Supplement F

The chemistry of amino, nitroso and nitro compounds and their derivatives

Part 2

Edited by Saul Patai

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Foreword

The present Supplement F includes material on nitrogen-containing functional groups such as amino, nitroso and nitro groups. In the main volumes of the Chemistry of the Functional Groups Series, these groups have been treated in the following books:

The Chemistry of the Amino Group (1968);

In addition, several functional groups which have not been treated in the main volumes have also been included, such as nitrones, nitronic acids, nitroxides, nitro-samines, nitrosoimines, enamines and ynamines.

With the exception of a chapter on ‘Ipso-attacks involving NO₂ groups’, all chapters planned for this Supplementary Volume actually materialized.

The editor will be very grateful to readers who would communicate to him omissions or mistakes relating to this volume as well as to other volumes in the series.

Jerusalem. July 1981  
SAUL PATAI
The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced post-graduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a complete coverage of the subject with no overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of deter-
mination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra: a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume The Chemistry of the Carbonyl Group, and a chapter on 'Ketenes' is included in the volume The Chemistry of Alkenes). In other cases certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in The Chemistry of the Ether Linkage, or 'Tetraaminoethylenes' in The Chemistry of the Amino Group.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of a supplementary volume, containing material on related functional groups, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The Chemistry of Alkenes (two volumes)
The Chemistry of the Carbonyl Group (two volumes)
The Chemistry of the Ether Linkage
The Chemistry of the Amino Group
The Chemistry of the Nitro and Nitroso Groups (two parts)
The Chemistry of Carboxylic Acids and Esters
The Chemistry of the Carbon–Nitrogen Double Bond
The Chemistry of the Cyano Group
The Chemistry of Amides
The Chemistry of the Hydroxyl Group (two parts)
The Chemistry of the Azido Group
The Chemistry of Acyl Halides
The Chemistry of the Carbon–Halogen Bond (two parts)
The Chemistry of Quinonoid Compounds (two parts)
The Chemistry of the Thiol Group (two parts)
The Chemistry of Amidines and Imidates
The Chemistry of the Hydrazo, Azo and Azoxy Groups (two parts)
The Chemistry of Cyanates and their Thio Derivatives (two parts)
The Chemistry of Diazonium and Diazo Groups (two parts)
The Chemistry of the Carbon–Carbon Triple Bond (two parts)
Supplement A: The Chemistry of Double-bonded Functional Groups (two parts)
Preface to the series

Supplement B: The Chemistry of Acid Derivatives (two parts)
The Chemistry of Ketenes, Allenes and Related Compounds (two parts)
Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues (two parts)
The Chemistry of the Sulphonium Group (two parts)
Supplement F: The Chemistry of Amino, Nitroso and Nitro Groups and their Derivatives (two parts)

Titles in press:
The Chemistry of Peroxides
The Chemistry of Organometallic Compounds
Supplement C: The Chemistry of Triple-bonded Functional Groups
Supplement D: The Chemistry of Halides and Pseudo-halides

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.
The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task, and who continues to help and advise me. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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Jerusalem, ISRAEL

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CHAPTER 16

Nitro-activated carbon acids

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I. INTRODUCTION

One of the notable properties of nitroalkanes is their perceptible acidity. This chapter will be devoted to the various aspects and manifestations, both equilibrium and kinetic, of this acidity.

A discussion of acidity requires a definition of acidity. Most of this chapter will be concerned with the Brønsted definition, that is, substances from which a proton can be removed. There will be a briefer mention of the Lewis acidity of some nitro compounds.

II. EQUILIBRIUM ACIDITY

A. Brønsted Acids

The nitro-activated carbon acids can be classified into three groups: firstly, nitromethane and its mono- and di-substituted derivatives, R₂CHNO₂; secondly the
vinyllogous substituted nitromethanes (in both of these classes there is an important resonance stabilization of the conjugate base), and thirdly carbon acids stabilized only by an inductive effect of the nitro group, of which there are few examples.

1. Nitromethane derivatives

A consideration of the structure of a nitroalkane (1) and its conjugate base (2) clarifies the source of both the resonance and the inductive effects.

\[
\begin{align*}
\text{(1)} & \\
R_2CH^-N\overset{+}{O}- & \leftrightarrow & R_2CH^-N\overset{O^{-}}{O}^- \\
\text{(2a)} & \\
R_2\overset{+}{C}^-N\overset{O}{O}^- & \leftrightarrow & R_2\overset{+}{C}^-N\overset{O^{-}}{O}^- \\
\text{(2b)} & \\
\text{(2c)} &
\end{align*}
\]

All the structures show the inductive effect derived from the formal positive charge on nitrogen. The major resonance stabilization of the anion arises from the additional structure 2c, which is important because the negative charge resides wholly on oxygen. The effect of the nitro group is very large, as shown in Table 1, which shows some approximate pKₐ values for a variety of substituted methanes. (These values are taken from Cram; they are rather uncertain at the high pKₐ end.)

The nitro group clearly has an enormous effect, of about 30 powers of ten on the equilibrium constant, although further nitro substitution is far less effective. This rather limited effect of the extra nitro group is probably attributable to a steric

<table>
<thead>
<tr>
<th>Methane substituent</th>
<th>pKₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Ph</td>
<td>35</td>
</tr>
<tr>
<td>CN</td>
<td>25</td>
</tr>
<tr>
<td>MeSO₂</td>
<td>23</td>
</tr>
<tr>
<td>MeCO</td>
<td>20</td>
</tr>
<tr>
<td>(MeSO₂)₂</td>
<td>14</td>
</tr>
<tr>
<td>(CN)₂</td>
<td>11.5</td>
</tr>
<tr>
<td>NO₂</td>
<td>10.2</td>
</tr>
<tr>
<td>(MeCO)₂</td>
<td>9</td>
</tr>
<tr>
<td>(MeCO)₃</td>
<td>6</td>
</tr>
<tr>
<td>(NO₂)₂</td>
<td>3.6</td>
</tr>
<tr>
<td>(MeSO₂)₃</td>
<td>~0</td>
</tr>
<tr>
<td>(NO₂)₃</td>
<td>~0</td>
</tr>
<tr>
<td>(CN)₃</td>
<td>&lt;0</td>
</tr>
</tbody>
</table>
effect which prevents coplanarity in the anion. A striking example of this steric inhibition of resonance is found in the comparison of trinitromethane, $pK_a$ about 0, with dinitro cyanomethane, $pK_a$ about $-6$; even though one nitro is more strengthening than one cyano, the third nitro group is much less effective than the linear cyano group. This argument and the crystallographic data on the two anions has been presented by Kaplan.33

The large steric requirements of the nitro group are in part responsible for the poor correlation of $K_a$ for substituted nitromethanes with ordinary substituent constants, such as $\sigma_1$. In cases where resonance interactions are eliminated, and the substitution is limited to relatively distant substitution on 1-nitroalkanes, a Taft treatment is modestly successful but 1-substitution is not simply treated. An interesting reversal of $\sigma_1$ correlation is found when alkyl substituents are introduced into nitromethane. The $pK_a$s of nitromethane, nitroethane and 2-nitropropane are 10.2, 8.5 and 7.7 respectively in water at 25°C, showing that the alkyl groups are acid-strengthening rather than -weakening as would be predicted from the negative $\sigma_1$ values. This peculiarity has long been recognized and is attributed to the stabilization by alkyl groups of the double bond (in structure 2c) of the nitronate anion. This stabilization is often attributed to hyperconjugation. We shall return to this peculiar effect of alkyl groups in the discussion of rates of ionization. The predominant contribution of the double-bonded structure is also relevant to the acidities of nitrocycloalkanes, which have been extensively studied recently by Bordwell and coworkers.6 The general problem of whether a methyl group is acid-strengthening or -weakening has also been discussed by this group, with consideration of medium changes, including the gas phase, DMSO, aqueous methanol and water.7

An idea of the range of acidities of various substituted nitromethanes can be obtained from Table 2, which contains data mostly from the older literature. Table 2 shows several of the effects already mentioned. Beyond that one can note that alkyl groups, except on the 1-carbon of 1-nitroalkanes, are acid-weakening, and fluorine is strongly acid-weakening at the 1-position.

<table>
<thead>
<tr>
<th>Nitroalkane</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$NO$_2$</td>
<td>10.2</td>
</tr>
<tr>
<td>CH$_3$CH$_2$NO$_2$</td>
<td>8.5</td>
</tr>
<tr>
<td>CH$_3$CH$_2$CH$_2$NO$_2$</td>
<td>9.0</td>
</tr>
<tr>
<td>(CH$_3$)$_2$CHNO$_2$</td>
<td>7.7</td>
</tr>
<tr>
<td>PhCH$_2$NO$_2$</td>
<td>6.8</td>
</tr>
<tr>
<td>CH$_2$(NO$_2$)$_2$</td>
<td>3.6</td>
</tr>
<tr>
<td>CH(NO$_2$)$_3$</td>
<td>0.1</td>
</tr>
<tr>
<td>NCCH(NO$_2$)$_2$</td>
<td>-6.2</td>
</tr>
<tr>
<td>CH$_2$ClNO$_2$</td>
<td>7.2</td>
</tr>
<tr>
<td>CHCl$_2$NO$_2$</td>
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</tr>
<tr>
<td>CH$_2$F$_2$NO$_2$</td>
<td>12.4</td>
</tr>
<tr>
<td>CF$_3$CH$_2$NO$_2$</td>
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</tr>
<tr>
<td>CH$_3$COCH$_2$NO$_2$</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Values are selected and rounded to 0.1 $pK_a$ units from Neilson.47.
2. Vinylogous substituted nitromethanes

There are in principle numerous examples of vinylogously activated carbon acids, for example 1-nitropropene (3) which might be thought to be acidic according to equation (1). The ionization however, also equilibrates 3 with 3-nitropropene by virtue of the possible protonation of the anion at the other carbon of the allylic system. The equilibrium (and kinetic) behaviour of 3-nitropropene and a number of its methylated derivatives have been studied by Bordwell and Hautala, but will not be further discussed here.

The most familiar of these vinylogous nitromethanes are the various derivatives of o- or p-nitrotoluene. The nitrotoluenes themselves have not been the subject of much study although p-nitrotoluene has been reported to exchange with ethanol-d and sodium hydroxide at elevated temperatures, but rather extensive studies have been made of 2,4,6-trinitrotoluene on the other hand and di- or tri-nitrophenylmethanes on the other. The latter system is the simplest to describe. The 4,4',4''-trinitrotriphenylmethane has been known to be significantly acidic for some time. However, the evaluation of the equilibrium constant could not be undertaken before a general understanding of this problem for all weak acids. The acidities of a number of these derivatives were measured by an acidity function method by Bowden and Stewart, as shown in Table 3, and the behaviour was so good that the compounds were recommended as indicators for an $H_-$ scale in solvents containing ethanol, dimethyl sulphoxide and sodium ethoxide.

The problem of 2,4,6-trinitrotoluene is more difficult, for there are several competing reactions when this is mixed with strong base. One is the proton transfer and the others are the formation of two addition products, as shown in equation (2).

The complexities introduced by these and other reactions have been studied intensively, especially in connection with the relation to the nitro-activated substitution reactions passing through Meisenheimer complexes. The $pK_a$ of trinitrotoluene is not reported, and indeed the identity of the trinitrobenzyl anion and a purple species produced rather rapidly is open to some question. Nevertheless it appears from these results that trinitrotoluene is slightly stronger than methanol in methanol, and considerably stronger than ethanol in ethanol. A report of $K_a = 1 \times 10^{-12}$ by Cuta and Beranek, is almost consistent with the earlier observations, but difficulties due to irreversible reactions have been

<table>
<thead>
<tr>
<th>Compound</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,4',4''-Trinitrotriphenylmethane</td>
<td>14.32</td>
</tr>
<tr>
<td>4,4'-Dinitrodiphenylmethane</td>
<td>15.85</td>
</tr>
<tr>
<td>2,4'-Dinitrodiphenylmethane</td>
<td>17.38</td>
</tr>
<tr>
<td>3,4'-Dinitrodiphenylmethane</td>
<td>17.62</td>
</tr>
</tbody>
</table>
reported. Apparently the polynitrophenyl systems encourage the formation of the addition complexes, thus confusing the simple ionization.

3. Inductively strengthened carbon acids

The nitro group, presumably because of the formal positive charge on nitrogen, can strengthen acids by virtue of an inductive effect alone. However, the resonance effect is normally so large that the inductive effect cannot easily be separated and evaluated. There are cases in which the inductive effect of a nitro group can be identified in the acid-strengthening of another type of carbon acid. As an example, in the ionization of substituted 1-phenyl-2-nitropropane the strongest acid is that with the p-nitrophenyl group. The nitro group in the ring is not conjugated with the carbanion centre, so its action must be inductive. Similarly, α,ω-dinitroalkanes are (even after statistical correction) perceptibly stronger than the 1-nitroalkanes. The magnitude of this inductive effect can be estimated using the σ values, which are large. Thus σ for nitro is +0.63, and the trinitromethyl group has σ = +2.04 (based on σ = σ*/2.22) as determined by Hine and Bailey. Nevertheless, there are few known aliphatic acids strengthened to a measurable level by nitro or even trinitromethyl groups.

One almost straightforward example of an inductively strengthened carbon acid is trinitrobenzene. The first hint that the 2,4,6-trinitrophenyl anion was perceptibly stable arose from the observation of facile decarboxylation of the 2,4,6-trinitrobenzoate ion (4). This decarboxylation appears to be a unimolecular
loss of carbon dioxide which is favoured when the product carbanion is stable, as in β-ketocarboxylates, nitroacetates, etc. An early report of catalysed deuterium exchange of 1,3,5-trinitrobenzene was initially not reproduced under milder conditions, but the problem has more recently been simply resolved. Trinitrobenzene reacts with hydroxide or alkoxide to give a rather stable Meisenheimer complex (5) which is of course not significantly acidic. Thus exchange can only occur on the rather small fraction of the free trinitrobenzene.

\[ \text{Meisenheimer complex (5)} \]

The competition between ionization and Meisenheimer complex formation is solvent-sensitive and the exchange can be made facile at room temperature. A more complete and up-to-date account is found in the review by Leffek.

Because of a different balance between base addition and proton abstraction, the presumably less acidic 1,3-dinitrobenzene exchanges faster at the 2-position than does trinitrobenzene, as has been explored by several workers, again described in the review by Leffek. The explanation confirms the identification of this acidity as being inductively enhanced; a third more remote nitro group enhances the acidity of 1,3-dinitrobenzene very little, but it adds substantial resonance stabilization to the Meisenheimer complex.

The acid dissociation constant of 1,3,5-trinitrobenzene is not given by these various data, and an equilibrium amount of the anion has not been seen. We may conclude that the pKₐ is probably substantially greater than 14.

B. Tautomerism and Dissociation Constant Measurements in Nitroalkanes

1. Nitronic acids as tautomers of nitroalkanes

A feature of the chemistry of nitroalkanes is the existence of tautomers, as shown in equation (3). The tautomers are now generally called nitronic acids; earlier they were called aci-nitro compounds. These tautomers are usually unstable with respect to the nitroalkanes, but are known because the interconversion is often slow.

\[ \text{Nitronic acids and the nitro compounds share the common anion, the nitronate ion, } R_2CNO}_2^- \text{ and like enols, are prepared by rapid acidification of solutions of this common anion.} \]

The conversion of the nitro compound to the nitronic acid via the nitronate ion is well established. By analogy with the keto–enol tautomerism, an acid-catalysed equilibration via a common cation (6) can be envisioned.

There is, however, no convincing evidence for this route although it has been claimed. Junell studied bromination of nitroalkanes in aqueous HBr. This reaction, zero order in bromine, presumably has a nitronic acid intermediate, but does not increase in rate with added acid. Pedersen, who studied the
base-catalysed reactions of nitroalkanes, estimated that Junell's rates were essentially the same as his own for base catalysis by the solvent water. Furthermore, nitromethane is not perceptibly protonated, as measured by freezing-point depression even in 100% sulphuric acid. The slow 'acid-catalysed' Nef reaction also presumably passes through the nitronic acid as do normal Nef reactions; it may also not have the rate accelerated by acid, although the acid is clearly necessary to suppress side-reactions.

2. Acid dissociation constants of nitronic acids and nitro compounds

The existence of tautomers has an important effect on the measurement of the acidity of nitro compounds. Consider the ionization constants of the nitro compounds, with carbon-bound proton, $K_C$ and those of the nitronic acids, with oxygen-bound proton, $K_O$:

$$K_C = \frac{[R_2\text{CNO}_2^-][H^+]}{[R_2\text{HCNO}_2]}$$

$$K_O = \frac{[R_2\text{CNO}_2][H^+]}{[R_2\text{CNO}_2\text{H}]}$$

These readily give equation (4).

$$K_C = \frac{[R_2\text{CNO}_2\text{H}]}{[R_2\text{HCNO}_2]} = K_{taut}$$

$K_{taut}$ is the equilibrium constant for the tautomerization of equation (3). The statement that the equilibrium usually favours the nitro compound is equivalent to saying that the nitronic acid is a stronger acid than the nitro compound.

The 'contamination' of a sample of a nitro compound by a stronger acid can clearly cause an error in the measurement of $K_C$, but corrections now to be described can be made.

Most methods of measurement of ionization constants of neutral acids measure the concentration of the ions, and if there are two neutral species in equilibrium with the same ions, an apparent equilibrium constant will be measured, $K_{app}$, defined by equation (5). This leads directly to equation (6), and then to the correction of equation (7). Thus $K_{app}$ is very close to $K_C$ when $K_{taut}$ is small, but if

$$K_{app} = \frac{[R_2\text{CNO}_2^-][H^+]}{[R_2\text{HCNO}_2] + [R_2\text{CNO}_2\text{H}]}$$

$$\frac{1}{K_{app}} = \frac{1}{K_C} + \frac{1}{K_O}$$

$$\frac{K_{app}}{K_C} = \frac{1}{1 + K_{taut}}$$

$K_{taut}$ is much larger than unity, $K_{app}$ is closer to $K_O$ than to $K_C$. As we shall see, $K_{taut}$ is usually $<10^{-2}$, and the error in assuming $K_C = K_{app}$ is less than 1%.
TABLE 4. Acid strengths of nitronic acids and nitro compounds

<table>
<thead>
<tr>
<th>Parent nitro compound</th>
<th>$pK_O$</th>
<th>$pK_C$</th>
<th>$\log K_{taut}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_2$NO$_2$</td>
<td>3.3</td>
<td>10.2</td>
<td>$-6.9$</td>
</tr>
<tr>
<td>C$_2$H$_5$NO$_2$</td>
<td>4.4</td>
<td>8.5</td>
<td>$-4.1$</td>
</tr>
<tr>
<td>CH$_3$CH$_2$CH$_2$NO$_2$</td>
<td>4.6</td>
<td>9.0</td>
<td>$-4.4$</td>
</tr>
<tr>
<td>(CH$_3$)$_2$CHNO$_2$</td>
<td>5.1</td>
<td>7.7</td>
<td>$-2.6$</td>
</tr>
<tr>
<td>$\text{c-C}<em>6\text{H}</em>{11}$NO$_2$</td>
<td>6.4</td>
<td>8.3</td>
<td>$-1.9$</td>
</tr>
<tr>
<td>PhCH$_2$NO$_2$</td>
<td>3.9</td>
<td>6.8</td>
<td>$-2.9$</td>
</tr>
<tr>
<td>CH$_2$(NO$_2$)$_2$</td>
<td>1.9</td>
<td>3.6</td>
<td>$-1.7$</td>
</tr>
<tr>
<td>CH$_3$CH(NO$_2$)$_2$</td>
<td>4.0</td>
<td>5.1</td>
<td>$-1.1$</td>
</tr>
<tr>
<td>CH$_3$CH$_2$CH(NO$_2$)$_2$</td>
<td>4.1</td>
<td>5.6</td>
<td>$-1.5$</td>
</tr>
</tbody>
</table>

In spite of the unimportance of nitronic acids at equilibrium, it is possible to establish both $K_O$ and $K_C$ in the same solution. If a solution of the nitronate ion is rapidly acidified with a half equivalent of strong acid, the solution initially contains equal amounts of nitronic acid and nitronate ion. Thus (with the usual corrections) $pH = pK_O$. In the course of time, which may be seconds or hours, the nitro compound is gradually formed and finally equilibrium is established between all species, and $pH = pK_{app}$. Of course data can be obtained similarly with other ratios of acid and nitronate. Conductivity and pH methods starting with the nitro compound rather than the nitronate ion reach equilibrium slowly and can give only $K_{app}$.

A number of compounds with their $K_C$ and $K_O$ (and $K_{taut}$) values are presented in Table 4. It can be seen, not surprisingly, that $K_O$ is far less sensitive to substituent than $K_C$, hence $K_C$ and $K_{taut}$ are somewhat correlated. The values presented in the table are taken from a table compiled from a number of different sources by Neilson$^{47}$ and are of uncertain accuracy. For this reason the acidities will not be pursued in further detail.

Another problem associated with these acidity measurements is that nitronic acids undergo irreversible decomposition to give ketones (the Nef reaction), oximes and other products. These reactions, usually slow, limit the accuracy of both $K_O$ and $K_C$ values, in some cases possibly seriously. Discussion of these problems is outside the scope of this chapter.

**C. Lewis Acidity of Nitro Compounds**

There are numerous examples of interaction of electron-rich compounds with nitro compounds. Some of these are not structurally clear, such as the use of tetranitromethane as a colour test for unsaturation. Some are clearly one-electron transfer reactions; both aliphatic and, especially, aromatic nitro compounds form significantly stable radical anions. Some are the 'complexes' formed by many aromatic hydrocarbons with trinitrobenzene, picric acid and the like. Those that are the clearest examples of single bond formation with bases, and hence Lewis acid reactions in the most rigorous sense, are the reactions of polynitroaromatics to form Meisenheimer complexes. Several examples have been mentioned in connection with the discussion of the proton activity of trinitrotoluene and trinitrobenzene. The additions to polynitroaromatics have been reviewed in this series by Hall and Poranski$^{26}$. In view of the fact that Lewis acidity has eluded an absolute quantitative treatment, no effort will be made in this direction here. However, equilibrium constants in a number of additions have been measured and are summarized in the above review.
III. RATES OF PROTON TRANSFER FROM NITROALKANES

A. Contrast between Nitroalkanes and other Carbon Acids

The acidity of many carbon acids has been estimated by their ‘kinetic acidities’. There is presumed a form of correlation between the rates of proton transfer from the acid (as measured by isotopic exchange, stereochemical change or a more drastic change attributable to the carbanion only) and the equilibrium constant for the reversible proton loss. A linear correlation between $\log k$ and $pK_a$ is the Brønsted relation, and Pearson and Dillon\(^4^8\) have made such a plot for a series of carbon acids ionizing in water. A group of carbonyl compounds defines roughly a straight line with Brønsted $\alpha = 0.6$, but there are major deviations, the worst of which are the nitroalkanes. Thus in this reaction with water, nitroethane, which is a slightly stronger acid ($pK_a = 8.7$) than acetylacetone ($pK_a = 9.0$), has a reaction rate about two million times slower.

It is this unexpectedly slow reaction of nitroalkanes with bases that has become a central item of interest in nitroalkane chemistry. The observation of a very slow reaction rate was noted by Hantzsch\(^2^9\) who coined the term pseudo acid. Nitro compounds represent the extreme of these slowly reacting acids, but the behaviour is not unique. Thus (with the data of Pearson and Dillon) from the rate constant ($3.7 \times 10^{-8}$ s\(^{-1}\)) for the reaction of nitroethane with water and its acid strength ($K_a = 2.5 \times 10^{-9}$), the reverse reaction rate of the nitronate ion with H\(_3\)O\(^+\) has a rate constant of $15 \text{ mol}^{-1}\text{s}^{-1}$, which is far below the diffusion-controlled rate. Acetylacetone anion reacts similarly with H\(_3\)O\(^+\) with $k = 1.7 \times 10^7$, still well below diffusion control. Dicyanomethane anion reacts with H\(_3\)O\(^+\) with a rate constant of $2.3 \times 10^9 \text{ mol}^{-1}\text{s}^{-1}$, close to the diffusion limit. In general, carbon acids activated by cyano or sulphonyl groups appear to react in the favoured direction at virtually the diffusional limit, carbonyl-activated compounds are slower, and the nitro compounds are by far the slowest, and do not come close to the diffusional limit in either direction. We may note, however, that nitronate ions are O-protonated very rapidly, probably at the diffusion-controlled rate and this great contrast between the rates of C-protonation and O-protonation accounts for the isolability of the nitronic acids.

B. Rates and Equilibria of Ionization of Nitro Compounds

1. Effect of changing substituents

Nitroalkanes deviate strongly from the rate–equilibrium relation defined by a group of carbonyl activated acids as described above, but even among themselves there is little semblance of a rate–equilibrium correlation. The first conspicuous example of this unexpected situation appeared in the reactions of nitromethane, nitroethane and 2-nitropropane with relative rates of 1, 0.16 and 0.009 respectively, although the acid dissociation constants increase in the same order: $6 \times 10^{-11}$, $3 \times 10^{-9}$, $2 \times 10^{-8}$. These values are quoted by Hammett\(^2^8\), who comments: ‘This is a most important case of failure of the usual rate–equilibrium parallelism’. An alternative expression of this unusual situation is to express the rate–equilibrium relation in terms of a three-point Brønsted plot, which leads to the Brønsted $\alpha = -0.5$. The reverse C-protonation correspondingly has $\beta = +1.5$. These Brønsted exponents, outside the expected limits of 0 to +1, were pointed out by Bordwell and coworkers\(^1^1\) and by Kresge\(^3^9\). A partial explanation offered earlier is that the rates show the normal inductive effect of the methyl groups, but the
equilibrium constants show the unusual acid-strengthening effect attributed to hyperconjugation in the nitronate anion, as described earlier in this chapter.

Our recent knowledge of both rate and equilibria in nitro compound ionization is greatly enhanced by the important and careful quantitative measurements of Bordwell and his coworkers. These are extensively but not comprehensively referred to in this chapter. The next unusual rate–equilibrium relation is in a series of more closely related compounds, the substituted 1-phenylnitroethanes in the reaction with hydroxide in aqueous methanol (equation 8)\(^{12,23}\). Both rates and equilibrium constants (expressed as \(K_a\)) fit the Hammett equation with the 
\[
\rho_{\text{rate}} = +1.44, \quad \rho_{\text{eq}} = +1.07.
\]
Thus the log \(k\) vs. \(\log K_a\) plot is linear with a slope 1.44/1.07 = +1.35, and this is the Brønsted \(\alpha\). Correspondingly, for the reverse C-protonation, \(\beta = -0.35\). These are again outside the expected zero to one range. Similarly for substituted 1-phenyl-2-nitropropanes, where there is now no resonance interaction between the anionic centre and the benzene ring, \(\rho_{\text{rate}} = +0.665, \quad \rho_{\text{eq}} = +0.395, \quad \alpha = +1.68, \quad \beta \) (for the reverse) = −0.68. These unusual values of \(\alpha\) have become known as the 'nitro anomaly'.

These results are clearly even more convincing than the methyl-ethyl-isopropyl series, in that there are more points and the substitutions are essentially free from special resonance and steric effects. The initial reaction is that the aliphatic series, with \(\alpha < 0\) cannot possibly be explained in the same way, yet a single explanation in fact serves for both.

If we compare \(\rho_{\text{eq}}\) for the 1-aryl-2-nitropropanes with that for the 1-arylnitroethanes, we find the former is smaller by a factor of 2.7. This is an example of the attenuation of substituent effects by moving the created charged farther from the benzene bearing substituents by the \(\text{CH}_2\) groups. Parenthetically, we may note that the rather large attenuation factor probably reflects a little resonance delocalization into the ring in the 1-arylnitroethane anion case. Thus the \(\rho\) values are relatively normal in this respect. The \(\rho_{\text{eq}}\) value for the arylnitroethanes is, however, quite small. In this aqueous methanol medium the value is less than would be expected for benzoic acid ionization (ca. +1.3), and applying the same argument as above, the negative charge is on the average farther from the benzene ring than it is in the benzoate ion. Thus the contribution of 7a must be much greater than that of 7b, which if predominant would lead to \(\rho > 2\). (The extra formal \(\begin{align*}
\text{CH}_3 & \quad \text{N} \quad \text{O}^- \\
\text{X} & \quad \text{C} \\
\text{CH}_3 & \quad \text{N} \quad \text{O}^-
\end{align*}\)

charges, positive on \(N\), negative on one \(O\), are present also in the neutral nitro compound and therefore do not contribute to \(\rho\).

It remains only to say that the larger \(\rho\) for the rate must mean that in the transition state for the proton transfer it must have either more than one net negative charge distributed like the nitronate ion, which is quite absurd, or the net negative charge must be closer to the ring. This leads to a transition state 8, with 8b contributing more than 8a. This description of the transition state is probably correct but leaves a number of questions open, such as what is the value of the partial negative charge \(\delta\), what are the relative contributions of 8a and 8b, and why do they differ so drastically from the relative contributions of 7a and 7b?
16. Nitro-activated carbon acids

\[
\begin{align*}
\text{ArC}^+\text{O}^-(1 + \delta) & \quad \text{Ar}^\delta\text{C}^+\text{O}(1 - \delta) \\
(1 - \delta) & \quad (1 - \delta)
\end{align*}
\]

The same explanation applies to the aliphatic case. The methyl groups substituted on nitromethane exert their usual destabilizing effect on the carbanionic transition state, which is greater than that on the product nitronate; in fact the product as described earlier is actually stabilized by the methyl groups, with the charge mostly located on oxygen. The negative $\alpha$ is only a reflection of the unusual acid-strengthening effect of the methyl groups.

This argument is original in wording only. Thus twenty-six years ago Ingold\textsuperscript{31} wrote with reference to the aliphatic case: '... it is the inductive effect of the alkyl groups which is controlling the rate of proton transfer from the nitro compounds ... it is chiefly the hyperconjugative effect of the alkyl groups which controls the equilibrium ... in the transition state of the proton transfer there is not yet sufficient growth of the CN double bond to furnish the degree of unsaturation needed to excite a dominating hyperconjugative effect in alkyl substituents'. Bordwell\textsuperscript{12} concluded that 'an appreciable negative charge must, therefore, have been developed on carbon, but this charge has not been delocalized to any marked degree to the nitro group'.

This ionization of nitroalkanes was quoted by Fuchs and Lewis\textsuperscript{22}, as an example of a reaction in which various measures of the position of the transition state do not coincide; the charge development on carbon and on oxygen do not keep in phase.

A nice presentation of the difference in the course of development of negative charge on carbon and on oxygen and the development of CN double-bond character has been presented by Davies\textsuperscript{20}, in connection with a study of secondary isotope effects in the ionization of 2-nitropropane.

There have been several applications of Marcus' theory\textsuperscript{44} to the nitroalkane ionization problem. This theory, with the assumption, common to most other applications, that there is a constant intrinsic barrier, requires that $\alpha$ lies between zero and one. The problem of accommodating Marcus' theory to the normal $\alpha$ values has been summarized by Kresge\textsuperscript{38} in a review in which eight examples of $\alpha$ outside the normal range are listed, of which seven are nitro compounds. The observations then require one of three conclusions: firstly, Marcus' theory is not applicable; secondly, the intrinsic barriers are highly variable; and thirdly, the work terms, in contrast to the usual situations, are structure-dependent. The second conclusion is advocated by Marcus\textsuperscript{45}. The reason for variable intrinsic barriers in this reaction is made plausible, and it is suggested that $\rho$ values for a nitro compound reacting with a variety of different oxygen or nitrogen bases should not have the problem, in agreement with experiment.

Kresge\textsuperscript{32} originally concluded that the unusual $\alpha$ values implied a special transition-state interaction between the base and the nitro compound, not present in reagent or product. A later extension by Kresge\textsuperscript{39} identified two interactions as the nitronate hyperconjugation, present in the product but only to a small extent in the transition state, and an electrostatic interaction between the negative charge on carbon and the substituents, which is important in the transition state but not the product. The treatment was made plausible by considering that the delocalization of
charge onto oxygen could well not be important until the system had become highly product-like. A quantitative treatment was able to reproduce both the \( \alpha \) for the alkylated nitromethanes and for the arylated systems. It improves on the Ingold treatment in that the development of the delocalization is quantitatively expressed.

Albery and coworkers\(^1\) have made a sophisticated application of Marcus' theory to diazo compound protonation and to \( C \)-protonation of nitronates in which the work terms are structure-sensitive. They divided the work terms into two parts, the usual structure-insensitive part and a part devoted to solvation and conformational changes on each side of the actual proton-transfer part. These distinct steps might also be to some extent merged, but not to the extent of allowing the reagents and products of the proton-transfer step to resemble very closely the separated reagents and products.

A possible, although by no means necessary, interpretation of the Albery work is that there is an extra real intermediate in the ionization process, namely a distinct, undelocalized carbanion as shown in equation (9), which then flattens out to the planar nitronate in reaction (10). This makes it clear that the transition state lies near the undelocalized carbanion and thus allows an immediate understanding of the anomalous \( \alpha \) values. However, it is unacceptable from several aspects. An estimate of the acidity of nitromethane with only the inductive contribution can be made, and thus an estimate of the very small equilibrium constant for equation (9). To reproduce the observed rate an unacceptably high rate for reaction (10) must be assigned, an argument communicated to me by Professor H. C. Gilbert. Secondly, the pyramidal carbanion would not appear to represent an energy minimum at all, whether the delocalization is prevented by the tetrahedral bond angles as shown, or by an unfavourable angle between the \( \text{CRR} \) plane and the \( \text{O}_2\text{NC} \) plane. Nevertheless, this two-step mechanism is a way of thinking about the single transition state, and Bordwell\(^8\) has used the description of the undelocalized carbanion as a 'virtual' intermediate, to emphasize the excess charge on carbon in the transition state.

2. Role of the solvent

The role of the solvent in this proton transfer cannot be ignored, and is difficult to describe. One possible specific role may be hydrogen bonding to the nitronate ion as in 9, which might be the source of the predominance of the charge on oxygen rather than on carbon. Against a major contribution from this effect is the
observation that nitromethane and phenol are comparably acidic in a number of different media from water to the gas phase. Furthermore, nitronic acids are fairly strong, thus the nitronates are not very basic on oxygen and might not form very strong hydrogen bonds. However, in dimethyl sulphoxide the rates and equilibria for the proton transfer from arylnitromethanes to benzoate ion have been measured and the Brønsted $\alpha$ is 0.92, compared to the value of 1.54 in water. The $\alpha$ value is no longer conspicuously anomalous, although still quite large, and Keefe believes that the ‘nitro compound anomaly’ is a consequence of the use of protic solvents. The high rate in DMSO also suggests reduction in the amount of solvent reorganization.

Slater and Chan have studied the effect of adding DMSO to water on the rate of the phenylnitromethane–hydride ion reaction. The rates increased with DMSO added to a concentration of about 67%, but only to the extent expected from the increasing basicity of the hydroxide ion, and they therefore concluded that solvent reorganization was not greatly altered. The question of extent and importance of hydrogen bonding in the nitronate ion cannot be regarded as entirely resolved.

3. Effect of the nature of the base

Two other approaches to the nature of the transition state for nitroalkane ionization have been extensively studied, and have been less informative than one might have hoped. The first is the measurement of the rates of a single nitro compound with a series of bases to yield a Brønsted $\beta$; many values of $\beta$ have been measured. The range is rather small, and they always have fallen within the normal range of 0–1. The $\beta$ values have not correlated well with the expected behaviour: small values associated with exothermic, fast, reagent-like transition states and values nearly unity for those that are product-like. Several of these $\beta$ values have been listed to show the unsatisfactory nature of the problem.

4. Isotope effect studies

There has been a considerable effort to use the hydrogen isotope effect to further define the transition state for the proton transfer from nitro compounds. The existence of a substantial isotope effect was one of the very first deuterium isotope effects measured, and the field has been reviewed by Leffek.

The effort has been to deduce the symmetry of the transition state based on the Westheimer argument that transition states, with nearly equal force constants (symmetrical transition states) to the transferring proton, should give nearly maximum isotope effects, and those with greatly unbalanced force constants in either direction should give almost no isotope effect. The method in principle relates, without much rigour, the symmetrical transition state to the transition state halfway between reagent and product, and therefore (by another nonrigorous argument) to the case of unit equilibrium constant. Isotope effects less than the maximum then correspond to reactions of equilibrium constants far removed from unity. This has led to the plot, presented by Bell and Goodall, of hydrogen isotope effect vs. $\Delta pK_a$ (the $pK$ for each equilibrium of the series of proton transfers). Such plots do often show maxima in the neighbourhood of $\Delta pK_a = 0$, but they are often broad, sometimes with much larger isotope effects than are allowed by the Westheimer treatment, and suffer from the fact that the measured isotope effect leads to an ambiguity in the sign of $\Delta pK_a$. The situation with respect to the nitro compounds is to some extent summarized by the following quotation: ‘The hope, which at one time seemed bright, for a simple general correlation of Brønsted...
coefficients, kinetic isotope effects, and solvent isotope effects with the extent of proton transfer in the transition state has proved vain\textsuperscript{10}. The difficulty is that the term 'extent of proton transfer' is vague. It is either an unmeasurable philosophical concept, or is the result of some kind of measurement, and as pointed out earlier, different methods of measurement do give different answers with these nitro compounds.

The further problem is that models have suggested that the Westheimer highly unsymmetrical situation is almost unattainable\textsuperscript{3,5,2}, and that observed maxima may result from a variable tunnel correction. The tunnel correction is certainly present and variable, as demonstrated both by very high isotope effects and their temperature dependences\textsuperscript{2,24,35,42,43,53}. Thus the variable tunnel contribution cannot be neglected as a factor in the magnitude of the isotope effect, and Bordwell and Boyle's discouraging statement\textsuperscript{10} is at least partly justified.

**IV. CONCLUSIONS**

There are no longer major questions about the equilibrium acidities of substituted nitromethanes. The problem of rates has been attacked from many aspects, and the slowness is certainly related to the extensive geometrical, orbital, and possibly, solvation changes that go on. In spite of many obstacles, the transition states are probably understood far better than the transition states for most reactions. The slowness of C-protonation of nitronate anions does not seem to be a peculiarity of the proton, it is shared by other electrophiles, since alkylation of nitronate anions occurs almost only on oxygen. Perhaps the major challenge is to understand why the nitro compounds are so exceptionally slow, and to find examples of anomalous Brønsted behaviour outside the nitroalkanes.

**V. REFERENCES**

16. Nitro-activated carbon acids

CHAPTER 17

Gas-phase basicity and acidity of amines

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I. INTRODUCTION

The last decade has witnessed a most important development in physical organic chemistry: laboratory techniques (finally) became available which allowed direct measurements of the kinetics and equilibria for the protonation and deprotonation of organic molecules in the gas phase. A substantial fraction of the measurements which have been reported to date have dealt with the amines and these are the subject of this chapter. They have provided the first quantitative indication of the gas-phase basicity and acidity of these compounds and, as such, have furnished important insights into the fundamental tendency of isolated amine molecules to gain or lose a proton.

A considerable variety of techniques have proven to be suitable for gas-phase studies of proton-transfer reactions involving amines. These include techniques of ion cyclotron resonance (ICR) spectroscopy\(^1,2\), high-pressure mass spectrometry (HPMS)\(^3,4\), trapped-ion mass spectrometry (TIMS)\(^5\), the selected-ion flow tube (SIFT)\(^6\) and the flowing afterglow (FA) technique\(^7,8\). These make use of a variety of modes of ion production, containment and detection, and encompass a wide
range of operating conditions such as total pressure, ion and neutral concentrations, temperature, reaction time, and ambient electric fields. No attempt is made here to provide details of construction, operation and data analysis, or to address concerns which have been expressed regarding the nature of the reaction and equilibrium conditions which are actually achieved with the various techniques. These have been discussed elsewhere in considerable detail. This article will concentrate on the presentation of experimental results which have been reported on various physicochemical aspects of proton-transfer reactions involving amines. Some consideration will be given to the interpretations which have been proposed to account for the gas-phase results in terms of various intrinsic effects arising from the molecular structures of the amines. These can be said to have had important consequences for structural theories of organic chemistry in general. No attempt will be made here to discuss the bearing of the gas-phase measurements on the interpretation of the behaviour of corresponding acid–base reactions proceeding in solution. This aspect has been discussed thoroughly in the more general context of acid–base chemistry in four excellent review articles which have recently been authored by Taft and by Arnett.

II. KINETICS OF PROTONATION AND DEPROTONATION

A. Protonation of Ammonia

Laboratory measurements of the gas-phase kinetics for the protonation of ammonia have been restricted largely to proton-transfer reactions involving inorganic acids, primarily because of their usefulness in the assessment of various classical theories of ion-molecule collisions. The measured rate constants are included in the compilation presented in Table 1 from which it is apparent that the protonation of ammonia by inorganic acids generally proceeds rapidly at room temperature, \( k > 1 \times 10^{-9} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1} \), without complications from other reaction channels. The information presently available on the dependence of these rate constants on translational and internal energy is insufficient to allow any generalizations to be made in this regard. However, attention should be drawn to a few specific observations.

(i) For the proton-transfer reactions (equation 1) where \( X = \text{H}_2, \text{CO}, \text{CH}_4, \text{O}_2 \)

\[
\text{XH}^* + \text{NH}_3 \rightarrow \text{NH}_4^* + \text{X}
\]

and \( \text{HO}_2 \), the rate constants have been observed to be quite insensitive to the mean relative kinetic energy from thermal to about 1 eV.

(ii) For the deuteron-transfer reaction of \( \text{D}_3^+ \) with \( \text{NH}_3 \), internal excitation of the ion has been shown to actually decrease the rate constant as is shown in Figure 1.

(iii) In one study of the overall temperature dependence of the rate constant for the proton transfer to \( \text{NH}_3 \) from \( \text{N}_2\text{H}^+ \), a small negative temperature dependence was observed between 320 and 640 K.

The large values of the rate constants indicated in Table 1 clearly suggest high probabilities of protonation at room temperature. Indeed, a comparison of these values with gas-kinetic collision rate constants predicted from a consideration of the classical electrostatic (ion-induced dipole and ion-permanent dipole) interaction between the ions and \( \text{NH}_3 \) indicates that proton transfer proceeds at essentially every collision. Such a comparison is shown in Figure 2 for which capture collision
### Table 1. Some rate constants (in units of $10^{-9}$ cm$^3$ molecule$^{-1}$ s$^{-1}$) for the protonation of ammonia at room temperature

<table>
<thead>
<tr>
<th>Reactant ion</th>
<th>$k_{total}^a$</th>
<th>Mode of reaction$^b$</th>
<th>Technique$^c$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_3^+$</td>
<td>4.2</td>
<td>PT</td>
<td>FA</td>
<td>12</td>
</tr>
<tr>
<td>D$_3^+$</td>
<td>3.1</td>
<td>PT</td>
<td>FA</td>
<td>24</td>
</tr>
<tr>
<td>H$_3$O$^+$</td>
<td>2.4, 2, 2.2</td>
<td>PT</td>
<td>FA, ICR</td>
<td>12, 15</td>
</tr>
<tr>
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<td>PT</td>
<td>FA, SIFT, ICR</td>
<td>12, 13, 15</td>
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<tr>
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<td>PT</td>
<td>FDT</td>
<td>20</td>
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<tr>
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<td>PT</td>
<td>FDT</td>
<td>21</td>
</tr>
<tr>
<td>N$_2$H$^+$</td>
<td>2.3</td>
<td>PT</td>
<td>FA</td>
<td>12</td>
</tr>
<tr>
<td>N$_2$OH$^+$</td>
<td>2.1</td>
<td>PT</td>
<td>FA</td>
<td>12</td>
</tr>
<tr>
<td>H$_2$COH$^+$</td>
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<td>PT</td>
<td>FA, SIFT, ICR</td>
<td>17, 13, 15</td>
</tr>
<tr>
<td>CH$_5^+$</td>
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<td>PT</td>
<td>FA, ICR, TIMS</td>
<td>12, 16, 22</td>
</tr>
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<td>CD$_5^+$</td>
<td>2.06</td>
<td>PT</td>
<td>TIMS</td>
<td>22</td>
</tr>
<tr>
<td>C$_2$H$_2$$^+$</td>
<td>2.1, 2.00</td>
<td>PT</td>
<td>FA, ICR</td>
<td>12, 16</td>
</tr>
<tr>
<td>C$_2$H$_3$$^+$</td>
<td>2.0</td>
<td>PT</td>
<td>FA</td>
<td>12</td>
</tr>
<tr>
<td>C$_3$H$_3$$^+$</td>
<td>1.9, 1.95</td>
<td>PT</td>
<td>FA, ICR</td>
<td>12, 16</td>
</tr>
<tr>
<td>CH$^+$</td>
<td>2.7</td>
<td>HCNH$^+$</td>
<td>SIFT</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>(0.68)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>(0.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>(0.15)</td>
<td></td>
</tr>
<tr>
<td>CH$_2^+$</td>
<td>2.8</td>
<td>CH$_2$NH$_2^+$</td>
<td>SIFT</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>(0.55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>(0.45)</td>
<td></td>
</tr>
<tr>
<td>CH$_3^+$</td>
<td>2.2</td>
<td>H$_4$CN$^+$</td>
<td>SIFT</td>
<td>14</td>
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<td>CH$_3^+$+NH$_3$</td>
<td>(0.70)</td>
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</tr>
<tr>
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<td></td>
<td>PT</td>
<td>(0.20)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PT</td>
<td>(0.10)</td>
<td></td>
</tr>
<tr>
<td>CH$_4^+$</td>
<td>2.8</td>
<td>CT</td>
<td>SIFT</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>(0.59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>(0.41)</td>
<td></td>
</tr>
<tr>
<td>CCl$_2$D$^+$</td>
<td>0.78</td>
<td>PT</td>
<td>ICR</td>
<td>18, 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>(0.57)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CClDNH$_2^+$</td>
<td>(0.24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCIH$^+$NH$_2^+$</td>
<td>(0.19)</td>
<td></td>
</tr>
<tr>
<td>CF$_2$H$^+$</td>
<td>1.00</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CFH$^+$NH$_2^+$</td>
<td>(trace)</td>
<td></td>
</tr>
</tbody>
</table>

*a Total rate constant for the disappearance of the reactant ion.

*b The observed product distribution is given in parentheses. Proton-transfer and charge-transfer products are indicated as PT and CT, respectively. Otherwise just the observed ion is indicated.

*c FA = flowing afterglow. SIFT = selected-ion flow tube, ICR = ion cyclotron resonance, FDT = flow-drift tube, TIMS = trapped-ion mass spectrometry.

Rate constants are calculated using the average-dipole-orientation (ADO) theory modified to include conservation of angular momentum approximately (the AADO theory$^{26}$). Figure 2 includes the predictions of the locked-dipole and the pure polarization (Langevin) theories which are known to overestimate and underestimate, respectively, the capture collision rate constants but nevertheless

*The ADO theory takes into account ion-permanent dipole interaction which strongly affects the rate constant. In this theory the average orientation of the dipole has a value intermediate between that achieved if the dipole simply locks into the direction of the approaching ion (the locked-dipole limit) and that corresponding to a perpendicular orientation with respect to the line of centres of collision in which the dipole has essentially no effect on the rate constant. The pure polarization limit in which the presence of the dipole is completely ignored is given by what has become known as the Langevin theory.*
D. K. Bohme

provide useful limiting values. Furthermore, since these proton-transfer reactions cover a wide range in exothermicity (standard enthalpy change, $\Delta H^0$) or exoergicity (standard free energy change, $\Delta G^0$), it follows that the probability of protonation at room temperature is virtually independent of the relative gas-phase proton affinity or basicity of $X$ and $NH_3$. The reactions in Figure 2 span a range in exothermicity from approximately 35 to 110 kcal mol$^{-1}$.

$CH_5^+$ and the related alkanonium ions have also been found to react with $NH_3$ at room temperature exclusively by proton transfer, again with essentially unit probability. However, with the less hydrogenated $CH_x^+$ ($x = 1-4$) and the halogenated $CCl_2D^+$ and $CF_2H^+$ species, proton transfer has been observed to proceed in competition with a variety of other reaction channels. These are also delineated in Table 1. In the case of $CH^+$, for example, proton transfer competes with both a charge-transfer and a condensation channel according to equation (2)$^{14}$.

$$CH^+ + NH_3 \xrightarrow{0.68} HCNH^+ + H_2 \tag{2a}$$

$$\xrightarrow{0.17} NH_3^+ + CH \tag{2b}$$

$$\xrightarrow{0.15} NH_4^+ + C \tag{2c}$$

In fact, the major route of reaction results in $C-N$ bond formation by condensation to form protonated HCN. The analogous route also predominates with $CH_2^+$ in which case the methyleneimmonium ion $[H_2C\equiv:CHNH_2]^+$ is presumed to be formed. The reaction of the methylcarbonium ion with $NH_3$ has been

FIGURE 1. The influence of internal excitation on the rate of protonation of ammonia by $D_3^+$. In the Tandem-Ion Cyclotron Resonance (ICR) experiments deexcitation proceeds by collisions with $D_2$ molecules while in the flowing afterglow (FA) experiments collisions with He atoms prevail. Reproduced with permission from D. K. Bohme in Interactions between Ions and Molecules (Ed. P. Ausloos), Plenum Press, New York, 1975, p. 489.
observed to exhibit still another channel. The product ion spectrum recorded in an inert helium buffer at total pressures between 0.2 and 0.7 Torr is shown in equation (3)\textsuperscript{14}. Under these conditions 20% of the reactive collisions result in the formation of an adduct stabilized by collision with helium atoms and/or by radiative deexcitation. Condensation is again the major reaction channel. Experiments performed at low pressure with mixtures of deuterated methane and ammonia have shown that the condensation proceeds in two distinct ways, one resulting in the

\[
\begin{align*}
\text{CH}_3^+ + \text{NH}_3 & \quad \xrightarrow{0.70} \quad \text{H}_4\text{CN}^+ + \text{H}_2 \\
& \quad \xrightarrow{0.20} \quad \text{CH}_3^+\text{NH}_3 \\
& \quad \xrightarrow{0.10} \quad \text{NH}_4^+ + \text{CH}_2
\end{align*}
\]
TABLE 2. Some rate constants (in units of $10^{-9}$ cm$^3$ molecule$^{-1}$ s$^{-1}$) for the protonation of amines at room temperature

<table>
<thead>
<tr>
<th>Reactants</th>
<th>$k_{\text{total}}^{a}$</th>
<th>Mode of reaction$^{b}$</th>
<th>Technique$^{c}$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_5^+$ + CH$_3$NH$_2$</td>
<td>2.25, 2.51</td>
<td>PT</td>
<td>ICR, TIMS</td>
<td>16, 22</td>
</tr>
<tr>
<td>CD$_5^+$ + CH$_3$NH$_2$</td>
<td>2.21</td>
<td>PT</td>
<td>TIMS</td>
<td>22</td>
</tr>
<tr>
<td>C$_2$H$_5^+$ + CH$_3$NH$_2$</td>
<td>1.87</td>
<td>PT</td>
<td>ICR</td>
<td>16</td>
</tr>
<tr>
<td>C$_3$H$_7^+$ + CH$_3$NH$_2$</td>
<td>1.65</td>
<td>PT</td>
<td>ICR</td>
<td>16</td>
</tr>
<tr>
<td>CH$_5^+$ + (CH$_3$)$_2$NH</td>
<td>2.15, 2.25</td>
<td>PT</td>
<td>ICR, TIMS</td>
<td>16, 22</td>
</tr>
<tr>
<td>CD$_5^+$ + (CH$_3$)$_2$NH</td>
<td>2.05</td>
<td>PT</td>
<td>TIMS</td>
<td>22</td>
</tr>
<tr>
<td>C$_2$H$_5^+$ + (CH$_3$)$_2$NH</td>
<td>1.88</td>
<td>PT</td>
<td>ICR</td>
<td>16</td>
</tr>
<tr>
<td>C$_3$H$_7^+$ + (CH$_3$)$_2$NH</td>
<td>1.64</td>
<td>PT</td>
<td>ICR</td>
<td>16</td>
</tr>
<tr>
<td>NH$_3$D$^+$ + NH$_3$</td>
<td>0.77</td>
<td>PT</td>
<td>TIMS</td>
<td>22</td>
</tr>
<tr>
<td>CH$_3$NH$_2$D$^+$ + CH$_3$NH$_2$</td>
<td>0.64</td>
<td>PT</td>
<td>TIMS</td>
<td>22</td>
</tr>
<tr>
<td>(CH$_3$)$_2$NH$^+$ + (CH$_3$)$_2$NH</td>
<td>0.31</td>
<td>PT</td>
<td>TIMS</td>
<td>22</td>
</tr>
<tr>
<td>CH$^+$ + CH$_3$NH$_2$</td>
<td>2.2</td>
<td>H$^-$</td>
<td>SIFT</td>
<td>28</td>
</tr>
<tr>
<td>CH$_2^+$ + CH$_3$NH$_2$</td>
<td>2.1</td>
<td>H$^-$</td>
<td>SIFT</td>
<td>28</td>
</tr>
<tr>
<td>CH$_3^+$ + CH$_3$NH$_2$</td>
<td>2.2</td>
<td>H$^-$</td>
<td>SIFT</td>
<td>28</td>
</tr>
<tr>
<td>CH$_4^+$ + CH$_3$NH$_2$</td>
<td>2.2</td>
<td>H$^-$</td>
<td>SIFT</td>
<td>28</td>
</tr>
<tr>
<td>CCl$_2$D$^+$ + CH$_3$NH$_2$</td>
<td>e</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td>CF$_2$H$^+$ + CH$_3$NH$_2$</td>
<td>e</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td>CCl$_2$D$^+$ + C$_2$H$_5$NH$_2$</td>
<td>~1.5</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td>CF$_2$H$^+$ + C$_2$H$_5$NH$_2$</td>
<td>e</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td>CCl$_2$D$^+$ + (CH$_3$)$_2$NH</td>
<td>e</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td>CF$_2$H$^+$ + (CH$_3$)$_2$NH</td>
<td>e</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td>CCl$_2$D$^+$ + (CH$_3$)$_3$N</td>
<td>1.37</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td>CF$_2$H$^+$ + (CH$_3$)$_3$N</td>
<td>e</td>
<td>PT</td>
<td>ICR</td>
<td>18</td>
</tr>
<tr>
<td>CCl$_2$D$^+$ + C$_6$H$_5$NH$_2$</td>
<td>1.0</td>
<td>PT</td>
<td>ICR</td>
<td>19</td>
</tr>
</tbody>
</table>

$^{a}$Total rate constant for the disappearance of the reactant ion.

$^{b}$The observed product distribution is given in parentheses. Proton-transfer, hydride-transfer (see text) and charge-transfer products are indicated as PT, H$^-$ and CT, respectively. Otherwise just the observed product ion is indicated.

$^{c}$ICR = ion cyclotron resonance. TIMS = trapped-ion mass spectrometry. SIFT = selection-ion flow tube.

$^d$Observed ternary association product. The quoted rate constant refers to the binary product channels only.

$^e$Not determined.
formation of CH$_3$NH$_2^+$ by loss of a hydrogen molecule across the C—N bond, and the other in the formation of CH$_3$NH$^+$ by loss of H$_2$ from the nitrogen end of the intermediate complex, approximately in the ratio 3.3 to 1$^{27}$.

**B. Protonation of Amines**

The available experimental data for the kinetics of protonation of amines indicates a pattern of reactivity which closely resembles that observed with ammonia. This is evident from the information provided in Table 2. In the absence of competing channels, the room-temperature protonation of the amines again proceeds at essentially every gas-kinetic capture collision except, it appears, at very low reaction exothermicities. For example, the R$^1$R$^2$NHD$^+$ ion produced in the special case of deuteron transfer from CD$_5^+$ or C$_2$D$_5^+$ to R$^1$R$^2$NH has been shown to react further with R$^1$R$^2$NH at a reduced rate by the 'symmetric' proton-transfer reaction shown in equation (4) where R$^1$ and R$^2$ may be CH$_3$ or H$^{22}$. The measurements are illustrated in Figure 3 for R$^1$ = CH$_3$ and R$^2$ = H. They were carried out with a trapped-ion mass spectrometer which discriminates against deuteron transfer in the sense that the latter is counted as a nonreaction. However, when the raw rate constants are multiplied by the statistical factor $n/(n - 1)$ to account for the fact that R$^1$R$^2$NHD$^+$ contains $n - 1$ labile H and one labile D, the resulting values still turn out to be approximately equal to only one-half of the collision rate constant. Such a probability would be predicted if the reaction proceeds through a symmetrical disolvated proton complex of the type I. If the complex is sufficiently long-lived the proton can be expected to have an equal chance of remaining with the amine to which it was bound originally (no reaction) or being transferred to the second amine (reaction) when the complex dissociates. The limiting rate for such symmetric proton transfer should therefore be one-half the collision rate (neglecting isotope effects)$^{22}$.

As was the case with NH$_3$, the reactions of CH$_x^+$(x = 1-4) with CH$_3$NH$_2$ are again less straightforward in that several other channels are observed to compete with proton transfer. The low ionization potential of CH$_3$NH$_2$ makes direct charge transfer energetically possible in all cases and, indeed, it is always observed to occur. Proton transfer to produce CH$_3$NH$_3^+$ is a minor channel and is observed to occur only with CH$_+$ and CH$_2^+$. The formation of CH$_2$NH$_2^+$ represents a major channel for the reactions of all the CH$_x^+$ ions. Formally it corresponds to the transfer of hydride ion to CH$_x^+$ according to equation (5) which is exothermic for all values of x. However, the actual reaction mechanism may also involve the dissociative charge-transfer reaction (6) or the dissociative proton-transfer reaction (7), both of which are exothermic with CH$^+$, CH$_2^+$ and CH$_4^+$. The production of CH$_2$NH$_2^+$ in the case of the reaction with CH$_3^+$ appears to be restricted on

\[ \text{CH}_x^+ + \text{CH}_3\text{NH}_2 \rightarrow [\text{CH}_3\text{NH}_2^+]^* + \text{CH}_x \]  \hspace{2cm} (6a)

\[ \downarrow \hspace{2cm} \text{CH}_2\text{NH}_2^+ + \text{H} \]  \hspace{2cm} (6b)

\[ \text{CH}_x^+ + \text{CH}_3\text{NH}_2 \rightarrow [\text{CH}_3\text{NH}_3^+]^* + \text{CH}_{x-1} \]  \hspace{2cm} (7a)

\[ \downarrow \hspace{2cm} \text{CH}_2\text{NH}_2^+ + \text{H}_2 \]  \hspace{2cm} (7b)
energetic grounds to proceed by $\text{H}^-$ transfer. It is interesting to note that, in this case only, a ternary association channel is also observed to compete, resulting in the adduct $\text{CH}_3^+ \cdot \text{CH}_3\text{NH}_2$ which conceivably may rearrange into, for example, protonated ethylamine. We have noted earlier the analogous channel in the reaction of $\text{CH}_3^+$ with $\text{NH}_3$.

The three options represented by equations (5)–(7) have been investigated by Huntress and Bowers\textsuperscript{29} in their studies of the reaction of $\text{H}_3^+$ with $\text{CH}_3\text{NH}_2$. These indicated that the product distribution and mechanism depends critically on the amount of excess internal energy of $\text{H}_3^+$. For highly excited $\text{H}_3^+$ ions the reaction proceeds mainly by the direct processes: by charge transfer and a process equivalent to $\text{H}^-$ abstraction. For partially or totally deactivated $\text{H}_3^+$ ions at hydrogen pressures above $\sim 2 \times 10^{-4}$ Torr in their ICR apparatus, the reaction appeared to proceed mainly via proton transfer to form a long-lived intermediate complex which decomposes by vicinal $\text{H}_2$ elimination to form $\text{CH}_2\text{NH}_2^+$ and by $\text{C} - \text{N}$ bond scission to produce $\text{CH}_3^+$ according to equation (8).

\[
\text{H}_3^+ + \text{CH}_3\text{NH}_2 \rightarrow \left[\text{CH}_3\text{NH}_3^+\right]^* + \text{H}_2 \quad (8a)
\]

\[
\rightarrow \text{CH}_2\text{NH}_2^+ + \text{H}_2 \quad (8b)
\]

\[
\rightarrow \text{CH}_3^+ + \text{NH}_3 \quad (8c)
\]

The relative importance of competing channels for the reactions of $\text{CCl}_2\text{H}^+$ and $\text{CF}_2\text{H}^+$ with ammonia and amines has been investigated and discussed by Lias and Ausloos\textsuperscript{18,19}. In these systems, the competing reactions which occur if they are exothermic are proton transfer, hydride transfer and charge transfer. When proton transfer and hydride transfer are the only two exothermic channels, proton transfer appears to predominate even though the corresponding hydride-transfer reactions are more exothermic.

### C. Deprotonation of Ammonia and Amines

Data available for the kinetics of deprotonation of amines are extremely sparse, in part because of the very low acidity of these compounds in the gas phase. Table 3 presents all of the rate constants which are presently available. They were measured with the flowing afterglow technique\textsuperscript{30,31}: the amine was added into a flowing $\text{NH}_3$–$\text{He}$ plasma in which $\text{H}^-$ and $\text{NH}_2^-$ were established as the major

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}^- + \text{NH}_3 \rightarrow \text{NH}_2^- + \text{H}_2$</td>
<td>0.00090 ± 0.00018</td>
</tr>
<tr>
<td>$\text{H}^- + \text{CH}_3\text{NH}_2 \rightarrow \text{CH}_3\text{NH}^- + \text{H}_2$</td>
<td>0.017 ± 0.009</td>
</tr>
<tr>
<td>$\text{H}^- + \text{C}_2\text{H}_5\text{NH}_2 \rightarrow \text{C}_2\text{H}_5\text{NH}^- + \text{H}_2$</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>$\text{H}^- + (\text{CH}_3)_2\text{NH} \rightarrow (\text{CH}_3)_2\text{N}^- + \text{H}_2$</td>
<td>4.3 ± 0.9</td>
</tr>
<tr>
<td>$\text{NH}_2^- + \text{CH}_3\text{NH}_2 \rightarrow \text{CH}_3\text{NH}^- + \text{NH}_3$</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>$\text{NH}_2^- + \text{C}_2\text{H}_5\text{NH}_2 \rightarrow \text{C}_2\text{H}_5\text{NH}^- + \text{NH}_3$</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td>$\text{NH}_2^- + (\text{CH}_3)_2\text{NH} \rightarrow (\text{CH}_3)_2\text{N}^- + \text{NH}_3$</td>
<td>3</td>
</tr>
<tr>
<td>$\text{NH}_2^- + (\text{CH}_3)_3\text{N} \rightarrow \text{products}$</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
negative ions. Figure 4 presents the observations recorded for the deprotonation of NH$_3$ by H$. This reaction proceeds slowly with $k = 9.0 \pm 1.8 \times 10^{-13}$ cm$^3$ molecule$^{-1}$ s$^{-1}$ as does the deprotonation of CH$_3$NH$_2$ by H$^-$ for which $k = 1.7 \pm 0.9 \times 10^{-11}$ cm$^3$ molecule$^{-1}$ s$^{-1}$, and the deprotonation of (CH$_3$)$_3$N by NH$_2^-$ for which $k < 1 \times 10^{-12}$ cm$^3$ molecule$^{-1}$ s$^{-1}$. Otherwise the deprotonation reactions which have been observed occur with high efficiency at specific rates close to gas-kinetic. In all cases deprotonation proceeded exclusive of any other competing reaction channels.
A. The Preferred Direction of Proton Transfer

Quantitative measurements of the gas-phase kinetics of the protonation and deprotonation of amines have become possible only fairly recently with developments in experimental techniques and associated kinetic analyses. The earlier experimental studies of these processes were able to provide only a qualitative indication of the preferred direction of proton transfer, i.e. the direction for which the equilibrium constant was greater than one or the standard free-energy change was less than zero. Nevertheless, these early studies provided the first direct indication of relative gas-phase basicity and acidity. The preferred direction was established either from an investigation of both directions of proton transfer or simply from its actual observation with the assumption that this was tantamount to a manifestation of its exoergicity ($\Delta G^0 < 0$).

In the first such study involving amines, Munson$^{32}$ was able to observe the proton-transfer reactions shown in equations (9)–(11). The protonated amines were established in the ion source of a mass spectrometer containing mixtures of two amines at total pressures of several tenths of a Torr. The reactions were identified from the pressure dependence of the protonated amines at constant composition. The following order of basicity was suggested:

$$(\text{CH}_3)_3\text{N} > (\text{CH}_3)_2\text{NH} > \text{CH}_3\text{NH}_2 > \text{NH}_3$$

This order was confirmed a few years later by Brauman and coworkers in a more comprehensive study of aliphatic amines$^{33,34}$. These authors employed the low-pressure ICR technique with which the occurrence and nonoccurrence of proton transfer was determined from the observation of double-resonance signals. The influence of the degree of methyl substitution on basicity reported by Munson was reproduced exactly and a similar order was obtained for ethyl substitution:

$$(\text{C}_2\text{H}_5)_3\text{N} > (\text{C}_2\text{H}_5)_2\text{NH} > \text{C}_2\text{H}_5\text{NH}_2 > \text{NH}_3$$

Furthermore, other orders of basicity involving a change in the size of the alkyl substituent(s) were also reported:

**Primary amines:**

$t\cdot\text{C}_4\text{H}_9\text{NH}_2 > (\text{CH}_3)_3\text{CCH}_2\text{NH}_2 > i\cdot\text{C}_3\text{H}_7\text{NH}_2 > n\cdot\text{C}_3\text{H}_7\text{NH}_2 >$

$\text{C}_2\text{H}_5\text{NH}_2 > \text{CH}_3\text{NH}_2 > \text{NH}_3$

**Secondary amines:**

$(\text{C}_2\text{H}_5)_2\text{NH} > (\text{CH}_3)_2\text{NH}$

**Tertiary amines:**

$(\text{C}_2\text{H}_5)_3\text{N} > (\text{CH}_3)_3\text{N}$

**Miscellaneous:**

$(\text{CH}_3)_3\text{N} > t\cdot\text{C}_4\text{H}_9\text{NH}_2$

$(\text{CH}_3)_2\text{NH} = i\cdot\text{C}_3\text{H}_7\text{NH}_2$

$(\text{CH}_3)_3\text{N} = (\text{C}_2\text{H}_5)_2\text{NH}$
These two sets of observations provided the first direct manifestation of molecular effects on the gas-phase basicity of amines and set the stage for the quantitative measurements of relative basicity which were to follow.

ICR and pulsed double-resonance spectroscopy also provided the first manifestation of the relative gas-phase acidity of amines from an analysis of the behaviour of various amide ions in the presence of a mixture of their conjugate acids\(^{35,36}\). Reactions of the type shown in equation (12) were observed to often proceed essentially in one direction only. These investigations provided the following orders of acidity:

\[
\text{[(C}_2\text{H}_5\text{)}_2\text{NH} > (\text{CH}_3)_2\text{CCH}_2\text{NH}_2 > t\text{-C}_4\text{H}_9\text{NH}_2 > (\text{CH}_3)_2\text{NH} >}
\]

\[
i\text{-C}_3\text{H}_7\text{NH}_2 > n\text{-C}_3\text{H}_7\text{NH}_2 > \text{C}_2\text{H}_5\text{NH}_2 > \text{CH}_3\text{NH}_2 > \text{NH}_3}
\]

\[
(\text{C}_2\text{H}_5\text{)}_2\text{NH} > \text{H}_2\text{O} > t\text{-C}_4\text{H}_9\text{NH}_2
\]

Experiments carried out with \(\text{C}_2\text{D}_5\text{NH}_2\) demonstrated that \(\text{N} - \text{H}\) protons were removed exclusively. Other experiments with saturated alkanes established that \(\text{NH}_3 > \text{CH}_4\). Support for the relative gas-phase acidity of \(\text{NH}_3\) was provided by a series of flowing afterglow experiments\(^{37-39}\) which established the following order of acidity:

\[
\text{H}_2\text{O} > \text{H}_2 > \text{NH}_3 > \text{CH}_4, \text{C}_2\text{H}_4, (\text{CH}_2)_3, \text{C}_8\text{H}_2
\]

B. Positive-ion Equilibria

Equilibrium constants for proton-transfer reactions of the type shown in equation (13) involving amines \(\text{B}^1\) and \(\text{B}^2\), began to be reported some six years after the pioneering studies of Munson\(^{32}\). They provided the first quantitative differences in gas-phase basicities of amines in terms of the change in standard free energy, \(\Delta G^0\), for reaction (13) which is related to the equilibrium constant according to the well-known equation (14). The equilibrium constants were determined from a measurement of the apparent equilibrium concentrations established in mixtures of the protonated amines and their conjugate bases according to the relationship in equation (15).

\[
\Delta G^0_T = -RT \ln K \quad (14)
\]

\[
K = \left( \frac{[\text{B}^2\text{H}^+][\text{B}^1]}{[\text{B}^1\text{H}^+][\text{B}^2]} \right)_{equilibrium} \quad (15)
\]

The measurements reported to date have been carried out either at low pressures (from \(10^{-6}\) to \(10^{-3}\) Torr) using techniques of ion cyclotron resonance or at moderately high pressures (from 1 to 5 Torr) with a pulsed ion source mass spectrometric method. Most of the measurements have been done at a single temperature, 300 K and 600 K respectively, but the latter technique has also allowed measurements of the equilibrium constant as a function of temperature.
which have provided values for the standard enthalpy change, $\Delta H^0$, and the standard entropy change, $\Delta S^0$ for reaction (13).

In the early application of the ICR technique\textsuperscript{40,41}, the relative intensities of the protonated amines were monitored as a function of pressure (from 2 to $8 \times 10^{-4}$ Torr) at a number of neutral concentration ratios (<4:1). Equilibrium appeared to be achieved for proton-transfer reactions with equilibrium constants <50 and rate constants > $2 \times 10^{-10}$ cm$^3$ molecule$^{-1}$ s$^{-1}$. Dimerization reactions began to interfere with the attainment of proton-transfer equilibrium outside of these limits at total pressures down to $1 \times 10^{-4}$ Torr. However, these could be avoided by performing experiments on the same mixtures using a pulsed ICR spectrometer fitted with a trapped ion-analysrer cell\textsuperscript{42}. This new technique allowed the trapping of protonated amines at pressures <$1 \times 10^{-5}$ Torr for up to 100 ms after their initial formation. The approach to equilibrium could then be followed as a function of storage time. Figure 5 shows the attainment of equilibrium in a mixture of azetidine and pyrrolidine for the proton-transfer reaction (16). The general experience has been that the high-pressure ICR measurements provide results which agree reasonably well with those obtained with the low-pressure trapped-ion technique and the high-pressure mass spectrometric technique. Figure 6 summarizes the

\begin{equation}
\begin{aligned}
\text{N}_2^+ &+ \text{NH} &\rightleftharpoons& \text{N}^+ &+ \text{NH}_2^+ \\
\text{N}_2^+ &+ \text{NH} &\rightleftharpoons& \text{N}^+ &+ \text{NH}_2^+
\end{aligned}
\end{equation}

Figure 5. Pulsed ICR data for the (CH$_2$)$_3$NH$_2^+$ and (CH$_2$)$_4$NH$_2^+$ peaks in a 6.4:1.0 mixture of (CH$_2$)$_3$NH and (CH$_2$)$_4$NH at approximately $1 \times 10^{-5}$ Torr. The protonated species ($m/e$ 58, 72) are formed by the reaction of parent ions ($m/e$ 57, 71) with the two neutral molecules. Reprinted with permission from M. T. Bowers, D. H. Aue, H. M. Webb and R. T. McIver, J. Amer. Chem. Soc., 93, 4314 (1971). Copyright by the American Chemical Society.
results obtained from pressure plots using the high-pressure ICR technique in an extensive investigation of a large number of coupled proton-transfer reactions of type (13) involving a variety of alkylamines.

Additional low-pressure ICR measurements have been reported by McMahon and Beauchamp\textsuperscript{13} who used a trapped ICR drift cell method and by Taft and coworkers who performed pulsed ICR measurements\textsuperscript{2}. Typical experiments were done at 10\textsuperscript{−6} Torr and the protonated amines were monitored over cell residence times of 200 to 1000 ms. The results obtained for amines are summarized in a recent review article by Taft\textsuperscript{2} and are presented here in Figure 7. In this article Taft also describes the various tests which have been made to establish that true equilibrium conditions can be achieved with low-pressure ICR techniques.

In the mass spectrometric method developed by Kebarle and his associates\textsuperscript{44,45}, the approach to equilibrium was monitored as a function of time for up to 1000 ms after the ion-formation pulse at the much higher total pressures of 1–5 Torr and at neutral ratios as large as 1000. Figure 8 shows the attainment of equilibrium for reaction (17). Equilibrium constants as large as 10\textsuperscript{5} could be measured over the

\[
\text{CH}_3\text{NH}_3^+ + \text{(CH}_3\text{)}_2\text{NH} \rightleftharpoons \text{(CH}_3\text{)}_2\text{NH}_2^+ + \text{CH}_3\text{NH}_2
\]  

(17)

FIGURE 8. The time dependence of normalized intensities of (CH\textsubscript{3})\textsubscript{3}NH\textsuperscript{+} (m/e 46) and CH\textsubscript{3}NH\textsubscript{3}\textsuperscript{+} (m/e 32) recorded with a high-pressure mass spectrometer at 600 K. ●: CH\textsubscript{4} at 4 Torr, methylamine at 31 mTorr, dimethylamine at 0.8 mTorr; ■: CH\textsubscript{4} at 4 Torr, methylamine at 340 mTorr, dimethylamine at 1.6 mTorr. Reprinted with permission from J. P. Briggs, R. Yamdagni and P. Kebarle, J. Amer. Chem. Soc., 95, 3504 (1973). Copyright by the American Chemical Society.
FIGURE 9. Temperature dependence of $\Delta G^0 = -RT \ln K$ for proton-transfer equilibria of the type $B^1H^+ + B^2 \rightleftharpoons B^2H^+ + B^1$ with $B^1/B^2 = CH_3NH_2/(CH_3)_2N$ (A); NH$_3$/CH$_3$NH$_2$ (B); CH$_3$NH$_2$/ (CH$_3$)$_2$NH (C); CH$_3$NH$_2$/C$_6$H$_5$NHCH$_3$ (D), and C$_6$H$_5$NH$_2$/ CH$_3$NH$_2$ (E). Reprinted with permission from J. P. Briggs, R. Yamdagni and P. Kebarle, J. Amer. Chem. Soc., 94, 5128 (1972). Copyright by the American Chemical Society.

temperature range from ~550 to 750 K. At these high temperatures dimer formation was suppressed sufficiently to avoid their interference. Figure 9 shows the van't Hoff plots generated for several reactions of type (13) involving NH$_3$, methylamines, aniline and pyridine. For these systems $\Delta G^0$ showed very little change with temperature from which it may be inferred that the reactions are essentially isentropic, $\Delta S^0 < 2.0 \text{cal mol}^{-1}\text{deg}^{-1}$. A much stronger dependence on temperature was indicated for reactions of type (13) involving monoamines and $\alpha, \omega$-diamines. This is evident from the van't Hoff plots shown in Figure 10 which lead to entropy changes of more than $12 \text{cal mol}^{-1}\text{deg}^{-1}$. The changes in thermodynamic state properties derived from these plots are given in Table 4. Table 5 presents the results reported for the systems studied only at the single temperature of 600 K. A separate study was made of the formation of proton-bound dimers corresponding to reactions of the type shown in equation...
FIGURE 10. Van't Hoff plots for proton-transfer equilibria of the type $B^1H^+ + B^2 \rightleftharpoons B^2H^+ + B^1$ with $B^1/B^2 = \text{dimethylamine}/1,2-$diaminoethane (O), trimethylamine/1,3-diaminopropane (●), trimethylamine/1,5-diaminopentane (△), and trimethylamine/1,7-diaminoheptane (■). Reprinted with permission from R. Yamdagni and P. Kebarle, J. Amer. Chem. Soc., 95, 3504 (1973). Copyright by the American Chemical Society.

(18), with $B = \text{NH}_3$, CH$_3$NH$_2$, (CH$_3$)$_2$NH and (CH$_3$)$_3$N, and reactions of the type shown in equation (19), with $B^1/B^2 = \text{CH}_3\text{NH}_2/\text{NH}_3$, (CH$_3$)$_2$NH/CH$_3$NH$_2$ and (CH$_3$)$_3$N/(CH$_3$)$_2$NH. The results of this study are summarized in Table 6 and presented as van't Hoff plots in Figure 11. The observed trends in $\Delta G^\circ$ and $\Delta H^\circ$ are consistent with the notion of a partial acid–base reaction in which the

<table>
<thead>
<tr>
<th>$B^1$</th>
<th>$B^2$</th>
<th>$-\Delta G^\circ_{298}$</th>
<th>$-\Delta H^\circ$</th>
<th>$-\Delta S^\circ$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethylamine</td>
<td>1,2-Diaminoethane</td>
<td>5.8</td>
<td>9.6</td>
<td>12.7</td>
</tr>
<tr>
<td>Trimethylamine</td>
<td>1,3-Diaminopropane</td>
<td>6.8</td>
<td>13.0</td>
<td>20.6</td>
</tr>
<tr>
<td>Trimethylamine</td>
<td>1,5-Diaminopentane</td>
<td>7.1</td>
<td>13.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Trimethylamine</td>
<td>1,7-Diaminoheptane</td>
<td>6.9</td>
<td>12.9</td>
<td>20.0</td>
</tr>
</tbody>
</table>

$\Delta H^\circ$ and $\Delta S^\circ$ are approximately temperature-independent over the temperature range indicated in Figure 10, $\Delta H^\circ$ and $\Delta G^\circ$ are in kcal mol$^{-1}$ and $\Delta S^\circ$ is in cal mol$^{-1}$ deg$^{-1}$.

TABLE 5. Summary of standard free energy changes (kcal mol\(^{-1}\)) for equilibria of the type \(B_1^+H^+ + B_2^2 \rightleftharpoons B_2^2H^+ + B_1^1\) derived at 600 K using high-pressure mass spectrometry\(^d\)

<table>
<thead>
<tr>
<th>(B_1^1)</th>
<th>(B_2^2)</th>
<th>(-\Delta G^0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{NH}_3)</td>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>10.8</td>
</tr>
<tr>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>(\text{C}_6\text{H}_5\text{NHCH}_3)</td>
<td>4.3</td>
</tr>
<tr>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>(\sigma)-Anisidine</td>
<td>4.3</td>
</tr>
<tr>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>((\text{CH}_3)_2\text{NH})</td>
<td>7.5</td>
</tr>
<tr>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>Pyridine</td>
<td>7.8</td>
</tr>
<tr>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>((\text{CH}_3)_3\text{N})</td>
<td>12.5</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{NH}_2)</td>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>1.9</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{NH}_2)</td>
<td>(\text{C}_6\text{H}_5\text{NHCH}_3)</td>
<td>6.2</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{NH}_2)</td>
<td>(\sigma)-Anisidine</td>
<td>6.5</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{NHCH}_3)</td>
<td>((\text{CH}_3)_2\text{NH})</td>
<td>3.5</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{NHCH}_3)</td>
<td>(\text{C}_6\text{H}_5\text{NHCH}_2\text{H}_5)</td>
<td>3.4</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{NHCH}_3)</td>
<td>(\text{C}_6\text{H}_5\text{N}((\text{CH}_3)_2)</td>
<td>6.6</td>
</tr>
<tr>
<td>((\text{CH}_3)_2\text{NH})</td>
<td>Cyclohexylamine</td>
<td>1.2</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{NH}_2\text{CH}_3)</td>
<td>Cyclohexylamine</td>
<td>1.3</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{N}((\text{CH}_3)_2)</td>
<td>((\text{CH}_3)_3\text{N})</td>
<td>1.6</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{N}((\text{CH}_3)_2)</td>
<td>(\text{C}_6\text{H}_5\text{N}((\text{CH}_3)(\text{CH}_5))</td>
<td>2.5</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{N}((\text{CH}_3)_2)</td>
<td>Piperidine</td>
<td>2.8</td>
</tr>
<tr>
<td>(\text{C}_6\text{H}_5\text{N}((\text{CH}_3)_2)</td>
<td>(\text{C}_6\text{H}_5\text{N}((\text{CH}_3)\text{H}_5))</td>
<td>5.2</td>
</tr>
<tr>
<td>Cyclohexylamine</td>
<td>Piperidine</td>
<td>4.8</td>
</tr>
<tr>
<td>Pyrrole</td>
<td>(\text{C}_6\text{H}_5\text{NH}_2)</td>
<td>1.75</td>
</tr>
</tbody>
</table>


17. Gas-phase basicity and acidity of amines

formation of the proton-bound dimer is viewed as a partial proton-transfer reaction from the proton donor \(B_1^1H^+\) to the proton acceptor \(B_2^2\).

**C. Negative-ion Equilibria**

Only a few equilibrium constant measurements have been reported for proton-transfer reactions of the type shown in equation (20) involving amines \(A^2\text{H}\) and \(A^1\text{H}\). They have been performed solely with the flowing afterglow technique at a total pressure of \(\sim 0.4\) Torr and room temperature \(^{39,31}\). The ions \(A^1\text{H}^-\) were generated by electron impact in a flowing helium buffer gas containing a fixed amount of the amine \(A^1\text{H}\). Equilibrium was approached by adding increasing amounts of \(A^2\text{H}\) into the reaction region at a fixed reaction time of a few milliseconds. Equilibrium constants were derived both from a measurement of equilibrium concentrations and an analysis of the decay of \(A^1\text{H}^-\) for the forward and reverse rate constants. Figures 12 and 13 show representative data obtained for the equilibrium (21). A fit to the decay of \(\text{CH}_3\text{NH}^-\) in Figure 12 provides a value.
TABLE 6. Summary of standard free energy and enthalpy changes (kcal mol\(^{-1}\)) derived\(^a\) from a temperature study of equilibria of the type \(B'H^+ + B^2 \rightleftharpoons (B'H^B)^+\) using high-pressure mass spectrometry

<table>
<thead>
<tr>
<th>(B'H^+)</th>
<th>(B^2)</th>
<th>(-\Delta G^0_{550})</th>
<th>(-\Delta H^0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH(_4^+)</td>
<td>NH(_3)</td>
<td>10.6</td>
<td>24.8</td>
</tr>
<tr>
<td></td>
<td>CH(_3)NH(_2)</td>
<td>17.9</td>
<td>(\approx) 32.0</td>
</tr>
<tr>
<td></td>
<td>(CH(_3)(_2))NH</td>
<td>(23.3)</td>
<td>(38.9)</td>
</tr>
<tr>
<td></td>
<td>(CH(_3)(_3))N</td>
<td>(27.3)</td>
<td>(43.3)</td>
</tr>
<tr>
<td>CH(_3)NH(_3^+)</td>
<td>NH(_3)</td>
<td>7.1</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>CH(_3)NH(_2)</td>
<td>8.7</td>
<td>21.7</td>
</tr>
<tr>
<td></td>
<td>(CH(_3)(_2))NH</td>
<td>13.8</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>(CH(_3)(_3))N</td>
<td>(17.0)</td>
<td>(32.5)</td>
</tr>
<tr>
<td>(CH(_3)(_2))NH(_2^+)</td>
<td>NH(_3)</td>
<td>5</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td>CH(_3)NH(_2)</td>
<td>6.3</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td>(CH(_3)(_2))NH</td>
<td>6.65</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>(CH(_3)(_3))N</td>
<td>9.4</td>
<td>23.3</td>
</tr>
<tr>
<td>(CH(_3)(_3))NH(_3^+)</td>
<td>NH(_3)</td>
<td>(4)</td>
<td>(20)</td>
</tr>
<tr>
<td></td>
<td>CH(_3)NH(_2)</td>
<td>(4.5)</td>
<td>(20)</td>
</tr>
<tr>
<td></td>
<td>(CH(_3)(_2))NH</td>
<td>4.8</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>(CH(_3)(_3))N</td>
<td>4.9</td>
<td>22.5</td>
</tr>
</tbody>
</table>

\(^a\)Numbers in parentheses are predicted values.


for \(K = k_d/k_f\), while the ion ratio plot in Figure 13 provides a measure of \(K\) in terms of equilibrium concentrations. Table 7 gives a summary of the equilibrium constants derived from the flowing afterglow measurements and the resulting changes in standard free energy.

**IV. GAS-PHASE BASICITIES OF AMINES**

The standard free energy change for reaction (13) provides a measure of the difference in the gas-phase basicity, \(GB\), of amines \(B'\) and \(B^2\), viz. \(\Delta G^0 = \Delta GB\) \((B', B^2)\) with the gas-phase basicity defined as the standard free energy change for process (22). It follows that continuous ladders of differences in gas-phase basicity

\[
B'H^+ \rightleftharpoons B + H^+ \quad (22)
\]

as shown in Figures 6 and 7 can yield absolute values for \(GB\) once the ladders are calibrated with an appropriate choice of an absolute reference value. In practice this choice is severely limited. Absolute values of gas-phase basicity may, in principle, be derived from (nonequilibrium) appearance potential measurements of the protonated amines but these have been very few and the protonated amine may not appear as a fragment ion. In recent years the basicity of \(NH_3\), itself referenced to the absolute basicity of isobutene, has been most commonly adopted as a reference value for the basicities of the amines\(^b\). This practice is retained here but the basicity of \(NH_3\) is derived from very recent appearance potential measurements\(^c\) for the \(NH_4^+\) fragment produced by the photoionization of the neutral dimer \(NH_3\) \cdot NH\(_3\) according to equation (23). These measurements have led to a standard enthalpy change for process (24) of \(203.6 \pm 1.3\) kcal mol\(^{-1}\) at 298 K.
17. Gas-phase basicity and acidity of amines

FIGURE 11. Van't Hoff plots for equilibria of the type $B^1H^+ + B^2 \rightleftharpoons (B^1HB^2)^+$ with $B^1/B^2 = \text{NH}_3/\text{NH}_3$ (a), $\text{CH}_3\text{NH}_2/\text{CH}_3\text{NH}_2$ (b), $(\text{CH}_3)_2\text{NH}/(\text{CH}_3)_2\text{NH}$ (c), $(\text{CH}_3)_2\text{N}/(\text{CH}_3)_2\text{N}$ (d), $\text{CH}_3\text{NH}_2/\text{NH}_3$ (A), $(\text{CH}_3)_2\text{NH}/\text{CH}_3\text{NH}_2$ (B), and $(\text{CH}_3)_3\text{N}/(\text{CH}_3)_2\text{NH}$ (C). (O) $B^1 = B^2$, total pressure due to amine only; (●) $B^1 = B^2$, major gas is CH$_4$. Reprinted with permission from R. Yamdagni and P. Kebarle, J. Amer. Chem. Soc., 95, 3504 (1972). Copyright by the American Chemical Society.

\[ \text{NH}_3\cdot\text{NH}_3 + \nu \longrightarrow \text{NH}_4^+ + \text{NH}_2 + \text{e} \]  \hspace{1cm} (23)

\[ \text{NH}_4^+ \iff \text{NH}_3 + \text{H}^+ \]  \hspace{1cm} (24)
FIGURE 12. The variation of the major negative ion signals recorded upon the addition of NH₃ into a flowing CH₃NH₂-He plasma in which CH₃NH⁻ is initially a dominant negative ion. The curve drawn through the observed CH₃NH⁻ decay represents a computed fit which yields a value for the ratio of rate constants, $k_1/k_r$, for the proton-transfer reaction \( CH₃NH⁻ + NH₃ \rightarrow NH₂⁻ + CH₃NH₂ \). The ion observed at m/e 44 is presumed to arise from the \((CH₃)₂N⁻\) impurity in CH₃NH₂ (\(T = 298\) K, \(P = 0.295\) Torr). Reproduced by permission of the National Research Council of Canada from G. I. Mackay, R. S. Hemsworth and D. K. Bohme, Can. J. Chem., 54, 1624 (1976).

This value is intermediate between the extreme values of 202.3 and 207.0 kcal mol⁻¹ which have been adopted previously. The conversion of $\Delta H_{298}^0$ to $\Delta G_{298}^0$ for reaction (24) may be accomplished by estimating the change in entropy to be equal to $S'(H⁺) + R \ln (12/3)$, where 12 and 3 are the rotational symmetry numbers for NH₄⁺ and NH₃, respectively. Thus the absolute gas-phase basicity of NH₃, $GB(NH₃)$, is 195.0 kcal mol⁻¹ with an uncertainty that
should be less than 2 kcal mol\(^{-1}\). This value is preferred as a reference in the compilation of absolute gas-phase basicities presented in Table 8. The compilation is based largely on the differences in gas-phase basicity reported in the extensive review by Taft.\(^2\)

The basicity \(\text{GB}(B)\) can provide a measure of the gas-phase proton affinity of \(B\), \(\text{PA}(B)\), which is defined as the standard enthalpy change for the deprotonation reaction (22). The standard entropy change required to make the connection, when not available from experiment, can often be estimated with reasonable accuracy.

### Table 7. Summary of equilibrium constants and standard free energy changes (kcal mol\(^{-1}\)) derived from a flowing afterglow study of equilibria of the type \((A^1)^- + A^2H \rightleftharpoons (A^2)^- + A^1H\) at 296 ± 2 K\(^3\)

<table>
<thead>
<tr>
<th>(A^2H)</th>
<th>(A^1H)</th>
<th>(K)</th>
<th>(-\Delta G^0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>(\text{NH}_3)</td>
<td>2.4 ± 0.4</td>
<td>0.51 ± 0.10</td>
</tr>
<tr>
<td>(\text{H}_2)</td>
<td>(\text{NH}_3)</td>
<td>26 ± 8</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>(\text{H}_2)</td>
<td>(\text{CH}_3\text{NH}_2)</td>
<td>12 ± 3</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>(\text{C}_2\text{H}_5\text{NH}_2)</td>
<td>(\text{NH}_3)</td>
<td>((1.3 ± 0.4) \times 10^3)</td>
<td>4.2 ± 0.2</td>
</tr>
<tr>
<td>(\text{C}_2\text{H}_5\text{NH}_2)</td>
<td>(\text{H}_2)</td>
<td>77 ± 14</td>
<td>2.6 ± 0.2</td>
</tr>
<tr>
<td>((\text{CH}_3)_2\text{NH})</td>
<td>(\text{H}_2)</td>
<td>((5.2 ± 1.1) \times 10^3)</td>
<td>5.0 ± 0.1</td>
</tr>
</tbody>
</table>
TABLE 8. Absolute and relative gas-phase basicities of amines in kcal mol\(^{-1}\) at 298 K. The preferred direction of proton transfer is towards the top of the table.\(^{2,4,5}\)

<table>
<thead>
<tr>
<th>B</th>
<th>GB(B)(^a)</th>
<th>(\Delta GB(\text{NH}_3, B))^{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary aliphatic amines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{t-C}_3\text{H}_7\text{NH}_2)</td>
<td>212.4</td>
<td>17.4</td>
</tr>
<tr>
<td>(\text{c-C}<em>6\text{H}</em>{11}\text{NH}_2)</td>
<td>211.3</td>
<td>16.3</td>
</tr>
<tr>
<td>(\text{t-BuNH}_2)</td>
<td>211.1</td>
<td>16.1</td>
</tr>
<tr>
<td>(\text{s-BuNH}_2)</td>
<td>210.2</td>
<td>15.2</td>
</tr>
<tr>
<td>(\text{i-PrNH}_2)</td>
<td>209.1</td>
<td>14.1</td>
</tr>
<tr>
<td>(\text{i-BuNH}_2)</td>
<td>209.0</td>
<td>14.0</td>
</tr>
<tr>
<td>(\text{n-BuNH}_2)</td>
<td>208.5</td>
<td>13.5</td>
</tr>
<tr>
<td>(\text{n-PrNH}_2)</td>
<td>208.0</td>
<td>13.0</td>
</tr>
<tr>
<td>(\text{EtNH}_2)</td>
<td>206.8</td>
<td>11.8</td>
</tr>
<tr>
<td>(\text{H}_2\text{C}≡\text{CH} \text{NH}_2)</td>
<td>206.3</td>
<td>11.3</td>
</tr>
<tr>
<td>(\text{MeNH}_2)</td>
<td>204.1</td>
<td>9.1</td>
</tr>
<tr>
<td>(\text{HC}≡\text{C} \text{NH}_2)</td>
<td>201.7</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Secondary aliphatic amines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>((\text{n-Pr})_2\text{NH})</td>
<td>217.2</td>
<td>22.2</td>
</tr>
<tr>
<td>(\text{Et}_2\text{NH})</td>
<td>215.2</td>
<td>20.2</td>
</tr>
<tr>
<td>((\text{H}_2\text{C}≡\text{CHCH}_2)_2\text{NH})</td>
<td>214.3</td>
<td>19.3</td>
</tr>
<tr>
<td>((\text{Me})_2\text{EtNH})</td>
<td>213.0</td>
<td>18.0</td>
</tr>
<tr>
<td>(\text{Me}_2\text{NH})</td>
<td>212.9</td>
<td>17.9</td>
</tr>
<tr>
<td>((\text{NC}≡\text{CCH}_2)_2\text{NH})</td>
<td>210.5</td>
<td>15.5</td>
</tr>
<tr>
<td>((\text{NC}≡\text{CCH}_2)_3\text{NH})</td>
<td>206.7</td>
<td>11.7</td>
</tr>
<tr>
<td><strong>Tertiary aliphatic amines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>((\text{n-Pr})_3\text{N})</td>
<td>223.7</td>
<td>28.7</td>
</tr>
<tr>
<td>(\text{Et}_3\text{N})</td>
<td>221.7</td>
<td>26.7</td>
</tr>
<tr>
<td>((\text{H}_2\text{C}≡\text{CH} \text{CH}_2)_3\text{N})</td>
<td>219.7</td>
<td>24.7</td>
</tr>
<tr>
<td>(\text{MeEt}_2\text{N})</td>
<td>219.6</td>
<td>24.6</td>
</tr>
<tr>
<td>(\text{Me}_2\text{EtN})</td>
<td>217.4</td>
<td>22.4</td>
</tr>
<tr>
<td>((\text{CD})_3\text{N})</td>
<td>215.3</td>
<td>20.3</td>
</tr>
<tr>
<td>((\text{CH})_3\text{N})</td>
<td>215.0</td>
<td>20.0</td>
</tr>
<tr>
<td>((\text{HC}≡\text{CCH}_2)_3\text{N})</td>
<td>210.0</td>
<td>15.0</td>
</tr>
<tr>
<td><strong>Cyclic tertiary aliphatic amines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinuclidine</td>
<td>222.1</td>
<td>27.1</td>
</tr>
<tr>
<td>Benzoquinuclidine</td>
<td>221.0</td>
<td>26.0</td>
</tr>
<tr>
<td>(\text{N-Methylpyrrolidin})</td>
<td>219.3</td>
<td>24.3</td>
</tr>
<tr>
<td>Diazabicyclooctane</td>
<td>218.5</td>
<td>23.5</td>
</tr>
<tr>
<td>(\text{N-Phenylpiperidin})</td>
<td>216.8</td>
<td>21.8</td>
</tr>
<tr>
<td>(\text{N-Phenylpyrrolidin})</td>
<td>214.3</td>
<td>19.3</td>
</tr>
</tbody>
</table>
TABLE 8.  continued

<table>
<thead>
<tr>
<th>B</th>
<th>$GB(B)^a$</th>
<th>$\Delta GB(NH_3,B)^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anilines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_6$H$_5$NMe$_2$</td>
<td>214.5</td>
<td>19.5</td>
</tr>
<tr>
<td>C$_6$H$_5$NHMe</td>
<td>207.9</td>
<td>12.9</td>
</tr>
<tr>
<td>p-MeC$_6$H$_4$NH$_2$</td>
<td>204.2</td>
<td>9.2</td>
</tr>
<tr>
<td>m-MeC$_6$H$_4$NH$_2$</td>
<td>203.9</td>
<td>8.9</td>
</tr>
<tr>
<td>C$_6$H$_5$NH$_2$</td>
<td>201.7</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Diamines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Me$_2$NCH$_2$)$_2$</td>
<td>225.3</td>
<td>30.3</td>
</tr>
<tr>
<td>1,5-Diaminopentane</td>
<td>217.6</td>
<td>22.6</td>
</tr>
<tr>
<td>1,7-Diaminoheptane</td>
<td>217.4</td>
<td>22.4</td>
</tr>
<tr>
<td>1,3-Diaminopropane</td>
<td>217.3</td>
<td>22.3</td>
</tr>
<tr>
<td>1,2-Diaminoethane</td>
<td>216.3</td>
<td>21.3</td>
</tr>
<tr>
<td>Me$_2$NNH$_2$</td>
<td>210.2</td>
<td>15.2</td>
</tr>
<tr>
<td><strong>Pyridines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,6-di-t-BuC$_5$H$_3$N</td>
<td>221.4</td>
<td>26.4</td>
</tr>
<tr>
<td>4-MeC$_5$H$_4$N</td>
<td>215.0</td>
<td>20.0</td>
</tr>
<tr>
<td>2-MeC$_5$H$_4$N</td>
<td>214.4</td>
<td>19.4</td>
</tr>
<tr>
<td>3-MeC$_5$H$_4$N</td>
<td>213.5</td>
<td>18.5</td>
</tr>
<tr>
<td>C$_5$H$_5$N</td>
<td>211.0</td>
<td>16.0</td>
</tr>
</tbody>
</table>

$^a$ Based on $GB(NH_3) = 195.0$ kcal mol$^{-1}$ (see text).

$^b$ The standard free energy change for the process $BH^+ + NH_3 \rightleftharpoons NH_4^+ + B$ as reported by Taft in Reference 2 and as derived from the results in Table 4 for the $\alpha,\omega$-diamines.

from a consideration of rotational symmetry numbers$^{49}$. However, this will not be the case when protonation is accompanied by intramolecular rearrangement such as cyclization$^{45}$. Values for the proton affinities of amines have been tabulated in a recent review article by Kebarle$^{46}$. These have a more direct relevance in discussions of ion thermochemistry and the experimental assessment of quantum-mechanical calculations of such properties.

Changes in the proton affinities of amines may be analysed in terms of changes in ionization potentials ($IP$) and hydrogen-atom affinities ($HA$). The proton affinity is a measure of the ionic heterolytic bond dissociation energy while the hydrogen-atom affinity is homolytic. Their relationship is demonstrated in the following thermochemical cycle and in equation (25):

$$PA(B^+) = HA(B^+) - IP(B^+) + IP(H^+)$$

A consistent set of vertical and adiabatic ionization potentials has now been measured for a series of alkylamines and related alicyclic and saturated heterocyclic amines using photoelectron spectroscopy, and it has been combined with experimental proton affinities to provide values of $HA$ for the corresponding amine.
TABLE 9. A comparison between experimental and calculated proton affinities (kcal mol\(^{-1}\)) of alkylamines

<table>
<thead>
<tr>
<th>B</th>
<th>Measured(^a)</th>
<th>Calculated(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>STO-3G</td>
</tr>
<tr>
<td>CH(_3)NH(_2)</td>
<td>212.6</td>
<td>269.0</td>
</tr>
<tr>
<td>C(_2)H(_4)NH(_2)</td>
<td>215.3</td>
<td>272.4</td>
</tr>
<tr>
<td>i-C(_3)H(_7)NH(_2)</td>
<td>217.8</td>
<td>275.0</td>
</tr>
<tr>
<td>r-C(_4)H(_9)NH(_2)</td>
<td>220.1</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)\(PA(B) = \Delta H^0_{298}\) for the reaction \(BH^+ \rightleftharpoons B + H^+\) based on \(PA(NH_3) = 203.6\) kcal mol\(^{-1}\) (see text and Reference 46).

\(^b\)\(PA(B) = \Delta E\) as calculated by Radom\(^57\).

Table 9.

radical cations\(^{41,50,51}\). Changes in \(PA\) for an homologous series of aliphatic amines have been found to correlate linearly with changes in \(IP\), which dominate \(HA\) changes in determining the \(PA\) changes\(^{41}\). Substituents which decrease the ionization potential increase the gas-phase proton affinity. Furthermore, it has been shown that there exists a linear correlation between values of \(PA\) and the inner-shell nitrogen 1\(s\) binding energies within a series of homologous amines\(^{52-54}\). This is attributed to a similarity in the relaxation effects initiated by the addition of a proton or ionization of a core electron. The correlations have been interpreted in terms of substituent effects and also promise to be useful for the prediction of proton affinities not available from experiment.

Experimental proton affinities of amines have found an important application in the testing of quantum-mechanical calculations of these properties. Indeed, it may be said that their availability has stimulated a renewed interest in such calculations. A number of semiempirical (CNDO/2)\(^{41,55}\) and \(ab\) initio\(^{56,57}\) quantum-mechanical calculations have now been reported for the simpler alkyl amines. Although they have predicted absolute proton addition energies considerably larger than the experimental values, the calculations have all been successful in reproducing the gas-phase order of \(PA\). Moreover, the energy changes, \(\Delta E\), calculated for proton transfer between two amines are quite close to the experimental enthalpy changes (\(\Delta PA\)). This is evident from the comparison between experiment and the \(ab\) initio calculations reported by Radom\(^57\) which is presented in Table 9. The experimental values for \(\Delta PA\) lie intermediate between the STO-3G and 4-31G values. Perhaps more significantly, the results of these calculations have provided useful insights into electron distributions in the alkylammonium ions, their equilibrium structures and sites of protonation\(^{41,57}\). Such information is not available from the gas-phase measurements described, except perhaps through inference. Clearly experiment and theory should proceed in concert for maximum mutual benefit. Such has been the case, for example, in a recent determination of the proton affinities of aniline and a variety of \(meta\)- and \(para\)-substituted anilines and their preferred sites of protonation\(^{59,60}\).

V. GAS-PHASE ACIDITIES OF AMINES

The standard free energy change for reaction (20) provides a measure of the difference in the gas-phase acidity, \(GA\), of amines \(A^2H\) and \(A^1H\), viz. \(\Delta G^0 = \Delta G A\) (\(A^2H, A^1H\)), with the gas-phase acidity defined as the standard free energy change...
for the process in reaction (26). Again it follows that a continuous ladder of $\Delta G_A$s can yield absolute values for $GA$ when the ladder is calibrated with an appropriate choice of absolute reference value. For the $\Delta G_A$s provided by the flowing afterglow studies of the aliphatic amines, $GA(H_2)$ is an obvious choice. Its value can be established with high accuracy from values for $D_0(H-H)$, the electron affinity ($EA$) of H, $IP(H)$ and the entropies ($S^0$) of $H_2$, $H^-$ and $H^+$ (equation 27), all of which are available from the JANAF thermochemical tables. The value of $GA(H_2)$ at 298 K derived in this manner is $394.2 \pm 0.5$ kcal mol$^{-1}$. It leads to the absolute gas-phase acidities shown in Table 10.

The acidity $GA(AH)$ can provide a measure of the gas-phase proton affinity of $A^-$, $PA(A^-)$, which is defined as the standard enthalpy change for the deprotonation of the amine. Again this involves an estimation of the corresponding standard entropy change. In this case the proton affinities are related to electron affinities ($EA$) and bond dissociation energies ($D$) as shown by the following thermochemical cycle and equation (28):

\[
PA(A^-) = D(A-H) + IP(H^+) - EA(A^-) - \int_0^{298} \Delta C_p dT
\]

Consequently the experimental determination of gas-phase acidities can be useful either for the determination of $A-H$ bond dissociation energies for amine molecules

<table>
<thead>
<tr>
<th>AH</th>
<th>$GA(AH)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(CH_3)_3N$</td>
<td>$&gt;396^b$</td>
</tr>
<tr>
<td>NH$_3$</td>
<td>$396.1 \pm 0.7$</td>
</tr>
<tr>
<td>CH$_3$NH$_2$</td>
<td>$395.7 \pm 0.7$</td>
</tr>
<tr>
<td>H$_2$</td>
<td>$394.2 \pm 0.5^c$</td>
</tr>
<tr>
<td>C$_2$H$_3$NH$_2$</td>
<td>$391.7 \pm 0.7$</td>
</tr>
<tr>
<td>$(CH_3)_2$NH</td>
<td>$389.2 \pm 0.6$</td>
</tr>
</tbody>
</table>

$^b$In this instance the acidity refers to the heterolytic dissociation of a C–H rather than an N–H bond.
$^c$Reference value (see text).
TABLE 11. A comparison between experimental and calculated proton affinities (kcal mol⁻¹) of anions

<table>
<thead>
<tr>
<th>A⁻</th>
<th>Measuredᵇ</th>
<th>Calculatedᶜ</th>
<th>Ref. 61</th>
<th>Ref. 57</th>
<th>Ref. 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>H⁻</td>
<td>400.4 ± 0.5</td>
<td>400.5ᵈ</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NH₂⁻</td>
<td>403.6 ± 0.9</td>
<td>421.9ᵈ</td>
<td>—</td>
<td>553.3</td>
<td></td>
</tr>
<tr>
<td>CH₃NH⁻</td>
<td>403.2 ± 1.0</td>
<td>—</td>
<td>442.8, 537.5</td>
<td>539.0</td>
<td></td>
</tr>
<tr>
<td>C₂H₅NH⁻</td>
<td>399.4 ± 1.0</td>
<td>—</td>
<td>439.3, 536.2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>(CH₃)₂N⁻</td>
<td>396.4 ± 0.9</td>
<td>—</td>
<td>—</td>
<td>523.8</td>
<td></td>
</tr>
</tbody>
</table>

ᵇPA(A⁻) = ΔH⁰₂₉₈ for the reaction AH ⇌ A⁻ + H⁺.
ᶜPA(A⁻) = ΔE.
ᵈΔE corrected for zero-point vibration.

or for the determination of electron affinities for amine radicals, providing the appropriate support data are available. This approach has been clearly demonstrated by the flowing afterglow studies of the amines which have yielded $D_{0}^{298}$ (NH₂—H) = 107.4 ± 1 kcal mol⁻¹ and electron affinities for CH₃NH⁻, C₂H₅NH⁻ and (CH₃)₂N⁻ of 13.1 ± 3.5, 17 ± 4 and 14.3 ± 3.4 kcal mol⁻¹, respectively. Such thermochemical quantities are not easily obtained using more conventional experimental techniques.

A number of quantum-mechanical calculations of proton removal energies have recently been reported for amines. Table 11 includes results of ab initio molecular orbital studies reported by Hopkinson and coworkers⁶¹, Hehre and Pople⁶⁶ and Radom⁵⁷. Although the calculations differ appreciably in quality according to the choice of the basis sets, they all correctly reproduce the observed order of proton affinity of the amide ions in the gas phase. However, the calculated absolute energies for proton removal are consistently higher than the experimental values by as much as ~35%. Better agreement is obtained with more extensive basis sets. Differences in proton affinity are also reproduced more exactly with the extensive sets. For example, the measured ΔPA of 3.8 ± 2.0 kcal mol⁻¹ for PA (CH₃NH⁻) – PA(C₂H₅NH⁻) compares more favourably (in fact, remarkably well) with the value of 3.5 kcal mol⁻¹ obtained by Radom⁵⁷ with the extended 4-31G set than the value of 1.3 kcal mol⁻¹ obtained with the minimal STO-3G set.

VI. INTRINSIC EFFECTS OF MOLECULAR STRUCTURE

The preferred direction of proton transfer as well as the actual position of equilibrium (the absolute magnitude of $K$) for the gas-phase acid–base reactions involving amines discussed in the previous sections represent a response solely to intrinsic structural effects. As such they can provide valuable insight into the nature of these effects. This has been thoroughly demonstrated for the protonation of amines in two excellent review articles by Taft to which the reader is referred for a detailed and comprehensive discussion³⁹. With one important exception, the substituent effects which operate have been previously identified through acid–base measurements in solution, albeit their influence is more distinct in the gas phase. The gas-phase measurements were the first to identify the so-called polarizability effect according to which proton transfer will be preferred in the direction which
places the most polarizable substituent with the charge type (positive or negative), i.e. if \( X \) is the most polarizable substituent, proton transfer is preferred in the direction shown in equations (29) and (30). This was first recognized in the early measurements of the orders of basicity and acidity for the primary, secondary and tertiary amines, all of which could be accounted for by this effect\(^3\). The polarizability effect arises from a charge induced dipole interaction, the energy of which in the point charge approximation is given by equation (31), where \( q \) is the charge, \( \alpha \) is the substituent polarizability, \( r \) is the distance of separation, and \( \epsilon \) is the effective dielectric constant. The charge stabilization calculated from equation (31) has been shown to be roughly of the right magnitude to account for the observed differences in the proton affinities of alkylamines and their remarkable regularity\(^4\). Further support of the polarizability effect has been forthcoming from quantum-mechanical calculations of charge distribution\(^5\). Trends in IPs of amines, the inner-shell nitrogen 1s binding energies of amines, and the electron affinities of amide ions have also been found to mimic the behaviour expected from polarization effects.

The contribution of other substituent effects may be best appreciated from a consideration of equilibria judiciously chosen to maximize the effect of interest. For example, Taft has shown that for proton-transfer equilibria involving contributions due to a polarizability effect \( P \), an inductive-field effect \( I \), and a resonance or \( \pi \)-electron delocalization effect \( R \), it is instructive to dissect the standard free energy change in the following manner\(^9\):

\[
-RT \ln K = \Delta G^0 = P + I + R
\]

The \( I \) effect is made predominant by choosing structures which minimize both \( P \) and \( R \) effects as is the case in the equilibria (33) and (34) involving distant \(-\text{CF}_3\) and \(\text{HC}≡\text{C}−\) substituents. In this case proton transfer is preferred in the direction

\[
\text{C}_2\text{H}_5\text{NMe}_2 + \text{CF}_3\text{CH}_2\text{N(Me)}_2\text{H}^+ \rightleftharpoons \text{C}_2\text{H}_5\text{N(Me)}_2\text{H}^+ + \text{CF}_3\text{CH}_2\text{NMe}_2
\]

\[
\text{n-C}_3\text{H}_7\text{NH}_2 + \text{HC}≡\text{CCH}_2\text{NH}_3^+ \rightleftharpoons \text{n-C}_3\text{H}_7\text{NH}_3^+ + \text{HC}≡\text{CCH}_2\text{NH}_2
\]

which minimizes the electrostatic charge–dipole destabilization (the large dipole moment localized in \( X \) is orientated with its positive end towards the cationic centre and contributes a favourable negative term to \( \Delta G^0 \) (i.e. \( I \) is negative). The equilibrium constants for reactions (33) and (34) are 10\(^8\) and 10\(^4\), respectively\(^2\). For alkyl substituents the inductive effects are stabilizing (electron-releasing) but considerably smaller than the predominating polarizability effects. Resonance effects are often found to be secondary to a predominant combination of \( I \) and \( P \) effects. Consequently, to obtain measures of the \( R \) effect the standards of comparison should have the same number of carbon atoms, as well as similar substituents and structures. This is the case in equilibrium (35) which is shifted towards the formation of the \( N \)-methylimidazolium ion which is strongly
resonance-stabilized. The equilibrium constant for this reaction is $10^{11.8}$. Examples have also been reported of proton transfer driven by preferential resonance stabilization of a neutral component.

Finally, attention should be drawn to stabilization (energy release) resulting from intramolecular cyclization which has been proposed to account for the high base strengths of diamines relative to monoamines of comparable structures. (Indeed, it has been proposed that gas-phase measurements of basicity may provide a general method for the detection of ring formation.) The large negative entropy changes associated with the protonation of diamines may be attributed almost entirely to the loss of freedom associated with the formation of proton-bound cyclic diamines according to equations (36) and (37). Step (36) should involve very little entropy change while step (37) involves entropy loss due to cyclization. The enthalpy change associated with the cyclization step, $\Delta H_{\text{cycl}}^0$, has been estimated assuming that $\Delta H_{36}^0$ is equal to $\Delta H^0$ for the proton transfer to the monoamine $\text{CH}_3(\text{CH}_2)_n\text{NH}_2$, so that

$$\Delta H_{\text{cycl}}^0 = \Delta H_{36}^0 = \rho_A(\text{NH}_2(\text{CH}_2)_n\text{NH}_2) - \rho_A(\text{NH}_2(\text{CH}_2)_n\text{CH}_3)$$

The values for $\Delta H_{\text{cycl}}^0$ obtained by equation (38) are shown in Table 12. Furthermore, the strain energies associated with cyclic protonated diamines have been estimated from a comparison of $\Delta H_{\text{cycl}}^0$ with $\Delta H^0$ associated with the formation of proton-bound dimers involving two alkylamines (equation 39) where

$$\text{C}_k\text{H}_{2k+1}\text{NH}_3^+ + \text{C}_k\text{H}_{2k+1}\text{NH}_2 \rightleftharpoons (\text{C}_k\text{H}_{2k+1}\text{NH}_2)_2^+$$

| TABLE 12. Thermodynamic aspects of the cyclization of protonated $\alpha,\omega$-diamines
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta S_{\text{cycl}}^0$</td>
<td>$\Delta H_{\text{cycl}}^0$</td>
<td>Strain</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1,2-Diaminoethane</td>
<td>12.7</td>
<td>12.6</td>
</tr>
<tr>
<td>1,3-Diaminopropane</td>
<td>20.6</td>
<td>20.5</td>
</tr>
<tr>
<td>1,5-Diaminopentane</td>
<td>20.0</td>
<td>20.1</td>
</tr>
<tr>
<td>1,7-Diaminohexane</td>
<td>20.0</td>
<td>20.0</td>
</tr>
</tbody>
</table>


In cal mol$^{-1}$ deg$^{-1}$.

In kcal mol$^{-1}$. 
strain energy \( = \Delta H_{\text{cycl}} - \Delta H_{39} = \Delta H_{\text{cycl}} + \approx 23 \text{ kcal mol}^{-1} \)  

(40)

\( k = n/2 \). The results are obtained from the approximation in equation (40) and are included in Table 12. It has been suggested that the strain energy for the proton-bound diaminoethane, which is much higher than that for the other diamines, and the entropy decrease associated with its formation, which is significantly smaller than those for the higher diamines, is consistent with a four-membered ring structure in which the \( \text{N-H}^+ - \text{N} \) hydrogen bond tends to be linear. A consideration of Dreiding models has indicated that a linear hydrogen bond may be accommodated only in a ring of somewhat large size (1,4-diaminobutane). Also, comparisons have been reported with thermodynamic data for the corresponding \( n \)-alkanes and cycloalkanes. It should be mentioned in closing that intrinsic effects of molecular structure (the position of equilibrium) will be modulated by solvation to a greater or lesser degree depending on the nature of the intrinsic effects and the nature of the competing interaction with solvent molecules. Indeed, this can result in striking anomalies between the gas phase and solution. The influence of solvation was considered to fall outside the scope of this article. The reader is referred to the review articles by Taft and Arnett for detailed treatments of this subject.

VII. REFERENCES

I. INTRODUCTION

This chapter emphasizes those aspects of the chemistry of di- and poly-amines*.

*To avoid ugly repetition, we shall frequently use the term diamine to include polyamines throughout this chapter; in practice diamines provide most of the examples with the exception of metal ion chelation.

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which depend on the presence of more than one lone pair$^\dagger$ of electrons. The interaction of lone pairs in diamines is always repulsive (antibonding), but this can be changed to a bonding interaction by oxidation, protonation or metal ion chelation (reaction 1).

We may therefore expect diamines to be more easily oxidised than monoamines, and to be stronger bases and more effective ligands towards metals. In practice some important distinctions and qualifications must be made. Diamines adopt structures and conformations which minimize lone-pair interactions unless molecular constraints prevent this. Vertical ionization potentials, as measured, for example, in photoelectron spectra, may therefore only be unusual in structurally constrained diamines.

Adiabatic ionization (oxidation), such as occurs in solution, might occur with formation of a stabilized three-electron bonded radical cation by structural change. In practice, however, an alternative pathway – proton transfer – often takes place (reaction 2) so that the formation of long-lived radical ions is limited to certain special situations. In protonation, there is no comparable competitive intramolecular reaction. However, in solution, stabilization of the monoprotonated ion by intramolecular hydrogen bonding has to compete with hydrogen bonding to the solvent. As a result, while in the gas phase diamines which can form hydrogen-bonded protonated ions are markedly more basic than monoamines, these effects are generally small for solution basicities except in special circumstances.

Lone pairs may not only interact directly (through space) by $\sigma$- or $\pi$-like orbital overlap but also via other $\sigma$- and $\pi$-bonding systems, and we shall first briefly review simple theories of these interactions. We shall then describe some structural consequences of the avoidance of lone-pair interactions in real diamines. We shall then discuss diamine oxidation and the structure of some of the radical cations formed. This is followed by a section on basicity and hydrogen bonding. Finally we shall consider metal ion chelation by di- and poly-amines with particular emphasis on nitrogen cryptands.

$^\dagger$We use the noncommittal term ‘lone pair’ deliberately. Lone pairs are never nonbonding in amines.
II. A SIMPLE THEORETICAL PICTURE OF INTERACTIONS AMONGST LONE PAIRS

Molecular orbital theory provides an almost too convenient framework for the discussion of lone-pair interactions. Direct, through-space interaction can occur in $\sigma$ (1), $\pi$ (2) or any intermediate geometry (3), and will, in detail, depend on the hybridization of the basis set lone-pair orbitals. Quite generally, however, there will

![Diagram of lone-pair interactions](image)

- **Diagram (a):** Mixing of lone-pair orbitals to generate $n_+$ and $n_-$. (b) Orbital energies; without overlap $n_+$ is stabilized to the same extent than $n_-$ is destabilized (dashed lines). Inclusion of overlap leads to greater destabilization of $n_-$. (c) Lone-pair interactions are always repulsive for diamines. The radical cation may have a weak three-electron bond, provided overlap is not too great ($s < \frac{1}{2}$). (d) The orbitals of a hydrogen bond, derived by mixing the hydrogen $1s$ orbital with $n_+$. Note that for the $N-H-N$ system, $\phi_1$, $\phi_2$, $\phi_3$, the positive charge lowers all orbital energies.
be one (bonding) orbital with two nodal surfaces and one (antibonding) orbital with three. As Figure 1 shows, the interaction is always overall antibonding for a diamine (four electrons), but can become weakly bonding with three electrons (radical cation of the diamine), and is strongly bonding for the dication. On the other hand introduction of a proton between the nitrogens (four electrons) leads to the familiar orbitals of the hydrogen bond.

Lone-pair orbitals may not only interact directly through space, but also via other orbitals in the molecule. Interaction via π-orbitals has been recognized for many years, but Hoffmann\(^3\) pointed out that interaction could also occur via σ-orbitals. As Figure 2 shows, there is no difference in principle. The degree of orbital mixing, according to perturbation theory, is inversely proportional to the energy difference between the unperturbed orbitals. Since π-orbitals are normally higher lying than σ-orbitals, their mixing with nonbonding orbitals will normally be larger. Nevertheless, through-bond mixing via σ-orbitals is now well established. Like classical conjugation, it is subject to strict geometrical limitations. In the example shown in Figure 2(b), the symmetric orbital, \(\psi_3\), related to \(n_1\) for through-space coupling, lies higher in energy. Thus through-space and through-bond interaction may be in conflict over the relative orbital energies, although both are destabilizing.

FIGURE 2. Through-bond mixing of lone-pair orbitals (a) via π-bonds, (b) via σ-bonds. Note that, especially for the σ-case (b), \(\psi_2\) and \(\psi_3\) are largely lone-pair orbitals, while \(\psi_1\) is largely a C—C bonding orbital.
for diamines as far as overall energy is concerned. Hoffmann has illustrated the orbital energy orderings for a number of common situations. In practice σ-type through-bond interaction is only dominant in the N—C—C—N situation shown in Figure 2(b) or in related cases which are rotameric about the C—C bond (but preserve the important overlaps).

Other theoretical analyses of through-bond coupling have been described. Wadt and Goddard have discussed the case of pyrazine in valence-bond terms. Their paper provides a useful antidote to the seductive interplay of molecular orbital theory with photoelectron spectroscopy via Koopmans' theorem, which almost persuades one of the reality of orbitals.

It is perhaps useful to see lone-pair interactions in terms of four limiting cases: π through-space, σ through-space, π through-bond and σ through-bond. These are shown as four classic examples in Figure 3.

### III. STRUCTURAL CONSEQUENCES OF THE AVOIDANCE OF LONE-PAIR REPULSION

In general terms, di- and poly-amines adopt structures which minimize interactions between lone pairs, unless strong molecular constraints dictate otherwise. As far as we are aware, no quantitative treatment of lone-pair repulsions as a function of geometry and hybridization has been reported and force-field calculations for amines are at present in a fairly primitive state. In this section therefore we shall simply describe some structures which show the effects of avoidance of lone-pair interactions.

While outside the strict scope of this chapter, hydrazines are really the simplest example. Where possible they adopt conformations in which the dihedral angle between the lone pairs is close to 90°. When this is impossible, a dihedral angle of 180° is adopted, but other changes occur (e.g. lengthening of the N—N bond) to minimize lone-pair overlap. Two recent structures illustrate these effects very nicely (Figure 4), and there is much evidence of a more indirect character which supports these trends.

In 1,1-diamines, conformations with parallel lone pairs are avoided.

![Figure 3. Limiting cases for different types of lone-pair interaction.](image-url)
18. Special properties of di- and poly-amines

(christened the ‘rabbit ear’ effect by Eliel\textsuperscript{12}). This is really one case of the anomeric effect\textsuperscript{13}. Discussions of the causes of this effect still continue, but it appears that, in an orbital description, mixing of lone-pair orbitals with the $\sigma^*$-orbitals of the polar C—X(C—N) bonds is important, as well as simple through-space lone-pair repulsion\textsuperscript{14}. The best experimental evidence comes from NMR studies of hexahydropyrimidines, and related heterocycles. Thus for (5), $R = \text{H}$, the ee conformation is only preferred by 0.4 kcal mol\textsuperscript{-1}, while for (5), $R = \text{Me}$, the ae conformation is preferred by 0.85 kcal mol\textsuperscript{-1}\textsuperscript{15}.

![Diagram](5(ee) and 5(ae))

In 1,2-diamines, structures which lead to through-space (6) and through-bond (7) interactions are avoided but this often occurs for other reasons than the lone-pair interactions themselves. Thus in hexahydropyrazines, conformations with both nitrogen substituents equatorial are preferred\textsuperscript{16,17}, and the triple constraint provided by the 1,4-diazabicyclo[2.2.2]octane is required to enforce the structure favourable to through-bond interaction. No diamine has been devised which is forced to adopt the through-space interactive structure.

The through-space interactive structure can only be enforced with severe constraints in 1,3-diamines. Partially alkylated 1,8-diaminonaphthalenes adopt conformations with N—H : N hydrogen bonds, but 1,8-bis (dimethylamino)naphthalene is forced to adopt a structure with some lone-pair interaction (Figure 5a)\textsuperscript{18}. In this and similar cases the situation is complicated by (favourable) $n-\pi$ overlap. In the radical anion\textsuperscript{19} (odd electron in a $\pi^*$-orbital), $n-\pi$ overlap is probably repulsive, accounting for the increase in the dihedral angle between $n$- and $\pi$-orbitals from ca. 30° to 60—70°. In the protonated ion\textsuperscript{20}, the lone pairs become coplanar, although the N—H : N bond is almost certainly not linear and has a symmetrical double-minimum potential (see Section VII); it is noteworthy that the nitrogens are still splayed apart (2.62 Å) relative to the naphthalene nucleus. The variable-temperature NMR behaviour of 1,8-bis(dimethylamino)naphthalene\textsuperscript{21} shows that it costs about 7.5 kcal mol\textsuperscript{-1} to achieve the C\textsubscript{2v} structure with directly opposed lone pairs. 2,7-Disubstitution as in 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene\textsuperscript{22} comes close to enforcing direct opposition of the lone pairs (Figure 5b), and this leads to extreme basicity for this diamine (see Section IX). Finally, directly opposed lone pairs are achieved in the naptho-1,5-diazabicyclo[3.3.3]undecane (Figure 5c)\textsuperscript{23}. Here the only avenue open for the relief of lone-pair interactions is outward pyramidalization of the nitrogens. This is strongly opposed by the rest of the structure, but nevertheless occurs to a limited extent.

There is no detailed structural information yet available on 1,5-diazabicyclo[3.3.3]undecane\textsuperscript{24} or 1,6-diazabicyclo[4.4.4]tetradecane\textsuperscript{25} but it seems certain that some degree of lone-pair interaction is enforced in these systems, and
FIGURE 5. (a) Structure of 1,8-bis(dimethylamino)naphthalene; the N—N distance is 2.79 Å. Reproduced by permission of the International Union of Crystallography from H. Einspahr, J.-B. Robert, R. E. Marsh and J. D. Roberts, Acta Cryst., B29, 1611 (1973). (b) Structure of 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene, the N—N distance is 2.76 Å. Structure of 1,8-naphtho[bc]1,5-diazabicyclo[3.3.3]undecane, the N—N distance is 2.89 Å and C—N—C bond angles average 118.5°.
the [4,4,4]system may have inwardly pyramidalized nitrogens. In macrobicyclic
diamines and cryptands direct N–N interaction becomes unimportant, but
in, in, in, out and out, out geometries are all found in the amines or their derivatives
(Figure 6). In one large cryptand a planar, planar geometry has been reported
(Figure 6d). This is rather remarkable since it requires the simultaneous
destabilization of both in and out geometries, and must always represent a finely
balanced situation.

IV. PHOTOELECTRON SPECTRA OF DIAMINES

Di- and poly-amines are electron-rich species which are amongst the most easily
oxidized of organic molecules. We are fortunate to be able to study electron
detachment by both UV photoelectron spectroscopy in the gas phase and, in sol-
ution, by electrochemical techniques, particularly cyclic voltammetry, for these give
quite distinct and complementary information. Photoionization is subject to the
usual Franck-Condon restrictions, so that the most accessible information is the
vertical ionization energy, the energy required to form the radical cation in the
geometry of the starting diamine. The very fact that the photoelectron bands
associated with ionization of lone-pair electrons are normally broad and featureless
shows that (a) these lone-pair electrons are rarely, if ever, ‘nonbonding’ and (b)
that radical cation equilibrium geometries are usually substantially different from
those of their parent diamines.

Saturated diamines show two low-energy photoelectron bands (Table 1), which,
using Koopmans’ theorem and the orbital picture, can be associated with the
removal of electrons from lone-pair orbitals. The ΔI between these bands is very
sensitive to the geometry and mode of interaction of the lone pairs. Hydrazines are
the simplest case and have been particularly thoroughly studied, especially by
Nelsen and Rademacher. When the dihedral angle between the lone pairs is
about 90° as in 8, ΔI is small, but it becomes large when the dihedral angle is near
180° (as in 9) or 0°. Enough confidence has now developed in this area to permit
the use of photoelectron spectra for conformational analysis. With certain hexahyd-
ropyridazines, the photoelectron spectrum is the superposition of spectra due to dif-
ferent conformers.

With 1,1-diamines, such as hexahydropyrimidines, ΔI is quite small when the
lone pairs are aa or ae as in 10 and 11 but is larger when they are ee as in 12 and
13. In the latter case it is the antisymmetric n–orbital which is of higher energy. As
has been pointed out earlier (Section II), the orbital interactions in 1,1-diamines
are complicated by n/n* overlap involving polar C=N bonds.

Diamine 12 contains an N–C–C–N unit fairly well aligned for through-bond
coupling; in this particular case it is believed that through-space coupling
dominate, putting n_ above n+. With two and three N–C–C–N coupling
pathways, through-bond coupling dominates, according to calculations. The classic
example is DABCO. Analysis of the vibrational fine structure in the DABCO
spectrum enabled Heilbronner and Muszkat to assign the 7.52 eV band to
formation of the A1(1)A2*(1) state of the radical cation with some assurance, and
thus to prove the dominance of through-bond coupling.

The finding of really significant through-space interactions uncontaminated by
through-bond effects had to wait for the synthesis of medium-ring bicyclic
diamines such as 16, 17, 18 and 19. These compounds show exceptionally low
ionization energies, and, in general terms, this is probably due to molecular strain
which (a) enforces flattened geometry at nitrogen (aminium cation radicals prefer
FIGURE 6. Cryptand structures showing (a) \textit{in,in} geometry in the free [2.2.2] cryptand, average C—N—C angles 112.2°; (b) \textit{out, out} geometry in [2.2.2]·2BH₃, average C—N—C angle 109.5° [reproduced by permission of the Chemical Society, London from B. Metz, D. Moras and R. Weiss, \textit{J. Chem. Soc., Perkin II}, 423 (1976)]; (c) [2.2.1]·BH₃ with \textit{in, out} geometry, average C—N—C angles 113.6° at the free nitrogen, and 110.6° at the complexed nitrogen [reproduced with permission from B. Metz and R. Weiss, \textit{Nouvea J. Chem.}, 2, 615 (1978)]; (d) a cryptand with planar geometry at nitrogen, average C—N—C bond angles 120.0° [reproduced with permission from G. R. Newkome, V. Majestic, F. Frongczek and J. L. Atwood, \textit{J. Amer. Chem. Soc.}, 101, 1047 (1979); copyright 1979 American Chemical Society].
### TABLE 1. Vertical ionization energies, $I_v$, of selected di- and polyamines

<table>
<thead>
<tr>
<th>Amine</th>
<th>$I_v$</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Me$_2$NNMe$_2$ (8)</td>
<td>8.27, 8.82</td>
<td>9</td>
</tr>
<tr>
<td>MeNMe$_2$N (9)</td>
<td>7.61, 9.92</td>
<td>9</td>
</tr>
<tr>
<td>MeMeN (10)</td>
<td>8.11, 8.51</td>
<td>30</td>
</tr>
<tr>
<td>MeMeNMe (11)</td>
<td>8.03, 8.41</td>
<td>30</td>
</tr>
<tr>
<td>N (12)</td>
<td>8.89, 9.64</td>
<td>30</td>
</tr>
<tr>
<td>N (13)</td>
<td>7.75, 8.78</td>
<td>30</td>
</tr>
<tr>
<td>(14) N</td>
<td>7.52, 9.65</td>
<td>31</td>
</tr>
<tr>
<td>(15)</td>
<td>7.43, 8.65</td>
<td>30</td>
</tr>
<tr>
<td>(16)</td>
<td>7.56, 8.8</td>
<td>23</td>
</tr>
<tr>
<td>(17)</td>
<td>6.85, 7.90</td>
<td>24, 32</td>
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</table>
### Table 1. (continued)

<table>
<thead>
<tr>
<th>Amine</th>
<th>( I_v )</th>
<th>Reference</th>
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<tbody>
<tr>
<td><img src="18" alt="Image" /></td>
<td>6.90, 7.76</td>
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<td><img src="19" alt="Image" /></td>
<td>6.75, 7.87</td>
<td>32</td>
</tr>
<tr>
<td><img src="20" alt="Image" /></td>
<td>8.08, 9.00</td>
<td>30</td>
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<tr>
<td><img src="21" alt="Image" /></td>
<td>8.53</td>
<td>30</td>
</tr>
<tr>
<td><img src="22" alt="Image" /></td>
<td>7.39, 8.66, 9.54</td>
<td>33</td>
</tr>
<tr>
<td>( \text{H}_2\text{C}=\text{C}(\text{NMe}_2)_2 )</td>
<td>7.5, 8.2, 10.3, 12.5</td>
<td>34</td>
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<tr>
<td>((\text{Me}_2\text{N})_2\text{C}=\text{C}(\text{NMe}_2)_2)</td>
<td>5.95, 7.5, 7.85, 8.5, 9.5</td>
<td>35</td>
</tr>
<tr>
<td>(\text{Me}_2\text{N}--\text{C}--\text{NMe}_2)</td>
<td>6.84, 8.36, 8.74, 10.0, 11.16</td>
<td>36</td>
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<tr>
<td>(\text{Me}_2\text{N}--\text{NMe}_2)</td>
<td>7.03, 7.47, 8.50, 9.01, 9.78</td>
<td>37, 38</td>
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planar geometry$^{39,40}$ so this favours ionization, raising both $n_+$ and $n_-$), and (b) also enforces through-space mixing, raising $n_-$ and lowering $n_+$. Very few polyamines have been examined by photoelectron spectroscopy. According to calculations, the most weakly bound electrons are in a degenerate $E$ orbital for $20^{30}$, in an orbital of $T_2$ symmetry for $21^{30}$ and in a $B_2$ orbital for $22^{33}$. The lowering of the ionization energies for $22$ vs. $21$ and $15$ vs. $14$ is probably again due to flattening at nitrogen.

In unsaturated and aromatic amines $n/\pi$ mixing complicates band assignment but leads to compounds with very low first ionization energies. The most weakly bound electrons in $24$ and $25$ lie in $\pi$-orbitals of the form shown below:

With the 1,8-naphthalenediamines $26$–$29$ there is only limited $n$–$\pi^*$ overlap. As we have seen (Section III), $26$ has $C_2$ symmetry with the lone pairs overlapping with opposite faces of the twisted naphthalene $\pi$-system. Diamine $27$ is probably almost planar while $28$ and $29$ have $C_5$ symmetry. Using simple symmetry arguments, it is possible to construct a correlation diagram for both conrotatory and disrotatory change from coplanar to perpendicular geometry for a simple model 1,8-naphthalenediamine (Figure 7). The observed photoelectron bands for $26$–$29$ fit on this diagram at very reasonable geometries. Unfortunately neither $16$ nor $18$ provide suitable models for the perpendicular geometry, the former because of

<table>
<thead>
<tr>
<th>Amine</th>
<th>$I_v$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Amine 27" /></td>
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<tr>
<td><img src="image" alt="Amine 28" /></td>
<td>6.72, 7.78, 8.38, 8.87, 9.90</td>
<td>38</td>
</tr>
<tr>
<td><img src="image" alt="Amine 29" /></td>
<td>6.85, 8.1, 8.5, 8.8, 9.83</td>
<td>38</td>
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</table>
through-bond coupling and the latter because of the effects of molecular strain (the model is taken to have sp2-hybridized nitrogen, whereas in practice only 18 approaches this). It should be noted that this correlation diagram leads to an assignment of the spectrum of 26 which is different from that of Maier37, who assumed perpendicular geometry.

Finally, those factors which raise orbital energies and lead to low ionization energies will also influence electronic spectra. Thus 18 is yellow, possibly due to an \( n \to \pi^* \) transition, and saturated diamines like 17 and 19 show absorption at exceptionally long wavelengths24,25. There is thorough discussion by Halpern of the electronic spectra of amines, including some diamines, elsewhere in this volume (Chapter 5).

V. ELECTROCHEMISTRY OF DI- AND POLY-AMINES

While the anodic oxidation of amines has been extensively studied41, our concern in this section is with the electrochemistry of those di- and poly-amines whose oxidation is electrochemically reversible (i.e. where radical cations with lifetimes greater than about 0.1 s are formed). Cyclic voltammetry has been the most frequently used technique although d.c. and a.c. polarography have also been employed. Most studies use acetonitrile or dichloromethane as solvent (butyronitrile is a superior low-temperature solvent), and gold or platinum electrodes and \( E^0 \) values are referred to either the standard calomel electrode or to a Ag/AgCl electrode. The data in Table 2 have all been referred to the standard calomel electrode. Corrections for different solvents have not been applied, but the use of any solvent other than acetonitrile is noted in the references.

In general terms compounds with low vertical ionization potentials (\( I_v \)) show low (more negative) values for \( E^0_1 \). The relationship between these quantities and the adiabatic ionization potential (\( I_a \)) is shown in Figure 8. The relaxation energy \( I_a - I_3 \) will be large if there are substantial differences between the structure of the diamine and its radical cation. The relaxation energy will be smallest for diamines
<table>
<thead>
<tr>
<th>Amine</th>
<th>$E^0_{1,2}$ vs. SCE</th>
<th>Reference</th>
</tr>
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<tr>
<td>Me$_2$NNMe$_2$ (8)</td>
<td>+0.28</td>
<td>9</td>
</tr>
<tr>
<td>(30)</td>
<td>-0.01, +1.18</td>
<td>42</td>
</tr>
<tr>
<td>(31)</td>
<td>+0.70</td>
<td>43</td>
</tr>
<tr>
<td>(14)</td>
<td>+0.57</td>
<td>43, 44</td>
</tr>
<tr>
<td>(17)</td>
<td>-0.17, +0.1</td>
<td>24</td>
</tr>
<tr>
<td>(18)</td>
<td>+0.11, +0.72</td>
<td>45</td>
</tr>
<tr>
<td>(19)</td>
<td>-0.1, +0.2</td>
<td>25</td>
</tr>
<tr>
<td>(22)</td>
<td>+0.56</td>
<td>43</td>
</tr>
<tr>
<td>(Me$_2$N)$_2$C=CMe$_2$ (32)</td>
<td>+0.05</td>
<td>46</td>
</tr>
<tr>
<td>(Me$_2$N)$_2$C=C(NMe$_2$)$_2$ (24)</td>
<td>-0.77, -0.65</td>
<td>46</td>
</tr>
<tr>
<td>[(Me$_2$N)$_2$C=CH]$_2$ (33)</td>
<td>-0.36, -0.18</td>
<td>46</td>
</tr>
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</table>
18. Special properties of di- and poly-amines

<table>
<thead>
<tr>
<th>Amine</th>
<th>$E^0_1$, $E^0_2$ vs. SCE</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_2$N-(\begin{array}{c} \text{NMe} \ \text{NMe} \end{array}) (25)</td>
<td>-0.01, +0.60</td>
<td>47</td>
</tr>
<tr>
<td>(\begin{array}{c} \text{NMe} \ \text{NMe} \end{array}) (34)</td>
<td>+0.60, +0.84</td>
<td>48</td>
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<tr>
<td>(\begin{array}{c} \text{N} \ \text{Me} \ \text{N} \ \text{Me} \end{array}) (35)</td>
<td>+0.36, +0.98</td>
<td>48</td>
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<tr>
<td>MeN-(\begin{array}{c} \text{NMe} \ \text{NMe} \end{array}) (36)</td>
<td>-0.87, -0.45</td>
<td>49</td>
</tr>
<tr>
<td>(\begin{array}{c} \text{N} \ \text{Me} \ \text{N} \ \text{Me} \end{array}) (37)</td>
<td>+0.61, +1.30</td>
<td>50</td>
</tr>
<tr>
<td>MeN-(\begin{array}{c} \text{NMe} \ \text{NMe} \end{array}) (38)</td>
<td>+0.61, +0.95</td>
<td>51</td>
</tr>
<tr>
<td>(\begin{array}{c} \text{Me} \ \text{N} \ \text{Me} \ \text{N} \ \text{Me} \end{array}) (39)</td>
<td>-0.11, +0.23</td>
<td>52</td>
</tr>
<tr>
<td>Tetraphenylporphin (40)</td>
<td>+1.05, +1.30</td>
<td>53</td>
</tr>
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</table>
containing large \( \pi \)-systems. Solvation energies are undoubtedly large, but differences in solvation energies between related systems may well be quite small; there is only one case where it is believed\(^{33} \) that the radical ion observed in solution is in a different electronic state from that in the gas phase (see Section VI).

The first oxidation potentials cover a wide range. In assessing the effects of different structural features it is helpful to have as a reference the oxidation potential for a simple tertiary amine. The only simple amine whose oxidation is electrochemically reversible is \( 41 \) which has \( E^0 = +0.74 \) V\(^{34} \).

Many unsaturated and aromatic diamines in which there is extensive conjugation have very low oxidation potentials. Tetraaminoethylenes\(^{55} \) are oxidized in two stages with exceptional ease, as are systems like \( 36 \), the reduced form of paraquat, which becomes aromatic in its oxidized ions. Deuchert and Hünig\(^{56} \) have reviewed these systems recently. They call any system which is a version or elaboration of system (3) a violene. It would now seem possible to design a violene system to have almost any values of \( E_1^0 \) and \( E_2^0 \) within a wide range. Of the three oxidation levels in a violene system, SEM makes the greatest demands on delocalization for

\[
\begin{align*}
\text{(41)}
\end{align*}
\]
18. Special properties of di and poly-amine

\[
\begin{align*}
\hat{X} = (CH=CH)_n \rightarrow \hat{Y} & \xrightarrow{\text{RED}} \hat{X} = (CH=CH)_n \rightarrow \hat{Y} & \xrightarrow{\text{OX}} \hat{X} = (CH=CH)_n \rightarrow \hat{Y} \\
\text{SEM} & \xrightarrow{\text{OX}} & \text{OX}
\end{align*}
\]

its stability, so that \(K_d\), the disproportionation constant for the radical cation \(= \exp (23.06 \times 10^3)/(1.987T) \times (E_0^\text{f} - E_1^\text{f})\] is low for systems like 33 and 34 where there is steric inhibition of resonance (compare 34 and 35)\textsuperscript{46.48}.

\(\text{RED} \) SEM ox

It is perhaps more surprising to find diamines without extensive conjugated systems which are oxidized with exceptional ease. Three cases can be distinguished (see Figure 3). Hydrazines form three-electron \( \pi \)-bonded radical cations; only one example, 30, has been found which reversibly forms a dication. Medium-ring systems like 17–19 form three-electron \( \sigma \)-bonded radical cations, which are readily oxidized further to dications that are hexaalkylated hydrazinium ions. There is no doubt that relief of strain in these medium-ring systems is responsible for the low values of \( E_0^\text{f} \) and \( E_1^\text{f} \). It is noteworthy that 42 is only irreversibly oxidized at +1.1 V. The startling contrast with 18 is presumably because the nitrogens in 42 cannot pyramidalize inward and form a three-electron \( \sigma \)-bond. However this does seem to happen in the more flexible 22. Finally, the DABCO radical cation is stabilized by through-bond effects as already discussed. Nelsen and Hintz\textsuperscript{43} examined a number of related bridgehead diamines (1,5-diazabicyclo[3.2.1]octane, 1,5-diazabicyclo[3.3.1]nonane, etc.) and apart from 31 found no other similar oxidized. Through-bond coupling implies easy fragmentation in the radical cation as shown in reaction (4). This is the decomposition pathway for the DABCO radical cation\textsuperscript{57}, and it probably occurs more rapidly in other cases where delocalization is not spread over three bridges.

Horner and Hünig\textsuperscript{58} have devised a most intriguing system (43) in which both through-space and \( \pi \)-electron delocalization effects are present.
It is amusing that in 43 ring strain destabilizes the (electronically-favoured) dication, whereas in 17–19, ring strain destabilizes the diamine. Obviously many more interesting redox systems could be devised along these lines.

Nelsen has recently reviewed ionization energy/oxidation potential comparisons for compounds containing amino nitrogen.

**VI. DIAMINE RADICAL CATIONS AND DICATIONS**

Many unsaturated and aromatic amines give long-lived radical cations and dications on oxidation, the classic example being tetramethyl-p-phenylenediamine which yields the blue Wurster's cation on oxidation. Much of the recent work in this field has been due to Hunig, who has studied the ESR and electronic spectra of the radical ions. Since this area has been recently reviewed, we shall not discuss it further, but will concentrate on those long-lived radical ions and dications which are derived from simple nonconjugated diamines.

Table 3 lists the approximate lifetime, nitrogen hyperfine coupling constants and absorption spectral data for some typical diamine radical ions. The radical ion 44 is by far the most stable of a large number of hydrazine radical cations which have been studied. This is undoubtedly because of the impossibility of α-deprotonation in this case. A crystal structure of 44 as the PF₆ salt has been reported; the N–N distance is remarkably short (1.27 Å) and the C₂N–NC₂ system is completely flat. The odd electron must lie in an orbital which is largely N–N antibonding in character and it is surprising that the N–N distance is very little longer than in many azo compounds (–N≡N–). Nelsen has examined the ESR spectra of many hydrazine radical cations. The nitrogen hyperfine splitting varies between 10 and 20 gauss and while some correlation with geometrical distortions have been discerned, some variations are not understood.

In the DABCO radical cation 45, the nitrogens remain equivalent down to 77 K, and it is presumed that the cation is symmetrical. The rather small nitrogen hyperfine coupling has caused comment, since in simple aminium ions low values of αₙ are expected for planar nitrogen, around 20 gauss, equivalent to 10 gauss per N in 45, while much higher values are expected for pyramidal ions. The cation 45 is unlikely to be nearly planar at nitrogen and indeed, if the ion is through-bond-coupled, this might induce a more pyramidal structure. The suggestion was made that in solution the through-space coupled ion was preferred, but this was later withdrawn. However Synons apparently believes that 45 is through-space-coupled, i.e. in a nₐ (∥) n₋ (1) state. One factor which needs consideration is that for these more complex systems maximum p character in the spin-bearing orbital (and thus minimum αₙ), need not, and indeed will not, correspond with planarity at nitrogen. These considerations also apply to the ions 46–48, although it does seem that the nitrogens in 48 must be much more pyramidal than those of 46 and 47. It seems very likely that 48 is strongly inwardly pyramidalized; this minimizes strain in the hydrocarbon bridges. Finally, it has recently been argued that, while 49 exists in a symmetrical state in the gas phase, in solution it exists in a geometry of lower symmetry with the odd electron in a σ*-orbital involving only one pair of nitrogens, the whole system undergoing rapid electron transfer/isomerization to an equivalent system to account for the simplicity of the ESR spectrum.

All the ions in Table 3 are coloured, and at least for 44–48, show one broad and quite intense absorption. It seems likely that this corresponds to the simple transition n₋(idences) → n₊(iones) for 44 and 46–48, and n₊(idences) → n₋(iones) for 45. The absorption bands for 46–48 cover the entire visible region.
<table>
<thead>
<tr>
<th>Cation</th>
<th>Approx. Lifetime in CH\textsubscript{3}CN at 25°C</th>
<th>(a_N) (gauss)</th>
<th>(\lambda_{\text{max}}) (nm)</th>
<th>(\varepsilon) (M\textsuperscript{-1} cm\textsuperscript{-1})</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Image" /></td>
<td>(~1) year</td>
<td>13.15</td>
<td>345 (95% EtOH)</td>
<td>3600</td>
<td>42</td>
</tr>
<tr>
<td><img src="image.png" alt="Image" /></td>
<td>(~1) second</td>
<td>17.02</td>
<td>465 (H\textsubscript{2}O)</td>
<td>2100</td>
<td>33, 44, 57, 60</td>
</tr>
<tr>
<td><img src="image.png" alt="Image" /></td>
<td>(~1) day</td>
<td>14.7</td>
<td>480 (H\textsubscript{2}O)</td>
<td>2600</td>
<td>24, 61</td>
</tr>
<tr>
<td>Cation</td>
<td>Approx. Lifetime in CH$_3$CN at 25°C</td>
<td>$a_N$ (gauss)</td>
<td>$\lambda_{max}$ (nm)</td>
<td>$\varepsilon$ (M$^{-1}$ cm$^{-1}$)</td>
<td>References</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------</td>
<td>-------------</td>
<td>------------------</td>
<td>-------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td><img src="47" alt="Diagram" /></td>
<td>~1 week</td>
<td>14.1</td>
<td>480 (CH$_3$CN)</td>
<td>&gt;1000</td>
<td>45</td>
</tr>
<tr>
<td><img src="48" alt="Diagram" /></td>
<td>~1 year</td>
<td>34.4</td>
<td>470 (H$_2$O)</td>
<td>4500</td>
<td>25, 61</td>
</tr>
<tr>
<td><img src="49" alt="Diagram" /></td>
<td>&lt;1 second</td>
<td>7.09 (4N)</td>
<td>(purple)</td>
<td>—</td>
<td>33</td>
</tr>
</tbody>
</table>
their exceptional width corresponds with a large change in structure on excitation, which, in turn, accords with transfer of an electron from an $N-N$ $\sigma$- to $\sigma^*$-orbital.

It would be most interesting to know the strength of the through-bond delocalization in 45 and of the ‘three-electron $\sigma$-bond’ in 46–48, and also to know the length of the bond in 46–48. No information is available on the latter point, but Staley and Beauchamp have pointed out that the difference in homolytic bond dissociation energies $D(N^+–H)$ for protonated quinuclidine and DABCO provide a measure of the stabilization of the DABCO radical cation. $D(N^+–H)$ values in the gas phase are derivable from knowledge of proton affinities and adiabatic ionization energies. Staley and Beauchamp have estimated that the stabilization energy of 45, due to delocalization, was 13 kcal mol$^{-1}$ (more recent data suggest a lower figure, around 9 kcal mol$^{-1}$). If a similar argument is applied to 46 and 48, the three-electron $\sigma$-bond seems to be worth 11 kcal mol$^{-1}$. An independent study of the generation (by pulse radiolysis) of 50 showed that this ion has a half-life of 5 ms in water at 25°C, and decays by a pH-independent, first-order process, corresponding to $\Delta G^+$ 14.5 kcal mol$^{-1}$. It seems likely that this process is fission of the three-electron $\sigma$-bond, followed by rapid decay of the unstabilized aminium radical ion. Thus this measurement suggests that the three-electron $\sigma$-bond in 50 is worth about 10–15 kcal mol$^{-1}$.

Radical ions 44 and 46–48 can be oxidized to dications. The dication from 44 is a dialkylated azocompound, while those from 46–48 are hexaalkylhydrazinium dications and undoubtedly contain a normal two-electron $N-N$ $\sigma$-bond. Dications 51 and 52 are isolable as stable, colourless, water-soluble salts and indeed the corresponding medium-ring diamines are made by their reduction.

VII. INTRAMOLECULAR HYDROGEN BONDING IN DIAMINES AND THEIR MONOPROTONATED IONS

Amines are poor hydrogen bond donors so that amine-to-amine hydrogen bonding is weak. Thus the dissociation energy of the $H_2N-H \cdots NH_3$ dimer in the gas phase is 4.5 kcal mol$^{-1}$. Intramolecular hydrogen bonding in diamines themselves is therefore only observed in favourable situations. For example the $N-H$ stretch for 53 is at 3280 cm$^{-1}$.

The ammonium ion-to-amine hydrogen bond is much stronger. Yamdagni and Kebarle have shown by high-pressure mass spectrometry that $\Delta H^0$ for dissociation
of 54 is 24.8 and of 55 20.2 kcal mol$^{-1}$. This can have important consequences for the basicity of diamines as we shall see (Sections VIII and IX). Protons involved in N$^+$—H$\cdots$N hydrogen bonds occur at very low fields in $^1$H NMR spectra. Thus the N—H proton in 56 appears at $\delta$ 19.5 in CF$_3$COOH solution$^{66}$, while that in 57 appears at $\delta$ 17.4$^{61}$. N$^+$—H$\cdots$N hydrogen bonds both inter- and intra-molecular, give rise to very broad infrared absorption in the 2000–1000 cm$^{-1}$ region. Inter-molecular examples have been extensively examined by Wood$^{67}$. These N$^+$—H$\cdots$N bonds are approaching the strength of the F—H$\cdots$F$^-$ and H$_2$O$^+$—H$\cdots$OH$_2$ cases and the interesting question arises for symmetrical situations like 56 and 57 as to whether the proton sits in a single- or double-minimum potential energy well. An ESCA study$^{68}$ on 56 showed two nitrogen 1s peaks at 400.1 and 401.5 eV, consistent with a double-minimum potential, the proton being instantaneously unsymmetrically located. Even so, the small difference between the nitrogen 1s peaks, compared with the 2.6 eV difference between the nitrogen 1s ionization energies for piperidine and the piperidinium cation, implies partial proton transfer in 56. Recently several ingenious NMR techniques have been devised to distinguish double- and single-minimum potential energy surfaces. These do not seek (as ESCA does) an 'instantaneous' picture of the N$^+$—H$\cdots$N system, but they make use of differences between the properties of time-averaged double-minimum and a genuine single-minimum situation$^{69,70}$. Thus, because of zero-point energy differences, the average lengths of N$^+$—H, N$^+$—D and N$^+$—T bonds will differ in the case of a double minimum, but will be the same if there is a single energy minimum. This leads to substantial isotope effects on chemical shifts in the double minimum case, and, in the case of 56 this was observed$^{69}$, in agreement with the ESCA result.

VIII. GAS-PHASE PROTON AFFINITIES OF DIAMINES

The proton affinities (PA) of some diamines and, for comparison, related monoamines are shown in Table 4 (see footnote for the scaling of these numbers). Diamines, such as H$_2$N(CH$_2$)$_2$NH$_2$, which can form unstrained intramolecularly hydrogen-bonded cations have proton affinities 20 kcal mol$^{-1}$ higher than comparable monoamines in good agreement with the expected strength of the N$^+$—H$\cdots$N bond (see Section VII). The hydrogen-bonded cyclic ions from H$_2$N(CH$_2$)$_3$NH$_2$ and H$_2$N(CH$_2$)$_3$NH$_2$ are somewhat strained, so the PA increases are less dramatic in these cases. Because of the loss of entropy on cyclization, the gas-phase basicities ($\Delta G^0$ for B + H$^+$ $\rightarrow$ BH$^+$; the proton affinity is $\Delta H^0$) are only $\sim$12 kcal mol$^{-1}$ higher than for comparable monoamines. This is nevertheless a very significant factor which if translated into solution would cause dramatic shifts in $pK_a$ values; in fact, as we shall see in Section IX, these shifts are rarely observed.

1-Aminonaphthalene is C-protonated in the gas phase; the PA for N-protonation is therefore $<221$. 1,8-Diaminonaphthalene is N-protonated and a considerably stronger base. Methylation increases the basicity so that 1,8-bis(dimethylamino)naphthalene has the highest recorded PA of a neutral com-
18. Special properties of di- and poly-amines

The pattern of increases in \( PA \) with methylation is as expected by comparison with simple amines, except that addition of the last methyl causes a much larger effect than might be anticipated. Since on methylation of \( 58 \) (which will be protonated on the tertiary amino group) the added methyl only replaces the hydrogen on the hydrogen-bonding nitrogen and does not directly affect the protonated

\[
\begin{align*}
\text{Table 4. Proton affinities (PA) of some diamines and comparable monoamines} \\
\text{Amine} & \quad PA^a & \text{Reference} \\
\hline
\text{H}_2\text{N(CH}_2\text{)}_2\text{NH}_2 & 232.0 & 71 \\
\text{CH}_3\text{(CH}_2\text{)}_2\text{NH}_2 & 222.3 & 71 \\
\text{H}_2\text{N(CH}_2\text{)}_3\text{NH}_2 & 238.3 & 71 \\
\text{CH}_3\text{(CH}_2\text{)}_3\text{NH}_2 & 222.8 & 71 \\
\text{H}_2\text{N(CH}_2\text{)}_4\text{NH}_2 & 243.3 & 71 \\
\text{CH}_3\text{(CH}_2\text{)}_4\text{NH}_2 & 223.1 & 71 \\
\text{H}_2\text{N(CH}_2\text{)}_5\text{NH}_2 & 241.3 & 71 \\
\text{CH}_3\text{(CH}_2\text{)}_5\text{NH}_2 & 223.2 & 71 \\
\text{H}_2\text{N(CH}_2\text{)}_6\text{NH}_2 & 242.1 & 71 \\
\text{H}_2\text{N(CH}_2\text{)}_6\text{NH}_2 & 223.2 & 71 \\
\text{NMe}_2 & 238.8 & 72 \\
\text{NMe}_2 & 227.9 & 72 \\
\text{NH}_2 & 221.0 & 72 \\
\text{H}_2\text{N} & 228.1 & 72
\end{align*}
\]
TABLE 4. (continued)

<table>
<thead>
<tr>
<th>Amine</th>
<th>PA$^a$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeHN NHMe</td>
<td>234.9</td>
<td>72</td>
</tr>
<tr>
<td>Me$_2$N NHMe</td>
<td>239.2</td>
<td>72</td>
</tr>
<tr>
<td>Me$_2$N NMe$_2$</td>
<td>246.2</td>
<td>72</td>
</tr>
<tr>
<td>N(14)</td>
<td>230.9</td>
<td>32</td>
</tr>
<tr>
<td>H-CI</td>
<td>233.6</td>
<td>32</td>
</tr>
<tr>
<td>N(17)</td>
<td>234.1</td>
<td>32</td>
</tr>
<tr>
<td>H-CN</td>
<td>233.4</td>
<td>32</td>
</tr>
<tr>
<td>N(19)</td>
<td>228.3</td>
<td>32</td>
</tr>
<tr>
<td>H-C</td>
<td>217</td>
<td>32</td>
</tr>
</tbody>
</table>

$^a$All PA values are in kcal mol$^{-1}$ and are referred to a value of 205.5 kcal mol$^{-1}$ for NH$_3$. This latter value is still uncertain$^{19}$. Relative PA values determined by different groups using ion cyclotron resonance and high-pressure mass spectrometry do not always agree within quoted error limits. In particular Reference 72 takes the PA of H$_2$N(CH$_2$)$_3$NH$_2$ to be only 233.2; thus the numbers in the table for the naphthalenediamines should be increased by 8.1 if the higher number is correct.
18. Special properties of di- and poly-amines

nitrogen itself, a rather small (< 2 kcal mol\(^{-1}\)) increase in \(\text{PA}\) might be expected. The large increase in \(\text{PA}\) is due to relief of steric strains (see Section III) in 1,8-bis-(dimethylamino)naphthalene and a corresponding increase in \(pK_a\) is observed in solution (Section IX).

The bicyclic diamines in Table 4 cannot form intramolecular hydrogen-bonded cations (inside protonation of 19 apparently cannot occur in the gas phase; if it did, 19 might have a very high \(\text{PA}\)). In this series we also see the operation of strain effects. In the absence of these we would expect \(\text{PA}\) to increase along the series 14, 17, 19, due to a decreasing inductive effect from the second nitrogen and because of increased polarizability. The lower \(\text{PA}\) of 19 is due to the strain induced in outward pyramidalization of a bridgehead atom in the [4.4.4] ring system. This is actually less of a problem for 19, which can adopt an \(\text{in},\text{out}\) conformation, with the unprotonated nitrogen inwardly pyramidalized, than for the corresponding mono-amine, where both bridgeheads must be \(\text{out}\) in the protonated ion.

**IX. BASICITY OF DIAMINES IN AQUEOUS SOLUTION**

The basicity of diamines, and the inductive (field) effect of \(-\text{NH}_3^+\) as a substituent in reducing \(pK_a\) have been discussed in an earlier volume in this series\(^73\). We shall only discuss here the effects of \(\text{N}^+-\text{H} \ldots \text{N}\) bonding on aqueous \(pK_a\) values. Considering the diamine in isolation, this bonding should increase \(pK_a\) and reduce \(pK_{a2}\). This is substantially modified by solvation (see Figure 9)\(^74,75\). The non-

![Figure 9](attachment:image.png)

**FIGURE 9.** Solvation effects on the energetics of diamine protonation; \(\Delta G_s\) = free energy of solvation.
intramolecularly hydrogen-bonded cation has the higher solvation energy (more sites for hydrogen bonding to water), and so the energetic advantage of the intramolecularly hydrogen-bonded cation is lost. Simple diamines do not show enhanced pK_a values and Hine and Li have shown that the fraction of cyclic ion present in aqueous solution is ~0 for Me_2N(CH_2)_3NH_2, 0.24 for Me_2NCH_2CHMeCH_2NH_2 and 0.71 for Me_2NCH_2CMe_2CH_2NH_2. The pK_a values for formation of Me_2NHCH_2CMe_2CH_2NH_3^+ and the cyclic hydrogen-bonded ion were estimated as 9.29, 9.08 and 9.88. Thus, in this case, the solvation energy differences almost exactly cancel the energetic advantage of the isolated cyclic ion. Again, although 1,2-bis(dimethylaminomethyl)benzene was protonated to give an ion which was almost completely cyclized (98.6%), the effects on pK_a values were small (pK_a 10.58, pK_a 4.97).

When protonation can relieve lone-pair interactions and/or other nonbonded interactions and strain effects (these effects are not attenuated in solution), dramatic effects on pK_a values can be observed. This is illustrated by a series of 1,8-diaminonaphthalenes as shown with the formulae below. The basicities of 59, 60 and 56 are essentially normal; the basicity shoots up only when the last methyl group is added. The free base is then strained (see Section III) and this strain is relieved by protonation. It is interesting that the solvation energy of protonated 26 is comparable to that of delocalized carbonium ions; protonated 26 has no sites for hydrogen bonding to water. The second pK_a of 26 is very low, protonation being half-complete in 86% H_2SO_4. Diprotonation breaks the hydrogen bond and

![Diagram of 1,8-diaminonaphthalenes]
18. Special properties of di- and poly-amines

reintroduces strain. Alkylation of 26 is also very difficult compared with amines of similar pKₐ. The compounds 28, 29, 61 and 62 nicely illustrate the effects of varying ring-size. Protonation of these compounds converts a medium ring into bicyclic system, relieving transannular interactions. Surprisingly, the pKₐ values of simple alyclic medium-ring diamines have not been reported. We have observed that the addition of 65 to a protonated salt of 63 in CDCl₃ causes partial proton transfer, so 65 is comparable in base strength to 63. The diamines 63 and 64 are the strongest known neutral bases. The buttressing effects of the methoxy groups induce more strain in these compounds than in 26 (see Section III for the structure of 63), and this strain is clearly relieved on protonation. When, as in 63, the nitrogen lone pairs are not in conjugation with the aromatic ring, an increase in basicity from this cause is expected. Clearly detailed dissection of the effects in 63 would be a formidable task.

Strain can also be increased by protonation. This arises not so much from differences in size of the proton and the lone pair, but in cases of unfavourable geometric and hybridization changes at the nitrogen. Thus the pKₐ values for outside protonation of 1,6-diazabicyclo[4.4.4]tetradecane (19) are ~6.5 and ~3.25. The exceptionally low pKₐ reflects the strain induced by outward pyramidalization of both nitrogens (see also Section VIII). An inside protonated ion can also be made from 19, but not by conventional methods and the pKₐ for inside protonation is unknown; it could be very high. Further outside protonation of this inside protonated ion to give 66 occurs in HSO₃F/SbF₅ but not in HSO₃F alone; 66 must count as the most acidic ammonium ion known.

When the ring-sizes in a bicyclic diamine increase beyond the medium-ring stage (8- to 11-membered), these steric strains should moderate. Indeed the pKₐ values for outside protonation of 67 are +7.1 and ~ +182. However, the major interest in these molecules is in the rates of proton transfer inside and outside the cage and this is discussed in the next section.

X. PROTON-TRANSFER RATES INVOLVING DIAMINES

The protonation of an amine is usually a diffusion-controlled process when it is thermodynamically favourable. It has been shown, however, that proton-transfer rates for certain diamines can be very much slower.

Hibbert and his coworkers have shown that the rates of protonation of some 1,8-diaminonapthalenes are well below diffusion control. For 2,7-dimethoxy-1,8-bis(diethylamino)naphthalene (reaction 5) the rates were slow enough to be followed in a conventional spectrometer.

\[
\begin{align*}
\text{MeO} & \quad \text{Et}_2\text{N} & \quad \text{NMe} \\
\end{align*}
\]

\[
\text{MeO} \quad \text{Et}_2\text{N} & \quad \text{NMe} \quad \text{OMe} \\
\]

\[
\begin{align*}
\label{eq:5}
\kappa_{30} & = 0.03 \text{ s}^{-1} \\
\kappa_{30} & = 3.3 \text{ mol}^{-1} \text{s}^{-1} \\
\text{(in 60% v/v Me}_2\text{SO}_4/\text{H}_2\text{O)}
\end{align*}
\]
By studying buffer catalysis of the proton transfers involving 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene (reaction 6), Hibbert and Robbins have provided evidence that protonation and deprotonation are two-step processes where an ammonium ion in which the hydrogen bond has broken plays the role of an intermediate. On the assumption of diffusion-controlled proton transfer in the latter step, one could derive the activation energy for breaking the hydrogen bond; however, it seems likely that the actual proton transfer to \( \text{OH}^- \) is sterically hindered and slower than diffusion-controlled.

Simmons and Park have studied the rates of inside-outside isomerism of macrobicyclic diamines, and the rate of proton exchange of the inside protonated ions. For the \( i^+i^{[8.8.8]} \) ion the rate of exchange of inside protons is \( \sim 10^4 \) times slower than for \( \text{Et}_3\text{NH}^+ \). Proton transfer to an inside lone pair seems to require (a) diffusion of a water molecule into the hydrophobic cavity (10^5 below normal bimolecular diffusion rates) and (b) protonation of the \( \text{H}_2\text{O} \) by \( \text{H}_3\text{O}^+ \) from outside, with simultaneous proton transfer onto nitrogen.

When the cavity inside the molecule becomes smaller, the barriers to inside protonation and deprotonation become even higher. Thus the doubly inside-protonated [1.1.1]cryptand (reaction 7) was only partially converted to the monoprotonated ion after 80 hours at 60°C in 5N KOH; further deprotonation did not seem to occur at all.

The inside-diprotonated cryptand is formed when the cryptand–BH₃ complex is refluxed in boiling 6N HCl for two hours, and an inside \( \text{H}^+ \), inside \( \text{D}^+ \) species is formed by refluxing the monoprotonated ion in concentrated D₂O/HCl for about 90 min. There is therefore no question but that the inside protons do originate from the solvent.

With 1,6-diazabicyclo[4.4.4]tetradecane 19, an inside-protonated ion is obtained on leaving the amine in 50% \( \text{H}_2\text{SO}_4/\text{H}_2\text{O} \) for several days. However labelling experiments show that the inside proton does not come from the solvent but from an \( \alpha-\text{CH}_2 \) group! The reaction is catalysed by one-electron oxidizing agents and is not a proton transfer at all. In fact no way has been found of inserting the proton in a conventional fashion, nor of removing it once inside.

Besides their intrinsic interest, these observations of slow proton transfers have an important practical implication. Compounds such as 1,8-bis(dimethylamino)naphthalene are potentially useful as strong bases without significant nucleophilic properties. If, however, their proton-transfer rates involving OH protons are slow, those involving CH protons will probably be very slow indeed. We have found that while good yields of olefins may be obtained by heating alkyl tosylates etc.
with 1,8-bis(dimethylamino)naphthalene in DMF, the diamine is never the kinetically active base even with Me₃N+CH₂CH₂CN. The trade name 'proton sponge' is indeed apt — sponges are not kinetically active in seeking water, they merely mop it up when it is presented to them!

XI. METAL COMPLEXATION BY DI- AND POLY-AMINES

The extensive complexation chemistry of amines with transition metals forms an important section of inorganic chemistry and clearly cannot be comprehensively treated here. Rather, this section will highlight some of the effects which specifically arise as a result of increased structural organization in the ligand, particularly the macrocyclic and macrobicyclic effects.

A. Chelation

The complex of Ni²⁺ with ethylenediamine is about 10¹⁰ times as stable towards hydrolysis as that with ammonia. This is an example of the well-known chelate effect and is quite general for bi- and poly-dentate ligands. The effect is largely entropic in origin and is dependent upon the size of the chelate ring formed. Five-membered rings are usually most favourable.

Linear polyamines can form 'wrap-around' complexes which may exist as several configurational and conformational isomers. Strain energy calculations have been successfully employed⁸⁷ to determine the most stable isomers of [Co(H₂N(CH₂CH₂NH)₃H)]³⁺. Branched polyamines have been used to stabilize certain coordination geometries around the metal ion. For example the tripodal ligand tren enforces trigonal bipyramidal-type geometry in five-coordinate Ni¹¹ complexes (68).

![Diagram of tren ligand](image)

B. Macrocycles

1. Synthesis

Nitrogen-containing macrocycles have been prepared by three principal methods:

(a) Condensation of a diamine with a diacid chloride under conditions of high dilution, followed by reduction of the macrocyclic diamide⁸⁸.

(b) Template reaction of a diamine with a dialdehyde (or diketone) in the presence of a suitable metal ion. This gives a macrocyclic imine encircling the template metal. Typically the imine functions can be reduced to amines with sodium borohydride and the metal decomplexed or exchanged⁸⁹.

(c) Reaction of a ditosylamide dianion with a ditosyloxyalkane in dimethylformamide without high dilution⁹⁰.
2. *Macrocyclic effect*

In general the metal complexes of macrocyclic polyamine ligands show an enhanced stability relative to their acyclic counterparts which is too large to be accounted for solely by the formation of one extra chelate ring. \([12-16]ane\, N_4\) macrocycles 69–72 have received considerable attention recently, both as interesting compounds in their own right and as models for porphyrin and corrin systems. Investigations have shown that the origin of the macrocyclic effect in these ligands can lie either in the enthalpy or entropy of complexation. Thus the enhanced stability of the Ni\(^{II}\) ([14]ane \(N_4\)) complex is enthalpic, and this has been explained in terms of poorer ligand solvation for the macrocycle than the corresponding linear tetramine\(^{91}\). On the other hand the Zn\(^{II}\) ([13]ane \(N_4\)) complex owes its stability largely to a favourable entropy of complexation\(^ {92}\), which is simply explained in terms of a favourable orientation of nitrogen atoms in the free ligand, and the displacement of four inner-sphere water molecules upon complexation.

Metal ions which prefer six-coordinate octahedral geometry form *cis* and/or *trans* complexes with the \([12-16]ane\, N_4\) ligands depending upon the ring-size. In the case of the *trans* complexes the size of the ring affects the metal–nitrogen interaction, and this shows up in the size of the ligand field splitting, \(Dq^{xy}\). It turns out that [4]ane \(N_4\) is the best size for Co\(^{3+}\) and the value of \(Dq^{xy}\) is about that of the complexes with acyclic tetramines. [13]ane \(N_4\) exerts a constrictive effect, enhancing \(Dq^{xy}\), whereas [15]- and [16]-ane \(N_4\) exert a dilative effect, reducing the value of \(Dq^{xy}\).\(^{93}\) Busch has developed additivity rules to predict changes in \(Dq^{xy}\).

\[
\text{For Co}^{3+}:
\begin{align*}
\text{trans} & : & [12]ane \, N_4 & \text{cis only} \\
& & [13-14]ane \, N_4 & \text{cis and trans} \\
& & [15-16]ane \, N_4 & \text{trans only}
\end{align*}
\]
18. Special properties of di- and poly-amines

with various structural changes in these systems\textsuperscript{94}. Reactivity in the axial positions is also influenced by the macrocycle. For the series \textit{trans}-Co(\textit{[}13–16\textit{]ane N}_4\text{Cl}_2^{+}
the rate of the first aquation reaction correlates with the calculated strain energies of the starting complexes, which is in accord with the formation of a five-coordinate transition state\textsuperscript{95}.

The rates of complexation of the unprotonated \textit{[}12–16\textit{]ane N}_4 macrocycles are comparable to those of the acyclic analogues\textsuperscript{96}. Thus the enhanced stability is manifested in slow rates of decomplexation. The protonated macrocycles react \textit{10}^3–\textit{10}^4 times more slowly than the open-chain ligands, and this appears to be a simple electrostatic effect in the case of the diprotonated ligands\textsuperscript{97}, but this correlation is not found for the monoprotonated compounds. By contrast, the unprotonated \textit{[}9–12\textit{]ane N}_3 macrocycles show accelerated rates of complexation and normal rates of decomplexation in acid solution\textsuperscript{98}.

3. Binuclear macrocyclic complexes

Larger macrocycles can often complex more than one metal atom. Such binuclear complexes have attracted much current interest, particularly with regard to the question of metal/metal exchange interaction and as models for some copper metalloproteins\textsuperscript{99}. Addition of a bidentate ligand to the binuclear complex may result in bridging of the metals and thereby provide a pathway for spin coupling. Macrocycles exhibiting these properties are typically in the 20–30-membered ring range and contain other heteroatoms such as oxygen and sulphur. Thus the azide-bridged (bis)Cu\textsuperscript{II} complex of the \textit{[}24\textit{]N}_2S_4 macrocycle \textit{73} is diamagnetic. The azide bridges enable strong antiferromagnetic coupling between the copper atoms\textsuperscript{100}. Imidazolate-bridged binuclear copper complexes are proposed to exist in certain metalloproteins and a macrocyclic model for this system has been prepared, and characterized by X-ray diffraction (\textit{74})\textsuperscript{101}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{73.png}
\includegraphics[width=\textwidth]{74.png}
\caption{(73) (74)}
\end{figure}

C. The Macrobicyclic or Cryptate Effect

Although the alkali and alkaline earth metal cations play an important role in chemistry and biology the complexation chemistry of these ions was little studied before 1965 as a consequence of the weakness of their complexation with simple ligands. The discovery by Pedersen\textsuperscript{102} that macrocyclic polyethers form stable complexes (\textit{K}_\text{f} between \textit{10}^2 and \textit{10}^6) with these metal ions marks the real beginning of this field. The crown ether forms a ring of oxygen atoms which can encircle and efficiently 'solvate' a suitable-sized metal ion. A surprisingly large proportion of the complexation behaviour can be qualitatively explained in terms of the fit between cation and hole. Lehn and coworkers elaborated these crown ethers by synthesizing macrobicyclic polyethers with nitrogen atom bridgeheads\textsuperscript{103}. By
varying the length of the bridges a series, 75–81, of these cryptands were prepared having polar three-dimensional cavities capable of encapsulating metal ions. The cryptands form extremely stable complexes with alkali and alkaline earth metal cations, the most stable being that of [2.2.2] with Ba\(^{2+}\) (log \(K_s\) = 9.5 in water). Just as the crown ethers can show a macrocyclic effect of some 10\(^4\), the extra bridge of the cryptand can lend a macrobicyclic effect of another 10\(^4\)–10\(^5\) to the stability constant. The nitrogen lone pairs in the free cryptands may be pointing more or less inside or outside the cavity, depending on the compound and its situation, however, in the metal complexes (cryptates) the lone pairs invariably point inside towards the cation. In acidic solution the cryptate nitrogen atoms become protonated and the metal ion is lost.

As well as forming very stable complexes the cryptands show a remarkable degree of selectivity\(^{104}\). Again the most stable complexes are formed between cations and cavities of similar size. The smaller cryptands show peak selectivity in the alkali metal series, disfavouring both cations too small and too large. [2.1.1], [2.2.1] and [2.2.2] form most stable complexes with Li\(^+\), Na\(^+\) and K\(^+\) respectively. The larger cryptands show plateau selectivity, binding large- and medium-sized cations equally well, but disfavouring the smaller cations. The alkaline earth metal cations are complexed with a selectivity which is typically the reverse of that shown by acyclic polyanionic ligands, hence (with the exception of [2.1.1]) Sr\(^{2+}\) and Ba\(^{2+}\) are preferred over Mg\(^{2+}\) and Ca\(^{2+}\). Selection between M\(^+\) and M\(^{2+}\) can also be unusual, thus [2.1.1] favours Li\(^+\) over Mg\(^{2+}\) and Na\(^+\) over Ca\(^{2+}\) although the larger cryptands prefer M\(^{2+}\) over M\(^+\) of similar size.

The free energies of complexation have been dissected into enthalpies and entropies by calorimetric studies\(^{105}\). The entropy of complexation for the small cations is large and favourable but decreases monotonically with increasing cation size, until it becomes disfavourable. This is accounted for in terms of two major effects: a favourable loss of the metal ion hydration sphere, which becomes less important as the size of the cation increases, and secondly an essentially constant disfavourable water structuring caused by the large hydrophobic cryptate cation. Favourable enthalpies of complexation are thought to arise principally from poor ligand solvation and a lack of interbinding site repulsions in the cryptate (as a consequence of the binding sites being built into the molecule). The enthalpies of complexation show grossly the same trends as the free energies; thus although the free energy of complexation may be largely entropic or enthalpic, the selectivity is enthalpic in origin, providing a basis for the empirical 'best fit' rule. The alkaline earth metal cations show similar behaviour. The preference of the larger cryptands for M\(^{2+}\) over M\(^+\) is almost entirely for reasons of entropy.

The rate of cryptate formation is several orders of magnitude slower than the complexation of alkali metal cations by simple ligands, which may be due to steric crowding during insertion of the metal. For the complexation of a series of cryptands with one metal \(K_s\) is usually reflected in the rate of dissociation, but in general the rates of formation vary substantially\(^{106}\). Activation parameters indicate that the transition state for cryptation lies nearer the reactants than the cryptate.
Cryptands [2.2.1] and [2.2.2] have also been found to be effective ligands for the encapsulation of the lanthanide metal cations. The Eu$^{3+}$ and Gd$^{3+}$ cryptates are the first kinetically inert lanthanide complexes and find some use as $T_1$ (shiftless) relaxation reagents in NMR. Cryptation by [2.2.1] renders the Eu$^{3+}$/Eu$^{2+}$ couple electrochemically reversible and 190 mV more positive than Eu$^{3+}$(aq)/Eu$^{2+}$(aq). Thus Eu$^{2+}\subset[2.2.1]^*$ is about $10^4$ times more stable than Eu$^{3+}\subset[2.2.1]$ which is explained in terms of a better fit for the larger Eu$^{2+}$ ion in the cavity and a lower free energy of solvation for free Eu$^{2+}$ than Eu$^{3+}$. Eu$^{3+}\subset[2.2.1]$ exhibits another intriguing property, namely complexation of small anions such as fluoride and hydroxide.

D. Applications of the Cryptands

1. Transport

Whereas the cryptands 75–81 show sufficiently strong and selective complexation behaviour to be considered as specific cation receptors, somewhat different properties are required of a specific cation carrier. A successful carrier must exhibit a high selectivity for the substrate in question but the stability of the complex must not be so high that the carrier becomes saturated or that the rates of exchange become prohibitively slow. Simple modification of [2.2.2] by replacement of the two oxygen atoms in one bridge by methylene groups gave a cryptand, [2.2.C$_8$], which retained a high selectivity for potassium but with a much reduced stability constant. [2.2.C$_8$] proved to be an efficient specific carrier for potassium picrate across a chloroform 'membrane'.

2. Detoxification

The high selectivity of the cryptands and the stability of their complexes makes them potentially useful agents for the removal of radioactive or heavy metals from living tissue. Indeed, [2.2.2] has been found to be effective in eliminating $^{85}$Sr$^{2+}$ and $^{224}$Ra$^{2+}$ from rats.

3. Solubilization

Cryptation may greatly increase the solubility of salts in polar and nonpolar media. Dramatic examples are the $10^4$ times increase in solubility of BaSO$_4$ in water caused by [2.2.2] and the solubilization of KMnO$_4$ in benzene by the same cryptand.

4. Anion activation

Anion activation by cryptation is even more effective than that shown by crown ethers because the complete encapsulation of the cation further reduces the tendency towards ion pairing. For example the hydrolysis of methyl mesitylate by KOH in dimethyl sulphoxide is greatly accelerated by [2.2.2].

*Lehn$^{27}$ has introduced the mathematical symbol for inclusion, $\subset$, to indicate cryptate formation.
5. Stabilization

Unusual species may be stabilized by a cryptate counterion. The most spectacular example is the isolation of alkali metal anions by Dye\textsuperscript{110}. Thus cooling a solution of sodium and [2.2.2] in ethylamine caused the growth of gold coloured crystals of Na\textsuperscript+ [2.2.2]⊂ Na\textsuperscript−.

6. Modification of binding sites

Substitution of the oxygen atoms in the cryptands by sulphur or nitrogen reduces their ability to complex alkali and alkaline earth metal cations and increases their affinity for the transition metal ions. Ligand (82) can be thought of as a derivative of [3.3.3] and consists of two tren units linked by ether bridges. This compound\textsuperscript{111} forms binuclear metal complexes with Co\textsuperscript{2+}, Cu\textsuperscript{2+} and Zn\textsuperscript{2+}. Addition of increasing amounts of Zn\textsuperscript{2+} to a solution of 82 results in the stepwise formation of an unsymmetrical mononuclear complex followed by the binuclear complex. The ESR spectrum of the binuclear Cu\textsuperscript{II} complex of 82 shows a weak $A_{ms} \frac{2}{5}$ transition at $g = 4.7$, indicating metal/metal interaction.

In its protonated form 82 can act as a complexing agent for anions. Inclusion complexes of anions were first observed by Simmons and Park with diprotonated macrobicyclic diamines 83\textsuperscript{26}. These compounds form stable and selective complexes with the halide ions. The observed selectivities correlate with cavity/anion size. 82 · 6 H\textsuperscript{+} is expected to be protonated on the secondary nitrogen atoms and the cavity defined by this ligand is large enough to accept small molecular anions. The observed selectivity sequence of 82 · 6 H\textsuperscript{+} is Cl\textsuperscript{−}, I\textsuperscript{−} < CH\textsubscript{3}CO\textsubscript{2}−, Br\textsuperscript{−} < HCO\textsubscript{2}− < NO\textsubscript{3}− < N\textsubscript{3}− which is neither the lyotropic series nor the sequence of hydration energies, indicating the topological discrimination of the ligand arising from the defined cavity size and shape. Molecular models suggest that linear triatomic molecules would fit best in the cavity and indeed azide ion shows the highest stability constant in this series, with log $K_s = 4.6$.

E. Macrotricyclic Cryptands

Increasing the cyclic order of the cryptands results in ligands with more highly defined cavity geometries. Macrotricyclic cryptands have been synthesized with spherical and cylindrical topologies.

1. Spherical

Ligand 84 has high (Td) symmetry and possesses a spherical cavity\textsuperscript{112}. This cryptand is an intriguing molecule. It forms stable complexes with the larger alkali
metals, with an affinity for Cs⁺ greater than any other known ligand. It also forms a molecular inclusion complex with ammonium ion, the tetrahedral array of nitrogen atoms providing an ideal receptor site. Diprotonated 84 complexes a water molecule, and the tetraprotonated species forms a very stable complex with chloride ion \( \log K_s > 4.0 \pm 0.5 \) with all four N⁺–H sites pointing inside the cavity towards the anion\(^{113}\).

2. Cylindrical

These ligands consist of two macrocycles linked face to face by two bridges, e.g. 85. A variety of these compounds have been synthesized containing different sized macrocycles and bridges. Compounds like 85 have the ability to form mononuclear and binuclear complexes with alkali metal cations\(^{114}\). Substitution of the oxygen atoms by sulphur leads to ligands which can form binuclear complexes with the transition metals\(^{115}\).

The binding of ammonium ions to crown ethers and azacrown ethers has been the subject of much research in recent years\(^{116,102}\). Ligands 86\(^{117}\) and 87\(^{118}\) can form 1:1 molecular complexes with simple diprotonated diamines (88), and these compounds show a selectivity which depends upon the length of the alkyl chain between the nitrogen atoms. Thus NMR measurements show that 87 complexes 88 \((n = 5 \text{ and } 6)\) in preference to 88 \((n = 4 \text{ and } 7)\) which are respectively too short and too long to fit well inside the cavity.

In conclusion it has been shown that a large variety of interesting ligands can be synthesized using the basic structural unit of a tertiary amine acting both as a binding site and a vertex in a three-dimensional structure. These macropolycyclic ligands show diverse properties including the ability to complex atomic and molecular cations and anions.
XII. REFERENCES


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18. Special properties of di- and poly-amines


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71. D. H. Aue, H. M. Webb and M. T. Bowers, J. Amer. Chem. Soc., 95, 2699 (1973); similar data for a more restricted set of diamines have been reported by Yampagni and Kebarle (Reference 65).
79. Values of $pK_a$ and rate constants for protonation and deprotonation of 61 and 62 were determined in 30% Me$_2$SO/H$_2$O (F. Hibbert, personal communication).
86. See footnote in Reference 22.
108. For a more comprehensive review see Reference 27.
CHAPTER 19

Alkyl nitrate nitration

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V. REFERENCES
The alkyl nitrate nitration is defined as the reaction of a nitrate ester in the presence of a base with active methylene compounds and with amines. With active methylene compounds the reaction enables the introduction of nitro groups at carbon atoms α to the activating group. In the case of amines the reaction leads to nitramines.

Historically, the reaction goes back to the 19th century. Angeli prepared the disodium salt of nitrohydroxylamine by the action of ethyl nitrate on hydroxylamine hydrochloride in the presence of excess sodium ethoxide (equation 1).

\[
H_2NOH \cdot HCl + EtONO_2 \xrightarrow{NaOEt \cdot EtOH} \left[ O_2NNO \right]^- + 2Na^+ \quad (1)
\]

A similar introduction of a nitro group into a carbon compound was first demonstrated by Thiele\(^2\), who converted cyclopentadiene into the sodium salt of nitrocyclopentadiene on treatment with ethyl nitrate and sodium ethoxide (equation 2).

\[
\begin{array}{c}
\text{C}_{5}H_{6} + \text{EtONO}_2 \xrightarrow{NaOEt \cdot EtOH} \text{Na}^+ \\
\end{array}
\quad (2)
\]

Wislicenus and coworkers\(^3\) reported the nitration of various phenylacetic esters, phenylacetonitriles and naphthylacetonitriles. The results with ethyl phenylacetate and p-bromophenylacetate were particularly significant. The expected α-nitrophenyl esters were not obtained. The products which were isolated after acidification of the crude reaction mixtures were phenylnitromethanes and diethyl carbonate.

The importance of base strength on the yield of product was indicated by the fact that the yield of phenylnitromethane was increased from 50% to 80% in the nitration of ethyl phenylacetate when sodium ethoxide was substituted by potassium ethoxide\(^4\) (equation 3). A similar improvement in yield from 30% with sodium ethoxide to 70% with potassium ethoxide was recognized in the nitration of o-bromophenylacetonitrile\(^5\). On the other hand a 90% yield of the salt of p-bromophenylacetonitrile was obtained with either base\(^6\). The reaction of phenylacetonitrile with sodium ethoxide and methyl nitrate and the subsequent hydrolysis of the sodium salt of phenylnitroacetonitrile has been adopted for the preparation\(^7\) of phenylnitromethane in an overall yield of 55% (equation 4).

\[
\begin{array}{c}
\text{PhCH}_2\text{CO}_2\text{Et} \xrightarrow{EtOK \cdot EtONO}_2 \left[ \text{Ph} - \text{C} \cdot \text{CO}_2\text{Et} \right]^- \xrightarrow{H^+} \text{PhCH}_2\text{NO}_2 + (\text{EtO})_2\text{CO} \\
\end{array}
\quad (3)
\]

Attempts by Wislicenus\(^4\) to extend the nitration to aliphatic esters by using potassium ethoxide as the base were unsuccessful; but he was able to convert fluorene to the potassium salt of 9-nitrofluorene in 70% yield. Nitration was, however, unsuccessful when sodium ethoxide was employed as the base\(^8\). Much later, the potassium salts of 2-bromo-9-nitrofluorene (62% yield)\(^9\), 2-benzoyl-9-nitrofluorene (84% yield) and 2,7-dibenzoyl-9-nitrofluorene (65% yield)\(^10\) were prepared.
On nitrating $p$-mercaptotolylacetophenone in ethanolic sodium ethoxide with ethyl nitrate at reflux temperature, Arndt and Rose\textsuperscript{11} reported that the benzoyl group had cleaved off during the reaction. The compound which was isolated after oxidation of the reaction mixture directly with hydrogen peroxide was $p$-tolyl nitromethyl sulphone (1). Similar results were obtained with $p$-mercaptotolylacetone. It is very likely that the cleavage was partially caused by the reaction conditions. For, in addition to 1, nitroketone 2 was obtained when a lower reaction temperature was employed during the nitration (equation 5).

\begin{equation}
\begin{align*}
\text{H}_2\text{O}_2 \\
\text{NaOEt}_{\text{EtONO}_2} \\
\text{p-MeC}_6\text{H}_4\text{SO}_2\text{CH}_2\text{NO}_2 \\
\text{p-MeC}_6\text{H}_4\text{S-CH}_2\text{COPh} \\
\rightarrow \quad \text{[p-MeC}_6\text{H}_4\text{S-CH=NO}_2^- \text{Na}^+] + \\
\text{p-MeC}_6\text{H}_4\text{S-CHNO}_2\text{COPh}
\end{align*}
\end{equation}

The nitration of a cyclic ketone was first achieved by Straus and Ekhard\textsuperscript{12}. $\alpha$-Tetralone was converted in 70% yield to the potassium salt of 2-nitrotetralone. Acidification of the salt with hydrochloric acid led to ring-opening with the formation of 2-(3-nitropropyl) benzoic acid (equation 6). About three years later, Wieland and coworkers\textsuperscript{13} reported that the nitration of cyclopentanone and cyclohexanone with two molar equivalents of nitrate ester and base afforded, respectively, the dipotassium salts of 2,5-dinitrocyclopentanone (3) and 2,6-dinitrocyclohexanone (3a). The yields of these salts were reported as quantitative and their purity was based only on potassium analyses. On nitrating cyclopentanone by Wieland's procedure, Klager\textsuperscript{14} found that the yield of 3 did not exceed 10%. The yield was ascertained by conversion of 3 to 1,1,4,4-tetrabromo-1,4-dinitrobutane on treatment with bromine in aqueous base (equation 7). This ring-opening reaction, essentially a haloform reaction, was established to proceed in a yield of about 88% with analytically pure 3a\textsuperscript{15}.

A short account of the importance of the alkyl nitration for the preparation of
primary nitramines has been presented by Wright\textsuperscript{16}. A more detailed discussion is presented in Section IV.

II. THE ALKYL NITRATE NITRATION OF ACTIVE METHYLENE COMPOUNDS

The developments of the last 25 years have been cursorily presented in various publications\textsuperscript{17}.

Prior to 1955 the reaction was limited to the nitration of aryl-substituted esters and nitriles, and to a few cyclic ketones. The results of a systematic study\textsuperscript{18} which appeared in 1956 set the stage for a much broader application of the reaction to other classes of compounds.

On considering the accepted mechanism of the alkyl nitrate reaction (equations 8–11), it is clear that for a successful reaction, important requirements have to be fulfilled, such as:

1. Generation of high concentrations of anion 4 by the choice of a strong base and a suitable aprotic solvent (equation 8).
2. Choice of a nitrate ester which would not be readily destroyed by the strong base and readily form intermediate 5 (equation 9), and which would then irreversibly collapse into the nitro compound and alkoxide ion (equation 10).
3. Choice of reaction conditions which would minimize the well-established interactions between base and nitrate ester\textsuperscript{19} and also side-reactions of the substrate, such as self-condensation of ketones and esters.

\begin{equation}
R^1-\text{CH}_2-X + B^- \rightarrow [R^1-\text{CH}_2-X]^- + HB
\end{equation}

(8)

(4)

\(X = \text{activating group, } B = \text{base}\)

\begin{equation}
4 + R^3\text{ONO}_2 \rightarrow R^1-\text{C}-\text{N}^\text{OR}^3
\end{equation}

(9)

(5)

\begin{equation}
5 \rightarrow R^1-\text{C}-\text{NO}_2 + \text{OR}^3
\end{equation}

(10)
19. Alkyl nitrate nitrations

\[
R^1\text{C}-\text{NO}_2 + \text{OR}^3 \text{ or } B^- \xrightarrow{\cdot} R^1\text{C}==\text{NO}_2^- + \text{HOR}^3 \text{ or } HB \quad (11)
\]

It should be emphasized that the formation of the nitronate salt in the final step (equation 11) is important in that it largely eliminates side-reactions.

A. Importance of Base and Solvent

1. Potassium t-butoxide

In considering suitable alkoxide bases to produce high concentrations of anion (equation 8), it is apparent that to fulfill this requirement such bases should be free of alcohol. Moreover, any reaction with the nitrating agent should be negligible.

Sublimed potassium t-butoxide, free from excess t-butyl alcohol, and dissolved in tetrahydrofuran (THF) has been found to be a suitable base–solvent combination for the nitration of ketones and nitriles. Primary alkyl nitrates are suitable nitrating agents since they are not affected by the base t-butoxide below \(-10^\circ C\). A tertiary nitrate such as t-butyl nitrate is unsuitable because it is converted to isobutylene by the base, even at \(-30^\circ C\).

The importance of solvent on the yield in the nitration of cyclopentanone is shown in Table 1. Reactions are performed at \(-30^\circ C\) since it has been established that side-reactions, such as the self-condensation of the ketone are minimized at this temperature. Except for THF, the yields of dipotassium 2,5-dinitrocyclopentanone (6) cannot be correlated with either the dielectric constant of the solvent or the solubility of the base in the solvent.

The advantage of sublimed potassium t-butoxide lies not only in its being a stronger base than potassium ethoxide but also in its ability to complex strongly with t-butyl alcohol which is formed during the reaction (equation 8). The removal of the alcohol ensures a favourable equilibrium for carbanion formation. The adverse effect of added t-butyl alcohol on the yield of 6 is shown in Table 2. The amount of added alcohol is only 1.5 times larger than the amount formed in the overall

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility</th>
<th>Dielectric constant at 20°C</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>2.27</td>
<td>2.38</td>
<td>21</td>
</tr>
<tr>
<td>Hexane</td>
<td>0.27</td>
<td>1.89</td>
<td>38</td>
</tr>
<tr>
<td>Ether</td>
<td>4.34</td>
<td>4.34</td>
<td>48, 55f</td>
</tr>
<tr>
<td>THF</td>
<td>25.00</td>
<td>7.58</td>
<td>62f</td>
</tr>
</tbody>
</table>

bSolubility of t-BuOK in g/100 g solvent at 25–26°C.
cIn all experiments the ketone is added to a 10% excess of base followed by a 10% excess of amyl nitrate at \(-30^\circ C\).
dDetermined by conversion of dipotassium 2,5-dinitrocyclopentanone to 1,1,4,4-tetrabromo-1,4-dinitrobutane.
eThe reaction time is 17 h.
fThe reaction time is 1 h.
TABLE 2. Effect of added t-butyl alcohol on the alkyl nitrate nitration of cyclopentanone

<table>
<thead>
<tr>
<th>t-BuOK</th>
<th>t-BuOH</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.110</td>
<td>—</td>
<td>39.0</td>
</tr>
<tr>
<td>0.110</td>
<td>0.11</td>
<td>15.5</td>
</tr>
<tr>
<td>0.165</td>
<td>—</td>
<td>55.0</td>
</tr>
<tr>
<td>0.165</td>
<td>0.15</td>
<td>17.0</td>
</tr>
</tbody>
</table>


b0.05 mole of ketone and a 10% excess of amyl nitrate are used in all experiments.

cDetermined by conversion of the dinitro salt 6 to 1,1,4,4-tetrambromo-1,4-dinitrobutane.

reaction. The data also indicate that an excess of base gives higher yields of 6; a 65% excess over the ketone is optimum.

The adverse effect of added alcohol is also observed in the nitration of adiponitrile; the yield of dipotassium 2,5-dinitroadiponitrile (7) decreases from 93% to 11%. Schaub and coworkers report that nitration of 17-methyltestosterone and of 20-ethylenedioxy-21-hydroxypregn-4-en-3-one gives 2α-nitro-17-methyltestosterone (8) and 20-ethylenedioxy-21-hydroxy-2α-nitropregn-4-en-3-one (9) in yields of 9% and 18%, respectively. It is very likely that the free hydroxyl groups interfere with the reaction, for conversion of the hydroxyl group in testosterone to the tetrahydropyranl ether affords 2α-nitro-17β-(tetrahydropyran-2-yloxy)androst-4-en-3-one (10) in 42% yield.

The importance of temperature and mode of addition in the nitration of cyclopentanone is indicated in Table 3. The highest yield of 6 is attained if the reaction temperature is maintained at −30°C and the ketone is added to the base followed by the nitrate. The temperature effect is further illustrated by the fact that in the nitration of acetophenone, the yield of potassium o-nitroacetophenone increases from 6.7% to 40.5% when the reaction temperature is decreased from −10°C to −40°C.
The effect of reaction time, especially in the nitration of ketones is of interest. Nitration of 2-tetralone at $-78^\circ$C, as monitored spectrophotometrically, shows that the concentration of the formed potassium salt of 2-nitrotetralone decreases with time. This is very likely due to a reaction between the product and the starting material. Indeed it is found that at ambient temperatures the amount of 2-nitrotetralone in a mixture with 2-tetralone decreases steadily and is virtually zero after six hours. Immediate work-up of the reaction mixture also increases the yield of 6 as shown in Table 4.

**a. Experimental procedure.** The reaction conditions which lead to high yields in the nitration of ketones and nitriles are as follows: a 65% excess of 100% potassium tert-butoxide is added to purified THF and the mixture is cooled to about $-50^\circ$C. The compound, dissolved in THF, is added followed by the rapid addition of a primary alkyl nitrate (10% excess) at $-40^\circ$C to $-50^\circ$C. Then the nitro salt is removed as soon as ambient temperatures are attained.

**TABLE 3. Effect of temperature and mode of addition on the yield of 6**

<table>
<thead>
<tr>
<th>Temp. ($^\circ$C)</th>
<th>-20</th>
<th>-30</th>
<th>-40</th>
<th>-30</th>
<th>-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (%)</td>
<td>28$^c$</td>
<td>38$^c$</td>
<td>36$^c$</td>
<td>34$^d$</td>
<td>44$^e$</td>
</tr>
</tbody>
</table>


$^b$Determined by conversion of 6 to 1,1,4,4-tetrabromo-1,4-dinitrobutane.

$^c$Ketone and nitrate are added to the base.

$^d$Ketone is added to a mixture of base and nitrate.

$^e$Nitrate is added to a mixture of base and ketone.
TABLE 4. Effect of reaction time on the yield of 6

<table>
<thead>
<tr>
<th>Reaction time (h)</th>
<th>Excess t-BuOK (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>62.0</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>60.0</td>
</tr>
<tr>
<td>16</td>
<td>65</td>
<td>57.0</td>
</tr>
</tbody>
</table>


b. Scope of the alkyl nitrate nitration in the potassium t-butoxide–THF system. In general, the nitration in the potassium t-butoxide–THF system gives good results with activated methylene compounds in the approximate acidity range of 18 to 25 pKₐ units. Thus, α-nitration, induced by this base, is also successful with N,N-disubstituted amides, N,N-disubstituted sulphonamides, and sulphones (Table 5). In the nitration of amides it is frequently advantageous to use diethyl ether as the solvent because the salts of the α-nitroamides precipitate during the reaction and can be easily removed. The high solubility in THF makes the isolation of the salts more difficult. The potassium salts of α-nitro-N,N-dialkyl substituted amides are highly hygroscopic. They tend to decompose with charring upon exposure to the atmosphere.

The nitration is unsuccessful with primary and secondary amides. Apparently the amido hydrogens interfere with the anion formation at the α-carbon atom which is essential for successful nitration to occur (equation 8). For instance, butyramide is recovered quantitatively when subjected to the alkyl nitration.

c. Acetone cyanohydrin nitrate. The failure of compounds of high acidity to undergo the alkyl nitration with primary nitrates in potassium t-butoxide can be explained by considering the second step in the reaction (equation 9). The reaction between the carbanion and alkyl nitrate leading to intermediate 5 is reversible. The position of the equilibrium lies far to the left with carbanions of highly acidic compounds. A more favourable position of this equilibrium is achieved with a
TABLE 5. Synthesis of nitro compounds by the alkyl nitration employing 100% $t$-BuOK

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>98</td>
<td>18, 30</td>
</tr>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>74</td>
<td>18, 30</td>
</tr>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>55</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>35</td>
<td>18, 25</td>
</tr>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>78</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>57</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>$^{+}\text{K} \text{O}_2\text{N}=\text{C} \text{C} \text{C} \text{C} \text{N} \text{O}_2^{-} \text{K}^{+}$</td>
<td>93</td>
<td>20</td>
</tr>
<tr>
<td>Reactant</td>
<td>Product</td>
<td>Yield (%)</td>
<td>Reference</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>(H₂C)₃(CH₂CN)₂</td>
<td>NC=C(CH₂)₃C-CN</td>
<td>45ᵇ</td>
<td>20</td>
</tr>
<tr>
<td>(H₂C)₄(CH₂CN)₂</td>
<td>NC=C(CH₂)₄C-CN</td>
<td>67ᶜ</td>
<td>20</td>
</tr>
<tr>
<td>(H₂C)₆(CH₂CN)₂</td>
<td>NC=C(CH₂)₆C-CN</td>
<td>48ᶜ</td>
<td>20</td>
</tr>
<tr>
<td>(H₂C)₂[CH₂CON(CH₃)₂]₂</td>
<td>(CH₃)₂N-C=C(CH₂)₂C-CN(CH₃)₂</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

**Mononitrations**

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>59</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44ᵇ</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55ⁱ</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32ᵏ</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65ˡ</td>
<td>27</td>
</tr>
</tbody>
</table>
19. Alkyl nitrate nitrations

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCH₃(ONO₂)⁻ K⁺</td>
<td></td>
<td>85</td>
<td>31</td>
</tr>
<tr>
<td>N-SO₂CH₂Ph</td>
<td>N-SO₂CHNO₂Ph</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>PhCH₂SO₂Ph</td>
<td>PhCHNO₂SO₂Ph</td>
<td>81</td>
<td>29</td>
</tr>
<tr>
<td>p-CH₃C₆H₄SO₂CH₂Ph</td>
<td>p-CH₃C₆H₄SO₂CHNO₂Ph</td>
<td>79</td>
<td>29</td>
</tr>
<tr>
<td>(PhCH₂)₂SO₂</td>
<td>PhCHNO₂SO₂CH₂Ph</td>
<td>82</td>
<td>29</td>
</tr>
<tr>
<td>PhCH₂SO₂Ph</td>
<td>PhCHNO₂SO₂Ph</td>
<td>42</td>
<td>29</td>
</tr>
<tr>
<td>n-PrSO₂Ph</td>
<td>CH₃CH₂CHNO₂SO₂Ph</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>(n-C₄H₉)₂SO₂</td>
<td>CH₃(CH₂)₂CHNO₂SO₂C₄H₉⁻n</td>
<td>33</td>
<td>29</td>
</tr>
</tbody>
</table>

*Unless stated otherwise, the solvent is purified THF.

*b Determined by conversion to NO₂Br₂C-(CH₂)ₙ-CBr₂NO₂.

*c 2-Nitrocyclooctanone (47% yield) is also formed.

*d Determined by conversion to CH₃CH₂-CBrNO₂-C-CBrNO₂-CCH₃.

*e Determined by conversion to NC-CBrNO₂-(CH₂)ₙ-CBrNO₂-CN.

*f Determined by conversion to (CH₃)₂N-C-CBrNO₂-(CH₂)₂-CBrNO₂-C-N(CH₃)₂.

*g One equivalent of RONO₂ is used.

*h Determined by conversion to CH₃CH₂CBrNO₂CN.

*i Determined by conversion to CH₃(CH₂)₃-CBrNO₂CN.

*j The solvent is absolute ether.

*k Determined by conversion to CBr₂NO₂-CON(CH₃)₂.

*l Determined by conversion to CH₃CH₂CBrNO₂-CON(CH₃)₂.

*m The yield is 79% when nitration is performed in the potassium amide-liquid ammonia system.

The successful nitration of several ethyl esters of substituted malonic and acetoacetic acids with 12 and an excess of sodium hydride in THF is reported. This reaction, which is performed at ambient temperatures, constitutes a general method for preparing ethyl esters of alpha-nitro acids in yields ranging between 42 and 70% (equation 12). It is suggested...
\[
\text{RCH(CO}_2\text{Et})_2 + (\text{Me})_2\text{C}^\text{ON}O_2 \text{NO}_2 \xrightarrow{2\text{NaH}} \text{RCHCO}_2\text{Et} + \text{Me}_2\text{CO} + \text{NaCN}
\]

\[
\text{or} \quad \text{RCHCO}_2\text{Et}
\]

\[
\text{COMe} \quad \text{R} = \text{alkyl, PhCH}_2, \text{ClCH}_2\text{CH}_2\text{CH}_2 \text{or CH} = \text{CHCH}_2
\]

(12)

that intermediate 5 (equation 9) is not involved in nitrations with 12 but that instead a direct displacement reaction takes place (equation 13).

\[
\text{A}^- + 12 \rightarrow \begin{array}{c}
\text{A}^\delta^- \\
\text{O}^\delta^- \\
\text{O}^\delta^-
\end{array}
\]

\[
\text{AN}_2 + (\text{Me})_2\text{CO} + \text{CN}^-
\]

(13)

A = Carbanion

Less acidic compounds such as \text{t}-\text{butyl acetate}, \text{acetophenone} and \text{diethyl succinate}
fail to undergo nitration with 12\textsuperscript{33}. Also, the choice of base in nitrations with 12
seems to be restricted to sodium hydride and potassium hydride\textsuperscript{34}. Alkoxide bases
cannot be used because they react rapidly with 12.

Nitration of \textit{N,N}-\text{dimethylbenzylsulphonamide} with potassium hydride and 12
gives the α-nitrosulphonamide in 25% yield, while the yield is 75% with ethyl nitrate\textsuperscript{34}.

2. \textit{Alkali amide–liquid ammonia systems}

Stronger bases than potassium \textit{t}-\text{butoxide} are required for the successful extension
of the alkyl nitrate nitration to active methylene compounds of low acidity. The use
of amide bases such as potassium or sodium amide in liquid ammonia enables
successful nitrations to compounds of pK\textsubscript{a} ~ 35\textsuperscript{35}. With very few exceptions
nitrations in the potassium amide–liquid ammonia system give higher yields than
those in the sodium amide system\textsuperscript{35–38}. Nitrations in lithium amide, the weakest base
in the series, give nitro compounds in very low yield\textsuperscript{37,38}.

Major advantages of the potassium amide–liquid ammonia system are:

(1) Increase of the scope of the alkyl nitrate nitration.
(2) Elimination of the time-consuming sublimation procedure to prepare 100%
potassium \textit{t}-\text{butoxide}. (This base has also been prepared \textit{in situ} from \textit{t}-\text{butyl}
alcohol and potassium amide in refluxing THF\textsuperscript{31}.)
(3) Elimination of operations mandatory in the handling and storage of dry THF
to prevent peroxide formation\textsuperscript{30}.

Disadvantages of the potassium amide system are:

(1) Reaction with the nitrating agent\textsuperscript{30}. the alkyl nitrate, even at −40°C (equation 14).
(2) Determination of the optimum ratio of the reactants for every class of
compounds.
19. Alkyl nitrate nitrations

(3) Careful control of the exothermal stage which occurs during the addition of nitrate to the reaction mixture; although it usually subsides after a few drops of the alkyl nitrate are added.

\[
\begin{align*}
\text{RONO}_2 & \xrightarrow{\text{KNH}_2-\text{NH}_3} \text{RO}^- & \xrightarrow{\text{NH}_4\text{Cl}, -33^\circ\text{C}} \text{ROH} \\
R & = \text{alkyl}
\end{align*}
\]

\(14\)

a. Experimental conditions. The required time for anion formation, optimum ratio of reactants, and work-up procedures vary with different classes of compounds. Otherwise experimental operations are rather simple. The substrate is added at \(-33^\circ\text{C}\) to the alkali amide which is prepared \textit{in situ} in liquid ammonia. Then, the nitrate ester is added as fast as is feasible by maintaining the reaction temperature at about \(-40^\circ\text{C}\). Replacement of ammonia by diethyl ether causes precipitation of the salt, which on acidification with glacial acetic acid is converted to the nitro compound. An alternate procedure for obtaining the nitro compound involves direct acidification of the reaction mixture with ammonium chloride.

b. Scope of the alkyl nitrate nitrations in the alkali amide–liquid ammonia system

(i) Ketones. Dinitrations\textsuperscript{30} of C\(_5\)–C\(_7\) cycloalkanones using potassium amide give the corresponding dinitro salts in yields which are comparable with or better than those using potassium t-butoxide as the base (Table 6). Essentially, equivalent amounts of base and alkyl nitrate are employed to obtain optimum yields and in the case of cyclopentanone and cyclohexanone, two equivalents of base suffice for generating high anion concentrations. With the less acidic cycloheptanone an excess of base (3.5 equiv.) is needed. A mixture of dinitro and mononitro salts is obtained when less base is used. In the case of cyclooctanone, nitration with an excess of base (3.5 equiv.) still gives a mixture of dinitro and mononitro salts\textsuperscript{30}.

The formation of mononitro compounds is a good indication that dinitration proceeds stepwise. This conclusion seems to be supported by the conversion of 2-nitrocyclooctane to dipotassium 2,7-dinitrocyclooctanone (28% yield) on further nitration.

The yield of dinitrated products reflects the acidity of the corresponding salt of the mononitrocyclanone which is converted into a dianion \textsuperscript{13} by proton removal (equation 15).

<table>
<thead>
<tr>
<th>Ketone\textsuperscript{a}</th>
<th>(\text{t-BuOK–THF} ) bromination product\textsuperscript{b}, yield (%)</th>
<th>Disal\textsuperscript{c}, yield (%)</th>
<th>(\text{KNH}_2-\text{NH}_3 ) bromination product\textsuperscript{b}, yield (%)</th>
<th>Disal\textsuperscript{c}, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopentanone</td>
<td>72</td>
<td>98</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>54\textsuperscript{d}</td>
<td>74</td>
<td>52\textsuperscript{d}</td>
<td>95</td>
</tr>
<tr>
<td>Cycloheptanone</td>
<td>55\textsuperscript{d}</td>
<td>—</td>
<td>80.5</td>
<td>85\textsuperscript{e}</td>
</tr>
<tr>
<td>Cyclooctanone</td>
<td>35\textsuperscript{d}</td>
<td>—</td>
<td>25\textsuperscript{d,e}</td>
<td>—</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Unless otherwise stated 2.0 equiv. of \text{KNH}_2 and 2.2 equiv. of amyl nitrate are used.

\textsuperscript{b}Bromination product is \(\text{O}_2\text{NBr}_2-(\text{CH}_2)_n-\text{Br}_2\text{NO}_2\).

\textsuperscript{c}Disal is 2-oxo-1,3-cycloalkanenedinitrionate.

\textsuperscript{d}Obtained on bromination of the crude disal.

\textsuperscript{e}\text{KNH}_2 (3.5 equiv.) and amyl nitrate (3.5 equiv.) are used.
The alkyl nitrate nitration leads to mononitroketones if equimolar amounts of ketone and base are used. At this ratio of reactants, however, the nitration is accompanied by a fragmentation reaction.

A comparison of the data compiled in Table 7 shows that in potassium amide less cleavage and more overall nitration occur than in potassium t-butoxide. Three products are obtained from the nitration of aliphatic ketones. Nitration of 4-heptanone, for instance, with ethyl nitrate gives 3-nitro-4-heptanone (14) (55%), 1-nitropropane (8%) and ethyl butanoate (8%) (equation 16).

Mononitration of cyclanones leads to α-nitrocyclanones and esters of ω-nitrocarboxylic acids (equation 17).

**TABLE 7. Mononitration of ketones in the potassium t-butoxide–THF and potassium amide–ammonia systems**

<table>
<thead>
<tr>
<th>Ketone</th>
<th>α-Nitroketone</th>
<th>ω-Nitrocarboxylic ester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t-BuOK–THF, yield (%)</td>
<td>KNH₂–NH₃, yield (%)</td>
</tr>
<tr>
<td>Cyclopentanone</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2,2,4-Trimethylcyclopentanone</td>
<td>82</td>
<td>trace</td>
</tr>
<tr>
<td>2,2,5-Trimethylcyclopentanone</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>2,5-Dimethylcyclopentanone</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>20%</td>
<td>59</td>
</tr>
<tr>
<td>Cycloheptanone</td>
<td>65</td>
<td>79</td>
</tr>
<tr>
<td>Cyclooctanone</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>Cyclononanone</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Cyclodecanone</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Cyclododecanone</td>
<td>54</td>
<td>64</td>
</tr>
<tr>
<td>Propiophenon</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>α-Tetralone</td>
<td>59</td>
<td>71</td>
</tr>
<tr>
<td>4-Heptanone</td>
<td>39</td>
<td>55</td>
</tr>
<tr>
<td>2,4-Dimethyl-3-pentanone</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

* t-BuOK (1.65 equiv.) and alkyl nitrate (1.1 equiv.) in THF at −40°C are used.
* KNH₂ (1.0 equiv.) and alkyl nitrate (2.0 equiv.) in NH₃ at −33°C are employed.
* Compound 6 (19%) is obtained in t-BuOK and 29% in KNH₂.
* Recovered 40% of ketone.
* Recovered 20% of ketone.
* Recovered 16% of ketone.
* Potassium 2-oxo-3-nitrocyclohexanenitronate (18%) is also formed.
* Recovered 59% of ketone.
* Ethyl benzoate (8%) and benzoic acid (7%) are formed (nitrating agent is EtONO₂).
* Recovered 34% of ketone.
* Amyl butyrate (25%) and 1-nitropropane (20%) are isolated (nitrating agent is AmONO₂).
* Ethyl butyrate (7%) and 1-nitropropane are formed (nitrating agent is EtONO₂).
* Recovered 16% of ketone.
* Amyl isobutyrate (84%) and 2-nitropropane (66%) are obtained.
19. Alkyl nitrate nitrations

\[
{\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}} \xrightarrow{1. \text{KHMnO}_4 - \text{NH}_3 \text{ or } r-\text{BuOK} - \text{THF}} {\text{CH}_3\text{CH}_2\text{CO}_2\text{Et} + \text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2} \xrightarrow{2. \text{EtONO}_2} \text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2 + 8\%
\]

\[
{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NO}_2} \xrightarrow{\text{H}^+} \text{CH}_3\text{CH}_2\text{CH}_2\text{C}-(\text{CH}_2)_2\text{CH}_3 + \text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2 \xrightarrow{\text{H}^+} \text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2 + 55\% \text{ and } 8\%
\]

\[
{\text{O}} \xrightarrow{1 \text{ KHMnO}_4 - \text{NH}_3 \text{ or } r-\text{BuOK} - \text{THF}} \xrightarrow{2. \text{RONO}_2} \xrightarrow{3 \text{ H}^+} \text{O}_2\text{NCH}_2\text{(CH}_2)_n+1\text{CO}_2\text{R} \xrightarrow{\text{H}^+} \text{O}_2\text{NCH}_2\text{(CH}_2)_n+1\text{CO}_2\text{R} \xrightarrow{\text{H}^+} \text{O}_2\text{NCH}_2\text{(CH}_2)_n+1\text{CO}_2\text{R} \]

\[
{n = 2-7 \text{ and } 9}
\]

\[
\text{R = alkyl}
\]

The following observations confirm that the fragmentation occurs during the nitration and not during the acidification step:

1. One of the reaction products, the carboxylic ester, can be isolated from the basic reaction mixture prior to acidification (equation 16).
2. Fragmentation is not a consequence of direct attack on the nitroketone by alkoxide derived from the alkyl nitrate. No cleavage products are formed when THF solutions of 2-nitrocyclooctanone or of 14 are added at \(-40^\circ\text{C}\) (the temperature maintained during the nitration) to varying ratios of a potassium \(r\)-butoxide–potassium ethoxide mixture or to potassium ethoxide alone, followed by acidification.
3. Cleavage is not caused by direct attack of alkoxide on the nitroketone which might be present in equilibrium with its salt. When in a nitration of cyclooctanone absolute ethanol is added immediately after the amyl nitrate, the only ester present after acidification is amyl 8-nitrooctanoate.

The foregoing results indicate clearly that the salt of a nitroketone, once formed during the nitration, does not participate in the cleavage reaction. A mechanism consistent with the experimental observations involves alkoxide attack at the carbonyl group of the intermediate 5 (equation 9 \(X = \text{CO}\)) which may have some stability at the temperature \((-40^\circ\text{C})\) at which nitrations are performed. Intermediate 5 also leads to the nitroketone after removal of the acidic \(\alpha\)-hydrogen by base (equation 18).

These two competing reactions should be influenced by the availability of \(\alpha\)-hydrogens and by any steric inhibition to alkoxide attack on the carbonyl group of 5. As shown in Table 7 and in equations (19)–(21), nitrations of 2,2,5-trimethylcyclopentanone and of 2,5-dimethylcyclopentanone in which no \(\alpha\)-hydrogens are available, lead mostly to the nitrocarboxylic esters 15 and 16, respectively. Nitration of 2,2,4-trimethylcyclopentanone, in which one of the \(\alpha\)-positions is blocked, gives the nitroketone 17 in high yield and only a trace of cleavage product.

Also consistent with the role of intermediate 5, it is reported that more of the
(ii) Aliphatic carboxylic and phenylacetic esters. Nitration of aliphatic carboxylic and phenylacetic esters affords α-nitro esters and the products of fragmentation (decarboxylation), namely nitroalkanes and dialkyl carbonates. Moreover, two α-nitro esters might form via transesterification if the alkoxy groups in the carboxylic and nitrate esters differ from each other (equation 22).

In nitrations of ethyl esters only a 10% excess of amide can be used without causing ammonolysis. Apparently this excess is insufficient for optimum anion formation because the total amount of nitration is not very high. It is, however, substantially increased when nitrations are carried out on t-butyl esters where amide formation is negligible even when a 100% excess of amide is employed. Moreover,
the nitration results for several tert-butyl esters and ethyl esters show that less fragmentation occurs in the nitration of tert-butyl esters except in the case of tert-butyl phenylacetate where the major product is phenyl nitromethane.

The nitration of p-nitrophenyl acetate is unsuccessful and 75% of the ester is recovered unchanged. Apparently as in the case of diethyl malonate, which also fails to undergo nitration, the equilibrium indicated in equation (9) lies far to the left of intermediate 5 (X = CO₂).

Based on several control experiments, it has been determined that the decarboxylation of the α-nitro esters does not occur in the acidification step. Also, it has been ascertained that at the conditions of the nitration reaction, the α-nitro ester salt, once formed, is not involved in the decarboxylation and transesterification reactions. A reasonable mechanism of these reactions is presented in Scheme 1.
TABLE 8. Nitration of \( \ell \)-butyl and ethyl esters, \( R^1CH_2CO_2R^2 \)\(^{40,a}\)

<table>
<thead>
<tr>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( \text{NO}_2 ) ( \text{yield} (%) )</th>
<th>( \text{NO}_2 ) ( \text{yield} (%) )</th>
<th>Total amount ( \alpha )-nitro esters, ( \text{yield} (%) )</th>
<th>( \text{RNO}_2 ) ( \text{yield} (%) )</th>
<th>Total nitration, ( \text{yield} (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Et</td>
<td>24</td>
<td>—</td>
<td>24</td>
<td>19</td>
<td>43(^b)</td>
</tr>
<tr>
<td>Me</td>
<td>Bu-( \ell )</td>
<td>22</td>
<td>26</td>
<td>48</td>
<td>14</td>
<td>62(^c)</td>
</tr>
<tr>
<td>Et</td>
<td>Et</td>
<td>41</td>
<td>—</td>
<td>41</td>
<td>14</td>
<td>55(^b)</td>
</tr>
<tr>
<td>Et</td>
<td>Bu-( \ell )</td>
<td>31</td>
<td>22</td>
<td>53</td>
<td>26</td>
<td>79(^c)</td>
</tr>
<tr>
<td>n-Bu</td>
<td>Et</td>
<td>42</td>
<td>—</td>
<td>42</td>
<td>14</td>
<td>56(^b)</td>
</tr>
<tr>
<td>n-Bu</td>
<td>Bu-( \ell )</td>
<td>33</td>
<td>22</td>
<td>55</td>
<td>33</td>
<td>88(^c)</td>
</tr>
<tr>
<td>s-Bu</td>
<td>Bu-( \ell )</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>72</td>
<td>72(^c)</td>
</tr>
<tr>
<td>H</td>
<td>Bu-( \ell )</td>
<td>22</td>
<td>18</td>
<td>40</td>
<td>33</td>
<td>73(^c)</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Bu-( \ell )</td>
<td>18</td>
<td>33</td>
<td>51</td>
<td>26</td>
<td>77(^c)</td>
</tr>
<tr>
<td>Ph</td>
<td>Et</td>
<td>23</td>
<td>—</td>
<td>23</td>
<td>49</td>
<td>72(^b)</td>
</tr>
<tr>
<td>Ph</td>
<td>Bu-( \ell )</td>
<td>3</td>
<td>36</td>
<td>39</td>
<td>49</td>
<td>88(^c)</td>
</tr>
<tr>
<td>( \ell )-MeOC(_6)H(_4)</td>
<td>Et</td>
<td>72(^d)</td>
<td>—</td>
<td>72(^d)</td>
<td>22</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\) Ratio of ethyl esters to \( \text{KNH}_2 \) to \( \text{EtONO}_2 \) is 1 to 1.1 to 1.5; in the case of \( \ell \)-butyl esters the ratio is 1 to 2 to 1.5.

\(^b\) About 20–30\% of starting ester is recovered.

\(^c\) About 1–8\% of starting ester is recovered.

\(^d\) Isolated as the potassium salt.

Intermediate 5 (equation 9, \( X = \text{CO}_2 \)) leads to intermediate Y which on fragmentation is converted to the nitroalkane salt and dialkyl carbonate. Removal of the \( \alpha \)-hydrogen in 5 by a base, such as amide, alkoxide or ammonia, would lead to the \( \alpha \)-nitro ester salt. As predicted by the mechanism, the fragmentation would predominate if there is no \( \alpha \)-hydrogen available in intermediate 5. This has been confirmed in the nitration of \( \ell \)-butyl 2-methylbutanoate. Only 2-nitrobutane is obtained and none of the nitro ester (Table 8).

The transesterification reaction might involve the collapse of intermediate Y, containing different alkoxy groups, via intermediate 5. There is some support of this from the results of an experiment in which potassium ethoxide is added prior to \( n \)-butyl nitrate in the nitration of \( \ell \)-butyl hexanoate (18)\(^40\). Three different \( \alpha \)-nitro esters are obtained, \( \ell \)-butyl 2-nitrohexanoate, \( n \)-butyl 2-nitrohexanoate (19) and ethyl 2-nitrohexanoate (20) (equation 23). It is uncertain whether ethoxide per se is

\[
\text{CH}_3(\text{CH}_2)\_4\text{CO}_2\text{Bu-}\_\ell \xrightarrow{1. \text{KNH}_2-NH_3; 2. KOEt; 3. nBuONO}_2; 4. H^+} \text{CH}_3(\text{CH}_2)\_3\text{CHNO}_2\text{CO}_2\text{Bu-}\_\ell +
\]

\( 3\% \)

\[
\text{CH}_3(\text{CH}_2)\_3\text{CHNO}_2\text{CO}_2\text{Bu-}n + \text{CH}_3(\text{CH}_2)\_3\text{CHNO}_2\text{CO}_2\text{Et} \quad \text{(23)}
\]

\( 19 \)

\( 23\% \)

\( 22\% \)

Actually involved in the formation of 20, for it has been reported that transesterification takes place between ethoxide and \( n \)-butyl nitrate at \(-33^\circ\)C in potassium amide–ammonia (equation 24). Thus it is possible that the formation of

\[
\text{n-BuONO}_2 + \_\cdot\text{OEt} \xrightarrow{\text{KNH}_2-NH_3} \text{n-BuO}^- + \text{EtONO}_2
\]

\( 24 \)
19. Alkyl nitrate nitrations

Esters 19 and 20 in the nitration of 18 is due to the presence of both n-butyl and ethyl nitrates. The equilibrium of the transesterification lies far to the right (equation 24); only a small amount of n-butyl nitrate forms when potassium n-butoxide is added to ethyl nitrate. This is explained by the low solubility of n-butoxide in liquid ammonia. The low solubility might account for the observation that only a small amount of 19 is formed if n-butoxide is added before the ethyl nitrate in the nitration of 18. It is also possible that some of nitro ester 20 originates from ethyl hexanoate (21) itself. This is indicated by the observation that 21 forms in ~23% yield from the t-butyl ester 18 and ethoxide under the conditions of the nitration reaction.

(iii) Alkylsulphonate esters. In contrast to carboxylic esters, alkylsulphonate esters are not subjected to desulphonation or transesterification in the alkyl nitrate nitrations. The choice of the ester group, however, is important to avoid the formation of α-nitroalkylsulphonic acids. Nitration of ethyl 1-butanesulphonate (22), using potassium amide as the base, gives two compounds, namely 55% of ethyl 1-nitro-1-butanesulphonate (23) and 11% of potassium 1-nitro-1-butanesulphonate (24) (equation 25). With sodium amide, the yield of 23 is only 36%. Similarly,

\[
\text{CH}_3\text{(CH}_2\text{)}_2\text{SO}_3\text{Et} \xrightarrow{1. \text{KOH-} \text{NH}_3} \xrightarrow{2. \text{RONO}_2} \xrightarrow{3. \text{NH}_4\text{Cl}} \text{CH}_3\text{(CH}_2\text{)}_2\text{CHNO}_2\text{SO}_3\text{Et} + \text{CH}_3\text{(CH}_2\text{)}_2\text{CHNO}_2\text{SO}_3\text{K} \quad (25)
\]

nitrations of n-octyl 1-butanesulphonate gives n-octyl 1-nitro-1-butanesulphonate (24) and 1-octene (25) (equation 26). The presence of 25 in the reaction mixture indicates that the loss of the ester group proceeds via a β-elimination reaction.

\[
\text{CH}_3\text{(CH}_2\text{)}_3\text{SO}_3\text{C}_8\text{H}_{17-n} \xrightarrow{1. \text{KOH-} \text{NH}_3} \xrightarrow{2. \text{RONO}_2} \xrightarrow{3. \text{NH}_4\text{Cl}} \text{CH}_3\text{(CH}_2\text{)}_2\text{CHNO}_2\text{SO}_3\text{C}_8\text{H}_{17-n} + 24 +
\]

\[
\text{CH}_3\text{(CH}_2\text{)}_5\text{CH}==\text{CH}_2 \quad (26)
\]

The choice of an ester group, such as neopentyl, in which β-elimination cannot occur during the nitration of alkylsulphonates, affords only neopentyl α-nitroalkylsulphonates (Table 9). In order to obtain high yields of α-nitrosulphonate esters containing 8–12 carbons in the acid part, more concentrated reaction mixtures have to be employed. For instance, the yield of neopentyl 1-nitro-1-dodecanesulphonate (26) increases from 3% to 33% when the concentration of potassium amide is increased from 0.3 M to ~0.7 M. Apparently, this is due to a slower rate of anion formation (equation 8), for the yield of 26 is further increased to 47% when the anion of neopentyl 1-dodecanesulphonate (27) is generated with potassium amide in THF at 65°C and then subjected to nitration at ~33°C. Similar treatment of neopentyl 1-hexadecanesulphonate (28) gives no nitrated product, and 95% of 28 is recovered. The failure of 28 to undergo nitration is accounted for by a lack of anion formation, as confirmed by a deuterium-exchange experiment. No deuterium is incorporated into 28 after treatment with potassium amide in liquid ammonia and subsequent acidification with deuterium oxide in anhydrous ether. Under similar reaction conditions, 75% of deuterium is incorporated into ester 27.

Since desulphonation does not take place in the nitration of alkylsulphonates it is possible to obtain tertiary α-nitroalkylsulphonates. Nitration of neopentyl 2-butanesulphonate affords neopentyl 2-nitro-2-butanesulphonate (equation 27).
TABLE 9. Alkyl nitrate nitration of neopentyl alkylsulphonates, RSO₃CH₂C(CH₃)₃, in potassium amide–liquid ammonia²,³

<table>
<thead>
<tr>
<th>R</th>
<th>yield (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂</td>
<td>74 (22)</td>
<td>—</td>
</tr>
<tr>
<td>n-C₄H₉</td>
<td>76 (22)</td>
<td>—</td>
</tr>
<tr>
<td>n-C₅H₁₁₃</td>
<td>56 (37)</td>
<td>75 (21)</td>
</tr>
<tr>
<td>n-C₆H₁₇</td>
<td>33 (62)</td>
<td>76 (22)</td>
</tr>
<tr>
<td>n-C₁₀H₂₁</td>
<td>17 (78)</td>
<td>56 (40)</td>
</tr>
<tr>
<td>n-C₁₂H₂₅</td>
<td>3 (93)</td>
<td>40 (63), 47f</td>
</tr>
<tr>
<td>CH₃CH₂CH(CH₃)</td>
<td>—</td>
<td>35 (60)</td>
</tr>
<tr>
<td>(CH₃)₂CCH₂O₃S(CH₂)₄</td>
<td>69</td>
<td>—</td>
</tr>
</tbody>
</table>


²The ratio of ester to base to nitrate is 1:2:3.
³Reactions are performed at −33°C in ca. 0.3 M solution of potassium amide. The nitration time is 5 min.
⁴The concentration of potassium amide is ca. 0.7 M. The nitration time is one hour.
⁵The numbers in parenthesis represent recovered starting material.
⁶Anion formation is carried out in THF at 65°C, and the nitration at −33°C.

Contrast, nitration of t-butyl 2-methylbutanoate leads entirely with decarboxylation to 2-nitrobutane (Table 8).

Regarding the β-elimination reaction which takes place in the ester part of alkylsulphonates, it has been confirmed that it occurs during the nitration step and not during anion formation or acidification. The important findings are: (a) ester 22 is recovered in 92% yield after treatment in the potassium amide–liquid ammonia system and acidification with ammonium chloride; (b) the potassium salt of 23 is converted in 97% yield to 23 on treatment with potassium amide in liquid ammonia and subsequent acidification with ammonium chloride; (c) on similar treatment, however, nitro ester 23 undergoes β-elimination to the potassium salt of 24 to the extent of 26%. A mechanism consistent with these observations is presented in Scheme 2. It shows in the first step the collapse of intermediate 5 (equation 9, X = SO₃) into nitrosulphonate 23 and alkoxide. Then, as suggested by the results of experiment (c) (see above), a competitive reaction takes place in which the base can attack the α-hydrogen (H₃) as shown in step (2), or alternately can abstract the β-hydrogen (H₄) in the ester part to give salt 24 and ethylene in step (3).

(iv) Activated toluenes. The alkyl nitrate nitration of toluenes³⁵ substituted in the \textit{ortho} or \textit{para} position with an electron-withdrawing group gives the corresponding α-nitrotoluenes in yields of about 40–55% (Table 10). The yield varies greatly with the particular activating group. With two substituted toluenes, higher yields are obtained in the weaker sodium amide–liquid ammonia system than in the stronger potassium amide–liquid ammonia system. This is encountered in the nitration of
19. Alkyl nitrate nitrations

\[
\begin{align*}
\text{CH}_3(\text{CH}_2)_2\text{C}^\text{-}\text{SO}_3\text{CH}_2\text{CH}_2 \quad \text{H}_a \\
\text{N}^\text{-} \quad \text{NO}_2 \quad \text{H}_b \\
\text{OR} \quad \text{(5)}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3(\text{CH}_2)_2\text{C}^\text{-}\text{SO}_3\text{CH}_2\text{CH}_2 + \text{OR} \quad \text{(1)}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3(\text{CH}_2)_2\text{C}^\text{-}\text{SO}_3\text{CH}_2\text{CH}_2 \quad \text{H}_a \\
\text{NO}_2 \quad \text{H}_b \\
\text{B}^- \\
\text{H}_3\text{C}(\text{CH}_2)_2\text{CHNO}_2^-\text{SO}_3^- + \text{CH}_2=\text{CH}_2 \quad \text{(24)}
\end{align*}
\]

SCHEME 2

\(N, N\)-dimethyl-\(p\)-toluenesulphonamide (29) and phenyl \(p\)-tolyl sulphone (30). The lower yields obtained in potassium amide are not due to side-reactions because the material balances are about 70–80%. The results have been explained by the ambident nature of the anions of 29 and 30. In one of the contributing structures of these anions, the negative charge resides on the oxygen. It is conceivable that the electrophilic attack of the nitrate would occur on oxygen rather than on carbon. The product of such nitration would very likely be unstable and revert to starting material (equation 28). According to the well-known cation effect, \(O\)-nitration predominates in potassium amide and as a consequence the yields in the nitration of 29 and 30 are lower than in sodium amide.

Toluene (\(pK_a\) \(\sim\) 37)\(^{44}\) fails to undergo nitration in potassium amide; diphenylmethane (\(pK_a\) \(\sim\) 35)\(^{45}\), however, is converted to diphenylnitromethane (31)
TABLE 10. Alkyl nitrate nitration of activated toluenes\textsuperscript{35,a}

\[
\begin{array}{cccc}
\text{X} & \text{yield (\%)} & \text{Yield (\%)} \\
-\text{CH}_3 & & \\
p-\text{CN} & 47 (36)^d & 42 (41)^d \\
o-\text{CN} & 38 (35) & - \\
p-\text{PhCO} & 16 (64) & 0 (100) \\
p-\text{Me}_2\text{NSO}_2 & 15 (55) & 40 (27) \\
p-\text{PhSO}_2 & 4 (84) & 55 (39) \\
\end{array}
\]

\textsuperscript{a}The molar ratio of substrate to base to alkyl nitrate is 1:1.5:2.
\textsuperscript{b}The base is potassium amide.
\textsuperscript{c}The base is sodium amide.
\textsuperscript{d}The number in brackets refers to recovered starting material.

(40%) Spectroscopically pure 31 decomposes to benzophenone\textsuperscript{46} when stored at 0°C; diphenylbromonitromethane, however, is stable when kept at 0°C.

Attempts to nitrate \textit{p}-nitrotoluene have been unsuccessful. Under the basic conditions of the nitration it is converted to \textit{p},\textit{\textit{p}}'-dinitrobenzyl\textsuperscript{47}.

The \textit{para}-substituted \textit{\alpha}-nitrotoluenes (Table 10) are readily converted in good yield into the corresponding stilbenes on treatment with a catalytic amount of potassium acetate in refluxing ethanol\textsuperscript{35} (equation 29). Under similar reaction conditions, \textit{o}-cyanophenylnitromethane is converted to 3-oximinophthalimide (92%) (equation 30).

\[
\text{X} = \text{CN (76\%), Me}_2\text{NSO}_2 (67\%), \text{PhSO}_2 (55\%), \text{PhCO (100\%)}
\]

\[(v)\text{ Amides and lactams.}\text{ There is only one example in the literature in which the nitration of an \textit{N}-substituted amide in potassium amide is described}\textsuperscript{48}. \textit{N}-Acetylpyrrolidine (32) is converted into \textit{N}-nitroacetylpyrrolidine in about 8\% yield and a considerable amount of starting material is recovered. It is possible that the low yield in the nitration of 32 is due to transamidation. For instance, when \textit{N},\textit{\textit{N}}-diphenylacetamide (33) is placed in potassium amide–liquid ammonia only 80\% is recovered and 20\% diphenylamine is isolated. However, nitration of 33 affords \textit{N},\textit{\textit{N}}-diphenylnitroacetamide (34) in 30\% yield\textsuperscript{49} (equation 31).

\[
\text{Ph}_2\text{NCOCH}_3 \xrightarrow{1 \text{ KNH}_2\text{-NH}_3} \xrightarrow{2 \text{ \textit{p}-PhNO}_2} \xrightarrow{3 \text{ H}^+} \text{Ph}_2\text{NCOCH}_2\text{NO}_2
\] (33) (34) 30\%
Attempts to nitrate \( o-N,N\)-dimethyltoluamide and its \( para \) isomer are unsuccessful because they are converted to \( o- \) and \( p \)-toluamides, respectively
\[^35\].

The conversion of several \( N \)-methyl-2-azetidinones to the \( N \)-methyl-3-nitroacetidinones has been reported
\[^48\]. It is of interest that the \( trans \) isomers are formed exclusively (equation 32). Also nitration of \( N \)\-methylcaprolactam and \( N \)-methylpyrrolidone afford \( N \)-methyl-3-nitrocaprolactam (37\%) and \( N \)-methyl-3-nitropyrrolidone (34\%).

\[
\begin{align*}
R^1 &= \text{Me}, R^2 = \text{H} (34\%); R^1, R^2 = \text{Me} (70\%); R^1 = \text{H}, R^2 = \text{Ph} (10\%); R^1 = \text{H}, R^2 = \text{MeS} (32\%)
\end{align*}
\]

\[
\text{(vi) Heterocyclic compounds. The alkyl nitrate nitration of } \pi \text{-deficient heterocyclic compounds such as 4-methylpyridine (35) and 4-methylpyrimidine and of } \pi \text{-excessive heterocyclic compounds such as 2-methylbenzoxazole and 2-methylbenzothiazole leads to } \alpha \text{-nitroalkyl heterocyclic} \text{ compounds. Both sodium amide and potassium amide have been found effective as bases in the nitration, but they are not equally effective in providing optimum yields (Table 11). For instance, in sodium amide, 35 is converted into 4-nitromethylpyridine (36) in 66\% yield while in}
\]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Starting material} & \text{Product}^b & \text{NaNH}_2 \text{-NH}_3^c, \text{yield} (%) & \text{KNH}_2 \text{-NH}_3^d, \text{yield} (%) \\
\hline
\text{4-Methylpyridine} & \text{4-Nitromethylpyridine} & 58 & 48^e \\
\text{4-Methylpyrimidine} & \text{4-Nitromethylpyridine} & 66 & 33 \\
\text{2-Methylbenzoxazole} & \text{2-Nitrobenzoxazole} & 69 & 53 \\
\text{2-Methylbenzothiazole} & \text{2-Nitrobenzothiazole} & 68 & 65 \\
\text{Pyridine} & \text{5-Nitropyridine} & 52^f & \text{---} \\
\hline
\end{array}
\]
TABLE 11. (continued)

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>NaNH&lt;sub&gt;2&lt;/sub&gt;-N&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;, yield (%)</th>
<th>KNH&lt;sub&gt;2&lt;/sub&gt;-NH&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtN&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtN&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0&lt;sup&gt;e&lt;/sup&gt;</td>
<td>42&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;-CH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Ph</td>
<td>N&lt;sub&gt;2&lt;/sub&gt;-CH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>90</td>
<td>74</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>71&lt;sup&gt;i&lt;/sup&gt;</td>
<td>54&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>58&lt;sup&gt;k&lt;/sup&gt;</td>
<td>58&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>58</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>Starting material</td>
<td>Product$^b$</td>
<td>NaNH$_2$–NH$_3$$^c$, yield (%)</td>
<td>KNH$_2$–NH$_3$$^d$, yield (%)</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>![image]</td>
<td>![image]</td>
<td>62</td>
<td>—</td>
</tr>
<tr>
<td>![image]</td>
<td>![image]</td>
<td>66</td>
<td>—</td>
</tr>
<tr>
<td>![image]</td>
<td>![image]</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>![image]</td>
<td>![image]</td>
<td>—</td>
<td>88</td>
</tr>
<tr>
<td>![image]</td>
<td>![image]</td>
<td>43</td>
<td>—</td>
</tr>
</tbody>
</table>


$^b$Reactions are performed in ca. 0.5 M amide concentration. The products are obtained from their salts without prior purification upon acidification with aqueous acetic acid.

$^c$The ratio of substrate to NaNH$_2$ to RONO$_2$ is 1:2.5:3.

$^d$The ratio of substrate to KNH$_2$ to RONO$_2$ is 1:2.0:2.5.

$^e$Obtained after acidification with acetic acid of the aqueous solution of pure salt.

$^f$Isolated as the picrate salt.

$^g$87% of starting material is recovered.

$^h$A 1.19 M concentration of KNH$_2$ is used.

$^i$Isolated as 2-(dibromonitromethyl)pyridine-N-oxide.

$^j$Impure compound.

$^k$Isolated as 4-(dibromonitromethyl)pyridine-N-oxide.

$^l$Only 1-(2-quinolyl)2-butanol is obtained (26%).

potassium amide the yield is only 33% and 42% of 35 is recovered. The sodium salt of 36 which can be readily purified is obtained in 92% yield (equation 33). This is not the case with the potassium salt of 36 which is highly hygroscopic.

On the other hand, in the nitration of 4-methylquinoline, potassium amide provides a higher yield of 4-nitromethylquinoline (37) (92%) than sodium amide (58%) (equation 34).

The nitration of 2-methylquinoline (38) is rather interesting. It is only successful in
potassium amide, and the concentration of the reaction mixture is rather important to obtain the potassium salt of 2-nitromethylquinoline in good yield (Table 12).

When sodium amide is used in the nitration of 38, the only compound isolated (26%) is 1-(2-quinolyl)-2-butanol (39). The formation of 39 is probably due to a base-catalysed reaction of 38 and propanal (equation 35). The aldehyde originates from the attack of base (NH\textsubscript{2}\textsuperscript{-}) on n-propyl nitrate via α-hydrogen abstraction. A similar reaction of the nitrate ester has been observed in the nitration of aldimines (see below, equation 52).

Nitration of heterocycles having more than one methyl group affords only mononitration products (Table 11) even if an excess of base and nitrate ester is used. As in oximation\textsuperscript{50} and side-chain alkylolation\textsuperscript{51}, the reactivity of the methyl group in pyridine is in the order of 4 > 2 > 3. Thus 2,4,6-trimethylpyridine and 2,3-dimethylpyridine are converted respectively to 2,6-dimethyl-4-nitromethylpyridine and 2-nitromethyl-3-methylpyridine.

### TABLE 12. Effects of potassium amide concentration on the nitration of 2-methylquinoline\textsuperscript{a}

<table>
<thead>
<tr>
<th>Concentration of KNH\textsubscript{2} (m)\textsuperscript{b}</th>
<th>Potassium salt of 2-nitromethylquinoline, yield (%)</th>
<th>Recovered 2-methylquinoline (38), yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35</td>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>0.59</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>1.58</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>2.84</td>
<td>50</td>
<td>37</td>
</tr>
</tbody>
</table>


\textsuperscript{b}Ratio of 38 to KNH\textsubscript{2} to n-PrONO\textsubscript{2} is 1.0:2.0:2.5.
The nitration of 4-ethylpyridine leads to a mixture consisting of 1-(4-pyridyl)nitroethane (40) and 4-acetylpyridine (41) (equation 36). Since according to the spectral data the material isolated from the basic nitration mixture does not indicate the presence of 41, it must be formed during the acidification step in a Nef-type reaction from 40. This is also confirmed by the observation that analytically pure 40 transforms slowly into 41. Pure 40 is obtained by reduction of 1-bromo-1-nitro-1-(4-pyridyl)ethane (42) with sodium borohydride. Compound 42 is prepared by bromination of the crude sodium salt of 40 (equation 37).

Attempts to nitrate 3-methylpyridine (43) have met with failure. This cannot be due to the lack of anion formation because 43 undergoes alkylation reactions in both sodium amide and potassium amide. It is possible that the anion of 43, being more basic than those of the 4- and 2-isomers reacts with the nitrating agent in an E2-type rather than in a S_N2-type fashion. The consequence of this is destruction of the alkyl nitrate.

3-Nitromethylpyridine (44) has, however, been prepared by the nitration of ethyl 3-pyridylacetate. A mixture is obtained consisting of 44 (65%) and ethyl α-nitro-3-pyridylacetate (45) (33%). The mixture is completely converted to 44 on heating in base followed by acidification (equation 38).

Nitrations of 4-isopropylpyridine (46) and 2-isopropylpyridine (47) do not give the expected tertiary isopropyl nitropyridines but instead lead to the dimers, 2,3-bis(4-pyridyl)-2,3-dimethylbutane (48) and 2,3-bis(2-pyridyl)-2,3-dimethylbutane (49) (equation 39). On the other hand, 3-isopropylpyridine is recovered unchanged. Convincing evidence is presented that the nitro compounds, 2-nitro-2-(4-pyridyl)propane (50) and 2-nitro-2-(2-pyridyl)propane (51) are intermediates in the formation of dimers 48 and 49. For instance, in the absence of the nitrating agent, 46 and 47 are recovered unchanged. Also, both compounds 48 and 50 are isolated.
when in an inverse addition the potassium salt of 46 is added to the nitrating agent in liquid ammonia (equation 40). Moreover, nitro compounds 50, 51 and 52, which have been prepared by direct nitration with 90% nitric acid53, are converted in high yields to the respective dimers 48, 49 and 50, 51 and 52.

2,3-bis(3-pyridyl)-2,3-dimethylbutane (53). The dimerizations occur in potassium amide—liquid ammonia or in the presence of the respective isopropylpyridine anions generated in the potassium or sodium amide—ammonia systems (equation 41).

Regarding the formation of dimers 48, 49 and 53, a direct displacement of the tertiary nitro group in compounds 50-52 by the tertiary carbanion of 46, 47 and 3-isopropylpyridine would seem unlikely because of steric considerations. It has been proposed53 that these dimerizations occur by electron-transfer processes related to reactions in which the tertiary nitro group of α,α-dinitrocumene is replaced by a variety of anions54 (see Chapter 10 in this volume).

Evidence that isopropylpyridines can participate in electron-transfer reactions in the amide—ammonia system is offered from two observations. In potassium amide—liquid ammonia, 46 is converted in the presence of oxygen to 2-(4-pyridyl)-2-propanol (54) (equation 42). Oxygenation of carbanions are considered to involve a radical—radical anion mechanism55. Moreover, the reaction of 46 and nitrobenzene in potassium amide—liquid ammonia affords dimer 48 (53%),
2-(4-nitrophenyl)-2-(4-pyridyl)propane (55) (10%) and potassium nitrobenzenide (56) (equation 43). The reddish-brown 56 decomposes to benzene on addition of water.\(^{56,57}\).

The essential steps which lead to the formation of dimers 48, 49 and 53 are shown in Scheme 3 by using the formation of 49 as an example. The reaction is initiated by an electron transfer of the anion 47a of 47 to the nitro compound 51 to give the radical anion A of 51 and radical B of 47. In step (2), A collapses into nitrite ion and B, which then couples with the anion 47a to produce the radical anion C of dimer 49 (step 3). Propagation of the radical chain by an electron transfer from C to 51 leads then to dimer 49 and regeneration of radical anion A (step 4).

\[ 46 + C_6H_5NO_2 \xrightarrow{1. KNH_2-NH_3} \xrightarrow{2. NH_4Cl} 48 + \begin{array}{c} \text{(55)} \\ \text{(56)} \end{array} \ \text{53\%} + \ \text{10\%} \]

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\[ \text{(42)} \]

\[ \text{(43)} \]
The combination of radicals \( B \) can also lead to dimer \( 49 \), but this process is considered less favourable in the highly diluted solution in which the experiments are performed.

In the direct formation of dimers \( 48, 49 \) and \( 53 \) from the nitro compounds \( 50, 51 \) and \( 52 \) on treatment with amide in liquid ammonia, it is suggested that the isopropylpyridine anion (the electron donor in step 1 of Scheme 3) is generated by displacement of the nitro group by amide ion (equation 44).

\[
\ce{C(CH3)2NO2 + NH2- + NH3 -> C^- + [NH2NO2]} \quad (44)
\]

The base–solvent system is rather critical for the dimerization to occur. Compound \( 50 \) is recovered unchanged after treatment with potassium methoxide in methanol at reflux. A reaction, however, does occur in DMSO at 75°C as well as at ambient temperatures with potassium \( t \)-butoxide in DMSO or HMPA. However, the product of these reactions is not the dimer \( 48 \) but the olefin 4-isopropenylpyridine \( 57 \) arising from the loss of nitrous acid (equation 45).

\[
\ce{CH3C=CH2 \rightarrow [r-BuOK, DMSO or HMPA]} \quad (45)
\]

\( 99\% \)

(vii) Arylmethylene, alkylidene and hetarylmerhylene phenylhydrazines. The alkyl nitrate nitration of arylmethylene, alkylidene and hetarylmethylene phenylhydrazines constitutes a general method for the introduction of the nitro group into the \( \alpha \)-position of these classes of compounds\(^{37} \) (equation 46). Nitration in several base–solvent systems with benzylidene phenylhydrazine \( 58 \) shows that highest yields (91%) of \( \alpha \)-nitrobenzylidene phenylhydrazine \( 59 \) are realized in potassium amide (Table 13). A high yield (80%) of \( 59 \) is obtained in potassium \( t \)-butoxide–THF but the reaction is accompanied by the formation (20%) of 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5- tetrazine \( 60 \) (equation 47). It is known that \( 59 \) is converted to \( 60 \) on heating in methanolic sodium hydroxide\(^{58} \), so it is possible that \( 59 \) is the precursor in the formation of \( 60 \) during the alkyl nitrate nitration. The mechanism of this conversion is not known. It is possible that \( 59 \) is converted to diphenyliminonitrile \( 61 \) which then undergoes a 1,3-dipolar head-to-tail coupling to give \( 60 \) (equation 48). \( 61 \) has been postulated as an intermediate in the conversion of \( \alpha \)-chlorobenzylidine phenylhydrazine to \( 60 \) on treatment with triethylamine in benzene\(^{59} \). It is of interest that \( 59 \) is recovered unchanged on similar treatment. However, on heating with sodium hydroxide in acetonitrile \( 59 \) is apparently
TABLE 13. Effect of base-solvent systems on the nitration of benzylidene phenylhydrazine (58)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Base-solvent\textsuperscript{b} system</th>
<th>PhC(NO\textsubscript{2})=N-NHPh (59), yield (%)</th>
<th>Recovered PhCH=N-NHPh (58), yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KNH\textsubscript{2}-NH\textsubscript{3}</td>
<td>91</td>
<td>3</td>
</tr>
<tr>
<td>NaNH\textsubscript{2}-NH\textsubscript{3}</td>
<td>45\textsuperscript{b}</td>
<td>45</td>
</tr>
<tr>
<td>LiNH\textsubscript{2}-NH\textsubscript{3}</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>t-BuOK-THF</td>
<td>80</td>
<td>\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{b}Ratio of 50 to base to nitrate is maintained at 1:1:2.
\textsuperscript{c}The yield is unchanged when the ratio of 50 to NaNH\textsubscript{2} to nitrate is 1:2:2.
\textsuperscript{d}A 20% yield of 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine is also obtained.

\[
\begin{align*}
\text{PhCH}=\text{N} &\xrightarrow{1. \text{t-BuOK}} \text{PhC(NO}_2\text{)=N-NHPh} \\
\text{(58)} &\xrightarrow{2. \text{CH}_2=\text{CHCO}_2\text{Me}} \text{59} \\
&\xrightarrow{3. \text{CH}_2=\text{CHCO}_2\text{Me}} \text{(62)} \\
&\text{75%}
\end{align*}
\]

converted to 61, for 59 reacts with methyl acrylate to give the 1,3-dipolar adduct, 5-carboxymethyl-4,5-dihydro-1,3-diphenyl-2-pyrazoline (62)\textsuperscript{60} (equation 49).

\[
\begin{align*}
\text{59} &\xrightarrow{1} \text{[Ph} &\xrightarrow{2} \text{C}\text{=}\text{N} &\xrightarrow{3} \text{N} &\xrightarrow{4} \text{Ph}\text{]} \\
&\text{(61)} &\text{(60)} \\
&\text{20%}
\end{align*}
\]

The data shown in Table 14 indicate the generality of the nitration in potassium amide with a variety of phenylhydrazines. As discussed (see above) in the nitration of alkylsulphonate esters\textsuperscript{42} and alkyl-substituted heterocyclic compounds\textsuperscript{36}, the yields of some of the nitro compounds are substantially higher when reactions are carried out in a more concentrated medium. For instance, the yield of $\alpha$-nitroethyldenedephylhydrazine is increased by 53\% when the concentration of potassium amide is increased from 0.3 M to 0.7 M. On the other hand, the yield of $\alpha$-nitrobutyldenedephylhydrazine has been found to decrease in the more concentrated reaction medium.

The data in Table 14 show that only $C$-nitro compounds are obtained in these nitrations. According to the accepted mechanism (equations 8–11), the initial
TABLE 14. Alkyl nitrate nitration of arylmethylene alkylidene and hetarylmethylene phenylhydrazines, \( R-\text{CH}=\text{N}-\text{NHPh} \)

<table>
<thead>
<tr>
<th>( R^b )</th>
<th>In 0.3 M KNH(_2), yield (%)</th>
<th>In 0.7 M KNH(_2), yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>91</td>
<td>—</td>
</tr>
<tr>
<td>2-MeOC(_6)H(_4)</td>
<td>28</td>
<td>65</td>
</tr>
<tr>
<td>4-MeOC(_6)H(_4)</td>
<td>74</td>
<td>—</td>
</tr>
<tr>
<td>2-MeC(_6)H(_4)</td>
<td>94</td>
<td>—</td>
</tr>
<tr>
<td>2-ClC(_6)H(_4)</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>4-ClC(_6)H(_4)</td>
<td>73</td>
<td>—</td>
</tr>
<tr>
<td>4-BrC(_6)H(_4)</td>
<td>16</td>
<td>58</td>
</tr>
<tr>
<td>4-(i-Pr)C(_6)H(_4)</td>
<td>94</td>
<td>—</td>
</tr>
<tr>
<td>4-CF(_3)C(_6)H(_4)</td>
<td>83</td>
<td>—</td>
</tr>
<tr>
<td>1-Naphthyl</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>2-Naphthyl</td>
<td>46</td>
<td>—</td>
</tr>
<tr>
<td>2-Furyl</td>
<td>19</td>
<td>47</td>
</tr>
<tr>
<td>2-Thienyl</td>
<td>83</td>
<td>—</td>
</tr>
<tr>
<td>3-Pyridyl</td>
<td>38</td>
<td>—</td>
</tr>
<tr>
<td>H</td>
<td>30</td>
<td>—</td>
</tr>
<tr>
<td>Me</td>
<td>30</td>
<td>83</td>
</tr>
<tr>
<td>( n)-Pr</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>


\(^b\)The ratio of substrate to amide to nitrate is 1:1:2. The nitro compounds are obtained from their crude salts upon aqueous acidification with acetic acid.

reaction in the case of the substituted phenylhydrazines involves proton abstraction with the formation of resonance-stabilized ambident anion \( 63 \). The exclusive formation of \( C \)-nitro compounds might be a consequence of the greater nucleophilicity of the carbanion over the anilide ion towards the nitrate ester (equation 9). One might also expect that a nitroamino compound resulting from an electrophilic attack of nitrate ester on nitrogen would revert to starting material because it cannot be stabilized by salt formation.

In contrast to the results in the alkyl nitrate nitration, alklylation reactions in alkaline media lead to exclusive substitution on nitrogen\(^b\). Apparently alklylation reactions are less influenced by the nucleophilicity of the anion. This fact is substantiated by experiments in which certain arylmethylene phenylhydrazines which fail to undergo nitration are readily alkylated. For example, 3-nitrobenzylidene phenylhydrazine (64) and 4-cyanobenzylidene phenylhydrazine (65) which are recovered unchanged from alkyl nitration experiments, are converted quantitatively to the respective \( N \)-methylated phenylhydrazines 66 and 67 when methyl iodide is added to the reaction mixture (equation 50).

(viii) Aldimines and alicyclic ketimines. The alkyl nitrate nitration of aldimines affords 1-alkylamino-2-nitro-1-alkenes\(^b\). \( N \)-Propylidene-\( t \)-butylamine (68) is converted to 1-(\( t \)-butylamino)-2-nitro-1-propene (69) in 53% yield if potassium
19. Alkyl nitrate nitration

\[ \text{RCH} = \text{N} - \text{NHPh} \quad \xrightarrow{1 \text{ KNH}_2 - \text{NH}_3 \text{ or t-BuOK-THF}} \quad \xrightarrow{2 \ n-\text{PrONO}_2; 3 \ \text{MeI}; 4 \ H^+} \quad \text{Me} \]

(64) \quad R = 3-nitrophenyl \quad (66)

(65) \quad R = 4-cyanophenyl \quad (67)

\[ \text{t-BuN} = \text{CHCH}_2\text{CH}_3 \quad \xrightarrow{1 \text{ KNH}_2 - \text{NH}_3} \quad \xrightarrow{2 \ n-\text{PrONO}_2; 3 \ \text{NH}_4\text{Cl}} \quad \text{t-BuNHCH} = \text{C} - \text{CH}_3 \quad (51) \]

(68)

(69)

amide is employed as the base (equation 51). In sodium amide the yield of 69 is 44%, while in lithium amide only tar-like material is obtained. In a control test only 18% of 68 is recovered when subjected to potassium amide in liquid ammonia. Thus it is rather remarkable that the nitration of 68 in this medium gives 53% of 69. The results of the nitration of various aldimines derived from primary aldehydes are shown in Table 15. Variations in the alkylamino part have some effect on the yield. The low yield (40%) of 1-(isopropylamino)-2-nitro-1-propene is due to its instability.

An interesting aldehyde interchange reaction is observed during the nitration if the alkyl group of the nitrate ester differs from that of the aldehyde moiety in the aldimine. In the nitration of N-ethylidene-t-butylamine (70) with n-propyl nitrate, in addition to 1-(t-butylamino)-2-nitroethene (71) there is also formed 10% of 69 (equation 52).

In a control test it has been established that aldehyde interchange can occur in the amide-liquid ammonia system. For instance aldimine 68 is formed in addition to considerable amounts of aldol-condensation products when N-butylidene-t-

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-Bu</td>
<td>H</td>
<td>21⁴⁺</td>
</tr>
<tr>
<td>n-Pr</td>
<td>Me</td>
<td>54⁴⁺</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Me</td>
<td>40⁴⁺</td>
</tr>
<tr>
<td>i-Bu</td>
<td>Me</td>
<td>70⁴⁺</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Me</td>
<td>51⁴⁺</td>
</tr>
<tr>
<td>C₆H₁₁</td>
<td>Me</td>
<td>50</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Et</td>
<td>51</td>
</tr>
<tr>
<td>n-Hex</td>
<td>Et</td>
<td>67</td>
</tr>
<tr>
<td>t-Bu</td>
<td>n-Pc</td>
<td>46</td>
</tr>
</tbody>
</table>


The ratio of substrate to KNH₂ to n-PrONO₂ is 1:2:1.5. NH₄Cl is the acidifying agent.

There is also formed 10% of 1-(t-butylamino)-2-nitro-1-propene (69).

The yield of 71 is 14% when ethyl nitrate is the nitrating agent.
butylamine (72) is treated with propanal (equation 53). The well-established α-hydrogen elimination reaction which primary alkyl nitrates undergo in basic media accounts for the formation of propanal from n-propyl nitrate.

Nitration of aldimines derived from α-branched aldehydes do not lead to t-α-nitroaldimines. Instead, products are obtained which arise both from dimerization of the aldimine and aldehyde interchange. For example, nitration of cyclohexylmethylene-t-butylamine (73) with n-propyl nitrate gives 1,1′-bis(cyclohexylmethylene-t-butylamine) (74) (18%), compound 69 (4%), cyclohexancarboxaldehyde (75) (2%) and unreacted 73 (23%) (equation 54). The mechanism of the formation of dimer 74 has not been established. The dimerization is reminiscent of the formation of dimers 48, 49 and 53 from the respective isomeric nitroiso-propylpyridines on treatment with potassium amide in liquid ammonia (equations 39–41). It is possible that a tertiary nitro compound such as N-(1-nitrocyclohexylmethylene)-t-butylamine (76) is the precursor and is converted to 74 in an electron-transfer process.

Only mononitratcd products are obtained in the alkyl nitrate nitration of cycloalkyl-t-butylamines. This is in contrast to the results with cyclanones where under appropriate conditions both mononitro and dinitro compounds are obtained. Nitrations of N-cyclopentylidene-t-butylamine (77), N-cyclohexylidene-t-butylamine (78), and N-cycloheptylidene-t-butylamine (79) give 1-nitro-2-(t-butylamino)cyclopentene (80), 1-nitro-2-(t-butylamino)cyclohexene (81) and 1-nitro-2-(t-butylamino)-cycloheptene (82) in yields of 35%, 44% and 50%, respectively (equation 55). The molar ratio of imine to base to nitrating agent employed is 1:2:1.5, and ammonium chloride is used in the acidification step.

The formation of compound 80 is of interest in view of the fact that attempts to prepare the ketone analogue 2-nitrocyclopentanone (83) by the alkyl nitrate nitration led to ring-opening and gave the ester of ω-nitropentanoic acid. However, 83 has been recently prepared and characterized as a yellow solid which decomposes at room temperature.
19. Alkyl nitrate nitrations

\[ \text{(77)} \quad n = 2 \]
\[ \text{(78)} \quad n = 3 \]
\[ \text{(79)} \quad n = 4 \]

The structures of the 1-alkylamino-2-nitro-1-alkenes are indicated by their spectral data\(^3\). NMR spectra confirm that in solution both \( Z \) and \( E \) isomers are present. The \( Z \) isomer predominates in nonpolar solvents because of its increased stability through intramolecular hydrogen bonding. The presence of the dipolar structure is also apparent in the solid-state infrared spectra.

The spectra of compounds \( 80-82 \) confirm that the dipolar structure is a very important contributor (equation 55). The NMR spectra in deuterated chloroform or deuterated dimethyl sulfoxide, \((\text{CD}_3)_2\text{SO}\), show the presence of the iminium proton of compounds \( 80-82 \) at 10.17, 12.00, and 12.30 ppm, respectively. The IR and UV spectra of these compounds also confirm the presence of the dipolar structure\(^6\)\(^2\).

Bromination of the alkylaminonitroalkene \( 69 \) in the presence of pyridine gives the \( \alpha \)-bromo-\( \alpha \)-nitroaldimine \( 84 \). It is suggested\(^6\)\(^3\) that the intermediate in the formation of \( 84 \) is a dibromo compound which eliminates hydrogen bromide (equation 56).

\[
\begin{align*}
\text{(69)} & \quad \text{Br} \quad \text{CHCl}_3, \text{o}^\circ \text{C} \\
\text{t-Bu} - \text{N} - \text{CH} = \text{C} - \text{CH}_3 + \text{Br}_2 & \quad \text{Br} \quad \text{NO}_2 \quad \text{CHCl}_3, \text{pyridine} \\
\end{align*}
\]

\[
\begin{align*}
\text{t-Bu} - \text{N} - \text{CH} = \text{C} - \text{CH}_3 & \quad \text{Br} \quad \text{NO}_2 \quad \text{Br} \\
\text{t-Bu} - \text{N} - \text{CH} = \text{C} - \text{CH}_3 & \quad \text{Br} \\
\end{align*}
\]

\[
\begin{align*}
\text{(69)} & \quad \text{Br} \quad \text{NO}_2 \\
\text{(84)} & \quad \text{Br} \\
\end{align*}
\]

In contrast, bromination of the dipolar aminonitrocycloalkene \( 81 \), in the presence of pyridine, does not occur as expected at the carbonitrone group. Instead it occurs at C-6 of \( 81 \) to give \( 1 \)-nitro-\( 2\)-(\( \text{t-buty} \text{l} \)amino)-\( 3 \)-bromocyclohexane \( 85 \) which exists mostly in the dipolar structure. The position of the bromine atom is clearly defined in the NMR spectrum of \( 85 \) by a multiplet at 5.30 ppm due to the methine hydrogen. This peak is absent in the NMR spectrum of \( 81 \).
It is proposed$^{62a}$ that the enamine $\text{86}$, which is generated from $\text{81}$ on treatment with pyridine is involved in the formation of $\text{85}$ (equation 57). Compound $\text{85}$ also results from the bromination of the sodium salt of $\text{81}$ whose spectral data indicate that it exists in the enamine structure $\text{86}$. The NMR spectrum of the salt taken in $(\text{CD}_3)_2\text{SO}$, shows a triplet at 4.34 ppm and a singlet at 8.10 ppm for the vinyl and amino protons, respectively.

<table>
<thead>
<tr>
<th>Sulphonamide</th>
<th>$\alpha$-Nitrosulphonamide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{SO}_2-N$</td>
<td>$\text{O}_2\text{NCH}_2\text{SO}_2-N$</td>
<td>31</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{SO}_2-N$</td>
<td>$\text{CH}_3\text{CHNO}_2\text{SO}-N$</td>
<td>36</td>
</tr>
<tr>
<td>$(\text{CH}_3)_2\text{CHSO}_2-N$</td>
<td>$(\text{CH}_3)_2\text{CNO}_2\text{SO}_2-N$</td>
<td>46</td>
</tr>
<tr>
<td>$(\text{CH}_3)_2\text{CHCH}_2\text{SO}_2-N$</td>
<td>$(\text{CH}_3)_2\text{CHCHNO}_2\text{SO}_2-N$</td>
<td>39</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{CH(\text{CH}_3)SO}_2-N$</td>
<td>$\text{CH}_3\text{CH}_2\text{CNO}_2(\text{CH}_3)\text{SO}_2-N$</td>
<td>35</td>
</tr>
<tr>
<td>$\text{CH}_3\text{SO}_2\text{N}[\text{CH}(\text{CH}_3)_2]_2$</td>
<td>$\text{NO}_2\text{CH}_2\text{SO}_2\text{N}[\text{CH}(\text{CH}_3)_2]_2$</td>
<td>25</td>
</tr>
</tbody>
</table>

$^a$Reactants are used in equimolar amounts. The nitrating agent is $\text{CH}_3\text{CH}_2\text{ONO}_2$. 
3. n-Butyllithium

n-Butyllithium (87) has been used with varying success in the alkyl nitrate nitrations of active methylene compounds.

While potassium t-butoxide is found adequate for nitrating benzylic sulphonamides (Table 5), it is necessary to use the stronger base 87 in THF for aliphatic sulphonamides (Table 16). Its greater effectiveness might be due to the formation of the anion in larger amounts and this is actually demonstrated in deuterium exchange experiments28. When morpholine methanesulphonamide (88) is treated with an equimolar amount of 87 followed by deuterium oxide, 77% of 87 is α-deuterated. Similar treatment of 88 in potassium t-butoxide gives only 18% deuteration.

In contrast, nitrations of certain sulphones, such as benzyl phenyl sulphone and dibenzyl sulphone give much lower yields of the corresponding α-nitrosulphones with 87 than with potassium t-butoxide29.

The nitrations of the phenylhydrazine 58 (Table 13) in the 87-ether system gives 1-phenylazo-1-phenylpentane (89) as the major product (40%) and 59 as the minor product (30%); about 21% of 58 is recovered. The formation of 89 arises from a nucleophilic attack of 87 on the azomethine carbon of 58, followed by air oxidation64 (equation 58).

\[
\begin{align*}
58 & \xrightarrow{1 \text{ Bu-Li-} \text{Et}_2\text{O}} \text{Bu-}n \+ \text{PhCH-} \text{NH} \+ \text{NPh} \\
& \xrightarrow{2 \text{ n-PrONO}_2} \text{Bu-}n \+ \text{PhCH-} \text{N} \text{NPh} \\
& \xrightarrow{3 \text{ H}^+} \text{PhCH-} \text{N} \text{NPh} \\
& \text{Bu-}n \\
& \text{PhCH-} \text{N} \text{NPh} \text{ (89)} \\
& \text{Bu-}n \\
& \text{PhCH-} \text{N} \text{NPh} \text{ (89)} \\
\end{align*}
\]

A similar addition on the azomethine carbon takes place when 87 in n-hexane is used as the base in the nitrations of aldimine 72. The product of the reaction (40%) is (N-t-butyl)-4-amino-octane (90) (equation 59).

\[
\begin{align*}
72 & \xrightarrow{1 \text{ n-BuLi-} \text{n-C}_6\text{H}_{14}} \text{NHBu-t} \\
& \xrightarrow{2 \text{ n-PrONO}_2} \text{CH}_3(\text{CH}_2)_2\text{CH}(\text{CH}_2)_3\text{CH}_3 \\
& \xrightarrow{3 \text{ H}^+} \text{NHBu-t} \\
& \text{CH}_3(\text{CH}_2)_2\text{CH}(\text{CH}_2)_3\text{CH}_3 \text{ (90)} \\
& \text{NHBu-t} \\
\end{align*}
\]

4. Lithium diisopropylamide

There are a few reports which describe the use of lithium diisopropylamide (91) as the base in nitrations reactions. Dideprotonation of carboxylic acids with 91 in THF and hexamethyldiphosphoramidc (HMPA) as cosolvents leads to dilithium salts of carboxylic acids which on subsequent treatment with n-propyl nitrate and acid are converted into nitroalkanes65 (equation 60).

The nitroaldimine 92 is obtained in 29% yield when 72 is nitrated with n-propyl nitrate in lithium diisopropylamide–THF (equation 61). In potassium amide the yield is 51% (Table 15).

Nitrations66 of alkylphosphonate dibutyl esters (93) with 91 as the base leads
directly to 1-nitroalkylphosphonates \((94)\). As in the case of carboxylic esters the nitration reaction of \((93)\) gives, in addition to \((94)\), cleavage products, namely, nitroalkanes and trialkyl phosphates \((\text{equation } 62)\). It is very likely that the cleavage reaction occurs by the mechanism shown in Scheme 1 except for the steps leading to transesterification, which is not observed in the nitration of \((93)\). Scheme 1 is supported by the observations that one of the fragmentation products, the trialkyl phosphate, is isolated prior to acidification, and that \((94)\) is quantitatively regenerated from its sodium or lithium salts on acidification with acetic acid.

In contrast to carboxylic esters, potassium amide has been found to be unsuitable as the base in the preparation of \((94)\) because it causes transamidation. Diethyl ethylphosphonate, for example, is converted to ethyl \(P\)-ethylphosphoramidate \((95)\) in 60% yield \((\text{equation } 63)\).

\[
\text{EtP(O)(OEt)}_2 + \text{K NH}_2 -> \text{EtP(O)(OEt)} + \text{NH}_2 \text{Cl} \]

\((95)\)

60%

### B. Intramolecular Alkyl Nitrate Nitration

The occurrence of an intramolecular nitration has been demonstrated \(^{67}\) with 10-nitro-2-nitratocamphane \((96)\). Treatment of \((96)\) with potassium hydroxide followed by acidification gives 10,10-dinitro-2-camphanol \((97)\) \((\text{equation } 64)\).
19. Alkyl nitrate nitrations

III. RELATED REACTIONS

A. Tetranitromethane

In alkaline media, tetranitromethane (98) is effective as a nitrating agent for aliphatic nitro compounds and for aromatic systems. Primary nitroalkanes and gem-dinitroalkanes are converted into dinitroalkanes and trinitroalkanes, respectively.

The reaction of p-cresol with 98 in a pyridine–ethanol mixture gives m-nitrocresol (60%) and pyridinium trinitromethide. Under similar reaction conditions in pyridine–acetone, isosafrole has been converted into β-nitroisosafrole (72%) (equation 65) and anethole into β-nitroanethole (64%)69. The reaction seems to be specific for conjugated arylalkenes. Nitration does not occur if the unsaturation in the arylalkene is in the allylic position70. Without additional base, 98 reacts with N,N-dialkyl-p-toluidines to give salts of trinitromethane and m-nitro-N,N-dialkyl-p-toluidines, which on treatment with base are converted into m-nitro-N,N-dialkyl-p-toluidines69.

A recent study of the kinetics and mechanism concerning the reaction of 98 with phenols in water and in 95% ethanol gives good indication of an electron-transfer process71.

The nitration of tyrosine with 98 affords 3-nitrotyrosine quantitatively at pH 8–9. At higher pH, 98 undergoes decomposition and below pH 7 no significant nitration occurs. The reaction seems to be highly specific72. Tryptophan and tryptophanyl peptides are unaffected by 98.

Azulene (99) and its derivatives are readily nitrated with 98 in the presence of pyridine. 99 is converted to 1-nitroazulene (81%)73, 2,4,8-trimethylazulene to 1-nitro-2,4,8-trimethylazulene (85%)74, and 1,3-di-r-butylazulene into 5-nitro-1,3-di-r-butylazulene (39%)75. A mixture of 5-nitro- and 7-nitrocyclopenta[b]thiapyran is obtained on treatment of the cyclopenta[b]thiapyran-1,3,5-trinitrobenzene addition compound with 98 and pyridine76.

B. Fluorotrinitromethane

Fluorotrinitromethane (100) in alkaline medium can function as a nitrating agent. 2,4,6-Trinitrotoluene on treatment with 100 and potassium hydroxide is converted in 89% to α,2,4,6-tetranitrotoluene (equation 66). The reaction is unsuccessful with 98 or alkyl nitrates77.
C. Methyldinitramine

Salts of primary nitroalkanes are converted into *gem*-dinitroalkanes on treatment with methyldinitramine (101) (equation 67). On similar treatment, secondary nitroalkanes undergo oxidative dimerization.

\[ \text{RCH}_2\text{NO}_2 + \text{MeN(NO}_2)_2 \xrightarrow{\text{KOH, MeOH, 0\text{--}20^\circ\text{C}}} \text{RC(NO}_2)_2^- + \text{MeNNO}_2^- + \text{K}^+ \]

(101)

\[ R = \text{H (34%), Me (47%), Et (55%), CH}_2\text{OH (45%)} \]

D. Intramolecular Alkyl Nitrations

The transformation of 1,1,1,3-tetranitroalkanes to 1,1,3,3-tetranitroalkanes on treatment with weak bases may be considered as an intramolecular alkyl nitrations. 1,1,1,3-Tetranitropropane (102, \( R = \text{H} \)) and the two higher homologues, for example, have been isomerized to the corresponding 1,1,3,3-tetranitro compounds in yields of \( \sim 35\% \) (equation 68). The isomerization of 102 is accompanied by an elimination reaction giving rise to the potassium salt of 1,1,3-trinitro-2-propene.

\[ (\text{NO}_2)_3\text{C}--\text{CH}--\text{CHNO}_2\text{R} \xrightarrow{\text{NH}_3, \text{EtOH}} \left[ \begin{array}{c} \text{CH}_2--\text{CHR} \\ \text{O} \end{array} \right] \xrightarrow{\text{KCl}} \left[ \begin{array}{c} \text{NO}_2 \\ \text{O}_2\text{N}--\text{C}--\text{CH}_2--\text{C}--\text{R} \end{array} \right] + 2\text{K}^+ \]

(102)

\[ R = \text{H (33%), Me (35%), Et (35%)} \]

1,1,1,3-Tetranitro-2-alkylpropanes do not undergo the isomerization reaction on treatment with base. Instead they undergo a retrograde Michael reaction with the formation of trinitromethide ion and the nitroalkene (equation 69).

\[ (\text{NO}_2)_3\text{C}--\text{CH}--\text{CH}_2\text{NO}_2 \xrightarrow{\text{B}^-} (\text{NO}_2)_3\text{C}^- + \text{RCH}--\text{CHNO}_2 \]

(69)

\[ R = \text{Me, Et, n-Pr} \]

\[ B = \text{--OH, --OCH}_3, \text{--OCOCH}_3, \text{C}_5\text{H}_5\text{N} \]

IV. ALKYL NITRATE NITRATION OF AMINES

A. Introduction

The first successful preparation of an aromatic nitramine by the alkyl nitrate nitrations is due to Angeli who converted aniline to phenyl nitramine with ethyl nitrate in the presence of sodium. Bamberger improved the procedure by replacing sodium with sodium ethoxide. This method of preparing aromatic nitramines...
19. Alkyl nitrate nitrations

avoids the rearrangement to \(o\)- and \(p\)-nitroarylamines which occurs on nitrination under the usual acidic conditions\(^{85}\).

A disadvantage of the nitrination of aromatic as well as aliphatic amines with alkyl nitrates lies in their ability to function also as alkylation agents; that is, nucleophilic attack of the amine occurs on carbon instead of on the nitrogen of the ester\(^{86}\). In recent years, however, these disadvantages have been somewhat overcome by the use of a unique nitrating agent\(^{87}\) such as \(\text{12}\) (Section II.A.1.c). and also by employing lithium bases in the conversion of the amine to its conjugate base\(^{88}\).

B. Nitration with Cyanohydrin Nitrates

Primary and secondary amines are converted in good yields to the corresponding nitramines using \(\text{12}\). During the nitrination reaction, the hydrogen cyanide and acetone produced react with the excess amine to form the corresponding aminonitrile (equation 70).

\[
R^1R^2\text{NH} + \text{12} \rightarrow R^1R^2\text{NNO}_2 + [\text{HCN} + \text{Me}_2\text{CO}]
\]

\[
R^1\text{R}^2\text{N} - \text{CMe}_2
\]

\[
R^1 = R^2 = \text{Me} (76\%), \text{Et} (60\%), \text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2 (64\%)
\]

\[
R^1 = \text{H}, R^2 = n-\text{Pr} (50\%)
\]

\[
R^1 = \text{H}, R^2 = n-\text{Bu} (52%)
\]

In the reaction with secondary amines, the amine is used in a fivefold excess, functioning as its own solvent. The reactivity of the primary amines is, however, affected by the solvent. In solvents with low dielectric constant yields do not exceed 20–25%. The yields are doubled in refluxing THF or acetonitrile.

It must be emphasized that nitrations with \(\text{12}\) are unsuccessful with aromatic amines and aliphatic amines with branching on the \(\alpha\)-carbon atom. The failure of the latter to undergo reactions might be steric in nature. However, even nitrate esters such as cyclopentanone cyanohydrin nitrate and the next higher homologue, for which interference would be decreased, fail to react with diisopropylamine or cyclohexylamine\(^{87}\).

C. Nitration with Alkyl Nitrates in the Presence of Lithium Bases

Aromatic nitramines have been prepared\(^{88}\) using phenyllithium as the base and amyl nitrate as the nitrating agent. The yields do not exceed 40%. The procedure is difficult to evaluate because the nitramines are not isolated as such but converted directly to the corresponding \(\text{N-methyl-N-nitroanilines}\). \(p\)-Toluidine is converted to \(\text{N-nitro-N-methyl-p-toluidine}\) in 44% yield, the latter is also obtained from nitrating the secondary amine, \(\text{N-methyl-p-toluidine}\) (35%) directly.

By a similar procedure, but using butyllithium \(^{87}\) and ethyl nitrate, \(\text{N-methyl-l-naphthylamine}\) and \(\text{1-naphthylamine}\) have been converted into the corresponding nitramines in yields of 60% and 65%. The yield of the \(\text{N-nitro-1-naphthylamine}\) is based on its barium salt. The free nitramine which is highly unstable has been obtained on acidifying the salt with carbon dioxide\(^{89}\). Employing \(\text{87}\) or phenyllithium and ethyl nitrate has made it feasible to prepare nitramines from aliphatic amines and also from amines with branching on the
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Henry Feuer

\[ R^1\text{NH}_2 \xrightarrow{1 \text{ R}^2\text{Li}} \xrightarrow{2 \text{ EiONO}_2} R^1\text{NHNO}_2 \]  

(71)

\[
R^1 = \text{Me (35\%), i-Pr (58\%), n-Bu (49\%), s-Bu (45\%), t-Bu (37\%)}
R^2 = \text{n-Bu or Ph}
\]

α-carbon atom \(^\text{\footnote{}}\) (equation 71). Isopropylamine is converted to isopropylnitramine in 58% when the ratio of amine to base to nitrate is 2:2:1 in an ether–hexane mixture (2:1 by volume). Essentially, the procedure is a one-step process. The nitramine is obtained directly upon acidification.

The main disadvantage of the method is that amines bearing functional groups which might react with the base \(^\text{87}\) do not form nitramines.

D. Nitration with Methylidinitramine (101)

Compound 101 is reported \(^{78}\) to convert primary and secondary amines to the corresponding nitramines (equation 72).

\[ R^1 R^2\text{NH} + 101 \xrightarrow{\text{THF}} 0{-20}^\circ\text{C} R^1 R^2\text{NNO}_2 \]  

(72)

\[
R^1 = \text{H, R}^2 = \text{Pr (54\%), R}^1 = \text{R}^2 = \text{Et (74\%), R}^1, R^2 = (\text{CH}_2)_4\text{O (70\%)}
\]

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# Aminals

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The term aminal was introduced in 1956 to designate the aminated equivalents of acetals and mercaptals. Aminals are gem-diamines, i.e. the aminal function is characterized by the presence of two di- or mono-substituted amino groups on the same carbon atom. Although their existence has been known for some time, the properties of aminals have been explored only for about the past two decades.

The term ‘cyclic’ is used when the aminal function is part of a heterocycle. The term ‘open-chain’ is used in all other cases even if one amino group is a heterocyclic amine such as piperidine. Because they can be considered as derivatives of carbonyl groups, they are called aldoaminals or ketoaminals according to their structures.

Aminals occur in natural products. Among the most thoroughly investigated compounds, members of the indole and quinoline alkaloid families may be cited as examples. Thus, physostigmine (1), found in Calabar bean, and chimonanthine (2a) folicanthine (2b) and calycanthine (2c), which occur in various species of calycanthus and chimonanthys, contain the aminal function.

Capreomycidine (3) is a component of the antitubercular polypeptide antibiotics capreomycin, tuberactinomycin N and tuberactinomycin O.

The aminal function also occurs in derivatives of 5,6,7,8-tetrahydrofolic acid, responsible for transporting single carbon units in biosynthesis. In many organisms serine is the major precursor of single carbon units. The ϒ-carbon of serine is removed as formaldehyde via direct transfer to tetrahydrofolate with formation of aminal 4 (equation 1).

Literature references on aminals are presented in some review articles.
II. PREPARATION

Open-chain aminals with at least one α-hydrogen atom are easily decomposed into enamine and amine by heating\(^{195}\) (equation 2), therefore drastic methods must be avoided in the course of their preparation. Conversely, aminals in which α-hydrogen atoms are absent can be isolated without difficulty.
Most aminals are solid compounds. Morpholine is the most preferred secondary amine because of its aptitude to form crystallized derivatives. Aminals are relatively stable compounds, but in aqueous acid solution, they are immediately decomposed into carbonyl compounds and amines.

A. Condensation of Carbonyl Compounds with Amines

This method is the most widely used.

1. Open-chain aminals

(a) Aldoaminals. The condensation of secondary amines with aldehydes proceeds rapidly on mixing of the reagents in the absence or in the presence of a solvent such as ethanol or pyridine (equation 3). The yields become nearly quantitative by using a dehydrating agent such as anhydrous potassium carbonate, boric anhydride, drierite or molecular sieves, or by removal of water by azeotropic distillation with benzene. This last technique was originally employed for the preparation of steroidal enamines.

Aldoaminals have also been prepared by reaction with As(NR₂)₃ or with Sb(NMe₂)₃. They have been obtained more readily by action of secondary amines together with TiCl₄, SbCl₃, AsCl₃ in an inert solvent, employing a technique initially used in the preparation of sterically hindered enamines (equation 4). These methods are attempted when the simpler ones fail.

Aminals (5) are generally obtained by mixing an aqueous solution of formaldehyde and secondary amines. Many structural variations are known. The intermediary carbinolamine (6) can be isolated by using

\[
\begin{align*}
\text{O} & \quad + \quad 2 \text{ AsCl}_3 \quad + \quad 12 \text{ HNR}_2 & \quad \rightarrow & \quad \text{R}^1 \quad \text{NR}_2 \quad + \quad \text{As}_2\text{O}_3 \quad + \quad 6 \text{ H}_2\text{NR}_2 \cdot \text{Cl}^- \\
\end{align*}
\]

(4)
equimolecular quantities of reagents\textsuperscript{133,134,148,175,280,281}. The utilization of a different secondary amine permits the formation of an unsymmetric aminal (7)\textsuperscript{280,281,383,284}. Aminals 5 of the weakly basic aziridine are also easily obtained\textsuperscript{175}. Those of 2-methylaziridine are formed with a very low yield\textsuperscript{284}. With 2,2-dimethylaziridine, only the carbinolamine 6 can be isolated\textsuperscript{176}.

Aminal 8 is obtained via reaction of \(\beta\)-chloroethylamine with paraformaldehyde, in the presence of triton B\textsuperscript{37}, and aminals 9 from aqueous solutions of formaldehyde and \(N\)-alkylhydroxylamines\textsuperscript{282}. Compounds with \(\beta\)-chloroethylamino groups were used in the treatment of cancer\textsuperscript{37,152}.

\[
\text{(8)}
\]

\[
\text{(9)}
\]

Aminals of benzaldehyde and dimethylamine\textsuperscript{139,188,275}, pyrrolidine\textsuperscript{238}, piperidine\textsuperscript{180,243,247}, morpholine\textsuperscript{135} and hexahydroazepine\textsuperscript{254} are readily obtained. However, under the same conditions, the more sterically hindered diethylamine and diisopropylamine appear to be inactive\textsuperscript{68,238}.

Numerous aminals derived from substituted benzaldehydes and heterocyclic aldehydes such as 10 and 11 are known\textsuperscript{46,72,79,92,135,137}. The reactivity of the carbonyl group is largely dependent on the substitution. Thus, in the reaction of \(p\)-chlorobenzaldehyde, or \(p\)-dimethylaminobenzaldehyde, or mesitylcarbaldehyde with morpholine, in benzene with azeotropic water elimination, the reflux times and the yields are respectively 1 h(92\%), 72 h(96\%), 120 h(51\%)\textsuperscript{92}. The nitrogen of 2-pyrrolocarbaldehyde is involved in the reaction of this aldehyde with secondary amines leading to the aminal 12\textsuperscript{136,137}.

\[
\text{(10)}
\]

\[
\text{(11)}
\]

\[
\text{(12)}
\]

\[\text{NR}_2 = \text{N}, \text{O}, \text{OH}, \text{OMe}, \text{SMe}, \text{NMe}_2, \text{NO}_2\]

\[\text{Y} = \text{Me}, \text{Cl}, \text{OH}, \text{OMe}, \text{SMe}, \text{NMe}_2, \text{NO}_2\]

\[\text{X} = \text{O, S, NMe}\]

(Bis)aminals 13, 14\textsuperscript{47a} and 15\textsuperscript{112,172} and functional aminals 16\textsuperscript{186} and 17\textsuperscript{49} have been prepared from the corresponding nonenolizable aldehydes, and piperidine or morpholine. The reaction of aqueous glyoxal with \(N\)-methylaniline does not lead to an aminal, as in the case of piperidine or morpholine, but to the aminooindole 18\textsuperscript{172}.

For aminals with an \(\alpha\)-hydrogen atom, the general method of Mannich\textsuperscript{195} (reaction of an aldehyde with at least two secondary amine equivalents, in presence of
K₂CO₃ is still the most commonly used, with occasional modifications of details. Some examples have been also prepared by the As(NR₂)₃ and TiCl₄ or AsCl₃-HNR₂ methods. These techniques are particularly useful in the case of volatile secondary amines.

Many aminals of structure 19 and 20 have been isolated from simple aldehydes or from α-alkyl- or α-aryl-substituted aldehydes.

α-Haloaminals 21 are available from α-halo aldehydes: one α-fluoroaminal was obtained by direct amination and α-chloro and α-bromo compounds by the AsCl₃-HNR₂ method. For very reactive α-chloro and α-bromo aldehydes, direct amination leads to halogen substitution with formation of a dialkylaminoaminal, which can also be prepared from the corresponding α-amino aldehydes (equation 6). Aminals 23–26 have been obtained from the corresponding heterocyclic amino aldehydes.
20. Aminals

Some aminals of primary aromatic amines are known. The condensation of aqueous formaldehyde and aniline leads to aminal 27 or to hexahydrotriazine (28, R = Ph)\(^{15,220c,260,265}\) (equation 7).

\[
\begin{align*}
\text{(27)} & \quad \begin{array}{c}
\text{NHR} \\
\text{NHR}
\end{array} & \quad \text{H}_2\text{NR (10 eq.)} & \quad \text{H}_2\text{NR (2 eq.)} & \quad \text{(28)} \\
\text{(27)} & \quad \text{O} & \quad \text{H} & \quad \text{N} & \quad \text{R} & \quad \text{R} \\
\text{(27)} & \quad \text{NHR} & \quad \text{H} & \quad \text{N} & \quad \text{R} & \quad \text{R}
\end{align*}
\]

The aminal 29 is obtained when very pure reagents and strictly defined experimental conditions avoiding acidic contaminations are used\(^{107,199}\). With 2-aminopyridine, aminals 30 (R = Ph, alkyl) are described\(^{114,168,244,249,255}\), whereas with 3-aminopyridine, only the Schiff base is obtained. Primary aliphatic amines do not lead to stable aminals, but to hexahydrotriazines\(^{215}\). However, primary aliphatic amines allow the preparation of aminals 31 from carbinolamines 6\(^{280}\).

\[
\begin{align*}
\text{(29)} & \quad \begin{array}{c}
\text{NHPh} \\
\text{NHPh}
\end{array} & \quad \text{(30)} & \quad \text{(31)} \\
\text{(29)} & \quad \text{(30)} & \quad \text{(31)}
\end{align*}
\]

(b) *Ketoaminals.* Only a few aminals have been prepared from ketones which are directly converted into enamines when treated with secondary amines.

Cyclopropanone is exceptionally reactive. The reactivity of its carbonyl group can be compared with that of the highly reactive formaldehyde. Cyclopropanone reacts readily with secondary amines such as dimethylamine and piperidine providing aminals 32\(^{261}\). When treated with an equivalent of secondary amine, the primary reaction product 33 can sometimes be isolated. It leads to mixed aminal 34, accompanied by small quantities of the two symmetrical aminals\(^{272}\) (equation 8).

Upon adding methylamine to an ethereal solution of cyclopropanone, the cyclic aminal 35 (48%) and the hexahydrotriazine 36 (3%) have been isolated\(^{261}\).

Aminals 32 have also been prepared by reaction of amines with cyclopropanone ethylhemiketal (NR\(_2 = \text{NHPH}\)\(^{271}\)) or with cyclopropanone hydrate in presence of molecular sieves (NR\(_2 = \text{NMe}_2\)\(^{261}\)).
The cyclopropanone aminals 37 and 38 are very well known, because they were the first Favorski intermediates isolated in the reaction of nucleophiles with haloketones. These aminals were obtained by reaction of piperidine or pyrrolidine with α-chlorocycloheptanone or α-chlorocyclohexanone (equation 9).

Indeed, the haloenamines 39, suggested as likely intermediates, lead effectively to aminals 37 or 38 when treated with secondary amines or with a dimethylamine–AgBF₄ complex. In the last case, the yield is nearly quantitative.

Aminal 38 (NR₂ = N[O]) is also obtained by reaction of morpholine with a derivative of α-dimethylsulphonium cycloheptanone (40) by reflux in acetonitrile.

Ketoaminals 41 and 42 have been synthesized by amination of the corresponding ketones, in the presence of TiCl₄. Aminals 42, characterized among other open-ring products, are generated with moderate yields (11–43%). Treatment of cyclopentanone with aziridine without TiCl₄ affords no aminal, but rather the imine 43.

The condensation of difluoroamine with ketones and aldehydes on reflux in the presence of sulphuric acid yields the corresponding aminals.
2. Cyclic aminals

The condensation of N,N'-disubstituted 1,2- or 1,3-diamines with aldehydes is simple and leads to 1,2,3-trisubstituted imidazolidines (44) or hexahydropyrimidines (45). The reaction is easier with 1,2-diamines, but does not occur with ketones.

(a) Imidazolidines. Since the solid derivatives are generally facile to purify and have sharp melting points, many 1,2-diamines have been proposed in the past for the rapid determination of aldehydes. Particularly useful are the 1,2-dianilinoethanes 46 (X = H, OMe, OEt, CI, Br, OMe, OEt, CI, Br). Other 1,2-diamines such as 47 (R = alkyl, benzy1, OMe, OEt) and the optically active 49 have also been tested.

1,2-Dianilinoethane (the Wanzlick reagent) is the most widely used. In methanol, the crystalline imidazolidine generally precipitates immediately after addition of a few drops of acetic acid.

Many cyclic aminals have been prepared with functional aldehydes. Imidazolidines 50 are obtained from α-substituted aldehydes (X = Cl, Br, OMe, N, O) \(^{103,239}\). However, for the hindered compound 51, the utilization of TiCl\(_4\) is necessary.\(^{239}\)
Aminals 52 have been prepared, from formaldehyde and the corresponding diamines, as model substances to study the mechanism of methylene transfer from tetrahydrofolic acid. The intermediary of an iminium cation in the formation of aminal 52 has been demonstrated\(^7\)\(^\text{--}\)\(^9\) (equation 10).

\[ X = \text{Me, Cl, CO}_2\text{Et} \]

Simple ketones do not react with 1,2-diamines (although an imidazolidine derived from acetone has been described\(^\text{11}\)) but α-halo- and α-hydroxy-ketones are directly transformed into tetrahydropyrazines\(^\text{103,121,194}\) such as 53 (equation 11), whereas α-dialkylaminoketones provide imidazolidines 54 (\(R^1 = \text{Me, Ph}\)), only in the presence of TiCl\(_4\)\(^\text{103}\).
(b) Hexahydropyrimidines. The condensation with \(N,N'\)-disubstituted 1,3-diamines is somewhat slower, yet many hexahydropyrimidines 45 have been prepared from aliphatic \(22,23,24,259\) and functional \(229\) aldehydes. The \(^1H\)-NMR spectrum of cyclic aminal 45a shows a \(\Delta \delta_{c-a} = 1.70\) ppm between the equatorial and axial protons \(H_e\) and \(H_a\). It is well established that a lone electron pair deshields an \(\alpha\)-proton in a gauche relationship with it relatively more than one in an anti position. In compound 45a, an important effect is observed because two lone pairs are antiperiplanar to \(H_a\) and gauche to \(H_e\)\(118\). The Tröger base 55 was obtained from formaldehyde and \(p\)-toluidine\(242\); it has been resolved chromatographically, by use of lactose, into the optically active isomers\(224\).

(c) \(1,3,4\)-Triazines. Hexahydro-1,3,5-triazines are obtained by trimerization of very reactive imines. Compounds 56 are prepared with cyclic imines, proceeding from \(N\)-chloropiperidine\(236\) or from pyrrolidine\(212\) (equation 12).

\[
\begin{align*}
\text{(12)}
\end{align*}
\]

We have already mentioned triazine 28 in the condensation of formaldehyde with primary amines.

Reactions of aliphatic aldehydes with aqueous ammonia\(221\a\) at \(-10^\circ\)C leads instantly to very unstable low-melting \(1\)-amino-\(1\)-alkanol hydrates 57 which upon standing in the same medium at \(0\) to \(5^\circ\)C are converted to hexahydrotriazines 58, usually isolated as hydrates\(210\) (equation 13). The triazine hydrate of isovaleraldehyde contains 24 water molecules (mass of water equal to nearly twice that of triazine); some of these triazine hydrates are the 'aldehyde ammonias' described by early workers. The first example, acetaldehyde ammonia, was discovered by Liebig in 1835\(189\). Delepine\(72-77\) was the first to suggest the correct structure 58 (\(R = Me\)) later confirmed by X-ray crystallographic studies\(196,211\). NMR studies of the anhydrous product indicate only one epimer having all alkyl groups equatorial\(210\).
When formaldehyde reacts with ammonia, the initially formed hexahydrotriazine reacts producing hexamethylenetetramine (59) (equation 74).

1,3,5-Triazaadamantane 61 is obtained by condensation of the triamines 60 (equation 15) and formaldehyde \((R = \text{Me}^{245}, \text{NO}_2^{143})\). 1,3-Diazaadamantane 63 is the product of diamine 62 and formaldehyde\(^{246}\) (equation 16).

B. Substitution of Dihalo Compounds by Amines

This important method (equation 17) has been used to prepare open-chain aminals containing no \(\alpha\)-hydrogen atoms. The amino groups are tertiary – generally morphilino or piperidino groups\(^{162,167}\).

When an \(\alpha\)-hydrogen atom is present in the dihalo compound, elimination occurs (equation 18). Likewise, the reaction of secondary amines with gem-dihalo-cyclopropanes leads to \(\beta\)-bromoallylamines by a ring-opening reaction\(^{179,231}\) (equation 19).
When the amine is in excess, formation of aminals takes place according to the $S_N2$ mechanism, and the reactivity of halogens is as expected $\text{Cl} < \text{Br} < \text{I}$.

1. Aldoaminals

Many aldoaminals 10 and 17 ($R = \text{Ar, } \tau\text{-Bu, 2-thienyl}$) have been prepared with excellent yields from substituted dihalomethylbenzenes$^{139,160}$ or $\alpha,\alpha$-dihaloketones$^{49,124,159,160,182,262}$.

Numerous aminals are obtained from dichloracetic acid derivatives: ester 16 from ethyl dibromoacetate, acid 64 from dichloroacetic acid, nitrile 65 from dibromoacetonitrile$^{160,162,163,186}$, amide 66 from methyl dichloroacetate, by condensation of secondary amine on the ester function arising simultaneously with substitution of the halogens, $(\text{NR}_2 = \text{NR}_2)^{127,128}$ or from dichloroacetyl chloride$^{83,96}$.

Reduction by $\text{LiAlH}_4$ of the amide function of aminal 66 leads to an $\alpha$-aminoaminal 67$^{83,96}$ which can also be readily prepared from $N,N$-dialkyltrichloroacetamides (68)$^{129}$ (equation 20).
Di- and tri-aminals 69–72 have been prepared from polymethylbenzenes via the corresponding dibromomethyl compounds (equation 21).

\[
\begin{align*}
(69) & \quad R_2N-NR_2 \\
(70) & \quad R_2N-NR_2 \\
(71) & \quad R_2N-NR_2 \\
(72) & \quad R_2N-NR_2
\end{align*}
\]

Compounds with two ortho aminal functions are readily partially hydrolysed. Thus aminal 70 can only be prepared under strictly anhydrous conditions. Otherwise, compound 73 is obtained. Similarly, the compound 74 is isolated on amination of octabromodurene.

\[
\begin{align*}
(73) & \quad R_2N-NR_2 \\
(74) & \quad R_2N-NR_2
\end{align*}
\]

2. Ketoaminals

Amination of dihalo compounds allows the preparation of many ketoaminals, such as 75, 76 and 77, which cannot be directly obtained from the corresponding ketones.

Transformation of β-dicarbonyl compounds into aminals 77 can be carried out without isolation of the dihalo compounds. When bromine is added to a solution of an active methylene compound in excess of an amine the dibromo compound is aminated as soon as it is formed (equation 22).

\[
\begin{align*}
(75) & \quad Ph-NR_2 \\
(76) & \quad Ph-\text{EtO}-\text{NR}_2
\end{align*}
\]
20. Aminals

\[
\begin{align*}
R^1 &= R^2 = \text{OMe, OEt, Me, Et} \\
R^1 &= \text{Me, Ph}; R^2 = \text{OEt, Me} \\
R^1, R^2 &= \text{Ph}
\end{align*}
\]

C. Addition of Amines to Iminium Salts

Reactions of secondary amines with iminium salts allow the preparation of mixed aminals such as 78 (X = H\textsuperscript{17,18}, Me, Cl\textsuperscript{38} (equation 23)). The condensation of 2,4,6-trichloro- (or trimethyl-)N-methylaniline with formaldehyde or with dichloromethane has been unsuccessful.

\[
\begin{align*}
\text{N}^+ \text{Br}^- + X^- \overset{\text{Br}_2}{\longrightarrow} \begin{array}{c}
\text{R}^1 \\
\text{R}^2
\end{array} \begin{array}{c}
\text{O} \\
\text{Br}
\end{array} \\
\overset{HNR_2}{\longrightarrow} \begin{array}{c}
\text{R}^1 \\
\text{R}^2
\end{array} \begin{array}{c}
\text{O} \\
\text{Br}
\end{array}
\end{align*}
\]

Aminals 15 \(\text{NR}_2 = \text{N}^-, \text{N}^=\) have been prepared by reaction of secondary amines with diiminium salts obtained by oxidation of 1,2-diaminoethylenes\textsuperscript{85,88} (equation 24).

\[
\begin{align*}
R_2N-N\overset{\text{Br}_2}{\longrightarrow} R_2N-N \overset{2\text{Br}^-}{\longrightarrow} R_2N-N\overset{HNR_2}{\longrightarrow} \begin{array}{c}
\text{NR}_2 \\
\text{NR}_2
\end{array}
\end{align*}
\]

With α-haloiminium salts, secondary amines lead to α-haloaminals 21 (R\textsuperscript{1} = t-Bu, X = Cl\textsuperscript{95-100}, or to α-aminoaminals 22 when the halogen is more reactive and the R\textsuperscript{1} group is less crowded (X = Br, R\textsuperscript{1} = Ph)\textsuperscript{97} (equation 25).

α,α-Dihaloaminals 79 have also been prepared from α,α-dihaloiminium salts obtained by halogenation of β-haloenamines or of the corresponding enamines (X = H), in the presence of two halogen equivalents and a tertiary amine\textsuperscript{222} (equation 26).
Presumably, iminium ion intermediates are also involved in reactions (27) and (28) yielding cyclic aminals 80\textsuperscript{130} and spiroaminals 81\textsuperscript{58}.

\begin{equation}
\text{R}_1^1 \text{NR}_2^1 + \text{RNH} \xrightarrow{\text{HNR}} \text{R} - \text{N} - \text{N} - \text{R} \quad (80)
\end{equation}

\begin{equation}
\text{R}_2^2 \text{NR}_2^2 \xrightarrow{\text{H}_2\text{O}^+} \text{R}^1\text{R}^1\text{N} - \text{R}^2 - \text{R}^2\text{N} - \text{R}^1 \quad (81)
\end{equation}

\textbf{D. Synthetic Methods}

Aminals have also been prepared by formation of a new C—C bond, when the amidinium salt 82, tris(dialkylamino)methane or tetra(dialkylamino)ethylene react with compounds containing nucleophilic carbon atoms (equation 29). Mechanistic
considerations suggest that the reactions of all three compounds proceed via the same amidinium salt 82.

Thus the aminal 83 has been prepared by reaction of phenyllithium with the formamidinium chloride isolated from the reaction of an acid halide with a triaminomethane85.

\[
\begin{align*}
\text{PhLi} & \quad \text{Ph} \quad \text{N-Ph} \\
& \quad \text{N-Ph} \quad \text{IPh} \\
& \quad \text{CI-} \quad \text{Ph-(N-Ph)} \quad (30)
\end{align*}
\]

Tris(dimethylamino)methane or bis(dimethylamino)-t-butoxymethane react with acetylenic carbon acids such as phenylacetylene or hydrogen cyanide leading to aminals 84 (equation 31) or 65 (NR₂ = NMe₂)55,277.

\[
\begin{align*}
\text{N} & + \quad \text{R-C≡C-H} \\
& \quad \text{N} \quad \text{R-C≡C-N} \quad (31)
\end{align*}
\]

\[\begin{align*}
\text{X} = \text{N} \quad \text{t-BuO} ; \quad \text{R} = \text{Ph}, \text{n-Bu}
\end{align*}\]

The condensation of tris(dimethylamino)methane with weaker carbon acids such as fluorene (pKₐ 25) or xanthene (pKₐ 29), although slower, yields the expected aminals 85 and 86276.
Electron-rich olefins such as 87 or tetramorpholinoethylene react with proton sources with cleavage of the central C=C double bond\textsuperscript{140-142,267}. Protonation of the double bond is probably the initial step, followed by decomposition into a cation and a carbene. The cation reacts with the nucleophile and the carbene can dimerize to give the starting olefin\textsuperscript{140} (equation 32).

\[
\text{H}^+ \quad (87) \quad \xrightarrow{} \quad \begin{array}{c} \text{N} \\ \text{R} \end{array} + \begin{array}{c} \text{N} \\ \text{R} \end{array} \quad (32)
\]

Aminals 88–92 have been prepared from olefin 87 and nitromethane\textsuperscript{257,267}, sulphones\textsuperscript{268}, cyclopentanone\textsuperscript{267}, 2,6-disubstituted phenols and 2-methylindole\textsuperscript{140,142,220b}.

Olefin 87 also reacts with aldehydes to give compounds 93\textsuperscript{267} formally regarded as 'C—H insertion products' (equation 33). Since the aldehydic hydrogen possesses practically no acidity, the initial step is probably electrophilic attack on the double bond by the carbonyl carbon atom\textsuperscript{140}.

\[
87 + \begin{array}{c} \text{R}^{1} \\ \text{O} \end{array} \quad \xrightarrow{} \quad \begin{array}{c} \text{N} \\ \text{R} \end{array} \quad \text{H} \quad \begin{array}{c} \text{N} \\ \text{R} \end{array} \quad (93) \quad (33)
\]

\[
X = \begin{array}{c} \text{R}^{1} \\ \text{O} \end{array}
\]
Ketoaminal 75 has been noted in the reaction of phenylmagnesium bromide with 1,3-benzodioxole derivatives (equation 34).

\[
\begin{array}{c}
\text{PhMgBr} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{NR}_2 \\
\text{NR}_2 \\
\text{OH} \\
\text{OH} \\
\text{Ph} \\
\text{Ph} \\
\text{NR}_2 \\
\end{array}
\quad
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{OH} \\
\text{OH} \\
\text{Ph} \\
\text{Ph} \\
\text{NR}_2 \\
\end{array}
\quad
\text{(75)}
\]

\text{(34)}

E. Reduction of Amidines and Amidinium Salts

The reduction of amidines to aminals is effected by Na–EtOH–NH₃, and provides a route to aldehydes. Unsubstituted amidines give the highest yields (equation 35).

\[
\begin{array}{c}
R-\text{NH} \\
\text{NH}_2 \\
\end{array}
\quad
\begin{array}{c}
R-\text{NH} \\
\text{NH}_2 \\
\end{array}
\quad
\begin{array}{c}
R-\text{CH} \quad (35)
\end{array}
\]

Amidinium salts react readily with sodium hydride to give aminals (equation 36). This reaction is one of the few known cases in which NaH smoothly reduces an organic compound.

\[
\begin{array}{c}
\text{Ar} \\
\text{N} \\
\text{Ar} \\
\text{N} \\
\text{X} \\
\end{array}
\quad
\begin{array}{c}
\text{Ar} \\
\text{N} \\
\text{Ar} \\
\text{N} \\
\text{Ar} \\
\end{array}
\quad
\begin{array}{c}
\text{NaH/MeO} \\
\text{OMe} \\
\end{array}
\quad
\begin{array}{c}
\text{Ar} \\
\text{N} \\
\text{Ar} \\
\text{N} \\
\text{Ar} \\
\end{array}
\quad
\text{(36)}
\]

Reduction of amidinium salts by NADPH also occurs in the reversible enzymatic formation of aminal 4 from a N-formyl derivative (equation 37). This reaction has also been studied with model compounds.

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{N} \\
\text{NR} \\
\text{R} \\
\end{array}
\quad
\begin{array}{c}
\text{N} \\
\text{H} \\
\end{array}
\quad
\text{NADPH} \\
\text{NAD}^{+}
\quad
\text{(4)}
\quad
\text{(37)}
\]

III. FORMATION OF AMMONIUM AND IMINUM SALTS

The presence of the two amino groups of an aminal such as 5 allows, with a suitable X–Y reagent, the formation of a monoammonium salt 94 or a biammonium salt 95 (equation 38). The presence of an electron acceptor group
NR₂ and an electron donor group NR₂ on the same carbon of the monoammonium salt 94 facilitates the cleavage of one C—N bond, with formation of an amino compound 96 and either an ionic derivative 97 or a covalent derivative 98. These compounds can also directly result from electrophilic attack of X—Y on aminal 5 (equation 39). We have used the iminium salt structure for the ionic compound 97, although in fact the positive charge is displaced between the carbon and nitrogen atoms. Formation of the ionic structure 97 in preference to the covalent structure 98 is directly proportional to the basicity of NR₂ and indirectly proportional to the basicity of X. Ionic and covalent compounds 97 and 98 are both very reactive.

Iminium salts participate in many reactions. Even before their preparation had been achieved, they were postulated as intermediates.

### A. Mono- and Bi-ammonium Salts

Monoammonium salts 94a, b and c are obtained by reaction of aminal 5

\[
\text{NR}_2 = N, NMe_2 \text{ with one equivalent of HCl, HBr, methyl bromide or }
\]

\[
\begin{align*}
\text{H} & \quad \text{CH}_3 & \quad \text{Cl} \\
\text{NR}_2 & \quad \text{NR}_2 & \quad \text{NR}_2 \\
\text{X}^- & \quad \text{X}^- & \quad \text{Cl}^- \\
\text{NR}_2 & \quad \text{NR}_2 & \quad \text{NR}_2 \\
\end{align*}
\]
halogen \((\text{Cl})_2\) in a non-polar aprotic solvent such as ether in which they precipitate.

Biammonium salts mentioned in the literature prior to 1953 were erroneously identified\(^{19}\). However, in polar solvents such as dimethylformamide or acetonitrile where monoammonium salts 94 are soluble, biammonium salts 95a and b can be prepared\(^{41}\) (equation 40).

\[
\begin{align*}
\text{NR}_2 & \quad \text{HCl} \quad \text{DMF or MeCN} \\
\text{NR}_2 & \quad \text{Me/MeCN} \quad \text{MeBr/DMF} \\
\text{NR}_2 & \quad \text{D}^+\text{BF}_4^- \quad \text{NO}_2\text{Me} \\
\text{NR}_2 & \quad 2 \text{X}^- \\
\end{align*}
\]

\((95a) \quad (5) \quad (95b) \quad (40)\)

\[
\begin{align*}
\text{NR}_2 &= \quad \text{N} \quad \text{N} \\
X &= \quad \text{Br, I, BF}_4^- \\
\end{align*}
\]

Similarly, mono- and bi-ammonium salts of imidazolidine \((44)\)\(^{48}\) and hexahydropyrimidine \((99)\)\(^{42}\) have been described (equation 41).

\[
\begin{align*}
\text{H}^- & \quad \text{N}^- \quad \text{N}^- \quad 2 \text{Cl}^- \\
\text{H}^- & \quad \text{N}^- \quad \text{N}^- \\
\text{H}^- & \quad \text{N}^- \quad \text{N}^- \quad 2 \text{I}^- \\
\end{align*}
\]

\((99) \quad (41)\)

Triammonium salts have been isolated when hexahydrotriazines 28 are treated with three equivalents of hydrogen chloride\(^{229}\) (equation 42).

\[
\begin{align*}
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} & \quad \text{R} \\
\end{align*}
\]

\((28) \quad (42)\)

Cyclic ammonium salts 101 are directly formed from aminals 100 possessing a halogen in a suitable position\(^{37}\) (equation 43).

Monoammonium salts are likewise obtainable by reaction of iminium salts 97a with tertiary amines\(^{39}\). In the case of \(\text{N}^-\text{alkylaziridines}\) or of \(\beta\)– or \(\gamma\)-chlorodialkylamines, the initially isolated monoammonium salts 102 or 104 can rearrange into cyclic mono- or bi-ammonium salts 103 or 105\(^{36,42}\) (equation 44).
Ammonium salts are hygroscopic and unstable. Generally, they have been isolated by working in the cold to avoid their transformation into iminium salts.

Formation of an ammonium salt by reaction of hexamethylenetetramine with primary halides is the first step of the Delepine synthesis of primary amines and the Sommelet synthesis of aldehydes (equation 45).

\[ \begin{align*}
\text{Ar} & \quad \text{AcOH, H$_2$O} \\
\text{Ar} & \quad \text{HCl, EtOH} \\
\end{align*} \]

B. Iminium Salts

1. Open-chain aminals

The monoammonium salt 94c obtained by chlorination of the aminal 5 at \(-50^\circ\text{C}\), undergoes decomposition at room temperature into the iminium chloride 97a and \(N\)-chlorodialkylamine \textsuperscript{20,21} (equation 46). The cleavage of aminals has been achieved by means of a large variety of compounds (Table 1).

Van't Hoff \(i\) factors near 4 have been reported in cryoscopic studies on aminals 5 at 0.02 M concentrations in concentrated sulphuric acid\textsuperscript{110}. The results agree with
TABLE 1. Compounds YX used for the formation of iminium salts

<table>
<thead>
<tr>
<th>Y—X</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>H—X</td>
<td>Hydrogen halides</td>
</tr>
<tr>
<td>Cl—Cl</td>
<td>Halogens</td>
</tr>
<tr>
<td>NC—Br</td>
<td>Cyanogen bromide</td>
</tr>
<tr>
<td>RCO—X</td>
<td>Acyl halides</td>
</tr>
<tr>
<td>RCOOC—Cl</td>
<td>Alkyl chlorocarbonates</td>
</tr>
<tr>
<td>Cl2O—Cl</td>
<td>Phosgene</td>
</tr>
<tr>
<td>ClSO2—Cl</td>
<td>Sulphonyl chlorides</td>
</tr>
<tr>
<td>Cl2SO—Cl</td>
<td>Sulphuryl chloride</td>
</tr>
<tr>
<td>Cl2S—Cl</td>
<td>Thionyl chloride</td>
</tr>
<tr>
<td>R2NS—Cl</td>
<td>Aminosulphur chlorides</td>
</tr>
<tr>
<td>NO—X</td>
<td>Nitrosyl halides</td>
</tr>
<tr>
<td>PX2—X</td>
<td>Phosphorus trihalides</td>
</tr>
<tr>
<td>Cl4P—Cl</td>
<td>Phosphorus pentachloride</td>
</tr>
<tr>
<td>NO—ClO4</td>
<td>Nitrosyl perchlorate</td>
</tr>
<tr>
<td>CCl3CO—OCOCl3</td>
<td>Trichloracetic anhydride</td>
</tr>
<tr>
<td>RSO2—OSO2R</td>
<td>Sulphonic acid anhydrides</td>
</tr>
<tr>
<td>(RO)2P—OP(OR)2</td>
<td>Tetraalkyl pyrophosphate</td>
</tr>
<tr>
<td>RCO—OSOR1</td>
<td>Mixed anhydrides</td>
</tr>
<tr>
<td>RSO—OSOR1</td>
<td></td>
</tr>
<tr>
<td>(EtO)2PO—OSOR1</td>
<td></td>
</tr>
<tr>
<td>RCO—OP(OEt)2</td>
<td>Alkyl halides</td>
</tr>
<tr>
<td>R—X</td>
<td></td>
</tr>
<tr>
<td>Me—OSO2F</td>
<td>Methyl fluorosulphonate</td>
</tr>
<tr>
<td>XCH2—X</td>
<td>Dihalomethanes</td>
</tr>
<tr>
<td>ROC2—X</td>
<td>α-Halo ethers</td>
</tr>
<tr>
<td>RSC2—X</td>
<td>α-Halo thioethers</td>
</tr>
</tbody>
</table>

\[
\text{Cl} \quad N_R^2 \quad + \quad \text{Cl}^- \quad \rightarrow \quad R_2N^+ \quad \text{Cl}^- \quad + \quad \text{Cl}^- \quad N_R^2
\]

(94c) (97a)
the dissociation shown in equation (47). Diamines \( \text{R}_2\text{N}-(\text{CH}_2)_n-\text{NR}_2 \) with \( n > 1 \) exhibit Van't Hoff \( i \) factors of about 3 under the same conditions.

With hydrogen chloride in excess in Et_2O, aminals are cleaved into iminium chlorides 97a and dialkylammonium chlorides 106 which can occasionally be separated by their different solubilities in polar solvents (DMF or MeCN)\(^{23,24} \) (equation 48).

\[
\begin{align*}
\text{NR}_2 &+ 2\text{HCl/Et}_2\text{O} \rightarrow \text{R}_2^+\text{N} \equiv \text{Cl}^- + \text{H}_2\text{NR}_2 \text{Cl}^- \\
(5) &\quad (97a) & (106)
\end{align*}
\]

The most convenient method for the preparation of iminium salts utilizes cleavage of aminals by acyl halides in ether (equation 49). The iminium salt 97 precipitates, whereas the dialkylamide 96a remains in solution. The yields are quantitative\(^{27,29} \).

\[
\begin{align*}
\text{NR}_2 &+ \text{R}^1\text{C}=\text{O} \rightarrow \text{R}_2^+\text{N} \equiv \text{X}^- + \text{R}^1\text{NR}_2 \\
(5) &\quad (97) & (96a)
\end{align*}
\]

\( X = \text{Cl, Br, I} \)

Iminium chlorides, bromides and iodides 97 have been prepared by this method\(^{27} \). With acyl fluorides the cleavage product 98 possesses a covalent structure, but in the presence of BF\(_3\) an iminium tetrafluoroborate is obtained\(^{27,44} \) (equation 50).

\[
\begin{align*}
\text{R}_2\text{N} \equiv \text{X}^- &+ \text{BF}_3 \rightarrow \text{R}_2^+\text{N} \equiv \text{X}^- + \text{R}^1\text{NR}_2 \\
\text{NR}_2 &+ \text{R}^1\text{C}=\text{F} \rightarrow \text{R}_2^+\text{N} \equiv \text{F}^- + \text{96a} \\
(97) &\quad (97) & (96a) & (98)
\end{align*}
\]

Iminium salts 97 (\( \text{NR}_2 = \text{N}< \)) can also be prepared by fragmentation of ammonium salts 107 (\( X = \text{Cl}^{47b}, \text{Br}^{41}, \text{I}^{237} \)) readily obtained from trimethylamine and dihalomethane (\( X = \text{Cl}^{22}, \text{Br} \text{ and I}^{232} \)) (equation 51).

\[
\begin{align*}
\text{N} + \text{X} \equiv \text{X} \rightarrow \text{N}^+\text{X} \equiv \text{X}^- \rightarrow \text{N}^+\text{N} \equiv \text{X}^- + \text{CH}_3\text{X} \\
(107) &\quad (97)
\end{align*}
\]

Cleavage of unsymmetric aminals 7 by acyl halides always leads to iminium salts 97 corresponding to the more basic amino group\(^{38,200,281,283,284} \).

These results suggest an equilibrium between the monoammonium salts 108 and 109. Monoammonium salt 109, although less abundant than 108 is decomposed into
the iminium salt more rapidly than 108. Yet the cleavage reaction (53) is observed for the unsymmetric acyl aminal 111 with acetyl chloride. It is likely that in this case, the NR1 group (phthalimido) is not sufficiently basic to allow formation of ammonium salt 109.

Cleavage of aminals by carboxylic anhydrides leads to covalent esters 112 (equation 54). However, in the case of trichloracetic anhydride, iminium trichloracetates are obtained.
Reaction of aminals 5 with \( \omega,\omega' \)-dihalides allows the preparation of cyclic quaternary ammonium salts (equation 55).

\[
\begin{align*}
\text{NR}_2 & \quad \rightarrow \quad \text{Br}^+ (\text{CH}_2)_n \text{Br}^- \\
\text{NR}_2 & \quad \rightarrow \quad \text{R}_2 \text{N}^+ \text{Br}^- + \quad \text{NR}_2 \quad (\text{CH}_2)_n \text{Br}^- \\
\end{align*}
\]

\[ n = 4, 5, 6 \]  

Mono- and bis-aminals 10–12, 13–17, 19–20 and 66 have been transformed into mono- or bis-iminium salts by cleavage with thionyl chloride (16, 66) or acyl halide (10, 27, 29, 40, 46, 92, 101, 114, 46, 92, 134, 47a, 101, 14, 15, 47a, 1749, 19, 20, 20, 30, 86, 92, 66). The cyclopropanone aminals 34 and 38 react with an excess of methyl fluorosulphonate at \(-78\,^\circ\text{C}\) forming cyclopropyliminium fluorosulphonates such as 113. These salts are relatively stable and can be stored many hours at \(35^\circ\text{C}\), without change in NMR (equation 56).

\[
\begin{align*}
\text{NR}_2 & \quad \rightarrow \quad \text{O}^- \text{SO}_2 \text{F} + \text{MeNR}_2 \\
\end{align*}
\]

The isolation of cyclopropyliminium salts and the substitutions observed without ring-opening are consistent with ab initio STO-3G orbital calculations. For \( X = \text{NH}_2 \), the cyclopropyl cation 114 is more stable than either the planar allylic cation 115 or the perpendicular allylic cation 116 (equation 57); the calculated relative energies of cations 114, 115 and 116 are respectively: \(-33.5, 0\) and \(+41.6\) kcal mol\(^{-1}\). For \( X = \text{H} \), 116 is more stable than 114.

\[
\begin{align*}
\text{114} & \quad \rightarrow \quad \text{H} \quad \text{H} \\
\text{115} & \quad \rightarrow \quad \text{H} \quad \text{H} \\
\text{116} & \quad \rightarrow \quad \text{H} \quad \text{H} \\
\end{align*}
\]

Aminals 27 when treated with excess phosgen are cleaved into phenyl isocyanate and carbamoyl chloride (equation 58).

\[
\begin{align*}
\text{NHR} & \quad \rightarrow \quad \text{R} \quad \text{N}^- \text{C} = \text{O} + \quad \text{Cl} \quad \text{N} \quad \text{C} = \text{O} \\
\text{27} & \quad \rightarrow \quad \text{117} \\
\text{R} & \quad = \quad \text{Ph} \\
\end{align*}
\]
2. Cyclic aminals

With cyclic aminals, the same types of cleavage occur.

Imidazolidines 44 are transformed by acyl chlorides into iminium salts 118 (equation 59).

\[
\begin{align*}
&\text{R}^1 = \text{H, Pr} \\
&R = \text{alkyl}
\end{align*}
\]

Cleavage of hexahydrotriazine 28 by hydrogen halides leads via the ammonium salt 99 to the corresponding unisolated iminium salt 119, characterized by its reaction products with nucleophiles\textsuperscript{229} [for a similar reaction with hexahydrotriazine 56 (n = 3) see Reference 26]. Reactions with phosphorus pentachloride\textsuperscript{116} yield bis(chloromethyl)alkylamine 120 and cleavage with excess phosgen affords compounds 121–123\textsuperscript{260} (equation 60).

\[
\begin{align*}
&\text{R} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{Cl} \\
&\text{R} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{Cl} \\
&\text{Cl} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \\
&\text{Cl} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \\
&\text{Cl} \quad \text{N} \quad \text{N} \quad \text{Cl} \quad \text{Cl} \\
&\text{R} = \text{Ph} \\
&\text{15\%} \\
&\text{R} = \text{alkyl} \\
&\text{24\%} \\
&\text{R} = \text{alkyl} \\
&\text{56\%}
\end{align*}
\]

Cleavage reactions of hexamethylenetetramine 59 have been achieved with acyl halides\textsuperscript{52} and phosphorus pentachloride\textsuperscript{115,116} yielding carboxamide 124 or tri(chloromethyl)amine 125 (equation 61).

\[
\begin{align*}
&\text{R} \quad \text{N} \quad \text{Cl} \\
&\text{R} \quad \text{N} \quad \text{Cl} \\
&\text{R} \quad \text{N} \quad \text{Cl} \\
&\text{R} \quad \text{N} \quad \text{Cl} \\
&\text{R} = \text{Ph} \\
&\text{15\%} \\
&\text{R} = \text{alkyl} \\
&\text{24\%} \\
&\text{R} = \text{alkyl} \\
&\text{56\%}
\end{align*}
\]
IV. FORMATION OF ENAMINES

A. The Aminal–Enamine Equilibrium

Equilibrium (62) has long been known for acetaldehyde aminals 19 \( (R^1 = H) \). On distillation, 1,1-dimorpholinoethane dissociates into morpholinoethylene (126)

\[
\begin{align*}
R^1 & \equiv \equiv R^1 \\
\text{NR}_2 & \equiv \equiv \text{NR}_2 + \text{HNR}_2
\end{align*}
\]

\( R^1 = H, \text{NR}_2 = \text{morpholino} \) and morpholine (both having similar boiling points) which immediately recombine exothermically to the starting aminal. The equilibrium has been confirmed by spectroscopic and reactivity studies.

The next higher aminal homologue \( (R^1 = \text{Me}; \text{NR}_2 = \text{morpholino}) \) partly dissociates into enamine and amine on dissolution in CDC\(_3\). The same composition \( 19/126 = 1 \) at 37°C is obtained from an equimolecular mixture of the enamine 126 and morpholine.

The ketoaminal 41 exists as such only in the solid state. In solution or when melted, it is in equilibrium with the corresponding enamine. The ketoaminal 127 could not be isolated from the amination of methyl ethyl ketone, but it was identified as the product of equilibrium (63) between the corresponding enamine and morpholine.

\[
\begin{align*}
\text{NR}_2 & \equiv \equiv \text{NR}_2 + \text{HNR}_2
\end{align*}
\]

\( \text{NR}_2 = \text{O} \)

Except for these few cases (see also Section IV.E), the dissociation equilibrium is almost always completely shifted toward the corresponding enamine.

B. Kinetics of the Dissociation into Enamine

The dissociation of aminal 20 into enamines 128-2 and 128-E has been studied. The dissociation rate \( (v) \) is very sensitive to the nature of the solvent: \( v(\text{CDC}3) > v(\text{C}_6\text{D}_6) \gg v(\text{NEt}_3) \). In DMSO, dissociation is accelerated by traces of hydrogen chloride and strongly retarded by addition of potassium t-butylate. In CDC\(_3\), the dissociation is first order with respect to aminal. The rate constant increases with the size of \( Y \) \( (Y = \text{Me}, k = 4.3 \times 10^{-4} \text{ s}^{-1}; Y = \text{C}_6\text{H}_{11}, k = 16.7 \times 10^{-4} \text{ s}^{-1}, \text{in CDC}3 \text{ at } 37^\circ\text{C}) \).

These results correspond with the formation of an iminium ion 129 as the rate-determining step, followed by a rapid deprotonation to yield enamines 128 (equation 64).
C. Stereochemistry of Amine Elimination

The ratio of enamines 128-$Z$ and 128-$E$ obtained immediately after heating aminals 20 or on their dissociation in solvents, is very different from the thermodynamic composition. For enamines 128 ($Y = Me$), the following data have been given:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$Z$</th>
<th>$E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equilibrium at 37°C</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>Aminal heating and distillation</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>Aminal dissociation in CDCl$_3$, CCl$_4$ or NEt$_3$ at 37°C</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

As expected from the proposed transition states 130-$E$ and 130-$Z$, the 128-$Z$ isomer (Ph and NR$_2$ in the cis position) is favoured when the size of $Y$ increases ($Y = C_6H_{11}$, 128-$Z$ = 100%; $Y = Me$, 128-$Z$ = 80%) (equation 65).

In agreement with the proposed mechanism, the iminium chloride 129 ($Y = Me$) when treated with triethylamine rapidly affords the enamines 128 in a $Z/E$ ratio of 80/20, corresponding to the kinetic ratio observed from the decomposition of the aminal 20 ($Y = Me$) in this solvent.
D. Enamines from Functional and Cyclic Aminals

α-Haloaminals 21 are transformed by heating into β-haloenamines 131 of exclusive or predominant Z configuration. Aminals 15 and 22 (R¹ = H) yield by distillation triaminoethylenes 132 and E-1,2-diaminoethylenes 133.

\[
\begin{align*}
R¹ & \equiv NR₂ \\
(131) & \\
R²N & \equiv NR₂ \\
(132) & \\
R₂N & \equiv NR₂ \\
(133) & 
\end{align*}
\]

Dissociation (66) of α-aminoaminals 134 with different NR₂ groups has been studied in CDC₃. In the kinetic product, the enamine 135-Z (Ph and NR₂ in the trans position) is predominant and its ratio varies only slightly with the size of NR₂ (61% (NMe₂) to 70% (NEt₂)). For these compounds, transition states such as 130 (Y = NR₂) are insufficient, because they take in consideration only the size of Y.

\[
\begin{align*}
\text{Ph} & \equiv NR₂ \\
(134) & \\
\text{Ph} & \equiv NR₂ + \text{Ph} \\
(135-Z) & \\
(136) & \\
\text{NR₂} & = \text{NMe₂, NEt₂, N, O; NR₂} = \text{N, O} \\
(137) & 
\end{align*}
\]

α-Aminoaminals 136 containing a β-H atom could lead to enamines 137 or 138, thus presenting in addition to the configurational isomerism a double-bond positional isomerism. The ratio 137/138 is 3 when R¹ is a methyl group and 4 when R¹ is hydrogen. Enamines 137 and 138 are in equilibrium (equation 67).

\[
\begin{align*}
R¹ & \equiv NR₂ \\
(136) & \\
R¹ & \equiv NR₂ + R¹ \\
(137) & \\
R¹ & \equiv NR₂ \\
(138) & \\
\text{NR₂} & = \text{R'YNR₂} \\
(139) & \\
\text{NR₂} & = \text{R'YNR₂} \\
(140) & \\
\end{align*}
\]

This type of isomerization can also be observed in enamines 139–144 derived from α-aminoaminals 23–26. Enamines 139, 140 and 142 with an exocyclic double bond and enamines 143 and 144 with an endocyclic double bond have been characterized. Both types of double bonds are present in enamine 141.
The particular behaviour of aminal 145 underlines the unstability of the four-membered heterocycle. Heating affords imine 146 isolated with 28% yield (equation 68). The same product was characterized by decomposition of aminal 145 in CDCl₃.

\[ \text{NR}_2 \text{N} \text{NR}_2 \xrightarrow{\Delta} \text{NR}_2 \text{N} \text{NR}_2 \]

(145) \hspace{1cm} (146)

Imidazolidines 44 and hexahydropyrimidines 45 can be distilled without decomposition. Imidazolidines 50a and 54 are transformed by heating into 1,2,4-trisubstituted tetrahydropyrazines 147. An internal transamination via open-chain iminium compounds is a plausible scheme (equation 69).

Tetrahydropiperazine 148 has been prepared either from imidazolidine 149 or from hexahydropiperazine 80 (equation 70).

Aminals 150 can be used as starting material for the synthesis of medium-ring diazaheterocycles such as 152. This is achieved via selective alkylation of the more basic nitrogen (formation of ammonium salt 151), followed by substruction of a proton leading to imine 152 in equilibrium with the corresponding enamine (equation 71).
E. Aminals Non-transformable into Enamines

Cyclopropanone aminals 32, cyclopropylcarbamins 53, 67, 145-147, 228 and azacyclopropylcarbamins 153, 269, 270 are not transformed by distillation or by prolonged heating into the expected enamines (equations 72 and 73).

\[
\begin{align*}
\text{(32)} & \\
\begin{align*}
NR_2 & \\
\end{align*}
\end{align*}
\]

\[
\begin{align*}
\text{(153)} & \\
\begin{align*}
NR_2 & \\
\end{align*}
\end{align*}
\]

\[
X = \text{CHR}^2, \text{NR}^2
\]
endocyclopropylaminals such as 154, 155 and 156 \((NR_2 = \bigcirc)\) undergo an

\[
\begin{align*}
\text{(154)} & \quad \xrightarrow{-HNR_2} \quad \text{(155)} & \quad \xrightarrow{HNR_2} \quad \text{(156)}
\end{align*}
\]

easy isomerization into the exoisomers. This isomerization sometimes occurs during the isolation of the aminal. It is catalysed by benzoic acid and is complete on distillation. It is considered to occur via a cyclopropylidene amine such as 158 with which the endo and exo aminals are in equilibrium\(^{146,228}\) (equation 74). The isomerization of aminal 154 in \(C_6D_6\) at 20°C is first order, with a rate coefficient of \(1.9 \times 10^{-3} \text{ min}^{-1}\).

For the aminal 156 an alternative mechanism (75) via the allylic cation 159 has been excluded, because the aminal 157 which can give such an allylic cation but cannot give an enamine such as 158, does not undergo the endo \(\rightleftharpoons\) exo isomerization\(^{145}\).

\[
\begin{align*}
\text{(156)} & \quad \xrightarrow{-HNR_2} \quad \text{(160)}
\end{align*}
\]

Under more drastic thermal conditions, cyclopropylcarbaminals with a vinylic double bond, such as 160–163, are decomposed with elimination of amine and formation of rearranged products 164–166\(^{145,147,228}\). Cyclopropylidene amines are considered to be plausible reactive intermediates (equation 76).

Aziridinoaminals 167 are recovered unchanged after heating at 200°C\(^\text{269}\), whereas aminal 168 is transformed into a pyrrole\(^\text{270}\) (equation 77).
\[
\text{NR}_2 = N\][; R^1 = i\text{-Pr}, t\text{-Bu}]
\]
F. Stability of Aminals in Strongly Basic Media

Aminals 169 and aminoimidazolidine 50 (X = NEt₂, R¹ = Et, R = Me) are stable in DMSO in the presence of potassium t-butylate, even after two hours at 170°C, while they are totally transformed into enamines in the absence of this base (equation 78).

\[
\begin{array}{c}
\text{DMSO, t-BuOK, 170°C} \\
\text{(169)} \\
\text{R¹ = Me, Ph, Ph, Ph} \\
\text{Y = H, H, Me} \\
\text{NR² = } \text{O, O, O} \\
\end{array}
\]

Similarly aminoaminal 169 (R¹ = Ph, Y = NR₂ = O, O, O) is unchanged after some hours of reflux in DMF containing potassium t-butyrate, or in ether, tetrahydrofurane or dioxane containing lithium aluminium hydride\(^{53,239}\).

This result suggests that decomposition of aminals into enamines does not occur when the formation of iminium ions is impossible. Therefore, an E₁ thermal mechanism with a four-electron transfer transition state is highly improbable, even at 170°C.

The haloimidazolidine 170 undergoes hydrogen halide elimination when treated with potassium t-butyrate. The tetrahydropyrazine 171 is obtained in a protic medium such as t-butanol in which the formation of iminium ions is allowed. However, in DMSO, the imidazolidine function is preserved, and the ethylenic compound 172 is formed exclusively\(^{103,239}\) (equation 79).

\[
\begin{array}{c}
\text{t-BuOK DMSO} \\
\text{(172)} \\
\text{(170)} \\
\text{Cl} \\
\end{array}
\]

V. REACTIONS

Aminals react with electrophilic reagents yielding iminium ions (Section III.B) and do not react with nucleophilic reagents. Therefore, reaction of aminals with nucleophilic reagents occurs only in conditions in which the iminium formation is possible.

Reaction of aminals with polarized double bonds leads to an addition compound 173 which formally corresponds to insertion of the double bond into the aminal C—N bond (equation 80).

A. Reactions with Heteroatom Nucleophilic Reagents

Mono- and di-substitution compounds 174 and 175 can be isolated by reaction of heteroatom nucleophilic reagents with aminals (equation 81).
1. Water

Generally, hydrolysis of aminals in acidic conditions is immediate. Hydrolysis of ketoaminals 75 and 77 seems somewhat more difficult.

Polyformylbenzenes (176) and para-substituted phenylglyoxals (177) have been advantageously prepared from polymethylbenzenes\textsuperscript{159,161,164,166,167,241} (equation 82) and \textit{para}-substituted acetophenones\textsuperscript{160,262} (equation 83) via aminals. In some cases, isolation of the aminal is not necessary, as the amination and hydrolysis steps may occur in the same pot.

Regeneration of the free aldehyde function from 1,2-diphenylimidazolidine derivatives has been achieved in mild conditions by treatment with 2.5–3 molar...
20. Aminals

Equivalents of $p$-toluenesulphonic acid monohydrate in acetone and methylene chloride. The diamine salt is removed by filtration and the aldehyde by aqueous extraction.

Hydrolysis of aminals with H$_2^{18}$O represents a useful method for the preparation of $^{18}$O-carbonyl compounds.

Monosubstitution products have been obtained by partial hydrolysis of $\alpha$-ketoaminals (equation 84).

\[
\begin{align*}
\text{(178)} & \quad \text{Y} = NR_2, \text{Ph} ; NR_2 = N\bigcirc N, N \\
\text{(179)} & \quad \text{Y} = NR_2, \text{Ph} ; NR_2 = N\bigcirc N, N \\
\end{align*}
\]

The cyclopropanone aminal (NR$_2$ = (N̕_N)) on treatment with hydrochloric acid affords the hemiaminal which permits a convenient synthesis of endonorcaranol (equation 85). Under similar conditions, (NR$_2$ = (N̕_N)) gives 2-chlorocyclohexanone. The unexpected formation of the exo-amine from is probably the result of a thermodynamically controlled isomerization. The isomeric endo-amine can be prepared from the fluorosulphonate in basic medium (equation 86). In the presence of traces of acid, it undergoes rapid
isomerization to 180. The endo–exo assignment of the bridge substituents is facile when a morpholino group is present. An exo morpholino group exhibits in 1H-NMR an AA’XX’ signal while an endo morpholino group shows an ABXY system.

The specific hydrolysis of tetramorpholinoethane (15; NR₂ = N[O]) into the aminoamide 183, according to equation (87), must be noted.

\[ \text{NR}_2 = \text{N} \]

\[ \text{HO} \]

\[ \begin{array}{c}
\text{HO} \\
\text{NR}_2 \\
\text{NR}_2
\end{array} \]

\[ \rightarrow \]

\[ \text{NR}_2 \]

\[ \begin{array}{c}
\text{HO} \\
\text{NR}_2 \\
\text{NR}_2
\end{array} \]

\[ \rightarrow \]

\[ \text{R}_2 \text{N} \]

\[ \begin{array}{c}
\text{R}_2 \\
\text{N}
\end{array} \]

(87)

NR₂ = N[O]

2. Alcohols

Monosubstitution products 184–186 have been obtained by successively adding acetyl chloride, triethylamine and methanol to aminal 5, by heating tetramorpholinoethane (15; NR₂ = N[O]) in alcohols or by reaction of methanol or ethanol with cyclopropanone aminal 38.

\[ \text{R'} = \text{Me, Et, Pr} \]

Many acetals have been prepared by reaction of aminals with alcohols in the presence of hydrogen chloride (equation 88). The reaction occurs at room temperature or at reflux, depending upon the structures.

Solvolysis by methanol of α-ketoaminals such as 17a is complex. Ketals 188 and 189 have been detected. Nevertheless, it has been possible to determine experimental conditions yielding exclusively acetal 187 (equation 89). Direct acetalization of phenylglyoxal by methanol has given, in the best case, an equal mixture of the ketal 188 and the starting material.

3. Thiols

Mono- and di-substitution products 190 and 191 have been obtained by reaction of thiols with aminals in the presence of acetyl chloride, hydrogen chloride or
20. Aminals

\[
\begin{align*}
R^1 \text{NR}_2 & \xrightarrow{\text{HCl, } R^2 \text{OH}} R^1 \text{OR}^2 \\
R^1 &= \text{X} - \text{phenyl}, \text{X} - \text{phenyl} - \text{CO}, \text{R}^3 \text{O} - \text{C} \\
R^2 &= \text{Me, Et, } n\text{-Pr, i-Pr} \\
\text{NR}_2 &= \text{N} \bigcirc \\
\end{align*}
\]

\[\text{equation 88}\]

sulphuric acid\textsuperscript{34,181,182,184} (equation 90). The reaction is rapid and the yields are often in excess of 80%. The method is useful for the preparation of \(\alpha\)-ketothioacetals which are difficult to obtain.

\[\text{equation 90}\]

4. Amines

Reaction of \(\alpha\)-aminoaminals 22 with primary and secondary amines leads to \(\alpha\)-amino imines 192 and enediamines 193 (equation 91). The amine exchange occurs on the aminal carbon involving an \(\alpha\)-aminoaaldinium cation 194\textsuperscript{98,102}.

\[\text{equation 91}\]

5. Amides

A variety of monosubstitution compounds 195 and amidals \((N,N\text{-diacylaminals})\) 196 have been prepared by reaction of aminals with amides\textsuperscript{183,185,238} (equation 92).
Reaction with succinimide results in rupture of the succinimide ring with formation of amide 197\textsuperscript{238} (equation 93).

\begin{equation}
\text{N-H} + \text{Ph-}\text{NR}_2 \rightarrow \text{O} \begin{array}{c}
\text{R}_2 \\
\text{H}
\end{array} \text{N} \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \text{NR}_2
\end{equation}

B. Reactions with Carbon Nucleophilic Reagents

These reactions lead to formation of a new C—C bond.

1. Grignard reagents

Grignard reagents react very slowly with aminals leading to a tertiary amine such as 198 isolated in low yield\textsuperscript{123} (equation 94).

2. Diazoalkanes

Reaction of aminals 5 with diazofluorene in the presence of carboxylic anhydrides yields $O$-acylethanolamines 199\textsuperscript{235} (equation 95).

An amino ester, e.g. 200, may be an intermediate (equation 96).
3. Isonitriles

The nucleophilic divalent carbon of isonitriles reacts with iminium cation intermediate giving a nitrilium ion, which in turn can react with a nucleophile Y⁻.\(^{258}\) (equation 97).

\[
\text{R}^1\text{N} = \text{C} + \text{YNR}_2 \rightarrow \text{R}^1 \text{N} = \text{C} \text{NR}_2 \rightarrow \text{R}^1 \text{N} = \text{C} \text{NR}_2 + \text{Y}^- \quad (97)
\]

Reaction of aminal 5 with an isonitrile yields an aminoacetamide 201.\(^{285}\) In the presence of hydrazoic acid, a tetrazole derivative 202 is obtained.\(^{258}\) (equation 98).
4. Trihaloacetic acids

Trichloro- and tribromo-acetic acids react with aminals at high temperature with evolution of carbon dioxide and formation of an α-(trihalo)methylamine (equation 99).

\[ \text{NR}_2 + \text{R}^1 \text{N} = \text{C} \rightarrow \Delta \rightarrow \text{R}_2 \text{N} - \text{C} = \text{N} - \text{NR}_2 \]

\( \text{R}^1 = \text{C}_6\text{H}_{11} \; ; \; \text{NR}_2 = \text{N} \quad \text{N} \quad \text{O} \)

5. C—H acidic compounds

The acid-catalysed Mannich reaction is believed to involve an iminium cation intermediate, which is formed from the condensation of the amine and the carbonyl compound (usually formaldehyde). The active hydrogen compound reacts as the enol with the iminium cations. The condensation product can be transformed into an α-ethylenic carbonyl compound by amine elimination (equation 100).

\[ \text{Ph} - \text{NR}_2 + \text{NR}_2 \xrightarrow{\text{X}_3\text{C} - \text{OH}} \text{Ph} - \text{NR}_2 \text{NR}_2 \xrightarrow{\text{X}_3\text{C} - \text{OH}} \text{Ph} - \text{N} = \text{C} = \text{N}_\text{R}_2 \text{NR}_2 \text{NR}_2 \xrightarrow{\text{X}_3\text{C} - \text{OH}} \text{Ph} - \text{NR}_2 \text{NR}_2 \]

\( \text{R}^1 = \text{C}_6\text{H}_{11} \; ; \; \text{NR}_2 = \text{N} \quad \text{N} \quad \text{O} \)

Instead of aldehydes and amines, this reaction may be carried out with the corresponding aminals which give iminium cations easily under acidic conditions.

Thus, treatment of compound 204 or ketone 206 with formaldehyde and dimethylamine hydrochloride under the usual Mannich conditions affords unsaturated compounds 205 and 207, with only fair yields, while excellent yields are obtained by using bis(dimethylamino)methane and acetic anhydride (equations 101 and 102).

Reaction of phenylacetone with aminal 10 yields a labile intermediate 208 which upon elimination provides the ethylenic ketone 209 (equation 103).
The aminal 10 (Ar = Ph) reacts with malonic acid affording cinnamic acid in a rapid reaction and good yield (equation 104). The intermediate has been isolated\(^{155}\).

\[
\begin{align*}
\text{Ph} & \text{NR}_2 + \text{O} \rightarrow \text{Ph} \text{NR}_2 \\
\text{NH} & \rightarrow \text{NH}
\end{align*}
\]

Aminals aminoalkylate the aromatic ring of phenols\(^{34}\), yielding substituted phenols such as 210\(^{269}\) (equation 105). In basic solutions (pH \(\sim 9\)), kinetic studies with varied concentrations of amine and formaldehyde seem to demonstrate the
intermediary role of an aminal, thus ruling out an iminium cation\textsuperscript{59}. The different behaviour of phenols and alcohols must be underlined.

With acetophenones such as 211, aminoalkylation can occur either on the aromatic ring or on the methyl group (equation 106). When the two hydroxyl groups are protected, the reaction takes place exclusively on the methyl group giving the chalcone 212. When the two hydroxy groups are free, a regiospecific aminoalkylation of the nucleus occurs, due to the tautomeric structure 213. Since the benzylic amino group of compound 214 can be removed by reduction, this method offers a selective route to C-methyl- or C-benzyl-acetophenone 215\textsuperscript{155-157}.

Reaction of chrysin (216) with aminals leads to mono- or di-aminoalkylation which, via removal of the amino group should allow the preparation of natural substituted flavanones\textsuperscript{155-157} (equation 107).

The condensation of imidazolidines 44a with dihydropyran proceeds similarly, yielding an perhydrodiazepine 217 and a secondary amine 218\textsuperscript{126} (equation 108).
The cyclopropanone aminal 38 readily undergoes reaction with ketones (acetone, methyl ethyl ketone, cyclopentanone) in the presence of an aqueous buffer of pH 5.5, to form addition products such as 219. 38 also reacts with nitromethane or nitroethane in the presence of methyl iodide (used to generate a cyclopropyliminium intermediate) leading to the nitro compound 220 (equation 109).

C. Reactions with Heterocumulenes

Aminals 5 react with heterocumulenes X=C=Y with formation of a 1:1 adduct (equation 110).

Addition products of this type (222–226) have been obtained with isocyanates (equation 111), isothiocyanates (equation 112), carbon disulphide (equation 113), ketene (equation 114) and ketene imines (equation 115). Generally, reaction occurs even at room temperature in the absence of a catalyst.
Compounds 222–224 are thermolabile and are cleaved into the starting materials on heating to 100 °C. The β-aminoamide 225 eliminates amine forming an α-unsaturated amide 227.

Cyclic aminals undergo analogous reactions yielding ring-enlargement products. Hexahydrodiazepinone 228 is formed from imidazolidines 44a and ketene (equation 116), and hexahydrotriazepine derivatives 229 are formed from 44a and isocyanate, isothiocyanate or ketene imine 221. These compounds are stable.

\[
\begin{align*}
894 & \quad \text{Lucette Duhamel} \\
S\equiv C\equiv S + 5 & \quad \rightarrow \quad R_2N\overset{S}{\equiv}S\overset{N}{\equiv}NR_2 \\
& \quad (224) \\
\text{O}=\text{C}=\text{CH}_2 + 5 & \quad \rightarrow \quad R_2N\overset{\text{C}}{\equiv}\overset{\text{C}}{\equiv}\overset{\text{N}}{\equiv}\overset{R'}{\equiv} + 5 \quad \rightarrow \quad R_2N\overset{\text{C}}{\equiv}\overset{\text{C}=\text{N}}{\equiv}R' \\
& \quad (225) \\
& \quad (227) \\
\text{EtO}_2\text{C}=\text{C}=\text{N}\overset{R_1}{\equiv} + 5 & \quad \rightarrow \quad \text{EtO}_2\text{C}\overset{\text{C}}{\equiv}\overset{\text{C}}{\equiv}\overset{\text{N}}{\equiv}R_2 \\
& \quad (221) \\
& \quad (226) \\
\end{align*}
\]

\[
\begin{align*}
\text{Compounds } 222–224 \text{ are thermolabile and are cleaved into the starting materials on heating to 100 °C. The } \beta\text{-aminoamide } 225 \text{ eliminates amine forming an } \alpha\text{-unsaturated amide } 227. \\
\text{Cyclic aminals undergo analogous reactions yielding ring-enlargement products. Hexahydrodiazepinone } 228 \text{ is formed from imidazolidines } 44a \text{ and ketene (equation } 116), \text{ and hexahydrotriazepine derivatives } 229 \text{ are formed from } 44a \text{ and isocyanate, isothiocyanate or ketene imine } 221. \text{ These compounds are stable.}
\end{align*}
\]

\[
\begin{align*}
\text{R} & = n\text{-Bu, PhCH}_2 \\
\end{align*}
\]
D. Reduction

Aminals are cleaved and reduced into both tertiary and secondary amines by catalytic hydrogenation, formic acid, or metal hydrides (equation 117).

\[ R^1NR_2 + [H] \rightarrow R^1NH + HNR_2 \quad \text{(117)} \]

Reduction of open-chain and cyclic aminals occurs by hydrogenation in the presence of platinium, palladium or Raney nickel\textsuperscript{174,286}. Splitting of the C—N bond of the spiroaminal 81a is easy, whereas more drastic conditions are required for the cleavage of the pyrrolidino ring\textsuperscript{174} (equation 118).

\[ \text{H}_2/\text{Pt} \quad r.f., 1 \text{ atm.} \quad \xrightarrow{} \quad \text{RNH(CH}_2)_2\text{NHR} \quad \text{H}_2/\text{Pt} \quad 50\text{oC}, 100 \text{ atm.} \quad \xrightarrow{} \quad \text{RNH(CH}_2)_2\text{NHR} \quad \text{(118)} \]

*Cis*— and *trans*-3(γ-aminopropyl)piperidines 231 are formed by reduction of decahydronaphthyridines 230. The *cis* isomer is largely predominant. The stereoselectivity is influenced by the catalyst used (Pt or Pd)\textsuperscript{286} (equation 119).

\[ \text{230} \quad \xrightarrow{\text{H}_2/\text{Pd/C or Pt/C}} \quad \text{231} \quad \text{(119)} \]

Reduction of aminals by formic acid was initially investigated in order to study the Leuckart–Wallach reaction (reductive amination of aldehydes and ketones) and the Eschweiler–Clarke reaction (reductive methylation of amines). Generally, animals react spontaneously with formic acid\textsuperscript{63,191,243}. An ionic mechanism involving the direct transfer of a hydride ion to the iminium cation is generally accepted (equation 120). A free-radical mechanism involving the transfer of an electron from the formate anion to the iminium cation, and decomposition of the formyloxyl radical has also been proposed: (equation 121). The thermal decomposition of an intermediate ester 232 has also been suggested\textsuperscript{191} (equation 122).

\[ \text{R}^1\text{NR}_2 + \text{HCOH} \quad \xrightarrow{\text{H}} \quad \text{R}^1\text{NR}_2 + \text{CO}_2 \quad \text{(120)} \]

\[ \text{R}^1\text{~N}^\ast\text{R}_2 \quad \xrightarrow{-\text{O}} \quad \text{R}^1\text{NR}_2 + \text{H}^+ + \text{CO}_2 \quad \xrightarrow{} \quad \text{R}^1\text{NR}_2 \quad \text{(121)} \]
The reduction of cyclopropylcarbaminal 162 by formic acid-d₂ yields a monodeuterioamine 233 and a biduterioamine 234 (equation 123) suggesting an equilibrium between the iminium cation and the not nonisolated cyclopropylidene amine (Section IV.E)¹⁴⁷.

1,3-Disubstituted and 1,2,3-trisubstituted imidazolidines 44 are cleaved and reduced to the corresponding diamine 235 upon exposure to sodium borohydride in boiling ethanol or lithium aluminium hydride in dioxane at reflux¹⁰³,²⁷⁹ (equation 124). The chloroimidazolidine 50 is transformed into piperazine 236 by these reagents¹⁰³ (equation 125). The proposed mechanism is shown in equation (126).

1,2,3-Trisubstituted hexahydropyrimidines 45 (R¹ = Me) are similarly cleaved by these two reducing agents. However, 1,3-disubstituted hexahydropyrimidines 45 (R¹ = H) are not affected under the same conditions²⁷⁹. Spiroaminoaminals 81a¹⁷⁴ (R¹ = R² = H) and α-aminoaminals 22 (R¹ = H, Ph)⁸³,⁹³ are recovered unchanged following treatment by lithium aluminium hydride, while cyclopropylcarbaminals are reduced⁶⁷.

Imidazolidines 44 are also cleaved to the diamines 235 by reduction with borane-tetrahydrofuran²¹³.
E. Oxidation

1. Without modification of the oxidation number of the aminal carbon atom

Aminals 27 formed in situ from formaldehyde and primary amines are transformed into diaziridines 237 by reaction with hypochlorite in a basic medium\(^2\) (equation 127). This reaction also occurs with the hexahydrotriazine
The hexahydrotriazine 58 reacts with nitrous acid to provide a fair yield of the trinitroso derivative 238. The nitration of hexamethylenetetramine 59 leads to the high-explosive cyclotrimethylene trinitroamine 239. N-Oxide aminals such as 240 have only been isolated from rigid systems such as polyazaadamantanes. Mono-, di- or tri-N-oxides are obtained by reaction of hexamethylenetetramine 59 with 3-chloroperoberzoic acid, depending on structural type and molar ratio between the reactants.

In other cases, the N-oxides are unstable and rearrange into oxazines such as 241 and 243 obtained from the aminals 1 and 242 (equations 130 and 131).

Triazines 28 are transformed into oxaziranes 244 by action of peracetic acid, via oxidation of formaldehyde imine (equation 132).

2. With modification of the oxidation number of the aminal carbon atom

1,3-Diarylimidazolidines are dehydrogenated by carbon tetrachloride to yield the corresponding imidazolidinium salt 245. Both free-radical (equation 133) and ionic (equation 134) mechanisms have been suggested. Dehydrogenation also occurs with potassium permanganate, peracetic acid in aqueous solutions, quinones, ethyl azodicarboxylate, mercuric
ethylenediaminetetracetate\textsuperscript{201,202}, and dimethyl sulphoxide in the presence of zinc chloride\textsuperscript{126}. In some cases \textit{N}-monoformyldiamine \textbf{246} is isolated, which can yield the imidazolidinium salt \textbf{245} after acidic treatment\textsuperscript{151,226} (equation 135).

Dehydrogenation of 2-substituted 1,3-diphenylimidazolidines \textbf{44} is more difficult, but is effected with 2,3-dichloro-5,6-dicyano-\textit{p}-benzoquinone\textsuperscript{226} and with mercuric ethylenediaminetetracetate\textsuperscript{201,202}.
3. With cleavage of the carbon chain

Isobutanal aminal 247 is cleaved in acetone and diphenylformamidine when stirred in the presence of pure oxygen or air (equation 136). The fragmentation of an intermediary hydroperoxide has been proposed. The presence of two α-alkyl groups in the aminal seems indispensable, because analogous ethanal and n-butanal aminals are stable under the same conditions\textsuperscript{233}.

\[
\begin{align*}
\text{PhNHNHPh} & \xrightarrow{\text{O}_2} \quad \text{O} \quad \text{H} \quad \text{N} \quad \text{H} \\
\text{PhNHNHPh} & \quad \text{Ph} \quad \text{N} \quad \text{H} \\
\text{PhNHNHPh} & \quad \text{Ph} \quad \text{N} \quad \text{H}
\end{align*}
\]

(136)

VI. AMINALS AS POTENTIAL AND PROTECTED CARBONYL COMPOUNDS

It has already been noted that aminals can be used as potential aldehydes for the easy synthesis of acetals and thioacetals (Section V.A.2.3).

Reaction of aminals with aromatic compounds in very concentrated aqueous solutions of sulphuric acid occurs via the hydrolysis products\textsuperscript{204,219} (equations 137 and 138).

\[
\begin{align*}
\text{PhNHNHPh} & \xrightarrow{\text{H}_2\text{SO}_4-\text{H}_2\text{O}} \quad \left[ \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array} \right] \\
\text{PhNHNHPh} & \quad \text{Ph} \\
\text{PhNHNHPh} & \quad \text{Ph}
\end{align*}
\]

(137)

\[
\begin{align*}
\text{PhNHNHPh} & \xrightarrow{\text{H}_2\text{SO}_4-\text{H}_2\text{O}} \quad \left[ \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array} \right] \\
\text{PhNHNHPh} & \quad \text{Ph} \\
\text{PhNHNHPh} & \quad \text{Ph}
\end{align*}
\]

(138)

In even more strongly acidic media such as anhydrous sulphuric acid, the aminal function does not react with aromatic compounds. This lack of reactivity is probably due to the protonation of both amino groups. This property permits the preparation of triarylacetaldehydes 248 from the α-ketoaminal 17a\textsuperscript{219} with good yields (equation 139).
In strongly basic media, the reactions of aminals are very sluggish, due to the difficulty of forming iminium cations (Section IV.F). Aminals can be used as aldehyde protecting groups in the presence of organometallic compounds. Thus, 2-chloro-3,5-diformylthiophene has been prepared from 2-chloro-3-formylthiophene via intermediate protection of the aldehyde group (equation 140).

α-Hydroxy aldehydes have been prepared in high optical yields by the reaction of α-ketoaminals with Grignard reagents and hydrolysis of the resulting hydroxyaminal. α-Ketoaminals have been obtained by treatment of the methoxycarbonylaminal with Grignard reagents in the presence of magnesium chloride (equation 141).

Protection of aldehydes in reducing media was realized by their transformation into imidazolidines. Reduction of nitriles or thio acid salts with Raney nickel was carried out in the presence of N,N'-diphenylethylenediamine, to trap the nascent aldehyde and thus, circumvent further reduction to the corresponding alcohol (equation 142). Penicillin aldehydes have been synthesized under these conditions.

Reduction of p-isopropylbenzaldehyde into the 2,5-dihydro derivative has been effected by metal ammonia after conversion into the 1,3-dimethylimidazolidine derivative.
Aminals have also been used to trap labile aldehydes. Thus, \( \alpha \)-amino aldehydes have been isolated from reaction mixtures as crystallized aminals \(^{22}\), in order to avoid their transformation into the more stable isomeric \( \omega \)-aminoketones\(^{84,90,95}\).

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20. Aminals

CHAPTER 21

Detection and determination of nitro and nitroso compounds

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I. INTRODUCTION

This chapter deals with detection and determination methods of nitro, C-nitroso and N-nitroso compounds. Reviews dealing with the analytical chemistry and spectroscopy of nitro and nitroso derivatives have appeared. The aim of this chapter is therefore to give a brief account of known methods without repeating details and procedures readily available in these sources. Recent developments (literature covered till the end of 1978) are emphasized, but as a rule we do not reproduce detailed procedures. The interested reader is referred to the specialized review literature and to the original works.

The analytical chemistry of explosives, most of them nitro derivatives, has been thoroughly covered by a recent review and will not be repeated here. Mass spectra of nitro and nitroso derivatives are treated in a separate chapter of this volume.

II. DETECTION AND IDENTIFICATION

A. Chemical Methods

This topic has been treated by several books and a recent review, so only a brief and selective summary is given here. For detailed procedures the reader is referred to the reviews and original works.

1. Nitro compounds

The most characteristic reaction of the nitro group, the reduction to amines (equation 1), is conveniently accomplished by using tin or zinc in hydrochloric acid. The resulting primary amine can then be detected. Nitroso, azoxy or azo compounds give the same results.

\[
\text{RNO}_2 + 6 \text{H}^+ + 6 \text{e}^- \rightarrow \text{RNH}_2 + 2 \text{H}_2\text{O} \quad (1)
\]

Tollén’s reagent or by the ferric hydroxamate test. Under the same conditions azoxy and azo compounds are reduced to hydrazo and hydrazine derivatives respectively, which also respond positively to Tollén’s test. However, only hydroxylamines give the ferric hydroxamate test. The application of both tests to the reduction products enables one to differentiate between nitro or nitroso derivatives, and azoxy or azo compounds. The original compound should be tested with Tollén’s reagent before the reduction step, to make sure that it does not affect the reagent.

Compounds containing one or more nitro groups give a positive ferrous hydroxide test (equation 3). Not all nitroparaffins give a positive response, whereas a positive test is given also by other oxidizing compounds.
21. Detection and determination of nitro and nitroso compounds

$\text{RNO}_2 + 6 \text{Fe(OH)}_2 + 4 \text{H}_2\text{O} \rightarrow \text{RNH}_2 + 6 \text{Fe(OH)}_3$ (3)

Distinction between primary, secondary and tertiary aliphatic nitro compounds can be accomplished by reacting the nitro derivative with nitrous acid$^{1,3-5}$. Primary nitroalkanes give a red colour, resulting from the formation of the salt of nitrolic acid; secondary nitroalkanes give a blue colouration resulting from the pseudonitrole formed in the reaction; tertiary nitroalkanes do not react with this acid. Primary and secondary nitroparaffins give a positive ferric chloride test$^4$. Secondary and some tertiary nitroparaffins liberate nitrous acid upon heating with sulphuric acid. The nitrous acid forms an intense purple product with resorcinol$^1$. Primary nitroparaffins couple in alkaline media with diazonium salts to yield coloured condensation products$^2$.

Aromatic mononitro derivatives can be detected without interference from nitroparaffins by reaction with sodium hydride$^1$. Dinitro and trinitro derivatives of benzene and its homologues can be classified by the acetone–sodium hydroxide test$^{3,4}$. Dinitro derivatives produce a purplish-blue colour and trinitro compounds show red colour. Mononitro compounds do not lead to colour development.

A sensitive spot test for aromatic nitro compounds is their reduction to nitroso derivatives by warming with calcium chloride and zinc, and the detection of the nitroso compound by a reaction with $\text{Na}_2[\text{Fe(CN)}_5\text{NH}_3]$ (purple, blue or green colour)$^2$.

Dinitro aromatic compounds give blue to green colour with tetraethylammonium hydroxide and fluorenone or butanone in dimethylformamide solution. Trinitro aromatics form red colours in this test$^2$. $m$-Dinitro aromatic compounds give a specific test with $\text{KCN}^2$, while $o$- and $p$-dinitrobenzenes can be identified through reduction with phenylhydrazine or other reducing organic compounds in alkaline media$^{1,2}$.

2. Nitroso compounds

$C$-Nitroso compounds (like their nitro analogues) can be reduced to amines and hydroxylamines, depending on reaction conditions$^{3-5}$ (equations 4 and 5). $N$-Nitroso compounds are reduced to hydrazines (equation 6). $N$-Nitroso and $C$-nitroso compounds can be distinguished by hydrazoic acid$^2$. The $N$-nitroso derivatives are easily denitrosated by the acid at room temperature (equation 7). $C$-Nitroso compounds are not altered by this reagent.

$\text{ArNO} + 4 \text{H}^+ + 6 \text{e} \xrightarrow{\text{Sn, HCl}} \text{ArNH}_2 + \text{H}_2\text{O}$ (4)

$\text{ArNO} + 2 \text{H}^+ + 2 \text{e} \xrightarrow{\text{Zn, CaCl}_2} \text{ArNHOH}$ (5)

$\text{R}_2\text{NNO} + 4 \text{H}^+ + 4 \text{e} \rightarrow \text{R}_2\text{NNH}_2 + \text{H}_2\text{O}$ (6)

compounds can be distinguished by hydrazoic acid$^2$. The $N$-nitroso derivatives are easily denitrosated by the acid at room temperature (equation 7). $C$-Nitroso compounds are not altered by this reagent.

$\text{R}_2\text{N—NO} + \text{HN}_3 \rightarrow \text{R}_2\text{NH} + \text{N}_2 + \text{N}_2\text{O}$ (7)

Aliphatic $C$-nitroso compounds can be detected by a rearrangement to the oximes and the identification of the latter with chlorourea$^1$. Aliphatic $N$-nitroso compounds liberate nitrous acid upon hydrolysis in an acid medium (equation 8). The nitrous acid can be detected with Griess reagent$^{1,2}$.

$\text{R}_2\text{NNO} + \text{H}_2\text{O} \rightarrow \text{R}_2\text{NH} + \text{HNO}_2$ (8)
Nitroso compounds can be distinguished from nitro compounds by their reaction with $[\text{Fe(CN)}_5\text{NH}_3]^{-3}$ or $[\text{Fe(CN)}_5\text{H}_2\text{O}]^{-3}$. A colour develops upon the exchange of $\text{NH}_3$ or $\text{H}_2\text{O}$ for the nitroso compound\(^1,2\) (equation 9). Aromatic amines or hydrazines will also give a positive test.

$$\text{Na}_3[\text{Fe(CN)}_5\text{NH}_3] + \text{RNO} \rightarrow \text{NH}_3 + \text{Na}_3[\text{Fe(CN)}_5\text{RNO}]$$ \hspace{1cm} (9)

Nitroso compounds give a positive Liebermann test (red colouration upon heating in conc. $\text{H}_2\text{SO}_4$ with phenol)\(^1,2\). A very sensitive test for nitroso compounds includes the reaction with diphenylbenzidine\(^1\). Oxidizing materials or compounds containing active halogens, interfere with this test since they give positive results. Aromatic nitroso compounds give a coloured product with resorcinol\(^1\).

Finally, some physical and chemical constants that can assist in the identification of the compounds, like melting and boiling points, refractive indices and densities, as well as properties of derivatives, can be found in Reference 15.

B. Infrared and Raman Spectroscopy

The infrared and Raman spectroscopy of nitro\(^1,2\) and nitroso\(^13\) compounds has been extensively reviewed.

1. Nitro compounds\(^12\)

The infrared and Raman fundamental frequencies of nitromethane are summarized in Table 1. Two characteristic bands of high intensity appear in the infrared spectra of alkyl nitro compounds; the symmetric stretching ($\nu_s$) in the region of $1300–1700 \text{ cm}^{-1}$, and the asymmetric stretching ($\nu_{as}$) in the region of $1500–1600 \text{ cm}^{-1}$. Generally primary and secondary nitro derivatives absorb at slightly higher frequencies than the tertiary derivatives, as seen in Table 2. $\alpha$-Halogen substituents increase the nitro group frequencies, whereas conjugation of the nitro group to an ethylenic double bond lowers the stretching frequencies.

Conjugation in aromatic compounds causes a shift in the $\text{NO}_2$ vibrations toward lower frequencies\(^17\). Coplanar aromatic nitro groups generally have their $\nu_{as}$ vibration in the region of $1520–1550 \text{ cm}^{-1}$. Strongly electron-withdrawing groups in the para position or bulky groups in the ortho position cause an increase in the $\nu_{as}$ frequency. Electron-releasing groups lower the $\nu_{as}$ frequency.

The nitro group frequencies can be shifted under the influence of a solvent. Usually the shift is negligible in the absence of hydrogen bonding\(^18\), though a

<table>
<thead>
<tr>
<th>Description</th>
<th>Infrared(^a) (cm(^{-1}))</th>
<th>Raman(^b) (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{NO}<em>2$ asym. stretching ($\nu</em>{as}$)</td>
<td>1586</td>
<td>1562</td>
</tr>
<tr>
<td>$\text{NO}_2$ sym. stretching ($\nu_s$)</td>
<td>1377</td>
<td>1377.3</td>
</tr>
<tr>
<td>C–N stretching</td>
<td>918</td>
<td>918.8</td>
</tr>
<tr>
<td>$\text{NO}_2$ sym. bending</td>
<td>658</td>
<td>656.5</td>
</tr>
<tr>
<td>$\text{NO}_2$ rocking</td>
<td>605</td>
<td>608</td>
</tr>
<tr>
<td></td>
<td>477</td>
<td>481</td>
</tr>
</tbody>
</table>

\(^{a}$Vapour. \(^{b}$Liquid.
TABLE 2. Infrared frequencies of aliphatic nitro compounds

<table>
<thead>
<tr>
<th>Nitro derivative</th>
<th>ν&lt;sub&gt;as&lt;/sub&gt; (cm&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>ν&lt;sub&gt;s&lt;/sub&gt; (cm&lt;sup&gt;-1&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>1550 ± 2</td>
<td>1379 ± 3</td>
</tr>
<tr>
<td>Secondary</td>
<td>1550 ± 2</td>
<td>1357</td>
</tr>
<tr>
<td>Tertiary</td>
<td>1536 ± 2</td>
<td>1348 ± 3</td>
</tr>
</tbody>
</table>

decrease in frequency in polar solvents has been recorded for para-substituted nitrobenzenes.

The infrared spectra of nitro derivatives have been recently reviewed. Several papers dealing with various aspects of the infrared and Raman spectra of nitro compounds have appeared recently.

2. Nitroso compounds

Owing to possibilities of dimerization and geometrical isomerism in nitroso compounds, their characteristic frequencies vary with temperature and concentration.

The most important group frequency in these derivatives is due to the N=O stretching vibration. In the nitrosomethane monomer the N=O stretching vibration is found at 1564 cm<sup>-1</sup>, whereas in the nitrosobenzene monomer it appears at 1506 cm<sup>-1</sup>. Generally aliphatic C-nitroso compounds show the free N=O stretching vibration in the region of 1538–1621 cm<sup>-1</sup>, while in aromatic C-nitroso compounds it appears at 1485–1515 cm<sup>-1</sup>. In aliphatic nitroso compounds substitution of an α-hydrogen by an acetyl group causes lowering in the N=O frequency, whereas substitution by a Cl, CN or NO<sub>2</sub> group increases this frequency.

The C—N stretching vibration appears in these compounds around 1100 cm<sup>-1</sup>, and the C—N=O bending in the region of 400–460 cm<sup>-1</sup>. The absorption frequencies of the cis and trans dimers of C-nitroso compounds are given in Table 3.

![Trans dimer](image1)

![Cis dimer](image2)

The trans dimers generally show high-intensity bands in the region 1180–1300 cm<sup>-1</sup>, while cis dimers do not have any remarkable bands in this region. Band intensities may thus serve for the assignment of cis and trans structures to unknown dimers. para-Substituted nitrosobenzenes show increased dimer band intensities with the electron-withdrawing ability of the substituent.

TABLE 3. Infrared characteristic frequencies of cis and trans dimers of C-nitroso compounds

<table>
<thead>
<tr>
<th>R</th>
<th>Trans dimer</th>
<th>Cis dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliphatic</td>
<td>Single band in the region 1176–1290 cm&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>Two bands in the regions 1323–1344 and 1330–1420 cm&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aromatic</td>
<td>Single band in the region 1253–1299 cm&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>Two bands in the regions 1389–1397 and 1409 cm&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
The infrared spectra of some nitroso derivatives are indicative of oxime formation. According to infrared spectroscopic evidence, \textit{p}-nitrosophenol (1) is present in the quinoid oxime structure (2).

\[
\begin{align*}
\text{OH} & \quad \text{NO} \\
\text{N} & \quad \text{OH}
\end{align*}
\]

(1)  

(2)

\(N\)-Nitrosamines in the monomeric state show the \(N\equiv O\) stretching frequency in the region 1430–1530 cm\(^{-1}\), whereas dimers absorb around 1300 cm\(^{-1}\). The \(N\equiv O\) stretching vibration of aliphatic nitrosamines appears around 1425–1460 cm\(^{-1}\), while that of aromatic nitrosamines around 1450–1500 cm\(^{-1}\). The intensity of this absorption and its frequency decrease on going to more polar solvents.

The \(N\equiv N\) stretching vibration of aliphatic nitrosamines appears around 1030–1150 cm\(^{-1}\), whereas in aromatic nitrosamines it appears around 925–1025 cm\(^{-1}\). The \(C\equiv N\) stretching of these compounds is assigned to a band in the region 1160–1200 cm\(^{-1}\), and the \(N\equiv N\equiv O\) deformation mode to a band around 660 cm\(^{-1}\).

The infrared spectra of nitroso derivatives have been reviewed recently\(^2\).

\section{Electronic Spectroscopy}

The electronic spectra of nitro and nitroso compounds have been extensively reviewed\(^12\,13\). A brief summary is presented here.

1. \textit{Nitro compounds}\(^12\)

Both \(n \rightarrow \pi^*\) and \(\pi \rightarrow \pi^*\) transitions are responsible for the observed absorption bands of nitro derivatives. In nitromethane the absorption band due to the \(n \rightarrow \pi^*\) transition appears at 270 nm (\(\log \epsilon = 1.3\)), while the band due to the \(\pi \rightarrow \pi^*\) transition appears at 210 nm (\(\log \epsilon = 4.2\)). In nitroaromatics the absorption bands due to the nitro groups are usually masked by the intense bands due to the \(\pi \rightarrow \pi^*\) transitions of the aromatic moiety.

The nitro group is highly electron-withdrawing, and causes bathochromic shifts of the aromatic absorption bands, and also considerable variation in the intensities. Nitrobenzene in inert solvents exhibits two absorption bands; at 260 nm (\(\epsilon = 8500\)) (probably corresponds to the 203 nm band of benzene), and at 290 nm (\(\epsilon = 1500\)) (corresponding to the forbidden \(\pi \rightarrow \pi^*\) transition of benzene, around 260 nm). \textit{para}-Substituted nitrobenzenes exhibit a bathochromic shift relative to nitrobenzene when substituted with an electron-donating substituent. The absorption spectra of \textit{ortho}-substituted benzenes are governed by electronic and steric effects of the substituents. Substituents in the \textit{meta} position have small effects on the spectra, relative to the parent compounds.

The electronic absorption spectra of 2,4-dinitrophenylhydrazones are utilized in the analysis of carbonyl compounds. 2,4-Dinitrophenylhydrazones of saturated carbonyl compounds absorb at 360 nm (\(\epsilon \sim 20,000\)) while those of \(\alpha,\beta\)-unsaturated derivatives absorb at 380 nm (\(\epsilon \sim 25,000\)).

Several papers dealing with the interpretation of electronic spectra of
21. Detection and determination of nitro and nitroso compounds

Nitroanilines\(^{28,29}\), \(N\)-phenylmaleimide derivatives\(^{30}\) and health-related compounds containing nitro groups\(^{31}\) have appeared recently.

2. Nitroso compounds\(^{13}\)

Monomeric aliphatic nitroso compounds are blue, while the aromatic derivatives have a green colour. Aliphatic nitroso monomers absorb at 220 nm with \(\epsilon \approx 5000\) (\(\pi \rightarrow \pi^*\) transition), at 270–290 nm with \(\epsilon \approx 80\) (\(n \rightarrow \pi^*\) oxygen lone-pair transition) and at 630–790 nm with \(\epsilon \approx 1–20\) (\(n \rightarrow \pi^*\) nitrogen lone-pair transition).

The visible absorption disappears upon oxidation of the nitroso group to the nitro group. The 700 nm band is affected markedly upon dimerization of the nitroso derivative.

In aromatic nitroso derivatives only the long-wavelength \(n \rightarrow \pi^*\) transition is seen distinctly. The lower wavelength \(n \rightarrow \pi^*\) transition is masked by the aromatic absorption bands. The nitrosobenzene monomer absorbs at 194 nm (\(\epsilon \approx 11,890\)), 280 nm (\(\epsilon \approx 10,330\)), 301–350 nm (\(\epsilon \approx 5200\)) and at 680–760 nm (\(\epsilon \approx 40–70\)). When a dimer is formed the \(n \rightarrow \pi^*\) band disappears and a new \(\pi \rightarrow \pi^*\) band emerges in the region of 270 nm (\(\epsilon \approx 1000\)). The change in absorption is expressed by the change in colour from blue to yellow. The wavelength of absorption is lower in the \(\text{cis}\) dimer than in its \(\text{trans}\) isomer.

\(N\)-Nitrosamines are characterized by bands at 235 nm (\(\pi \rightarrow \pi^*\) transition) and at 360 nm (\(n \rightarrow \pi^*\) transition with fine structure). The 360 nm band is affected markedly by dimerization of the nitrosamine.

The electronic structures of nitrosomethane, nitrosoethylene and nitrosobenzene have been studied by the PPP and CNDO/2 methods\(^{32}\).

D. Nuclear Magnetic Resonance

1. Proton NMR

The \(^1\text{H}-\text{NMR}\) spectra of nitro and nitroso compounds have been reviewed\(^{12,13}\). The nitro group exerts an inductive effect on the alkane moiety, and causes a deshielding effect on the protons of the carbon adjacent to it. The chemical shift of the methyl protons of nitromethane is \(\delta = 4.28\) ppm. The effect of the nitro group on the \(^1\text{H}\) chemical shifts of benzene is a combination of inductive, resonance and magnetic anisotropy effects. The chemical shifts of the protons of nitrobenzene with respect to benzene (\(\delta = 7.27\) ppm) are as follows: \(\delta_{\text{ortho}} = 0.92\), \(\delta_{\text{meta}} = 0.25\) and \(\delta_{\text{para}} = 0.38\) ppm\(^{33}\).

\(N\)-Nitrosamines have been studied by \(^1\text{H}-\text{NMR}\) spectroscopy with respect to hindered rotation about the N–N bond. Generally, protons within two bonds removed from the nitroso group and \(\text{cis}\) to it are shielded, and protons \(\text{trans}\) to the nitroso group are deshielded in \(N\)-nitrosodialkylamines. The resonance structure 3 accounts for these findings. C-Nitroso compounds exist as \(\text{cis}\) and \(\text{trans}\) dimers having distinguishable \(^1\text{H}-\text{NMR}\) spectra.

Several papers dealing with the structure and barriers to hindered rotation in \(N\)-nitrosamines have appeared recently\(^{34-38}\).

\[\text{trans, deshielded}: \text{H}_3\text{C}^-\text{N}^+\text{CH}_3 \quad \text{cis, shielded}: \text{H}_3\text{C}^-\text{N}^-\text{CH}_3\]

(3)
2. Carbon-13 NMR

The nitro group exhibits the largest effect of any substituent examined on the carbon of an aliphatic chain. The effect of the NO₂ group on the ¹³C chemical shifts of the aliphatic chain, relative to the parent alkane is as following:

\[ \delta_{O_2N-C(1)-C(2)} = 64.5 \text{ ppm} \]

The ¹³C chemical shifts of the carbons of nitrosobenzene are:\n\[ \delta_{(1)} = 148.3, \delta_{(2)} = 123.4, \delta_{(3)} = 129.5 \text{ and } \delta_{(4)} = 134.7 \text{ ppm.} \]

N-Nitrosamines and N-nitrosoanilines have been studied by ¹³C-NMR spectroscopy with respect to their structure, cis-trans isomerism and the effect of the N—NO group on ¹³C chemical shifts. It has been suggested that apart from the magnetic anisotropic effect of the N—NO group, it also exerts an electronic field effect. Both effects contribute to the ¹³C chemical shifts of the carbons close to the nitroso group. These effects were taken into account in deriving the empirical substituent parameter for the N—NO group.

3. Nitrogen-14 NMR

The ¹⁴N-NMR spectra of nitroalkanes, nitroaromatic compounds as well as various nitroso compounds have been extensively reviewed.

Nitromethane serves as a standard for ¹⁴N-NMR chemical shifts. Generally the ¹⁴N-NMR resonances of nitro compounds appear at higher fields with increasing electronegativity of the group R in R—NO₂. ¹⁴N resonance signals of nitroaromatic compounds occur at higher fields than those of nitroalkanes. The ¹⁴N chemical shift of nitrobenzene is 8 ppm (from CH₃NO₂). Studies of aromatic nitro compounds have indicated little effect on the chemical shifts due to the π-electron conjugation between the substituents.

A double bond exerts a general shielding effect on the ¹⁴N resonance of the nitro group. A double bond at the carbon atom β to the nitro group results in a shielding of about 4 ppm relative to the corresponding nitroalkane or nitrocycloalkane; whereas a double bond at the carbon α to the nitro group causes a high-field shift of about 15 ppm. High-field ¹⁴N chemical shifts observed for anions derived from nitroalkanes have been attributed to an appreciable double-bond character of the carbon—nitrogen bond in the nitro group. The ¹⁴N chemical shifts of several nitroalkanes have been calculated according to the Pople MO theory and compared with experimental values.

The mutually isomeric structures of oximes (4), nitrones (5) and nitroso compounds (6) may be differentiated on the basis of their ¹⁴N chemical shifts: for

- oximes 0 to 50 ppm,
- nitrones 70 to 110 ppm,
- nitroso compounds −400 to −550 ppm (referred to CH₃NO₂ or NO₃⁻ on the screening constant scale).

The tautomeric equilibria present in oxime–nitroso systems may thus be easily observed by means of ¹⁴N-NMR spectroscopy.
The $^{14}$N chemical shifts of some nitroso compounds have been correlated for the nuclear quadrupole coupling constants$^{48}$.

**E. Nuclear Quadrupole Resonance**

Nitrogen-14 nuclear quadrupole effects have been extensively reviewed$^{49}$. The $^{14}$N-NQR spectra of a group of substituted nitrobenzenes and of nitromethane have been reported and analysed in the framework of the Townes and Dailey theory$^{50}$. It has been suggested, that the $z$ direction of the principal axis system, for the electric field gradient tensor at the nitrogen of the nitro group, is in the plane of the molecule and perpendicular to the C—N bond, whereas the $x$ direction is along the C—N bond. The variations of the calculated $\pi$-electron density at the nitrogen of the NO$_2$ group, with changing the substituents on the benzene ring, have been found to be in good agreement with the theories of resonance and inductive effects of the substituents. Satisfactory correlations of the NQR data with the Hammett $\sigma$ and $\sigma_R$ constants have been found.

**III. QUANTITATIVE DETERMINATION**

The quantitative determination of nitro and nitroso compounds has been extensively reviewed$^{1,6-11,51,52}$. We shall mention only briefly the well-established methods. The reader is referred to the cited literature for details and procedures, as well as for other known methods. Recent developments will be emphasized here.

**A. Titrimetric Methods**

1. *Nitro compounds*

Reductive techniques$^{1,6,7,9-11}$ are the most popular for the determination of nitro compounds. The overall reduction to the amine can be accomplished in various ways, depending on the type of compound. The analysis may be based on the determination of the excess of reductant, or the amine, or water formed in the reaction.

The most popular reducing agents employed are: Sn$^{2+}$, Ti$^{3+}$, Cr$^{2+}$ and V$^{2+}$. Usually a standard ferric ammonium sulphate solution is used for the back-titration of the excess reducing titrants. The whole procedure has to be carried out in the absence of oxygen. Detailed procedures using titanous chloride (most popular) and chromous chloride are given by Siggia$^7$ and by Gawargious$^9$. The reductive methods are applicable to aliphatic and aromatic nitro compounds, on micro and macro scales. If solubility problems in aqueous solutions arise in some cases, alcoholic or alcohol–water media may be used.

Primary and secondary nitroalkanes can be accurately determined by the chlorination reaction with excess sodium hypochlorite, and subsequent estimation of the unconsumed reagent by titrimetry$^1$.

Aliphatic nitro compounds with the nitro function attached to a primary or secondary carbon atom, can enolize to the *aci* form $7$. The *aci* form is titratable as acid
in nonaqueous basic medium, thus enabling the direct determination of the nitro derivative\(^1\).\(^9\).\(^11\).

Procedures for the determination of aromatic nitro compounds by measurement of water produced in their reduction or condensation reactions have been described\(^1\).\(^6\).\(^7\).\(^9\).\(^11\).

2. **Nitroso compounds**

C-Nitroso compounds can be reduced to the corresponding amine. \(N\)-Nitroso compounds are usually reduced to the corresponding substituted hydrazines; but a few undergo cleavage at the \(N\)\(\longrightarrow\)\(N\) bond under reducing conditions, yielding the corresponding amine.

Reductive titrimetric methods for the determination of nitroso compounds, similar in principle to the methods applicable to nitro compounds, are well established\(^1\).\(^6\).\(^7\).\(^9\).\(^11\). An iodometric method for the determination of \(C\)-nitroso compounds has also been described by several authors\(^1\).\(^6\).\(^9\).\(^11\).

3. **Recent developments**

\(Fe^{+2}\) in acidic or alkaline medium is a suitable reducing agent for the quantitative titrimetric microdetermination of aromatic nitro groups according to equations (10) and (11)\(^5\).\(^3\). The same method is also suitable for the microdetermination of aromatic

\[
\text{Ph-NO}_2 + 6 \text{Fe}^{+2} + 6 \text{H}^+ \rightarrow \text{Ph-NH}_2 + 6 \text{Fe}^{+3} + 2 \text{H}_2\text{O} \quad (10)
\]

\[
\text{Ph-NO}_2 + 6 \text{Fe(OH)}_2 + 4 \text{H}_2\text{O} \rightarrow \text{Ph-NH}_2 + 6 \text{Fe(OH)}_3 \quad (11)
\]

\[
\text{Ph-NO} + 4 \text{Fe}^{+2} + 4 \text{H}^+ \rightarrow \text{Ph-NH}_2 + 4 \text{Fe}^{+3} + \text{H}_2\text{O} \quad (12)
\]

\[
\text{Ph-NO} + 4 \text{Fe(OH)}_2 + 3 \text{H}_2\text{O} \rightarrow \text{Ph-NH}_2 + 4 \text{Fe(OH)}_3 \quad (13)
\]

\(C\)-nitroso compounds according to equations (12) and (13). The acidic medium is found suitable for the reduction of mononitro aromatic compounds substituted with electron-attracting groups, and for di- and poly-nitro aromatic compounds. Nitro hydrocarbons and aromatic nitro compounds substituted with electron-releasing groups are not reduced quantitatively. The alkaline medium is found to be suitable for the reduction of nitro hydrocarbons and mononitro aromatic compounds substituted with electron-attracting or -releasing groups. Di- and poly-nitro aromatic compounds are not reduced quantitatively. The nitroso compounds are satisfactorily reduced in both acidic and alkaline media. After the reduction step thiocyanate is added and the \(Fe^{+3}\) formed by the reduction is titrated with \(Ti^{+3}\) solution to the disappearance of the red colour of the \(Fe^{+3}\)\(\longrightarrow\)SCN\(^-\) complex\(^5\).\(^3\).

A method similar to that given above, based on the reduction of nitro and nitroso compounds with \(Fe(OH)_2\) has been described by Bartha\(^5\).\(^4\). The reduction is performed in a boiling alkaline solution of \(FeSO_4\) to avoid the oxidation of \(Fe(OH)_2\) by atmospheric oxygen and the resulting \(Fe^{+3}\) is determined by titration with \(Hg_2(\text{NO}_3)_2\).

Determination of aromatic mono-, di-, and tri-nitro compounds on the microscale by direct reduction with \(Fe^{+2}\) using potentiometric or amperometric end-point detection has been described by Velikov and coworkers\(^5\).\(^5\). The direct titration of the nitro group with \(Fe^{+2}\) to yield amino derivatives is possible by using alkaline solutions of sorbitol as the titration medium. In this medium the \(Fe^{+3}\) formed is bound in a strong complex, and the formal redox potential of the \(Fe^{+3}/Fe^{+2}\) system is
21. Detection and determination of nitro and nitroso compounds

decreased enough to permit the reduction. This method eliminates the need for unstable reductants for the titration, or an indirect determination.

A quantitative and specific microdetermination of \( m \)-dinitro aromatics by reaction with KCN has been developed by Hassan. \( m \)-Dinitro aromatics react with cyanide in a 1:1 molar ratio, whereas \( sym \)-trinitro aromatics consume 2 moles of KCN per mole. The excess cyanide is determined by a potentiometric titration with \( \text{AgNO}_3 \) using a silver sulphide or silver cyanide selective electrode.

Nitro and nitroso compounds have been determined by reduction with a known excess of \( \text{Ti}^{+3} \) solution and thermometric titration of the excess with \( \text{Fe}^{+3} \) solution. The thermometric detection of the end-point has some advantages over a visual indication, especially for some industrial materials and for highly coloured samples.

1,2,4,6-Tetraphenylpyridinium acetate has been evaluated recently for the potentiometric precipitation titration of semimicro amounts of organic anions. The method allows determination of nitrophenols, some dinitro- and trinitro-phenols and various halogenated nitrophenols.

A microdetermination of nitro compounds based on reduction with \( \text{TiCl}_3 \) in dimethylformamide solution and subsequent titration of the water formed in the reaction has been described. The \( \text{TiCl}_3 \) is generated from \( \text{TiCl}_4 \) in dimethylformamide by electrolysis with an Hg cathode. The water is determined by Karl Fischer titration.

B. The Modified Kjeldahl Method

Nitro and nitroso compounds can be determined by reduction and decomposition to ammonia, and determination of the latter by the Kjeldahl method (equation 14). The method is completely nonselective and can be specific only when other nitrogenous species are absent.

\[
\text{RNO}_2 + \frac{1}{2} \text{H}_2\text{SO}_4 \rightarrow \text{RNH}_2 + \frac{1}{2} \text{H}_2\text{SO}_4 + \text{Na}_2\text{SO}_4 \rightarrow \text{NH}_3
\]

C. Gasometric Methods

Nitro and nitroso functions attached to an amino liberate NO on treatment with Hg in \( \text{H}_2\text{SO}_4 \). Aliphatic and aromatic nitro compounds can be decomposed to nitrite or nitrate which liberate NO on treatment with the same reagent. The volume of the evolved NO gas is measured in a nitrometer, thus enabling the determination of the nitro function.

A gasometric micro method applicable to aromatic nitro and nitroso compounds has recently been described by Hassan and coworkers. The method is based on the reduction of the compounds with zinc in HCl to the corresponding amino compounds, and the subsequent deamination reaction with \( \text{HNO}_3 - \text{HCl} \). The \( \text{N}_2\text{O} \) gas evolved upon the deamination reaction is collected in a nitrometer. Samples of 3–5 mg have been determined by this method within 0.2% absolute of the theoretical nitrogen content.

D. Electroanalytical Methods

Polarographic and coulometric reductions can serve for sensitive determination of aliphatic and aromatic nitro compounds, as well as for nitroso derivatives, in aqueous or organic solvents. For details and procedures of well-established methods the reader is referred to References 1 and 9.

A selective coulometric titration of mixtures of nitro and nitroso aromatic
compounds has been described by Bourg and coworkers\textsuperscript{62}. The nitroso aromatic derivatives were determined in the presence of their parent nitro analogues by titration with Ti\textsuperscript{+3}, which was generated coulometrically from Ti\textsuperscript{+4} in an aqueous EDTA solution. A subsequent coulometric titration with Cr\textsuperscript{+3} enabled the determination of total nitro and nitroso content, and the estimation of the nitro derivatives by difference.

A coulometric determination of individual nitro and nitroso compounds, and their mixtures, with externally generated Ti\textsuperscript{+3} has been described by Mitev and coworkers\textsuperscript{63}. Both the nitro and the nitroso groups were found to react quantitatively with Ti\textsuperscript{+3} in a citrate buffer solution, whereas only the nitroso group reacted in 6M HCl. The method thus enables a selective determination of nitro and nitroso compounds.

The analysis of organic water pollutants including nitroso and nitro derivatives\textsuperscript{64}, the polarographic determination of some aromatic nitro derivatives in corresponding amines\textsuperscript{65} and the simultaneous polarographic determination of N-unsubstituted and N-substituted nitroazoles\textsuperscript{66} are well described in the literature.

Walters and coworkers have described a procedure for the separation of volatile and nonvolatile N-nitrosamines, and their determination at low levels by differential polarography in acidic media\textsuperscript{67}.

E. Spectroscopic Methods\textsuperscript{1,6,9,11}

1. Nitro compounds

   Most procedures for the spectrophotometric determination of aliphatic nitro compounds are based on their conversion to nitrite, followed by determination of the latter by the Griess reaction\textsuperscript{1,9}. \textit{m}-Dinitro aromatics can be determined colorimetrically via their reaction with diethylamine in dimethyl sulphoxide\textsuperscript{1}. Aromatic nitro compounds can also be determined colorimetrically after their conversion to the corresponding amines\textsuperscript{1}.

2. Nitroso compounds

   C-Nitroso compounds form coloured solutions in some organic solvents and can thus be measured directly\textsuperscript{1}. One colorimetric method for determining these compounds is based on their conversion to the coloured azoxy derivative\textsuperscript{1}. Another reaction that yields a coloured product is condensation of an aromatic nitroso derivative with a primary aromatic amine to yield a coloured azo compound, which can be determined spectrophotometrically.

3. Recent developments

   Aliphatic and aromatic nitro compounds have been determined photometrically at 470 nm in \(\mu\)g amounts\textsuperscript{68}. The sample was used to oxidize Fe\textsuperscript{3+} in alkaline solution to Fe\textsuperscript{3+}, and the latter was determined photometrically after reaction with KSCN.

   LiAlH\textsubscript{4} in tetrahydrofuran has been used to reduce aromatic nitro compounds to yield coloured azo compounds, which were determined spectrophotometrically\textsuperscript{69}. The method enables analysis in \(\mu\)g quantities within 2.5\%. NaBH\textsubscript{4} in ethanol has been used for a specific spectrophotometric determination of \textit{meta} di- and tri-nitro aromatic compounds\textsuperscript{70}. The coloured products of the reaction were measured at 520–530 nm. The method enables the determination of \(\mu\)g amounts within 2\%.
Zinc in the presence of NH₄Cl has been used as the reducing agent to convert aromatic nitro compounds to arylhydroxylamines, which form violet complexes with Fe⁺³ and acetyl chloride⁷¹. Spectrophotometric determination of the complexes enables the determination of the aromatic nitro derivatives in μg amounts within 1.2%. Aromatic nitro compounds have been determined by reduction with formamidine–sulphinic acid, and subsequent spectrophotometric determination of the Schiff bases formed was by condensation of the resulting amines with \( \textit{p}-\text{dimethylaminobenzaldehyde} \)⁷².

A separate spectrophotometric determination of the three isomeric nitrophenols⁷³ and simultaneous determination of nitropyrazoles⁷⁴ have been described.

An automatic colorimetric analysis of \( \text{\textit{N}} \)-nitroso compounds, based on their cleavage by UV irradiation followed by determination of the released nitrite has been described⁷⁵. The nitrite was determined using its diazotization reaction with sulphanilic acid. The coupling of the product with \( \textit{N}-1\)-naphthylethylenediamine yielded the azo dye which was determined colorimetrically.

Aromatic nitro compounds on the μg scale have been determined by a fluorimetric method consisting of the steps shown in equation (15). The fluorescent enediol (8) was determined fluorimetrically⁷⁶.

\[
\begin{align*}
\text{ArNO}_2 & \xrightarrow{\text{Fe}^{+2}} \text{ArNH}_2 \\
\text{ArNH}_2 & \xrightarrow{\text{SO}_3\text{Na}} \text{NHAr} \\
\text{NHAr} & \xrightarrow{\text{KBH}_4} \text{ArHO} \\
\text{ArHO} & \xrightarrow{} \text{ArOH} \\
\end{align*}
\]

\[(15)\]

**F. Gravimetric Determination⁷¹,⁷⁶,⁹,¹¹**

The gravimetric method of analysis is suitable for the determination of aromatic nitro and nitroso compounds. It is based on the reduction of these groups by metals (usually tin or copper) in acidic solutions. The weight of the consumed metal (by the reduction process) is directly related to the amount of nitro or nitroso compounds present. The method is simple and generally applicable on the macro scale. For procedures the reader is referred to the literature⁷¹,⁷⁶,¹¹.

**G. Other Methods of Determination**

Aromatic nitro compounds can be determined indirectly by reduction to the amine stage and subsequent determination of the latter. Primary and secondary aliphatic nitroso compounds rearrange readily to the corresponding oximes and are most conveniently determined as such⁷¹.
IV. DETECTION AND DETERMINATION BY CHROMATOGRAPHIC METHODS

Nitro and nitroso compounds rearrange and decompose relatively easily on heating or by contact with chromatographic supports. The most suitable method for the separation of nitro or nitroso compounds from other compounds, or from each other, is thus dependent on the characteristics of the sample, and no general procedure can be given. Some representative examples of the use of chromatographic methods for the detection and quantitative determination of nitro and nitroso compounds will be mentioned here. Practical information concerning the application of various chromatographic methods to the analysis of these compounds can be found in the Handbook of Chromatography.

A. Gas Chromatography (GC)

As many nitro compounds have low volatility or decompose to some extent on heating, direct GC determination is sometimes impossible. Siggia and coworkers have described a method for the determination of nonvolatile nitro compounds that uses carbohydrazide reduction of the nitro group to the amino group, and GC analysis of the products. The analysis is specific and enables resolution of mixtures of nitro and azo compounds.

The ortho, meta and para isomers of chloronitrobenzenes and nitroanilines are separated on columns packed with 3% cyclohexanedimethanol succinate on Gas-Chrom Q. A quantitative method for collection of air pollutants, including nitrobenzene, on a porous polymer (Tenax GC) trap, and their analysis by GC has been described by Parsons and Mitzner. Fusion reaction GC including its application to nitro compounds has been reviewed by Whitlock and Siggia. The effect of the dipole moment of nitroaromatic hydrocarbons on their retention in gas-liquid chromatography, has been the subject of a recent work.

B. Liquid Chromatography (LC)

LC has the advantage of being applicable to thermally unstable compounds and to the separation of nonvolatile compounds. Due to the high performances achieved using the HPLC (High Performance LC) technique, it is a promising method for fast detection and quantitative determination of nitro and nitroso compounds, in the presence of other organic compounds.

The HPLC technique has been used for the separation and qualitative analysis of various nitroaromatics and other constituents of explosive formulations. Toluene, p-nitrotoluene, 2,4-dinitrotoluene and 2,4,6-trinitrotoluene were separated on Corasil II within 15 minutes, using 60% hexane/40% CH$_2$Cl$_2$ as the mobile phase, with a refractive index detector.

Ortho, meta and para nitroanilines have been separated on a chemically bonded Corasil I stationary phase using HPLC. The mobile phase was 0.5% isopropanol in heptane, and a UV monitor was used for detection. HPLC has been used for the separation and quantitative determination of 2-nitrodiphenylamine (a stabilizer used in explosives) and its nitro derivatives, on Corasil II with a mobile phase of 20% CH$_2$Cl$_2$/80% cyclohexane, by one group, and on Microbondapack C18 with a mobile phase of 67.5 methanol in water by another group.

β-Nitroso-α-naphthol and its isomer α-nitroso-β-naphthol have been separated by ligand exchange chromatography, using a strong acid-type resin in the Fe$^{3+}$ form as the stationary phase. 50% ethanolic ammonia solutions (pH 9.5 and 12.0) have been used for the stepwise elution of the isomeric nitroso compounds.
21. Detection and determination of nitro and nitroso compounds

C. Paper and Thin-layer Chromatography

These methods enable qualitative identification and quantitative determination. Their main advantage is their simplicity and sensitivity; however they are very dependent on the experimental conditions, so it is compulsory to run standards together with the unknown. For a given mixture of compounds it is usually difficult to achieve a separation of all the components in one run, and sometimes several runs using different conditions are needed. The quantitation of the methods is also quite difficult.

A mechanistic model of liquid–solid chromatography has been proposed and given experimental verification. The model assumes that adsorption complexes are formed between the surface of the thin layer, and an electron-donor function on the solute. The chromatographic behaviour of aromatic nitro compounds on thin layers of silica, alumina, Florisil and magnesium silicate, has been examined and interpreted. The mobile phase was a mixture of a polar solvent and a nonpolar diluent. The adsorption was analysed in terms of the mole fraction of the polar solvent and the number and positions of nitro groups. Typically, polynitro compounds are retained longer and the selectivity of separation is generally higher with dilution of the polar component in the developing solvent.

Jäger has used TLC on silica and cellulose plates for the detection and characterization of nitro derivatives of some polycyclic aromatic hydrocarbons from airborne particulates (application to air pollution analysis). The nitro derivatives were reduced to their fluorescent amino analogues on the plate, and their subsequent treatment with the quenching reagents aniline and phenylhydrazine served as a basis for their characterization.

Schutz and Schindler have developed a method for the detection and separation of sixteen nitropesticides. The compounds were separated on silica TLC plates, and then converted with TiCl₃ to primary aromatic amines, which were detected by diazotization and subsequent coupling with Bratton–Marshall reagent. The resulting dyes were eluted with dimethylformamide and determined quantitatively by photometry.

A method for the quantitative determination of a nitro-group containing drug in blood and plasma by TLC has been developed by Haefelfinger. The method is generally applicable to aromatic nitro compounds. The determination is based on TLC separation, subsequent reduction of the nitro group with SnCl₂, and reaction of the resulting primary aromatic amine with fluorescamine. A direct fluorimetric scanning of the resulting fluorescent spots enables the determination of the drug with high sensitivity.

Klemm and coworkers have measured the $R_F$ values of 43 nitro-substituted arenes on alumina and on silica gel TLC plates in an atmosphere of constant relative humidity. They have found that adsorbability increases with substitution of a second nitro group on the benzene ring, and that $R_F$ values on alumina plates are more sensitive to the substitution pattern than on silica gel plates. It was concluded from the experimental data that nitro-substituted arenes are adsorbed on alumina and on silica gel preferentially in a flat manner, with the nitro group in a coplanar arrangement with the aromatic ring. The twisting of the nitro group from coplanarity with the ring resulted in a lower retention. Separability was found to be better on alumina plates than on silica gel plates under the same conditions. The spots of nitroarenes were detected by spraying the developed plates with Rhodamine B and observation in UV light.

An examination of 60 nitro derivatives and the products of their incomplete reduction, by chromatography on thin layers of gypsum-bound silica gel, and
detection by reaction on the plates, has led to the conclusion that detection by reaction is superior to examination in UV light. The reaction sequence used was reduction of the nitro group, diazotization of the resulting amino derivative and azo coupling to yield a dye. It has been found that Sn\(^{+2}\) in conc. HCl is a superior reducing agent to zinc, and that \(N-(1\text{-naphthyl})\text{ethylenediamine}\) is superior to \(\beta\text{-naphthol}\) for the azo coupling reaction. The detection sensitivity was 0.05 μg.

Nitroso derivatives were not reduced under the above conditions, and do not interfere with the determination.

Other methods for the detection of nitro compounds on TLC plates are spraying with 30% 3,3'-iminobispropylamine in pyridine, or with an acetone solution of tetrathylammonium hydroxide (10% aqueous solution), 1:1 by volume.

D. Paper Electrophoresis

The number of nitro groups in nitrophenols, nitrobenzoic acids and nitronaphthalenes can be detected by reduction of the nitro derivatives with zinc in acetic acid, and comparison of the mobilities of the reduced compounds with those of the starting materials in paper electrophoresis.

V. RECENT DEVELOPMENTS IN THE DETECTION AND DETERMINATION OF N-NITROSO COMPOUNDS

The investigations concerned with the role of N-nitroso compounds in human cancer have prompted the development of selective methods for the trace analysis of both volatile and nonvolatile N-nitroso compounds in foods and other biological mixtures, and in the environment. The subject has been covered extensively by books, reviews and articles, thus only a brief introduction will be given here.

The most recent methods for detection and determination of N-nitroso compounds are based on the thermal energy analyser (TEA), a selective detector for the N-nitroso group, developed by Fine and coworkers. The detection is based on the decomposition of the N-nitroso compound into a nitrosyl radical (\(\cdot\text{NO}\)), and its reaction with ozone to yield electronically excited NO\(_2\). The emitted light, in the near infrared region of the spectrum, by the decay process of the excited NO\(_2\) to its ground state, is detected and measured by means of an S-20 photomultiplier tube. The intensity of the emission is proportional to the \(\cdot\text{NO}\) concentration, and hence to the N-nitroso compound concentration. The method enables the detection of N-nitroso compounds below 1 μg/kg in foodstuffs and other biological materials.

The TEA technique has been combined with GC and with HPLC, and has so enabled the analysis of a wide variety of N-nitroso compounds. Problems of artifacts in the analysis of N-nitroso compounds have been discussed in a recent review.

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21. Detection and determination of nitro and nitroso compounds

CHAPTER 22

Deaminations (carbon–nitrogen bond cleavages)

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I. INTRODUCTION

The organic chemist, like the biochemical cell, frequently encounters the problem of carbon–nitrogen bond cleavage. Thus, academic and industrial organic chemists deal with deaminations during syntheses, degradations, and analyses; and also as mechanistic problems. Biochemists likewise frequently encounter a wide variety of biological deaminations. More recently, deaminations, especially those involving nitrosations and nitrosamines, have been the centre of much study with respect to environmental chemistry, toxicology and related areas.

In some ways the problems of carbon–nitrogen bond cleavage are similar to the problems involved in carbon–oxygen bond breakage, but unlike the inventory of dehydroxylations, the inventory of deaminations which are both simple in execution and high-yielding in products is relatively small. In fact until the 1950s there were few if any nonaromatic deamination methods which were comparable in facility and efficiency to dehydroxylation methods. Nonetheless many deamination procedures such as the nitrous acid reaction and the Hoffmann elimination date from the early years of organic chemistry. These historical and still useful reactions were almost certainly discovered via empirical techniques, since mechanistic
predictions as we use them today were all but totally unknown in the 19th century. However, mechanistic logic is the best and most interesting way to analyse deamination reactions both with respect to a review of known methods and to predicting future deamination techniques. Thus, by using mechanistic reasoning, the large number of deamination reaction procedures, most of which at first glance appear to be unrelated, neatly sort themselves into only a few reaction types, many of which have analogous procedures in dehydroxylation chemistry.

A. The Principle of Activation

Amines must first be activated before deamination can occur under laboratory conditions. This activation principle is best observed by analogy to the alcohol and ether series. In particular, alcohols, ethers and amines do not normally undergo simple substitutions at the carbon to heteroatom bond without some form of activation, since $S_N$ reactions on the unactivated compounds give rise to strongly basic, and consequently very poor, leaving groups (equation 1)\(^3\).

\[
\begin{align*}
ROH + X^- & \rightleftharpoons RX + OH^- \\
ROR' + X^- & \rightleftharpoons RX + OR' \\
RNH_2 + X^- & \rightleftharpoons RX + NH_2^-
\end{align*}
\] (1)

With the above-type functional groups, however, the carbon–oxygen or the carbon–nitrogen bonds can be thermodynamically and/or kinetically weakened by using at least one of the following activating principles.

1. The heteroatom may be altered in some fashion, as for example, by forming an isolable sulphonate (1) or disulphonimide (2) derivative (equations 2 and 3) (see Sections II.A–C and II.G)\(^{31,109}\).

\[
ROH + R'\text{SO}_2\text{Cl} \rightleftharpoons ROSR' + HCl
\] (2)

\[
RNH_2 + 2 R'\text{SO}_2\text{Cl} \stackrel{\text{base}}\longrightarrow R-N\text{SO}_2\text{R}'+ 2 \text{HCl}
\] (3)

2. The carbon bonded to the heteroatom and the heteroatom may simultaneously be altered in some way, as for example, by oxidation (equations 4–6) (see Section IV).

\[
R_2C-OH \stackrel{[\text{o}]\text{[o]}}\longrightarrow R_2C=O \stackrel{R'\text{NH}_2}{\text{H}^+} \longrightarrow R_2C=NR' \] (4)

\[
R_2C-NH_2 \stackrel{[\text{o}]}\longrightarrow R_2C=NH \stackrel{H_2O}{\longrightarrow} R_2C=O + NH_3
\] (5)
It is interesting to note that in these oxidation reactions, the carbon to heteroatom bond is activated from a kinetic viewpoint, while being strengthened from a thermodynamic standpoint.

(3) The procedures wherein only the organic portions of the molecules are altered to labilize the molecule for carbon–nitrogen bond cleavage have rarely been exploited in deamination chemistry. However, new general procedures for deamination may be found by reasoning along these lines. Thus, for example, the activation of the alkyl moieties of amines might occur at the α-, β, or γ-positions.

(a) Activation at the α-position: Most of the dehydroxylation and deaminations in the literature, which at first glance appear to be occurring on nonactivated alcohols or amines, are in fact occurring on activated alcohols or activated amines wherein the activation is on the organic moiety of the molecules. Thus, the catalytic hydrogenolysis of benzyl alcohols and the catalytic hydrogenolysis of tertiary amines having at least one N-benzyl group are in actuality examples of labilization to dehydroxylation or deamination via some activating substituent at the position α to the heteroatom, with the activating group being the phenyl group (e.g. see Section III.D).

Another example of α-activation with respect to dehydroxylation of alcohols involves one of the oldest and most common synthetic procedures in organic chemistry – namely the conversion of a primary alcohol into some activated carboxylic acid derivative (equation 7). Thus, for example, alcohols may be converted to a variety of amines by this procedure, without the complications of eliminations, rearrangements, etc.

Similarly, oxidizing reagents which might convert amines to amides would lead to kinetic weakening of the carbon–nitrogen bond with analogous synthetic utility (equation 8). No reagents, however, are currently known which accomplish this conversion in good yield, although oxidations of primary carbinamides to carboxylic acids with basic potassium permanganate and other reagents, are known, and may very well proceed via amides as intermediates (see Section IV.E).

Yet another activation for deamination via the α-position would involve the conversion of a saturated amine to an enamine (equation 9), since the enamine is readily hydrolysed to the corresponding carbonyl compound. Such procedures are modifications of the procedures summarized in equation (6), and would appear to be a very promising approach for innovations in the field (see also Sections IV.F and IV.C).
(b) **Activation at the β-position**: The reaction scheme described in equation (9) might also be considered as an example of initial activation at the β-position. Yet another type of β-activation might be considered, however, since Mannich-type amines are more susceptible to eliminations (via reverse 1,4-additions) than are most other amines (equation 10) (see Section II.J.3).

(c) **Activations at the γ-position**: Similarly Mannich-type bases may be produced via the sequence in equation (11), wherein R represents an unsaturated functionality such as phenyl.

### B. Oxidation States in Deamination

Deaminations may be organized according to changes in oxidation state which occur in the alkyl group during the deamination process. Thus, deaminations resulting in every oxidation state change have been observed.

1. **Deaminations without any change in oxidation state at the alkyl carbon**

   The most common deamination techniques, such as the Hofmann elimination, the nitrous acid reaction, the nitrosoamide and triazene decompositions, and the disulphonimide and triphenylpyridine substitutions, involve either substitution or elimination without changes in oxidation state of the alkyl products, although of
22. Deaminations (carbon–nitrogen bond cleavages)

course the leaving activated nitrogen moiety is frequently oxidized during these procedures (see Section II).

(2) Reductive deamination
Several processes have been developed for converting amines into alkanes (Section III).

(3) Oxidative deamination
(a) Conversions to aldehydes or ketones. A variety of procedures are known wherein primary or secondary amines are first oxidized to imines, which are then hydrolysed to the corresponding carbonyl compound (Sections IV.A, B, C and F).
(b) Conversions to carboxylic acids. Many oxidizing agents have been found which convert primary carbamines to either carboxylic acids, nitriles or their oxidation state equivalents (Sections IV.A, D and E).

C. Deaminations of Arylamines

Aromatic amine deaminations most commonly involve a different set of problems and mechanisms than do the aliphatic amine deaminations. Almost all deaminations of arylamines centre around the gaseous nitrogen leaving group, but the few exceptions will also be briefly discussed.

D. The Scope and Organization of this Chapter

A number of excellent reviews on various aspects of deamination have appeared within the last few years including one by White and Woodcock, emphasizing nitrogen gas leaving groups, in the earlier volume in this series and one by Wulfman, covering aspects of aromatic deaminations, in a recent volume in this series. Other reviews have discussed yet other aspects of gaseous nitrogen leaving groups. Thus, while this chapter will be comprehensive in scope, it will be selective in emphasis. Those topics which have been previously reviewed will only be briefly summarized here, with appropriate references to the relevant reviews.

The main topic organization of the chapter is according to change in oxidation states. Subheadings in Sections II and III and to a lesser extent in Section IV are based on leaving groups. Furthermore, the aliphatic and aromatic cases are usually divided into separate subheadings where applicable. A final topic (Section V) is devoted to biochemical, bioorganic, and environmental tie-ins.

We wish to thank Dr. Phillip J. DeChristopher for reading an early draft of Sections I and II of the manuscript and for making some helpful suggestions as well as forwarding some useful references (especially those pertaining to industrial aromatic deaminations). We also wish to thank Professor Alan R. Katritzky for a preprint copy of his excellent review for Tetrahedron on his deaminations via pyrillium cations. Since this highly versatile procedure is reviewed by its developer, somewhat less space is being devoted to it here than would otherwise have been the case. We also wish to thank all those others, too numerous to mention individually, who sent us reprints of their articles.

II. DEAMINATIONS OF AMINES, WHICH INVOLVE NO CHANGE IN OXIDATION STATE IN THE ALKYL OR ARYL MOIETIES

Most of the well-known and practical deaminations fall under this topic. A variety of leaving groups ranging from one of the worst (the NH₂⁻ anion) to one of the
best leaving groups (nitrogen), have been observed during carbon–nitrogen bond cleavages. The oldest deamination techniques centre around nitrogen gas (via nitrous acid) and trialkylamine leaving groups. In fact until the mid 1960s these were still the only commonly observed leaving groups during deamination procedures, although a number of more sophisticated modifications were devised in the 1950s and 1960s towards activating amino groups with the end goal of forming the gaseous nitrogen leaving group\textsuperscript{31,88,231,264,297,298,394}. In 1966, however, a prediction was made that a whole new category of nitrogenous leaving groups should be possible by forming activated derivatives of amines, which would be analogous to the well-known sulphonate ester activating groups in the alcohol series (equations 2 and 3). These predictions were based upon a consideration of the $K_a$s of a variety of potential leaving groups. From this type of an analysis, such leaving groups as the anions derived from disulphonimides, carboximides, saccharin, sulphonamides, barbituric acid and uracil should be fair-to-good leaving groups\textsuperscript{31,32,34}. All these anions, with the exception of the last two, have since been observed.

<table>
<thead>
<tr>
<th>Leaving group</th>
<th>pK$_a$ of the conjugate acid of leaving group</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH$_2^-$</td>
<td>&gt;35</td>
<td>316</td>
</tr>
<tr>
<td>R-NH$^-$</td>
<td>&gt;35</td>
<td>316</td>
</tr>
<tr>
<td>iNH$_3^-$; RNH$_2$</td>
<td>-9–11</td>
<td>316</td>
</tr>
<tr>
<td>R$_2$NH; R$_3$N</td>
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<td>316</td>
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<tr>
<td>Aziridinc</td>
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<td>316</td>
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<tr>
<td>R–C–NR$^-$</td>
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<td>316, 87</td>
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<tr>
<td>Acetamidine</td>
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<td>316</td>
</tr>
<tr>
<td>Amidine</td>
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<td>N-Phenylurea</td>
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<tr>
<td>Succinimide anion</td>
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<td>Phthalimide anion</td>
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<td>Saccharin anion</td>
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<td>$N,N$-Disulphonimides</td>
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<tr>
<td>Uracil anion</td>
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<td>Barbituric acid anion</td>
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<tr>
<td>Purine</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<td>$o$-Nitroaniline</td>
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</tr>
<tr>
<td>2,4,6-Trinitroaniline</td>
<td>-9.4</td>
<td>316</td>
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observed at least once in a variety of new deamination procedures. And while heterocyclics, such as barbituric acid and uracil, have not yet been incorporated in any deamination scheme, Katritzky and coworkers have recently developed an analogous scheme wherein pyridine derivatives become leaving groups. Table I lists the pKₐ's of the conjugate acids of several amines and amine derivatives which have already been observed as leaving groups, or which may possibly be used as leaving groups in the future. Of the several new nitrogenous leaving groups, the various disulphonimide types and the pyridine types have demonstrated the most synthetic promise. This section of the chapter is organized with respect to leaving groups.

A. N,N-Diarylsulphonimide Anion (3) Leaving Groups

As predicted from the pKₐ's in Table 1, several disulphonimides (2) have been treated with a variety of nucleophiles under a wide diversity of conditions to give the corresponding substitution and/or elimination products (equation 12). Since the overall deamination process which involves activation of the primary amine by forming the disulphonimide (2) followed by treatment of 2 with nucleophiles has proved to be simple in execution, versatile in scope, and often high-yielding, this deamination technique will be discussed in some detail.

\[
R \rightarrow N(SO₂R')₂ + Y^- \rightarrow RY + N(SO₂R')₂ (\text{+ alkenes})
\] (12)

1. Synthesis and properties of N-alkyl-N,N-disulphonimides

A variety of crystalline, stable disulphonimides (2) may be prepared by a simple two-step procedure (equation (13)). The yields are generally excellent for most primary and secondary carbinamines. More recently, Bartsch has reported a one-step variation on this procedure. Diarylsulphonimides (2) derived from such sterically hindered amines as tertiary carbinamines, adamantyl amine, exo-2-aminonorbornane and aminodiphenylmethane, however, cannot be prepared, even though there are no problems in obtaining the corresponding arylsulphonamides. In an effort to obtain these difficult cases, Hutchins and his research group introduced a variety of modifications, including one...
originally devised by Pan and Fletcher\textsuperscript{322} employing thallium salts, without any success. A few other procedures for disulphonimide synthesis have been reported\textsuperscript{2,174,234,347b,370}. Finally a technique for synthesizing polymeric diarylsulphonimides has been described\textsuperscript{295}, as has one for \(\sigma\)-benzenedisulphonimides\textsuperscript{182,198}.

Some chemical and physical properties of a large number of disulphonimides have been reported, including IR and PMR properties\textsuperscript{110,112,113}.

Besides deamination, the most characteristic chemical properties of disulphonimides are their resistance to acid-catalysed hydrolysis, and their partial saponification when they are treated with basic nucleophiles such as hydroxide, cyanide, hydrides or mercaptide\textsuperscript{100,101,110,113,156,199,200}.

2. Scope of the reaction with respect to \(R, R'\) and \(Y\)

The yields of substitution products are highest when the \(R\) groups are unhindered primary alkyls. Unhindered secondary alkyls also give fair-to-good yields of substitution products. Both the primary and secondary cases react with little or no skeletal rearrangement. As might be predicted, cyclohexyl derivatives give high yields of alkene, but poor yields of substitution products, regardless of the nucleophile. Since diarylsulphonimides of tertiary carbinamines and other hindered amines could not be prepared, these deaminations are not applicable to bulky carbinamines\textsuperscript{7,36,109,112–114,199,200}.

The nucleophiles, \(Y^-\), which have given the best yields in these substitution reactions, are iodide, bromide, chloride, thiophenoxide and phenylselenide ions\textsuperscript{7,109,112–114,436}. Fair-to-good yields of 3,5-dinitrobenzoates have also been obtained\textsuperscript{101,102}. Other substitutions have been observed with the homocysteine thiolate anion, azide, mercaptide, tosylate, triphenylphosphine and aniline\textsuperscript{12,102,109,111–113,278,436,439}. In addition, hydrides and certain solvents have been observed to act as nucleophiles; these will be discussed in connection with other leaving groups, and also with reductive and oxidative deaminations.

In the presence of basic nucleophiles such as hydroxide anions, cyanide, malonic ester anions and mercaptides, sulphur–nitrogen bond partial hydrolysies have been observed rather than carbon–nitrogen bond deaminations. However, alternate procedures have been developed for converting amino groups to all these functionalities. One such example is the conversion of carbon–nitrogen bonds to carbon–oxygen bonds via 3,5-dinitrobenzoate anion rather than via hydroxide anion. Other examples will be discussed under other topics\textsuperscript{101,102,111–113,439}.

Finally it is worth noting that various \(N\)-2-butyl-\(N\),\(N\)-disulphonimides only give unspecified amounts of 1-butene when treated with a variety of alkoxides at 50°C, which indicates that sulphur–nitrogen bond cleavage is not always the exclusive pathway with strongly basic nucleophiles\textsuperscript{30}.

Some representative cases are summarized in Table 2.

3. The effect of strongly acidic conditions on these deaminations – carbon–nitrogen to carbon–oxygen conversions

Under strongly acidic conditions, it would be expected that \(N\)-alkyldisulphonimides (2) would exist to a small, but significant, degree as the protonated cations 2a. Reactions of the latter with nucleophiles should lead to the neutral disulphonimide (3a) leaving groups (equation 14). 3a are much weaker bases than their conjugate anions (3), and, thus, should be better leaving groups\textsuperscript{111–113}. 
TABLE 2. Sample conditions and yields for selected deaminations with various disulphonimides

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>Y</th>
<th>Solvent</th>
<th>Temp., time</th>
<th>Products, yield</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Hexyl</td>
<td>p-Nitrobenzene</td>
<td>KI</td>
<td>DMF</td>
<td>95-105°C, 2-4 h</td>
<td>1-Iodohexane, 85-90%</td>
<td>109, 112, 113, 439</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>p-Nitrobenzene</td>
<td>LiCl</td>
<td>DMF</td>
<td>100°C, 2 h</td>
<td>1-Chlorohexane, 93.5%</td>
<td>112, 113, 439</td>
</tr>
<tr>
<td>dl-2-Heptyl</td>
<td>p-Nitrobenzene</td>
<td>LiBr</td>
<td>DMF</td>
<td>25°C, 7 days</td>
<td>2-Bromoheptane, 73.7%</td>
<td>112, 113, 439</td>
</tr>
<tr>
<td>l-2-Octyl</td>
<td>p-Nitrobenzene</td>
<td>LiCl</td>
<td>DMF</td>
<td>43°C, 1 day</td>
<td>l-2-Octyl chloride, 87%</td>
<td>112, 113, 439</td>
</tr>
<tr>
<td>Benzyl</td>
<td>p-Nitrobenzene</td>
<td>NaN₃</td>
<td>DMSO</td>
<td>70°C, 40 h</td>
<td>Benzyl azide, 56.5%</td>
<td>112, 113, 439</td>
</tr>
<tr>
<td>2-Phenylethyl</td>
<td>p-Nitrobenzene</td>
<td>LiCl</td>
<td>DMF</td>
<td>60°C, 1 day</td>
<td>2-Phenylethyl chloride, 46.3%</td>
<td>112, 113, 439</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>p-Toluene</td>
<td>Aniline</td>
<td>DMF</td>
<td>R flank, 3 days</td>
<td>N-Cyclohexylaniline, 75.5%</td>
<td>109, 112, 113, 439</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>p-Toluene</td>
<td>Aniline</td>
<td>DMF</td>
<td>145°C, 72 h</td>
<td>Cyclohexyl chloride, ~7-12%</td>
<td>36</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>m-Nitrobenzene</td>
<td>LiCl</td>
<td>DMF</td>
<td>68°C, 7 days</td>
<td>Cyclohexane, 90.3%</td>
<td>112, 113, 439</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>p-Nitrobenzene</td>
<td>KI</td>
<td>DMF</td>
<td>90°C, 41 h</td>
<td>n-Hexyl acetate, 100%</td>
<td>7</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>p-Toluene</td>
<td>KI + CH₃COO⁻</td>
<td>HMPA</td>
<td>115°C, 1 day</td>
<td>1-Hexanethiol, 24.7%</td>
<td>112, 113, 439</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>p-Toluene</td>
<td>NaSH</td>
<td>DMF</td>
<td>60°C, 17 h</td>
<td>Cyclohexyl 3,5-di-nitrobenzoate, ~12%; cyclohexene, 60%</td>
<td>101, 102, 439</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>p-Nitrobenzene</td>
<td>Lithium 3,5-di-nitrobenzoate</td>
<td>DMF</td>
<td>107°C, 24 h</td>
<td>Cyclohexyl 3,5-di-nitrobenzoate, ~12%; cyclohexene, 60%</td>
<td>101, 102, 439</td>
</tr>
<tr>
<td>n-Dodecyl</td>
<td>p-Nitrobenzene</td>
<td>Lithium 3,5-di-nitrobenzoate</td>
<td>DMF</td>
<td>140°C, 24 h</td>
<td>n-Dodecyl 3,5-dinitrobenzoate, 60%</td>
<td>101, 102, 439</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>p-Nitrobenzene</td>
<td>Lithium tosylate</td>
<td>DMF</td>
<td>Reflux, 1 h</td>
<td>n-Hexyl tosylate, 18.5%</td>
<td>101, 102, 439</td>
</tr>
<tr>
<td>n-Decyl</td>
<td>p-Toluene</td>
<td>NaBH₄</td>
<td>HMPA</td>
<td>175°C, 8 h</td>
<td>n-Decane, 91%</td>
<td>200</td>
</tr>
<tr>
<td>R</td>
<td>R¹</td>
<td>Y</td>
<td>Solvent</td>
<td>Temp., time</td>
<td>Products, yield</td>
<td>References</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>----------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Cyclooctyl</td>
<td>p-Nitrobenzene</td>
<td>Neat</td>
<td>Pyrolysis</td>
<td>200°C, 30 min</td>
<td>cis-Cyclooctene, &gt;91%</td>
<td>101, 103, 439</td>
</tr>
<tr>
<td>1,2-Diphenylethyl</td>
<td>p-Nitrobenzene</td>
<td>Neat</td>
<td>Pyrolysis</td>
<td>200°C, 25 min</td>
<td>trans-Stilbene, 99%</td>
<td>101, 103, 439</td>
</tr>
<tr>
<td>n-Dodecyl</td>
<td>p-Nitrobenzene</td>
<td>Lithium tosylate</td>
<td>DMF</td>
<td>Reflux, 18 h</td>
<td>n-Dodecyl formate, 57%; n-Dodecanol, 25%</td>
<td>101, 102, 439</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>p-Toluene</td>
<td>HI</td>
<td>H₂O–HI–DMF</td>
<td>125°C, 94 h</td>
<td>1-Hexanol, 60.3%; 1-hexyl formate</td>
<td>111, 113, 439</td>
</tr>
<tr>
<td>Benzyl</td>
<td>CF₃</td>
<td>CN⁻</td>
<td>HMPA</td>
<td>R.t.</td>
<td>Benzyl cyanide, 80%</td>
<td>157</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>CF₃</td>
<td>CH(CO₂Et)₂</td>
<td>HMPA</td>
<td>R.t.</td>
<td>n-Hexyldiethyl malonate, 57%</td>
<td>157</td>
</tr>
<tr>
<td>Methyl</td>
<td>‘Mixed’ p-toluene and p-nitrobenzene</td>
<td>CH(CO₂Et)₂</td>
<td>HMPA</td>
<td>R.t.</td>
<td>Methyl diethylmalonate, 60%</td>
<td>388</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>p-Toluene</td>
<td>PhS⁻</td>
<td>DMF</td>
<td>150°C, 1.5 h</td>
<td>n-Hexyl phenyl sulphide, 68%</td>
<td>436</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>p-Toluene</td>
<td>PhSc⁻</td>
<td>DMF</td>
<td>150°C, 1.5 h</td>
<td>n-Hexyl phenyl selenide, 96%</td>
<td>436</td>
</tr>
<tr>
<td>Benzyl</td>
<td>p-Toluene</td>
<td>Ph₃P, LiI</td>
<td>AcOH</td>
<td>Reflux, 2.4 h</td>
<td>PhCH₂PPh₃, 53%</td>
<td>436</td>
</tr>
<tr>
<td>n-Hexyl</td>
<td>CF₃</td>
<td>NaI</td>
<td>CH₃CN</td>
<td>25°C, 2 h</td>
<td>1-Iodohexane, 76%</td>
<td>112, 113, 439</td>
</tr>
</tbody>
</table>
22. Deaminations (carbon-nitrogen bond cleavages)

\[
R\mathcal{N}(\text{SO}_2\text{Ar})_2 + \text{HX} \rightleftharpoons R\mathcal{N}(\text{SO}_2\text{Ar})_2 X^- \quad (2)
\]

\[
R\mathcal{N}(\text{SO}_2\text{Ar})_2 \rightleftharpoons R-X + H\mathcal{N}(\text{SO}_2\text{Ar})_2 \quad (3a)
\]

\[
\text{X}^- + R\mathcal{N}(\text{SO}_2\text{Ar})_2 \rightleftharpoons R-X + H\mathcal{N}(\text{SO}_2\text{Ar})_2 \quad (3a)
\]

Results obtained when a variety of alkyldiarylsulphonimides (2) were treated with aqueous HI in DMF, confirm these predictions. Under these conditions, yields of up to 97.6% of deaminations to alcohols and/or esters have been obtained without any skeletal rearrangement. For example, \(N-(n\text{-hexyl})-N,N\text{-di(p-toluene)}\) sulphonimide gives with HI in DMF, 60.3% of 1-hexanol and 37.6% of 1-hexyl formate. A likely scheme to rationalize these results is given in equation (15). This scheme may represent the first example of the ‘Aa12’ amide hydrolysis mechanism.\(^{11-113,204}\)

\[
R\mathcal{N}(\text{SO}_2\text{Ar})_2 + \text{HI} \rightleftharpoons R\mathcal{N}(\text{SO}_2\text{Ar})_2 I^- \quad (2a)
\]

\[
I^- + 2a \rightleftharpoons Rl + H\mathcal{N}(\text{SO}_2\text{Ar})_2 \quad (3a)
\]

\[
\text{RI} + \text{H}_2\text{O} \rightleftharpoons [\text{ROH}_2^+] I^- \text{ base} \rightarrow \text{ROH}
\]

\[
\text{ROH} + \text{HCOOH} \overset{\text{H}^+}{\rightleftharpoons} \text{ROOCH} + \text{H}_2\text{O}
\]

(from DMF hydrolysis)

4. Alkene formation

The degree of alkene formation in these reactions is dependent largely upon the nature of the alkyl group. Thus, under most conditions, primary and unhindered secondary alkyamine derivatives give either no, or minor amounts of, alkenes.\(^{7,109,111-113}\). On the other hand, hindered secondary amine derivatives such as cyclohexyl and cyclododecyl give cycloalkenes as the major products. In fact, the best yield of \(S_N\) product with such cycloalkylamine derivatives was 35%, obtained from the reaction of \(N\text{-}(\text{cyclohexyl})-N,N\text{-di(p-nitrobenzene)}\) sulphonimide with aniline.\(^{109}\). Most runs with these cycloalkyl derivatives give 0-12% yields of substitution products.\(^{7,36,109,112,113}\)

While no tertiary derived diarylsulphonimides have been successfully isolated, there is some indication that isobutylene may be forming during the attempted preparation of \(N\text{-}t\text{-butyl}d\text{iarylsulphonimides}\) (see also the discussion under ‘triflimide’ leaving groups in Section II.B.2).\(^{113}\)

Although strong bases under most conditions give sulphur–nitrogen bond cleavage, alkene formation has also been observed, including a highly stereospecific
β-elimination of unspecified yield [see also the discussions involving the stereochemistry (Section II.A.5) and the mechanisms (Sections II.C.3) of these reactions]10,113.

Disulphonimides (2) derived from secondary carbinamincs give good to excellent yields of alkenes when pyrolysed neat at 160–200°C. These conditions are much milder than the 400–500°C temperatures required for the pyrolyses of most esters and carboxamidcs. This reaction is stereoselective. For example, N-cyclooctyl-N,N-di(p-nitrobenzene)sulphonimide gives over 91% cis-cylooctene when pyrolysed at 175°C, and the corresponding 1,2-diphenylethyl derivative gives 99% trans-stilbene at 200°C. The analogous primary carbinaminc derivatives do not give this reaction101,103. N-Cyclohexyl-N,N-di(p-nitrobenzene)sulphonimide gives cyclohexene in 70% yield when refluxed in pure DMF111,113.

Small amounts of mostly Saytzeff alkenes are obtained with some nucleophiles113. Finally, alkenes are obtained in 22–88% yields as unwanted by-products during oxidations with DMSO–NaHCO3 (see Section IV.J)100,101.

5. Stereochemical considerations

Only limited stereochemical data are currently available for these deaminations. The available stereochemical data indicate that the substitutions occur with predominant inversion of configuration. Thus, runs done with LiCl in dry DMF on N-(l)-(2-octyl)-N,N-di(p-nitrobenzene)sulphonimide, indicate that the deamination to 2-chlorooctane occurs with at least ~80–90% inversion of configuration112,113. More recently it has been shown that chiral methyl transfer from N-methyl-N,N-di(p-toluene)sulphonimide to homocysteine thiolate in HMPA proceeds with clean inversion12,278, and Townsend and Theis388 have proposed and obtained some data extending this concept towards the syntheses of a variety of complex substances bearing labelled methyl groups by using mixed tosyltrifluoromethyldisulphonimides (see also Section V.B.3).

With respect to the β-elimination pathway in these deaminations, Bartsch and coworkers30 have made the remarkable observation that the reaction of N-(2-butyl)-N,N-di(p-toluene)sulphonimide with t-BuOK–DMSO and other base–solvent systems at 50°C, yields entirely 1-butene, although Bartsch did not specify the alkene yields as opposed to SN or other products. To date no other leaving group has demonstrated such exclusive Hofmann orientation in eliminations. The N,N-dimethylsulphonimide leaving group also gave exclusive Hofmann orientation under identical conditions, while the di(m-nitrobenzene)sulphonimide leaving group gave 98.8% 1-butene and 1.2% 2-butene. This latter result was expected, since more reactive leaving groups tend to give smaller proportions of terminal alkenes. Bartsch attributes the overwhelming Hofmann orientation to the steric effect of the —N(SO2-)2 portion of the leaving group. The steric bulk of the —N(SO2-)2 group is also suggested by the difficulties encountered in all attempted preparations of disulphonimides derived from hindered alkylamines110,113,200. Nonetheless, the small amounts of alkene obtained with less bulky and less basic nucleophiles were the Saytzeff oriented alkenes113.

B. N-Alkyl-N,N-di(trifluoromethane)sulphonamide Anion Leaving Groups ('Triflimides') (2b)

The development of the trifluoromethanesulphonyl group as an activating group in deaminations has arisen concurrently with the development of the diarylsulphonyl activating groups112,113,136,157,180,181. While in a general sense the two types
of activating groups behave similarly, there are several important differences between them.

1. *Synthesis of triflimides* (2b)

The triflimides 2b may be prepared via the same procedure as other disulphonimides. However, trifluoromethanesulphonyl chloride is handled with considerable difficulty and the trifluoromethanesulphonic anhydride is used instead (equation 16). In many cases yields are not as good as the yields obtained in the preparations of diarylsulphonimides (2).

\[ 2 \text{RNH}_2 + (\text{CF}_3\text{SO}_2)\text{O} \rightarrow \text{RNHSO}_2\text{CF}_3 + \text{RNH}_3\text{O}_3\text{SCF}_3 \]

(16)

While most diarylsulphonimides (2) are crystalline solids, most triflimides (2b) are liquids. Finally, crystalline mixed aryl-'trifyl'-sulphonimides (2c) have been prepared.

2. *Carbon–nitrogen bond cleavages*

As a general rule, triflimides 2b are more reactive in deaminations than are any of the other disulphonimides so far studied. The first triflimide prepared and studied, *N-(n-hexyl)-N,N-di(trifluoromethyl)sulphonimide*, gives carbon–nitrogen bond cleavage by merely treating the compound with sodium iodide in acetonitrile at 25°C for two hours; 1-iodohexane is produced in 76% yield. By contrast, *N-(n-hexyl)-N,N-di(m-nitrobenzene)sulphonimide* requires heating to 100°C in DMF with KI to give 85–90% yields of 1-iodohexane over a period of two hours, and *N-(n-hexyl)-N,N-di(methyl)sulphonimide* gives only trace amounts of 1-iodohexane and 1-hexene after 44 h with KI at 100°C in DMF. Since these initial studies, it has been observed that triflimides may give deaminations under conditions in which other disulphonimides either give no reaction or react with sulphur–nitrogen rather than carbon–nitrogen bond cleavage. Synthetically most useful of triflimide deaminations are alkylation and nitrile formations. Thus, Glass and Swedo have alkylated malonic ester anions in poor-to-good yields using alkyl triflimides in HMPA (equation 17). Müller and Phuong have obtained somewhat better alklylation yields using lithium dimethyl cuprate and lithium diphenylcuprate (equation 18). Most recently, Townsend and Theis have alkylated potassium salts of various malonic esters with the mixed disulphonimides 2c in 19
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\[ R - \text{N} \left( \text{SO}_2\text{CF}_3 \right)_2 + R'_2\text{CuLi} \longrightarrow R - R' + :\text{N} \left( \text{SO}_2\text{CF}_3 \right)_2 \quad (18) \]

12–73% to 60% yields. Another type of carbon–carbon bond formation, nitrile formation, has been achieved by reacting these triflimides with cyanide in HMPA.\textsuperscript{156}

Other types of deamination utilizing triflimides have been reported. Thus, Hendrickson and his group\textsuperscript{180} have obtained indirect evidence for the synthesis of the \( r \)-amine derivative, \( N-(r\text{-butyl})-N,N\text{-di}(\text{ trifluoromethane})\text{sulphonimide} \), by observing quantitative isobutylene formation during its attempted preparation at \(-78^\circ\text{C}\). Since gas evolution is noted during the attempted preparation of other disulphonimides derived from tertiary carbinamines, this one reported case may not be unique.\textsuperscript{113} Hendrickson and coworkers have reported the only example of a successful substitution of disulphonimides with alkoxides.\textsuperscript{180}

Many of the results involving triflimides in HMPA may involve intermediate salt formation due to the reaction of the triflimide with the HMPA. This will be considered further under the discussion of mechanisms.

Glass and coworkers\textsuperscript{156,158} and Hendrickson and coworkers\textsuperscript{180,181} have investigated other areas of triflimide and triflamide chemistry, and certain aspects of triflimide and triflamide chemistry have been briefly discussed as parts of general reviews on trifluoromethylsulphonyl chemistry.\textsuperscript{178,179,182}

C. Mechanisms of the Deaminations Utilizing Various Disulphonimide Leaving Groups

1. Probable \( S_N2 \) character

Limited data involving nucleophile substitution with disulphonimides suggest that these reactions proceed via mechanisms of essentially \( S_N2 \) character. Thus, skeletal rearrangements occur minimally if at all, and the reactions proceed best with the disulphonimides derived from unhindered primary carbinamines. Similarly, the stereochemical results show that the reactions proceed with predominant inversion of configuration (see Section II.A.5). In addition kinetic studies involving the reactions at different temperatures of various \( N-(n\text{-hexyl})-N,N\text{-di}(\text{benzene})\text{-sulphonimides} \) with KI in DMF indicate that the reaction rate is dependent on both reactants. Related results have also been obtained which demonstrate that the reactions are Hammett-correlated for the various diarylsulphonimides investigated, which implies that the mechanism is invariant throughout the series. Furthermore a positive \( \rho \) value in these runs shows, as expected, that the reactions are facilitated by electron-withdrawing groups. Arrhenius plots of runs at three different temperatures have also been obtained. The resulting activation parameters also expectedly parallel those seen for the reactions of the corresponding alkyl sulphonates.\textsuperscript{112,114}

2. Solvent participation

The choice of solvent is often crucial for these runs. Thus, most nucleophilic substitutions occur faster in HMPA than in other solvents.\textsuperscript{156,318} In particular some of the deaminations involving basic nucleophiles only give good results in this solvent. This has been especially true for the carbon–carbon bond formations of Glass\textsuperscript{156,157} and the \( \text{NaBH}_4 \) reductions of Hutchins.\textsuperscript{199,200} In fact in some cases the HMPA may itself act as a nucleophile to form intermediate salts (4) with the HMPA.\textsuperscript{156}
Anselmi and Glass caution that other reported substitutions in HMPA may involve similar solvent participation. However, the work of Arigoni and Townsend and Theis indicates clean inversion in HMPA in respect to their chiral methyl transfers. Apparently no salts form here, and perhaps this only can happen with specially reactive sulphonimides such as the triflimides (see also Section II.A.5).

In most cases, DMF gives excellent results and is the solvent of choice based on its relatively low cost and low toxicity. Unlike tosylates and most other good leaving groups, most sulphonimides are not solvolysed by nucleophilic solvents, and they may even be recrystallized from them. DMSO, however, may act as a nucleophile in oxidative deaminations (see Section IV.I).

3. Alkene formation

Under most of the observed deamination conditions, the small amounts of alkene products probably arise via E2-type eliminations. As discussed previously, Bartsch and coworkers have noted an extreme regioselectivity in respect to the elimination of the diarylsulphonimide leaving group upon treatment with t-butoxides so that only the Hofmann alkene is produced. Apparently the $\text{-N(SO}_2\text{)}^+$ portion of the leaving group equals or surpasses the trimethylammonium ion in its steric requirements (see Section II.A.5). When less bulky and less basic nucleophiles initiate the eliminations, however, Saytzeff orientation predominates.

4. Carbon–nitrogen vs. sulphur–nitrogen bond cleavage

Under most conditions, strongly basic nucleophiles react with disulphonimides to give primarily sulphur–nitrogen bond cleavages. Exceptions to this rule include the NaBH$_4$ reductions in HMPA, alkylations in HMPA, alkylations with organocuprates, nitrile formations in HMPA, sulphide and selenide formations in DMF, and one case of alkoxide formation.

The different selectivities of phenyl sulphide and selenide as compared with certain other bases with respect to competing attack rates on carbon versus sulphur atoms, have been rationalized by Müller and Nguyen Thi on the grounds of Pearson's hard and soft acid–base theories. All or most of the other examples mentioned in this section involving competing carbon–nitrogen versus nitrogen–sulphur bond cleavages with nucleophiles may be similarly rationalized according to hard and soft acids and bases.

D. Other Imides as Leaving Groups

The first imide investigated as an activating group for the deamination of amines was saccharin. Unfortunately, nonbasic nucleophiles did not react at all with N-alkylsaccharins (5), while basic nucleophiles (i.e. hydroxide anion) react with
most alkylsaccharins to give the sulphamic acid derivatives derived from attack at the carbonyl group. However, when the $N$-alkylsaccharin 5 is properly activated in respect to the alkyl moiety (e.g. via an sp² system to the nitrogen, as with $N$-2-phenylethylsaccharin), alkenes are formed upon heating with potassium hydroxide pellets. Shortly after the very limited activating effect of saccharin was reported, the $\alpha$-benzenedisulphonimide (6) activating group was observed to have an even weaker activating ability in respect to carbon–nitrogen bond cleavage. However, when $Y$ is Br or Cl, this sulphonimide does act as a good leaving group.

The earliest example in the literature of a cyclic sulphonimide leaving group was the one associated with 1,3-propane disulphonimide. In this case, though, only the leaving group was sought and identified.

Carboximides such as phthalimide also do not ordinarily give alkyl carbon–nitrogen bond cleavage with nucleophiles. Yet, $N$-2-phenylethylphthalimide gives styrene in ca. 50–70% yield when heated with potassium hydroxide pellets. Similarly, arylaminomethylsuccinimides have been shown to give alkyl carbon–nitrogen bond cleavage upon treatment with NaBH₄ in DMSO (see also Section III.B, since this is a 'reductive deamination').

E. Sulphonamides as Leaving Groups

As might be predicted from the poor activating ability of saccharin and related compounds, most $N$-alkyl-$N$-sulphonamides rarely give carbon–nitrogen bond cleavages with nucleophiles. Nonetheless, alkylsulphonamides which are suitably activated in the alkyl moiety do occasionally give carbon–nitrogen bond cleavage. Thus, $N$-(2-phenylethyl)-$p$-toluenesulphonamide gives 50–70% yields of styrene, and $N$-(1,2-diphenylethyl)-$p$-nitrobenzenesulphonamide gives 29% of trans-stilbene, when pyrolysed with KOH. Similarly, benzenesulphonamides derived from tertiary carbinamines and benzylic amines give $S_n_1$ and $E_1$-type products during acid-catalysed hydrolysis.

The trifluoromethanesulphonyl group is a more potent activator than arylsulphonyl groups towards deaminations. Thus, $N$-acyltrifluoromethanesulphonamides have been observed to act as excellent acylating agents (equation 19). Although this acylation process is not a true deamination due to the formation of 7 from acyl halides and triflamides, we feel this scheme has the potential for becoming a good deamination technique if some simple process can be found for oxidizing $RCH_2N(R')SO_2CF_3$ to $RCON(R')SO_2CF_3$. Such potential schemes for deamination via activation at both the alkyl and amino portion of a molecule were discussed in Section I.A.3.a.

F. Carboxamides as Leaving Groups

Earlier reviews have discussed alkyl carbon–nitrogen bond cleavages wherein carboxamides or carboxamide anions are the leaving groups. Thus
N-alkylamides have been pyrolysed with and without acid catalysts to give alkenes. In addition certain amides give nitrate esters on treatment with 100% nitric acid or nitric acid-sulphuric acid mixtures. The nature of the leaving group has not been identified for these nitrate ester formations, so that it may be the carboxamide group, $N_2O$ and acetic acid, or some other species.

More recently it has been found that tertiary amines which have an alkyl group capable of forming a stable carbonium ion (such as benzyl or tertiary) can be cleaved with acetic anhydride. The leaving group is the carboxamide (equation 20a). A related reaction involves the degradation of tertiary amines with phenyl chloroformate and related reagents. (equation 20b)

\[
\text{PhCH}_2\text{NMe}_2 + (\text{MeCO})_2\text{O} \rightarrow \text{PhCH}_2\text{O}_2\text{CMe} + \text{Me}_2\text{NCOMe} \quad (20a)
\]

\[
\text{R}_3\text{N} + \text{ClCOOPh} \rightarrow \text{RCl} + \text{R}_2\text{NCOOPh} \quad (20b)
\]

G. 2,4,6-Triphenylpyridine and Related Leaving Groups (8b)

1. Scope of the reaction

A relatively new deamination procedure features the 2,4,6-triphenylpyridine leaving group (8b) (equation 21). Although Ziegler and Fries were the first to report an example of this reaction, Susan and Balaban were the first to realize the synthetic possibilities of the process. It remained, however, for Katritzky and coworkers to develop the reaction into an especially useful synthetic procedure. Some examples are given in Table 3 which illustrate the versatility of the reaction. As with most other deamination procedures, this deamination technique is not applicable to tertiary carbinamines.

An extensive review by Katritzky of this highly useful and interesting reaction through June, 1979, is in press as of this writing. In addition to the deaminations listed in Table 3, this article gives preliminary results for deaminations via thiourea, sulphonate anion, phthalimide anion, azide anion, malonate anions, oxidizing and reducing agents, and others. Eliminations, oxidations and reductions are discussed as well as a variety of nondeaminative processes (see also Sections III.C, III.F, and IV.K).

Katritzky and coworkers have also mentioned some preliminary results which indicate that this method should be subtly selective in deaminating polyfunctional natural products which contain one or more amino groups under conditions which may be mild enough to be termed 'pseudophysiological conditions' (see also Section V.B.5).
TABLE 3. Selected examples of pyrolytic substitution reactions of \( N \)-substituted 2,4,6-triphenylpyridinium salts with various nucleophiles

<table>
<thead>
<tr>
<th>( N )-Substituent</th>
<th>Nucleophile</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>Acetate</td>
<td>Methyl acetate</td>
<td>65</td>
<td>212</td>
</tr>
<tr>
<td>( n )-Butyl</td>
<td>Benzoate</td>
<td>( n )-Butyl benzoate</td>
<td>85</td>
<td>212</td>
</tr>
<tr>
<td>2-Butyl</td>
<td>I(^{-})</td>
<td>2-Iodobutane</td>
<td>83</td>
<td>213, 220</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>I(^{-})</td>
<td>Cyclohexene</td>
<td>66</td>
<td>213, 220</td>
</tr>
<tr>
<td>Phenyl</td>
<td>I(^{-})</td>
<td>Iodobenzene</td>
<td>75</td>
<td>213, 220</td>
</tr>
<tr>
<td>3-Hydroxypropyl</td>
<td>Br(^{-})</td>
<td>3-Bromo-1-propanol</td>
<td>72</td>
<td>214</td>
</tr>
<tr>
<td>Benzyl</td>
<td>Cl(^{-})</td>
<td>Benzyl chloride</td>
<td>50</td>
<td>214, 220</td>
</tr>
<tr>
<td>( n )-Heptyl</td>
<td>Piperidine</td>
<td>Benzylpiperidine</td>
<td>85</td>
<td>27</td>
</tr>
<tr>
<td>( n )-Hexyl</td>
<td>NO(_3)(^{-})</td>
<td>( n )-Hexyl nitrate</td>
<td>68</td>
<td>220</td>
</tr>
<tr>
<td>Benzyl</td>
<td>( \beta )-Napthoxide</td>
<td>Benzyl ( \beta )-naphthyl ether</td>
<td>71</td>
<td>220</td>
</tr>
<tr>
<td>Methyl</td>
<td>SCN(^{-})</td>
<td>Methyl thiocyanate</td>
<td>95</td>
<td>217, 220</td>
</tr>
<tr>
<td>Phenyl</td>
<td>SCN(^{-})</td>
<td>Phenyl thiocyanate</td>
<td>98</td>
<td>220, 221</td>
</tr>
<tr>
<td>( n )-Butyl</td>
<td>Xanthate</td>
<td>( n )-Butyl xanthate</td>
<td>80</td>
<td>217, 220</td>
</tr>
<tr>
<td>( n )-Hexyl</td>
<td>Succinimide</td>
<td>( n )-Hexyl succinimide</td>
<td>65</td>
<td>220, 222</td>
</tr>
<tr>
<td>( n )-Butyl</td>
<td>Anion of 2-nitropropane</td>
<td>C-alkylated product</td>
<td>73</td>
<td>220</td>
</tr>
<tr>
<td>2-Phenylethyl</td>
<td>Base</td>
<td>Styrene</td>
<td></td>
<td>220</td>
</tr>
</tbody>
</table>

2. Related leaving groups

Theoretically, the parent alkylpyridinium salts 9 should also be capable of pyrolytic deaminations, and rare examples of pyridine acting as a leaving group have been observed (equation 22)\(^{201,246}\). Katritzky has analysed several serious problems involved with utilizing unsubstituted pyridine as a leaving group for deamination\(^ {210}\). With such major obstacles, there is little doubt that the 2,4,6-triphenylpyridine (8b) or related leaving groups are the choice ones for these deaminations. 2,3,4,5,6-Pentaphenylpyridinium salts have also been prepared and pyrolysed by Katritzky but the deamination yields are poor in these cases\(^ {214}\).

3. Arylamines to aryl iodides and aryl thiocyanates

An important synthetic feature of this reaction is an apparently useful new procedure for converting arylamines into iodides and thiocyanates\(^ {213,221}\). None of the other modern activating techniques such as the ones using disulphonimides have so far been shown to be useful for the deamination of arylamines.
4. Mechanistic considerations

Susan and Balaban\textsuperscript{381} were the first to suggest an $S_N2$ mechanism for the deaminations using halides as nucleophiles. Katritzky likewise suggests an $S_N2$ mechanism for the reactions of the alkylpyridinium salts with halides. For those cases where arylamines are converted to aryl halides, Katritzky\textsuperscript{212} proposes a charge-transfer complex promoted $S_{RN1}$ mechanism. Some kinetic mechanistic data are discussed in the review by Katritzky\textsuperscript{220}.

H. Pyrrole Derivatives as Potential Leaving Groups

Since pyrrole is a much weaker base than pyridine (see Table 1), $N$-alkylpyrroles (10) might very well undergo alkyl carbon-nitrogen bond cleavages, especially under strongly acidic conditions (equation 23). A complicating factor arises in the evidence for the greater base strength of the $\alpha$-position than the nitrogen for many pyrroles.

\begin{equation}
\text{O} \quad \text{O} \quad \text{R}^1\text{NH}_2 \\
\text{RC(\text{CH}_2)\text{CR}_2} \quad \underset{\text{R}_1^1}{\longrightarrow} \quad \underset{\text{R}_1^2}{\underset{\text{H}^X}{\longrightarrow}} \quad \underset{\text{R}_1^3}{\underbrace{\text{H}}} \quad \underset{\text{R}^1 X}{\text{R}^1^X}
\end{equation}

Nonetheless, there is an example of the related azaindole (11) acting as a leaving group (equation 24).\textsuperscript{133} In this reaction, the authors were only concerned with the azaindole leaving group, and, thus did not characterize the benzyl-derived product.

\begin{equation}
\text{CH}_2 \quad \text{N} \quad \text{N} \quad \text{H} \quad \text{N} \\
\text{N} \quad \text{CH}_2 \quad \text{N} \quad \text{H} \quad \text{N} \\
\text{KOH} \quad \text{NH}_3\text{OH}
\end{equation}

J. Amines and Ammonia as Leaving Groups

Under this category are two of the most famous and important types of deamination. In particular, when trialkylamines are leaving groups, we have the familiar Hofmann elimination, and when dialkylhydroxylamines are the leaving groups, we have the equally useful Cope elimination\textsuperscript{91,186}. Examples where other amines, ammonia, and/or their conjugate anions are leaving groups are much less frequent and commonly require special activating groups in the alkyl portion of the amines and/or severe conditions.

1. Tertiary alamines as leaving groups

The Hofmann \textit{trans} (or \textit{anti} or antarafacial) elimination is represented by equation (25a)\textsuperscript{186,187}. This reaction and the competing substitution pathway have been reviewed previously and will not be discussed further\textsuperscript{31,91,116,394}. A variety of related
Reactions such as the Stevens rearrangements, the Sommelet–Hauser rearrangement, the von Braun degradation, and the substitution reactions of quaternary amine salts and tertiary amines with a variety of nucleophiles, have also been reviewed previously. More recent examples involve the pyrolyses of quaternary ammonium halides to give alkyl halides (equation 25b) and the pyrolyses of quaternary ammonium salts with acetate ions in aprotic solvents.

\[ R_4N^+X^- \xrightarrow{\text{heat}} R_3N + RX \]  

(25b)

2. Dialkylhydroxylamines (13) as leaving groups

Wernick and Wolfenstein first observed the formation of alkenes when tertiary amine oxides (12) were pyrolysed, but it remained for Cope and coworkers to fully develop this reaction (equation 26). This cis (syn, suprafacial) elimination has also been reviewed and will not be discussed further.

\[ R_2NC(=O)CH_2R' \xrightarrow{\text{heat}} R_2NO + CH_2=CHR' \]  

(26)

(12) (13)

3. Ammonia, primary and secondary amines and/or their conjugate anions as leaving groups

In the alcohol and ether series, water and alcohols are facile leaving groups; in the amine series, ammonia and amine leaving groups are not as common. Nonetheless, some examples exist in the literature wherein ammonia and primary and secondary amines, as well as possibly their conjugate anions, act as leaving groups. Most of these examples occur with amines which have at least one activating group, such as an unsaturated group to the leaving ammonia or amine group (see Section 1). Thus, Mannich bases (14) may undergo elimination and/or substitution at the carbon–nitrogen bond under basic or acidic conditions (equations 27–29). Tramontini's discussion of Mannich base deaminations is especially useful. Particularly noteworthy are the alkylations of the Mannich bases. Deaminations of this type have received considerable use in respect to the
22. Deaminations (carbon–nitrogen bond cleavages)

syntheses and degradations of a variety of alkaloids and other natural products.\textsuperscript{15,31,78,87,105,106,385}

Activated amines, such as \(N\)-benzylic tertiary amines, readily undergo reductive deaminations (see also Section III).\textsuperscript{31,168,394}

Arylamines are much weaker bases and thus should be better leaving groups than most alkylamines. Some examples have been reported (equations 30a–c), although occasionally the investigators are only interested in the arylamine leaving groups and do not bother to characterize the alkyl moiety as in equation (30c). These deaminations are related to ether cleavages in acidic media.

\[
\begin{align*}
\text{ArNR}_2 + \text{HBr} & \rightarrow \text{RBr} + \text{ArNHR} \quad (30a) \\
\text{ArNHR} + \text{HBr} & \rightarrow \text{RBr} + \text{ArNH}_2 \quad (30b) \\
\text{ArNHR} & \rightarrow \text{RBr} + \text{ArNH}_2 \quad (30c)
\end{align*}
\]

Even amines which are totally unactivated deaminate with the loss of ammonia when conditions are severe enough (equations 31–33).\textsuperscript{139,241,269,270,385}

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{NH}_2 + \text{HBr} & \xrightarrow{500-540^\circ\text{C}} \text{CH}_2=\text{CH}_2 + \text{NH}_3 + \text{HBr} \quad (31) \\
(\text{CH}_3)_2\text{CNH}_2 + \text{HBr} & \xrightarrow{395-460^\circ\text{C}} \text{CH}_2=\text{C(\text{CH}_3)_2} + \text{NH}_3 + \text{HBr} \quad (32) \\
\text{CH}_3(\text{CH}_2)_3\text{NH}_2 + \text{HBr} & \xrightarrow{\text{Al}_2\text{O}_3, \text{heat}} \text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2 + \text{NH}_3 \quad (33)
\end{align*}
\]

Photochemical dealkylations of amines have also been reported. Many of these involve oxidations of the alkyl moiety and will, thus, be discussed in Section IV.M.\textsuperscript{78,83,84,87,105,106,355}

It is also interesting to note that biochemical deaminations of phenylalanine, tyrosine, histidine and aspartic acid in certain organisms involve the apparent loss of ammonia from only moderately activated amines to give alkenes (equation 34).\textsuperscript{17,267,282} (see also Sections V.A.2 and V.B).

\[
\begin{align*}
\text{RCH}_2\text{CH(\text{NH}_2)COOH} & \xrightarrow{\text{enzyme}} \text{RCH}=\text{CHCOOH} + \text{NH}_3 \quad (34)
\end{align*}
\]

Finally the ammonia leaving group has been proposed in connection with theories pertaining to the origin of certain organic compounds on prebiotic earth (equation 35).\textsuperscript{1,17} While most amino acids pyrolytically decompose with \(\text{CO}_2\) evolution, aspartate decomposes with loss of ammonia (equation 35). The kinetics of this reaction have been used to estimate the minimum concentration of ammonium ion on prebiotic earth.\textsuperscript{1,17}

\[
\begin{align*}
\text{O}_2\text{CCH}_2\text{CH(\text{NH}_3)CO}_2^- & \rightleftharpoons \text{O}_2\text{CCH}=\text{CHCO}_2^- + \text{NH}_3 + \text{H}^+ \quad (35)
\end{align*}
\]

K. Nitrogen Gas as Leaving Group

Although yields are often poor, the most facile leaving group in deaminations is nitrogen. This is also the oldest, the most extensively studied, the best known, and the
most complex in respect to mechanisms of formation, of all the leaving groups in both the aliphatic and aromatic series. A number of excellent reviews of deamination via the nitrogen leaving group have appeared, and, thus, these types of deaminations will only be briefly discussed here.

Of special note is the earlier two-part volume in this series, The Chemistry of Diazonium and Diazo Groups.

Deaminations involving the nitrogen leaving group may be divided into the aliphatic series and the aromatic series. Then the aliphatic series may be further subdivided in respect to the numerous variations by which amines are oxidatively activated to the many isolable and nonisolable intermediates which eventually lead to nitrogen gas evolution, followed by product formation.

1. Nitrogen as the leaving group in the deamination of aliphatic amines

a. Nitrosations of primary amines. A somewhat simplified representation of the direct nitrosation of primary amines is given in equation (36). The older investigations featured nitrosation in water. These almost always led to complex mixtures of products which usually included rearranged R groups as well as the promiscuous variety of functionalities. More recently nonaqueous protic and aprotic conditions have been utilized along with a variety of modifications employed in the generation of nitrosating agents. These newer nonaqueous nitrosations often greatly simplify the product mixtures. The investigations in aprotic solvents have proven to be especially promising with respect to generating respectable yields of unrearranged substitution products. Much of the pioneer work on aprotic conditions was done by Friedman and group and Bakke. More recently, Doyle and coworkers have improved on these early techniques by developing a method for generating nitrosyl chloride which minimizes typical side-reactions such as rearrangement, elimination and oxidation. This technique utilizes alkyl nitrites, titanium tetrachloride (or other halides), and DMF for the generation of nitrosyl chloride. The yields of unrearranged halide range from 48–80% (equation 37). Similarly, the research groups of Wudl, Barton, and White have greatly advanced the utility of dinitrogen tetroxide as a synthetically useful nitrosating agent. For example, Barton and Narang have converted cyclohexylamine to a cyclohexanol-cyclohexyl nitrate mixture in 81–89% yield, and 3β-aminocholestanate to the corresponding alcohol-nitrate ester mixture in 87% yield, by treating the amines with dinitrogen tetroxide in the presence...
22. Deaminations (carbon–nitrogen bond cleavages) of a tertiary amine of stronger base strength (amidine) than the reactant amine in ether at $-78^\circ$C (equation 38).

\[
\begin{align*}
\text{RNH}_2 + \text{N}_2\text{O}_4 & \rightarrow \text{ROH} + \text{RNO}_2 + \text{N}_2 \\
\text{(38)}
\end{align*}
\]

In another modification unrearranged carboxylate esters are produced in fair-to-good yields. To achieve this conversion, Jacobson has treated a variety of amines with a small excess of carboxylic acid and isoamyl nitrite in refluxing benzene (equation 39). Alkylnitrates as nitrosating agents had earlier been reported by the groups of Cadogan, Friedman and Curtin.

Yet another technique for exerting some control over the highly promiscuous nitrous acid deaminations involves the designing of micellar aqueous conditions. In this approach, pioneered and largely developed by Moss and coworkers, significant stereochemical control may be exerted, even though no claims are made for improved yields of products. For example, the stereochemistry of the 2-aminoctane to 2-octanol conversion can be changed from 24% net inversion (nonmicellar conditions) to 6% net retention (micellar conditions). To effect these stereochemical changes, counterions such as perchlorate, $p$-tosylate, fluoroborate, or $d$-10-camphorsulphonate are necessary. Micellar conditions also catalyse deamination rates about 15-fold. Kirmse and coworkers have also studied the effect of micelles on nitrous acid deaminations. Kirmse has observed that some micelles tend to increase the overall yields of alkenes and rearranged products. On the other hand, Kirmse has found that alkyl shifts may be suppressed under certain micellar conditions.

b. Decompositions of diazoalkanes (15). Since one of the many procedures for generating diazoalkanes is by nitrosation of the parent amine, the chemistry of diazoalkanes is relevant to any discussion of deaminations. In any event, diazoalkanes and/or their corresponding diazonium ions (15a) are important intermediates in the many procedures used to generate the nitrogen leaving group. The typical diazoalkane decomposition under acidic conditions is represented by equation (40). Carbonium ions generated from diazoalkanes are among the hottest carbonium ions known.

\[
\begin{align*}
\text{R}_2\text{C}N_2 & \stackrel{\text{H}^+}{\longrightarrow} [\text{R}_2\text{CHN}_2^+] \stackrel{\text{x}}{\longrightarrow} \text{elimination products} + \text{N}_2 \\
\text{(15)} & \quad \text{various substitution and elimination products} + \text{N}_2 \\
\text{(15a)} & \quad \text{(40)}
\end{align*}
\]

Diazooalkanes, and their possible participation in the various mechanisms involving nitrogen leaving groups, have been much discussed, and, thus, will not be considered further here.

Readers of this section are especially referred to the chapter by Hegarty in the recent volume in this series The Chemistry of the Diazonium Ion and Diazo Groups. Also, a section of Wulfman's chapter in the same volume deals with alkylidiazonium ions.

c. Decompositions of N-nitrosoamides (16). N-nitrosoamides (16) are easily prepared from the corresponding amines in two steps (equation 41). While nitrosoamides of most primary carbinamines are reasonably stable at room temperature, the nitrosoamides of most secondary and tertiary carbinamines decompose between ca. $-40^\circ$C.
and 30°C. The pyrolytic decomposition of nitrosoamides results in deamination involving nitrogen loss as briefly formulated in equation (42). Pathway (a) predominates with nitrosoamides of primary amines, attaining yields of unrearranged ester often approaching 80%. Ester yields from the pyrolyses of nitrosoamides of secondary and tertiary carbinamines are much less satisfactory (20–65%), with alkenes being important products. Nitrosamide pyrolyses were pioneered by Huisgen and coworkers\(^\text{195,196}\) and White and coworkers\(^\text{394,395,397-401}\). The many fascinating mechanistic subtleties have been mainly elucidated by White and his research group\(^\text{248,394,396,399,400,402,403,407-410}\).

Nitrosoamides and related compounds will be briefly discussed in Section V.C.

Nitrosocarbamates, nitrososulphonamides, nitrosohydrazone, nitrosohydroxylamines and the corresponding N-nitro derivatives behave in an analogous fashion\(^\text{264,297,394,396,416}\) (see also Section II.M).

The photochemistry of nitrosoamides and other properties of nitrosoamides have also been discussed\(^\text{79}\).

d. Decompositions of triazenes (17). Triazenes (17) are easily prepared in one step (equation 43). They readily deaminate under acidic conditions (equation 44).

\[
\text{RNH}_2 + \text{ArN}_2^+ \rightarrow \text{RNHN}=\text{NAr} \tag{43}
\]

\[
\text{RNHN}=\text{NAr} + \text{HX} \rightarrow \text{RX} + \text{alkenes} + \text{ArNH}_2 + \text{N}_2 \tag{44}
\]

With carboxylic acids, esters are obtained in 35–95% yields. As in other deamination pathways, the highest yields are obtained from triazenes derived from primary carbinamines, while the lowest yields are obtained from the tertiary carbinamine derivatives.

White and coworkers have pioneered and done many of the subsequent studies on, the triazene deamination technique. White and others have investigated the mechanism of this reaction\(^\text{31,33,227,250,297,394,412,413}\).

e. Alkane diazotates (18). The most recent of the indirect methods for activating amines for the purpose of breaking carbon–nitrogen bonds with the production of nitrogen as leaving group involves the treatment of alkane diazotates (18) with acids (equation 45)\(^\text{298,300}\).

Alkane diazotates are formed by treating N-nitrosocarbamates (19a) with strong base (equation 46).\(^\text{167,298,300,306}\).
22. Deaminations (carbon–nitrogen bond cleavages)

Deaminations (carbon–nitrogen bond cleavages)

\[
\text{RN} = \text{NO}^- \xrightarrow{\text{H}^+} \text{RN} + \text{N}_2 + \text{H}_2\text{O} \quad (18)
\]

\[
\text{[RN} = \text{N} = \text{N} = \text{O}^- \xrightarrow{\text{substitution and elimination products}} + \text{RN} + \text{N}_2 + \text{H}_2\text{O} \quad (45)
\]

\[
\text{NO} \xrightarrow{\text{R}^2\text{O}^- K^+} \text{RN} = \text{N} = \text{N} = \text{O}^- \quad (46)
\]

Alkane diazotates (18) are the conjugate bases of the unstable \text{RN} = \text{N} = \text{N} = \text{OH} intermediates in nitrous acid deaminations. However, while certain similarities exist between nitrous acid deamination products and diazotate deaminations, the product distributions are usually quite different. Thus, for example, diazoalkanes are rarely isolated in nitrous acid deaminations, while they are important products in alkane diazotate deaminations, especially when the \text{R} group is primary.298

Another interesting aspect of alkane diazotates is that they apparently give extensive amounts of \text{S}_\text{N}2 substitutions under certain conditions. Thus, the reactions of alkane diazotates with such nucleophiles as ammonia, hydrazine, azide anions and Grignard reagents, give the corresponding substitution products with ca. 40–70% net inversion. Complete inversion is not observed, due to the competing internal return process. Perhaps the synthetically most promising of these \text{S}_\text{N}2 displacements is the reaction of 1-phenylethyl diazotate (18a) with Grignard reagents to give the corresponding 2-phenylbutane with 70% inversion (equation 47). The overall yield, however, of 2-phenylbutane is only 25%.299

\[
\text{(S)-(−)18} \xrightarrow{\text{EtMgBr}} \text{(S)-(+)19} \quad (18a)
\]

\[
\text{(S)-(+)20} \xrightarrow{\text{PhMgBr or Ph}_2\text{Mg}} \text{(R)-(−)19} \quad (18b)
\]

White and coworkers have generated diazotate intermediates, from nitrosoamide precursors, in their studies on enzyme active-site inhibition and labelling. The diazotates generate carbonium ions which alkylate the enzyme (see Section V.B.2).415

Most of the work on diazotates has been reported by Moss and his group. Moss has also extensively reviewed the subject.297,298

f. Nitrosations of secondary amines. When secondary amines are nitrosated under a variety of conditions, \text{N},\text{N}-dialkyl-\text{N}-nitrosamines (19b) are produced (equation 48).9,146,390

\[
\text{R}_2\text{NH} \xrightarrow{\text{nitrosation}} \text{R}_2\text{NNO} \quad (19b)
\]
Nitrosamines (19b) have elicited much recent interest due to the unhealthy combination of their presence in our natural and unnatural environment, and their extraordinarily high mutagenicity and carcinogenicity. These nitrosamines are apparently precarcinogens which are oxidatively activated in vivo to compounds which are nitrogen-emitting alkylating agents. Most nitrosamines (19b) do not behave as alkylating agents under nonbiological conditions. Nonetheless a few very special types of nitrosamines (19c and d) do deaminate and act as alkylating agents or potential alkylating agents in vitro (equations 49 and 50). Nitrosamine 19d is believed to be similar to oxidized nitrosamine metabolites.

\[
\begin{align*}
\text{O} & \quad \text{CH}_3\text{CCH}_2\text{Cl(CH}_3\text{)_2} \quad \text{N} \quad \text{NO} \quad \xrightarrow{\text{HCl} \quad \text{H}_2\text{O}} \quad (\text{CH}_3)_2\text{C} \equiv \text{CHCCH}_3 + \text{CH}_2 \equiv \text{CH}_2 + \text{H}_2\text{O} + \text{N}_2 \\
(19c) & \\
\text{CH}_3\text{N(NO)CH}_2\text{OOCCH}_3 & \quad \xrightarrow{\text{H}_2\text{O} \quad \text{(H}^+ \text{ or base)}} \quad \text{CH}_3\text{COOH} + \text{HCHO} + \text{CH}_3\text{OH} + \text{N}_2 \quad (50) \\
(19d)
\end{align*}
\]

Stereochemical effects on N-nitrosamine chemistry have also been surveyed. Bioorganic alkylations with nitrosamines 19b will be further discussed in Section V.C.

The chemical and physical properties of nitrosamines have been reviewed by Fridman, and most recently in an ACS symposium report.

Finally, certain aspects of nitrosamine chemistry are discussed in the chapter by Challis in this volume.

**g. Alkylsulphinylamines (20).** Alkylsulphinylamines (20) may be prepared from primary amines and SOCl₂ (equation 51).

\[
\text{R} \text{NH}_2 + \text{SOCl}_2 \quad \xrightarrow{\text{RNSO}} \quad \text{(20)} \\
(51)
\]

When sulphinylamines (20) have been treated with certain nitrosating agents, they have been observed to alkylate aromatics via carbonium ion mechanisms in 25–45% yields (equation 52).

\[
\text{ArH} + \text{RNSO} + \text{NO}^+\text{SbF}_6^- \quad \xrightarrow{\text{(20)}} \quad \text{ArR} + \text{N}_2 + \text{SO}_2 + \text{HSbF}_6 \\
(52)
\]

**h. Alkyl isocyanates (21).** Alkyl isocyanates (21) may be formed from primary amines by treatment with COCl₂ (equation 53).

\[
\text{R} \text{NH}_2 + \text{COCl}_2 \quad \xrightarrow{\text{RNCO}} \quad \text{(21)} \\
(53)
\]

Isocyanates (21) behave similarly to sulphinylamines (20) when treated with certain nitrosating reagents (equation 54).

\[
\text{ArH} + \text{RNCO} + \text{NO}^+\text{SbF}_6^- \quad \xrightarrow{\text{(21)}} \quad \text{ArR} + \text{N}_2 + \text{CO}_2 + \text{HSbF}_6 \\
(54)
\]
2. Aromatic deaminations via dediazoniations

Virtually all the synthetically useful aromatic deaminations occur via the conversion of aromatic amines to diazonium ions followed by homolytic or heterolytic nitrogen loss with subsequent substitution by some nucleophile or free radical (equation 55).

\[
\text{ArNH}_2 + \text{HNO}_2 \rightarrow \text{ArN}_2^+ \quad \xrightarrow{\alpha \rightarrow \chi} \quad \text{ArX} + \text{N}_2
\]  

The conditions and mechanisms by which nitrogen loss may be effected are extraordinarily diverse. Thus, it is an oversimplification to break these mechanisms down into the two textbook categories of 'homolytic' and 'heterolytic', since within each of these categories may be found many subtle variations. Not only will the mechanisms often change upon only slight changes in reaction conditions, but often so will the products. Some of the many variations in conditions employed which have been shown to greatly influence mechanisms and/or products include: the nature of the solvents, the pH, oxygen concentrations, the absence or presence of light, the absence or presence of metallic ions, the nature of the reaction vessel, the concentrations of reactants, etc. And new mechanistic surprises occur constantly. For example, it has been found that aryl carbonium ions can reversibly combine with nitrogen. The fascinating story of the mechanisms of aromatic dediazoniation is worth whole review articles, and such articles have been excellently written by Zollinger. In addition Wulfman has extensively reviewed the replacements of the aryl diazo group by a large number of substituents in a recent volume in this series.

\[a. \text{Scope of the reaction.} \]
Preparative and industrial chemists are more concerned with the synthetic aspects of aromatic deaminations. A number of famous name reactions such as the Sandmeyer reactions, the Gatterman reaction, the Schiemann reaction, the Meerwein reaction, the Gomberg reaction and the Pschorr ring-closure are aromatic dediazoniations. Some of the substituents represented by these name reactions as well as some others are: OH, RO, SH, RS, SCN, N₃, Br, Cl, I, F (via BF₄⁻), CN, NO₂, Ar, alkene, H and metals. Polymerizations are also very important, especially in industrial chemistry.

Textbooks often state that Sandmeyer-type dediazoniations which utilize Cu(I) proceed via homolytic mechanisms, while dediazoniations in water proceed via heterolytic mechanisms. However, Zollinger's reports reveal these statements to be oversimplifications. Factors affecting yields in Sandmeyer reactions have been discussed.

In addition to Wulfman's recent chapter in this series and Zollinger's reviews, a number of other surveys of aromatic deaminations in general, and also of specific cases, have appeared. Furthermore, the process of diazotization has also been reviewed.

\[b. \text{One-pot aromatic deaminations.} \]
Most aromatic deaminations involve two separate synthetic steps. Recently, however, one-step procedures utilizing alkyl nitriles and copper (II) halides have been reported (equation 56). Yields are generally excellent, ranging up to 99.5% halide production. Earlier one-pot conversions to halides have been published, but apparently are of only limited use.

\[
2 \text{ArNH}_2 + 2 \text{RONO} + \text{CuX}_2 \rightarrow 2 \text{ArX} + 2 \text{ROH} + \text{CuO} + \text{H}_2\text{O} + \text{N}_2
\]  

Another one-step deamination resulting in mostly good to excellent halide yields.
involves the use of $t$-butyl thionitrite or $t$-butyl thionitrate as the diazotizing reagent (equation 57).230

\[
\begin{align*}
\text{CH}_2\text{CN}^+ + \text{ArNH}_2 + \text{CuX} & \xrightarrow{\text{CH}_3\text{CN}} \text{ArX} + \text{N}_2 + (t\text{-Bu})_2\text{S}_3 + (t\text{-Bu})_2\text{S}_2 \\
\text{ArNH}_2 + \text{H}_2\text{C}==\text{CHY} & \xrightarrow{\text{RONO}} \text{ArCH}_2\text{CHY} + \text{N}_2
\end{align*}
\]

(57)

A one-pot Meerwein arylation of alkenes using alkyl nitrites and copper (II) halides has similarly been developed (equation 58)\textsuperscript{124}.

\[
\begin{align*}
\text{RON0} + \text{ArNH}_2 + \text{H}_2\text{C}==\text{CHY} & \xrightarrow{\text{CuCl}_2} \text{ArCH}_2\text{CHY} + \text{N}_2 + \text{Cl} \\
\text{ArNH}_2 + \text{H}_2\text{C}==\text{CHY} + \text{H}_2\text{O} & \xrightarrow{\text{hv}} \text{ArH} + \text{ArCH}_2\text{CH}_2\text{OH} + \text{ArOCH}_3 + \text{ArCHOH} + \text{N}_2
\end{align*}
\]

(58)

Analogous displacements of the aryl amino group with hydrogen have been reported and will be briefly discussed under 'reductive deaminations' (Section III).\textsuperscript{71,125,220,223}

c. \textit{Photochemical dediazonation and the photorearrangements of diazoketones.} The photochemistry of diazonium ions has been reviewed by Ando\textsuperscript{8}, and by Dinaburg\textsuperscript{119}. Two representative examples of photodediazonation are given in equations (59a) and (59b)\textsuperscript{8,24,253,333,363,425}. When the anions in these photochemical deaminations are derived from Lewis acids, as in equation (59a), the Lewis acid

\[
\begin{align*}
\text{BF}_3^- & \xrightarrow{\text{hv}} \text{F} + \text{BF}_3 + \text{N}_2 \\
\text{ArN}_2^+ + \text{C}_2\text{H}_5\text{OH} & \xrightarrow{\text{hv}} \text{ArH} + \text{ArCH}_2\text{CH}_2\text{OH} + \text{ArOCH}_3 + \text{ArCHOH} + \text{N}_2
\end{align*}
\]

(59a)

(59b)

is released as a by-product. This method of generating Lewis acids \textit{in situ} has found much application in industrial polymer chemistry (see Section II.K.2.e)\textsuperscript{224,355}.

Aryl-1,2-diazooxides ('o-quinone diazides') (22), give Arnlt–Eistert-type ring-contractions on photolysis (equation 60)\textsuperscript{363}. This reaction has also been found to be useful to industrial chemists (see Section II.K.2.e).

\[
\begin{align*}
\text{CON} & \xrightarrow{\text{hv}} \text{N}_2 + \text{COOH}
\end{align*}
\]

(60)

(d. \textit{Arynes from certain aryldiazonium salts.} Special diazonium salts, such as those prepared from anthranilic acid or its derivatives, photochemically or thermally decompose to give arynes (equation 61)\textsuperscript{148,161,266,374,375,424}.

e. \textit{Industrial applications of aromatic deaminations.} The photochemical and thermal decompositions of aromatic diazonium salts and diazoketones have found extensive use in industrial chemistry. In particular, many polymerizations make use of the photolysis of diazoketones or diazonium salts. The photographic and related industries have made considerable use of these types of dediazoniations and related
22. Deaminations (carbon–nitrogen bond cleavages)

\[
\begin{align*}
\text{COOH} & \xrightarrow{\text{HNO}_2} \text{COO}^- \\
\text{NH}_2 & \xrightarrow{\text{hv or heat}} \begin{cases} 
\text{[C]}
\end{cases} \\
+ \text{CO}_2 & + \text{N}_2
\end{align*}
\]

processes\textsuperscript{24,363}. Many of the details of these procedures are trade secrets, but much information can be found in several reviews as well as in the voluminous patent literature\textsuperscript{24,72,119,155,239,245,335,351}.

A particularly interesting example of the applied chemistry of dediazoniation is partly given in equation (59a). In this case the important product is the boron trifluoride, which is generated for use as a Lewis acid catalyst for cationic polymerizations such as the polymerizations of various epoxides\textsuperscript{335}.

L. Miscellaneous Leaving Groups in Aromatic Deaminations

1. Photochemical deaminations of aromatic amines

Whereas photochemical dealkylation of amines is commonly observed, photochemical dearylation of arylamines is a rarely observed process\textsuperscript{355,365}. An example of the latter involves the photodegradation of certain quarternary amine salts with easily oxidizable counterions such as iodide\textsuperscript{392}.

2. 2,4,6-Triphenylpyridine and related leaving groups

It has already been mentioned that arylamines can be converted to aryl iodides and thiocyanates by forming 2,4,6-triphenylpyridinium salts and then pyrolysing them (equation 62) (see also Section II.G)\textsuperscript{213,221}. A variant on 8b has recently been found to give better yields\textsuperscript{221}.

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{ArNH}_2} \text{Ph} \\
\text{Ph} & \xrightarrow{\text{heat}} \text{ArI} + \text{Ph}
\end{align*}
\]

M. Dinitrogen Oxide (N\textsubscript{2}O) Gas as Leaving Group

1. Pyrolyses of N-nitroamides and related compounds (23)

\(N\)-Nitroamides (23) and \(N\)-nitrocarbamates pyrolyse similarly to \(N\)-nitrosoamides with \(\text{N}_2\text{O}\) being expelled instead of nitrogen (equation 63)\textsuperscript{411,416} (see also Section II.K.1.c).

\[
\begin{align*}
\text{R} & \xrightarrow{\text{heat}} \text{ROOCR}^1 + \text{alkenes} + \text{N}_2\text{O}
\end{align*}
\]

White and Field\textsuperscript{396} have proposed for these reactions mechanisms involving ion-pair intermediates which are analogous to those proposed for nitrosoamide
decompositions. The product distributions for different R groups indicate a gradual change in mechanism with carboxonium ion stability, but there are no discontinuities in the series as a function of substituents.

N-Nitroamides (23) and N-nitrocarbamates are readily prepared by nitrating the parent amides (equation 64)^396.

\[
\text{RNHCON}^1 + \text{NO}_2 \rightarrow \text{RNH}_{2-N} \text{C} \leftarrow \text{O}
\]

(64)

\[\text{RNHCOR}^1 \xrightarrow{\text{NO}_2} \text{RNCH} \rightleftharpoons \text{C} \]

(23)

2. Reactions of tertiary amines with nitrosating agents

The reactions of most tertiary amines with nitrous acid produce complex mixtures of products, the most important of which are \(N,N\)-dialkylnitrosamines (19) and carbonyl compounds. The leaving group is \(N_2O\) (equation 65)^146,172,394 (see also Sections IV.M and V.C.4).

\[
\text{RNHCHR}^1 \xrightarrow{\text{HONO}} \text{N}_2\text{O} + \text{RN} \rightleftharpoons \text{N} \leftarrow \text{NO} + \text{R}^1\text{C} \rightleftharpoons \text{O}
\]

(65)

(19)

3. The reaction of aziridines (24) with certain nitrosating agents

Aziridines (24) react with nitrosating agents such as nitrosyl chloride or methyl nitrite to give alkenes and \(N_2O\) (equation 66). The reactions are completely stereospecific with retention of configuration^68,80,130,345,347a,394.

\[
\text{C} \leftrightharpoons \text{N} \rightarrow \text{C} \xrightarrow{\text{NOCl}} \text{C} \leftrightharpoons \text{N} + \text{N}_2\text{O}
\]

(66)

\[\text{R}^1\text{C} \leftrightharpoons \text{N} \leftrightharpoons \text{C} \xrightarrow{\text{ClC}_6\text{H}_5\text{CO}_2\text{H}} \text{R}^1\text{C} \leftrightharpoons \text{C} + (\text{R}^1\text{NO})_2
\]

(24a)

(67a)

N. Nitrile Leaving Group

The von Braun degradation which involves the heating of secondary or tertiary amides with \(\text{PCl}_3\) or \(\text{PBr}_3\) expels nitrile leaving groups (equations 67b and 67c)^31,50,54,55,327,391,394.
22. Deaminations (carbon–nitrogen bond cleavages)

\[
\text{ArCONR}_2 \xrightarrow{\Delta} \text{RX} + \text{ArCX} = \text{NR} \quad \xrightarrow{\Delta} \text{ArCN} + \text{RX} \quad (67b)
\]

\[
\text{ArCONHR} \xrightarrow{\text{PCl}_5} \text{ArC} = \text{NR} \xrightarrow{\Delta} \text{ArCN} + \text{RCI} \quad (67c)
\]

O. Some Potentially Good Leaving Groups

A number of other leaving groups derived from amines should be fair-to-good leaving groups. Some of these activated amines may even have been 'unintentionally' observed to give carbon–nitrogen bond cleavage. Rigorous literature searches, particularly of the older literature, thus, might prove fruitful in suggesting 'new' deamination procedures. It has already been pointed out here that heterocycles such as pyrrole and the barbiturates might be good leaving groups. Other candidates may be suggested by perusing pKₐ tables or by structural analysis. One example of the latter approach would involve groups such as nitroamide leaving groups (26) in S_N2 reactions (equation 68) (hypothetical equation). Of course, the pathway wherein such compounds rearrange and evolve N₂O are well known and have already been discussed.

\[
\text{RC-N-R} + \text{Y}^- \rightarrow [\text{R-C-N} = \text{NO}_2]^- + \text{RY} \quad (68)
\]

Not all groups which appear to be good leaving groups on paper, however, turn out to be good leaving groups in fact. Thus, some trial runs with \text{N,N-di(2,4-nitrophenyl)alkylamines (27)} with a variety of nucleophiles gave no evidence for carbon–nitrogen bond cleavage^{113,114}.

\[
\text{(27)}
\]

P. N-Containing Leaving Groups Compared with Other Leaving Groups

It has already been mentioned that aryl disulphonimidates (2), unlike most compounds with good leaving groups, can be readily recrystallized from a variety of nucleophilic solvents without solvolysis^{111,113}. Similarly Katritzky's 2,4,6-triphenylpyridinium salts are recrystallized from ethanol^{210}.

Various nitrogen-containing groups have been compared with a variety of other leaving groups in a review by Stirling^{376}, and Beak, Adams and Barron^{40} have compared gaseous nitrogen with other especially facile leaving groups.
III. REDUCTIVE DEAMINATIONS

Most of the generally useful aliphatic reductive deamination procedures are of recent vintage. Reductions reported before 1960, with few exceptions, were observed to occur only with amines with special activating features such as benzyl or carbonyl. More recent reductive techniques are much more general in scope. Reductive deaminations through around 1968 have been previously reviewed\textsuperscript{31,154,394.}

As in the previous section, reductive deaminations are organized according to leaving group.

A. Sulphonimide Anion (3) Leaving Groups

Hutchins and coworkers have recently reported that hydride (from BH\textsubscript{4}\textsuperscript{-}) may displace diarylsulphonimide anions and triflimides (3) (equation 69)\textsuperscript{199,200}. Yields in these reductions are fair to excellent, with unhindered primary amine derivatives giving the best results. As discussed in Section II.A, sulphonimides 2 derived from hindered amines cannot be prepared or give poor yields of substitution products. The mechanisms of these reductions have also been discussed\textsuperscript{156,200}.

B. Succinimide Leaving Group (28b)

In the course of developing a new monomethylation procedure for aromatic amines, Kadin\textsuperscript{209} has found that certain succinimides derived from Mannich bases (28a) may be reductively deaminated with NaBH\textsubscript{4} (equation 70). Functionalities such as ester, nitrile, or amide do not interfere with the reaction. Circumstantial evidence suggests the mechanism shown in equation (71) for this reduction\textsuperscript{209}.

C. Pyridine-derived Leaving Groups (8b)

Katritzky and coworkers have reported a novel procedure for reducing benzyl-, allyl- and heteroarylmethyl-aminies via substituted dihydropyridines (29) (equation...
22. Deaminations (carbon–nitrogen bond cleavages)

\[
\text{RCH}_2\text{NH}_2 + \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{N} \\
\text{CH}_2\text{R} \\
\end{array}
\stackrel{\text{NaBH}_4}{\longrightarrow}
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{N} \\
\text{CH}_2\text{R} \\
\end{array}
\text{(29)}
\]

(72)

Yields are generally very good\cite{52,215}. (This method is related to the reaction described in Section II.G; see also Section III.F.)

Katritzky has proposed the mechanism shown in equation (73) for this reaction\cite{52,215}.

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{N} \\
\text{CH}_2\text{R} \\
\end{array}
\stackrel{\text{H}_2\text{C}=	ext{H}}{\longrightarrow}
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{N} \\
\text{CH}_2\text{R} \\
\end{array}
\text{(8b)}
\]

(73)

D. Ammonia and Amines as Leaving Groups

Amines and ammonium salts which are appropriately activated in the R group(s) bonded to the nitrogen may be reduced to the corresponding alkyl moiety by catalytic hydrogenation, metals and various hydrides. These methods have been reviewed\cite{31,154,273,387,394}. Furthermore, certain enamines have been reduced via \text{AlH}_3 or diborane to the corresponding alkene\cite{64,262,292}.

Electrolytic reductions are also known and have been briefly reviewed\cite{394}. A more recent example involves the electrolytic reduction of \(\alpha\)-acylamino acid esters to the corresponding \(\beta\)-keto esters in good yields (equation 74)\cite{280}.

\[
\begin{array}{c}
\text{RCOC}\\(\text{R'})\text{COOR}^2 \\
\text{NH}_3 \text{ Cl}^- \\
\end{array}
\rightarrow
\begin{array}{c}
\text{RCOC}\\(\text{R'})\text{COOR}^2 + \text{NH}_4\text{Cl} \\
\end{array}
\]

(74)

Hutchins and group have developed a synthesis of tertiary amines derived from aniline (30), using \text{NaBH}_4 as the reducing agent. Yields are good (71–79%) (equation 75)\cite{200}.
E. Nitrogen Gas Leaving Groups

1. Aliphatic cases

With the exception of the reduction of special diazoalkanes, reported amine reductions which emit nitrogen as the leaving group probably proceed via diimide (31) intermediates.

a. The reaction of primary amines with difluoramine. The difluoramine procedure for generating diimide (31)-type reductions looks very promising on paper, but in actuality it is a very difficult and potentially dangerous procedure (equation 76). This reaction and its mechanism have been previously discussed.31,67,98,240,256,394

\[ \text{RNH}_2 + \text{HNF}_2 \rightarrow [R-N=NH] \rightarrow \text{RH} + \text{N}_2 \]  
(31)

b. The reaction of hydroxylamine-O-sulphonic acid or chloramine with arylsulphonamides. The first reported deamination procedure for reducing amines to alkanes via the probable diimide (31) intermediate is summarized in equation (77). Similar reductions are observed when alkylhydrazines are oxidized to alkylidymines.98

\[ \text{RNH}_2 \xrightarrow{\text{ArSO}_2\text{Cl}} \text{RNHSO}_2\text{Ar} \xrightarrow{\text{OH}^-} \text{RH} + \text{ArSO}_3\text{H} + \text{N}_2 \]  
(77)

X = OSO_3H or Cl

c. The reaction of primary amines with hydroxylamine-O-sulphonic acid. A reaction similar to the previously described case has recently been reported and is summarized in equation (78). This procedure is also believed to proceed via a diimide intermediate.

\[ \text{RNH}_2 \xrightarrow{\text{NH}_2\text{OSO}_3\text{H}} \text{RH} + \text{SO}_4^{2-} + \text{N}_2 \]  
(78)

Seven amines were reported to be reduced in 26–72% yield. Carboxyl and amide groups apparently do not seriously interfere with the reductions of 2-aminobenzoic acid to benzoic acid and 2-amino-3-methylbenzoic acid to 3-methyl-benzoic acid.122

Trace amounts of cupric ion give a reaction which appears to be a disproportionation (equation 79).

\[ \text{PhCH}_2\text{NH}_2 \xrightarrow{\text{NH}_2\text{OSO}_3\text{H}} \text{OH}^- \text{Cu}^{2+} \rightarrow \text{PhCHO} + \text{PhCH}==\text{NCH}_2\text{Ph} + \text{PhCH}_2\text{CH}_2\text{Ph} \]  
(79)

d. The reaction of diazoketones with HI. Diazoketones may be reduced to methyl ketones by HI (equation 80).332 Since diazoketones may be obtained from the parent amines, this constitutes a possibly useful type of deamination.

\[ \text{RCOCHN}_2 + 2 \text{HI} \rightarrow \text{RCOCH}_3 + \text{N}_2 + \text{I}_2 \]  
(80)
2. Aromatic cases

Reductive dediazoniations are generally discussed with other aromatic deaminations and most of the reviews cited in Section II.K.2 discuss these.

Until recently, aromatic reductive deaminations were accomplished in two steps; the first was formation of the diazonium ion and the second involved the reductive dediazoniation. Hypophosphorous acid has been the most popular reducing agent, although a number of others have been reported (equation 81a).41,125,237,238,274.

$$\text{ArNH}_2 + \frac{\text{HNO}_2}{2} \rightarrow \text{ArH} + \text{N}_2$$  \hspace{1cm} (81a)

In newer one-pot procedures, the arylamines are treated with alkyl nitrites in solvents such as ethers or DMF.71,125. In the modification by Doyle and coworkers125, yields are generally good (equation 81b).

$$\text{ArNH}_2 + \text{RONO} \rightarrow \text{ArH} + \text{ROH} + \text{N}_2 + \text{H}_2\text{O}$$ \hspace{1cm} (81b)

Doyle and coworkers125 have obtained evidence for a free-radical mechanism for this reaction (equation 82).

$$\text{ArNH}_2 + \text{RONO} \rightarrow \text{ArN}==\text{NOR} + \text{H}_2\text{O}$$

$$\text{ArN}==\text{NOR} \rightarrow \text{ArN}_2^+ + \text{RO}.$$ \hspace{1cm} (82)

The alkyl nitrite reductive dediazoniations have been applied to the conversion of adenine derivatives to the corresponding purines by Nair and Richardson.308a (equation 83a). This type of deamination had reportedly failed under a variety of previously tried conditions.351,428

$$\text{NH}_2$$

$$\text{H}$$

$$\text{Et}$$

$$\text{CH}_3\text{CH}_2\text{ONO}$$

$$\text{THF}$$

$$\text{N} + \text{N}_2$$ \hspace{1cm} (83a)

This procedure has been used to synthesize the antibiotic, nebularine and other nucleosides.308a Nair and Richardson have also found that Cl, Br and I may replace nitrogen using this procedure.308b

F. Aromatic Reductions via 2,4,6-Triarylpyridine Leaving Groups

The amazingly versatile procedure of Katritzky and coworkers utilizing 2,4,6-triarylpyridine leaving groups may be used to reduce arylamines (equation 83b).220,223 Yields of reduced arylamine are 57–62% (see also Sections III–C and II.G).

G. Alkylations

When the amino group is replaced by an alkyl group; there is a reductive change
in the oxidation state of the molecule. These deaminations have been discussed in other sections of this chapter (see Sections II.B.2. II.K.1.e and Table 3).

**IV. OXIDATIVE DEAMINATIONS**

Until recently there were essentially no practical laboratory methods for oxidatively deaminating most amines. However, over the last few years procedures have been developed to convert many types of amines into ketones, aldehydes, carboxylic acids, etc, including simple photochemical oxidation which converts many amines into aldehydes or ketones, in excellent yields.

Amines may be oxidized by a large inventory of reagents to aldehydes, ketones and carboxylic acids (or other functionalities of equivalent oxidation states). Most of these oxidations proceed via intermediate imines, nitriles or amides, and in some cases the unsaturated nitrogen compounds are isolated. Virtually all the imine and nitrile intermediates may be hydrolysed, and the conditions for the hydrolysis of Schiff bases and related functionalities have been discussed. Thus, the ultimate leaving group in Sections A–F below is ammonia or an amine.

In addition to oxidations via imine-type intermediates, a few newer procedures effect oxidations via totally different mechanistic paths.

A number of reviews of oxidative deaminations and related topics have appeared.

Since a recent comprehensive review by Chow and coauthors on amine oxidations which proceed via nonaromatic ammonium radical intermediates has been published, this type of oxidation will not be specifically discussed here (however, see Chapter 25 in this volume).

**A. Oxidations of Amines by Direct Dehydrogenation**

Dehydrogenations of amines are represented by equations (84)–(86). The leaving group in these cases is ammonia or an amine.

$$\begin{align*}
\text{RCH}_2\text{NH}_2 & \xrightarrow{-2\text{H}^+} \text{RHC}=\text{NH} & \xrightarrow{\text{H}_2\text{O}} & \text{RHC}=\text{O} + \text{NH}_3 \\
\text{R}_2\text{CHNHR'} & \xrightarrow{-2\text{H}^+} \text{R}_2\text{C} = \text{NR} & \xrightarrow{\text{H}_2\text{O}} & \text{R}_2\text{C}=\text{O} + \text{R'}\text{NH}_2 \\
\text{RCH}_2\text{NH}_2 & \xrightarrow{-4\text{H}^+} \text{RCH}=\text{N} & \xrightarrow{\text{H}_2\text{O}} & \text{RCOOH} + \text{NH}_3
\end{align*}$$

A representative list of inorganic oxidizing reagents used in these types of dehydrogenation includes: Ag(NO$_3$)$_2$, Ag$_2$CO$_3$, KMnO$_4$, MnO$_2$, NiO$_2$, Pb(OAc)$_4$, chromic oxide, copper chromite–nickel–K$_2$P$_4$, mercuric oxide, Hg(OAc)$_2$, potassium peroxydisulphate, IF$_5$, other peroxides, NaNH$_2$–NH$_3$, Ni, Pt, Cr$_2$, Pd, Sc, ruthenium and other transition metals, chromic acid, FeCl$_3$, silver oxide, S$_2$O$_8^{2-}$/Ag$^{+}$. Not all these reagents work in all cases, and in those cases where they do work, yields are often...
Deaminations (carbon–nitrogen bond cleavages) Of the above, the Ag(1) salts give the best yields (30–60%). The mechanisms involving some of the above dehydrogenations most probably involve more complex pathways than simple hydrogen abstractions (e.g. some oxidations proceed via ammonium radical intermediates) also see Section IV.C.

In addition to the above large inventory of inorganic reagents which may dehydrogenate amines, some organic oxidizing agents convert amines to carbonyl compounds via imines. These include hexamethylenetetramine, various derivatives of formic acid, derivatives of diaminomethane, o'-bromoanisole, t-butyperoxide, quinones, nitrosobenzene, and photochemically with benzophenone (see next topic). Oxidation may also occur via transamination (see Section IV.F). Furthermore a key step in the Sommelet–Hauser rearrangement involves dehydrogenation (equation 87). This and related rearrangements have been reviewed.

\[
\text{ArCH}_2\text{NH}_2 + [\text{CH}_2=\text{NH}] \rightarrow \text{ArCH=NH} + \text{CH}_3\text{NH}_2 \quad (87)
\]

A procedure has also been developed for oxidizing enamines to α-acetoxyketones with thallium triacetate. A number of oxidizing agents may oxidize primary amines and/or hydroxylamines to imines.

The Strecker degradation of α-amino acids involves a simultaneous oxidation and decarboxylation (equation 88). The various reagents which may be used in this reaction have been discussed in reviews. Some of these reactions proceed via transamination mechanisms which will be discussed later (Section IV.F).

\[
\begin{align*}
\text{NH}_2 \\
\text{R-CH-COOH} & \quad [\text{O}] \quad \text{RCH=NH} + \text{CO}_2 \quad \overset{\text{H}_2\text{O}}{\rightarrow} \quad \text{RCH=O} + \text{NH}_3
\end{align*} \quad (88)
\]

The direct oxidation of amino acids and amines via enzymatic dehydrogenation in biochemistry is a well-known process and will be briefly discussed under Section V.A.

B. Photochemical Oxidations of Amines to Aldehydes and Ketones

A reaction well known to photochemists, but surprisingly neglected by synthetic chemists, involves the photodehydrogenation of amines by benzophenone and related compounds (equation 89). By this technique, both aldehydes and ketones may be obtained simply and in good yield.

\[
\begin{align*}
2 \text{RR'C(NH)NH}_2 + \text{Ph}_2\text{C}=\text{O} & \overset{\text{hv}}{\rightarrow} \text{Ph}_2\text{C(OH)}\text{C(OH)}\text{Ph}_2 + 2 \text{RR'C=NNHR} \\
\text{RR'C=NNHR} & \overset{\text{H}_2\text{O}}{\rightarrow} \text{RCR} + \text{RR'C(NH)NH}_2
\end{align*} \quad (89)
\]

When these photooxidations are run under anhydrous conditions, the maximum yield of aldehyde or ketone is only 50% due to the stoichiometric requirement of a 2:1 molar ratio of amine to benzophenone. Fortuitously, however, this reaction proceeds as efficiently in aqueous media, so that quantitative yields of acetone and 2-butanone have been obtained by irradiation in an aqueous media with 4-carboxybenzophenone (equation 90). The products and mechanisms of these reactions are different in aqueous media from those observed under anhydrous conditions. Many interesting aspects as well
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\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_3 + \text{CH}_2\text{=C}+\text{NH}_3 + \text{H}_2\text{O} &\xrightarrow{\text{hv}} \text{CH}_3\text{CH}=\text{CH}_2 \text{COPh} \\
&\xrightarrow{4\text{-carboxybenzophenone}} \text{CH}_3\text{SCH}_2\text{CH}_2\text{CHO} + \text{CO}_2 + \text{NH}_3
\end{align*}
\]

(91)

as the mechanisms of these and related reactions have been investigated by Cohen and coworkers and reviewed by Cohen, Parola and Parsons\textsuperscript{84}. Preparative organic chemists should note the following advantages of this oxidative procedure:

(1) Yields are not only potentially quantitative, but work-ups are easy, and no corrosive or sensitive reagents are involved. Toxicity levels are also probably on the relatively low side.

(2) Most oxidations of amines give little or no aldehyde products. Here aldehyde yields may be good.

(3) The procedure is excellent for the degradation of secondary amines. Tertiary amines are also efficiently and selectively degraded (see Section IV.M).

(4) In these energy-conscious times it is interesting to note that these reactions may at least theoretically be performed using only direct solar energy.

Drawbacks are the probable interference of many types of functional groups and the sensitivity of aldehydes to the basic conditions employed in the aqueous runs.

A further interesting application of this reaction is in essence a photochemical variation of the Strecker degradation of \(\alpha\)-amino acids, as Cohen and Ojanpera\textsuperscript{86} have reported that methionine can be oxidatively deaminated to the corresponding aldehyde (equation 91).

\[
\text{CH}_3\text{SCH}_2\text{CH}_2\text{CH}\text{(NH}_2\text{)}\text{CO}_2^- \xrightarrow{\text{hv}, \text{H}_2\text{O}} \text{CH}_3\text{SCH}_2\text{CH}_2\text{CHO} + \text{CO}_2 + \text{NH}_3
\]

(91)

Other varieties of photochemical amine oxidations involving ammonium ion radical intermediates from \(N\)-haloamines have been reviewed\textsuperscript{78}.

Yet another interesting photooxidation is apparently more limited in scope. Hyatt\textsuperscript{203} has reported that salts of certain amines are converted to aldehydes or ketones by a Norrish type II photolysis (equation 92).

\[
\text{R}_2\text{CHNH}_2\text{CH}_2\text{COPh} \xrightarrow{\text{hv}} \text{R}_2\text{C}=\text{O} + \text{PhCOCH}_3
\]

(92)

The photochemistry of nitrosoamides is rather complex; among the many products isolated have been aldehydes, amides and \(N\)-arylimines\textsuperscript{79}.

Nonoxidative photochemical dealkylations are also known\textsuperscript{355}.
C. Oxidations of Amines to Imines via the Generation of Good Leaving Groups

In these reactions, one or two NH and/or CH bonds are replaced by some functionality such as halogen, which can then be eliminated, for example, as HX (equation 93) (see also Section I).

\[
\begin{align*}
R_2C\text{-}N\text{-}H & \xrightarrow{[\text{X}^+]} R_2C\text{-}N\text{-}X \\
& \xrightarrow{\text{base}} R_2C\text{-}NR (+ \text{HX}) \\
& \xrightarrow{H_2O} R_2CO + \text{RNH}_2
\end{align*}
\] (93)

1. Oxidations with halogens and related species – HX as leaving groups

In general most N-haloamines are readily converted to imines by merely heating or by treating with base\textsuperscript{108,164,206,265,372}. Thus, any procedures which convert amines to N-haloamines are potentially deamination procedures. Some of the halogen species which have been used to oxidize amines are: Br\textsubscript{2}\textsuperscript{346a}, N-bromosuccinimide\textsuperscript{135,177}, t-butyl hypochlorite\textsuperscript{13,60,170,260}, hypochlorous acid\textsuperscript{43} and NaOCl with phase-transfer catalysts\textsuperscript{251}.

Deaminations via N-haloamines are sometimes called the ‘Ruschig reaction’\textsuperscript{346b}. Labler and Sorm\textsuperscript{244}, and Bachmann, Cava and Dreiding\textsuperscript{13} have successfully applied this reaction to a variety of systems.

Corey and coworkers\textsuperscript{32} have used this type of oxidative deamination as a key step in their syntheses of prostaglandins of the E\textsubscript{1} and F\textsubscript{1} series (equation 94). The overall yield of ketone in this process is 25%.

\[
\begin{align*}
\text{H}_3\text{N}^+ & (\text{CH}_2)_6\text{COO}^- \\
\text{THPO} & \xrightarrow{1. \text{NBS}} \xrightarrow{2. \text{H}_2\text{O}, \text{base}} \text{HO} (\text{CH}_2)_6\text{COOH}
\end{align*}
\] (94)

Amino acids give a Strecker-type oxidative decarboxylation with hypohalites\textsuperscript{247}.

Examples of HX elimination from α-haloamines are much harder to find in the literature. One such rare case is given in equation (95)\textsuperscript{329}.

\[
\text{CF}_3\text{N}=\text{CF}_2 \xrightarrow{\text{KF}} \text{CF}_3\text{N}^\text{+}=\text{CF}_2 (+ \text{HF})
\] (95)

2. Sulphonic acids as leaving groups – oxidations with sulphonyl peroxides

Sulphonyl peroxides (32) oxidize primary and secondary amines to the corresponding aldehydes and ketones in 37–96% yield (equation 96). This reaction

\[
\text{RCH}_2\text{NHR}^1 + (\rho\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_3)_2 \rightarrow \text{RCH}=\text{NR}^1 + 2 \rho\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_3\text{H}
\] (32)

\[
\text{R}^1 = \text{H or alkyl}
\]
was reported by Hoffman who proposed the mechanistic sequence shown in equation (97).

\[ R'\text{CH}_2\text{NHR} + (\text{ArSO}_3)_2 \rightarrow R'\text{CH}_2\text{NHR} + \text{ArSO}_3^- \]  
\[ \text{(32)} \]

\[ R'\text{CH}_2\text{NHR} \rightarrow R'\text{CH}=\text{NR} + \text{ArSO}_3^- \]  
\[ \text{Ar} = p-\text{O}_2\text{NC}_6\text{H}_4^- \]  
\[ \text{(97)} \]

3. Sulphonates as leaving groups – eliminations of sulphonates and sulphinates from sulphonamides and sulphonimides

Certain arylsulphonamides (33) activated via an electron-attracting R group give imines by eliminating sulphonates when treated with strong bases (equation 98). The reaction usually fails when R is hydrogen.

\[ R'\text{CH}_2\text{NSO}_2\text{Ar} \rightarrow \text{RCH}=\text{NR} + \text{ArSO}_3^- \]  
\[ \text{base} \]  
\[ \text{(33)} \]  
\[ \text{(98)} \]

More recently Glass and Hoy have found that N-benzyl-N,N-diarylsulphonimides (2) may eliminate either the arylsulphonate anion, or both arylsulphonate anion and the arylsulphinate anion (34) to give either imino derivatives (35) or nitriles (equations 99 and 100). The details of this mechanism have also been discussed by Glass and Hoy.

\[ \text{PhCH}_2\text{N(SO}_2\text{Ar)}_2 \rightarrow \text{PhCH}=\text{NSO}_2\text{Ar} \]  
\[ \text{base} \]  
\[ \text{OCMe}_2 \]  
\[ \text{PhCH}=\text{N(SO}_2\text{Ar)}_2 \rightarrow \text{PhC}=\text{N} + \text{ArSO}_2^- \]  
\[ \text{CN}^- \]  
\[ \text{(34)} \]  
\[ \text{(35)} \]  
\[ \text{(99)} \]  
\[ \text{(100)} \]

The following reaction is probably related to the reactions in this section (equation 101).

\[ \text{Me}_-\text{SONHCH}_2\text{-} \rightarrow \text{Ph-} + \text{K}_2\text{SO}_3 + \text{Me} \]  
\[ \text{KOH} \]  
\[ \text{(101)} \]
22. Deaminations (carbon–nitrogen bond cleavages)

4. Active methylene compounds (or their anions) as leaving groups

Diacetylmethane (and its derivatives) (36) have been observed as leaving groups to give imines from certain Mannich-type bases (equation 102)\(^{225,226}\).

\[
\begin{align*}
\text{PhCHCH(COMe)}_2 + \text{NHPh} & \xrightarrow{\Delta} \text{PhCH=NP} + \text{CH}_2\{\text{COMe}\}_2 \\
(102) & \text{(36)}
\end{align*}
\]

This reaction looks like a reverse Mannich reaction and is, thus, yet another example of deamination activated by substituents in the R moiety of the amine. It would not be surprising to observe this reaction with a variety of other Mannich bases and in fact, thermal retro-Mannich reactions have been reported\(^{64,65}\).

5. Elimination of halogens

An imine formation from a substituted amine occurs in the reductive defluorination of the exceptionally stable perfluoroazaalkanes (37). The reducing agent for the process is ferrocene (equation 103)\(^{290}\).

\[
\begin{align*}
\text{CF}_3\{\text{CF}_2\}_2\text{NF}_2 + \text{ferrocene} & \xrightarrow{} \text{CF}_3\{\text{CF}_2\}_2\text{NF} + (2\text{F}) \\
(103) & \text{(37)}
\end{align*}
\]

D. Nitrile Formation

Some of the oxidizing procedures previously described may oxidize amines to nitriles as well as to imines, and a few produce nitriles but no imine. Thus, Pb(OAc)\(_4\)\(^{288}\), NBS\(^{162}\), IF\(_3\)\(^{371}\), Br\(_2\)\(^{188}\), Ni and other catalysts\(^{326,348}\), Ni peroxide\(^{310}\), Ag(II)picolinate\(^{252}\), and Cl\(_2\)-NaHCO\(_3\) followed by CsF\(^{357}\) oxidize primary amines to nitriles in usually poor yield. The best results are most commonly obtained with Pb(OAc)\(_4\). In addition small amounts of nitriles are obtained as by-products when primary carbinamines are treated with Cu(II) halide nitrosyls (see also Section IV.L)\(^{126,137}\).

With NBS, Strecker degradations of amino acids have been observed to give nitriles along with the more commonly observed aldehyde products\(^{373}\).

The anomalous oxidations of certain sulphonimides, described in Section IV.C.3, give some benzonitrile\(^{158}\). Certain ruthenium-promoted oxidations lead to nitriles\(^{117}\).

Finally the degradation of \(N,N\)-di-n-butylamine shown in equation (104) gives 1-cyanobutane\(^{37}\).

\[
\begin{align*}
\text{(C}_4\text{H}_9\text{)}_2\text{NH} + \text{NH}_3, \text{Zn and} & \xrightarrow{\text{Cr oxide}} 2 \text{C}_3\text{H}_7\text{CN} \\
(104)
\end{align*}
\]

E. Carboxylic Acid and Amide Formation

Some of the oxidizing reagents described under Section IV.A may convert primary carbinamines to carboxylic acids or their derivatives. Yields are, however, usually poor. Probably the most useful of these techniques involves the treatment of primary carbinamines with basic permanganate (equation 105). These conditions have been used in degradation schemes for locating \(^{14}\)C\(^{334,353,354}\).

\[
\begin{align*}
\text{RCH}_2\text{NH}_2 + \text{KMnO}_4 & \xrightarrow{\text{OH}^-} \text{RCOO}^- + (\text{NH}_3) \\
(105)
\end{align*}
\]
Oxidations of primary carbinamines to amides are much more rarely observed. The example given in equation (106) is one which gives low yields of the amide. If, however, a reagent can be found which will effect conversions to amides in good yields, this would constitute an excellent deamination method (see Section I).

\[
\text{CH}_3(\text{CH}_2)_3\text{NH}_2 + \text{(NH}_4)_2\text{S} \rightarrow \text{CH}_3(\text{CH}_2)_2\text{CNH}_2
\] (106)

Some secondary and tertiary amines have been oxidized to amides via a variety of reagents.

F. Imines via Transamination

The most common biochemical deaminations involve transaminations. A few analogous organic chemical deaminations have been reported. The general idea of oxidative transamination is summarized in equation (107). Bioorganic considerations will be further discussed in Section V.B, while the organic chemical cases will be emphasized here.
1. Transaminations with aldehydes and ketones

Pyridoxal is the biochemical coenzyme most commonly used by cells to oxidize amines to aldehydes and ketones via transamination, and a number of in vitro experiments utilizing pyridoxal and pyridoxal analogues have been successfully performed. Not all biochemical transaminases, however, necessarily utilize pyridoxal as the transaminating agent. Thus, the active transaminating agent in histidine decarboxylase (from Lactobacillus 30a) may very likely be the N-terminal pyruvylphenylalanine residue336. Also, Owen and Young320 have demonstrated in vitro decarboxylation and deamination utilizing pyruvamide and N-substituted pyruvamides (38), as transaminating reagents. For example, poor-to-fair yields of benzaldehyde and acetophenone were obtained from the corresponding amines. The imine from n-butylamine did not lead to aldehyde. These transaminations are summarized in equation (108a)320,336.

Corey and Achiwa93 have developed an elegant transamination scheme which utilizes highly hindered conjugated carbonyl compounds for imine formation, followed by facile prototropic interconversion. The isomerized imines are then hydrolysed in mostly good yields. Thus, 3,5-di-i-butyl-1,2-benzoquinone (39a), mesitylglyoxal and nitro mesitylglyoxals (39b), have been employed to convert a variety of primary amines to ketones and aldehydes in 33–97% yields (equations 108b and 108c)93. Yields of ketones are markedly better than those of aldehydes, which is just the opposite of what Bacon and coworkers14,16 observed for direct Ag(II) picolinate oxidations.

\[
\begin{align*}
\text{(39a)} & \quad \text{+} \quad \text{R}_2\text{CHNH}_2 \quad \longrightarrow \\
\text{(39b)} & \quad \text{NCHR}_2
\end{align*}
\]

\[
\begin{align*}
\text{Y} & = \text{Z} = \text{H} \\
\text{Y} & = \text{NO}_2; \text{Z} = \text{H} \\
\text{Y} & = \text{Z} = \text{NO}_2
\end{align*}
\]

\[
\begin{align*}
\text{Y} & = \text{Me} \\
\text{Z} & = \text{Me} \\
\text{Me} & = \text{Me}
\end{align*}
\]
The key to the success of these transamination oxidations lies in the ingenious choice of specially hindered quinones and aldehydes since the selective hindrance suppresses competing reactions while driving the transamination equilibrium towards the desired isomer.

Calo and Todesco\textsuperscript{434} have reported yet another transamination system analogous to the Corey-Achiwa system.

Most recently Panetta and Dixit\textsuperscript{323} have reported the deamination of simple aliphatic and cycloalkylamines, as well as L-glutamic acid and L-alanine, to the corresponding carbonyl compounds utilizing 9-fluorenone-1-carboxylic acid (39c) as the transaminating oxidizing agent (equation 109). The L-amino acids in turn convert 39c to the corresponding amine with some asymmetric induction.

![Equation 109](image)

Amino acids and other amines are oxidized by ninhydrin. The mechanism again most probably involves transamination\textsuperscript{151,283,356}. Those cases (i.e. \(\alpha\)-amino acids) which give simultaneous \(\text{CO}_2\) loss and deamination are called Strecker degradations\textsuperscript{283,378}. Besides ninhydrin and pyridoxal other transaminating reagents capable of effecting Strecker degradations are alloxan and \(p\)-nitrosalicylaldehyde\textsuperscript{93,283,356,378}. Yields of amine to carbonyl compound conversion are poor for amines other than amino acids\textsuperscript{305}.

Transaminations involving such systems as pyruvic acid and glycine have also been reported (equation 110a)\textsuperscript{309}.

![Equation 110a](image)

2. Transamination oxidations via imines and oxaziridines (40)

Dinizio and Watt\textsuperscript{120} have devised a novel transamination procedure for converting a variety of amines to ketones in 42\textendash77% yield. The procedure consists of the initial condensation of the amine with 2-pyridinecarboxyaldehyde to form the aldmine. \(m\)-Chloroperoxybenzoic acid then oxidizes the aldmine to the oxaziridine (40), after which base followed by acid gives the ketone via another imine (equation 110b).

![Equation 110b](image)
G. Primary Amines to Aldehydes via Triazoles

Doeschall has reported a procedure wherein primary carbinamines have been converted to aldehydes in good yields via triazole activation (equation 110c).

\[
\begin{align*}
\text{C}_3\text{H}_7\text{-NH}_2 + \text{Br}^{-} & \quad \xrightarrow{2 \text{Et}_3\text{N}} \quad \text{C}_3\text{H}_7\text{-N} = \text{N} - \text{COOEt} \\
\text{CH}_3\text{-CH}_2\text{-CH} = \text{N} \quad \xrightarrow{H^+/\text{H}_2\text{O}} \quad \text{CH}_3\text{-CH}_2\text{-CH} = \text{O} +
\end{align*}
\]

H. The Pyrolysis of Certain N-Nitroamides

N-Nitroamides may be obtained from the parent amines in two steps. Pyrolyses of some N-nitroamides (i.e. those derived from certain amino acid esters), result in aldehydes or ketones (equation 111)\textsuperscript{35,411}. The mechanism of this reaction possibly involves a nitrosoimine intermediate (41).

J. Dimethyl sulfoxide (DMSO) Oxidations of Disulphonimid es (2) (Disulphonimide Anion Leaving Groups)

All the oxidations considered up to now most probably proceed via imine or nitrile intermediates. DMSO-mediated oxidations of disulphonimid es (2), however, most probably do not proceed via imine intermediates at all. A typical DMSO oxidation of 2 is summarized in equation (112)\textsuperscript{100,101}. As suggested by the equation, this oxidation only proceeds on sulphonimid es derived...
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\[
R_2C\text{--N(SO}_2\text{R}^1\text{)}_2 + \text{DMSO} \quad \text{NaHCO}_3 \rightarrow R_2C\text{=O} + \frac{\text{H}_2\text{O} + \text{CO}_2 + \text{Me}_2\text{S}}{(+ \text{alkenes})}\quad (112)
\]

from secondary carbinamines. Derivatives of the activated primary carbinamine, benzylamine, did, however, give benzaldehyde. Yields of the carbonyl product ranged from 5 to 67% with cyclohexyl derivatives surprisingly giving the best results. The other deaminations with sulphonimides derived from cyclohexylamine gave predominantly alkenes as described in Section II of this chapter.100,101,113,439. Alkene by-products in these oxidations range from 22% to 88%.100,101

The mechanisms for most DMSO oxidations apparently proceed with DMSO acting as nucleophile (equation 113)138. The failure of most primary carbinamine derivatives to give this oxidation suggests that the intermediate may have significant carbonium ion character. The tendency for the benzylamine derivative to give the oxidation easily, reinforces this suggestion.

Epstein and Sweat have reviewed earlier DMSO oxidations138. Bosworth and Magnus51 have suggested an alternative mechanism for some DMSO oxidations, which involves the action of bicarbonate anion as a nucleophile, as well as a base. This alternative mechanism may be operating in at least some of these oxidations.

K. Oxidations of N-Substituted 2,4,6-Triphenylpyridinium Tetrafluoroborates (8a) [2,4,6-Triphenylpyridine Leaving Group (8b)]

Another example of an amine oxidation which probably does not involve intermediate imines is the pyrolysis of various 8a with sodium 1-oxo-4,6-diphenyl-2-pyridone. Yields are 3–59% of aldehydes. This reaction provides one more example of the expulsion of the 2,4,6-triphenylpyridine leaving group, which is apparently even more versatile than the disulphonimide leaving group218–220. A variation on this reaction involves the treatment of 1-benzyl-2,4,6-triphenylpyridiniums with K$_2$Cr$_2$O$_7$ to give benzaldehyde224 (see also Section II.G).

L. Conversions of Amines to Geminal Dihalides via the Gaseous Nitrogen Leaving Group

An unusual oxidation of amines involves the treatment of primary carbinamines with either alkyl nitrites and copper (II) halides or the treatment with copper halide
22. Deaminations (carbon–nitrogen bond cleavages)

\[
RCH_2NH_2 + 2 \text{CuX} + R^1\text{ONO} \rightarrow RCHX_2 + 2 \text{CuX} + N_2 \tag{114}
\]

\[
RCH_2CH_2NH_2 \cdot \text{CuX}_2 + (\text{CuX} \cdot \text{NO})_2 \xrightarrow{\text{CH}_3\text{CN} \atop 29^\circ C} RCH_2\text{CH}_2\text{X} + RCH_2\text{CN} + RCH_2\text{CH}_2\text{OH} \tag{115}
\]

nitrosyls (equations 114 and 115). The products are geminal dihalides which like imines are in essence masked aldehydes due to the ease with which they are hydrolysed to the carbonyl functionality. Yields are 38–67% with the alkyl nitrite procedure and 14–58% with the copper halide nitrosyls. The leaving group is gaseous nitrogen in both procedures\textsuperscript{126,127}. Yields of nitrile in equation (115) are low (3–7%), and thus, this procedure is not recommended for that purpose. The alkyl halide and alcohol products probably arise via the well-known diazonium ion intermediates. Doyle, Siegfried and Hammond\textsuperscript{126} suggest that the geminal dihalide is produced by reaction of a diazoalkane intermediate and copper (II) chloride, by analogy to the previously reported\textsuperscript{349} reaction of ethyl diazoacetate with copper (II) chloride to produce ethyl dichloroacetate.

M. Oxidative Degradations of Tertiary Amines

A few representative examples of tertiary amine oxidative degradations are briefly covered here.

When tertiary amines are treated with nitrous acid, a complex degradation reaction ensues with the production of a carbonyl compound as one of the main products (equation 116). This reaction has been reviewed elsewhere\textsuperscript{146,172,360,361,394}.

\[
R_2\text{NCHR}_1^1 \xrightarrow{\text{HONO}} R_2\text{C}=\text{O} + R_2\text{NO} + H_2O + H_2O \tag{116}
\]

A variety of other oxidizing agents cleave tertiary amines to secondary amines and an aldehyde or ketone. Electrophilic reagents such as NBS or chlorine dioxide are especially useful in these degradations\textsuperscript{197,346a,361}. These and similar oxidations have been reviewed\textsuperscript{78,108,394}. Examples of oxidations of cyclic tertiary amines to iminium salts utilizing mercuric acetate have found application in the study of alkaloids\textsuperscript{47,259}. Oxidation of certain secondary and tertiary amines to amides have been reported\textsuperscript{431,432}.

Substituted diaminomethanes may be degraded via iminium salts utilizing chlorine or acyl halides (equation 117)\textsuperscript{48,49}. This reaction is related to the von Braun amide reaction (Section II.N).

\[
(R_2\text{N})_2\text{CH}_2 + R^1\text{COCl} \rightarrow R_2^+\text{N}=\text{CH}_2 + R_2\text{NCOR}^1 \tag{117}
\]

A complex novel method involves treating a tertiary amine with 2-nitropropane and $\text{H}_2\text{O}_2$–CuCl\textsuperscript{145}.

A procedure has been reported for obtaining aldehydes or ketones from $\alpha$-dialkyaminonitriles (42) (equation 118)\textsuperscript{66}. Yields range from 65 to 94%.

![Equation 118](image-url)
A very promising oxidative degradation of tertiary amines, developed by Cohen and coworkers involves the photooxidation of these amines by such oxidants as benzophenone or fluorenone (equation 119) \(^{82-84}\). This interesting reaction which

\[
(\text{CH}_3)_2\text{NCH(CH}_3)\text{CH}_2\text{CH}_3 \xrightarrow{\text{benzophenone} \text{hv}} \text{H}_2\text{CO} + \text{CH}_3\text{NHCH(CH}_3)\text{CH}_2\text{CH}_3 \quad (119)
\]

has already been discussed in relation to the oxidation of primary and secondary amines, has been reviewed\(^{84}\). Cleavage usually occurs at the least substituted carbon. The reaction works well for both tertiary alkylamines and tertiary arylalkylamines. This reaction has been recommended for stepwise degradations of both tertiary and secondary amines\(^{83}\).

Many tertiary amine oxidations proceed via aminium radical intermediates. These oxidations have been reviewed\(^{78}\).

Nonoxidative degradations of tertiary amines such as the Hofmann elimination, the Cope elimination, and a few other reactions have been discussed in Sections II.F, II.J.1, II.J.2 and III.D. Another non-oxidative degradation is the von Braun cyanogen bromide reaction which has been reviewed elsewhere\(^{165,394}\).

**V. BIOCHEMICAL, BIOORGANIC, TOXICOLOGICAL, ENVIRONMENTAL AND RELATED CONSIDERATIONS**

Deamination chemistry is of special importance in a variety of areas associated with the life sciences. For example, hardly a day goes by when even the layman does not hear some reference to nitrosamines and/or nitrosoamides as carcinogenic and mutagenic agents. Similarly some of the most interesting areas of biochemistry are concerned with the deaminations of amino acids and other biological amines.

Scientists in the life sciences often get mechanistic clues to biochemical reactions from organic chemical mechanisms. On the other hand, whole categories of reactions, as well as synthetic pathways, may be suggested to organic chemists by individual biochemical reactions as well as by complete biosynthetic or catabolic pathways.

Deaminations and related processes comprise vast areas of study in the voluminous life science field, and, thus, only selected examples of such deaminations will be outlined here.

**A. Biochemical Deaminations**

1. Oxidative deaminations

   By far the most important and common biochemical deaminations are oxidative deaminations. There are two major categories of biochemical oxidative deaminations and both of these categories have several subcategories. The first category consists of the transaminations which utilize pyridoxal phosphate as a cofactor. The second category consists of a variety of oxidases (or dehydrogenases). These oxidases require such cofactors as NAD\(^+\), NADP\(^+\), FMN or FAD. It is also worth noting that there are different enzyme systems operating for the L-amino acids and the far less common D-amino acids. Discussions of these deaminations have appeared\(^{26,57,255,383,284}\).

   The most common deamination mechanism in cells is the transamination wherein \(\alpha\)-ketoglutarate (or another keto acid) is the ultimate recipient of \(\text{NH}_3\) via pyridoxal phosphate (PLP) (equation 120)\(^{225}\). The mechanisms of these reactions involving
Deaminations (carbon–nitrogen bond cleavages)

\[
\text{HOOCCH(NH}_2\text{)CH}_2\text{COOH} \xrightarrow{\text{PLP}} \text{HOOCCH}_2\text{COOH} + \\
\text{HOOCCH}_2\text{CH}_2\text{COOH} \xleftarrow{\text{transaminase}} \text{HOOCCH(NH}_2\text{)CH}_2\text{CH}_2\text{COOH}
\]  

Schiff bases derived from pyridoxal phosphate have been discussed. Over 50 pyridoxal-requiring transaminase enzymes have already been reported. Although the transamination mechanism is most important for amino acids, other amines may oxidatively deaminate by this mechanism. Prosthetic groups in place of or in addition to pyridoxal may be at least partly involved in some transaminases.

Dehydrogenation (via dehydrogenases or amine oxidases) of amines to ketones or aldehydes are also very common in biochemistry (equation 121). Four coenzymes (NAD+, NADP+, FMN, FAD) have been observed to be cofactors for various dehydrogenases.

\[
\text{R} - \text{CH(NH}_2\text{)R}^1 \xrightarrow{\text{oxidase and one of: NAD}^+, \text{NADP}^+, \text{FMN}, \text{FAD}} \text{RCR}^1
\]

Amines which have a leaving group \(\beta\) to the amino group may be converted to the carbonyl group by elimination to form the enamine, followed by tautomerization and hydrolysis (equation 122). These deaminations also require pyridoxal. However, these conversions are not true oxidative deaminations, since the carbon \(\beta\) to the amine is reduced while the carbon bearing the amino group is oxidized. Y groups which have been observed as leaving groups include water (from serine and threonine), \(\text{H}_2\text{S}\) (from cysteine), propanethial S-oxide, the onion lachrymatory factor [from \(\text{trans-}\rightarrow\text{(1-propenyl)-L-cysteine sulfoxide}\)], and indole (from tryptophan).

2. Deaminations involving no change in oxidation state of the carbon bearing the amine

Although these deaminations are not nearly as common as oxidative deaminations in biochemistry, a number of important examples of nonoxidative deaminations are known. Most commonly in these cases ammonia is eliminated to form the \(\alpha,\beta\)-unsaturated acids (equation 123). Amino acids which may deaminate by this route include phenylalanine (to \(\text{trans}\)-cinnamic acid), tyrosine (to \(p\)-coumarate), histidine (to \(\text{urocanic acid}\)), aspartic acid (to \(\text{fumarate}\)) and
β-hydroxyaspartate (to oxaloacetate)\textsuperscript{236,267,282,283}. These deaminations are most commonly observed in plants and certain 'lower' organisms. Mechanisms have been proposed\textsuperscript{121,166}.

3. A reductive deamination

Reductive biological deaminations are very rare. However, one remarkable example in \textit{Clostridium sticklandii} involves the reduction of glycine to acetate with the aid of a dithiol, ATP and a selenoprotein (equation 124)\textsuperscript{367}.

\[
\text{H}_2\text{NCH}_2\text{COOH} + \text{R(SH)}_2 \xrightarrow{selenoprotein \ ATP} \text{CH}_3\text{COOH} + \text{NH}_3 + \text{R} \quad \quad (124)
\]

B. Bioorganic Chemistry

1. Comparisons of biochemical and organochemical deaminations

Sections IV.F and IV.A, B, and C provide a number of analogous organochemical cases to the important biochemical oxidative deaminations and oxidative transaminations. Some of the transamination studies described in Section IV.F were probably prompted by, or inspired by, the biochemical models. In turn the biochemical mechanisms which have been proposed were, no doubt, suggested by what was known about imine chemistry at the time. One of the most obvious symbiotic relationships between organo- and bio-chemistry can be found in the work with pyridoxal, as evidenced by the studies of Metzler, Ikawa and Snell\textsuperscript{285}. Also, many of the newer transamination schemes described in Section IV.F, such as the Corey–Achiwa transaminations\textsuperscript{93}, and the recent use of 9-fluorenone-1-carboxylic acid as a transaminating agent\textsuperscript{323}, were probably influenced by the biochemical models. Yet it still appears as if there remains much virgin territory to explore in this area. Other related possibilities were mentioned in Section I.

Analogies to the biochemical deaminations of α-substituted amino acids are worth considering for enamine preparations as well as for the conversions of amines to carbonyls.

The intriguing reduction described in Section V.A.3 is wide open to speculation. Does the ATP form a phosphoramide, or even a phosphorimide, so as to make the nitrogen a better leaving group in analogy to the sulphonimides described in Topic II.A? For that matter, sulphonimides may yet be found in some of the lower forms such as Clostridia. Far more surprising functionalities (i.e. nitrosoureas and diazoalkanes) have been isolated in certain species. Similarly, one might look for analogies to Katritzky's pyridine-type leaving groups (Section II.G).

2. Enzyme inhibition and active-site mapping

A recent method for irreversibly inhibiting enzyme active sites makes use of a deamination reaction. In particular, White and his research group have achieved ~99% inhibition of chymotrypsin by treating it with certain \textit{N}-nitrosoamides (16). The idea is the following: the nitrosoamide itself does not alkylate the nucleophilic functionalities at the active site. Rather, the chymotrypsin hydrolyses the nitrosoamide to a diazotate anion (18) (see Section II.K.1.e). The diazotate anion then rapidly decomposes to a 'hot' carbonium ion which alkylates the nucleophiles.
22. Deaminations (carbon–nitrogen bond cleavages)

(especially oxygen) at the active site (equation 125)\[^{405,406,414,415}\]. Analogous inhibitors have been called 'suicide-type' inhibitors\[^{25}\].

\[
\begin{align*}
\text{H} & \quad \text{NO} \\
\text{PhCH}_2\text{C} & \quad \text{C} \quad \text{N} \quad \text{R} \\
\text{NHCOCHMe}_2 & \\
\text{(16)} & \\
+ & \\
\text{Chymotrypsin} & \\
\downarrow & \\
\text{N}-\text{Isobutyrylphenylalanylchymotrypsin} & + \quad \text{PhCH}_2\text{N}^- \\
\text{H}_2\text{O} & \\
\text{Chymotrypsin} & \\
\downarrow & \\
\text{PhCH}_2\text{N}_2^+ & \\
\downarrow & \\
\text{PhCH}_2^+ & \\
\text{Alkylates chymotrypsin}
\end{align*}
\]

(125)

In addition to inhibiting the enzyme's active site, these alkylating agents provide a valuable tool for the mapping of active sites. The preferential points of attack are apparently the oxygens of imidate anions derived from the peptide bonds. The alkylated imidates can then be hydrolysed at pH 5 into two easily analysable fragments. White suggests that a variety of enzymes such as other proteolytic enzymes and oxidases should be amenable to this type of active-site mapping\[^{405,406}\].

Finally it should be pointed out that with some nitrosoamides the D isomer is a more potent inhibitor than the L isomer, while with other nitrosoamides, the L isomer is more effective. Apparently the alignment of the N-nitroso portion of the inhibitor in the hydrophobic enzyme clefts of the active site is crucial for determining the degree of inhibition\[^{405}\].

3. The synthesis and application of chiral methyl carriers in biosynthetic studies

A process has been developed for synthesizing methionine with a chiral methyl group carrier. The key step in the synthetic sequence is a deamination which involves the transfer of the chiral methyl group to the anion of homocysteine thiol. The deamination is accomplished by treating the homocysteine thiolate anion with the \(N,N\)-ditoluenesulphonimide derivative of chiral methylamine (equation 126)\[^{12,278}\]. This methionine (43) with its chiral methyl carrier can then be employed to investigate the mechanism of methyl transferase biosynthetic processes. Thus, Mascaro and coworkers\[^{278}\] have used a chiral methyl carrier to determine the steric
course of the enzymatic C-methylation of indole pyruvate during the biosynthesis of
the antibiotic indolymcin.

Townsend and Thei\textsuperscript{388} have also discussed this technique, and have further
demonstrated the feasibility of transferring chiral methyl groups via disulphonimide
derivatives, by using a variety of organic chemical models (see also Section II.A.5).

4. \textit{Deaminations of amino sugars}

The deamination of amino sugars is a well-explored area which has been
reviewed\textsuperscript{418}. A discussion of the specific use of the Corey–Achiwa method for
deaminating aminodeoxy sugars has also appeared\textsuperscript{257}.

5. 'Pseudophysiological' deaminations via pyridinium salts

Katritzky and coworkers\textsuperscript{220,433} have predicted from preliminary data that highly
selective deaminations may be observed under conditions mild enough to be termed
'pseudophysiological' on such polyfunctional natural products as nucleic acids and
polyamino compounds. Katritzky also draws analogies between his \textit{in vitro}
deamination technique and enzyme-active sites (see also Section II.G).

C. \textbf{Environmental Considerations}

Environmental studies indicate that all life forms are actual or potential victims
of a variety of mostly man-made mutagens, carcinogens, teratogens and other
toxins. Among the most notoriously dangerous of these poisons are a variety of
\textit{N}-nitroso and related compounds, some of which have been shown to be the most
powerful mutagens yet discovered. However, while the dangers of \textit{N}-nitroso
compounds should never be minimized, they are quite possibly less environmentally
dangerous than ecological poisons such as radioactive chemicals, many heavy metal
compounds and most halogenated aromatics, due to the fact that most of them
have relatively short half-lives in the environment. Furthermore, \textit{N}-nitroso
compounds do not tend to be stored in fatty or other tissues to the extent of many
other environmental toxins and their very danger is at least partly related to their
tendency to be rapidly metabolized to compounds with very short half-lives. Many
other amines and amine derivatives such as triazenes, 2-naphthalenamine and
benzidine have similarly high mutagenicity and/or carcinogenicity.

1. \textit{Nitrosamines, nitrosoamides and related compounds}

\textit{N,N}-Diethyl-\textit{N}-nitrosoamines, \textit{N}-nitrosoamides and related compounds are
astonishingly potent mutagens and/or carcinogens as shown by a large volume of
data based on Ames and other types of tests. In fact, ethyl nitrosourea has been reported to be the only chemical more potent than radiation for causing mammalian mutations. Since that report certain N-nitrosoamides have been shown to be over ten times more mutagenic than the corresponding N-nitrosoureas via Ames tests! N-Nitrosoamides are ineffective as antitumour agents, while the nitrosoureas are effective in this respect. Side-effects of a usually very unpleasant nature are a major characteristic of these and most other antitumour agents. A number of reports pertaining to the mutagenicity etc. of N-nitroso compounds have appeared including many reviews. Extreme caution is always recommended in handling these compounds. For example, no visible effects may be evident on initial exposure. But on repeated contact, even of minute amounts, effects such as nasty skin rashes may occur, as actually did happen when this author was repeatedly exposed to N-nitrosocarbamate derivatives of amino acid esters. The long latency period for cancer development is, of course, well known (see also Sections II.K.1.c and II.K.1.f).

The ACS Symposium on 'N-nitrosamines' and related compounds reviews a wide range of topics relevant to this whole section.2

2. Other amine derivatives as mutagens, carcinogens and teratogens

A number of linear and cyclic triazenes (see Section II.K.1.d) have been shown to be powerful mutagens, carcinogens and teratogens by Ames-type and other studies. Evidence has been presented for the formation of triazenes from the treatment of diamines, polyamines and amine derivatives with nitrous acid \textit{in vivo} and \textit{in vitro}. A variety of monofunctional and bifunctional disulphonimides have been tested for antitumour activity. None of these disulphonimides were particularly active against tumours in the tests performed.

A number of amines (especially certain aromatic amines), have long been known to be carcinogenic. The mechanisms of their carcinogenic action may very well not involve deaminations for many of these compounds.

3. Teratogens

Lists of teratogens, including many amines and amine derivatives, have been published.

4. Mechanisms of action

It appears as if most of the amine-derived mutagens and carcinogens discussed here do their damage by acting as direct or indirect alkylating agents. Alkylating agents which have two or more good leaving groups on the same molecule are especially potent mutagens or carcinogens.

The \textit{N},\textit{N}-dialkynitrosamines are good examples of indirect mutagens. These do not normally undergo deamination \textit{in vitro} (see Section II.K.1.f). However, indirect evidence has been obtained to show that they are enzymatically oxidized \textit{in vivo} to C-hydroxy compounds. It is these metabolites which then, most likely, rapidly decompose to carbonium ions which alkylate nucleophilic portions of enzymes and/or nucleic acids.

Tertiary amines may also be mutagenic agents in the presence of nitrosating agents, since they react with nitrous acid to give \textit{N},\textit{N}-dialkynitrosamines (see Sections II.M.2 and IV.M).
Triazenes are probably direct-acting mutagens and carcinogens, as only acid is required to convert them into labile nitrogen-emitting alkylating agents\textsuperscript{386} (see Section II.K.1.d).

There are at least two mechanisms by which nitrosoamides may act as mutagens. One possibility involves enzymatic or nonenzymatic hydrolysis to give the unstable diazotate anions, which then act as potent alkylating agents [see Section V.B.2 (equation 125) and Section II.K.1.c]. Some nitrosoamides are far more mutagenic or carcinogenic than others. For example, the relatively stable $N$-nitroso-$N$-methyl-$p$-toluene sulphonamide is far less carcinogenic than the relatively unstable $N$-nitroso-$N$-methylurethane. In the latter case it is believed that diazomethane is produced on hydrolysis, which then acts as the alkylating agent. Hence, the $N$-nitrosotoluene sulphonamide is now recommended as the reagent to use for generating diazomethane in the laboratory\textsuperscript{131}.

$N$-Nitroamides probably behave in an analogous manner expelling dinitrogen oxide instead of nitrogen.

5. Environmental sources of $N$-nitroso compounds and similar carcinogens, and nutritional factors

$N$-Nitrosamines, $N$-nitrosoamides and related compounds are carcinogenic and mutagenic at very low levels. They have been detected in widely diverse sources, such as cured meats, cured fish, cosmetics, drugs, herbicides, industrial areas, many vegetables (especially when not fresh), drinking water, beer, polluted air, cigarette smoke, soil and many more. Their prevalence is not surprising when one considers that amines, nitrates, nitrites and nitrogen oxides are common compounds in the environment. In addition, nitrites are added intentionally to food, water and soil (chiefly in the form of fertilizers). Nitrites, in small amounts, are used as preservatives and meat-colouring agents. Amines are not only naturally occurring, but may also be introduced into the environment from industrial sources, or as food additives, drugs, etc. Nitrites are not ordinarily dangerous, and they do not figure in any nitrosation mechanisms. However, under certain conditions (e.g. via certain intestinal and salivary bacteria) nitrates may be converted to nitrites, and under appropriately acidic conditions, nitrites become nitrosating agents. Nitrosamines possibly form in the stomach if foods containing amines are consumed along with any source of nitrite ion. One such possible source of nitrite is the reduction of nitrates to nitrites by salivary bacteria. Perhaps nitrosation of amines in the stomach is not an important source of most nitrosamines, since the low $p$H($\sim 1-3$) of gastric juice is below the optimum $p$H for nitrosations of aliphatic amines. Nitrosoamides and aryl diazonium ions may, however, form under such acidic conditions. Stale foods (and most meats, and to a lesser extent other foods, are consumed in varying degrees of putrefaction) contain higher proportions of amines, nitrites and nitrosamines. While nitrosamines and related compounds have probably always been present in the environment, the amounts consumed in industrial societies are most likely much higher.
than in most primitive societies. Nitroso compounds in the environment have been reviewed 9,137,242,263,420,438.

An example of a naturally occurring $N1$-nitrosourea derivative of an amino sugar is the antitumour agent, Streptozotocin (45) (from Streptomyces achromagenes) 183.

![Chemical structure of Streptozotocin](image)

Two equally surprising and better known naturally occurring alkylating agents are L-azaserine (46) and 6-diazo-5-oxo-L-norleucine (47) 284.

\[
N_2CHCOOCH_2CH(NH_3^+)COO^- \\
(46)
\]

\[
N_2CHCOCH_2CH_2CH(NH_3^+)COO^- \\
(47)
\]

Other aspects related to the potency of nitroso compounds as mutagens and carcinogens are nutritional factors. Certain vitamins (especially C and E) protect against nitrosamines and certain other mutagens 137. There is much evidence to support this statement 23,61. Apparently ascorbic acid inhibits the formation of nitrosamines. Certain theories consider the presence or absence of other vitamins, minerals and naturally occurring anticancer agents in whole foods (especially certain vegetables, fruits and soy beans). Still other theories emphasize the importance of low-fat, high-fibre diets. It is very likely that all these factors are important in determining whether a malignancy will arise. For example, the dietary deficiency of even one vitamin or mineral could upset the body's immunological capacity.

An area of nutritional chemistry which is directly related to oxidative deaminations (as well as many other metabolic processes) is the vitamin $B_6$ (pyridoxine) requirement. This vitamin is sometimes called the 'master vitamin' since it is involved with at least sixty enzymes 23,350. It may be that most modern diets are deficient in this key vitamin.

Finally, there is a question as to what is the best technique for identifying the vast number of potential mutagens and carcinogens in our environment, which, of course, include numerous functional groups in addition to $N$-nitroso and related functionalities. In particular, over 50,000 synthetic chemicals are currently produced and in use, with close to 1,000 new chemicals being introduced every year. Most of these compounds are untested. Thorough animal tests require over $250,000 per chemical and three years to perform. Thus the current method of
choice for screening mutagens appears to be the Ames test on salmonella and related short-term tests. These tests can be performed at a tiny fraction of the cost of animal tests and in a small fraction of the time period. The correlation between mutagenicity and carcinogenicity is high\textsuperscript{5,6}. Another highly promising, inexpensive, rapid and potentially reliable alternative to the use of animal models, is the chick embryonic skin (CES) organ culture assay for cellular neoplasia\textsuperscript{430}. Finally, Meyers and Meyers\textsuperscript{286} point out that the prediction level for teratogens based on animal studies is often very poor.

6. Other environmental considerations

Modern organic chemists are concerned with more than ‘yields’ and ‘costs’. In the old days, only the most obviously toxic or explosive chemicals were treated with any degree of respect, and then only with regard to those researchers immediately exposed. Today industrial and laboratory chemists must consider health and safety factors as well as the effects of their products and by-products on the environment. In addition, the cost factors have changed. Until recently, only the visible costs of reagents and equipment were considered. Now with rapidly escalating energy costs the cost of the energy required to run a process or perform a reaction is also considered, as are hopefully the hidden costs to the health and safety of the community. Also, it is no longer acceptable to promiscuously dump or bury wastes. Of course the rising costs of energy are partly reflected in the rising costs of organic chemicals, but some chemicals will rise at faster rates than others. due not only to their source, but also to the energy expense in their preparation, as well as the cost of essential safety and health precautions which must be taken into account. As a result many old favourite type reactions may eventually be priced out of practicality. For a while it looked as if reactions requiring silver such as the Hofmann elimination might fall in this category. Now it is not so certain that this will be the case, since silver is falling in price as of this writing. On the other hand, reactions which take place without the need for heating or cooling will take on new economic importance. Others which make use of potentially free or cheap forms of energy such as photochemical reactions, might soon assume greater importance than they have in the past. On the basis of this discussion, certain reactions discussed in this chapter receive relatively poor grades due to negative environmental considerations. Thus, all reactions which involve \textit{N}-nitroso compounds, nitrous acid, triazenes, etc. fall in this category. When these reactions are conducted it is very important to protect not only those immediately in contact with these toxins, but also to render these toxic materials harmless before disposing of them, especially when done on a large industrial scale. From energy utilization considerations, however, these reactions are relatively economical. On the other hand, many of the oxidative deaminations discussed environmentally rate relatively high. This is especially true for those types which consist of biological transaminations, or the photooxidations of amines. If the 2,4,6-triphenylpyridinium ions and the corresponding leaving groups are relatively nontoxic, the Katritzky reactions also rate high. The diarylsulphonimide procedure probably rates somewhere in the middle of the scale, environmentally speaking.

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22. Deaminations (carbon–nitrogen bond cleavages)

CHAPTER 23

Chiroptical properties of amino, nitroso and nitro compounds

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I. INTRODUCTION

In the early part of the nineteenth century, John Baptiste Biot discovered that chiral substances rotate the plane of plane-polarized light and that the rotatory power changes with a change in the wavelength of the light used\(^1\). The rotatory power of a substance over a range of wavelengths is known as its optical rotatory dispersion (ORD)\(^1\). During Biot's life nearly all measurements of optical rotatory power, including those of his pupil, Louis Pasteur, were of the ORD type, utilizing light in the visible part of the spectrum. After Biot's death in 1862 and the invention in 1866 of the Bunsen burner, it became much easier to work with the nearly monochromatic light of the sodium flame (589 nm) and thus the more laborious study of ORD was for the most part abandoned\(^1\). Historically and even today, the chiroptical property most frequently reported for chiral substances is their rotatory power for sodium D light.

Useful compilations of this chiroptical property for natural products, including \(\alpha\)-amino acids\(^2\), alkaloids\(^3\) and amino sugars\(^4\), have appeared. More recently the absolute configuration of a host of chiral substances, including chiral amino, nitroso and nitro compounds, have been presented in two collections\(^5,6\). In the earlier of these\(^5\), the absolute configurations of approximately 6000 compounds, the method by which each configurational assignment was made, the sign of the rotatory power for a particular enantiomer, and appropriate literature references are given. In the second\(^6\), the absolute configurations, the sign of the rotatory power for given states (liquids or as solutions in various solvents) and literature references are tabulated for nearly 6000 compounds, each compound having only one chiral centre (asymmetric carbon atom).

Rotatory power (with sodium D light) comparison\(^7\) for the establishment of absolute configuration is not as reliable a tool as ORD and circular dichroism (CD) methods and is little used today, and then only within well-defined compound classes\(^8\). Brewster\(^9\) has developed a more involved method to relate the rotatory powers of chiral substances to their absolute configurations. The application of Brewster's rules does not necessitate the use of chiral structures of known configuration closely related to that being studied and is sometimes used when other methods for configurational assignment cannot be easily utilized.

Prior to 1950, ORD curves were measured with ease in the visible spectral region (380–780 nm) but only with great difficulty in the near ultraviolet region (200–380 nm)\(^1\). In 1953, a commercially manufactured spectropolarimeter capable of routine rotatory power measurements from 700 to about 280 nm became available\(^10\). With improvements, measurements are easily made to 185 nm\(^11\). Circular dichroism (CD) was not commonly measured before 1960 except in a few laboratories\(^11\). The description of the first recording circular dichrograph\(^12\) led to a rapid development in this field and the commercial availability of instruments.
capable of routine CD measurements in the visible and near ultraviolet spectral regions, 185–600 nm$^{11,13}$.

The focus of this chapter then is a brief outline of the sources of chiral amino, nitroso and nitro compounds, application of Brewster's rules used for the assignment of the absolute configurations to a few chiral amines, and a discussion of the ORD and CD in the visible and near ultraviolet of amino compounds and some of their derivatives and of nitroso and nitro compounds. Other chiroptical measurements such as magnetic circular dichroism$^{14}$ (MCD), far-ultraviolet circular dichroism$^{15}$ (FUCD), infrared (vibrational) circular dichroism$^{16}$ (VCD), VCD observations using a Fourier transform infrared (FT IR) spectrometer$^{17}$ and Raman circular intensity differential (CID) scattering$^{18}$ are just beginning to have an impact on stereochemical problems. These methods, however, have not been widely used with chiral amino, nitroso and nitro compounds and will not be discussed here.

II. CHIRAL AMINO COMPOUNDS

A. Sources of Chiral Amino Compounds

Many chiral amino compounds occur as natural products, including α-amino acids$^2$, alkaloids$^3$ and amino sugars$^4$. Other pure chiral amines are prepared by the introduction of an amino group into a symmetrical (achiral) or chiral substrate by an appropriate reaction$^5$, e.g. the reductive amination of a ketone such as menthone (1) with formamide–formic acid (Leuckart reaction$^20$). Diastereomers (2 and 3) are separated by physical methods, and enantiomers are usually resolved by fractional crystallization of diastereomeric salts formed with chiral acids. There are a recent review$^21$ and collections$^{22,23}$ of the application of this and other techniques for the resolution of amines.

B. Application of Brewster's Rules

Brewster$^9$ concluded that two contributions, atomic and conformational asymmetry, in general make up the rotatory power (with sodium D light) of a chiral substance. The atomic asymmetry contribution for absolute configuration 4 is dextrorotatory when the polarizability of the substituent attachment atoms decreases in the order $A > B > C > D$. Brewster also tabulated the rotational
ranking of a number of common substituents, including deuterium, the rankings being established for the most part empirically. The conformational asymmetry contribution is given by conformational units, unit 5 being dextrorotatory. The contribution for each unit is summed algebraically over an entire conformer such that the molecular rotatory contribution for conformer 6 is given by a simple equation involving the polarizabilities of A, A' and H (hydrogen). Conformer 6 is dextrorotatory when the polarizabilities of A and A' are greater than that of H. A flexible chain compound generally has a relatively small rotatory power because its molecules can assume many conformations with different and opposed rotatory contributions. In order to estimate the rotatory power of the compound, the contribution of each conformer must be added algebraically. For this summation simple conformational rules are used.

With the attachment atom polarizability sequence decreasing in the order phenyl > methyl (alkyl) > amino > hydrogen, (R)-α-phenylethylamine [(R)-7] and (R)-α-phenylneopentylamine [(R)-8], having only atomic asymmetry, are correctly predicted to be dextrorotatory. On the other hand (R)-2-aminobutane [(R)-9] has no atomic asymmetry since it has two alkyl groups attached at the chiral centre. The two alkyl groups, however, provide a sterically asymmetric environment for the development of conformational asymmetry. Considering only the two allowed conformers 10 and 11, the molecular rotation of (R)-9 is calculated as +3°.

Experimentally the molecular rotation of (R)-9 is −5° and thus the conformational asymmetry rule fails to predict even the correct sign for the rotatory power of this amine and for similar methylalkylcarbinamines.

Using the polarizability sequence alkyl > amino > hydrogen > deuterium, the atomic asymmetry rule has been used to assign the R absolute configuration to (+)-1-aminoethane-1-d [(R)-12] and (+)-1-amino-2,2-dimethylpropane-1-d [(R)-14] and [(R)-15].
When the laevorotation of (R)-benzylamine-$\alpha$-d$^{27,28}$ [(R)-14] is considered, an alternate polarizability sequence, amino > phenyl > hydrogen > deuterium, is required$^{24}$, the amino group being assigned a rotational rank higher than that of the carbon sequence when it is $\alpha$ to a phenyl group. This suggests the occurrence of a rotationally significant interaction of the amino group with the phenyl group. This amendment of the empirical atomic asymmetry rule necessitates no change in the treatment of (R)-7 and (R)-8 above. For (R)-aminobutane-1-$d^{29}$ [(R)-15], the atomic asymmetry predicts a positive rotatory contribution, and the observed small laevorotation of (S)-15 indicates only a small conformational asymmetry contribution$^{24}$.

C. Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD)

1. Amino chromophore

Although it was recognized very early on the basis of ORD measurements$^{30,31}$ that, for some chiral amines, Cotton effects are associated with the electronic transition below 250 nm of the lone pair of electrons on the nitrogen atom, only on observation of the CD spectra of chiral tertiary amines such as 16 and 17 were Cotton effects observed$^{32}$. The spectra are characterized by two oppositely signed dichroic absorption bands in the region 190–240 nm corresponding to absorption maxima of trimethylamine in the gas phase at 227 and 199 nm$^{33}$. The amines were classified into two categories depending on the intensities of their respective Cotton effects. Those of category a, typified by 16 with positive and negative CD maxima at 196 and 225 nm respectively, have a preponderance of one conformation as compared to that arising from inversion of the nitrogen lone pair of electrons. The Cotton effects observed with the amines of category b, represented by 17, are much weaker in intensity since there is less of an energy difference between the conformational diastereomers arising from the conformational mobility of the nitrogen lone pair of electrons. The disappearance of the CD bands on protonation of the amino group supports the conclusion that the dichroic absorption is associated with electronic transitions of the lone-pair electrons on the nitrogen atom.

Subsequent ORD$^{34,35}$ and CD$^{35,36}$ measurements with cyclic secondary and tertiary amines and acyclic secondary amines, such as (R)-N,3,3-trimethyl-2-aminobutane$^{36}$ [(R)-18], confirm that the observed Cotton effects for chiral amines are associated with the amino chromophore. On the basis of a comprehensive study of chiral 2-alkyl-substituted piperidines$^{37}$, such as (S)-$\alpha$-pipercoline [(S)-19], and their $N$-methyl derivatives, the sign of the strong Cotton effect near 200 nm, assigned to an $n \rightarrow \sigma^*$ transition of the amino group$^{37}$,
is empirically correlated with the absolute configuration at C-2. For an N-methyl-2-alkylpiperidine, the N-methyl group has an equatorial conformation (21), and the Cotton effect near 200 nm for the configuration shown in 21 [(S)-20, R = CH₃] is positive. For the cyclic secondary amines in which the 2-alkyl group is larger than a methyl group, the lone pair of electrons on nitrogen is equatorial (22), and the Cotton effect is negative. Thus, a clockwise (positive) direction (21) from the lone-pair electrons to the C-2 alkyl group results in a positive Cotton effect; a counterclockwise (negative) direction (22) gives a negative Cotton effect.

2. Amino group influence on other chromophores

a. Carbonyl chromophore. In connection with the study of the stereochemistry of the alkaloid lycopodine 23 and of its 6α-bromo derivative 24, an unexpected interaction of an ammonium group β to a carbonyl group was detected in the ORD spectrum. Lycopodine (23) in methanol shows, as anticipated by application of the octant diagram 25, a positive Cotton effect associated with the carbonyl n → π* transition at about 300 nm. In fact the absolute configuration of 23 was first established on this basis. 6α-Bromolycopodine hydrobromide (24·HBr) in methanol also shows a positive Cotton effect at about 300 nm, but with an intensity less than that of 23 and thus substantially less than that expected by application of the α-haloketone rule. The bromine atom in octant diagram 26 lying in a far lower right octant and expected to make a strong, positive
contribution to the Cotton effect. Further, since lycopodine hydrobromide (23·HBr) has a negative Cotton effect at about 300 nm, it was concluded that a positively charged nitrogen, in this case in a far, upper left octant, makes a disignate (antioctant) contribution to the Cotton effect. In agreement with this conclusion, lycopodine methiodide and lycopodine perchlorate in methanol also show negative Cotton effects at about 300 nm, and a solution of lycopodine in acetic acid also exhibits a negative Cotton effect. As predicted by the α-haloketone rule, 6α-bromolycopodine (24) in methanol shows a stronger positive Cotton effect than does lycopodine (23) itself.

When the ORD curves of a number of α-amino-D-homoketo steroids and their salts (27a–d, 27g, 28a–d and 29a–f) were compared with the corresponding ketols (27h, 28h and 29h), good correlations were found except with salts 29b and 29d. The unusual ORD spectra for 29b and 29d were explained by the presence of the positively charged nitrogen atom which makes a disignate contribution to the Cotton effect. The reduced magnitude, as compared to that of 17-keto steroids, of the positive Cotton effect associated with the n → π* transition of 16β-amino-17-keto steroid hydrochlorides was also explained on the basis of an antioctant contribution of the ammonium group.

Application of the octant rule for the establishment of the absolute configuration of a series of oxoquinolizidines (30–32), each showing a strong CD maximum at about 300 nm, leads to the incorrect configurational assignment for (−)-30. The latter’s configuration was independently established as (R)-30 by synthesis, and its CD could only be explained on the basis of a strong antioctant contribution of the nitrogen atom. Similar results are encountered in the CD study of six-membered heterocyclic saturated ketones [33], all having the hetero group predominantly in the upper-left-rear sector of the octant projection but showing small negative Cotton effects centred at 305 nm in all solvents investigated.

Recently an empirical analysis of the UV and CD spectra of the available chiral α- and β-aminocyclohexanones has suggested how an amino group can interact with a carbonyl group depending on their relative orientation. This interaction is
reflected in both the UV and CD spectra. Octant (consignate\textsuperscript{42}) behaviour with respect to the \( n \rightarrow \pi^* \) carbonyl transition is to be expected of an \( \alpha \)-amino group when the lone pair of electrons on the nitrogen atom is \textit{trans} diaxial to the \( C_\alpha-CO \) bond (35) or of a \( \beta \)-amino group, as in lycopodine (23), when the lone pair is \textit{trans} diaxial to the \( C_\alpha-C_\beta \) bond. Antioctant (dissignate\textsuperscript{42}) behaviour of an \( \alpha \)- or \( \beta \)-amino group is observed when the lone pair on nitrogen is \textit{cis} to the \( C_\alpha-CO \) (36) or \( C_\alpha-C_\beta \) bond (37), respectively. For \( \beta \)-aminocyclohexanones, antioctant behaviour will also apply when the \( C_\beta-N \) bond is axial (i.e. \textit{cis}) to the \( C_\alpha-CO \) bond (38). When the lone pair on the nitrogen atom is removed by protonation, the change from octant to antioctant or increased antioctant behaviour is observed.

Verification of this analysis has appeared\textsuperscript{50}, and the CD spectra displayed by chiral acyclic \( \alpha-(N,N\text{-dialkylamino}) \) ketones\textsuperscript{51} and \( \beta \)-aminoketones\textsuperscript{52} and their salts can be interpreted using this analysis. This also appears to be true for chiral \( \alpha \)-trimethylammonio aldehydes as well\textsuperscript{53}.

\textit{b. Carboxyl chromophore.} Since the first observation of the complete Cotton effect at about 210 nm associated with the carboxyl chromophore of \( \alpha \)-amino acids\textsuperscript{54}, their ORD and CD have been extensively studied. Included in the CD
23. Chiroptical properties of amino, nitroso and nitro compounds

studies were surveys of the more common and less common \( \alpha \)-amino acids. These studies have shown that these acids with the \( L \) configuration (L-39), which is

\[
\text{CO}_2\text{H} \\
\text{H}_2\text{N} \xrightarrow{\text{C}} \text{H} \\
\text{R}
\]

(L-39)

usually, but not always, equivalent to the \( S \) configuration, give a positive Cotton effect at about 200 nm in water and at 208–210 nm with added acid, provided that there is no unusual conformational constraint and that no other interfering chromophore is present. When one of the latter, such as an \( \alpha \)- or \( \beta \)-aryl sulphone, disulphide, or seleno group, is present, additional CD bands are observed and the influence of these chromophores must be taken into account.

Recently, the rotatory strengths of L-alanine (L-39, \( \text{R} = \text{CH}_3 \)) (witterionic and nonwitterionic forms), L-alanine cation and L-alanine anion as a function of the angle between the \( \text{O}_2\text{C} \) and the \( \text{C}_2\text{N} \) planes have been calculated by a semiempirical quantum-mechanical method. These rotational strengths have been compared with the experimental CD spectra for L-alanine and compared with predictions based on a sector rule proposed for \( \alpha \)-amino acids.

c. Benzene chromophore. In chiral benzene-ring-containing compounds, the benzene chromophore gives rise to observable Cotton effects associated with the benzene \( \text{L}_b \) and \( \text{L}_a \) \( \pi \rightarrow \pi^* \) transitions at about 260 and 210 nm, respectively.

In the ORD spectra of (R)-\( \alpha \)-phenylalkylamines, (R)-7, (R)-8 and (R)-\( \alpha \)-phenyl-n-propylamine [(R)-40] (Figure 1), and (R)-\( \alpha \)-benzylethylamine [(R)-41] display multiple, negative Cotton effects associated with the totally symmetric vibrational progression of the \( \text{L}_b \) benzene transition. For (S)-1-aminoindane [(S)-42] these Cotton effects are also negative. In the ORD spectrum of these amines, the \( \text{L}_b \) Cotton effects are superimposed on strong background curves which are the long-wavelength wings of transitions below 240 nm. These short-wavelength contributions far override in intensity its rotatory
contribution at 240–270 nm and in general give the sign to the rotatory power at the sodium D line (589 nm). For \((R)\)-\(\alpha\)-phenylethylamine \([(R)-7]\) and \((R)\)-\(\alpha\)-phenyl-\(n\)-propylamine \([(R)-40]\), the plain dispersion curve from 225 to 240 nm is positive and the rotatory power using sodium D light is positive\(^{65}\). Below 240 nm the plain dispersion curve for \((R)\)-\(\alpha\)-phenyleopentylamine \([(R)-8]\) is negative, but the rotatory power at 589 nm is positive\(^{65}\), indicating oppositely signed contributions from the transitions below 240 nm.

There are slight changes in the magnitude of the rotational strength for the respective \(^1\)L_{\(b\)} Cotton effects of \(\alpha\)- and \(\beta\)-phenylalkylamines on protonation of the amino group, but the sign remains unchanged\(^{65-67}\). These Cotton effects are
assumed to arise by a combination of static (one-electron) as well as dynamic (coupled oscillator) mechanisms, the one-electron contribution being dominant. For the para-substituted derivatives of (S)-α-phenylethylamine [(S)-43] and their respective hydrochloride salts, the 1Lb transition moment becomes larger, and the negative-signed contribution of the coupled oscillator mechanism becomes dominant. Thus the 1Lb Cotton effects of (S)-43 and its salts are opposite in sign (negative) to those of (S)-α-phenylethylamine [(S)-7] and its salt.

The negative Cotton effect at about 215 nm in the CD spectrum of (S)-1-methylindane [(S)-44] is clearly due to the 1La benzene transition. The shorter wavelength and the larger moment of the 1La transition, as compared to those of the 1Lb transition, suggest the dominance of the coupled oscillator mechanism for generation of this Cotton effect, and as predicted by the coupled oscillator mechanism, this Cotton effect is negative. For (S)-1-aminooindane [(S)-42], the positive CD maximum in this same spectral region is due to the coupling of the benzene 1La transition with the n → σ* transition of the amino group at about 210 nm. Protonation of the amino group eliminates its n → σ* transition and (S)-1-aminooindane hydrochloride [(S)-42-HCl] displays a negative Cotton effect near 215 nm. The same is true for (S)-α-phenylethylamine [(S)-7] and its para-substituted derivatives [(S)-43]. For (S)-7 and (S)-43, the 215-nm Cotton effect is positive in cyclohexane but negative in 10% hydrochloric acid.

Sometimes the amino group also affects the sign of the plain ORD curve between 225 and 240 nm of α- and β-phenylalkylamines (Figure 1). The curve for the hydrochloride salt of (R)-α-phenylethylamine [(R)-7-HCl] and (R)-α-phenyleopentylamine [(R)-8-HCl] in methanol and isopropyl alcohol, although opposite in sign to each other, are of the same sign as the respective amines in methanol and isopropyl alcohol. The plain dispersion curve of the hydrochloride salt of (R)-α-phenyl-n-propylamine [(R)-40-HCl] is negative in both solvents, but the curve is opposite in sign to that of the free base (R)-40 in methanol and isopropyl alcohol. (S)-α-Benzylethylamine, hydrochloride [(S)-41-HCl], frequently referred to as d-amphetamine hydrochloride, in water and methanol shows a positive plain dispersion curve from about 225 to 240 nm, similar to that shown by (S)-41 in methanol and isopropyl alcohol. In isopropyl alcohol, however, the plain curve for (S)-41-HCl is negative. This solvent effect is also reflected in the rotatory power at the sodium D line of (S)-41-HCl, positive in water and methanol and negative in absolute ethanol and isopropyl alcohol.

3. Chromophoric derivatives

a. Isolated derivatives. Since the longest wavelength transition at about 225 nm associated with the amino group gives rise to only a feeble Cotton effect, unless some conformational restriction is present (Section II.C.1), and since this Cotton effect and that at about 200 nm may be masked by the dichroic absorption of other groups, much attention has focused on chromophoric derivatives of chiral amines for the establishment of their absolute configurations by ORD and CD measurements. Use is made of empirical correlations and the formulation of sector rules based on model compounds of known absolute configurations. To be effective the chromophoric derivative must show at least one Cotton effect, the sign of which can be related unambiguously to the stereochemical disposition of groups situated in the environment of the chromophore. Another requirement is optical and chemical stability during chiroptical measurements. In some circumstances, the ability to prepare the derivative suitable for ORD and CD measurements utilizing micromole quantities of the amine under investigation is of great importance.
The synthetic operations leading to some of these derivatives are such that the derivative must be isolated before use in chiroptical measurements. Important ones of this type are the N-phthaloyl derivatives of primary amines (45)\textsuperscript{70,71}, the dithiocarbamate derivatives of primary and secondary amines and of α-amino acids (46)\textsuperscript{70,72} and the N-nitroso derivatives of N-acyl-α-amino acid esters\textsuperscript{73} (47) and of secondary amines\textsuperscript{74} (48). The N-phthaloyl and N-dithiocarbamate derivatives are easily prepared, but only for the latter has a sector rule been formulated for the interpretation of the CD spectra\textsuperscript{72}. The preparation of N-nitroso compounds is somewhat cumbersome, and the derivatives are sometimes unstable\textsuperscript{73} (Section III.A.3). For examination of an N-nitroso derivative, the requirement that a primary amine be converted to a secondary or N-acylamine is a limitation in itself. The N-nitroso derivatives also occur as a mixture of syn and anti forms\textsuperscript{75} and there has been some question concerning the usefulness of the sector rule developed for the interpretation of the CD spectra (Section III.B.3).

Other chromophoric derivatives, used after isolation, have been reviewed\textsuperscript{76}. Significant among these for chiral amines are the dimitedonyl derivatives of primary amines and of α-amino acid esters\textsuperscript{77} (49), the N-chloro derivatives of secondary amines\textsuperscript{78} (50) and the Schiff base, N-benzylidene (51) and N-salicylidene (52),

\begin{align*}
\text{R'-CH-R} & \quad \text{R2} = \text{alkyl or carboxyl} \\
\text{R3-N-\text{CS2}R} & \quad \text{R3 = H or alkyl}
\end{align*}

derivatives of primary amines\textsuperscript{79,80}. Reaction of an amine or α-amino acid ester with dimitedone (53) to form 49 requires heat but the condensation appears to be almost

\begin{align*}
\text{H3C} & \quad \text{CH3} \\
\text{N-\text{CH-R}} & \quad \text{R1} = \text{alkyl, aryl or alkoxy carbonyl}
\end{align*}
The requirement of a free base or an \( \alpha \)-amino acid ester, an amine salt or zwitterion being unreactive, is inconvenient when dealing with milligram quantities of amine. Further, since the sign of the Cotton effect in the CD spectra depends on both the configuration and the conformational distribution of the derivative, the substantial conformational mobility of the system may not lend itself to an unambiguous interpretation of the spectrum\(^{77} \). The \( N \)-chloroamines (50) are easily prepared, but they are frequently oils and have not been widely utilized\(^{78} \). The \( N \)-salicylidene derivatives, prepared from salicylaldehyde (54) and the free base, are perhaps the most widely used chromophoric derivatives of chiral primary amines. The derivatives can also be formed by the reaction of the sodium salt of salicylaldehyde (55) with an amine salt or an \( \alpha \)-amino acid\(^{80} \). The absolute configuration of the chiral centre to which the nitrogen atom is attached can be deduced when the ORD or CD spectrum of the derivative is interpreted using the salicylidenimino chirality rule\(^{79} \) (Section II.C.4).

Other chromophoric derivatives of interest are the \( N \)-(2-pyridyl-\( N \)-oxide) derivatives of \( \alpha \)-amino acids\(^{81} \) and chiral primary and secondary amines (56)\(^{82} \), including heterocyclic amines\(^{78,83} \), and the \( N \)-2,4-dinitrophenyl derivatives of \( \alpha \)-amino acids\(^{84,85} \) and chiral primary amines (57)\(^{86} \). 2-Fluoropyridine \( N \)-oxide (58) reacts slowly at room temperature with an \( \alpha \)-amino acid or a primary or secondary amine to form 56\(^{83} \). The sign of the CD maximum near 330 nm for the derivative, however, can be correlated with the configuration of an amine only if the nitrogen atom in the amine moiety is attached to a chiral centre\(^{83} \). 2,4-Dinitrofluorobenzene (59) reacts somewhat more rapidly than 58 with \( \alpha \)-amino acids and primary amines, and the \( N \)-2,4-dinitrophenyl derivatives (57) may have substantial use in connection with the determination of the absolute configurations of abnormal \( \alpha \)-amino acids.
found as components of peptide antibiotics. The derivatives are found directly from the protein hydrolysate mixture of α-amino acids and separated by chromatography.

In connection with establishment of the absolute configuration of chiral diamines, the CD of certain classes of metal complexes have been useful, and the configuration of (S)-trans-1,2-cyclohexanediamine [(S)-60] was established on this basis.

![Structure of (S)-60]

**b. Derivatives formed in situ.** As a matter of convenience and when the amount of chiral amine is extremely small, it is possible to form chromophoric derivatives of chiral amines suitable for ORD and CD studies in the reaction medium. A number of such studies of metal chelates of α-amino acids and peptides have been reported. As an extension of this technique, when a chiral, vicinal amino alcohol is added to a solution of di(acetylacetonato)nickel(II) [Ni(acac)₂] or tris(dipivalomethanato)praseodymium(III) [Pr(dpm)₃] in an organic solvent, a complex is formed which results in an induced Cotton effect originating in the inorganic ligand. Correlations between the sign of the Cotton effect shown by amino alcohols of known absolute configuration lead to an empirical method for the determination of the absolute configurations of other vicinal amino alcohols. [Pr(dpm)₃] also shows Cotton effects with chiral primary and secondary amines, but in order to establish the usefulness of these complexes it will be necessary to study additional amines possessing various types of substituents.

Complexes prepared in methylene chloride from chiral primary amines and disuccinimidatodisopropylaminecopper(I) [Cu(ip)₂] or disuccinimidatodipyridinecopper(I) [Cu(py)₂] and used in situ show a number of Cotton effects, the signs of those near 600 and 700 nm being correlated with the absolute configuration of α-amino acid esters and a number of steroidal amines. Although model studies for this procedure have not been extensive, the sign of the induced Cotton effect appears to depend on the effective bulk size of the groups at the chiral centre to which the nitrogen atom is attached. The need to use the free base and the empirical nature of these methods are serious limitations.

Fluorescamine (FLURAM) (61) easily forms chromophoric derivatives (62) with chiral primary amines. Secondary amine, including cyclic amine, derivatives can also be formed in situ for CD measurements. Configurational assignments for primary and secondary amines using these derivatives, however, can be made only
on the basis of comparison of the CD spectrum of a derivative of unknown configuration with that of a close structural analogue of known absolute configuration.  

2-Methoxy-2,4-diphenyl-3(2H)-furanone (MDPF) (63) reacts with α-amino acids to form chromophoric derivatives 64 which for a substantial variety of α-amino acids always show a positive Cotton effect at about 385 nm for the L configuration (L-39). For the D configuration, this longest wavelength Cotton effect is negative.  

The N-salicylidene derivatives (52) of chiral primary amines may also be formed in situ by mixing sodium salicylaldehyde (55) with the amine salt in methanol.  

\[
\text{CHO} + \text{H}_2\text{N-R} \quad \text{NaCl} + \text{H}_2\text{N-R} \quad \text{CHO} + \text{H}_2\text{N-R} \quad \text{OH} \quad \text{OH} \quad \text{OH} \quad \text{N-R} \quad \text{H}_2\text{O} \quad \text{(52)}
\]

This procedure obviates the conversion of a crystalline amine salt to a usually noncrystalline free base, and since both reactants are solids, one or two milligram amounts can be conveniently weighed before mixing. Using 55, measurements of the CD spectra of α-amino acid and α-amino acid ester derivatives are also possible. In these cases the α-amino acid and α-amino acid ester hydrochloride are used. The CD spectra in all cases show maxima essentially the same as those of the isolated derivatives except that the observed molecular ellipticities for the derivatives formed in situ are somewhat lower due to the incomplete formation of the derivative. Application of the salicylidenimino chirality rule (Section II.4) allows the sign of the Cotton effects to be correlated with the absolute configuration of a wide variety of primary amines, including α-amino acids and esters and terpene and steroidal amines.

4. Salicylidenimino chirality rule  

a. Salicylidenimino chromophore. The isotropic electronic absorption (EA) spectra of the N-salicylidene derivatives of primary amines (52) in hexane exhibit characteristic absorption bands at about 315 (log ε_{max} 3.68-3.73), 255 (4.12-4.21) and 215 nm (4.36-4.49), designated as bands I, II and III, respectively (Figure 2), which are assigned to transitions of the intramolecularly hydrogen-bonded salicylidenimino chromophore (65). In polar solvents such as dioxane,
methanol and ethanol, a broad band at about 400 nm (log $\varepsilon_{\text{max}}$ 1.32–1.89 in dioxane and 3.06–3.08 in methanol and ethanol) and a shoulder near 280 nm (log $\varepsilon_{\text{max}}$ 3.49–3.67 in ethanol) become evident and the other three bands show a slight decrease in intensity. The two additional bands are attributed to the presence of a quinoid tautomer (66) in the polar solvent. The EA spectra of N-5-bromosalicylidene derivatives are the same except for the positions of the two longest wavelength bands at 328 and 415 nm.

Corresponding CD maxima are observed for bands I and II and for the band
near 400 nm (Figure 3). The Cotton effect associated with band III is difficult to measure and is frequently not observed. In some CD spectra there is an additional CD maximum, opposite in sign to that of bands I and II and centred at about 275 nm. This Cotton effect is not assigned to the quinoid tautomer since it persists in hexane, but on the basis of spectral observations on related Schiff bases and CNDO/S calculations on the azomethine and conjugated azomethine chromophore, it is assigned to the $n \rightarrow \pi^*$ transition of the conjugated azomethine group. For $N$-salicylidene derivatives containing unsaturated groups in the amine moiety, the 275-nm CD maximum may also be due to transition of this unsaturated group. This is definitely the case for the $N$-salicylidene derivative of (S)-$\alpha$-(1-naphthyl)ethylamine [(S)-67] in which the strong negative Cotton effect at 285 nm (Figure 3) is due to the $^1L_a$ transition of the naphthalene group.

b. Planar sector rule. When an N-salicylidene derivative is used as a chromophoric derivative to deduce the absolute configuration of a chiral primary amine, the sign of CD bands I (315 nm) and II (255 nm) may be related to the spatial distribution of the perturbing groups about the salicyldeniminino chromophore using a planar sector rule (68)\textsuperscript{79}. The distribution of groups with respect to the chromophore depends on the preferred conformation of the salicyldeniminino group about its attachment bond to the chiral centre and the absolute configuration of the chiral centre to which the chromophore is attached\textsuperscript{79}. On the basis of experimental observations with a substantial number of derivatives of known absolute configurations and on conformational analysis considerations, the sector signs were deduced as shown in 68, the plane in 68 being defined by the plane of the salicyldeniminino chromophore.

Thus for the N-salicylidene derivative of structure and configuration 69, the conformational equilibrium may be represented as 69a–69c. Conformer 69a is that of lowest energy whether the R group is larger or smaller in effective bulk size than the Ar group. With structure and configuration 69 (Ar = 1-naphthyl, phenyl, benzyl, substituted benzyl, 2- or 4-pyridyl, 2-thienyl, 2-thienylimethyl, 2-furanyl or 4-imidazolylmethyl group, R = alkyl, carboxylate, alkoxycarbonyl or alkoxycarbonylmethyl group), the Cotton effects near 255 and 315 nm are positive, the rotatory perturbation of the chromophore by an aryl or arylmethylene group
being greater than that of an alkyl, carboxylate, alkoxy carbonyl or alkoxy carbonylmethyl group.\textsuperscript{79,80,104,105} For the enantiomer of 69, the sign of the Cotton effects is negative. As predicted by this analysis, only a weak Cotton effect near 315 nm was detected for (S)-N-salicylidene-\(\alpha\),\(\beta\)-diphenylethylamine [(S)-70]\textsuperscript{106}, the perturbing effect of the \(\alpha\)-phenyl group being essentially cancelled by the \(\alpha\)-benzyl group.

\[
\text{[(S)-70]}
\]

For (S)-N-salicylidene-s-butylamine [(S)-71] and (R)-N-salicylidene-2,2-dimethyl-3-aminobutane [(R)-72], corresponding but less intense CD maxima are observed.\textsuperscript{79} Since both (S)-71 and (R)-72 have preferred conformations similar to 69a, and the rotatory perturbation by an ethyl group and by a \(t\)-butyl group is larger than that of a methyl group, the same planar sector rule for the salicylideneimino chromophore (68) also predicts the sign of the observed Cotton effects, positive for (S)-71 and negative for (R)-72.\textsuperscript{79}

Assuming a similar preferred conformation of the salicylideneimino group about its attachment bond and the same planar sector rule, the sign of the Cotton effect near 315 nm shown by a number of 20-aminopregnane derivatives\textsuperscript{107} is also predicted. A completely similar application of the planar sector rule is possible when the aryl group in 69 is replaced by an ethynyl or ethenyl group, these derivatives also showing positive Cotton effects for bands I and II.

An aliphatic \(L\)-\(\alpha\)-amino acid derivative with a preferred conformation (L-73) similar to 69a always shows positive Cotton effects for bands I and II\textsuperscript{80}. Thus in the CD spectrum of the derivative L-73 (alkyl = CH\(_3\)) formed by condensation of

\[
\text{[(S)-71]}
\]
\[
\text{[(R)-72]}
\]

\(L\)-alanine (L-74) with sodium salicylaldehyde (55) in methanol, bands I and II are positive (Figure 4), the perturbation of the chromophore by a carboxylate group being greater than that by an alkyl group. The quinoid CD band centred at 402 nm is positive and band III at 229 nm is negative. The CD band centred at 273 nm is assigned to the \(n \rightarrow \pi^*\) transition of the salicylideneimino chromophore.\textsuperscript{101}
A β-hydroxyl group on an aliphatic α-amino acid derivative has little effect on the CD spectrum, but the effect of a β-sulphur atom can be substantial. The sign of band I in the CD spectrum of the L-S-methionylcysteine (L-75) derivative is opposite that of the L-alanine (L-74) derivative, and no CD maximum near 275 nm was detected. A couplet structure for band II in the derivative of L-75 also arises from a sulphide transition in this spectral region.

For aliphatic α-amino acid ester derivatives, such as that formed with methyl L-alaninate hydrochloride (L-76) and sodium salicylaldehyde (55) in methanol, CD bands I and II are predicted to be positive on the basis of a preferred conformation similar to L-73 and a stronger influence on the chromophore by an alkoxy carbonyl group than by an alkyl group. For the few aliphatic α-amino acid ester derivatives studied, band I is positive, but the CD band near 265 nm is negative. Although
23. Chiroptical properties of amino, nitroso and nitro compounds

This latter band has been assigned to transition II of the salicylidenimino chromophore, it in fact may be due to the \( n \rightarrow \pi^* \) transition of the salicylidenimino group.

c. Coupled oscillator mechanism. The planar salicylidenimino chirality rule was in its earliest development based on empirical observation, and the wide range of its applicability was due to the availability of sufficient \( N - \text{salicylidene} \) derivatives of chiral amines of known absolute configuration. Later, the signs of the observed Cotton effects were rationalized in terms of the coupled oscillator mechanism for the generation of the observed Cotton effects. Using the exciton splitting in the CD spectra of the \( N,N' - \text{disalicylidene} \) derivatives of \((R)-\text{trans-1,2-cyclohexanediamine} \) and \((R)-1,2\)-propanediamine and CNDO/S calculations, the transition moment directions for the salicylidenimino chromophore were determined. The Cotton effects associated with the transitions near 315 (band I) and 255 nm (band II) are the result of coupling of these respective moments, both approximately along the attachment bond of the salicylidenimino group, with transition moments in the other groups attached to the chiral centre. For \( \beta \)-phenylalkylamine derivatives the important transition moments are those of the \( ^1L_a \) and \( ^1B_{ab} \) transitions of the benzene group, and the effective direction of these moments is along the phenyl group attachment bond. The \( ^1B_{ab} \) transition has a moment with components both along and perpendicular to the phenyl group attachment bond, but the interaction due to the perpendicular component is cancelled by rotation of the phenyl group about its attachment bond.

Newman projection formulae of the three conformers of lowest energy for an \((S)-N - \text{salicylidene-\beta-phenylalkylamine} \) are shown as \( 78a-78c \). For each particular conformer, the sign of the corresponding Cotton effect for bands I and II is shown. These signs can be easily determined when the transition moment directions for both the salicylidenimino chromophore and the phenyl group are oriented away from their respective attachment bonds. The interaction energy is positive and the sign of the CD maxima is determined by the chirality of the two attachment bonds, a right-handed screw giving a positive Cotton effect, and a left-handed screw giving a negative Cotton effect. Conformer \( 78a \) will be of higher energy than \( 78b \) and \( 78c \) due to steric interaction, and \( 78a \) will have a negligible population compared to the others. Conformer \( 78b \) will have a negligible rotational strength because of the near anticollinearity and large separation between the transition moments of the sali-
cylidenimino and phenyl groups. Conformer \(78c\) will thus dominate the CD spectrum, and \(N\)-salicylidene derivatives of \(\beta\)-phenylalkylamines of the configuration shown in \(78\) display positive Cotton effects near 315 and 255 nm \(^{79}\).

A similar coupled oscillator analysis for the \(N\)-salicylidene derivatives of other chiral \(\alpha\)- and \(\beta\)-arylalkylamines \(^{79,108}\), 1-alkyl-2-propynylamines \(^{108}\) and \(\alpha\)-amino acids \(^{80}\) predicts the sign of the respective Cotton effects, the dominant contribution to the CD arising from the coupling of the transition moments of the salicylidimenimino chromophore with those of \(\pi \rightarrow \pi^*\) transitions of the aryl, ethynyl, ethenyl and carboxylate groups.

The Cotton effects associated with bands \(I\) and \(II\) in spectra of chiral \(N\)-salicylidenealkylamines also arise by the coupled oscillator mechanism \(^{98}\). Since the polarizability of a carbon–hydrogen bond is small compared with that of a carbon–carbon bond \(^{98}\), only the latter near the chromophore attachment bond (vicinal or homovicinal) need be considered as inducing dichroic absorption in the chromophore \(^{80,98,99}\).

### III. CHIRAL NITROSO COMPOUNDS

#### A. Preparation of Chiral Nitroso Compounds

1. C-Nitroso compounds

Although the CD of caryophyllene and bornylene nitrosite (nitroso nitrite) was studied many years ago \(^{109}\), chiral C-nitroso compounds \((79)\) were not generally available until a careful study was made of their preparation by oxidation of chiral amines \((80)\) with \(m\)-chloroperbenzoic acid or peracetic acid \(^{110}\). Great care must be taken since overoxidation yields the nitro compound \((81)\), dimerization to \(82\) is facile, and tautomerization to the oxime \((83)\) can also occur. In this synthesis the configuration at the chiral centre is probably the same as that in the amine \(^{110}\), but the great instability of these compounds makes their use for chiroptical studies of limited value. Chiral C-nitroso compounds in which the nitroso group is attached to a tertiary carbon atom are more stable \(^{111}\) but the chiral amines are not readily available.

Treatment of a chiral ketoxime with \(N\)-bromosuccinimide in cold pyridine–ethanol gives the \(\alpha\)-bromo-C-nitroso compound \(^{110}\). For a series of monoterpene and steroidal oximes only \(5\alpha\)-cholestan-3-one oxime yielded a stable, crystalline monomeric derivative \((84)\). The reaction leading to \(84\) and the other \(\alpha\)-halo derivatives is such that the halogen atom occupies an axial position \(^{110}\). All chiral \(\alpha\)-halo-C-nitroso compounds are extremely unstable and even \(84\) could not be obtained in analytical purity \(^{110}\).
2. O-Nitroso compounds, nitrite esters

Although chiral nitrites are produced in the reaction of silver nitrite with chiral bromides\textsuperscript{112}, the most efficient method for the preparation of nitrites is the reaction of the chiral alcohol with nitrosyl chloride (NOCl) in dry pyridine at $-20^\circ$C\textsuperscript{113,114}. Although (R)-2-octyl nitrite [(R)-85] can be purified by distillation at reduced pressure\textsuperscript{112} and some steroidal nitrites may be recrystallized in the usual way\textsuperscript{113}, other steroidal nitrites are reported as recrystallized only at room temperature\textsuperscript{114}. Dioxane solutions of nitrite esters used for spectroscopic measurements should be stabilized by the addition of 0.2% pyridine\textsuperscript{114}.

3. N-Nitroso compounds

a. N-Nitrosoamides. The N-nitroso derivatives of primary amines are unstable but the N-nitroso-N-acyl-\textalpha-amin acid esters (86) are easily prepared using nitrogen tetroxide (N\textsubscript{2}O\textsubscript{4}) in carbon tetrachloride in the presence of sodium acetate\textsuperscript{73}. These compounds in general are unstable oils which must be stored at low temperature. Similarly the N-nitroso-N-acetyl derivatives of a number of chiral primary aralkylamines [(R)-87] have also been prepared as chromophoric derivatives of the primary amines\textsuperscript{73,115-117}.

b. Nitrosamines. The N-nitroso derivatives of chiral secondary amines may be prepared by treatment of the amine with nitrous acid\textsuperscript{117,118} (sodium nitrite in hydrochloric acid\textsuperscript{117} or acetic acid\textsuperscript{74}). These nitrosamines are frequently oils\textsuperscript{117,118} but sometimes they can be distilled at reduced pressure\textsuperscript{74}. Thus the N-nitroso derivatives of steroidal alkaloids\textsuperscript{74,119}, (R)-\textalpha-pipecoline\textsuperscript{74} [(R)-88] and (R)-\textbeta-pipecoline\textsuperscript{120} [(R)-89], and other chiral secondary amines\textsuperscript{117,120-122} have been prepared. It is to be recognized that chiral nitrosamines occur as conformational diastereomers and
that (R)-88 exists in carbon tetrachloride essentially in three conformations, 90a–c, 27% 90a, at least 37% 90b and the rest 90c123. Crystalline L-N-nitrosoproline is 80% syn (L-91a) and 20% anti (L-91b), the ratio being deduced on the basis of \(^1\)H-NMR studies using freshly prepared solutions at 0°C124. The diastereomers L-91a and L-91b have been separated by column chromatography at low temperature125.

B. Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD)

1. C-Nitroso compounds

The C-nitroso chromophore shows an n → π* transition at 680 nm126, and in the few ORD73 and CD110 studies that have been reported, this absorption band was found to be optically active. These derivatives were suggested as chromophoric derivatives of aliphatic and alicyclic amines110, but due to the instability of the compounds when the nitroso group is attached to a secondary carbon, it proved difficult to obtain CD spectra with reproducible intensities110.

Circular dichroism measurements110 with chiral α-bromo-C-nitroso compounds such as 84 indicate that the n → π* transition127 near 650 nm is optically active, but again, the instability of the compounds precludes the observation of spectra with reproducible intensities110.
23. Chiroptical properties of amino, nitroso and nitro compounds

2. O-Nitroso compounds, nitrite esters

The earliest circular dichroism studies with chiral nitrite esters are those of Elkins and Kuhn. These compounds, showing an $n \rightarrow \pi^*$ transition with much vibrational fine structure centred at about 360 nm, also show multiple Cotton effects in the same region. Thus 5α-pregnan-3β,20α- (92) and 5α-pregnan-3β,20β-diol 3-acetate 20-nitrite (93) show oppositely signed, multiple Cotton effects in this spectral region, and the O-nitroso group has been suggested as a chromophoric derivative for chiral alcohols. The conformational mobility of the nitrite group about its attachment bond to the chiral centre makes the interpretation of the Cotton effect in terms of a sector rule difficult. Reported spectra, for the most part of nitrite esters of steroidal alcohols, may be used as reference spectra for the stereochemical study of steroidal alcohols, where the relevant hydroxyl group of unknown configuration is located in an environment similar to that of one of the reference nitrites.

3. N-Nitroso compounds

a. N-Nitrosoamides. Chiral N-nitrosoamides show an isotropic electronic absorption band at about 415 nm which in ORD and CD studies is found to be optically active. The derivatives most extensively studied are those of the N-acetyl- and N-benzoyl-α-amino acid esters and α- and β-phenylalkylamines. Again the conformational mobility of the N-nitrosoamide group about its attachment bond and the nature of the chromophore itself is such that the presently reported curves can only be used as standards for comparison with ORD and CD curves of closely related compounds of unknown configuration. Thus the N-nitrosoacetamide derivative of (S)-amphetamine [(S)-94] and of (+)-norfenfluramine [(S)-96] show identical ORD and CD curves in isooctane, supporting the assignment of the S configuration to (+)-norfenfluramines.

b. Nitrosamines. In the case of chiral nitrosamines the $n \rightarrow \pi^*$ transition at 370 nm is also optically active, and (S)-nitrosofenfluramine [(S)-96] shows a strong positive Cotton effect at about 370 nm. Similar spectra were obtained with the N-nitroso derivatives for secondary amines in which the amino group is part of a ring, and the derivative is conformationally more rigid. Considering the sign of
the Cotton effects in these spectra and the symmetry of the chromophore, a sector rule (97) was proposed for the nitrosamino chromophore\textsuperscript{24}. As discussed for

(R)-N-nitroso-\alpha-pipecoline [(R)-88] and (S)-N-nitroso-2-ethylpiperidine [(S)-98] which both show positive Cotton effects near 350 nm, application of this sector rule to a chiral nitrosamine requires that all conformers that possibly could make a contribution to the Cotton effect be considered\textsuperscript{122}. However, a careful analysis of the three lowest energy conformers of (R)-88\textsuperscript{122}, and the CD spectra of other more conformationally rigid nitrosamines, suggests that the sector signs in 97 should be reversed\textsuperscript{124,132}. More recently a different sector rule for the nitrosamino chromophore (99) was suggested\textsuperscript{75}. Successful application of this rule to N-nitroso derivatives of \(\alpha\)-amino acids, chiral piperidines, and other naturally occurring chiral secondary amines also requires that the equilibrium distribution of conformational diastereomers of the derivative be taken into account\textsuperscript{75}.

It is to be noted that there is sometimes an additional difficulty in the interpretation of the Cotton effects for chiral nitrosamines\textsuperscript{75}. (S)-N-Nitrosoprolinol [(S)-100] in methanol, shown by IR and NMR measurements to occur in a fixed \textit{anti} conformation with hydrogen bonding of the hydroxyl group to the nitrogen atom of the nitroso group, gives a strong negative Cotton effect centred at about 340 nm along
with a positive Cotton effect at longer wavelength (384 nm). The 340-nm Cotton effect, conforming to sector rule 99, is at a substantially shorter wavelength than the absorption maximum in the ultraviolet absorption spectrum of (S)-100 and is assigned to the usual $n \rightarrow \pi^*$ transition, while that at 384 nm is tentatively assigned to an $n \rightarrow \pi^*$ transition from an excited vibrational ground state.

Quantum-mechanical calculations also suggest that a clear-cut sector rule cannot be applied to the nitrosamine chromophore. The calculated results for chiral alkyl-substituted $N$-nitrosopiperidines reflect the extreme sensitivity of the $n \rightarrow \pi^*$ rotatory strength to the position of ring substitution, the number and relative disposition of ring substituents, and the rotameric isomerism of individual substituent groups.

IV. CHIRAL NITRO COMPOUNDS

A. Preparation of Chiral Nitro Compounds

1. C-Nitro compounds

In the direct introduction of a nitro group at a chiral centre attention must be paid to the stereospecificity of the reaction. The reaction of (S)-2-octyl bromide [(S)-101] with silver nitrite leads to (R)-2-nitrooctane [(R)-102] and (R)-2-octyl nitrite [(R)-85], both with complete or almost complete inversion of configuration. In contrast, the same reaction using (S)-alpha-phenylethyl chloride [(S)-103] leads to (R)-alpha-phenylnitroethane [(R)-104] and also to (S)-alpha-phenylethyl nitrite [(S)-105], both of these compounds being far from optically pure. A direct displace-
(107) \( R = \text{OCOCH}_3, X = \text{H} \)
(108) \( R = \text{COCH}_3, X = \text{H} \)
(109) \( R = \text{C}_8\text{H}_{17}, X = \text{H} \)
(110) \( R = \text{OCOCH}_3, X = \text{NO}_2 \)
(111) \( R = \text{COCH}_3, X = \text{NO}_2 \)
(112) \( R = \text{C}_8\text{H}_{17}, X = \text{NO}_2 \)

\[
\begin{align*}
\text{HCIO}_4/\text{CH}_3\text{OH} & \rightarrow \\
\text{AcO} & \rightarrow \\
\text{NO}_2 & \\
(110) R = \text{OCOCH}_3 \quad (111) R = \text{COCH}_3 \\
\text{OH} & \rightarrow \\
\text{NO}_2 & \\
(113) R = \text{OH} \quad (114) R = \text{COCH}_3 \\
\text{OH} & \rightarrow \\
\text{NO}_2 & \\
(115) R = \text{OH} \quad (116) R = \text{COCH}_3 \\
\text{[0]} & \rightarrow \\
\text{NO}_2 & \\
(119) R = \text{OH} \quad (120) R = \text{COCH}_3 \\
\text{OH} & \rightarrow \\
\text{NO}_2 & \\
(121) R = \text{OH} \quad (122) R = \text{COCH}_3
\end{align*}
\]
Acidic hydrolysis of 110 and 111 removes the acetate groups (113 and 114). Treatment of 110, 111, 113 and 114 with alkali forms the anions of the aci form (115 and 116) of the respective nitro compounds. Acidification gives the thermodynamically less stable 6β-nitro steroids (117 and 118), steric hindrance to prototopic attack at the β-face being the product-controlling factor. Oxidation of 117 and 118 yields the 6β-nitro-α,β-unsaturated ketones (119 and 120) which are isomerized with base to the 6α-nitro compounds (121 and 122). The acetate of 121 (123) may also be formed directly by the action of fuming nitric acid on 3,5-androstadiene-3,17-diol diacetate (124).

Oxidative reactions for the formation of C-nitro compounds employ either an oxime or a primary amine. A very successful method for the preparation of steroidal nitro compounds is the nitration of an oxime (125) with fuming nitric acid to form the pseudo-nitrole (126) which is easily oxidized with hydrogen peroxide to form the gem-dinitro compound (127). The latter is then reduced with hydrogen over platinum to the mononitro compound (128). In 7α-nitro-5α-cholestan (128), the configuration at C-7 is controlled by the stereochemical features in 127.
Oxidation of an amine using peracetic acid (Emmons oxidation) preserves the chirality at the centre to which the amino group is attached. Thus oxidation of (+)-neomenthylamine \((+)-2\) gives \((1R,3S,4S)-3\)-nitro-\(\beta\)-menthane \([(1R,3S,4S)-129]\), which on treatment with a catalytic amount of sodium bicarbonate in boiling ethanol is isomerized to \((1R,3R,4S)-3\)-nitro-\(\beta\)-menthane \([(1R,3R,4S)-130]\). \([141]\)

\[
\begin{align*}
\text{(+)-2} & \xrightarrow{\text{CH}_3\text{CO}_3\text{H}} \text{[(+)-2]} & \xrightarrow{\text{NO}_2} & \text{[(1R, 3S, 4S)-129]} & \xrightarrow{\text{NaHCO}_3} & \text{[(1R, 3R, 4S)-130]}
\end{align*}
\]

2. O-Nitro compounds, nitrate esters

Chiral nitrate esters are synthesized from the corresponding chiral alcohol either with anhydrous nitric acid in acetic acid–acetic anhydride at \(-10^\circ\text{C}\) \([142,143]\) or via the corresponding chloroformate and silver nitrate \([143]\), the latter reaction leaving the carbon–oxygen bond predominantly intact \([144]\). Thus, reaction of \((S)-2\)-octyl chloroformate \([(S)-131]\) with silver nitrate in acetonitrile gives 2-octyl nitrate with 68% retention \([(S)-132]\) and 32% inversion of configuration \([144]\). For chiral compounds with more than one chiral centre the separation of diastereoisomers may be necessary. For those with one chiral centre a partially racemic product may be formed.

\[
\begin{align*}
\text{n-C}_6\text{H}_{13} & \xrightarrow{\text{H}} \text{O} & \text{O} & \text{Cl} \xrightarrow{\text{AgNO}_3/\text{CH}_3\text{CN}} & \text{n-C}_6\text{H}_{13} & \xrightarrow{\text{H}} \text{O} & \text{NO}_2
\end{align*}
\]

\[(S)-131 \rightarrow (S)-132\]

3. N-Nitro compounds, nitramines

Both primary \((133)\) and secondary \((134)\) nitramines are known \([145]\), but only the latter may be prepared by direct nitration of an amine in acidic media \([145]\). Analogous to the formation of chiral nitrate esters from chiral alcohols, secondary nitramines may be formed by the action of nitric acid on a secondary amine in acetic anhydride \([146]\) or of silver nitrate on a dialkylcarbamyl chloride \((135)\) in acetonitrile \([147]\), but chiral nitramines seem to have been prepared only by oxidation of the corresponding chiral nitrosamine \([148,149]\) with trifluoroperacetic acid \([150]\). With this reagent \((R)-\text{N-nitro-}\alpha\text{-pipecoline} \([(R)-88]\) was converted to \((R)-\text{N-nitro-}\alpha\text{-pipecoline} \([(R)-136]\) \([149]\).
B. Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD)

1. C-Nitro compounds

An early review of the ORD of chiral C-nitro compounds\(^1\) has been augmented
by extensive ORD\(^{14,10,15}\) and CD measurements\(^{14,15,154}\) of a substantial number
of C-nitro steroids and ORD measurements of 1-nitro-1-deoxy monosaccharide
derivatives\(^{155,156}\).

For C-nitro compounds the absorption band at 270–280 nm is assigned to an
\(n \rightarrow \pi^*\) transition of the nitro group, the assignment recently confirmed by magnetic
circular dichroism measurements\(^{157}\). On the basis of the CD curves for the saturated
nitro steroids a generalization of the octant rule\(^3\) was suggested\(^{154}\) as applying to
this transition.

For the 1-nitro-1-deoxy monosaccharide derivatives the sign of the observed
Cotton effect centred at about 280 nm correlates with the absolute configuration at
C-2, adjacent to the nitromethylene group. Thus for 1-nitro-1-deoxy-D-mannitol
(D-137) the Cotton effect is negative while that for 1-nitro-1-deoxy-D-glucitol
(D-138) is positive\(^{155}\).

2. O-Nitro compounds, nitrate esters

The ORD\(^{158,159}\) and CD\(^{160}\) spectra of the nitrate esters of a number of hexoses
and the ORD spectra of \(\alpha\)-hydroxy acids\(^{161}\) show that the observed Cotton effect at
about 270 nm, due to the weak \(n \rightarrow \pi^*\) transition of the nitrato chromophore\(^{162}\),
can be correlated with the configuration of the particular compound under study.

For the nitrate esters of other chiral alcohols, including those of steroidal
alcohols\(^{142,143}\), monoterpenoid alcohols\(^{143}\) and \(\alpha\)-hydroxy acids\(^{143}\), three optically
active absorption bands, at 270, 230 and 200–210 nm, are observed. Using con-
formational analysis based on X-ray and spectrographic data, it is found that a
planar sector rule\(^{(139)}\) correlates the molecular geometry of 42 nitrate esters and
the sign of the Cotton effect associated with the transition at 230 nm\(^{143}\). For appli-
cation of the rule the nitrate ester is viewed down the O—C bond with the nitro
group uppermost (139). Rotatory contributions to the 230-nm band are positive for
perturbing groups to the right and negative for those to the left of the nitrato sym-
metry plane\(^{143}\).
3. N-Nitro compounds, nitramines

The CD spectra of chiral nitramines\textsuperscript{148,149}, showing a strong absorption band near 240 nm, also reveals an optically active, forbidden transition near 270 nm\textsuperscript{148}, the position agreeing with the energy of an \( n \rightarrow \pi^* \) transition predicted by semi-empirical calculations\textsuperscript{133}. The planar arrangement of the nitramino chromophore (C\(_{2v}\) symmetry) suggests an octant rule\textsuperscript{148}, similar to that for chiral ketones\textsuperscript{39}, to correlate the sign of the observed Cotton effect near 270 nm with the molecular geometry of a particular compound. The sector signs, however, are opposite to those of the octant rule for ketones\textsuperscript{39}. Thus, (S)-N-nitro-\( \beta \)-pipecoline [(S)-140] with its methyl group preferably in an equatorial conformation is, on the basis of octant projection \textsuperscript{141}, predicted to show, in agreement with experiment, a positive Cotton effect near 270 nm\textsuperscript{148}. As is suggested by quantum-mechanical calculations on chiral nitramines\textsuperscript{133}, more recent CD measurements\textsuperscript{149} indicate that this rule does not apply in all cases since it fails to predict the observed negative Cotton effect at 278 nm for (R)-N-nitro-\( \alpha \)-pipecoline [(R)-136], the methyl group in (R)-136 preferably in an axial conformation. On the other hand, a quadrant rule (142)

predicts, as is observed for (R)-136, a negative Cotton effect at 240 nm associated with the \( \pi \rightarrow \pi^* \) transition of the nitramino chromophore\textsuperscript{149}. Similar predictions, based on this quadrant rule, of the sign of the Cotton effect near 240 nm are confirmed by CD measurement with other chiral \( \alpha \)-alkyl-substituted N-nitropiperidines\textsuperscript{149}. Quantum-mechanical calculations also support the application of sector rule 142 for the prediction of the sign of the Cotton effect associated with the \( \pi \rightarrow \pi^* \) transition of the nitramino chromophore\textsuperscript{133}.
V. ACKNOWLEDGEMENTS

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23. Chiroptical properties of amino, nitroso and nitro compounds

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CHAPTER 24

Thermochemistry of nitro compounds, amines and nitroso compounds

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I. INTRODUCTION

Although the thermochemistry of nitrogen-containing compounds has not been so intensively studied as that of hydrocarbons, it is important for a number of reasons. Many of these compounds are explosive or decompose hazardously, and in order to predict the exothermicity of a reaction or the detonation properties of a compound it is necessary to know its heat of formation. Use of nitrogen-containing compounds in industrial processes (for example, in the manufacture of dyes) also requires knowledge of thermodynamic properties. Where the thermochemical properties of a compound have not been measured it is very useful to be able to predict these properties; collections of results have been used by Benson and coworkers to derive rules which permit heats of formation, standard entropies and heat capacities in the ideal gas state to be estimated. In order to have confidence in properties estimated in this way it is necessary that new thermochemical results obtained experimentally be compared with estimated values, so that the method of estimation may be improved if necessary. Knowledge of accurate values of heats of formation, standard entropies, heat capacities and bond dissociation energies is also essential for the correct interpretation of results obtained in kinetic studies, permitting realistic mechanisms of reaction to be postulated.

For the reaction (1):

\[ AB \rightarrow \dot{A} + \dot{B} \] (1)

when the reverse reaction, a radical combination reaction (2):

\[ \dot{A} + \dot{B} \rightarrow AB \] (2)

may be assumed to have zero activation energy, the A—B bond dissociation energy, \( D(A—B) \), is frequently equated with the activation energy of reaction (1), \( E_1 \). The implication is that the enthalpy of reaction (1) is equal to \( E_1 \). However, for a system at constant volume the difference between the activation energies for the forward and reverse processes will be equal to the change in internal energy of the system \( \Delta U^0(T) \), which will be given by:

\[ \Delta U^0(T) = E_1 - E_2 = \Delta H_1(T) - \Delta nRT \]

where \( \Delta H_1(T) \) is the enthalpy change during reaction (1) at the mean reaction temperature \( T \), and \( \Delta n \) is the change in the number of moles during reaction (1). Hence, for the case where \( E_2 \) is equal to zero:

\[ \Delta H_1(T) = E_1 + \Delta nRT \]

In order to obtain the standard enthalpy change at 298 K, account must be taken of any change in the difference between the heat capacities of the products and reactants at 298 K and \( T \). Hence:

\[ \Delta H_1^0(298) = E_1 + \Delta nRT + \Delta C_p(298 - T) \] (A)

where \( \Delta C_p \) is the mean change between the heat capacities of the products and
24. Thermochemistry of nitro compounds, amines and nitroso compounds

reactant over the temperature range $298 \text{ K}$ to $T$. (We assume that the measured high-pressure activation energy, $E_1$, refers to a standard state of one atmosphere.) For a bond-breaking process, $\Delta H_\circ^\ddagger(298)$ may be equated with the dissociation energy of the bond broken in the reaction, $D(A\rightarrow B)$. Expression (A) only holds if the activation energy for the reverse process is zero, and if the activation energy measured is that for the homogeneous, unimolecular reaction (1): the reaction conditions must be such that the reaction is at its high-pressure limit and free from surface reactions. The heat capacity correction term is generally found to be less than $\pm 1 \text{ kcal/mol}$; the $\Delta nRT$ term, for $\Delta n$ equal to one, ranges from 0.6 to 3.0 kcal/mol between 298 and 1500 K. Thus the assumption that $D(A\rightarrow B)$ is equal to $E_1$ is in many cases a reasonable approximation, but values which differ by up to 4 kcal/mol from the true value of $D(A\rightarrow B)$ may be obtained in other cases, especially where the mean reaction temperature is high. Knowledge of the heats of formation of the radicals $\dot{A}$ and $\dot{B}$ and the reactant $AB$ allows calculation of $D(A\rightarrow B)$ from the thermochemistry:

$$D(A\rightarrow B) = \Delta H_\circ^\ddagger(\dot{A}) + \Delta H_\circ^\ddagger(\dot{B}) - \Delta H_\circ^\ddagger(AB) \quad (B)$$

It is interesting to compare bond dissociation energies obtained from kinetic results with those calculated from the thermochemistry.

In this review we have chosen to focus attention on heats of formation of nitro compounds, amines and nitroso compounds in the solid, liquid and gas phases, together with standard entropies and heat capacities in the gas phase (of which there are rather few results), and the bond dissociation energies of the $C\rightarrow N$ bonds in these compounds. We have also chosen to include in our review sections on alkyl nitrites and alkyl nitrates (which may be considered to be $O$-nitroso and $O$-nitro compounds), because of the importance of the kinetics of these compounds\(^2\). We have not extended our review to cover nitramines and nitrosamines.

The thermochemical literature up to the late 1960s has been exhaustively covered by two valuable reviews: those of Stull, Westrum and Sinke\(^3\) and Cox and Pilcher\(^4\). Stull, Westrum and Sinke have covered heats of formation, standard entropies, heat capacities and the thermodynamic functions $-\Delta G^\circ(T) - \Delta H^\circ(298)/T$ and $\Delta H^\circ(T) - \Delta H^\circ(298)$, while Cox and Pilcher have reviewed very thoroughly results on heats of formation and heats of vaporization. In the present review we have attempted to update these compilations, and have made use of the reviews to draw general conclusions concerning the thermochemistry of the compounds considered. In the preparation of this chapter the following publications have been searched: the American Chemical Society's Chemical Abstracts, the Bulletin of Thermodynamics and Thermochemistry published annually by IUPAC, the Journal of Chemical Thermodynamics, Thermochimica Acta, the Russian Journal of Physical Chemistry and other Russian journals. There will inevitably be omissions, which we ask the reader to forgive.

We have had to reach a decision on which units to use: calories or joules. We have chosen to quote values in terms of calories, since to quote both calories and joules would be too cumbersome. Throughout, 1 thermochemical calorie $= 4.185 \text{ J}$. A decision had also to be reached regarding the notation for standard states. McGlashan\(^5\) recommends use of the symbol $^\circ$ to represent standard states and we have adopted this convention. We have denoted the standard heat of formation as $\Delta H_\circ^\circ$, as this seems more satisfactory than $\Delta q^\circ$. For standard heats of sublimation and vaporization we have used $\Delta H_\circ^{s}$ and $\Delta H_\circ^{v}$. 
II. NITRO COMPOUNDS

A. Nitroalkanes

Stull, Westrum and Sinke\textsuperscript{3} and Cox and Pilcher\textsuperscript{4} list thermochemical data on several nitroalkanes and, more recently, Shaw\textsuperscript{6} has reviewed heats of formation of nitroalkanes obtained up to 1972. In the section which follows these exhaustive reviews will be updated, and in the subsequent section the C—N bond strength in nitroalkanes will be discussed.

1. Thermochemical properties of nitro derivatives of methane

The value selected by Cox and Pilcher\textsuperscript{4} and Stull, Westrum and Sinke\textsuperscript{3} for the heat of formation of liquid nitromethane is the unpublished National Bureau of Standards value of $-27.03 \pm 0.15$ kcal/mol quoted by McCullough and coworkers\textsuperscript{7}. On the basis of a value of $9.17 \pm 0.01$ kcal/mol for the heat of vaporization of nitromethane\textsuperscript{7} a value of $\Delta H_f^\circ$ for gaseous nitromethane of $-17.86 \pm 0.15$ kcal/mol is obtained. Two more recent determinations of the heat of formation of nitromethane have been carried out by Russian groups. Knobel' and coworkers\textsuperscript{8} determined the heat of combustion of nitromethane from which a value of $\Delta H_f^\circ$ for gaseous nitromethane of $-19.3 \pm 0.3$ kcal/mol was obtained. Lebedeva and Ryadnenko\textsuperscript{9} obtained a value of $\Delta H_f^\circ$ for liquid nitromethane of $-26.9 \pm 0.1$ kcal/mol giving $\Delta H_f^\circ$ equal to $-17.73 \pm 0.11$ kcal/mol for gaseous nitromethane. No experimental details are available about the second of these studies, but the results are in excellent agreement with the earlier National Bureau of Standards value.

Knobel' and coworkers\textsuperscript{8} also measured the heat of combustion of dinitromethane, from which they obtained a value of $-25.2 \pm 0.2$ kcal/mol for the heat of formation of liquid dinitromethane. On the basis of an estimated value of $11$ kcal/mol for the heat of evaporation of dinitromethane they estimated the enthalpy of formation of dinitromethane in the gas phase to be $-14.2$ kcal/mol.

Values in the range $-6.2$\textsuperscript{10} to $-18.6$ kcal/mol\textsuperscript{11} have been obtained for the heat of formation of liquid trinitromethane. The most thorough examination of the thermochemistry of trinitromethane was carried out by Miroshnichenko and coworkers\textsuperscript{12} who obtained $\Delta H_f^\circ = -11.5 \pm 0.5$ kcal/mol for the solid, $\Delta H_f^\circ = -7.0 \pm 0.4$ kcal/mol for the liquid and $-0.2 \pm 0.5$ kcal/mol for gaseous trinitromethane.

The value selected by Cox and Pilcher\textsuperscript{4} for the heat of formation of liquid tetranitromethane is that of $+8.9 \pm 0.7$ kcal/mol obtained by Gardner and Grigger\textsuperscript{13}. Using the value of $9.7$ kcal/mol for the heat of vaporization of tetranitromethane obtained by Edwards\textsuperscript{14} a value of $18.6 \pm 0.8$ kcal/mol for the heat of formation of gaseous tetranitromethane is obtained. A more recent determination of the enthalpies of formation of liquid and gaseous tetranitromethane was carried out by Lebedev and coworkers\textsuperscript{15}. Using a semimicrocalorimeter they obtained $\Delta H_f^\circ$ equal to $9.2 \pm 0.4$ kcal/mol for liquid tetranitromethane. With $\Delta H_f^\circ$ equal to $10.5 \pm 0.1$ kcal/mol they obtained a value of $19.7 \pm 0.5$ kcal/mol for the heat of formation of gaseous tetranitromethane, in agreement within experimental error with the results of Gardner and Grigger\textsuperscript{13}.

The heat of formation of fluorodinitromethane was determined by Pepekin and coworkers\textsuperscript{16}. They found that the heat of formation of liquid fluorodinitromethane was $-66.5 \pm 0.6$ kcal/mol. They obtained the heat of vaporization of the compound and thus found a value of $-56.1 \pm 0.8$ kcal/mol for the heat of formation of gaseous fluorodinitromethane.
The preferred values of the heats of formation of nitro derivatives of methane are summarized in Table 1.

The only nitro derivative of methane for which the standard entropy and heat capacity have been obtained is nitromethane. For the ideal gas state, $S^\circ(298)$ has been determined to be 65.73 cal/(mol K)$^7$ and $C_p^\circ(298) = 13.70$ cal/(mol K)$^7$. Stull, Westrum and Sinke$^3$ list thermodynamic functions for nitromethane (ideal gas state) from 298 to 1000 K.

2. Thermochemical properties of higher nitroalkanes

Shaw$^6$, in his review of the thermochemistry of nitroalkanes, listed the heats of formation of the nitro alkanes studied up to 1972 and showed that in general the heats of formation obeyed group additivity, not only in the gas phase but in the solid and liquid phases also. Group values for nitro compounds were listed. Since his article was written a few more values of heats of formation of nitroalkanes have been published; these have been added to Shaw’s list in Table 2. In some cases the new results have allowed new group values to be derived, and in other cases have led to modification of the group values derived by Shaw. Table 3 gives the group values which seem, at present, to be best. It has been assumed that the destabilizing effect of an alkyl–nitro gauche interaction in the solid and liquid phases is the same as that for an alkyl–alkyl gauche interaction in the solid and liquid phases, and that there is no destabilizing effect of alkyl–alkyl or alkyl–nitro gauche interactions in the gas phase. More results are required to refine the group values derived, and to give more accurate estimations of the effects of gauche interactions.

From Table 2 it may be seen that, in general, heats of formation of solid, liquid and gaseous nitroalkanes can be estimated to ±2 kcal/mol using group additivity, with some exceptions. The sterically crowded 1,1,1,3,5,5,5-heptanitropentane is considerably less stable than predicted by group additivity, probably because of steric interactions between groups separated by more than two carbon atoms. The
TABLE 2. Heats of formation of nitroalkanes obtained experimentally and estimated by group additivity rules (g.a.r.) (kcal/mol)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solid</th>
<th>Liquid</th>
<th>Gas</th>
</tr>
</thead>
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<tr>
<td></td>
<td>$\Delta H_f^o$ (exp.)</td>
<td>$\Delta H_f^o$ (g.a.r.)</td>
<td>$\Delta H_f^o$ (exp.)</td>
</tr>
<tr>
<td></td>
<td>Reference</td>
<td>$\Delta H_f^o$ (exp.) - $\Delta H_f^o$ (g.a.r.)</td>
<td>Reference</td>
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<td>1-Nitroalkanes</td>
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<tr>
<td>Nitromethane</td>
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<td>-34.4</td>
<td>9</td>
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<td>-39.7</td>
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<td></td>
<td>-40.0</td>
<td>9</td>
<td>-39.7</td>
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<td>-45.8</td>
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<td>-51.9</td>
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<td>3</td>
<td>-44.4</td>
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<td>-49.6</td>
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<td>-39.7</td>
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<td>18</td>
<td>-51.9</td>
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<td>1,1,1-Fluoronitroalkanes</td>
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$a^{a}$ Reference
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<tr>
<th>Compound</th>
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<th>Error</th>
<th>Value</th>
<th>Error</th>
<th>Value</th>
<th>Error</th>
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<td>1,3-Dinitropropane</td>
<td>-59.6</td>
<td>18</td>
<td>-51.3</td>
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<td>1,4-Dinitrobutane</td>
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<td>-46.5</td>
<td>+0.5</td>
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<td>2,2-Dinitropropane</td>
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<td>18</td>
<td>-42.7</td>
<td>-0.9</td>
<td>-40.1</td>
<td>18</td>
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<tr>
<td>2,2,3,3-Tetrinitrobutane</td>
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<td>18</td>
<td>-49.9</td>
<td>+13.2</td>
<td>-33.7</td>
<td>18</td>
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<td>1,1,1-Trinitropropane</td>
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<td>-38.7</td>
<td>+0.1</td>
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<td>18</td>
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<td>1,1,1,3,4,5,5,5-Heptanitropentane</td>
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<td>+0.1</td>
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<td>18</td>
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<tr>
<td>Hexanitroethane</td>
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<td>+7.8</td>
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<td>1,1,1-Trinitropropane</td>
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<tr>
<td>1,1,1-Trinitropropane</td>
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<tr>
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<tr>
<td>Tertiary nitroalkanes</td>
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<td>2-Methyl-2-nitropropane</td>
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<td>22</td>
<td>-55.6</td>
<td>+0.7</td>
<td>-51.9</td>
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<td>2-Methyl-2,3,3-trinitropentane</td>
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<td>Phenyl-substituted nitroalkanes</td>
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<td></td>
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</table>

Values shown in brackets indicate that groups were determined from single experimental values and thus the group additivity value must necessarily agree with the experimental value.

Heat of formation of liquid 1,2-dinitroethane based on estimated heat of fusion of 3 kcal/mol.
TABLE 3. Group values for the estimation of heats of formation of nitroalkanes (kcal/mol)\(^a\)

<table>
<thead>
<tr>
<th>Group</th>
<th>(\Delta H_f^0) (solid)</th>
<th>(\Delta H_f^0) (liquid)</th>
<th>(\Delta H_f^0) (gas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(-)(C)(H)(_2)(NO(_2))</td>
<td>-22.2</td>
<td>-22.0</td>
<td>-14.4</td>
</tr>
<tr>
<td>C(-)(C)(_2)(H)(NO(_2))</td>
<td>-21</td>
<td>-21.2</td>
<td>-13.6</td>
</tr>
<tr>
<td>C(-)(C)(H)(_3)(NO(_2))</td>
<td>-16.2</td>
<td>-17.7</td>
<td>-11.6</td>
</tr>
<tr>
<td>C(-)(C)(_2)(H)(NO(_2))(_2)</td>
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<td>-10.7</td>
<td></td>
</tr>
<tr>
<td>C(-)(C)(_3)(H)(NO(_2))(_2)</td>
<td>-22</td>
<td>-13.7</td>
<td></td>
</tr>
<tr>
<td>C(-)(C)(F)(NO(_2))(_2)</td>
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<td>-10.7</td>
<td></td>
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<td>C(-)(C)(H)(NO(_2))(_2)</td>
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<td>C(-)(C)(_2)(F)(NO(_2))(_2)</td>
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<tr>
<td>C(-)(C)(_3)(NO(_2))(_3)</td>
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<td>C(-)(C)(H)(_3)(_2)</td>
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<td>C(-)(C)(_2)(H)(_2)</td>
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<tr>
<td>C(_B)(-)(C)</td>
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</tr>
<tr>
<td>C(_B)(-)(H)</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Gauche interactions*

| Alkyl–alkyl | 2 | 2 | 0 |
| Alkyl–NO\(_2\) | 2 | 2 | 0 |
| NO\(_2\)–NO\(_2\) | 8 | 8 | 6.6 |

*Based on the review by Shaw\(^6\).*

The value for the heat of formation of hexanitroethane given by Shaw\(^6\) differs by 8.6 kcal/mol from the value obtained by Pepekin and coworkers\(^9\), which agrees well with the estimated value, and is therefore preferred. The value for 2-methyl-2,3,3-trinitropentane quoted by Cox and Pilcher\(^4\) also disagrees with the estimated value by a considerable amount, and may be suspect, for this reason. As noted by Shaw\(^6\) the heat of formation of liquid 1,2-dinitroethane disagrees with the group additivity value; another determination of this quantity would be useful. Finally, the heats of formation of the fluorodinitroalkanes do not obey group additivity very satisfactorily.

Insufficient data on entropies and heat capacities of nitroalkanes have been obtained to construct group values for the estimation of these properties. Stull, Westrum and Sinke\(^3\) list thermodynamic functions for six nitroalkanes including nitromethane: values of \(\Delta H_f^0\), \(S^0\) (298) and \(C_p^0\) for these compounds are listed in Table 4. The thermodynamic functions for the nitroalkanes other than nitro-

TABLE 4. Thermochemical properties of nitroalkanes (ideal gas state)\(^a\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\Delta H_f^0) kcal/mol</th>
<th>(S^0) (298) cal/(mol K)</th>
<th>(C_p^0) [cal/(mol K)]</th>
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</thead>
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<tr>
<td>Nitromethane</td>
<td>-17.8</td>
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<td>13.70 19.56 25.56 28.17</td>
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<td>Nitroethane</td>
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<td>18.69 27.92 36.81 40.67</td>
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<td>24.41 36.24 47.96 53.06</td>
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</tr>
<tr>
<td>1-Nitrobutane</td>
<td>-34.4</td>
<td>94.28</td>
<td>29.85 44.48 59.03 65.39</td>
</tr>
<tr>
<td>2-Nitrobutane</td>
<td>-39.1</td>
<td>91.62</td>
<td>29.51 44.61 59.44 65.96</td>
</tr>
</tbody>
</table>

\(^a\)Values taken from Stull, Westrum and Sinke\(^3\).
Thermochemistry of nitro compounds, amines and nitroso compounds were estimated by Stull, Westrum and Sinke on the basis of substitution constants for the nitro compound relative to the appropriate alkane, and will be subject to uncertainty because of this method of estimation.

3. The C—N bond dissociation energy

The C—N bond dissociation energy, \( D(C-N) \), in nitroalkanes may be obtained by considering the reactions:

\[
\begin{align*}
\text{RNO}_2 & \longrightarrow \text{R} + \text{NO}_2 \quad (3) \\
\text{R} + \text{NO}_2 & \longrightarrow \text{RNO}_2 \quad (4)
\end{align*}
\]

\( D(C-N) \) may be calculated from the thermochemistry, using:

\[
\Delta H^\circ (298) = D(C-N) = \Delta H^\circ_1(\text{R}, \text{g}) + \Delta H^\circ_2(\text{NO}_2, \text{g}) - \Delta H^\circ(\text{RNO}_2, \text{g})
\]

and knowing the heats of formation of the alkyl radical (from group additivity or published values), of nitrogen dioxide \((7.91 \pm 0.2 \text{ kcal/mol}^{24})\) and of the gaseous nitroalkane (Table 2). Thus for nitromethane, using the most recent value for the heat of formation of the methyl radical\(^{25}\) of \(35.1 \pm 0.15 \text{ kcal/mol}\), and using a value of \(-17.8 \pm 0.15 \text{ kcal/mol}\) for the heat of formation of nitromethane, \( D(C-N) \) is calculated to be \(60.8 \pm 0.3 \text{ kcal/mol}\). Values of \( D(C-N) \) for various mono-nitroalkanes are listed in Table 5.

If the activation energy for reaction (3) is known, the relationship discussed in the introduction:

\[
D(C-N) = \Delta H^\circ (298) = E_3 - E_4 + R\overline{T} + \overline{\Delta C}_{p}^\circ(298 - \overline{T})
\]

may be used to derive the bond dissociation energy. This may be simplified to:

\[
D(C-N) = E_3 + R\overline{T} + \overline{\Delta C}_{p}^\circ(298 - \overline{T}) \quad (C)
\]

since it may be assumed that the activation energy for the combination reaction (4) between alkyl radicals and nitrogen dioxide is zero. The above relationship only gives a true value of \( D(C-N) \) if the activation energy measured is that of the homogeneous, unimolecular reaction. In early studies of the decomposition of nitroalkanes the rate constant measured was not simply that for the rate of breaking of the C—N bond. More recent studies have allowed the high-pressure limiting rate constant for process (3) to be obtained. In Table 6 the high-pressure

| TABLE 5. C—N bond dissociation energies for mononitroalkanes (kcal/mol) |
|-----------------|-----------------|--------|-----------------|-----------------|--------|
| Compound        | \( D(C-N) \) (thermochemical)\(^{a}\) | \( E_1 \) | \( E_1 + R\overline{T} \) | \( \Delta H^\circ (298) = D(C-N) \) (kinetic)\(^{b}\) | Reference |
| Nitromethane    | 60.8            | 58.5   | 60.4            | 59.5            | 27     |
| Nitroethane     | 58.6            | 57     | 59.2            | 60.1            | 27     |
| 1-Nitropropane  | 58.7            | 55     | 57.1            | 57.5            | 27     |
| 2-Nitropropane  | 59.0            | 54     | 56.1            | 56.3            | 27     |
| 2-Nitrobutane   | 60.7            |        |                 |                 |        |
| 2-Methyl-2-nitropropane | 58.5 |        |                 |                 |        |

\(^{a}\)Mean \( D(C-N) \) (thermochemical) = 59.4 \pm 1.4 \text{ kcal/mol.} \\
\(^{b}\)Mean \( D(C-N) \) (kinetic) = 58.4 \pm 2.0 \text{ kcal/mol.}
activation energies for the decomposition of nitroalkanes are listed with the corresponding values of the bond dissociation energies derived using equation (C). Heat capacities for the alkyl radicals are tabulated or may be estimated by group additivity\(^2\); for nitrogen dioxide the heat capacity is tabulated\(^2\), while for the nitroalkanes the heat capacities derived by Stull, Westrum and Sinke\(^3\) are used. It may be seen from Table 5 that the ‘thermochemical’ bond dissociation energies for the series are constant. The ‘kinetic’ bond dissociation energies show a tendency to decrease with increasing length of the hydrocarbon chain. This may suggest that the reverse process has a small activation energy, increasing with increasing size of the alkyl group. The mean thermochemical and kinetic values are in reasonably good agreement. We conclude that for mononitroalkanes the C—N bond energy is \(59.4 \pm 1.4\) kcal/mol, independent of \(R\). There seems to be no clear reason for the trend observed in the kinetic results.

A number of kinetic studies have been carried out on the decomposition of polynitroalkanes: the activation energies obtained are listed in Table 6. For the polynitroalkanes and the nitroalkyl radicals no information is available about heat capacities. No attempt is made here to estimate the \(\Delta C_p(T)\) term, since the errors involved in estimating this quantity would probably be larger than the quantity itself, which is generally found to be less than \(\pm 1\) kcal/mol. We therefore make the approximation that \(\Delta H(T)\) is equal to \(\Delta H^0(298)\) for these reactions. It may be seen from Table 6 that for the geminal dinitroalkanes \(D(C—N)\) is constant.

| TABLE 6. C—N bond dissociation energies for polynitroalkanes from kinetic studies (kcal/mol) |
|---------------------------------|-----------------|------------------|----------------|
| **Compound**                    | \(E_1\)         | \(E_1 + \frac{RT}{2} - D(C—N)\) (kinetic)\(^a\) | **Reference** |
| **Geminal dinitroalkanes**      |                 |                  |               |
| 1,1-Dinitroethane               | 47.1 ± 2.5      | 48.1             | 28            |
| 1,1-Dinitropropane              | 47              | 48\(^b\)         | 29            |
| 1,1-Dinitropropane              | 48.0 ± 2.5      | 49.0             | 28            |
| 2,2-Dinitropropane              | 46              | 47\(^b\)         | 29,30         |
| 2,2-Dinitropropane              | 50.5            | 51.4             | 31            |
| 1,1-Dinitrobutane               | 48.2 ± 2.5      | 49.2             | 28            |
| **Mean \(D(C—N)\) (kinetic)\) = 48.8 ± 2.5 kcal/mol** |                 |                  |               |
| **Geminal trinitroalkanes**     |                 |                  |               |
| Trinitromethane                 | 42.4            | 43.1             | 32            |
| 1,1,1-Trinitroethane            | 43.2 ± 0.5      | 44.1             | 33            |
| 1,1,1-Trinitropropane           | 42.3 ± 1.0      | 43.2             | 33            |
| 1,1,1-Trinitrobutane            | 43.6 ± 1.0      | 44.5             | 33            |
| **Mean \(D(C—N)\) (kinetic)\) = 43.7 ± 1.3 kcal/mol** |                 |                  |               |
| Tetranitromethane               | 38.2            | 39.0             | 34            |
| Tetrinitromethane               | 40.9            | 41.8             | 35            |
| Hexanitroethane                 | 35.8            | 36.6             | 34            |
| Hexanitroethane (solid)         | 38.9 ± 3.9      | 39.6             | 36            |
| Hexanitroethane (in CCl\(_4\))  | 37.8 ± 3.8      | 38.5             | 36            |

\(^a\)No information on heat capacities available so we assume \(\Delta C_p(T) = 0\).
\(^b\)No experimental details available for these unpublished results so we assume \(T = 235^\circ C\) as in Reference 28.
24. Thermochemistry of nitro compounds, amines and nitroso compounds

at 48.8 ± 2.5 kcal/mol independent of R, and for geminal trinitroalkanes $D(C-N)$ is 43.7 ± 1.3 kcal/mol, again independent of R.

For these reactions no information is available for the heat of formation of the nitroalkyl radicals formed. For some of these species, estimates may be made which allow an approximate thermochemical bond dissociation energy to be calculated. For the CH$_3$CH$_2$CHNO$_2$ radical an approximate value for the heat of formation may be arrived at by considering the process:

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2 \longrightarrow \text{CH}_3\text{CH}_2\text{CHNO}_2 + \text{H}$$

and assuming that the C—H bond strength is equal to that in propane (98 kcal/mol). (This is an oversimplification but serves as a first approximation.) Using the results in Table 2, with $\Delta H^\circ_f (\text{H})$ equal to 52.1 kcal/mol, we find that $\Delta H^\circ_f (\text{CH}_3\text{CH}_2\text{CHNO}_2)$ is 16.1 kcal/mol. Hence, with $\Delta H^\circ_f$ for 1,1-dinitropropane equal to $-25.0$ kcal/mol, we obtain an approximate value of 49.0 kcal/mol for the C—N bond dissociation energy in 1,1-dinitropropane, in exact agreement with the ‘kinetic’ bond dissociation energy. For 2,2-dinitropropane a similar argument leads to a value of $\Delta H^\circ_f (\text{CH}_3\text{CHNO}_2\text{CH}_3)$ equal to 8.5 kcal/mol based on $D(C-H)$ for the secondary H in 2-nitropropane equal to 94.5 kcal/mol. Hence we obtain an approximate value of 46.8 kcal/mol for the C—N bond dissociation energy in 2,2-dinitropropane, considerably lower than the ‘kinetic’ value.

Several studies have been carried out on the decomposition of halonitroalkanes which yield activation energies for C—NO$_2$ bond-breaking processes. The activation energies obtained in these studies are listed in Table 7. Again, no correction for

<table>
<thead>
<tr>
<th>TABLE 7. C—N bond dissociation energies for halonitroalkanes and halopolynitroalkanes (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
</tr>
<tr>
<td>Mononitro compounds</td>
</tr>
<tr>
<td>Nitromethane</td>
</tr>
<tr>
<td>Trichloronitromethane</td>
</tr>
<tr>
<td>Dinitro compounds</td>
</tr>
<tr>
<td>1,1-Dinitroethane</td>
</tr>
<tr>
<td>Fluorodinitromethane</td>
</tr>
<tr>
<td>Difluorodinitromethane</td>
</tr>
<tr>
<td>Chlorodinitromethane</td>
</tr>
<tr>
<td>Dichlorodinitromethane</td>
</tr>
<tr>
<td>1,1,1-Trifluorodinitroethane</td>
</tr>
<tr>
<td>Trinitro compounds</td>
</tr>
<tr>
<td>Trinitromethane</td>
</tr>
<tr>
<td>Fluorotrinitromethane</td>
</tr>
<tr>
<td>Chlorotrinitromethane</td>
</tr>
<tr>
<td>Bromotrinitromethane</td>
</tr>
<tr>
<td>Iodotrinitromethane</td>
</tr>
<tr>
<td>Hexinitroethane</td>
</tr>
<tr>
<td>1,2-Difluorotetranitroethane</td>
</tr>
<tr>
<td>Fluoropentanitroethane</td>
</tr>
</tbody>
</table>

$^a$No information on heat capacities available so we assume $\Delta C_p(298 - T) \sim 0$. 

at 48.8 ± 2.5 kcal/mol independent of R, and for geminal trinitroalkanes $D(C-N)$ is 43.7 ± 1.3 kcal/mol, again independent of R.
changes in heat capacities between 298 K and the reaction temperature is made for these reactions. For comparison, for each class of halonitroalkane the bond dissociation energy in the analogous nitroalkane is also listed. It may be seen from Table 7 that α-substitution of one or two fluorine atoms has very little effect on the C—N bond dissociation energy relative to the unsubstituted nitroalkane, while α-substitution of one or more chlorine atoms lowers the C—N bond strength considerably. Likewise, substitution of a bromine or iodine atom in trinitromethane results in lowering of the first C—N bond dissociation energy by 6.1 and 7.9 kcal/mol respectively. Overall it may be seen that substitution of an α-hydrogen atom by a nitro group or halogen other than fluorine lowers the C—N bond dissociation energy, and the more highly substituted the carbon atom is by these groups, the weaker is the C—N bond.

B. Aromatic Nitro Compounds

1. Heats of formation

There exist in the literature many more results from studies of the thermochemistry of aromatic nitro compounds than aliphatic nitro compounds, and these have been collected by Cox and Pilcher and by Stull, Westrum and Sinke. Shaw has derived group values for solid and gaseous aromatic nitro compounds and has compared measured heats of formation for several of these compounds in the solid phase with values estimated in two ways: using ideal gas group values with measured heats of sublimation, and using solid group values. He concluded that the latter was the more satisfactory method. When considering polysubstituted aromatic compounds resonance and steric factors may have to be considered in addition to group values in the estimation of heats of formation. Shaw did not consider steric effects in his study. Where resonance occurs in a molecule the resonance energy cannot be estimated simply and thus group additivity is not appropriate.

Recent values of heats of formation of aromatic nitro compounds are listed in Table 8. The arrangement of the compounds is that used by Stull, Westrum and Sinke. Nitroaromatic amines are also included in Table 8.

TABLE 8. Heats of formation of some aromatic nitro compounds

<table>
<thead>
<tr>
<th>Formula</th>
<th>Name</th>
<th>State</th>
<th>ΔHf° (kcal/mol)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H3N3O6</td>
<td>1,3,5-Trinitrobenzene</td>
<td>s</td>
<td>-8.9 ± 0.3</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l</td>
<td>-4.9 ± 0.4</td>
<td>40</td>
</tr>
<tr>
<td>C6H4N2O4</td>
<td>m-Dinitrobenzene</td>
<td>s</td>
<td>-6.5 ± 0.1</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l</td>
<td>-1.6 ± 0.2</td>
<td>40</td>
</tr>
<tr>
<td>C6H2N3O4</td>
<td>α-Dinitrobenzene</td>
<td>s</td>
<td>-0.4 ± 0.15</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l</td>
<td>+5.1 ± 0.25</td>
<td>40</td>
</tr>
<tr>
<td>C6H4N2O4</td>
<td>p-Dinitrobenzene</td>
<td>s</td>
<td>-9.2 ± 0.1</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l</td>
<td>-1.2 ± 0.4</td>
<td>40</td>
</tr>
<tr>
<td>C6H3NO2</td>
<td>Nitrobenzene</td>
<td>l</td>
<td>+2.32 ± 0.10</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>g</td>
<td>+15.72 ± 0.10</td>
<td>41</td>
</tr>
<tr>
<td>C6H3N3O6</td>
<td>1,3-Diamino-2,4,6-trinitrobenzene</td>
<td>s</td>
<td>-23.4 ± 0.8</td>
<td>42</td>
</tr>
<tr>
<td>C6H6N2O2</td>
<td>m-Nitroaniline</td>
<td>s</td>
<td>-9.2 ± 0.1</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l</td>
<td>-3.5 ± 0.3</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>g</td>
<td>+16.3 ± 1.8°</td>
<td>44</td>
</tr>
</tbody>
</table>
24. Thermochemistry of nitro compounds, amines and nitroso compounds

TABLE 8. continued

<table>
<thead>
<tr>
<th>Formula</th>
<th>Name</th>
<th>State</th>
<th>$\Delta H_f^\circ$ (kcal/mol)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_6H_6N_2O_2$</td>
<td>$\alpha$-Nitroaniline</td>
<td>s</td>
<td>$-6.3 \pm 0.1$</td>
<td>43</td>
</tr>
<tr>
<td>$C_6H_6N_2O_2$</td>
<td>$\beta$-Nitroaniline</td>
<td>l</td>
<td>$-2.3 \pm 0.3$</td>
<td>43</td>
</tr>
<tr>
<td>$C_6H_6N_2O_6$</td>
<td>1,3,5-Triamino-2,4,6-trinitrobenzene</td>
<td>s</td>
<td>$-33.4 \pm 1.2$</td>
<td>42</td>
</tr>
<tr>
<td>$C_7H_4N_2O_6$</td>
<td>3,5-Dinitrobenzoic acid</td>
<td>l</td>
<td>$-103.4 \pm 0.1$</td>
<td>40</td>
</tr>
<tr>
<td>$C_7H_5NO_4$</td>
<td>$m$-Nitrobenzoic acid</td>
<td>s</td>
<td>$-98.0 \pm 0.3$</td>
<td>40</td>
</tr>
<tr>
<td>$C_7H_5NO_4$</td>
<td>$\alpha$-Nitrobenzoic acid</td>
<td>l</td>
<td>$-94.3 \pm 0.4$</td>
<td>40</td>
</tr>
<tr>
<td>$C_7H_5NO_4$</td>
<td>$\beta$-Nitrobenzoic acid</td>
<td>s</td>
<td>$-95.3 \pm 0.15$</td>
<td>40</td>
</tr>
<tr>
<td>$C_7H_5NO_4$</td>
<td>$\gamma$-Nitrobenzoic acid</td>
<td>l</td>
<td>$-90.6 \pm 0.45$</td>
<td>40</td>
</tr>
<tr>
<td>$C_7H_5N_3O_6$</td>
<td>2,4,6-Trinitrotoluene</td>
<td>s</td>
<td>$-15.1 \pm 1.2$</td>
<td>42</td>
</tr>
<tr>
<td>$C_7H_5N_3O_6$</td>
<td>2,4,6-Trinitrotoluene</td>
<td>s</td>
<td>$-19.25 \pm 0.74$</td>
<td>45</td>
</tr>
<tr>
<td>$C_7H_5N_3O_6$</td>
<td>2,4,6-Trinitrotoluene</td>
<td>g</td>
<td>$+5.75 \pm 0.84$</td>
<td>45</td>
</tr>
<tr>
<td>$C_7H_5N_3O_6$</td>
<td>2,4,6-Trinitrotoluene</td>
<td>g</td>
<td>$+7.7 \pm 0.8^a$</td>
<td>46</td>
</tr>
<tr>
<td>$C_7H_5N_3O_6$</td>
<td>2,4,6-Trinitrotoluene</td>
<td>g</td>
<td>$+5.8 \pm 0.7^a$</td>
<td>46</td>
</tr>
<tr>
<td>$C_{10}H_4N_2O_8$</td>
<td>1,4,5,6-Tetranitronaphthalene</td>
<td>s</td>
<td>$+11.3 \pm 2.0$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{12}H_4N_6O_{12}$</td>
<td>2,2',4,4',6,6'-Hexanitrobi phenyl</td>
<td>s</td>
<td>$+16.3 \pm 2.0$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{12}H_4N_8O_{12}$</td>
<td>2,2',4,4',6,6'-Hexanitroazobenzene</td>
<td>s</td>
<td>$+69.2 \pm 1.3$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{12}H_6N_8O_{12}$</td>
<td>3,3'-Diamino-2,2',4,4',6,6'-Hexanitrobu phenyl</td>
<td>s</td>
<td>$+61.087 \pm 0.26$</td>
<td>47</td>
</tr>
<tr>
<td>$C_{13}H_5N_5O_{11}$</td>
<td>2,2',4,4',6-Pentanitrobenzoph enone</td>
<td>s</td>
<td>$-27.4 \pm 1.2$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{14}H_6N_6O_{12}$</td>
<td>2,2',4,4',6,6'-Hexanitrostilbene</td>
<td>s</td>
<td>$+16.2 \pm 2.5$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{18}H_5N_9O_{18}$</td>
<td>2,2',2'',4,4',4'',6,6',6''-Nona nitroterphenyl</td>
<td>s</td>
<td>$+31.6 \pm 2.6$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{18}H_6N_8O_{16}$</td>
<td>2,2',4,4',6,6',6''-Octanitro- m-terphenyl</td>
<td>s</td>
<td>$+22.6 \pm 4.4$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{23}H_6N_{12}O_{24}$</td>
<td>2,2',2'',2''',4,4',4'',6,6',6'',6''-Dodec anitroquaterphenyl</td>
<td>s</td>
<td>$+50.9 \pm 2.4$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{24}H_6N_{14}O_{24}$</td>
<td>Azobis(2,2',4,4',6,6'-hexanitrobi phenyl)</td>
<td>s</td>
<td>$+114.8 \pm 1.9$</td>
<td>42</td>
</tr>
<tr>
<td>$C_{24}H_6N_{16}O_{24}$</td>
<td>2,2',2'',2''',4,4',4'',4'',6,6',6'',6''-Dodecanitro-3,3'-bis(pheny lazo)-biphenyl</td>
<td>s</td>
<td>$+189.2 \pm 2.6$</td>
<td>42</td>
</tr>
</tbody>
</table>

*Standard enthalpy of sublimation was measured by these workers. Values of $\Delta H_f^\circ$ (g) are based on the values given by Cox and Pilcher* for $\Delta H_f^\circ$ (s).
Previous values of the heats of formation of several of these compounds have been published. For 1,3,5-trinitrobenzene, Cox and Pilcher selected, after making corrections, a value of $-10.4 \pm 0.45$ kcal/mol for the heat of formation of the solid compound, 1.5 kcal/mol lower than the more recent value of Lebedeva and coworkers, for which experimental details are not easily available. For $m$-dinitrobenzene, Cox and Pilcher corrected results by Badche to obtain a value of $-8.1 \pm 0.6$ for the heat of formation of the solid, lower by 1.6 kcal/mol than the value of Lebedeva and coworkers. Stull, Westrum and Sinke list heats of formation for $o$- and $p$-dinitrobenzene of 2.7 and $-9.05$ kcal/mol, given by Kharasch. The more current values by Lebedeva and coworkers of $-0.4$ and $-9.2$ kcal/mol will probably be more reliable. For nitrobenzene the only other value for the heat of formation of the liquid appears to be that quoted by Parks and coworkers of 2.7 kcal/mol, which compares well with the value of Lebedeva and coworkers of $2.32 \pm 0.10$ kcal/mol (correcting the sign of this quantity which seems to be wrong in the Russian paper). For $o$-, $m$- and $p$-nitroaniline, Cox and Pilcher list heats of formation of $-6.29 \pm 0.77$, $-6.8 \pm 1.5$ and $-9.91 \pm 0.17$ kcal/mol respectively, compared with the values of $-6.3 \pm 0.1$, $-9.2 \pm 0.1$ and $-10.3 \pm 0.2$ kcal/mol obtained by Lebedeva and coworkers; the values for $o$- and $p$-nitroaniline agree within experimental error while the value for $m$-nitroaniline differs by 2.4 kcal/mol. Stull, Westrum and Sinke list heats of formation of $o$-, $m$- and $p$-nitrobenzoic acid of $-98.9$, $-101.2$ and $-100.6$ kcal/mol respectively, from the compilation of Kharasch, written in 1929. These values are not very far removed from the results of Lebedeva and coworkers of $-95.3 \pm 0.15$, $-98.9 \pm 0.1$ and $-102.1 \pm 0.2$ kcal/mol respectively. These latter, more recent, values will probably be more reliable. For 2,4,6-trinitrotoluene, Cox and Pilcher select a value of $-16.03 \pm 0.65$ kcal/mol for the heat of formation of the solid, which agrees within experimental error with the value of $-15.1 \pm 1.2$ kcal/mol obtained by Rouse. The value of $-19.25 \pm 0.74$ kcal/mol obtained by Lenchitz and coworkers differs considerably from the value selected by Cox and Pilcher: Lenchitz and coworkers suggest that sample purity is a factor in this comparison. The heat of sublimation given by Cox and Pilcher for 2,4,6-trinitrotoluene is $28.3 \pm 1.0$ kcal/mol. Lenchitz and Velicky found $\Delta H^\circ$ equal to $25.0 \pm 0.4$ kcal/mol, using a Knudsen effusion cell, while Pella obtained a value of $23.7 \pm 0.5$ kcal/mol, using an electron-capture gas chromatographic method. These last two results are in fairly good agreement, while the value given in Cox and Pilcher, by Edwards, is probably too high. The heat of formation of gaseous 2,4,6-trinitrotoluene is selected here to be $7.7 \pm 0.8$ kcal/mol, bearing in mind the relative precision of the various determinations. For solid 2,4-dinitrotoluene Cox and Pilcher select a heat of formation of $-17.10 \pm 0.65$ kcal/mol. Lenchitz and coworkers measured the heat of combustion of the solid compound and hence obtained a value of $-15.38 \pm 0.74$ kcal/mol for its heat of formation, in reasonable agreement with the value preferred by Cox and Pilcher. The heat of sublimation measured by Lenchitz and Velicky of $23.8 \pm 0.3$ kcal/mol for 2,4-dinitrotoluene is in good agreement with the value of $-22.9 \pm 0.3$ kcal/mol obtained by Pella. Using the value selected by Cox and Pilcher for the heat of formation of the solid, and using a mean value of $23.3 \pm 0.3$ kcal/mol for its heat of sublimation we arrive at a value of $6.2 \pm 0.7$ kcal/mol for the heat of formation of gaseous 2,4-dinitrotoluene. For $p$-nitrotoluene Stull, Westrum and Sinke list a value by Kharasch of $-8.9$ for the heat of formation of the solid. The more recent value by Lenchitz and coworkers of $-11.52 \pm 0.72$ kcal/mol is more reliable. For 2,2',4,4',6,6'-hexanitroazobenzene the result of Rouse differs considerably from that of Baroody and Carpenter.
24. Thermochemistry of nitro compounds, amines and nitroso compounds

Rouse could not attribute this discrepancy to an impurity in his sample. Lastly, for 2,2',4,4',6,6'-hexanitrostilbene, Cox and Pilcher\(^4\) list a value of 13.8 ± 1.0 kcal/mol for the heat of formation of the solid, in agreement with the value of 16.2 ± 2.5 kcal/mol obtained by Rouse\(^4\), when the uncertainty in the values is considered.

2. The C—N bond dissociation energy

For the simplest of these compounds, nitrobenzene, the C—N bond dissociation energy may be calculated from the thermochemistry:

\[
D(C—N) = \Delta H_f^0(C_6H_5^*, g) + \Delta H_f^0(NO_2, g) - \Delta H_f^0(C_6H_5NO_2, g)
\]

Using heats of formation of 78.5, 7.91 and 15.72 kcal/mol for the phenyl radical\(^26\), nitrogen dioxide\(^24\) and nitrobenzene\(^4\) respectively we arrive at a value of 70.7 ± 1 kcal/mol for the standard C—N bond dissociation energy in nitrobenzene.

As discussed earlier for aliphatic nitro compounds, the standard bond dissociation energy is related to the activation energy for the reaction (5):

\[
C_6H_5NO_2 \rightarrow C_6H_5^* + NO_2
\]

by the expression

\[
D(C—N) = E_5 + R\overline{T} + \Delta C_p^0(298 - \overline{T})
\]

Matveev and Nazin\(^53\) have studied the decomposition of nitrobenzene and have determined the reaction conditions where heterogeneous effects are minimized and chain reactions are inhibited. Under these conditions they were able to obtain rate constants for the unimolecular reaction (5) from which a value of 69.7 kcal/mol for the activation energy over the temperature range 410–480°C was deduced. This gives a value of 71.1 kcal/mol for \(\Delta H_f(720)\). If we assume that \(\Delta C_p(298 - \overline{T})\) is negligibly small, then \(\Delta H_f(720)\) may be taken to be approximately equal to \(\Delta H_f^0(298)\). Thus the kinetic value of \(D(C—N)\) is in close agreement with the thermochemical value. This study has shown that it is only with the greatest care that aromatic nitro compounds may be persuaded to decompose unimolecularly and homogeneously. In a more recent study, Matveev and coworkers\(^54\) were able to obtain rate constants for the unimolecular homogeneous loss of nitrogen dioxide from \(p\)-nitrotoluene and \(m\)-nitrotoluene. They obtained activation energies for these reactions of 65.9 ± 1.1 and 68.0 ± 1.3 kcal/mol respectively. These values correspond to enthalpies of reaction of 67.3 and 69.4 kcal/mol for \(p\)-nitrotoluene and \(m\)-nitrotoluene at the temperatures of reaction, indicating that the C—N bond strength is reduced by the introduction of a CH\(_3\) group, particularly in the para-position. In the case of the decomposition of \(o\)-nitrotoluene they obtained a much lower activation energy, 49.5 kcal/mol, which they attributed to a different and possibly heterogeneous mechanism which left the C—N bond intact.

Other studies have been carried out on the kinetics of the decomposition of aromatic nitro compounds which allow general conclusions about the reactivity of these compounds to be drawn but which do not give values of \(D(C—N)\) because of the complicating effects of surface decomposition and pressure dependence. Thus Maksimov\(^55\) could conclude from his study of the gas-phase decomposition of several aromatic nitro compounds that the rate of decomposition of an aromatic nitro compound is enhanced by the presence of methyl, amino, hydroxyl and halogen substituents and that the greater the number of nitro groups the higher the rate of decomposition. The rate of decomposition is further enhanced by crowding.
Where intramolecular reaction is possible, as in \( o \)-nitrotoluene, the rate of reaction is enhanced and the C—N bond is left intact.

### III. AMINES

#### A. Thermochemical Properties

1. **Group additivity**

   Benson and coworkers\(^1\) determined group values for the heats of formation of amines in the gas phase on the basis of published heats of formation of twelve aliphatic and six aromatic amines. They also estimated group values for the standard entropies and heat capacities of amines on the basis of measurements of one aromatic and three aliphatic amines together with interpolated values. Since Benson and coworkers published their article several more studies of amines have been carried out, and the results obtained in these studies may be used to test the group values obtained earlier. These more recent results are listed in Table 9, together with the values predicted on the basis of the group values of Benson and coworkers.

   It may be seen from Table 9 that, in general there is good agreement between the predicted and observed values. As far as heats of formation are concerned, for the monofunctional noncyclic amines agreement is within \( \pm 1 \) kcal/mol, if no correction is made for \( \text{NH}_2-R \) or \( \text{RNH}_2-R \) gauche interactions. For the diamines, agreement is best for the unbranched compounds, again not correcting for gauche interactions. In each case the estimated \( \Delta H^\circ_f \) is higher, by \( \sim 0.5 \) kcal/mol, for all except 2-methyl-1,2-propanediamine. For the cyclic amines the estimated values include corrections for strain which are those for the unsubstituted rings: this is not necessarily valid. The agreement between observed and estimated values is best for cyclohexylamine, where no strain correction is required. As far as diethyl(2-hydroxyethyl)amine is concerned, the estimated and measured \( \Delta H^\circ_f \) 's differ by so much that it is clear that some stabilizing influence arises from intramolecular interactions. From perfluoroaminomethane, benzylamine and triphenylamine we may estimate values of \( \Delta H^\circ_f \) for the groups C(N)(F)\(_3\), C(N)(H)\(_2\)(C\(_9\)) and N(C\(_8\))\(_3\) of \(-161.2\), \(-5.83\) and \(30.1\) kcal/mol respectively.

   For the standard entropies, agreement between observed and estimated values is better than \( \pm 1 \) cal (mol K) for all but 2-methyl-1,2-propanediamine. With this one exception these results show that the group values for C(N)(C)(H)\(_2\), C(N)(C)\(_2\)(H) and C(N)(C)\(_3\) which were estimated by Benson and coworkers\(^1\) by interpolation may be used with confidence.

   The agreement between estimated and observed heat capacities at 298 K is good in all cases, showing that the group values predict thermochemical properties of amines accurately.

   Stull, Westrum and Sinke\(^3\) list thermodynamic functions for methyl-, ethyl-, dimethyl- and trimethyl-amines based upon molecular data, and of propyl-, butyl-, \( \alpha \)-butyl-, \( t \)-butyl-, diethyl- and triethyl-amines on the basis of substituent constants and thermodynamic values for the analogous hydrocarbons.

2. **Recent results**

   In Table 10 we list recent thermochemical results for amines (nitroaromatic amines have been included in Table 8). Previous values exist for some of these
<table>
<thead>
<tr>
<th>Compound</th>
<th>( \sigma^a )</th>
<th>( \Delta H_f^\circ ) (kcal/mol)</th>
<th>( \Delta H_f^\circ ) (g.a.r.)</th>
<th>( \Delta H_f^\circ ) (obs.) - ( \Delta H_f^\circ ) (g.a.r.)</th>
<th>( S^\circ ) (298) (cal/(mol K))</th>
<th>( S^\circ ) (298) (g.a.r.)</th>
<th>( S^\circ ) (obs.) - ( S^\circ ) (g.a.r.)</th>
<th>( C_p^\circ ) (298) (cal/(mol K))</th>
<th>( C_p^\circ ) (298) (g.a.r.)</th>
<th>( C_p^\circ ) (obs.) - ( C_p^\circ ) (g.a.r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluoroaminomethane</td>
<td>3</td>
<td>-169.0</td>
<td>-169.0</td>
<td>0.0</td>
<td>68.03</td>
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<td>67.74</td>
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<td>17.35</td>
<td>58</td>
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<td>Ethylamine</td>
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<td>-11.9</td>
<td>0.55</td>
<td>16.16</td>
<td>63</td>
<td>16.16</td>
<td>0.04</td>
<td>22.16</td>
<td>63</td>
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<td>Ethylenediamine</td>
<td>2</td>
<td>-4.07</td>
<td>17.3</td>
<td>1.12</td>
<td>76.92</td>
<td>60</td>
<td>77.64</td>
<td>-0.72</td>
<td>21.8</td>
<td>63</td>
</tr>
<tr>
<td>Propylamine</td>
<td>3</td>
<td>-16.77</td>
<td>-16.83</td>
<td>0.06</td>
<td>77.9</td>
<td>63</td>
<td>77.16</td>
<td>0.74</td>
<td>21.8</td>
<td>63</td>
</tr>
<tr>
<td>1,2-Propanediamine</td>
<td>2</td>
<td>-20.02</td>
<td>-20.56</td>
<td>0.54</td>
<td>74.7</td>
<td>63</td>
<td>74.46</td>
<td>0.23</td>
<td>22.6</td>
<td>63</td>
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<tr>
<td>Cyclohexylamine</td>
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<td>-12.81</td>
<td>-12.28</td>
<td>-0.53</td>
<td>86.07</td>
<td>60</td>
<td>87.12</td>
<td>-1.05</td>
<td>22.6</td>
<td>63</td>
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<tr>
<td>Cyclobutylamine</td>
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<td>-23.57</td>
<td>-23.86</td>
<td>0.29</td>
<td>78.3</td>
<td>63</td>
<td>78.1</td>
<td>0.2</td>
<td>28.8</td>
<td>63</td>
</tr>
<tr>
<td>2-Methyl-1-aminopropane</td>
<td>3</td>
<td>-28.9</td>
<td>-28.64</td>
<td>-0.26</td>
<td>88.34</td>
<td>60</td>
<td>91.57</td>
<td>-3.28</td>
<td>28.8</td>
<td>63</td>
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<tr>
<td>Triphenylamine</td>
<td>2</td>
<td>-13.13</td>
<td>-13.9</td>
<td>0.77</td>
<td>88.34</td>
<td>60</td>
<td>91.57</td>
<td>-3.28</td>
<td>28.8</td>
<td>63</td>
</tr>
</tbody>
</table>

\( a \) \( \sigma \) is the symmetry of the molecule which is required in calculating \( S^\circ \) (298). \( R \ln \sigma \) is subtracted from the group additivity value of \( S^\circ \) (298).

\( b \) From this value of the heat of formation of perfluoroaminomethane we may derive a value of \( \Delta H_f^\circ \) for the group C(N)(F)\(_3\) of -161.2 kcal/mol.

\( c \) From this value of the heat of formation of benzylamine we may derive a value of \( \Delta H_f^\circ \) for the group C(N)(H)\(_2\)(C\(_6\)H\(_5\)) of -5.83 kcal/mol, assuming no gauche interaction between the amino group and the benzene ring.

\( d \) From this value of the heat of formation of triphenylamine we may derive a value of \( \Delta H_f^\circ \) for the group N(C\(_6\)H\(_5\))\(_3\) of 30.1 kcal/mol, on the assumption that there is no steric destabilization in the molecule.
TABLE 10. Recent thermochemical results for amines

<table>
<thead>
<tr>
<th>Formula</th>
<th>Name</th>
<th>State</th>
<th>$\Delta H^\circ$ (kcal/mol)</th>
<th>Reference</th>
<th>$\delta^\circ$ (298) [cal/(mol K)]</th>
<th>Reference</th>
<th>$C_p^\circ$ (298) [cal/(mol K)]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF$_3$N</td>
<td>Difluoroaminotrifluoromethane</td>
<td>g</td>
<td>−169.0 ± 0.6</td>
<td>57</td>
<td>68.03</td>
<td>58</td>
<td>17.36</td>
<td>58</td>
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<tr>
<td>C$_5$H$_7$N</td>
<td>Ethylamine</td>
<td>g</td>
<td>−15.06 ± 0.13</td>
<td>59</td>
<td>76.92</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_2$H$_8$N$_2$</td>
<td>Ethylenediamine</td>
<td>l</td>
<td>−4.07 ± 0.14</td>
<td>59</td>
<td>10.95 ± 0.12</td>
<td>61</td>
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<td></td>
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<tr>
<td>C$_3$H$_7$N</td>
<td>Cyclopropylamine</td>
<td>l</td>
<td>18.42 ± 0.16</td>
<td>61</td>
<td>24.26 ± 0.09</td>
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<tr>
<td>C$_3$H$_9$N</td>
<td>Propylamine</td>
<td>l</td>
<td>−16.77 ± 0.13</td>
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<td>26.83 ± 0.16</td>
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<td></td>
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<tr>
<td>C$_3$H$_9$N</td>
<td>Isopropylamine</td>
<td>l</td>
<td>−20.02 ± 0.19</td>
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<td>23.8 ± 0.10</td>
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<td>86.07 ± 0.2</td>
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<tr>
<td>C$<em>3$H$</em>{11}$N$_2$</td>
<td>1,2-Propanediamine</td>
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<td>−12.81 ± 0.11</td>
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<tr>
<td>C$_2$H$_5$F$_3$N$_5$O$_8$</td>
<td>Bis(2-fluoro-2,2-dinitroethyl)amine</td>
<td>s</td>
<td>−126.952 ± 0.49</td>
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<td>C$_4$H$_9$N</td>
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<td>9.8 ± 0.1&quot;</td>
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<td>C$<em>4$H$</em>{11}$N</td>
<td>2-Methyl-1-aminopropane</td>
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<td>−31.68 ± 0.12</td>
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<td>C$<em>4$H$</em>{12}$N$_2$</td>
<td>1,2-Butanedi amine</td>
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<td>78.3 ± 0.2</td>
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<td>2-Methyl-1,2-propanediamine</td>
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<td>C$<em>6$H$</em>{12}$N$_4$</td>
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<tr>
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<td>Chemical Formula</td>
<td>Chemical Name</td>
<td>Phase</td>
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<td>$C_6H_{13}N$</td>
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<td>$C_6H_{15}N$</td>
<td>Dipropylamine</td>
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<td>$-37.33 \pm 0.10$</td>
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<td>$C_6H_{15}N$</td>
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<td>$C_6H_{15}NO$</td>
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<td>$C_7H_{17}NO_2$</td>
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<tr>
<td>$C_8H_9N$</td>
<td>Benzylamine</td>
<td>l</td>
<td>$8.18 \pm 0.41$</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_8H_{19}N$</td>
<td>Dibutylamine</td>
<td>l</td>
<td>$-49.27 \pm 0.09$</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_8H_{19}N$</td>
<td>Diisobutylamine</td>
<td>l</td>
<td>$-52.24 \pm 0.11$</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_9H_{18}N$</td>
<td>Tripropargylamine</td>
<td>l</td>
<td>$160.4 \pm 1.4$</td>
<td>74</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_9H_{13}N$</td>
<td>Dipropargylpropylamine</td>
<td>l</td>
<td>$90.1 \pm 0.5$</td>
<td>74</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_9H_{17}N$</td>
<td>Dippargylpropylamine</td>
<td>l</td>
<td>$20.1 \pm 0.6$</td>
<td>74</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_9H_{18}N_2$</td>
<td>Diethyl(1-cyanobutyl)amine</td>
<td>l</td>
<td>$-14.8 \pm 0.2$</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{10}H_{23}NO_2$</td>
<td>Ethyl 2-(diethylamino)butanoate</td>
<td>l</td>
<td>$-134.3 \pm 0.15$</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{12}F_{27}N$</td>
<td>Perfluorotributylamine</td>
<td>l</td>
<td>$-1328$</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{12}F_{27}N$</td>
<td>Perfluorotributylamine</td>
<td>g</td>
<td>$-1313.6$</td>
<td>77, 72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{18}H_{15}N$</td>
<td>Triphenylamine</td>
<td>s</td>
<td>$56.1 \pm 0.8$</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{18}H_{15}N$</td>
<td>Triphenylamine</td>
<td>g</td>
<td>$78.1 \pm 1.0$</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on estimated enthalpy of vaporization calculated as the mean of the values of $\Delta H^\circ_v$ for cyclopropyl- and cyclopentyl-amines.

$^b\Delta H^\circ_v$ was obtained from early boiling-temperature data (see Ref. 68).
compounds. For the trans isomer of ethylamine*, Petrov and Vvedenskii calculated thermodynamic functions from published vibrational frequencies. Their values for $C_p^\circ$ and $S^\circ$ do not differ significantly from those listed by Stull, Westrum and Sinke. For propylamine, Stull, Westrum and Sinke list thermodynamic functions based upon a substitution constant; the values listed by Scott are based upon vibrational assignments of molecular spectra together with calorimetric determinations of $\Delta H^\circ$ and $S^\circ$. For $p$-aminobenzoic acid a value of the heat of formation of the solid $-78.4$ kcal/mol determined by Pushkareva and Kokoshko is listed by Stull, Westrum and Sinke, a value considerably higher than that of $-97.99$ kcal/mol obtained by Nabavian and coworkers. For benzylamine the only other value of the heat of formation in the liquid state is the value listed by Kharasch in 1929 of $2.0$ kcal/mol; the more recent value of $8.18$ kcal/mol obtained by Carson and coworkers is preferred. Kharasch listed a value of $-51.9$ kcal/mol for the heat of formation of liquid diisobutylamine, very close to the value of $-52.24$ kcal/mol obtained by Lebedeva and coworkers. Lastly, for the heat of formation of solid triphenylamine an early value of $58.7$ kcal/mol is quoted by Stull, Westrum and Sinke, in fair agreement with the value of $56.1$ kcal/mol obtained by Steele. The latter value is preferred.

### B. The C—N Bond Dissociation Energy

#### 1. Kinetic studies

The C—N bond dissociation energy in amines can, in principle, be obtained by either kinetic or thermochemical methods. However, it will be seen from the review by Batt that there are few definitive kinetic studies on amines. Also, there is still uncertainty regarding the thermochemistry of the amino radicals formed by fission of the C—N bond, as will be discussed later.

Early values of kinetic parameters for C—N bond-breaking processes in amines were obtained using toluene and aniline carrier techniques. Benson and O'Neal noted that the preexponential factors obtained in these experiments were unacceptably low and warned against using the activation energies obtained in this way to determine the heats of formation of the amino radicals thus formed. The most definitive studies on the decomposition of amines appear to be the very-low-pressure pyrolysis (VLPP) studies of Benson, Golden and coworkers. Tsang has made use of the assumption that for amines the crosscombination to combination ratios of the alkyl, aminoalkyl and amino radicals will be equal. Using the measured rate constants for the decomposition of $t$-amylamine he has derived Arrhenius parameters for the C—N bond-breaking reaction of several amines using a derived relationship between the enthalpies and activation energies of related reactions of the amines. He has pointed out that this method of obtaining rate parameters is by no means rigorous, but the derived values serve as a useful first approximation for systems where experimental results are lacking. In Table 11 the activation energies derived by Benson, Golden and coworkers and by Tsang are listed, together with the C—N bond dissociation energies calculated from these.

*Ethylamine can exist in two rotameric forms. The gas and the liquid consist of mixtures of the gauche isomer and the trans isomer, the latter being more stable. Only the trans isomer is present in the crystalline state.
TABLE 11. C—N bond dissociation energies for certain amines from kinetic studies

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$E$ (kcal/mol)</th>
<th>Ref.</th>
<th>$\Delta H^\circ (T)$ (kcal/mol)</th>
<th>$D(C-N)$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_6H_5CH_2NH_2 \rightarrow C_6H_4CH_2 + NH_2$</td>
<td>71.9</td>
<td>83</td>
<td>74.2</td>
<td>73.1</td>
</tr>
<tr>
<td>$C_6H_5CH_2NHCH_3 \rightarrow C_6H_5CH_2 + NHCH_3$</td>
<td>68.7</td>
<td>83</td>
<td>70.9</td>
<td>70.9</td>
</tr>
<tr>
<td>$C_6H_5CH_2N(CH_3) \rightarrow C_6H_5CH_2 + N(CH_3)_2$</td>
<td>60.9</td>
<td>83</td>
<td>62.8</td>
<td>63.1</td>
</tr>
<tr>
<td>$C_6H_5CH_2CH_2NH_2 \rightarrow C_6H_5CH_2 + CH_2NH_2$</td>
<td>63.9</td>
<td>84</td>
<td>66.1</td>
<td>65.5</td>
</tr>
<tr>
<td>$C_6H_5NHCH_3 \rightarrow C_6H_5NH + CH_3$</td>
<td>66.7</td>
<td>85</td>
<td>68.9</td>
<td>68.9</td>
</tr>
<tr>
<td>$C_6H_5N(CH_3) \rightarrow C_6H_5NHCH_3 + CH_3$</td>
<td>64.7</td>
<td>85</td>
<td>66.8</td>
<td>66.6</td>
</tr>
<tr>
<td>$t-C_6H_{11}NH_2 \rightarrow t-C_6H_{11} + NH_2$</td>
<td>78.9</td>
<td>86</td>
<td>81.0</td>
<td>81.5</td>
</tr>
<tr>
<td>$C_2H_3NH_2 \rightarrow C_2H_5 + NH_2$</td>
<td>80.7</td>
<td>86</td>
<td>82.8</td>
<td>82.8</td>
</tr>
<tr>
<td>$t-C_4H_7NH_2 \rightarrow t-C_4H_7 + NH_2$</td>
<td>80.7</td>
<td>86</td>
<td>82.8</td>
<td>82.8</td>
</tr>
<tr>
<td>$t-C_6H_{19}NH_2 \rightarrow t-C_4H_9 + NH_2$</td>
<td>80.1</td>
<td>86</td>
<td>82.2</td>
<td>82.5</td>
</tr>
<tr>
<td>$C_6H_5CH_2NH_2 \rightarrow C_6H_5CH_2 + NH_2$</td>
<td>70.5</td>
<td>86</td>
<td>72.6</td>
<td>71.6</td>
</tr>
</tbody>
</table>

Results using the relationship:

$$E = \Delta H^\circ(T) + R\overline{T}$$

$$\Delta H^\circ(298) = D(C-N) = \Delta H^\circ(T) + \overline{C_p}(298 - \overline{T})$$

Values of $\overline{C_p}$ are calculated using group additivity rules or tabulated values\(^{26}\).

2. Heats of formation of amino radicals

The C—N bond dissociation energies obtained from the kinetic studies may be used to obtain the heats of formation of the various amino radicals formed in these reactions. The heats of formation of amino radicals have been the subject of uncertainty for some time\(^{83}\).

For many years the heat of formation of the amino radical, NH$_2$, was accepted to be 40.1 ± 3 kcal/mol\(^{24}\), a value based on results obtained from the study of the decomposition of hydrazine using the toluene carrier technique, now accepted to give low Arrhenius parameters. Benson and O'Neal\(^{82}\) 'scaled' the kinetic parameters obtained in this study of hydrazine decomposition and in studies of the decomposition of some amines and hydrazine derivatives which produced NH$_2$ radicals using toluene and aniline carriers, to obtain realistic $A$ factors and activation energies for these reactions. They thus deduced C—N bond dissociation energies which allowed them to select a value of 45 kcal/mol for the heat of formation of the amino radical.

The heat of formation of the amino radical may be calculated using the C—N bond dissociation energy obtained from the VLPP study of benzyamine\(^{83}\), knowing the heats of formation of benzylamine and the benzyl radical. A recent determination of the heat of formation of benzylamine\(^{88}\) which used early vapour-pressure results to obtain the heat of vaporization of the compound, yielded $\Delta H^\circ$ for gaseous benzylamine equal to 20.98 kcal/mol, in agreement with the value given by Benson and O'Neal\(^{82}\) of 21.0 kcal/mol. The heat of formation of the benzyl radical is generally accepted to be 45.0 kcal/mol\(^{82}\). This value has recently been questioned, however\(^{86}\). Tsang\(^{37}\) obtained an activation energy of 69.1 kcal/mol.
(1100 K) for the reaction

\[
\text{C}_6\text{H}_5\text{CH}_2\text{CH}(	ext{CH}_3)_2 \rightarrow \text{C}_6\text{H}_5\dot{\text{C}}\text{H}_2 + \dot{\text{C}}\text{H}(	ext{CH}_3)_2
\]

Hence \(\Delta H(1100) = 71.3\) kcal/mol and \(\Delta C_p^\circ = -0.48\) cal/(mol K), whence \(\Delta H_f^\circ\) (benzyl) = 48.9 kcal/mol. The heat of formation of the benzyl radical obtained by Walsh and coworkers\(^8\), of 45 kcal/mol, was based on a study of reactions (6) and (7):

\[
\begin{align*}
\text{I}^+ + \text{C}_6\text{H}_5\text{CH}_3 & \rightarrow \text{C}_6\text{H}_5\dot{\text{C}}\text{H}_2 + \text{H}\text{I} \\
\text{C}_6\text{H}_5\dot{\text{C}}\text{H}_2 + \text{H}\text{I} & \rightarrow \text{I}^+ + \text{C}_6\text{H}_5\text{CH}_3
\end{align*}
\]

A preliminary value of \(E_6\) of 14.4 kcal/mol was obtained. On the basis of an assumed value of \(E_7\) of 1.5 \(\pm\) 1.0 kcal/mol the heat of formation of the benzyl radical was calculated to be 44.9 kcal/mol, assuming that \(\Delta C_p^\circ = 0\) for the reaction. They did not pursue this study to refine their results because the value they obtained agreed well with the kinetic results of Esteban and coworkers\(^8\) and of Szwarc\(^9\). Esteban and coworkers\(^8\) used the aniline carrier technique to examine the decomposition of ethylbenzene and (in more detail) \(n\)-propylbenzene. For the second of these reactions:

\[
\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_3 \rightarrow \text{C}_6\text{H}_5\dot{\text{C}}\text{H}_2 + \dot{\text{C}}\text{H}_2\text{CH}_3
\]

they obtained an activation energy of 68.6 kcal/mol (860–1008 K). On the basis of heats of formation available at that time they obtained \(\Delta H_f^\circ\) (benzyl) = 44.5 kcal/mol. The result of Esteban and coworkers may now be used to calculate \(\Delta H_f^\circ\) (benzyl) using:

\[
\Delta H_f^\circ(T) = E_8 + RT
\]

\[
\Delta H_f^\circ(298) = \Delta H_f^\circ(T) + \Delta C_p\Delta T
\]

and using more recent thermochemical data. From their result, \(\Delta H_f^\circ(930) = 70.7\) kcal/mol. Group additivity gives \(\Delta C_p^\circ = -0.8\) cal/(mol K) and hence \(\Delta H_f^\circ(298) = 71.2\) kcal/mol. Using \(\Delta H_f^\circ\) (\(n\)-propylbenzene) = 1.87 kcal/mol\(^1\) and \(\Delta H_f^\circ\) (\(C_2H_5^+\)) = 26.5 kcal/mol\(^2\) we arrive at \(\Delta H_f^\circ\) (benzyl) = 46.6 kcal/mol. Since the aniline carrier technique has proved to give low activation energies in some systems it seems unlikely that the activation energy quoted by Esteban and coworkers is too high and thus this heat of formation of the benzyl radical should be a lower limit. We select a value of 47.7 \(\pm\) 1.5 kcal/mol for the heat of formation of the benzyl radical, the mean of the values derived from the results of Tsang\(^8\) and Esteban and coworkers\(^9\). If this value for the heat of formation of the benzyl radical is used, the results of Benson, Golden and coworkers from the VLPP study of benzylamine\(^8\) yield a value of 46.4 \(\pm\) 2.0 kcal/mol for the heat of formation of the amino radical.

Tsang\(^8\)\(^6\) study of the shock-tube decomposition of \(t\)-amylamine leads to \(D(C\rightarrow N) = 81.5\) kcal/mol, from which the heat of formation of the amino radical may be calculated to be 44.9 kcal/mol, using heats of formation of \(t\)-amylamine and the \(t\)-amyl radical of –33.9 and 2.7 kcal/mol respectively (from group additivity). Tsang\(^8\)\(^6\) used his result from the decomposition of \(t\)-amylamine to obtain the heat of formation of the amino radical in a rather more complex manner. He compared the activation energies for the two reactions:

\[
\text{t-}C_6\text{H}_{11}\text{NH}_2 \rightarrow \text{t-}C_6\text{H}_{11}^+ + \text{NH}_2
\]
24. Thermochemistry of nitro compounds, amines and nitroso compounds

\[ t-\text{C}_9\text{H}_{11}\text{CH}_3 \rightarrow t-\text{C}_9\text{H}_{11}^+ + \text{CH}_3 \]  

(10)

and assumed that for these reactions

\[ E_9 - E_{10} = \Delta H_f^0(\text{NH}_2) - \Delta H_f^0(\text{CH}_3) - [\Delta H_f^0(t-\text{C}_9\text{H}_{11}\text{NH}_2) - \Delta H_f^0(t-\text{C}_9\text{H}_{11}\text{CH}_3)] \]  

(D)

whence

\[ 78.9 - 81.5 = \Delta H_f^0(\text{NH}_2) - \Delta H_f^0(\text{CH}_3) - (33.9 + 44.75) \]

giving \( \Delta H_f^0(\text{NH}_2) \) at 298 K = 43.4 kcal/mol. No heat capacity changes are included and thus the result obtained may be subject to considerable uncertainty. The result for \( \Delta H_f^0(\text{NH}_2) \) derived earlier from Tsang’s result in the more straightforward way is likely to be more reliable.

Values of the heat of formation of the amino radical have been obtained from systems other than the C—N bond-breaking reactions of hydrazines and amines. For the reaction (11):

\[ \text{NH}_2^- + \text{H}_2 \rightarrow \text{H}^- + \text{NH}_3 \]

(11)

the equilibrium constant has been measured by Bohme and coworkers. From their result a value of \( \Delta H_f^0(298) \) for the reaction of \( -3.2 \pm 0.3 \) kcal/mol was obtained. Using the measured electron affinities of the hydrogen atom and the amino radical \( \bar{D}(\text{NH}_2^- - \text{H}) \) was calculated to be 107.4 \pm 1.1 kcal/mol, and hence a value of 44.3 \pm 1.1 kcal/mol for \( \Delta H_f^0(\text{NH}_2) \) was obtained. The activation energy for the reaction (12):

\[ \text{O} + \text{NH}_3 \rightarrow \text{NH}_2 + \text{OH} \]

(12)

was measured over the temperature range 361–677 K by Kurylo and coworkers. They found \( E_{12} = 6.6 \pm 0.1 \) kcal/mol. Assuming zero activation energy for the reverse of this process \( \Delta H_{12}^o(520) \) is calculated to be 7.6 kcal/mol, which yields \( \Delta H_f^0(298) = 7.4 \) kcal/mol, when heat capacity corrections are made. Thus the heat of formation of the amino radical is calculated to be 46.6 \pm 0.4 kcal/mol.

Franklin and Sharma measured the appearance potential of the methyl ion for the process (13):

\[ \text{CH}_3\text{NH}_2 \rightarrow \text{CH}_3^+ + \text{NH}_2^- + e^- \]

(13)

After making a correction for excess energy they obtained \( \Delta H_f^0(\text{NH}_2) = 41 \) kcal/mol, but considered that the appearance potential might be in error. Applying the correction for excess energy to an earlier appearance potential obtained by Haney and Franklin they obtained \( \Delta H_f^0(\text{NH}_2) = 46 \) kcal/mol.

It will be seen from the foregoing compilation of results for the heat of formation of the amino radical that there is no clear consensus over the value of \( \Delta H_f^0(\text{NH}_2) \). What does seem clear, however, is that the value of this quantity quoted by JANAF is undoubtedly too low. The most reliable value will be that based upon the most accurate measurements and most reliable ancillary heats of formation. The method of Benson, Golden and coworkers offers an elegant route to accurate activation energies. It is therefore unfortunate that there is still some uncertainty associated with the heat of formation of the benzyl radical – a VLPP study of, say, \( \alpha \)-propylbenzene would help to clear up this uncertainty. The value of \( \Delta H_f^0(\text{NH}_2) \) of 46.6 \pm 0.4 kcal/mol which results from the study by Kurylo and coworkers would be expected to be reliable, since the heats of formation of O, NH$_3$ and OH are well known. Their result is in excellent agreement with the value derived from the result of Benson, Golden and coworkers. We therefore select a value of
46.6 ± 2.0 kcal/mol for the heat of formation of the amino radical. On the basis of this value for $\Delta H^\circ (\text{NH}_2)$, the first bond dissociation energy in ammonia is estimated to be 109.7 kcal/mol, which seems to be reasonable when compared with the C—H bond dissociation energy in methane of 104 kcal/mol.

For the heat of formation of the methylamino radical, CH$_3$NH, the value recommended by JANAF$^{24}$ is 34.5 kcal/mol. Benson and O'Neal$^{82}$ derived a value of 41.7 kcal/mol for the heat of formation of the radical, based on adjustment of kinetic results on the decomposition of N-methylbenzylamine and methylhydrazine obtained using the toluene carrier technique, similarly to the adjustments described previously for amino radical systems.

Franklin and Sharma$^{93}$ obtained a value for the heat of formation of the methylamino radical of 43.6 kcal/mol from the appearance potential of the methyl ion in the reaction (14):

$$\text{(CH}_3\text{)}_2\text{NH} \longrightarrow \text{CH}_3^+ + \text{CH}_3\text{NH} + \text{e}^- \quad (14)$$
corrected for excess energy.

Golden and coworkers' value of 68.7 kcal/mol for the activation energy for the reaction (15)$^{83}$:

$$\text{C}_6\text{H}_5\text{CH}_2\text{NHCH}_3 \longrightarrow \text{C}_6\text{H}_5\text{CH}_2 + \text{CH}_3\text{NH} \quad (15)$$
leads to $\Delta H^\circ (1100 \text{ K}) = 70.9$ kcal/mol. With $\Delta C_p = 0$ cal/(mol K), $\Delta H^\circ (298) = 70.9$ kcal/mol, and so using $\Delta H_f$ (benzyl) = 47.7 kcal/mol and $\Delta H_f$ (N-methylbenzylamine) = 21.5 kcal/mol (by group additivity), we obtain $\Delta H^\circ (\text{CH}_3\text{NH}) = 44.7 \pm 2.0$ kcal/mol, a full 10 kcal higher than that previously accepted, and this value is selected. This result leads to a value of 102.3 kcal/mol for the N—H bond dissociation energy in methylamine, compared with the value of the C—H bond dissociation energy in ethane of 98 kcal/mol$^{26}$.

For the heat of formation of the dimethylamino radical Benson and O'Neal$^{82}$ selected a value of 37.4 kcal/mol to explain the adjusted parameters obtained by them from early kinetic results on 1,1-dimethylhydrazine. Franklin and Sharma$^{93}$ used the appearance potential of the methyl ion for the process (16):

$$\text{(CH}_3\text{)}_3\text{N} \longrightarrow \text{CH}_3^+ + (\text{CH}_3\text{)}_2\text{N} + \text{e}^- \quad (16)$$
to deduce $\Delta H^\circ$ for the dimethylamino radical to be 39 kcal/mol. The results of Golden and coworkers$^{83}$ on the decomposition of N,N-dimethylbenzylamine, leading to $\Delta H^\circ (298) = 63.1$ kcal/mol for the process (17):

$$\text{C}_6\text{H}_5\text{CH}_2\text{N(CH}_3\text{)}_2 \longrightarrow \text{C}_6\text{H}_5\text{CH}_2 + \text{N(CH}_3\text{)}_2 \quad (17)$$
together with $\Delta H^\circ (\text{N,N-dimethylbenzylamine}) = 26.25$ kcal/mol (by group additivity) and $\Delta H^\circ (\text{benzyl}) = 47.7$ kcal/mol, lead to $\Delta H^\circ [\text{N(CH}_3\text{)}_2] = 41.6 \pm 2.0$ kcal/mol. Using this preferred value we may calculate the N—H bond dissociation energy in dimethylamine to be 98.2 kcal/mol. This value seems reasonable when compared with the secondary C—H bond dissociation energy in propane of 94.5 kcal/mol$^{26}$.

For the heat of formation of the aminomethyl radical, CH$_2$NH$_2$, Benson$^{26}$ selects a value of 33.5 kcal/mol. Franklin and Sharma$^{93}$ measured the appearance potential of the methyl ion for the process (18):

$$\text{C}_2\text{H}_5\text{NH}_2 \longrightarrow \text{CH}_3^+ + \text{CH}_2\text{NH}_2 + \text{e}^- \quad (18)$$
and hence derived $\Delta H^\circ (\text{CH}_2\text{NH}_2) = 43$ kcal/mol. In a VLP$^{2}$ study, Colussi and Benson$^{84}$ obtained a value of 63.9 kcal/mol for the high-pressure activation energy
for the reaction (19):

\[
\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2 \rightarrow \text{C}_6\text{H}_5\dot{\text{C}}\text{H}_2 + \dot{\text{CH}}_2\text{NH}_2 \quad (19)
\]

over the temperature range 960–1245 K. Hence \(\Delta H_{190}^{o}(1100 \text{ K}) = 66.1 \text{ kcal/mol}\), and making a heat capacity correction of \(\Delta C_p = 0.7 \text{ cal/(deg mol)}\), \(\Delta H_{19}(298) = 65.5 \text{ kcal/mol}\). Then using heats of formation of 2-phenylethylamine and the benzyl radical of 15.84 and 47.7 kcal/mol respectively we obtain \(\Delta H_{19}^{o}(\text{CH}_2\text{NH}_2) = 33.3 \pm 2.0 \text{ kcal/mol}\), in exact agreement with the value selected by Benson.26

This value is considerably lower than the value quoted by Colussi and Benson, who used \(\Delta H_{19}^{o}(\text{benzyl}) = 44.2 \text{ kcal/mol}\), now believed to be too low, to obtain \(\Delta H_{19}^{o}(\text{CH}_2\text{NH}_2) = 37.0 \text{ kcal/mol}\). The value of 33.3 kcal/mol is nearly 10 kcal/mol lower than the value of Franklin and Sharma, and it is suspected that the appearance potential work may be in error. The aminomethyl radical is believed to be stabilized by interaction between the half-filled molecular orbital of the carbon atom and the nitrogen lone pair.95 This stabilization of the radical leads to lowering of the C—H bond strength in amines compared with ethane: using \(\Delta H_{19}^{o}(\text{CH}_2\text{NH}_2) = 33.3 \pm 2.0 \text{ kcal/mol}\) we obtain \(D(\text{C—H})\) for methylamine equal to 91 ± 2 kcal/mol, compared with the C—H bond dissociation energy in ethane of 98 kcal/mol. Thus in methylamine the C—H bond is weaker than the N—H bond by ~11 kcal/mol.

Franklin and Sharma93 measured appearance potentials for the processes (20) and (21):

\[
\begin{align*}
(\text{C}_2\text{H}_5)_2\text{NH} & \rightarrow \text{CH}_3^+ + \dot{\text{C}}\text{H}_2\text{N}(\text{C}_2\text{H}_5)\text{H} + e^- \quad (20) \\
(\text{C}_2\text{H}_5)_3\text{N} & \rightarrow \text{CH}_3^+ + \dot{\text{C}}\text{H}_2\text{N}(\text{C}_2\text{H}_5)_2 + e^- \quad (21)
\end{align*}
\]

from which they obtained heats of formation of 37 and 23 kcal/mol for the \(\text{CH}_2\text{N}(\text{C}_2\text{H}_5)\text{H}\) and \(\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\) radicals respectively, but they do not consider these values to be very satisfactory. A rough group additivity calculation using the approximation that \(\dot{\text{C}}\) is equivalent to \(\text{C}\) and that \(\text{N}\) is equivalent to \(\text{C}\), predicts a value of 34.4 kcal/mol for the first of these radicals and 26.6 kcal/mol for the second: reasonable agreement in both cases. It seems overall that the use of appearance potentials to obtain radical heats of formation is still beset by problems, so that reliable heats of formation cannot yet be obtained in this way.

In a further VLPP study of the decomposition of aromatic amines, Colussi and Benson85 obtained high pressure activation energies for the reactions (22) and (23):

\[
\begin{align*}
\text{C}_6\text{H}_5\text{NHCH}_3 & \rightarrow \text{C}_6\text{H}_5\dot{\text{N}}\text{H} + \dot{\text{CH}}_3 \quad (22) \\
\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2 & \rightarrow \text{C}_6\text{H}_5\dot{\text{N}}\text{CH}_3 + \dot{\text{CH}}_3 \quad (23)
\end{align*}
\]

of 66.7 and 64.7 kcal/mol respectively, giving \(\Delta H_{22}(1100 \text{ K}) = 68.9 \text{ kcal/mol}\) for the first of these reactions and \(\Delta H_{23}(1070 \text{ K}) = 66.8 \text{ kcal/mol}\) for the second. No heat capacity correction is needed for the first reaction40, so \(\Delta H_{22}(298) = 68.9 \text{ kcal/mol}\). Using \(\Delta H_{19}^{o}(\text{N-methylaniline}) = 20.4 \text{ kcal/mol}\)3 and \(\Delta H_{19}^{o}(\text{CH}_3) = 35.1 \text{ kcal/mol}\)25 a value of 54.2 kcal/mol for the heat of formation of the anilino radical is obtained. This value is lower than that obtained by Colussi and Benson because they used \(\Delta H_{19}^{o}(\text{CH}_3) = 34.3 \text{ kcal/mol}\) which now appears to be too low. Using the value of 54.2 kcal/mol for the heat of formation of the anilino radical and using the heat of formation of aniline (20.76 kcal/mol)3 the N—H bond dissociation energy is calculated to be 85.5 kcal/mol, compared with that in methylamine of 102.4 kcal/mol (see above). For the second
reaction $\Delta C_p^o = 0.25$ cal/(mol K) and thus $\Delta H_{298}^o(\text{N,N-dimethylaniline}) = 20.1$ kcal/mol and $\Delta H_{298}^o(\text{CH}_3) = 35.1$ kcal/mol$^{25}$, the heat of formation of the N-methylanilino radical is calculated to be 51.6 kcal/mol, again lower than the value of Colussi and Benson, who found $\Delta H_{298}^o(\text{N-methylanilino}) = 53.2 \pm 2.0$ kcal/mol, using the earlier value of $\Delta H_{298}^o(\text{CH}_3)$ and making a different correction for $\Delta C_p^o$.

Using the value of 51.6 kcal/mol for the heat of formation of the N-methylanilino radical the N—H bond dissociation energy in N-methylaniline may be calculated. Using $\Delta H_{298}^o(\text{N-methylaniline}) = 20.4$ kcal/mol$^3$, $D(\text{N—H})$ for N-methylaniline is calculated to be 83.3 kcal/mol, 2.2 kcal/mol less than that in aniline, showing that N-methyl substitution has very little effect on the N—H bond strength in anilines.

The heats of formation of the various amino radicals derived here from the kinetic studies discussed are summarized in Table 12. The errors quoted represent estimates of uncertainties in thermochemical data and activation energies.

3. The C—N bond dissociation energy from thermochemical results

The heats of formation of the various amino radicals may be used together with published heats of formation of the amines and alkyl radicals to obtain C—N bond dissociation energies for a number of amines. In Table 13 C—N bond dissociation energies calculated using the most recently published heats of formation of the amine, the heat of formation of the relevant amino radical as selected above and the heat of formation of the alkyl radical given by Benson or calculated using group additivity$^{26}$ are listed. Where kinetic studies have been carried out or kinetic arguments have been used to derive activation energies for C—N fission, the bond dissociation energies calculated from these results are given also, for comparison.

It may be seen that for primary alkylamines, except methylamine and the strained cyclic amines cyclopropylamine and cyclobutylamine, the C—N bond strength is 84.2 ± 1.3 kcal/mol, independent of R. The C—N bond dissociation energy is calculated to be 3 kcal/mol higher than this in methylamine, where the alkyl radical formed has no alkyl groups attached to the radical centre to stabilize the radical by inductive effects. The higher C—N bond strength in cyclopropylamine and cyclobutylamine may be a reflection of the uncertainties in the heats of formation of the cyclic alkyl radicals$^{26}$ which may be too high. The calculations of Tsang$^6$ give C—N bond dissociation energies which are considerably lower than the thermochemical values by around 1.5 kcal/mol, except for methylamine for which the discrepancy is greater. This may suggest that the combination reactions between NH$_2$ and the alkyl radicals have a small activation energy, or may indicate a flaw in Tsang's method.

For the secondary alkylamines the C—N bond strengths are 1.9 to 3.9 kcal/mol lower than for the corresponding primary amines. Again the first member of the

<table>
<thead>
<tr>
<th>Radical</th>
<th>$\Delta H_{298}^o$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH$_3$</td>
<td>46.6 ± 2.0</td>
</tr>
<tr>
<td>CH$_3$NH</td>
<td>44.7 ± 2.0</td>
</tr>
<tr>
<td>(CH$_3$)$_2$N</td>
<td>41.6 ± 2.0</td>
</tr>
<tr>
<td>CH$_2$NH$_2$</td>
<td>33.3 ± 2.0</td>
</tr>
<tr>
<td>C$_6$H$_5$NH</td>
<td>54.2 ± 2.0</td>
</tr>
<tr>
<td>C$_6$H$_5$NCH$_3$</td>
<td>51.6 ± 2.0</td>
</tr>
</tbody>
</table>
TABLE 13. C—N bond dissociation energies in amines obtained from kinetic studies and calculated from the thermochemistry

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$D(C-N)$(thermochemical) (kcal/mol)</th>
<th>$E$ (kcal/mol)</th>
<th>$D(C-N)$(kinetic) (kcal/mol)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$NH$_2$ $\rightarrow$ CH$_3$ + NH$_2$</td>
<td>87.2</td>
<td>83.8</td>
<td>83.0</td>
<td>86</td>
</tr>
<tr>
<td>C$_2$H$_5$NH$_2$ $\rightarrow$ C$_2$H$_5$' + NH$_2$</td>
<td>84.4</td>
<td>80.7</td>
<td>82.8</td>
<td>86</td>
</tr>
<tr>
<td>n-C$_3$H$_7$NH$_2$ $\rightarrow$ n-C$_3$H$_7$' + NH$_2$</td>
<td>84.4</td>
<td>80.7</td>
<td>82.8</td>
<td>86</td>
</tr>
<tr>
<td>i-C$_3$H$_7$NH$_2$ $\rightarrow$ i-C$_3$H$_7$' + NH$_2$</td>
<td>84.2</td>
<td>80.7</td>
<td>82.8</td>
<td>86</td>
</tr>
<tr>
<td>c-C$_3$H$_7$NH$_2$ $\rightarrow$ c-C$_3$H$_7$' + NH$_2$</td>
<td>94.2 $\pm 6^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-C$_4$H$_9$NH$_2$ $\rightarrow$ n-C$_4$H$_9$' + NH$_2$</td>
<td>85.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-C$_4$H$_9$NH$_2$ $\rightarrow$ t-C$_4$H$_9$' + NH$_2$</td>
<td>83.9</td>
<td>80.1</td>
<td>82.5</td>
<td>86</td>
</tr>
<tr>
<td>c-C$_4$H$_9$NH$_2$ $\rightarrow$ c-C$_4$H$_9$' + NH$_2$</td>
<td>87.8$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i-C$<em>5$H$</em>{11}$NH$_2$ $\rightarrow$ i-C$<em>5$H$</em>{11}$' + NH$_2$</td>
<td>83.0</td>
<td>78.9</td>
<td>81.5</td>
<td>86</td>
</tr>
<tr>
<td>c-C$<em>7$H$</em>{15}$NH$_2$ $\rightarrow$ c-C$<em>7$H$</em>{15}$' + NH$_2$</td>
<td>83.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-C$<em>7$H$</em>{15}$NH$_2$ $\rightarrow$ n-C$<em>7$H$</em>{15}$' + NH$_2$</td>
<td>84.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-C$<em>6$H$</em>{11}$NH$_2$ $\rightarrow$ c-C$<em>6$H$</em>{11}$ + NH$_2$</td>
<td>84.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_6$H$_5$NH$_2$ $\rightarrow$ C$_6$H$_5$' + NH$_2$</td>
<td>104.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_6$H$_5$CH$_2$NH$_2$ $\rightarrow$ C$_6$H$_5$CH$_2$' + NH$_2$</td>
<td>73.2</td>
<td>70.5</td>
<td>71.6</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>73.2</td>
<td>71.9</td>
<td>73.1</td>
<td>83</td>
</tr>
<tr>
<td>Reaction</td>
<td>$D(C-N)$(thermochemical) (kcal/mol)</td>
<td>$E$ (kcal/mol)</td>
<td>$D(C-N)$(kinetic) (kcal/mol)</td>
<td>Reference</td>
</tr>
<tr>
<td>----------</td>
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<td>----------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Secondary amines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(CH_3)_2NH \rightarrow \hat{CH}_3 + CH_3\hat{NH}$</td>
<td>82.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(CH_3)_2NH \rightarrow C_2H_5^+ + C_2H_3\hat{NH}$</td>
<td>82.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(i-C_3H_7)_2NH \rightarrow i-C_3H_7^+ + i-C_3H_7\hat{NH}$</td>
<td>82.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(n-C_4H_9)_2NH \rightarrow n-C_4H_9^+ + n-C_4H_9\hat{NH}$</td>
<td>81.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(i-C_3H_7)_2NH \rightarrow i-C_3H_7^+ + i-C_3H_7\hat{NH}$</td>
<td>81.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(i-C_4H_9)(n-C_4H_9)NH \rightarrow i-C_4H_9^+ + n-C_4H_9\hat{NH}$</td>
<td>82.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_6H_5CH_2NHCH_3 \rightarrow C_6H_5\hat{CH}_3 + \hat{NH}CH_3$</td>
<td>70.9</td>
<td>68.7</td>
<td>70.9</td>
<td>83</td>
</tr>
<tr>
<td>$C_6H_5NHCH_3 \rightarrow C_6H_5\hat{NH} + \hat{CH}_3$</td>
<td>68.9</td>
<td>66.7</td>
<td>68.9</td>
<td>85</td>
</tr>
<tr>
<td>$\rightarrow C_6H_5^+ + NHCH_3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(C_6H_5)_2NH \rightarrow C_6H_5^+ + C_6H_5\hat{NH}$</td>
<td>78.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tertiary amines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(CH_3)_3N \rightarrow (CH_3)_2\hat{N} + \hat{CH}_3$</td>
<td>82.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(CH_3)_3N \rightarrow (CH_3)_2\hat{N} + C_2H_5^+$</td>
<td>79.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_6H_5CH_2N(CH_3)_2 \rightarrow C_6H_5\hat{CH}_3 + \hat{N}(CH_3)_2$</td>
<td>63.1</td>
<td>60.9</td>
<td>63.1</td>
<td>83</td>
</tr>
<tr>
<td>$C_6H_5N(CH_3)_2 \rightarrow C_6H_5\hat{N}CH_3 + \hat{CH}_3$</td>
<td>66.6</td>
<td>64.7</td>
<td>66.6</td>
<td>85</td>
</tr>
<tr>
<td>$\rightarrow C_6H_5^+ + \hat{N}(CH_3)_2$</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Using $\Delta H^0$ (cyclopropyl) = 66 ± 6 kcal/mol calculated by Benson. A value of 94.2 kcal/mol is obtained for the C—N bond dissociation energy; using $\Delta H^0$ (cyclopropyl) = 55.2 kcal/mol calculated by group additivity, with a strain energy of 27.6 kcal/mol the resulting $D(C-N)$ is 83.4 kcal/mol.

*b Using $\Delta H^0$ (cyclobutyl) = 51 kcal/mol, listed by Benson. A value of 87.8 kcal/mol is obtained; using $\Delta H^0$ (cyclobutyl) = 48.8 kcal/mol calculated by group additivity, with a strain energy of 26.2 kcal/mol the resulting $D(C-N)$ is 85.6 kcal/mol.

*Approximate values. Heat of formation of the alkylamino radicals calculated assuming $D(N-H)$ in methylamine = $D(N-H)$ in RNH$_2$, i.e. 102.4 kcal/mol (see text).

*Thermochemical $D(C-N)$ and kinetic $D(C-N)$ are equal because kinetic value was used to determine the heat of formation of the relevant amino radical.
series, dimethylamine, has a higher C—N bond strength than the higher members of the series. The C—N bond strength for the secondary amines is 82 ± 1 kcal/mol. For the tertiary alkylamines only two C—N bond strengths can be calculated. Again, the value for the methylamine is higher than for the higher alkylamine by ~3 kcal/mol.

It would be predicted, on the assumption that the C—N bond strength is unaffected by the nature of R for groups other than methyl, that for tertiary alkylamines $D(C-N)$ would be 79 ± 1 kcal/mol. Thus we see a gradual weakening of the C—N bond in alkylamines in going from primary to secondary to tertiary amines of approximately 84 to 82 to 79 kcal/mol. The C—N bond strength is considerably lower, by more than 11 kcal/mol, where one of the product radicals is capable of being stabilized by conjugation, as in the case of benzylamine, $N$-methylbenzylamine and $N,N$-dimethyl benzylamine, where benzyl radicals are formed, and $N$-methylaniline and $N,N$-dimethylaniline, where anilino radicals are formed. Conversely, the C—N bond strength is increased by around 20 kcal/mol in aniline which is stabilized by resonance:

Likewise, in $N$-methylaniline and $N,N$-dimethylaniline the aryl carbon–nitrogen bond is strengthened by this resonance. In all these cases fission of the (strengthened) aryl C—N bond is made less favourable by the fact that the phenyl radical, which is incapable of stabilization by resonance, is formed. In the case of diphenylamine, which is resonance-stabilized, a radical capable of resonance stabilization (anilino) and one incapable of stabilization (phenyl) are formed. Interestingly these effects seem to balance out so that the C—N bond strength is not far away from that in other secondary amines, at 78.5 kcal/mol.

It is partly because in many amines the C—N bond strength is comparable to that of C—C bonds in the molecule that the decomposition of certain amines is complex and hence the kinetics are not yet well understood.

IV. C-NITROSO COMPOUNDS

In contrast to nitro compounds and amines, very few studies have been carried out on the thermochemistry of C-nitroso compounds, despite the importance of this subject. In systems where nitric oxide is used as a trap for alkyl radicals$^2$ the C—N bond strength is an important quantity. The lack of information on the thermochemistry of these compounds is due to:

1. the tendency of these compounds to dimerize:

$$2 RNO \rightleftharpoons R\equiv N\equiv O \quad \text{or} \quad R\equiv N\equiv O$$

(1) the reactivity of primary and secondary nitrosoalkanes towards isomerization to the oxime, e.g.:

$$\text{CH}_3\text{NO} \longrightarrow \text{CH}_2\text{NOH}$$
At the time of the reviews by Cox and Pilcher and Stull, Westrum and Sinke there had been no determination of the heat of formation of any gaseous monomeric nitroso compound. Stull, Westrum and Sinke list a value for the heat of formation of solid nitrosobenzene of $-7.0$ kcal/mol. Evans, Fairbrother and Skinner carried out a combustion study of the cis dimer of solid nitroisobutane (2-methyl-1-nitrosopropane) and obtained a heat of formation for the solid dimer of $-46.2 \pm 1$ kcal/mol. For the trans dimer of nitrosocyclohexane they obtained an approximate value of $57.7 \pm 8$ kcal/mol for the solid. Médard and Thomas obtained the heat of formation of solid $p$-nitrosodiphenylamine in a bomb calorimetry experiment: they found a value of $50.93 \pm 0.80$ kcal/mol for the solid compound.

Heats of formation of gaseous monomeric nitroso compounds may be determined (a) by obtaining the heat of formation of the solid dimer and knowing the enthalpy change $\Delta H_{298}^\circ$ for the reaction

\[ (\text{RNO})_2 \rightarrow 2 \text{RNO} \]  

or (b) by obtaining a value for the C—N bond strength of the nitroso compound either from the kinetics of the decomposition:

\[ \text{RNO} \rightarrow \text{R} + \text{NO} \]  

or from electron impact studies which yield the C—N bond dissociation energy, whence:

\[ \Delta H_{298}^\circ(\text{RNO}) = \Delta H_{298}^\circ(\text{R}) + \Delta H_{298}^\circ(\text{NO}) - D(C—N) \]

Thus Benson and coworkers derived approximate group values for C-nitrosoalkanes on the basis of a 'judicious guess' that the C—N bond strength in secondary nitrosoalkanes was equal to 37 kcal/mol, and estimated C—N bond strengths in primary and tertiary nitrosoalkanes of 38.5 and 35.5 kcal/mol respectively. In the next section heats of formation of C-nitroso compounds determined by method (a) will be reviewed, while in the following two sections results which yield C—N bond dissociation energies in C-nitroso compounds will be discussed.

### A. Calorimetric Studies

Batt and Milnegn carried out a bomb calorimetric study on the trans dimer of nitrosomethane, from which they obtained a value of $+0.2 \pm 0.4$ kcal/mol for the heat of formation of the solid dimer. Earlier vapour pressure data led to a value for the heat of sublimation of the compound and hence they determined the heat of formation of the gaseous dimer to be $16.9 \pm 1$ kcal/mol. Using the enthalpy change for the equilibrium (26):

\[ \text{trans-}(\text{CH}_3\text{NO})_2 \rightleftharpoons 2 \text{CH}_3\text{NO} \]  

obtained by Christie and coworkers, they estimated a value of $16.7 \pm 0.8$ kcal/mol for the heat of formation of gaseous monomeric nitrosomethane. This value may be used to obtain the C—N bond dissociation energy in nitrosomethane:

\[ \Delta H_{298}^\circ = D(C—N) = \Delta H_{298}^\circ(\text{CH}_3) + \Delta H_{298}^\circ(\text{NO}) - \Delta H_{298}^\circ(\text{CH}_3\text{NO}) \]

\[ = 35.1 + 21.6 - 16.7 \]

\[ = 40.0 \pm 0.8 \text{ kcal/mol} \]

Pepekin and coworkers carried out a calorimetric study on dimeric 2-methyl-2-nitrosopropane and nitrosobenzene. For the first of these compounds
24. Thermochemistry of nitro compounds, amines and nitroso compounds

they carried out only two experiments to obtain the heat of combustion, which yielded a heat of formation of solid dimeric 2-methyl-2-nitrosopropane of \(-50.1 \pm 0.4 \text{ kcal/mol}\). Coupled with a value of \(18.2 \pm 0.2 \text{ kcal/mol}\) for the heat of sublimation of the compound, this yielded a value of \(-31.9 \pm 0.6 \text{ kcal/mol}\) for the heat of formation of the gaseous dimer of 2-methyl-2-nitrosopropane. Pepekin and coworkers assumed a value of \(+25.6 \text{ kcal/mol}\) for the enthalpy change for the reaction (27):

\[
(t-C_4H_9NO)_2 \rightarrow 2 t-C_4H_9NO \quad (27)
\]

on the basis of the result of Batt and coworkers\(^{101}\), who studied the decomposition of the \textit{trans} dimer of 2-methyl-1-nitrosopropane. They obtained an activation energy of 25.6 kcal/mol for the reaction (28):

\[
(i-C_4H_9NO)_2 \rightarrow 2 i-C_4H_9NO \quad (28)
\]

The reverse of this process would however be expected to have a small activation energy and thus the enthalpy change would not be equal to the activation energy for the decomposition. No information exists on the equilibrium constant for the equilibrium (29):

\[
(i-C_4H_9NO)_2 \rightleftharpoons 2 i-C_4H_9NO \quad (29)
\]

but we may estimate a value of \(4.6 \pm 1.0 \text{ kcal/mol}\) for the enthalpy of the dimerization reaction by analogy with the nitrosomethane equilibrium\(^{99}\). Thus

\[
\Delta H_{29}^0 = E_{28} - E_{30} + R\bar{T} = 25.6 - 4.6 + 0.8 = 21.8 \pm 1.0 \text{ kcal/mol at 385 K}
\]

Assuming heat capacity corrections to be negligible and assuming that the enthalpy changes for dimerization for the two isomers are equal, we may calculate the heat of formation of gaseous monomeric 2-methyl-2-nitrosopropane to be \(-5.0 \pm 1.6 \text{ kcal/mol}\). This value must be considered to be subject to considerable uncertainty, bearing in mind the assumptions made and the number of combustion experiments carried out. Using the value of \(-5.0 \text{ kcal/mol}\) for the heat of formation of gaseous monomeric 2-methyl-2-nitrosopropane, the C—N bond dissociation energy in this compound may be calculated to be \(37 \pm 2 \text{ kcal/mol}\), using a value of 10.5 kcal/mol for the heat of formation of the \(t\)-butyl radical\(^{26}\).

Pepekin and coworkers\(^{100}\) also considered how the result of Evans and coworkers\(^{96}\) on the heat of formation of solid dimeric 2-methyl-1-nitrosopropane could be used to obtain the heat of formation of the gaseous monomer. If it is assumed that the heats of sublimation of the two isomeric solid dimers are equal (18.2 \pm 0.2 kcal/mol), a value of \(-28.0 \pm 1.2 \text{ kcal/mol}\) for the heat of formation of gaseous dimeric 2-methyl-1-nitrosopropane is obtained. Using the result of Batt and coworkers\(^{101}\) to obtain the enthalpy change for dimerization as above \((-21.8 \pm 1.0 \text{ kcal/mol})\), the heat of formation of the gaseous monomeric compound is estimated to be \(-31.8 \pm 2.2 \text{ kcal/mol}\). On this basis and using a value of 13.7 kcal/mol for the heat of formation of the \(i\)-butyl radical\(^{26}\), the C—N bond dissociation energy in 2-methyl-1-nitrosopropane is calculated to be \(38.4 \pm 2.2 \text{ kcal/mol}\).

Pepekin and coworkers carried out seven combustion experiments on dimeric nitrosobenzene from which they calculated a value of \(57.7 \pm 0.5 \text{ kcal/mol}\) for the heat of formation of the solid compound\(^{100}\). They determined the heat of
sublimation to be $20.8 \pm 0.2 \text{kcal/mol}$ from which they calculated the heat of formation of the gaseous dimer to be $78.5 \pm 0.7 \text{kcal/mol}$. No information exists on the equilibrium constant for the equilibrium (31):

$$
(C_6H_5NO)_2 \leftrightarrow 2 C_6H_5NO \quad (31)
$$

Pepekin's group assume a value of $24.5 \text{kcal/mol}$ for the enthalpy of the process (32):

$$
(C_6H_5NO)_2 \rightarrow 2 C_6H_5NO \quad (32)
$$
on the basis of the results of Batt and coworkers$^{101}$ on dimeric nitrosoalkanes. It is difficult to see how they arrived at this value, which seems to be too high. Using this value, however, they calculated the heat of formation of gaseous monomeric nitrosobenzene to be $51.5 \pm 2.0 \text{kcal/mol}$. Hence the C—N bond dissociation energy may be calculated to be $48.6 \pm 2.0 \text{kcal/mol}$, using a value of $78.5 \text{kcal/mol}$ for the heat of formation of the phenyl radical$^{26}$.

It is clear that while some progress has been made since the reviews of Cox and Pilcher$^4$ and Stull, Westrum and Sinke$^3$, there is still a lack of information on the thermochemistry of C-nitroso compounds, because not only do combustion experiments have to be carried out on the dimeric compounds, but a value for the enthalpy change for the reaction:

$$
(RNO)_2 \rightarrow 2 RNO
$$
is also required. The heat of formation of nitrosomethane$^{98}$ is now firmly established, but the heats of formation of the other nitroso compounds obtained by Pepekin and coworkers$^{100}$ are based on too many assumptions to be reliable. Thus it is not possible to improve upon the group values for nitroso compounds of Benson and coworkers$^1$ using these more recent results.

### B. Electron Impact Studies

C—N bond dissociation energies in C-nitroso compounds have been determined using electron impact methods$^{102,103}$. The bond dissociation energy $D(R—NO)$ was obtained from the appearance potential $(AP)$ of the alkyl ion or NO$^+$ ion in some cases, and the ionization potential $(IP)$ of the radical using the relationship

$$
D(R—NO) = AP(R^+) \text{ or } (NO^+) - IP(R)
$$

The results they obtained are listed in Table 14.

### C. Kinetic Studies

Early studies of the decomposition of nitrosoalkanes were beset by difficulties of heterogeneous decomposition and secondary reactions$^{104,105}$ so that it was not possible to isolate the reaction (25):

$$
RNO \rightarrow \cdot R + NO \quad (25)
$$

and obtain an activation energy from which the C—N bond dissociation energy could be obtained. More recent techniques have allowed this initial step to be isolated.

Glänzer, Maier and Troe$^{106}$ carried out a shock wave study of the decomposition of trifluoronitrosomethane in the fall-off region. They found that their results were
TABLE 14. C—N bond dissociation energies obtained from electron impact measurements

<table>
<thead>
<tr>
<th>Compound</th>
<th>$D(R—NO)$ (kcal/mol)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i$-C$_3$H$_7$NO</td>
<td>36.5 ± 3</td>
<td>102</td>
</tr>
<tr>
<td>$r$-C$_4$H$_9$NO</td>
<td>34 ± 3; 46 ± 3$^a$</td>
<td>102</td>
</tr>
<tr>
<td>$t$-C$_3$H$_7$NO</td>
<td>36 ± 3</td>
<td>102</td>
</tr>
<tr>
<td>C$_6$H$_5$NO</td>
<td>41 ± 3</td>
<td>102</td>
</tr>
<tr>
<td>CF$_3$NO</td>
<td>31 ± 3</td>
<td>103</td>
</tr>
<tr>
<td>CCl$_3$NO</td>
<td>32 ± 3</td>
<td>103</td>
</tr>
<tr>
<td>C$_6$F$_5$NO</td>
<td>62 ± 5$^b$</td>
<td>103</td>
</tr>
</tbody>
</table>

$^a$The higher value for the bond dissociation energy arises from the use of a more recent value of the ionization potential of the $t$-butyl radical$^{102}$.  
$^b$This high value seemed to the authors to have arisen because of excess energy carried by one or both fragments produced by electron impact.

best fitted when $\Delta H^f_{298}(0)$ for the process

$$\text{CF}_3\text{NO} \rightarrow \text{CF}_3 + \text{NO} \quad (33)$$

was equal to 42 ± 2 kcal/mol. At 800 K they quote a value of 41.5 ± kcal/mol for $\Delta H^f_{298}$. After making heat capacity corrections, using F$_3$CCH=CH$_2$ as a model compound and making corrections for the loss of the vibrations of three hydrogen atoms, a value of $\Delta H^f_{298}(298)$ for the above reaction of 42.8 ± 2 kcal/mol is obtained, which corresponds to the C—N bond dissociation energy in trifluoronitrosomethane. Using this value for $D(C—N)$ and with the heat of formation of the trifluoromethyl radical equal to $-112.5 ± 1$ kcal/mol$^{26}$, the heat of formation of trifluoronitrosomethane is calculated to be $-133.7 ± 3$ kcal/mol at 298 K.

Choo and coworkers$^{107}$ carried out a study of the decomposition of 2-methyl-2-nitrosopropane using the VLPP technique, thus eliminating heterogeneous decomposition and secondary reactions. Values of $k_{34}$ and $k_{35}$ for the reactions (34) and (35):

$$t$-C$_4$H$_9$NO \rightarrow t$-C$_4$H$_9^* + \text{NO} \quad (34)$$

$$t$-C$_4$H$_9^* + \text{NO} \rightarrow t$-C$_4$H$_9$NO \quad (35)$$

were obtained in the temperature range 550–850 K. After choosing a suitable value for the high-pressure $A$ factor for reaction (34), they carried out an RRKM (Rice, Ramsperger, Kassel, Marcus) calculation which yielded a high-pressure activation energy of 36.0 ± 1.0 kcal/mol for reaction (34) at 600 K. Hence $\Delta H^\circ_{298}(600) = 37.2 ± 1.0$ kcal/mol. They were also able to obtain the enthalpy change during reaction (34) using the relationship:

$$\ln K = \frac{-\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R}$$

from which they found $\Delta H^\circ_{298}(600) = 38.5 ± 1.5$ kcal/mol. They selected an average value of these two results and obtained $\Delta H^\circ_{298}(600) = 38.0 ± 1.5$ kcal/mol. After
Leslie Batt and Gillian N. Robinson

heat capacity corrections, using the isoelectronic \( t\text{-C}_2\text{H}_5\text{CH}==\text{CH}_2 \) as a model compound and correcting for the loss of vibration of the three hydrogen atoms, they obtained a value of \( 39.5 \pm 1.5 \text{ kcal/mol} \) for \( \Delta H_{36}^0(298) \), and hence \( D(\text{C}==\text{N}) \) for 2-methyl-2-nitrosopropane is \( 39.5 \pm 1.5 \text{ kcal/mol} \). If the heat of formation of the \( t\text{-butyl radical} \) is taken to be \( 10.5 \text{ kcal/mol} \) then making heat capacity corrections, using the isoelectronic styrene as a model compound and correcting for the loss of the vibrations of three hydrogen atoms, they obtained \( \Delta H_{36}^0(298) = 51.5 \pm 1.0 \text{ kcal/mol} \), which is the \( \text{C}==\text{N} \) bond dissociation energy of nitrosobenzene. Using \( \Delta H_F^0(\text{C}_6\text{H}_5') = 78.5 \text{ kcal/mol} \) we obtain \( \Delta H_F^0(\text{nitrosobenzene, g}) = 48.6 \pm 1 \text{ kcal/mol} \), which is not far removed from the result of Pepekin’s group which yielded \( \Delta H_F^0(\text{nitrosobenzene, g}) = 51.5 \pm 2 \text{ kcal/mol} \).

In another VLPP study, Choo and coworkers studied the decomposition of nitrosobenzene and pentafluoronitrosobenzene. For the first of these compounds they obtained unimolecular rate constants for the reaction (36) (763–953 K):

\[
\text{C}_6\text{H}_5\text{NO} \rightarrow \text{C}_6\text{H}_5^- + \text{NO}
\]  

(36)

After estimating the high-pressure \( A \) factor for this reaction, and carrying out an RRKM calculation, their results yielded a high-pressure activation energy at 700 K of 49.0 \( \pm 1.0 \) kcal/mol. Assuming zero activation energy for the reverse of this reaction, \( \Delta H_{36}^0(700) \) is calculated to be \( 50.4 \pm 1.0 \) kcal/mol. Then making heat capacity corrections, using the isoelectronic styrene as a model compound and correcting for the loss of the vibrations of three hydrogen atoms, they obtained \( \Delta H_{36}^0(298) = 51.5 \pm 1.0 \text{ kcal/mol} \), which is the \( \text{C}==\text{N} \) bond dissociation energy of nitrosobenzene. Using \( \Delta H_F^0(\text{C}_6\text{H}_5') = 78.5 \text{ kcal/mol} \) we obtain \( \Delta H_F^0(\text{nitrosobenzene, g}) = 48.6 \pm 1 \text{ kcal/mol} \), which is not far removed from the result of Pepekin’s group which yielded \( \Delta H_F^0(\text{nitrosobenzene, g}) = 51.5 \pm 2 \text{ kcal/mol} \).

For pentafluoronitrosobenzene the unimolecular rate constants for the reaction (37) (698–943 K):

\[
\text{C}_6\text{F}_5\text{NO} \rightarrow \text{C}_6\text{F}_5^- + \text{NO}
\]  

(37)

were subjected to RRKM calculations which yielded a value of \( 48.0 \pm 1.0 \text{ kcal/mol} \) for the high-pressure activation energy for this reaction at 700 K. Thus \( \Delta H_{36}^0(700) = 49.4 \pm 1.0 \text{ kcal/mol} \) and \( \Delta H_{36}^0(298) = 50.5 \pm 1.0 \text{ kcal/mol} \), after heat capacity corrections. Using \( \Delta H_F^0(\text{C}_6\text{F}_5') = -130.9 \pm 2 \text{ kcal/mol} \), the heat of formation of pentafluoronitrosobenzene was calculated to be \( -160 \pm 3 \text{ kcal/mol} \).

D. The \( \text{C}==\text{N} \) Bond Dissociation Energy and Heats of Formation

The values of the heats of formation of gaseous nitroso compounds and \( \text{C}==\text{N} \) bond dissociation energies obtained by the methods discussed above are summarized in Table 15. Bearing in mind the difficulties inherent in calorimetric studies of \( \text{C}==\text{N} \) nitroso compounds, it is considered that the heats of formation and bond strengths obtained from the kinetic studies of 2-methyl-2-nitrosopropane and nitrosobenzene are more reliable than those obtained from the calorimetric studies. Electron impact studies in some cases give results which agree with values obtained by other methods, but in other cases do not, so this method cannot always be relied upon to always give reliable results.

It was stated earlier that Benson and coworkers had derived group values for nitroso compounds based upon a ‘judicious guess’ that for secondary nitrosoalkanes \( D(\text{C}==\text{N}) \) was equal to 37 kcal/mol, with \( D(\text{C}==\text{N}) \) for primary and tertiary nitrosoalkanes equal to 38.5 and 35.5 kcal/mol respectively. The most reliable values in Table 15 for \( D(\text{C}==\text{N}) \) will be the result for nitrosomethane and the kinetic results for trifluoronitrosomethane and 2-methyl-2-nitrosopropane: these results are in the range \( 39.5 \pm 1.5 \) to \( 42.8 \pm 2 \text{.0 kcal/mol} \). It is therefore concluded that the \( \text{C}==\text{N} \) bond dissociation energy in nitrosoalkanes is \( 40 \pm 2 \text{ kcal/mol} \)
### TABLE 15. Thermochemical properties of C-nitroso compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta H_f^\circ$ (kcal/mol)</th>
<th>Method</th>
<th>$D$(C–N) (kcal/mol)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrosomethane</td>
<td>16.7 ± 0.8</td>
<td>Calorimetry + equilibrium constant</td>
<td>40.0 ± 0.8</td>
<td>98</td>
</tr>
<tr>
<td>Trifluoroniitrosomethane</td>
<td>−122 ± 4</td>
<td>Electron impact</td>
<td>31 ± 3</td>
<td>103</td>
</tr>
<tr>
<td>Trifluoronitrosomethane</td>
<td>−133.7 ± 3</td>
<td>Shock wave</td>
<td>42.8 ± 2</td>
<td>106</td>
</tr>
<tr>
<td>Trichloroniitrosomethane</td>
<td>8 ± 4</td>
<td>Electron impact</td>
<td>32 ± 3</td>
<td>103</td>
</tr>
<tr>
<td>2-Nitrosopropane</td>
<td>2.7 ± 3</td>
<td>Electron impact</td>
<td>36.5 ± 3</td>
<td>102</td>
</tr>
<tr>
<td>2-Methyl-1-nitrosopropane</td>
<td>−3.1 ± 2.2</td>
<td>Calorimetry + equilibrium constant</td>
<td>38.4 ± 2.2</td>
<td>100</td>
</tr>
<tr>
<td>2-Methyl-2-nitrosopropane</td>
<td>−5.0 ± 1.6</td>
<td>Calorimetry + equilibrium constant</td>
<td>35 ± 2</td>
<td>100</td>
</tr>
<tr>
<td>2-Methyl-2-nitrosopropane</td>
<td>−4 ± 3; −16 ± 3”</td>
<td>Electron impact</td>
<td>34 ± 3; 46 ± 3</td>
<td>102</td>
</tr>
<tr>
<td>2-Methyl-2-nitrosopropane</td>
<td>−9.5 ± 1.5</td>
<td>VLPP</td>
<td>39.5 ± 1.5</td>
<td>107</td>
</tr>
<tr>
<td>2-Methyl-2-nitrosobutane</td>
<td>−10.9 ± 3</td>
<td>Electron impact</td>
<td>36 ± 3</td>
<td>102</td>
</tr>
<tr>
<td>Nitrosobenzene</td>
<td>51.5 ± 2</td>
<td>Calorimetry + equilibrium constant</td>
<td>48.6 ± 2.0</td>
<td>100</td>
</tr>
<tr>
<td>Nitrosobenzene</td>
<td>59.1 ± 3</td>
<td>Electron impact</td>
<td>41 ± 3</td>
<td>102</td>
</tr>
<tr>
<td>Nitrosobenzene</td>
<td>48.6 ± 1</td>
<td>VLPP</td>
<td>51.5 ± 1.0</td>
<td>108</td>
</tr>
<tr>
<td>Pentafluoroniitrosobenzene</td>
<td>−171 ± 7</td>
<td>Electron impact</td>
<td>62 ± 5</td>
<td>103</td>
</tr>
<tr>
<td>Pentafluoronitrosobenzene</td>
<td>−160 ± 3</td>
<td>VLPP</td>
<td>50.5 ± 1.0</td>
<td>108</td>
</tr>
</tbody>
</table>

*See Table 14, footnote a.*
independent of R. On the basis of this conclusion, and group values for nitrosoalkanes obtained by Benson and coworkers\textsuperscript{1} may be amended: we select $\Delta H^\circ_p [(C(H)(C(NO))] = 17.7$ kcal/mol, $\Delta H^\circ_p [(C(H)(C)(NO))] = 19.6$ kcal/mol and $\Delta H^\circ_p [(C(C)(NO))] = 20.6$ kcal/mol on the basis of calculated heats of formation of 1-nitrosopropane of 2.6 kcal/mol, of 2-nitrosopropane of $-0.8$ kcal/mol and of 2-methyl-2-nitrosopropane of $-10.0$ kcal/mol.

The most reliable values for the C—N bond strengths in nitrosobenzene and pentafluoronitrosobenzene must be those of Choo and coworkers\textsuperscript{108} of $51.5 \pm 1.0$ and $50.5 \pm 1.0$ kcal/mol respectively. Thus it may be concluded that the C—N bond strength is unaffected by the presence of fluorine atoms in the benzene ring. Choo and coworkers\textsuperscript{108} estimate the heat of formation of the $C_B(NO)$ group to be 31.6 kcal/mol on the basis of their results.

\section*{V. ALKYL NITRITES}

\subsection*{A. Methyl Nitrite}

\subsubsection*{1. Heat of formation}

A flame calorimetric study of methyl nitrite by Geiscler and Thierfelder\textsuperscript{109} yielded $\Delta H^\circ_p (\text{methyl nitrite, } g) = -16.8 \pm 0.8$ kcal/mol. Other values for the heat of formation of methyl nitrite have been deduced from measurements of equilibrium constants. Gray and Pratt\textsuperscript{110} used the equilibrium constant for:

$$\text{CH}_3\text{OH} + \text{NOCl} \rightleftharpoons \text{CH}_3\text{ONO} + \text{HCl}$$

obtained by Leermakers and Ramsperger\textsuperscript{111} together with unpublished results on an enthalpy of hydrolysis\textsuperscript{112} to obtain a value of $-14.93 \pm 0.26$ kcal/mol for the heat of formation of methyl nitrite. Ray and Gershon\textsuperscript{113} also used the enthalpy of the above reaction and obtained $\Delta H^\circ_p (\text{methyl nitrite, } g) = -15.64 \pm 0.20$ kcal/mol.

Silverwood and Thomas\textsuperscript{114} examined the reaction between methanol and nitrogen dioxide:

$$\text{CH}_3\text{OH} + 2 \text{NO}_2 \rightleftharpoons \text{CH}_3\text{ONO} + \text{HNO}_3$$

Values of the equilibrium constant yielded a value of $15.9 \pm 0.1$ kcal/mol for the enthalpy change for the above reaction and hence $\Delta H^\circ_p (\text{methyl nitrite, } g) = -16.05 \pm 0.2$ kcal/mol. This value is preferred.

\subsubsection*{2. Standard entropy}

The value of the standard entropy of methyl nitrite is an important quantity since group values for values of $S^\circ (298)$ for the higher nitrites depend upon this value. Equilibrium studies have yielded values in the range $64.2\textsuperscript{111}$ to $71.5 \pm 0.9\textsuperscript{110}$ cal/(mol K). Silverwood and Thomas\textsuperscript{114} obtained a value of $S^\circ (298)$ for methyl nitrite of $69.7 \pm 0.3$ cal/(mol K) in their study of the equilibrium between methanol and nitrogen dioxide. The standard entropy of methyl nitrite has been calculated by Gray and Pratt\textsuperscript{110}. It is known\textsuperscript{73} that alkyl nitrates exist in two isomeric forms, \textit{cis} and \textit{trans}:

\begin{itemize}
  \item \textit{cis} \hspace{2cm} \textit{trans}
\end{itemize}
demonstrating that there is a barrier to rotation of the NO group. In the absence of barriers to rotation of the NO group and the methyl group, and including the entropy of mixing of the two isomers, Gray and Pratt calculated $S^{\circ}(298)$ to be $74.1 \pm 0.14$ cal/(mol K). By comparing this result with their experimentally derived value of $71.5$ cal/(mol K) they concluded that the barrier to rotation of the NO group was $\sim 7.8$ kcal/mol. A subsequent proton magnetic resonance study\textsuperscript{115} yielded a value of $10.5$ kcal/mol for the barrier to rotation of the NO group, and this agreed well with a value of $11.1$ kcal/mol for the barrier height determined later by Temussi and Tancredi\textsuperscript{116}. There is also a barrier to rotation of the methyl group in the cis isomer (the more stable isomer) of $\sim 2.1$ kcal/mol\textsuperscript{117}. These two barriers to rotation lead to reductions in the standard entropy of methyl nitrite of $2.9$ and $0.8$ cal/(mol K) respectively\textsuperscript{118}. Thus the standard entropy of methyl nitrite is calculated to be $74.1 - 2.9 - 0.8 = 70.4$ cal/(mol K), in good agreement with the value obtained by Silverwood and Thomas\textsuperscript{114}.

Stull, Westrum and Sinke\textsuperscript{3} list thermodynamic functions for methyl nitrite.

B. Higher Alkyl Nitrites

For ethyl nitrite, Rossini and coworkers\textsuperscript{119} quote a value of $-24.8$ kcal/mol for the heat of formation of the gaseous compound, determined at the end of the last century. Gray and Williams\textsuperscript{120} quote an unpublished result of Baldrey, Lotzgesell and Style of $\Delta H_f^\circ = -24.2$ kcal/mol for gaseous ethyl nitrite. This latter value is preferred. Gray and Williams\textsuperscript{120} quote an unpublished value by Baldrey, Lotzgesell and Style for the heat of formation of liquid $n$-propyl nitrite of $-38.01$ kcal/mol and Benson and coworkers calculated the heat of vaporization of $n$-propyl nitrite and hence arrived at a value of $-30.1$ kcal/mol for the heat of formation of gaseous $n$-propyl nitrite. In a bomb calorimetry study of $n$-propyl nitrite, Batt and coworkers\textsuperscript{121} obtained a value of $-36.0$ kcal/mol for the heat of formation of the liquid; coupled with a value of $7.6$ kcal/mol for the heat of vaporization, they obtained a value of $-28.4 \pm 1$ kcal/mol for the heat of formation of gaseous $n$-propyl nitrite, and this is the preferred value. For $i$-propyl nitrite, Batt and coworkers\textsuperscript{121} obtained a value of $-39.3$ kcal/mol for the heat of formation of the liquid. They calculated the heat of vaporization to be $7.4$ cal/mol and hence found $\Delta H_f^\circ$ for gaseous $i$-propyl nitrite was $-31.9 \pm 1.0$ kcal/mol. Batt and coworkers\textsuperscript{121} also carried out bomb calorimetric studies on the four isomeric butyl nitrites: they obtained heats of formation in the liquid phase of $-43.6$, $-44.4$, $-45.0$ and $-49.2$ for $n$-butyl, $i$-butyl, $s$-butyl and $t$-butyl nitrites respectively. Together with their respective heats of vaporization these values yielded heats of formation of $-34.8 \pm 1.0$, $-36.1 \pm 1.0$, $-36.5 \pm 1.0$ and $-41.0 \pm 1.0$ kcal/mol for gaseous $n$-butyl, $i$-butyl, $s$-butyl and $t$-butyl nitrites. Lastly, Islam\textsuperscript{122} obtained a value of $-53.8$ for the heat of formation of liquid $t$-pentyl nitrite by bomb calorimetry from which, with $\Delta H_f^\circ = 7.98$ kcal/mol, a value of $-45.8 \pm 0.8$ kcal/mol for the heat of formation of gaseous $t$-pentyl nitrite was obtained.

Benson and coworkers\textsuperscript{1} derived group additivity rules for the heats of formation of alkyl nitrites on the basis of the heats of formation of methyl, ethyl and $n$-propyl nitrite. Group values for the standard entropies of alkyl nitrites were derived on the basis of the entropy of formation of methyl nitrite, and heat capacity group values were likewise based upon methyl nitrite. In Table 16 the selected heats of formation of alkyl nitrites determined experimentally are listed together with the values of the heats of formation of the nitrites calculated using the group additivity
TABLE 16. Heats of formation of alkyl nitrites obtained experimentally and estimated by group additivity rules (g.a.r.) (kcal/mol)

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \Delta H_f^o ) (exp.)</th>
<th>( \Delta H_f^o ) (g.a.r.) (^a)</th>
<th>( \Delta H_f^o ) (corr.) (gauche)</th>
<th>( \Delta H_f^o ) (exp.) - ( \Delta H_f^o ) (calc., corr.)</th>
<th>( \Delta H_f^o ) (corr., g.a.r.) (^b)</th>
<th>( \delta )</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)ONO</td>
<td>-16.05</td>
<td>-16.0</td>
<td>-16.0</td>
<td>-0.05</td>
<td>-15.7</td>
<td>-0.35</td>
<td>114</td>
</tr>
<tr>
<td>C(_2)H(_3)ONO</td>
<td>-24.2</td>
<td>-24.2</td>
<td>-24.2</td>
<td>0.0</td>
<td>-23.9</td>
<td>-0.3</td>
<td>120</td>
</tr>
<tr>
<td>n-C(_3)H(_7)ONO</td>
<td>-28.4</td>
<td>-29.1</td>
<td>-29.1</td>
<td>+0.7</td>
<td>-28.8</td>
<td>+0.4</td>
<td>121</td>
</tr>
<tr>
<td>i-C(_3)H(_7)ONO</td>
<td>-31.9</td>
<td>-33.5</td>
<td>-32.7</td>
<td>+0.8</td>
<td>-32.4</td>
<td>+0.5</td>
<td>121</td>
</tr>
<tr>
<td>n-C(_4)H(_9)ONO</td>
<td>-34.8</td>
<td>-34.1</td>
<td>-34.1</td>
<td>-0.7</td>
<td>-33.8</td>
<td>-1.0</td>
<td>121</td>
</tr>
<tr>
<td>i-C(_4)H(_9)ONO</td>
<td>-36.1</td>
<td>-36.3</td>
<td>-36.3</td>
<td>+0.2</td>
<td>-36.0</td>
<td>-0.1</td>
<td>121</td>
</tr>
<tr>
<td>s-C(_4)H(_9)ONO</td>
<td>-36.5</td>
<td>-38.4</td>
<td>-37.6</td>
<td>+1.1</td>
<td>-37.3</td>
<td>+0.8</td>
<td>121</td>
</tr>
<tr>
<td>t-C(_4)H(_9)ONO</td>
<td>-41.0</td>
<td>-43.1</td>
<td>-41.5</td>
<td>+0.5</td>
<td>-41.2</td>
<td>+0.2</td>
<td>121</td>
</tr>
<tr>
<td>t-C(_4)H(_11)ONO</td>
<td>-45.8</td>
<td>-48.0</td>
<td>-46.4</td>
<td>+0.6</td>
<td>-46.1</td>
<td>+0.3</td>
<td>122</td>
</tr>
</tbody>
</table>

\(^a\) Using \( \Delta H_f^o \) [O(NO)(C)] = -5.9 kcal/mol.

\(^b\) Using \( \Delta H_f^o \) [O(NO)(C)] = -5.6 kcal/mol.

\(^c\) \( \delta = \Delta H_f^o \) (exp.) - \( \Delta H_f^o \) (corr., g.a.r.).
values of Benson\(^1\) (column 3). Inspection of these values shows that agreement between experimental and estimated values is improved if a correction of +0.8 kcal/mol is made for each gauche interaction between the NO group and an alkyl group. The values of \(\Delta H^\circ\) obtained when this correction is made are listed in column 4. Column 5 gives the difference between the experimental and gauche-corrected heats of formation. Because the majority of these differences are positive, a correction was made to the group value for O(NO)(C) to minimize the mean difference, giving a value of \(\Delta H^\circ_{\text{est}}[\text{O(NO)}(\text{C})]\) of -5.6 kcal/mol instead of -5.9 kcal/mol. After these corrections are made agreement between experimental and estimated heats of formation of alkyl nitrites is within ±1 kcal/mol, a satisfactory result.

C. The RO—NO Bond Dissociation Energy

The heats of formation of the alkyl nitrites listed above may be used to obtain the RO—NO bond dissociation energies of the nitrites, if the heats of formation of the relevant alkoxy radicals are known:

\[
D(\text{RO—NO}) = \Delta H^\circ_{\text{RÒ}} + \Delta H^\circ_{\text{NO}} - \Delta H^\circ_{\text{RONO}}
\]

The heats of formation of the alkoxy radicals may be derived from the thermochemistry of the decomposition of the dialkyl peroxides:

\[
\text{ROOR} \rightarrow 2 \text{RÒ}
\]

(38)

Where the activation energy for this reaction is known the RO—OR bond dissociation energy at 298 K may be calculated, and knowing the heat of formation of the dialkyl peroxide, the heat of formation of the alkoxy radical may be determined. Where the activation energy for the decomposition of the relevant dialkyl peroxide has not been determined the heat of formation of the alkoxy radical may be calculated using group additivity rules\(^26\). The heats of formation of alkoxy radicals are listed in Table 17. The activation energies obtained in kinetic studies have been converted to enthalpies of reaction at the mean reaction temperature, assuming that the activation energies for alkoxy radical combination reactions are equal to zero. Standard enthalpy changes at 298 K were obtained using heat capacities for the peroxides and alkoxy radicals estimated by group additivity. It may be seen, in passing, that the RO—OR bond dissociation energy is constant at 38.2 ± 0.7 kcal/mol, independent of R, with the exceptions of di-s-butyl and di-t-pentyl peroxides for which the activation energies seem too low by around 1 kcal/mol (because of the likelihood of chain decomposition under the reaction conditions employed in the first case\(^125\), and because of the uncertainty inherent in the selection of the preexponential factor for the reaction in the second case\(^127\)). To obtain the RO—NO bond dissociation energies for the nitrites, heats of formation of alkoxy radicals obtained in kinetic studies were used in preference to those obtained from group additivity, except for s-butoxy and t-pentoxy, for which the kinetically determined heat of formation may be suspect. The values of \(D(\text{RO—NO})\) obtained in this way are listed in Table 18.

Also in Table 18 are RO—NO bond dissociation energies obtained from the most recent kinetic studies of the decomposition of alkyl nitrites\(^129—135\):
TABLE 17. Heats of formation of alkoxy radicals (kcal/mol)

<table>
<thead>
<tr>
<th>Radical</th>
<th>$\Delta H^*_f$ (g.a.r.)</th>
<th>$E$</th>
<th>Reference</th>
<th>$E + R\bar{T}$</th>
<th>$\Delta H^*$ (298)</th>
<th>$\Delta H^*_f$ (ROOR)</th>
<th>Reference</th>
<th>$\Delta H^*_f$ (RO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$O</td>
<td>-</td>
<td>37.0</td>
<td>123</td>
<td>37.8</td>
<td>38.0</td>
<td>-30.0</td>
<td>128</td>
<td>4.0</td>
</tr>
<tr>
<td>C$_2$H$_5$O</td>
<td>-4.1</td>
<td>37.3</td>
<td>124</td>
<td>38.1</td>
<td>38.3</td>
<td>-46.1</td>
<td>128</td>
<td>-3.9</td>
</tr>
<tr>
<td>C$_3$H$_7$O</td>
<td>-9.03</td>
<td>37.2</td>
<td>82</td>
<td>38.0</td>
<td>38.2</td>
<td>-55.5</td>
<td>g.a.r.</td>
<td>-8.6</td>
</tr>
<tr>
<td>i-C$_3$H$_7$O</td>
<td>-12.6</td>
<td>37.1</td>
<td>124</td>
<td>37.9</td>
<td>38.1</td>
<td>-64.2</td>
<td>g.a.r.</td>
<td>-13.0</td>
</tr>
<tr>
<td>C$_4$H$_9$O</td>
<td>-14.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i-C$_4$H$_9$O</td>
<td>-16.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s-C$_4$H$_9$O</td>
<td>-17.5</td>
<td>36.4</td>
<td>125</td>
<td>37.2</td>
<td>37.4</td>
<td>-74.1</td>
<td>g.a.r.</td>
<td>-18.3</td>
</tr>
<tr>
<td>i-C$_4$H$_9$O</td>
<td>-21.7</td>
<td>37.4</td>
<td>126</td>
<td>38.2</td>
<td>38.4</td>
<td>-81.5</td>
<td>128</td>
<td>-21.6</td>
</tr>
<tr>
<td>i-C$<em>5$H$</em>{11}$O</td>
<td>-26.9</td>
<td>36.4</td>
<td>127</td>
<td>37.0</td>
<td>37.2</td>
<td>-93.3</td>
<td>g.a.r.</td>
<td>-28.1</td>
</tr>
</tbody>
</table>
24. Thermochemistry of nitro compounds, amines and nitroso compounds

**TABLE 18. Values of RO—NO bond dissociation energies of alkyl nitrates (kcal/mol)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>(D(\text{RO—NO})) (thermochemical)(^a)</th>
<th>(E)</th>
<th>(E + RT)</th>
<th>(\Delta H_{298}^o = D(\text{RO—NO})) (kinetic)(^b)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3\text{ONO})</td>
<td>41.7</td>
<td>41.2</td>
<td>42.1</td>
<td>42.1</td>
<td>129</td>
</tr>
<tr>
<td>(\text{C}_2\text{H}_5\text{ONO})</td>
<td>41.9</td>
<td>41.8</td>
<td>42.2</td>
<td>42.2</td>
<td>130</td>
</tr>
<tr>
<td>(\text{C}_3\text{H}_7\text{ONO})</td>
<td>41.4</td>
<td>41.0</td>
<td>41.8</td>
<td>41.8</td>
<td>131</td>
</tr>
<tr>
<td>(\text{i-C}_3\text{H}_7\text{ONO})</td>
<td>40.5</td>
<td>40.3</td>
<td>41.2</td>
<td>41.2</td>
<td>133</td>
</tr>
<tr>
<td>(\text{C}_4\text{H}_9\text{ONO})</td>
<td>41.0</td>
<td>40.3</td>
<td>41.1</td>
<td>41.1</td>
<td>134</td>
</tr>
<tr>
<td>(\text{s-C}_4\text{H}_9\text{ONO})</td>
<td>41.0</td>
<td>40.3</td>
<td>41.1</td>
<td>41.1</td>
<td>135</td>
</tr>
<tr>
<td>(\text{i-C}_4\text{H}_9\text{ONO})</td>
<td>40.3</td>
<td>40.3</td>
<td>41.1</td>
<td>41.1</td>
<td>135</td>
</tr>
</tbody>
</table>

\(^a\) Mean \(D(\text{RO—NO})\) (thermochemical) = 41.3 ± 0.7 kcal/mol.

\(^b\) Mean \(D(\text{RO—NO})\) (kinetic) = 41.6 ± 0.6 kcal/mol.

\(^c\) Assumed \(E_x = 41.0\) kcal/mol for purposes of the RRKM calculation.

The activation energies obtained in these studies are converted to bond dissociation energies as before, assuming that the activation energy for the reverse of this process is equal to zero. For these reactions heat capacity corrections were negligibly small, with \(\Delta C_p(298 - T)\) being of the order of 0.03 kcal/mol. It should be noted that the result of Baldwin and Golden\(^{132}\) was from a VLPP study in which RRKM calculations were carried out to obtain \(A_x\) on the basis that \(E_x\) was 41.0 kcal/mol, by analogy with the results of Batt and coworkers\(^{129}\). Thus the bond dissociation energy obtained in this way is not a directly determined result.

It may be seen from Table 18 that the mean values for the thermochemical and kinetic bond dissociation energies are in very close agreement, within experimental error, confirming the assumption made that the activation energy for the process:

\[
\text{RO} + \text{NO} \rightarrow \text{RONO}
\]

is very close to zero. (The activation energies obtained in earlier studies by Steacie and coworkers\(^{136,137}\) would give bond dissociation energies inconsistent with the thermochemical results.) The conclusion is drawn that the RO—NO bond dissociation energy in alkyl nitrates is 41.5 ± 1 kcal/mol. It is interesting to note that there is a slight decrease in \(D(\text{RO—NO})\) with increasing size of the alkyl group, this trend being more marked in the kinetic results. There may be some relationship between weakening of the RO—NO bond and gauche interactions, but there are insufficient results to confirm this and the difference is probably too small to be significant.

**VI. ALKYL NITRATES**

**A. Thermochemical Properties**

Thermochemical properties have been determined for the C\(_1\)—C\(_3\) alkyl nitrates. The studies carried out are described by Stull, Westrum and Sinke\(^3\), so will not be discussed here. Stull, Westrum and Sinke estimated heat capacities for ethyl nitrate and thermodynamic functions of propyl nitrate and isopropyl nitrate. The values recommended by these workers are summarized in Table 19, together with the heat
Leslie Batt and Gillian N. Robinson

**TABLE 19. Thermochemical properties of gaseous alkyl nitrates**

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta H^o$ (g) [kcal/mol]</th>
<th>$S^o$ (298) [cal/(mol K)]</th>
<th>$C_p^o$ [cal/(mol K)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>300</td>
</tr>
<tr>
<td>CH$_3$ONO$_2$</td>
<td>-28.8</td>
<td>72.15</td>
<td>18.34</td>
</tr>
<tr>
<td>C$_2$H$_5$ONO$_2$</td>
<td>-36.8</td>
<td>83.25</td>
<td>(23.36)</td>
</tr>
<tr>
<td>C$_3$H$_7$ONO$_2$</td>
<td>-41.6</td>
<td>(92.1)</td>
<td>29.1</td>
</tr>
<tr>
<td>i-C$_3$H$_7$ONO$_2$</td>
<td>-45.65</td>
<td>(89.20)</td>
<td>28.95</td>
</tr>
<tr>
<td>C$_3$H$_5$(ONO$_2$)$_3$</td>
<td>-64.7</td>
<td>$\pm$ 1.2$^c$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Values taken from Stull, Westrum and Sinko$^3$.  
$^b$Estimated values.  
$^c$Reference 4.

of formation of gaseous nitroglycerine which appears to be the only other gaseous alkyl nitrate for which the heat of formation has been measured. Benson's group$^1$ made use of the heats of formation of the four alkyl moninitrates to derive the group value for O(NO$_2$)(C) which gave heats of formation of the alkyl nitrates within ±0.7 kcal/mol of the observed heats of formation. Not unexpectedly, the heat of formation of nitroglycerine cannot be derived from the O(NO$_2$)(C) group value (group additivity would predict a heat of formation of −81.6 kcal/mol).

**B. The RO—NO$_2$ Bond Dissociation Energy**

The RO—NO$_2$ bond dissociation energy may be calculated from the heats of formation of the alkyl nitrates:

$$D(\text{RO—NO}_2) = \Delta H^o(\text{NO}_2) + \Delta H^o(\text{RO}) - \Delta H^o(\text{RONO}_2)$$

Bond dissociation energies calculated in this way, using the heats of formation of the alkoxy radicals listed in Table 17, and $\Delta H^o(\text{NO}_2) = 7.9$ kcal/mol$^{24}$, are listed in Table 20. Kinetic studies have been carried out on the C$_1$—C$_3$ alkyl nitrates$^{138-143}$. On the assumption that the activation energy for the combination reactions of alkoxy radicals with nitrogen dioxide is zero, activation energies for the

**TABLE 20. RO—NO$_2$ bond dissociation energies for alkyl nitrates obtained from thermochemical and kinetic studies (kcal/mol)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>$D(\text{RO—NO}_2)$ (thermochem.$^a$)</th>
<th>$E$</th>
<th>$E + \bar{R}T$</th>
<th>$\Delta H^o (298) = D(\text{RO—NO}_2)$ (kinetic)$^b$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$ONO$_2$</td>
<td>40.7</td>
<td>39.5</td>
<td>40.5</td>
<td>40.9</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40.0</td>
<td>40.9</td>
<td>41.2</td>
<td>139</td>
</tr>
<tr>
<td>C$_2$H$_5$ONO$_2$</td>
<td>40.8</td>
<td>39.9</td>
<td>40.8</td>
<td>41.0</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>38.9</td>
<td>39.1</td>
<td>141</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39.3</td>
<td>40.2</td>
<td>40.4</td>
<td>142</td>
</tr>
<tr>
<td>C$_3$H$_7$ONO$_3$</td>
<td>40.5</td>
<td>40.0</td>
<td>40.5</td>
<td>40.5</td>
<td>143</td>
</tr>
<tr>
<td>i-C$_3$H$_7$ONO$_2$</td>
<td>40.9</td>
<td>38.1</td>
<td>38.9</td>
<td>40.0</td>
<td>139</td>
</tr>
</tbody>
</table>

$^a$Mean $D(\text{RO—NO}_2)$ (thermochem.) = 40.7 ± 0.2 kcal/mol.  
$^b$Mean $D(\text{RO—NO}_2)$ (kinetic) = 40.4 ± 1.3 kcal/mol.
TABLE 21. Activation energies (kcal/mol) obtained for RO—NO₂ bond breaking in dinitrates and trinitrates

<table>
<thead>
<tr>
<th>Compound</th>
<th>$E$</th>
<th>$E + RT$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene glycol dinitrate</td>
<td>39</td>
<td>39.7</td>
</tr>
<tr>
<td>Trimethylene glycol dinitrate</td>
<td>38.1</td>
<td>38.8</td>
</tr>
<tr>
<td>Propylene glycol dinitrate</td>
<td>37.4</td>
<td>38.1</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>40.3</td>
<td>41.0</td>
</tr>
<tr>
<td>Trimethylol nitromethane trinitrate</td>
<td>36.3</td>
<td>37.0</td>
</tr>
</tbody>
</table>

Reaction (41):

\[
\text{RONO}_2 \rightarrow \text{RO} + \text{NO}_2
\]

may be converted to bond dissociation energies as before. In making the heat capacity corrections, the values of $C_p^\infty$ derived by Stull, Westrum and Sinke³ for ethyl, propyl and isopropyl nitrates have been used, with heat capacities for the alkoxy radicals estimated by group additivity. It may be seen from Table 20 that the thermochemical bond dissociation energies are very close together; while there is rather more scatter in the kinetic results the mean thermochemical value is very close to the mean kinetic value (hence the activation energy for the combination reaction between alkoxy radicals and nitrogen dioxide is confirmed to be close to zero). Thus it may be seen that for alkyl nitrates, $D(\text{RO—NO}_2)$ is equal to 40.7 ± 0.2 kcal/mol independent of R.

Phillips¹⁴⁴ carried out a series of studies on dinitrates and trinitrates and the activation energies he obtained for the RO—NO₂ bond-breaking step are listed in Table 21. The activation energies have been converted to enthalpies of reaction at the mean reaction temperature. No attempt is made here to convert these enthalpies to values of $\Delta H^\circ(298)$. It is expected that the heat capacity correction required would be small, however, so that the values of $E + RT$ will be close to the RO—NO₂ bond dissociation energies at 298 K. It appears that for these compounds the RO—NO₂ bond dissociation energy is virtually the same as in the mononitrates.

VII. CONCLUSIONS

Since the reviews of Stull, Westrum and Sinke³ and Cox and Pilcher⁴ were compiled numerous studies of the thermochemistry of nitro compounds, amines and nitroso compounds have been carried out which enable general conclusions to be drawn.

New results on the heats of formation of these compounds in the gas phase have allowed us to refine the group additivity rules of Benson and coworkers¹⁴¹: we have been able to modify certain group values and derive new ones. The amended group values are listed in Table 22. We have found that agreement between experimental and group additivity values is best when no correction is made for gauche interactions between alkyl and alkyl, alkyl and nitro, and alkyl and amino groups for compounds in the gas phase. A correction of +6.6 kcal/mol is required for nitro-nitro gauche interactions and a correction of +0.8 kcal/mol is required for alkyl-nitrito gauche interactions. Having made these adjustments to the group additivity rules we feel that heats of formation of the compounds covered in this review may be estimated to ±1 kcal/mol, except in the case of sterically crowded
molecules. Where differences between estimated and experimental values are large this may indicate that the experimental value is suspect. As far as heats of formation in the solid and liquid phases are concerned, reliable results can only be estimated for nitroalkanes. Here corrections must be made for gauche interactions between alkyl and alkyl and nitro and alkyl groups. For nitroalkanes in the solid and liquid phases group additivity values are generally within ±2 kcal/mol of the experimental values of the heats of formation, with some exceptions. Values of \( S^\circ(298) \) and \( C^\circ_p(298) \) for amines calculated by group additivity are in excellent agreement with values determined by other means.

In this review we have concentrated entirely on the method of group additivity devised by Benson and coworkers. This is not the only system, however: for example, a new method has recently been devised by Yoneda, based upon an earlier method of Anderson, Beyer and Watson. This system has the advantages that heats of formation, entropies and heat capacities of gaseous compounds containing only one carbon atom may be estimated and an estimate of reliability is also obtained, but has the disadvantage of being more complex than Benson’s method to operate. Yoneda states that his method gives more accurate values of heats of formation than do other methods. The method of Benson, which has the advantage of being simple to operate, gives results which are probably adequate for most purposes.

We have considered C—N and RO—N bond dissociation energies in two ways: from kinetic and thermochemical results. In most cases agreement between the two types of bond dissociation energy has been good. This emphasizes that the expression

\[
D = E + R\bar{T} + \Delta C^\circ_p(298 - \bar{T})
\]
TABLE 23. C—N bond dissociation energies in nitro compounds, amines and C-nitroso compounds and RO—N bond dissociation energies in alkyl nitrites and nitrates

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond dissociation energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H—NO₂</td>
<td>~78a</td>
</tr>
<tr>
<td>R—NO₂</td>
<td>59.4 ± 1.4</td>
</tr>
<tr>
<td>Ph—NO₂</td>
<td>71</td>
</tr>
<tr>
<td>H—NH₂</td>
<td>109.7</td>
</tr>
<tr>
<td>R—NH₂</td>
<td>84.2 ± 1.3</td>
</tr>
<tr>
<td>R—NHR</td>
<td>82 ± 1</td>
</tr>
<tr>
<td>R—NR₂</td>
<td>79 ± 1</td>
</tr>
<tr>
<td>Ph—NH₂</td>
<td>104.3</td>
</tr>
<tr>
<td>Ph—NHR</td>
<td>102.8</td>
</tr>
<tr>
<td>Ph—NR₂</td>
<td>100.0</td>
</tr>
<tr>
<td>H—NO</td>
<td>49.9</td>
</tr>
<tr>
<td>R—NO</td>
<td>40 ± 2</td>
</tr>
<tr>
<td>Ph—NO</td>
<td>51.5 ± 1.0</td>
</tr>
<tr>
<td>HO—NO</td>
<td>49.6</td>
</tr>
<tr>
<td>RO—NO</td>
<td>41.5 ± 1.0</td>
</tr>
<tr>
<td>HO—NO₂</td>
<td>49.4</td>
</tr>
<tr>
<td>RO—NO₂</td>
<td>40.7 ± 0.2</td>
</tr>
</tbody>
</table>

*Based on an approximate value of 18 kcal/mol for $\Delta H_f^\circ$ (HNO₂) (see Ref. 26, p. 115).

must be used to obtain the best value of the bond dissociation energy from an activation energy relating to a bond-breaking process, where the reverse reaction has zero activation energy. Where kinetic and thermochemical bond dissociation energies differ, this is maybe an indication that the mechanism proposed is wrong and that, for example, surface reactions or intramolecular rearrangements are playing a part, and the reaction is not simply a unimolecular bond-breaking process. We have observed in the case of nitroalkanes and possibly amines a lowering of the ‘kinetic’ bond dissociation energy with increasing size of the alkyl group, while the thermochemical bond dissociation energy remained constant. This may be an indication that the combination reactions

\[
\hat{R} + \text{NO}_2 \rightarrow \text{RNO}_2 \\
\hat{R} + \hat{\text{NH}}_2 \rightarrow \text{RNH}_2
\]

may have small activation energies when R is larger than ethyl. We list in Table 23 the values of $D(C—N)$ and $D(\text{RO—N})$ for the compounds considered in this review together with $D(\text{H—N})$ or $D(\text{HO—N})$ for the relevant parent compounds. It may be seen that the H—N bond is stronger by around 30% than the R—N bond, while the strength of the Ph—N bond is of the same order of magnitude as the H—N bond. The RO—N bonds are around 20% weaker than the corresponding HO—N bonds.

We have been able to conclude that for the compounds considered in this review the bond dissociation energies of the R—N and RO—N bonds are unaffected by the nature of R where R is a simple alkyl group. Where R is substituted, except by fluorine atoms, this conclusion no longer applies.
The authors wish to acknowledge correspondence with S. W. Benson and K. Glänzer and the comments of D. W. Thompson.

IX. REFERENCES

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24. Thermochemistry of nitro compounds, amines and nitroso compounds

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120. L. Médard and M. Thomas, Mem. Poudres, 38, 45 (1956).


24. Thermochemistry of nitro compounds, amines and nitroso compounds


CHAPTER 25

Oxidation of amines

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I. INTRODUCTION

The choice of reactions to review as amine oxidations is somewhat arbitrary. Two general categories of reactions are treated in this chapter: oxidations at the \( \alpha \)-carbons of alkyl groups attached to the amine nitrogen, and attachment of oxygen to the nitrogen. Excluded are nitrosations of primary and secondary amines, certain oxidative deaminations, aromatic ring oxidations and reactions of the Hofmann–Löffler or similar types. Some of the areas discussed here were covered in the original chapter of this series, ‘Substitution at the amino nitrogen’, by Challis and Butler\(^5\), but have, in the dozen years since that time, shown significant progress; others were not addressed.

The subject matter may be considered either in terms of applications – such as synthetic methods, detoxification of water pollutants or explanation of reaction by-products – or in terms of reaction pathways and mechanisms. With regard to mechanisms, reagents are categorized as two-electron or one-electron oxidants. The latter may attack the nitrogen or an \( \alpha \)-hydrogen; confusion has sometimes arisen because the mode of attack depends on the structure of the amine as much as on the nature of the oxidant. The correlation of structure with reactivity for some amine oxidations and the realization that the most stable configuration for the aminium radical is usually planar are among the more important advances recorded in the past twelve years. This chapter continues the practice of subdivision by reagent.

II. CHLORINE DIOXIDE IN AQUEOUS SOLUTION

Though unknown to most organic chemists, the volatile (b.p. 11°C) and quite water-soluble free radical, chlorine dioxide, \( \text{ClO}_2 \), is consumed in quantity as a bleach for wood pulp and flour, and as a water disinfectant. It is normally generated at the point of use, for example, from a chlorite salt and hypochlorous acid\(^2\) (equation 1). Its reactions with secondary and especially tertiary nonaromatic amines in aqueous solution were investigated over a decade ago during the evaluation of potential decontaminants for toxic nitrogen-containing chemical agents in potable water\(^7\)\(^8\)\(^9\)\(^15\)\(^16\)\(^17\)\(^25\)\(^7\)\(^26\)\(^26\)\(^3\). Aqueous chlorine dioxide is easily measured spectrophotometrically (\( \lambda_{\text{max}} \) 358.3 nm, \( \varepsilon \) 1250). It is stable up to about pH 9 (disproportionating above that pH to chlorate and chlorite ions); its one-electron reduction product, chlorite ion, is stable above pH 5 in the absence of excessive concentrations of aldehydes, strong oxidants and certain reducing agents\(^11\). Kinetic measurements of chlorine dioxide consumption in reactions with amines are conveniently made under pseudo-first-order conditions; the amines are present in excess, but may be maintained largely in the form of the unreactive water-soluble protonated species. The magnitudes of the observed rates can be varied by increasing or decreasing pH, which controls the equilibrium of protonated with free amine\(^7\)\(^8\)\(^9\)\(^15\)\(^16\)\(^17\)\(^25\)\(^7\)\(^26\)\(^26\)\(^3\).

Oxidative dealkylation is typically seen in reactions of chlorine dioxide with tertiary and secondary nonaromatic amines; reactivity is in the order \( \text{R}_3\text{N} > \text{R}_2\text{NH} > \text{RNH}_2 \), with \( \text{RNH}_2 \) relatively unreactive\(^15\)\(^6\)\(^26\)\(^26\)\(^3\). Anticipated complexities, analogous to those observed with phenols, precluded extensive experimentation with aromatic amines, but the ready conversion of tris-(\(p\)-dimethylaminophenyl)amine and \( N,N,N',N''-p\)-phenylenediamine to stable free radicals has been demonstrated\(^15\)\(^6\). The first such reaction to be studied was the conversion of triethylamine
by aqueous chlorine dioxide to diethylamine and acetaldehyde, as shown in reaction (2). Addition of chlorite ion at constant pH and a constant excess of amine
\[
\text{ClO}_2 + \text{Et}_3\text{N} \overset{k_1}{\rightarrow} \text{ClO}_2^- + \text{Et}_3\text{N}^+ \quad \text{(1)}
\]
helped to demonstrate that the initial step was reversible; this modification retarded the overall reaction. In agreement with the mechanism, a plot of the half-time for chlorine dioxide disappearance against chlorite ion concentration was linear. The second and third steps of reaction (2) were evidently rapid and irreversible. Despite the overall stoichiometry (see reaction 3), the reaction was first order in both chlorine dioxide and amine. The kinetic rate law was
\[
\frac{-d[\text{ClO}_2]}{dt} = \frac{2k_1k_2[\text{Et}_3\text{N}][\text{ClO}_2]}{(k_{-1}[\text{ClO}_2^-] + k_2)}
\]
For the analogous oxidation of trimethylamine, the kinetic deuterium isotope effect was 1.3, providing additional strong evidence for electron abstraction in the first (reversible) step. Thus, the transient, but certainly real, aminium radical was indirectly proven to be a key intermediate.
Chlorine dioxide's reaction with a series of ring-substituted N,N-dimethylbenzylamines at 27°C and ionic strength 0.2 provided an unprecedented demonstration of linear free energy relationships in nonaromatic amine oxidations. The Brønsted plot gave an equation (corrected for a factor of 2 not accounted for in the original reference) of
\[
\log k_1 = 2.598 + 0.812 pK_a
\]
with a correlation coefficient of 0.991, and a Hammett plot (corrected for a factor of 2 not accounted for in the original reference) of
\[
\log k_1 = 4.15 - 0.924 \sigma
\]
with a correlation coefficient of 0.976. Surprisingly, the product distribution indicated that proton loss by the aminium radical was statistical; loss of benzylic, as opposed to methyl, hydrogens was not favoured.

The limitations to extrapolating a mechanism from the reaction of one compound to that of another apparently similar one were exemplified with certain benzylamines. Ring-substituted N,N-dimethylbenzylamines had indeed exhibited the same sort of kinetics with chlorine dioxide as had triethylamine; only one-electron abstraction was observed for the first step. When related secondary amines were permitted to react, however, both electron abstraction and hydrogen abstraction occurred in the initial step, e.g. reactions (7) and (8). These reactions represent parallel pathways from the same starting materials, through intermediate 2, to the same products. Only reaction (7), constituting 65% of the reaction in the absence of added chlorite ion at pH 7.08 and 40.7°C, was retarded when chlorite was added. Reaction (8) was unaffected by the addition, either because the chlorous acid concentration was not high enough to reverse the initial step in solutions near neutral
pH or because the abstraction of a hydrogen atom by chlorine dioxide is by nature not reversible. The electron abstraction reaction for benzyl-t-butylamine showed a kinetic deuterium isotope effect of 1.8, whereas the hydrogen abstraction reaction gave a value of 4.97. Thus, the duality of the mechanisms was demonstrated by two independent means. In another example, the oxidative deamination of benzylamine by chlorine dioxide at 25°C and pH 8.96 proceeded about 23% by electron abstraction, the remainder by hydrogen abstraction.

In both electron abstraction and hydrogen abstraction, a planar configuration of the bonds about the nitrogen should be energetically favoured; these involve sp2-orbitals, with the odd electron in a p-orbital. In retrospect, therefore, the low reactivity of quinuclidine and its anomalous products with chlorine dioxide should not have been too surprising (reaction 9).

![Chemical structure](image)

It had been surmised that the very similar compound, triethylenediamine (3), should behave like quinuclidine. In one sense, this was certainly not so. The rate constant for the initial step of the reaction with chlorine dioxide, i.e. to form an aminium radical, was about 50 times that predicted on the basis of the Taft $\sigma^*$ constants, as calculated for oxidative dealkylations. This was quite unexpected, since the bonds around the nitrogens could not become coplanar; the stability of this aminium radical had to be explained, at least in part, by the distribution of the odd electron over both nitrogens. In this unusual case, the aminium radical was such that its red colour could be observed ($\lambda_{\text{max}}$ 465 nm, $\epsilon$ 2,104 ± 231) and its electron spin resonance (ESR) spectrum measured259,261, though not in the presence of chlorine dioxide. [The inference of an aminium radical intermediate in reaction (2) was thereby strengthened.] In another sense, there was an important resemblance to the behaviour of quinuclidine. A proton could not be lost from a carbon adjacent to nitrogen. This, or subsequent one-electron oxidation, would have amounted to a violation of Bredt's rule (reaction 10). Instead, a new mechanism
was observed, i.e. oxidative fragmentation\(^{82}\) (reaction 11). The kinetic rate law for reaction (11) in the presence of added chlorite ion was\(^{261}\):

\[
\frac{-d[\text{ClO}_2]}{dt} = \frac{2 k_1 k_2 [\text{ClO}_2]^2 [3]}{k_{-1}[\text{ClO}_2^-]} \tag{12}
\]

This second-order rate law for the oxidation of 3 in the presence of added chlorite stands in contrast to the first-order kinetics described for the previously cited oxidative dealkylations. The measured rate constants applicable to equation (12) at 25°C, in mol\(^{-1}\) s\(^{-1}\), were \(k_1 = 4.05 \times 10^4\), \(k_{-1} = 4.57 \times 10^5\) and \(k_2 = 1.31 \times 10^4\). Separation of these constants was made possible by stopped-flow kinetic examination of the reaction under both presteady-state and steady-state conditions.

Oxidative fragmentation is evidently always to be considered in the oxidation of an amine containing a \(\beta\)-heteroatom such as N or O\(^{82}\).

In both oxidative dealkylation and oxidative fragmentation, the C\(=\)N bond of the oxidized product is ordinarily too labile, in aqueous solution, to resist hydrolysis. Cyclic carbinolamines and Schiff bases can be exceptions to this rule. Reactions (13)–(15) have been observed\(^{118}\).

\[
\text{N-Bu-}n + \text{H}_2\text{O} \rightarrow \text{N-Bu-}n \tag{13}
\]

\[
\text{NH} \rightarrow \text{Trimer of } \Delta^2\text{-piperideine} \tag{15}
\]

\[
\text{N-Bu-}n \text{OH} \tag{14}
\]
As may be readily imagined, various characteristics of amine oxidations are repeated or modified to a degree in oxidations with other oxidants, especially those that operate in one-electron steps. A review by Chow and coworkers\(^5\), which focused on the intermediate nonaromatic aminium radicals, served to compare a number of these and to integrate a corpus of relevant information. In a different sort of comparison with the effects of other oxidants, a few one-electron amine oxidations in aqueous solution, including chlorine dioxide reactions, were correlated by means of the following equations with the ionization potentials \((IP)\) or Taft \(\sigma^*\) values of the amines and the redox potentials of the oxidants\(^1\):

\[
\log k_1 = -7.84 E^0 - 5.31 IP + 3.85
\]

or

\[
\log k_1 = -7.64 E^0 - 4.78 \Sigma \sigma^* - 3.47
\]

### III. HALOGENATING AGENTS

The halogenating agents of major interest are chlorine, bromine and iodine (to a far lesser degree), the corresponding hypohalous acids and a variety of \(N\)-halogenated amines and amides. In most cases, these agents transfer positive halogen to unshared amine electrons, with formation of \(N\)-haloammonium ions from tertiary amines and haloamines from primary or secondary amines. The tertiary amine-derived \(N\)-chloroammonium ions are usually unstable; thus, although Ellis and Soper\(^9\) observed that dry trimethylchloroammonium chloride, formed in carbon tetrachloride, is stable for several days, the triethyl analogue could not be prepared. Both \(N\)-chloroammonium ions form in aqueous solution; these ions decompose oxidatively, as described later, but also react with chloride ion in a partial reversal of the chlorination reaction\(^3\). \(N\)-Chloroquinuclidinium ion \((4)\) is exceptional; it can be hydrolysed to quinuclidine but does not undergo oxidative decomposition\(^1\) (equation 18).

\[
\begin{align*}
\text{Cl} & \quad \text{N}^+ \\
\text{Cl} & \quad \text{N}^+ \\
& \quad \text{OH}^- & + & \text{OCI}^- \\
\end{align*}
\]

Crane and coworkers\(^6\) reported that amines containing the \(\beta\)-chloroethyl group underwent both \(\alpha\)- and \(\beta\)-chlorination in carbon tetrachloride, the latter reaction slightly predominating; hydrolysis of the resultant products produced aldehydes and secondary amines. This has been the only report in recent years to suggest that chlorine is introduced directly to the \(\alpha\)- or \(\beta\)-carbons of aliphatic amines, but it is also one of the few concerned with chlorination in nonpolar media. Detailed examination of the oxidative dealkylation of tertiary amines in acidic aqueous hypochlorous acid solution suggested the sequence shown in reactions \((19)-(23)\). The 'product' \(7\) remained undefined because reaction \((20)\) could be interpreted as either abstraction of an \(\alpha\)-proton from \(6\) by \(5\) (reaction \(24\)) to give \(8\), or electrophilic attack by \(6\) on the \(\alpha\)-carbon of \(5\) to yield \(9\) (reaction \(25\)). Both \(8\) and \(9\) (i.e. versions of \(7\)) would hydrolyse to \(R_2NH\) and \(R^1CHO\). Although reaction \((24)\)

\[
\begin{align*}
R_2(R^1CH_2)N+: + HOCI & \rightarrow R_2(R^1CH_2)^N+ - Cl \\
(5) & \quad (6)
\end{align*}
\]
25. Oxidation of amines

\[ \text{R}_2\text{R'}\text{CH}_2\text{Cl} + 5 \rightarrow \text{R}_2\text{NH} + \text{R'}\text{CHO} \]  

(20)

\[ \text{R}_2\text{NH} + \text{HOCl} \rightarrow \text{R}_2\text{NCl} \]  

(21)

\[ \text{R}_2\text{NH} + \text{R}_2\text{R'}\text{CH}_2\text{Cl} \rightarrow \text{R}_2\text{NCl} + \text{R}_2\text{R'}\text{CH}_2\text{NH}^+ \]  

(23)

\[ \text{R}_2\text{N}^+\text{C}^\text{R'}\text{H} + \text{R'}\text{CHO} \rightarrow \text{R}_2\text{N}^+\text{C}^\text{R'}\text{H} + \text{Cl}^- \]  

(24)

\[ \text{R}_2\text{N}^+\text{C}^\text{R'}\text{H} + \text{H}^+ \rightarrow \text{R}_2\text{N}^+\text{C}^\text{R'}\text{H} + \text{H}^+ \]  

(25)

is more attractive than (25), Taraszka excluded it. He reasoned that if the tertiary amine played the role of a general base catalyst, acetate ion should also be a general base catalyst here; yet it is not.

Differences from the foregoing are seen with Br. Lee and Srinivasan, in studies on dimethylbenzylamines, confirmed speculation by Deno and Fruit to the effect that BrZ attacks the nitrogen electron pair in concert with general base attack on an \( \alpha \)-hydrogen (reaction 26). Both BrZ and HOCl show preferred benzyl cleavage of dimethylbenzylamines, whereas ClO cleavage is proportional to the number of \( \alpha \)-hydrogens. Moreover, BrZ attack favours ring oxidation of \( N \)-methylpyrrolidine and \( N \)-methylpipеридine, in contrast to a greater tendency towards \( N \)-methyl oxidizations by HOCl and ClOZ, thus, Deno and Fruit concluded that the BrZ reaction is not promising for \( N \)-demethylation of alkaloids, unlike HOCl. The pronounced selectivity for ring oxidation over demethylation by BrZ was demonstrated by studies on the alkaloids nicotine and conamine by Picot and Luschini on reactions of alkaline BrZ and IZ and sodium hypochlorite with conamine and related alkaloids provide examples of the diversity of possible reactions. When a methyl proton is eliminated, loss of formaldehyde quickly ensues (reaction 27). However, with elimination of a ring proton, complex products can result, e.g. reaction (28).

\[ \text{N-Haloamides oxidize tertiary amines in a manner very similar to that of hypo-} \]
halous acids. Inasmuch as these reactions are usually carried out in nonaqueous media, vinylamine-type products (enamines) are often the result.

Purine and pyrimidine bases also undergo sequential halogenation reactions. Initially, N- and C-halogenated intermediates are formed, which are often quite stable. However, when the reaction mixtures stand for a long time, especially in the continued presence of excess active halogen species, more extensive reactions take place, accompanied by ring disruption. For example, nitrogen trichloride, carbon dioxide and trichloroacetic acid are produced by HOCl from uracil at pH 7 and chloroform at higher pH; acetic acid, trichloroacetic acid and isobutyramidinium ion, along with a little chloroform, result from HOCl attack on 2-isopropyl-4-methyl-6-pyrimidinol. Guanine, adenine and xanthine slowly form parabanic acid, whereas caffeine and theophylline produce N,N'-dimethylparabanic acid when treated with the same reagent.

A number of other nitrogenous water supply constituents yield chloroform on treatment for several hours with hypochlorous acid/hypochlorite ion at neutral pH, indicating extensive oxidation; chloroform yields increase as the pH is raised to 11. Notable among these water supply constituents are hydroxyproline, tryptophane, indole, m-aminophenol and chlorophyll. Several other compounds produce chloroform only at elevated pH, with maximum yields at pH 8.5–10.5. Chlorine consumption also indicates that other oxidations occur, though they do not lead to chloroform.

In addition to such oxidative dealkylations or ring oxidations as were shown previously, 1,2-diamines can undergo oxidative fragmentation. An outstanding example is reaction (29). The intermediate, 11, also appears to undergo reversible homolysis, as discussed later. Perchloryl fluoride is another oxidant capable of
Consensus seems to favour two-electron pathways in these oxidations, in particular, evidence for this is the fact that light has no effect on the bromination reaction. Nevertheless, homolytic cleavage of the N—Cl bond may give rise to the free radicals in the reaction mixtures, as demonstrated by the ability of a mixture of HOCl and triethylamine to initiate acrylonitrile polymerization and by the easily observed formation of the red aminium radical intermediate when triethylenediamine reacts with HOCl. Moreover, one-electron transfer to give aminium ion intermediates was implicated in the amine-catalysed bromination of olefins by N-bromosuccinimide and in amine oxidations by 1-chlorobenzotriazole.
Product and kinetic studies by Ogata and Nagura on the secondary amine N-benzylaniline demonstrated that hypohalite attack in methanol cannot involve an N-halogenated intermediate; when solutions of such intermediates are made alkaline, aniline ring substitution (halogen or methoxy) invariably results. Based on product isolation and on kinetics with only iodine-containing solutions (because chlorine and bromine are rapidly consumed in organic solvents), they proposed the mechanism shown in reaction (30).

At pH 7, HCl elimination from 14 is general base-catalysed (reaction 31).

\[
\begin{align*}
\text{CH}_3\text{N} &\text{CH}_2\text{CO}_2\text{CH}_3 \xrightarrow{\text{H}_2\text{PO}_4^-} \text{CH}_3\text{N} = \text{CHCO}_2\text{CH}_3 \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{NH}_2 + \text{HC} = \text{CO}_2\text{CH}_3 \quad (31)
\end{align*}
\]

(14)

A slight change from structure 14 gives a compound 15, whose decomposition is unaffected by general base. The nitrenium ion pathway suggested by Kaminski and coworkers (equation 32) borrows from the nitrene mechanism proposed by Pinchuk and coworkers (equations 33 and 34).

\[
\begin{align*}
\text{H} &\text{N} = \text{CH}_2\text{CO}_2\text{Et} \xrightarrow{-\text{Cl}^-} \text{H}: \text{N} = \text{CH}_2\text{CO}_2\text{Et} \xrightarrow{15} \text{H} \xrightarrow{-\text{H}^+} \text{N} = \text{N} = \text{CH} = \text{O} \text{Et}_2 \quad (15)
\end{align*}
\]

(32)

\[
\begin{align*}
\text{EtO}_2\text{CCH}_2\text{N} &\text{CH} = \text{CH}_2\text{CO}_2\text{Et} \xrightarrow{-\text{HCl}} \text{EtO}_2\text{CCH}_2\text{N} = \text{N} = \text{CH} = \text{O} \text{Et}_2 \quad (32)
\end{align*}
\]

(33)

\[
\begin{align*}
\text{H}_2\text{N} &\text{CH} = \text{NCl}_2 \xrightarrow{\text{OH}^-} \text{R}_2\text{C} = \text{N} &\text{Cl} \xrightarrow{\text{Y}} \text{R}_2\text{C} = \text{N} : \text{Y} \quad (33)
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{CN}, \text{PO}(\text{OEt})_2 \text{ or } \text{CO}_2\text{Me}
\end{align*}
\]

(34)

These equations, (33) and (34), do not exclude the numerous examples wherein N-chlorinated secondary or primary amines undergo conversion to imines (and thence by hydrolysis to carbonyl compounds). Here, the initial step could well be attack of base on an α-hydrogen, e.g. equations (35)–(37).

\[
\begin{align*}
\text{RCH}_2\text{NCl} \xrightarrow{\text{base}} \text{RCH}_2\text{NH} &\text{Cl} \quad (35)
\end{align*}
\]

(35)

\[
\begin{align*}
\text{RCH}_2\text{NHCl} \xrightarrow{\text{base}} \text{RCH} &= \text{NH} \quad (36)
\end{align*}
\]

(36)

\[
\begin{align*}
\text{RCH}_2\text{NCl} \xrightarrow{\text{base}} \text{RCH} &= \text{NCl} \xrightarrow{\text{base}} \text{RCN} \quad (37)
\end{align*}
\]

(37)
Although a number of mono- and di-chloroamines and bromoamines have been prepared, pure or in aqueous solution, they are not very stable; this seems to be especially true of the bromoamines. Excess bromine in pH 6 buffer converted dipropylamine to a mixture of pyruvic and propionic acids; propylamine gave propionic acid as the sole product, even with equimolar Br₂.

In the literature of amine halogenation, the reactions of amino acids and peptides occupy a special place. As early as 1909, Langheld reported the oxidative decarboxylation of α-amino acids at neutral pH (reaction 38). Dakin showed that chlorosulphonamides could also act as the chlorinating agents, and later that two moles of sodium hypochlorite, or chlorosulphonamide produced nitriles (reaction 39). Hypobromite oxidations gave the same types of decarboxylation products (16 or 17)\(^\text{106,117}\). N,N-Dichloropeptides (18), which decomposed on standing to N-chloroimides (19), were isolated on treatment of dipeptides with hypochlorous acid. Goldschnidt and coworkers elaborated on the bromination of dipeptides as shown in reaction (40).
They found carbamino acid (20) to be moderately stable in alkaline solution; the amino group was thus protected from further attack by hypobromite. Loss of the N-carboxy function as carbon dioxide occurred quickly on acidification. With tripeptides, a hydantoin and then a dehydroxydantoin were obtained\(^{115,116}\) (reaction 41).

\[
\text{HOBr} + \text{H}_2\text{N-C-C-M-C-C-N-C-CO}_2\text{H} \rightarrow \text{HOBr} + \text{H}_2\text{N-C-C-M-C-C-N-C-CO}_2\text{H}
\]

Glycine and certain of its peptides show some atypical chemistry, which cannot be fully presented here. It is most important to remember, however, that the product of type 17, in the case of glycine, is HCN, which undergoes further reaction with hypohalites to form the cyanogen halide\(^{66}\) or cyanate ion\(^{117}\). Culver\(^{66}\) concluded that \(N\)-chloroglycine forms iminocacetate in strongly alkaline solution (equation 42); it rapidly disproportionates in acidic solution to glycine and \(N,N\)-dichloroglycine. The latter appears by a first-order process in the pH range 5.1–8.5 to form HCN and CO\(_2\) as discussed earlier. Culver\(^{66}\) was less certain about the mode of decomposition of \(N,N\)-dichloroglycine, but slightly favoured reaction (43) over (44). In a very similar reaction, van Tamelen and coworkers\(^{297}\) reported that

\[
3\text{Cl}_2\text{N-C-CO}_2\text{H} + 2\text{H}_2\text{O} \rightarrow \text{H}_2\text{N-C-CO}_2\text{H} + 2\text{HCl} + 2\text{NHCl}_2 + 2\text{O-C-CO}_2\text{H}
\]

(43)

\[
3\text{Cl}_2\text{N-C-CO}_2\text{H} + 2\text{H}_2\text{O} \rightarrow \text{H}_2\text{N-C-CO}_2\text{H} + 2\text{NHCl}_2 + 2\text{HCl} + 2\text{CH}_2\text{O} + 2\text{CO}_2
\]

(44)

oxidation of \(N,N\)-dimethylglycine with one mole of hypochlorous acid in the pH range 1.5–6.3 showed maximum decarboxylation at pH 1.5 (reaction 45).

\[
\text{Me}_2\text{N-CH}_2\text{CO}_2\text{H} + \text{HOCI} \rightarrow \text{Me}_2\text{NH} + \text{CH}_2\text{O} + \text{CO}_2 + \text{HCl}
\]

(45)
Among recent studies on the mechanism of such amino acid oxidations, that of Stanbro and Smith\textsuperscript{286} is noteworthy for its integration of the kinetics of \( N \)-chloroalanine decomposition with product identification to formulate a picture of the variation of reaction pathways with pH. They indicated the existence of two decarboxylative pathways, the second of which was earlier suggested by Fox and Bullock\textsuperscript{105} (reaction 47). Although Fox and Bullock\textsuperscript{105} explained the higher pH formation of pyruvic acid by a carbanion intermediate (equation 48), Stanbro and

\[
\begin{align*}
\text{H}_2\text{C}-\text{N}^+\text{Cl}^- + \text{CO}_2^- &\xrightarrow{\text{Me}} \text{Cl}^- + \text{CO}_2 + \text{H}^+\text{N}^+\text{C}^-\text{H} \\
&\xrightarrow{\text{Me}^+} \text{MeCHO} + \text{NH}_3
\end{align*}
\]

Stanbro and Smith\textsuperscript{286} found that the kinetics did not justify such a mechanism. The scheme of Stanbro and Smith\textsuperscript{286} also required kinetic terms for the autodecomposition and acid-catalysed decomposition of the most protonated species (24), though they wrote no mechanism and did not specify the products (probably those of oxidative
decarboxylation). They completely described the kinetics at 25°C over the pH range 1.5–7.5 by an equation involving species 21, 22 and 24.

The importance of halogen transfer to, from and among amino nitrogens is apparent in the foregoing discussion. Rates and equilibria of chlorine transfer have been determined by a number of investigators, most notably Soper and Smith284, Weil and Morris303,304, Culver66, Friend107, Higuchi and coworkers144, Kaminski and coworkers165, Higuchi and Hasegawa143, Pitman and coworkers246, Hussain and coworkers158, Gray119, Gray and coworkers120 and Margerum and coworkers210. Particularly significant has been the development of values and correlations for chlorine potential, $-\log_{10} K_{cp}$, where:

$$K_{cp} = \frac{[R_2NH][HOCl]}{[R_2NCI]}$$

Although chlorine transfer could occur via hydrolysis to HOCl, Hussain and coworkers158 and Margerum and collaborators210 showed conclusively that direct nitrogen-to-nitrogen transfer occurs much more rapidly.

Hypobromous acid appears to halogenate amines about 3–5 times faster than hypochlorous acid216, but the evidence so far is Fragmentary.

IV. POTASSIUM FERRICYANIDE

Lindsay Smith’s group6,7,8,203,204 has produced the most important mechanistic studies of the ferricyanide oxidation of tertiary alkylamines. The concentration of ferricyanide ion is easy to follow spectrophotometrically at the 420 nm absorption maximum. Unlike many other complexed metal ions, neither the oxidized (ferricyanide) nor the reduced (ferrocyanide) form readily loses its ligands. Ferricyanide is not a particularly reactive oxidant (compared, for example, to chlorine dioxide). For this reason, most of the oxidation experiments have been conducted at high pH, where enough of the amine free base can be present to react with reasonable speed. To dissolve the required concentrations of amines, it has usually been necessary to employ mixed organic–aqueous solvents, such as t-butylamine–water or methanol–water55.

The ferricyanide oxidation mechanisms (equations 50–53) parallel corresponding chlorine dioxide mechanisms in many details (see equation 2). One notable
exception is the irreversibility of ferricyanide's initial electron-abstraction step, as shown by the failure of ferrocyanide to retard reaction in high pH experiments\textsuperscript{6}; this stands in contrast to the large effect of ferrocyanide at pH 8.8\textsuperscript{154}. Other important characteristics of these reactions include:

1. Stoichiometry of the dealkylation (2 moles of oxidant per mole of tertiary amine)\textsuperscript{6.7}.
2. First order, each, in oxidant and amine\textsuperscript{6.7,203,204}.
3. Rate control by electron density on nitrogen (very small $\alpha$-deuterium isotope effect)\textsuperscript{203}.
4. Product control by acidity of the $\alpha$-protons, with associated preference for demethylation\textsuperscript{6}.
5. $\alpha$-Deuterium isotope effect on the nature of the products ($k_H/k_D = 3.6$)\textsuperscript{203}.
6. Lack of any effect by molecular oxygen\textsuperscript{7}.
7. Formamide formation from N-methyl when oxidant is in excess, presumably via the carbinolamine\textsuperscript{6}.
8. Values of $\rho^*$ and $\rho$\textsuperscript{6,7} similar to those for chlorine dioxide\textsuperscript{155,263}.
9. Large cation salt effects\textsuperscript{6}.
10. Clear indication that aminium ions are intermediates\textsuperscript{6}.
11. Decrease in reaction rate from 5- to 6-membered rings, but sizeable increases from 6- to 7- to 8-membered rings (which is probably a planarity effect, as discussed later)\textsuperscript{203,204}.

The inductive effect of amino or hydroxy groups in the $\beta$-position reduces reactivity somewhat; this effect falls off with increasing distance along a chain\textsuperscript{204}. The reactivity is increased, however, when a strong base causes a $\beta$-hydroxyl or $\beta$-oxo (in the enol form) to ionize\textsuperscript{204,260}.

Showing similarity to its reactivity with chlorine dioxide, the bridgehead nitrogen of quinuclidine reacts over 70 times more slowly with ferricyanide ion than does the nitrogen of N-methylpiperidine\textsuperscript{205}. This is attributable to the energetics of the rate-determining step, since aminium radical cations are planar unless constrained by the geometry of the molecules to be otherwise. The cage structure distorts the nitrogen atom from the preferred planar configuration, thereby increasing the enthalpy of activation for electron abstraction. With triethylenediamine (3), however, reactivity is enhanced, despite ring constraints and the unfavourable inductive effect of the second nitrogen atom\textsuperscript{203}. This ready oxidation of triethylenediamine must arise from a through-bond coupling between the two nitrogens, which stabilizes the intermediate-like transition state relative to the ground state\textsuperscript{55,206}.

Like chlorine dioxide\textsuperscript{82}, ferricyanide causes oxidative fragmentation of triethanolamine to formaldehyde\textsuperscript{260}. For the alkaline medium used, one can write reaction (54).

Haynes and Hewgill\textsuperscript{130–132} have described oxidation of three substituted anilines (compounds 25, 26 and 27) by ferricyanide ion. In each instance, the corresponding
azobenzene was isolated, along with phenazines and other products. No oxidation mechanism was discussed.

Abramovitch and Vinutha\(^1\) used alkaline ferricyanide to oxidize \(N\)-methylpyridinium hydroxides to 2-(or 6)-pyridones, presumably via pseudobases of type \(28\). The experiments were insufficient to permit conclusions concerning the oxidation mechanism.

\[
\begin{align*}
\text{azobenzene} & \\
\text{NH}_2 \quad \text{NH}_2 \quad \text{NH}_2 \\
\text{NH}_2 \quad \text{MeO} \quad \text{MeO} \\
\text{Bu-t} \quad \text{Bu-t} \quad \text{t-Bu}
\end{align*}
\]

(25) (26) (27)

IV. MERCURIC ACETATE

Prior to the extensive studies of Leonard and coworkers more than two decades ago\(^{1129, 186-189, 192-197}\), mercuric acetate had been employed occasionally in the modification of alkaloid structures, but little was known of the nature of its oxidative action, and its utility as a synthetic tool for cyclic enamines and iminium salts had not been considered. An example is the first reported treatment of quinolizidine \((29)\) with mercuric acetate in hot dilute acetic acid, followed by addition of alkali and purification of the resulting enamine \((30)\) via the iminium perchlorate \((31)\). The reaction is general for cyclic tertiary amines having one or more protons on carbon adjacent to nitrogen, and the mechanism has been shown to involve abstraction of \(\alpha\)-H in the rate-determining step\(^{192}\). The pathway originally proposed\(^{194}\) (Scheme 1) pictures abstraction by acetate as 4-centre concerted attack with cleavage of the \(N\)-Hg bond in the initially formed \(\pi\)-complex \((32)\) to give iminium cation \(33\) and mercury in a two-electron process; the latter is then oxidized rapidly to insoluble mercurous acetate. The two-electron pathway was later substantiated by the isolation of mercury (and no mercurous acetate) from a similar mercuric acetate oxidation conducted under nitrogen\(^{129}\). The order of ease of \(\alpha\)-H removal is tertiary \(>\) secondary \(>\) primary.

In cases where a tertiary carbon is present \(\beta\) as well as \(\alpha\) to nitrogen, the oxidation may take a different course, a combined dehydrogenation and hydroxylation leading to carbinolamines\(^{193, 195}\). The example of 1-methyldecahydroquinoline\(^{196}\) is illustrative (Scheme 2). A prior equilibrium between \(34a\) and the corresponding base \(34b\) is interrupted by formation of a mercurated \(\pi\)-complex of the latter. Attack of acetate at the double bond may be concerted with cleavage of the \(N\)-Hg bond to give iminium salt \(35\) and \(\text{Hg}^2\), the latter reacting rapidly to give mercurous acetate as above. Addition of base results in proton abstraction at C-8 and hydrolysis of acetate to yield \(36\). In a similar case, hydroxyiminium perchlorate \(38\) was found as a minor product of perchloric acid treatment of the mixture of enamines
25. Oxidation of amines

obtained on oxidation of 4-methylquinolizidine (Scheme 3)\textsuperscript{193}. However, in the case of bicyclic pyrrolidine 39\textsuperscript{121} and in two cases of decahydroquinoline derivatives where the β-carbon was tetrasubstituted (40 and 41)\textsuperscript{173,213}, enamines were the only products isolated.

The effect of substituents on the course of oxidation has been studied with a number of substituted 1-alkyl-piperidines\textsuperscript{187} and -pyrrolidines\textsuperscript{186}. Monosubstitution at the 2 and/or 6(5) positions led to the expected enamines, whereas the unsubstituted and 2,2-substituted compounds gave dimers as the major products (Scheme 4). In the case of 1-methylpyrrolidine, approximately equal amounts of dimer and

SCHEME 1

SCHEME 2
Scheme 3

\[
\text{D-a} \xrightarrow{1 \ \text{Hg(OAc)}_2, \ 2 \ . \ \text{OH}^-} \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array} +
\begin{array}{c}
\text{OH}^- \\
\text{ClO}_4^-
\end{array}
\]

(37) 90%  
(38) 10%

Scheme 4

\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array} \xrightarrow{\text{C}_{16} \text{H}_{17}} \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]

(39)

(40)

(41)
25. Oxidation of amines

trimer (42) were found. These oxidations provide synthetically useful routes to substituted Δ²-tetrahydroanabasines and, after treatment of the pyrrolidine products with ethyl acetoacetate, substituted hygrines. While cyclic secondary amines were inert to Leonard's conditions, Bonnett and coworkers found that certain pyrrolidines (2-methyl-, 2,6-dimethyl- and 2,4,4-trimethyl-) could be forced to give fair yields of the corresponding enamines. Another useful synthetic application was the oxidative cyclization of \(N\)-(3-hydroxypropyl)- and \(N\)-(2-hydroxyethyl)-piperidine derivatives to tetrahydro-1,3-oxazines and -oxazolidines, respectively (Scheme 5). The reagent is also effective in aromatization of certain \(N\)-heterocyclic systems, notably bisbenzylisoquinoline alkaloids and 2-dehydroisoemetine.

![Scheme 5](image)

It should be pointed out that, while noncyclic tertiary amines, e.g. \(N,N\)-dimethylcyclohexylamine and \(N,N\)-dimethylbenzylamine, are reactive, the resulting iminium salts (43) are not stable and lead to the corresponding carbonyl compounds on workup. As for noncyclic secondary amines, one report cites low and variable yields of carbonyl compounds.

![Equations](image)

Experiments by Leonard and by others have served to define the steric requirements for the dehydrogenation reaction, and the results strongly substantiate the proposed 4-centre elimination mechanism requiring trans coplanarity of the \(\alpha\)-H and the \(N\)--Hg bond. Sparticine (44), with two nonequivalent bridgehead tertiary \(\alpha\)-hydrogens (C-6 hydrogen axial-axial to the adjoining rings and C-11 hydrogen equatorial-axial) was shown to lose the former hydrogen more readily. Further, in the yohimbine–reserpine series, alkaloids bearing an axial (\(\alpha\)) hydrogen at C-3 (shown in 45) are more readily oxidized than their \(\beta\) C-3 epimers,
although the possibility of epimerization of the less stable β-epimer may present a complication\(^{94,308}\). Finally, the synthesis and oxidation of 11-methyl-11-azabicyclo[5.3.1]hendecane (46a)\(^{188}\) proved conclusively the requirement for elimination of a proton in \textit{trans} diaxial relationship to the N—Hg bond in the mercurated complex. From the conformational representation (46b), it can be readily seen that both tertiary hydrogens (at C-1 and C-7) are locked into positions equatorial to either a \textit{syn} or \textit{anti} N—Hg bond. In addition to unchanged 46a, the only product isolated after prolonged heating with four molar equivalents of mercuric acetate was the desmethylamine 47 (60%). Thus, while neither tertiary hydrogen can become \textit{trans} coplanar with the N—Hg bond, virtually unrestricted rotation of the N—CH\(_3\) allows one of the primary hydrogens to become aligned favourably for abstraction (Scheme 6). The fact that a primary hydrogen is lost preferentially to a tertiary, by exception to the normal rule, emphasizes the importance of steric requirements in the dehydrogenation reaction. The overall demethylation of 46a to 47 was seen as a six-electron oxidation with the methyl group ultimately converted to \textit{CO}_2\(^{188}\).
VI. MANGANESE SPECIES

A. Manganese Dioxide

Primary aliphatic amines, e.g. ethylamine$^{27}$ and benzylamine$^{142}$, were oxidized in moderate yields to the corresponding carbonyl compounds, and spectral evidence for an imine precursor was reported$^{142}$. Primary aromatic amines, including o- and p-phenylenediamines, on the other hand, gave good yields of azobenzenes$^{27,38,309}$. 2,2'-Diaminobiphenyl was oxidatively cyclized to pyridazine $^{48,38}$. Secondary and tertiary alkyl- and alkylaryl-amines gave a variety of products, notably N-formyl compounds, Schiff bases, carbonyl compounds and oxidation products believed to arise from enamines$^{138}$. A series of substituted benzylanilines (49) gave the corresponding benzilidineanilines (50) in 70–90% yields$^{250}$. The examples in Scheme 7 summarize the oxidative cleavage of substituted ethylenediamines reported by Henbest and coworkers$^{67,138}$.

A series of tri-N-alkylamines $R_N^3$ where $R = n-C_3H_7$ through $n-C_7H_{15}$ gave the respective formamides $R_N^2N—CHO$ in yields improving with increase in chain length (27–54%)$^{136}$. Variation of conditions for (n-C$_4$H$_9$)$_3$N showed better yields (65–74%) at higher temperatures$^{137}$. The lower yields of lower molecular weight compounds were attributed to stronger adsorption and/or further reaction at the catalyst surface. The oxidation is believed to proceed via carbinolamine (51) and enamine (52) intermediates$^{136,137}$.

\[
\begin{align*}
\text{(51)} & \quad \text{OH} \\
\text{(52)} & \quad \text{R}_2\text{N}—\text{CHO} \quad \text{R}_2\text{N}—\text{CHR} \\
\end{align*}
\]

Manganese dioxide has found some synthetic utility in selective dehydrogenation of certain heteroaromatic systems (Scheme 8). Tricyclic ketone 53, which readily
aromatizes to a naphthalene system or undergoes oxidative polymerization, gave a 64% yield of indole 54 on treatment with MnO₂ in CH₂Cl₂ at room temperature. Similarly, tetrahydroquinazoline 55 gave the dihydro derivative 56, and dihydrobenzodiazepine oxide 57 was dehydrogenated without loss of the labile N-oxide.

The oxidative cyclization of a series of N,N'-diaryl-1,3-propanediamines (59) to the respective 1,2-diarylpyrazolidines (60) has also been reported. For additional examples the reader is referred to an earlier review.

B. Potassium Permanganate

Neutral or alkaline permanganate oxidation of amines having hydrogen on carbon bonded to nitrogen (α-H) leads to complex mixtures of products dependent on the structure of the amine and the reaction conditions. More recent work suggests that the mechanistic pathway to the initially formed iminium species, which then reacts further, may also vary depending on the structure of the amine. Considering only the reaction in nearly neutral or weakly basic solution, it is clear from the kinetic studies of Wei and Stewart on substituted benzylamines that the mechanism involves reaction of the amine (free base) with permanganate ion in the rate-determining step; but it is not clear whether α-hydrogen atom or hydride
abstraction\textsuperscript{302}, or electron abstraction from nitrogen\textsuperscript{260} is the predominant process. In the former case, as proposed for benzylamine (Scheme 9), either a hydrogen atom may be transferred in a slow step to give Mn(VI) and a radical intermediate followed by rapid oxidation of the latter, or a hydride ion may be transferred to give Mn(V) and a cationic intermediate in a single slow step. The observed primary kinetic isotope effect of 7.0 is in agreement with this proposal. In the latter case, as proposed for trimethylamine (Scheme 10), the amination cation radical (61), formed in a slow step, rapidly loses a proton giving 62, which is further oxidized to iminium cation 63. The Mn(VI) formed in steps 1 and 3 is subject to rapid disproportionation: \(3 \text{MnO}_4^{-2} + 2 \text{H}_2\text{O} \rightarrow 2 \text{MnO}_4^{-} + \text{MnO}_2 + 4 \text{OH}^{-}\). A secondary kinetic isotope effect of 1.8 was observed for the trimethylamine oxidation, comparable to the relatively large secondary isotope effects (1.3–1.8) found in the generation of amination cation radicals from chlorine dioxide\textsuperscript{156}. The relative rates
for oxidation in buffered permanganate of triethylamine, diethylamine and ethylamine were 31, 0.9 and 0.08, respectively. This order of reactivity conforms to that observed for chlorine dioxide and ferricyanide, where involvement of aminium cation radicals has been demonstrated independently, and is opposite to that inferred from earlier data for permanganate. In summary, in view of these observations and other considerations, a dual mechanism of α-hydrogen abstraction and electron abstraction appears most likely, with the latter dominating for tertiary amines and the former becoming more important as one goes to secondary and then to primary amines.

Rawalay and Shechter have reported a modification of their earlier procedure, which gives optimum yields of carbonyl compounds from appropriately substituted amines. It is suggested as a convenient alternative to more lengthy degradative procedures and may also have some synthetic utility.

The course of oxidation of N-aryl-2-naphthylamines, first investigated by Wieland, has been clarified by Bridger and coworkers more than 60 years later. The structures of the major products (64 and 65, Scheme 11) were conclusively proven and are attributed to C–C and C–N coupling of amino radical. The observed p of −0.68 suggests that transfer of hydrogen to permanganate in a single step is most probable in formation of the latter.

C. Manganic Acetate

Oxidation of N,N-dialkylanilines, the only amine substrates so far investigated for Mn(III) species, evidently follows different courses under different experimental conditions. In addition to polymeric material, the only product isolated from oxidation of N,N-dimethylaniline with two molar equivalents of Mn(OAc)₃ in acetic acid in the presence of air was 67, derived by condensation of a formaldehyde unit with the substrate.

On the other hand, under conditions where N,N-dialkylanilines are known to
undergo oxidative dealkylation on treatment with Pb(OAc)$_4$ to $N$-aryl-$N$-alkylacetamides as major products$^{151}$, Mn(OAc)$_3$ was shown to give the same products, generally in higher yields$^{255}$. Thus, treatment of $N,N$-dimethylaniline with two molar equivalents of Mn(OAc)$_3$ in CHCl$_3$–acetic anhydride (1:1) solution under N$_2$ gave $N$-phenyl-$N$-methylacetamide in 58% yield. In cases of unsymmetrically substituted $N,N$-dialkylanilines, both Pb(OAc)$_4$ and Mn(OAc)$_3$ showed high selectivity in removal of the methyl group in preference to a higher alkyl group; yields of $N$-phenyl-$N$-methylacetamide were <10%. A series of $p$-substituted $N,N$-dialkylanilines (68) was also studied$^{109}$, and the results for Mn(OAc)$_3$ are summarized in Table 1.

![Chemical structure](Image)

**TABLE 1.** Percentage yields of substituted $N$-phenyl-$N$-alkylacetamides 69

<table>
<thead>
<tr>
<th>Para substituent</th>
<th>R</th>
<th>H</th>
<th>OMe</th>
<th>NO$_2$</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>58</td>
<td>55</td>
<td>36</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Et</td>
<td>61</td>
<td>69</td>
<td>43</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>$n$-Bu</td>
<td>83</td>
<td>50</td>
<td>33</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

The mechanism of this oxidation has not been investigated, but kinetic studies of the apparently similar Pb(OAc)$_4$ oxidation (Section VII) show a rate-determining electron-transfer step and suggest an aminium cation intermediate$^{116,110}$. For the oxidation of dimethylaniline in acetic acid, an electron-transfer process was also suggested without elaboration$^5$. Clearly, additional work is desirable to further our understanding of these oxidative processes.

### VII. LEAD TETRAACETATE

A series of primary aliphatic amines as well as benzylamine have been oxidized to nitriles in 40–60% yields with two molar equivalents of Pb(OAc)$_4$ (LTA) in refluxing benzene$^{289}$. Isolation of benzaldehyde (in addition to benzonitrile in 59% yield) constituted evidence for an intermediate imine, and the observed lower yields of low molecular weight nitriles reflected the relatively greater instability of lower molecular weight imines to polymerization$^{289}$. Thus, the reaction may be of some synthetic utility for substituted benzonitriles and higher aliphatic nitriles.

In contrast, primary aromatic amines were oxidized to either azobenzenes$^{17,241}$ or quinones and derivatives$^{241}$ as major products, depending on the ring substituents, but the yields were low and variable. $o$-Phenylenediamines bearing electron-donating substituents have been oxidized in 35–40% yields to $Z,Z$-1,4-dicyano-butadienes by LTA$^{219,220}$; optimization of this conversion will be described in Section VIII.

With arylalkylamines oxidative cleavage takes place, and in the example of dibenzylamine the major products were benzaldehyde (60%) and benzonitrile...
As described in Section VI.C, N,N-dialkylanilines undergo oxidative dealkylation with preferential demethylation to N-aryl-N-alkylacetamides on treatment with LTA in CHCl₃/acetic anhydride. However, in 10 of the 12 cases reported, yields were substantially higher with Mn(OAc)₃. Based on kinetic studies of the oxidation of a number of meta- and para-substituted N,N-dimethylanilines by LTA under these conditions, a mechanism (Scheme 12) involving rate-determining abstraction of an electron from nitrogen to give aminium cation radical, followed by rapid proton loss and a second (rapid) electron transfer, has been proposed. Experimental substantiation for the intermediacy of aminium cation radicals has been obtained from electron spin resonance (ESR) studies of a number of mono-, di- and tri-arylamines in solution with LTA. Furthermore, the ρ value (~2.4 ± 0.5) found for ring-substituted dimethylanilines is indicative of a high degree of positive charge on nitrogen in the transition state.

**SCHEME 12**

Primary and secondary 1,2-amino alcohols undergo carbon–carbon cleavage to aldehydes and imines, the latter generally being further oxidized to nitriles, while tertiary 1,2-amino alcohols are cleaved at carbon–nitrogen to secondary amines and α-hydroxycarbonyl compounds.

Baumgarten and coworkers have studied the oxidative cleavage of a series of α-aminoketones (71) by LTA in CH₂Cl₂ with and without addition of an alcohol (Scheme 13). The products were aryl esters (72a) or acids (72b) derived from the acyl moiety and nitriles derived from the carbinamine moiety. In the absence of an alcohol, yields of cleavage products were lower and acetylation of the aminoketone became competitive.

Oxidation of cis- or trans-2-phenylcyclopropylamine with LTA at −78°C gave high yields of trans-cinnamaldehyde (84% and 79%, respectively), while under the
same conditions, 1-phenylcyclopropylamine gave benzonitrile (69%) and ethylene. Both reactions are believed to proceed via nitrenium ions (Scheme 14). A similar oxidation of 2-phenylaziridine gave benzaldehyde as the only product isolated (42% yield).

A novel LTA-promoted cyclization of steroidal amine 73 to aziridine 74a was extended to simpler cases and proved to be a useful general procedure for conversion of cyclic δ,ε-unsaturated primary amines to highly strained bridged aziridines (Scheme 15). While the steroidal aziridines (74a, b) were stable solids obtained in excellent yields (80–90%), the lower yields (55–60%) of the simpler compounds (75, 76a, b) were attributed to their instability and volatility.

LTA-promoted oxidative fragmentations and demethylations have been observed in a number of complex alkaloid systems and have been of some utility in structural correlations. For example, indole alkaloids have been readily aromatized on treatment with excess LTA in acetic acid. However, on treatment with one equivalent of LTA in CH₂Cl₂ acetoxyindolenines (77) were isolated and characterized, and could be aromatized on further treatment with LTA or converted to dehydro compounds 78 or rearranged to oxindoles 79 (Scheme 16). Thus, reserpilne (80) was
rearranged to carpanaubine (81). In contrast, certain ajmaline derivatives (82) were found to yield 2-hydroxy compounds (83) that underwent demethylation on further treatment with LTA$^{32}$.

VIII. OTHER METALS

A. Copper

Aliphatic amines, with the exception of α-aminoketones, are generally inert to Cu(II). The latter are oxidized to dicarbonyl compounds by Cu(II) in alkaline solution$^{160}$. Aromatic amines are oxidized by Cu(II) in hydroxylic solvents in the presence of O$_2$ to complex mixtures (Scheme 17). Aniline gave quinone anil 84 as a major product in addition to azobenzene and phenoxazine 85$^{92}$, the latter being analogous to 86, obtained from a similar oxidation of o-phenylenediamine$^{314}$. 
The results of a detailed study of the kinetics and product distribution in the oxidation of N,N-dimethylaniline (87) by cupric chloride in ethanol by Lindsay Smith and coworkers\textsuperscript{206} provide compelling evidence for multiple two-electron transfer processes in formation of the products 88–91. A 1:1 complex of the reactants (92) was isolated and characterized, and was converted to 88–91 on warming in ethanol. It was suggested that both Cu(II) species in the complex undergo one-electron reduction facilitated by electron transfer through the chloride bridge resulting in a two-electron oxidation of one molecule of 87 to cation 93, which reacts with 87 to give diamine 88 (Scheme 18). N-Methylaniline (94) was also present among the oxidation products, and when diamine 88 was subjected to the oxidation conditions, a higher yield of methyl violet (90) was found than could be accounted for by oxidation of 87 alone. Thus, 88 is believed to undergo retro-Mannich reaction to 94 and cation 95, which reacts with 87 to give 89 (Scheme 19).
Further sequential two-electron transfers lead to the violet dyes 90 and 91 as shown in Scheme 19.

Cuprous chloride in pyridine in the presence of O₂ was used to oxidize substituted benzylamines to the corresponding benzonitriles and was found to be the reagent of choice for conversion of o-phenylenediamines (96) to Z,Z-1,4-dicyanobutadienes (97). Yields were 62–96% in the unsubstituted case and for electron-donating substituents. Similarly, o-cyano-Z-cinnamonic nitrile (98) was obtained (72% yield) from 1,2-naphthalenediamine. A molar ratio CuCl/96 greater than 2 was necessary to minimize competitive polymerization, and the CuCl complex was regenerated on completion.
of the oxidation. To account for these observations and for the stereoselective formation of Z,Z isomers, a mechanism was proposed (Scheme 20) in which electron transfer from nitrogen to oxidized copper species takes place within the coordination sphere of complex 99.

The extensively studied Cu(II)-catalysed reaction of amines with carbon tetrachloride gave a variety of products believed to arise from an initial radical chain reaction followed by a number of further ionic processes\textsuperscript{200}. The role of the catalyst is yet unclear.

B. Silver

Argentic oxidants will be treated here as three general classes that differ significantly in methods of preparation and properties as oxidants. Silver persulphate,
prepared *in situ* by addition of sodium persulphate to a catalytic amount of aqueous alkaline silver nitrate solution containing the amine, is a useful reagent for the conversion of low molecular weight primary amines to carbonyl compounds (60–95% yields)\(^1\), and the intermediate aldimines (but not ketimines) may be isolated if the solution is allowed to remain basic. These conditions, however, were not found useful for preparation of carbonyl compounds from secondary amines\(^1\). Intermediacy of Ag(III) in persulphate oxidations has been suggested\(^2\), but the mechanistic picture is unclear. Alternatively, argentie ion may be isolated as the red solid picolinate 100 prepared by persulphate treatment of an alkaline solution of silver nitrate and picolinic acid. With this reagent, primary amines were found, in contrast to earlier observation\(^4\), to give mixtures of nitriles and aldehydes with the former predominating except in the case of *p*-nitrobenzylamine, where hydrolysis of the intermediate imine evidently competed favourably with further oxidation\(^5\). Water\(^14,18\), DMSO\(^184\) and ethanol\(^14\) have been used as solvents. Mechanistically, Ag(II) picolinate oxidations were viewed as one-electron transfer processes without experimental substantiation, but recent evidence from a study by Challis and Outram\(^3\), which demonstrated the intermediacy of amine radical cations derived from Ag(II)–amine complexes in the nitrosation of secondary amines, suggests the probable involvement of radical cation intermediates in these oxidations.

Argentic oxide has been reported to oxidize low molecular weight amines in aqueous solution in unspecified yields\(^5\). The products appeared similar to those of

\[
\text{CuCl} \quad \text{O}_2, \text{pyr.} \\
(CuCl)\text{C}_6\text{H}_4(\text{NH}_2)_2\text{C}_5\text{H}_5\text{N}_n \quad \text{yellow} \\
(CuCl)\text{C}_6\text{H}_4(\text{NH}_2)_2\text{C}_5\text{H}_5\text{N}_n \quad \text{green} \\
\text{O}_2, \text{pyr.} \\
\text{Ag} \quad \text{O} \\
\text{N} \quad \text{C} = \text{O} \\
\text{O} \\
\text{C} = \text{N} \\
\text{O} \\
\text{Ag} \\
\text{O} \\
\text{N} \quad \text{C} = \text{O} \\
(100)
\]
Ag(II) picolinate for amines having α-hydrogen, and in addition t-butylamine was oxidized to a 2:1 mixture of t-butyl alcohol and 2-methyl-2-nitropropene. Certain ring-substituted anilines were converted to the respective azobenzenes in 15–59% yields on treatment with AgO in organic media (benzene or ether)\textsuperscript{235} (Scheme 21).

Oxidation of ring-substituted anilines (101a–e) by Ag\textsubscript{2}CO\textsubscript{3}/celite, reported by two French groups\textsuperscript{97,133}, also gave azobenzenes (102a–e, Scheme 21) and is believed to proceed by a radical coupling process. Unless both ortho and para positions were substituted, yields were only moderate, and minor products (103c, 103d, 104b) resulting from C–N couplings of the initial radical were also isolated\textsuperscript{133}.

Treatment of a number of substituted N-phenylaminooindoles (105, R = H or Me) with silver(1) perchlorate in acetonitrile gave rise to aminium radical cations (106), some of which (R' = OMe or NMe\textsubscript{2}) were sufficiently stable to be isolated and characterized\textsuperscript{47}. Aminium perchlorate 106a in acetonitrile was further oxidized to iminium perchlorate 107 by molecular oxygen (Scheme 22)\textsuperscript{46}.

**C. Miscellaneous Metal Oxidants**

Ruthenium tetroxide was shown to be a useful reagent for the oxidation of various N-substituted pyrrolidines and piperidines (108, n = 2, 3) to the respective amides (109), and in some cases further to imides\textsuperscript{276}. Amides were also isolated in lower yields from certain azetidines (108, n = 1). 1,2-Di-t-butylaziridine (110) was oxidized to amide 111 in 77% yield. Application of this procedure to determination of the absolute configuration of cyclic 3-arylamines (112) gave imides (113), which were hydrolysed to optically active acids of established configurations\textsuperscript{35}. 
A ruthenium tetroxide–sodium periodate reagent has been employed to oxidize arylalkylamines with electron-donating substituents to amino acids (Scheme 23). In acidic solution the amino group was not affected and the aryl group was readily oxidized.

Nickel peroxide was found useful for the preparation of nitriles from primary aliphatic amines and substituted benzylamines, but was a poor choice for conversion of o-phenylenediamines (96) to dinitriles (97). Tetraarylhydrazines were obtained in moderate yields from diarylamines.

Rates of oxidation of a number of amino acids by Co(III) in perchloric acid solution were very rapid compared to benzylamine, and aliphatic amines were essen-
25. Oxidation of amines

1119

\[
\begin{align*}
\text{HO-} & \quad \text{(CH}_2\text{)}_n\text{CH}_2\text{NH}_3 & \to & \text{HO}_2\text{C(CH}_2\text{)}_n\text{CH}_2\text{NH}_3 \\
n = 1, & \quad 86\% \\
n = 2, & \quad 69\% \\
\text{MeO-} & \quad \text{CH-} \quad \text{NH}_3 & \to & \text{HO}_2\text{CCH-} \quad \text{NH}_3 \\
& & & \quad 50\%
\end{align*}
\]

SCHEME 23

tially inert. The amino acids are believed to be oxidized by a mechanism similar to that proposed for carboxylic acids, and of the amines only benzylamine, due to resonance stabilization of an α-aryl radical, can be attacked at α-C−H.

An investigation of aqueous potassium ferrate as an oxidant for alcohols and amines reported isolation of benzaldehyde and acetophenone in 70% yields from benzylamine and α-methylbenzylamine, respectively, and a ‘high’ yield of 3,4-dihydroisquinoline from 1,2,3,4-tetrahydroisquinoline. Tertiary amines were not oxidized.

A comparison of oxidations of eight primary amines to carbonyl compounds with PdCl₂ and AuCl₃ in water was made, and in five cases AuCl₃ at pH 4.5–6 gave higher yields. Exceptions were cyclopentylamine and α-methylbenzylamine (each requiring addition of 10% Pd on charcoal to the PdCl₂) and cycloheptylamine. Indoline underwent Pd-promoted dehydrogenation to indole in 83% yield.

In the course of investigation of UF₆ as a selective oxidant for organic compounds, five N,N-dimethylalkylamines were oxidized to the respective carbonyl compounds (16–70% yields). A two-electron pathway via an iminium ion intermediate was suggested.

A number of examples of metal-catalysed O₂ oxidations in the liquid phase have been reported. The methyl group in N-methyl tertiary amines was selectively oxidized to N-formyl at ambient temperatures in benzene over platinum black. The same selective conversion took place in N,N-dimethylformamide with dissolved catalysts at 100–150°C and air pressures up to 35 atmospheres; reported catalysts were CuCl₂, Cu₂Cl₂, CuBr₂, Cu₂I₂, FeCl₃, NiCl₂, CoBr₂, CoCl₂, AgCl, AuCl₃, ZnCl₂, HgCl₂, MnCl₂, Re₃Cl₃, PdCl₂ and PtCl₂, anhydrous or hydrated. Although the synthesis of N,N-dimethylformamide from trimethylamine was studied in greatest detail, other examples, such as N-formylpipercidine from N-methylpipercidine and N-methyl-N-phenylformamide from N,N-dimethylaniline, showed the breadth of possibilities.

At about 100°C and 2–3 atm of oxygen, hydrated RuCl₃ in toluene catalysed conversion of RCH₂NH₂ to RCN and RCONH₂, and RR¹CHNH₂ to RR¹C=O and RR¹C=NH.

IX. Peroxy Species

A. Hydroperoxides – Peroxy Acids and Hydrogen Peroxide

The peracid oxidant of choice for conversion of primary aliphatic amines RCH₂NH₂ or R₂NCHNH₂ to primary and secondary nitroalkanes, respectively, is
without question \( m \)-chloroperbenzoic acid (MCPBA), with addition of a solution of amine to a large excess of peracid in the refluxing solvent being necessary to minimize stoppage at the nitroso stage due to dimerization\(^{18,256} \). Oxidation of chiral amines proceeded with retention of configuration at the chiral centre, as demonstrated in the cases of epimeric 3α,3β- and 20α,20β-steroidal amines\(^{256} \) and of four amino sugar derivatives\(^{18} \). Gilbert and Borden\(^{114} \) have recently reported that higher temperatures (refluxing 1,2-dichloroethane) and longer reaction times than used previously gave higher yields of primary and secondary nitroalkanes relative to nitroso compounds. While tertiary nitroalkanes are generally better prepared by \( \text{KMnO}_4 \) oxidation of tertiary carbinamines\(^{174} \), it is worth noting that in one case (\( t \)-BuNH\(_2 \)) sodium tungstate-catalysed \( \text{H}_2\text{O}_2 \) oxidation gave only a somewhat lower yield (70%)\(^{290} \) compared to \( \text{KMnO}_4 \) (83%)\(^{174} \).

Of various peracid oxidants employed for conversion of secondary amines to stable nitroxyl free radicals\(^{207,266} \), the most generally useful appear to be MCPBA and sodium tungstate-catalysed \( \text{H}_2\text{O}_2 \) in methanol/acetonitrile\(^{251} \). The yields for some substituted piperidines (Table 2) show a dramatic improvement in comparison with aqueous sodium tungstate-catalysed \( \text{H}_2\text{O}_2 \) for the less water-soluble compounds\(^{251} \).

Progress has been made recently in synthetic methodology for oxidation of poly-nitroanilines to polynitrobenzenes (toluenes). Trifluoroperacetic acid was found to effect nearly quantitative conversion (94–98%) of aminodinitrotoluenes to the respective trinitrotoluenes\(^{86} \). For similar syntheses of tetrinitrobenzenes and penta-nitrobenzene, the oxidant of choice was nearly anhydrous peroxydisulphuric acid (78–95% yields)\(^{227} \). For oxidation of penta-nitroaniline a new reagent, peroxytrifluoromethanesulphonic acid, gave hexanitrobenzene in 90% yield\(^{228} \), compared to 58% obtained with peroxydisulphuric acid\(^{227} \).

Oxidation of 2-aminopyridines to the corresponding nitropyridines (60–68%) with Caro's acid has been reported\(^{312} \), but later work\(^{57,140} \) indicates that further oxidation to \( N \)-oxides as major products may present a complication. Hindered aromatic amines have been oxidized to nitroso compounds with perbenzoic acid and MCPBA: 2,4,6-tri-\( t \)-butylaniline\(^{232} \) and 4-fluorenylamine\(^{316} \) in 80% yields, and other less hindered 2-\( t \)-butylanilines in 43–73% yields\(^{232} \).

A recent kinetic comparison of oxidations of \( N,N \)-dimethylaniline and \( N \)-methyl-

### Table 2. Yields (%) of nitroxyl radicals from some substituted piperidines

<table>
<thead>
<tr>
<th>( R )</th>
<th>( R' )</th>
<th>( \text{H}_2\text{O/aq.} )</th>
<th>( \text{H}_2\text{O/MeOH/MeCN} )</th>
<th>MCPBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>O</td>
<td>50</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>H</td>
<td>OH</td>
<td>80</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>H</td>
<td>CO(_2)Me</td>
<td>15</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>H</td>
<td>CO(_2)Bu-( t )</td>
<td>10</td>
<td>88</td>
<td>83</td>
</tr>
</tbody>
</table>
25. Oxidation of amines

\[ R, R' \quad \text{N-phenylaniline} \quad \text{with peroxymonophosphoric acid}^{230} \text{ has shown a rate-determining nucleophilic attack of neutral amine on peracid oxygen similar to that well established for other peracid oxidations of primary amines}^{247}. \]

Behrman and Behrmam\(^{34}\) have recently clarified the course of oxidation of aromatic amines (114) by peroxydisulphate in alkaline media (Boyland-Sims oxidation). Earlier work had shown the reaction proceeded via electrophilic attack of peroxydisulphate anion on the neutral amine, and since the product was \( o \)-aminoaryl sulphate (115) (Scheme 24), arylhydroxylamine-\( O \)-sulphonate (116) was proposed as an intermediate. Support included kinetic studies on ring-substituted anilines, which excluded rate-limiting attack at the \( \text{ortho} \) carbon. However, independent synthesis of 116a and the finding that it did not rearrange to 115a under Boyland-Sims conditions excluded 116a as an intermediate for tertiary amines. The Behrmans then conducted kinetic studies on ring-substituted \( N,N \)-dimethylanilines, which excluded rate-limiting attack at the \( \text{ortho} \) carbon for tertiary amines as well as for primary. Rather, the reaction is now viewed as proceeding by \( \text{ipso} \) attack with rearrangement via 117 for tertiary amines and perhaps also for primary and secondary.

Oxidation of primary aromatic amines by peroxydisulphate in acetic acid follows a different course, leading to \( N \)-aryl-\( p \)-benzoquinonedimines as initial products, and is believed to proceed by a radical mechanism\(^{285}\).

An earlier report\(^{177}\) that tertiary amines were oxidized to \( N \)-oxides by \( t \)-butyl hydroperoxide at low temperatures in the presence of vanadium or molybdenum catalysts has been confirmed\(^{278}\), and, under similar conditions, anilines were oxidized to nitrobenzenes\(^{152}\). Thus, the reaction takes a very different course from \( t \)-butyl hydroperoxide oxidations under conditions known to promote free-radical oxidations\(^{79}\) and is similar to oxidation by other hydroperoxides. Kinetic studies supported a mechanism involving rapid, reversible formation of a peroxide-catalyst complex followed by rate-determining nucleophilic attack of amine lone pair and heterolytic \( O-O \) bond cleavage\(^{152}\).

Six products of oxidation of \( N \)-phenyl-2-naphthylamine (118) with peroxy radicals generated from \( t \)-butyl hydroperoxide were separated and identified by Ingold and
coworkers (Scheme 25)\(^\text{42}\). Three were radical coupling products, two identical with the major products of permanganate oxidation of 118 (Section VI) and the third (119) identical to a trace permanganate product. Products 120, 121 and 122 are believed to result from attack of radicals and/or various nucleophiles on an intermediate quinone imine (123).

**B. Diacyl Peroxides**

The complex and extensively investigated reactions of diacyl peroxides with amines were reviewed in 1971\(^\text{141}\). Since then, the course of oxidation of amines by diarylsulphonyl peroxides (124) has been studied comprehensively by Hoffman and coworkers\(^\text{143h,146-149}\), and detailed pictures of the mechanisms of competing elimination and rearrangement processes have been well documented. Primary and
secondary alkyl- and alkylaryl-amines (substituted benzylamines) having α-hydrogen gave as major products carbonyl compounds resulting from hydrolysis of the intermediate imine\textsuperscript{145b}. An exception was p-methoxybenzylamine in which rearrangement (40%) competed favourably with elimination (12%)\textsuperscript{149} (Scheme 26). In cases where no α-hydrogen was present (tritylamines), only rearrangement products were found, and for certain substituted benzhydrylamines, the products were mixtures of benzophenone and benzaldehydes resulting from elimination and rearrangement, respectively\textsuperscript{148,149}. Kinetic studies and the results of substituent effects in the oxidation of a series of benzylamines with p-nitrobenzenesulphonyl peroxide support a 2-step, 2-electron mechanism (Scheme 26) where rapid nucleophilic attack by amine yielding hydroxylamine-O-2-nitrobenzenesulphonyl adduct (125) (similar to the O-acylhydroxylamine adduct in diacyl peroxide oxidations)\textsuperscript{81} is followed by rate-determining elimination to imine\textsuperscript{147}. Kinetic and isotope effect studies with substituted benzylamines and substituted arylsulphonyl peroxides support an 'unsymmetrical' transition state for elimination in which the leaving group is largely removed and there is substantial benzylic proton transfer. At the same time, a lack of benzylic charge development implies significant π-bond character in the transition state\textsuperscript{146}. As to the observed rearrangements of aryl groups, determination of migratory aptitudes in a series of substituted benzhydrylamines and tritylamines indicates that aryl migration in the hydroxylamine-O-p-nitrobenzenesulphonate intermediate is concerted with loss of arylsulphonate anion\textsuperscript{148}.

**X. QUINONES**

Henbest and coworkers investigated the oxidation of aliphatic tertiary amines in benzene by a variety of quinones\textsuperscript{48,49,135}. These reactions are of special interest because they produce colours that may be useful in visualizing amines on thin-layer chromatograms or otherwise characterizing them.
When triethylamine reacts with chloranil, two distinct events occur in sequence (reactions 55 and 56).

\[
(C_2H_5)_3N + (C_2H_5)_2N\cdot C=CH_2 \rightleftharpoons [AQ] \rightarrow (A)
\]

\[
(C_2H_5)_2N\cdot C=CH_2 + (C_2H_5)_3N\cdot HCl (56)
\]

(126)

\[
126 + A + Q \rightarrow \begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{Cl} \\
\text{C}=\text{C} - \text{N}(C_2H_5)_2 \\
\text{H} \\
\text{H}
\end{array} + (C_2H_5)_3N\cdot HCl (56)
\]

(127)

The ethyl group of \(N\)-ethylpiperidine similarly loses hydrogen and the product forms a blue diethylaminovinylquinone, but \(N\)-methylpiperidine, in the absence of light, does not react. Thus, neither the methyl group nor the heterocyclic ring is easily oxidized by chloranil. Trimethylamine is believed to form the initial complex in higher concentration than triethylamine, but is oxidized much more slowly, and cannot form a blue conjugate. Other oxidants can perform the oxidizing function, for example, benzoyl peroxide, 3,3',5,5'-tetrachlorodiphenoquinone or \(N\)-bromosuccinimide. When triethylamine is oxidized by benzoyl peroxide in the presence of 127, a purple product, 128, is formed.

\[
(C_2H_5)_2N\cdot C=NC=C\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\]

(128)

Triethylamine forms a complex with 129, but 129 lacks the oxidation potential to dehydrogenate the amine in the dark (although it does so under strong illumination); when benzoyl peroxide is added, however, 130 forms easily, owing to
reaction 57. Thus, formation of a blue conjugate from 129 in the presence of a suitable amine and an oxidant is evidence of an enamine intermediate.

Diethylamine also reacts with quinones, but the vinyl group formed by oxidation can transfer to a molecule of unoxidized diethylamine to form 126. For example, the products of 131 and diethylamine included 132 and 133, and under appropriate conditions 134 and 135 could be obtained.

In some cases, where vinylamine intermediates such as 126 could not be formed, it was nevertheless possible to isolated aldehydes as their 2,4-dinitrophenylhydrazones. For example, from tribenzylamine, the ionic intermediate 136 must have been formed, albeit slowly.

Bromnanil reacts substantially as chloranil; iodanil seems to react much more slowly, owing to steric factors.
XI. MOLECULAR AND ATOMIC OXYGEN

Although amines are not normally very reactive (without catalysis) with molecular oxygen at ambient temperatures, certain structural features favour oxidation. Thus, enamine 137 underwent air oxidation in benzene to 138 through a postulated free-radical chain-mechanism involving an aminium radical. The reaction was accelerated by ferric and cupric salts.

(137) (138)

N-Alkylisoindolines are especially subject to autoxidation. Kochi and Singleton studied the effect of \( \text{O}_2 \) on \( N-n \)-butylisoindoline (139) in a variety of solvents at 38°C. Oxidation proceeded rapidly in 'hydrogen-donor' solvents, such as methyl ketones, alkenes and isopropyl alcohol, but not in several other solvents, such as benzene, toluene, cumene, pyridine, benzaldehyde or nitriles. The reaction sequence appeared to involve cooxidation of at least some of the solvents. A complex chain mechanism carried the starting material, 139, through \( N-n \)-butylisoindole (140) to the reaction products, \( N-n \)-butylphthalimidinc (141), \( N-n \)-butylphthalimide (142) and, to a lesser extent, \( N-n \)-butyl-3-hydroxyphthalimide (143).

(139) (140) (141) (142) (143)

Under more severe conditions than the foregoing, a study was made of the reaction kinetics of \( \text{O}_2 \) with 1-naphthylamine, \( N \)-phenyl-1-naphthylamine, \( N \)-phenyl-2-naphthylamine and \( N,N' \)-di-2-naphthyl-p-phenylenediamine in benzene. Air or oxygen pressures up to 30 atm and temperatures from 120 to 220°C were employed. The reactions were first order, each, in amine and oxygen.

Cullis and Waddington studied the gas-phase reactions of triethylamine and trimethylamine with oxygen. Triethylamine oxidation became measurable above 200°C, and 'slow' reaction persisted to 280°C; 280-360°C was an explosive region, but slow consumption took place between 360 and 400°C, with explosion again above that range. Kinetics at 211°C indicated two concurrent oxidation
pathways in the early stages, one represented in part by equation (58) and the other by equation (59). The overall process, reflecting principally equation (58), produced mainly ethylamine and acetaldehyde.

\[
\begin{align*}
\text{Me} & \quad \text{H} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} \\
\text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} & \quad \text{H} & \quad \text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{H} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} & \quad \text{H} & \quad \text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} \\
\text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} & \quad \text{Me} & \quad \text{H} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} & \quad \text{Me} & \quad \text{H} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{CHO} & \quad \text{O} & \quad \text{OH} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} & \quad \text{Me} & \quad \text{H} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} \\
\text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} & \quad \text{Me} & \quad \text{H} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} & \quad \text{Me} & \quad \text{H} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{CHO} & \quad \text{O} & \quad \text{OH} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} & \quad \text{Me} & \quad \text{H} & \quad \text{Et} & \quad \text{N} & \quad \text{C} \quad \text{Me} \\
\end{align*}
\]

The reaction of trimethylamine with oxygen was rapid even at 165°C, but did not go to completion; at initial pressures of 100 mm in each reactant, 75% of the initial amine and 65% of the oxygen were unconsumed when reaction ceased. Small amounts of formaldehyde, dimethylamine and nitrogen were found in the products.\(^{65}\)

Kirchner and coworkers\(^{169,170}\) reported the reaction rates of atomic oxygen (from \(N + NO \rightarrow N_2 + O\)) with amines over the temperature range 300–450 K. Reactivity at 300 K was of the order trimethylamine > dimethylamine > ethylamine > methylamine > ammonia. The activation energy for ammonia was considerably higher than for the primary amines. Reaction products for methylene were reported as \(\text{CH}_4, \text{NH}_3, \cdot \text{OH}, \text{H}_2\text{O}, \text{H}_2\) and \(\text{O}_2\).

**XII. OZONE**

Ozonation as a synthetic tool for conversion of primary or aromatic amines to nitro compounds\(^{12}\) generally rates poorly in comparison to peracid oxidation (Section IX). However, a recently described procedure for ozonation of the amine adsorbed on dry silica gel, which gave 65–70% yields for certain primary aliphatic amines\(^{166}\), may be of potential utility.

As to mechanisms of ozonation of aliphatic amines, the systematic investigations of Bailey and coworkers over the past decade\(^{19–26}\) have contributed substantially to our understanding of a variety of complex processes operating in competition. The initial amine–ozone adduct \((144a, b)\) may undergo decomposition by three different pathways (Scheme 27) giving species that generally react further: (a) loss of molecular oxygen yielding amine oxide or hydroxylamine, (b) homolytic dissociation to aminium cation and ozonate anion radicals and (c) intramolecular oxidative rearrangement to \(\alpha\)-hydroxyamine \(^{145}\), which yields \(\alpha\)-cleavage (side-chain oxidation) products. In cases of secondary and tertiary amines with secondary alkyl substituents (e.g. isopropyl), a 1,3-dipolar addition process (Scheme 28) is believed to be the preferred pathway to intermediate
145. With secondary amines in halocarbon solvents, a fourth pathway (d, Scheme 29) leading to nitroxyl radical, ammonium ion and superoxide ion was found to be important. The identities and relative amounts of products resulting from these competitive processes varied widely with the solvent and temperature as well as with the structure of the amine. The amine oxide pathway being more important in polar solvents and at lower temperatures. Thus, n-butylamine and i-propylamine gave nitroalkanes (pathway a), ammonium salts and isocyanates.
(pathway b, the products arising by a succession of reactions involving aminium cation and ozonate anion radicals, and solvent derived species) and carbonyl compounds (pathway c) as major products\(^{19}\); similar mixtures of products from pathways a and b were obtained from \(t\)-butylamine\(^{19}\). In contrast, products of pathways c (\(N\cdot n\)-butylidene-\(n\)-butylamine, 146, and nitrone 147 from \(n\)-butylamine,
\[
\begin{align*}
n\cdot \text{PrCH} = \text{NBu-n} & \quad n\cdot \text{PrCH} = \text{NBu-n} \\
(146) & \quad (147)
\end{align*}
\]
and acetone from \(di\cdot i\)-propylamine) and d (ammonium salts from \(di\cdot i\)-propylamine and \(di\cdot i\)-butylamine) predominated for secondary amines\(^{12,16}\). In addition, 2-nitropropane and 2-methyl-2-nitropropane, isolated in significant amounts from ozonation of the latter two amines, were shown to be derived from oxidation of the respective nitroxides\(^{10}\). The presence of nitroxides as important intermediates in ozonation of secondary amines had been demonstrated earlier by Russian workers\(^{23,3}\). Amine oxides and alkyl cleavage products were predominant for tertiary alkylamines\(^{24,25}\).

Ozonation of tertiary aromatic amines, however, was found to follow a different course, and further studies by Kerr and Meth-Cohn\(^{167}\) have cast some light upon the mechanisms involved. The major products of a series of substituted \(N\cdot N\)-dimethylanilines were \(N\)-methylformanilides (148) and bis(\(N\)-methylanilino)methyl peroxides (149); no \(N\)-oxides were found. Relative amounts of the two products were solvent-dependent, 148 predominating in polar solvents and 149 becoming more important with decreasing solvent polarity. Thus, it is believed that both cationic and radical intermediates are involved as precursors of 148 and 149, respectively. The absence of \(N\)-oxide products was attributed to greater stability of...
the initial ozone adduct 150 relative to an aliphatic counterpart, resulting in proton abstraction from the N—CH₃ group, rather than O—O bond cleavage, being the dominant mode of reaction (Scheme 30).

Ozonation of N-arylpyrrolidines gave mixtures of dimers (151) and N-aryl-2-pyrrolidones (152)⁶⁸. The initial adduct 153 was envisioned to undergo proton abstraction and loss of O₂, followed by dimerization or further oxidation of the resulting iminium species (154) (Scheme 31).

XIII. ELECTROCHEMISTRY

A. 'Inert' Electrodes: Platinum, Glassy Carbon, Lead Dioxide

Electrochemical oxidations of aromatic amines and amino acids have long been studied, and are detailed in four recent reviews⁵⁴,⁷⁳,⁸⁸,⁹². Thus, this discussion is limited to a few papers in the former category that were not reviewed or were published subsequently. Nelsen and coworkers²²⁴ have measured free energies of formation of cation radical (E⁰⁺) and dication (E⁰⁺) for a number of alkyl-substituted o-phenylenediamines by cyclic voltammetry (CV). The results were interpreted in terms of steric and electronic effects and evidence was presented both from CV and nuclear magnetic resonance (NMR) data that the dications, in contrast to the cation radicals, are significantly nonplanar. For geometry of the neutral molecules, a
correlation of downfield shifts in $^{13}$C-NMR of the two carbons bonded to nitrogen with decreased conjugation of the nitrogen lone pairs with the ring was made.

$N$-Substituted diarylamines have been oxidized to carbazoles (155) at a platinum anode in acetonitrile$^{254}$, and the results compare interestingly with the photochemical process (Section XIV). The electrochemical cyclization requires that all $para$ positions be blocked; otherwise $p,p'$-benzidines (156) are formed nearly quantitatively by coupling of the initially formed cation radicals (Scheme 32)$^{272}$. In contrast, $p,p'$-disubstituted diphenylamines and $p,p',p''$-substituted triphenylamines form extremely stable radical cations that neither cyclize or couple. On further oxidation, however, the dications react extremely rapidly, giving carbazoles among other products. Since the dication is a $4n$-electron system, ring-closure is a conrotatory process (Scheme 32).

Anodic oxidation of secondary $p$-substituted diphenylamines showed that the

\[
\begin{align*}
\text{(155)} \\
\text{(156)}
\end{align*}
\]

\[
\begin{align*}
\text{(a) } R = p \cdot C_6H_4X, \text{ alkyl} \\
\text{(b) } R = H
\end{align*}
\]

\[
\begin{array}{c}
\text{SCHEME 32}
\end{array}
\]
initially formed cation radical could give rise to four possible types of product (156b, 157–159) depending on the nature of the substituent and the alkalinity of the medium (Scheme 33)\(^{273}\). Diaryldihydrophenazines (157) or tetraarylhydrazines (159) were obtained from \(p,p'\)-disubstituted diphenylamines\(^{51}\). A nitrenium ion (\(\text{Ar}_2\text{N}^+\)) is believed to be an intermediate in the formation of types 157 and 158\(^{51,273}\).

The overall process in anodic oxidation of tertiary alkylamines in acetonitrile or in aqueous alkaline solutions is oxidative dealkylation to carbonyl compounds and secondary amines\(^{54}\). The latter also undergo similar dealkylation\(^{301}\). In methanol, however, \(\alpha\)-methoxylation may be a predominant process\(^{305}\). Mechanistically, both processes have elicited some controversy, but most evidence presented recently supports a mechanism strictly analogous to that proposed for chemical one-electron oxidants and not involving electrode surface phenomena (Scheme 34)\(^{201}\). Correlations of logarithms of rate constants of a number of one-electron oxidations of amines with the amine polarographic peak potentials have been made\(^{155}\). Disproportionation of two aminoalkyl radicals to amine and enamine intermediate was also suggested\(^{248}\), but later work does not support this possibility\(^{212,249,264,265}\). Some evidence for preferential dealkylation of methyl versus higher alkyl groups was cited\(^{212}\), but more definitive work showed a nearly statistical distribution of products. The combination of this observation and a low primary isotope effect for the deprotonation step supports a transition state with a nearly intact \(\alpha\)-C—H bond, resembling the aminium cation radical more than the \(\alpha\)-amino radical\(^{201}\).

The complex course of \(\alpha\)-methoxylation of \(N,N\)-dimethylbenzylamine has been analysed by Ross and coworkers\(^{29}\), and the results were found to depend on both the anodic potential and the nature of the base present. At low potentials, the
mechanism is similar to that depicted in Scheme 34, involving proton loss from the initially formed aminium radical followed by electron transfer to give cations that react with methanol yielding the final products 160 and 161. The relative amounts of the α-amino radical precursors are determined by the nature of the base participating in proton transfer. In neutral solution, where amine substrate is the base, transfer from CH₂, yielding 160, is highly favoured, whereas in alkaline media, a nearly statistical product distribution results. At higher potentials, a competitive mechanism involving abstraction of H· from neutral amine molecule by solvent-derived hydroxymethyl radicals becomes important and 161 is favoured. Anodic oxidation of N,N-dialkylcarbamates in methanol gave predominantly α-methoxylation and in a few cases dealkylation products.

In the case of nortropane (162), the α-protons are considered to lie nearly perpendicular to the charge-bearing orbital in the radical cation, and α-deprotonation becomes an unimportant process. The products isolated on anodic oxidation in acetonitrile (163 and 164, Scheme 35) were believed to arise from adduct 165 formed by coupling of nortropyl radical and solvent-derived ·CH₂CN.

Geometrical factors influencing the stability (longevity) of nonaromatic aminium radical cations have been extensively investigated by Nelsen and coworkers using cyclic voltammetry and photoelectron spectroscopy. Of a number of complex polycyclic tertiary amines studied, only 3, 166, and 167 gave stable radicals. Stability was shown to depend on favourable (parallel) alignments for lone pair-σₐ interactions, i.e. through-bond rather than through-space interactions. A later study by Lindsay Smith and Masheder of oxidation of cyclic and noncyclic polyamines and amino alcohols by linear sweep voltammetry concluded that, in general, introduction of an electron-withdrawing heteroatom into a tertiary amine destabilizes the aminium radical and raises the oxidation peak potential. However, in some cases through-bond interactions occur, and the net effect is stabilization of the...
incipient radical cation. Thus, while peak potentials for six-membered heterocycles were dominated by the inductive effect of an additional heteroatom (N-methylpiperidine < N,N'-dimethylpiperazine < N,N'-dimethylhexahydropyrimidin < N,N',N''-trimethylhexahydro-s-triazine), in the eight-membered ring case the stabilizing effect of a transannular 1,5-interaction between a nitrogen lone pair and the incipient radical cation was the dominant factor, and the peak potential of N,N'-dimethyl-1,5-diazacyclooctane was lower than that of N-methylazocyclooctane. The low peak potential of N,N,N',N'-tetraethyl-1,2-diaminoethane relative to triethylamine was attributed to stabilization by a through-bond interaction between the nitrogens, which was substantiated by isolation of formaldehyde (and no acetaldehyde) as the carbonyl oxidation product. Thus, the oxidation proceeded via Grob fragmentation (Scheme 36), which has the same stereochemical requirement as a through-bond interaction.

B. 'Active' Electrodes: Silver, Copper, Nickel, Cobalt

Oxidations of amines have been observed at oxide-covered silver, copper, nickel and cobalt anodes in aqueous alkaline solution. Both products and processes appear to be similar in the cases investigated. Primary amines with α-hydrogen gave exclusively nitriles or mixtures of nitriles and aldehydes, and t-butylamine gave a mixture of nitro compound, alcohol and olefin. Secondary amines reacted more slowly, giving N-alkyl cleavage products, and tertiary amines appeared to be inert. Evidence was presented that the electrolytic reaction involves oxidation of the metal oxide to a higher level [Ag(I) → Ag(II), Cu(II) → Cu(III)] etc., and that the organic compound is adsorbed and reacts with the higher oxide. A primary isotope effect was observed for oxidation of CD₃OH at a nickel electrode, implying a rate-determining hydrogen transfer, but an amine was not similarly studied.

XIV. PHOTOCHEMISTRY

A. Anaerobic Photooxidations

Photoreduction of carbonyl compounds by amines has been extensively investigated, and was reviewed by Cohen's research group. Substantial evidence has
25. Oxidation of amines

\[
\text{Ar}_2\text{C}=\text{O}(S_0) + \text{R}_2\text{NCH}_2\text{R}' \xrightarrow{\text{hv}} \text{Ar}_2\text{C}=\text{O}(T_1) + \text{R}_2\text{NCH}_2\text{R}'
\]

\[
[\text{Ar}_2\dot{\text{C}}-\text{O}^- + \text{R}_2\dot{\text{NCH}}_2\text{R}'] \xrightarrow{\text{H transfer}} \text{Ar}_2\dot{\text{C}}-\text{OH} + \text{R}_2\text{NCH}_2\text{R}'
\]

**SCHEME 37**

accumulated\(^{61}\) in support of a mechanism (Scheme 37) involving rapid charge-transfer interaction of amine with triplet carbonyl followed by α-hydrogen transfer to radicals \(^{169}\) and \(^{170}\). α-Amino radical \(^{170}\) may react with a ground-state carbonyl compound donating a second reducing group in a number of ways (equations 60–63)\(^{60}\), and a variety of radical coupling processes may occur\(^{59,61,239}\).

\[
\text{Ar}_2\text{C}=\text{O}(S_0) + \text{R}_2\text{NCH}_2\text{R}' \quad \text{if } R = \text{H} \quad \text{RN}=\text{CHR}' + \text{Ar}_2\dot{\text{C}}-\text{OH} \quad (60)
\]

\[
\text{Ar}_2\text{C}=\text{O}(S_0) + \text{R}_2\text{NCH}_2\text{R}' \quad \text{if } R' = \text{CH}_3 \quad \text{R}_2\dot{\text{N}}=\text{CHR}' + \text{Ar}_2\dot{\text{C}}-\text{O}^- \quad (61)
\]

\[
\text{Ar}_2\text{C}=\text{O}(S_0) + \text{R}_2\text{NCH}_2\text{R}' \quad \text{if } R = \text{H} \quad \text{R}_2\text{NCH}=\text{CH}_2 + \text{Ar}_2\dot{\text{C}}-\text{OH} \quad (62)
\]

\[
\text{Ar}_2\text{C}=\text{O}(S_0) + \text{R}_2\text{NCH}_2\text{R}' \quad \text{if } R' = \text{CH}_3 \quad \text{Ar}_2\dot{\text{C}}-\text{O}^-\text{CHR}^1\text{NR}_2 \quad (63)
\]

Both aqueous and organic media have been used, and high yields of pinacols have been obtained in the latter\(^{58}\). In aqueous solutions, benzhydrols also arise via disproportionation (equation 64)\(^{60}\). In cases of photoreductions involving unsymmetrical amines, product analysis after acid hydrolysis has shown that the less hindered α-hydrogen is transferred preferentially (to give the less stable α-amino radical), e.g. \(N, N\)-dimethylbenzylamine gave \(N\)-methylbenzylamine and formaldehyde and no benzaldehyde\(^{60}\). In this regard, results of a recent comparative study\(^{199}\) of the photochemical reaction of \(trans\)-stilbene with five tertiary amines are informative. Radical cations of highly hindered amines (\(i\)-Pr\(_2\)NMe and \(i\)-Pr\(_2\)NEt) were deprotonated highly selectively to the less stable α-amino radicals, while in less hindered cases (Et\(_2\)NMe, Me\(_2\)NMe and \(i\)-PrNMe\(_2\)), deprotonation was relatively nonselective. In extremely hindered cases (\(i\)-Pr\(_3\)N and 3) there was no reaction.

Photochemical cleavage reactions of arylaminoketones \(^{171,298}\) and \(^{172,237}\) have been shown to proceed via an initial fast intramolecular charge-transfer process (Scheme 38) characterized by low quantum yields and high chemical yields. Photochemical conversion of 3-aryloazetidines \(^{(173}\) to pyrroles \(^{(174}\) is believed to follow a similar course\(^{236}\).

An example of a reaction proceeding via an aminium charge-transfer complex that does not follow a α-hydrogen transfer pathway is the photoinduced dechlorination of 4-chlorobiphenyl (Scheme 39)\(^{231}\).

Photoreductions of a number of aromatic nitro compounds by diethyl- and triethyl-amine gave mixtures of up to as many as four of the products shown (Scheme 40)\(^{28}\). A mechanism involving initial hydrogen abstraction, rather than electron...
transfer, by a nitro compound \( \pi-\pi^* \) triplet was favoured on energetic grounds\(^{28}\), but a charge-transfer process cannot be ruled out\(^{61}\).

**B. Aerobic Photooxidations**

The first definitive product study of dye-sensitized photooxidation of primary, secondary and tertiary alkylamines revealed complex mixtures of products resulting from further reactions of the initially formed imine\(^ {270} \). Predominant processes were (a) hydrolysis to alkylamines and aldehydes, (b) \( \beta \)-oxidation of \( N \)-alkylidene groups to give hydroperoxides that led to formamides or \( \alpha \)-keto aldehydes and (c) addition of hydroperoxide to imine followed by base-catalysed rearrangement to amides. Predominant products of aerobic oxidation of alkylarylamines sensitized by benzophenone were carbonyl compounds and arylamines resulting from \( N \)-dealkylation\(^ {30} \).

Mechanistic investigations of dye-sensitized photooxidations have generated some controversy, and the most recent papers present evidence for two concurrent mechanisms\(^ {25,76} \). A mechanism similar to that of aerobic photooxidations (Scheme 37) involving hydrogen transfer to give amino radical 170 via a triplet dye-amine charge-transfer complex was first suggested (type I)\(^ {31} \). Later kinetic studies were interpreted in terms of reaction of singlet oxygen with amine in a charge-transfer process to give the same radical 170 (type II)\(^ {283} \) (equation 65). Utilizing a kinetic scheme to separate the contribution of singlet oxygen from other processes, Davidson and Trethewey\(^ {75,76} \) have shown that in the case of triethylamine the two processes are operative simultaneously.
A similar duality of mechanism in the photooxidation of 4,5-bis(N,N-dimethylamino)-o-xylene (175) was easier to demonstrate because the two processes gave rise to different products. Thus, the yield of N-formyl derivative 176 depended on the type of sensitizer but was unaffected by known singlet oxygen quenchers, and formation of epoxyenone 177 was independent of sensitizer type but was inhibited by singlet oxygen quenchers. The type II process was believed to proceed via successive rearrangement of a 1,4-singlet oxygen adduct (178) (Scheme 41). In contrast, the 1,2-cleavage product 179 isolated in 60% yield from 2,4-dimethoxy-N,N-dimethylaniline (180) was attributed to 1,2-addition of singlet oxygen (Scheme 42).

Dye-sensitized photooxidation of cyclohexylamine and dicyclohexylamine in organic media gave the respective hydroperoxides 181 and 182 as primary products (50% isolated yield in each case). Further treatment of 181 and 182 with the respective amines, or prolonged oxidations, gave complex mixtures of nonphoto-derived products. In contrast, on irradiation of O₂-saturated cyclohexylamine (neat)
at the wavelength of the charge-transfer band, \( N \)-cyclohexylidene cyclohexylamine and cyclohexanone oxime were the products isolated\(^{178}\). The former was shown to originate from hydroperoxides and/or peroxides; origin of the latter is uncertain.

Dye-sensitized photooxidations of tropinone (183a) and pseudopelletierine (183b)\(^{100}\) and related polycyclic \( N \)-methylamines and steroidal \( N, N \)-dimethylamines\(^{139}\) gave mixtures of demethylation products (secondary amines) and \( N \)-formyl derivatives, with the latter generally predominating. It is not clear to what extent singlet oxygen\(^{100}\) and triplet dye\(^{31}\) processes contribute. Singlet oxygen has been reported to be involved in dye-sensitized photooxidations resulting in formation of stable nitroxyl radicals\(^{159}\).

Aziridines have been shown to undergo sensitized photooxidation to a variety of products depending on the nature of the ring substituents\(^{36}\). These investigations have recently been extended to certain bicyclic aziridines that can give rise to azomethine intermediates under photochemical conditions\(^{37}\).

### C. Photooxidations Involving Chloromethanes

Oxidations of amines in polyhalomethane solvents have been studied under a variety of conditions and may involve thermal, photochemical or meta-ion-catalysed processes\(^{209}\). Thus, a variety of mechanistic pathways are possible, and this discussion is limited to two examples illustrative of electron-transfer processes in photooxidation.

\( p \)-Phenylenediamines 184a–c were oxidized in \( CHCl_3 \) or \( CCl_4 \) to coloured species believed to be aminium cation radicals\(^{101}\). The results in degassed and oxygenated solutions were similar except for higher quantum yields in the latter. There was no oxidation in nonhalogenated solvents; only fluorescence was observed. Mechanistically, the key step was viewed as electron transfer via excited singlet-state amine to solvent, accompanied by dissociation to chloride ion and formation of aminium cation radical (equation 66)\(^{101}\). The fate of the latter was not addressed, and no products resulting from the amines were described.
Photocyclization of N-substituted diphenylamines 185a, b to carbazoles 155a, b was first studied in nonhalogenated solvents, and the results supported a mechanism involving conversion of triplet amine to dihydrocarbazole 186, which formed 155 by both aerobic and anaerobic processes (Scheme 43)104. In the presence of increasing amounts of CCl₄, however, the intramolecular triplet pathway was suppressed and intermolecular electron-transfer processes were favoured, leading to complex mixtures of products315.

**XV. RADIATION CHEMISTRY**

The radicals generated by high-energy radiolysis of amines in solution and in solid matrices have been studied by ESR methods. On irradiation of acidic solutions of di- and tri-methylamine with high-energy electrons, aminium cation radicals (R₃N⁺) were formed; in neutral and alkaline media only aminoalkyl radicals (R₂NCH₂) were found225. Radicals of the type R-CO₂H and R-CO₂⁻ were observed for a number of amino acids in acidic and alkaline solutions, respectively. The aminium radicals result from attack of ·OH on protonated nitrogen (equation 67a), whereas in neutral or basic solution, abstraction of α-hydrogen is favoured due to the resonance-stabilizing effect of the adjacent nitrogen lone pair (equation 67b)35.

\[
\begin{align*}
\text{Me}_3\text{NH} + \cdot\text{OH} & \rightarrow \text{Me}_3\text{N}⁺ + \text{H}_2\text{O} \\
\text{RCH}_2-\bar{\text{NR}}_2 + \cdot\text{OH} & \rightarrow \text{RCH}_2-\bar{\text{NR}}_2 \rightarrow \text{RCH}-⁺\bar{\text{NR}}_2(67b)
\end{align*}
\]

Aminoalkyl radicals were also generated on room-temperature irradiation of aliphatic amines in adamantane matrices313. In unsymmetrical cases, only one
radical was observed, and the order of stability with respect to carbon substitution
was primary > secondary > tertiary.

γ-Irradiation of primary amines frozen at 77 K gave alkylamino radicals
\((\text{R}_2\text{CH}—\text{NH})\) that isomerized to aminoalkyl radicals \((\text{R}_2\text{C}—\text{NH}_2)\) on warming\(^{299}\). Dimethylamine under these conditions gave mixtures of radicals \((\text{CH}_3)_2\text{N}\) and \(\text{CH}_3\text{NHCH}_3\), and trimethylamine gave aminoalkyl radical \(\text{CH}_2\text{N}(\text{CH}_3)_2\) exclusively. Results of γ-irradiation of amines adsorbed on silica gel at 77 K were similar except for trimethylamine, where only the aminium cation radical \((\text{CH}_3)_3\text{N}^+\) was observed\(^{300}\). In contrast, ultraviolet irradiation of methyl-, dimethyl- and trimethyl-

amine frozen at 77 K gave exclusive rise to alkylamino radicals\(^{123}\).

Pulse radiolysis investigations of aromatic amines in chlorinated hydrocarbon
solutions have demonstrated good yields of aminium cation radicals, which are
believed to arise by charge transfer from an initially formed solvent cation radical
(equation 68)\(^{50}\).

\[
\text{CCl}_4^+ + \text{A} \rightarrow \text{CCl}_4 + \text{A}^+ \quad (68)
\]

The products of γ-radiolysis of a number of primary, secondary and tertiary
alkylamines and arylalkylamines have been extensively studied by Swan and
coworkers\(^{2,95,96,281,292}\). In all but two cases, the products were attributable to further
reactions of the initially formed α-aminoalkyl radicals: coupling, disproportionation
and, in two cases where hydrazines were isolated\(^2\), abstraction of \(\text{H}^+\) from amine
(equation 69). The finding of \(\text{N},\text{N},\text{N}',\text{N}'\text{-tetramethylenediamine (187) (but}\n
\[
\text{RNHCHR}^1 + \text{RNHCH}_2R^1 \rightarrow \text{RNCH}_2R^1 + \text{RNHCH}_2R^1 \quad (69)
\]

\[
\text{Me}_2\text{NCH}_2\text{NMe}_2 \quad (187)
\]
o no tetramethylhydrazine) on radiolysis of trimethylamine\(^{281}\), however, indicates
that radiolytic C—N cleavage may sometimes take place. When no α-hydrogen was
present (\(t\)-butylamine), two of the three products isolated were derived from
coupling of two β-aminoalkyl radicals and coupling of a β-aminoalkyl radical and an
alkylamino radical \((\text{Me}_3\text{CNH})^ {281}\). In certain symmetrical cases, the initial α-alkyl-
amino radicals were trapped by \(\text{N}\)-phenylmalicimide\(^{96}\).

**XVI. MISCELLANEOUS OXIDATIONS**

Treatment of primary amines with IF₅ gave nitriles (or, in the absence of α-hydro-
gen, azoalkanes)\(^{287,288}\); carbonyl compounds were obtained from secondary\(^ {287,288}\)
and tertiary\(^ {233}\) amines. A novel periodinane, \(188^3\), gave carbonyl compounds with
both primary and secondary amines; in most cases, yields with the two reagents
were only fair.
Three primary amines (diphenylamine, 9-fluorenylamine and 2-adamantylamine) were oxidized to the respective ketones in 97–100% yields by diphenylselenic anhydride and diphenylseleny1 chloride, but the reagents lacked general synthetic utility. Peroxyacetyl nitrate gave high yields of acetamides from primary amines. Oxidation of aromatic amines adsorbed on various oxide surfaces was studied by ESR, and the identity of the desorbed product was shown to depend on the oxide surface, e.g. diphenylamine gave diphenyl nitroxide on alumina and N,N-diphenylbenzidine on alumina–silica. Quinones and quinoneimines were obtained from aromatic amines and potassium nitrosodisulphonate (Fremy's salt). A re-investigation of the reaction of benzylamines with nitrosobenzene, which was reported earlier to give azoxybenzenes and aldehydes derived from the amine, failed to detect the latter product. Rather, azoxybenzene and substituted imines, the latter shown to arise from amine exchange with the initial amine, were the products isolated.

Benzylammonium salts \([\text{PhCH}(R)NR: X^-]\), on prolonged heating with dimethyl sulfoxide, underwent oxidation to carbonyl compounds (PhCOR) and, in some instances, elimination to olefins. Evidence was presented for an ionic pathway.

XVII. REFERENCES

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25. Oxidation of amines


David H. Rosenblatt and Elizabeth P. Burrows


25. Oxidation of amines

CHAPTER 26

N-Nitrosamines and N-nitrosoimines

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I. INTRODUCTION

This review is primarily concerned with the chemistry of N-nitrosamines (1), where \( R_1 \) and \( R_2 \) are alkyl or aryl groups. The related N-nitrosoimines (2) are discussed in Section V, but these compounds are unstable and little is known about their chemistry.

\[
\begin{align*}
\text{(1)} & \quad \text{N-nitrosamines} \\
\text{(2)} & \quad \text{N-nitrosoimines}
\end{align*}
\]

Primary aromatic N-nitrosamines (1, \( R_1 = H, R_2 = \text{aryl} \)) are tautomeric with aryl diazohydroxides (Ar\( \text{N} = \text{NOH} \)). One or two examples are known at very low temperatures\(^1\)\(^-\)\(^3\), but otherwise they are too unstable to detect and rapidly decompose to aryl diazonium or diazohydroxide ions in acid and alkali, respectively (see the chapter by Baumgarten and Curtis in this volume). Heteroaromatic primary N-nitrosamines (1, \( R_1 = H, R_2 = \text{heteroaryl} \)) are better known and are more stable when electron-withdrawing substituents are present\(^3\). Primary aliphatic N-nitrosamines (1, \( R_1 = H, R_2 = \text{alkyl} \)) also decompose below room temperature to give products of deamination as discussed in the above mentioned chapter. None of the primary N-nitrosamines will be further discussed here.

Secondary aliphatic, heterocyclic and aromatic N-nitrosamines (1, \( R_1, R_2 = \text{alkyl, aryl} \)) are usually regarded as derivatives of secondary amines, from which they are prepared by nitrosation (see Section II). Such characterization is of limited utility, however, in understanding their properties and reactions because the amino-N lone-pair electrons are delocalized through the \( \pi \)-electron system of the nitroso
N-Nitrosamines and N-nitrosoimines

function. This strengthens the N—N bond and attenuates the properties associated with isolated amino and nitroso groups. Consequently, secondary N-nitrosamines are rather stable compounds of limited chemical reactivity.

N-Nitrosamines have been known since the last century but they attracted little interest until the 1960s when it was found that many were powerful carcinogens. This stimulated interest in both their chemical and biological properties. The present review deals mainly with advances made in N-nitrosamine chemistry since 1970. It supplements other recent brief reviews \(^4^-^7\) and the extensive survey by Fridman and colleagues \(^8\) of the earlier chemical literature. Recent developments in their biological properties are only briefly reviewed because these aspects have been extensively discussed elsewhere (see Section IV).

Following IUPAC nomenclature, N-nitrosamines are named as N-nitroso derivatives of the parent amines throughout this review. This nomenclature applies equally well to simple alkyl- and aryl-amine derivatives and to more complex heterocyclic amines. The alternative method of naming them as alkyl or aryl derivatives of N-nitrosamines (e.g. \(N,N\)-dimethylnitrosamine) becomes unwieldy for heterocyclic compounds. It should be noted that since 1972, Chemical Abstracts has indexed acyclic amines as the parent carbon skeleton with suffix ‘amine’. Thus methylamine becomes methanamine, aniline becomes benzenamine and secondary amines are indexed as \(N\)-alkyl or \(N\)-aryl derivatives of the corresponding primary amine, e.g., dimethylamine becomes \(N\)-methylmethanamine, diisopropylamine becomes \(N\)-(1-methylethyl)-2-propanamine and diphenylamine becomes \(N\)-phenylbenzenamine. The corresponding \(N\)-nitroso derivatives are indexed as \(N\)-nitroso-\(N\)-methylmethanamine, \(N\)-nitroso-\(N\)-(1-methylethyl)-2-propanamine and \(N\)-nitroso-\(N\)-phenylbenzenamine. Heterocyclic \(N\)-nitrosamines are indexed as 1-nitroso derivatives of the heterocyclic amine, e.g. 1-nitrosopiperidine, 1-nitrosomorpholine. The IARC, in their Scientific Publication No. 19, has recommended the usage of the following acronyms based on the IUPAC system of nomenclature for \(N\)-nitrosamines:

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDMA</td>
<td>(N)-Nitrosodimethylamine</td>
</tr>
<tr>
<td>NDBA</td>
<td>(N)-Nitrosodi-n-butylamine</td>
</tr>
<tr>
<td>NDi-BA</td>
<td>(N)-Nitrosodisobutylamine</td>
</tr>
<tr>
<td>NEMA</td>
<td>(N)-Nitrosocethyimethylamine</td>
</tr>
<tr>
<td>NPYR</td>
<td>(N)-Nitrosopyrrolidine</td>
</tr>
<tr>
<td>NPIP</td>
<td>(N)-Nitrosopiperidine</td>
</tr>
<tr>
<td>NMOR</td>
<td>(N)-Nitrosomorpholine</td>
</tr>
<tr>
<td>M-NPZ</td>
<td>Mononitrosopiperazinc</td>
</tr>
<tr>
<td>D-NPZ</td>
<td>Dinitrosopiperazinc</td>
</tr>
<tr>
<td>NPRO</td>
<td>(N)-Nitrosoproline</td>
</tr>
<tr>
<td>NSAR</td>
<td>(N)-Nitrososarcosine</td>
</tr>
<tr>
<td>NHPRO</td>
<td>(N)-Nitrosohydroxyproline</td>
</tr>
<tr>
<td>NPCIC</td>
<td>(N)-Nitrosopicolic acid</td>
</tr>
<tr>
<td>NHPYR</td>
<td>(N)-Nitrosohydroxyprolilidine</td>
</tr>
<tr>
<td>NNN</td>
<td>(N)-Nitrosonornicotine</td>
</tr>
<tr>
<td>NDELA</td>
<td>(N)-Nitrosodichanolamine</td>
</tr>
</tbody>
</table>

II. FORMATION OF \(N\)-NITROSAMINES

\(N\)-Nitrosamines are usually obtained by N—N bond formation between an amino compound and the NO function. The most common method involves interaction of a secondary amine \((R_2\text{NH})\) with an NO\(^+\) entity. Free NO\(^+\) (nitrosonium ion) can
be obtained only in strong acids or as solid salts (e.g. \( \text{NO}^+\text{BF}_4^- \)). It is readily available, however, from labile nitrosating agents of the type \( \text{Y—NO} \) (where \( \text{Y} \) is either a stable anion such as \( \text{Cl}^- \) or \( \text{NO}_2^- \), or a neutral molecule such as \( \text{ROH} \) or \( \text{R}_2\text{NH} \)) which can be regarded as carriers of \( \text{NO}^+ \). These reactions involve nucleophilic (SN₂) displacement at the nitroso nitrogen atom by the secondary amine as in Scheme 1. Neither nitrous acid itself (\( \text{HO—NO} \)) nor nitrite ion (\( \text{NO}_2^- \)) interacts as a nitrosating agent directly with amines, and other activating transformations must take place prior to their reaction. For example, in moderately acidic solutions of nitrite salts the nitrosating agent (\( \text{Y—NO} \)) is \( \text{N}_2\text{O}_3 \) formed from two molecules of \( \text{HNO}_2 \) (Section II.A.1). Otherwise, photolysis of gaseous \( \text{HNO}_2 \) (Section II.B.2) and photolysis or radiolysis of aqueous nitrite solutions (Section II.E.1) can generate nitrogen oxide reagents which may then react with secondary amines. Other potential carriers of \( \text{NO}^+ \) include the conjugate acids of alkyl nitrates and \( \text{N} \)-nitrosamines (e.g. \( \text{Y—NO} \), where \( \text{Y} = \text{ROH} \) or \( \text{R}_2\text{NH} \)) and gaseous reagents such as nitrosyl chloride (\( \text{NOCl} \)), dinitrogen trioxide (\( \text{N}_2\text{O}_3 \)) and dinitrogen tetroxide (\( \text{N}_2\text{O}_4 \)). These reactions are discussed in Sections II.C and II.B, respectively.

There is also good evidence that \( \text{N} \)-nitrosamines can be obtained from the interaction of secondary amines with several organic nitroso and nitro compounds under thermal conditions. These reactions, as discussed in Section II.C, probably involve nitrogen oxide (e.g. \( \text{N}_2\text{O}_3 \) and \( \text{N}_2\text{O}_4 \)) intermediates. Formation of \( \text{N} \)-nitrosamines from nitric oxide (\( \text{NO} \)) is less common, but in principle it may occur with amine anions (\( \text{R}_2\text{N}^- \), equation 1), or when oxidants generate either amino radicals (\( \text{R}_2\text{N}^- \), equation 2) or amino radical cations (\( \text{R}_2\text{NH} \), equation 3) from secondary amines (Section II.B.5).

\[
\begin{align*}
\text{R}_2\text{NH} & \quad \rightleftharpoons \quad \text{N} = \text{O} & \quad \text{R}_2\text{NH} \quad \text{N} = \text{O} \end{align*}
\]

\[\quad \text{R}_2\text{N}^- \quad \text{N} = \text{O} \quad \text{R}_2\text{N} = \text{N} = \text{O} \quad (1)\]

\[
\begin{align*}
\text{R}_2\text{N}^- \quad \text{N} = \text{O} & \quad \rightarrow \quad \text{R}_2\text{N} = \text{N} = \text{O} \quad (2) \end{align*}
\]

\[\begin{align*}
\text{R}_2\text{NH} & \quad \rightarrow \quad \text{R}_2\text{N} = \text{N} = \text{O} \quad \text{R}_2\text{NH} \quad \text{N} = \text{O} \quad \text{R}_2\text{N} = \text{N} = \text{O} \quad (3) \quad + \text{H}^+ \end{align*}
\]

Amino compounds other than secondary amines can also generate \( \text{N} \)-nitrosamines under appropriate circumstances, but these reactions are much less extensive than those with secondary amines. Finally, there are a few examples in which reaction of nitrite ion with amines can be brought about by catalysts such as carbonyl compounds or metal salts, or in which nitrate salts can be reduced \textit{in situ} to generate nitrosating agents (Section II.E).

Because of widespread concern about the carcinogenic properties of many \( \text{N} \)-nitrosamines (Section IV) methods of inhibiting their formation are discussed in Section II.A.3.
A. Nitrosation of Secondary Amines by Aqueous HNO₂

The best known reagent for nitrosating amines is sodium nitrite (nitrous acid) in aqueous acidic solutions at pH < 5. This reagent has been widely investigated from a mechanistic standpoint. Neither HNO₂ nor NO₂⁻ reacts with the secondary amine and the effective nitrosating agent (Y⁻NO) is formed from the nucleophilic catalyst (Y⁻) and protonated nitrous acid in a rapid pre-equilibrium step (Scheme 2). In the absence of other nucleophiles, nitrite ion itself can act as the catalyst Y⁻ in which case the reactive species is N₂O₃. The presence of nucleophiles such as I⁻ or SCN⁻ may increase the rate of nitrosation, whereas N-nitrosamine formation can be inhibited by reagents which reduce HNO₂ to either N₂ or NO or bind the NO⁺ group irreversibly.

\[
\begin{align*}
\text{NO}_2^- & \overset{\text{H}_2\text{O}^+}{\rightarrow} \text{HO-N=O} \overset{\text{H}_2\text{O}^+}{\rightarrow} \text{H}_2\text{O-N=O} \overset{Y^-}{\rightarrow} \text{Y-N=O} + \text{H}_2\text{O} \\
Y^- &= \text{NO}_2^-, \text{Cl}^-, \text{SCN}^-, \text{etc.}
\end{align*}
\]

SCHEME 2. General mechanism for the nitrosation of secondary amines in aqueous HNO₂.

1. Mechanisms and reactivities

N-Nitrosamine formation from secondary alkyl and heterocyclic amines and NaN₂O₃ in aqueous buffers at pH 2–5 has been widely examined. The reaction rates approximate to equation (4) where the [HNO₂]² term shows that the nitrosating agent is N₂O₃ (nitrous anhydride) formed in equilibrium with HNO₂ (equation 5). Thus the mechanism in Scheme 2 applies with Y⁻ = NO₂⁻. For the more basic amines (pKₐ > 5), the rates of these reactions calculated from the gross amounts of amine and nitrite salt added (rate = \(k₃\text{[amine][nitrite]}\)) have a characteristic pH dependence with a maximum value at ca. pH 3.4 (Figure 1). This reflects the counteracting effects of acidity, which increases the amount of HNO₂ (pKₐ 3.4) but decreases the amount of unprotonated amine. The level of observed rates over the whole pH range, however, is dependent on the amine basicity (pKₐ) which determines the proportion of unprotonated amine available for reaction. Data in Table 1 from the review by Mirvish show clearly that: (1) N-nitrosamines form most rapidly (i.e. largest \(k₃\) values) from the least basic amines, and (2) amines of widely different basicities have surprisingly similar reactivities (\(k₃\) values) towards N₂O₃. The second observation suggests that the rate is governed by factors (possibly diffusion through the solvent) other than the ease of amine attack on N₂O₃. This conclusion has important ramifications in explaining the effect of catalysts (see Section II.A.2), and implies that evidence for steric retardation of N-nitrosamine formation needs to be reexamined. Mirvish formulated a...
FIGURE 1. Variation in the yield of Me$_2$NNO with pH after 3 h for reaction of 0.02 M Me$_2$NH with 0.1 M NaNO$_2$ at 25°C. Reproduced from Reference 10 by permission of the author.

TABLE 1. Rates ($k_3$) and reactivities ($k_3^*$) for nitrosation of secondary amines at the optimum pH and 25°C (taken from Mirvish's review$^4$)

<table>
<thead>
<tr>
<th>Amine</th>
<th>pK$_3$</th>
<th>Optimum pH</th>
<th>$k_3^b$ (l$^2$ mol$^{-2}$ s$^{-1}$)</th>
<th>$10^{-5} k_3^c$ (l$^2$ mol$^{-2}$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrrolidine</td>
<td>11.27</td>
<td>3.0</td>
<td>0.0053</td>
<td>21</td>
</tr>
<tr>
<td>Piperidine</td>
<td>11.2</td>
<td>3.0</td>
<td>0.00045</td>
<td>1.4</td>
</tr>
<tr>
<td>Dimethylamine</td>
<td>10.72</td>
<td>3.4</td>
<td>0.0017</td>
<td>1.5</td>
</tr>
<tr>
<td>N-Methylbenzylamine</td>
<td>9.54</td>
<td>3.0</td>
<td>0.013</td>
<td>0.92</td>
</tr>
<tr>
<td>Proline</td>
<td>2.5</td>
<td>2.5</td>
<td>0.037</td>
<td>1.4</td>
</tr>
<tr>
<td>Morpholine</td>
<td>8.7</td>
<td>3.4</td>
<td>0.42</td>
<td>2.3</td>
</tr>
<tr>
<td>N-Nitrosopiperazine</td>
<td>6.8</td>
<td>3.0</td>
<td>6.7</td>
<td>0.83</td>
</tr>
<tr>
<td>Piperazinium ion</td>
<td>5.57</td>
<td>3.0</td>
<td>83</td>
<td>0.62</td>
</tr>
<tr>
<td>N-Methylaniline</td>
<td>4.85</td>
<td>3.0</td>
<td>250</td>
<td>18</td>
</tr>
</tbody>
</table>

$^a$At 0°C and pH 1.

$^b$Calculated from the experimental data using gross concentrations of reactants (i.e. rate = $k_3[\text{amine}][\text{nitrite}]$).

$^c$Calculated from the experimental data using actual concentrations of free amine and HNO$_2$ (i.e. rate = $k_3[R_2NH][HNO_2]^2$).

simple expression (equation 6) for estimating the approximate maximum rate (at pH 3.4), which reflects the overriding importance of unprotonated amine concentration.

$$\log k_3 = 7.8 - pk_{\text{amine}}$$  (6)

The kinetic dependences of equation (4) apply to most secondary alkyl- and heterocyclic amines at pH 2–5 in the absence of catalysts such as SCN$^-$ and I$^-$. Significantly, neither the type nor concentration of buffer seems to have an appreciable effect. This may be a consequence of the high nitrite concentrations required to obtain measurable rates, which leads to swamping by N$_2$O$_3$.

Many weakly basic compounds (e.g. some aromatic amines) are too unreactive to combine readily with N$_2$O$_3$$^{14,13}$. At about pH 2, however, they react by another pathway which follows equation (7) and is attributed to a direct reaction of the
26. N-Nitrosamines and N-nitrosoimines

rate = \( k_3 [R^1R^2NH] [\text{HNO}_2] [\text{H}_3\text{O}^+] \)  

\[
\text{RArNH}_2^+ \xrightarrow{H_2O^+} \text{RArNH} + \text{NO}^+(\text{H}_2\text{O}) \xrightarrow{\text{slow}} \text{RArNNO} + \text{H}_3\text{O}^+
\]

SCHEME 3. Acid-catalysed nitrosation of weakly basic amines by aqueous HN\(_2\)O.

neutral substrate with either H\(_2\)ONO\(^+\) or NO\(^+\) (Scheme 3). Usually these reactions are quite slow at pH > 3, but they become progressively faster with increasing acidity.

2. Catalysis of N-nitrosamine formation

In the presence of anionic (Y\(^-\)) or nucleophilic (HY) entities, HNO\(_2\) forms additional YNO reagents (Scheme 2). These accelerate nitrosation principally by increasing the concentration of NO\(^+\) carriers\(^{14}\), but most are potentially more reactive than N\(_2\)O\(_3\). It should be noted, too, that the strength of the catalysis is strongly dependent on the structure and basicity of the amino substrate.

Catalysis of N-nitrosamine formation by anions at pH 2–5 has been widely observed (for leading references see the review of Douglass and colleagues\(^5\)). Reaction rates follow equation (8) and the catalytic order is usually SCN\(^-\) > I\(^-\) >> Br\(^-\) > Cl\(^-\) >> phosphate or carboxylate. Strong accelerations by SCN\(^-\) and I\(^-\) have attracted attention because of their possible \textit{in vivo} relevance\(^{11,15}\). Salivary SCN\(^-\) levels are known to be enhanced for smokers and I\(^-\) is present in gastric secretion. For strongly basic substrates such as morpholine, 2.5 mM KSCN shifts the maximum rate of nitrosation from pH 3.4 to 2.3 and increases its value by a factor of ca. 6 at pH 4, however, its catalytic effect is negligible\(^{11}\). These changes are best related to an increased concentration of NO\(^+\) carriers rather than the higher reactivity of NOSCN (relative to N\(_2\)O\(_3\)) to be consistent with previous conclusions (see above) that morpholine may react with N\(_2\)O\(_3\) on encounter. Much stronger SCN\(^-\) catalysis is observed for less basic substrates such as N-methyl- aniline and the maximum rate is shifted to ca. pH 0\(^{15b}\). This probably reflects that both carrier concentration and reactivity are important, in line with earlier observations that N\(_2\)O\(_3\) reacts sluggishly with amines of pK\(_a\) << 2.16.

Although many neutral, electron-rich compounds other than amines also react readily with acidified nitrite, examples leading to catalysis are rare. Usually the nitroso product is too stable to react further or so unstable that spontaneous decomposition ensues before reaction with an amino substrate can proceed. In both cases, the outcome is inhibitory rather than catalytic. As a general rule, reactions at carbon atoms give stable products whereas reactions at heteroatoms produce unstable intermediates with catalytic potential. An interesting example of both effects is found with phenol. This compound reacts readily with aqueous HN\(_2\)O at pH < 4 (equation 9) to give the stable quinone monoxime (3)\(^{17}\). Subsequently, it has been shown that 3 catalyses the nitrosation of pyrrolidine\(^{18}\) and diethylamine\(^{19}\). A plausible explanation for the catalysis (equation 10) is rapid formation of an O-nitroso derivative (4) which reacts slowly with the secondary amine. Other recent work shows that the formation of N-nitrosodimethyamine at pH 4 is strongly
catalysed by thioureas, possibly via an S-nitroso adduct (5) which could be a powerful reagent (equation 11)\textsuperscript{20}.

\[(H_2N)_2C=S + N_2O_3 \rightarrow [(H_2N)_2C=S-NO]^+NO_2^- \rightarrow Me_2NNO + (H_2N)_2C=S + HNO_2 \quad (11)\]

Substances capable of forming micelles also catalyse \(N\)-nitrosamine formation in acid solution. For dihexylamine at pH 3.5 an 800-fold increase in rate is observed in the presence of decyltrimethylammonium bromide, but smaller effects apply to other secondary amines with shorter alkyl substituents\textsuperscript{21}. Catalysis by microorganisms under similar conditions has been explained by an analogous hydrophobic interaction between the amine and cellular constituents\textsuperscript{22}.

3. Inhibition of \(N\)-nitrosamine formation

The simplest way to inhibit \(N\)-nitrosamine formation is to convert amino substrates to their unreactive conjugate acids by raising the solvent acidity. This is only feasible, however, for the most basic compounds and then with limited success because the nitrosating ability of aqueous nitrite also increases with acidity. Another simple method is to reduce the acidity below pH 6 to convert nitrosating agents to inactive \(NO_2^-\). This, too, is only partially successful because hydrolysis of the nitrosating agents (including \(N_2O_3\)) is substantially slower than their reactions with many amines. Thus some early analytical studies may overestimate \(N\)-nitrosamine concentrations because alkaline conditions were used for quenching or work-up. The best procedure is to remove all the nitrosating agents with a suitable scavenger (see below) before adding base. Effective inhibition therefore requires materials (scavengers) which react readily with and convert nitrosating agents to innocuous products. Generally this implies compounds which either reduce \(HNO_2\) to \(N_2\) or \(NO\), or bind the \(NO^+\) group irreversibly.

Reduction to \(N_2\) takes place with ammonia, primary amines, hydrazine, urea, sulphamic acid and its salts, hydroxylamine and azides. Ammonia is a poor inhibitor, however, because of extensive protonation at low pH. A similar reser-
Amination applies to primary amines (unless aromatic) and alkylation reactions concurrent with deamination produce small amounts of secondary amines and, ultimately, $N$-nitrosamines\textsuperscript{23}. The remaining compounds are more useful, but urea and sulphamic acid appear to be really effective only below pH 2 and, further, recent findings suggest that sulphamic acid may even stimulate $N$-nitrosamine formation from some drugs above pH 4\textsuperscript{24}. Hydroxylamines\textsuperscript{25}, hydrazoic acid (azide)\textsuperscript{26} and hydrazine\textsuperscript{27} all react rapidly with HNO$_2$ over a wide pH range. The relative reactivities of some of these reagents towards NOCl in 3.05M HCl decrease in the order $\text{N}_3\text{H} > \text{NH}_2\text{SO}_3\text{H} > \text{PhNH}_2 > \text{NH}_2\text{OH} > \text{CO(NH}_2)_2$\textsuperscript{28}. It must be remembered, however, that the order will be different at lower acidity.

A wider range of compounds reduce HNO$_2$ to NO under mildly acidic conditions. In this category are sulphur dioxide and bisulphite ion, ascorbic acid, tocopherols, gallic acid, thiols, several dihydroxyphenols and some other well-established synthetic and natural 'antioxidants'. Their inhibition of $N$-nitrosamine and $N$-nitrosamide formation both \textit{in vitro} and \textit{in vivo} has been examined intensively and much more is known about these aspects than the actual reduction of HNO$_2$. An excellent compilation of this work is given in a recent review\textsuperscript{5}. Mirvish and his colleagues first championed the application of ascorbic acid as an inhibitor. It remains one of the best because both the free acid and ascorbate ion rapidly reduce Y—NO to NO\textsuperscript{29} as shown in Scheme 4, and it is therefore effective over a wide pH range. For lipophilic matrices, however, there is some evidence that $\alpha$-tocopherol may be superior\textsuperscript{30,31}. Other recent work\textsuperscript{32} has cleared up confusing results concerning the effect of polyhydroxylated phenols on $N$-nitrosamine formation. In particular, Pignatelli and her colleagues\textsuperscript{32} have shown that 1,2- and 1,4-dihydroxyphenols (including naturally occurring flavanols) inhibit $N$-nitrosamine formation at pH 4 and that previous reports of catalysis by 4-methylcatechol\textsuperscript{33} and gallic acid\textsuperscript{34} are incorrect because of artifactual formation during work-up. The inhibition again relates to reduction of the nitrosating agent (e.g. N$_2$O$_3$) to NO (equation 12). 1,3-Dihydroxyphenols (e.g. resorcinol), however, are powerful catalysts under similar conditions. This is attributed to rapid formation of a nitroso derivative (possibly 6) which interacts with more N$_2$O$_3$ to generate a powerful nitrosating agent analogous to that proposed for catalysis by quinone monoxime (compare equations 9 and 13). The reduction of HNO$_2$ to NO leads to inhibition because NO is an ineffectual nitrosating agent in the absence of catalysts (see below). To be effective, however, it is necessary to add excess reducing agent because the ready

\begin{center}
\includegraphics[width=\textwidth]{scheme4.png}
\end{center}

\textbf{SCHEME 4.} Reduction of Y—NO to NO by ascorbic acid.
oxidation of NO back to NO₂ and subsequent formation of N₂O₃ (NO + NO₂ \xrightleftharpoons{\text{K}} N₂O₃) quickly restores nitrosating capability. This effect has been noted for the formation of \textit{N}-nitrosomorpholine in the presence of ascorbic acid\textsuperscript{35}.

Inhibition by irreversible binding of the NO⁺ group seems less effective than the reductive methods discussed above. An early suggestion\textsuperscript{36} that phenolic materials might be useful in this respect needs to be viewed cautiously in view of findings (discussed above) that nitrosophenols (or quinone monoximes) catalyse \textit{N}-nitrosamine formation. It has been reported, however, that pyrrole inhibits the formation of \textit{N}-nitrosomorpholine\textsuperscript{37} and other reactive heteroaromatic compounds may behave similarly.

**B. Nitrosation of Secondary Amines by Gaseous Nitrosyl Chloride and Nitrogen Oxides**

Several oxides of nitrogen are known but only four appear to be implicated in the formation of \textit{N}-nitroso compounds. These are nitrogen dioxide (NO₂), dinitrogen tetraoxide (N₂O₄), dinitrogen trioxide (N₂O₃) and nitric oxide (NO). The first three oxides and also gaseous nitrosyl chloride (NOCl) are much more reactive than nitric oxide towards amines. They combine readily with them without the need for catalysts, but under certain conditions β-substituted alcohols enhance the extent of reaction. Nitric oxide becomes an effective nitrosating agent only following rapid oxidation to NO₂ or in the presence of certain metal salts, iodine or hydrogen iodide. Reactions by the nitrogen oxides and gaseous nitrosyl chloride do not require acidic conditions and generally \textit{N}-nitrosamine formation is much faster and more extensive than with aqueous HNO₂.

1. **Nitrosation by gaseous nitrosyl chloride (NOCl)**

Nitrosation reactions employing nitrite salts in HCl involve NOCl generated \textit{in situ} as explained in Section II.A.2. NOCl can also be obtained as a compressed gas
and in this form it is an established, synthetically useful reagent for nitrosation in organic solvents\(^{38,39}\) and in alkaline media\(^{40}\). Gaseous NOCl is much less dissociated \([K_p(\text{NOCl}) \approx 7.8 \times 10^{-8} \text{ atm. at } 25^\circ\text{C}^{41}]\) than either \(\text{N}_2\text{O}_3\) or \(\text{N}_2\text{O}_4\) (equation 14)

\[
2 \text{NOCl} \longrightarrow 2 \text{NO} + \text{Cl}_2
\]

and it exists only as a single molecular isomer. Thus it should be a good reagent for comparative studies in acidic and nonacidic media. This is borne out by recent findings for primary and secondary amines, which give substantial amounts of either diazonium ion or \(N\)-nitroso products in alkaline and neutral aqueous solutions\(^{42}\). The results are similar to those discussed below for gaseous \(\text{N}_2\text{O}_3\) and \(\text{N}_2\text{O}_4\). For example, the reactions are very rapid and reach completion in a few seconds. Further, amine basicity has only a small effect on the extent of reaction for compounds more basic than \(N\)-methyl-4-nitroaniline (\(pK_a = 1.49\)). This behaviour suggests that diffusion of the amine and NOCl reactants through solution is rate-limiting in most cases. This conclusion is corroborated by independent rate measurements from the diazotization of anilines by nitrite in HCl, which proceeds via the NOCl reagent formed \textit{in situ}\(^{43}\).

2. \textit{Nitrosation by nitrogen oxides in the gaseous phase or in organic solvents}

These reactions are of particular interest because nitrogen oxides are common environmental pollutants produced by combustion and are probably formed in the microbiological reduction of nitrate ion (Section II.E.2).

Both \(\text{N}_2\text{O}_3\) \([K_p(\text{N}_2\text{O}_3) = 1.91 \text{ atm. at } 25^\circ\text{C}^{44}]\) and \(\text{N}_2\text{O}_4\) \([K_p(\text{N}_2\text{O}_4) = 0.15 \text{ atm. at } 25^\circ\text{C}^{45}]\) are highly dissociated in the gas phase at ambient temperatures and pressures (equations 15 and 16, respectively). Dissociation of both decreases sharply, however, when dissolved in either aqueous or organic solvents\(^{45-47}\). Recent work has shown that in the absence of catalysts NO reacts very slowly with secondary amines under anaerobic conditions (\(t_{1/2}\) ca. 8 days at \(25^\circ\text{C}\)). Injection of air into the reaction vessel, however, results in complete conversion to \(N\)-nitrosamine within 4 min\(^{13}\). Thus rapid nitrosation is connected with the formation of \(\text{NO}_2\) (equation 17) and NO itself, is a poor reagent. \(\text{NO}_2\) may dimerize to \(\text{N}_2\text{O}_4\) (equation 16) or combine with NO to give \(\text{N}_2\text{O}_3\) (equation 15) both of which are powerful nitrosating agents as discussed below. Thus reactions of nitric oxide require careful evaluation unless anaerobic conditions are employed.

\[
\text{N}_2\text{O}_3 \rightleftharpoons \text{NO} + \text{NO}_2
\]

\[
\text{N}_2\text{O}_4 \rightleftharpoons 2 \text{NO}_2
\]

\[
2 \text{NO} + \text{O}_2 \longrightarrow 2 \text{NO}_2
\]

In organic solvents secondary amines react with gaseous \(\text{N}_2\text{O}_3\) to give high yields of \(N\)-nitrosamine\(^{13,48}\) whereas \(\text{N}_2\text{O}_4\) gives a mixture of \(N\)-nitroso- and \(N\)-nitroamines\(^{49,50}\). Little is known about the mechanisms of these reactions but some insight comes from similar studies in aqueous media (Section II.B.3).

The formation of \(N\)-nitrosamines from nitrogen oxides in the gas phase has also been examined, principally in relation to cigarette smoking and atmospheric pollution. Both Neurath and Spencer and their colleagues\(^{51,52}\) have shown that NO by itself is unreactive, whereas equimolar mixtures of NO and \(\text{NO}_2\) (i.e. \(\text{N}_2\text{O}_3\)) lead to rapid formation of \(N\)-nitrosamines. Also, low concentrations of diethylamine and
NO₂ form N-nitrosodiethylamine rapidly at ambient temperatures. Other work designed to mimic atmospheric conditions shows that moist gases containing dimethylamine and diethylamine, NO, NO₂ and HNO₃ (at concentrations of 0.5 to 2 ppm) produce a mixture of N-nitroso- and N-nitro- amines. N-Nitrosamine formation under these conditions has been attributed to free-radical processes arising from photodissociation of HNO₂, where activation of the amine by production of an amino radical facilitates reaction with nitric oxide (equation 18).

\[
\text{HONO} \xrightarrow{hv} \text{NO}^+ + \text{HO}^- \xrightarrow{R_2NH} \text{H}_2\text{O} + R_2N' \xrightarrow{\text{NO}} R_2\text{NNO} \quad (18)
\]

3. Nitrosation by dinitrogen trioxide and dinitrogen tetraoxide gases in aqueous media

Nitrosation by gaseous N₂O₃ and N₂O₄ in aqueous solution is a recent development probably because both were expected to undergo rapid hydrolysis at pH > 5 to innocuous NO₂⁻ (equations 19 and 20). Hydrolysis does occur, but less rapidly

\[
\text{N}_2\text{O}_3 + 2 \text{HO}^- \rightarrow 2 \text{NO}_2^- + \text{H}_2\text{O} \quad (19)
\]

\[
\text{N}_2\text{O}_4 + 2 \text{HO}^- \rightarrow \text{NO}_3^- + \text{NO}_2^- + \text{H}_2\text{O} \quad (20)
\]

than the nitrosation of many amines. Data in Table 2 show that substantial yields of diazo and N-nitrosamine products, respectively, are obtained within four minutes from reaction with primary and secondary amines in neutral and alkaline solution. With N₂O₄, small amounts of N-nitramine form concurrently. Only the unprotonated substrates react, but product yields are not strongly dependent on substrate basicity (pKₐ) except for very feebly basic compounds (pKₐ < 1). Analysis of these data suggests that N₂O₃ and N₂O₄ react about 2000 times more rapidly with most amines than with H₂O and that N₂O₃ formed by recombination of NO and NO₂ is more reactive than the reagent produced by dehydration of HNO₂ (equation 5).

TABLE 2. Nitrosation of amino compounds by gaseous N₂O₃ and N₂O₄ in aqueous 0.1 M NaOH at 25°C³

<table>
<thead>
<tr>
<th>Amine</th>
<th>pKₐ</th>
<th>N₂O₄</th>
<th>N₂O₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperidine</td>
<td>11.12</td>
<td>39(0)⁺</td>
<td>65(0)⁺</td>
</tr>
<tr>
<td>Morpholine</td>
<td>8.33</td>
<td>19</td>
<td>52</td>
</tr>
<tr>
<td>N-Methylpiperazine</td>
<td>9.8, 5.11</td>
<td>33(44)⁺</td>
<td>39(45)⁺</td>
</tr>
<tr>
<td>Aniline</td>
<td>4.65</td>
<td>27</td>
<td>45</td>
</tr>
<tr>
<td>N-Methyl-4-nitroaniline</td>
<td>1.19</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>4-Nitroaniline</td>
<td>0.99</td>
<td>24(38)⁺</td>
<td>29(31)⁺</td>
</tr>
<tr>
<td>Diphenylamine</td>
<td>0.78</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3,5-Dinitroaniline</td>
<td>0.35</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2-Nitroaniline</td>
<td>-0.3</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>2-Chloro-4-nitroaniline</td>
<td>-1.0</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>2,4-Dinitroaniline</td>
<td>-4.53</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>N-Butylacetamide</td>
<td>-0.29</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

⁺Based on [amine].

Figures in parentheses refer to reaction in phosphate buffer at pH 6.85.
These observations can be rationalized if $N_2O_3$ and $N_2O_4$ each exist in two tautomeric forms ($7 \rightleftharpoons 8$ and $9 \rightleftharpoons 10$) with the less stable and therefore more reactive isomers ($7$ and $9$) being formed from gaseous NO and NO$_2$ components. The mechanism proposed for concurrent nitrosation and nitration by $N_2O_4$ is illustrated by Scheme 5. Formation of $N$-nitrosamines is considered to involve tautomer $9$, and $N$-nitramines tautomer $10$ or possibly NO$_2$ radicals.

\[
\begin{align*}
O=N-O&O \rightleftharpoons O=N-NO_2 \quad O=N-O&NO_2 \rightleftharpoons O_2N-N&NO_2 \\
(7) & \quad (8) & \quad (9) & \quad (10)
\end{align*}
\]

Subsequent work$^{58}$ has shown that the reactions in aqueous media are inhibited by added acids, NaN$_3$, sodium ascorbate, phenols, simple alcohols and primary amines. They are catalysed, however, by nucleophilic anions (e.g. SCN$^-$), and by 1,2-alkanolamines and 1,2-dihydroxy compounds as discussed further below (Section II.B.4). Also, tertiary amines (e.g. triethylamine, $N,N$-dimethylaniline) react as rapidly as secondary amines to give lower, but nonetheless significant, yields of $N$-nitrosamines$^{58}$.

\[
\begin{align*}
O_2N-N&NO_2 \rightleftharpoons NO_2 + NO_2 \\
(11) & \quad (12)
\end{align*}
\]


Nitrosation by gaseous $N_2O_3$ and $N_2O_4$ in aqueous media follow the general mechanism of Scheme 2, where NOY refers to either ONONO, ONNO$_2$ or ONONO$_2$. The rapidity of their reactions relates more to the nonacidic nature of the reaction media than any other factor. This provides much higher concentrations of unprotonated amine than do acidic conditions. It is apparent from Table 2, however, that amines of widely different basicity ($pK_a$) show remarkably similar reactivities towards gaseous $N_2O_3$ and $N_2O_4$. This behaviour also characterizes the $k_3$ values in Table 1 obtained for nitrosation by $N_2O_3$ at pH 2. Both sets of data suggest that the nitrosation of secondary amines is governed by factors other than reactivity, such as the diffusion of reagents through solution.

4. Catalysis by 1,2-diols, carbohydrates and $\beta$-alkanolamines

Simple alcohols such as MeOH and EtOH have been observed to reduce the formation of $N$-nitrosamines from secondary amines and gaseous $N_2O_3$, $N_2O_4$ or NOCl under neutral and alkaline conditions$^{59-61}$. This arises because the alcohols combine with the nitrosyl gases to form a nitrite ester (equation 21) before they can react with the amines to form $N$-nitrosamines. The simple nitrite esters (e.g.
EtONO) are poor nitrosating agents in the absence of acids (see Section II.C.3). Other alcohols which bear an electron-withdrawing group $\beta$ to the hydroxyl function, however, usually increase the yield of $N$-nitrosamines under similar conditions.$^{59-62}$ Significantly, a wide range of common chemicals, drugs and food components have this structural feature, including 1,2-diols (e.g. ethylene glycol), $\beta$-alkanolamines (e.g. ethanolamine) and carbohydrates (sugars). Most increase the yield of $N$-nitrosamine as exemplified for piperidine in 0.1 M NaOH in Table 3. Mechanistic studies suggest that the corresponding nitrite ester (11) is formed, but activation by the $\beta$-substituent renders it reactive towards amines under nonacidic conditions (Scheme 6). This conclusion is supported by independent measurements showing that 2-ethoxyethyl nitrite (EtOCH$_2$CH$_2$ONO) effects the nitrosation of

$$ROH + YNO \xrightarrow{\text{HO}^-} RONO + Y^- + H_2O$$  \hspace{1cm} (21)

<table>
<thead>
<tr>
<th>[Alcohol] (M)</th>
<th>$10^4$[N-Nitrosopiperidine] (M)$^a$</th>
<th>$t_{1/2}$ (min)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>7.0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>0.05 D-Glucose</td>
<td>11.6</td>
<td>2.0</td>
</tr>
<tr>
<td>0.25 D-Glucose$^c$</td>
<td>20</td>
<td>3.0</td>
</tr>
<tr>
<td>0.05 D-Mannose</td>
<td>12.2</td>
<td>4.1</td>
</tr>
<tr>
<td>0.05 D-Galactose</td>
<td>11.4</td>
<td>2.2</td>
</tr>
<tr>
<td>0.05 Sucrose</td>
<td>18.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Table sugar (0.86 g/5 ml)</td>
<td>18.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Milk (1.5 ml/5 ml)</td>
<td>10</td>
<td>4.0</td>
</tr>
<tr>
<td>0.26 Ethylene glycol</td>
<td>17.8</td>
<td>25</td>
</tr>
<tr>
<td>0.05 Triethanolamine</td>
<td>12.1</td>
<td>19</td>
</tr>
<tr>
<td>0.05 Diethanolamine</td>
<td>3.75</td>
<td>24</td>
</tr>
<tr>
<td>0.05 N-Nitrosodiethanolamine</td>
<td>17.5</td>
<td>4.0</td>
</tr>
<tr>
<td>0.05 N-Nitrosodiethanolamine$^c$</td>
<td>4.9</td>
<td>3.5</td>
</tr>
<tr>
<td>0.05 Choline chloride</td>
<td>10.0</td>
<td>3.0</td>
</tr>
<tr>
<td>0.25 2,2,2-Trifluoroethanol</td>
<td>17.0</td>
<td>1.2</td>
</tr>
<tr>
<td>0.25 2-Fluoroethanol</td>
<td>16</td>
<td>8.0</td>
</tr>
</tbody>
</table>

$^a$Maximum yield for reaction of $2 \times 10^{-3}$M piperidine with $1.14 \times 10^{-2}$M NOCl.

$^b$Time to obtain 50% of the maximum yield.

$^c$Using $10^{-2}$M $N_2O_4$ in place of NOCl.

$$XCH_2CH_2OH + YNO \xrightarrow{\text{HO}^-} XCH_2CH_2ONO + Y^- + H_2O$$  \hspace{1cm} (11)

$$X = \text{OH, NH}_2, \text{etc}$$

$$Y = \text{Cl, ONO, ONO}_2$$

$$R_2NNO + XCH_2CH_2OH$$

SCHEME 6. Catalysis of nitrosyl gas nitrosation of amines by $\beta$-hydroxyalkyl compounds.
piperidine and morpholine in 0.1 M NaOH, and of the N-methylpiperazinium ion in phosphate buffer at pH 6.85. The data in Table 3, together with observations that simple alkyl nitrites (e.g. EtONO) are ineffectual under non-acidic conditions, show that the reactivity of these reagents increases with electron-withdrawing ability of the β-substituent. Further, the extent of reaction (and the ability to catalyse nitrosation by nitrosyl gases) is strongly dependent on the reactivity of the amine. For example, morpholine (pKₐ 8.33) is about 100 times less reactive than piperidine (pKₐ 11.12) towards 2-ethoxyethyl nitrite.

The scope of these reactions requires further study but their involvement with N-nitrosamine formation in vivo and in consumer products seems highly probable. Both gaseous N₂O₃ and N₂O₄ form N-nitrosamines in blood and plasma and these reactions are likely to be mediated by carbohydrates. Further, they suggest the pathway by which N-nitroso compounds may form from gaseous NOₓ pollutants in the presence of common materials such as glycerine and alkanolamines. Triethanolamine, for example, has been recommended for both the removal and estimation of NO₂ in studies of atmospheric pollution.

5. Catalysed nitrosation by nitric oxide

Early work by Drago and Paulik established that secondary amines react with excess NO in EtOH to give first N-nitrosamines and then ammonium salts (R₂NN₂O₂⁻ R₂NH₂⁺). Subsequently, Brackman and Smit showed that the N-nitrosamine formation was catalysed by CuCl₂ and proposed a complex mechanism involving several redox processes. Related reactions were the subject of innumerable patents.

Under anaerobic conditions, the reaction of NO with heterocyclic amines is either catalysed or promoted by ZnI₂, ZnBr₂, CuCl₂, CuCl, Fe(NO₃)₃, AgNO₃, AgClO₄, CoSO₄, SnCl₂, NiCl₂, CdCl₂, HgCl₂ and Hg(OAc)₂. Some of these reactions are retarded by H₂O, and all are inhibited by added acids. The mechanisms by which several occur are now understood. For AgNO₃ and AgClO₄, the initial step is disproportionation to give a Ag(II)–amine complex (12) plus Ag(0) (silver mirror). Subsequent redox processes generate an amino radical cation (R₂N⁺) which combines directly with NO to produce the N-nitrosamine as shown in Scheme 7. Other work shows that oxidative activation of amine ligands to either a radical or a radical cation intermediate also applies to catalysis by Cu(I), Cu(II), Fe(II) and Fe(III) salts.

Apart from O₂ (cf. equation 17), two of the best promoters for nitrosation by NO are I₂ and HI. With I₂, quantitative yields of N-nitrosamine are obtained from heterocyclic amines in EtOH at 25°C in ca. 20 min. These reactions have been shown to proceed via nitrosyl iodide (NOI) which, like NOCl, reacts readily with the unprotonated amine (Scheme 8). Since only the unprotonated amine is reactive,
it is surprising that N-nitrosamine formation is also promoted by HI. The ex-planation lies in the discovery that HI is reduced to I₂ by NO in organic solvents (equation 22). This effectively reduces the acidity of the reaction solutions by con-verting HI (strong acid) to H₂O (weak acid). The formation of N-nitrosamines then

\[ 2\text{HI} + 2\text{NO} \rightarrow \text{N}_2\text{O} + \text{H}_2\text{O} + \text{I}_2 \]  

(22)

proceeds via the reaction of NO with I₂ as described in Scheme 8. Rapid N-nitrosamine formation in the presence of metal iodides and bromides (e.g. ZnI₂ and ZnBr₂) proceeds similarly following solvolysis of the salt to HI or HBr (e.g. equation 23).

\[ \text{ZnI}_2 + 2\text{EtOH} \rightarrow \text{Zn(OEt)}_2 + 2\text{HI} \]  

(23)

Reactions using NO can be very much faster than conventional N-nitrosamine formation using acidified nitrite because under neutral conditions the concentration of unprotonated amine is higher. Nonetheless, the powerful NOI nitrosating agent can be generated in the presence of I₂, HI and metal iodides. This behaves like other YNO reagents and reacts in accordance with Scheme 2. With other metal salts, rapid reactions relate to the formation of metal amine complexes in which oxidative activation of the amino ligand results in ready combination with the normally unreactive NO reagent.

C. Nitrosation of Secondary Amines by Organic Nitroso and Nitro Compounds

Nitrosation reactions by aromatic N-nitrosamines, nitrite esters, thionitrite esters and certain other organic nitro and nitroso compounds have been known for many years and some find application in organic synthesis. Few, however, have been systematically investigated, and their mechanisms may therefore be speculative.

1. Nitrosation by N-nitrosamines

Denitrosation by aqueous acid, thermally as in the TEA" Analyzer and photochemically, implies that all N-nitrosamines are potential nitrosating agents under the appropriate conditions. Interaction with other amines leading to new N-nitrosamines (often termed transnitrosation) is only significant, however, when the N–N(O) bond is weakened by electron-withdrawing substituents.

Transnitrosation occurs in dilute acid (pH < 3) decreasing along the series \( \text{Ph}_2\text{NNO} > \text{PhMeNNO} > \text{N-nitrosopiperazine} > \text{N-nitrosomorpholine} > \text{N-nitrosopiperidine} \) in line with decreasing bond strength. The reactions tend to be sluggish because the amino substrates are extremely protonated, but catalysis by anions and nucleophiles (I⁻ ≈ thiourea > SCN⁻ > Br⁻ > Cl⁻) has been demon-
N-Nitrosamines and N-nitrosoimines

26. N-Nitrosamines and N-nitrosoimines

\[ R_2\text{NNO} + \text{HY} \leftrightarrow \left[ \begin{array}{c} R \\text{H} \\ \text{N} \\text{NO} \end{array} \right]^+ \quad \text{Y}^- \leftrightarrow R_2\text{NH} + \text{YNO} \quad \text{R}_2^1\text{NNO} + \text{HY} \quad (24) \]

This implies that release of \( \text{YNO} \) is involved (equation 24) so the scope and limitations of these reactions can be assessed from direct investigations of nitrosation using \( \text{HNO}_2 \). Under certain conditions (e.g. in \( \text{EtOH} \) or with excess \( \text{Y}^- \)) protonation of the \( \text{N-nitrosamine} \) appears to become rate-limiting for \( \text{N-nitrosodiphenylamine} \) and \( \text{N-nitroso-N-methylaniline} \). The conditions under which these transnitrosations occur are not too dissimilar from those in the stomach. It follows that many noncarcinogenic materials (e.g. \( \text{N-nitrosodiphenylamine} \), \( \text{N-nitrosoamino acids} \)) may produce carcinogenic compounds by reacting with secondary amines \( \text{in vivo} \). Transnitrosation can also be effected in non-aqueous solvents by heating the more labile \( \text{N-nitrosamines} \) (e.g. \( \text{N-nitrosocarbazole} \), \( \text{N-nitrosodiphenylamine} \)) with another secondary amine. Temperatures in the region of 50–80°C are usually required. Unpublished work shows that these reactions proceed via release of \( \text{NO} \), which requires either oxidation to \( \text{NO}_2 \) (\( \equiv \text{N}_2\text{O}_4 \)), or catalysis by metal salts (see Section II.B.5) to react with another amine (equation 25). Aromatic \( \text{N-nitrosamines} \) find industrial application as antioxidants and retardants. It is conceivable that thermal reactions similar to equation (25) may explain, for example, the detection of \( \text{N-nitrosomorpholine} \) in some rubber factories.

2. Nitrosation by \( \text{N-nitrosamides and related compounds} \)

\( \text{N-Nitrosamides} \), \( \text{N-methyl-N-nitroso-p-toluenesulphonamide} \), and \( \text{N-nitrosoureas} \) have been shown to undergo denitrosation and (sometimes) concurrent deamination in mildly acidic conditions (\( \text{pH} < 4 \)) as in equation (26). Usually \( \text{H}^+ \) transfer to form the conjugate acid intermediate (e.g. 13) is rate-limiting. In principle, this could result in transnitrosation to another amino substrate, but, thus far, the reaction has been demonstrated only for \( \text{N-nitrosoureas} \) and \( \text{N-nitroso-methylurethane} \). Above \( \text{pH} 4 \), deamination is dominant for most compounds.
Further, homolytic fission of the \(N\text{--}N(=O)\) bond has not been reported (other than in the TEA\(^6\) Analyzer) possibly because of preferential rearrangement reactions. For example, \(N\)-nitrosamides rearrange to diazo ester intermediates (14) that rapidly lose \(N_2\) (equation 27).^90

\[
\begin{align*}
R^1\text{CON(NO)R}^2 & \quad \xrightarrow{\Delta}\quad [R^1\text{C=ON}=NR^2] \quad \xrightarrow{} \quad R^1\text{CO}_2\text{R}^2 + N_2 \\
(14) &
\end{align*}
\]

3. Nitrosation by nitrite esters

These compounds have found synthetical application as nitrosating agents largely because of their good solubility in organic solvents. They have been used to prepare \(N\)-nitrosamines, but reliable mechanistic investigations are lacking. Compounds derived from simple monohydric alcohols (e.g. EtONO, \(n\)-AmONO) are reactive under acidic, thermal and photolytic conditions. In aqueous acid, formation of an \(O\)-conjugate acid (15) is probably involved, but it is not known whether 15 reacts directly with the amino substrate, via the YNO carrier, or by both pathways (equation 28). The \(O\)-conjugate acid 15 should behave very much like the nitrous acidium ion \((H_2O\text{NO}^+)\). Simple nitrite esters undergo homolytic fission both thermally and photolytically to generate alkoxy radicals \((RO^+)\) and NO. Since these reactions are rarely carried out under anaerobic conditions, it is possible that ensuing nitrosation reactions proceed via \(N_2O_4\) following oxidation of NO to \(NO_2\) (equation 29).

\[
\begin{align*}
2\text{R}^1\text{ONO} & \quad \xrightarrow{\Delta \text{or } hv} \quad 2\text{R}^1\text{O}^+ + 2\text{NO} \quad \xrightarrow{O_2} \quad \text{N}_2\text{O}_4 \quad \xrightarrow{R_2^2\text{NH}} \quad \text{R}_2^2\text{NNO} + \text{HNO}_3
\end{align*}
\]

As discussed in Section II.B.4, nitrite esters bearing electron-withdrawing \(\beta\)-substituents \((X)\) are more reactive. They effect \(N\)-nitrosamine formation at ambient temperatures in the absence of acid catalysts by direct nucleophilic attack of the amine on the neutral ester (equation 30). For example, 2-ethoxyethyl nitrite \((\text{EtOCH}_2\text{CH}_2\text{ONO})\) reacts with both piperidine and morpholine in 0.1 M NaOH and with the \(N\)-methylpipperazinium ion at pH 6.85 to give significant yields of the corresponding \(N\)-nitrosamines in ca. 30 min. Base-catalysed hydrolysis of \(\text{EtOCH}_2\text{CH}_2\text{ONO}\) competes with the \(N\)-nitrosation, but piperidine and morpholine react 320 and 3.7 times faster, respectively, than \(\text{HO}^-\). Related reactions have been reported for \(\beta\)-phenethyl nitrite in aqueous dioxan and nitrite esters derived from a variety of vicinal diols, \(\beta\)-alkanolamines and carbohydrates. Esters of similar
structure find some application as antianginal drugs, but the possibility that they may act as in vivo nitrosating agents has not been widely recognized.

4. Nitrosation by thionitrite esters

Nitrosation by thionitrite esters is less well known probably because of their instability. Intrinsically, however, they should be more reactive than regular nitrite esters because RS\(^-\) is a better leaving group (i.e. more stable) than RO\(^-\). This conclusion is partially borne out by reports that alkyl- and aryl-thionitrites convert piperidine to its N-nitroso derivative in organic solvents at ambient temperatures\(^9\) and that nitrosocysteine produces N-nitrosamines in acidic, neutral and alkaline aqueous solutions\(^95,96\). Thus, there is clear evidence that activation by acids is not necessary, but other mechanistic aspects remain unclear. Direct nitrosation by the thionitrite ester cannot be excluded, yet formation of disulphide coproducts (RSSR) and catalysis by air and light\(^8\) suggest that release of NO followed by oxidation to NO\(_2\) (\(\Rightarrow\)N\(_2\)O\(_3\)) may also be important.

5. Nitrosation by organic nitro compounds

Early work reviewed by Fridman\(^8\) and his colleagues showed that some aliphatic nitro compounds act as nitrosating as well as nitrating agents. Findings for tetranitromethane \([\text{C(NO}_2\text{)}_4]\) are relevant; it converts \(N,N\)-dimethylaniline to \(N\)-methyl-\(N\)-nitroso-aniline on heating in pyridine\(^9\) yet effects the nitration of phenols in aqueous solution at pH 8 and 25°C\(^9\). The nitration is considered to involve charge-transfer intermediates\(^9\) but little is known about the nitrosation reaction. More recently, the formation of \(N\)-nitrosomorpholine from tetranitromethane, 2,2-dinitropropanol and 2-bromo-2-nitropropane-1,3-diol (bronopol) on heating at 70°C with morpholine in both aqueous and organic solvents has been described\(^10\). The propensity for reaction appears to depend on the presence of additional electron-withdrawing substituents at the carbon atom bearing the nitro group, which weaken the C—NO\(_2\) bond. The mechanism of these reactions is also unclear, but one obvious explanation is that release of NO\(_2\) leads to formation of N\(_2\)O\(_4\), which then effects nitrosation. For bronopol (2-bromo-2-nitropropene-1,3-diol), an alternative pathway involving formaldehyde and NO\(_2\)\(^-\) has been suggested\(^10\), but this may be exceptional.

A priori, any nitro compound that releases NO\(_2\) may be expected to form an \(N\)-nitrosamine from secondary and tertiary amines, but few examples are known. \(N\)-Nitrodimethylamine, however, is reported to give \(N\)-nitrosodimethylamine both by heating at 165–200°C in the gas phase\(^10\) and by UV photolysis at ambient temperature in the solid state\(^10\). The thermolysis is considered to involve radicals produced by breakage of the N—N bond\(^10\), whereas isotopic scrambling experiments suggest that the photolysis proceeds by direct reduction with N—O bond cleavage\(^103\). Further, several antianginal drugs with a nitrate ester structure have recently been shown to produce \(N\)-nitrosamines in dilute acid\(^10\), but these reactions appear to proceed via the release of HNO\(_2\).

D. Nitrosation of Primary, Tertiary and Quaternary Amino Compounds

At first sight, the formation of \(N\)-nitrosamines from these substrates seems unlikely, but there is good evidence to show otherwise. These reactions are less facile and/or less extensive, however, than those with secondary amino compounds.
1. Primary amines

Nitrosation of primary aliphatic amines leads to deamination via an unstable diazonium ion intermediate (16), which reacts with nucleophiles to give substitution, elimination and rearrangement products (Scheme 9). One of these decomposition pathways can result in alkylation of the starting material to give a secondary amine and, subsequently, an N-nitrosamine (equation 31). The kinetic characteristics of the initial deamination (including catalysis and inhibition) should be similar to N-nitrosamine formation, but yields of N-nitrosamines obtained from primary amines are very low because the intermediate 16 reacts by several competitive pathways other than equation (31). Higher yields might be anticipated for reaction in organic (aprotic) solvents, but this awaits confirmation. These reactions could be of some importance to the formation of heterocyclic N-nitrosamines from primary diamine precursors. Putrescine, for example, gives ca. 1.6% N-nitrosopyrrolidine (equation 32) on heating with HNO₂ in an aqueous slurry compared to 0.01% N-nitroso-di-n-butylamine from n-butylamine under similar conditions.

2. Tertiary amines

Early work on the interaction of tertiary amines with acidified nitrite has been reviewed, but these reactions have attracted further attention because of N-nitrosamine formation. Such products may arise from the sequence of reactions outlined in Scheme 10, in which an iminium salt (17) undergoes hydrolysis to a secondary amine, or by a direct reaction of 17 with NO₂-. The hydrolysis hypothesis is supported by recent identification of secondary amines as co-products to aldehydes, N₂O₂ (2HNO → N₂O + H₂O) and N-nitrosamines. An alternative pathway involving electron transfer rather than N-nitrosation to form 17 has been proposed and this could be favoured for aromatic amines. Usually quite stringent conditions (50–100°C) are required for tertiary alkylamines and it has been estimated that these compounds are ca. 10,000 times less reactive than comparable secondary amines. This implies that either formation or hydrolysis of 17 is rate-limiting (Scheme 10). Most investigations (e.g. References...
26. N-Nitrosamines and N-nitrosoimines

\[
R_2NCH_2R' + YNO \xrightarrow{\text{fast}} \left[ R_2NCH_2R' \right]^+ + Y^- \xrightarrow{\text{slow?}} R_2N\equiv C = \text{CHR}^2 + [\text{HNO}]
\]

(17)

\[
HY + R_2NNO \xrightleftharpoons{\text{YNO}} R_2NH + R^2CHO
\]


109 and 110) find maximum rates with HNO\(_2\) at pH 3-3.4 (as for secondary amines) but there is considerable disagreement as to the kinetic dependence on [HNO\(_2\)] (cf. References 110, 111 and 114). This may relate to different experimental conditions or to inadequate attention to concurrent thermal decomposition of HNO\(_2\). Further, if the initial N-nitrosation is rapid as suggested in Scheme 10, the kinetic data will not identify the nitrosating agent (possibly \(N_2O_3\)) and nucleophilic anions (e.g. SCN\(^-\)) may not catalyse N-nitrosamine formation.

Much faster reactions are observed for tertiary amines bearing other than simple alkyl substituents. This applies, for example, to the formation of \(N\)-nitrosodimethylamine at ambient temperatures from aminopyrine\(^{107}\), oxytetracycline\(^{107}\) and minocycline\(^{115}\). For aminopyrine, rapid reaction has been attributed\(^4\) to facile addition of \(N_2O_3\) to the enamine moiety to give an intermediate (18) which collapses directly to \(N\)-nitrosodimethylamine (equation 33). Alternative mechanisms

\[
\begin{align*}
\text{Me}_2N \text{Ph} & \xrightarrow{\text{N}_2\text{O}_3} \text{Me}_2N \text{Ph} \\
\text{Me}_2N \text{Ph} & \xrightarrow{\text{H}_2\text{O}} \text{Me}_2N \text{Ph} \\
& + \text{Me}_2\text{NNO} + \text{HNO}_2
\end{align*}
\]

have been discussed\(^{116}\) and may be required to explain strong SCN\(^-\) catalysis\(^{117}\). A pathway similar to equation (33) would apply to oxytetracycline. For minocycline (19), rapid \(N\)-nitrosodimethylamine formation probably relates to the presence of 7-dimethylamino and 10-hydroxy substituents. Aromatic amines are less basic than aliphatic analogues, and are therefore much more reactive towards nitrosating
agents in dilute acid. Further, hydrolytic cleavage of the 7-dimethylamino group is facilitated by the 10-hydroxy substituent. This effect has been observed with 4-hydroxy-\(N,N\)-dimethylaniline, which undergoes rapid oxidative hydrolysis by \(\text{HNO}_2\) at pH 3 and 25°C (equation 34)\(^{118}\). The interaction of other aromatic tertiary amines (e.g. \(N,N\)-dimethylaniline) with acidified nitrite has not been widely examined, but dealkylation should be favoured by their low basicity and ready oxidation to radical cation intermediates. Subsequent nitrosation would produce an aromatic \(N\)-nitrosamine (e.g. \(N\)-methyl-\(N\)-nitrosoaniline).

3. Quaternary amine salts and amine oxides

\(N\)-Nitrosodimethylamine has also been obtained from reactions of acidified nitrite with both quaternary methylammonium salts and trimethylamine-\(N\)-oxide\(^{108,114,119}\). As for tertiary amines, forcing conditions of high reagent concentrations and high temperatures are required. Surprisingly, the \(N\)-oxide seems to be more reactive than trimethylamine, itself\(^{114}\), whereas the quaternary salts are less reactive\(^{119}\). Comparative data for reaction after 4 h with a five-fold excess of \(\text{NaNO}_2\) at pH 5.6 and 78°C are given in Table 4. Very little is known about the mechanism of these reactions.

4. Tertiary amides and related compounds

These compounds have only been superficially examined, but there is good evidence that \(N\)-nitrosamines (and in some cases \(N\)-nitrosamides) form on reaction with acidified nitrite at elevated temperatures\(^{107,120,121}\). Trialkylureas usually give the corresponding \(N\)-nitrosourea, whereas dialkyl- and trialkyl-thioureas, 1,1-dialkylureas, 1,1-dialkyl-3-phenylureas and tetralkylureas produce \(N\)-nitrosamines.

<table>
<thead>
<tr>
<th>Amino substrate</th>
<th>Yield of (\text{Me}_2\text{NNO}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Me}_2\text{NH})</td>
<td>9.6</td>
</tr>
<tr>
<td>(\text{Me}_3\text{N})</td>
<td>0.9</td>
</tr>
<tr>
<td>(\text{Me}_4\text{N}^+)</td>
<td>0.6</td>
</tr>
<tr>
<td>(\text{Me}_2\text{NCH}_2\text{CH}_2\text{OH})</td>
<td>1.6</td>
</tr>
<tr>
<td>(\text{Me}_3\text{NCH}_2\text{CH}_2\text{OH})</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
26. N-Nitrosamines and N-nitrosoimines

E. Miscellaneous Methods of N-Nitrosamine Formation

1. Catalysed reactions of nitrite ion

Reactions by NO$_2^-$ proceed in the presence of certain carbonyl compounds, chlorinated solvents or metal salts and under the influence of radiation. Formaldehyde, pyridoxal and several benzaldehydes (but not acetone or acetaldehyde) produce N-nitrosamines from secondary amines in neutral and alkaline solutions of NO$_2^-$\textsuperscript{122,123}. The reaction rates vary with steric accessibility to the nitrogen atom, but all are much slower than regular nitrosations in acidic solutions. The mechanism first proposed involved nucleophilic attack by NO$_2^-$ on an iminium ion intermediate (20) followed by collapse of the adduct to the N-nitrosamine (Scheme 11). Alternative mechanisms have been discussed elsewhere\textsuperscript{116}. This type of reaction may also explain the unexpected formation of N-nitrosamines from secondary amines and solid NaN$O_2$ in halogenated solvents (e.g. CH$_2$Cl$_2$)\textsuperscript{124} and small amounts of N-nitrosodiethanolamine in cosmetics containing the bactericide 2-bromo-2-nitropropane-1,3-diol (bronopol) which decomposes to release NO$_2^-$ and formaldehyde\textsuperscript{101}.

NaN$O_2$ has also been shown to produce N-nitrosamines from secondary amines at pH 11 in the presence of ferrocyanide ion\textsuperscript{125} and in 2,2'-bipyridine in the presence of cupric nitrate\textsuperscript{126}. In both cases, interaction of NO$_2^-$ with the metal salt is believed to generate a powerful nitrosating agent such as [Fe$^{III}$(CN)$_5NO$]$^+$ and Cu$^{II}$(bipy)(ONO)$_2$, respectively. Many transition metals other than Fe are known to form diverse nitrosyl complexes, but their ability to nitrosate amino compounds has not been extensively investigated.

\[
\text{R}_2\text{NH} + \text{R}_2\text{CHO} \xrightleftharpoons{\text{H}^+} \text{R}_2\text{N}^+=\text{CHR}^2 + \text{H}_2\text{O} \tag{20}
\]

\[
\begin{align*}
\text{R}_2\text{N}^+\text{CHR}^2 \quad &\xrightarrow{\text{NO}_2^-} \quad \text{R}_2\text{NNO} + \text{R}_2\text{CHO} \\
\end{align*}
\]

\textbf{SCHEME 11.} Formation of N-nitrosamines from nitrite ion, carbonyl compounds and amines.

Recent work demonstrates that N-nitrosamines form rapidly from neutral aqueous NaN$O_2$ and heterocyclic amines both on $\gamma$-irradiation\textsuperscript{59} and on UV photolysis\textsuperscript{127}. It seems probable that HO radicals and solvated electrons generated from H$_2$O convert NO$_2^-$ to NO$_2$ and NO. These combine to form N$_2$O$_3$ which effects the nitrosation.

2. Reduction of nitrate ion

Nitrosation by nitrate salts or nitric acid requires reductive conditions and, in principle, the formation of either NO$_2^-$, NO$_2$, or NO intermediates. Reduction of NO$_3^-$ is difficult to achieve under mild conditions, but it can be effected microbiologically, and there is good evidence for the formation of N-nitrosamines from aqueous solutions of nitrate salts and secondary amines in the presence of bacteria\textsuperscript{128,129}. 

Other recent work reveals that N-nitrosamines are readily formed when neutral aqueous solutions of NaNO₃ and secondary amines are exposed either to γ-radiation⁵⁹ or to UV photolysis¹²⁷. The highest yields apply to experiments with excess NaNO₃. These reactions are thought to result from reduction of NO₃⁻ to NO₂, which then dimerizes to form the N₂O₄ reagent. This conclusion is supported by the concurrent formation of N-nitramines⁵⁹,¹²⁷.

### III. PROPERTIES AND REACTIONS OF N-NITROSAMINES

Aliphatic and heterocyclic N-nitrosamines are either yellow liquids or low-melting solids, soluble in water and organic solvents. Their aromatic counterparts are usually low-melting solids, insoluble in water and thermally unstable. Because of their potential carcinogenicity (see Section IV), great care is necessary in handling all N-nitrosamines.

N-Nitrosamines are close analogues of tertiary amides and it is instructive to compare their structure and chemistry. For both classes the amino nitrogen lone-pair electrons are delocalized into the π-electron system of a doubly bonded oxygen atom and the two major contributing valence structures are those shown in Figure 2. Both N···X···O chains are therefore planar with considerable 1,3-dipolar ion character and the N···X bond orders are about 1.5. The bond orders explain the existence of configurational isomers (E) and (Z) for N-nitrosamines (see Section III.A) and tertiary amides¹³⁰ and the 1,3-dipolar nature of both N···X···O systems is manifest in physical properties and reactions. Thus, self-association in condensed phases and complexation with Lewis and Brønsted acids are characteristic of both N-nitrosamines (see Section III.B) and tertiary amides¹³⁰. Further, both classes exhibit ambident basic and nucleophilic properties with the oxygen atom being more reactive than the amino nitrogen atom (Sections III.C, III.D and Reference 130). Nonetheless, nucleophilic interactions with N-nitrosamines are generally more difficult than with tertiary amides and only organometallic and hydride reagents are effective (Sections III.E and III.F) probably because of repulsion by the lone-pair nitroso nitrogen electrons.

An important property of aliphatic and heterocyclic N-nitrosamines, so far unreported for tertiary amides, is the lability of the (C)—H atom α to the amino nitrogen atom. Thus strong bases generate carbanions, such as R₁⁺R₂N=N=O, which lead to α-substituted derivatives of sufficient importance to be discussed separately in Section III.J. Other reactions of N-nitrosamines, without parallels in the chemistry of tertiary amides, are oxidation to N-nitramines (Section III.G) and...

---

**FIGURE 2.** Comparison of resonance structures of secondary N-nitrosamines and tertiary amides.
homolysis of the N—N(O) bond, brought about thermally or photolytically (Section III.H).

A. Structure, Stereochemistry and Spectra

By analogy with tertiary amides the structure and stereochemistry of \( N \)-nitrosamines should reflect extensive delocalization of the amino nitrogen lone-pair electrons into the \( \pi \)-system of the \( N=O \) group. This is borne out by the limited evidence available. Thus an electron diffraction study of gaseous \( N \)-nitroso-dimethylamine (Figure 3) shows an essentially planar (i.e. trigonal) amino nitrogen atom with bond angles close to 120°. The N—N bond length (134 pm) is intermediate between those for \( N=\text{N} \) (125 pm) and \( N—\text{N} \) (145 pm) and the N—O bond length (123 pm) is also intermediate between those for \( N=O \) (114 pm)* and \( N—O \) (136 pm). Thus both N—N and N—O bond orders are ca. 1.5 implying a structure intermediate between the valence structures 21 and 22 and therefore of partial 1,3-dipolar ion character. Independent evidence for considerable charge development in the ground state comes from dipole moments of 4.0–4.4 D for aliphatic \( N \)-nitrosamines, which are significantly larger than those for tertiary amides (3.75 D). \( N \)-Nitrosodiphenylamine, however, has a lower dipole moment (3.39 D) implying reduced charge development arising from competitive delocalization of the amino lone-pair electrons into the aromatic nucleus. Condensed-phase infrared spectra of \( N \)-nitrosamines are very complex because of self-association and hydrogen bonding, but the highest frequency band at 1445–1490 cm\(^{-1}\), attributed to \( N=O \) stretching in both condensed- and gaseous-phase spectra is much lower than those for \( C \)-nitroso compounds (\( \nu_{N=O} \) 1620–1605 cm\(^{-1}\)) and for alkyl nitrites (\( \nu_{N=O} \) 1620–1605 cm\(^{-1}\)). This is further evidence of intermediate bond order for the \( N=O \) group in \( N \)-nitrosamines.

![FIGURE 3. Structure of \( N \)-nitrosodimethylamine from electron diffraction data. (Bond lengths in pm.)](image)

*Unambiguous bond lengths for \( N=O \) are not available, the best being in nitric oxide (115 pm) and nitrosyl chloride (114 pm).
Free rotation about the N—N bond should be hindered by its partial double-bond character and lead to the existence of configurational isomers 23 and 24.

\[
\begin{align*}
\text{(R')ZR_2) & \text{ (23)} \\
\text{(R')ZR_2) & \text{ (24)}
\end{align*}
\]

\[(R^1 \neq R^2)\]. Good evidence to this effect is the observation of nonequivalent signals in the \(^1\text{H}-\text{NMR}\) spectra of symmetrical N-nitrosamines \((R^1 = R^2)\). For example, N-nitrosodimethylamine shows two CH₃ signals separated by 19 ppm and their temperature dependence gives a rotational barrier \((\Delta G^\circ)\) of 96 kJ mol\(^{-1}\).\(^{134}\) Although the methyl group assignments in this study for (E) and (Z) isomers has been challenged\(^{135}\), a separate investigation\(^{136}\) using total line-shape analysis confirms that rotational barriers for dialkyl-N-nitrosamines are in the range 96–121 kJ mol\(^{-1}\). N-Isopropyl-N-nitrosoaniline also lies in this range\(^{137}\) but the lower value for N-nitrosodiphenylamine \((\Delta G^\circ = 79.9 \text{ kJ mol}^{-1})\) is consistent with a decreased N—N double-bond character. Another investigation of heterocyclic N-nitrosamines\(^{139}\) shows that \(\alpha\)-substitution also lowers the rotational barriers \((\Delta G^\circ = 77–92 \text{ kJ mol}^{-1})\). In general, however, the barriers to rotation in N-nitrosamines are slightly higher than those for \(N,N\)-dimethylamines \((\Delta G^\circ = 75 \text{ kJ mol}^{-1})\) and considerably lower than for ethylene \((\Delta G^\circ = 167 \text{ kJ mol}^{-1})\).

The proportion of \((E)\) to \((Z)\) isomer (i.e. 23 to 24) depends mainly on the relative size of \(R^1\) and \(R^2\) and it is generally assumed\(^{135,137}\) that isomers with the less bulky group adjacent to oxygen predominate. This ratio can be altered by photolysis and for several \(N\)-methyl-N-nitrosamines the proportion of (Z) isomer increases by 10–30% on irradiation in organic solvents over 6 h\(^{140}\). Because of their rapid interconversion \((t_{1/2} \text{ ca. } 1–2 \text{ h in solution at } 36^\circ\text{C})\), (E) and (Z) isomers have rarely been separated, except for 23, 24 \((R^1 = \text{PhCH}_2, R^2 = 2,6\text{-Me}_2\text{C}_6\text{H}_4)\) by thin-layer chromatography\(^{141}\) and for the chiral \(N\)-nitrosamine (25) by crystallization with an optically pure amine\(^{142}\). Separation of (E) and (Z) isomers of \(\alpha\)-\(N\)-nitrosamino acids is easier and can be accomplished by either t.l.c.\(^{143}\) or h.p.l.c.\(^{144}\).

Both UV and mass spectra of \(N\)-nitrosamines have characteristic features of diagnostic value. Their UV spectra have two bands in the region of 230–240 nm \((\log \epsilon \text{ ca. } 4)\) or 330–370 nm \((\log \epsilon \text{ ca. } 2)\)\(^{8,145,146}\). The first is assigned to a \(\pi \rightarrow \pi^*\) transition and is found at longer wavelengths for aromatic compounds and the second (which is very sensitive to solvent effects) to an \(n \rightarrow \pi^*\) transition. The mass spectra of aliphatic \(N\)-nitrosamines show both molecular ion and \(M^+ - 17\) (due to loss of OH) peaks plus others at some point in the fragmentation pattern corresponding to \(\alpha\)-cleavage. Heterocyclic compounds also give satisfactory molecular ion and \(M^+ - 17\) peaks as well as ones at \(M^+ - 30\) (loss of NO), \(M^+ - 31\) (loss of NOH) and due to \(\alpha\)-cleavage. Aromatic \(N\)-nitrosamines, however, exhibit weak
molecular ions but relatively strong \( M^+ - 29 \) and \( M^+ - 30 \) signals. The \( M^+ - 29 \) peak is attributed to hydrogen abstraction by the \( M^+ - 30 \) ion\(^{147}\).

**B. Acid–Base, Hydrogen-bonding and Complexing Properties**

Although both the acidic and basic properties are well characterized, reliable quantitative data (i.e., \( pK \) values) are generally lacking. In alkaline solution \( N \)-nitroso derivatives of either heterocyclic amines or open-chain amines bearing at least one primary or secondary alkyl substituent undergo hydrogen exchange at the \( \alpha \)-carbon atom\(^{148,149}\) (e.g., equation 35), and in the presence of very strong bases (such as NaH or organometallic reagents) the corresponding carbanions (26) are generated\(^{149,150}\) as in equation (36). This prototropic behaviour is reminiscent of diazoalkanes:

\[
\begin{align*}
\text{CH}_2\text{N}^+\text{N}^- & \rightarrow \text{CH}_2\text{N}^-\text{N}^+ \text{H}_2\text{O}^+ \rightarrow \text{CH}_3\text{N}^-\text{N}^+. \\
R^1\text{CH}_2^+\text{N}^-\text{N}^- & + \text{D}_2\text{O} \xrightarrow{\text{base}} R^1\text{CD}_2^+\text{N}^-\text{N}^- \rightarrow \text{H}_2\text{O} \\
R^1\text{CH}_2\text{N}^-\text{N}^- & \xrightarrow{\text{base}} R^1\text{CH}_2^+\text{N}^-\text{N}^- \rightarrow R^1\text{CD}_2^+\text{N}^-\text{N}^- (26) \\
(26) & \rightarrow (27)
\end{align*}
\]

although the \( N \)-nitrosamines are significantly weaker acids. The lability of the \( \alpha \)-protons in \( N \)-nitrosamines was originally attributed to an ylid-type stabilization of the carbanion 26 by the adjacent positive end of the 1,3-dipole\(^{148}\), but differences in the rate of hydrogen exchange of \( \text{syn} \) - and \( \text{anti} \)-\( \alpha \)-protons suggest that stabilization of the dianion 27 is of overriding importance\(^{151}\). These results are discussed in more detail in Section III.J. The carbanions (26) are important as synthetic intermediates (Section III.J) and they may also play a significant role in the metabolic activation of \( N \)-nitrosamines (Section IV).

\( N \)-Nitrosamines are very much weaker bases than the parent amines and they undergo extensive protonation only in strong acid. Early investigations by Jaffe and his colleagues\(^{152}\) on the effect of strong acids on the UV spectra of \( N \)-nitrosodialkylamines in both aqueous and organic solvents, showed that protonated complexes form, but gave little information about their structure. They suggested that several hydrogen-bonded complexes formed in addition to a conjugate acid and obtained an approximate value of \( pK_a \approx -0.62 \) for \( N \)-nitrosodimethylamine in water. Thus \( N \)-nitrosamines appear to be ca. 10\(^{10}\) less basic than the corresponding amines and of approximately the same basicity as amides, but this estimate requires independent confirmation. Until recently, there has also been considerable doubt about the site of protonation of \( N \)-nitrosamines, reminiscent of the controversy surrounding the protonation of amides\(^{130}\). The best available evidence, however, now suggests that the most stable conjugate acid for \( N \)-nitrosamines (like amides) is that resulting from \( O \)-protonation (28) where resonance stabilization of the positive

\[
\begin{align*}
R^1 & \text{N}^-\text{N}^+ \text{OH} \leftrightarrow R^1 & \text{N}^+\text{N}^- \text{OH} (28)
\end{align*}
\]
charge is feasible. The alternative conjugate acids 29 and 30 cannot undergo similar resonance stabilization and they are expected to be of higher energy. This conclusion is supported by closed-shell INDO calculations showing that for N-nitrosodiphenylamine, structure 29 is 67 kJ mol\(^{-1}\) more energetic than the O-conjugate acid (28)\(^76\). Other convincing evidence for preferential O-conjugate acid formation in strong acids such as fluorosulphuric acid and H\(_2\)SO\(_3\)F:SbF\(_5\) ("magic acid") comes from \(^1\)H-NMR studies by Kuhn and McIntyre\(^153\) and by Olah and his colleagues\(^154\). Both groups report that on protonation the methyl groups of N-nitrosodimethylamine remain nonequivalent. Thus rotation about the N—N bond of the conjugate acid cannot be free as required for structures 29 and 30. However, since formation of an N-conjugate acid (29) is necessary to explain N—N bond fission in denitrosation processes (Section III.C), a small amount (<5\%) of this species must be present in acidic media.

As acids, N-nitrosamines are apparently too weak to act as donors in hydrogen-bonded complexes, but they are sufficiently basic to act as hydrogen-bond acceptors under the appropriate conditions. Equilibrium constants for 1:1 complexes between N-nitrosamines and alcohols, phenols and amines in hydrocarbon solvents have been measured by Basu and his colleagues\(^155\) using UV spectrophotometry. Formation of a weak 1:1 complex between achiral N-nitrosamines and chiral alcohols and carbohydrates has also been measured by circular dichroism studies\(^156\).

As Lewis bases, N-nitrosamines also form 1:1 and 1:2 complexes with metal salts such as CuCl\(_2\), ZnBr\(_2\), CdCl\(_2\)\(^157\) and PdCl\(_2\)\(^158\) and with Lewis acids such as BF\(_3\)\(^159\), PCl\(_3\) and AlCl\(_3\)\(^157\). An X-ray study\(^160\) of the crystalline 1:1 complex between CuCl\(_2\) and N-nitrosodimethylamine (Figure 4) shows unequivocally that each metal atom

---

**FIGURE 4.** Structure of the 1:1 complex between N-nitrosodimethylamine and CuCl\(_2\). (From X-ray diffraction data\(^160\); bond lengths in pm.)
coordinates with nitroso nitrogen and oxygen atoms from two \( N \)-nitrosodimethylamine molecules. The coordination to oxygen is substantially stronger (\( r = 282 \) pm) than that to nitrogen (\( r = 302 \) pm). The amino nitrogen atom is not bonded to the metal but the \( N-N \) bond is shortened (126 pm) compared with free \( N \)-nitrosamine (134 pm) as expected with increased delocalization of amino nitrogen lone-pair electrons towards oxygen.

\(^1\)H-NMR studies of the adducts between \( N \)-nitrosodimethylamine and \( BF_3, PCl_5, SbCl_5, AlCl_3 \) and \( ZnBr_2 \) show that rotation about the \( N-N \) bond remains restricted in the complex. By arguments similar to those advanced for protonation of \( N \)-nitrosamines, this implies coordination at the nitroso oxygen atom (31) rather than at either nitrogen atom.

\[
R^1R^2 occurrence\rightleftharpoons R^1R^2\overset{\text{N}}{\text{N}} \overset{\text{N}}{\text{O}}X^- \\
(31)
\]

\( X = BF_3, AlCl_3, ZnBr_2 \) etc.

C. Reaction with Inorganic Acids

\( N \)-Nitrosamines are much less reactive than tertiary amides towards nucleophilic reagents. Hydrolysis, for example, can only be brought about via the conjugate acid intermediate, and for alkyl and heterocyclic \( N \)-nitrosamines, only in the presence of a relatively strong nucleophile, such as \( Cl^- \), \( Br^- \) or \( SCN^- \), as well. The resultant \( N-N \) bond fission to amine and YNO is the reverse of the synthesis of \( N \)-nitrosamines from YNO reagents. By the principle of microscopic reversibility, this reaction (equation 37) must involve an \( N \)-protonated nitrosamine intermediate (29)

\[
R^1R^2\overset{\text{H}}{\text{N}}\overset{\text{H}}{\text{O}} + Y^- \\
\overset{\text{H}}{\text{O}} \rightleftharpoons R^1R^2\overset{\text{H}}{\text{N}}\overset{\text{H}}{\text{O}} + Y^- \\
(29)
\]

\( Y^- = Cl-, Br-, SCN-, H_2O \) etc.

presumably formed at low concentration in equilibrium with the \( O \)-conjugate acid (28, Section III.B). For complete reaction, removal of YNO or \( R_2NH \) is necessary. In the absence of strong nucleophiles, the conjugate acids of \( N \)-nitrosamines are stable unless strongly heated, in which case other types of fragmentation can occur (see below).

1. Reactions with anhydrous acids

Despite the formation of an \( O \)-conjugate acid, most \( N \)-nitrosamines are stable in strong acids at ambient temperatures provided good nucleophiles are absent. On heating to 80–140°C, however, various decomposition reactions are observed\(^{154} \), whose occurrence and rate depend on both the \( N \)-nitrosamine structure and the type of acid medium. For compounds bearing \( N \)-alkyl groups higher than ethyl, \( N \)-alkyl bond fission proceeds in \( SO_2\text{ClF} \) plus 'magic acid' (\( HSO_3\text{F} \cdot SbF_3 \)) catalyst with the evolution of \( N_2 \) and a carbocation. The latter undergoes condensation and
fragmentation to form ultimately the tert-butyl carbocation as the principal identifiable product (Scheme 12). In FHSO₃ or 100% H₂SO₄ these N-nitrosamines decompose by a different pathway (Scheme 13) resulting in loss of [HNO] and formation of an iminium ion (32). This presumably proceeds via an N-conjugate acid (33) present at low concentration in equilibrium with the O-conjugate acid. Further, N-nitrosodimethylamine and N-nitrosodiethylamine are atypical in that their decomposition follows Scheme 13 even in 'magic acid', and for N-nitrosodiethylamine a small amount of denitrosation occurs concurrently. This difference probably relates to the low stability of methyl and ethyl carbocations even in 'magic acid'.

The presence of strong nucleophiles such as Cl⁻ or Br⁻ has a profound effect on the acid-catalysed decompositions and results in smooth denitrosation of all N-nitrosamines irrespective of their structure (equation 38). Further, the reaction is quantitative and can therefore be used for N-nitrosamine assay. In Walter's procedure¹⁶¹, for example, a 5–10% solution of HBr in glacial acetic acid added to the

$$\text{R}_2\text{NNO} \xrightarrow{(a) \text{H}_2\text{O}^+} \text{R}_2\text{N}^+ \text{NO} \xrightarrow{(b) \text{Y}^-} \text{R}_2\text{NH} + \text{YNO}$$  (38)
N-nitrosamine in an organic solvent releases NOBr which can be estimated by an ‘NO chemiluminescence’ detector. Related procedures employ either NaI plus H₃PO₄ or gaseous HCl to react with the N-nitrosamine dissolved in an organic solvent.

Few kinetic studies of these reactions have been reported but Williams and his coworkers have examined the denitrosation of aryl-N-nitrosamines by HCl in ethanol. The reaction rate follows equation (39), and the absence of catalysis by added Br⁻ or SCN⁻ is interpreted as evidence for rate-limiting proton transfer to N-nitrosamine (equation 38, step a) followed by rapid release of NOCl (equation 38, step b). This contrasts with denitrosation in aqueous HCl (see below) where protonation is usually rapid and attack by Cl⁻ rate-limiting.

2. Reaction with aqueous acids

N-Nitrosamines are remarkably stable in water and alkaline solutions, but hydrolysis to the parent amine and HNO₂ (equation 40) does occur in aqueous acid at pH < 3. The reactions are reversible, usually sluggish and dependent on temperature and the nature of both the N-nitrosamine and the added acid. The most labile N-nitrosamines are those derived from weakly basic amines and the best catalysts are acids with relatively strong nucleophilic anions. Thus aryl-N-nitrosamines hydrolyse readily in most aqueous acids, whereas N-nitroso-di-n-propylamine requires fairly concentrated (1-5 M) HCl or HBr; 50-80% H₂SO₄; 40% H₃PO₄; formic and acetic acids are all largely ineffective.

The mechanism of hydrolysis has been specifically examined for aryl-N-nitrosamines only, but indirect information for alkyl analogues is available from transnitrosation studies (see below). Because the hydrolysis is reversible, it is advantageous to remove HNO₂ by means of a ‘trap’ such as HN₃, sulphamic acid or urea. Under these conditions, the observation of both acid catalysis and a dependence on the presence of nucleophiles (Y⁻) is consistent with the mechanism in Scheme 14. With low [Y⁻], the hydrolyses of several N-nitrosanilines in 0.5-3 M acid show a first-order dependence on [Y⁻], and the efficacy of various nucleophiles decreases in the order I⁻ > SCN⁻ > Br⁻ > Cl⁻ >> H₂O. This is consistent with rapid formation of the N-conjugate acid followed by rate-limiting reaction with Y⁻. At high [Y⁻], however, the rate becomes independent of Y⁻ which suggests that N-conjugate acid formation is then rate-limiting, reminiscent of the reaction in ethanolic HCl (Section III.C.1). Significantly, there is no evidence for hydrolysis via the O-conjugate acid and this is supported by the low amount of¹⁸O exchange between N-nitrosamines and aqueous acids.

\[
R_2NNO + H_2O \rightleftharpoons HNO_2 + R_2NH
\]

SCHEME 14. Acid-catalysed hydrolysis of N-nitrosamines.
In concentrated aqueous acids (2–5 M), the hydrolysis of aryl-N-nitrosoamines is complicated by concurrent Fisher–Hepp rearrangement, whereby the nitroso group migrates intramolecularly to the para position of the benzene ring (equation 41). This rearrangement is discussed in detail in another chapter in this volume.

\[
\text{RNNO} + \text{RNH} \xrightarrow{\text{H}_2\text{O}^+} \text{RNH} \xrightarrow{\text{H}_2\text{O}} \text{RNH} + \text{H}_3\text{O}^+ \quad (41)
\]

Treatment of N-nitrosoamines with aqueous acid in the presence of nucleophilic organic materials such as phenols or amines often results in the formation of new nitrosated products. These reactions are often described as 'transnitrosations'. With phenol, transnitrosation provides a spot test for N-nitrosoamines, well-known as the Lieberman reaction\(^{166}\) (Scheme 15). Here \( p \)-nitrosophenol (34) (probably produced from \( \text{HNO}_2 \) obtained by hydrolysis of the N-nitrosoamine) condenses with a second molecule of phenol to give a highly coloured quinone-imine derivative. Alternatively, in the presence of secondary amines, transnitrosation under acidic conditions may lead to the formation of a new N-nitrosoamine (equation 42) (see also Section II.C.1). As for hydrolysis these reactions are reversible and, in order to obtain an appreciable amount of product, the reagent N-nitrosoamine must have a weaker N–N bond than that of the product N-nitrosoamine. This condition is met when aryl-N-nitrosoamines react with heterocyclic and aliphatic amines\(^{77,82}\) or when substituted N-nitroso-morpholines or -piperazines react with morpholine\(^{78,167}\). Two potential pathways for transnitrosation between amines, shown in Scheme 16, are either direct interaction of the \( N \)-protonated \( N \)-nitrosoamine (35) with the amine substrate (path a) or intermediate formation of an inorganic nitrosating agent (YNO) from an external nucleophile such as \( \text{Cl}^- \), \( \text{Br}^- \) or \( \text{SCN}^- \) (path b). Direct transnitrosation (path a) has been invoked to explain absence of nucleophilic catalysis in the reaction between \( N \)-nitrosodiphenylamine and \( N \)-methylaniline in 0.1 M HCl or HClO\(_4\)\(^{77,82}\), but indirect transnitrosation (path b) is implicit in the

\[
\text{R}_2\text{NNO} + \text{R}_2\text{NH} \xrightarrow{\text{H}_2\text{O}^+} \text{R}_2\text{NNO} + \text{R}_2\text{NH} \quad (42)
\]

![Scheme 15. Lieberman's spot test for N-nitrosoamines.](image)
26. N-Nitrosamines and N-nitrosoimines

\[
\begin{align*}
(a) R_2NH & \rightarrow R_2^NNO + R_2^NNO \\
R_2^NNO & \xrightleftharpoons{H^+} R_2^NNO \\
(b) Y^- & \rightarrow R_2^N + YNO \rightarrow R_2^NNO + HY
\end{align*}
\]


strong SCN\(^-\) catalysis observed for reactions of N-nitrosomorpholines and N-nitrosopiperazines\(^{78,167}\).

Other nucleophiles such as HN\(_3\), NH\(_2\)OH, ascorbic or sulphamic acid and urea also participate in transnitrosation reactions with N-nitrosamines\(^{14,82}\) usually by path (b) of Scheme 16. Here, however, the reactions are irreversible and such reagents find application as HNO\(_2\) ‘traps’ in studying the mechanism of hydrolysis reactions (see above).

D. Nucleophilic Reactions

Again, by analogy with tertiary amides, the most basic atom in N-nitrosoamines, i.e., the oxygen should also be the most nucleophilic. This is borne out in practice for reaction with alkylating agents (equation 43) where the usual product is the salt 36. Less is known about acylating agents but it is probable that they react similarly.

\[
R_2^NNO + R^2X \rightarrow R_2^{N=NC}X^\text{OR}\ (36)
\]

1. Alkylation

N-Nitrosamines react under mild conditions with powerful alkylating agents such as triethyl oxonium tetrafluoroborate\(^{168}\), triethyl oxonium hexafluoroantimonate\(^{169}\) and dimethyl sulphate\(^{169}\) to form salts (36) (X = BF\(_4^-\), SbF\(_6^-\) or MeSO\(_4^-\); equation 43), which occur as (E) and (Z) isomers. The spectral properties and reactions of these salts with alkali, carboxylate ion and pyridine have been described by Hünig and his colleagues\(^{168,170}\); it is clear that the formation and properties of 36 are very similar to analogous salts formed between tertiary amides and reactive alkylating agents\(^{130}\).

Intermolecular interaction of N-nitrosamines with less reactive alkylating agents has not been widely investigated, but amino-N-alkylated products are reported to arise from reaction of either methyl iodide\(^{169}\) or pyrimidines\(^{171}\) with N-nitrosodimethylamine. It is not known, however, whether these form via an O-alkyl salt (36) which subsequently rearranges to the N-alkyl product (cf. O to N rearrangements during alkylation of amides\(^{130}\)) or by direct N-alkylation. We favour the former explanation because intramolecular alkylation\(^{172}\), involving displacement of tosylate ion by a neighbouring N-nitroso group results in quantitative formation of the five-membered heterocyclic salt (37) rather than the three-membered salt (38) which would result from nucleophilic substitution by amino nitrogen (Scheme 17). Further, nucleophilic participation of nitroso oxygen rationalizes formation of similar types of five- and six-membered cyclic intermediates during the facile acetylation of β- and γ-(tosyloxy)-N-nitrosamines in acetic acid and sodium acetate (equation 44).
2. Acylation

It is reasonable to suppose that acylation of $N$-nitrosamines proceeds by an analogous route to alkylation whereby reaction at the nitroso oxygen atom gives an $O$-acyl intermediate (39) (equation 45). However, as with tertiary amides, this intermediate is expected to be considerably more labile than its $O$-alkyl counterpart (36) and evidence for its existence is therefore indirect (see below).

$$
\begin{align*}
R^1\leftarrow N\rightarrow NO + R^3COX & \rightarrow \left[ R^1\leftarrow N\rightarrow NO \right]_{\text{O}} + R^3COX \\
\text{X} & = \text{Cl, OCOR, etc.}
\end{align*}
$$

Very few examples of $N$-nitrosamines reacting with typical acylating agents are known. Thus far, most investigations have concerned acid anhydrides, but the variety of reaction conditions and products make mechanistic speculation unfruitful without further information. Examples of these reactions include heating $N$-alkyl-$N$-nitrosoanilines in acetic anhydride alone\(^{173}\) (equation 46), heating the $N$-nitroso-

$$
\begin{align*}
\text{Ph} & \rightarrow N\rightarrow NO + (\text{MeCO})_2O \xrightarrow{3/7\text{h}} \text{Ph} \rightarrow N\text{COMe} \\
\text{R} & = \text{alkyl}
\end{align*}
$$
piperidine (40) with acetic anhydride in acetic acid\textsuperscript{174} (equation 47) and using the more reactive heptafluorobutyric anhydride in pyridine at room temperature to acylate \( N \)-nitrosodialkylamines\textsuperscript{175} (equation 48).

In contrast, much information is available about intramolecular acylations resulting in the formation of mesoionic sydrones (41) (Scheme 18)\textsuperscript{176,177}. There seems little doubt that these reactions proceed by nucleophilic attack by the nitroso oxygen atom on the neighbouring activated carbonyl group to form the \( N-O \)-acyl intermediate (42) which forms the more stable mesoionic sydnone (41) by loss of HX. This is good evidence that, as with tertiary amides, acylation of \( N \)-nitrosamines proceeds preferentially at the oxygen atom (\( C=O \) or \( N=O \), respectively) rather than at the amino nitrogen atom.

Another interesting study\textsuperscript{178} concerns the reactions of reactive acid chlorides (e.g. phosgene, ethyl chloroformate, chloroacetyl chloride, dichloroacetyl chloride, chlorocarbonyl isocyanate, \textit{p}-toluenesulphonyl chloride and oxalyl chloride) with \( N \)-nitroso derivatives of substituted 1,3-oxazolidines and tetrahydro-1,3-oxazines (43; \( n = 2, 3 \), respectively) whereby \( N-N \) bond fission occurs with release of NOCl. Presumably the nitroso oxygen atom is first acylated (as in the formation of sydrones above), but subsequent rearrangements and \( N-N \) bond fission occur to give the products described in equations (49–51). These reactions parallel the denitrosation of \( N \)-nitrosamines by inorganic acids (Section III.C) and it is of considerable interest to know whether acyclic \( N \)-nitrosamines behave similarly.

\[ R^1N\begin{array}{c} \text{CHR}^2 \end{array} \text{C}^\circ \text{O}_2H \xrightarrow{X Y} R^1N\begin{array}{c} \text{CHR}^2 \end{array} \text{N}_\text{C}^\circ \text{O}_2 \xrightarrow{X^-} R^1N\begin{array}{c} \text{CHR}^2 \end{array} \text{N}_\text{O}_2 \text{C}^\circ \text{O} \]

\[ X = \text{MeCO}_2, \text{SOCl}, \text{COCI}, \text{etc.} \]
\[ Y = \text{MeCO}, \text{Cl} \]

\textbf{SCHEME 18.} Intramolecular acylation of \( N \)-nitrosamines to give sydrones.
3. Reaction with other electrophiles

*N*-Nitrosamines have recently been reported to react with other electrophiles such as molecular halogens and phosphorus oxychloride, but both products and mechanisms have yet to be established. A close analogue to sydnone formation (i.e. Scheme 18), is the acid-catalysed cyclization of *N*-alkyl-*N*-nitroso-α-aminoacetonitriles to give sydnone imines (44), which are stabilized as the salt 45 (Scheme 19). Here again, the more nucleophilic nitroso oxygen atom appears to attack the activated electrophilic carbon atom to give the five-membered ring. Interestingly, the immediate higher homologue (*N*-nitroso-3-methylaminopropionitrile) undergoes denitrosation rather than cyclization to the larger six-membered ring in methanolic HCl, (Scheme 20) (cf. Section III.C.1). A sydnone imine intermediate (44a) is believed to participate in the facile hydrolysis of *N*-nitroso-2-methylaminoacetonitrile in aqueous KOH (equation 52).

E. Reaction With Organometallic Reagents

In contrast to the hydroxide ion (Section III.C.2), Grignard and alkyl- or phenyl-lithium reagents are sufficiently powerful nucleophiles to add across the *N*=*O
group of \(N\)-nitrosamines. Unfortunately, they also abstract a proton from the \(\alpha\)-carbon atom of \(N\)-nitrosoalkylamines\(^{180}\), thereby reducing the amount of organometallic reagent available for nucleophilic addition. Attempts to compensate for this depletion by using excess reagent are often hindered by subsequent transformations of the primary products to give a complex mixture. By and large, however, all the products can be rationalized by Scheme 21, in which the organometallic reagent initially adds to the \(N\)-nitrosamine to give an intermediate (46) which then undergoes \(N\text{--}O\) bond fission. The ultimate products depend on the nature of both \(N\)-substituents (\(R^1\) and \(R^3\)). Thus, loss of hydride ion from the \(\alpha\)-carbon of \(R^1\) leads to an azomethine imine (47) which can be trapped by ethanol or 1,3-dipolarophiles\(^{181}\), dimerize to a hexahydrotetrazine (48)\(^{181,182}\) or add to further Grignard
SCHEME 21. Reaction of organolithium or Grignard reagents with N-nitrosamines.

reagent to give a trialkylhydrazine (49). Alternatively, loss of H⁺ from the α-carbon of R₃ produces the hydrazone 50 which on reaction with further organometallic reagent gives the trialkylhydrazine 51. The structure of 51 differs from 49 obtained via the azomethine imine intermediate 47.

In contrast to Grignard and alkyl- or phenyl-lithium reagents, phenylcopper induces N—N bond fission with formation of secondary amines, diphenylhydroxylamine and other products (equation 53). The mechanism of these transformations has not been established, but formation of biphenyl implies a radical pathway.

\[
R₂NNO + PhCu \rightarrow R₂NH + Ph₂NH + Ph₂NOH + PhOH + Ph-Ph
\]

F. Reduction

Although N-nitrosamines will react with many different reducing agents, only the few annotated in Scheme 22 are of synthetic utility. Depending on the strength of
26. *N*-Nitrosamines and *N*-nitrosoimines

![Scheme 22](image)

**Scheme 22.** Usual products from the reduction of *N*-nitrosamines.

the reagent, the main product is either the parent amine or the corresponding 1,1-disubstituted hydrazine, and the amine probably results from further reduction of the hydrazine.

Lithium aluminium hydride is the most convenient reagent for reducing *N*-nitrosamines to 1,1-disubstituted hydrazines. The reactions are carried out under neutral conditions at low temperatures\(^{186-188}\) and usually one molar proportion of reagent is adequate. The formation of a coloured intermediate suggests that addition across the \(N=O\) bond gives 52 which is analogous to the complex formed from lithium aluminium hydride and tertiary amides\(^ {130}\). On decomposition of the coloured complex in alkali, the 1,1-disubstituted hydrazine is obtained in good yield (Scheme 22, route a). *N*-Nitrosodiphenylamine is exceptional insofar as 1,1-diphenylhydrazine is obtained with one molar proportion of lithium aluminium hydride whereas excess reagent gives diphenylamine\(^ {186}\), possibly by further reduction of the hydrazine. Good yields of hydrazine (Scheme 22, route a) can also be obtained by electrochemical reduction in acidified ethanolic solution, provided the *N*-nitrosamine does not undergo rapid hydrolysis in the acidic medium\(^ {189}\). Other reagents such as zinc in acetic acid\(^8\), hydrazine with Raney nickel\(^ {190}\) or zinc with ammonia and ammonium carbonate\(^ {191}\) are preparatively less useful, providing lower yields of hydrazines along with other products.

The reduction of *N*-nitrosamines to parent amines (Scheme 22, route b) can be achieved in high yield either by treatment of an acidic ethanolic solution of the *N*-nitrosamine with cuprous chloride\(^ {192}\), or in neutral solution by catalytic hydrogenation over Raney nickel\(^ {193}\). One other method involving the production of radical anions (53) (detected by electron spin resonance) from the *N*-nitrosamine and alkali metals\(^ {194}\) is of mechanistic rather than preparative interest. The radical anions 53 react with further alkali metal to ultimately give a small amount of amine (equation 54)\(^ {195}\).

Other mechanistically interesting reductive reactions arise from the interaction of *N*-nitrosamines with alkaline sodium dithionite\(^ {196}\), lithium in liquid ammonia\(^ {196}\), iron
\[ R_2N-N\text{NO} \xrightarrow{M} R_2N-N\tilde{O}\text{M}^+ \xrightarrow{M} R_2N^\text{M}^+ + [\text{MNO}] \rightarrow R_2\text{NH} \]  
(53)

\[ M = \text{Li, K} \]

pentacarbonyl\textsuperscript{197}, aryl azides\textsuperscript{198a} or phenacyl bromides in the presence of silver hexafluoroantimonate\textsuperscript{198b}. Although the last three reagents are not regarded as conventional reducing agents, all induce N–O bond fission to give a nitrene intermediate (54). The formation of bibenzyls from N-nitrosodibenzylamines and alkaline sodium dithionite (equation 55) was first demonstrated by Overberger and coworkers\textsuperscript{196}, but any reagent capable of producing the intermediate nitrene 54 also gives these products. Other N-nitrosamines are reduced by alkaline sodium dithionite to the corresponding hydrazine\textsuperscript{196}, and iron pentacarbonyl produces parent amines in high yield from N-nitroso derivatives of diphenylamine, N-phenylbenzylamine, N-methylaniline and carbazole\textsuperscript{199}. These reactions probably proceed via nitrenes similar to 54 but the exact mechanism remains in dispute\textsuperscript{197,199}.

**G. Oxidation**

Powerful oxidizing agents, particularly peroxides, react with most N-nitrosamines to give the corresponding N-nitramines (equation 56). The best preparative procedure is probably that described by Emmons\textsuperscript{200}, using peroxys trifluoroacetic acid prepared \textit{in situ} from trifluoroacetic anhydride and 90% H\textsubscript{2}O\textsubscript{2}. The reactivity of this reagent compared with hydrogen peroxide alone may relate to an initial acylation of the nitroso oxygen atom which would then place the peroxidic oxygen atom in close proximity to the weakly nucleophilic nitroso nitrogen atom (equation 57). Other work shows that respectable yields of N-nitramines are also obtained on prolonged treatment with \( t \)-amyl hydroperoxide in the presence of MoCl\textsubscript{5}\textsuperscript{201}. The readily available 2-butanone peroxide is also effective but the yields of N-nitramine are only moderate\textsuperscript{202}. Oxidation reactions other than those leading to N-nitramines are also known and some may be important in the metabolic activation of N-nitrosamines. In this context a recent report that \( \alpha \)-hydroperoxy-N-nitrosoalkylamines can be obtained by
treatment of the lithium salts of N-nitrosodialkylamines with oxygen\textsuperscript{203} is particularly interesting and has an analogy in the oxidation of enolate ions\textsuperscript{204}. Further, treatment of N-nitrosodialkylamines with the Udenfriend hydroxylating mixture (ascorbic acid, ferrous iron, EDTA and molecular oxygen) produces $\gamma$-hydroxy and $\gamma$-keto derivatives and, possibly, very unstable $\alpha$-substituted analogues\textsuperscript{205, 206}.

**H. Homolysis of the N—N(O) Bond**

Molar N—N(O) bond enthalpies are of the order of 217–225 kJ mol\textsuperscript{-1} for heterocyclic and aliphatic N-nitrosoamines, but only 46 kJ mol\textsuperscript{-1} for N-nitrosodiphenylamine\textsuperscript{207}. All are significantly lower than values for C—N, C—C or C—H bonds (which lie in the range 250–450 kJ mol\textsuperscript{-1}) and it is not surprising that cleavage of the N—N(O) bond (equation 58) can be effected for virtually all N-nitrosamines by heating and for many on photolysis as well. Further, these reactions form the basis of degradative procedures and some important analytical methods. Nonetheless, most aliphatic and heterocyclic N-nitrosamines can be successfully distilled under atmospheric pressure at temperatures of ca. 150–175°C and usually they do not decompose during g.l.c. analysis. Aromatic analogues (b.p. ca. 180°C), however, are much less stable and they readily decompose unless distilled at reduced pressure and rarely survive g.l.c. analysis.

Homolysis of the N—N(O) bond can also be effected by photolysis under acidic conditions. This procedure, which is a useful method for destroying N-nitrosoamines under certain conditions\textsuperscript{208}, gives the primary products, nitric oxide and an aminium radical cation (equation 59). Neither the amino radical (equation 58) nor the radical cation (equation 59) can be isolated but both undergo the further transformations discussed below.

\[\text{R}_2\text{NNO} \xrightarrow{\Delta \text{ or } \text{hv}} \text{NO} + \text{R}_2\text{N}^* \longrightarrow \text{Products}\]  (58)

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\[\text{R}^1\text{R}^2\text{NNO} \xrightarrow{\text{H}_2\text{O}^+} \left[\begin{array}{c} \text{R}^1 \text{N} \\ \text{R}^2 \text{N} \end{array} \right] \xrightarrow{\text{hv}} \text{NO} + \text{R}^1\text{R}^2\text{N}^* \longrightarrow \text{products}\]  (59)

1. **Thermolysis**

All N-nitrosoamines decompose on heating under neutral conditions in accordance with equation (58), but for most nonaromatic compounds high temperatures (ca. 300°C) are required. When coupled to the lability of amino radicals, this means that few reactions have found synthetic application. Further, under aerobic conditions oxidation of NO to NO\textsubscript{2} ensues and this leads to the formation of nitrated as well as nitrosated products.

The thermolysis of N-nitrosobenzylamines has been examined, however, both for neat materials at 190–240°C under N\textsubscript{2}\textsuperscript{209} and in the vapour phase at 325°C\textsuperscript{210}. The major products are NO, the parent amines and the corresponding imines, presumably formed by disproportionation of the amino radical (55) obtained by initial N—N(O) bond homolysis (equation 60). Thermolysis in organic solvents at temperatures of 50–150°C is restricted to the less stable N-nitrosoarylamines. These

\[\text{PhCHR}^1\text{R}^2\text{NNO} \xrightarrow{} \text{NO} + \text{PhCHR}^1\text{R}^2\text{N}^* \xrightarrow{\text{PhCHR}^1\text{R}^2\text{N}^*} \text{PhCHNHR}^2 \]  (60)

\[\text{PhR}^1\text{C}==\text{NR}^2\]
reactions for N-nitrosodiarylamines have been investigated by Welzel in solvent chlorobenzene under nitrogen (to prevent oxidation of NO to NO₂). The production of various arylamine products can be ascribed to reactions of the diaryl-amine radical (56) formed by homolysis of the N—N(0) bond (equation 61). For instance, the products obtained from thermolysis of N-nitrosodiphenylamine are the same as those obtained from thermolysis of tetraphenylhydrazine (also expected to give the diphenylamino radical) as outlined in Scheme 23.

When similar reactions are carried out in polar solvents under oxygen, N—N(0) bond cleavage again occurs but NO₂ produced by oxidation of the NO results in the formation of nitroaromatic products (equation 62).

Measurement of NO released by thermolysis is the basis of the TEAc₉ procedure for N-nitrosamine analysis. The N-nitrosamine is heated in the gas phase at ca. 300°C in the presence of catalysts, and the NO evolved reacts with ozone to form NO₂ in an electronically excited state. Light emitted when NO₂ returns to its ground electronic state is proportional to the amount of N-nitrosamine.

2. Transnitrosation

Thermolysis of aromatic N-nitrosamines in the presence of other secondary amines or compounds bearing active methylene groups generates N-nitroso or C-nitroso products, respectively. The term ‘transnitrosation’ has been coined for these reactions. Thus, on heating in organic solvents in the presence of dimethylamine, piperidine, morpholine or N-methylaniline, N-nitrosodiphenylamine gives high yields of the corresponding N-nitrosamines (equation 63). The mechanism...
of these reactions is not properly understood, but it seems unlikely that the amine substrate is involved in the rate-limiting step because N-methylaniline (despite its lower reactivity) reacts ca. ten times faster than the other amines. The observation of ESR spectra may indicate a free-radical pathway but reaction via N₂O₃ (following partial oxidation of NO to NO₂) has not been excluded. N-Nitroso-3-nitrocarmazol also converts N-methylaniline to its N-nitroso derivative.

N-Nitrosodiphenylamine and its 4-substituted derivatives also react with compounds such as 1,2,3,4-tetrachloropentadiene or deoxybenzoin, containing an active methylene group, to form an oxime (e.g. equation 64). Reaction rates are slowest for aromatic N-nitrosamines bearing electron-donating 4-substituents possibly because the N-N bond is strengthened, but these reactions also require mechanistic investigation.

3. Photolysis

In general, neutral N-nitrosamines are fairly resistant to photolysis although a few examples of decomposition in the gas phase or in organic solvents are known. Early work by Bamford showed that photolysis of neutral N-nitroso-diethyl- and -dimethyl-amins in the vapour phase at 100°C gave mainly nitric oxide, dialkylamines and polymeric material. The organic products were considered to result from dialkylamino radicals formed by homolysis of the N-N(0) bond. The dialkylamino radical should disproportionate to the secondary amine and the corresponding imine with the latter polymerizing (equation 65). This sequence of reactions is very similar to that for thermolysis in equation (60). Photolytic decomposition of these N-nitrosodialkylamines in methanol or cyclohexane solutions (Φ = 0.05–0.72) has also been reported, but the products were not identified. Photolysis of N-nitrosodibenzylamine, either neat or in hydrocarbon solvents, gives equal proportions of dibenzylamine and N-benzylidenebenzylamine, presumably as in equation (65) but without polymerization. In the presence of oxygen, however, the photolysis of N-nitrosodibenzylamine yields dibenzylammonium nitrate in addition to dibenzylamine and N-benzylidenebenzylamine, probably as a result of oxidation of NO to NO₂.
In contrast to the above, photolysis of N-nitrosamines in the presence of HCl, or trichloro- or trifluoro-acetic acids proceeds readily to form nitric oxide and aminium radical cations (equation 59) which, with suitable substrates can result in elimination, reduction or addition reactions. These transformations are discussed by Chow in a review and in a chapter in this volume.

J. α-Substituted N-Nitrosamines

Two factors have stimulated interest in the syntheses and reactions of α-substituted N-nitrosamines. Firstly, Seebach and Enders recognized that the C—H acidity α to the nitrosamino group could be utilized to effect substitution at the α-carbon atom, a reaction not normally possible for amines themselves. After substitution, the N-nitroso group can be removed (e.g. Section III.C or III.F) to give the amine (equation 66). Seebach and Enders coined the term ‘Umpolung’ meaning ‘polarity reversal’ for this activation of secondary amines by nitrosation. Secondly, it is now widely believed that biological activation of N-nitrosamines involves enzymatic α-hydroxylation (see Section IV). This has attracted much attention to both the synthesis and the properties of α-hydroxy-N-nitrosamines and related compounds, some of which is summarized and discussed in Reference 220.

1. α-Hydrogen exchange reactions

The lability of protons on the α-carbon atom to the N-nitrosamino group, first reported by Keefer and Fodor and Rademacher and Lüttke from facile exchange in alkaline D₂O (equation 67), has been the subject of some discussion.

Originally, this lability was attributed to stabilization of the intermediate carbanion (57) by an inductive interaction with the adjacent positively charged nitrogen atom of the N—N—O dipole (58). However, subsequent findings that the hydrogen exchange is subject to stereoelectronic control led Fraser and Ng to conclude that delocalization involving structure 59 was of overriding importance. Fraser and Ng studied the rigid N-nitrosodibenzazepine derivative (60), where relative hydrogen exchange rates with respect to 61 lie in the order H₂ (syn—axial) > H₁ (syn—equatorial) > H₃ (anti—axial) > H₄ (anti—equatorial). The axial hydrogen atoms exchange more readily than the equatorial hydrogen atoms by a factor of 100 (H₂ > H₁ and H₃ > H₄) whereas the syn hydrogen atoms exchange faster than the anti hydrogen atoms by a factor of 1000 (H₂ > H₃ and H₁ > H₄). These differences were rationalized by considering the carbanion intermediate as a four-atom, six π-electron system whose stability is determined by the ‘through-space’ overlap between the terminal lobes of the HOMO. This overlap should be enhanced when the developing carbanion is either axial or syn to the N=O function.
Further, Fraser and Ng\(^{15}\) discount both the importance of inductive stabilization in 58 (because the ammonium ion, 62, fails to exchange even under more stringent conditions) and the importance of ion-pair formation with K\(^+\) (because exchange rates are insensitive to the presence of crown ether).

Independent support for Fraser and Ng's conclusions comes from findings\(^{221}\) that the bicyclic N-nitrosamine 63 (where charge delocalization would require an unfavourable bridgehead double bond) does not form an \(\alpha\)-carbanion. Stereoelectronic control is also evident for N-nitroso-4-\(t\)-butylpiperidine where exchange of axial, but not equatorial, H-2 atoms with alkaline D\(_2\)O has been demonstrated\(^{222}\). Nonetheless, the labilization of hydrogen at the \(\alpha\)-carbon atom in N-nitrosamines must be finely balanced, because thus far similar hydrogen exchange reactions have not been reported for tertiary amides.

For unsymmetrical N-nitrosamines, hydrogen atoms on the least substituted \(\alpha\)-carbon atom appear to be more labile unless carbanion-stabilizing groups are present\(^{150}\). This also implies that the preferred stereochemistry is one where the N—N(O) group is syn to the least hindered carbon atom. Thus far, quantitative hydrogen exchange data for these compounds have not been reported.

2. Preparation

The most important method for the synthesis of \(\alpha\)-substituted N-nitrosamines is that of electrophilic substitution of the \(\alpha\)-carbanion intermediate, usually generated using lithium diisopropylamide as base. The reactions have been widely reported...
and a compilation of the products and yields obtained under various reaction conditions is given in Beak and Reitz's review\textsuperscript{222}. The carbanions readily undergo electrophilic substitutions such as alkylation, hydroxyalkylation, acylation and thioalkylation as outlined in Scheme 24, and recently, reactions with methyl chloroformate\textsuperscript{224} and oxygen\textsuperscript{203} have also been reported. The products obtained from these reactions reflect the regio- and stereo-specificities noted previously for hydrogen exchange. In fact, Barton and his colleagues\textsuperscript{225} were the first to show that regioselectivity controlled by the stereochemistry of the N-nitrosamine is important for alkylation. Thus sequential double alkylation of N-nitrosodimethylamine anion with benzyl bromide yielded only the asymmetric product 64 from two successive \textit{syn} substitutions (Scheme 25). Subsequently, a preference for \textit{syn–axial} substitutions has been demonstrated with N-nitrosopiperidines\textsuperscript{226,227}. The carbanion from 4-phenyl-N-nitrosopiperidine, for example, gives yields of 76, 79 and 72\% on

\begin{equation}
\text{SCHEME 24. Preparation of } \alpha\text{-substituted } N\text{-nitrosamines via an } \alpha\text{-carbanion.}
\end{equation}

\begin{equation}
\text{SCHEME 25. Regioselective alkylation of the } \alpha\text{-syn carbanion of } N\text{-nitrosodimethylamine.}
\end{equation}
reaction with CO₂, methyl iodide and benzophenone, respectively, and <1% of the corresponding equatorial products²²⁶.

Few other methods are available for the synthesis of α-substituted N-nitrosamines but nitrosation of suitably substituted amines is one alternative that has proved practical for N-nitroso-α-amino acids²²⁸ or α-amino aldehydes²²⁹. An interesting and convenient way of obtaining α-alkoxy-N-nitrosamines from simple precursors involves nitrosation of a mixture of a primary amine, an aldehyde and an alcohol (equation 68) presumably by way of a Mannich-type condensation. A modification of this method employing acetic acid in place of the alcohol gives the α-acetoxy-N-nitrosamine²³¹. Generally, however, the yields of α-alkoxy and α-acetoxy products are low. One other procedure using readily available starting materials involves the addition of NOCl to an imine to give the α-chloro-N-nitrosamine (65). The chlorine substituent can then be readily substituted by nucleophilic entities as shown in equation (69)²³². Finally, N-nitrosamines can be converted into α,β-un-saturated derivatives by rearrangement of allylic isomers, elimination of β-tosylates or oxidative elimination of α-phenylselenyl derivatives (e.g. equations 70–72)²³³.

\[
\text{R}^1\text{CH}_2\text{NH}_2 + \text{R}^2\text{CHO} + \text{R}^3\text{CHOH} \xrightarrow{\text{YNO}} \text{R}^3\text{R}^4\text{CHOCHR}^2\text{NNO} \quad (68)
\]

3. Reactions

Cyclisation of the α-carboxy and α-cyano derivatives of N-nitrosamines to give sydnones and sydnone imines, respectively, has already been mentioned (Section III.D). The α-carboxy derivatives can also be decarboxylated to the parent N-nitrosamine by heating either alone or as the sodium salt in solution²³⁴. On heating the α-carboxy derivatives with lead tetraacetate, the intermediate N-nitrososiminium ion is trapped to give an α-acetoxy derivative (equation 73) in varying
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\[ \begin{align*}
R^1\text{NCHR}^2\text{CO}_2\text{H} & \xrightarrow{\text{Pb(OAc)}_4} \left[ R^1\text{N} = \text{CHR}^2 \text{OAc}^- \right] + R^1\text{NCHR}^2\text{OAc} \\
\text{NO} & \text{NO}
\end{align*} \]  
(73)

yield (depending on the structure of the \( N \)-nitrosamine), along with other products.\(^{235}\)

The most widely examined reactions of these compounds concern the production and decomposition of \( \alpha \)-hydroxy-\( N \)-nitrosamines \((66)\), the putative metabolites obtained by microsomal activation. These \( \alpha \)-hydroxy-\( N \)-nitrosamines appear to be very unstable and thus far they have been isolated in only one instance.\(^{203}\) As well as being geminal disubstituted compounds, the favourable stereochemistry for intramolecular proton transfer from the hydroxy group to the nitroso oxygen atom may facilitate \( \text{C} = \text{N} \) bond fission (equation 74), leading to the generation of an alkylating agent. Useful precursors to the \( \alpha \)-hydroxy-\( N \)-nitrosamines are the \( \alpha \)-acetoxy derivatives and studies on their hydrolysis, reaction with amines and conversion to \( \alpha \)-hydrperoxy derivatives have all been reported. Hydrolysis with conventional reagents under mild conditions is usually difficult but hog liver esterase has proved efficacious.\(^{231,236,237}\) The products commonly found are attributable to the formation and decomposition of an \( \alpha \)-hydroxy-\( N \)-nitrosamine. An unusually labile \( \alpha \)-acetoxy compound \((67)\) which hydrolyses rapidly in water alone (\( t_{1/2} \) 19 min)\(^{237}\), probably reacts via less common alkyl-oxygen fission (equation 75) favoured here by the

\[ \text{MeN-CHPhOCOMe} \xrightarrow{\text{H}_2\text{O}} \text{MeN-CHPhOAc} \xrightarrow{\text{MeN-CHPhOH}} \text{MeN-CHPhOH} \]  
(67)

\[ \xrightarrow{\text{[CH}_3^+]} + \text{N}_2 + \text{PhCHO} + \text{HO}^- \]  
(75)

stabilizing benzylic function. \( \alpha \)-Acetoxy compounds react very readily with \( n \)-propylamine to give \( N-\text{n-propylacetamide} \) in good yields, the facility of the reaction being attributed to the inductive effect of the nitrosamino group.\(^{237}\) Treatment of the \( \alpha \)-acetoxy or \( \alpha \)-methoxy compounds with hydrogen peroxide in acetic acid provides the very interesting \( \alpha \)-hydrperoxyxides \((68)\).\(^{203}\) One of these compounds has been deoxygenated using sodium bisulphite (equation 76) to give first reported isolation of an \( \alpha \)-hydroxy-\( N \)-nitrosamine \((69; \text{R}^1 = \text{n-Pr, R}^2 = \text{Me})\).\(^{203}\)
Much of the current interest in the chemistry of N-nitrosamines stems from their biological properties. The striking carcinogenicity of many of these compounds has attracted most attention, but various other adverse effects can be produced, such as acute tissue injury, foetal malformations and diabetes. Most N-nitrosamines are also mutagenic towards standard bacterial tester strains following enzymatic activation with liver microsomal preparations. The toxicology of N-nitroso compounds has been the subject of several comprehensive reviews and aspects of their teratogenicity and mutagenicity have been discussed recently.

No direct link between human cancer and exposure to N-nitrosamines has been established, but it is widely suspected because of their ready formation from common precursors under both environmental and in vivo conditions (see Section II). Further, N-nitrosamines have been detected in the environment and in biological fluids such as blood, faeces and urine, they can be metabolized by cultured human tissue and they are systemic carcinogens, inducing tumours in certain organs regardless of the route of administration.

As indicated above, both the carcinogenic and mutagenic action of N-nitrosamines results from interaction of a metabolite (rather than the N-nitrosamine itself) with cellular tissue. The structure and reactivity of this metabolite(s), as well as the biomechanisms of its formation and interaction with cellular constituents such as nucleic acids, are matters of intense, current interest.

A. Toxicity and Carcinogenicity

Studies by Freund in the 1930s showed that N-nitrosodimethylamine induced pronounced liver damage. This finding was later confirmed by Barnes and Magee and is now known to be the main acute biological action of most dialkyl- and heterocyclic N-nitrosamines. Subsequently, Magee and Barnes, along with many others, showed that N-nitrosamines are also carcinogenic. About 100 analogues have been tested thus far. Most show carcinogenic action and no test species (including mice, rats, hamsters, rabbits, guinea pigs, dogs, pigs, monkeys and fish) has proven resistant to N-nitrosamine-induced cancer. These results have been thoroughly documented and it is clear that this class of compounds has many special features as a carcinogen.

Generally, N-nitrosamines exhibit organ specificity which is dependent on their molecular structure. Thus, most asymmetrical dialkyl-N-nitrosamines are liver carcinogens, whereas unsymmetrical dialkyl and heterocyclic compounds tend to attack the oesophagus and nasal cavity, respectively. Other target organs include the trachea, lung, urinary bladder and kidney.

The carcinogenic potency of N-nitrosamines (which can vary over several orders of magnitude) is also related to their molecular structure as well as the species and sex of the test animal. With male B-D rats, for example, the mean tumorigenic dose for N-nitrosodiethylamine is ca. 6 x 10^-3 mol/kg body weight whereas that for N-nitrosodiethanolamine is ca. 1 mol/kg body weight. Further, carcinogenic action results both from single, relatively large doses and from long-term chronic exposure to lower doses. Wishnok and his colleagues have suggested that the potency of N-nitrosamines be expressed as log(1/D50) [where D50 = mean total carcinogenic dose (in mol/kg body weight) for production of tumours in 50% of the test animals] so that larger numbers indicate higher potency. These indices for several representative compounds are summarized in Table 5. Generally, substituents α to the nitrosamino group lower the potency of hetero-
### Table 5. Carcinogenic activity of some N-nitrosamines

<table>
<thead>
<tr>
<th>N-Nitrosamine</th>
<th>log ((1/D_{50})^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highly potent: log ((1/D_{50}) &gt; 3)</strong></td>
<td></td>
</tr>
<tr>
<td>MeN(NO)CH₂CH₂Cl</td>
<td>3.2</td>
</tr>
<tr>
<td>Et₂NNO</td>
<td>3.2</td>
</tr>
<tr>
<td>MeN(NO)CH₂Ph</td>
<td>3.1</td>
</tr>
<tr>
<td>MeN(NO)CH₂CH₂Ph</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Potent: log ((1/D_{50}) 2.0 to 3.0)</strong></td>
<td></td>
</tr>
<tr>
<td>MeN(NO)CH=CH₂</td>
<td>3.0</td>
</tr>
<tr>
<td>MeN(NO)CH=CH₂</td>
<td>2.9</td>
</tr>
<tr>
<td>EtN(NO)CH=CH₂</td>
<td>2.6</td>
</tr>
<tr>
<td>MeN(NO)C₅H₁₁-n</td>
<td>2.6</td>
</tr>
<tr>
<td>MeN(NO)Et</td>
<td>2.3</td>
</tr>
<tr>
<td>Me₂NNO</td>
<td>2.3</td>
</tr>
<tr>
<td>MeN(NO)CH₂CN</td>
<td>2.2</td>
</tr>
<tr>
<td>EtN(NO)Bu-n</td>
<td>2.1</td>
</tr>
<tr>
<td>MeN(NO)CH₂CH=CH₂</td>
<td>2.1</td>
</tr>
<tr>
<td>n-Pr₂NNO</td>
<td>2.05</td>
</tr>
<tr>
<td><strong>Moderately potent: log ((1/D_{50}) 1.0 to 2.0)</strong></td>
<td></td>
</tr>
<tr>
<td>ONN</td>
<td>1.95</td>
</tr>
<tr>
<td>ONN O</td>
<td>1.95</td>
</tr>
<tr>
<td>ONN NCO₂Et</td>
<td>1.9</td>
</tr>
<tr>
<td>n-Bu₂NNO</td>
<td>1.9</td>
</tr>
<tr>
<td>MeN(NO)Ph</td>
<td>1.6</td>
</tr>
<tr>
<td>MeN(NO)C₇H₁₅-n</td>
<td>1.6</td>
</tr>
<tr>
<td>EtN(NO)Pr-i</td>
<td>1.5</td>
</tr>
<tr>
<td>n-BuN(NO)(CH₂)₄OH</td>
<td>1.5</td>
</tr>
<tr>
<td>ONN</td>
<td>1.4</td>
</tr>
<tr>
<td>n-BuN(NO)C₅H₁₁-n</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Weakly potent: log ((1/D_{50}) &lt; 1)</strong></td>
<td></td>
</tr>
<tr>
<td>i-Pr₂NNO</td>
<td>1.0</td>
</tr>
<tr>
<td>ONN NMe</td>
<td>0.95</td>
</tr>
<tr>
<td>(AcOCH₂CH₂)₂NNO</td>
<td>0.7</td>
</tr>
<tr>
<td>((n-C₅H₁₁)₂NNO)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
26. *N*-Nitrosamines and *N*-nitrosoimines

<table>
<thead>
<tr>
<th>N-Nitrosamine</th>
<th>( \log(1/D_{50})^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtN(NO)CH₂CH₂OH</td>
<td>0.2</td>
</tr>
<tr>
<td>(HOCH₂CH₂)₂NNO</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Probably noncarcinogenic**

<table>
<thead>
<tr>
<th>N-Nitrosamine</th>
<th>( \log(1/D_{50})^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph₂NNO</td>
<td>—</td>
</tr>
<tr>
<td>(PhCH₂)₂NNO</td>
<td>—</td>
</tr>
<tr>
<td><img src="image" alt="Chemical structure" /></td>
<td>—</td>
</tr>
<tr>
<td>(HO₂CCH₂)₂NNO</td>
<td>—</td>
</tr>
</tbody>
</table>

\( D_{50} \) = mean total carcinogenic dose, expressed in mol/kg body weight, for production of tumours in 50% of the test animals.

Cyclic *N*-nitrosamines⁴⁵¹,²⁵⁷ and highly substituted dialkyl or aromatic compounds without hydrogen on the \( \alpha \)-carbon atom (e.g. \( t-\text{Bu}_2\text{NNO}, \text{Ph}_2\text{NNO} \)) are noncarcinogenic¹⁴⁵. Nonetheless, these compounds should be handled with considerable care because transnitrosation *in vivo* may generate other, carcinogenic *N*-nitrosamines⁸¹. Substituents \( \beta \) to the nitrosamino group, irrespective of their electronic properties, generally increase the potency of heterocyclic *N*-nitrosamines²⁵⁷,²⁵⁸. With one or two exceptions, there is no simple explanation for the \( \alpha \)- and \( \beta \)-substituent effects. Several investigations, however, have shown that \( \alpha \)-deuteriated *N*-nitrosamines are less carcinogenic than regular analogues²⁵⁹,²⁶⁰ and this difference has been regarded as evidence that \( \alpha \)-hydrogen abstraction is kinetically important in the metabolic activation of *N*-nitrosamines. In an interesting extension of this work, Lijinsky and Reuber²⁶¹ have shown that the deuteriated metabolite, itself, is a more potent carcinogen.

Attempts have been made recently to develop structure–activity relationships for *N*-nitrosamines²⁶². Wishnok and his colleagues²⁵⁵ find that the carcinogenic potency of acyclic compounds correlates reasonably well with a linear combination of their hexane–water partition coefficients and Taft (\( \sigma^* \)) substituent parameters. The significance of the correlation coefficients for each term, however, is far from clear. Earlier, Wishnok and Archer²⁶³ demonstrated that the carcinogenic potency of acyclic *N*-nitrosamines is inversely related to the number of carbon atoms, but Lijinsky²⁶⁴ found the reverse applied to heterocyclic compounds where larger molecules are more potent concurrent with changes in organ specificity.

Some *N*-nitrosamines also induce tumours in the offspring of treated pregnant animals (teratogenesis or transplacental carcinogenesis), but only when the dose is administered during the last days of gestation²⁴¹,²⁶⁵,²⁶⁶. This may relate to a deficiency of activating enzymes until the foetus is well developed.

**B. Mutagenicity**

The mutagenic action of *N*-nitrosamines has been demonstrated both in microorganisms (bacteria) and in some higher systems such as insects. For bacterial tests
**C. Metabolism**

The biological properties of many chemical compounds relate to products arising from *in vivo* decomposition rather than the compounds themselves. This concept applies to most chemical carcinogens and it is widely accepted that these substances are transformed into chemically reactive electrophiles, which exert their biological actions by interacting with the nucleophilic sites of cellular constituents.

Because of their chemical stability (see Section III), N-nitrosamines require enzyme activity to decompose under mild biological conditions and may remain unchanged *in vivo* for relatively long periods. Experiments using radiolabelled materials show that distribution throughout animals occurs fairly rapidly and whereas complete metabolism to $^{14}$CO$_2$ usually takes several hours or even days depending on the compound's structure. Further, the labelled N-nitrosamines or their metabolites persist in organs susceptible to tumour formation.

Early work by Magee and Vandekar established that the metabolism of N-nitrosodimethylamine is mediated by liver microsomes and is dependent on NADPH and molecular oxygen. Similar findings apply to most other N-nitrosamines and prior treatment with either the S-9 fraction or microsomal pellet from rat livers (or preferably hamster livers) has become a standard procedure for activating N-nitrosamines in bacterial mutagenicity tests (see Section IV.B). Subsequently, it has been shown that many other tissues, including cultured human bronchus, colon and oesophagus, can metabolize N-nitrosamines, and it has been suggested that the susceptibility to tumour induction may correlate with an organ's ability to decompose a particular N-nitrosamine.

Although neither the enzyme system nor the mechanism of activation of N-nitrosamines has been explicitly defined, much evidence points to an oxidative dealkylation (Scheme 26) mediated by a cytochrome P-450 dependent mixed-function oxidase. Gangolli and his colleagues, however, have drawn attention to the fact that the metabolism of N-nitrosodimethylamine and N-nitrosopyrrolidine is not reduced by the usual mixed-function oxidase inhibitors and suggest that the enzyme is a microsomal amine oxidase. These findings may not be contradictory because investigations by both Arcos and coworkers and Kroeger-Koepke and Michejda demonstrate that N-nitrosodimethylamine is demethylated.
by more than one microsomal enzyme whose relative importance depends on the dosage. Other work suggests that N-nitrosamines can also be denitrosated by a reductive process in which cytochrome P-450 is involved and that the so-called pH-5 enzymes (solid material obtained from postmicrosomal supernatant by lowering the pH from 7.4 to 5.2) reduce N-nitrosodimethylamine to dimethylhydrazine among other products. Thus N-nitrosamines appear to be metabolized by several different enzymes, but the relationship of some to the biological actions has yet to be established.

For the pathway outlined in Scheme 26, the enzyme is considered to effect hydroxylation of an α-carbon atom to the nitrosamino group. The α-hydroxylated N-nitrosamine decomposes by spontaneous C–N bond cleavage to yield the reactive diazohydroxide metabolite and an aldehyde (72). The diazohydroxide can either be trapped by water to form an alcohol or react with nucleophilic sites on cellular material such as an amino acid, protein, RNA or DNA (see Section IV.D). The aldehyde is further metabolized, ultimately with the formation of CO₂. A substantial body of evidence has accumulated in support of this pathway, particularly for N-nitrosodimethylamine. Thus HCHO, MeOH and high (ca. 70%) yields of nitrogen (contrary to earlier reports) have been detected for its metabolism both in vitro and in vivo, a deuterium isotope effect applies to the generation of formaldehyde in vitro from hexadeuterio-N-nitrosodimethylamine which correlates with similar isotope effects for mutagenic and carcinogenic actions (see Sections IV.A and IV.B), both nucleic acids and proteins are methylated in vivo and an intact CD₃ group is transferred to guanine bases of hepatic nucleic acids following the administration of hexadeuterio-N-nitrosodimethylamine to rats. Further indirect support for Scheme 26 comes from
observations that the α-acetoxy derivative 73 hydrolyses to a mixture of HCHO, MeOH, MeCO₂H and nitrogen²³¹ (equation 77), is mutagenic towards bacteria

\[
\text{MeC(O)OCH₂} \xrightarrow{\text{esterase}} \text{HCHO} + \text{MeOH} + \text{MeCO₂H} + N₂ \quad (77)
\]

without metabolic activation³⁰⁷,³⁰⁸, and is both a DNA-methylating agent³⁰⁹ and a carcinogen in the rat³⁰⁸,³¹⁰, with a different organ specificity from N-nitrosodimethylamine itself³¹⁰.

**TABLE 6. Urinary metabolites from the administration of symmetrical N-nitrosodialkylamines to rats**

*From Et₂NNO*

*From n-Pr₂NNO*

*From i-Pr₂NNO*

*From n-Bu₂NNO*

*From n-Pe₂NNO*
The metabolic activation outlined in Scheme 26 appears to be general and not confined to N-nitrosodimethylamine. It certainly applies to longer-chain acyclic and heterocyclic compounds, where generation of the corresponding alkylating intermediates (71) following activation both in vivo and in vitro has been frequently demonstrated. For example, ethyl-, n-propyl- and n-butyl-guanine bases are recovered from rat livers following the administration of N-nitroso-diethylamine\(^{311}\), -di-n-propylamine\(^{312}\) and -di-n-butylamine\(^{312}\), respectively. For these and related N-nitrosamines, however, metabolic oxidation also proceeds at carbon atoms remote from the nitrosamino group. This is evident from the urinary metabolites (Table 6, identified by Blattman and Preussmann\(^{313}\)), whose formation can be rationalized by concurrent enzymatic hydroxylation at the penultimate and terminal carbon atoms, followed by further oxidation and decarboxylation to effect chain-shortening\(^{299}\). The relevance of these metabolites to carcinogenic action is not understood, but chain-shortening is required to account for the formation of methylated guanine bases from hepatic nucleic acids following the administration of N-nitroso-di-n-propylamine and N-nitroso-di-n-butylamine to rats. This finding, first reported by Krüger\(^{312}\), also applies to the 2-hydroxy (74)\(^{314}\) and 2-oxo (75)\(^{315}\) derivatives, and radiolabelling establishes that only the \(^{14}\)C-1 atom is transferred to the guanine base\(^{312}\). Krüger\(^{312}\) hypothesized that long-chain N-nitrosodialkylamines are metabolically degraded via \(\beta\)-oxidation to an N-nitrosomethylalkylamine, which acts as the methylating agent after activation by the established \(\alpha\)-oxidative process (Scheme 26). Other, more recent, work\(^{316,317}\) lends support to this hypothesis.

Enzymatic hydroxylation at either the \(\alpha\)- or \(\beta\)-carbon atom is also observed for several heterocyclic compounds. The most complete evidence for \(\alpha\)-hydroxylation relates to some tobacco-specific N-nitrosamines examined by Hecht and his colleagues\(^{318}\). For example, the products obtained from N-nitrosonornicotine (76) can all be rationalized by transformations (Scheme 27) of either the 2- or 5-hydroxy derivatives (77 and 78) whose formation are both subject to a significant deuterium isotope effect\(^{319}\). Other related cases include the isolation of 2-hydroxytetrahydrofuran from N-nitrosopyrrolidine\(^{320,321}\), 5-hydroxypentanal from N-nitrosopiperidine\(^{322}\) and several products including 1,6-hexanediol (79) \(\varepsilon\)-caprolactam (80) and \(\varepsilon\)-aminocaproic acid (81) from N-nitrosohexamethylenimine\(^{323,324}\) (Scheme 28). Krüger and Bertram\(^{325}\), however, have shown that N-nitroso-3-hydroxy-pyrrolidine (i.e. \(\beta\)-oxidation product) is a urinary metabolite of N-nitrosopyrrolidine administered to rats. Other examples of \textit{in vivo} \(\beta\)-oxidation to the nitrosamino group are the formation of N-nitrosobis(2-hydroxy)propylamine (82) and N-nitroso-(2-hydroxypropyl)(2-oxopropyl)amine (83) from N-nitroso-2,6-dimethylmorpholine\(^{326}\) and N-nitrosodiehthanolamine (84) from N-nitrosomorpholine\(^{327}\). However, earlier reports\(^{328}\) that administration of some heterocyclic N-nitrosamines to rats leads to the formation of methylguanine bases from hepatic nucleic acids (as for acyclic analogues) have not been confirmed\(^{329}\).

There has been considerable speculation about the structure of the metabolic alkylating agent (so-called 'ultimate carcinogen') that interacts with cellular constituents. Recent work, however, points towards the diazohydroxide (71) rather
than the diazoalkane (85) or the unstable carbocation (86) (equation 78). The diazoalkane is firmly discounted by observations that both CD$_3$ and C$_2$D$_5$ substituents transfer intact to the guanine bases of nucleic acids when (CD$_3$)$_2$NNO$^{306}$ and (C$_2$D$_5$)$_2$NNO$^{330}$ are incubated with rat-liver slices. 

A priori, reaction via the carbo-
SCHEME 28. Proposed pathways involving α-hydroxylation for the metabolism of \( N \)-nitrosohexamethyleneimine in rats.

\[
\begin{align*}
\text{N-} & \quad \text{N}^0 \quad \text{No} \\
\text{HNO} + \text{OHC(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}N=N} & \xrightarrow{\text{H\textsubscript{2}O}} \text{H\textsubscript{2}N(CH\textsubscript{2})\textsubscript{6}CO\textsubscript{2}H} \\
\text{enzyme} & \rightarrow \text{OHC(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}N=N--OH} \\
& \xrightarrow{\text{H\textsubscript{2}O}^+} \text{OHC(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}OH} + \text{N\textsubscript{2}} + \text{H\textsubscript{2}O} \\
& \xrightarrow{\text{reductase}} \text{HOCH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{2}OH} \\
& \quad \text{(79)}
\end{align*}
\]
cation in vivo seems unlikely because of its low stability. Tentative confirmation of this view comes from the detection of 7-n-propylguanine without any 7-i-propylguanine in hepatic DNA following administration of N-nitroso-di-n-propylamine to rats, but products bearing the rearranged alkyl group are obtained when the same reaction is carried out with liver microsomes in vitro. The origin of this difference requires clarification. Affirmative evidence in favour of the diazo-hydroxide metabolite is that hydrolysес of chiral \( \text{MeCH(Ph)N(NO)CH}_2\text{OAc} \) and \( \text{MeCH(Ph)N(NO)CO}_2\text{Et} \) proceed with similar stereochemical consequences for the 1-phenylethanol product. Further, the observation that \( \text{88} \) but not \( \text{87} \) inhibits the hog-liver esterase used in their hydrolysis leads Gold and Linder to conclude that \( \alpha \)-hydroxy-\( N \)-nitrosamines may be transportable metabolites of \( N \)-nitrosodialkylamines.

### D. Interactions with Cellular Constituents

The idea that \( N \)-nitrosamines exert their adverse biological properties via the alkylation of cellular constituents is widely accepted and evidence for it has been critically reviewed. Attention has focused on the interaction with DNA because it is considered to be the critical cellular target for the induction of tumours. It has also been shown, however, that \( N \)-nitrosamines alkylate the nuclear proteins of rat liver and kidney. Administration of [\( ^{14}\text{C}-1 \)]-labelled \( N \)-nitrosodimethylamine, for example, produces labelled S-methylcysteine, 1-methylhistidine, 3-methylhistidine and \( \varepsilon \)-N-methyllysine in the liver histones.

There are several nucleophilic sites on the bases of nucleic acids and 1-methyladenine, 3-methyladenine, 7-methyladenine, 3-methylcytosine, 6-methylguanine and 7-methylguanine have all been identified as hepatic products following the administration of [\( ^{14}\text{C}-1 \)]- \( N \)-nitrosodimethylamine to rats. Most alkylation seems to occur at the N-7 position of DNA guanine, but recent studies, summarized in an excellent review by Pegg, suggest that tumour formation (associated with mispairing during subsequent replications of the alkylated DNA molecules) is best correlated with alkylation at the O-6 position of guanine.

The active removal of 6-methylguanine from DNA in vivo appears to be due to an enzymic mechanism, which varies in activity from tissue to tissue and is lowest in organs most susceptible to tumour formation. There is also evidence to suggest that this enzyme system can be both inhibited by exposure to large doses of \( N \)-nitrosodimethylamine and stimulated by continuous exposure to low doses.
Most N-nitrosoimines (89) are unstable compounds which decompose readily (often spontaneously) to a ketone and nitrogen gas (see Section V.C). Only a few examples (where $R^1$ and $R^2$ form part of a heterocyclic ring) are sufficiently stable to be handled with impunity. Neither dialkyl-N-nitrosoketimines (89; $R^1, R^2 =$ alkyl) nor alkyl-N-nitrososaldimines (89; $R^1 =$ alkyl, $R^2 =$ H) are known, and

\[
\begin{align*}
R^1 & \quad C \equiv N \\
R^2 & \quad \phantom{C} \quad N = O
\end{align*}
\]

(89)

although diaryl-N-nitrosoketimines (89; $R^1, R^2 =$ aryl) and mixed alkylaryl-N-nitrosoketimines (89; $R^1 =$ alkyl, $R^2 =$ aryl) have been isolated they decompose at room temperature within a few weeks. Not surprisingly, relatively little is known about the properties and reactions of most compounds.

A. Preparation

$N$-Nitrosoketimines are usually prepared by nitrosation using regular reagents such as acidified sodium nitrite or gaseous NOCl of either the parent ketimine or an organometallic derivative.

The most stable $N$-nitrosoketimines (e.g. 90–93), derived from imino-substituted dihydrothiazoles and the corresponding thiazoles, are conveniently prepared by direct nitrosation of the substrate with aqueous sodium nitrite in glacial acetic acid.\(^{340-342}\) For less stable $N$-nitrosoimines, the use of either gaseous nitrosyl chloride plus a base such as triethylamine or sodium acetate in an inert solvent at ca. $-20^\circ C$ or of nitrite esters is advantageous. This procedure was first used by Thoman and Hunsberger\(^{343}\) to prepare diaryl- and alkylaryl-$N$-nitrosoimines (equation 79) and applied subsequently to $N$-nitrosoimines bearing $\alpha$-nitrogen

\[
\begin{align*}
R^1 & \quad C \equiv NH \\
R^2 & \quad \phantom{C} \quad \text{NOCI/NaOAc} \quad \text{CCl}_4/ -10^\circ C \quad \text{CCl}_4/ -10^\circ C
\end{align*}
\]

(79)

\[
R^1 \quad C \equiv N \quad \text{NO} + \text{HOAc}
\]

$R^1 =$ aryl
$R^2 =$ aryl, $i$-Pr, $t$-Bu
atoms. For example, 2-iminopyrrolidines give N-nitroso derivatives (94) in the presence of triethylamine \(^{344}\) and 1,1,3,3-tetrasubstituted guanidines give N-nitroso derivatives such as 95 in the presence of sodium acetate \(^{345}\). The related S-alkylthioureas can be converted to N-nitroso derivatives (96) (which decompose spontaneously) by isopentyl nitrite \(^{346}\).

\[
\begin{align*}
\text{(94)} \\
\text{(95)} \\
\text{(96)}
\end{align*}
\]

\[R = \text{Ar, } C_6H_{11}\]

Other work \(^{347}\) shows that organometallic derivatives of ketenimines (97) also react with nitrosyl chloride in ether at room temperature. This procedure may prove beneficial when the parent imine is unstable.

\[
\begin{align*}
\text{(97)} \\
R^1 = \text{alkyl, aryl} \\
R^2 = \text{Me, Et, Ph} \\
M = \text{Si, Sn, Pb}
\end{align*}
\]

**B. Properties**

N-Nitrosoketimines are highly coloured oils or crystals of red, orange and purple hue. Major contributing resonance structures are 98, the 1,3-dipolar ion 99 and the 1,4-dipolar ion 100. The 1,4-dipolar ion is thought to be more important than 99 because N-nitrosoketimines fail to add to 1,3-dipolarophiles such as ketene or dimethyl acetylenedicarboxylate \(^{343}\). This conclusion is supported by both the proposed mechanism for thermal rearrangements (see Section V.C) and the reaction of tetraphenyl-N-nitrosoguanidine with phenyl isocyanate (equation 80) which appears to proceed via a 1,4-addition intermediate \(^{345}\).

Although no bond lengths for N-nitrosoimines have been reported, contributions from 99 and/or 100 should confer partial N=N character and lengthen the N=O bond, whereas 100 but not 99 will lengthen the C=N bond. Tentative spectroscopic evidence is consistent with conjugation between the imino and nitroso groups, resulting in both the lengthening of the C=N and N=O bonds and the shortening of the N=N bond and therefore implies that 100 is an important contributing structure. For example, the IR absorption bands of compound 94 at 1563–1592 cm\(^{-1}\), assigned to C=N stretching, are much lower than those for other conjugated ketenimines (1660–1630 cm\(^{-1}\)), and N=O stretching bands at 1418–1439 cm\(^{-1}\)
N-Nitrosamines and N-nitrosoimines

\[ \text{Ph}_2\text{N} = \text{C} = \text{N} \text{N}=\text{O} + \text{PhN}=\text{C}=\text{O} \rightarrow \text{Ph}_2\text{N} = \text{C} = \text{N} \text{N}=\text{O} \rightarrow \text{Ph}_2\text{N} = \text{C} = \text{NPh} + \text{N}_2 + \text{CO}_2 \quad (80) \]

are much lower than in other nitroso compounds but comparable with N-nitrosamines (see Section III.A)\(^{344}\). Further, absorption bands in the UV-visible spectrum\(^{343,345}\) at 284–354 nm (log \( \varepsilon \) ca. 4) and 423–454 nm (log \( \varepsilon \) ca. 2) (assigned\(^{345}\) to the \( \pi \rightarrow \pi^* \) and \( n \rightarrow \pi^* \) transitions, respectively) appear at longer wavelengths than the corresponding bands in N-nitrosamines (235 and 340–385 nm, respectively). Like N-nitrosamines, partial N=N character in N-nitrosoketimines should lead to (\( E \)) and (\( Z \)) isomers but so far none have been detected even by NMR\(^{343}\).

**C. Reactions**

As noted above, many N-nitrosoimines are unstable and usually decompose below room temperature to a ketone and nitrogen gas (equation 81). In a single instance, however, additional products (equation 82) have been reported\(^{347}\). Their thermal stability, however, is markedly influenced by structure. It is increased when the \( R^1 \) and \( R^2 \) substituents are either bulky (e.g. t-Bu, i-Pr or 2-substituted phenyl) or electron-withdrawing (e.g. 4-NO\(_2\)-C\(_6\)H\(_4\)) and is decreased by electron-donating 4-substituted phenyl groups. Stabilities range from 6–8 weeks at room temperature (89; \( R^1 = \text{t-Bu}, R^2 = 2\text{-MeC}_6\text{H}_4 \)) to a few minutes at \(-10^\circ\text{C} \) (89; \( R^1 = 4\text{-MeOC}_6\text{H}_4, R^2 = 2\text{-MeOC}_6\text{H}_4 \))\(^{343}\). N-Nitrosoimines bearing heteroatoms (N or S) adjacent to the imino carbon atom are also labile (e.g. 94, \( R = \text{C}_6\text{H}_{11} \), is stable for a few hours\(^{344}\) and 95 for a few minutes\(^{345}\) at room temperature), except when both nitrogen and sulphur are part of a five-membered ring; for example, compounds 90–93 are indefinitely stable at room temperature but decompose in boiling toluene\(^{348}\).

Mechanistic studies\(^{343}\) reveal that decomposition of compound 101 in cyclohexane at 23°C has a first-order dependence on [substrate]. This implies an intramolecular attack by the nucleophilic oxygen atom on the electrophilic carbon atom, followed by elimination of nitrogen to ketone (equation 83). For diaryl- and alkylaryl-N-
nitrosoketimines, the only other reaction studied thus far is that with triethyl-
oxonium tetrafluoroborate to give substituted propylene oxide and nitrogen\textsuperscript{343}. A plausible mechanism, outlined in equation (84), involves initial alkylation of the nucleophilic nitroso oxygen atom followed sequentially by intramolecular rearrangement with elimination of nitrogen and then loss of H\textsuperscript+ to give the propylene oxide.

Much more is known about the chemistry of the relatively stable heterocyclic N-nitrosoimines 90–93 and it is summarized in the review by Akiba and Inamoto\textsuperscript{348}. For example, photolysis of 90 or 91 produces the disulphide 102 and nitric oxide\textsuperscript{340,342}, implying homolysis of the N–N(O) bond (as in photolysis of N-nitroso-
amines, Section III.H), followed by radical rearrangement and recombination. Treatment of 90 with nucleophilic reagents such as lithium aluminium hydride\textsuperscript{349}, organo-
lithium\textsuperscript{350} and Grignard reagents\textsuperscript{351–353}, however, produces several products resulting from both attack at more than one site and subsequent transformations between products, reagents and substrates. Thus with lithium aluminium hydride, 90 yields a mixture of 103, 104 and 105\textsuperscript{349}, possibly through initial attack by hydride ion at both the imino carbon atom and the nitroso nitrogen atom. With organometallic...
reagents, a multitude of products is obtained from 90 but Inamoto and his colleagues suggest that these arise from nucleophilic attack at three sites as shown in Scheme 29. Reaction at the sulphur atom is restricted to organolithium reagents, whereas reaction at the imino carbon atom is found for both organolithium and Grignard reagents and leads to either ring-opening or N–O bond fission. Reaction at the nitroso nitrogen atom applies only to Grignard reagents, and it has a parallel in N-nitrosamine chemistry (Section III.E). A fuller account of these complex reactions is found in Akiba and Inamoto’s review, but reasons for the high specificity of the different nucleophilic reagents need confirmation.

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CHAPTER 27

The role of Meisenheimer or \( \sigma \)-complexes in nitroarene-base interactions

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I. INTRODUCTION AND SCOPE

The nature of the interaction between nitroarenes and bases is governed to a large extent by the electron-withdrawing character of the nitro group which depletes the aromatic ring of electron density, imparting to it the properties of an electron – or electron-pair acceptor. Hence, depending on the structure and nature of the base \( (Y^-) \), as well as the nitroarene, one (or more) of several possible interactions can take place, as follows:

1. A charge-transfer type of interaction results in a donor–acceptor complex, 1.
2. Electron transfer from \( Y^- \) leads to a radical anion, 2.
3. Abstraction of a proton can occur from a ring-carbon yielding the aryl
carbanion 3, while a benzylic carbanion, 4, results when the proton is removed from an $\alpha$-carbon.

(4) Finally, covalent bond formation gives rise to adduct 5. In 4, as well as in 5, negative charge is delocalized over the ring as well as on the nitro groups.

Donor–acceptor complexes will not be considered in the present account. A monograph published in 1970 was devoted largely to that topic and such species are also featured in a recent edited work. Also, only scant reference to radical anions is made in this chapter since their role in Meisenheimer-complex-forming processes is as yet unclear; this aspect is treated in a recent review. Discussion of the carbanions 3 and 4 is included here, but largely in the context of competition with processes leading to adducts such as 5.

II. MEISENHEIMER OR $\sigma$-COMPLEXES

A. Historical Review

The current structural formulation of the covalent adducts resulting from nucleophilic addition of bases such as alkoxide ion to nitroarenes such as 1,3,5-trinitrobenzene (TNB) or 2,4,6-trinitroanisole (TNA) dates back to around 1900. Even before the end of the last century, several authors had described the isolation of solid, red adducts from the reaction of TNB with methanolic KOH, and speculated as to the structure. However, definitive formulations were made independently and almost concurrently by Jackson and by Meisenheimer, both formulating the structure of the adduct obtained from addition of alkoxide to picryl ether as 6. In accord with this structure, Meisenheimer showed that the same adduct was obtained from reaction of methyl picryl ether with EtOK–EtOH, and of ethyl picryl ether with MeOK–MeOH. By analogy with 6, the adduct derived from
Mcisenheimer or  \( \sigma \)-complexes in nitroarene–base interactions

TNB and methoxide was assigned as structure 7. These types of covalent adducts have been commonly called Meisenheimer complexes, although the designation Jackson–Meisenheimer complexes acknowledges their discovery and structural formulation more correctly. In recent years such adducts have often been called anionic \( \sigma \)-complexes, or simply \( \sigma \)-complexes, which is the terminology adopted in this account.

\( \sigma \)-Complexes as a subject of investigation developed rather slowly for 50 years or more following their discovery. However, from ca. 1960 on a great deal of activity has centred on this subject and in 1966 the first review dealing with \( \sigma \)-complexes appeared\(^\text{11}\). Over the next five years no less than seven other reviews were published dealing wholly or partly with this topic\(^\text{12-18}\), and two of these appeared in this series of volumes.

As a result of this activity and the vast amount of material currently available, it has become impractical, if not impossible, to treat all aspects of the subject in one chapter. Therefore, rather than attempting a cursory treatment, we will instead focus on a few selected aspects and follow their development in some detail.

Following a brief review of the salient structural features of \( \sigma \)-complexes, and the methods currently used for their investigation, we shall describe some of the important \( \sigma \)-complexes that have been synthesized during the past decade. This will be followed by consideration of nitroarene–base systems where \( \sigma \)-complex formation is in competition with other interactions, namely nucleophilic displacement, and nuclear and benzylic proton-transfer processes.

### B. Structural Features and Methods of Investigation

The main structural features of \( \sigma \)-complexes are now established, though significant refinements continue to be made. The results of X-ray crystallographic studies reported for the potassium ethoxide and methoxide adducts of the corresponding picryl ethers\(^\text{19,20}\) essentially confirmed the formulation of Jackson\(^\text{9}\) and Meisenheimer\(^\text{10}\), when written in current form (i.e. \( =\text{NO}_2^- \) at C-4). The ring was found to be essentially planar, the two alkoxy oxygens being contained in a perpendicular plane, in accord with \( sp^3 \) hybridization at C-1. A significant shortening of the C—N bond length at C-4 relative to C-2 and C-6 was found, indicative of considerable negative-charge localization on the oxygens of the nitro group at C-4. The C-2 and C-6 \( \text{NO}_2 \) groups were found to be nearly coplanar with the ring.

However, a recent X-ray crystal structure determination of the potassium methoxide adduct of TNB shows a boat-like conformation of the ring, with significant displacement from coplanarity of C-1 and C-4\(^\text{21}\). This deviation from coplanarity greatly reduces the interaction between the methoxy group and the C-2 and C-4 nitro groups. This type of interaction will also be present in the alkoxide complexes of picryl ethers discussed above, but in these symmetrical structures the steric compressions involving the two alkoxy groups will be balancing, with zero net effect. The parameters for the TNB·OMe\(^-\) \( K^+ \) complex are shown in Figure 1\(^\text{21}\).

The \( ^1\text{H}-\text{NMR} \) spectra of typical \( \sigma \)-complexes generally provide definitive evidence of their structure. This can be illustrated for the case of the methoxide adduct of TNB as follows\(^\text{22,23}\) [chemical shifts are given in ppm relative to tetramethylsilane for a solution of TNB·OMe\(^-\) \( K^+ \) in \( (\text{CD}_3)_2\text{SO} \)]. The C-3,5 protons appear as a doublet at \( \delta \ 8.48 \ (J = 1 \text{ Hz}) \), the C-1 proton appears at \( \delta \ 6.17 \) as a triplet \( (J = 1 \text{ Hz}) \), and the methoxyl protons appear as a singlet at \( \delta \ 3.22 \). In comparison with TNB which displays a single resonance at \( \delta \ 9.20 \), the moderate upfield shift of the \( sp^3 \) hydrogens in the TNB·OMe\(^-\) complex is in accord
with increased negative charge on the ring, while the much larger upfield shift for the C-1 proton resonance is in accord with a change in hybridization, from sp² to sp³, on complex formation. The resonance of the methoxyl protons occurs ca. 1 ppm upfield from that in TNA.

NMR was also the tool which first revealed that the initial complex formed in the addition of MeO⁻ to TNA was not the C-1 but the C-3 adduct. It was thus found that in DMSO–methanol medium the adduct 8 is formed first and is subsequently transformed into the more stable adduct 9 (Scheme 1). A number of other systems have been found to obey this type of relationship, though some exceptions have been noted.

¹³C-NMR spectroscopy has been applied recently to the study of σ-complexes, and ¹³H-NMR as well. An important development is the application of flow NMR spectroscopy to nitroarene–base interactions, as this method yields structural information in chemically reacting systems. Use of this method is described in Section III.A.
Electron absorption spectroscopy has been used extremely widely in the investigation of $\sigma$-complexes. Though UV–visible spectra generally do not give direct structural information, they are normally characteristic of a given species. For example the TNB·OMe$^-$ complex in methanol exhibits absorption maxima at 425 and 495 nm, the shorter wavelength absorption being the more intense ($\varepsilon_1 = 31,200$, $\varepsilon_2 = 21,000 \text{ mol}^{-1} \text{ cm}^{-1}$); this relationship is typical of 1:1 adducts of TNB. The wavelength maxima and extinction coefficients are dependent on the solvent and also on the nature of the nucleophilic atom$^{11-18}$. As a quantitative method, UV–visible spectroscopy is the method of choice in kinetic and equilibrium studies. The use of stopped-flow and temperature-jump relaxation methods$^{37}$ has brought into range the majority of kinetic processes pertaining to the formation and transformation of $\sigma$-complexes. Moreover, stopped-flow spectrophotometry allows one to determine the spectra of transient species, by performing experiments at a number of wavelengths and extrapolating the absorbances to zero time. The spectrum of the TNA·OMe$^-$ C-3 adduct (8) obtained by this method is reproduced in Figure 2$^{30}$ which shows also the spectrum of the C-1 adduct for comparison. The spectra of the corresponding ethoxy complexes are quite similar$^{29}$. Visible absorption spectra of 1,3-complexes have also been obtained by means of a continuous flow technique$^{38}$. Use of fast reaction techniques has given quantitative expression to Servis' findings through NMR$^{24}$, that the TNA·OMe$^-$ C-3 adduct is formed with a high rate coefficient but a relatively low equilibrium constant, whereas formation of the C-1 adduct is characterized by a relatively low rate coefficient and a high equilibrium constant$^{27}$. The same relationship holds, for example, for methoxide addition to cyano-substituted nitroarenes$^{38,39a}$. The bases of these observations have been discussed$^{28,38,39}$.

Dipolar aprotic media such as DMSO and DMF have been found to be of great value in study of $\sigma$-complexes. Equilibrium constants for $\sigma$-complex formation typically show very large increases in such media$^{40}$. For example, in formation of the TNB·OH$^-$ $\sigma$-complex, $K_{eq}$ increases from $3 \text{ mol}^{-1}$ in pure water to ca. $10^4 \text{ mol}^{-1}$ in 70 vol % DMF$^{40b}$. Similarly, for the TNB·OMe$^-$ $\sigma$-complex, $K_{eq}$ increases from $15 \text{ mol}^{-1}$ in methanol to $10^4 \text{ mol}^{-1}$ in 40 vol % DMSO$^{41}$. It has been shown that increasing the dipolar aprotic component increases primarily the rate of the forward, $\sigma$-complex formation process, while the rate of the reverse,
FIGURE 2. Absorption spectra of 2,4,6-trinitroanisole-methoxide ion σ-complexes in 96% DMSO–4% methanol; — 1,1-complex, ---- 1,3-complex. Reprinted with permission from C. F. Bernasconi and M. C. Muller, J. Amer. Chem. Soc., 100, 5530 (1978). Copyright by the American Chemical Society.

σ-complex decomposition process, is relatively unaffected\textsuperscript{38,39b}. These medium effects can be attributed largely to desolvation of the anionic reagent in the dipolar aprotic media, though stabilization of the σ-complex relative to the parent nitroarene may also be a contributing factor\textsuperscript{38–42}.

C. Hydride Ion Adducts

In 1970, Taylor described the preparation of the prototype anionic σ-complex of TNB, namely the product of hydride ion addition to the ring, 10\textsuperscript{38a}. This complex was readily obtained, as the tetramethylammonium salt, on addition of TNB to a stirred dispersion of Me\textsubscript{4}N\textsuperscript{+} BH\textsubscript{4}\textsuperscript{−} in MeCN. The purple product (m.p. 131–132°C) has a typical UV–visible spectrum $\lambda_{\text{max}}$ 478 nm ($\varepsilon$ 3.1 x 10\textsuperscript{4} I mol\textsuperscript{-1} cm\textsuperscript{-1}) and 585 nm ($\varepsilon$ 1.5 x 10\textsuperscript{4} I mol\textsuperscript{-1} cm\textsuperscript{-1}), in MeCN. The NMR spectrum consists of two triplets, the C-3,5 protons appearing at $\delta$ 8.26 ($J \sim 0.5$ Hz) and the C-1 protons at $\delta$ 3.88 ($J \sim 0.5$ Hz). Complex 10 was also obtained by H\textsuperscript{−} transfer to TNB from 1-propyl-1,4-dehydronicotinamide\textsuperscript{44} as well as from dehydro derivatives of other nitrogen heterocycles\textsuperscript{45}.

It is interesting that the decomposition of complex 10 is accelerated by a factor of ca. 10\textsuperscript{4} by bovine serum albumin (BSA) in the pH range 7–10\textsuperscript{46}. This catalytic activity of BSA is highly sensitive to the conformational integrity of the protein. This finding is but one example of the application of σ-complexes as biophysical and biochemical probes\textsuperscript{47}.

The corresponding alkyl-2,4,6-cyclohexatrienate adducts 11, R = Me, n-Bu, with an alkyl group coordinated to the ring, were obtained when the appropriate
tetralkylboron salts were used in the reaction with TNB. The NMR spectra of these complexes were likewise definitive.

Hydride adducts are also obtained for a series of 1-X-2,4-dinitro-substituted benzenes, by the action of NaBH₄ in DMSO medium. The NMR parameters are consistent with formation of complexes 12 and/or 13, depending on the nature of the substituent X. For example, when X = H only 12 is observed, and when X = OMe only 13 is formed, while for X = halogen a mixture of the two adducts is obtained.

The NMR spectra in these systems undergo changes on prolonged reaction times, and it has been shown that there is either displacement of the 2-nitro group by hydrogen or ring-reduction. The proposed reaction mechanism is given in Scheme 2 and involves a novel internal displacement of NO₂⁻ by H⁻ in the anionic species 12. This pathway was confirmed by various hydrogen isotope labelling experiments.

Last in this series is the hydride ion adduct of nitrobenzene itself, i.e. 14. This species is implicated as an intermediate by the occurrence of isotopic exchange
between nitrobenzene and tritium-labelled sodium borohydride in DMSO solution.

**D. Spiro Complexes**

There has been a great deal of interest in spiro σ-complexes, in part because of their relationship to the intramolecular aromatic nucleophilic substitution reaction known as the Smiles rearrangement.

An example of an in-depth study is illustrated in Scheme 3 which depicts the rearrangement of \( N \)-methyl-\( \beta \)-aminoethyl picryl ether (15) into \( N \)-methyl-\( N \)-\( \beta \)-hydroxyethylpicramide (19) through the action of base. The overall conversion is rapid, requiring study by a combined stopped-flow temperature-jump method; this has shown that the reaction occurs in two stages. The first stage is the formation of spiro complex 17, via the intermediate zwitterionic species 16, while the second, slower, stage involves the conversion of 17 into rearranged product 19. Rate constants of all elementary steps could be determined in this system. One of the significant conclusions is that the deprotonation of 16 to 17 is partially rate-limiting. A number of related kinetic studies have been reported, giving considerable insight into mechanisms of spiro complex formation and decomposition as well as into \( S_N \)Ar processes in general (see below).
Spiro complexes of various structural types have been characterized by spectroscopic techniques including NMR, having been prepared either as stable compounds or *in situ* by the action of base on the appropriate open-chain derivative. A partial listing of such spiro complexes is given below together with the appropriate references.

The zwitterionic complex 29 is actually the cyclized form of the picryl ether of 3,5,7-trimethyltropolone. A number of structure-reactivity studies are included among the references cited, for example concerning the effect of the number of methylene groups on complex stability, and the effect of naphthyl vs. phenyl substitution.

Competitive processes involving spiro complex formation, and concurrent intramolecular displacement of a nitro group, have been observed in several cases. For example, in the reaction of *N*,*N*-dimethyl-*N*-picrylhydrochloride (30) with Et₃N, there is rapid conversion to spiro complex 32, followed by slow formation of 33, the product of intramolecular NO₂ displacement. Some possible mechanisms are given in Scheme 4. Displacement of NO₂ could occur either via the open-chain base 31, or directly from the spiro complex 32. The latter possibility would have some analogy to the intramolecular displacement of NO₂⁻ by H⁻ found in hydride *σ*-complexes (see above).

Reaction of spiro complexes with nucleophiles has been reported in a few cases, yielding adducts such as 34 and 35. The prototype spiro complex 36 containing
no NO₂ groups to stabilize negative charge has been prepared by reaction of 4-(4-chlorobutyl)biphenyl with lithium at \(-70^\circ\text{C}\)\textsuperscript{2}.

E. Ambident Nucleophiles in \(\sigma\)-Complex Formation

Acetonate complexes of nitroarenes have been widely investigated, their origin dating to the finding in 1886 by Janovsky and Erb of an intense purple colour in the reaction of acetone with \(m\)-dinitrobenzene in alkaline solution\textsuperscript{23}. After a period of controversy as to whether the structure of the species formed was \textsuperscript{37}\textsuperscript{24} or \textsuperscript{38}\textsuperscript{25},
the latter was proved unambiguously by NMR. The corresponding TNB adduct, which is obtained readily also on solvolysis of the TNB-OMe- complex in acetone, was similarly shown through NMR to have structure.

It is evident from the above that the α-carbon of the enolate anion has much greater nucleophilicity towards the electron-deficient carbon of DNB or TNB than the enolate oxygen. This has been confirmed also through thermodynamic measurements.

Acetonate adducts such as 39, and the analogues 40 (R = Me, Ph, CO₂Me etc.), have been found to undergo very interesting and useful cyclization processes in basic media. As indicated in Scheme 5, abstraction of a γ-hydrogen by base leads to a carbanion which is favourably situated for bonding with the meta carbon of the nitroarene moiety. Bond formation gives rise to the cyclized species 42 which on protonation yields the bicyclic product 43.

A variety of bicyclic and tricyclic products (the latter formed via a second internal nucleophilic addition) have been obtained in this manner, affording a number of products of biological significance, e.g. potential narcotic antagonists. In no instance was cyclization found to occur via the enolate oxygen.

The reaction of phenoxide ion with picryl chloride has been the normal method of preparing phenyl picryl ether. In accord with nucleophilic attack by phenoxy oxygen, Shein and Byval’kevich reported that PhO⁻ reacts with TNB in DMSO solution to yield the complex 44. However, Buncel and Webb found that in DMSO–methanol the initially formed TNB-OMe⁻ adduct (through solvolysis) gives way to another species whose structure was proven to be the carbon-bonded adduct 46.

The above results can be explained by the reactions in Scheme 6. Though attack by PhO⁻ via oxygen could be kinetically favoured, the adduct 44 would form in a reversible process. However, carbon attack followed by proton loss from 45 gives rise to the aromatized product 46 in an effectively irreversible process. Hence 46 will be the product of thermodynamic control in this system. The stability of 46 to
dilute acid readily permits its isolation and characterization. In moderately concentrated acid, protonation in a nitro group occurs giving rise to a nitronic acid.

\[
\text{PhO}^- + \xrightarrow{\text{MeOH}} \xleftarrow{\text{MeO}^-} \text{PhOH}
\]

\[\text{44} \quad \text{45} \quad \text{46}\]

**SCHEME 6**

Spectroscopic evidence has been presented of initial oxygen attack in the reaction of TNB and TNA with phenoxide, and of TNB with 2,4,6-trimethylphenoxide. However, in the reaction of TNB with 1-naphthoxide only the 1:1 and 2:1 carbon-bonded adducts 47 and 48 were observed.

Another instance of ambident reactivity towards arenes has been reported recently, concerning indolyl anions. Thus reaction of 2-methylindolyl anion 49 with TNB in DMSO has been found to give three products, namely 50, the product of N-attack, 51 the product of C-attack, and 52 in which one indolyl unit is joined via nitrogen and the other via carbon (Scheme 7). Both \(^1\)H- and \(^{13}\)C-NMR have been used to characterize these products.
F. Other σ-Complexes

It is important to emphasize the great diversity in σ-complex structural types that have been characterized over the past two decades. In this section a brief selection is made of some of these unusual complexes.

The gem-difluoro adduct 53 is readily obtained by reaction of picryl fluoride with potassium fluoride/18-crown-6 ether in acetonitrile. The gem-diamino and -di(alkythio) adducts 54 and 55 are likewise obtained from the parent nitroarenes and the respective anions.

Both the cis and trans forms of the 2:1 sulphite adduct of TNB, 56, have been characterized. The evidence includes NMR, absorption spectroscopy, reaction rates and equilibrium properties.

The scope of nitroarene σ-complexes has been extended through addition to TNB of organometallic compounds of the type $R_3EM$ where $R = \text{alkyl}$, $E = \text{Si, Ge}$,
Sn and $M = Li, K$ (equation 1)$^{104}$. $\sigma$-Complexes have also been obtained from reaction of TNB with organophosphorus compounds$^{105}$.

Electron-withdrawing groups other than NO$_2$ can serve to stabilize, to varying extents, the negative charge on anionic $\sigma$-complexes. A number of studies have been directed towards establishing quantitative structure-reactivity relationships following such structural changes. For example, Fendler$^{106}$, Terrier$^{107}$, and their coworkers have compared rate and equilibrium constants in formation and decomposition of cyano-substituted aromatics, e.g. 58, with the nitro analogues. The trifluoromethanesulphonyl group is one of the most powerful electron-withdrawing substituents, and adduct 59 is formed from 1,3,5-tris(trifluoromethanesulphonyl)benzene in neutral methanol$^{108}$.

$\sigma$-Complexes can also result in molecules lacking specific electron-withdrawing groups, negative charge being stabilized by some characteristic property of the system. The complex 60$^{109}$ serves as an interesting example of such a system.

$\sigma$-Complexes of heteroaromatic compounds have been extensively investigated. Indeed, this area has developed into a field of study in its own right$^{110}$. Some of the heterocycles which have been found to give rise to $\sigma$-complexes on reaction with anionic reagents are pyrrole$^{111}$, thiophene$^{112-116}$, selenophene$^{115}$, pyridine$^{117,118}$,
pyrimidine\textsuperscript{119}, triazole\textsuperscript{120,121} benzofurazan and benzofuroxan\textsuperscript{122-126} and various purine derivatives\textsuperscript{127,128}.

In the case of the heterocycles containing only one heteroatom, such as pyridine and thiophene, the presence of at least one strongly electron-withdrawing substituent such as nitro is required in order for stable $\sigma$-complexes to be formed. However, when several heteroatoms are present, as in triazole and purine, then $\sigma$-complexes can be observed without the necessity of further electron withdrawing substituents. Examples of complexes of this type are $\text{61}\textsuperscript{120,127}$ and $\text{63}\textsuperscript{128}$.

\begin{align*}
\text{(61)} & \quad \begin{array}{c}
\text{H}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\quad \begin{array}{c}
\text{MeO}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\quad \begin{array}{c}
\text{H}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\quad \begin{array}{c}
\text{Ome}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\end{align*}

\begin{align*}
\text{(62)} & \quad \begin{array}{c}
\text{MeO}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\quad \begin{array}{c}
\text{Ome}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\quad \begin{array}{c}
\text{CH}_{2}\text{OME}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\end{align*}

\begin{align*}
\text{(63)} & \quad \begin{array}{c}
\text{H}
\end{array}
\quad \begin{array}{c}
\text{NH}_{2}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\quad \begin{array}{c}
\text{N}
\end{array}
\end{align*}

A number of $\sigma$-complexes in the heterocyclic series are of biological interest. For example, $\sigma$-complexes have been implicated in the observed antileukaemic activity of nitrobenzofurazan and furoxan derivatives\textsuperscript{129}. As well, a number of molecular rearrangements that occur through the action of nucleophiles with heterocyclic derivatives have been shown to occur via $\sigma$-complex intermediates\textsuperscript{130,131}.

III. COMPETITIVE PROCESSES INVOLVING $\sigma$-COMPLEXES

A. Nucleophilic Displacement versus $\sigma$-Complex Formation

For many years interest in $\sigma$-complexes had focused on their role in aromatic nucleophilic substitution ($S_{N}\text{Ar}$) processes. This situation came about largely as a result of the appearance in 1951 of two comprehensive reviews concerned with $S_{N}\text{Ar}$ processes\textsuperscript{132,133}, both pointing to an addition–elimination mechanism for activated aromatic substrates, in contrast to the concerted mechanism accepted for bimolecular nucleophilic substitution at saturated carbon centres. The Jackson–Meisenheimer $\sigma$-complex thus served as the model of the adduct formed in $S_{N}\text{Ar}$ processes. A number of kinetic studies during the 1950s and 60s of the structure–reactivity type\textsuperscript{134,135} were interpreted on this basis. Particularly interesting was the observation of base catalysis in $S_{N}\text{Ar}$ processes involving amines as nucleophiles, providing kinetic evidence for a reaction intermediate\textsuperscript{136-140}. Studies of the latter type are still continuing\textsuperscript{141-144}.

However, difficulties arose in obtaining unambiguous spectroscopic evidence for the formation of $\sigma$-complexes as \textit{bona fide} intermediates in $S_{N}\text{Ar}$ processes. A claim that a spectrally detectable coloured species ($\lambda_{\text{max}} 397 \text{ nm}$) corresponding to structure 64 was formed in the reaction of 1-fluoro-4-nitrobenzene with azide ion in DMF\textsuperscript{145} was subsequently withdrawn\textsuperscript{146}. The reaction of 1-chloro-2,4-dinitrobenzene with hydroxide ion in aqueous medium does not give rise to a spectrally detectable intermediate\textsuperscript{147}. Thus, if an adduct is formed in these processes, then nucleophilic attack at C-1 must be rate-determining and leaving-group expulsion occurs in a fast step.

A spectral species formed in the reaction of 1-fluoro-2,4-dinitrobenzene with diethyl malonate in the presence of Et$_3$N, and which was earlier assigned as corresponding to structure 65\textsuperscript{148}, was subsequently reassigned as corresponding to the final reaction products\textsuperscript{149a}. However, at very short reaction times (<0.2 s), the
intervention of another transient spectral species was later observed and this was assigned as 65. The reaction sequence in the system is given by Scheme 8, values of $k_1$, $k_2$ and $k_3$ being derived from the kinetic data. The final reaction product is the anion of diethyl 2,4-dinitrophenylmalonate, 66.

![Scheme 8](image)

Coloured solutions are generally obtained in $S_N$Ar reactions of trinitro-substituted benzene derivatives containing a potential leaving group, and it is on such systems that most attention has been focused. However, a problem which arises in such systems can be illustrated with reference to Scheme 9. Thus, consider that in the study of the reaction $ArX + Nu -> ArNu + X$ ($Ar = 2,4,6$-trinitrophenyl) a spectrally detectable intermediate is observed; is the structure of the transient species given by 68 or 69? While species 68 leads directly to product, 69 may not be on the reaction pathway, being involved instead in a side-equilibrium. A further difficulty lies in the fact that the UV-visible spectrum is usually not greatly different for the species 68 and 69 (see Figure 2). These considerations can be illustrated with respect to the following studies.

In a kinetic study of the alkaline hydrolysis of picryl chloride a transient coloured species was observed and was presumed to be 68 ($X = Cl, Nu = OH$). However, an NMR study of the interaction of picryl chloride with MeO$^-$ in DMSO solution showed that the structure of the coloured species formed corresponds actually to 69 ($X = Cl, Nu = OH$), rather than to 68.

A careful kinetic study of the reaction of picryl chloride with MeONa-MeOH followed by stopped-flow and UV-visible spectroscopy showed that there is only one distinct...
processes could be discerned\textsuperscript{152}. The first process, which was the faster one, was assigned to formation of the C-3 adduct 69. The second, slower process corresponded to formation of the C-1 adduct of 2,4,6-trinitroanisole with MeO\textsuperscript{-}. This product is formed via the sequence of reactions shown in Scheme 10\textsuperscript{152}. It is apparent that of the two complexes 68 and 69, the C-3 adduct (69) is kinetically preferred relative to the C-1 adduct (68). These observations are in agreement with the original findings by Servis using \textsuperscript{1}H-NMR, pertaining to the reaction of 2,4,6-trinitroanisole with MeO\textsuperscript{-} in DMSO–MeOH\textsuperscript{24}, as noted previously.

An extensive study\textsuperscript{147} of the alkaline hydrolysis of 1-X-2,4,6-trinitrobenzene derivatives (X = Cl, NO\textsubscript{2}, OMe) by stopped-flow spectroscopy has confirmed the rapid formation of the 3-hydroxy adduct as the first coloured species obtained in these systems. The kinetic results, however, provide strong evidence for the occurrence of nucleophilic substitution of X\textsuperscript{-} in the 3-hydroxy complexes (71), in the oxy anions formed on deprotonation (72), as well as in the parent substrate (67). The overall scheme which encompasses these processes is given in Scheme 11\textsuperscript{147}.

Picrate ion, which is the final product in each case, is formed by attack of OH\textsuperscript{-} at the 1-position, in a slower step. This would entail formation of intermediates 73–75, corresponding to attack on the substrate, the 3-hydroxy adduct, and the deprotonated species, respectively. There is no evidence for a build-up in
concentration of the species 73–75, indicating that hydroxide attack at the 1-position is rate-determining in all cases in the overall substitution reaction.

It was noted previously (Scheme 8) that reaction of diethyl malonate anion with 1-fluoro-2,4-dinitrobenzene, which gives rise to the anion of diethyl 2,4-dinitrophenylmalonate as the final product, proceeds via a coloured intermediate species whose structure was assigned as the C-1 adduct \(^{(73)}\). \(^{149}\) The reaction of picryl chloride with diethyl malonate anion in benzene–DMSO solution was subsequently interpreted on a similar basis. \(^{153}\) This contrasts with the hydroxide and methoxide ion results discussed above, although it should be noted that the solvent systems in the various studies are not kept constant and that solvent can preferentially stabilize certain intermediates. \(^{154,155}\)

It is of interest, therefore, that a kinetic study of the reaction of picryl chloride with dimethyl malonate and sodium methoxide in DMSO–methanol solutions, using stopped-flow and UV–visible spectroscopy, has received a different interpretation. \(^{156}\) The proposed Scheme 12 invokes the formation of mono(C-3)- and di(C-3,5)-malonate adducts as the spectrally detectable intermediates. A separate study of the reaction of 2,4,6-trinitroanisole with dimethyl malonate and methoxide ion in DMSO–methanol solutions indicates that this reaction proceeds by a similar pathway. The adducts (C-3 and C-5) derived from malonate ion as well as from methoxide ion are given as kinetically and spectrally detectable intermediates. \(^{157}\)

In view of these different interpretations, an approach by some other method is clearly desirable. Pertinent evidence has been obtained by the flow NMR method developed by Fyfe and his coworkers. \(^{36,158–161}\) The flow NMR method allows high-resolution spectra of reliable intensities to be measured in rapidly flowing, chemically reacting systems. Hence, in suitable systems, transient reaction intermediates can be definitively characterized. The technique has now been used to elucidate the mechanisms of a variety of reactions.
In SNAr processes, one of the most interesting applications of flow NMR relates to the reaction of 1-ethoxy-2,4-dinitronaphthalene with n-butylamine, in 75% DMSO-25% methanol solution. This reaction had previously been studied by Orvik and Bunnett by stopped-flow and UV-visible spectroscopy. They observed that reaction occurs in two stages and determined the rate of formation of an intermediate species and also its decay. Structure 77 was assigned to the transient species and Scheme 13 proposed for the overall reaction.

The results of the flow NMR experiment are in complete accord with the formulations in Scheme 13, including the structure assigned to the transient
intermediate. Thus a series of spectra obtained under flowing conditions at 0.1-0.5 s intervals from the time of mixing showed proton resonances characteristic of structure 77, in addition to those assignable to the reactant 76, and products, 78 ⇌ 79. For example, at the intermediate reaction times, three separate signals (singlets) are observed (δ 8.8, 8.9 and 9.1) characteristic of the H-3 environments in 76, 77, and 78 ⇌ 79. The position of this signal in the transient (δ 9.1) readily rules out the possibility of base addition at C-3 (cf. Scheme 9), as this would have resulted in H-3 absorption at considerably higher field (≈ δ 6.5), by analogy with related systems.

From the measurement of the relative intensities of the absorptions assigned to the H-3 protons, it was possible to construct a complete time evolution of the system in terms of the time dependence of the relative concentrations of the reactant, intermediate and product. The plots, shown in Figure 3158, are in complete agreement with the reaction in Scheme 13. It should be pointed out, however, that plots of the type found in Figure 3 would also follow if the intermediate were one formed in a side-equilibrium, rather than on the reaction pathway. This problem is a general one pertaining to the demonstration of reaction intermediates and in no way detracts from the usefulness of the flow NMR method.

It was mentioned in the introductory paragraph in this section that study of base catalysis in SNAr reactions involving amine nucleophiles has provided kinetic evidence for the formation of intermediate adducts. This principle can be illustrated with respect to Scheme 14.

It becomes apparent that the catalytic processes that are implicated in Scheme 14 are also inherent in Scheme 15, which is applicable to the formation of amine σ-complexes of nitroarenes. Noteworthy in both schemes is the initial formation of a zwitterionic species which is then transformed through action of base into the anionic σ-complex. This proton-transfer step is a key process pertaining to base catalysis observed in these systems, and in some cases has been found to be the rate-limiting step.

A variety of studies exemplified in Scheme 15 have been reported70.163–167, and
FIGURE 3. Percentage composition of the reaction mixture during the reaction of 0.20 M 1-ethoxy-2,4-dinitronaphthalene (75% DMSO–25% MeOH) with n-butylamine (0.4 M in 75% DMSO–25% MeOH) at 0°C, from measurement of the relative intensities of the singlet low-field absorptions assigned to the H-3 protons of the reactant, intermediate and product species. Reproduced by permission of the National Research Council of Canada from C. A. Fyfe, A. Koll, S. W. H. Damji, C. D. Malkiewich and P. A. Forte, Can. J. Chem., 55, 1468 (1977)

\[
\begin{align*}
\text{SCHEME 14:} \\
\text{\begin{align*}
X &+ \text{R}_2\text{NH} &\xrightarrow{k_1} \text{XNH}_2^+ \\
&\xleftarrow{k_{-1}} &
\end{align*}}
\end{align*}
\]
have demonstrated that kinetic investigations involving \( \sigma \)-complexes, in which no displaceable group is present, provide very useful insight into \( S_NAr \) processes which do involve displaceable groups. The detailed kinetic arguments are outside the scope of the chapter and the interested reader is referred to the original references.

Other aspects of \( S_NAr \) processes which have received attention recently and which intimately involve \( \sigma \)-complex intermediates include micellar catalysis\(^{168}\) and the occurrence of tele\(^{169,170}\) and cine substitution\(^{171-173}\). Several reviews of \( S_NAr \) processes, including in heteroaromatic systems, have appeared\(^{174-177}\). Photoaromatic substitution has also been reviewed\(^{178}\).

### B. 'Vicarious' Nucleophilic Substitution of Hydrogen

Displacement of hydride ion from a nitroarene through nucleophilic displacement is generally considered as an energetically prohibitive process. This, indeed, is the basis of the formation of stable \( \sigma \)-complexes of compounds containing no readily displaceable leaving group, as exemplified by the stable complexes of TNB and so on.

However, in an interesting discovery Golinski and Makosza\(^{179}\) have reported what is in effect a formal displacement of hydride ion. Thus 1-haloalkylphenyl sulphones and \( N,N \)-dialkyl-1-haloalkanesulphonamides react with nitrobenzene in DMSO in the presence of KOH to yield the product arising from chloride displacement in the reagent, and hydride ion displacement in the nitroarene (equation 2). A possible reaction mechanism involves abstraction of the acidic proton in 80 by base, followed by addition of the carbanion to the aromatic ring to form the \( \sigma \)-complex 82. Expulsion of chloride from 82, with concurrent migration of hydride to the \( \alpha \)-carbon would yield the reaction products (equation 3)\(^{179}\).

Confirmation of this mechanism, for example through investigation of the intramolecularity of hydride migration, has not yet been obtained. However, the reaction has been extended to other \( C-H \) acids containing potential leaving groups as substituents (MeS, PhS, PhO), as illustrated in equation 4\(^{180}\).

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{NO}_2 \quad + \quad \text{R}_2\text{NH} & \quad \text{K}_1 & \quad \text{K}^{-1} \\
\text{O}_2\text{N} & \quad \text{H} \quad \text{NHR}_2 \quad \text{NO}_2 \quad \text{K}_3\text{[B]} & \quad \text{K}^{-3}\text{BH}^+ \quad \text{[BH}^+\text{]} \\
\end{align*}
\]

\text{SCHEME 15}

\[\text{R-CHCISO}_2\text{Y} + \quad \text{NO}_2 \quad \overset{\text{KOH \ DMSO}}{\longrightarrow} \quad \text{R-CHSO}_2\text{Y} + \quad \text{Cl}^- \]

\((80)\)  \(\text{Y = Ph}\) \(\text{NO}_2\) \(\text{NO}_2\)  \(\text{Cl}^-\)  

\((81)\)
A somewhat related process, which involves overall replacement of hydride by an aryl moiety, derives from the reaction of TNB with ambident phenoxide ion mentioned previously. The carbon-bonded phenoxide adduct 46 can be readily oxidized by reagents such as benzoquinone to yield the diphenyl derivative 83 (Scheme 16).

C. Aromatic Proton Abstraction versus σ-Complex Formation

In 1940, Lewis and Seaborg advanced the possibility of ionization of an aryl hydrogen in a polynitroarene, through action of base, in order to account for the conducting properties of solutions in liquid ammonia. The observed cryoscopic properties of TNB in 2-aminoethanol were similarly explained according to equation (5) by Baliah and Ramakrishnan.

However, Wheland and coworkers suggested that the conductivity of solutions of 1,3-dinitrobenzene (DNB) in liquid ammonia was a result of σ-complex
formation by NH$_3^-$, while Briegleb and coworkers$^{185}$ interpreted on such a basis the conductance and UV–visible spectroscopic properties of TNB interacting with piperidine in acetonitrile. Quite recently$^{186}$, $^1$H-NMR studies of polynitroarenes in liquid ammonia have given conclusive evidence of adduct formation and have further revealed that both 1:1 and 1:2 adducts are formed with NH$_2^-$, as shown in equation (6) for the case of TNB. Other nitroarenes examined in this way included

\[
\begin{align*}
\text{H}_2\text{NCH}_2\text{CH}_2\text{OH} &\rightarrow \text{H}_3\text{NCH}_2\text{CH}_2\text{OH} \\
+ \text{NO}_2 &\rightarrow \text{H}_2\text{NCH}_2\text{CH}_2\text{OH} + \text{NO}_2
\end{align*}
\]

$N,N$-dimethylpicramide, 2,4,6-trinitrotoluene (TNT) and TNA. As in the case of TNB, both 1:1 and 1:2 interactions are observed. The 1:2 adduct can exist as either the cis or trans isomer.

The use of isotopic exchange as a criterion of proton abstraction in nitroarenes was first examined by Kharasch and coworkers$^{187}$. Extensive exchange was found to occur on treatment of TNB with NaOH–EtOH–D$_2$O at 110°C for 68 h. However, the uniqueness in interpretation of this result was subsequently questioned$^{188}$ on the basis that under the conditions of this exchange, nucleophilic displacement of a nitro group in TNB by hydroxide ion occurs readily. Exchange was not observed on treatment of TNB with 8M NaOH in D$_2$O at room temperature$^{189}$. However, complete exchange occurred when TNB (0.5M) was treated with NaOD (0.01M) in DMF–D$_2$O (90:10) at 100°C for 1 h$^{190}$. Under these conditions, nucleophilic displacement of NO$_2$ occurred only to a small extent, if at all. Deuterium exchange in DNB in the NaOD–D$_2$O–DMF system occurred under even milder conditions$^{191,192}$. Other basic systems in which isotopic exchange in DNB was found to occur include liquid ND$_3$$^{193}$, MeONa–MeOT–DMSO$^{188}$ and NaOD–D$_2$O–DMSO$^{192}$. In these studies, it was either shown through $^1$H-NMR in the case of the deuterium experiments, or otherwise inferred in the case of the tritium experiments, that DNB undergoes exchange only at the 2-position.

However, a combination of tritium exchange and $^3$H-NMR has revealed that isotopic exchange in DNB can occur in the 4(6)-positions, as well as the 2-position$^{194}$. Thus, whereas in a medium of MeONa–HTO–dioxan exchange was confined to the 2-position, use of the more strongly basic MeONa–HTO–HMPA system led to complete exchange at the 2-position and 7% exchange at the equivalent 4- and 6-positions. This could be shown definitively through $^3$H-NMR examination of the recovered 1,3-dinitrobenzene. However, under these more vigorous conditions displacement of NO$_2$ also occurred, as demonstrated by partial formation of m-nitroanisole, which was also tritiated in the 2-position.

A kinetic study performed with DNB tritiated in the 2- as well as 4(6)-positions, in aqueous NaOH at 60°C, showed that exchange from the 2-position occurred 2000 times more rapidly than from the 4(6)-positions$^{194}$. This reactivity factor in favour of the 2-position would presumably explain why exchange at the 4(6)-positions had not been detected previously.
A contrasting result was observed when tritium exchange was examined in 1,3-dinitronaphthalene (DNN) in combination with $^3$H-NMR. The $^3$H-NMR spectrum of the DNN recovered following exchange in the NaOT-HOT-HMPA system showed that exchange again occurred in two positions, but now exchange at the 4-position had taken place to a greater extent (85%) than at the 2-position (15%).

An explanation of this contrasting behaviour can be proposed when one considers the possibility of stabilization of the nitroaryl carbanions through resonance structures entailing carbenoid delocalization. Thus, as shown in Scheme 17, for the carbanions derived from DNB, two carbenoid structures can be written following deprotonation from either the 2- or 4(6)-positions. Hence the exchange process will be governed by a combination of inductive and steric factors at the respective positions. On the other hand, in the case of DNN the carbanion derived on proton loss at C-2 can partake in only one carbenoid form without disrupting aromaticity in the second ring, whereas for deprotonation from the 4-position, two such carbenoid structures are possible. Hence proton abstraction from the 4-position in DNN would be favoured relative to DNB. It is noteworthy that carbenoid resonance has previously been invoked in a variety of heterocyclic systems, but this appears to be the first such evidence in the case of nitroaryl carbanions.

Solutions of TNB and DNB in basic media are typically coloured red, as for example in the NaOD-D$_2$O-DMF system described above. What is the relationship between carbanion formation, leading to isotopic exchange, and $\sigma$-complex formation? Some workers had inferred that carbanion formation was the predominant process in such systems and that the colour of the solution could be attributed mainly to this species. However, the unambiguous characterization of $\sigma$-complexes via their spectral properties (see above) has shown unambiguously that $\sigma$-complexes are in fact present in such systems, at least to an important extent.

Quantitatively, the problem was approached by measurement of rates of isotopic exchange concurrently with $\sigma$-complex formation, via measurement of absorbance due to the latter species. The first such study concerned tritium exchange in DNB in MeONa-MeOT-DMSO mixtures, keeping constant [MeONa] and varying the DMSO content to change the basicity of the medium. The plots of log $k$ vs. $H_-$, and of log $\epsilon$ vs. $H_-$, both showed initial increasing tendency, but then both levelled off at about the same $H_-$ value, corresponding to practically complete conversion to coloured species. However, throughout the composition range the colour formation was virtually instantaneous (<1 s), which would rule out the dinitrophenyl anion as the species chiefly responsible for the solution colour.

Contrasting results were obtained in another study of concurrent exchange and $\sigma$-complex formation, for the case of TNB in the NaOD-D$_2$O-DMF system. In this case $\sigma$-complex formation increased steadily as the DMF composition was increased from 0–20 mol %, and then levelled off as expected. The exchange process, however (which could only be studied by the sampling techniques employed at >20 mole % DMF due to low solubility of TNB), showed a decreasing tendency with increasing DMF content. It is noteworthy that the degree of complexation in this system had already reached ~99% in 20 mol % DMF. Hence it could be presumed that if the method had allowed measurement of exchange rates in <20 mol % DMF, an increasing plot would first be obtained, passing through a maximum prior to the decline that was actually observed over the region 20–80 mole % DMF.

A recent study of the concurrent exchange and $\sigma$-complex formation processes in DNB in the NaOD-D$_2$O-DMF system has in fact revealed the behaviour anticipated in the earlier work with TNB. The kinetic data for exchange now do
show the initial rate increase, following which a maximum in rate is attained at ca. 70 mole % DMF, and then there is a rate decrease (Figure 4). The concurrent σ-complex formation process increases to ~99% of the maximum value by ~70 mole % DMF, and then levels off.

It is apparent that the principles governing the TNB and DNB systems are
analogous and the differences arise at the quantitative level, from the different
degrees of complexation in the two systems and as a function of medium basicity.

The origin of the decreasing exchange rate in the media of high DMF content is
shown in an alternative fashion in Figure 5, which is applicable to the DNB ease in
the NaOD–D₂O–DMF system (0.5 M DNB, 0.004 M NaOD)¹⁹⁹. From the \( K_{eq} \) values
for \( \sigma \)-complex formation, one can calculate the extent of complexing of OD⁻, and
hence the free [OD⁻] can be evaluated. Plotting the function \( \log (k_{obs}/[OD^-]_{free}) \)
in effect \( \log k_2 \) representing the second-order rate constant for exchange), versus
\( H^- \), one obtains an initial linear portion followed by a downward curving plot
(Figure 5). In contrast, as seen from the figure, the plot of \( \log K_{eq} \) versus \( H^- \) remains
linear over the entire range of medium composition. It follows, therefore, that it is
the steeper dependence of \( \sigma \)-complex formation on medium basicity, compared to
proton exchange, which is the underlying reason for the decreasing exchange rate in
media of high DMF content.

The sum of the evidence points to isotopic exchange occurring via the aryl
carbanion intermediate and the involvement of the \( \sigma \)-complex in a side-equilibrium
as an unreactive species. This is illustrated in Scheme 18.

\[ \text{SCHEME 18} \]

D. Benzylic Proton Abstraction versus \( \sigma \)-Complex Formation

In the interaction of nitrobenzyl compounds with bases, \( \sigma \)-complex formation
can potentially compete with \( \alpha \)-hydrogen abstraction. The latter possibility arises
from increased acidity of \( \alpha \)-hydrogens due to delocalization of negative charge in
the anion by ortho and para nitro substituents. For the anion derived from TNT
one can write:

\[ \text{etc.} \]

Formation of the TNT⁻ anion from TNT under alkaline conditions is implicated in
the reported isolation of 2,2',4,4',6,6'-hexanitrobenzyl²⁰³ and 2,2',4,4',6,6'-hexa-
nitrostilbene²⁰¹, the latter having the properties of a thermally stable explosive
with possible application in space research²⁰². Another kind of evidence for the
intervention of TNT⁻ in TNT–base systems derives from the observation of
27. Meisenheimer or σ-complexes in nitroarene–base interactions

hydrogen–deuterium exchange, as in the pyridine–D₂O\(^{203}\), NaOD–D₂O–DMF\(^{204}\) or NaOD–D₂O–MeOD–THF\(^{205}\) systems.

What of σ-complex formation in TNT–base systems? A number of early attempts to use NMR to elucidate the structure(s) of species formed in TNT–base systems were unsuccessful\(^{14}\), apparently as a result of radical anion formation (see below). However, the use of electron absorption spectroscopy in combination with fast kinetic methods for detection of spectral species has yielded the desired information. Moreover, it has been found that several types of σ-complexes can be formed, depending on the reaction conditions.

With TNT in excess of base, in a medium of 50% dioxan–50% water or in methanolic or ethanolic media containing the respective lyate ions, the processes that have been identified are shown in equation (7)\(^{206}\). The TNT\(^−\) anion generated in the first step reacts with another mole of TNT to yield the Janovsky type σ-complex \(\text{84}\).

stopped-flow and temperature-jump techniques. At molar ratios of RO\(^−\):TNT > 1, another faster process emerged and was tentatively ascribed to σ-complex formation involving alkoxide ion, but the resulting complex(es) could not be identified spectrally.

In a series of studies by stopped-flow techniques involving TNT and TNT-d\(_3\) with EtO\(^−\), i-PrO\(^−\) and t-BuO\(^−\) in the respective alcohols, with alkoxide in large excess, the concurrent formation of a σ-complex and the TNT\(^−\) anion was proved unequivocally\(^{207–209}\). A gradation of behaviour as a function of solvent–base was also apparent in this work. For example, in the TNT–EtO\(^−\)–EtOH system σ-complex formation could only be inferred from the perturbing effect on the kinetics of formation of TNT\(^−\). However, use of i-PrO\(^−\) or t-BuO\(^−\) in conjunction with TNT-d\(_3\) enabled actual observation of the spectrum of the σ-complex. Kinetic measurements showed that the σ-complex (‘brown species’) is formed more rapidly relative to the TNT\(^−\) anion (‘purple species’). The competing processes can be illustrated simplistically in Scheme 19. However, this scheme does not accurately reflect the detailed kinetic results, including the effect of added salts, which showed that the data have to be analysed in terms of the reactivities of ion pairs as well as of free ions. σ-Complex formation is thus represented in Scheme 20, while a corresponding scheme is applicable to TNT\(^−\) anion formation. Interestingly, it is found that, for the i-PrONa/i-PrOH system, in σ-complex formation the ion-paired sodium alkoxide has a reactivity comparable to that of dissociated ions, while in proton transfer free ions are the more reactive species. These results can be explained on the basis of the transition-state structures \(\text{87 and 88}\) applicable to σ-complex formation and TNT\(^−\) anion formation respectively. It is seen that in the
former case the metal cation stabilizes the incipient negative charge on the aromatic ring in a favourable six-membered transition state, unlike the latter case.

It is also interesting that whereas proton abstraction from TNT by alkoxide ions in the respective alcohols is subject to a 'normal' primary kinetic isotope effect of

\[
\frac{k_{i}}{k_{p}} = 7-8 \text{ at } 25^\circ C \text{ to } 20^\circ C, \text{ use of 1,1',3,3'-tetramethylguanidine as base in DMF solvent led to a KIE of 16.9 at } 20^\circ C \text{ and 24.3 at } 0^\circ C, \text{ apparently as a result of tunnelling}^{210}.
\]

A reexamination of the TNT–alkoxide system by means of flow NMR spectroscopy has led to the discovery of yet another species. It was thus found\textsuperscript{211} that whereas reaction between equimolar proportions of TNT and MeO\textsuperscript{-} in 87.5% DMSO–12.5% MeOH led to the formation of a σ-complex and of TNT\textsuperscript{-}, according
to the previously discussed Scheme 18, doubling the proportion of MeO\(^-\) resulted in formation of the dianionic species 89. The latter was unambiguously identified by its NMR spectrum, and its electronic absorption spectrum was also obtained. This new species apparently is formed from 85 or 86, as in Scheme 21. It is noteworthy that in this study\(^{211}\) the presence of free radicals was also detected, although these could not be structurally identified.

An NMR study of nitromethylnaphthalene compounds has yielded interesting results\(^{212}\). 1,5-Dimethyl-2,4,8-trinitronaphthalene (90) on reaction with one mole of methoxide in DMSO solution is reported to yield initially the deprotonated species 91. Addition of further methoxide yields the dianionic species 92, in analogy with the TNT system (equation 8).

1,5-Dimethyl-2,4,6,8-tetranitronaphthalene yielded two \(\sigma\)-complexes (via addition of MeO\(^-\) at C-1 and at C-3) in a minor process, the major process giving rise to the anion 93, via proton abstraction. However, this species is unstable and gives rise to another species which is formulated as 94 on the basis of the NMR evidence. The pathway in Scheme 22 involving intramolecular reaction between the carbanionic centre and NO\(_2\) at C-8 is proposed\(^{212}\).
IV. ACKNOWLEDGEMENTS

I wish to express my sincere thanks to my coworkers named in the accompanying references for their contributions. Exchange of ideas with colleagues in the field of Meisenheimer complexes, including unpublished information, is warmly acknowledged. Thanks are also due to the Natural Sciences and Engineering Research Council of Canada for continuing support of our research in this area.

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CHAPTER 28

Uses of isotopically labelled amino, quaternary ammonium and nitro compounds

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III. THE USE OF ISOTOPE TRACER EXPERIMENTS AND ISOTOPE EFFECT MEASUREMENTS FOR THE DETERMINATION OF MECHANISM FOR AN ELIMINATION PROCESS FROM A QUATERNARY AMMONIUM SALT

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   1. Deuterium exchange at the \(\beta\)-carbon
   2. Nitrogen kinetic isotope effects
I. THEORY OF KINETIC ISO TOPE EFFECTS AND THEORETICAL APPROACHES TO THE EFFECT OF SUBSTITUENTS ON TRANSITION-STATE GEOMETRY

A. Theory of Kinetic Isotope Effects

1. Heavy-atom kinetic isotope effects

Several monographs1-4 have detailed discussion dealing with heavy-atom and primary and secondary hydrogen–deuterium kinetic isotope effects. The recent monograph by Melander and Saunders4 covers the entire area particularly well. For this reason, only a brief summary of the theory of kinetic isotope effects as well as their important uses in the determination of reaction mechanism and transition-state geometry will be presented.

The Bigeleisen treatment5-7, based on Eyring and coworkers' absolute rate theory8, assumes that there is a single potential energy surface along which the reaction takes place, and that there is a potential energy barrier separating the reactants from the products of the reaction. The reaction occurs along the path corresponding to the lowest potential energy, i.e. it passes over the lowest part of the barrier. The transition state is located at the top of the barrier on the reaction path, i.e. it lies at the energy maximum along the reaction coordinate but at an energy minimum in all other directions, and is assumed to have all the properties of a stable molecule except that one vibrational degree of freedom has been converted into motion along the reaction coordinate.
28. Isotopically labelled amino, quaternary ammonium and nitro compounds

The expression for the rate constant ‘k’ of the reaction according to these assumptions may be expressed by equation (1).

\[ k = \frac{\dot{k}TK'}{h} \]  

where \( \dot{k} \) is the Boltzmann constant, \( T \) is the absolute temperature, \( h \) is Planck’s constant, \( \kappa \) is the so-called transmission coefficient and \( K' \) is the equilibrium constant between the activated complex (the molecule at the transition state) and the reactants. It is assumed that the transition-state complex is in equilibrium with the reactants. The degree of freedom corresponding to the reaction path is not included for the activated complex, \( \kappa \) represents a factor which takes into account the nonclassical correction required to allow molecules with insufficient classical energy to surmount the barrier – to ‘tunnel’ through it. Using equation (2) with a knowledge of the potential energy surface, \( K' \) may be calculated using the methods of statistical mechanics, since:

\[ K' = \frac{Q'}{Q_AQ_B} \]  

where the \( Q \)s are the complete partition functions for reactants A, B, ..., etc. and \( Q' \) is the partition function for the transition-state complex, omitting again the one vibrational energy level corresponding to the translational motion along the decomposition pathway.

The calculation of the potential energy surface from first principle is, at present, insufficiently accurate to allow this approach to yield reliable values of \( Q' \) and therefore of \( K' \). However, the effect of isotopes on these quantities can be predicted more accurately than can the quantities themselves and isotopic rate ratios may be calculated for fairly complex reactions with some confidence. For the reaction:

\[ A + B + C \ldots \rightleftharpoons \text{Transition state} \rightleftharpoons \text{Products} \]

\[ \frac{k_1}{k_2} = \frac{\kappa_1 \cdot \frac{Q_A}{Q_A^1} \cdot \frac{Q_B}{Q_B^2} \cdot \frac{Q_C}{Q_C^2}}{\kappa_2 \cdot \frac{Q_A}{Q_A^2} \cdot \frac{Q_B}{Q_B^1} \cdot \frac{Q_C}{Q_C^1}} \]

where the subscripts 1 and 2 refer to the molecules containing the lighter and heavier isotopes, respectively.

The assumption is that \( \kappa_1 = \kappa_2 \) initially, although these transmission coefficients are not known with certainty. To correct for any error introduced in this assumption, a ‘tunnelling correction’ factor is introduced. Bigeleisen and Goeppert-Mayer expressed the partition functions in terms of the vibrational frequencies of the molecules in the gas phase. Applying the harmonic approximation to all nonlinear gas molecules leads to an expression for \( Q_2/Q_1 \) (equation 4), where \( S_1 \) and \( S_2 \) are the symmetry numbers of the respective molecules, the \( M \)s are the molecular weights, the \( I \)s are the moments of inertia about the three principal axes of the \( n \)-atom molecules and the \( \nu \)s are the fundamental vibrational frequencies of the molecules in wave numbers.

\[ \frac{Q_2}{Q_1} = \frac{S_1}{S_2} \left( \frac{I_{A2}I_{B2}I_{C2}}{I_{A1}I_{B1}I_{C1}} \right)^{1/2} \left( \frac{M_2}{M_1} \right)^{3/2} \pi_i^{3n-6} \exp \left[ \frac{(\nu_1 - \nu_2)h\epsilon}{2kT} \right] \left[ 1 - \exp(-h\nu_1/kT) \right] \left[ 1 - \exp(-h\nu_2/kT) \right] \]

(4)
Using various approximations, a solution to the isotopic rate ratio equation can be obtained. It is found that the isotope rate ratio, $k_{1}/k_{2}$, is dependent on the force constant changes which occur in passing to the transition state. Consequently, if C—X bond rupture, where the isotopically labelled atom X can be halogen, sulphur, nitrogen, etc., has not progressed at the transition state of the slow or rate-determining step of the overall reaction, there is no change in the force constants involving the isotopic atom and a rate ratio $k_{X1}/k_{X2}$ equal to one is expected. Accordingly, a value of the isotope rate ratio greater than one will be observed if there is a decrease in the force constants at the transition state of the slow step. The greater the decrease in the force constant the larger will be the magnitude of the isotope effect.

The observation of a heavy-atom isotope effect, therefore, allows one to determine whether C—X bond weakening (a decrease in force constant) has progressed at the activated complex of the rate-determining step. The magnitude of the isotope effect provides information concerning the structure of the transition state. Saunders has recently calculated the dependence of the leaving-group isotope effect on the extent of C—X bond rupture for concerted elimination reactions where the leaving groups were trimethylamine and dimethyl sulphide. It was found that the magnitude of the heavy-atom isotope effect varied linearly with the extent of C—X bond rupture. Sims and coworkers, in a similar calculation, found that the same relationship between the magnitude of the leaving-group isotope effect and the extent of C—X bond rupture existed for a nucleophilic substitution reaction.

2. Primary hydrogen–deuterium kinetic isotope effects

Transition-state force constants can be calculated with some confidence if a large computer is available. For some purposes, however, it is sufficient to have only a qualitative estimate of the changes in force constants which have occurred at the transition state, and acceptable estimates of the isotope effect can be obtained without recourse to a complex calculation. While the zero-point energy differences between the isotopic molecules' vibrations are not the only contribution to the isotope effect, they are however often the dominant term. This is particularly true for hydrogen–deuterium kinetic isotope effects where the zero-point energy difference is large, and also for large molecules where isotopic substitution does not effect the mass and moment of inertia term significantly. It is usual to assume that the stretching modes are the most important in determining the isotope effect. This is based on the two assumptions: (i) that the bending vibrations are generally of a lower frequency and therefore have smaller zero-point energy differences for isotopic molecules, and (ii) the bending motions in the transition state will be largely similar to those in the substrates.

Applying these approximations to the rupture of a single C—H bond in a unimolecular process leads to equation (5),

$$\frac{k_{H}}{k_{D}} = \exp\left[-\frac{\hbar c}{2kT}(\nu_{H} - \nu_{D})\right]$$

where $\nu_{H}$ and $\nu_{D}$ are the ground-state symmetric stretching frequencies for the C—H and C—D bonds, respectively. Substitution into equation (5) leads to an expected isotope effect of approximately seven at 25°C.

For reactions involving a proton transfer from one molecule to another, however, the situation is more complex. Westheimer and Melander have independently pointed out that, because bond formation and breaking are occurring concurrently,
new stretching vibrations in the transition state which are not present in the reactants must be considered.

They considered the reaction:

\[
AH + B \rightarrow [A \cdots H \cdots B] \rightarrow A + HB
\]

where \([A \cdots H \cdots B]\) is a linear transition state. If this transition state is regarded as a linear molecule, there would be two independent stretching vibrational modes which may be illustrated as follows:

\[
\begin{array}{c}
\text{Symmetric} \\
\text{Antisymmetric}
\end{array}
\]

Neither of these vibrations corresponds to stretching vibrations of AH or BH. The translational mode in the transition state may be identified with the 'antisymmetric' vibrational mode, but the 'symmetric' mode is a real vibration with a positive force constant. Both Melander and Westheimer, and more recently More O’Ferrall\(^{14}\), show that the 'symmetric' transition-state vibration may or may not involve motion of the central H(D) atom. If the motion is truly symmetric, the central atom will be motionless in the vibration and thus the frequency of the vibration will not depend on the mass of this atom i.e. the vibrational frequency will be the same for both isotopically substituted transition states. It is apparent that under such circumstances there will be no zero-point energy differences between deuterium – and hydrogen-substituted compounds for the symmetric vibration in the transition state. Hence an isotope effect of seven at room temperature is expected since the difference in activation energy is the difference between the zero-point energies of the symmetric stretching vibrations of the initial states, i.e.

\[
\frac{1}{2}h\nu_H - \frac{1}{2}h\nu_D.
\]

In instances where bond breaking and bond making at the transition state are not equal, i.e. the bond breaking is either more or less advanced than the bond formation, the 'symmetric' vibration will not be truly symmetric. In these cases, the frequency will have some dependence on the mass of the central atom and there will be a zero-point energy difference for the vibrations of the isotopically substituted molecules at the transition state. Hence:

\[
\frac{k_H}{k_D} = \exp\{\frac{-hc}{2kT}[(\nu_H - \nu_D) - \Delta\nu]\}
\]

where \(\Delta\nu\) corresponds to the frequency difference of the symmetric mode of the transition state on isotopic substitution. For such situations, \(k_H/k_D\) will have values smaller than seven.

It may be concluded that for reactions where the proton is less or more than one-half transferred in the transition state, i.e. the A—H and H—B force constants are unequal, the primary hydrogen–deuterium kinetic isotope effect will be less than the maximum of seven. The maximum isotope effect will be observed only when the proton is exactly half-way between A and B in the activated complex.

3. Secondary alpha hydrogen–deuterium kinetic isotope effects

In the preceding sections the bond involving the isotopic atom is broken or formed in the rate-determining step of the reaction. In these cases, the change in rate is referred to as the primary kinetic isotope effect. Isotope substitution at
other sites in the molecule gives smaller rate effects and these are collectively referred to as secondary kinetic isotope effects.

As with primary isotope effects, the origin of secondary isotope effects is considered to be mainly due to changes in forces constants upon going from reactants to the transition state. For the most part secondary isotope effects depend on the change in zero-point energy ($\Delta ZPE$). Smaller force constants for the isotopic nuclei in the transition state than in the reactant leads to an isotope effect greater than one (Figure 1a). On the other hand, when the force constants are greater in the transition state than in the reactant an isotope effect less than one is observed (Figure 1b).

Secondary alpha hydrogen-deuterium kinetic isotope effects are determined when hydrogen is replaced by deuterium at the $\alpha$- or reacting carbon. The generally accepted view originally proposed by Streitwieser and coworkers\textsuperscript{15} is that the alpha deuterium kinetic isotope effects are primarily determined by the changes in the out-of-plane bending vibrations in going from the reactants to the transition state. Solvolysis reactions proceeding via a carbocation are expected to give isotope effects, $(k_H/k_D)_o$, of approximately 1.15. The maximum values expected for various leaving groups are 1.22 for fluoride, 1.15 for chloride, 1.13 for bromide, 1.09 for iodide, 1.19 for ammonia and 1.22 for benzenesulphonate\textsuperscript{16,17}.

Smaller alpha deuterium isotope effects are observed for reactions proceeding via the $S_{N2}$ mechanism. This is presumed to be due to steric interference by the leaving group and/or the incoming nucleophile with the out-of-plane bending motion of the $\alpha$-carbon–hydrogen bonds. This leads to an increased force constant at the $S_{N2}$ transition state, $1$ (see Figure 1b). In fact, small or inverse isotope effects, $(k_H/k_D)_{oD} = 0.95–1.04$, are observed for the $S_{N2}$ reactions of primary substrates\textsuperscript{18}.

\begin{equation}
\text{Nu} \cdots \text{X}
\end{equation}
4. Secondary beta hydrogen—deuterium kinetic isotope effects

Secondary beta-deuterium kinetic isotope effects arise when the hydrogen(s) on the β-carbon (adjacent to the carbon where the C—X bond rupture is progressing) are replaced by deuterium(s). These isotope effects \( (k_H/k_D)_P \) are greater than unity for nucleophilic substitution reactions. In addition, the magnitude of the isotope effect increases as the amount of positive charge (carbonium-ion character) on the α-carbon in the transition state \( 2 \) is increased. For example, the isotope effect per

\[
\frac{1}{2} \begin{array}{c}
\beta C \vdash \cdots \vdash X^5- \\
(D)H
\end{array}
\]

(D)H

\[ (2) \]

CD₃ group increases from about 1.03 for ethyl compounds, which undoubtedly react by an \( sN_2 \) mechanism, to approximately 1.37 for a \( t \)-butyl compound, which reacts by a limiting \( sN_1 \) mechanism²⁰. A wealth of experimental evidence²¹ indicates that these isotope effects are primarily, if not completely, a result of hyperconjugative electron release from the \( C_p-H \) bonds²². Other studies by Shiner and coworkers²²,²³ have demonstrated that the magnitude of these isotope effects vary with the dihedral angle between the \( C_p-H \) orbital and the developing p-orbital on the α-carbon. The maximum isotope effect in any system is observed when the dihedral angle is either 0° or 180°, i.e. where the overlap between the \( C_p-H \) and the p-orbital on the α-carbon is a maximum.

5. Kinetic isotope effects arising from the difference in basicity between \( DO^- \) in \( D_2O \) and \( HO^- \) in \( H_2O \)

As already noted in the discussion dealing with the primary hydrogen—deuterium kinetic isotope effect, it is generally agreed that small hydrogen—deuterium isotope effects can arise when the proton is more than or less than one-half transferred to base at the transition state. As a consequence, it is necessary to determine, using other criteria, the particular side of the symmetrical situation on which the transition state lies. This is necessary in order to interpret the magnitude of the primary hydrogen—deuterium isotope effects in terms of the degree of carbon—hydrogen bond rupture at the transition state. Steffa and Thornton²⁴ approached this problem by comparing the relative reaction rates with \( DO^- \) in \( D_2O \) and \( HO^- \) in \( H_2O \).

The relative basicity of the hydroxide and deuteroxide ion is determined by the equilibrium (8). The related equilibrium for the conversion of one \( OD^- \) bond of

\[
2 \text{OD}^- + \text{H}_2\text{O} \rightleftharpoons \text{OH}^- + \text{D}_2\text{O}
\]

the solvated deuteroxide ion to one OD bond of heavy water is shown in equation (9) and \( K \), therefore, must be the direct measure of the relative basicities of \( OD^- \)

\[
\text{OD}^- + \frac{1}{2} \text{H}_2\text{O} \rightleftharpoons \text{HO}^- + \frac{1}{2} \text{D}_2\text{O}
\]

and \( \text{OH}^- \). Since \( \text{OD}^- \) is the stronger base, \( K = K_B^{1/2} = k_{\text{OD}^-}/k_{\text{OH}^-} > 1 \). The magnitude of this secondary isotope effect for complete proton transfer to the base can be calculated using the self-ionization constants of \( D_2O \) and \( H_2O \) (equations 10 and 11 respectively) and the equilibrium constant \( L \) (defined by equation 12).
From equations (10) and (11) it is seen that:

\[
\frac{K_H}{K_D} = \frac{[\text{OH}^-][\text{H}_3\text{O}^+]}{[\text{H}_2\text{O}]^2} \cdot \frac{[\text{D}_2\text{O}]^2}{[\text{D}_3\text{O}^+][\text{OD}^-]}
\]  

(13)

In fact \(K_H/K_D\) is the equilibrium constant, \(K_{eq}\), for the exchange reaction (14):

\[
2 \text{H}_2\text{O} + \text{OD}^- + \text{D}_3\text{O}^+ \rightleftharpoons 2 \text{D}_2\text{O} + \text{OH}^- + \text{H}_3\text{O}^+
\]  

(14)

From equations (14), (13), (12) and (8) it is evident that:

\[
K_B = K_{eq}^2/L
\]  

(15)

Since the equilibrium constants \(K_{eq}\) and \(L\) can be measured, \(k^{\text{OD}^-}/k^{\text{OH}^-} = K_B^{1/2}\) can be calculated using values of \(L = 9.6\), \(K_H = 1 \times 10^{-14}\) and \(K_D = 1.56 \times 10^{-15}\).

The maximum isotope effect, \(k^{\text{OD}^-}/k^{\text{OH}^-}\), will occur when the proton is completely transferred from \(\text{H}_2\text{O}\) to \(\text{DO}^-\), i.e. it only holds for the equilibrium reaction shown in equation (8) for reaction at 25°C, \(K_B^{1/2} = 2.07\). At 80°C, this value is expected to be 1.88 for complete proton transfer at the transition state. For a transition state in which the proton is half-transferred between the substrate and base, the isotope effect should be \(1.88^{1/2} = 1.37\). Consequently, the observation of the secondary effects, \(k^{\text{OD}^-}/k^{\text{OH}^-}\), which are greater than 1.37 at 80°C, indicates that the proton is more than one-half transferred to base at the transition state. This allows an interpretation of the primary hydrogen–deuterium isotope effects to be made in terms of the degree of carbon–hydrogen bond rupture.

B. Effect of Substituents on the Geometry of Transition States

Several theories predicting the effect of substituents on the geometry of transition states have been put forward. This section will deal briefly with two of these theoretical studies.

Thornton considered the influence of substituents on the motion along the reaction coordinate, designated as 'parallel' motion (vibration), and on the normal modes of vibration, or 'perpendicular' vibrations, of the transition states.

He demonstrated that it is a valid approximation to describe the effect of a substituent on a bond by the addition of a linear perturbation to the parabolic potential energy function for that bond. For motion along the reaction coordinate, the potential energy as a function of distance can be approximated by an inverted parabola in the region of the potential energy maximum (transition state). Because the parabola is inverted at the transition state, the effect of a substituent on bond length which results from its effect on the motion along the reaction coordinate, is exactly the opposite to its effect on the normal vibrational modes of the transition state. This led Thornton to the following rule for predicting geometric changes at the transition state: 'Any substituent change which makes an increase (decrease) in the coordinate X of a transition state more difficult will lead to a perturbed equilibrium geometry in which X is decreased (increased) if the force constant for
X motion is positive, but in which X is increased (decreased) if the force constant for X motion is negative'.

The effect of substituents on both the parallel and perpendicular motions must be considered for a complete description of the change in bond lengths at the transition state, but usually a consideration of the former is all that is necessary. This arises from the fact that the magnitude of the change in coordinate X is inversely proportional to the force constant (the curvature of the potential energy surface in the region of the transition state). Since in most systems this curvature is considerably smaller for parallel than for perpendicular motion, the change in bond length is determined largely by the substituent effect on the former. Thus, on examination of Thornton's rule, it is concluded that a substituent change which makes cleavage of a bond more difficult (or easier) results in that bond being more ruptured (or less ruptured) at the transition state.

This theory is readily applicable to substituent effects in bimolecular elimination reactions. Only the two reacting bonds closest to the substituent are considered in this treatment. The other bonds are assumed to 'follow along'. The parallel motion can be described as follows:

\[
\begin{align*}
B & \quad H \\
C_b & \quad C_a & \quad X
\end{align*}
\]

where B is the base and X is the leaving group. An electron-withdrawing substituent at C_a will weaken the C_b−H bond and thus make the motion which extends this bond easier. It will also make compression of the C_b−C_a bond more difficult. The latter effect on the parallel motion cannot be expected to be too important since the σ-bond already present prohibits large changes in C_b−C_a bond length. Since, for parallel motion, a substituent change which makes cleavage of a bond easier results in that bond being less ruptured at the transition state, it follows that an electron-withdrawing substituent on C_b will shorten the C_b−H bond. Electron-releasing substituents on the other hand will lengthen the C_b−H bond in the transition state. The B−H and C_a−X bonds will follow along in the direction of coordinate motion set by the C_b−H bond, i.e. the B−H bond is lengthened and the C_a−X bond shortened to complete the change to a more reactant-like transition state.

The theory predicts that increasing the base strength (making compression of the B−H bond easier) will increase the B−H bond length and shorten both the C_b−H and C_a−H bonds making the transition state more reactant-like. Another prediction arising from Thornton's treatment is that a more product-like transition state will have relatively more carbanion than carbonium-ion character by making H move more relative to C_a, and C_b move more relative to X; a more product-like transition state will have relatively more carbanion character at C_b than carbonium ion character at C_a, that is, it becomes more Elcb-like.

Thornton and Winey recently expanded the theory in order to consider data which suggest that in some cases the influence of a substituent change is greater on the perpendicular motion than on the parallel motion. This updated theory considers the concept of differential sensitivity of geometry of the transition state towards structural changes, depending on the character of the transition state, i.e. whether the transition state is central or Elcb-like. The specific predictions of Thornton's theory will be considered in the section dealing with the experimental studies on transition states.

The other commonly considered theory dealing with substituent effects was originally advanced by More O’Ferrall for β-elimination reactions. Its predictions, for the most part, agree with those of Thornton's theory even though the rationale of the two are quite different. Thornton considered the direct effect of substituents...
upon the length of bonds at the transition state whereas More O’Ferrall considered
the effect of substituents on the energy of reactants, products and possible
intermediates which, in turn, affect the energy and structure of the transition state.
This latter approach was first introduced by Hammond and applied to reactions
involving the cleavage of a single bond. Now the same principles are applied to
congerred elimination reactions with the additional consideration directed at the
possible intermediate carbanion and carbonium ion structures that would be formed
if the mechanism were not concerted, but stepwise.

More O’Ferrall begins with the basic premise that there need be no gradual
transition from an E2 mechanism with an ‘Elcb-like’ transition state to the Elcb
mechanism as a result of small structural changes in the reactants. In other words,
he proposes that at the point of mechanistic change reaction by the two
mechanisms can proceed side-by-side through transition states which, although of
the same energy, have quite different structures.

A schematic potential energy surface, which forms the basis of More O’Ferrall’s
model for predicting the influence changes in the structure of reactants has on the
transition state structure of an elimination process, is shown in Figure 2. In this
model, the surface is considered to be of such flexibility as to transmit across its
length and breadth the effect of energy changes at any point. As a result, the
structure of the transition state for a concerted elimination process is influenced,
not only by the relative stabilities of reactants and products, but also by the
stabilities of the reactive intermediates that would be formed if the mechanism
were not concerted.

By reference to this representation of the potential energy surface, it can be seen
that an increase in the stability of the elimination product, R, will correspond to a
‘downward pull’ at the top right-hand corner of the figure. As a result, the energy
of the transition state is decreased and its structure moves towards the bottom
left-hand corner, that is, toward point ‘b’ and the transition state becomes more
reactant-like. On the other hand, an increase in the stability of the carbanion, R−,
will correspond to a downward pull at the bottom right-hand corner of the surface, again resulting in a lower transition-state energy but a transition-state structure which is closer to that of the carbanion, point 'c' in the figure. It is seen that the transition state has a greater \( \text{C}_9 - \text{H} \) and shorter \( \text{C}_a - \text{X} \) bond distance than in the transition state on the potential energy surface represented by point 'a' on the figure.

II. KINETIC ISOTOPE EFFECTS IN NUCLEOPHILIC SUBSTITUTION REACTIONS INVOLVING ISOTOPICALLY LABELLED AMINES AND QUATERNARY AMMONIUM SALTS

Although most of the isotopically labelled quaternary ammonium salts have been used to elucidate the mechanisms and structures of the transition states of elimination reactions, isotopes have also been used to study the Menschutkin reaction and the reverse process. The Menschutkin reaction is a nucleophilic substitution reaction in which an amine displaces a leaving group 'X' to form a quaternary ammonium salt (equation 16). In the reverse of the Menschutkin reaction, an amine is removed from a quaternary ammonium salt in a nucleophilic substitution reaction (equation 17). Of these two reactions, the Menschutkin reaction has been the most widely studied.

\[
\begin{align*}
\text{R}_3\text{N} + \text{R} - \text{X} & \quad \rightarrow \quad \text{R} - \text{NR}_3 \quad \text{X}^- \\
\text{R} - \text{NR}_3 + \text{X}^- & \quad \rightarrow \quad \text{R} - \text{X} + \text{NR}_3
\end{align*}
\]

A. Isotope Effects in the Menschutkin Reaction

Several types of primary and secondary kinetic isotope effects have been used to probe the properties of the transition states of Menschutkin reactions. Primary carbon\(^{32,33}\) and chlorine kinetic isotope effects\(^{34,35}\) have been used to determine the structural changes that occur at the \( \alpha \)-carbon and in the \( \alpha \)-carbon–leaving group bond in the transition state for these reactions. In addition, a few primary nitrogen (incoming group) kinetic isotope effects have been determined\(^{36}\). Most of the work, however, has involved the use of secondary hydrogen–deuterium kinetic isotope effects. In these studies, the isotopes have been placed at several different positions in the nucleophile and in the substrate\(^{37,44}\).

Bender and Hoeg\(^{32}\) reported the first kinetic isotope effect in a Menschutkin reaction in 1957. These workers found large primary carbon-14 kinetic isotope effects of 1.10 and 1.14 in the Menschutkin reaction between methyl-\(^{14}\)C iodide and (i) trimethylamine and (ii) pyridine in benzene. The large isotope effects indicate that these processes occur by the one-step (S\(_{N2}\)) mechanism\(^{45}\).

1. Secondary hydrogen–deuterium kinetic isotope effects

The first secondary hydrogen–deuterium kinetic isotope effects in Menschutkin reactions were reported simultaneously in 1959 by Lewis\(^{37}\) and by Simon and Palm\(^{44}\). Lewis reported an inverse secondary hydrogen–deuterium kinetic isotope effect of 0.93 in the reaction between diethyl(ethyl-\( \alpha \)-d\(_{2}\))amine and methyl \( p \)-bromobenzensulphonate. The work by Simon and Palm substantiated the inverse isotope effects reported by Lewis. These workers reported an inverse secondary hydrogen–tritium kinetic isotope effect 0.96/tritium in the reaction of methyl-\( \text{t}_1 \)
iodide and pyridine in benzene. In fact all of the secondary hydrogen–deuterium kinetic isotope effects measured in Menschutkin reactions have been inverse.

Extensive work by Brown and coworkers\textsuperscript{39,46} and by Kaplan and Thornton\textsuperscript{40} has illustrated that the secondary hydrogen–deuterium kinetic isotope effects in Menschutkin reactions are primarily caused by the steric crowding in the transition states of these $S_{N}2$ reactions. Brown and McDonald\textsuperscript{39} measured the secondary hydrogen–deuterium kinetic isotope effects in the reactions between 4-methyl-d$_3$-, 3-methyl-d$_3$-, 2-methyl-d$_3$-, 2,6-dimethyl-d$_6$-, 4-deutero- and perdeutero-pyridine with alkyl iodides in nitrobenzene. Their results are given in Table 1.

Brown and McDonald attributed the inverse isotope effects to an increased steric crowding in the transition state. Replacing hydrogen by deuterium in the nucleophile can have two different effects; an inductive and/or a steric effect on the reaction. The inductive effect occurs because deuterium is more electron-donating than hydrogen and will therefore increase the electron density (nucleophilicity) of the pyridine and reduce the partial positive charge on the nitrogen in the transition state. Thus, the deuterated pyridine should react faster in the Menschutkin reaction. The steric effect arises because C–D bonds are shorter than C–H bonds. Thus, a change from hydrogen to deuterium will reduce the steric crowding in the transition state and pyridines with deuterium at the 2 and/or 6 positions should react faster than undeuterated pyridines.

The results of Brown and McDonald\textsuperscript{39} indicate that the inductive effect is less important than the steric effect in determining the magnitude of the isotope effects. The virtual absence of a isotope effect when the CD$_3$ group is placed in the 3- or 4-position of pyridine and the larger isotope effect in the 2-methyl-d$_3$-pyridine reaction cannot be explained by the inductive effect. In fact, the $pK_a$s of 4-methyl- and 2-methyl-pyridine are almost identical (6.02 and 5.97 respectively) and thus the inductive effect from the CD$_3$ group is essentially the same in both pyridines. Obviously, if inductive effects were predominant, the isotope effects for the reactions involving the 4-methyl- and the 2-methyl-pyridines would be almost identical. The much larger isotope effect in the reaction between 2-methylpyridine and methyl iodide, is therefore, only consistent with the steric explanation, i.e. the deuterated nucleophile reduces the steric crowding in the $S_{N}2$ transition state and reacts faster than the undeuterated amine. In addition, the isotope effect in the 2,6-dimethylpyridine reaction is more than twice the isotope effect in the

<table>
<thead>
<tr>
<th>Pyridine</th>
<th>Substrate</th>
<th>Temp ($^\circ$C)</th>
<th>$k_{H}/k_{D}$\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Methyl-d$_3$-</td>
<td>CH$_3$I</td>
<td>25</td>
<td>0.999</td>
</tr>
<tr>
<td>3-Methyl-d$_3$-</td>
<td>CH$_3$I</td>
<td>25</td>
<td>0.991</td>
</tr>
<tr>
<td>2-Methyl-d$_3$-</td>
<td>CH$_3$I</td>
<td>25</td>
<td>0.971</td>
</tr>
<tr>
<td>2,6-Dimethyl-d$_6$-</td>
<td>CH$_3$I</td>
<td>25</td>
<td>0.913</td>
</tr>
<tr>
<td>4-Deutero-</td>
<td>CH$_3$I</td>
<td>25</td>
<td>0.988</td>
</tr>
<tr>
<td>2,3,4,5,6-Pentadeutero-</td>
<td>CH$_3$I</td>
<td>25</td>
<td>0.970</td>
</tr>
<tr>
<td>2-Methyl-d$_3$-</td>
<td>C$_2$H$_5$I</td>
<td>75</td>
<td>0.965</td>
</tr>
<tr>
<td>2,6-Dimethyl-d$_6$-</td>
<td>C$_2$H$_5$I</td>
<td>75</td>
<td>0.933\textsuperscript{b}</td>
</tr>
<tr>
<td>2-Methyl-d$_3$-</td>
<td>(CH$_3$)$_2$CHI</td>
<td>100</td>
<td>0.945\textsuperscript{c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The isotope effects are accurate to $\pm$ 1%.

\textsuperscript{b}This isotope effect is accurate to $\pm$ 2%.

\textsuperscript{c}This isotope effect is accurate to $\pm$ 3%.
28. Isotopically labelled amino, quaternary ammonium and nitro compounds

2-methylpyridine-methyl iodide reaction. This is also more consistent with a steric origin for the isotope effect. The inverse isotope effect observed in the perdeuteropyridine reaction is also attributed to reduced steric crowding in the transition states with deuterium atoms at the 2- and 6-positions of pyridine. Finally, the larger (more inverse) isotope effects in the reactions with the more sterically crowded substrates, ethyl iodide and isopropyl iodide with the same nucleophile, are only consistent with the steric origin for the isotope effects.

Kaplan and Thornton came to the same conclusion. These workers found a large inverse secondary hydrogen-deuterium kinetic isotope effect ($k_H/k_D = 0.883 \pm 0.008$) in the Menschutkin reaction between $N,N'$-dimethyl-d$_6$-aniline and methyl $p$-toluenesulphonate in nitrobenzene at 51.3°C. Although the inductive effect of the deuteriums in the $N$-methyl groups would increase the electron density on the nitrogen and reduce the positive charge on the nitrogen atom in the transition state, Kaplan and Thornton preferred a steric explanation for two reasons. Firstly, the smaller (less inverse) isotope effect of 0.952 in the corresponding reaction between dimethyl-d$_6$-phenyl phosphine and methyl $p$-toluenesulphonate is consistent with the lower steric crowding in the transition state in the phosphine reaction where the CD$_3$ groups on the larger phosphorus atom are further away from the methyl group of the substrate. Secondly, a vibrational analysis of the reactants and products from the Menschutkin reaction also convinced Kaplan and Thornton that the isotope effect was primarily caused by steric effects. The C—H and C—D stretching frequencies were the same in the reactants and products whereas the bending force constants for these bonds were significantly different. This indicated that the isotope effect resulted from changes that occurred in the bending vibrations in going to the transition state. This is only consistent with a steric origin for the isotope effect. Finally, this was confirmed since the secondary hydrogen-deuterium kinetic isotope effect measured experimentally was the same as the isotope effect calculated using the force constants found in the vibrational analysis.

The steric origin for the inverse secondary hydrogen-deuterium kinetic isotope effects in the Menschutkin reaction was also substantiated by the isotope effects on the enthalpies of reaction ($\Delta H_H^\circ - \Delta H_D^\circ$) for the formation of the acid-base complex between methyl-d$_3$-substituted pyridines and boron trifluoride in nitrobenzene (equation 18)

\[
\begin{align*}
\text{CD}_3 \text{N} + \text{BF}_3 & \rightleftharpoons \text{CD}_3 \text{N}^+ \tilde{\text{B}}\text{F}_3 \\
\end{align*}
\] (18)

This reaction is relevant to this discussion because the nitrogen is effectively quaternized just as it is in the Menschutkin reaction. The isotope effects on the enthalpy of reaction were measured for the reactions involving 4-methyl-d$_3$, 3-methyl-d$_3$, 2-methyl-d$_3$ and 2,6-dimethyl-d$_6$-pyridines. The isotope effects on the enthalpy of reaction were effectively zero ($-0.04$ and $-0.10$ kcal/mol) for the reaction of the 4-methyl- and 3-methyl-pyridines, whereas a positive and significant isotope effect of 0.16 kcal/mol was observed for the reaction involving the 2-methylpyridine. The isotope effect for the 2,6-dimethylpyridine reaction was even larger (0.23 kcal/mol). Although these isotope effects are equally consistent with an inductive and a steric explanation, Brown's group rationalized the isotope effects using an argument based on steric crowding. The steric explanation was favoured for three reasons. Firstly, the failure to observe an isotope effect in the 4-methylpyridine reaction when a significant
isotope effect is observed in the 2-methylpyridine reaction, is only consistent with a steric isotope effect. This is because 4-methyl- and 2-methyl-pyridine have the same $pK_a$ and therefore the same inductive effect. Secondly, there was no isotope effect in the reaction between 2,6-dimethylpyridine and diborane (equation 19). An

$$\text{N} + \frac{1}{2} \text{B}_2\text{H}_6 \rightleftharpoons \text{N} \text{BH}_3 \quad (19)$$

$$L = H, D$$

isotope effect of close to 0.26 kcal/mol would have been expected if the inductive effect was the major cause of the isotope effect. Brown and coworkers suggested that there was no isotope effect in this reaction because the shorter B—H bonds on the boron are too short to interfere stericly with the 2- and 6-methyl groups on the pyridine ring. Finally, the steric origin of the isotope effect was also favoured because deuteration in both the acid and base components increased the stability of the addition compound. Deuterating the 2- and 6-methyl groups in the nucleophile or base (2,6-dimethylpyridine) lowers the enthalpy of formation of the complex with trifluoroboron (equation 18). Substituting deuterium in the methyl groups of trimethylboron (the acid portion of the complex) increases the stability of the equilibrium complex with trimethylamine (equation 20). In fact, the equilibrium

$$(\text{CH}_3)_3\text{N} + \text{B(\text{CL})}_3 \rightleftharpoons (\text{CH}_3)_3\text{N}:\text{B(\text{CL})}_3 \quad (20)$$

$$L = H, D$$

constant is 1.25 times larger for the deuterated trimethylboron–trimethylamine reaction. Obviously, the inductive effect cannot explain the increased stability of the complexes when the more electron-donating deuterium is placed both in the acid and in the base components. The steric effect is, however, consistent with the results.

Leffek and MacLean measured the secondary hydrogen–deuterium kinetic isotope effects with the isotope in the substrate. The actual reactions involved treating methyl-$d_3$ iodide with tertiary aliphatic amines or pyridines in benzene at 50°C. The isotope effects were all inverse. They varied over a narrow range, i.e. from 0.88 to 0.90 for the tertiary aliphatic amines: triethylamine (0.88), tripropylamine (0.89) and tributylamine (0.90). The isotope effects in the pyridine reactions increased in magnitude from 0.92 for pyridine to 0.88 for 2-methylpyridine and 2,6-dimethylpyridine. In the pyridine series, larger (more inverse) isotope effects are found in the reactions with the more sterically hindered amines, 2-methylpyridine and 2,6-dimethylpyridine. It is surprising however, that the isotope effects are identical for the 2-methyl- and 2,6-dimethylpyridine reactions. Unfortunately, the opposite trend is observed when the nucleophiles are tertiary amines. The smallest inverse isotope effect is obtained when the most sterically hindered nucleophile (tri-$n$-butylamine) is used. Although, the largest (most inverse) kinetic isotope effect would be expected in the reaction with the most sterically hindered amine, the steric crowding in the transition state (magnitude of the isotope effect) is dependent on two factors. An increase in the bulk of the reacting amine would increase the frequency of the C—H out-of-plane bending vibrations in the transition state (this assumes that there is no change in the $\alpha$-carbon–nucleophile and $\alpha$-carbon–leaving-group transition-state bond lengths)
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and lead to a more inverse isotope effect. Secondly, a more open (looser) transition state with longer nucleophile-α-carbon and/or α-carbon-leaving-group bonds would reduce the frequency of the C—H out-of-plane bending vibrations in the transition state and lead to a less inverse (smaller) kinetic isotope effect. A different balance between these two factors could be responsible for the different trends observed in the two series of reactions.

Leffek and MacLead also measured the temperature dependence of the rate constants for reactions of deuterated and undeuterated methyl iodide with 2-methylpyridine. To their surprise, they found a larger isotope effect on the entropy of activation term $T(\Delta S^0_0 - \Delta S^0_1) = 75$ cal/mol at 300 K than on the enthalpy of activation term $(\Delta H^0_0 - \Delta H^0_1) = -2$ cal/mol. These results suggested that the isotope effect was not caused by changes in the vibrational energies of the C—H and C—D bonds (steric effects). Vibrational changes would lead to a significant isotope effect on the enthalpy of activation term. Although it was realized that the small change in $\Delta H^e$ could arise from a cancellation of changes in the vibrational energies, the authors suggested that the isotope effect was more likely caused by differences in solvation or differences in the internal rotation of the CH$_3$ and CD$_3$ groups in the transition state.

In an extension of this work, Leffek and Matheson measured the temperature dependence of the secondary hydrogen-deuterium kinetic isotope effect on the reaction between dimethyl-d$_6$-aniline and methyl p-toluenesulphonate in nitrobenzene. This reaction was chosen because Kaplan and Thornton had concluded that the secondary hydrogen-deuterium kinetic isotope effect in this reaction was primarily determined by steric effects on the C—H out-of-plane bending vibrations in the transition state. The results indicated that this isotope effect was indeed enthalpy-controlled, i.e. $(\Delta H^0_0 - \Delta H^0_1)$ was equal to $-134$ cal/mol whereas $T(\Delta S^0_0 - \Delta S^0_1)$ was only equal to $-45$ cal/mol at 300 K. This result is consistent with a steric origin for the isotope effects in this Menschutkin reaction. In fact, Leffek and Matheson concluded that the magnitudes of the hydrogen-deuterium kinetic isotope effects in all nonsolvolytic $S_N2$ reactions were determined by changes in steric crowding in going from the reactants to the transition state.

Leffek and Matheson also examined the effect of solvent on the secondary hydrogen-deuterium kinetic isotope effects in the Menschutkin reaction between pyridine and methyl-d$_3$ iodide at 50°C. As expected, all the isotope effects were inverse; they varied from 0.919 in benzene to 0.891 in nitrobenzene to 0.882 in ethanol to 0.857 in 2-butanone. This change in isotope effect was attributed to differences in the solvation of the developing charges on the nitrogen and iodine atoms in the transition state and to a change in transition-state structure. In fact, Leffek and Matheson proposed that earlier transition states would be observed when the reaction was carried out in a solvent that interacted more strongly with the developing charges. This solvation was thought to increase the steric crowding around the C—H bonds in the transition state. This would increase the energy of the C—H out-of-plane bending vibrations in the transition state and lead to a more inverse isotope effect. Presumably the less inverse isotope effect in ethanol occurs because ethanol, which solvates the developing iodide ion by hydrogen bonding, would increase the steric crowding around the α-carbon less than 2-butanone which solvates both developing charges by an ion—dipole interaction. Finally, it is interesting to note that these results are consistent with the solvation rule for $S_N2$ reactions which predicts that the structure of Menschutkin transition states are solvent-dependent.

Leffek and Matheson also measured the secondary alpha, beta and gamma hydrogen-deuterium kinetic isotope effects in the Menschutkin reactions of several
different alkyl halides and pyridine in nitrobenzene. The secondary alpha hydrogen–deuterium kinetic isotope effects for primary (methyl and ethyl) substrates were inverse regardless of the leaving group. The isotope effects were less inverse or zero for isopropyl compounds. The secondary alpha hydrogen–deuterium kinetic isotope effects decrease (become less inverse) as the substrate become more highly substituted at the α-carbon because (i) the out-of-plane bending vibrations would be stiffer in the initial state (the zero-point energy difference would be greater in the initial state) and (ii) because the transition state is looser (longer nucleophile–α-carbon and/or α-carbon–leaving-group bonds when the α-carbon is more highly substituted). The latter effect leads to lower energy Cα–H out-of-plane bending vibrations and reduces the zero-point energy difference in the transition state. Both effects indicate that smaller (less inverse) kinetic isotope effects should be observed when the α-carbon is more highly substituted and this trend has been observed.

The magnitude of the secondary alpha hydrogen–deuterium kinetic isotope effects in the reactions involving methyl compounds decreased in magnitude from 0.962 when the leaving group was iodide ion (the best leaving group from a kinetic point of view) to 0.975 when bromide ion was the leaving group to 0.994 when the leaving group was tosylate (the poorest leaving group). The authors suggested that a more crowded transition state exists in the reactions with the more polarizable (better) leaving group. This suggests that there is a tighter transition state with a better leaving group. This anti-Hammond response to changing to a better leaving group in SN2 reactions has been reported by Westaway and Ali.

Unlike the secondary alpha deuterium kinetic isotope effects, the secondary beta hydrogen–deuterium kinetic isotope effects for the reactions of ethyl-β-d3, propyl-β-d2 and isopropyl-β-d6 halides with pyridine are small but normal. They vary from 1.00/β-D to 1.015/β-D. The larger isotope effects are observed in the isopropyl halide reactions where hyperconjugation is more important. This occurs because the transition states for the isopropyl halide reactions are looser and have a larger amount of positive charge on the α-carbon than the transition states for the ethyl and propyl halides. It is worth noting that the secondary beta hydrogen–deuterium kinetic isotope effect is significantly smaller when the substrate is isopropyl iodide (kH/kD per β-D = 1.005) than when the substrate is isopropyl bromide. Again, the smaller isotope effect and tighter transition state is observed with the better leaving group.

Finally, the secondary gamma hydrogen–deuterium kinetic isotope effect in the reaction between propyl-γ-d3 bromide and pyridine was too small to measure. The actual isotope effect was kH/kD = 0.995 or 0.9985 per γ-D.

Finally, Vitullo, Grabowski and Sridharan have determined how substituents in the alkyl halide influence the magnitude of the secondary alpha hydrogen–deuterium kinetic isotope effects for Menschutkin reactions. These workers measured the isotope effects for the reaction of the p-methoxy-, p-hydrogen- and p-nitro-benzyl bromides with triethylamine in 80% (V/V) dioxane–water at 25°C. The isotope effect decreased from 1.014 ± 0.003 for p-methoxybenzyl bromide to 0.993 ± 0.006 for benzyl bromide to only 0.988 ± 0.009 for the reaction of p-nitrobenzyl bromide. The decrease in the magnitude of the isotope effect indicates a more crowded transition state when a more electron-withdrawing group is on the benzene ring of the substrate.

2. Primary nitrogen entering-group kinetic isotope effects

Bourns and Hayes measured the primary nitrogen (entering-group) kinetic
isotope effects in the Menschutkin reaction between tertiary aliphatic amines and alkyl bromides and iodides in benzene (Table 2).

Although all of these nitrogen kinetic isotope effects are very close to zero, they are still significant. Bigeleisen\(^{52}\) was able to simplify the heavy-atom kinetic isotope effect equation by applying several valid approximations to the basic expression shown in equation (4). The final expression (equation 21)\(^{52,53}\), shows that the nitrogen heavy-atom kinetic isotope effects measured by Bourns and Hayes are determined by the magnitude of two terms:

$$\frac{k^{14}}{k^{15}} = \left(\frac{\mu^{15}}{\mu^{14}}\right)^{1/2} \left[ 1 + \sum_i^{3n-6} G(u_i)\Delta u_i - \sum_i^{3n-7} G(u_i^\dagger)\Delta u_i^\dagger \right]$$  \hspace{1cm} (21)

where \(\mu^{14}\) and \(\mu^{15}\) are the effective masses of the transition state containing the \(\text{C}^{14}\text{N}\) and \(\text{C}^{15}\text{N}\) bonds, respectively. The \(\Sigma^{3n-6} G(u_i)\Delta u_i\) term gives the difference in the vibrational energies of the \(^{14}\text{N}\) and \(^{15}\text{N}\) bonds in the reactants. The \(\Sigma^{3n-7} G(u_i^\dagger)\Delta u_i^\dagger\) term is the corresponding term for the \(^{14}\text{N}\) and \(^{15}\text{N}\) bonds in the transition state\(^{52}\). The first term is the temperature-independent term. It is always greater than one. The second term (in the square brackets) is the temperature-dependent term because its magnitude is determined by the isotope effect on the individual vibrational frequencies of the initial and transition states. For an entering-group kinetic isotope effect, the \(\Sigma^{3n-6} G(u_i)\Delta u_i\) term will be determined by the stretching and bending frequencies of the \(\text{C}^{\alpha}\text{N}\) bonds in the free amine (there is no bond between the \(\alpha\)-carbon of the alkyl halide and the nitrogen of the amine). In the transition state however, the \(\alpha\)-carbon–nitrogen bond has partially formed and changing the isotope will also affect the vibrational frequencies of the partially formed \(\text{C}_\cdot\cdot\cdot\text{N}^+\) bond. As a result, the \(\Sigma^{3n-7} G(u_i^\dagger)\Delta u_i^\dagger\) term will be larger than the \(\Sigma^{3n-6} G(u_i)\Delta u_i\) term and the temperature-independent factor will be less than unity. Moreover, more complete bond formation in the transition state increases the value of the \(\Sigma^{3n-7} G(u_i^\dagger)\Delta u_i^\dagger\) term and decreases the magnitude of the temperature-dependent term. This would in turn, lead to a smaller isotope effect. Finally, since the magnitude of an entering-group kinetic isotope effect is determined by the magnitude of the temperature-independent term and the temperature-dependent term, an isotope effect of approximately one can still be found for \(S_n2\) reactions where the \(\alpha\)-carbon–nitrogen bond is partially formed in the transition state. The entering-group nitrogen kinetic isotope effects measured by Bourns and Hayes\(^{36}\) are very small. This indicates that the temperature-independent term and the temperature-dependent term nearly cancel for these reactions. This means that the temperature-dependent term is significantly less than one and that there is substantial \(\alpha\)-carbon–nitrogen bond formation in the transition states of these reactions.
It is interesting to note that slightly larger isotope effects are observed in the alkyl iodide reactions. Since the temperature-independent factor for the ethyl bromide reaction must be equal to or larger than that for the reactions involving the alkyl iodides, the temperature-dependent term must be smaller for the ethyl bromide–trimethylamine reaction. The smaller isotope effect in the ethyl bromide–trimethylamine reaction means that the α-carbon–nucleophile transition-state bond is longer in the reactions with the best leaving group (iodide ion). This conclusion is contrary to the results obtained in other studies by Leffek and Matheson and Ballisteri and coworkers in the Menschutkin reaction and by Westaway and Ali in the reverse of the Menschutkin reaction. It is worth noting however, that both the nucleophile and the leaving group are different in the trimethylamine–ethyl bromide reaction than those in the ethyl iodide reaction where the nucleophile was triethylamine. Perhaps the change in nucleophile is responsible for this unexpected behaviour.

3. Chlorine leaving-group kinetic isotope effects

Leaving-group primary chlorine kinetic isotope effects have also been used to probe the structure of the transition states of Menschutkin reactions. Le Noble and Miller measured the chlorine kinetic isotope effect in the reactions between pyridine or 2,6-dimethylpyridine and methyl chloride in bromobenzene at 100°C. The isotope effects were \( k^{35}/k^{37} = 1.00355 \pm 0.0008 \) for the pyridine reaction and \( 1.00384 \pm 0.00026 \) for the reaction involving 2,6-dimethylpyridine. These isotope effects, which are significantly different at the 95% confidence level, were attributed to a longer C–Cl transition-state bond (a more product-like transition state) in the 2,6-dimethylpyridine reaction. Le Noble and Miller concluded that the transition state of a Menschutkin reaction will be later (more product-like) when a more sterically crowded amine is used as the reactant.

These results are opposed to the earlier results of Swain and Hershey, who found a larger chlorine kinetic isotope effect and concluded that the transition state was later or more product-like when a less sterically hindered amine was used as the nucleophile in the Menschutkin reaction. The chlorine isotope effect \( (k^{35}/k^{37}) \) was only \( 1.00640 \pm 0.00009 \) in the more sterically crowded Menschutkin reaction between triethylamine and methyl chloride whereas a larger isotope effect of \( 1.00709 \pm 0.00011 \) was found for the reaction of the less crowded amine, quinuclidine.

In Swain and Hershey's experiments, care was taken to use nucleophiles with the same base strength, i.e. the same nucleophilicity. Unfortunately, this is not the case in the study reported by Le Noble and Miller. Brown and Mihm found that the pK\(_a\) of pyridine was 5.15 whereas the pK\(_a\) of 2,6-dimethylpyridine was 6.75. Thus, 2,6-dimethylpyridine is a much better nucleophile than pyridine and the changes in the magnitude of the chlorine isotope effect reported by Le Noble and Miller cannot be attributed entirely to an increase in the steric crowding in the transition state. In fact, it seems more likely that the change in nucleophilicity rather than the change in steric crowding is the major cause of the change in the chlorine leaving-group kinetic isotope effect.

4. Carbon kinetic isotope effects

Yamataka and Ando have measured the primary carbon-14 kinetic isotope effects in several Menschutkin reactions between para-substituted N,N-dimethylanilines (3) and benzyl para-substituted benzenesulphonates (4) in
Isotope-effect theory indicates that the magnitude of the carbon isotope effects in an $S_N2$ reaction is a maximum when the transition state is symmetrical and that smaller isotope effects are observed when the transition states are unsymmetrical, i.e. the magnitude of the isotope effect follows the Melander and Westheimer treatments$^{1,13}$ and passes through a maximum in the same way that primary hydrogen–deuterium kinetic isotope effects in proton-transfer reactions vary with transition-state structure.

The carbon-14 kinetic isotope effects for the reactions between $N,N$-dimethyl-$p$-toluidine ($Y = CH_3$) and several benzyl $para$-substituted benzenesulphonates in acetone at $45^\circ C$ pass through a maximum when the $para$ substituent on the leaving group is hydrogen (Table 3).

Thus, the transition state is symmetrical when the leaving group is benzenesulphonate and the transition states with more electron-donating and more electron-withdrawing groups are less symmetrical. The problem is to decide which transition states are product-like and which are reactant-like. In spite of the authors' claims it is impossible to determine with any certainty the structure of the unsymmetrical transition states without additional information such as that provided by leaving-group or incoming-group kinetic isotope effects.

We have used Yamataka and Ando's rate constants to calculate the Hammett $\rho$ values observed when the $para$ substituent in the incoming nucleophile is changed for each leaving group. In fact, the Hammett $\rho$ values obtained by substitution in the nucleophile decrease as a more electron-withdrawing substituent is placed in the leaving group, i.e. the $\rho$ value decreases from $-3.57$ for $X = CH_3$ to $-2.54$ for $X = H$ to $-2.33$ for $X = Cl$ to $-1.60$ for $X = m$-$NO_2$. Since a larger $\rho$ value is indicative of a transition state with a more complete nucleophile–$\alpha$-carbon bond$^{50}$, it would appear that the transition states with electron-withdrawing substituents $X'$ have longer nucleophile–$\alpha$-carbon bonds and are more reactant-like, whereas the

<table>
<thead>
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<th>X</th>
<th>$p$-$CH_3$O</th>
<th>$p$-$CH_3$</th>
<th>H</th>
<th>$p$-$Cl$</th>
<th>$m$-$NO_2$</th>
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<tr>
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<td>1.140</td>
<td>1.142</td>
<td>$-$</td>
</tr>
<tr>
<td>$p$-$CH_3$</td>
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<td>1.162</td>
<td>1.149</td>
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<tr>
<td>H</td>
<td>$-$</td>
<td>$-$</td>
<td>1.135</td>
<td>1.143</td>
<td>1.158</td>
</tr>
<tr>
<td>$p$-$Br$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>1.139</td>
<td>$-$</td>
</tr>
<tr>
<td>$m$-$NO_2$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>1.127</td>
</tr>
</tbody>
</table>

*The error limits range from ±0.001 to ±0.008. Most of the errors are ±0.002 and ±0.003.*

28. Isotopically labelled amino, quaternary ammonium and nitro compounds acetone at 35 and 45°C (equation 22).
nucleophile–α-carbon bonds are more completely formed in the transition states with electron-donating substituents. The shorter α-carbon–nucleophile bonds that are observed when electron-donating groups are present means that product-like transition states exist in these reactions. These results suggest that changing to a better leaving group (‘X’ is more electron-withdrawing) leads to a more reactant-like transition state for the Menschutkin reaction. This behaviour is consistent with the prediction based on Hammond’s thermal postulate, Thornton’s reacting bond rule and the More O’Ferrall-type of energy surface as applied to $S_N2$ reactions.

A consideration of the above conclusions enabled us to predict the structure of the other transition states in the reactions studied by Yamataka and Ando. An examination of the other transition states showed the opposite trend when the leaving group was changed. In fact, changing to a better leaving group (X is more electron-withdrawing) leads to a more product-like transition state in the reaction series where the nucleophile is $N,N$-dimethyl-p-anisidine and $N,N$-dimethylaniline. The changes in transition-state structure in these two series of reactions agree with the changes found in studies by Leffek and Matheson and by Westaway and Ali, but do not agree with the predictions based on Hammond’s postulate, Thornton’s rule or the More O’Ferrall energy surface.

The carbon-14 kinetic isotope effects associated with changing the nucleophile in three reaction series (X = H, Cl and $m$-NO$_2$) also display curved (Westheimer-type) plots, i.e. pass through a maximum as a more electron-withdrawing substituent is placed on the nucleophile.

Extending the results described above to these transition states has led us to conclude that adding a more electron-withdrawing substituent to the nucleophile (going to a poorer nucleophile) leads to a more product-like transition state in the reaction series where X = m-NO$_2$, but to more reactant-like transition states in the series where X = Cl, H and CH$_3$. Only the reactions where the leaving group is $m$-nitrobenzene sulphonate follow the predictions based on Hammond’s postulate, Thornton’s rules or More O’Ferrall’s theory of substituent effects.

Finally, Yamataka and Ando concluded that the transition-state structure was influenced more strongly by changing the substituent ‘Y’ on the nucleophile than by changing the substituent ‘X’ on the leaving group. This is reasonable because the substituent is closer to the reacting atom in the nucleophile (four bonds) whereas it is five bonds away from the reacting atom in the leaving group.

Bender and Hocg and Buist and Bender have measured carbon-14 kinetic isotope effects in the Menschutkin reactions between methyl iodide and several different amines. These large isotope effects which are in the same range as those measured by Yamataka and Ando, i.e. between 1.10 and 1.14, do not shed any additional light on the transition states or properties of the Menschutkin reaction and will not be discussed in detail.

**B. Kinetic Isotope Effects in Nucleophilic Substitution Reactions of Quaternary Ammonium Salts**

Kinetic isotope effects have also been used to determine the mechanisms and to study substituent effects on the transition-state structure of the nucleophilic substitution reactions of quaternary ammonium salts. Ko and Leffek reported the first kinetic isotope effect in a nucleophilic substitution reaction of a quaternary ammonium salt in 1971. These workers measured the secondary alpha hydrogen–deuterium kinetic isotope effects in the reaction between
28. Isotopically labelled amino, quaternary ammonium and nitro compounds

benzyldimethylphenylammonium ion and bromide ion in chloroform and acetone (equation 23).

\[
\begin{align*}
\text{PhCl}_2 - N(CH_3)_2 Ph \text{Br}^- & \quad \longrightarrow \quad \text{PhCl}_2 \text{Br} + (CH_3)_2 NPh \\
L = H, D
\end{align*}
\]

They found very large isotope effects of 1.20 (1.10/α-D) in acetone and 1.25(1.12/α-D) in chloroform. Because the maximum secondary alpha hydrogen–deuterium kinetic isotope effect for an SN2 reaction was thought to be 1.04 per α-D^{18}, and because the corresponding 1-phenylethylidimethylphenylammonium bromide reacted 22 times faster than the benzyl compound^{9}, Ko and Leffek suggested that the benzyl compound reacted by way of the ‘ionic internal nucleophilic substitution’ mechanism shown in equation (24)^{58,59}. The carbonium ion is produced in the slow step within a triple-ion complex. The ion pair collapses to form product in the fast step of the reaction.

\[
\begin{align*}
\text{PhCH}_2 \text{N}((CH_3)_2 \text{Ph})_2 \text{Br}^- \quad \longrightarrow \quad [(\text{PhCH}_2 \text{N}((CH_3)_2 \text{Ph})_2 \text{Br})^+] + [(\text{PhCH}_2 \text{N}((CH_3)_2 \text{Ph} \text{Br})_2)^-] \\
\text{PhCH}_2 \text{N}((CH_3)_2 \text{Ph})_2 \text{Br}^- \quad \text{slow} \quad \text{fast} \\
\text{PhCH}_2 \text{Br} \quad + \quad (CH_3)_2 NPh \\
\text{PhCH}_2 \text{N}((CH_3)_2 \text{Ph})_2 \text{Br}^- \\
\text{PhCH}_2 \text{N}((CH_3)_2 \text{Ph})_2 \text{Br}^- \\
\text{PhCH}_2 \text{Br} \quad + \quad (CH_3)_2 NPh
\end{align*}
\]

Westaway and Poirier^{50} have studied the nucleophilic substitution reaction of the same substrate, benzyldimethylphenylammonium ion, with thiophenoxide ion in N,N-dimethylformamide at 0°C. A large primary nitrogen kinetic isotope effect of 1.0200 indicated that the α-carbon–nitrogen bond was breaking in the rate-determining step of the reaction. Clean second-order kinetics, first order in the nucleophile (thiophenoxide ion) and first order in substrate, indicated that the nucleophile was also involved in the slow step of the reaction. These conclusions were also supported by other data^{16,50,60} and it was concluded that this reaction is a simple SN2 reaction (equation 25).

\[
\begin{align*}
\text{PhS}^- + \text{PhCH}_2 \text{N}((CH_3)_2 \text{Ph}) & \quad \longrightarrow \quad ([\text{PhS}^- \cdots \text{N}((CH_3)_2 \text{Ph})]^k) \\
\text{PhS}^- + \text{PhCH}_2 \text{N}((CH_3)_2 \text{Ph}) & \quad \longrightarrow \quad \text{PhSCH}_2 \text{Ph} + (CH_3)_2 NPh
\end{align*}
\]

When the secondary alpha hydrogen–deuterium kinetic isotope effect was measured in the thiophenoxide ion reaction, an unexpectedly large value of 1.179 or 1.09 per α-deuterium was observed^{16}. In fact, this isotope effect was more than twice the magnitude of the maximum value predicted for secondary alpha hydrogen–deuterium kinetic isotope effects in SN2 reactions^{16,18}. The isotope effect of 1.179 measured by Westaway and Ali^{16} is close to that measured by Ko and Leffek^{58} for the reaction of the same substrate with bromide ion in chloroform (k_H/k_D = 1.25) and in acetone (k_H/k_D = 1.20). The close agreement between these isotope effects indicates that the secondary alpha hydrogen–deuterium kinetic isotope effects are large for the nucleophilic substitution reactions of this substrate and suggests that the actual substitution process in all three reactions must occur by the same mechanism. Because the thiophenoxide ion reaction in DMF occurs by
the simple $S_N2$ mechanism, it is now believed that the actual substitution reaction with the bromide ion in chloroform and acetone occurs by an internal $S_N2$ process within the triple ion formed from two quaternary ammonium cations and one bromide ion (equation 26)\textsuperscript{16}.

\[
[(\text{PhCH}_2\text{N(CH}_3\text{)}_2\text{Ph})_2\text{Br}]^+ \\
\text{PhCH}_2\text{N(Ch}_3\text{)}_2\text{Ph} \\
\downarrow \\
\text{PhCH}_2\text{Br} + (\text{CH}_3)_2\text{NPh} + \text{PhCH}_2\text{N(Ch}_3\text{)}_2\text{Ph}
\]

The conclusion that all three substitution steps occur by way of a concerted ($S_N2$) mechanism is supported by the theoretical calculations performed by Hartshorn and Shiner\textsuperscript{17}. These workers calculated the maximum secondary alpha hydrogen–deuterium kinetic isotope effects for the ionization of methylammonium ion to methylcarbonium ion and ammonia. The calculations predicted that the isotope effect for this reaction would be 1.19 per $\alpha$-deuterium or 1.42 per $\text{CD}_2$ group. This means that the minimum secondary alpha deuterium kinetic isotope effect for the ionization of an ammonium ion (an $S_N1$ reaction with the ionization to the intimate ion pair fully rate-determining) would be $(1.19)^{0.75} = 1.14$ per $\alpha$-deuterium or 1.30 per $\text{CD}_2$ group\textsuperscript{61}.

The isotope effects for all three reactions are below this minimum value and are therefore in the range expected for an $S_N2$ mechanism. In addition, a much larger secondary alpha hydrogen–deuterium kinetic isotope effect than 1.30 would be expected for the ionization (an $S_N1$ reaction) of the benzylidimethylphenylammonium ion to yield a benzyl carbonium ion and dimethylaniline. This occurs because the $Cα-H$ and $Cα-D$ bonds in the substrate are in a very crowded environment and the $Cα-H$ out-of-plane bending vibrations, which are primarily responsible for the secondary alpha deuterium isotope effect, will be of a very high energy. This means that the zero-point energy difference between the $Cα-H$ and $Cα-D$ out-of-plane bending vibrations will be much larger for the benzylidimethylphenylammonium ion than they are for the methylammonium ion and a much larger isotope effect would be expected for the $S_N1$ reaction of the benzyl compound. Thus, it is safe to conclude that the isotope effects for the three reactions studied by Ko and Leffek\textsuperscript{58} and by Westaway and Ali\textsuperscript{16} are significantly below those expected for carbonium ion processes and the authors believe that all three of these substitution reactions occur by the concerted $S_N2$ mechanism.

Finally, Westaway and Ali concluded that the isotope effect for the thiophenoxide ion reaction is unexpectedly large because the extreme crowding around
the C\textsubscript{a}–H bonds is reduced in going to the S\textsubscript{N}2 transition state\textsuperscript{16}, because the C\textsubscript{a}–\textsuperscript{+}N\textsuperscript{+} bond is quite long in the transition state (the nitrogen kinetic isotope effect is approximately half of the theoretical maximum) and the very bulky leaving group has been effectively removed from the area around the C\textsubscript{a}–H bonds. Other work\textsuperscript{16,50} has shown that the S–C\textsubscript{a} bond is also long in the transition state. This means that the relief of steric crowding by removing the very bulky leaving group more than compensates for the increased steric crowding associated with the approach of the smaller nucleophile, and a large normal secondary alpha hydrogen–deuterium kinetic isotope effect is observed. Presumably, this is also the reason for the unusually large isotope effects in the reactions studied by Ko and Leffek\textsuperscript{58}. It is worth noting that these results clearly demonstrate that the magnitude of a secondary alpha hydrogen–deuterium kinetic isotope effect cannot be used blindly as a criterion of mechanism. In practice, the magnitude of the isotope effects for carbonium ion reactions may have to be established for each substrate and its leaving group.

If the actual substitution reaction between the benzylidimethylphenylammonium ion and bromide ion in chloroform and acetone occurs by way of an S\textsubscript{N}2 mechanism and the 1-phenylethyl compound reacts by the same mechanism, it is surprising that the 1-phenylethylidimethylphenylammonium ion reacts with bromide ion in chloroform (equation 27) 22.5 times faster than the benzylidimethylphenylammonium ion\textsuperscript{61}. Westaway and Joly\textsuperscript{49} have used secondary alpha and beta hydrogen–deuterium kinetic isotope effects to determine the mechanism of the nucleophilic substitution reaction between 1-phenylethylidimethylphenylammonium ion and bromide ion in chloroform.

The observed rate of the 1-phenylethylidimethylphenylammonium ion–bromide ion reaction could be faster than the rate of the benzylidimethylphenylammonium ion for any one of four reasons. The larger rate constant could be a result of (i) a slow concerted (E2) elimination followed by the rapid addition of the elimination product (HBr) to the styrene; (ii) the 1-phenylethylidimethylphenylammonium bromide reacting by an S\textsubscript{N}1 mechanism which is faster than the S\textsubscript{N}2 reaction of benzylidimethylphenylammonium bromide; (iii) the 1-phenylethyl compound reacting by an S\textsubscript{N}2 mechanism that is unexpectedly fast; and (iv) the observed rate being the sum of the rates for the elimination–addition and the substitution reactions. The three possible mechanisms are illustrated in Scheme 1.

Initially, the beta hydrogen–deuterium kinetic isotope effect was measured in an effort to distinguish between the four possible mechanisms. No styrene could be isolated from the reaction mixture and moreover, the addition of hydrogen bromide to styrene was found to be very rapid in chloroform. Thus, if the elimination–addition pathway is followed, the elimination must occur in the slow or rate-determining step of the overall reaction. This means that a \( \beta \)-hydrogen is removed in the slow step of the overall reaction and a large primary hydrogen–deuterium kinetic isotope effect of between three and seven would be expected. If the substitution occurs by way of an S\textsubscript{N}1 or an S\textsubscript{N}2 mechanism on the other hand, a secondary beta hydrogen–deuterium kinetic isotope effect would be observed. An S\textsubscript{N}1 reaction would have a secondary beta deuterium kinetic isotope effect of between 1.2 and 2.5 whereas an S\textsubscript{N}2 reaction would have an isotope effect between 0.95 and 1.1. Finally, even a small amount of elimination would lead to a reasonably large observed isotope effect; if five per cent of the reaction were to
\[
\text{Scheme 1}
\]

\[
\begin{align*}
\text{CL}_3 \text{CH}_3 + (\text{CH}_3)_2\text{N}^- & \rightarrow \text{CL}_3 \text{CHX}^+ + (\text{CH}_3)_2\text{N}^- \\
\text{CH}═\text{CL}_2 + LX + (\text{CH}_3)_2\text{N}^- & \rightarrow \text{CH}═\text{CL}_2 + L + (\text{CH}_3)_2\text{N}^- \\
\text{Cl}_3 & \rightarrow \text{Cl}_3 \\
\text{X}^- & \rightarrow \text{X}^- \\
\end{align*}
\]
The observed secondary beta hydrogen–deuterium kinetic isotope effect for this reaction was $1.144 \pm 0.0095$ per $\beta$-CD$_3$ at 25°C. This very small isotope effect clearly rules out the elimination–addition mechanism for this reaction; it also rules out the combination of elimination–addition and substitution mechanisms.

Thus, the problem is reduced to distinguishing between the $S_N1$ and $S_N2$ mechanisms. Shiner and collaborators reported that the secondary beta hydrogen–deuterium kinetic isotope effect for the $S_N1$ solvolysis of 1-phenylethyl chlorides in various solvents varied between 1.22 and 1.23 per $\beta$-CD$_3$ group. Since the leaving group is nearly removed or has been removed from the $\alpha$-carbon in the transition state, the isotope effects for $S_N1$ reactions should be the same regardless of the leaving group. Thus, the isotope effect of 1.44 per $\beta$-CD$_3$ is smaller than the expected value of 1.2 per $\beta$-CD$_3$ for an $S_N1$ reaction of 1-phenylethyl substrates.

Unfortunately, only one secondary beta hydrogen–deuterium kinetic isotope effect has been measured for an $S_N2$ reaction of a secondary substrate. Shiner and coworkers found that the isotope effect was 1.13 per $\beta$-CD$_3$ group for the $S_N2$ ethanolysis of isopropyl $p$-bromobenzenesulphonate. Although the magnitude of the isotope effect in the 1-phenylethylidimethylphenylammonium bromide reaction is closer to the magnitude of the isotope effect found in the $S_N2$ reaction than to those found for carbonium ion reactions, one cannot unequivocally conclude that the 1-phenylethyl quaternary ammonium salt reacts via the $S_N2$ mechanism.

A secondary alpha hydrogen–deuterium kinetic isotope effect was determined in an effort to remove the uncertainty concerning the mechanism. Unfortunately, this experiment did not provide a clear answer to this question. A reasonably large secondary alpha deuterium isotope effect $(k_H/k_D)_a = 1.178 \pm 0.006$ at 25°C was found. Several studies have shown that adding a methyl group to the $\alpha$-carbon increases the secondary alpha hydrogen–deuterium kinetic isotope effect by approximately four per cent for an $S_N2$ reaction. If this factor is applied to the secondary alpha hydrogen–deuterium kinetic isotope effect of 1.12 observed for the benzyl compound, the isotope effect for the $S_N2$ reaction of the 1-phenylethyl compound should be $(k_H/k_D)_a = 1.16$. Using the same factor, the minimum secondary alpha hydrogen–deuterium kinetic isotope effect for a carbonium ion reaction, i.e. an $S_N1$ reaction where the ionization step is rate-determining would be $(k_H/k_D)_a = (1.19 \times 1.04)^{0.75} = 1.18$. Again, the observed isotope effect was between the values expected for an $S_N1$ and $S_N2$ mechanism. In fact, a larger isotope effect than 1.18 would be expected for an $S_N1$ reaction of the 1-phenylethylidimethylphenylammonium bromide because the substrate is extremely crowded in the region around the $C_\alpha$–H(D) bond and the out-of-plane $C_\alpha$–H(D) bending vibration would be very high-energy. This, of course, would lead to a very large zero-point energy difference in the initial state and thus, to a minimum isotope effect of greater than 1.18. Thus, the observed isotope effect is not consistent with an $S_N1$ mechanism. The observed isotope effect could be consistent with an $S_N2$ mechanism because the increased steric crowding in the substrate of the 1-phenylethyl system is greater than that in the benzyl compound which is already very sterically crowded. This might cause the additional methyl group to increase the magnitude of the isotope effect by more than the usual four per cent.

Although the secondary alpha hydrogen–deuterium kinetic isotope effect seemed more consistent with the $S_N2$ than the $S_N1$ mechanism, it was also between the magnitudes of the kinetic isotope effects expected for the two mechanisms and it was therefore impossible to distinguish clearly between the $S_N1$ and $S_N2$ mechanisms for the 1-phenylethylidimethylphenylammonium bromide reaction. This
meant that another method of distinguishing between these mechanisms had to be found. The problem was resolved by measuring the secondary alpha and beta hydrogen–deuterium kinetic isotope effects for the nucleophilic substitution reaction between 1-phenylethylidimethylphenylammonium ion and iodide ion under the same conditions used for the bromide ion reaction (equation 28).

\[
\text{CH}_3 \quad \text{PhCHN(CH}_3\text{)}_2\text{Ph}^- \quad \overset{25^\circ C}{\longrightarrow} \quad \text{CH}_3 \quad \text{PhCH} + (\text{CH}_3\text{)}_2\text{NPh} 
\]

(28)

The rationale for measuring these isotope effects was to learn whether the nucleophile was involved in the rate-determining step of the reaction. If the 1-phenylethylidimethylphenylammonium iodide reacted by an \( S_{N1} \) mechanism with the ionization step rate-determining (this is suggested because the isotope effects are just under the minimum values expected for a carbonium ion mechanism), the nucleophile was not involved in the transition state of the rate-determining step and the secondary alpha and secondary beta hydrogen–deuterium kinetic isotope effects should be the same when the nucleophile is bromide ion or iodide ion. If the actual substitution reaction occurs by an \( S_{N2} \) mechanism on the other hand, the nucleophile is involved in the transition state of the rate-determining step and the transition-state structure and thus the magnitudes of both the secondary alpha and secondary beta hydrogen–deuterium kinetic isotope effects should be different when the nucleophile is changed from bromide ion to iodide ion. The secondary alpha and secondary beta hydrogen–deuterium kinetic isotope effects for these two reactions are given in Table 4.

<table>
<thead>
<tr>
<th>Halide ion</th>
<th>((k_{DD}/k_{DD})_\alpha)</th>
<th>((k_{DD}/k_{DD})_\beta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>1.178 ± 0.006</td>
<td>1.144 ± 0.0095</td>
</tr>
<tr>
<td>I</td>
<td>1.187 ± 0.005</td>
<td>1.169 ± 0.0125</td>
</tr>
</tbody>
</table>

A statistical analysis using the Wilcoxin test \(^64\) indicates that the secondary alpha hydrogen–deuterium kinetic isotope effects are significantly different at the 94% confidence level and that the secondary beta hydrogen–deuterium kinetic isotope effects are significantly different at the 99.9% confidence level. The different magnitudes of the isotope effects for the bromide and iodide ion reactions demonstrate conclusively that \((i)\) the nucleophile is involved in the transition state of the substitution reaction and \((ii)\) that the substitution step of the overall reaction is concerted, i.e. occurs by way of a one-step \( S_{N2} \) mechanism. Thus, the decomposition of the 1-phenylethylidimethylphenylammonium halides in chloroform occurs in two steps. The first step is the pre-equilibrium formation of a triple ion composed of two quaternary ammonium ions and a halide ion. The second step is an \( S_{N2} \) reaction within the triple-ion complex (equation 26).

The unexpectedly rapid reaction observed for the 1-phenylethylidimethylphenylammonium ion (it reacts 23 times faster than the benzylidimethylphenylammonium ion) is attributed to the greater steric crowding that exists in the 1-phenylethylidimethylphenylammonium ion. Other work \(^49\,^65\) shows that the
α-carbon–nucleophile and α-carbon–leaving-group transition-state bonds are significantly longer in the 1-phenylethyl compound than they are in the corresponding reaction of the benzyl compound. As a result, the relief of steric crowding in going to the transition state is much greater for the 1-phenylethyl compound than for the benzyl compound and the 1-phenylethyldimethylphenylammonium ion reacts faster.

Finally, a comparison of the isotope effects for the reactions between the 1-phenylethyldimethylphenylammonium ion and the bromide or iodide ion suggests that the transition state for the reaction involving iodide ion is looser than the transition state for the bromide ion reaction. The larger secondary alpha deuterium isotope effect for the iodide ion reaction (Table 4) indicates that there is less steric crowding around the α-carbon–hydrogen bonds in the transition state. Since the iodide ion is larger than the bromide ion, the smaller steric hindrance to the Cα–H out-of-plane bending vibration in the iodide ion transition state indicates that the nucleophile–α-carbon and/or the α-carbon–leaving-group bonds are longer in the transition state of the iodide ion reaction.

This conclusion is supported by the magnitudes of the secondary beta hydrogen–deuterium kinetic isotope effects for the bromide and iodide ion reactions. A loose transition state with longer nucleophile–α-carbon and/or α-carbon–leaving-group bonds would obviously have a greater positive charge on the α-carbon in the transition state. This larger charge should be delocalized to a greater extent by hyperconjugation. If this occurred, the secondary beta hydrogen–deuterium kinetic isotope effect, which is primarily a result of hyperconjugation, should be larger. This is, in fact, what is observed (Table 4). Unfortunately, the isotope effects do not indicate which of the α-carbon–nucleophile and the α-carbon–leaving-group bonds are longer in the transition state of the iodide ion reaction, and thus we cannot use these results to test the predictions based on Thornton's reacting bond rule or the More O'Ferrall-type of energy surface.

Kinetic isotope effects have also been used to illustrate how changing the leaving groups in an SN2 reaction of a quaternary ammonium salt effects the structure of the transition state. Westaway and Ali50 have measured the secondary alpha hydrogen–deuterium and the primary nitrogen (leaving-group) kinetic isotope effects in the SN2 reactions between para-substituted phenylbenzyltrimethylammonium ions and thiophenoxide ions in N,N-dimethylformamide at 0°C (equation 29). The isotope effects found for these reactions are shown in Table 5.

All of the primary nitrogen kinetic isotope effects are large. In fact, they are approximately half of the theoretical maximum nitrogen kinetic isotope effect at 0°C and indicate that there is a substantial Cα--N+ bond rupture in the transition state of all three reactions. Although the nitrogen kinetic isotope effects are not significantly different, they do increase in magnitude as a more electron-withdrawing substituent 'Z' is added to the leaving group. These isotope effects are complicated because there is some C--N+ bond formation between the nitrogen and the carbon of the phenyl ring in the transition state. The increased conjugation that occurs between the developing lone pair of electrons on the nitrogen and the carbon of the phenyl ring as a more electron-withdrawing substituent is added to the benzene ring of the leaving group means that the magnitude of the observed kinetic isotope effect will be smaller than expected for a particular amount of Cα--N+ bond rupture in the transition state. This effect, coupled with the slight increase in the observed kinetic isotope effect, has led the authors to conclude that the Cα--N+ bond is slightly longer in the transition state when a more electron-withdrawing substituent is present in the leaving group.
The magnitude of the secondary alpha hydrogen-deuterium kinetic isotope effect increases as a more electron-donating substituent ‘Z’ is added to the leaving group. Changing the substituent ‘Z’ in the leaving group would not be expected to influence the $C_a-H(D)$ out-of-plane bending vibrations in the substrate because the point of structural change occurs too far away (six bonds) from the $\alpha$-carbon. This means that the magnitudes of these isotope effects are determined by the structure of the transition state. The magnitude of secondary alpha hydrogen-deuterium kinetic isotope effects is primarily determined by the $C_a-H(D)$ out-of-plane bending vibrations. The energy (frequency) of these vibrations would be increased if either or both of the nucleophile and the leaving group are closer to the $\alpha$-carbon. This suggests that the magnitude of the isotope effect would be related to the nucleophile–leaving-group distance in the transition state, i.e. a short nucleophile–leaving-group distance would lead to high-energy out-of-plane bending vibrations. As a result, the zero-point energy difference would be large in the transition state and a small isotope effect would be observed. A long nucleophile–leaving-group distance on the other hand would lead to low-energy $C_a-H$ bending vibrations and a large isotope effect\(^\text{50}\). In fact, this idea is supported by experimental\(^\text{68}\) as well as two different theoretical calculations\(^\text{67,68}\).

Applying this criterion to the data presented in Table 5 indicates that the longest $\cdot S \cdots N^+$ distance in the transition state is observed when the \textit{para} substituent is

| Para substituent | $(k_H/k_D)_a$ | $k_{14}/k_{15}$
|------------------|---------------|-----------------
| OCH\textsubscript{3} | 1.207 ± 0.020 | 1.0197 ± 0.00034 |
| H | 1.179 ± 0.007 | 1.0200 ± 0.0007 |
| Cl | 1.151 ± 0.014 | 1.0202 ± 0.0009 |

\(^a\)The errors are the standard deviation.
TABLE 6. The influence of a change in substituent (Z) in the leaving group on the structure of the S_N2 transition state

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Relative ( C_\alpha-N ) bond length in transition state</th>
<th>Relative S(-)N distance in transition state</th>
<th>Relative transition-state structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCH₃</td>
<td>( k_{14}^{15} )</td>
<td>( k_{14}^{15} )</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>1.0197</td>
<td>1.207</td>
<td>S--( \cdots )N--C--( \cdots )N</td>
</tr>
<tr>
<td>Cl</td>
<td>1.0200</td>
<td>1.179</td>
<td>S--( \cdots )N--C--( \cdots )N</td>
</tr>
</tbody>
</table>

*The relative lengths of the sulphur-a-carbon transition-state bonds have been confirmed by measuring the Hammett \( \rho \) values obtained by changing the substituent in the thiophenoxide ion.

methoxy (the poorest leaving group) and that the shortest \( \cdots S\cdots N^+ \) distance occurs with the best leaving group, i.e. when the substituent on the leaving group is chlorine.

Combining these conclusions with the results from the nitrogen kinetic isotope effects enabled the authors to propose the transition states shown in Table 6. The kinetic isotope effects indicate that changing to a better leaving group (a more electron-withdrawing substituent 'Z') leads to a transition state with a slightly longer \( \alpha \)-carbon-leaving-group (\( C_\alpha\cdots N^+ \)) bond and a much shorter nucleophile-a-carbon (\( S\cdots C_\alpha \)) bond. These results are surprising for two reasons. First, the major change in structure occurs in the bond more remote from the point of structural change and secondly, because the shortest \( S\cdots C_\alpha \) bond is observed in the transition state with the best leaving group, i.e. where \( X = Cl \). The unexpected conclusion is that the most nucleophilic assistance is required in the reaction with the best leaving group.

The results found in this study can be compared with the substituent effects predicted for S_N2 reactions with a better leaving group by Thornton's reacting bond rule and the More O'Ferrall-type energy surface for S_N2 reactions. Both Thornton's rules and the More O'Ferrall-type energy surface predict that changing to a better leaving group should lead to a transition state with a much longer \( \alpha \)-carbon-nucleophile (\( S\cdots C_\alpha \)) bond and a slightly longer \( \alpha \)-carbon-leaving-group (\( C_\alpha\cdots N^+ \)) bond. (This assumes that the perpendicular effect and parallel effect contribute equally in Thornton's reacting bond rule.) Although the theories predict the slightly longer \( C_\alpha\cdots N^+ \) bond, they do not predict that the \( S\cdots C_\alpha \) bond would be shorter. Reasons for the possible failure of these rules were presented.

Finally, the authors suggest that the \( S\cdots C_\alpha \) transition-state bond might be more sensitive to a change in substituent than the \( C_\alpha\cdots N^+ \) bond because the \( S\cdots C_\alpha \) bond is weaker than the \( C_\alpha\cdots N^+ \) bond. The shorter \( S\cdots C_\alpha \) bond in the transition state with the best leaving group (a more electron-withdrawing substituent 'Z') might arise because the nitrogen and the \( \alpha \)-carbon would be more positively charged when a more electron-withdrawing substituent is present in the leaving group. If the position of the nucleophile in the transition state is determined by the charge on the \( \alpha \)-carbon, the shortest nucleophile-\( \alpha \)-carbon (\( S\cdots C_\alpha \)) bond would be expected in the transition state with the most electron-withdrawing substituent.
TABLE 1. Secondary alpha hydrogen-deuterium kinetic isotope effects and rate constants for the SN2 reactions of various nucleophiles with the N-methoxymethyl-N,N-dimethyl-m-nitroanilinium ion in water at 25°C

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>((k_H/k_D)_0) per D</th>
<th>(10^5 k_2(1 \text{ mol}^{-1} \text{s}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>I(^-)</td>
<td>1.18</td>
<td>278</td>
</tr>
<tr>
<td>Br(^-)</td>
<td>1.16</td>
<td>85.9</td>
</tr>
<tr>
<td>HOCH(_2)CH(_2)S(^-)</td>
<td>1.14</td>
<td>751</td>
</tr>
<tr>
<td>CH(_3)O(_2)CCH(_2)S(^-)</td>
<td>1.14</td>
<td>1140</td>
</tr>
<tr>
<td>Cl(^-)</td>
<td>1.13</td>
<td>39.6</td>
</tr>
<tr>
<td>H(_2)O</td>
<td>1.11</td>
<td>0.434</td>
</tr>
<tr>
<td>CH(_3)(CH(_2))(_2)NH(_2)</td>
<td>1.08</td>
<td>196</td>
</tr>
<tr>
<td>NC(CH(_2))(_2)NH(_2)</td>
<td>1.07</td>
<td>78.4</td>
</tr>
<tr>
<td>CN(^-)</td>
<td>1.08</td>
<td>52</td>
</tr>
<tr>
<td>PhO(^-)</td>
<td>1.08</td>
<td>237</td>
</tr>
<tr>
<td>OH(^-)</td>
<td>1.07</td>
<td>90.6</td>
</tr>
<tr>
<td>AcO(^-)</td>
<td>1.07</td>
<td>24</td>
</tr>
<tr>
<td>F(^-)</td>
<td>0.99</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Recently, Knier and Jencks\(^70\) have reported the secondary alpha hydrogen-deuterium kinetic isotope effects for the SN2 reactions between several different nucleophiles and the N-methoxymethyl-N,N-dimethyl-m-nitroanilinium ion (equation 30). Their results are given in Table 7.

\[ \text{Nu}^- + \text{CH}_3\text{OCH}_2\text{N(CH}_3)_2^- \rightarrow \text{NuCH}_2\text{OCH}_3 + \text{(CH}_3)_2\text{N}^- \]

These results are interesting for several reasons. The most striking feature is that these isotope effects are extremely large for SN2 reactions. With the exception of the reaction with fluoride ion, all of the isotope effects are much larger than the maximum value of 1.04 per \(\alpha\)-D originally predicted for SN2 reactions\(^18\). In fact, these isotope effects are equal to or significantly greater than those reported by Westaway and Ali (1.07–1.10 per \(\alpha\)-D)\(^16,50\) or by Ko and Leffek (1.10 and 1.12 per \(\alpha\)-D\(^58\)) for the SN2
28. Isotopically labelled amino, quaternary ammonium and nitro compounds

reactions of the closely related benzylidimethylanilinium ions (see equations 29 and 23). These results confirm that very large isotope effects are observed in the S_N2 reactions of anilinium ions and again demonstrate that large secondary alpha hydrogen–deuterium kinetic isotope effects, originally thought to be indicative of S_N1 reactions, can be observed for S_N2 processes. The fact that all of the S_N2 reactions displaying large secondary alpha deuterium kinetic isotope effects have large bulky leaving groups\(^{16,70,71}\) suggests that the explanation provided by Westaway\(^{72}\) for these large isotope effects is correct, i.e. that the relief of steric crowding caused by lengthening the bond to the bulky leaving group is greater than the increased steric crowding resulting from the approach of the nucleophile.

Another interesting observation is that there is no correlation between the rate constants and the magnitude of the isotope effect. For example, the best nucleophiles from a kinetic point of view (the thiolate anions) have associated with their reaction smaller isotope effects than the iodide ion reaction but much larger isotope effects than the phenoxide ion reaction. The rates of the iodide ion and the phenoxide ion reactions are approximately the same.

Another interesting observation is that changes in the substituent on a nucleophile have little or no effect on the magnitude of the isotope effect and thus transition-state structure. For example, the isotope effects are effectively constant when the nucleophile is changed from OH\(^-\) to OAc\(^-\) to PhO\(^-\) ion. The same behaviour is observed for CH\(_3\)(CH\(_2\))\(_3\)NH\(_2\) and NC(CH\(_2\))\(_2\)NH\(_2\) and identical isotope effects are observed for the nucleophiles HOCH\(_2\)CH\(_2\)S\(^-\) and CH\(_3\)O\(_2\)CH\(_2\)S\(^-\).

Changes in the proximal atom of the nucleophile, on the other hand, cause large changes in the magnitude of the isotope effect. The isotope effect is larger for water than for the oxy anion or the amine nucleophiles and the thiolate anion reactions have much larger isotope effects than the oxy anions etc. A plausible explanation for this behaviour is presented below.

First, however, it is necessary to estimate the general structure of the transition states for these reactions. The large secondary alpha hydrogen–deuterium kinetic isotope effects indicate that there is significantly less steric crowding around the C\(_\alpha\)–H bonds in the transition state than in the reactants. This suggests that these transition states are very loose, i.e. have long \(\alpha\)-carbon-nucleophile and \(\alpha\)-carbon-leaving-group bonds. The long \(\alpha\)-carbon–leaving-group bond is required because the approaching nucleophile increase the steric crowding around the \(\alpha\)-carbon. The large reduction in the steric crowding at the C\(_\alpha\)–H bonds must, therefore, result from a substantial increase in the \(\alpha\)-carbon–leaving-group bond, i.e. moving the large bulky leaving group away from the C\(_\alpha\)–H bonds.

Although there is insufficient information to prove whether the \(\alpha\)-carbon–nucleophile bonds are also long in the transition state, the isotope effects for the thiolate anion–N-methoxymethyl-N,N-dimethyl-m-nitroanilinium ion reaction \((k_D/k_H = 1.14 \text{ per } \alpha-D)\) are significantly larger than those reported for the S_N2 reaction between thiophenoxide ion and benzylidimethylanilinium ion \((k_D/k_H = 1.09 \text{ per } \alpha-D)\). Since the steric requirements of the nucleophiles and leaving groups are similar in these two reactions, the former reaction must have a looser transition state. Previous work has shown that both the \(\alpha\)-carbon–nucleophile and the \(\alpha\)-carbon–leaving-group bonds are long in the transition state of the thiophenoxide ion–benzylidimethylanilinium ion reaction. The much larger isotope effect for the methoxymethyl compound suggests that both the \(\alpha\)-carbon–nucleophile and \(\alpha\)-carbon–leaving-group bonds are longer in the transition state for the methoxymethyl compound. It is not known whether the looser transition state occurs because the methoxy group is able to stabilize the partial positive charge on the \(\alpha\)-carbon in the transition state\(^{48,73}\) or because a more ionizing solvent was used in the methoxymethyl reactions\(^{50,58}\).
The largest isotope effects in this series of SN2 reactions are found in the reactions where the proximal atoms in the nucleophile are softer or more polarizable. The largest isotope effect is observed when the nucleophile is iodide ion and the magnitude of the isotope effect decreases as less polarizable (harder) nucleophiles are used, e.g., the isotope effect decreases from 1.18 for iodide ion to 1.16 for bromide ion to 1.13 for chloride ion and to 0.99 for fluoride ion. The same trend is observed in the thiolate anion–oxy anion series, i.e., the isotope effects are 1.14 for the thiolate anion reactions whereas they are only 1.08 or 1.07 per α-D for the oxy anions. These results suggest that the α-carbon–nucleophile transition-state bonds are longer when a more polarizable nucleophile is used. Although this conclusion is qualitatively satisfying, it is not required by the experimental data. A larger secondary alpha deuterium kinetic isotope effect simply indicates a looser transition state. In fact, the nucleophile–α-carbon bonds could be the same length or even shorter if the α-carbon–leaving-group bonds were significantly longer in the transition states with the more polarizable nucleophile.

Finally, the very small (inverse) isotope effect in the fluoride ion reaction indicates that the steric crowding around the Cα—H bonds is not altered significantly in going from the reactant to the transition state. This requires much more steric crowding around the Cα—H bonds in the transition state of this reaction and thus much shorter α-carbon–nucleophile and α-carbon–leaving-group bonds. It is possible, however, that solvent molecules hydrogen-bonded to the fluoride ion increase the size of the fluoride ion significantly. This could increase the energy of the Cα—H out-of-plane bending vibrations and reduce the magnitude of the isotope effect even if the α-carbon–fluoride ion and α-carbon–leaving-group bonds were long in the transition state. Perhaps secondary solvent hydrogen–deuterium kinetic isotope effects would indicate the reason for the very small isotope effect in the fluoride ion reaction.

Knier and Jencks70 have also measured the secondary solvent hydrogen–deuterium kinetic isotope effects for the reactions between water, acetate ion or n-propylamine and N-methoxymethyl-N,N-dimethyl-m-nitroanilinium ion in water at 25°C. The isotope effects, k(H2O)/k(D2O), were 1.07 for the water and acetate ion reactions and 0.94 for the n-propylamine reaction. These isotope effects are in the range reported for SN2 reactions of methyl substrates and are significantly smaller than the solvent isotope effects of 1.2 to 1.4 reported for SN1 reactions74. These results confirm that the nucleophilic substitution reactions of the methoxymethyl compounds proceed via an SN2 mechanism and illustrate that the solvent isotope effects for the SN2 reactions of anilinium ions are normal.

C. Substituent Effects on the Geometry of SN2 Transition States

Two different theories are commonly used to predict substituent effects on transition-state structure. One of these is Thorton's reacting bond rule which considers how the change in substituent affects the parallel and perpendicular vibrations of the SN2 transition state28. The second method, which is an extension69 of the method devised by More O’Ferrall to predict substituent effects in β-elimination reactions, considers how the substituent affects the energy of the reactants, the products and the two hypothetical intermediates (a pentavalent complex and a carbocation). The effect of changing the substituent on the energy surface is then used to predict the change in transition-state geometry60,69.

Recently, Westaway and Ali50 published a study describing how changes in the leaving group altered the geometry of the SN2 transition state in the reaction between para-substituted phenylbenzyldimethylammonium ion and thiophenoxide ion (Figure 3). The results of this study describe the structure of the transition states in sufficient
detail to test Thornton's reacting bond rules and More O’Ferrall’s energy surface method of predicting how changes in substituent affect the structure of $S_N2$ transition states.

In applying Thornton’s rule one considers the substituent effect on the stretching vibrations of the $S_N2$ transition state, perpendicular (A) and parallel (B) to the reaction coordinate:

$$\begin{align*}
\text{Nu} & \cdots \text{C} \cdots \cdots \text{L} \\
\text{C} & \cdots \text{N} & \cdots \text{L}
\end{align*}$$

Adding a more electron-attracting substituent to the leaving group reduces the ionic character of the perpendicular vibration. This makes an increase in vibration A easier (Thornton states that the effect on the nearest bond is most important). As a result, the transition state with the more electron-attracting substituent would have a longer nucleophile-$\alpha$-carbon and $\alpha$-carbon-leaving-group bond. For the parallel vibration, B, a more electron-attracting substituent will make an increase in the vibration easier and the transition state should have a longer nucleophile-$\alpha$-carbon and a shorter $\alpha$-carbon-leaving-group bond. Whether one assumes that the parallel effect is more or that the parallel and perpendicular effects are equally important, Thornton’s theory predicts a longer $S\cdots C_a$ bond in the transition state with a better leaving group. The change in the $C_a\cdots N^+$ bond, on the other hand, is less certain. If the parallel effect is greater, a shorter $C_a\cdots N^+$ bond would be expected, whereas there should be almost no change in the $C_a\cdots N^+$ bond if the parallel and perpendicular effects are equally important. An examination of the relative transition-state structure in Figure 3 indicates that the $S\cdots C_a$ bond is significantly shorter and that the $C_a\cdots N^+$ bond is slightly longer in the transition state with a more electron-attracting substituent in the leaving group. The reacting bond rule predicts correctly that the $S\cdots C_a$ bond will change more than the $C_a\cdots N^+$ bond. Moreover, the observed change in the $C_a\cdots N^+$ bond is described if the perpendicular effect is slightly more important than the parallel effect. Obviously, the change in the $S\cdots C_a$ bond cannot be accommodated by Thornton’s theory since the theory predicts a longer $S\cdots C_a$ bond and a shorter $S\cdots C_a$ bond is observed.

The predictions of the More O’Ferrall-type energy surface method for $S_N2$ reactions can be obtained from Figure 4. The first problem in applying this method is to place
the transition state on the energy surface. Both the $S\cdots C_a$ and $C_a\cdots N^+$ bonds are long (weak) in the transition state. The means that the bond order at the $\alpha$-carbon, $n_{C_a}$, given by the sum of the $S\cdots C_a$ and $C_a\cdots N^+$ bond orders $n_{SC}$ and $n_{CN}$, respectively, must be equal to or less than one (the bond order in the reactant and product). As a result, the transition state must either be near the centre of the diagonal joining the reactant and product (a constant total bonding transition state with $n_{C_a} = 1.00^{69}$) or in the lower right-hand part of the energy surface where $n_{C_a}$ is less than one, i.e. a decreased total bonding transition state in the upper left portion of the energy surface.

The major effect of making the substituent 'Z' in the leaving group more electron-withdrawing (going to a weaker lower energy base as the leaving group) is to lower the energy of the top right and bottom right corners of the energy surface. The perpendicular effect for both of the possible transition states (a central transition state at A and a carbonium-ion-like transition state at B) is to move the transition state towards the bottom right-hand corner of the energy surface (arrows a and b) and longer $S\cdots C_a$ and $C_a\cdots N^+$ bonds would be anticipated. Lowering the top right-hand corner will produce a parallel effect that will move the transition states back towards the reactants (arrows c and d) and thus to a transition state with a longer $S\cdots C_a$ and a shorter $C_a\cdots N^+$ bond. Thus More O’Ferrall’s type of energy surface, like Thornton’s perpendicular effects are shown by arrows e and f. For transition state A, adding a more electron-withdrawing substituent should lead to a transition state with a longer $S\cdots C_a$ bond and a slightly longer $C_a\cdots N^+$ bond (the perpendicular effect is slightly more important). A transition state with a longer $S\cdots C_a$ bond and a slightly shorter $C_a\cdots N^+$ bond is predicted if the original transition state is at B.

Changing ‘Z’ to a more electron-withdrawing group should lead to a longer $S\cdots C_a$ bond whether the transition state is at A or B and the $C_a\cdots N^+$ bond should not change appreciably. Thus More O’Ferrall’s type of energy surface, like Thornton’s rule, predicts that the bond more remote from the point of structural change (the $S\cdots C_a$ bond) will change more than the closer $C_a\cdots N^+$ bond. It also suggests correctly that the $C_a\cdots N^+$ bond should be slightly longer in the transition state with
the better leaving group, provided that the transition state is near point A on the diagram. However, this theory predicts the change in the $S\cdots C_9$ bond incorrectly. A shorter $S\cdots C_9$ bond is observed in the transition state with a better leaving group whereas a longer $S\cdots C_9$ bond is predicted.

Thus, neither theory is able to predict the results observed in this study. Further results describing the substituent effects on the transition-state geometry of $S_N2$ reactions will have to be obtained before it can be determined whether these rules can be used successfully for predicting substituent effects for $S_N2$ reactions.

III. THE USE OF ISOTOPE TRACER EXPERIMENTS AND ISOTOPE EFFECT MEASUREMENTS FOR THE DETERMINATION OF MECHANISM FOR AN ELIMINATION PROCESS FROM A QUATERNARY AMMONIUM SALT

A. Reaction of 2-Arylethyltrimethylammonium Ions with Ethoxide Ion

The use of isotope tracer studies and kinetic isotope effect determinations to establish the mechanism of an elimination process was first demonstrated by Buncel and Bourns who studied the carbonyl elimination reaction of benzyl nitrate to give benzaldehyde. Subsequently, Bourns and Smith used the same techniques to investigate the mechanisms of the reaction of 2-phenylethyltrimethylammonium salts with ethoxide ion (equation 31). Their results will be discussed in the following section.

$$\beta PhCH_2CH_2\text{N(CH}_3)_3 + \text{EtO}^- \rightarrow Ph\text{CH}=\text{CH}_2 + \text{N(CH}_3)_3 \quad (31)$$

1. Deuterium exchange at the $\beta$-carbon

Two important mechanisms which must be considered for an elimination reaction exhibiting second-order kinetics are the concerted one-step process, designated E2 (equation 32) and the carbanion mechanism, Elcb (equation 33). In the concerted process, the carbon–hydrogen and carbon–nitrogen bonds are ‘weakened’ at the transition state while the carbon–carbon double bond is forming. For the Elcb mechanism a true intermediate, a carbanion, intervenes between the reactants and products. The carbanion can either revert back to starting material in a $k_2$ step or proceed to product in a $k_3$ step. If the reaction is carried out with deuterium
substituted in the β-position of the substrate and stopped partway to completion, then deuterium loss from substrate should be found if the carbanion mechanism is operative and $k_2 \gg k_3$.

2-Phenylethyltrimethylammonium-2,2-d$_2$ bromide containing 1.88 atoms D/molecule was treated with $0.1\text{~M}$ sodium ethoxide in ethanol at 40°C and the reaction allowed to proceed halfway to completion. The unreacted salt was isolated and was found to have the same deuterium content as the original reactant. From these results, it can be concluded that there is no significant exchange of the hydrogens at the β-carbon. The Elcb mechanism involving a freely solvated zwitterionic intermediate, PhCH=CH$_2$–N(CH$_3$)$_3$, in partial or complete equilibrium with the reactant, is therefore excluded.

It should be noted that a primary hydrogen–deuterium isotope effect is expected for both the concerted mechanism and the carbanion mechanism when the rate of reaction of carbanion to product is fast relative to its rate of return to starting material, i.e. $k_3 \gg k_2$. For the carbanion mechanism, the rate of reaction = $k_3$ [carbanion] and if the carbanion is present in steady-state concentration:

$$\text{Rate of reaction} = \frac{k_1k_3[\text{substrate}][\text{EtO}^-]}{k_2[\text{EtOH}] + k_3}$$

If $k_3 \gg k_2[\text{EtOH}]$ then:

$$\text{Rate of reaction} = k_1[\text{substrate}][\text{EtO}^-]$$

Consequently, the slow (rate-determining) step for the carbanion mechanism where $k_3 \gg k_2$, as well as for the concerted process, involves rupture of the carbon–hydrogen bond at the transition state. A primary hydrogen–deuterium kinetic isotope effect therefore, is expected and in fact, Saunders and Edison$^{77}$ found a value of $k_{1d}/k_{1s} = 3$ at 50°C for this reaction.

2. Nitrogen kinetic isotope effects

In order to distinguish between the two mechanisms, (the E2 and Elcb) dictated by the deuterium exchange test, the primary nitrogen isotope effect, $[[k_{1s}^4/k_{1s}^{15}] - 1]100$, was determined. The concerted mechanism has carbon–nitrogen bond rupture occurring at the transition state while the carbanion process with $k_3 \gg k_2$ does not have any carbon–nitrogen bond rupture at the energy maximum for the rate-determining ($k_1$) step. A large nitrogen isotope effect of $[[k_{1s}^4/k_{1s}^{15}] - 1]100 = 1.33$ was found for the reaction of 2-phenylethyltrimethylammonium ion with ethoxide ion at 40°C. This result is only consistent with the concerted E2 process$^{26}$. 

$$\text{PhCH}_2\text{CH}_2^+\text{N(CH}_3)_3 + \text{EtO}^- \xrightleftharpoons{k_1}{k_2} \text{PhCH}_2\text{CH}_2^+\text{N(CH}_3)_3 + \text{EtOH} \quad (33)$$

$$\xrightarrow{k_3} \text{PhCH=CH}_2 + \text{N(CH}_3)_3$$
3. Deuterium exchange at the α-carbon

Although in the preceding discussion the E2 mechanism was distinguished from the Elcb process, two other less common mechanisms must be considered. The first of these is the carbene (α-elimination) mechanism illustrated in equation (34). It is

\[
\text{PhCH}_2\text{CD}_2\text{N(CH}_3\text{)}_3 + \text{EtO}^- \rightleftharpoons \text{PhCH}_2\text{CDN(CH}_3\text{)}_3 \rightarrow \text{PhCH}_2\text{CD} + \text{N(CH}_3\text{)}_3
\]

seen that the zwitterionic intermediate, formed by loss of an α-hydrogen can expel trimethylamine to give a carbene.

An exchange test similar to that described for β-exchange was carried out with 2-phenylethyltrimethylammonium-1,1-d₂ bromide and it was found that no significant exchange occurs at the α-position. Consequently, the zwitterion, PhCH₂CDN(CH₃)₃, if formed, does not abstract a proton from the solvent under elimination reaction conditions. Its intermediacy in an α-elimination process is still a possibility however, provided it were formed in the rate-determining step of the reaction.

Deuterium tracer studies provide an unequivocal test for this reaction pathway, since a β-elimination involves the loss of one hydrogen (deuterium) from the β-carbon whereas an α-elimination involves the loss of one hydrogen (deuterium) from the α-carbon and a migration of a hydrogen (deuterium) from the β- to the α-carbon. This test was applied to the reactions of 2-phenylethyltrimethylammonium-1,1-d₂ and 2-phenylethyltrimethylammonium-2,2-d₂ ions. The position of the deuterium in the styrene was determined by NMR analysis of the styrene dibromide formed by reacting the unstable styrene with bromine. The results are shown in Table 8. The absorption at 5.15 ppm, corresponding to the resonance of the -CH₂Br hydrogens, is compared to that expected for the product from each of the two reaction pathways. It is seen that the results clearly eliminate an α-elimination mechanism and are in complete accord with a β-elimination process.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>N₁</th>
<th>N₂</th>
<th>N₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCD₂CH₂N(CH₃)₃</td>
<td>2.04</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PhCH₂CD₂N(CH₃)₃</td>
<td>0.00</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

4. Test for the ylide α',β-mechanism

The other possible less common mechanism for β-elimination is the α',β-mechanism (equation 35), where an ylide is formed by abstraction of an α'-hydrogen with base. This ylide can act as an internal base by removing a β-hydrogen via a cyclic transition state to give the elimination products. It is seen
that if the starting material is deuterated in the β-position then the eliminated trimethylamine will contain deuterium.

\[
\text{PhCD}_2\text{CH}_2\text{N(CH}_3\text{_})_3 + \text{EtO}^- \rightarrow \text{PhCDCH}_2 + \text{EtOH}
\]

The reaction of 2-phenylethyltrimethylammonium-2,2-d$_2$ bromide with ethoxide ion in ethanol at 40°C was allowed to proceed to completion and the trimethylamine, recovered as the hydrochloride, was analysed for deuterium. No deuterium enrichment was found in this product and hence the α',β-pathway was excluded.


The reaction of several 9-(4-substituted-benzyl)fluorenyl-9-trimethylammonium ions (5) with ethoxide ion has been investigated in order to determine the effect of substituents on transition-state geometry. The results, which will be discussed in Section IV.B, indicated an unusual substituent effect behaviour and it was considered that steric effects must be important. It was suspected that the steric interaction of the ortho hydrogens on the phenyl ring with the 1- and 8-hydrogens of the fluorene ring are responsible for this effect.

In order to test this hypothesis, Pradhan and Smith prepared a series of ortho-substituted analogues of 5. These salts, unlike the 4-substituted compounds which were unreactive in ethanol, reacted in absolute ethanol in the absence of base to give both the alkene and ether products. The observed rate constants, $k_{\text{obs}}$, for the formation of the alkene from several ortho-substituted quaternary ammonium salts and their β,β-d$_2$ analogues, as well as the percentage alkene, are given in Table 9. In addition, the $k^E_{\text{alkene}}/k^S_{\text{ether}}$ ratio (equation 36) calculated from the ratio of products together with the hydrogen–deuterium kinetic isotope effects, $k_{11}^{D}/k_{0D}^{D}$, and $k_{11}^{E}/k_{0E}^{E}$ are included.

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TABLE 9. Rate constants, percentage alkene and hydrogen-deuterium isotope effects for reaction of 9-(ortho-substituted-benzyl)fluorenyl-9-trimethylammonium salts in absolute ethanol at 57.3°C

<table>
<thead>
<tr>
<th>Ortho substituent</th>
<th>$10^5k_{obs}$(s$^{-1}$)</th>
<th>% Alkene</th>
<th>$(k_E/k_S)^a$</th>
<th>$(k_{R}/k_{D})^b$</th>
<th>$k_{obs}^{bs}/k_{D}^{bs}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Methyl</td>
<td>2.35</td>
<td>56.2</td>
<td>1.28</td>
<td>1.54</td>
<td>1.22</td>
</tr>
<tr>
<td>2-Methyl-β,β-d$_2$</td>
<td>1.92</td>
<td>42.8</td>
<td>0.748</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-Dimethyl</td>
<td>2.85</td>
<td>56.8</td>
<td>1.31</td>
<td>1.76</td>
<td>1.16</td>
</tr>
<tr>
<td>2,4-Dimethyl-β,β-d$_2$</td>
<td>2.45</td>
<td>40.1</td>
<td>0.669</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,6-Dichloro</td>
<td>9.60</td>
<td>28.6</td>
<td>0.401</td>
<td>2.10</td>
<td>1.45</td>
</tr>
<tr>
<td>2,6-Dichloro-β,β-d$_2$</td>
<td>6.60</td>
<td>14.7</td>
<td>0.172</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,6-Dimethyl</td>
<td>268</td>
<td>28.8</td>
<td>0.404</td>
<td>2.78</td>
<td>2.35</td>
</tr>
<tr>
<td>2,6-Dimethyl-β,β-d$_2$</td>
<td>114</td>
<td>11.6</td>
<td>0.131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4,6-Trimethyl</td>
<td>248</td>
<td>25.4</td>
<td>0.340</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$See text and equation (36).  
$^b$Calculated with the assumption that $k_R/k_D = 0.9$.

The E2b, ylide and α-elimination mechanisms are not possible because these compounds react in the absence of strong base. In addition, the E2 mechanism with ethanol as the base can be ruled out because the 4-substituted benzylfluorenyl compounds, which could react by an E2 mechanism, are inert in ethanol. As a result, it was concluded that these reactions must occur via the carbocation or E1 mechanism. This is only the second example of a trimethylammonium salt (poor leaving group) undergoing solvolysis to give an alkene in an E1 process.

The observed rate constants for the formation of the alkene from the 2-methyl and 2,4-dimethyl salts are very similar and are approximately one hundred times less than the corresponding rate constants for the 2,6-dimethyl and 2,4,6-trimethyl substrates. It appears, therefore, that since ortho methyl groups accelerate the reaction (the salts are completely stable in ethanol when there are no ortho substituents) and the para substituent has very little effect, the rate enhancement is due to steric acceleration. An examination of Dreiding stereomodels indicates that there is considerable interaction between the ortho methyl groups and the 1,8-hydrogens on the fluorene ring as well as the methyl groups of the trimethylammonium ions. Thus, the reaction is promoted by a relief of steric interactions and not only by the formation of a favourable carbocation.

The reaction of the 2,6-dichloro substrate with ethanol is slower than the reaction of the 2,6-dimethyl compound, but is faster than the reaction of the 2,4-dimethyl compound. These observations can be accommodated by the steric argument since chlorine is smaller than methyl (Taft $E_s$ values). Also, it is seen that the percentage alkene decreases when both ortho positions bear a substituent: e.g. % alkene = 56.2 and 28.8 for the 2-methyl and 2,6-dimethyl compounds, respectively. This is also consistent because the ortho substituents lead to an increase in the nonplanarity of the alkene due to interactions with the 1,8-hydrogens on the fluorene ring. In addition, the presence of the ortho groups provides a steric hindrance to the removal of the β-hydrogen from the carbocation by base.

The carbocation mechanism for the formation of the alkene and ether products can be represented by equation (36). If it is assumed that all steps are irreversible

$$
S \xrightarrow{k_1} C^+ \quad \xrightarrow{k_E} \text{alkene} \\
\quad \xrightarrow{k_S} \text{ether}
$$

(36)
then it can be shown that the observed rate constant for alkene formation is given by:

\[ k_{\text{obs}} = k^1k^E/(k^E + k^S) \]

If \( k^E > k^S \), then:

\[ k_{\text{obs}}^{\text{H}}/k_{\text{obs}}^{\text{D}} = k_{\text{H}}^1/k_{\text{D}}^1 \]

and the observed isotope effects will mainly be secondary \( \beta \)-deuterium isotope effects, i.e. when \( k^E/k^S = 1.28 \) then \( k_{\text{obs}}^{\text{H}}/k_{\text{obs}}^{\text{D}} = 1.22 \) for the 2-methyl substrate. However, when \( k^E < k^S \) and if \( k^S/k_D^S = 1 \), then:

\[ k_{\text{obs}}^{\text{H}}/k_{\text{obs}}^{\text{D}} = (k_{\text{H}}^1/k_{\text{D}}^1)(k^E/k^E). \]

A larger observed isotope effect is expected since the observed isotope effect is the product of a secondary isotope effect and a primary isotope effect associated with the removal of a proton from the carbocation (\( k^E \)). When \( k^E/k^S = 0.404 \) then \( k_{\text{obs}}^{\text{H}}/k_{\text{obs}}^{\text{D}} = 2.35 \) for the 2,6-dimethyl salt. The isotope effects for loss of hydrogen from the carbocation (\( k_{\text{H}}^S/k_{\text{D}}^S \)) can be calculated from the product ratios. Isotope effects ranging from 1.54 to 2.78 are found. These are reasonable primary isotope effects for the loss of a proton from a high-energy carbocation.

IV. USE OF KINETIC ISOTOPE EFFECTS IN THE DETERMINATION OF E2 TRANSITION-STATE STRUCTURE

A. Effect of \( \text{para} \) Substituents of the Nature of the E2 Transition State for the Reaction of 2-Arylethyltrimethylammonium Salts with Ethoxide Ion

It was concluded in an earlier section that 2-phenylethyltrimethylammonium bromide reacts with ethoxide ion via a concerted E2 process. Consequently, Smith and Bourns\(^2\) initiated a study concerning the effect of substituents on the nature of the E2 transition state for the reaction of a series of \( \text{para} \)-substituted 2-phenylethyltrimethylammonium ions with ethoxide. One of the most direct ways of obtaining information on the transition state is by measuring the isotope effect associated with an atom whose bond is undergoing rupture in the reaction. As a result both the primary hydrogen–deuterium and nitrogen kinetic isotope effects (Table 10) were determined in order to gain an insight into the relative degree of both \( \text{C}_\text{p} - \text{H} \) and \( \text{C}_\text{a} - \text{N}^+ \) bond rupture at the E2 transition state (6)

\[ \text{OEt} \]

\[ \text{(6)} \]

The results of the nitrogen isotope effect study on the 2-arylethyl system show a relationship between the magnitude of the isotope effect and the electron-withdrawing or -donating ability of the \( \text{para} \) substituent. Although the effects for the \( \text{p-H} \) or \( \text{p-OCH}_3 \) compounds are the same within experimental error, there is a significant decrease in the magnitude of the isotope effect when electron-withdrawing substituents are placed on the benzene ring, i.e.
28. Isotopically labelled amino, quaternary ammonium and nitro compounds

TABLE 10. Isotope effects found for the E2 reaction of 2-arylpropyltrimethylammonium ions [ZC6H4CH2CH2N(CH3)3] with sodium ethoxide in ethanol at 40°C

<table>
<thead>
<tr>
<th>Para substituent ‘Z’</th>
<th>[(k14/k15) - 1]100</th>
<th>kH/kD</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCH3</td>
<td>1.37 ± 0.09</td>
<td>2.64 ± 0.05b</td>
</tr>
<tr>
<td>H</td>
<td>1.33 ± 0.02</td>
<td>3.23 ± 0.06</td>
</tr>
<tr>
<td>CI</td>
<td>1.14 ± 0.09</td>
<td>3.48 ± 0.07</td>
</tr>
<tr>
<td>CF3</td>
<td>0.88 ± 0.06</td>
<td>4.16 ± 0.07</td>
</tr>
</tbody>
</table>

*aThe limits shown are standard deviations.

bRatio of rates of elimination; deviation = ±(kH/kD)[(rH/kH)^2 + (rD/kD)^2]^{1/2}, where r is the standard deviation in k.

[(k14/k15) - 1]100 is 1.33 and 0.88 for the p-H and p-CF3 compounds, respectively. In fact, the magnitude of the nitrogen isotope effect is approximately linearly related to the effect of the para substituent on the free energy of activation for the elimination process. The experimental results show that the extent of carbon–nitrogen bond rupture in the transition state decreases as the para substituent becomes more electron-withdrawing.

As indicated earlier it is necessary to know whether the hydrogen is more than or less than one-half transferred to base before the interpretation of primary hydrogen–deuterium isotope effects in terms of the degree of C–H bond rupture can be made. This information was obtained by Steffea and Thornton24 who determined the secondary isotope effect, kOD/kOH, for the reaction of several quaternary ammonium ions at 80°C. The secondary isotope effects, kOD/kOH, and the primary β-deuterium isotope effect, kH/kD, for the elimination reactions of three phenylethyl derivatives are presented in Table 11. It is noted that the secondary effects are greater than 1.37 suggesting that for reaction of the three substrates the proton is more than one-half transferred at the transition state. Furthermore, the magnitude of the secondary effects, kOD/kOH, decreases as one proceeds down the table, indicating a decrease in the extent of carbon–hydrogen bond rupture at the potential energy maximum. At the same time, the values of the primary hydrogen–deuterium isotope effects increase. This relationship of the two effects clearly establishes that the proton is more than one-half transferred at the transition state, since only in this circumstance can a decrease in the extent of proton transfer, as shown by the kOD/kOH values, result in an increase in the kH/kD ratio. It follows from the trend in the hydrogen–deuterium isotope effects in Table 11 that electron-withdrawing para substituents in the reaction of the 2-arylethyltrimethylammonium ions result in a decrease in the extent of proton transfer to base at the transition state.

TABLE 11. Secondary and primary kinetic isotope effects in the reaction of 2-phenylethyl derivatives

<table>
<thead>
<tr>
<th>Substrate</th>
<th>(kOD/kOH)^a</th>
<th>(kH/kD)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH2CH2N(CH3)3</td>
<td>1.79</td>
<td>3.23</td>
</tr>
<tr>
<td>p-CIC6H4CH2CH2N(CH3)3</td>
<td>1.73</td>
<td>3.48</td>
</tr>
<tr>
<td>PhCH2CH2N(CH3)2Ph</td>
<td>1.62</td>
<td>4.50c</td>
</tr>
</tbody>
</table>

*aReference 24.

bMeasured with ethoxide ion in ethanol at 40°C.

cReference 83.
The isotope effects show that electron-withdrawing substituents lead to a decrease in the extent of both carbon-hydrogen and carbon-nitrogen bond rupture at the transition state. This conclusion is in complete accord with the Thornton model for predicting the effect of a substituent on the nature of the activated complex. The removal of the $\beta$-hydrogen is made easier by placing electron-withdrawing substituents on the benzene ring and this effect, when considering motion along the reaction coordinate, should lead to a more reactant-like transition state, i.e. less C–H and less C–N$^+$ bond weakening.

A consideration of the More O’Ferrall potential energy diagram (Figure 2, Section 1.B) can also accommodate the isotope effect results. The energy diagram can be represented schematically, (Figure 5), in terms of the various mechanisms for elimination.

It is reasonable to consider that the transition state for the E2 reaction of the 2-arylethyl salts is Elcb-like since the isotope effects and a large Hammett $\rho$ of +3.66 indicate that there is extensive C–H bond rupture in the transition state. The effects of para substituents on the stability of the alkene products is considered to be small and, hence, it is necessary to consider the effect of the increased stabilization of the carbanion on motion perpendicular to the reaction coordinate and on the parallel motion for carbanion formation, in order to predict the effect of the substituent on transition-state geometry. Adding a more electron-withdrawing substituent would be equivalent to a downward push at the lower right-hand corner of the energy surface. The transition state would shift towards the lower right hand corner, arrow ‘a’, because of the perpendicular effect. This gives rise to a transition state with increased C–H and decrease C–N bond rupture (an anti-Hammond effect) when the para substituent is made more electron-withdrawing. The effect of an electron-withdrawing substituent on the parallel motion for carbanion
formation, however (arrow 'b'), would give rise to a transition state with decreased 
C—H bond weakening. Since the transition state for the elimination reaction is 
close to the reaction coordinate for carbanion formation, an electron-withdrawing 
substituent would have a similar parallel effect on the energy surface at the 
transition state. The resultant of the parallel and perpendicular effects at the 
transition state is represented by arrow 'c' leading to a transition state 'Y' where 
there is decreased carbon—hydrogen and carbon—nitrogen bond rupture. This 
conclusion is in accord with that obtained from a consideration of the kinetic 
isotope effect results.

B. Effect of Substituents on the Nature of the E2 Transition State for 
the Reaction of 9-(4-Substituted-benzyl)fluorenyl- 
9-trimethylammonium Ions with Ethoxide Ion 

The elimination reaction of 9-(4-substituted-benzyl)fluorenyl-9-trimethyl-
ammonium ions (5) with sodium ethoxide in ethanol has recently been 
investigated. The mechanism was shown to be the normal concerted E2 process

![Diagram](image)

(5)

and hence the primary hydrogen—deuterium and nitrogen isotope effects were 
measured for reaction of several 4-substituted compounds in an effort to determine 
how substituents affect transition-state geometry (Table 12).

The trend in the magnitude of $k_H/k_D$ with the electron-donating or -withdrawing 
ability of the 4-substituent is the opposite to that found for the 2-arylethyl system 
just discussed. For the benzylfluorenyl system the magnitude of $k_H/k_D$ decreases 
with increasing electron-withdrawing ability of the 4-substituent while, for the 
2-arylethyl series, the magnitude of $k_H/k_D$ increased when the para substituent was 
made more powerfully electron-withdrawing.

<table>
<thead>
<tr>
<th>Substituent 'Z'</th>
<th>$k_H/k_D$ (60°C)</th>
<th>$[(k^{14}/k^{15}) - 1]100$ (70°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCH$_3$</td>
<td>5.91 ± 0.09$^a$</td>
<td>0.80 ± 0.03$^b$</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>5.75 ± 0.10</td>
<td>0.91 ± 0.09</td>
</tr>
<tr>
<td>H</td>
<td>5.61 ± 0.08</td>
<td>0.92 ± 0.04</td>
</tr>
<tr>
<td>F</td>
<td>0.95 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>5.34 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>5.10 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>CF$_3$</td>
<td>4.15 ± 0.12</td>
<td>1.24 ± 0.07</td>
</tr>
</tbody>
</table>

$^a$Ratio of rates of elimination; deviation = $\pm (k_H/k_D) [(r_H/r_D) + (r_D/r_H)]^{1/2}$ where $r$ is the 
standard deviation.

$^b$Standard deviation.
The rate of reaction of compound 5 with ethoxide is surprisingly slower than the corresponding reaction of the 2-phenylethyl salt. Dreiding stereomodels indicate that there is considerable steric interaction between the phenyl ring and the fluorene nucleus when they are in the same plane. Hence, the phenyl ring is probably twisted out of the plane of the fluorenyl ring at the transition state. Consequently the developing p-orbital at the benzylic carbon, as C—H bond rupture advances, will not be able to effectively overlap with the \( \pi \)-system of the phenyl ring. This is consistent with the observation of a small value of \( \rho \) (+1.33) for the reaction of 5.

Assuming that \( \rho \) does not provide a measure of the degree of \( \text{C—H} \) bond rupture at the transition state for the reaction of 5, it is reasonable to conclude that the proton is more than one-half transferred to base at the transition state. The decrease in the magnitude of the \( k_H/k_D \) effect, as the 4-substituent is made more electron-withdrawing, indicates increased \( \text{C—H} \) bond weakening at the transition state.

The trend in the magnitude of the nitrogen isotope effects with changes in the 4-substituent was unexpected because the largest effect was observed for the best electron-withdrawing substituent. Hence, the degree of \( \text{C—N}^+ \) bond rupture is the greatest for the reactions with the strongest electron withdrawers. This trend is opposite to that found in the 2-arylethyl system. The conclusion is reached that electron-withdrawing substituents increase both carbon—hydrogen and carbon—nitrogen bond rupture at the transition state (anti-Hammond behaviour).

On the assumption that the parallel and perpendicular effects in Thornton’s reacting bond rule are important, Winey and Thornton predicted how a more electron-withdrawing substituent would alter the structure of an Elcb-like transition state. Their predictions suggested that adding a stronger electron withdrawer would

---

**FIGURE 6.** Transition-state map for the various elimination mechanisms of the 9-(4-substituted-benzyl)fluorenyl-9-trimethylammonium ions.
lead to a perturbed equilibrium geometry with less C—H and C—N\(^+\) bond weakening in the transition state. Their predictions are obviously inconsistent with the above conclusions.

On the other hand, the treatment of More O-Ferrall\(^{26}\) can predict the experimental results. The transition states for this series of reactions are more E1cb-like and occur later along the reaction coordinate than the transition states for the 2-arylethyl compounds (Figure 6). A more electron-withdrawing substituent will stabilize the carbanion and lead to the perpendicular effect shown by arrow ‘a’, i.e. to increased C—H and decreased C—N\(^+\) bond rupture in the transition state. In this reaction series, the Hammond or parallel effect is determined from the substituent effect on the reaction coordinate representing the slow decomposition of the carbanion. A consideration of the effect of electron withdrawers on the parallel motion for carbanion decomposition gives arrow ‘b’, i.e. to move the transition state towards product. Again since the transition state for elimination is on a reaction coordinate very close to that for carbanion decomposition, the parallel effect will be similar to that found for the decomposition of the carbanion, i.e. the transition state will have a longer C—N\(^+\) bond and there would be little or no change in the C—H bonds. Combining the parallel and perpendicular effects leads to the change in transition-state structure shown by arrow ‘c’. Thus, the transition state should have longer C—H and C—N\(^+\) bonds when a more electron-withdrawing substituent is present. This is in fact, what is observed.

C. Effect of Substituents on the Nature of the E2 Transition State for the Reaction of 2-Phenylethylidimethylanilinium Salts with Ethoxide Ion

Schmid and Bourns\(^{83}\) recently considered the effect of the leaving group on the E2 transition state by determining both the primary hydrogen-deuterium and nitrogen kinetic isotope effects (Table 13) for the reaction of a series of 2-phenylethylidimethylanilinium salts with ethoxide in ethanol at 40°C (equation 37).

The nitrogen isotope effect results show that an electron-withdrawing group in the aniline ring leads to an increased magnitude of the leaving-group isotope effect. Consequently, the extent of carbon—nitrogen bond rupture is greater for the more electron-withdrawing substituents, i.e. the ‘better’ the leaving group.

The authors, after a consideration of the \(k^{OD}/k^{OH}\) values of Steffa and

<table>
<thead>
<tr>
<th>Substituent 'Z'</th>
<th>(k_{H}/k_{D})</th>
<th>([(1/k^{14}) - (1/k^{15})]100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(p)-OCH(_3)</td>
<td>4.70 ± 0.06(^a)</td>
<td>1.19 ± 0.07(^b)</td>
</tr>
<tr>
<td>(p)-CH(_3)</td>
<td>4.61 ± 0.04</td>
<td>1.13 ± 0.06</td>
</tr>
<tr>
<td>H</td>
<td>4.50 ± 0.04</td>
<td>1.12 ± 0.08</td>
</tr>
<tr>
<td>(p)-Cl</td>
<td>4.53 ± 0.09</td>
<td>1.30 ± 0.07</td>
</tr>
<tr>
<td>(m)-CF(_3)</td>
<td>5.00 ± 0.07</td>
<td>1.32 ± 0.06</td>
</tr>
<tr>
<td>(p)-CF(_3)</td>
<td>5.39 ± 0.07</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\) Ratio of specific rates of elimination; deviation = \(\pm (k_{H}/k_{D})(r_{H}/k_{H})^2 + (r_{D}/k_{D})^2)\)^{1/2} where \(r\) is the standard deviation in \(k\).

\(^b\) Limits shown are the standard deviation.
Thornton, and the variation of the primary $k_{1H}/k_D$ values with substituents, concluded that the proton was more than one-half transferred to base at the transition state for reaction of each substrate. Furthermore, the large value of $k_{1H}/k_D = 4.50$ and a smaller Hammett $\rho$ value of $+2.69$ (compared with $+3.66$ for reaction of the 2-arylethyltrimethylammonium compounds) led to the conclusion that the proton is only slightly more than one-half transferred in the transition state. In other words, the transition state is a central one with slight carbanion character. This is in contrast to what was found for the reaction of the 2-arylethyltrimethylammonium salts where the poorer leaving group (trimethylamine) led to a transition state which is very carbanion-like with extensive C—H bond rupture.

The isotope effects for reaction of the anilinium compounds can be considered in terms of the degree of C—H and C—N bond weakening at the transition state. When an electron-withdrawing substituent 'Z' is present in the leaving group both $k_{1H}/k_D$ and the nitrogen effect increase. This means that an increase in C—N bond length is coupled with a decrease in C—H bond length at the transition state. Changing to a better leaving group would lower the energy of both the top right-hand and left-hand corners of the energy surface. For a central transition state, therefore, it appears that the effect of a substituent change is primarily felt in the direction perpendicular to the reaction coordinate.

D. Effect of Different Amine Leaving Groups on the Nature of the E2 Transition State for the Reaction of 2-Phenylethyl Quaternary Ammonium Salts with Ethoxide Ion

Grover and Smith extended the study of the effect of the leaving group on the nature of the E2 transition state by measuring the primary deuterium isotope effects for the reaction of 2-phenylethyl quaternary ammonium salts with different amine leaving groups. The rate constants and $k_{1H}/k_D$ values, together with the $pK_a$ values for the amine leaving groups are shown in Table 14.

There is a reasonably linear relationship between log ($k_{1H}/k_D$) and the $pK_a$ of the leaving group. The better leaving groups (lower $pK_a$ values) have associated with them larger values for the primary hydrogen–deuterium isotope effects.

### TABLE 14. Rate constants, $k_{H}/k_D$ effects and $pK_a$ values of the amine leaving groups for the reaction of 2-phenylethyl quaternary ammonium salts with ethoxide ion at 40°C

<table>
<thead>
<tr>
<th>Leaving groups</th>
<th>$k_2 \times 10^4$ (1 mol$^{-1}$ s$^{-1}$)</th>
<th>$k_{H}/k_D$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triethylamine</td>
<td>2.99 ± 0.03</td>
<td>2.82</td>
<td>11.01</td>
</tr>
<tr>
<td>Quinuclidine</td>
<td>1.12 ± 0.08</td>
<td>2.47</td>
<td>10.58</td>
</tr>
<tr>
<td>N-Methylpyrrolidine</td>
<td>2.29 ± 0.05</td>
<td>2.80</td>
<td>10.32</td>
</tr>
<tr>
<td>N-Methylpipерidine</td>
<td>4.06 ± 0.04</td>
<td>2.96</td>
<td>10.08</td>
</tr>
<tr>
<td>Trimethylamine</td>
<td>5.27 ± 0.05</td>
<td>3.02</td>
<td>9.81</td>
</tr>
<tr>
<td>N,N-Dimethylbenzylamine</td>
<td>11.23 ± 0.09</td>
<td>3.31</td>
<td>9.02</td>
</tr>
<tr>
<td>N-Methylmorpholine</td>
<td>18.09 ± 0.01</td>
<td>3.19</td>
<td>7.40</td>
</tr>
<tr>
<td>N-Methyl-N-ethylaniline</td>
<td>54.30 ± 0.03</td>
<td>4.50</td>
<td>6.00</td>
</tr>
<tr>
<td>N,N-Dimethylaniline</td>
<td>70.90 ± 0.03</td>
<td>4.50</td>
<td>5.15</td>
</tr>
</tbody>
</table>
Consequently, considering that the proton is more than one-half transferred at the transition state, the conclusion is reached, in agreement with Bourns, that the better the leaving group the less the degree of C—H bond weakening at the transition state.

V. THE USE OF OXYGEN-18, NITROGEN-15, CARBON-13 AND DEUTERIUM AS TRACERS IN THE DETERMINATION OF MASS SPECTRAL FRAGMENTATION PATHWAYS

A. Fragmentation Mechanisms of Nitroarenes

1. A deuterium tracer study

The loss of ·OH is observed from the molecular ion of o-nitrotoluene whereas there is no observed loss of ·OH from the molecular ions of the meta and para isomers. A cyclic mechanism (equation 38) has been proposed to account for these results. Recently it was found that α-d₃-o-nitrotoluene lost only ·OD it was concluded, in support of the above mechanism, that loss of the hydroxyl radical involves only the hydrogen atoms of the methyl group.

In a further test of the mechanism shown in equation (38), Butcher and Thomas examined the spectra of α,α-d₂-o-nitro-n-propylbenzene (7) and α-d-o-nitrocumene (8) which should show exclusive loss of ·OD. However 7 lost 73% ·OD and 27% ·OH while 8 lost 45% ·OD and 55% ·OH. Complete randomization of the hydrogens in the side-chain does not give rise to the observed values. It was reasoned that, because o-nitrotoluene loses hydrogen exclusively from the side-chain, it is unlikely that the ring hydrogens are involved. To account for their results, the authors suggested that partial randomization occurs in the side-chain followed by exclusive abstraction from the benzylic carbon.

Furthermore, it was found that several m- and p-alkynitrobenzenes also lost ·OH from the molecular ion in contrast to the behaviour of the isomeric nitrotoluenes. For example, the mass spectrum of n-propynitrobenzene gave ions with intensity (% total ion current) corresponding to [M—OH]⁺ as follows: ortho = 11.5, meta = 3.3 and para = 1.3. Also, the molecular ion of the para isomer deuterated in the benzylic position gave [M — OH]⁺ corresponding to 18% loss of ·OD and 82% loss of ·OH.

To account for these results, the authors proposed that isomerization occurs in the molecular ions and only after rearrangement to the ortho structure can the
hydroxyl group be lost. On this basis, the observed extent of loss of ·OH from the three isomers seems reasonable as no rearrangement is necessary for loss of ·OH from the ortho isomer and the meta isomer can rearrange to the ortho compound more easily than the para substrate. A general mechanism to account for the rearrangement is shown in equation (39).

\[
\begin{align*}
\text{D-C-D} & \quad \text{H} \quad \text{H} & \quad \text{H} \quad \text{D} \\
\text{NO}_2 & \quad \text{H} \quad \text{D} & \quad \text{H} \quad \text{D} \\
\text{rearrangement} & \quad \text{etc. (39)}
\end{align*}
\]

2. Carbon-13 and oxygen-18 labelling

Benoit and Holmes\textsuperscript{66} investigated the mechanism for the formation of the \textit{m/e} 93 ion from the molecular ion of \textit{o}-nitrobenzoic acid. On the basis of labelling experiments they suggested two mechanisms (equations 40 and 41).

\[
\begin{align*}
\text{\textit{o}}\text{-}\text{CO}_2\text{H} & \quad \text{\textit{o}}\text{-}\text{OH} \quad \text{\textit{o}}\text{-}\text{CO}_2 \quad \text{\textit{o}}\text{-}\text{OH} \\
\text{\textit{o}}\text{-}\text{CO}_2 \quad \text{\textit{o}}\text{-}\text{OH} \quad \text{\textit{o}}\text{-}\text{OH} \quad \text{\textit{o}}\text{-}\text{CO}_2 \\
\text{m/e 65} & \quad \text{m/e 93} \\
\text{(40)} & \quad \text{(41)}
\end{align*}
\]

Djerassi and coworkers\textsuperscript{87} suggested two alternate pathways (equations 42 and 43), which are consistent with the data of Benoit and Holmes\textsuperscript{66}. It is seen that the \textit{o}CO is lost in the mechanisms shown in equations (40) and (41) while for mechanisms (42) and (43) the \textit{a}CO is lost.
Djerassi's group prepared the substrate with $^{13}$C at the ring carbon to which the carboxyl group is attached, i.e. the $\alpha$-carbon. It was found that the $m/e$ 65 ion completely retained the label and it was concluded that the processes (40) and (41) are operative.

Benoit and Holmes also investigated the formation of the $m/e$ 123 ion from $o$-nitroanisole and proposed two mechanisms to account for the fact that 80% of the $m/e$ 123 ion arises via CH$_2$O loss (equation 44) and the remainder comes from NO$^-$ expulsion (equation 45).

In order to gain further information concerning the two proposed mechanisms, Djerassi determined the mass spectrum of $o$-nitroanisole labelled with $^{18}$O in the methoxy group. Surprisingly, the products contained all of the label, i.e. the only ion observed was $m/e$ 125. This was expected for NO$^-$ loss but it was totally
unexpected that formaldehyde loss did not involve the ether oxygen. The following pathway was postulated to account for the experimental results (equation 46).

\[
\begin{align*}
\text{NO}_2^{18} & \xrightarrow{\text{H}^+} \text{H}O\text{N}=\text{O} \xrightarrow{\text{NO}^*} \text{H}O\text{N}\text{O}^{18} \\
& \xrightarrow{\text{OH}} \text{H}O\text{N}\text{O}^{18} \xrightarrow{-\text{CH}_2\text{O}} \text{H}O\text{N}\text{O}^{18}
\end{align*}
\]

\[m/e 125\]

(B) Fragmentation of Monocyanopyridines

1. Carbon-13 and nitrogen-15 labelling

The mass spectra of the three isomeric monocyanopyridines show that the loss of HCN from the molecular ion is the most important process. The mechanism of this reaction has recently been investigated using carbon-13 and nitrogen-15 labelling.

When the mass spectra of the 2-, 3- and 4-cyanopyridines labelled with $^{15}\text{N}$ in the cyano group were examined, it was found that the retention of the label in the $[\text{M} - \text{HCN}]^+$ ions was 64–66%. Thus the neutral HCN lost from $\text{M}^+$ in the ion source contains preferentially the nitrogen from the pyridine ring.

In order to test whether skeletal rearrangement was significant before the loss of HCN from $\text{M}^+$, the mass spectra of 2-, 3- and 4-cyanopyridines labelled with $^{13}\text{C}$ in the cyano group were determined. It was found that the percentage retention of $^{13}\text{C}$ in the $[\text{M} - \text{CN}]^+$ ions was very similar to the corresponding $^{15}\text{N}$ retention, i.e. 67% for 2-$^{13}\text{CN}$-pyridine, 69% for 3-$^{13}\text{CN}$-pyridine and 66% for 4-$^{13}\text{CN}$-pyridine. It was concluded that destruction of the original cyano group for reactions proceeding in the ion source is at the most a very minor process.

Carbon-13 labelling in one of the ring carbons adjacent to the ring-nitrogen atom of the 2- and 4-cyanopyridines, however, revealed that in both cases about 78% of the label is retained in the fragment ions after loss of HCN from the corresponding molecular ions. This percentage is different from 68% $^{13}\text{C}$ retention that would be expected if all of the eliminated hydrogen cyanide came from the ring-nitrogen and an adjacent ring-carbon. It was concluded that the difference between the expected and observed degree of $^{13}\text{C}$ retention was due to the loss of the positional identity of the ring-carbons prior to the loss of HCN.

VI. REFERENCES

28. Isotopically labelled amino, quaternary ammonium and nitro compounds 1311


77. K. C. Westaway and Z. Waszyylo, unpublished results.
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