Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
Edited by Saul Patai

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);
The Chemistry of the Nitro and Nitroso Groups, Part 1 (1969) and Part 2 (1970).

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

With the exception of a chapter on 'Ipso-attacks involving NO_2 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*)

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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Contents

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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

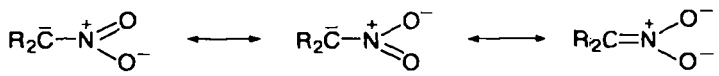
The nitro-activated carbon acids can be classified into three groups: firstly, nitromethane and its mono- and di-substituted derivatives, R_2CHNO_2; secondly the

vinylogous 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.

(1)



(a) (b) (c)

(2)

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 pK_a values for a variety of substituted methanes. (These values are taken from Cram[17]; they are rather uncertain at the high pK_a 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 1. pK_a values for various substituted methanes

Methane substituent	pK_a
H	>40
Ph	35
CN	25
$MeSO_2$	23
MeCO	20
$(MeSO_2)_2$	14
$(CN)_2$	11.5
NO_2	10.2
$(MeCO)_2$	9
$(MeCO)_3$	6
$(NO_2)_2$	3.6
$(MeSO_2)_3$	~0
$(NO_2)_3$	~0
$(CN)_3$	<0

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 dinitrocyanomethane, 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 σ_1[5]. 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 σ_1 correlation is found when alkyl substituents are introduced into nitromethane. The pK_as 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 σ_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.

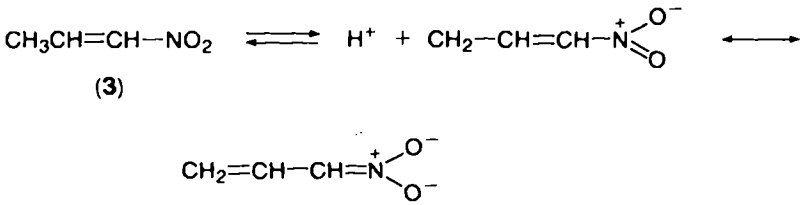
TABLE 2. pK_a values for various nitroalkanes[a]

Nitroalkane	pK_a
CH_3NO_2	10.2
$CH_3CH_2NO_2$	8.5
$CH_3CH_2CH_2NO_2$	9.0
$(CH_3)_2CHNO_2$	7.7
$PhCH_2NO_2$	6.8
$CH_2(NO_2)_2$	3.6
$CH(NO_2)_3$	0.1
$NCCH(NO_2)_2$	−6.2
CH_2ClNO_2	7.2
$CHCl_2NO_2$	6.0
CHF_2NO_2	12.4
$CF_3CH_2NO_2$	7.4
$CH_3COCH_2NO_2$	5.1

[a]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



(**3**) (1)

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[13], but will not be further discussed here.

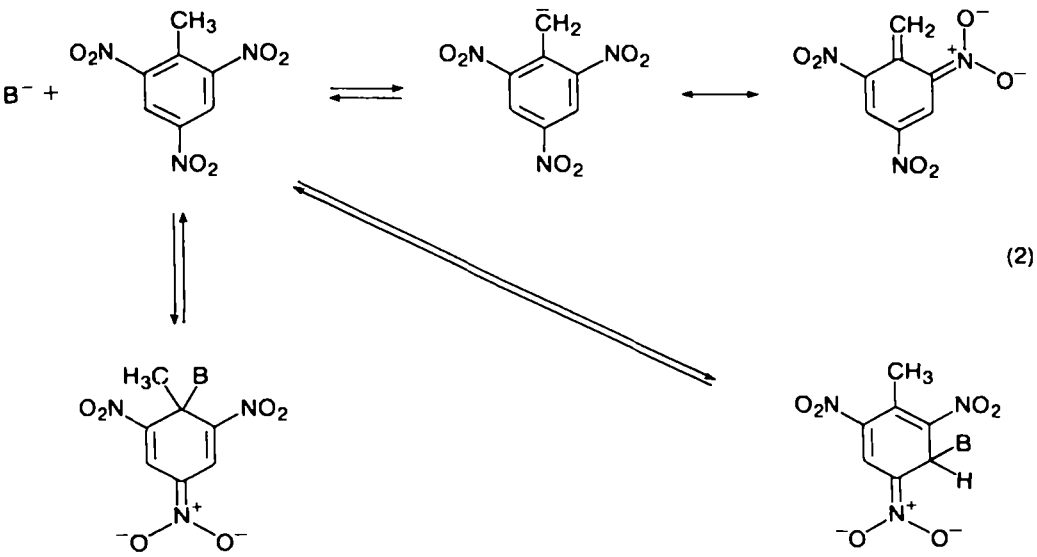
The most familiar of these vinylogous nitromethanes are the various derivatives of *o*- or *p*-nitrotoluene. The nitrotoluenes themselves have not been the subject of much study although *p*-nitrotoluene has been reported to exchange with ethanol-d and sodium hydroxide at elevated temperatures[36], but rather extensive studies have been made of 2,4,6-trinitrotoluene on the one 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[14], 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[4,15,18,25]. 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[19], is almost consistent with the earlier observations, but difficulties due to irreversible reactions have been

TABLE 3. pK_a values for nitrophenylmethanes

Compound	pK_a
4,4′,4″-Trinitrotriphenylmethane	14.32
4,4′-Dinitrodiphenylmethane	15.85
2,4′-Dinitrodiphenylmethane	17.38
3,4′-Dinitrodiphenylmethane	17.62



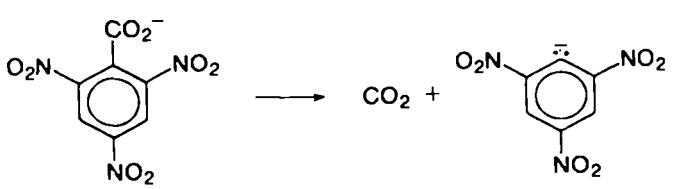
(2)

reported. Apparently the polynitrophenyl systems encourage the formation of the addition complexes, thus confusing the simple ionization.

3. *Inductively strengthened carbon acids*

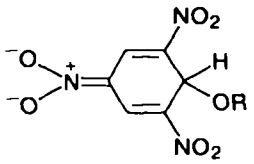
The nitro group, presumably because of the formal positive charge on nitrogen, can strengthen acids by virtue of an inductive effect alone. However, the resonance effect is normally so large that the inductive effect cannot easily be separated and evaluated. There are cases in which the inductive effect 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[12]. 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_1 values, which are large. Thus σ_1 for nitro is +0.63, and the trinitromethyl group has σ_1 = +2.04 (based on $\sigma_1 = \sigma^*/2.22$) as determined by Hine and Bailey[30]. 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



(**4**)

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[36] was initially not reproduced[46] 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.



(5)

The competition between ionization and Meisenheimer complex formation is solvent-sensitive and the exchange can be made facile at room temperature[16]. A more complete and up-to-date account is found in the review by Leffek[40].

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[40]. 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 pK_a is probably substantially greater than 14.

B. Tautomerism and Dissociation Constant Measurements in Nitroalkanes

1. *Nitronic acids as tautomers of nitroalkanes*

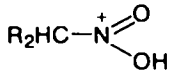
A feature of the chemistry of nitroalkanes is the existence of tautomers, as shown in equation (3). The tautomers are now generally called nitronic acids; earlier they were called *aci*-nitro compounds. These tautomers are usually unstable with respect to the nitroalkanes, but are known because the interconversion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

(3)

The nitronic acids and the nitro compounds share the common anion, the nitronate ion, $R_2CNO_2^-$ 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[32] 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[49], who studied the



(6)

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[27]. The slow 'acid-catalysed' Nef reaction[21] 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:

$$K_C = \frac{[R_2CNO_2^-][H^+]}{[R_2HCNO_2]}$$

$$K_O = \frac{[R_2CNO_2][H^+]}{[R_2CNO_2H]}$$

These readily give equation (4).

$$\frac{K_C}{K_O} = \frac{[R_2CNO_2H]}{[R_2HCNO_2]} = K_{taut} \tag{4}$$

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

$$K_{app} = \frac{[R_2CNO_2^-][H^+]}{[R_2HCNO_2] + [R_2CNO_2H]} \tag{5}$$

$$\frac{1}{K_{app}} = \frac{1}{K_C} + \frac{1}{K_O} \tag{6}$$

$$\frac{K_{app}}{K_C} = \frac{1}{1 + K_{taut}} \tag{7}$$

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

Parent nitro compound	pK_O	pK_C	$\log K_{taut}$
CH_3NO_2	3.3	10.2	−6.9
$C_2H_5NO_2$	4.4	8.5	−4.1
$CH_3CH_2CH_2NO_2$	4.6	9.0	−4.4
$(CH_3)_2CHNO_2$	5.1	7.7	−2.6
$c\text{-}C_6H_{11}NO_2$	6.4	8.3	−1.9
$PhCH_2NO_2$	3.9	6.8	−2.9
$CH_2(NO_2)_2$	1.9	3.6	−1.7
$CH_3CH(NO_2)_2$	4.0	5.1	−1.1
$CH_3CH_2CH(NO_2)_2$	4.1	5.6	−1.5

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.

A further 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[48] 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[29] 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_3O^+ has a rate constant of $15\ mol^{-1}\ s^{-1}$, which is far below the diffusion-controlled rate. Acetylacetone anion reacts similarly with H_3O^+ with $k = 1.7 \times 10^7$, still well below diffusion control. Dicyanomethane anion reacts with H_3O^+ with a rate constant of $2.3 \times 10^9\ mol^{-1}\ s^{-1}$, 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: 6×10^{-11}, 3×10^{-9}, 2×10^{-8}. These values are quoted by Hammett[28], 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[11] and by Kresge[39]. 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.

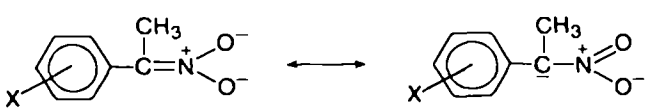
Our recent knowledge of both rate and equilibria in nitro compound ionization is greatly enhanced by the important and careful quantitative measurements of Bordwell and his coworkers. These are extensively but not comprehensively referred to in this chapter. The next unusual rate–equilibrium relation 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

$$ArCHNO_2CH_3 + OR^- \xrightarrow{MeOH-H_2O} Ar\bar{C}NO_2CH_3 + HOR \qquad (8)$$

equilibrium constants (expressed as K_a) fit the Hammett equation with the $\rho_{rate} = +1.44$, $\rho_{eq} = +1.07$. 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 α. 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, $\rho_{rate} = +0.665$, $\rho_{eq} = +0.395$, $\alpha = +1.68$, β (for the reverse) $= -0.68$. These unusual values of α 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.

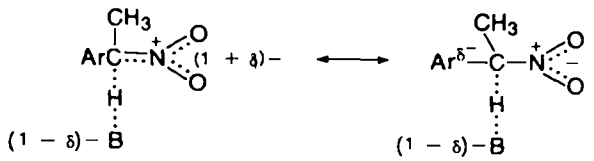
If we compare ρ_{eq} for the 1-aryl-2-nitropropanes with that for the 1-arylnitroethanes, we find the former is smaller by a factor of 2.7. This is an example of the attenuation of substituent effects by moving the created charge farther from the benzene bearing substituents by the CH_2 groups. Parenthetically, 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 ρ values are relatively normal in this respect. The ρ_{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



(7a) **(7b)**

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

It remains only to say that the larger ρ 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 δ, what are the relative contributions of **8a** and **8b**, and why do they differ so drastically from the relative contributions of **7a** and **7b**?



(8a) (8b)

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 α 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[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[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[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[20], in connection with a study of secondary isotope effects in the ionization of 2-nitropropane.

There have been several applications of Marcus' theory[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 α lies between zero and one. The problem of accommodating Marcus' theory to the normal α values has been summarized by Kresge[38] in a review in which eight examples of α 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[45]. The reason for variable intrinsic barriers in this reaction is made plausible, and it is suggested that ρ values for a nitro compound reacting with a variety of different oxygen or nitrogen bases should not have the problem, in agreement with experiment.

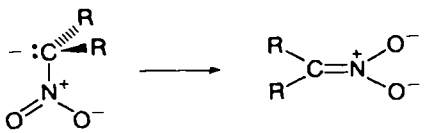
Kresge[37] originally concluded that the unusual α values implied a special transition-state interaction between the base and the nitro compound, not present in reagent or product. A later extension by Kresge[39] identified two interactions as the nitronate hyperconjugation, present in the product but 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 α 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

(9)

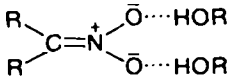


(10)

near the undelocalized carbanion and thus allows an immediate understanding of the anomalous α 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 CRR plane and the O_2NC 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



(**9**)

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[34] and the Brønsted α is 0.92, compared to the value of 1.54 in water. The α value is no longer conspicuously anomalous, although still quite large, and Keefe[34] 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[50] 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 β; many values of β have been measured. The range is rather small, and they always have fallen within the normal range of 0–1. The β 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 β values have been listed to show the unsatisfactory nature of the problem[9].

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[41].

The effort has been to deduce the symmetry of the transition state based on the Westheimer argument[51] 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[2], of hydrogen isotope effect vs. ΔpK_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 ΔpK_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'[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[3,52], 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[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[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.

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
Edited by Saul Patai

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[1-8]. 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[2,9] and by Arnett[10,11].

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, $k > 1 \times 10^{-9}$ cm^3 molecule^{-1} s^{-1}, without complications from other reaction channels[12]. 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 = H_2, CO, CH_4, O_2

$$XH^+ + NH_3 \longrightarrow NH_4^+ + X \qquad (1)$$

and HO_2, the rate constants have been observed to be quite insensitive to the mean relative kinetic energy from thermal to about 1 eV[20,21].

(*ii*) For the deuteron-transfer reaction of D_3^+ with NH_3, internal excitation of the ion has been shown to actually decrease the rate constant as is shown in Figure 1[23,24].

(*iii*) In one study of the overall temperature dependence of the rate constant for the proton transfer to NH_3 from N_2H^+, a small negative temperature dependence was observed between 320 and 640 K[25].

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 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

Reactant ion	k_{total}[a]	Mode of reaction[b]		Technique[c]	Reference
H_3^+	4.2	PT		FA	12
D_3^+	3.1	PT		FA	24
H_3O^+	2.4, 2.2	PT		FA, ICR	12, 15
HCO^+	2.4, 1.9, 2.6	PT		FA, SIFT, ICR	12, 13, 15
O_2H^+	2.0	PT		FDT	20
$H_2O_2^+$	1.8	PT		FDT	21
N_2H^+	2.3	PT		FA	12
N_2OH^+	2.1	PT		FA	12
H_2COH^+	1.7, 2.0, 2.3	PT		FA, SIFT, ICR	17, 13, 15
CH_5^+	2.5, 2.33, 2.31	PT		FA, ICR, TIMS	12, 16, 22
CD_5^+	2.06	PT		TIMS	22
$C_2H_5^+$	2.1, 2.00	PT		FA, ICR	12, 16
$C_2H_7^+$	2.0	PT		FA	12
$C_3H_7^+$	1.9, 1.95	PT		FA, ICR	12, 16
CH^+	2.7	$HCNH^+$	(0.68)	SIFT	14
		CT	(0.17)		
		PT	(0.15)		
CH_2^+	2.8	$CH_2NH_2^+$	(0.55)	SIFT	14
		PT	(0.45)		
CH_3^+	2.2	H_4CN^+	(0.70)	SIFT	14
		$CH_3^+ \cdot NH_3$	(0.20)		
		PT	(0.10)		
CH_4^+	2.8	CT	(0.59)	SIFT	14
		PT	(0.41)		
CCl_2D^+	0.78	PT	(0.57)	ICR	18, 19
		$CClDNH_2^+$	(0.24)		
		$CClHNH_2^+$	(0.19)		
CF_2H^+	1.00	PT	(>0.99)	ICR	18
		$CFHNH_2^+$	(trace)		

[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.

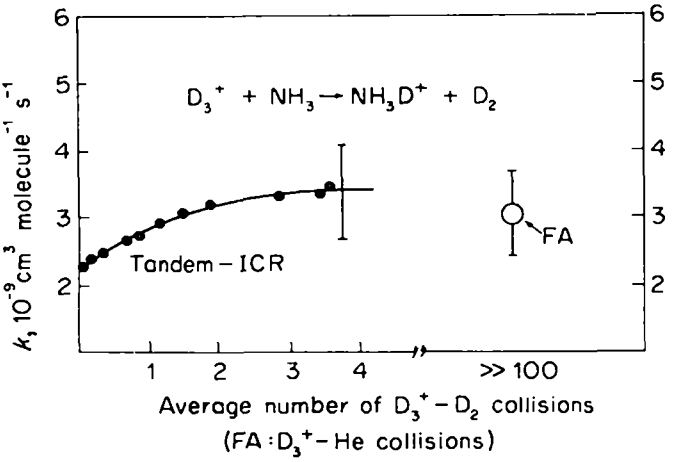


FIGURE 1. The influence of internal excitation on the rate of protonation of ammonia by D_3^+. In the Tandem-Ion Cyclotron Resonance (ICR) experiments deexcitation proceeds by collisions with D_2 molecules while in the flowing afterglow (FA) experiments collisions with He atoms prevail. Reproduced with permission from D. K. Bohme in *Interactions between Ions and Molecules* (Ed. P. Ausloos), Plenum Press, New York, 1975, p. 489.

provide useful limiting values[24]. Furthermore, since these proton-transfer reactions cover a wide range in exothermicity (standard enthalpy change, ΔH^0) or exoergicity (standard free energy change, ΔG^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 exothermity 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].

$$CH^+ + NH_3 \xrightarrow{0.68} HCNH^+ \quad H_2 \qquad (2a)$$

$$\xrightarrow{0.17} NH_3^+ + CH \qquad (2b)$$

$$\xrightarrow{0.15} NH_4^+ + C \qquad (2c)$$

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 $[H_2C{=}NH_2]^+$ is presumed to be formed. The reaction of the methylcarbonium ion with NH_3 has been

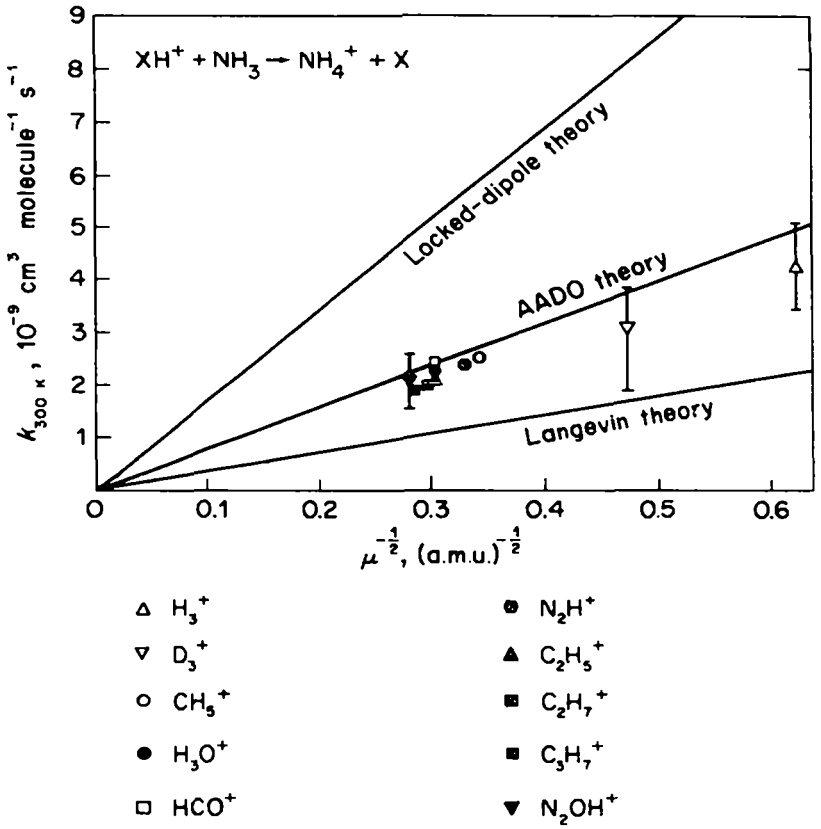


FIGURE 2. A comparison of experimental rate constants for the protonation of ammonia (the solid bars represent the estimated accuracy) with collision rate constants predicted by various classical theories. Reproduced with permission from D. K. Bohme in *Interactions between Ions and Molecules* (Ed. P. 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)[14]. Under these conditions 20% of the reactive collisions result in the

$$CH_3^+ + NH_3 \xrightarrow{0.70} H_4CN^+ + H_2 \quad (3a)$$

$$\xrightarrow{0.20} CH_3^+.NH_3 \quad (3b)$$

$$\xrightarrow{0.10} NH_4^+ + CH_2 \quad (3c)$$

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

TABLE 2. Some rate constants (in units of 10^{-9} cm^3 molecule^{-1} s^{-1}) for the protonation of amines at room temperature

Reactants	k_{total}[a]	Mode of reaction[b]		Technique[c]	Reference
$CH_5^+ + CH_3NH_2$	2.25, 2.51	PT		ICR, TIMS	16, 22
$CD_5^+ + CH_3NH_2$	2.21	PT		TIMS	22
$C_2H_5^+ + CH_3NH_2$	1.87	PT		ICR	16
$C_3H_7^+ + CH_3NH_2$	1.65	PT		ICR	16
$CH_5^+ + (CH_3)_2NH$	2.15, 2.25	PT		ICR, TIMS	16, 22
$CD_5^+ + (CH_3)_2NH$	2.05	PT		TIMS	22
$C_2H_5^+ + (CH_3)_2NH$	1.88	PT		ICR	16
$C_3H_7^+ + (CH_3)_2NH$	1.64	PT		ICR	16
$NH_3D^+ + NH_3$	0.77	PT		TIMS	22
$CH_3NH_2D^+ + CH_3NH_2$	0.64	PT		TIMS	22
$(CH_3)_2NHD^+ + (CH_3)_2NH$	0.31	PT		TIMS	22
$CH^+ + CH_3NH_2$	2.2	H^-	(0.50)	SIFT	28
		PT	(0.40)		
		CT	(0.10)		
$CH_2^+ + CH_3NH_2$	2.1	H^-	(0.55)	SIFT	28
		CT	(0.35)		
		PT	(0.10)		
$CH_3^+ + CH_3NH_2$	2.2	CT	(0.55)	SIFT	28
		H^-	(0.45)		
		$CH_3^+.CH_3NH_2$[d]			
$CH_4^+ + CH_3NH_2$	2.2	CT	(0.60)	SIFT	28
		H^-	(0.40)		
$CCl_2D^+ + CH_3NH_2$	e	PT	(0.63)	ICR	18
		H^-	(0.25)		
		$CH_3NHCClD^+$	(0.12)		
$CF_2H^+ + CH_3NH_2$	e	PT	(>0.98)	ICR	18
		H^-	(<0.02)		
$CCl_2D^+ + C_2H_5NH_2$	~1.5	PT	(0.73)	ICR	18
		H^-	(0.27)		
$CF_2H^+ + C_2H_5NH_2$	e	PT	(>0.98)	ICR	18
		H^-	(<0.02)		
$CCl_2D^+ + (CH_3)_2NH$	e	PT	(0.59)	ICR	18
		H^-	(0.25)		
		CT	(0.16)		
$CF_2H^+ + (CH_3)_2NH$	e	PT	(0.80)	ICR	18
		H^-	(0.10)		
		CT	(0.10)		
$CCl_2D^+ + (CH_3)_3N$	1.37	PT	(0.08)	ICR	18
		H^-	(0.22)		
		CT	(0.70)		
$CF_2H^+ + (CH_3)_3N$	e	PT	(0.76)	ICR	18
		H^-	(0.12)		
		CT	(0.12)		
$CCl_2D^+ + C_6H_5NH_2$	1.0	PT	(0.01)	ICR	19
		CT	(0.99)		

[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.

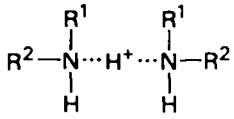
formation of $CH_2NH_2^+$ by loss of a hydrogen molecule across the C—N bond, and the other in the formation of CH_3NH^+ by loss of H_2 from the nitrogen end of the intermediate complex, approximately in the ratio 3.3 to 1[27].

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 $R^1R^2NHD^+$ ion produced in the special case of deuteron transfer from CD_5^+ or $C_2D_5^+$ to R^1R^2NH has been shown to react further with R^1R^2NH 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

$$R^1R^2NHD^+ + R^1R^2NH \longrightarrow R^1R^2NH_2^+ + R^1R^2ND \quad (4)$$

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 $R^1R^2NHD^+$ 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 **1**. If the



(1)

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_3NH_2 are again less straightforward in that several other channels are observed to compete with proton transfer. The low ionization potential of CH_3NH_2 makes direct charge transfer energetically possible in all cases and, indeed, it is always observed to occur. Proton transfer to produce $CH_3NH_3^+$ is a minor channel and is observed to occur only with CH^+ and CH_2^+. The formation of $CH_2NH_2^+$ 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

$$CH_x^+ + CH_3NH_2 \longrightarrow CH_2NH_2^+ + CH_{x+1} \quad (5)$$

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 $CH_2NH_2^+$ in the case of the reaction with CH_3^+ appears to be restricted on

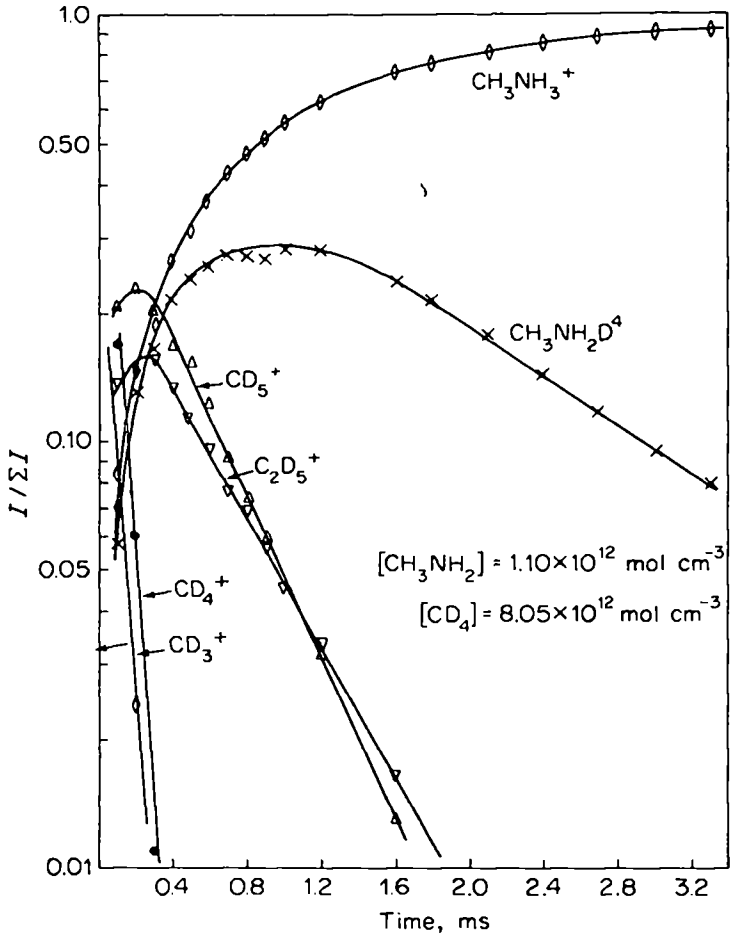


FIGURE 3. Ion intensities in a mixture of CD_4 and CH_3NH_2 measured as a function of time with a trapped-ion mass spectrometer. Reproduced by permission of Elsevier Scientific Publishing Company, Amsterdam from A. G. Harrison, P.-H. Liu and C. W. Tsang, *Intern. J. Mass Spectrom. Ion Phys.*, **19**, 23 (1976).

$$CH_x^+ + CH_3NH_2 \longrightarrow [CH_3NH_2^+]^* + CH_x \qquad (6a)$$

$$[CH_3NH_2^+]^* \longrightarrow CH_2NH_2^+ + H \qquad (6b)$$

$$CH_x^+ + CH_3NH_2 \longrightarrow [CH_3NH_3^+]^* + CH_{x-1} \qquad (7a)$$

$$[CH_3NH_3^+]^* \longrightarrow CH_2NH_2^+ + H_2 \qquad (7b)$$

energetic grounds to proceed by 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 $CH_3^+ . CH_3NH_2$ which conceivably may rearrange into, for example, protonated ethylamine. We have noted earlier the analogous channel in the reaction of CH_3^+ with NH_3.

The three options represented by equations (5)–(7) have been investigated by Huntress and Bowers[29] in their studies of the reaction of H_3^+ with CH_3NH_2. These indicated that the product distribution and mechanism depends critically on the amount of excess internal energy of H_3^+. For highly excited H_3^+ ions the reaction proceeds mainly by the direct processes: by charge transfer and a process equivalent to H^- abstraction. For partially or totally deactivated 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 H_2 elimination to form $CH_2NH_2^+$ and by C—N bond scission to produce CH_3^+ according to equation (8).

$$H_3^+ + CH_3NH_2 \longrightarrow [CH_3NH_3^+]^* + H_2 \quad (8a)$$

$$[CH_3NH_3^+]^* \longrightarrow CH_2NH_2^+ + H_2 \quad (8b)$$

$$[CH_3NH_3^+]^* \longrightarrow CH_3^+ + NH_3 \quad (8c)$$

The relative importance of competing channels for the reactions of CCl_2H^+ and CF_2H^+ with ammonia and amines has been investigated and discussed by Lias and Ausloos[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 prodominate 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[30,31]: the amine was added into a flowing NH_3–He plasma in which H^- and NH_2^- were established as the major

TABLE 3. Rate constants (10^{-9} cm^3 molecule^{-1} s^{-1}) for the deprotonation of NH_3 and several aliphatic amines at room temperature[30,31]

Reaction	k
$H^- + NH_3 \rightarrow NH_2^- + H_2$	0.00090 ± 0.00018
$H^- + CH_3NH_2 \rightarrow CH_3NH^- + H_2$	0.017 ± 0.009
$H^- + C_2H_5NH_2 \rightarrow C_2H_5NH^- + H_2$	1.1 ± 0.3
$H^- + (CH_3)_2NH \rightarrow (CH_3)_2N^- + H_2$	4.3 ± 0.9
$NH_2^- + CH_3NH_2 \rightarrow CH_3NH^- + NH_3$	>0.1
$NH_2^- + C_2H_5NH_2 \rightarrow C_2H_5NH^- + NH_3$	2.6 ± 0.8
$NH_2^- + (CH_3)_2NH \rightarrow (CH_3)_2N^- + NH_3$	≈ 3
$NH_2^- + (CH_3)_3N \rightarrow$ products	<0.001

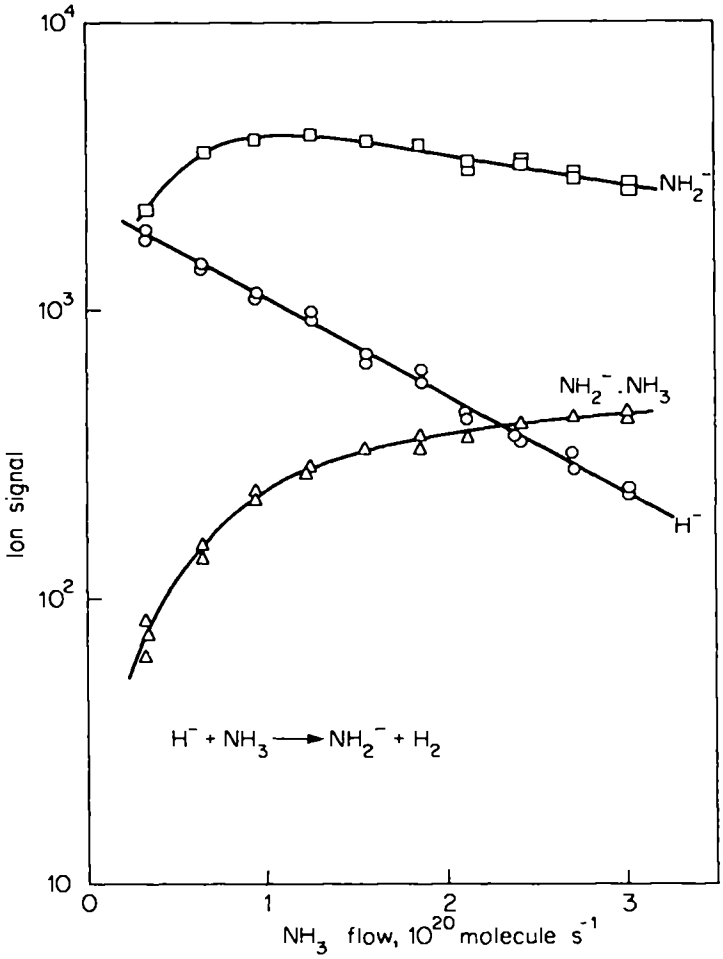


FIGURE 4. The variation of the H^-, NH_2^- and $NH_2^-.NH_3$ signals recorded upon the addition of NH_3 into a flowing He–NH_3 plasma in which H^- is initially a major ion (T = 297 K, P = 0.301 Torr). Reproduced by permission of the American Institute of Physics from D. K. Bohme, R. S. Hemsworth, H. W. Rundle and H. I. Schiff, *J. Chem. Phys.*, **59**, 77 (1973).

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_3NH_2 by H^- for which $k = 1.7 \pm 0.9 \times 10^{-11}$ cm^3 molecule^{-1} s^{-1}. and the deprotonation of $(CH_3)_3N$ 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.

III. PROTON-TRANSFER EQUILIBRIA

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

$$NH_4^+ + CH_3NH_2 \longrightarrow CH_3NH_3^+ + NH_3 \quad (9)$$

$$CH_3NH_3^+ + (CH_3)_2NH \longrightarrow (CH_3)_2NH_2^+ + CH_3NH_2 \quad (10)$$

$$(CH_3)NH_2^+ + (CH_3)_3N \longrightarrow (CH_3)_3NH^+ + (CH_3)_2NH \quad (11)$$

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:

$$(CH_3)_3N > (CH_3)_2NH > CH_3NH_2 > NH_3$$

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:

$$(C_2H_5)_3N > (C_2H_5)_2NH > C_2H_5NH_2 > NH_3$$

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

Primary amines: $t\text{-}C_4H_9NH_2 > (CH_3)_3CCH_2NH_2 > i\text{-}C_3H_7NH_2 > n\text{-}C_3H_7NH_2 > C_2H_5NH_2 > CH_3NH_2 > NH_3$

Secondary amines: $(C_2H_5)_2NH > (CH_3)_2NH$

Tertiary amines: $(C_2H_5)_3N > (CH_3)_3N$

Miscellaneous: $(CH_3)_3N > t\text{-}C_4H_9NH_2$

$(CH_3)_2NH \approx i\text{-}C_3H_7NH_2$

$(CH_3)_3N \approx (C_2H_5)_2NH$

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

$$R^1R^2N^- + R^3R^4NH \rightleftharpoons R^1R^2NH + R^3R^4N^- \quad (12)$$

proceed essentially in one direction only. These investigations provided the following orders of acidity:

$$(C_2H_5)_2NH > (CH_3)_3CCH_2NH_2 > t\text{-}C_4H_9NH_2 > (CH_3)_2NH >$$

$$i\text{-}C_3H_7NH_2 > n\text{-}C_3H_7NH_2 > C_2H_5NH_2 > CH_3NH_2 > NH_3$$

$$(C_2H_5)_2NH > H_2O > t\text{-}C_4H_9NH_2$$

Experiments carried out with $C_2D_5NH_2$ demonstrated that N—H protons were removed exclusively. Other experiments with saturated alkanes established that $NH_3 > CH_4$. Support for the relative gas-phase acidity of NH_3 was provided by a series of flowing afterglow experiments[37–39] which established the following order of acidity:

$$H_2O > H_2 > NH_3 > CH_4, C_2H_4, (CH_2)_3, C_6H_{12}$$

B. Positive-ion Equilibria

Equilibrium constants for proton-transfer reactions of the type shown in equation (13) involving amines B^1 and B^2, began to be reported some six years after the

$$B^1H^+ + B^2 \rightleftharpoons B^2H^+ + B^1 \quad (13)$$

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, ΔG^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

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

measurement of the apparent equilibrium concentrations established in mixtures of the protonated amines and their conjugate bases according to the relationship in equation (15).

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

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, ΔH^0, and the standard entropy change, ΔS^0 for reaction (13).

In the early application of the ICR technique[40,41], the relative intensities of the protonated amines were monitored as a function of pressure (from 2 to 8×10^{-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 1×10^{-4} Torr. However, these could be avoided by performing experiments on the same mixtures using a pulsed ICR spectrometer fitted with a trapped ion-analyser cell[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

(16)

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

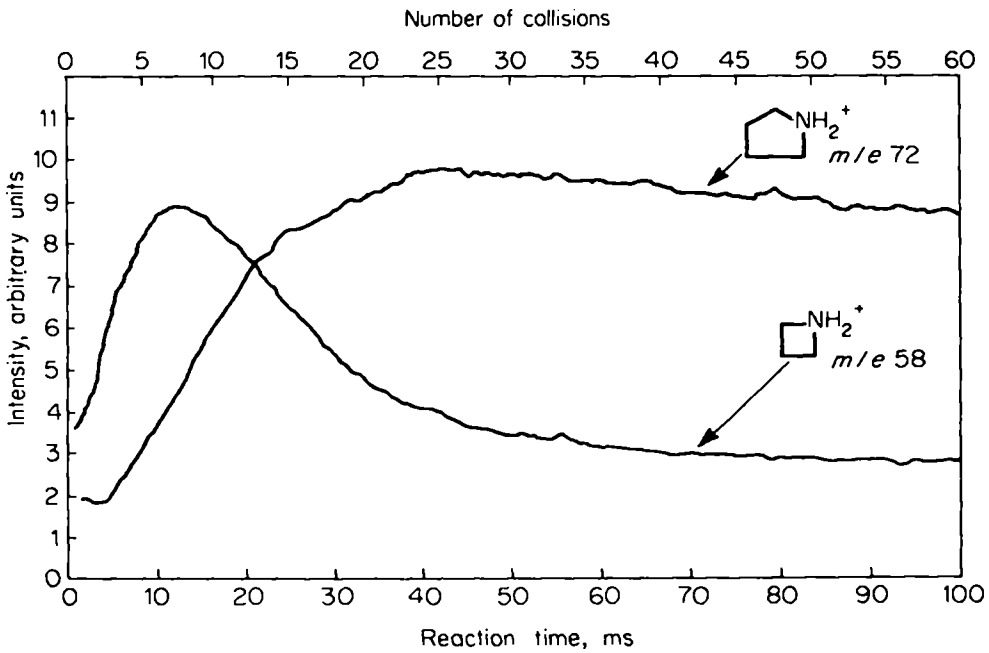


FIGURE 5. Pulsed ICR data for the $(CH_2)_3NH_2^+$ and $(CH_2)_4NH_2^+$ peaks in a 6.4:1.0 mixture of $(CH_2)_3NH$ and $(CH_2)_4NH$ at approximately 1×10^{-5} Torr. The protonated species (*m/e* 58, 72) are formed by the reaction of parent ions (*m/e* 57, 71) with the two neutral molecules. Reprinted 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.

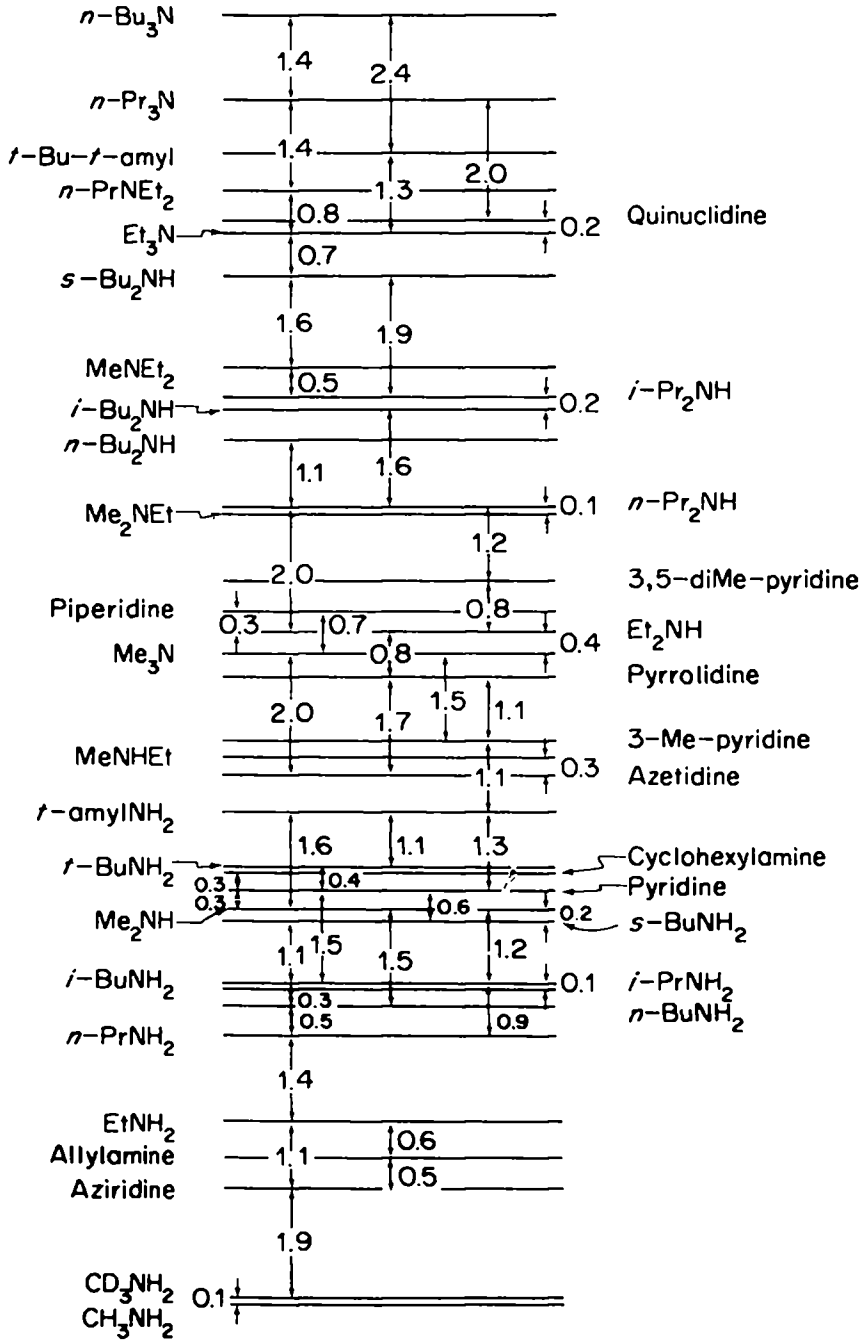


FIGURE 6. Summary of values of ΔG^0 (kcal mol^{-1}) between alkylamines derived using high-pressure ICR techniques. Reprinted with permission from D. H. Aue, H. M. Webb and M. T. Bowers, *J. Amer. Chem. Soc.*, **98**, 311 (1976). Copyright by the American Chemical Society.

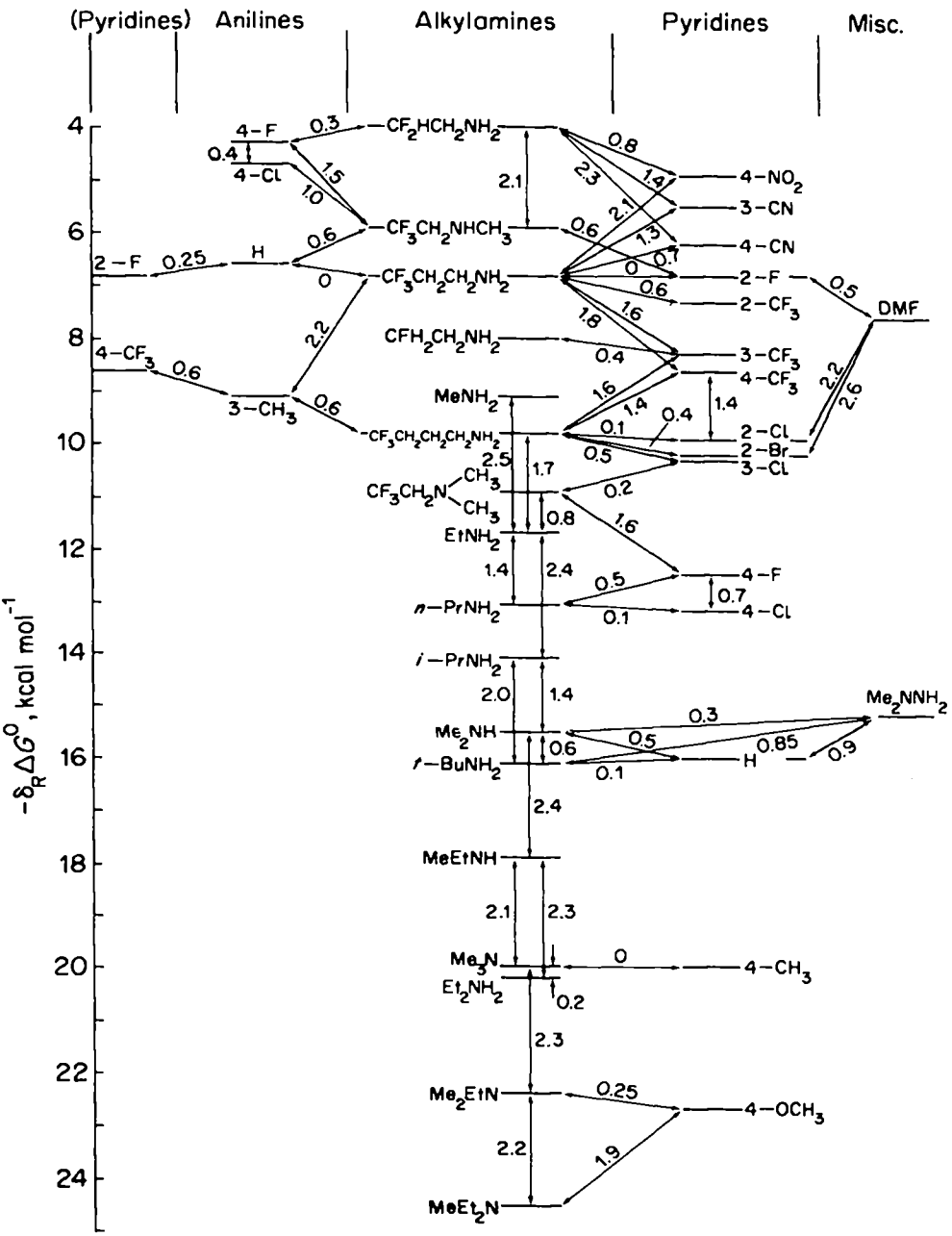


FIGURE 7. Summary of values of ΔG^0 (kcal mol^{-1}) derived using low-pressure ICR techniques. Reproduced with permission from R. W. Taft in *Proton-transfer Reactions* (Eds. E. Caldwin and V. Gold), Chapman and Hall Ltd., London, 1975, p. 31.

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[43] who used a trapped ICR drift cell method and by Taft and coworkers who performed pulsed ICR measurements[2]. Typical experiments were done at 10^{-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[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[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 10^5 could be measured over the

$$CH_3NH_3^+ + (CH_3)_2NH \rightleftharpoons (CH_3)_2NH_2^+ + CH_3NH_2 \qquad (17)$$

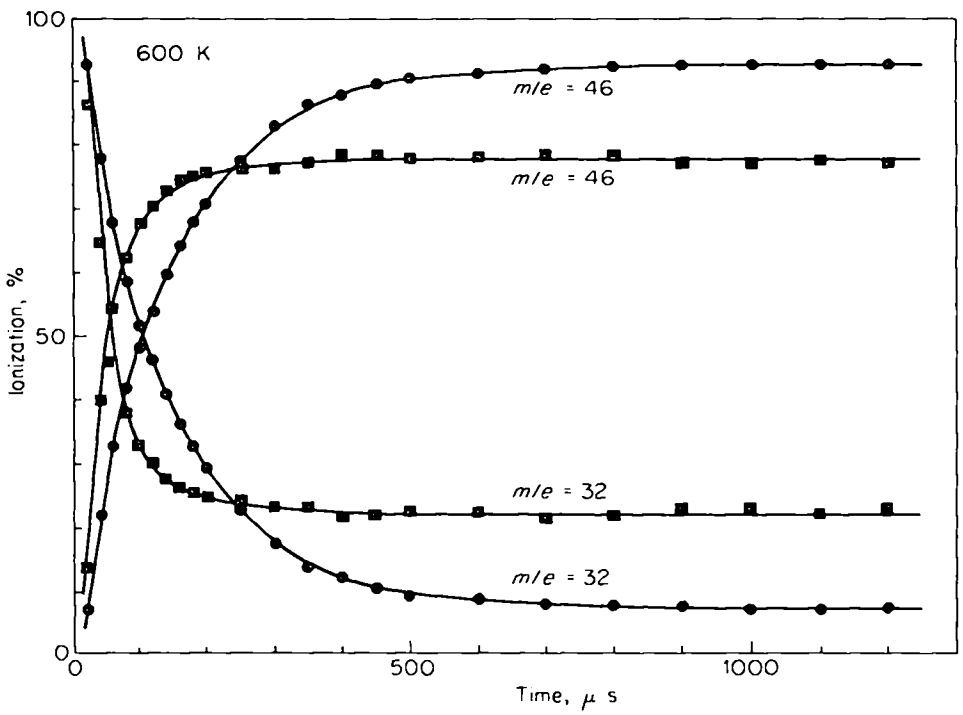


FIGURE 8. The time dependence of normalized intensities of $(CH_3)_2NH_2^+$ (*m/e* 46) and $CH_3NH_3^+$ (*m/e* 32) recorded with a high-pressure mass spectrometer at 600 K. ●: CH_4 at 4 Torr, methylamine at 31 mTorr, dimethylamine at 0.8 mTorr; ■: CH_4 at 4 Torr, methylamine at 340 mTorr, dimethylamine 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.

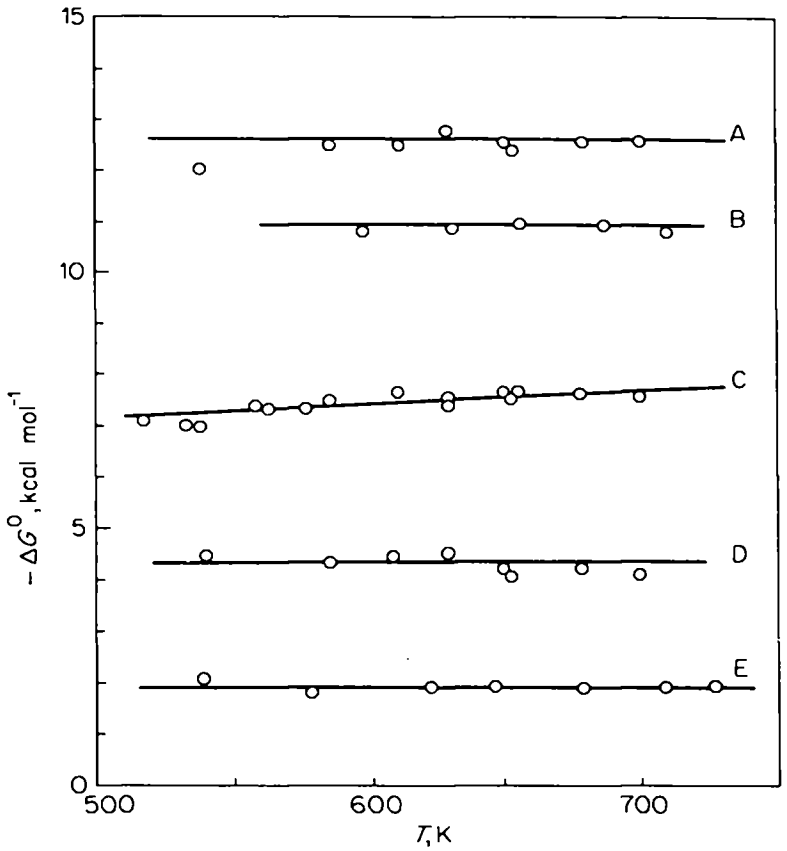


FIGURE 9. Temperature dependence of $\Delta G^0 = -RT \ln K$ for proton-transfer equilibria of the type $B^1H^+ + B^2 \rightleftharpoons B^2H^+ + B^1$ with $B^1/B^2 = CH_3NH_2/(CH_3)_3N$ (A); NH_3/CH_3NH_2 (B); $CH_3NH_2/(CH_3)_2NH$ (C); $CH_3NH_2/C_6H_5NHCH_3$ (D), and $C_6H_5NH_2/CH_3NH_2$ (E). Reprinted 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 ΔG^0 showed very little change with temperature from which it may be inferred that the reactions are essentially isentropic, $\Delta S^0 < 2.0$ cal mol^{-1} deg^{-1}. A much stronger dependence on temperature was indicated for reactions of type (13) involving monoamines and α,ω-diamines. This is evident from the van't Hoff plots shown in Figure 10 which lead to entropy changes of more than 12 cal mol^{-1} 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

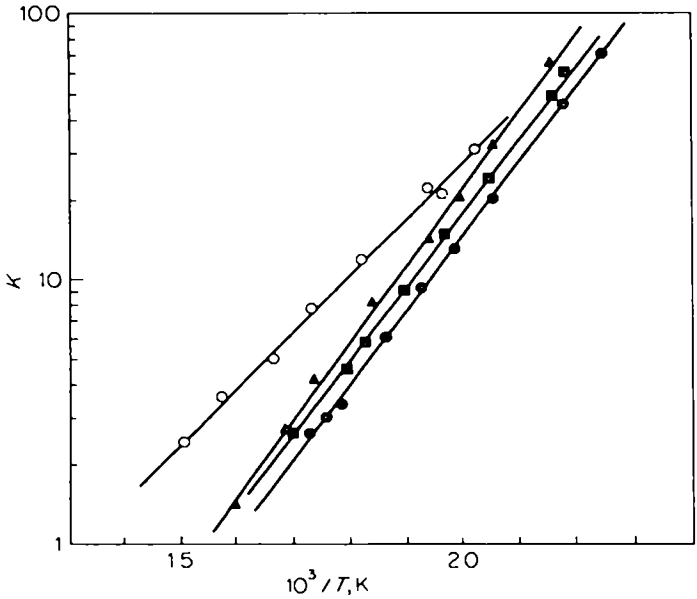


FIGURE 10. Van't Hoff plots for proton-transfer equilibria of the type $B^1H^+ + B^2 \rightleftharpoons B^2H^+ + B^1$ with B^1/B^2 = dimethylamine/1,2-diaminoethane (○), trimethylamine/1,3-diaminopropane (●), trimethylamine/1,5-diaminopentane (▲), and trimethylamine/1,7-diaminoheptane (■). Reprinted with permission from R. Yamdagni and P. Kebarle, *J. Amer. Chem. Soc.*, **95**, 3504 (1973). Copyright by the American Chemical Society.

(18), with B = NH_3, CH_3NH_2, $(CH_3)_2NH$ and $(CH_3)_3N$, and reactions of the type shown in equation (19), with B^1/B^2 = CH_3NH_2/NH_3, $(CH_3)_2NH/CH_3NH_2$ and $(CH_3)_3N/(CH_3)_2NH$. The results of this study are summarized in Table 6 and presented as van't Hoff plots in Figure 11. The observed trends in ΔG°_9 and ΔH°_9 are consistent with the notion of a partial acid–base reaction in which the

TABLE 4. Summary of the thermodynamics[a] derived from a temperature study of equilibria of the type $B^1H^+ + B^2 \rightleftharpoons B^2H^+ + B^1$ involving α,ω-diamines using high-pressure mass spectrometry[b]

B^1	B^2	$-\Delta G^0_{298}$	$-\Delta H^0$	$-\Delta S^0$
Dimethylamine	1,2-Diaminoethane	5.8	9.6	12.7
Trimethylamine	1,3-Diaminopropane	6.8	13.0	20.6
Trimethylamine	1,5-Diaminopentane	7.1	13.0	20.0
Trimethylamine	1,7-Diaminoheptane	6.9	12.9	20.0

[a] ΔH^0 and ΔS^0 are approximately temperature-independent over the temperature range indicated in Figure 10, ΔH^0 and ΔG^0 are in kcal mol^{-1} and ΔS^0 is in cal mol^{-1} deg^{-1}.
[b] Reprinted with permission from R. Yamdagni and P. Kebarle, *J. Amer. Chem. Soc.*, **95**, 3504 (1973). Copyright by the American Chemical Society.

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

B^1	B^2	$-\Delta G^0$
NH_3	CH_3NH_2	10.8
CH_3NH_2	$C_6H_5NHCH_3$	4.3
CH_3NH_2	*o*-Anisidine	4.3
CH_3NH_2	$(CH_3)_2NH$	7.5
CH_3NH_2	Pyridine	7.8
CH_3NH_2	$(CH_3)_3N$	12.5
$C_6H_5NH_2$	CH_3NH_2	1.9
$C_6H_5NH_2$	$C_6H_5NHCH_3$	6.2
$C_6H_5NH_2$	*o*-Anisidine	6.5
$C_6H_5NHCH_3$	$(CH_3)_2NH$	3.5
$C_6H_5NHCH_3$	$C_6H_5NHC_2H_5$	3.4
$C_6H_5NHCH_3$	$C_6H_5N(CH_3)_2$	6.6
$(CH_3)_2NH$	Cyclohexylamine	1.2
$C_6H_5NHC_2H_5$	Cyclohexylamine	1.3
$C_6H_5N(CH_3)_2$	$(CH_3)_3N$	1.6
$C_6H_5N(CH_3)_2$	$C_6H_5N(CH_3)(C_2H_5)$	2.5
$C_6H_5N(CH_3)_2$	Piperidine	2.8
$C_6H_5N(CH_3)_2$	$C_6H_5N(C_2H_5)_2$	5.2
Cyclohexylamine	Piperidine	4.8
Pyrrole	$C_6H_5NH_2$	1.75

[a]Reprinted with permission from R. Yamdagni and P. Kebarle, *J. Amer. Chem. Soc.*, **95**, 3504 (1973). Copyright by the American Chemical Society.

$$BH^+ + B \rightleftharpoons (BHB)^+ \quad (18)$$

$$B^1H^+ + B^2 \rightleftharpoons (B^1HB^2)^+ \quad (19)$$

formation of the proton-bound dimer is viewed as a partial proton-transfer reaction from the proton donor B^1H^+ to the proton acceptor B^2[45].

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^2H

$$(A^1)^- + A^2H \rightleftharpoons (A^2)^- + A^1H \quad (20)$$

and A^1H. They have been performed solely with the flowing afterglow technique at a total pressure of ~0.4 Torr and room temperature[30,31]. The ions $(A^1)^-$ were generated by electron impact in a flowing helium buffer gas containing a fixed amount of the amine A^1H. Equilibrium was approached by adding increasing amounts of A^2H 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 $(A^1)^-$ 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 CH_3NH^- in Figure 12 provides a value

$$CH_3NH^- + NH_3 \rightleftharpoons NH_2^- + CH_3NH_2 \quad (21)$$

TABLE 6. Summary of standard free energy and enthalpy changes (kcal mol^{-1}) derived[a] from a temperature study of equilibria of the type $B^1H^+ + B^2 \rightleftharpoons (B^1HB^2)^+$ using high-pressure mass spectrometry

B^1H^+	B^2	$-\Delta G^0_{550}$	$-\Delta H^0$
NH_4^+	NH_3	10.6	24.8
	CH_3NH_2	17.9	~32.0
	$(CH_3)_2NH$	(23.3)	(38.9)
	$(CH_3)_3N$	(27.3)	(43.3)
$CH_3NH_3^+$	NH_3	7.1	21.4
	CH_3NH_2	8.7	21.7
	$(CH_3)_2NH$	13.8	27.5
	$(CH_3)_3N$	(17.0)	(32.5)
$(CH_3)_2NH_2^+$	NH_3	5	20.6
	CH_3NH_2	6.3	27.4
	$(CH_3)_2NH$	6.65	20.8
	$(CH_3)_3N$	9.4	23.3
$(CH_3)_3NH^+$	NH_3	(4)	(20)
	CH_3NH_2	(4.5)	(20)
	$(CH_3)_2NH$	4.8	20.5
	$(CH_3)_3N$	4.9	22.5

[a]Numbers in parentheses are predicted values.
[b]Reprinted with permission from R. Yamdagni and P. Kebarle, *J. Amer. Chem. Soc.*, **95**, 3504 (1973). Copyright by the American Chemical Society.

for $K = k_f/k_r$ 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^1 and B^2, viz. $\Delta G^0 = \Delta GB$ (B^1, 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

$$BH^+ \rightleftharpoons B + H^+ \qquad (22)$$

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[46]. This practice is retained here but the basicity of NH_3 is derived from very recent appearance potential measurements[47] 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 ± 1.3 kcal mol^{-1} at 298 K.

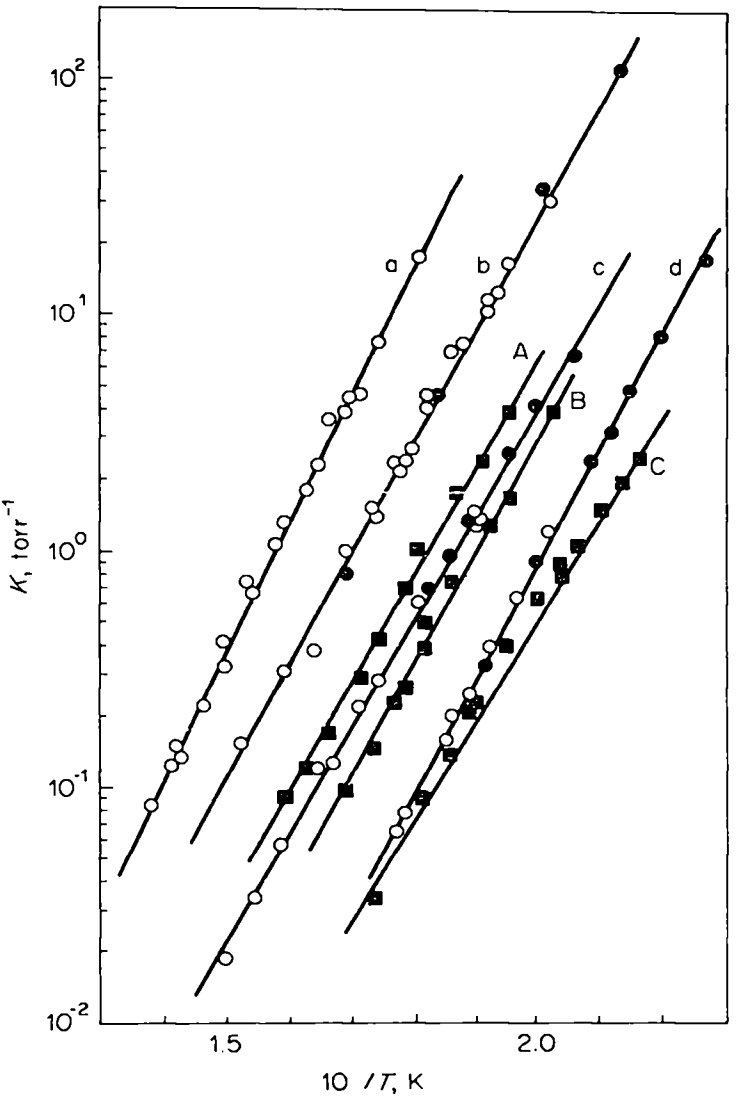


FIGURE 11. Van't Hoff plots for equilibria of the type $B^1H^+ + B^2 \rightleftharpoons (B^1HB^2)^+$ with $B^1/B^2 = NH_3/NH_3$ (a), CH_3NH_2/CH_3NH_2 (b), $(CH_3)_2NH/(CH_3)_2NH$ (c), $(CH_3)_3N/(CH_3)_3N$ (d), CH_3NH_2/NH_3 (A), $(CH_3)_2NH/CH_3NH_2$ (B), and $(CH_3)_3N/(CH_3)_2NH$ (C). (○) $B^1 = B^2$, 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.

$$NH_3.NH_3 + h\nu \longrightarrow NH_4^+ + NH_2 + e \qquad (23)$$

$$NH_4^+ \rightleftharpoons NH_3 + H^+ \qquad (24)$$

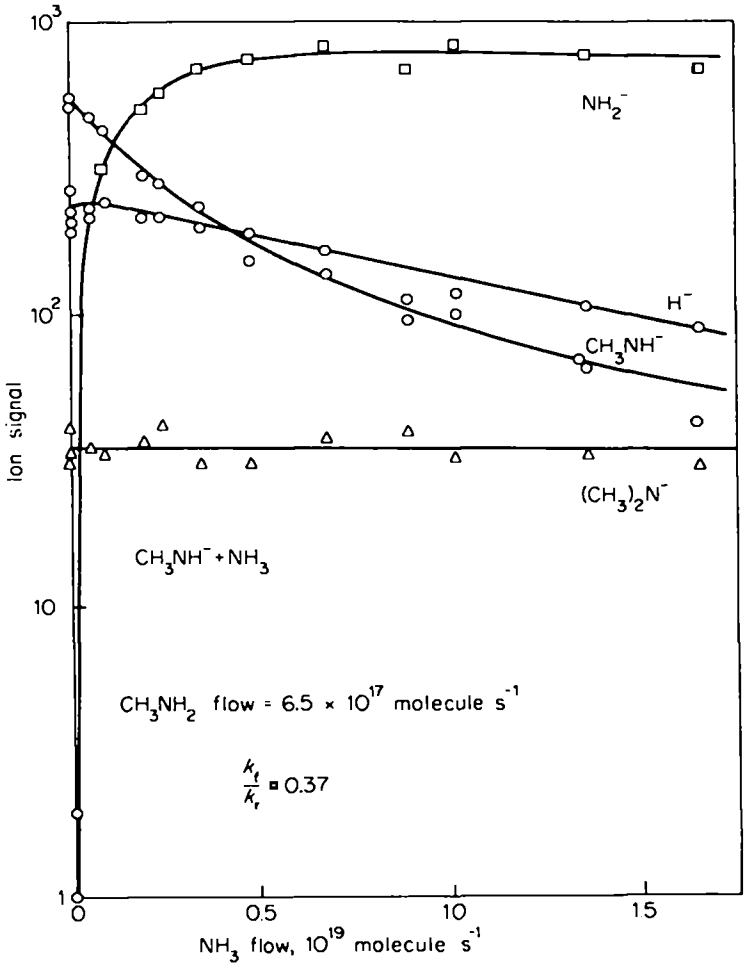


FIGURE 12. The variation of the major negative ion signals recorded upon the addition of NH_3 into a flowing CH_3NH_2–He plasma in which CH_3NH^- is initially a dominant negative ion. The curve drawn through the observed CH_3NH^- decay represents a computed fit which yields a value for the ratio of rate constants, k_f/k_r, for the proton-transfer reaction $CH_3NH^- + NH_3 \rightleftharpoons NH_2^- + CH_3NH_2$. The ion observed at m/e 44 is presumed to arise from the $(CH_3)_2NH$ impurity in CH_3NH_2 (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[46,48]. The conversion of ΔH^0_{298} to ΔG^0_{298} for reaction (24) may be accomplished by estimating the change in entropy to be equal to $S^0(H^+) + R$ ln (12/3), where 12 and 3 are the rotational symmetry numbers for NH_4^+ and NH_3, respectively[49]. Thus the absolute gas-phase basicity of NH_3, $GB(NH_3)$, is 195.0 kcal mol^{-1} with an uncertainty that

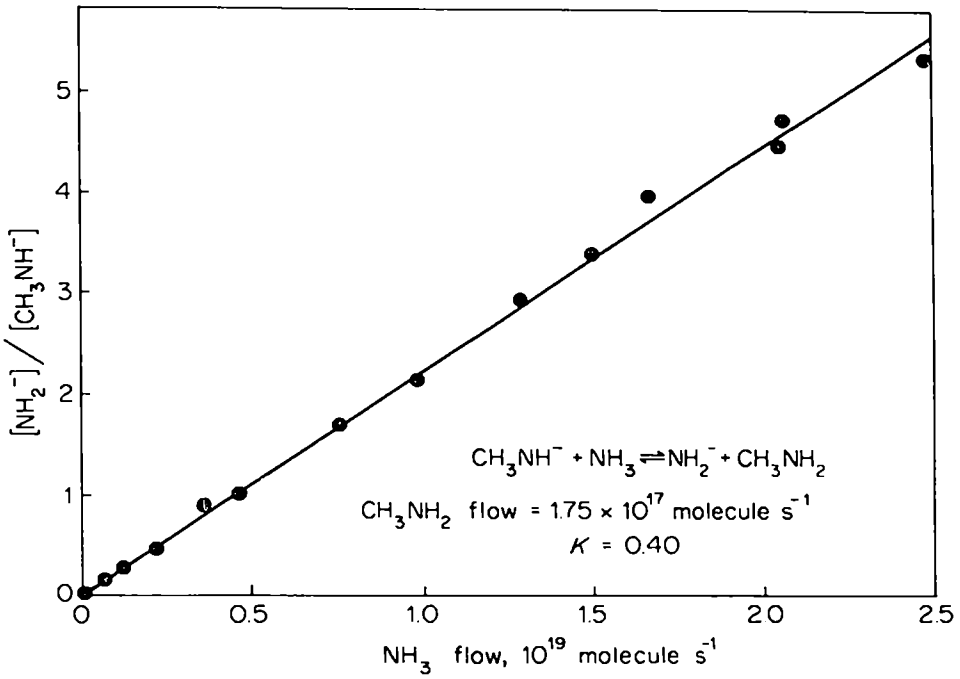


FIGURE 13. The observed variation of the ion concentration ratio with NH_3 addition. The linearity of this plot indicates attainment of equilibrium at all measured flows of NH_3 (T = 297 K, P = 0.287 Torr). Reproduced by permission of the National Research Council of Canada from G. I. Mackay, R. S. Hemsworth and D. K. Bohme, *Can. J. Chem.*, **54**, 1624 (1976).

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 GB(B) can provide a measure of the gas-phase proton affinity of B, 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[31]

A^2H	A^1H	K	$-\Delta G^0$
CH_3NH_2	NH_3	2.4 ± 0.4	0.51 ± 0.10
H_2	NH_3	26 ± 8	1.9 ± 0.2
H_2	CH_3NH_2	12 ± 3	1.5 ± 0.2
$C_2H_5NH_2$	NH_3	(1.3 ± 0.4) × 10^3	4.2 ± 0.2
$C_2H_5NH_2$	H_2	77 ± 14	2.6 ± 0.2
$(CH_3)_2NH$	H_2	(5.2 ± 1.1) × 10^3	5.0 ± 0.1

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[2,45]

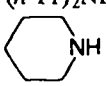
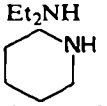
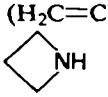
B	$GB(B)^a$	$\Delta GB(NH_3,B)^b$
Primary aliphatic amines		
t-$C_5H_{11}NH_2$	212.4	17.4
c-$C_6H_{11}NH_2$	211.3	16.3
t-$BuNH_2$	211.1	16.1
s-$BuNH_2$	210.2	15.2
i-$PrNH_2$	209.1	14.1
i-$BuNH_2$	209.0	14.0
n-$BuNH_2$	208.5	13.5
n-$PrNH_2$	208.0	13.0
$EtNH_2$	206.8	11.8
$H_2C{=}CH{-}CH_2NH_2$	206.3	11.3
$MeNH_2$	204.1	9.1
$HC{\equiv}C{-}CH_2NH_2$	201.7	6.7
Secondary aliphatic amines		
(*n*-$Pr)_2NH$	217.2	22.2
	216.2	21.2
Et_2NH	215.2	20.2
	215.1	20.1
$(H_2C{=}CHCH_2)_2NH$	214.3	19.3
	213.0	18.0
MeEtNH	212.9	17.9
Me_2NH	210.5	15.5
$(NC{\equiv}CCH_2)_2NH$	206.7	11.7
	206.2	11.2
Tertiary aliphatic amines		
(*n*-$Pr)_3N$	223.7	28.7
Et_3N	221.7	26.7
$(H_2C{=}CH{-}CH_2)_3N$	219.7	24.7
$MeEt_2N$	219.6	24.6
Me_2EtN	217.4	22.4
$(CD_3)_3N$	215.3	20.3
$(CH_3)_3N$	215.0	20.0
$(HC{\equiv}CCH_2)_3N$	210.0	15.0
Cyclic tertiary aliphatic amines		
Quinuclidine	222.1	27.1
Benzoquinuclidine	221.0	26.0
N-Methylpyrrolidine	219.3	24.3
Diazabicyclooctane	218.5	23.5
N-Phenylpiperidine	216.8	21.8
N-Phenylpyrrolidine	214.3	19.3

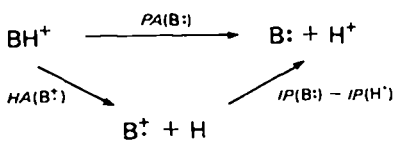
TABLE 8. *continued*

B	$GB(B)^a$	$\Delta GB(NH_3,B)^b$
Anilines		
$C_6H_5NMe_2$	214.5	19.5
C_6H_5NHMe	207.9	12.9
p-$MeC_6H_4NH_2$	204.2	9.2
m-$MeC_6H_4NH_2$	203.9	8.9
$C_6H_5NH_2$	201.7	6.7
Diamines		
$(Me_2NCH_2)_2$	225.3	30.3
1,5-Diaminopentane	217.6	22.6
1,7-Diaminoheptane	217.4	22.4
1,3-Diaminopropane	217.3	22.3
1,2-Diaminoethane	216.3	21.3
Me_2NNH_2	210.2	15.2
Pyridines		
2,6-di-t-BuC_5H_3N	221.4	26.4
4-MeC_5H_4N	215.0	20.0
2-MeC_5H_4N	214.4	19.4
3-MeC_5H_4N	213.5	18.5
C_5H_5N	211.0	16.0

[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 α,ω-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):



$$PA(B:) = HA(B^{+}) - IP(B:) + IP(H^{\cdot}) \qquad (25)$$

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

B	Measured[a]	Calculated[b]	
		STO-3G	4-31G
CH_3NH_2	212.6	269.0	232.6
$C_2H_5NH_2$	215.3	272.4	234.9
i-$C_3H_7NH_2$	217.8	275.0	236.5
t-$C_4H_9NH_2$	220.1	277.5	—

[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].

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, ΔE, calculated for proton transfer between two amines are quite close to the experimental enthalpy changes (ΔPA). 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 ΔPA 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. $\Delta G^0 = \Delta GA$ (A^2H, A^1H), with the gas-phase acidity defined as the standard free energy change

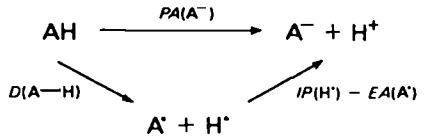
$$AH \rightleftharpoons A^- + H^+ \quad (26)$$

for the process in reaction (26). Again it follows that a continuous ladder of ΔGAs can yield absolute values for GA when the ladder is calibrated with an appropriate choice of absolute reference value. For the ΔGAs provided by the flowing afterglow studies of the aliphatic amines, $GA(H_2)$ is an obvious choice[31]. 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

$$GA(H_2) = D_0^0(H—H) + IP(H) - EA(A) + \int_0^{298} \Delta C_p dT + S^0(H^+) + S^0(H^-) - S^0(H_2) \quad (27)$$

which are available from the JANAF thermochemical tables[58]. The value of $GA(H_2)$ at 298 K derived in this manner is 394.2 ± 0.5 kcal mol^{-1} [31]. 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):



$$PA(A^-) = D(A—H) + IP(H^\cdot) - EA(A^\cdot) \quad (28)$$

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 10. Absolute gas-phase acidities of amines in kcal mol^{-1} at 298 K[a]

AH	$GA(AH)$
$(CH_3)_3N$	>396[b]
NH_3	396.1 ± 0.7
CH_3NH_2	395.7 ± 0.7
H_2	394.2 ± 0.5[c]
$C_2H_5NH_2$	391.7 ± 0.7
$(CH_3)_2NH$	389.2 ± 0.6

[a]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).
[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[a]

		Calculated[c]		
A^-	Measured[b]	Ref. 61	Ref. 57	Ref. 56
H^-	400.4 ± 0.5	400.5[d]	—	—
NH_2^-	403.6 ± 0.9	421.9[d]	—	553.3
CH_3NH^-	403.2 ± 1.0	—	442.8, 537.5	539.0
$C_2H_5NH^-$	399.4 ± 1.0	—	439.3, 536.2	—
$(CH_3)_2N^-$	396.4 ± 0.9	—	—	523.8

[a]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).
[b]$PA(A^-) = \Delta H^0_{298}$ for the reaction $AH \rightleftharpoons A^- + H^+$.
[c]$PA(A^-) = \Delta E$.
[d]ΔE 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} $(NH_2—H) = 107.4 \pm 1$ kcal mol^{-1} and electron affinities for $CH_3NH\cdot$, $C_2H_5NH\cdot$ and $(CH_3)_2N\cdot$ of 13.1 ± 3.5, 17 ± 4 and 14.3 ± 3.4 kcal mol^{-1}, respectively[30,31]. 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 coworkers[61], Hehre and Pople[56] and Radom[57]. 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 $PA(CH_3NH^-) - PA(C_2H_5NH^-)$ compares more favourably (in fact, remarkably well) with the value of 3.5 kcal mol^{-1} obtained by Radom[57] 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 discussion[2,9]. 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

$$Y{-}BH^+ + X{-}B \longrightarrow X{-}BH^+ + Y{-}B \quad (29)$$

$$Y{-}A^- + X{-}AH \longrightarrow X{-}A^- + Y{-}AH \quad (30)$$

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[33–36]. 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

$$E = \frac{\alpha q^2}{2\varepsilon r^4} \quad (31)$$

charge, α is the substituent polarizability, r is the distance of separation, and ε 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[41]. Further support of the polarizability effect has been forthcoming from quantum-mechanical calculations of charge distributions[41,57]. Trends in *IP*s 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 π-electron delocalization effect R, it is instructive to dissect the standard free energy change in the following manner[9]:

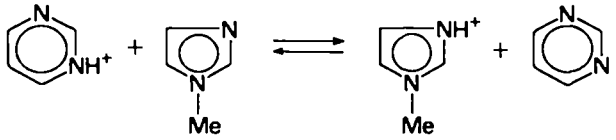
$$-RT \ln K = \Delta G^0 = P + I + R \quad (32)$$

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 $-CF_3$ and $HC{\equiv}C-$ substituents. In this case proton transfer is preferred in the direction

$$C_2H_5NMe_2 + CF_3CH_2N(Me)_2H^+ \rightleftharpoons C_2H_5N(Me)_2H^+ + CF_3CH_2NMe_2 \quad (33)$$

$$n\text{-}C_3H_7NH_2 + HC{\equiv}CCH_2NH_3^+ \rightleftharpoons n\text{-}C_3H_7NH_3^+ + HC{\equiv}CCH_2NH_2 \quad (34)$$

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 ΔG^0 (i.e. I is negative). The equilibrium constants for reactions (33) and (34) are $10^{8.8}$ and $10^{4.8}$, respectively[2,62]. 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



(35)

resonance-stabilized. The equilibrium constant for this reaction[9] is $10^{11.8}$. Examples have also been reported of proton transfer driven by preferential resonance stabilization of a neutral component[9].

Finally, attention should be drawn to stabilization (energy release) resulting from intramolecular cyclization which has been proposed to account for the high base strenths of diamines relative to monoamines of comparable structures[45,63]. (Indeed, it has been proposed that gas-phase measurements of basicity may provide a general method for the detection of ring formation[63].) 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

$$BH^+ + NH_2(CH_2)_nNH_2 \rightleftharpoons B + NH_3^+(CH_2)_nNH_2 \tag{36}$$

$$NH_3^+(CH_2)_nNH_2 \rightleftharpoons \underset{NH_2\cdots H^+\cdots NH_2}{\overset{(CH_2)_n}{\frown}} \tag{37}$$

entropy change while step (37) involves entropy loss due to cyclization. The enthalpy change associated with the cyclization step, ΔH^0_{cycl}, has been estimated assuming that ΔH^0_{36} is equal to ΔH^0 for the proton transfer to the monoamine $CH_3(CH_2)_nNH_2$, so that

$$\Delta H^0_{cycl} = \Delta H^0_{37} = PA(NH_2(CH_2)_nNH_2) - PA(NH_2(CH_2)_nCH_3) \tag{38}$$

The values for H^0_{cycl} 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 ΔH^0_{cycl} with ΔH^0 associated with the formation of proton-bound dimers involving two alkylamines (equation 39) where

$$C_kH_{2k+1}NH_3^+ + C_kH_{2k+1}NH_2 \rightleftharpoons (C_kH_{2k+1}NH_2)_2H^+ \tag{39}$$

TABLE 12. Thermodynamic aspects of the cyclization of protonated α,ω-diamines[a]

	$-\Delta S^0_{cycl}$[b]	$-\Delta H^0_{cycl}$[c]	Strain[c]
1,2-Diaminoethane	12.7	12.6	10.4
1,3-Diaminapropane	20.6	20.5	2.5
1,5-Diaminopentane	20.0	20.1	2.9
1,7-Diaminoheptane	20.0	20.0	3.0

[a]Reprinted with permission from R. Yamdagni and R. Kebarle, *J. Amer. Chem. Soc.*, **95**, 3504 (1973). Copyright by the American Chemical Society.
[b]In cal mol^{-1} deg^{-1}.
[c]In kcal mol^{-1}.

$$\text{strain energy} = \Delta H_{cycl} - \Delta H_{39} = \Delta H_{cycl} + \approx 23 \text{ kcal mol}^{-1} \quad (40)$$

$k \approx n/2$. 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 N—H⁺—N hydrogen bond tends to be linear[45]. 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)[63]. Also, comparisons have been reported with thermodynamic data for the corresponding *n*-alkanes and cycloalkanes[45,63].

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[2,9] and Arnett[10,11] for detailed treatments of this subject.

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **18**

Special properties of di- and poly-amines

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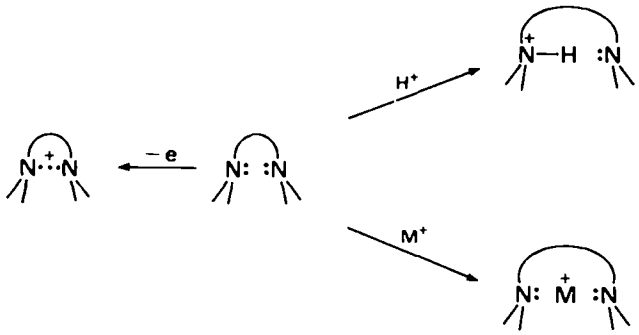
I. INTRODUCTION

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.

which depend on the presence of more than one lone pair† 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).



(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 σ- or π-like orbital overlap but also via other σ- and π-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.

†We use the noncommital term 'lone pair' deliberately. Lone pairs are never nonbonding in amines.

II. A SIMPLE THEORETICAL PICTURE OF INTERACTIONS AMONGST LONE PAIRS[1]

Molecular orbital theory provides an almost too convenient framework for the discussion of lone-pair interactions. Direct, through-space interaction can occur in σ (**1**), π (**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

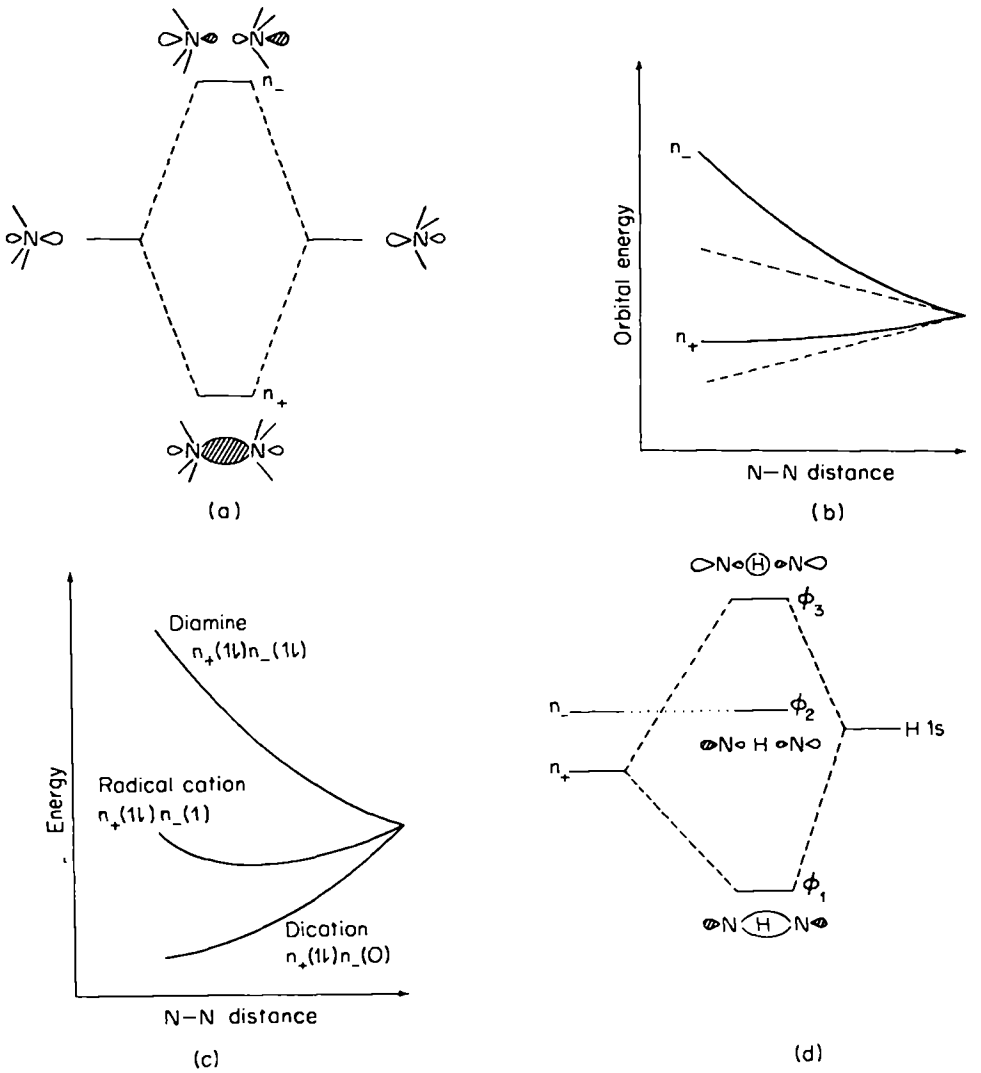
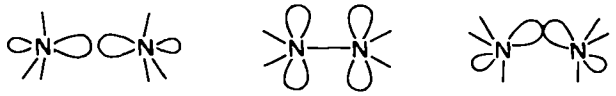


FIGURE 1. (a) Mixing of lone-pair orbitals to generate n_+ and n_-. (b) Orbital energies; without overlap n_+ is stabilized to the same extent than n_- is destabilized (dashed lines). Inclusion of overlap leads to greater destabilization of n_-. (c) Lone-pair interactions are always repulsive for diamines. The radical cation may have a weak three-electron bond, provided overlap is not too great ($s < \frac{1}{3}$)[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, $\phi_1(\uparrow\downarrow)$ $\phi_2(\uparrow)$, the positive charge lowers all orbital energies.



(1) (2) (3)

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, ψ_3, related to n_+ 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

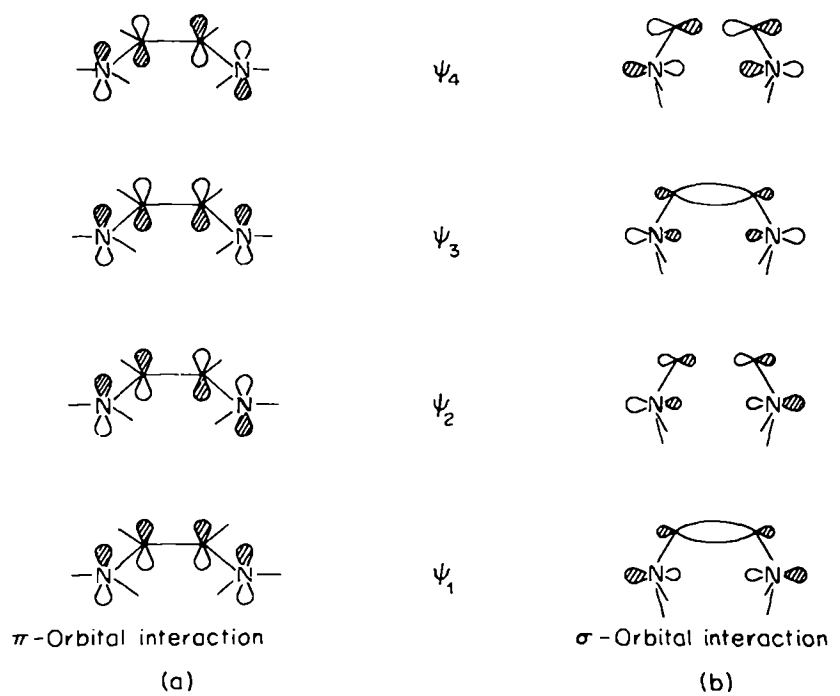


FIGURE 2. Through-bond mixing of lone-pair orbitals (a) via π-bonds, (b) via σ-bonds. Note that, especially for the σ-case (b). Ψ_2 and Ψ_3 are largely lone-pair orbitals, while Ψ_1 is largely a C—C bonding orbital.

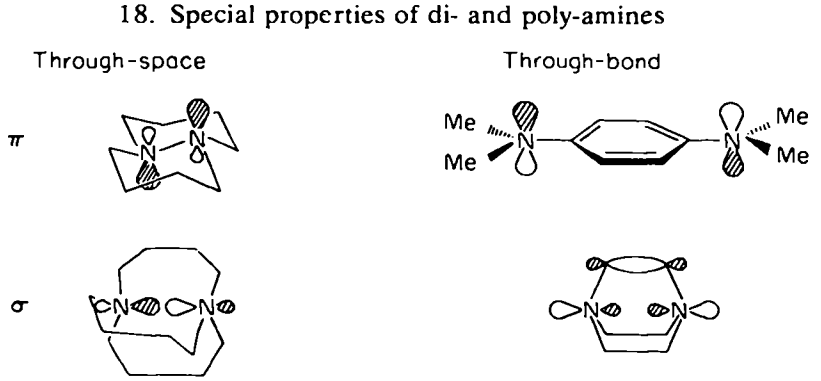


FIGURE 3. Limiting cases for different types of lone-pair interaction.

for diamines as far as overall energy is concerned. Hoffmann[1] 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[4]. Wadt and Goddard[5] 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.

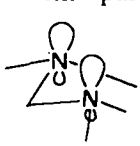
It is perhaps useful to see lone-pair interactions in terms of four limiting cases:– π through-space, σ through-space, π through-bond and σ through-bond. These are shown as four classic examples in Figure 3.

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[6]. 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[7,8] illustrate these effects very nicely (Figure 4), and there is much evidence of a more indirect character which supports these trends[9–11].

In 1,1-diamines, conformations with parallel lone pairs (**4**) are avoided



(**4**)

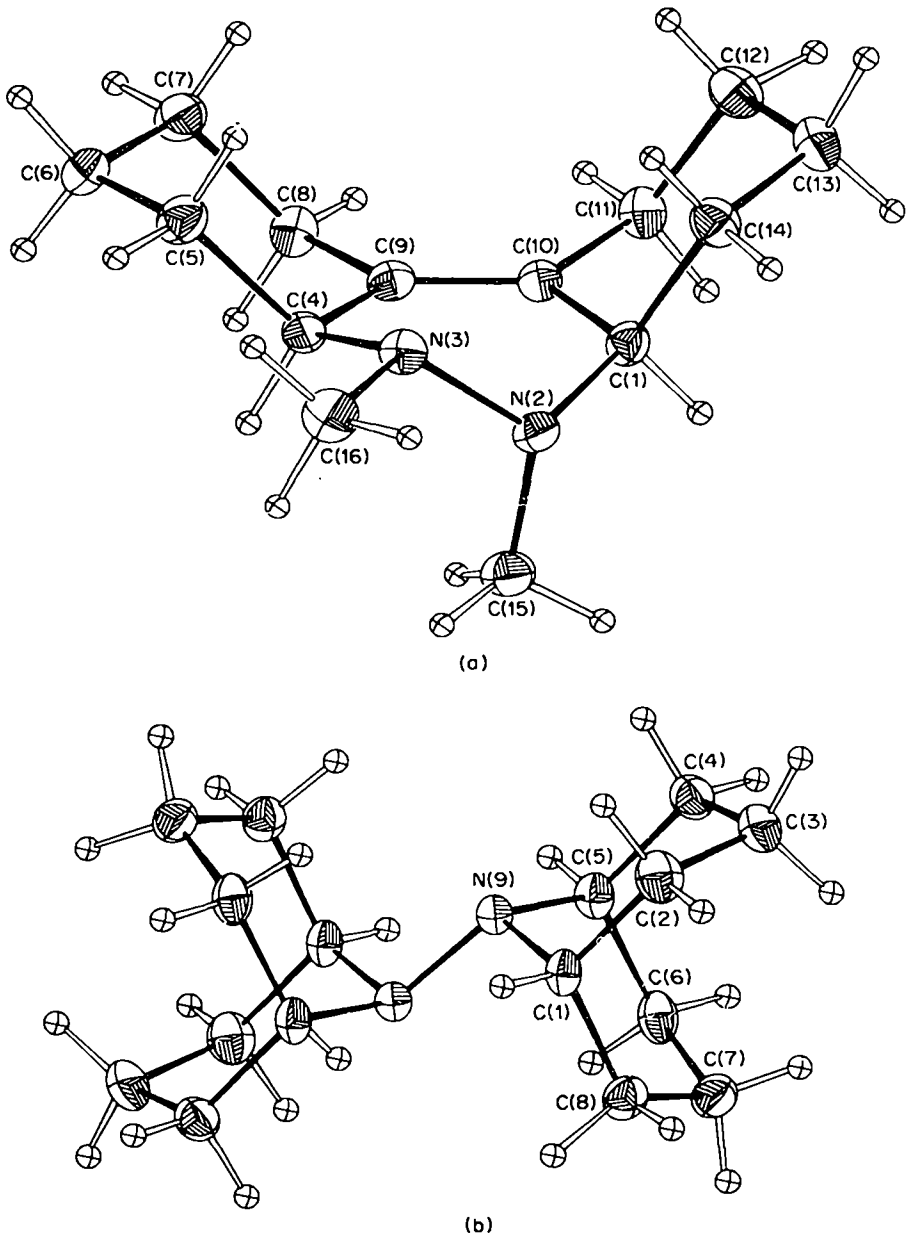
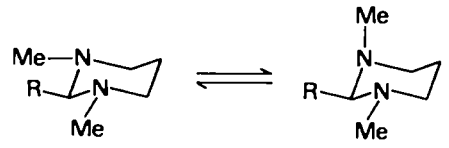


FIGURE 4. (a) Structure of 2,3-dimethyl-2,3-diazatricyclo[8.4.0.$0^{4,9}$] tetradec-9-ene. The N—N bond length is 1.45 Å, and the dihedral angle between the lone pairs about 70°. Reprinted with permission from S. F. Nelsen, W. C. Hollinsed and J. C. Calabrese, *J. Amer. Chem. Soc.*, **99**, 4461 (1977). Copyright 1977 American Chemical Society. (b) Structure of 9,9′-bis-9-azabicyclo[3.3.1]-nonane. The N—N bond length is 1.50 Å and the lone-pair dihedral angle is 180°. Reprinted with permission from S. F. Nelsen, W. C. Hollinsed, C. R. Kessel and J. C. Calabrese, *J. Amer. Chem. Soc.*, **100**, 7876 (1978). Copyright 1978 American Chemical Society.

(christened the 'rabbit ear' effect by Eliel[12]). This is really one case of the anomeric effect[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 σ^*-orbitals of the polar C—X(C—N) bonds is important, as well as simple through-space lone-pair repulsion[14]. The best experimental evidence comes from NMR studies of hexahydropyrimidines, and related heterocycles. Thus for (5), R = H, the *ee* conformation is only preferred by 0.4 kcal mol^{-1}, while for (5), R = Me, the *ae* conformation is preferred by 0.85 kcal mol^{-1} [15].



(5)(*ee*) (5)(*ae*)

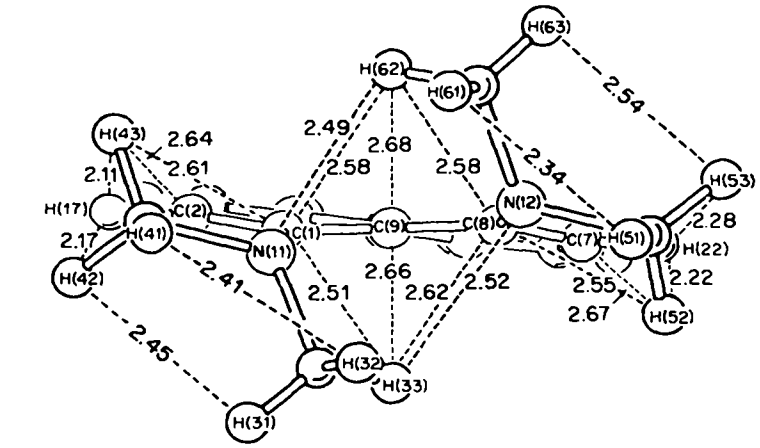
In 1,2-diamines, structures which lead to through-space (6) and through-bond (7) interactions are avoided but this often occurs for other reasons than the lone-pair

(6) (7)

interactions themselves. Thus in hexahydropyrazines, conformations with both nitrogen substituents equatorial are preferred[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)[18]. In this and similar cases the situation is complicated by (favourable) n—π overlap. In the radical anion[19] (odd electron in a π^*-orbital), n–π overlap is probably repulsive, accounting for the increase in the dihedral angle between n-and π-orbitals from ca. 30° to 60–70°. In the protonated ion[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[21] shows that it costs about 7.5 kcal mol^{-1} to achieve the C_{2v} structure with directly opposed lone pairs. 2,7-Disubstitution as in 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene[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)[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[24] or 1,6-diazabicyclo[4.4.4]tetradecane[25] but it seems certain that some degree of lone-pair interaction is enforced in these systems, and



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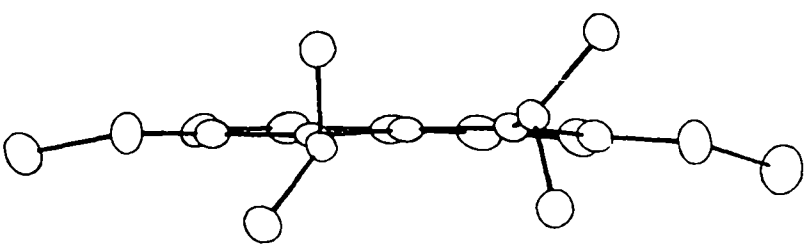

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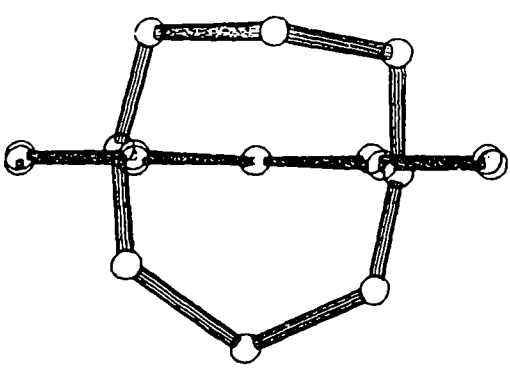


(c)

FIGURE 5. (a) Structure of 1,8-bis(dimethylamino)naphthalene; the N—N distance is 2.79Å. 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[22], the N—N distance is 2.76 Å. Structure of 1,8-naphtho[*bc*]1,5-diazabicyclo[3.3.3]-undecane[23], 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[26] and cryptands[27] 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)[28]. In one large cryptand a *planar,planar* geometry has been reported (Figure 6d)[29]. 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

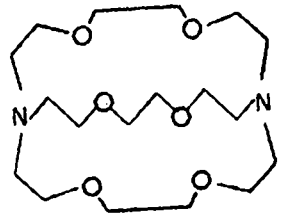
Di- and poly-amines are electron-rich species which are amongst the most easily oxidized of organic molecules. We are fortunate to be able to study electron detachment by both UV photoelectron spectroscopy in the gas phase and, in solution, by electrochemical techniques, particularly cyclic voltammetry, 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.

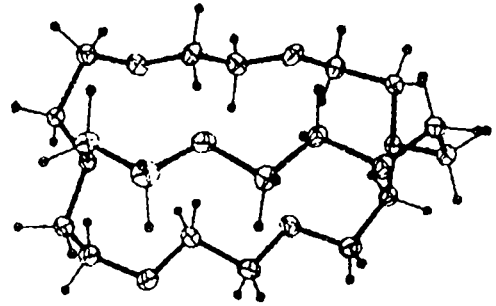
Saturated diamines show two low-energy photoelectron bands (Table 1), which, using Koopmans' theorem and the orbital picture, can be associated with the removal of electrons from lone-pair orbitals. The ΔI between these bands is very sensitive to the geometry and mode of interaction of the lone pairs. Hydrazines are the simplest case and have been particularly thoroughly studied, especially by Nelsen[9,10] and Rademacher[11]. 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 hexahydropyridazines, the photoelectron spectrum is the superposition of spectra due to different 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/σ^* 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 dominates, putting n_- above n_+. With two and three N—C—C—N coupling pathways, through-bond coupling dominates, according to calculations[30]. The classic example is DABCO **14**. Analysis of the vibrational fine structure in the DABCO spectrum enabled Heilbronner and Muszkat[31] to assign the 7.52 eV band to formation of the $A_1'(\uparrow)A_2''(\uparrow\downarrow)$ 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[23–25] 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





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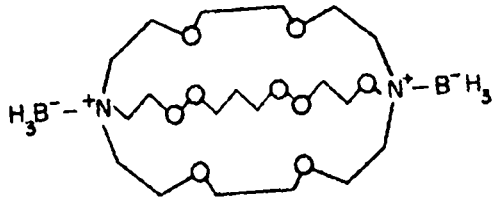

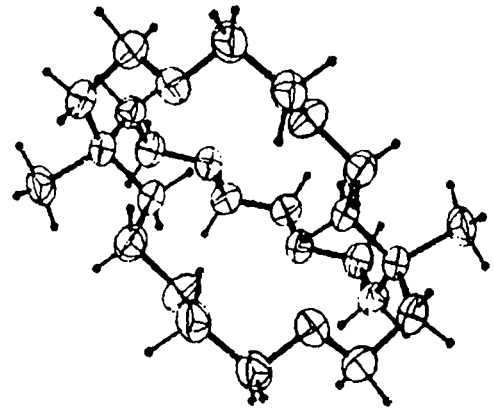

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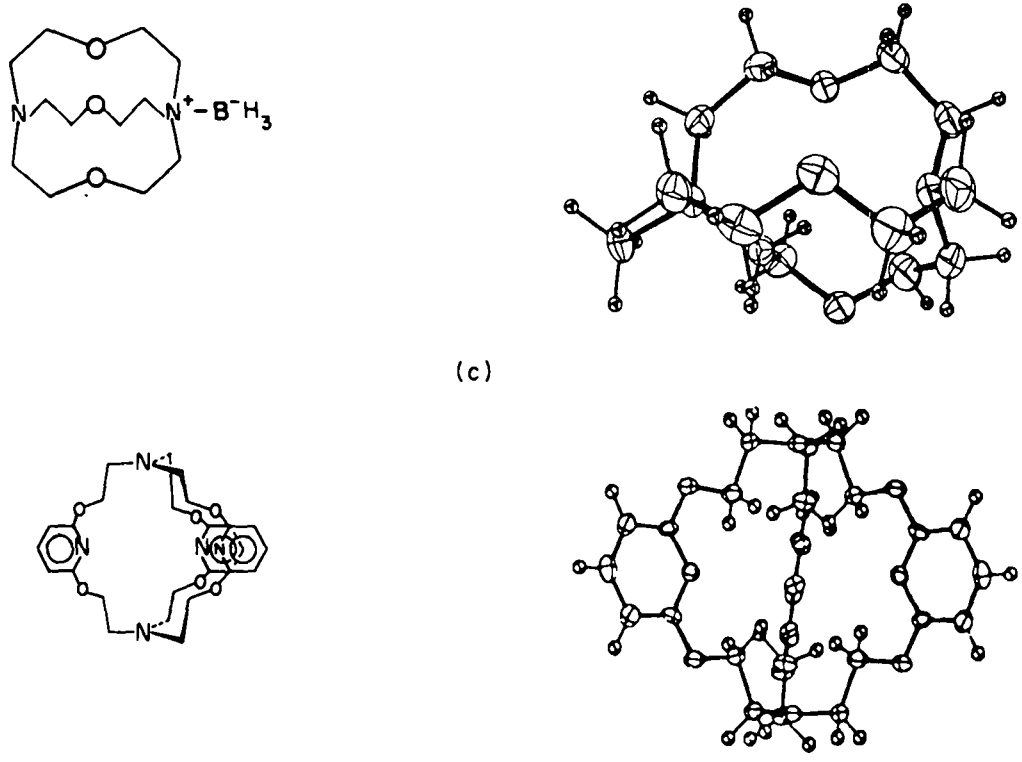


FIGURE 6. Cryptand structures showing (a) *in,in* geometry in the free [2.2.2] cryptand, average C—N—C angles 112.2°; (b) *out,out* geometry in [2.2.2] · 2 BH_3, average C—N—C angle 109.5° [reproduced by permission of the Chemical Society, London from B. Metz, D. Moras and R. Weiss, *J. Chem. Soc., Perkin II*, 423 (1976)]; (c) [2.2.1] · BH_3 with *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, *Nouveau 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. Fronczek and J. L. Atwood, *J. Amer. Chem. Soc.*, **101**, 1047 (1979); copyright 1979 American Chemical Society].

TABLE 1. Vertical ionization energies, I_v, of selected di- and poly-amines

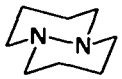
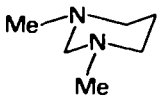
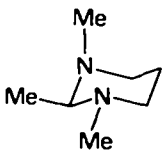
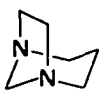
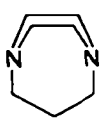
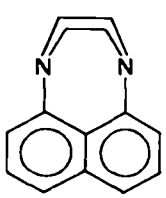
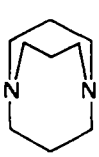
Amine		I_v	Reference
Me_2NNMe_2	**(8)**	8.27, 8.82	9
	**(9)**	7.61, 9.92	9
	**(10)**	8.11, 8.51	30
	**(11)**	8.03, 8.41	30
	**(12)**	8.89, 9.64	30
	**(13)**	7.75, 8.78	30
	**(14)**	7.52, 9.65	31
	**(15)**	7.43, 8.65	30
	**(16)**	7.56, 8.8	23
	**(17)**	6.85, 7.90	24, 32

TABLE 1. (*continued*)

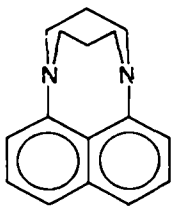
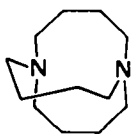
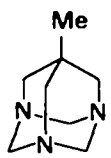
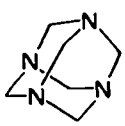
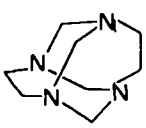
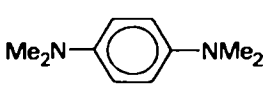
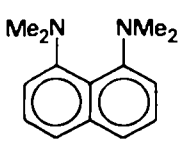
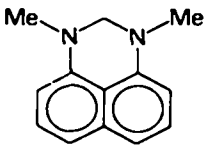
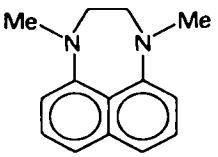
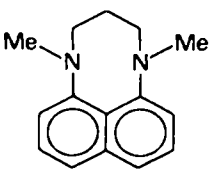
Amine		I_v	Reference
	**(18)**	6.90,7.76	23
	**(19)**	6.75, 7.87	32
	**(20)**	8.08, 9.00	30
	**(21)**	8.53	30
	**(22)**	7.39, 8.66, 9.54	33
$H_2C{=}C(NMe_2)_2$	**(23)**	7.5, 8.2, 10.3, 12.5	34
$(Me_2N)_2C{=}C(NMe_2)_2$	**(24)**	5.95, 7.5, 7.85, 8.5, 9.5	35
	**(25)**	6.84, 8.36, 8.74, 10.0, 11.16	36
	**(26)**	7.03, 7.47, 8.50, 9.01, 9.78	37, 38

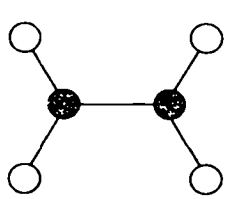
TABLE 1. (*continued*)

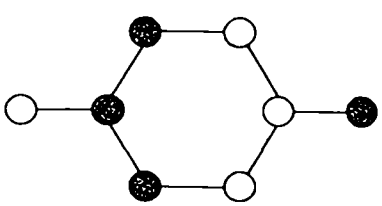
Amine		I_v	Reference
	**(27)**	6.84, 7.76, 8.47, 9.37, 10.14	38
	**(28)**	6.72, 7.78, 8.38, 8.87, 9.90	38
	**(29)**	6.85, 8.1, 8.5, 8.8, 9.83	38

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 photoelectronspectroscopy. 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/π 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 π-orbitals of the form shown below:





With the 1,8-naphthalenediamines **26–29** there is only limited n–π* overlap. As we have seen (Section III), **26** has C_2 symmetry with the lone pairs overlapping with opposite faces of the twisted naphthalene π-system. Diamine **27** is probably almost planar while **28** and **29** have C_S 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

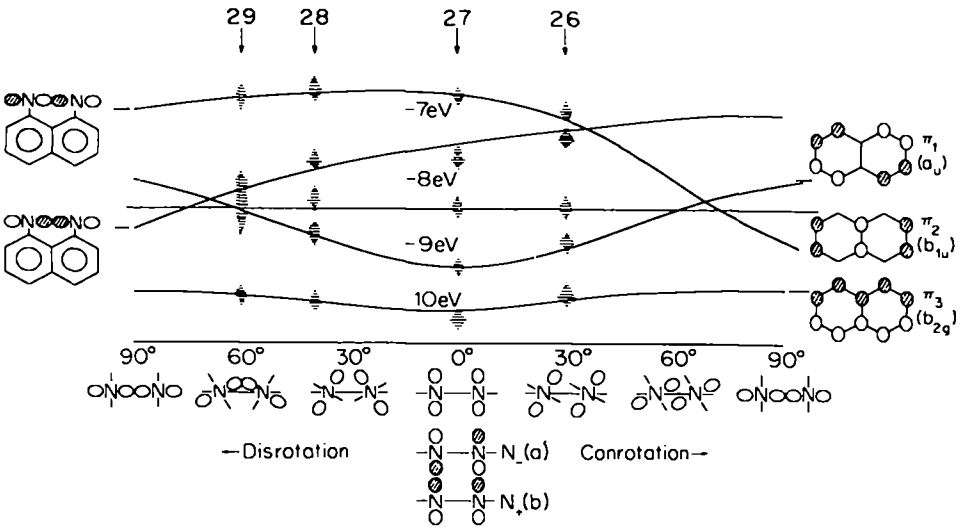


FIGURE 7. Correlation diagram for 1,8-diaminonaphthalenes.

through-bond coupling and the latter because of the effects of molecular strain (the model is taken to have sp^2-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 Maier[37], 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 $n \rightarrow \pi^*$ transition, and saturated diamines like **17** and **19** show absorption at exceptionally long wavelengths[24,25]. 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 studied[41], 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[9] 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_1^0. The relationship between these quantities and the adiabatic ionization potential (I_a) is shown in Figure 8. The relaxation energy $I_v - I_a$ 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 2. E^0 values for di- and poly-amines showing reversible electrochemical oxidation

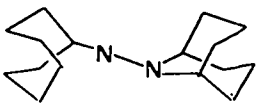
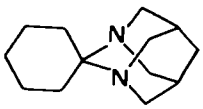
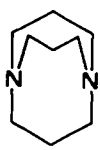
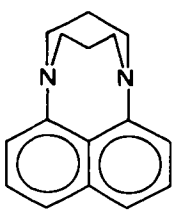
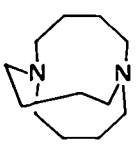
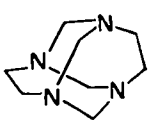
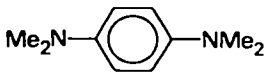
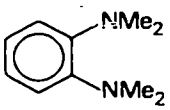
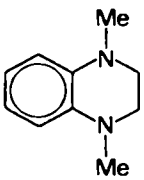
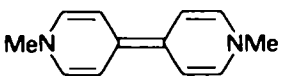
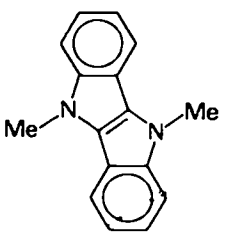
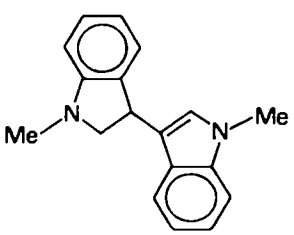
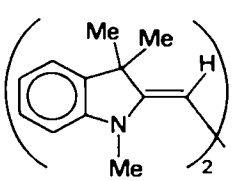
Amine		E_1^0, E_2^0 vs. SCE	Reference
Me_2NNMe_2	**(8)**	+0.28	9
	**(30)**	−0.01, +1.18	42
	**(31)**	+0.70	43
	**(14)**	+0.57	43, 44
	**(17)**	−0.17, +0.1	24
	**(18)**	+0.11, +0.72	45
	**(19)**	−0.1, +0.2	25
	**(22)**	+0.56	43
$(Me_2N)_2C{=}CMe_2$	**(32)**	+0.05	46
$(Me_2N)_2C{=}C(NMe_2)_2$	**(24)**	−0.77, −0.65	46
$[(Me_2N)_2C{=}CH]_2$	**(33)**	−0.36, −0.18	46

TABLE 2. (*continued*)

Amine		E_1^0, E_2^0 vs. SCE	Reference
	**(25)**	−0.01, +0.60	47
	**(34)**	+0.60, +0.84	48
	**(35)**	+0.36, +0.98	48
	**(36)**	−0.87, −0.45	49
	**(37)**	+0.61, +1.30	50
	**(38)**	+0.61, +0.95	51
	**(39)**	−0.11, +0.23	52
Tetraphenylporphin	**(40)**	+1.05, +1.30	53

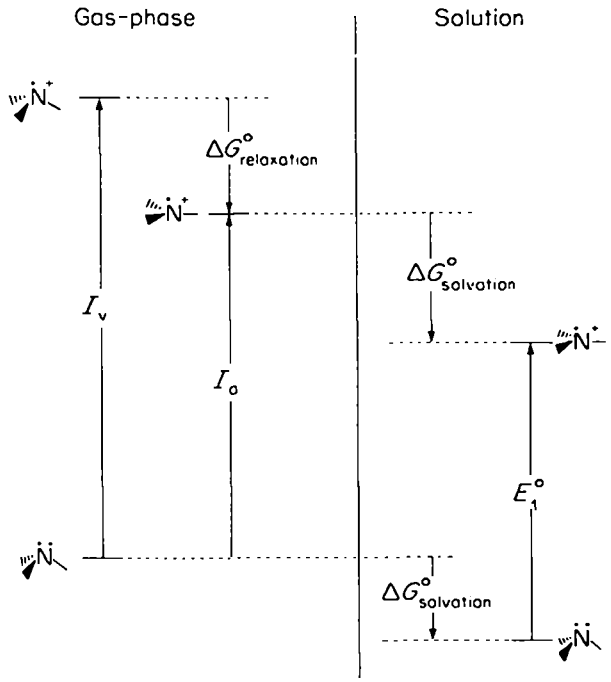
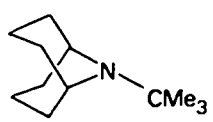


FIGURE 8. Relationships between I_v, the vertical ionization energy I_a, the adiabatic ionization energy, and E^0_1, the oxidation potential for the amine in solution.

containing large π-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[54].



(41)

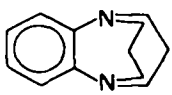
Many unsaturated and aromatic diamines in which there is extensive conjugation have very low oxidation potentials. Tetraaminoethylenes[55] are oxidized in two stages with exceptional ease, as are systems like **36**, the reduced form of paraquat, which becomes aromatic in its oxidized ions. Deuchert 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^0_1 and E^0_2 within a wide range. Of the three oxidation levels in a violene system, SEM makes the greatest demands on delocalization for

$$\ddot{X}-(CH{=}CH)_n-\ddot{Y} \underset{}{\overset{-e}{\rightleftharpoons}} \dot{X}-(CH{=}CH)_n-\ddot{Y} \overset{-e}{\rightleftharpoons} \overset{+}{X}{=}(CH-CH)_n{=}\overset{+}{Y} \qquad (3)$$

RED SEM OX

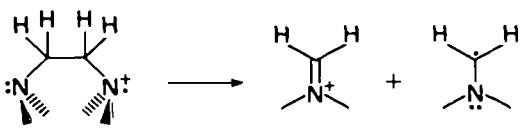
its stability, so that K_d, the disproportionation constant for the radical cation [$= \exp\ (23.06 \times 10^3)/(1.987T) \times (E_2^0 - E_1^0)$] is low for systems like **33** and **34** where there is steric inhibition of resonance (compare **34** and **35**)[46,48].

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 π-bonded radical cations; only one example, **30**, has been found which reversibly forms a dication. Medium-ring systems like **17–19** form three-electron σ-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_1^0 and E_2^0. 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**



(42)

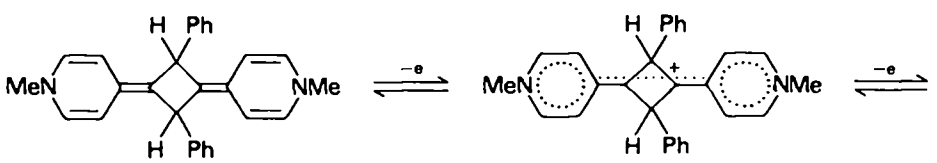
cannot pyramidalize inward and form a three-electron σ-bond. However this does seem to happen in the more flexible **22**. Finally, the DABCO radical cation is stabilized by through-bond effects as already discussed. Nelsen and Hintz[43] examined a number of related bridgehead diamines (1,5-diazabicyclo[3.2.1]octane, 1,5-diazabicyclo[3.3.1]nonane, etc.) and apart from **31** found no other similar diamine which is reversibly oxidized. Through-bond coupling implies easy fragmentation in the radical cation as shown in reaction (4). This is the



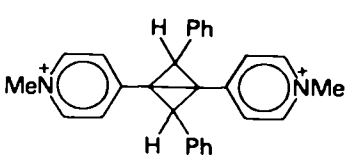
(4)

decomposition pathway for the DABCO radical cation[57], and it probably occurs more rapidly in other cases where delocalization is not spread over three bridges.

Horner and Hünig[58] have devised a most intriguing system (43) in which both through-space and π-electron delocalization effects are present.



(43)



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[59] 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[56], 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 PF_6^- salt has been reported; the N—N distance is remarkably short (1.27 Å) and the $C_2N—NC_2$ 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[62].

In the DABCO radical cation **45**, the nitrogens remain equivalent down to 77 K[60], and it is presumed that the cation is symmetrical. The rather small nitrogen hyperfine coupling has caused comment[33], since in simple aminium ions low values of a_N 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[40]. 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[31]. The suggestion was made that in solution the through-space coupled ion was preferred[33a], but this was later withdrawn[33b]. However Symons apparently believes that **45** is through-space-coupled, i.e. in a n_+ (↑↓) n_- (↑) state[60]. One factor which needs consideration is that for these more complex systems maximum p character in the spin-bearing orbital (and thus minimum a_N), 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[33b] 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 elctron 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 $n_+(↑↓)\, n_-(↑) \rightarrow n_+(↑)\, n_-(↑↓)$ for **44** and **46–48**, and $n_+(↑)\, n_-(↑↓) \rightarrow n_+(↑↓)\, n_-(↑)$ for **45**. The absorption bands for **46–48** cover the entire visible region;

TABLE 3. Diamine radical cations: lifetimes, nitrogen hyperfine coupling constants and absorption spectra

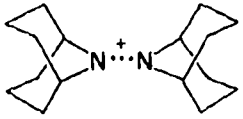
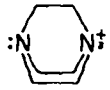
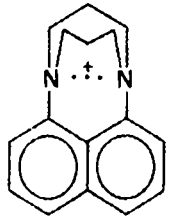
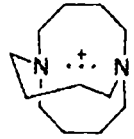
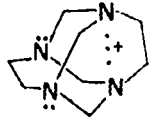
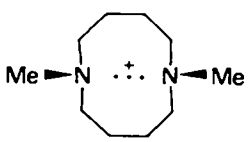
Cation	Approx. Lifetime in CH_3CN at 25°C	a_N (gauss)	λ_{max} (nm)	ε (M^{-1} cm^{-1})	References
 (44)	~1 year	13.15	345 (95% EtOH)	3600	42
 (45)	~1 second	17.02	465 (H_2O)	2100	33, 44, 57, 60
 (46)	~1 day	14.7	480 (H_2O)	2600	24, 61

TABLE 3. (*continued*)

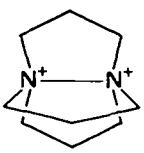
Cation	Approx. Lifetime in CH_3CN at 25°C	a_N (gauss)	λ_{max} (nm)	ε (M^{-1} cm^{-1})	References
 (47)	~1 week	14.1	480 (CH_3CN)	>1000	45
 (48)	~1 year	34.4	470 (H_2O)	4500	25, 61
 (49)	<1 second	7.09 (4N)	(purple)	—	33

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 σ- to σ*-orbital.

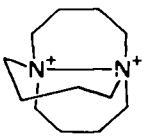
It would be most interesting to know the strength of the through-bond delocalization in **45** and of the 'three-electron σ-bond' in **46–48**, and also to know the length of the bond in **46–48**. No information is available on the latter point, but Staley and Beauchamp[63] have pointed out that the *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[32] suggest a lower figure, around 9 kcal mol^{-1}). If a similar argument is applied to **46** and **48**, the three-electron σ-bond seems to be worth[32] about 11 kcal mol^{-1}. An independent study[61] 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 $\Delta G^{\dagger}$ 14.5 kcal mol^{-1}. It seems likely that this process is fission of the three-electron σ-bond, followed by rapid decay of the unstabilized aminium radical ion. Thus this measurement suggests that the three-electron σ-bond in **50** is worth about 10–15 kcal mol^{-1}.



(50)



(51)

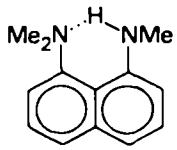


(52)

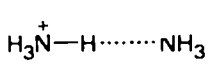
Radical ions **44** and **46–48** can be oxidized to dications. The dication from **44** is a dialkylated azocompound, while those from **46–48** are hexaalkylhydrazinium dications and undoubtedly contain a normal two-electron N—N σ-bond. Dications **51** and **52** are isolable as stable, colourless, water-soluble salts and indeed the corresponding medium-ring diamines are made by their reduction[24,25].

VII. INTRAMOLECULAR HYDROGEN BONDING IN DIAMINES AND THEIR MONOPROTONATED IONS

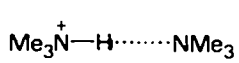
Amines are poor hydrogen bond donors so that amine-to-amine hydrogen bonding is weak. Thus the dissociation energy[64] of the $H_2N—H \ldots NH_3$ dimer in the gas phase is 4.5 kcal mol^{-1}. Intramolecular hydrogen bonding in diamines themselves is therefore only observed in favourable situations. For example the N—H stretch for **53** is at 3280 cm^{-1}.



(53)



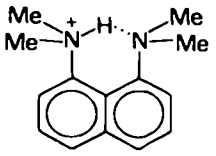
(54)



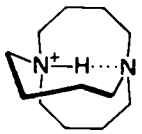
(55)

The ammonium ion-to-amine hydrogen bond is much stronger. Yamdagni and Kebarle[65] have shown by high-pressure mass spectrometry that ΔH^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 $N^+—H\ldots N$ hydrogen bonds occur at very low fields in ^1H NMR spectra. Thus the N—H proton in **56** appears at δ 19.5 in CF_3COOH solution[66], while that in **57**



(56)



(57)

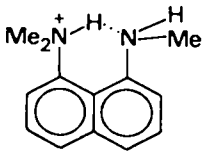
appears at δ 17.4[81]. $N^+—H\ldots N$ hydrogen bonds both inter- and intra-molecular, give rise to very broad infrared absorption in the 2000–1000 cm^{-1} region. Intermolecular examples have been extensively examined by Wood[67]. These $N^+—H\ldots N$ bonds are approaching the strenth of the $F—H\ldots F^-$ and $H_2O^+—H\ldots OH_2$ 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 $N^+—H\ldots N$ 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 $H_2N(CH_2)_4NH_2$, 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 $N^+—H\ldots N$ bond (see Section VII). The hydrogen-bonded cyclic ions from $H_2N(CH_2)_2NH_2$ and $H_2N(CH_2)_3NH_2$ 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 (ΔG^0 for $B + H^+ \rightarrow BH^+$; the proton affinity is ΔH^0) are only ~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-

pound. 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



(**58**)

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

TABLE 4. Proton affinities (*PA*) of some diamines and comparable monoamines

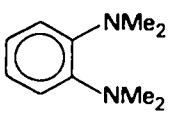
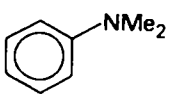
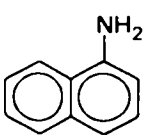
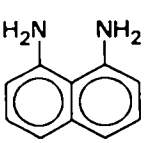
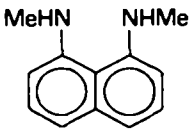
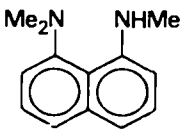
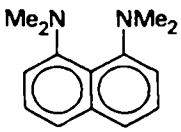
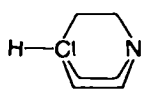
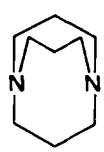
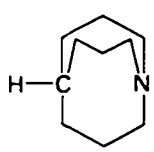
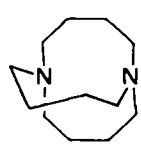
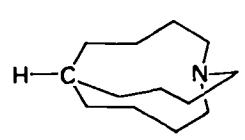
Amine	*PA*[a]	Reference
$H_2N(CH_2)_2NH_2$	232.0	71
$CH_3(CH_2)_2NH_2$	222.3	71
$H_2N(CH_2)_3NH_2$	238.3	71
$CH_3(CH_2)_3NH_2$	222.8	71
$H_2N(CH_2)_4NH_2$	243.3	71
$CH_3(CH_2)_4NH_2$	223.1	71
$H_2N(CH_2)_5NH_2$[b]	241.3	71
$CH_3(CH_2)_5NH_2$	223.2	71
$H_2N(CH_2)_6NH_2$	242.1	71
$H_2N(CH_2)_6NH_2$	223.2	71
	238.8	72
	227.9	72
	221.0	72
	228.1	72

TABLE 4. (*continued*)

Amine	*PA*[a]	Reference
	234.9	72
	239.2	72
	246.2	72
 (**14**)	230.9	32
	233.6	32
 (**17**)	234.1	32
	233.4	32
 (**19**)	228.3	32
	217	32

[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[119]. 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 $H_2N(CH_2)_5NH_2$ 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.

nitrogen itself, a rather small (< 2 kcal mol^{-1}) increase in *PA* might be expected. The large increase in *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 *PA*). In this series we also see the operation of strain effects. In the absence of these we would expect *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 *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 *in,out* conformation, with the unprotonated nitrogen inwardly pyramidalized, than for the corresponding monoamine, where both bridgeheads must be *out* in the protonated ion.

IX. BASICITY OF DIAMINES IN AQUEOUS SOLUTION

The basicity of diamines, and the inductive (field) effect of $-NH_3^+$ as a substituent in reducing pK_{a2}, have been discussed in an earlier volume in this series[73]. We shall only discuss here the effects of $N^+-H \ldots N$ bonding on aqueous pK_a values. Considering the diamine in isolation, this bonding should increase pK_{a1} and reduce pK_{a2}. This is substantially modified by solvation (see Figure 9)[74,75]. The non-

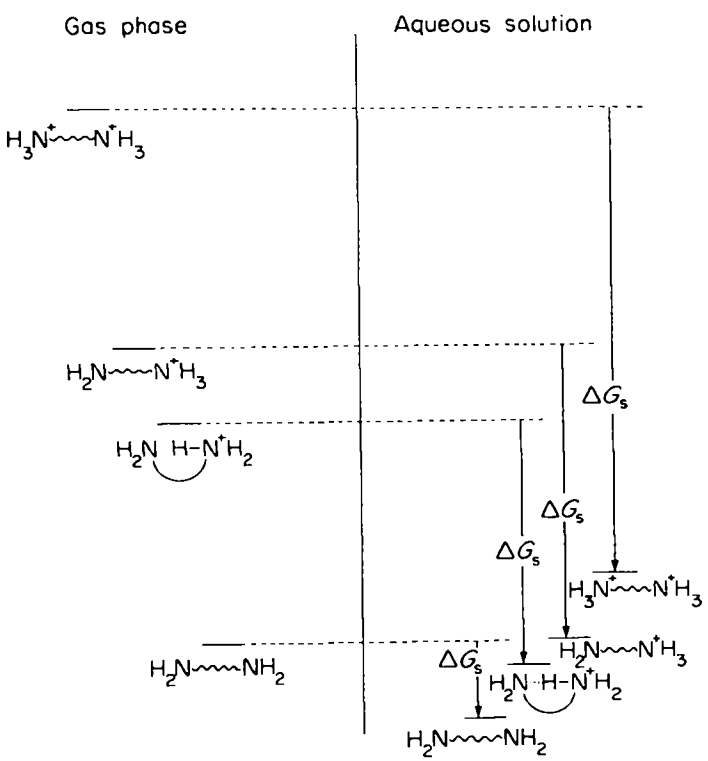
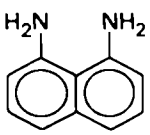


FIGURE 9. Solvation effects on the energetics of diamine protonation; ΔG_s = free energy of solvation.

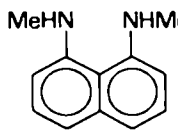
intramolecularly hydrogen-bonded cation has the higher solvation energy (more sites for hydrogen bonding to water), and so the energetic advantage of the intramolecularly hydrogen-bonded cation is lost. Simple diamines do not show enhanced pK_{a1} values[73] and Hine and Li[76] have shown that the fraction 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 $Me_2NHCH_2CMe_2CH_2NH_2$, $Me_2NCH_2CMe_2CH_2NH_3^+$ 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_{a1} 10.58, pK_{a2} 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[66]; 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[72]. The second pK_a of **26** is very low, protonation being half-complete in 86% H_2SO_4. Diprotonation breaks the hydrogen bond and



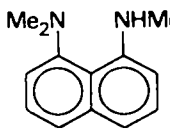
4.61

(**59**)



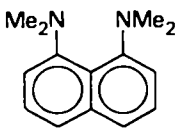
5.61

(**60**)



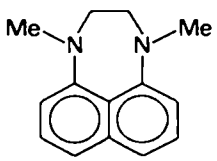
6.43

(**53**)



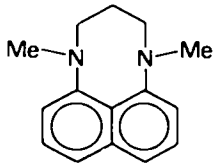
12.34

(**26**)



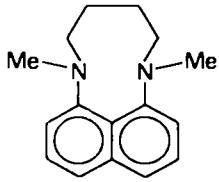
4.61

(**28**)



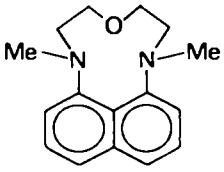
10.30

(**29**)



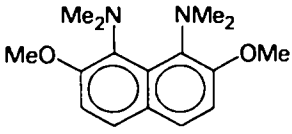
13.6

(**61**)



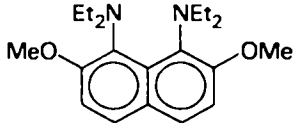
13.0

(**62**)



16.3

(**63**)

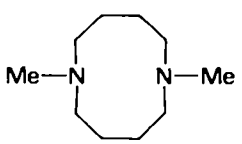


16.6

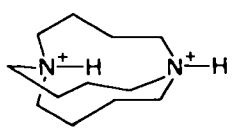
(**64**)

reintroduces strain. Alkylation of **26** is also very difficult compared with amines of similar pK_a[66,77]. The compounds **28**, **29**[78], **61** and **62**[78,79] nicely illustrate the effects of varying ring-size. Protonation of these compounds converts a medium ring into bicyclic system, relieving transannular interactions. Surprisingly, the pK_a values of simple alicyclic medium-ring diamines have not been reported. We have observed that the addition of **65** to a protonated salt of **63** in $CDCl_3$ 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 butressing 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[80]. Clearly detailed dissection of the effects in **63** would be a formidable task.

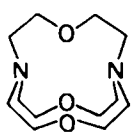
Strain can also be *increased* by protonation. This arises not so much from differences in size of the proton and the lone pair, but in cases of unfavourable geometric and hybridization changes at the nitrogen. Thus the pK_a values for outside protonation of 1,6-diazabicyclo[4.4.4]tetradecane (**19**) are ~6.5 and −3.25[81]. The exceptionally low pK_{a2} 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 pK_a for inside protonation is unknown; it could be very *high*. Further outside protonation of this inside protonated ion to give **66** occurs in HSO_3F/SbF_5 but not in HSO_3F alone; **66** must count as the most acidic ammonium ion known.



(**65**)



(**66**)



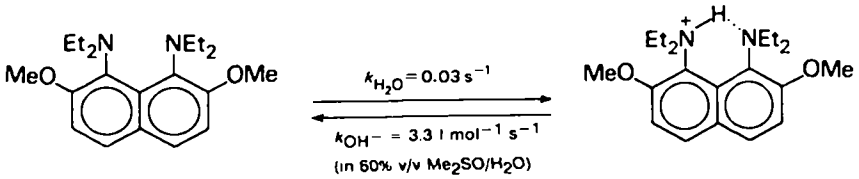
(**67**)

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 pK_a values for outside protonation of **67** are +7.1 and ~ +1[82]. 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

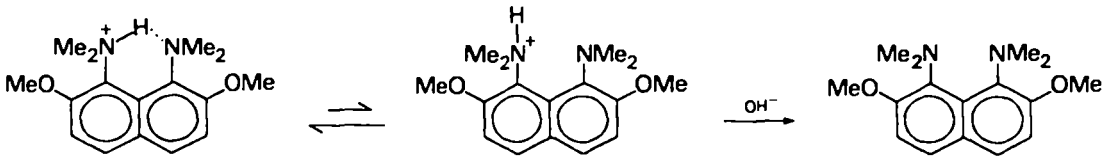
The protonation of an amine is usually a diffusion-controlled process when it is thermodynamically favourable. It has been shown, however, that proton-transfer rates for certain diamines can be very much slower.

Hibbert and his coworkers have shown that the rates of protonation of some 1,8-diaminonapthalenes are well below diffusion control[22,83,84]. For 2,7-dimethoxy-1,8-bis(diethylamino)naphthalene (reaction 5) the rates were slow enough to be followed in a conventional spectrometer[22].



(5)

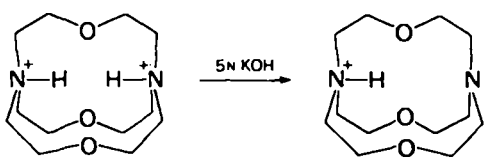
By studying buffer catalysis of the proton transfers involving 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene (reaction 6), Hibbert and Robbins[85] have provided evidence that protonation and deprotonation are two-step processes where an ammonium ion in which the hydrogen bond has broken plays the role 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 OH^- is sterically hindered and slower than diffusion-controlled.



(6)

Simmons and Park[26] 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 Et_3NH^+. 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 H_2O by H_3O^+ 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[82].



(7)

The inside-diprotonated cryptand is formed when the cryptand–BH_3 complex is refluxed in boiling 6N HCl for two hours, and an inside H^+, inside D^+ species is formed by refluxing the monoprotonated ion in concentrated D_2O/DCl 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% H_2SO_4/H_2O for several days[81]. However labelling experiments show that the inside proton does not come from the solvent but from an α-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[86] 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 $Me_3N^+CH_2CH_2CN$. 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!

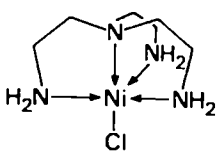
XI. METAL COMPLEXATION BY DI- AND POLY-AMINES

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 Ni^{2+} with ethylenediamine is about 10^{10} 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 employed[87] to determine the most stable isomers of $[Co(H_2N(CH_2CH_2NH)_5H)]^{3+}$. 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 Ni^{II} complexes (**68**).



(**68**)

B. Macrocycles

1. *Synthesis*

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

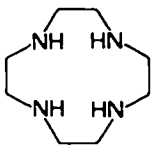
(*a*) Condensation of a diamine with a diacid chloride under conditions of high dilution, followed by reduction of the macrocyclic diamide[88].

(*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 exchanged[89].

(*c*) Reaction of a ditosylamide dianion with a ditosyloxyalkane in dimethylformamide without high dilution[90].

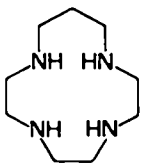
2. Macrocyclic effect

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



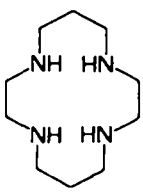
[12]ane N_4

(69)



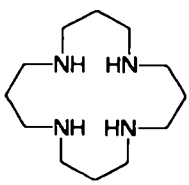
[13]ane N_4

(70)



[14]ane N_4

(71)

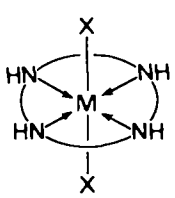


[16]ane N_4

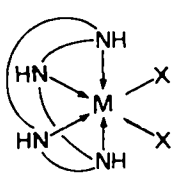
(72)

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}



trans



cis

For Co^{3+}:

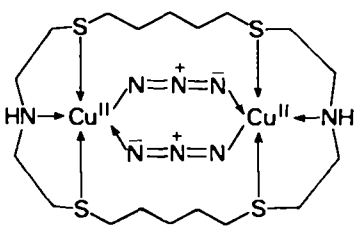
[12]ane N_4	*cis* only
[13–14]ane N_4	*cis* and *trans*
[15–16]ane N_4	*trans* only

with various structural changes in these systems[94]. Reactivity in the axial positions is also influenced by the macrocycle. For the series *trans*-Co([13–16]ane N_4)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[95].

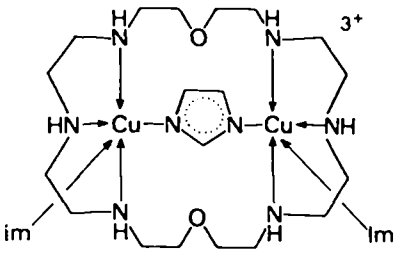
The rates of complexation of the unprotonated [12–16]ane N_4 macrocycles are comparable to those of the acyclic analogues[96]. Thus the enhanced stability is manifested in slow rates of decomplexation. The protonated macrocycles react 10^3–10^4 times more slowly than the open-chain ligands, and this appears to be a simple electrostatic effect in the case of the diprotonated ligands[97], but this correlation is not found for the monoprotonated compounds. By contrast, the unprotonated [9–12]ane N_3 macrocycles show accelerated rates of complexation and normal rates of decomplexation in acid solution[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[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^{II} complex of the [24]N_2S_4 macrocycle **73** is diamagnetic. The azide bridges enable strong antiferromagnetic coupling between the copper atoms[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 (**74**)[101].



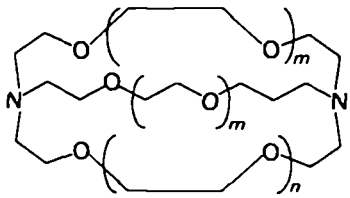
(**73**)



(**74**)

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[102] that macrocyclic polyethers form stable complexes (K_s between 10^2 and 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[103]. By



(**75**) [1.1.1] $m = n = 0$
(**76**) [2.1.1] $m = 0, n = 1$
(**77**) [2.2.1] $m = 1, n = 0$
(**78**) [2.2.2] $m = n = 1$
(**79**) [3.2.2] $m = 1, n = 2$
(**80**) [3.3.2] $m = 2, n = 1$
(**81**) [3.3.3] $m = 2, n = 2$

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 monotanically 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 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[107]. 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[108]

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'[109].

2. *Detoxification*

The high selectivity of the cryptands and the stability of their complexes makes them potantially 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].

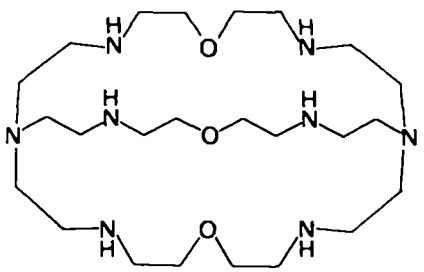
*Lehn[27] has introduced the mathematical symbol for inclusion, $\subset$, to indicate cryptate formation.

5. *Stabilization*

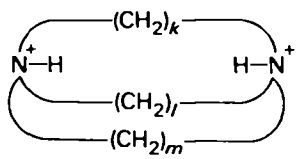
Unusual species may be stabilized by a cryptate counterion. The most spectacular example is the isolation of alkali metal anions by Dye[110]. Thus cooling a solution of sodium and [2.2.2] in ethylamine caused the growth of gold coloured crystals of $Na^+C[2.2.2]C\,Na^-$

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[111] forms binuclear metal complexes with Co^{2+}, Cu^{2+} and Zn^{2+}. Addition of increasing amounts of Zn^{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^{II} complex of **82** shows a weak $\Delta m_s \pm 2$ transition at $g = 4.7$, indicating metal/metal interaction.



(**82**)



(**83**)

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**[26]. These compounds form stable and selective complexes with the halide ions. The observed selectivities correlate with cavity/anion size. **82** · 6 H^+ 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^+ is Cl^-, $I^- < CH_3CO_2^-$, $Br^- < HCO_2^- < NO_3^- \ll N_3^-$ 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 $K_s = 4.6$.

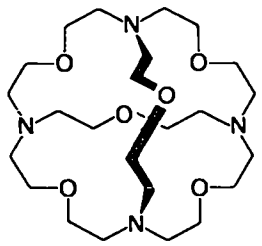
E. Macrotricyclic Cryptands

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.

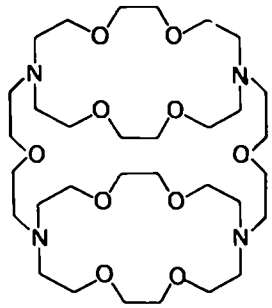
1. *Spherical*

Ligand **84** has high (Td) symmetry and possesses a spherical cavity[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].



(**84**)

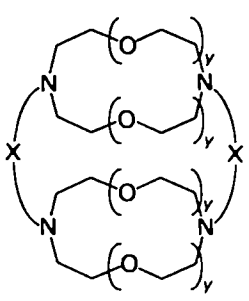


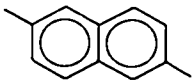
(**85**)

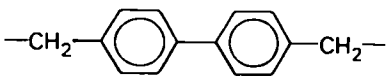
2. *Cylindrical*

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 and 6) in preference to **88** (n = 4 and 7) which are respectively too short and too long to fit well inside the cavity.



(**86**) y = 2, X = 

(**87**) y = 1, X = 

$H_3\overset{+}{N}-(CH_2)_n-\overset{+}{N}H_3$

(**88**)

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.

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
Edited by Saul Patai

CHAPTER **19**

Alkyl nitrate nitrations

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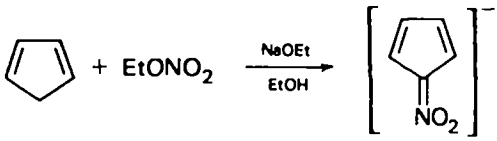
I. INTRODUCTION

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[1] (equation 1).

$$H_2NOH \cdot HCl + EtONO_2 \xrightarrow[EtOH]{NaOEt} [O_2NNO]^{=} \; 2\,Na^{+} \qquad (1)$$

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).



(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

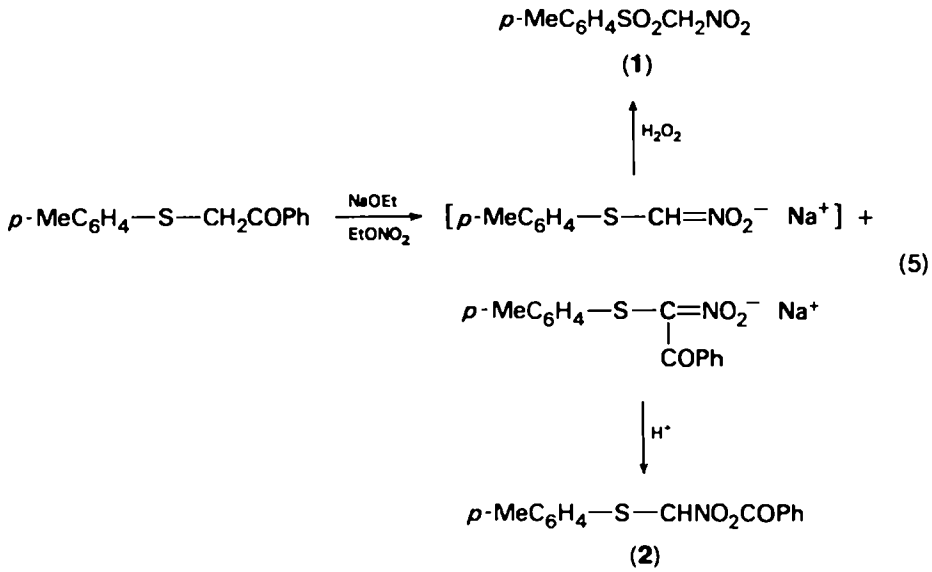
$$PhCH_2CO_2Et \xrightarrow[EtONO_2]{EtOK} \left[Ph{-}\overset{\displaystyle NO_2^{-}\;K^{+}}{\overset{\|}{C}}{-}CO_2Et \right] \xrightarrow{H^{+}} \underset{80\%}{PhCH_2NO_2} + (EtO)_2CO \qquad (3)$$

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*-bromophenylnitroacetonitrile 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).

$$PhCH_2CN \xrightarrow[MeONO_2]{NaOEt} \underset{CN}{PhC{=}NO_2^{-}}\;Na^{+} \xrightarrow[2\ HCl]{1\ NaOH} \underset{55\%}{PhCH_2NO_2} \qquad (4)$$

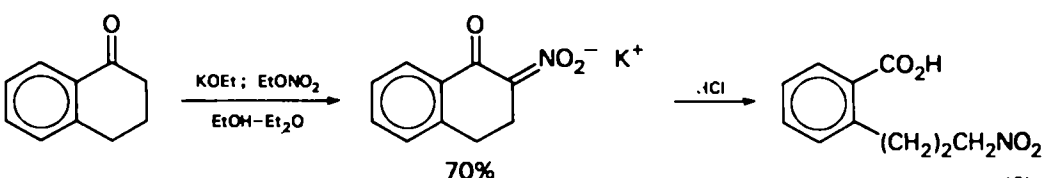
Attempts by Wislicenus[4] to extend the nitration to aliphatic esters by using potassium ethoxide as the base were unsuccessful; but he was able to convert fluorene to the potassium salt of 9-nitrofluorene in 70% yield. Nitration was, however, unsuccessful when sodium ethoxide was employed as the base[8]. 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[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).



(5)

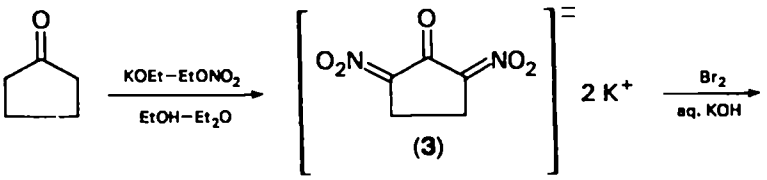
The nitration of a cyclic ketone was first achieved by Straus and Ekhard[12]. α-Tetralone was converted in 70% yield to the potassium salt of 2-nitrotetralone. Acidification of the salt with hydrochloric acid led to ring-opening with the formation of 2-(3-nitropropyl) benzoic acid (equation 6). About three years later, Wieland and



(6)

coworkers[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[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**[15].

A short account of the importance of the alkyl nitration for the preparation of



(3)

$$O_2NCBr_2(CH_2)_2CBr_2NO_2 + K_2CO_3 \quad (7)$$

primary nitramines has been presented by Wright[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[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[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[19] and also side-reactions of the substrate, such as self-condensation of ketones and esters.

$$R^1{-}CH_2{-}\underset{\displaystyle R^2}{\overset{\displaystyle |}{X}} + B^- \rightleftharpoons [R^1{-}\underset{\displaystyle R^2}{\overset{\displaystyle |}{CH}}{-}X]^- + HB \quad (8)$$

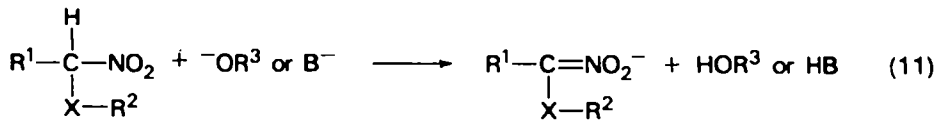
(4)

X = activating group, B = base

$$4 + R^3ONO_2 \rightleftharpoons R^1{-}\underset{\displaystyle R^2{-}X}{\overset{\displaystyle H}{C}}{-}\overset{\displaystyle O^-}{N}{-}OR^3 \quad (9)$$

(5)

$$5 \longrightarrow R^1{-}\underset{\displaystyle R^2{-}X}{\overset{\displaystyle H}{C}}{-}NO_2 + {}^-OR^3 \quad (10)$$



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[18] and nitriles[20]. Primary alkyl nitrates are suitable nitrating agents since they are not affected by the base *t*-butoxide below −10°C. A tertiary nitrate such as *t*-butyl nitrate is unsuitable because it is converted to isobutylene by the base, even at −30°C.

The importance of solvent on the yield in the nitration of cyclopentanone is shown in Table 1. Reactions are performed at −30°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[21,22].

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[23] (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 1. Solvent effects in the alkyl nitrate nitration of cyclopentanone[a]

Solvent	Solubility[b]	Dielectric constant at 20°C	Yield (%)[c,d]
Toluene	2.27	2.38[21]	21[e]
Hexane	0.27	1.89	38[e]
Ether	4.34	4.34	48[e], 55[f]
THF	25.00	7.58[22]	62[f]

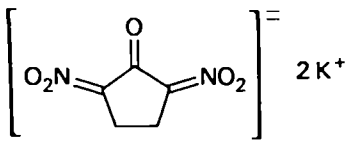
[a]Reprinted with permission from H. Feuer, J. W. Shepherd and Ch. Savides, *J. Amer. Chem. Soc.*, **78**, 4364 (1956). Copyright 1956 American Chemical Society.
[b]Solubility of *t*-BuOK in g/100 g solvent at 25–26°C.
[c]In all experiments the ketone is added to a 10% excess of base followed by a 10% excess of amyl nitrate at −30°C.
[d]Determined by conversion of dipotassium 2,5-dinitrocyclopentanone to 1,1,4,4-tetrabromo-1,4-dinitrobutane.
[e]The reaction time is 17 h.
[f]The reaction time is 1 h.

TABLE 2. Effect of added *t*-butyl alcohol on the alkyl nitrate nitration of cyclopentanone[a]

t-BuOK[b]	*t*-BuOH	Yield (%)[c]
0.110	—	39.0
0.110	0.11	15.5
0.165	—	55.0
0.165	0.15	17.0

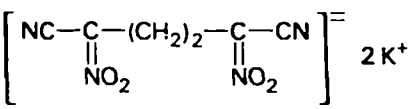
[a]Reprinted with permission from H. Feuer, J. W. Shepherd and Ch. Savides, *J. Amer. Chem. Soc.*, **78**, 4364 (1956). Copyright 1956 American Chemical Society.
[b]0.05 mole of ketone and a 10% excess of amyl nitrate are used in all experiments.
[c]Determined by conversion of the dinitro salt **6** to 1,1,4,4-tetrabromo-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[18].



(**6**)

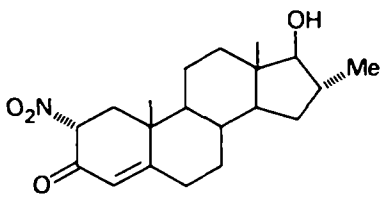
The adverse effect of added alcohol is also observed in the nitration of adiponitrile[20]; the yield of dipotassium 2,5-dinitroadiponitrile (**7**) decreases from 93% to



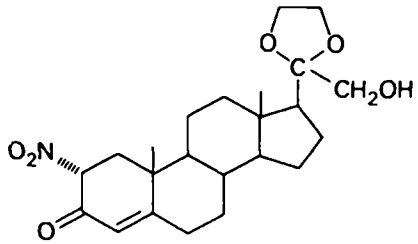
(**7**)

11%. Schaub and coworkers[24] 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 tetrahydropyranyl ether affords 2α-nitro-17β-(tetrahydropyran-2-yloxy)androst-4-en-3-one (**10**) in 42% yield.

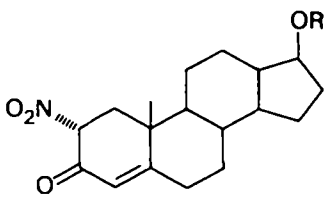
The importance of temperature and mode of addition in the nitration of cyclopentanone is indicated in Table 3. The highest yield of **6** is attained if the reaction temperature is maintained at −30°C and the ketone is added to the base followed by the nitrate. The temperature effect is further illustrated by the fact that in the nitration of acetophenone, the yield of potassium ω-nitroacetophenone increases from 6.7% to 40.5% when the reaction temperature is decreased from −10°C to −40°C.



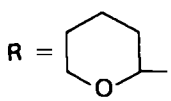
(8)



(9)



(10)



The effect of reaction time, especially in the nitration of ketones is of interest. Nitration of 2-tetralone at −78°C, as monitored spectrophotometrically, shows that the concentration of the formed potassium salt of 2-nitrotetralone decreases with time[20]. 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 *t*-butoxide is added to purified THF and the mixture is cooled to about −50°C. The compound, dissolved in THF, is added followed by the rapid addition of a primary alkyl nitrate (10% excess) at −40°C to −50°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**[a]

Temp. (°C)	−20	−30	−40	−30	−30
Yield (%)[b]	28[c]	38[c]	36[c]	34[d]	44[e]

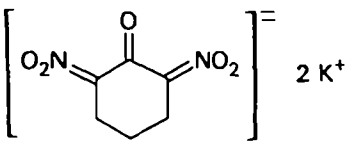
[a]Reprinted with permission from H. Feuer, J. W. Shepherd and Ch. Savides, *J. Amer. Chem. Soc.*, **78**, 4364 (1956). Copyright 1956 American Chemical Society.
[b]Determined by conversion of **6** to 1,1,4,4-tetrabromo-1,4-dinitrobutane.
[c]Ketone and nitrate are added to the base.
[d]Ketone is added 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**[a]

Reaction time (h)[b,c]	Excess *t*-BuOK (%)	Yield (%)[d]
0	65	62.0
4	65	60.0
16	65	57.0

[a]Reprinted with permission from H. Feuer, J. W. Shepherd and Ch. Savides, *J. Amer. Chem. Soc.*, **78**, 4364 (1956). Copyright 1956 American Chemical Society.
[b]Reaction temperature is −30°C.
[c]An additional one-hour period required to attain ambient temperature is not included.
[d]Determined by conversion of **6** to 1,1,4,4-tetrabromo-1,4-dinitrobutane.

High yields (Table 5) of pure **6** and dipotassium 2,6-dinitrocyclohexanone (**11**) are



(11)

obtained by dissolving the crude salts in a minimum amount of equal parts water and methanol followed by precipitation with acetone[25]. An alternate method involves converting disalts **6** and **11** to the monosalts directly in the reaction mixture with acetic acid, dissolving the dried salts in aqueous potassium hydroxide, and precipitating the disalts with methanol[26]. These procedures, however, do not give pure dipotassium salts of 2,7-dinitrocycloheptanone and 2,8-dinitrocyclooctanone.

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 pK_a units. Thus, α-nitration, induced by this base, is also successful with *N,N*-disubstituted amides[27], *N,N*-disubstituted sulphonamides[28] and sulphones[29] (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[27].

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[a]

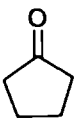
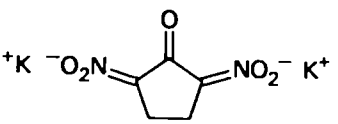
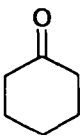
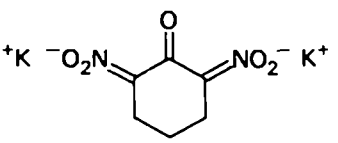
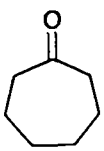
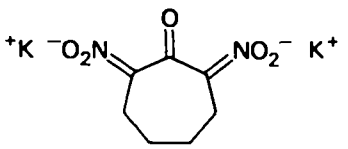
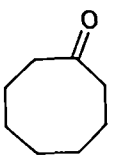
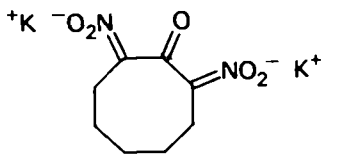
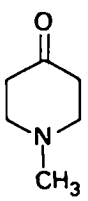
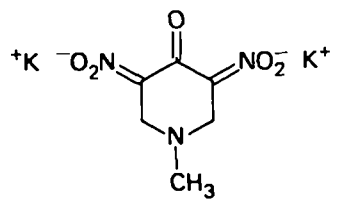
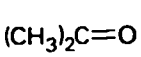
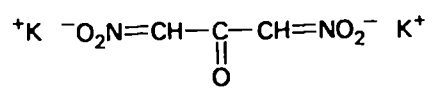
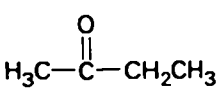
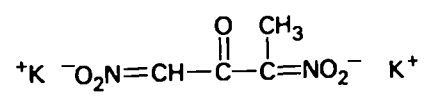
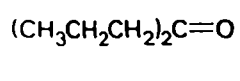
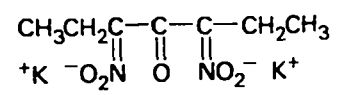
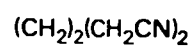
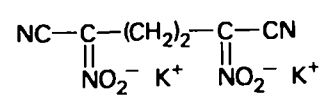
Reactant	Product	Yield (%)	Reference
Dinitration			
		98	18, 30
		74	18, 30
		55[b]	18
		35[b,c]	18, 25
		78	31
		49	20
		57	20
		50[d]	20
		93	20

TABLE 5. (*continued*)

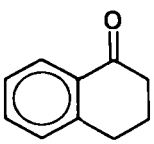
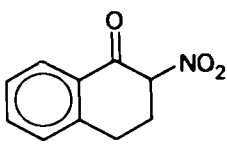
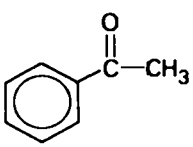
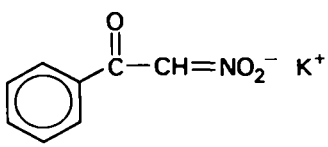
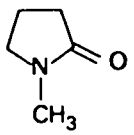
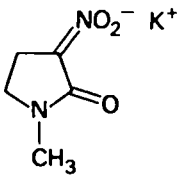
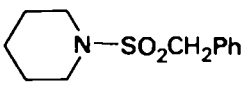
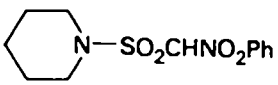
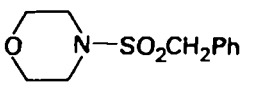
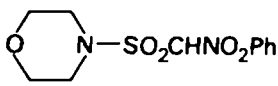
Reactant	Product	Yield (%)	Reference
$(H_2C)_3(CH_2CN)_2$	$NC-C(=NO_2^- K^+)-(CH_2)_3-C(=NO_2^- K^+)-CN$	45[b]	20
$(H_2C)_4(CH_2CN)_2$	$NC-C(=NO_2^- K^+)-(CH_2)_4-C(=NO_2^- K^+)-CN$	67[e]	20
$(H_2C)_6(CH_2CN)_2$	$NC-C(=NO_2^- K^+)-(CH_2)_6-C(=NO_2^- K^+)-CN$	48[e]	20
$(H_2C)_2[CH_2CON(CH_3)_2]_2$	$(CH_3)_2N-C(=O)-C(=NO_2^- K^+)-(CH_2)_2-C(=NO_2^- K^+)-C(=O)-N(CH_3)_2$		27
Mononitration[g]			
		59	32
		40	20
$CH_3(CH_2)_2CN$	$CH_3CH_2-C(=NO_2^- K^+)-CN$	44[h]	20
$CH_3(CH_2)_4CN$	$CH_3(CH_2)_3-C(=NO_2^- K^+)-CN$	55[i]	20
$CH_3CON(CH_3)_2$[j]	$HC(=NO_2^- K^+)-CON(CH_3)_2$	32[k]	27
$CH_3(CH_2)_2CON(CH_3)_2$[j]	$CH_3CH_2-C(=NO_2^- K^+)-CON(CH_3)_2$	65[l]	27

TABLE 5. (*continued*)

Reactant	Product	Yield (%)	Reference
		85	31
		64	28
		66	28
$PhCH_2SO_2Ph$	$PhCHNO_2SO_2Ph$	81	29
$p\text{-}CH_3C_6H_4SO_2CH_2Ph$	$p\text{-}CH_3C_6H_4SO_2CHNO_2Ph$	79	29
$(PhCH_2)_2SO_2$	$PhCHNO_2SO_2CH_2Ph$	82	29
$PhCH_2SO_2Ph$	$PhCHNO_2SO_2Ph$	42	29
$n\text{-}PrSO_2Ph$	$CH_3CH_2CHNO_2SO_2Ph$	8	29
$(n\text{-}C_4H_9)_2SO_2$	$CH_3(CH_2)_2CHNO_2SO_2C_4H_9\text{-}n$	33[m]	29

[a]Unless stated otherwise, the solvent is purified THF.
[b]Determined by conversion to $NO_2Br_2C—(CH_2)_n—CBr_2NO_2$.
[c]2-Nitrocyclooctanone (47% yield) is also formed.
[d]Determined by conversion to $CH_3CH_2—CBrNO_2—\overset{\overset{O}{\|}}{C}—CBrNO_2—CH_2—CH_3$.
[e]Determined by conversion to $NC—CBrNO_2—(CH_2)_n—CBrNO_2—CN$.
[f]Determined by conversion to $(CH_3)_2N—\overset{\overset{O}{\|}}{C}—CBrNO_2—(CH_2)_2—CBrNO_2—\overset{\overset{O}{\|}}{C}—N(CH_3)_2$.
[g]One equivalent of $RONO_2$ is used.
[h]Determined by conversion to $CH_3CH_2CBrNO_2CN$.
[i]Determined by conversion to $CH_3(CH_2)_3—CBrNO_2CN$.
[j]The solvent is absolute ether.
[k]Determined by conversion to $CBr_2NO_2—CON(CH_3)_2$.
[l]Determined by conversion to $CH_3CH_2CBrNO_2—CON(CH_3)_2$.
[m]The yield is 79% when nitration is performed in the potassium amide–liquid ammonia system.

nitrating agent such as acetone cyanohydrin nitrate[33] (**12**). 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[33]. This reaction, which is performed at ambient temperatures, constitutes a general method for preparing ethyl esters of α-nitro acids in yields ranging between 42 and 70% (equation 12). It is suggested[33]

$$\text{RCH(CO}_2\text{Et)}_2 \text{ or } \begin{matrix}\text{RCHCO}_2\text{Et}\\ |\\ \text{COMe}\end{matrix} + \underset{\text{CN}}{\underset{|}{(\text{Me})_2\text{C}-\text{ONO}_2}} \xrightarrow{2\,\text{NaH}} \underset{}{\overset{\text{NO}_2}{\overset{|}{\text{RCHCO}_2\text{Et}}}} + \text{Me}_2\text{CO} + \text{NaCN} \quad (12)$$

(12)

R = alkyl, $PhCH_2$, $ClCH_2CH_2CH_2$ or $CH_2=CHCH_2$

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

$$A^- + \mathbf{12} \longrightarrow \left[A^{\delta-} \cdots \overset{\overset{O^{\delta-}}{\vdots}}{\underset{\underset{O^{\delta-}}{\vdots}}{N}} \cdots O = \overset{\overset{Me}{|}}{\underset{\underset{Me}{|}}{C}} \cdots CN^{\delta-} \right] \longrightarrow$$

$$ANO_2 + (Me)_2CO + CN^- \quad (13)$$

A = Carbanion

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

Nitration of *N,N*-dimethylbenzylsulphonamide with potassium hydride and **12** gives the α-nitrosulphonamide in 25% yield, while the yield is 75% with ethyl nitrate[34].

2. *Alkali amide–liquid ammonia systems*

Stronger bases than potassium *t*-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 $pK_a \sim 35$[35]. With very few exceptions nitrations in the potassium amide–liquid ammonia system give higher yields than those in the sodium amide system[35–38]. Nitrations in lithium amide, the weakest base in the series, give nitro compounds in very low yield[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 *t*-butoxide. (This base has also been prepared *in situ* from *t*-butyl alcohol and potassium amide in refluxing THF[31])
(3) Elimination of operations mandatory in the handling and storage of dry THF to prevent peroxide formation[20].

Disadvantages of the potassium amide system are:

(1) Reaction with the nitrating agent[30], the alkyl nitrate, even at −40°C (equation 14).
(2) Determination of the optimum ratio of the reactants for every class of compounds.

(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.

$$RONO_2 \xrightarrow{KNH_2-NH_3} RO^- \xrightarrow[-33°C]{NH_4Cl} ROH \qquad (14)$$

R = alkyl

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°C to the alkali amide which is prepared *in situ* in liquid ammonia. Then, the nitrate ester is added as fast as is feasible by maintaining the reaction temperature at about −40°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 nitration in the alkali amide–liquid ammonia system (i) Ketones. Dinitrations[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[30].

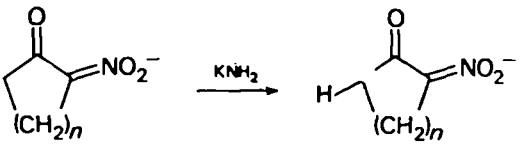
The formation of mononitro compounds is a good indication that dinitration proceeds stepwise. This conclusion seems to be supported by the conversion of 2-nitrocyclooctane to dipotassium 2,7-dinitrocyclooctanone (28% yield) on further nitration.

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

TABLE 6. Comparison of dinitration of cyclanones in *t*-BuOK–THF and KNH_2–NH_3[30]

Ketone[a]	*t*-BuOK–THF bromination product[b], yield (%)	Disalt[c], yield (%)	KNH_2–NH_3 bromination product[b], yield (%)	Disalt[c], yield (%)
Cyclopentanone	72	98	89	94
Cyclohexanone	54[d]	74	52[d]	95
Cycloheptanone	55[d]	—	80.5	85[e]
Cyclooctanone	35[d]	—	25[d,e]	—

[a]Unless otherwise stated 2.0 equiv. of KNH_2 and 2.2 equiv. of amyl nitrate are used.
[b]Bromination product is $O_2NCBr_2-(CH_2)_n-CBr_2NO_2$.
[c]Disalt is 2-oxo-1,3-cycloalkanedinitronate.
[d]Obtained on bromination of the crude disalt.
[e]KNH_2 (3.5 equiv.) and amyl nitrate (3.5 equiv.) are used.



(15)

(13)

The alkyl nitrate nitration leads to mononitroketones if equimolar amounts of ketone and base are used[30,32]. 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[30, a,b]

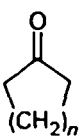
Ketone	α-Nitroketone		ω-Nitrocarboxylic ester	
	t-BuOK–THF, yield (%)	KNH_2–NH_3, yield (%)	*t*-BuOK–THF, yield (%)	KNH_2–NH_3, yield (%)
Cyclopentanone[c]	0	0	10	11
2,2,4-Trimethylcyclopentanone[d]	82	—	trace	—
2,2,5-Trimethylcyclopentanone[e]	0	—	53	—
2,5-Dimethylcyclopentanone[f]	10	—	58	—
Cyclohexanone	20[g]	59	10	2
Cycloheptanone	65	79	4	1
Cyclooctanone	35	60	37	21
Cyclononanone	14	26	60	46
Cyclodecanone	14	17	58	50
Cyclododecanone	54	64	23	17
Propiophenone[h]	16	30	0[i]	—
α-Tetralone[j]	59	71	—	—
4-Heptanone	39	55	0[k]	0[l]
2,4-Dimethyl-3-pentanone[m]	0	—	0[n]	—

[a] *t*-BuOK (1.65 equiv.) and alkyl nitrate (1.1 equiv.) in THF at −40°C are used.
[b] KNH_2 (1.0 equiv.) and alkyl nitrate (2.0 equiv.) in NH_3 at −33°C are employed.
[c] Compound **6** (19%) is obtained in *t*-BuOK and 29% in KNH_2.
[d] Recovered 40% of ketone.
[e] Recovered 20% of ketone.
[f] Recovered 16% of ketone.
[g] Potassium 2-oxo-3-nitrocyclohexanenitronate (18%) is also formed.
[h] Recovered 59% of ketone.
[i] Ethyl benzoate (8%) and benzoic acid (7%) are formed (nitrating agent is $EtONO_2$).
[j] Recovered 34% of ketone.
[k] Amyl butyrate (25%) and 1-nitropropane (20%) are isolated (nitrating agent is $AmONO_2$).
[l] Ethyl butyrate (7%) and 1-nitropropane are formed (nitrating agent is $EtONO_2$).
[m] Recovered 16% of ketone.
[n] Amyl isobutyrate (84%) and 2-nitropropane (66%) are obtained.

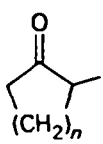
$$(CH_3CH_2CH_2)_2CO \xrightarrow[2.\ EtONO_2]{1.\ KNH_2-NH_3 \text{ or } t\text{-BuOK-THF}} CH_3(CH_2)_2CO_2Et + \quad 8\%$$

$$\text{'nitro salts'} \xrightarrow{H^+} CH_3CH_2\underset{NO_2}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-(CH_2)_2CH_3 + CH_3CH_2CH_2NO_2 \qquad (16)$$

55% (14) 8%



$$\xrightarrow[2\ RONO_2\ 3.\ H^+]{1\ KNH_2-NH_3 \text{ or } t\text{-BuOK-THF}}$$



$$+ O_2NCH_2(CH_2)_{n+1}CO_2R \qquad (17)$$

n = 2–7 and 9
R = alkyl

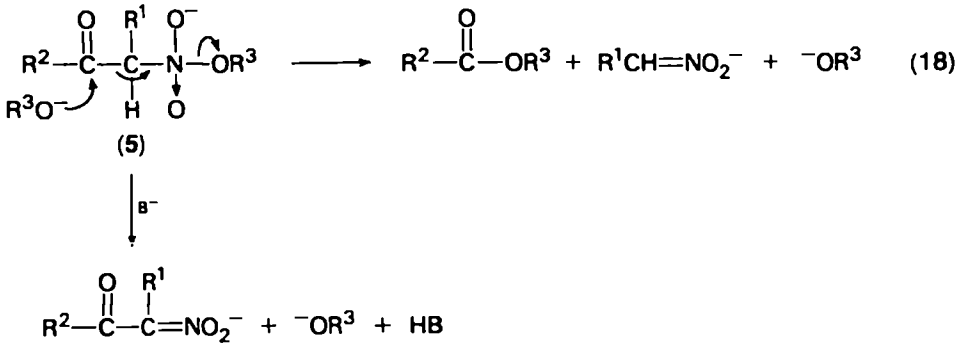
The following observations confirm that the fragmentation occurs during the nitration and not during the acidification step:

(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°C (the temperature maintained during the nitration) to varying ratios of a potassium *t*-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[39]. When in a nitration of cyclooctanone absolute ethanol is added immediately after the amyl nitrate, the only ester present after acidificatioan is amyl 8-nitrooctanoate.

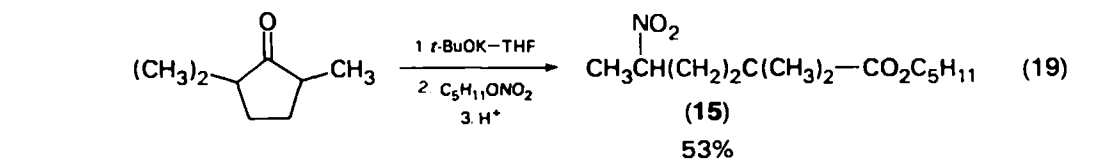
The foregoing results indicate clearly that the salt of a nitroketone, once formed during the nitration, does not participate in the cleavage reaction. A mechanism consistent with the experimental observations involves alkoxide attack at the carbonyl group of the intermediate **5** (equation 9 X = CO)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

These two competing reactions should be influenced by the availability of α-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 α-hydrogens are available, lead mostly to the nitrocarboxylic esters **15** and **16**, respectively. Nitration of 2,2,4-trimethylcyclopentanone, in which one of the α-positions is blocked, gives the nikroketone **17** in high yield and only a trace of cleavage product.

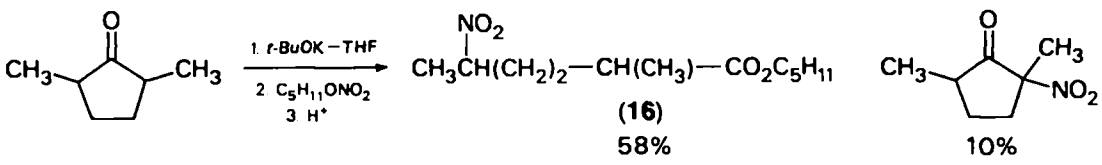
Also consistent with the role of intermediate **5**, it is reported that more of the



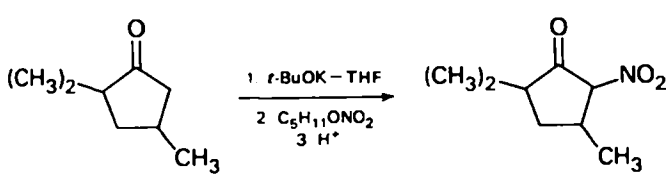
(18)



(19)



(20)

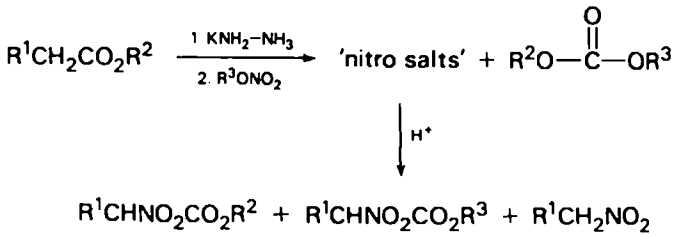


(21)

nitroketone forms in nitrations in potassium amide than in potassium *t*-butoxide; in the stronger basic medium removal of the acidic hydrogen in **5** occurs at a faster rate than the attack of alkoxide at the carbonyl group[30].

(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[40]. 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[41]. Moreover,

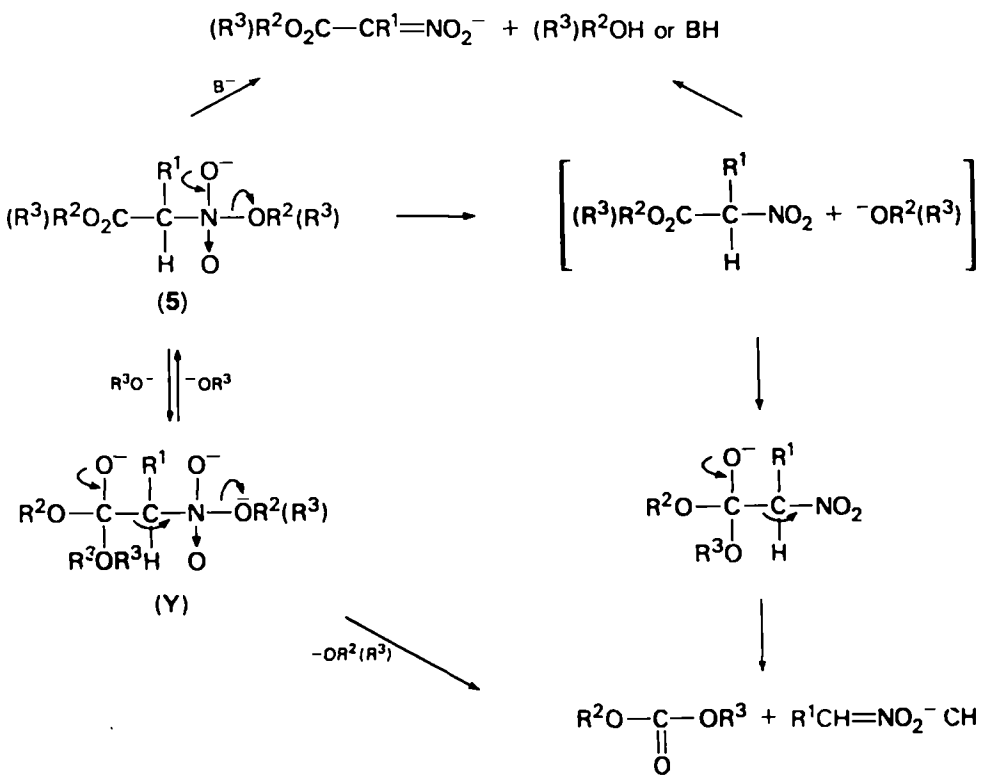


(22)

the nitration results for several *t*-butyl esters and ethyl esters show that less fragmentation occurs in the nitration of *t*-butyl esters except in the case of *t*-butyl phenylacetate where the major product is phenylnitromethane.

The nitration of *p*-nitrophenyl acetate is unsuccessful[40] 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 = CO_2).

Based on several control experiments[40] 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. Nucleophilic attack of alkoxide (from the nitrating agent) at the carboxyl group of



SCHEME 1

TABLE 8. Nitration of *t*-butyl and ethyl esters, $R^1CH_2CO_2R^2$ [40,a]

R^1	R^2	$RCHCO_2Et$ (NO_2) yield (%)	$RCHCO_2Bu\text{-}t$ (NO_2) yield (%)	Total amount of α-nitro esters, yield (%)	RNO_2 yield (%)	Total nitration, yield (%)
Me	Et	24	—	24	19	43[b]
Me	Bu-*t*	22	26	48	14	62[c]
Et	Et	41	—	41	14	55[b]
Et	Bu-*t*	31	22	53	26	79[c]
n-Bu	Et	42	—	42	14	56[b]
n-Bu	Bu-*t*	33	22	55	33	88[c]
s-Bu	Bu-*t*	0	0	0	72	72[c]
H	Bu-*t*	22	18	40	33	73[c]
i-Pr	Bu-*t*	18	33	51	26	77[c]
Ph	Et	23	—	23	49	72[b]
Ph	Bu-*t*	3	36	39	49	88[c]
p-$MeOC_6H_4$	Et	72[d]	—	72[d]	22	94

[a]Ratio of ethyl esters to KNH_2 to $EtONO_2$ is 1 to 1.1 to 1.5; in the case of *t*-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, $X = CO_2$) leads to intermediate **Y** which on fragmentation is converted to the nitroalkane salt and dialkyl carbonate. Removal of the α-hydrogen in **5** by a base, such as amide, alkoxide or ammonia, would lead to the α-nitro ester salt. As predicted by the mechanism, the fragmentation would predominate if there is no α-hydrogen available in intermediate **5**. This has been confirmed in the nitration of *t*-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 *t*-butyl hexanoate (**18**)[40]. Three different α-nitro esters are obtained, *t*-butyl 2-nitrohexanoate, *n*-butyl 2-nitrohexanoate (**19**) and ethyl 2-nitrohexanoate (**20**) (equation 23). It is uncertain whether ethoxide *per se* is

$$\underset{\textbf{(18)}}{CH_3(CH_2)_4CO_2Bu\text{-}t} \xrightarrow[3\ n\text{-}BuONO_2;\ 4.\ H^+]{1.\ KNH_2\text{–}NH_3;\ 2.\ KOEt} \underset{3\%}{CH_3(CH_2)_3CHNO_2CO_2Bu\text{-}t} + \underset{\textbf{(19)}\quad 23\%}{CH_3(CH_2)_3CHNO_2CO_2Bu\text{-}n} + \underset{\textbf{(20)}\quad 22\%}{CH_3(CH_2)_3CHNO_2CO_2Et} \qquad (23)$$

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

$$n\text{-}BuONO_2 + {}^-OEt \xrightleftharpoons{KNH_2\text{–}NH_3} n\text{-}BuO^- + EtONO_2 \qquad (24)$$

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 nitration[42]. 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,

$$\underset{\textbf{(22)}}{CH_3(CH_2)_3SO_3Et} \xrightarrow[3.\ NH_4Cl]{1.\ KNH_2-NH_3;\ 2.\ RONO_2} \underset{\textbf{(23)}}{CH_3(CH_2)_2CHNO_2SO_3Et} + \underset{\textbf{(24)}}{CH_3(CH_2)_2CHNO_2SO_3K} \quad (25)$$

nitration 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.

$$CH_3(CH_2)_3SO_3C_8H_{17}\text{-}n \xrightarrow[3.\ NH_4Cl]{1.\ KNH_2-NH_3;\ 2.\ RONO_2} CH_3(CH_2)_2CHNO_2SO_3C_8H_{17}\text{-}n + \textbf{24} + CH_3(CH_2)_5CH{=}CH_2 \quad (26)$$

(25)

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). In

TABLE 9. Alkyl nitrate nitration of neopentyl alkylsulphonates, $RSO_3CH_2C(CH_3)_3$, in potassium amide–liquid ammonia[a,b]

R	Neopentyl 1-nitrosulphonates	
	yield (%)[c]	yield (%)[d]
CH_3CH_2	74 (22)[e]	—
n-C_4H_9	76 (22)	—
n-C_6H_{13}	56 (37)	75 (21)[e]
n-C_8H_{17}	33 (62)	76 (22)
n-$C_{10}H_{21}$	17 (78)	56 (40)
n-$C_{12}H_{25}$	3 (93)	40 (63), 47[f]
$CH_3CH_2CH(CH_3)$	—	35 (60)
$(CH_3)_3CCH_2O_3S(CH_2)_4$	69	—

[a]Reprinted with permission from H. Feuer and M. Auerbach, *J. Org. Chem.*, **35**, 2552 (1970). Copyright 1970 American Chemical Society.
[b]The ratio of ester to base to nitrate is 1:2:3.
[c]Reactions are performed at −33°C in ca. 0.3 M solution of potassium amide. The nitration time is 5 min.
[d]The concentration of potassium amide is ca. 0.7 M. The nitration time is one hour.
[e]The numbers in parenthesis represent recovered starting material.
[f]Anion formation is carried out in THF at 65°C, and the nitration at −33°C.

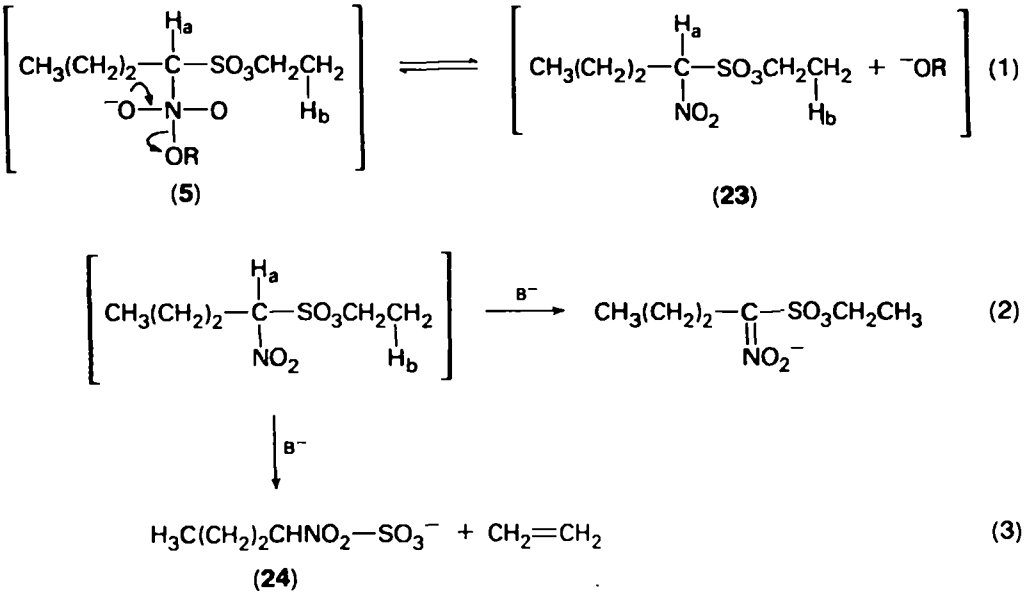
$$CH_3CH_2CH(CH_3)SO_3CH_2C(CH_3)_3 \xrightarrow[2.\ RONO_2\ \ 3.\ NH_4Cl]{1.\ KNH_2-NH_3} CH_3CH_2\overset{\displaystyle NO_2}{\underset{\displaystyle CH_3}{C}}-SO_3CH_2C(CH_3)_3 \quad (27)$$

35%

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 = SO_3) 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 (H_a) as shown in step (2), or alternately can abstract the β-hydrogen (H_b) in the ester part to give salt **24** and ethylene in step (3).

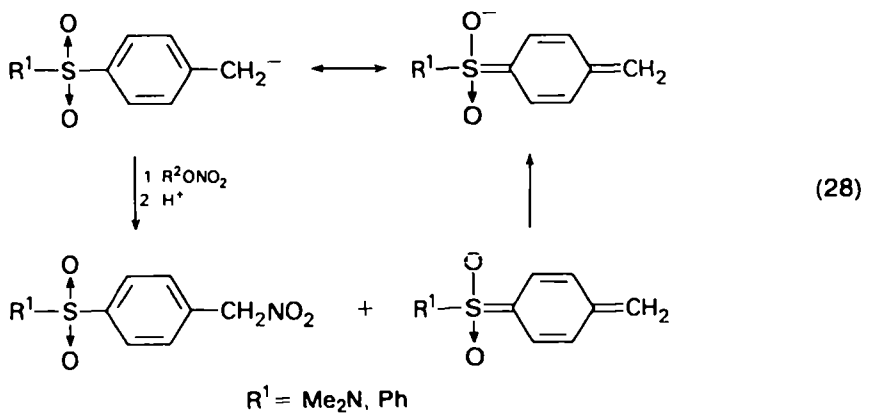
(iv) Activated toluenes. The alkyl nitrate nitration of toluenes[35] substituted in the *ortho* or *para* position with an electron-withdrawing group gives the corresponding α-nitrotoluenes in yields of about 40–55% (Table 10). The yield varies greatly with the particular activating group. With two substituted 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 nitrations of



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[43], *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.

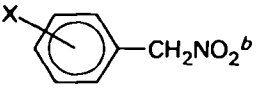
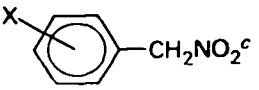
Toluene (pK_a ~37)[44] fails to undergo nitration in potassium amide; diphenylmethane (pK_a ~35)[45], however, is converted to diphenylnitromethane (**31**)



(28)

R^1 = Me_2N, Ph

TABLE 10. Alkyl nitrate nitration of activated toluenes[35,a]

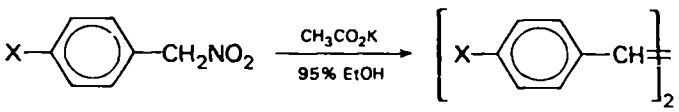
X	yield (%)	yield (%)
		
p-CN	47 (36)[d]	42 (41)[d]
o-CN	38 (35)	—
p-PhCO	16 (64)	0 (100)
p-Me_2NSO_2	15 (55)	40 (27)
p-$PhSO_2$	4 (84)	55 (39)

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

(40%). Spectroscopically pure **31** decomposes to benzophenone[46] when stored at 0°C; diphenylbromonitromethane, however, is stable when kept at 0°C.

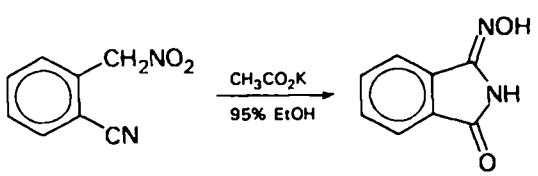
Attempts to nitrate *p*-nitrotoluene have been unsuccessful. Under the basic conditions of the nitration it is converted to *p,p'*-dinitrobibenzyl[47].

The *para*-substituted α-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[35] (equation 29). Under similar reaction conditions *o*-cyanophenylnitromethane is converted to 3-oximinophthalimide (92%) (equation 30).



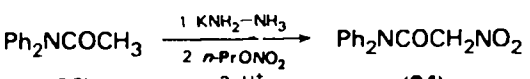
(29)

X = CN (76%), Me_2NSO_2 (67%), $PhSO_2$ (55%), PhCO (100%)



(30)

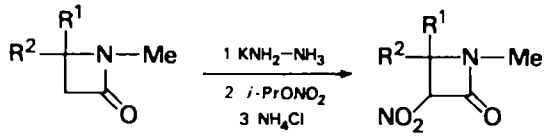
(v) Amides and lactams. There is only one example in the literature in which the nitration of an *N*-substituted amide in potassium amide is described[48]. *N*-Acetylpiperidine (**32**) is converted into *N*-nitroacetylpiperidine in about 8% yield and a considerable amount of starting material is recovered.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



Ph_2NCOCH_3 (**33**) → $Ph_2NCOCH_2NO_2$ (**34**), 30% (31)

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 nitrations of *N*-methylcaprolactam and *N*-methylpyrrolidone afford *N*-methyl-3-nitrocaprolactam (37%) and *N*-methyl-3-nitropyrrolidone (34%).



(32)

R^1 = Me, R^2 = H (34%); R^1, R^2 = Me (70%); R^1 = H, R^2 = Ph (10%); R^1 = H, R^2 = MeO (30%); R^1 = H, R^2 = MeS (32%)

(vi) Heterocyclic compounds. The alkyl nitrate nitration of π-deficient heterocyclic compounds such as 4-methylpyridine (**35**) and 4-methylpyrimidine and of π-excessive heterocyclic compounds such as 2-methylbenzoxazole and 2-methylbenzothiazole leads to α-nitroalkyl heterocyclics[36]. 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

TABLE 11. Alkyl nitrate nitration of alkyl-substituted heterocyclic compounds[a]

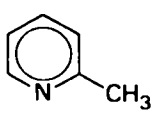
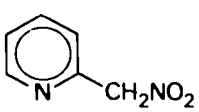
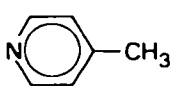
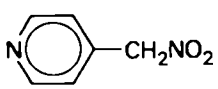
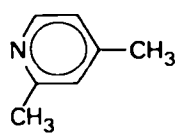
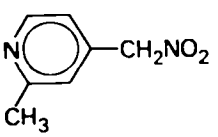
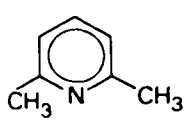
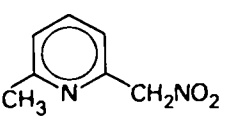
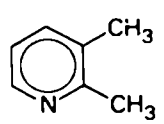
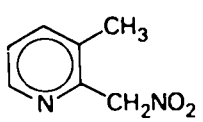
Starting material	Product[b]	$NaNH_2$–NH_3[c], yield (%)	KNH_2–NH_3[d], yield (%)
		58	48[e]
		66	33
		69	53
		68	65
		52[f]	—

TABLE 11. (*continued*)

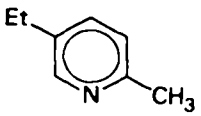
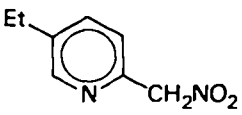
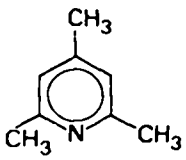
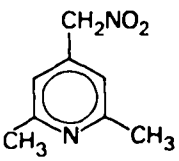
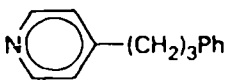
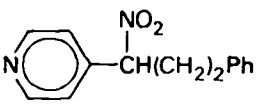
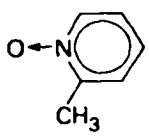
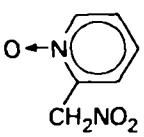
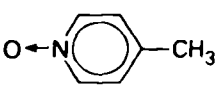
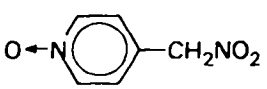
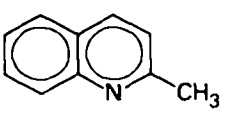
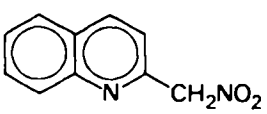
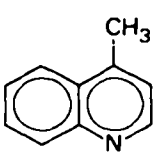
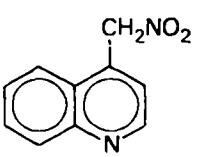
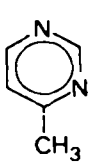
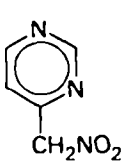
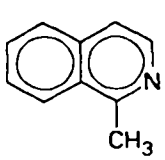
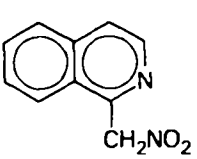
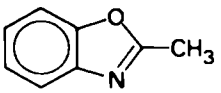
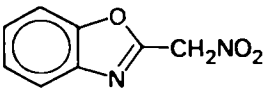
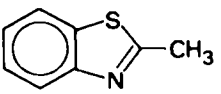
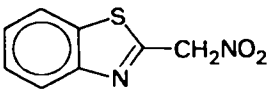
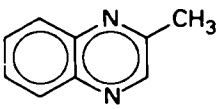
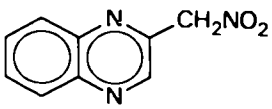
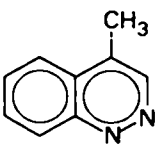
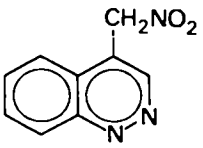
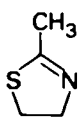
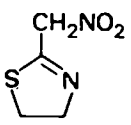
Starting material	Product[b]	$NaNH_2$–N_3[c], yield (%)	KNH_2–NH_3[d], yield (%)
		0[g]	42[h]
		76	55
		90	74
		71[i]	54[j]
		58[k]	58[k]
		*l*	33[e]
		58	93
		—	71
		54	50

TABLE 11. (*continued*)

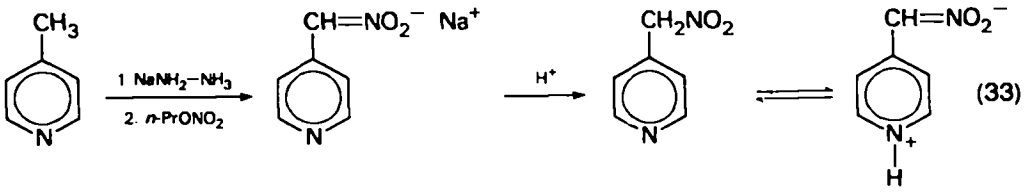
Starting material	Product[b]	$NaNH_2$–NH_3[c], yield (%)	KNH_2–NH_3[d], yield (%)
		62	—
		66	—
		55	58
		—	88
		43	—

[a]Reprinted with permission from H. Feuer and J. P. Lawrence, *J. Org. Chem.*, **37**, 3663 (1972). Copyright 1972 American Chemical Society.
[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%).

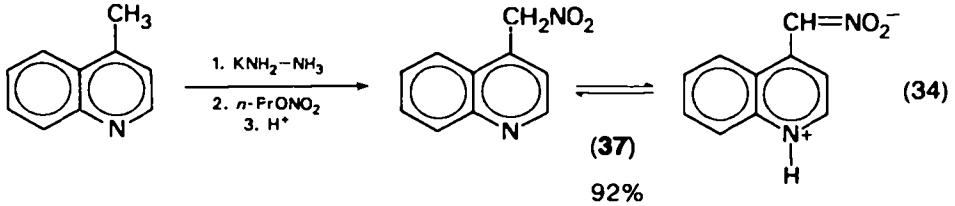
potassium amide the yield is only 33% and 42% of **35** is recovered. The sodium salt of **36** which can be readily purified is obtained in 92% yield (equation 33). This is not the case with the potassium salt of **36** which is highly hygroscopic.

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



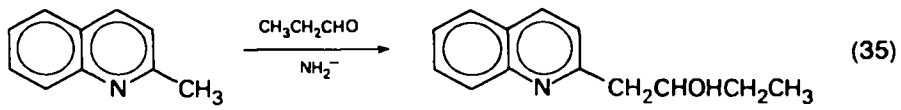
(35) 92% (36) 66% (33)



(37) 92% (34)

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



(38) (39) (35)

from the attack of base (NH_2^-) 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).

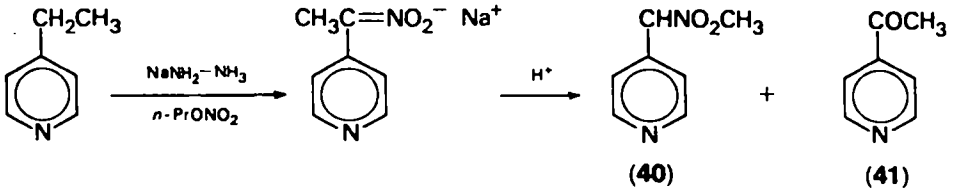
Nitration of heterocycles having more than one methyl group affords only mononitration products (Table 11) even if an excess of base and nitrate ester is used. As in oximation[50] and side-chain alkylation[51], the reactivity of the methyl group in pyridine is in the order of 4 > 2 > 3. Thus 2,4,6-trimethylpyridine 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[a]

Concentration of KNH_2 (M)[b]	Potassium salt of 2-nitromethylquinoline, yield (%)	Recovered 2-methylquinoline (**38**), yield (%)
0.35	0	88
0.59	42	42
1.58	43	43
2.84	50	37

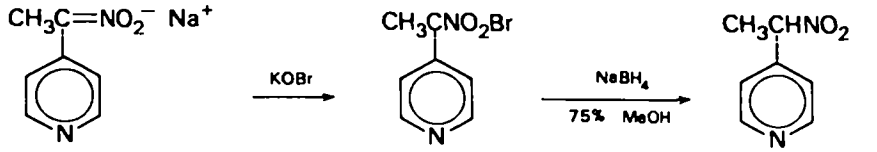
[a]Reprinted with permission from H. Feuer and J. P. Lawrence, *J. Org. Chem.*, **37**, 3663 (1972). Copyright 1972 American Chemical Society.
[b]Ratio of **38** to KNH_2 to *n*-$PrONO_2$ is 1.0:2.0:2.5.

The nitration of 4-ethylpyridine leads to a mixture consisting of 1-(4-pyridyl)nitroethane (**40**) and 4-acetylpyridine (**41**) (equation 36). Since



(40) (41) (36)

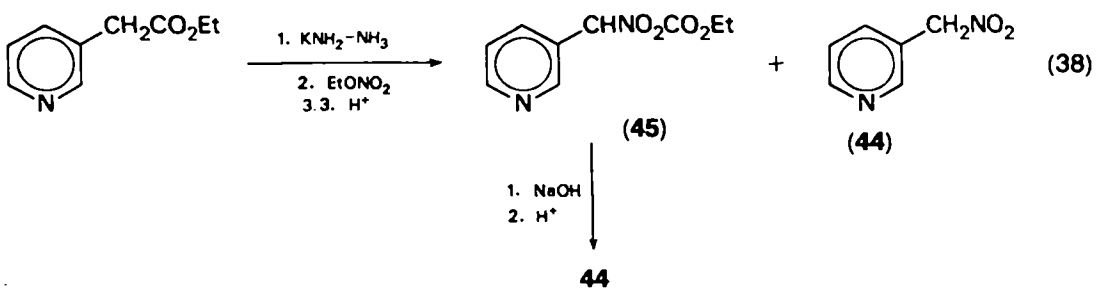
according to the spectral data the material isolated from the basic nitration mixture does not indicate the presence of **41**, it must be formed during the acidification step in a Nef-type reaction from **40**. This is also confirmed by the observation that analytically pure **40** transforms slowly 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).



(42) (40) (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[52]. 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 E_2-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).

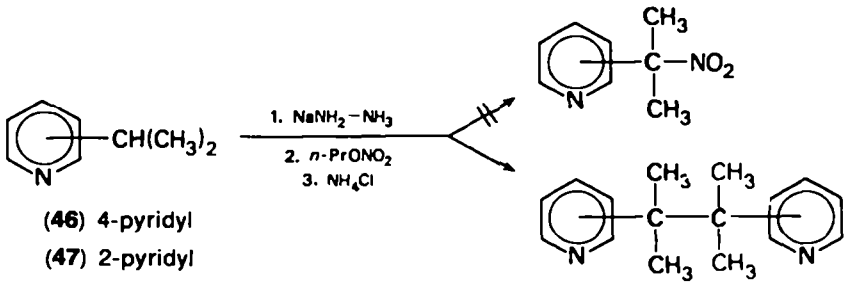


(45) (44) (38)

44

Nitrations[53] of 4-isopropylpyridine (**46**) and 2-isopropylpyridine (**47**) do not give the expected tertiary isopropylnitropyridines 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

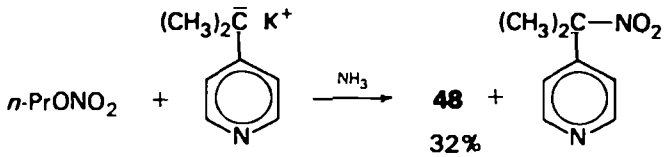


(46) 4-pyridyl
(47) 2-pyridyl

(48) 4-pyridyl, 88%
(49) 2-pyridyl, 91%

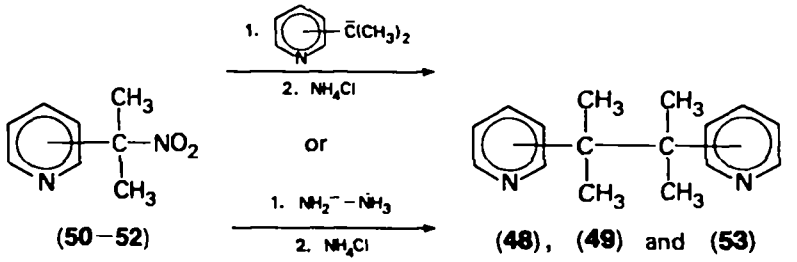
(39)

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



(40)

2-nitro-2-(3-pyridyl)propane (**52**), which have been prepared by direct nitration with 90% nitric acid[53], are converted in high yields to the respective dimers **48**, **49** and 2,3-bis(3-pyridyl)-2,3-dimethylbutane (**53**). The dimerizations occur in potassium amide–liquid ammonia or in the presence of the respective isopyropylpyridine anions generated in the potassium or sodium amide–ammonia systems (equation 41).



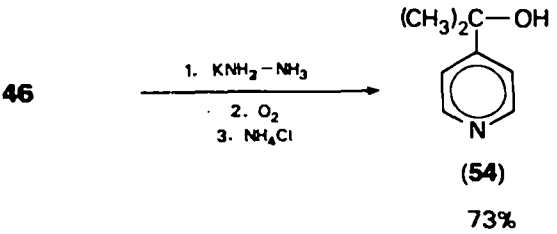
(50–52)

(48), (49) and (53)

(41)

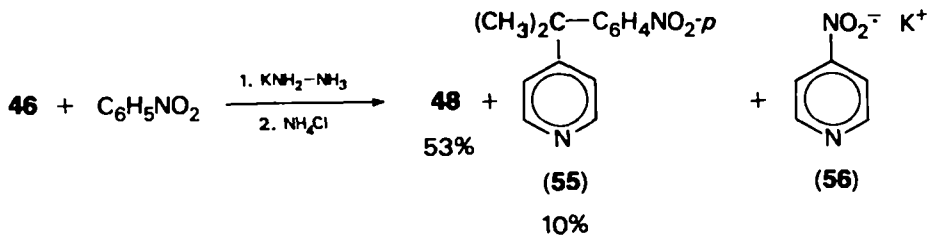
Regarding the formation of dimers **48**, **49** and **53**, a direct displacement of the tertiary nitro group in compounds **50–52** by the tertiary carbanion of **46**, **47** and 3-isopropylpyridine would seem unlikely because of steric considerations. it has been proposed[53] that these dimerizations occur by electron-transfer processes related to reactions in which the tertiary nitro group of α,p-dinitrocumene is replaced by a variety of anions[54] (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 mechanism[55]. Moreover, the reaction of **46** and nitrobenzene in potassium amide–liquid ammonia affords dimer **48** (53%),



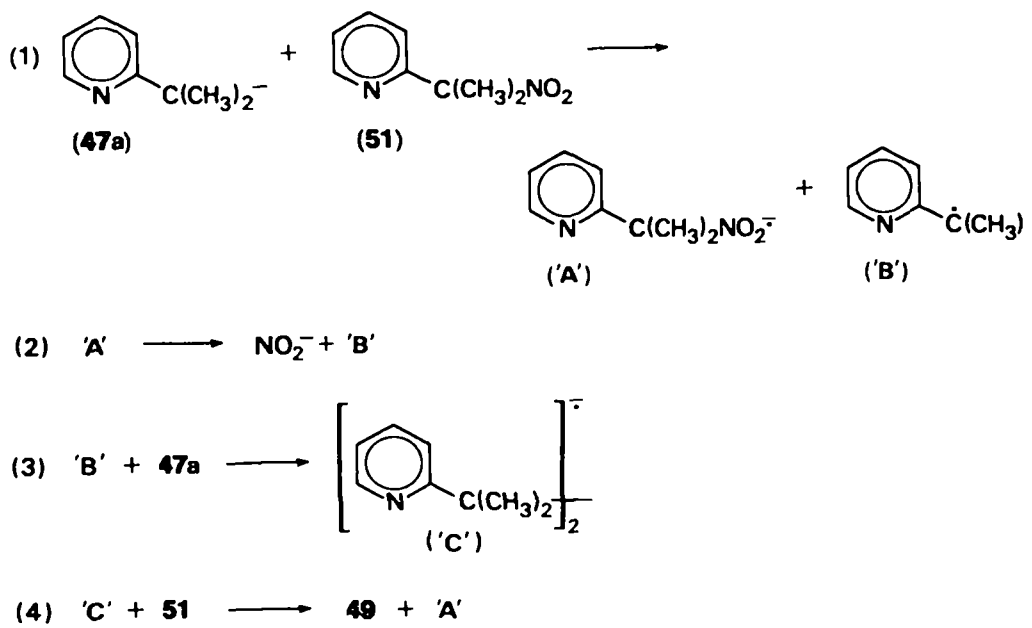
(42)

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].



(43)

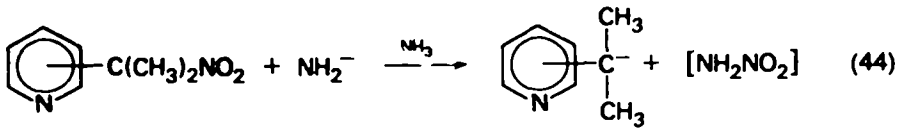
The essential steps which lead to the formation of dimers **48**, **49** and **53** are shown in Scheme 3 by using the formation of **49** as an example. The reaction is initiated by an electron transfer of the anion **47a** of **47** to the nitro compound **51** to give the radical anion **A** of **51** 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).



SCHEME 3

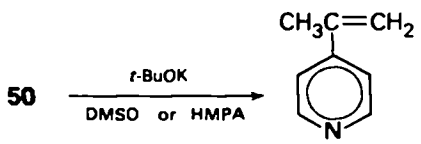
The combination of radicals **B** can also lead to dimer **49**, but this process is considered less favourable in the highly diluted solution in which the experiments are performed.

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).



(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).

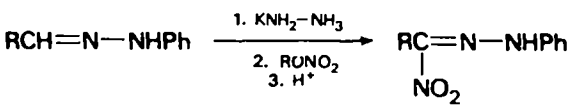


(45)

(**57**)

99%

(vii) Arylmethylene, alkylidene and hetarylmethylene phenylhydrazines. The alkyl nitrate nitration of arylmethylene, alkylidene and hetarylmethylene phenylhydrazines constitutes a general method for the introduction of the nitro group into the α-position of these classes of compounds[37] (equation 46). Nitration in several



(46)

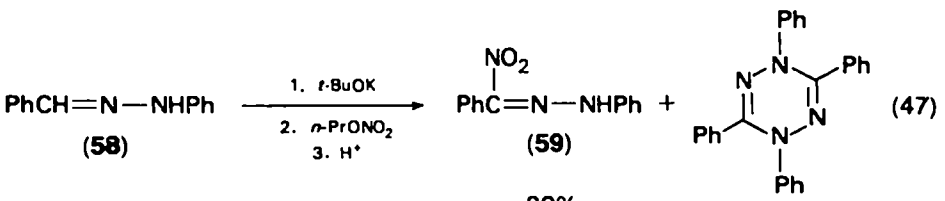
R = aryl, alkyl, hetaryl

base–solvent systems with benzylidene phenylhydrazine (**58**) shows that highest yields (91%) of α-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 α-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

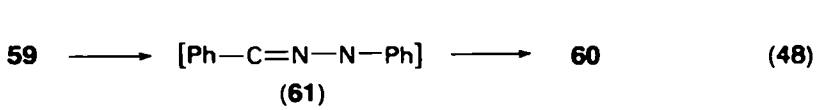
TABLE 13. Effect of base–solvent systems on the nitration of benzylidene phenylhydrazine (58)[a]

Base–solvent[b] system	$PhC(NO_2)$=N-NHPh (59), yield (%)	Recovered PhCH=N-NHPh (58), yield (%)
KNH_2–NH_3	91	3
$NaNH_2$–NH_3	45[b]	45
$LiNH_2$–NH_3	2	90
t-BuOK–THF	80	[d]

[a]Reprinted with permission from H. Feuer and L. F. Spinicelli, *J. Org. Chem.*, **41**, 2982 (1976).
[b]Ratio of **50** to base to nitrate is maintained at 1:1:2.
[c]The yield is unchanged when the ratio of **50** to $NaNH_2$ to nitrate is 1:2:2.
[d]A 20% yield of 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine is also obtained.

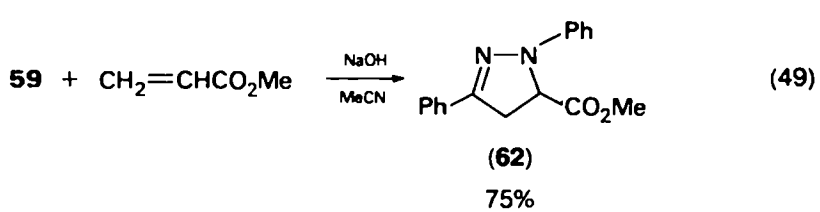


(47)



(48)

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**)[60] (equation 49).



(49)

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[42] and alkyl-substituted heterocyclic compounds[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 α-nitroethylidene phenylhydrazine 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 α-nitrobutylidene phenylhydrazine 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—CH=N—NHPh[a]

	R—C(NO$_2$)=N—NHPh	
R[b]	In 0.3 M KNH_2, yield (%)	In 0.7 M KNH_2, yield (%)
Ph	91	—
2-$MeOC_6H_4$	28	65
4-$MeOC_6H_4$	74	—
2-MeC_6H_4	94	—
2-ClC_6H_4	21	45
4-ClC_6H_4	73	—
4-BrC_6H_4	16	58
4-(*i*-Pr)C_6H_4	94	—
4-$CF_3C_6H_4$	83	—
1-Naphthyl	14	14
2-Naphthyl	46	—
2-Furyl	19	47
2-Thienyl	83	—
3-Pyridyl	38	—
H	30	—
Me	30	83
n-Pr	30	15

[a]Reprinted with permission from H. Feuer and L. F. Spinicelli, *J. Org. Chem.*, **41**, 2982 (1976). Copyright 1976 American Chemical Society.
[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

$$[R—CH=N—\bar{N}—Ph \longleftrightarrow R—\bar{C}H—N=N—Ph]$$
(63)

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, alkylation reactions in alkaline media lead to exclusive substitution on nitrogen[61]. Apparently alkylation 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[38]. *N*-Propylidene-*t*-butylamine (**68**) is converted to 1-(*t*-butylamino)-2-nitro-1-propene (**69**) in 53% yield if potassium

$$\underset{\textbf{(64)}}{RCH{=}N{-}NHPh} \xrightarrow[2\ n\text{-}PrONO_2;\ 3\ MeI;\ 4\ H^+]{1\ KNH_2-NH_3\ \text{or}\ t\text{-}BuOK-THF} \underset{\textbf{(66)}}{RCH{=}N{-}\overset{\overset{Me}{|}}{N}{-}Ph} \qquad (50)$$

(64) R = 3-nitrophenyl **(66)**

(65) R = 4-cyanophenyl **(67)**

$$\underset{\textbf{(68)}}{t\text{-}BuN{=}CHCH_2CH_3} \xrightarrow[2\ n\text{-}PrONO_2\ 3\ NH_4Cl]{1\ KNH_2-NH_3} \underset{\textbf{(69)}}{t\text{-}BuNHCH{=}\overset{\overset{NO_2}{|}}{C}{-}CH_3} \qquad (51)$$

53%

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 15. Alkyl nitrate nitration of $R^1N{=}CHCH_2R^2$ to $R^1NHCH{=}C(NO_2)R^2$ [a]

R^1 [b]	R^2	Yield (%)
t-Bu	H	21[c,d]
n-Pr	Me	54
i-Pr	Me	40
i-Bu	Me	70
t-Bu	Me	51
C_6H_{11}	Me	50
t-Bu	Et	51
n-Hex	Et	67
t-Bu	*n*-Pe	46

[a] Reprinted with permission from A. I. Fetell and H. Feuer, *J. Org. Chem.*, **43**, 497 (1978). Copyright 1978 American Chemical Society.

[b] The ratio of substrate to KNH_2 to *n*-$PrONO_2$ is 1:2:1.5. NH_4Cl is the acidifying agent.

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

[d] The yield of **71** is 14% when ethyl nitrate is the nitrating agent.

$$t\text{-BuN=CHCH}_3 \xrightarrow[2.\ n\text{-PrONO}_2\ \ 3.\ NH_4Cl]{1.\ KNH_2-NH_3} t\text{-BuNHCH=CHNO}_2 + \mathbf{69} \qquad (52)$$

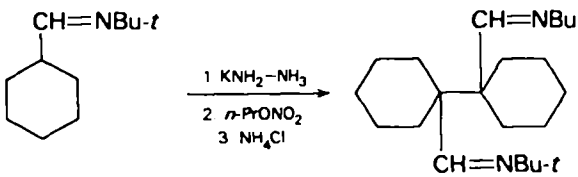
(70) (71)

21% 10%

$$t\text{-BuN=CH(CH}_2)_2CH_3 + CH_3CH_2CHO \xrightarrow[2.\ NH_4Cl]{1.\ KNH_2-NH_3} \mathbf{68} + \mathbf{72} \qquad (53)$$

butylamine (**72**) is treated with propanal (equation 53). The well-established[19] α-hydrogen elimination reaction which primary alkyl nitrates undergo in basic media accounts for the formation of propanal from *n*-propyl nitrate.

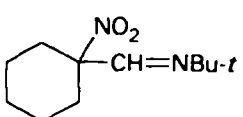
Nitrations of aldimines derived from α-branched aldehydes do not lead to *t*-α-nitroaldimines. Instead, products are obtained which arise both from dimerization of the aldimine and aldehyde interchange. For example, nitration of cyclohexylmethylene-*t*-butylamine (**73**) with *n*-propyl nitrate gives 1,1′-bis(cyclohexylmethylene-*t*-butylamine) (**74**) (18%), compound **69** (4%), cyclohexanecarboxaldehyde (**75**) (2%) and unreacted **73** (23%) (equation 54). The mechanism



$$+ \mathbf{69} + C_6H_{11}CHO \qquad (54)$$

(73) (74) (75)

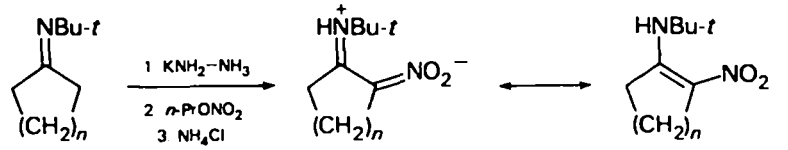
of the formation of dimer **74** has not been established. The dimerization is reminiscent of the formation of dimers **48**, **49** and **53** from the respective isomeric nitroisopropylpyridines on treatment with potassium amide in liquid ammonia (equations 39–41). It is possible that a tertiary nitro compound such as *N*-(1-nitrocyclohexylmethylene)-*t*-butylamine (**76**) is the precursor and is converted to **74** in an electron-transfer process.



(76)

Only mononitrated products are obtained in the alkyl nitrate nitration of cycloalkyl-*t*-butylamines[62a]. This is in contrast to the results with cyclanones where under appropriate conditions both mononitro and dinitro compounds are obtained[18,20,30,32]. 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[32]. However, **83** has been recently prepared and characterized as a yellow solid which decomposes at room temperature[62b].

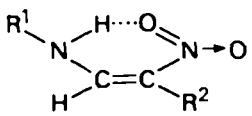


(55)

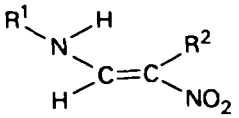
(**77**) n = 2
(**78**) n = 3
(**79**) n = 4

(**80**) n = 2, 35%
(**81**) n = 3, 44%
(**82**) n = 4, 50%

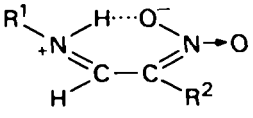
The structures of the 1-alkylamino-2-nitro-1-alkenes are indicated by their spectral data[38]. NMR spectra confirm that in solution both Z and E isomers are present. The Z isomer predominates in nonpolar solvents because of its increased stability through intramolecular hydrogen bonding. The presence of the dipolar structure is also apparent in the solid-state infrared spectra.



Z isomer



E isomer

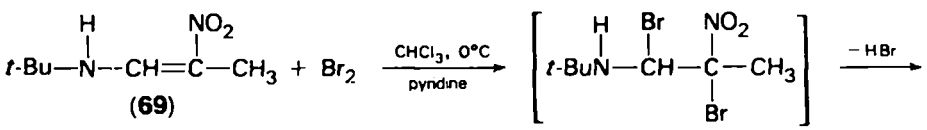


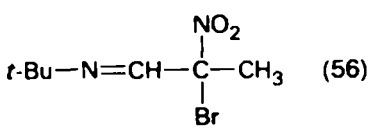
Dipolar structure

R^1 = alkyl; R^2 = H, alkyl

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 sulphoxide, $(CD_3)_2SO$, 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[62a].

Bromination of the alkylaminonitroalkene **69** in the presence of pyridine gives the α-bromo-α-nitroaldimine **84**. It is suggested[63] that the intermediate in the formation of **84** is a dibromo compound which eliminates hydrogen bromide (equation 56).



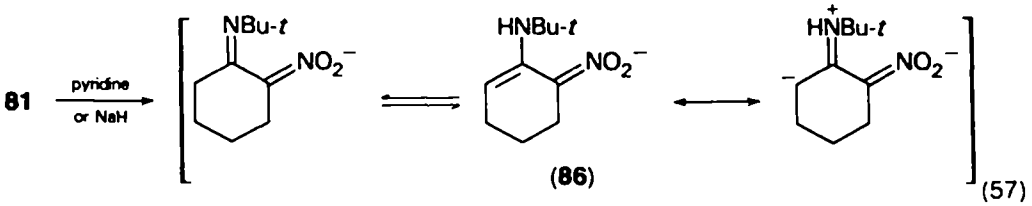


(56)

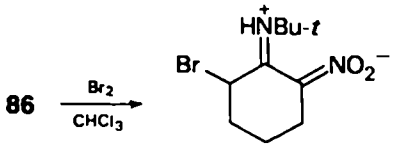
(**84**)
77%

In contrast, bromination of the dipolar aminonitrocycloalkene **81**, in the presence of pyridine, does not occur as expected at the carbonitronate group. Instead it occurs at C-6 of **81** to give 1-nitro-2-(*t*-butylamino)-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 **86**, which is generated from **81** on treatment with pyridine is involved in the formation of **85** (equation 57). Compound **85** also results



(57)



(**85**)
80%

from the bromination of the sodium salt of **81** whose spectral data indicate that it exists in the enamine structure **86**. The NMR spectrum of the salt taken in $(CD_3)_2SO$, shows a triplet at 4.34 ppm and a singlet at 8.10 ppm for the vinyl and amino protons, respectively.

TABLE 16. Alkyl nitrate nitration of aliphatic sulphonamides in the butyllithium–THF system[28]

Sulphonamide	α-Nitrosulphonamide	Yield (%)
CH_3SO_2—N⟨O⟩	$O_2NCH_2SO_2$—N⟨O⟩	31
$CH_3CH_2SO_2$—N⟨O⟩	CH_3CHNO_2SO—N⟨O⟩	36
$(CH_3)_2CHSO_2$—N⟨O⟩	$(CH_3)_2CNO_2SO_2$—N⟨O⟩	46
$(CH_3)_2CHCH_2SO_2$—N⟨O⟩	$(CH_3)_2CHCHNO_2SO_2$—N⟨O⟩	39
$CH_3CH_2CH(CH_3)SO_2$—N⟨O⟩	$CH_3CH_2CNO_2(CH_3)SO_2$—N⟨O⟩	35
$CH_3SO_2N[CH(CH_3)_2]_2$	$NO_2CH_2SO_2N[CH(CH_3)_2]_2$	25

[a] Reactants are used in equimolar amounts. The nitrating agent is $CH_3CH_2ONO_2$.

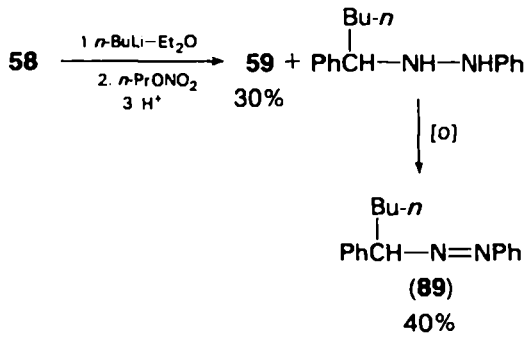
3. n-Butyllithium

n-Butyllithium (**87**) has been used with varying success in the alkyl nitrate nitration 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 experiments[28]. 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.

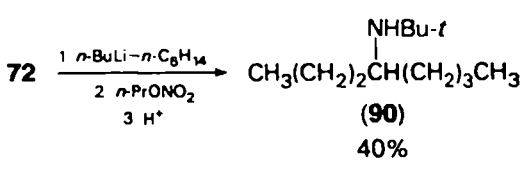
In contrast, nitrations of certain sulphones, such as benzyl phenyl sulphone and dibenzyl sulphone give much lower yields of the corresponding α-nitrosulphones with **87** than with potassium *t*-butoxide[29].

The nitration 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 oxidation[64] (equation 58).



(58)

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



(59)

4. Lithium diisopropylamide

There are a few reports which describe the use of lithium diisopropylamide (**91**) as the base in nitration reactions. Dideprotonation of carboxylic acids with **91** in THF and hexamethylphosphoramide (HMPA) as cosolvents leads to dilithium salts of carboxylic acids which on subsequent treatment with *n*-propyl nitrate and acid are converted into nitroalkanes[65] (equation 60).

The nitroaldimine **92** is obtained[30] 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).

Nitration[66] of alkylphosphonate dibutyl esters (**93**) with **91** as the base leads

$$RCH_2{-}CO_2H \xrightarrow[\text{THF–HMPA}]{(i\text{-}Pr)_2NLi;\ -70^\circ C} [RCHCO_2]^{=}\ 2\,Li^+ \xrightarrow[H^+]{n\text{-}PrONO_2} RCH_2NO_2 \quad (60)$$

R = C_7H_{15} (68%), $C_{10}H_{21}$ (53%), $C_{12}H_{25}$ (50%),
cis-$CH_3(CH_2)_7CH = CH(CH_2)_6$ (45%)

$$\mathbf{72} \xrightarrow[3.\ H^+]{1.\ (i\text{-}Pr)_2NLi\text{–}THF;\ 2.\ n\text{-}PrONO_2} t\text{-}Bu{-}NH{-}CH{=}CNO_2CH_2CH_3 \quad (61)$$

(**92**)

28%

directly to 1-nitroakylphosphonates (**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 (equation 62). It is very likely that the cleavage

$$RCH_2{-}P(O)(OBu)_2 \xrightarrow[3.\ H^+]{1.\ (i\text{-}Pr)_2NLi\text{–}THF;\ 2.\ n\text{-}PrONO_2} \underset{\mathbf{(94)}}{\overset{NO_2}{\overset{|}{RCH}}{-}P(O)(Bu)_2} + RCH_2NO_2 + PrOP(O)(OBu)_2 \quad (62)$$

(**93**)

R = Pr (41%)
R = Bu (47%)

23%

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.

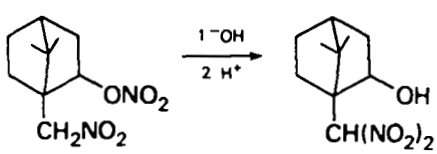
In contrast to carboxylic esters, potassium amide has been found to be unsuitable as the base in the preparation of **94** because it causes transamidation. Diethyl ethylphosphonate, for example, is converted to ethyl *P*-ethylphosphoramidate (**95**) in 60% yield (equation 63).

$$EtP(O)(OEt)_2 \xrightarrow[2.\ NH_4Cl]{1\ KNH_2{-}NH_3} \underset{\mathbf{(95)}}{\overset{NH_2}{\overset{|}{EtP}}(O)OEt} \quad (63)$$

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**) (equation 64).



(64)

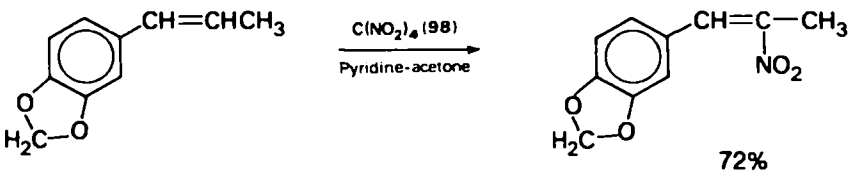
(**96**) (**97**)

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[68].

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



(65)

specific for conjugated arylalkenes. Nitration does not occur if the unsaturation in the arylalkene is in the allylic position[70]. 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*-toluidines[69].

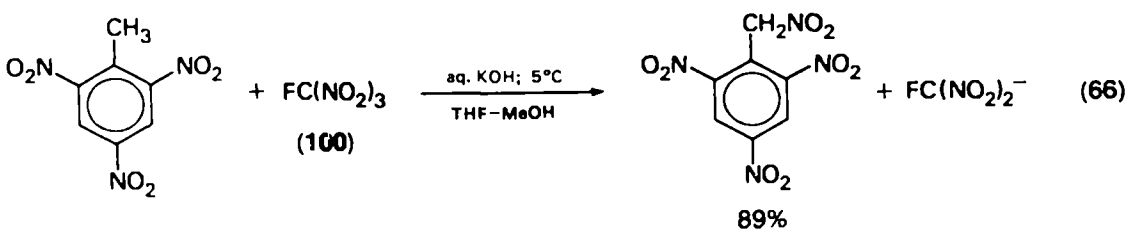
A recent study of the kinetics and mechanism concerning the reaction of **98** with phenols in water and in 95% ethanol gives good indication of an electron-transfer process[71].

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 specific[72]. 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-*t*-butylazulene into 5-nitro-1,3-di-*t*-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 pyridine[76].

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 nitrates[77].



(66)

C. Methyldinitramine

Salts of primary nitroalkanes are converted into *gem*-dinitroalkanes on treatment with methyldinitramine (**101**)[78] (equation 67). On similar treatment, secondary nitroalkanes undergo oxidative dimerization.

$$RCH_2NO_2 + MeN(NO_2)_2 \xrightarrow[0-20°C]{KOH,\ MeOH} RC(NO_2)_2^-\ K^+ + MeNNO_2^-\ K^+ \quad (67)$$

(**101**)

R = H (34%), Me (47%), Et (55%), CH_2OH (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 nitration[79]. 1,1,1,3-Tetranitropropane (**102**, R = H) and the two higher homologues, for example, have been isomerized to the corresponding 1,1,3,3-tetranitro compounds[80,81] in yields of ~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[79].

$$(NO_2)_3C-CH_2-CHNO_2R \xrightarrow[EtOH]{NH_3} \left[(NO_2)_2C\overset{CH_2}{\diagdown\!\diagup}\overset{-}{C}HR \leftrightarrow (NO_2)_2C\overset{O}{\diagdown\!\diagup}N{=}O\right] \xrightarrow{KCl} \quad (68)$$

(**102**)

$$\left[O_2N-\overset{NO_2}{\overset{\|}{C}}-CH_2-\overset{NO_2}{\overset{\|}{C}}-R\right]^= 2K^+$$

R = H (33%), Me (35%), Et (35%)

1,1,1,3-Tetranitro-2-alkylpropanes do not undergo the isomerization[80] reaction on treatment with base. Instead they undergo a retrograde Michael reaction with the formation of trinitromethide ion and the nitroalkene[82] (equation 69).

$$(NO_2)_3C-\overset{R}{\overset{|}{C}}H-CH_2NO_2 \xrightarrow{B^-} (NO_2)_3C^- + RCH{=}CHNO_2 \quad (69)$$

R = Me, Et, *n*-Pr

B = ^-OH, $^-OCH_3$, $^-OCOCH_3$, C_5H_5N

IV. ALKYL NITRATE NITRATION OF AMINES

A. Introduction

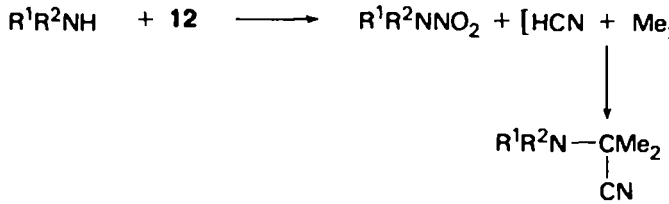
The first successful preparation of an aromatic nitramine by the alkyl nitrate nitration is due to Angeli[83] who converted aniline to phenylnitramine with ethyl nitrate in the presence of sodium. Bamberger improved the procedure by replacing sodium with sodium ethoxide[84]. This method of preparing aromatic nitramines

avoids the rearrangement to *o*- and *p*-nitroarylamines which occurs on nitration under the usual acidic conditions[85].

A disadvantage of the nitration of aromatic as well as aliphatic amines with alkyl nitrates lies in their ability to function also as alkylating 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 **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 **12**. During the nitration reaction, the hydrogen cyanide and acetone produced react with the excess amine to form the corresponding aminonitrile (equation 70).



(70)

$R^1 = R^2 =$ Me (76%), Et (60%), $CH_3CH(CH_3)CH_2CH_2$ (64%)
$R^1 =$ H, $R^2 = n$-Pr (50%) $R^1 =$ H, $R^2 = n$-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 **12** are unsuccessful with aromatic amines and aliphatic amines with branching on the α-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 *N*-methyl-*N*-nitroanilines. *p*-Toluidine is converted to *N*-nitro-*N*-methyl-*p*-toluidine in 44% yield, the latter is also obtained from nitrating the secondary amine, *N*-methyl-p-toluidine (35%) directly.

By a similar procedure, but using butyllithium (**87**) and ethyl nitrate, *N*-methyl-l-naphthylamine and 1-naphthylamine have been converted into the corresponding nitramines in yields of 60% and 65%. The yield of the *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 **87** or phenyllithium and ethyl nitrate has made it feasible to prepare nitramines from aliphatic amines and also from amines with branching on the

$$R^1NH_2 \xrightarrow[2\ EtONO_2\ 3\ H^+]{1\ R^2Li} R^1NHNO_2 \qquad (71)$$

R^1 = Me (35%), *i*-Pr (58%), *n*-Bu (49%), *s*-Bu (45%), *t*-Bu (37%)
R^2 = *n*-Bu or Ph

α-carbon atom[90] (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 **87** do not form nitramines.

D. Nitration with Methyldinitramine (101)

Compound **101** is reported[78] to convert primary and secondary amines to the corresponding nitramines (equation 72).

$$R^1R^2NH + \mathbf{101} \xrightarrow[0-20°C]{THF} R^1R^2NNO_2 \qquad (72)$$

R^1 = H, R^2 = Pr (54%), R^1 = R^2 = Et (74%), R^1, R^2 = $(CH_2)_4O$ (70%)

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
Edited by Saul Patai

CHAPTER **20**

Aminals

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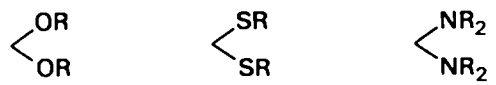
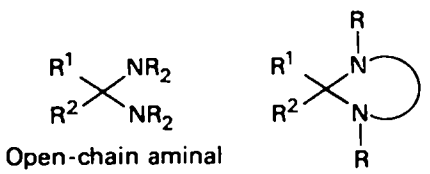
I. INTRODUCTION

The term aminal[20] 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.



Acetal Mercaptal Aminal

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.



Open-chain aminal Cyclic aminal

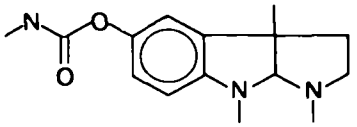
R^1 or/and R^2 = H: aldoaminal
$R^1, R^2 \neq$ H; ketoaminal

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[3].

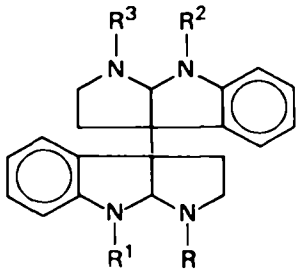
Capreomycidine (**3**) is a component of the antitubercular polypeptide antibiotics capreomycin, tuberactinomycin N and tuberactinomycin O[197].

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 β-carbon of serine is removed as formaldehyde via direct transfer to tetrahydrofolate with formation of aminal **4** (equation 1)[198,220a].

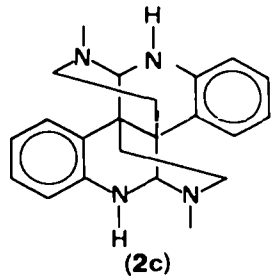
Literature references on aminals are presented in some review articles[66,240].



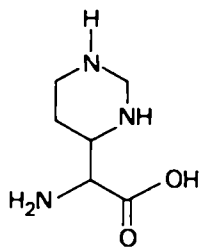
(1)



(2a) R = R^3 = Me, R^1 = R^2 = H
(2b) R = R^1 = R^2 = R^3 = Me



(2c)



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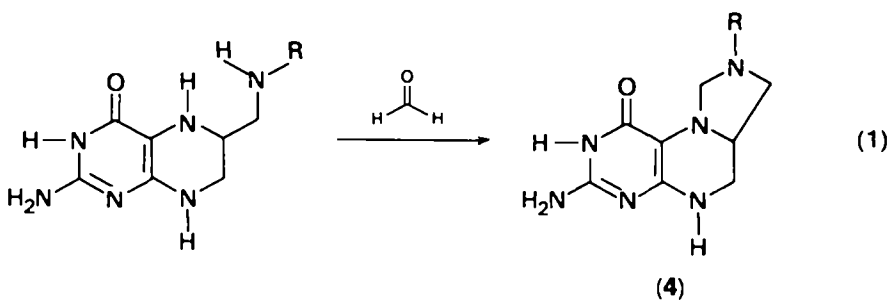
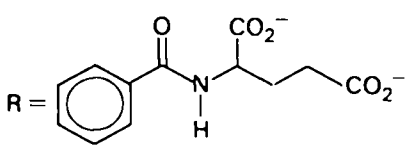


(1)

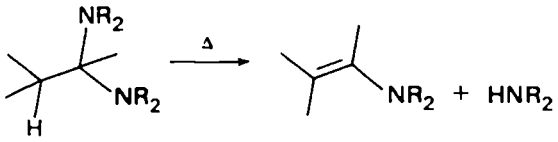
(4)



or polyglutamates

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.



(2)

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

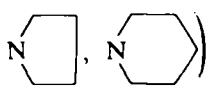
This method is the most widely used.

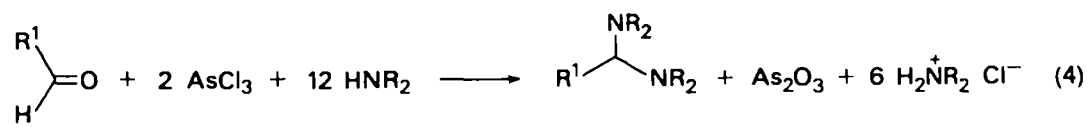
1. *Open-chain aminals*

(a) Aldoaminals. The condensation of secondary amines with aldehydes proceeds rapidly on mixing of the the reagents[180] in the absence or in the presence of a solvent such as ethanol[135] or pyridine[68] (equation 3). The yields become nearly

(3)

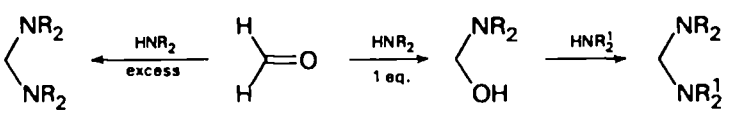
quantitative by using a dehydrating agent such as anhydrous potassium carbonate[188,195], boric anhydride[238], drierite[167] or molecular sieves, or by removal of water by azeotropic distillation with benzene[247]. This last technique was originally employed for the preparation of steroidal enamines[138].

Aldoaminals have also been prepared by reaction with $As(NR_2)_3$ (NR_2 = )[139,275] or with $Sb(NMe_2)_3$[173]. They have been obtained more readily by action of secondary amines together with $TiCl_4$, $SbCl_3$, $AsCl_3$ in an inert solvent, employing a technique initially used in the preparation of sterically hindered enamines[278] (equation 4). These methods are attempted when the simpler ones fail.



(4)

Aminals (5) are generally obtained by mixing an aqueous solution of formaldehyde and secondary amines[132]. Many structural variations are known[23,132,148,280]. The intermediary carbinolamine (6) can be isolated by using



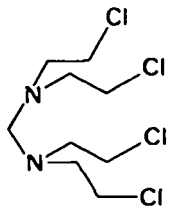
(5)

(5) (6) (7)

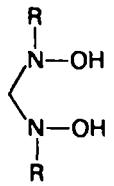
equimolecular quantities of reagents[133,134,148,175,280,281]. The utilization of a different secondary amine permits the formation of an unsymmetric aminal (**7**)[280,281,283,284].

Aminals **5** of the weakly basic aziridine are also easily obtained[175]. Those of 2-methylaziridine are formed with a very low yield[284]. With 2,2-dimethylaziridine, only the carbinolamine **6** can be isolated[176].

Aminal **8** is obtained via reaction of β-chloroethylamine with paraformaldehyde, in the presence of triton B[37], and aminals **9** from aqueous solutions of formaldehyde and *N*-alkylhydroxylamines[282]. Compounds with β-chloroethylamino groups were used in the treatment of cancer[37,152].



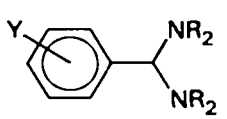
(**8**)



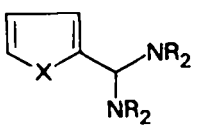
(**9**)

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

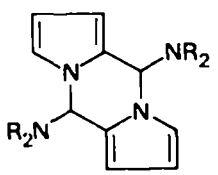
Numerous aminals derived from substituted benzaldehydes and heterocyclic aldehydes such as **10** and **11** are known[46,72,79,92,135,137]. The reactivity of the carbonyl group is largely dependent on the substitution. Thus, in the reaction of *p*-chlorobenzaldehyde, or *p*-dimethylaminobenzaldehyde, 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%)[92]. The nitrogen of 2-pyrrolcarbaldehyde is involved in the reaction of this aldehyde with secondary amines leading to the aminal **12**[136,137].



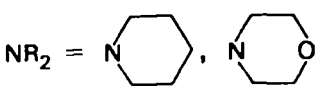
(**10**)



(**11**)



(**12**)

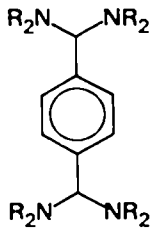


Y = Me, Cl, OH, OMe, SMe, NMe_2, NO_2

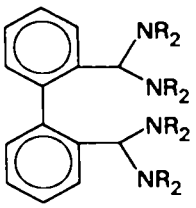
X = O, S, NMe

(Bis)aminals **13**, **14**[47a] and **15**[112,172] and functional aminals **16**[186] and **17**[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 aminoindole **18**[172].

For aminals with an α-hydrogen atom, the general method of Mannich[195] (reaction of an aldehyde with at least two secondary amine equivalents, in presence of



(13)



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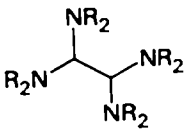

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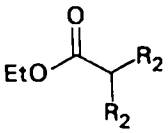

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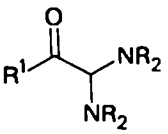
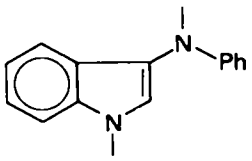


(17)

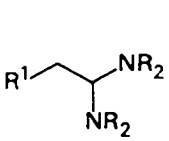


(18)

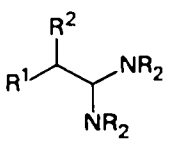
R^1 = Me, Ph

K_2CO_3) is still the most commonly used, with occasional modifications of details. Some examples have been also prepared by the $As(NR_2)_3$ and $TiCl_4$ or $AsCl_3$–HNR_2 methods[275,278]. These techniques are particularly useful in the case of volatile secondary amines.

Many aminals of structure **19** and **20** have been insolated from simple aldehydes or from α-alkyl- or α-aryl-substituted aldehydes[26,70,86,195].

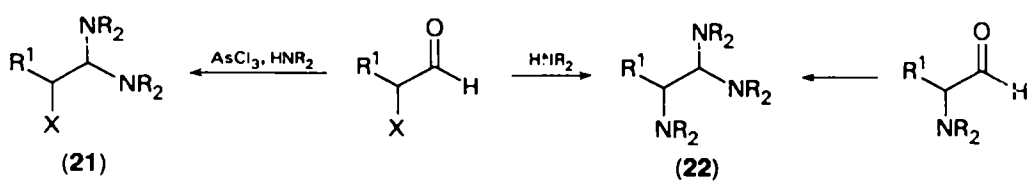


(19)



(20)

α-Haloaminals **21** are available from α-halo aldehydes: one α-fluoroaminal was obtained by direct amination[108] and α-chloro and α-bromo compounds by the $AsCl_3$–HNR_2 method[94,99]. For very reactive α-chloro and α-bromo aldehydes, direct amination leads to halogen substitution with formation of a dialkylaminoaminal **22**[81,83,87,169], which can also be prepared from the corresponding α-amino aldehydes[81,82,169] (equation 6). Aminals **23–26** have been obtained from the corresponding heterocyclic amino aldehydes[89,90,91,208,269,270].

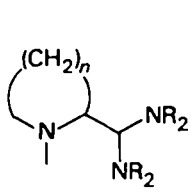


(21) (22)

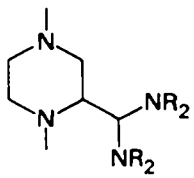
R^1 = C_5H_{11}; X = F
R^1 = Et; X = Cl
R^1 = *t*-Bu; X = Cl, Br

R^1 = Ph; X = Cl
R^1 = H, Et; X = Br

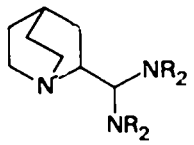
(6)



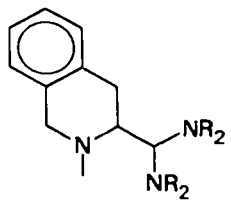
(23)



(24)



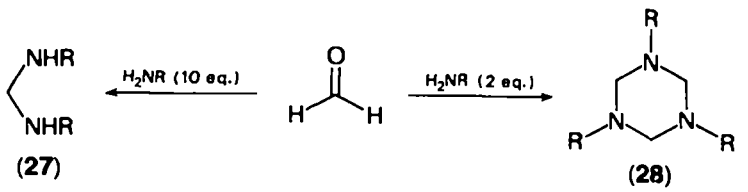
(25)



(26)

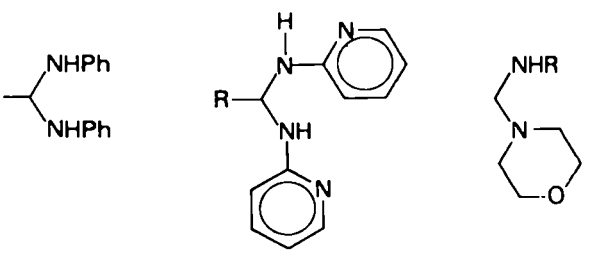
n = 0, 1, 2, 3, 4

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).



(27) (28) (7)

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].



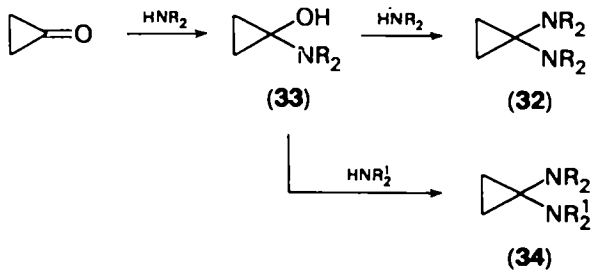
(29) (30) (31)

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

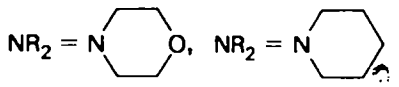
Cyclopropanone is exceptionally reactive. The reactivity of its carbonyl group can be compared with that of the highly reactive formaldehyde. Cyclopropanone reacts readily with secondary amines such as dimethylamine and piperidine providing aminals **32**[261]. When treated with an equivalent of secondary 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).

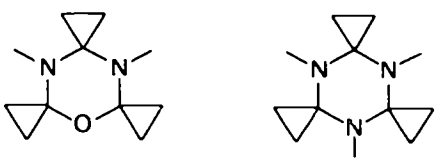
Upon adding methylamine to an etheral solution of cyclopropanone, the cyclic aminal **35** (48%) and the hexahydrotriazine **36** (3%) have been isolated[261].

Aminals **32** have been also prepared by reaction of amines with cyclopropanone ethylhemiketal (NR_2 = NHPh[271]) or with cyclopropanone hydrate in presence of molecular sieves (NR_2 = NMe_2[261]).



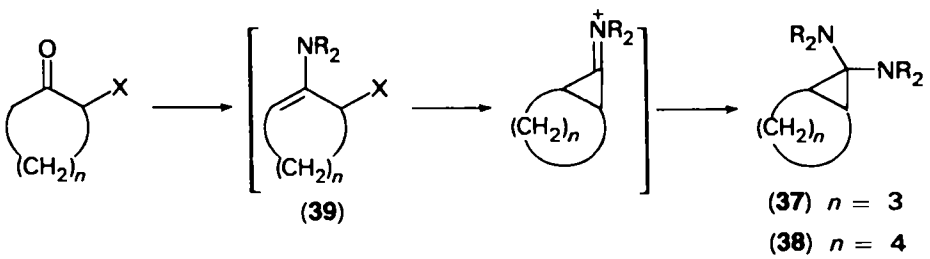
(33) (32) (34) (8)





(35) (36)

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[250,251] (equation 9).

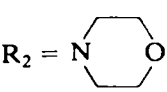


(39) (9)

(37) $n = 3$

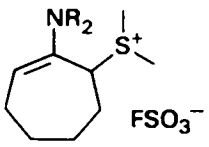
(38) $n = 4$

Indeed, the haloenamines **39**, suggested as likely intermediates, lead effectively to aminals **37** or **38** when treated with secondary amines[16,61] or with a dimethylamine–$AgBF_4$ complex. In the last case, the yield is nearly quantitiative[154].

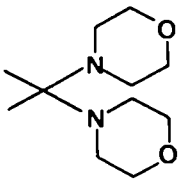
Aminal **38** ($NR_2 =$ ) is also obtained by reaction of morpholine with a derivative of α-dimethylsulphonium cycloheptanone (**40**) by reflux in acetonitrile[263].

Ketoaminals **41**[10] and **42**[178] have been synthesized by amination of the corresponding ketones, in the presence of $TiCl_4$. Aminals **42**, characterized among other open-ring products, are generated with moderate yields (11–43%). Treatment of cyclopentanone with aziridine without $TiCl_4$ affords no aminal, but rather the imine **43**.[178]

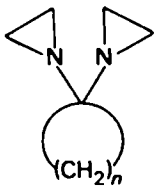
The condensation of difluoroamine with ketones and aldehydes on reflux in the presence of sulphuric acid yields the corresponding aminals[6,117].



(40)

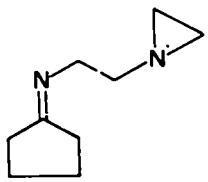


(41)



(42)

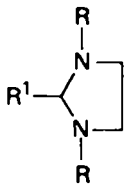
n = 4, 5, 6



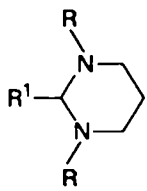
(43)

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.

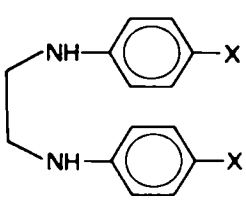


(44)

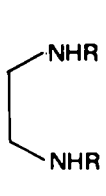


(45)

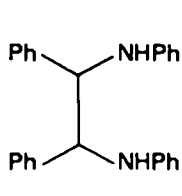
(a) Imidazolidines. Since the solid derivatives are generally facile to purify and have sharp melting points, many 1,2-diamines have been proposed in the past for the rapid determination of aldehydes. Particularly useful are the 1,2-dianilinoethanes **46** (X = H[14,80,203,266], OMe[11], OEt[14], Cl[12], Br[253]). Other 1,2-diamines such as **47** (R = alkyl[80], benzyl[11,190]), **48**[149,150] and the optically active **49**[206,207] have also been tested.



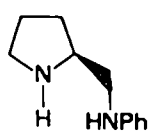
(46)



(47)



(*meso*-48)

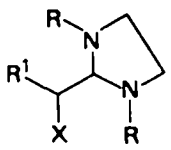


(49)

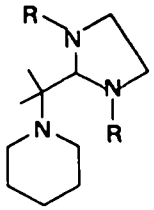
1,2-Dianilinoethane (the Wanzlick reagent[266]) is the most widely used. In methanol, the crystalline imidazolidine generally precipitates immediately after addition of a few drops of acetic acid.

Many cyclic aminals have been prepared with functional aldehydes[266,267].

Imidazolidines **50** are obtained from α-substituted aldehydes (X = Cl, Br, OMe,  , )[103,239]. However, for the hindered compound **51**, the utilization of $TiCl_4$ is necessary[239].

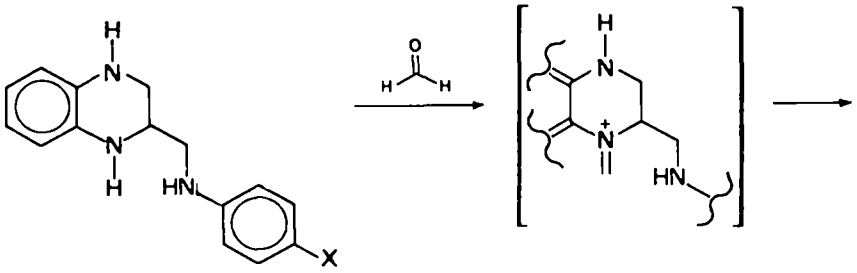


(50)

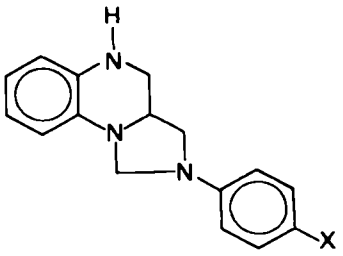


(51)

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[7-9] (equation 10).

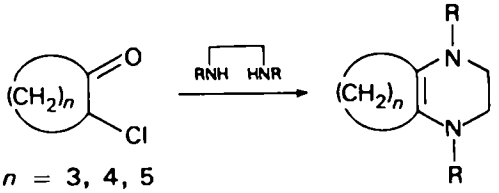


X = Me, Cl, CO_2Et



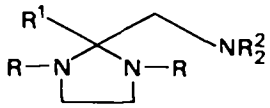
(52) (10)

Simple ketones do not react with 1,2-diamines (although an imidazolidine derived from acetone has been described[11]) but α-halo- and α-hydroxy-ketones are directly transformed into tetrahydropyrazines[103,121,194] such as **53** (equation 11), whereas α-dialkylaminoketones provide imidazolidines **54** (R^1 = Me, Ph), only in the presence of $TiCl_4$[103].



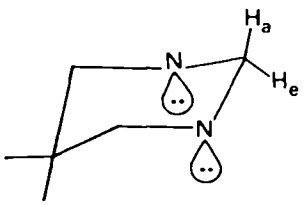
n = 3, 4, 5

(53) (11)

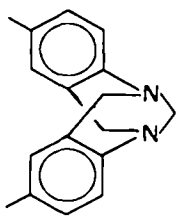


(54)

(b) Hexahydropyrimidines. The condensation with *N,N'*-disubstituted 1,3-diamines is somewhat slower, yet many hexahydropyridimidines **45** have been prepared from aliphatic[42,234,279] and functional[239] aldehydes. The ^{1}H-NMR spectrum of cyclic aminal **45a** shows a $\Delta\delta_{e-a} = 1.70$ ppm between the equatorial and axial protons H_e and H_a. It is well established that a lone electron pair deshields an α-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].

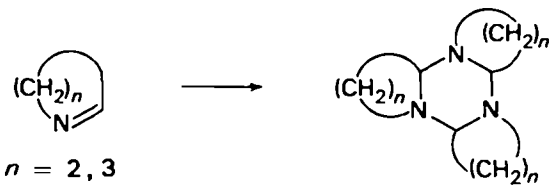


(45a)



(55)

(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).

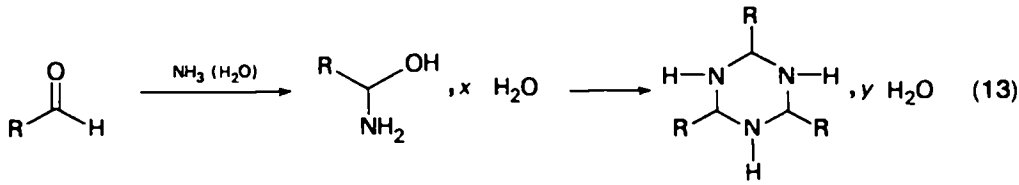


(12)

(56)

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

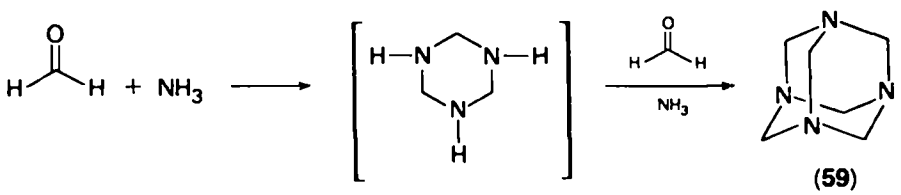
Reactions of aliphatic aldehydes with aqueous ammonia[221a] at −10°C leads instantly to very unstable low-melting 1-amino-1-alkanol hydrates **57** which upon standing in the same medium at 0–5°C are converted to hexahydrotriazines **58**, usually isolated as hydrates[210] (equation 13). The triazine 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[73–77] 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].



(13)

(57) (58)

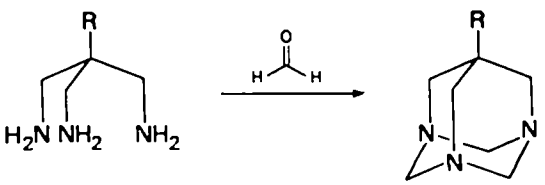
(d) Polyazaadamantanes. When formaldehyde reacts with ammonia, the initially formed hexahydrotriazine reacts producing hexamethylenetetramine (**59**) (equation 74).



(14)

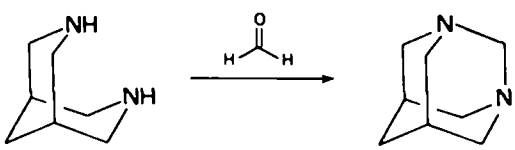
(59)

1,3,5-Triazaadamantane **61** is obtained by condensation of the triamines **60** (equation 15) and formaldehyde (R = Me[245], NO_2[143]). 1,3-Diazaadamantane **63** is the product of diamine **62** and formaldehyde[246] (equation 16).



(15)

(60) (61)

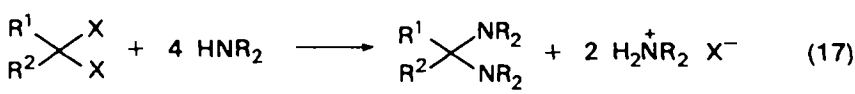


(16)

(62) (63)

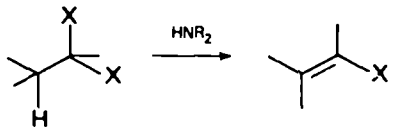
B. Substitution of Dihalo Compounds by Amines

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

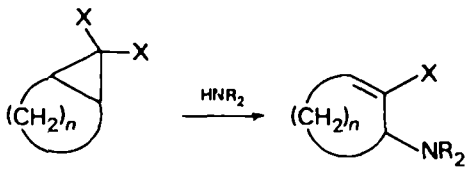


(17)

When an α-hydrogen atom is present in the dihalo compound, elimination occurs (equation 18). Likewise, the reaction of secondary amines with gem-dihalocyclopropanes leads to β-bromoallylamines by a ring-opening reaction[179,231] (equation 19).



(18)



(19)

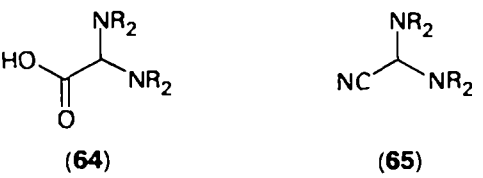
When the amine is in excess, formation of aminals takes place according to the S_N2 mechanism, and the reactivity of halogens is as expected Cl < Br < I[167].

1. Aldoaminals

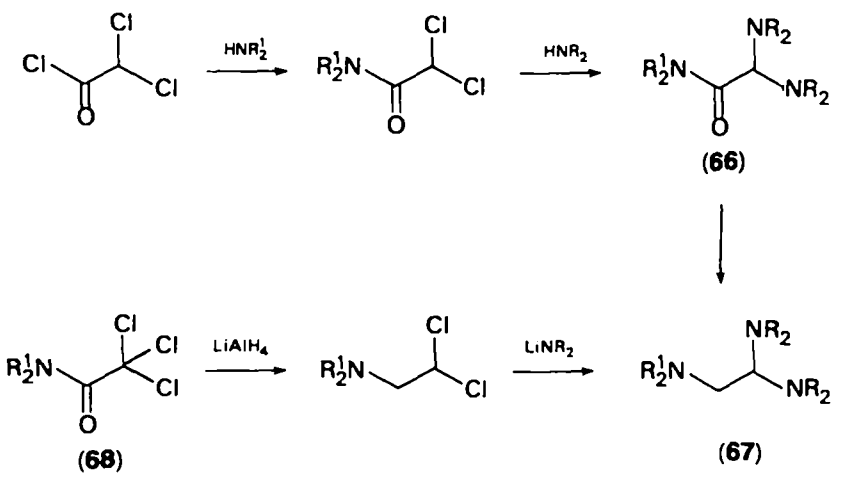
Many aldoaminals **10** and **17** (R = Ar, *t*-Bu, 2-thienyl) have been prepared with excellent yields from substituted dihalomethylbenzenes[159,160] or α,α-dihaloketones[49,124,159,160,182,262].

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, ($NR'_2 = NR_2$[127,128]) or from dichloroacetyl chloride[83,96].

Reduction by $LiAlH_4$ of the amide function of aminal **66** leads to an α-aminoaminal **67**[83,96] which can also be readily prepared from *N,N*-dialkyltrichloroacetamides (**68**)[129] (equation 20).

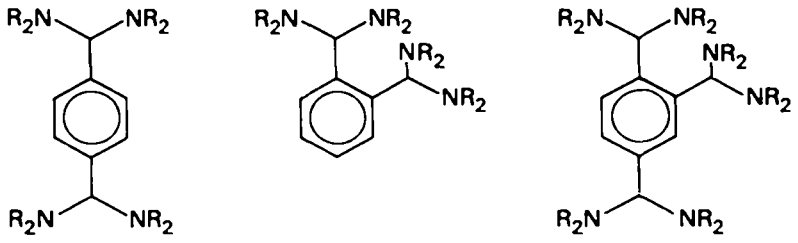


(**64**) (**65**)

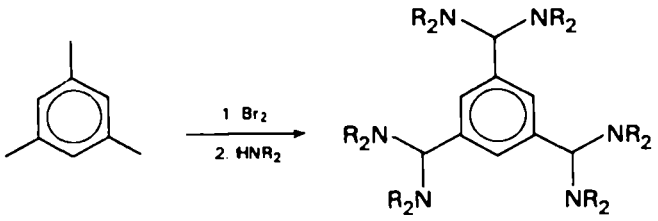


(20)

Di- and tri-aminals **69–72** have been prepared from polymethylbenzenes via the corresponding dibromomethyl compounds[162,167] (equation 21).

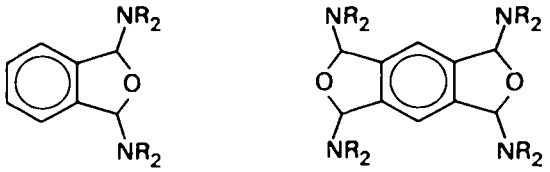


(69) **(70)** **(71)**



(72) (21)

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[165]. Similarly, the compound **74** is isolated on amination of octabromodurene[166].

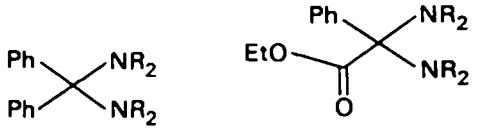


(73) **(74)**

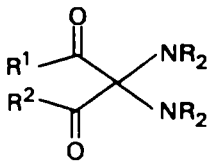
2. *Ketoaminals*

Amination of dihalo compounds allows the preparation of many ketoaminals, such as **75**[119,162], **76** and **77**[158,162,167], 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[205] (equation 22).



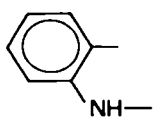
(75) **(76)**

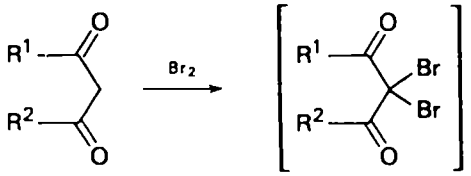


(77)

$R^1 = R^2$ = OMe, OEt, Me, Et

R^1 = Me, Ph; R^2 = OEt, Me

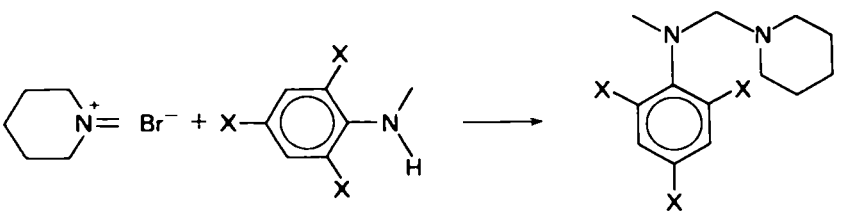
R^1, R^2 = 



(22)

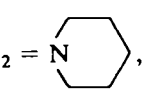
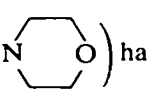
C. Addition of Amines to Iminium Salts

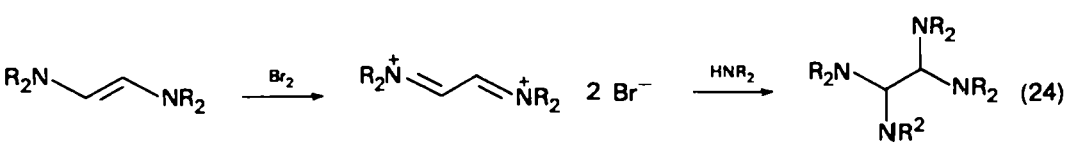
Reactions of secondary amines with iminium salts allows the preparation of mixed aminals such as **78** (X = H[17,18], Me, Cl[38] (equation 23)). The condensation of 2,4,6-trichloro- (or trimethyl-)*N*-methylaniline with formaldehyde or with dichloromethane has been unsuccessful.



(78)

(23)

Aminals **15** (NR_2 =  , ) have been prepared by reaction of secondary amines with diiminium salts obtained by oxidation of 1,2-diaminoethylenes[85,88] (equation 24).

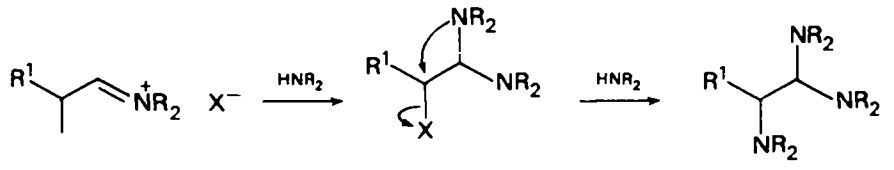


(15)

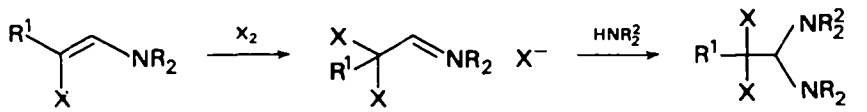
(24)

With α-haloiminium salts, secondary amines lead to α-haloaminals **21** (R^1 = *t*-Bu, X = Cl)[99–100], or to α-aminoaminals **22** when the halogen is more reactive and the R^1 group is less crowded (X = Br, R^1 = Ph)[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[222] (equation 26).



(21) (22) (25)

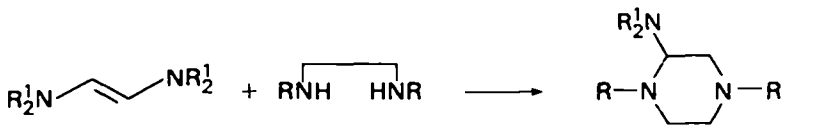


(79) (26)

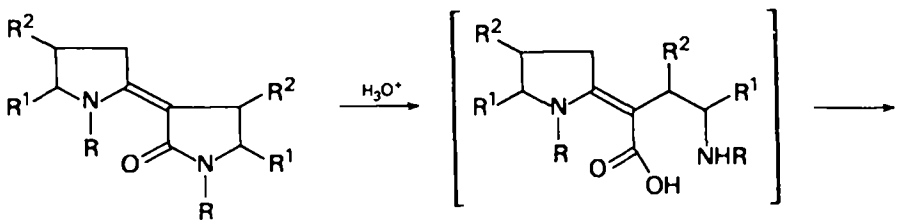
R^1 = Et, X = Cl, NR_2 = NR_2^2 = NEt_2

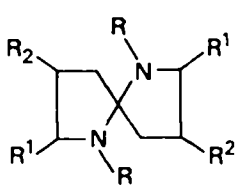
R^1 = *t*-Bu, X = Cl, NR_2 = NMe_2, NR_2^2 = NEt_2

Presumably, iminium ion intermediates are also involved in reactions (27) and (28) yielding cyclic aminals **80**[130] and spiroaminals **81**[58].



(80) (27)

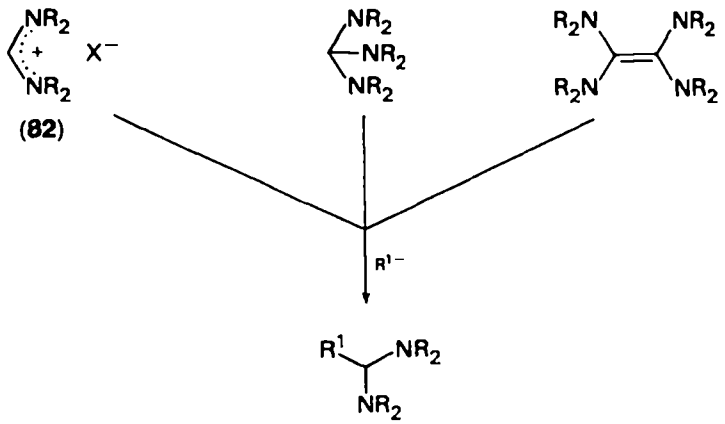




(81) (28)

D. Synthetic Methods

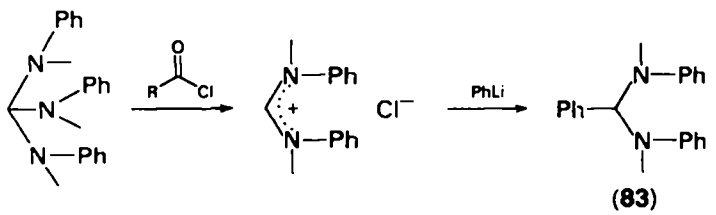
Aminals have also been prepared by formation of a new C—C bond, when the amidinium salt **82**, tris(dialkylamino)methane or tetra(dialkylamino)ethylene react with compounds containing nucleophilic carbon atoms (equation 29). Mechanistic



(29)

considerations suggest that the reactions of all three compounds proceed via the same amidinium salt **82**.

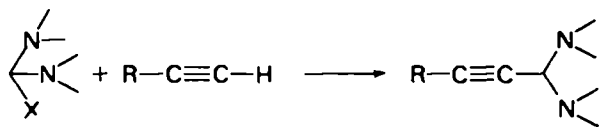
Thus the aminal **83** has been prepared by reaction of phenyllithium with the formamidinium chloride isolated from the reaction of an acid halide with a triaminomethane[65].



(30)

(83)

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** ($NR_2 = NMe_2$)[55,277].

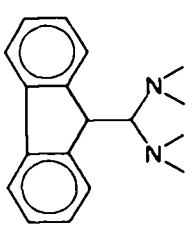


(31)

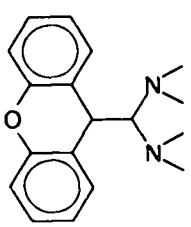
(84)

X = N⟨ , *t*-BuO; R = Ph, *n*-Bu

The condensation of tris(dimethylamino)methane with weaker carbon acids such as fluorene (pK_a 25) or xanthene (pK_a 29), although slower, yields the expected aminals **85** and **86**[276].

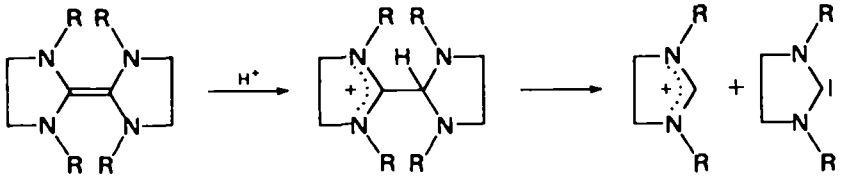


(85)



(86)

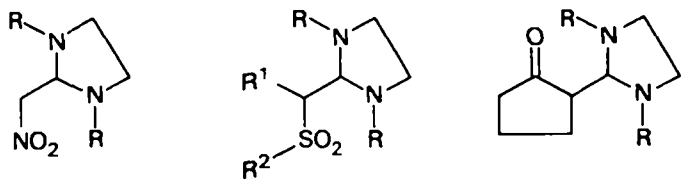
Electron-rich olefins such as **87** or tetramorpholinoethylene react with proton sources with cleavage of the central C=C double bond[140–142,267]. Protonation of the double bond is probably the initial step, followed by decomposition into a cation and a carbene. The cation reacts with the nucleophile and the carbene can dimerize to give the starting olefin[140] (equation 32).



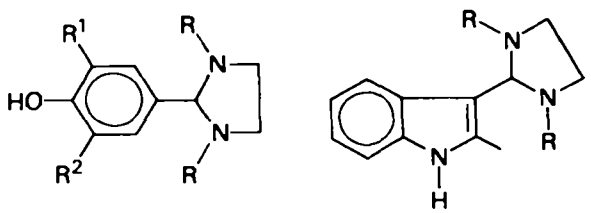
(32)

(87)

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

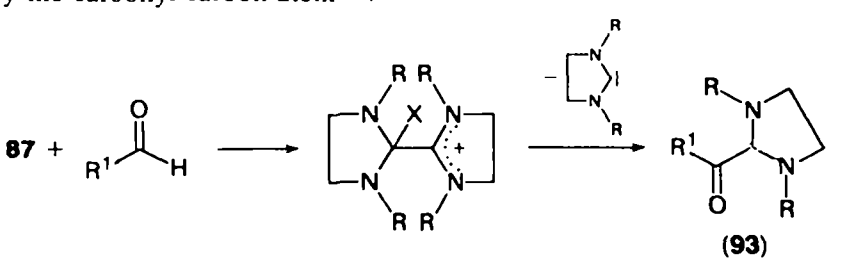


(88) **(89)** **(90)**



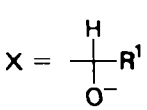
(91) **(92)**

Olefin **87** also reacts with aldehydes to give compounds **93**[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[140].

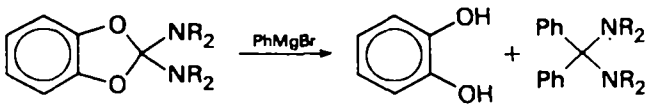


(33)

(93)



Ketoaminal **75** has been noted in the reaction of phenylmagnesium bromide with 1,3-benzodioxole derivatives[60] (equation 34).

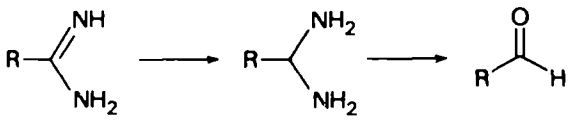


(34)

(75)

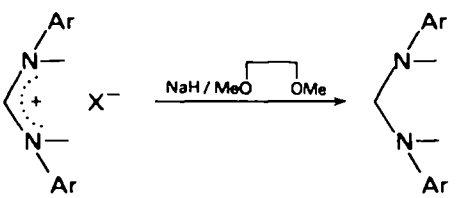
E. Reduction of Amidines and Amidinium Salts

The reduction of amidines to aminals is effected by Na–EtOH–NH_3, and provides a route to aldehydes. Unsubstituted amidines give the highest yields[4] (equation 35).



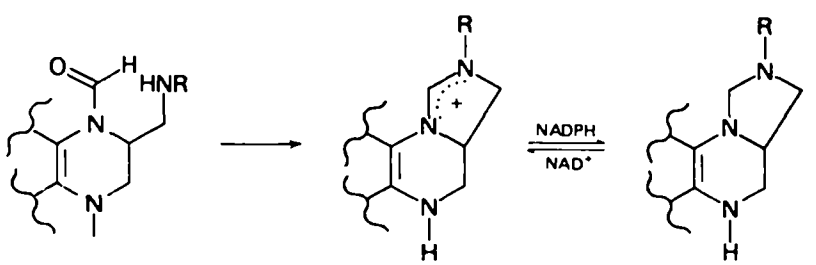
(35)

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[65].



(36)

Reduction of amidinium salts by NADPH also occurs in the reversible enzymatic formation of aminal **4** from a *N*-formyl derivative[198] (equation 37). This reaction has also been studied with model compounds[200].

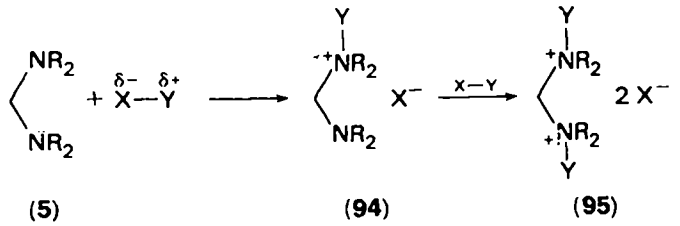


(37)

(4)

III. FORMATION OF AMMONIUM AND IMINIUM SALTS

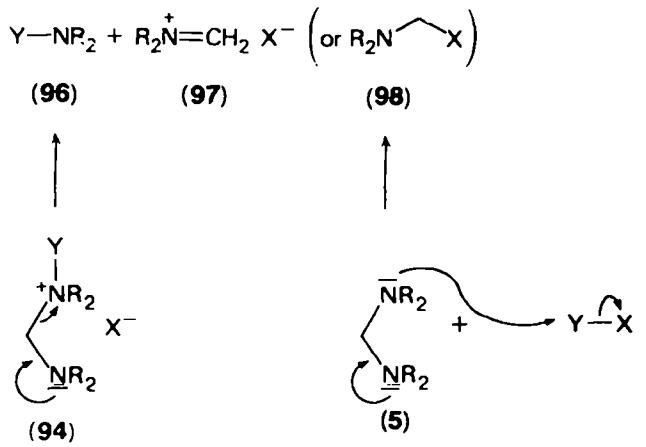
The presence of the two amino groups of an aminal such as **5** allows, with a suitable X—Y reagent, the formation of a monoammonium salt **94** or a biammonium salt **95** (equation 38). The presence of an electron acceptor group



(38)

(5) (94) (95)

$^+NR_2Y$ and an electron donor group NR_2 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



(39)

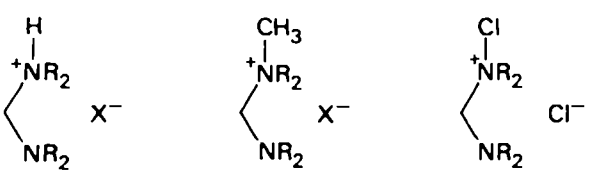
(96) (97) (98) (94) (5)

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 NR_2 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[264], they were postulated as intermediates.

A. Mono- and Bi-ammonium Salts

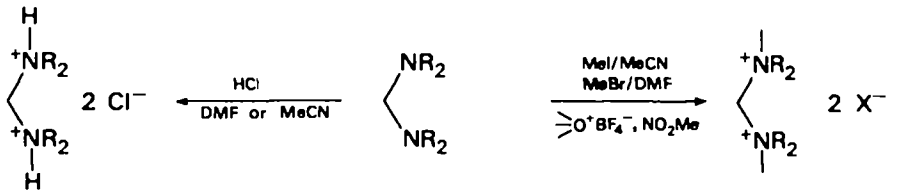
Monoammonium salts **94a, b** and **c** are obtained by reaction of aminal **5** ($NR_2 = N\langle\rangle$, NMe_2) with one equivalent of HCl[106], HBr[17], methyl bromide[17,18] or



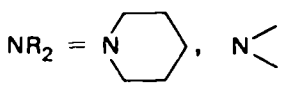
(94a) (94b) (94c)

halogen (Cl_2)[20,21] in a non-polar aprotic solvent such as ether in which they precipitate.

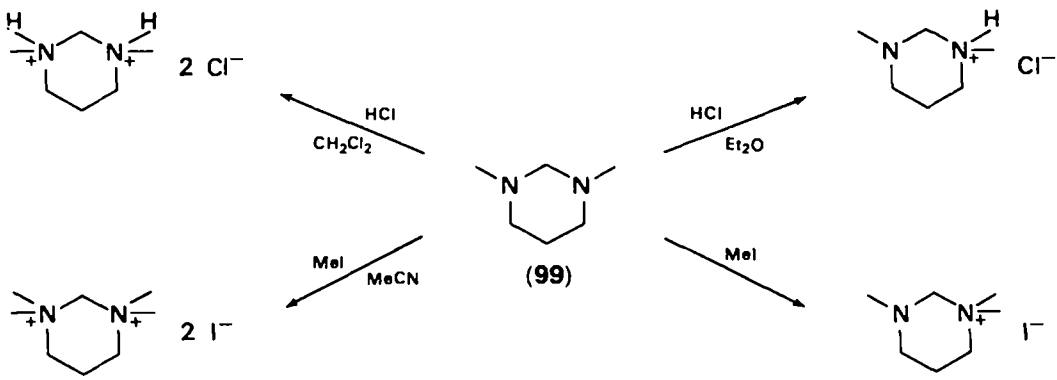
Biammonium salts mentioned in the literature prior to 1953 were erroneously identified[19]. However, in polar solvents such as dimethylformamide or acetonitrile where monoammonium salts **94** are soluble, biammonium salts **95a** and **b** can be prepared[41] (equation 40).



(95a) (5) (95b) (40)

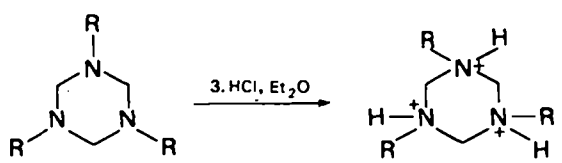
NR_2 =  ; X = Br, I, BF_4

Similarly, mono- and bi-ammonium salts of imidazolidine (**44**)[38] and hexahydropyrimidine (**99**)[42] have been described (equation 41).



(99) (41)

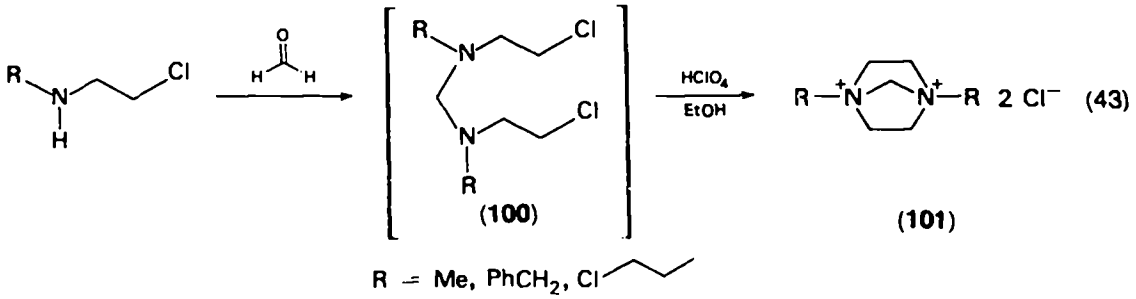
Triammonium salts have been isolated when hexahydrotriazines **28** are treated with three equivalents of hydrogen chloride[229] (equation 42).

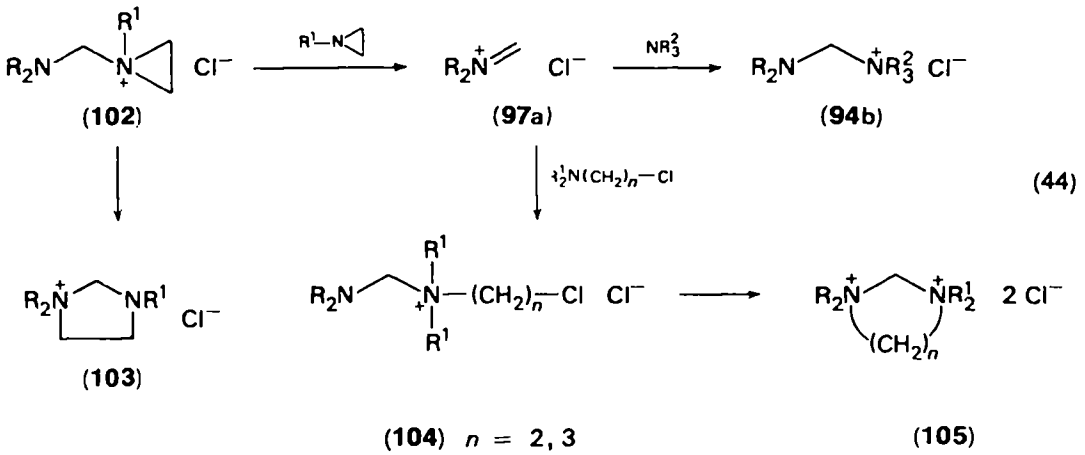


(28) (42)

Cyclic ammonium salts **101** are directly formed from aminals **100** possessing a halogen in a suitable position[37] (equation 43).

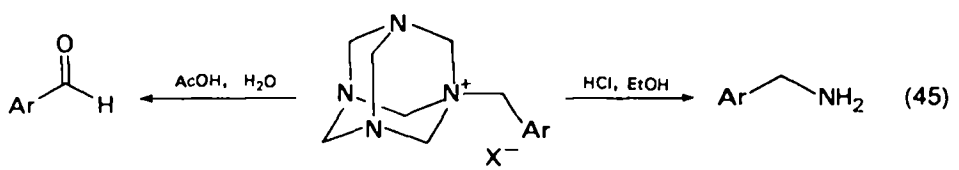
Monoammonium salts are likewise obtainable by reaction of iminium salts **97a** with tertiary amines[39]. In the case of *N*-alkylaziridines or of β- or γ-chlorodialkylamines, the initially isolated monoammonium salts **102** or **104** can rearrange into cyclic mono- or bi-ammonium salts **103** or **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[1,256] (equation 45).

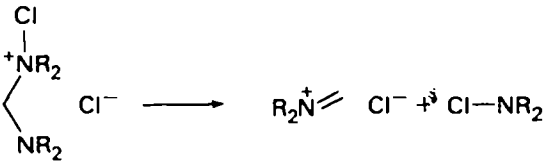


B. Iminium Salts

1. Open-chain aminals

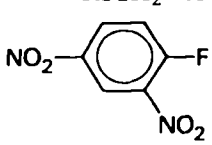
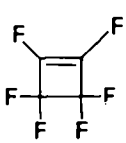
The monoammonium salt **94c** obtained by chlorination of the aminal **5** at −50°C, undergoes decomposition at room temperature into the iminium chloride **97a** and *N*-chlorodialkylamine[20,21] (equation 46). The cleavage of aminals has been achieved by means of a large variety of compounds (Table 1).

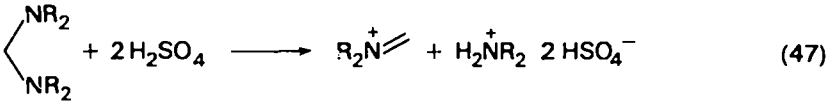
Van't Hoff *i* factors near 4 have been reported in cryoscopic studies on aminals **5** at 0.02 M concentrations in concentrated sulphuric acid[110]. The results agree with



(94c) (97a) (46)

TABLE 1. Compounds YX used for the formation of iminium salts

Y—X		References
H—X	Hydrogen halides	23, 24, 26
Cl—Cl	Halogens	20, 21
NC—Br	Cyanogen bromide	21, 54
RCO—X	Acyl halides	27, 29, 44
ROCO—Cl	Alkyl chlorocarbonates	27
ClCO—Cl	Phosgene	30, 31, 260
RSO_2—Cl	Sulphonyl chlorides	51
$ClSO_2$—Cl	Sulphuryl chloride	31
ClSO—Cl	Thionyl chloride	31
ClS—Cl	Dichlorosulphane	51
R_2NS—Cl	Aminosulphur chlorides	51
NO—X	Nitrosyl halides	31
PX_2—X	Phosphorus trihalides	31
Cl_4P—Cl	Phosphorus pentachloride	115, 116
NO—ClO_4	Nitrosyl perchlorate	51
CCl_3CO—$OCOCl_3$	Trichloracetic anhydride	50
RSO_2—OSO_2R	Sulphonic acid anhydrides	35
$(RO)_2P$—$OP(OR)_2$	Tetraalkyl pyrophosphate	35
RCO—OSO_2R^1	Mixed anhydrides	35
RCO—$OSOR^1$		
RSO—OSO_2R^1		
$(EtO)_2PO$—OSO_2R^1		
RCO—$OPO(OEt)_2$		
R—X	Alkyl halides	17, 18
Me—OSO_2F	Methyl fluorosulphonate	153, 154
XCH_2—X	Dihalomethanes	47b
$ROCH_2$—X	α-Halo ethers	45
$RSCH_2$—X	α-Halo thioethers	45
	1-Fluoro-2,4-dinitrobenzene	44
	Perfluorocyclobutene	230

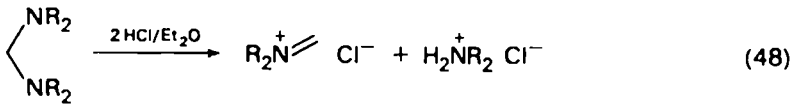


(47)

(5)

the dissociation shown in equation (47). Diamines $R_2N-(CH_2)_n-NR_2$ with $n > 1$ exhibit Van't Hoff *i* factors of about 3 under the same conditions.

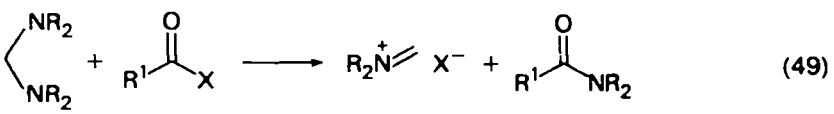
With hydrogen chloride in excess in Et_2O, aminals are cleaved into iminium chlorides **97a** and dialkylammonium chlorides **106** which can occasionally be separated by their different solubilities in polar solvents (DMF or MeCN)[23,24] (equation 48).



(48)

(5) (97a) (106)

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].

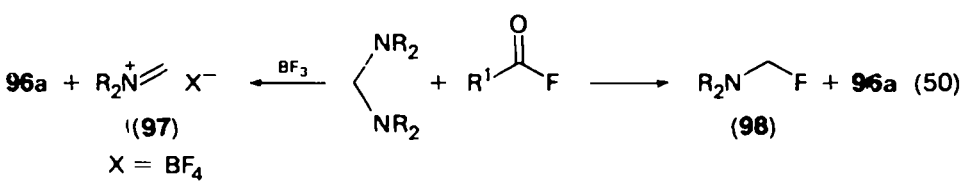


(49)

(5) (97) (96a)

X = 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).



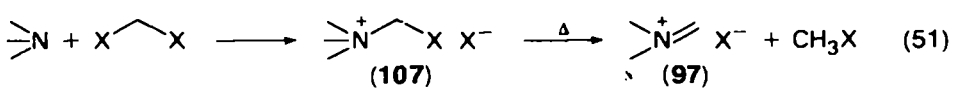
(50)

(97)

X = BF_4

(98)

Iminium salts **97** (NR_2 = N<) can also be prepared by fragmentation of ammonium salts **107** (X = Cl[47b], Br[41], I[237]) readily obtained from trimethylamine and dihalomethane (X = Cl[22], Br and I[232]) (equation 51).

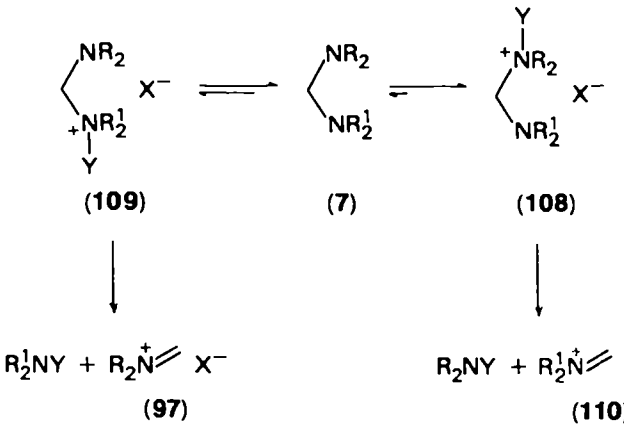


(51)

(107) (97)

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



(52)

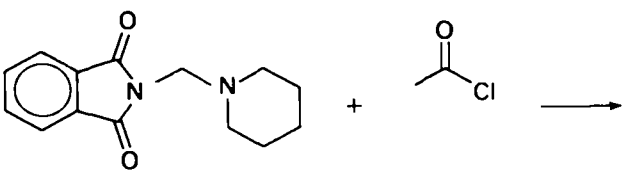
(109) (7) (108)

$R_2^1NY + R_2\overset{+}{N}{=}\ X^-$ (97)

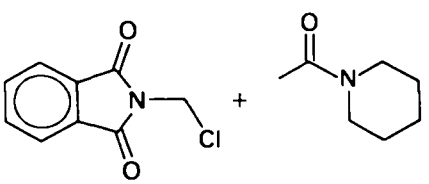
$R_2NY + R_2^1\overset{+}{N}{=}\ X^-$ (110)

NR_2 more basic than NR_2^1

the iminium salt more rapidly than **108**. Yet the cleavage reaction (53) is observed for the unsymmetric acyl aminal **111** with acetyl chloride[32]. It is likely that in this case, the NR_2^1 group (phthalimido) is not sufficiently basic to allow formation of ammonium salt **109**.

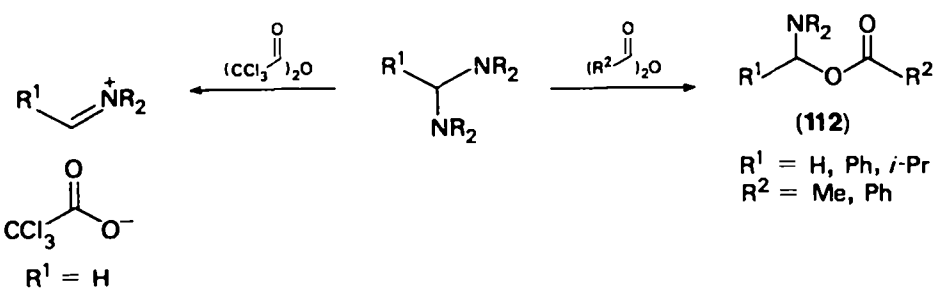


(111)



(53)

Cleavage of aminals by carboxylic anhydrides leads to covalent esters **112**[28,33,50] (equation 54). However, in the case of trichloracetic anhydride, iminium trichloracetates are obtained[50].



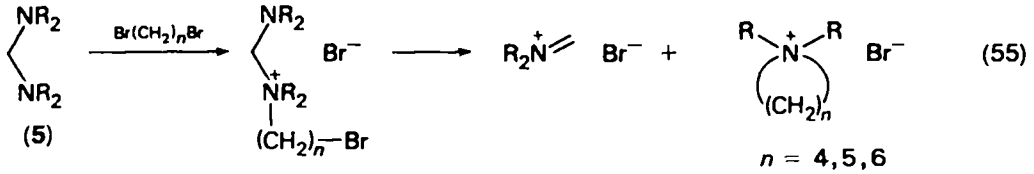
(54)

(112)

R^1 = H, Ph, *i*-Pr
R^2 = Me, Ph

R^1 = H

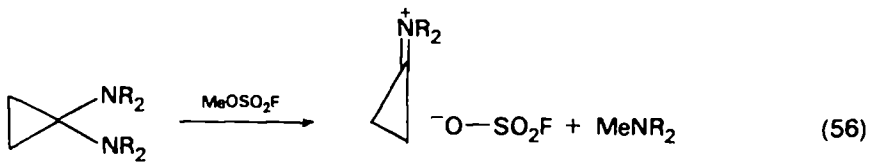
Reaction of aminals **5** with ω,ω'-dihalides allows the preparation of cyclic quaternary ammonium salts[216] (equation 55).



(55)

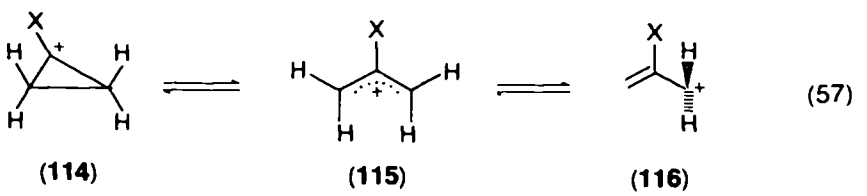
Mono- and bis-aminals **10–12, 13–17, 19–20** and **66** have been transformed into mono- or bis-iminium salts by cleavage with thionyl chloride (**16, 66**)[127,128] or acyl halide (**10**[27,29,40,46,92,101], **11**[46,92], **13**[47a,101], **14, 15**[47a], **17**[49], **19**[92], **20**[30,86,92], **66**[92]).

The cyclopropanone aminals **34** and **38** react with an excess of methyl fluorosulphonate at −78°C forming cyclopropyliminium fluorosulphonates such as **113**. These salts are relatively stable and can be stored many hours at 35°C, without change in NMR[153,154] (equation 56).



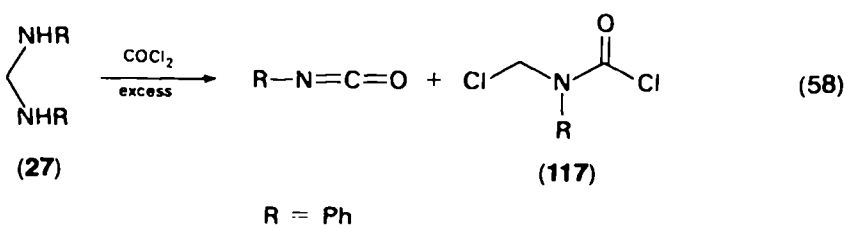
(56)

The isolation of cyclopropyliminium salts and the substitutions observed without ring-opening are consistent with *ab initio* STO-3G orbital calculations. For X = 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 = H, **116** is more stable than **114**[227].



(57)

Aminals **27** when treated with excess phosgen are cleaved into phenyl isocyanate and carbamoyl chloride **117**[260] (equation 58).

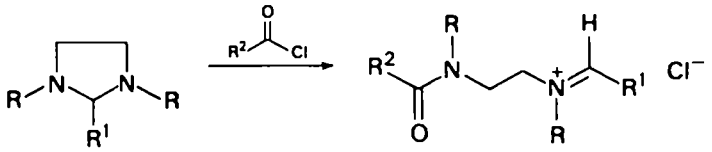


(58)

2. Cyclic aminals

With cyclic aminals, the same types of cleavage occur.

Imidazolidines **44** are transformed by acyl chlorides into iminium salts **118**[48] (equation 59).

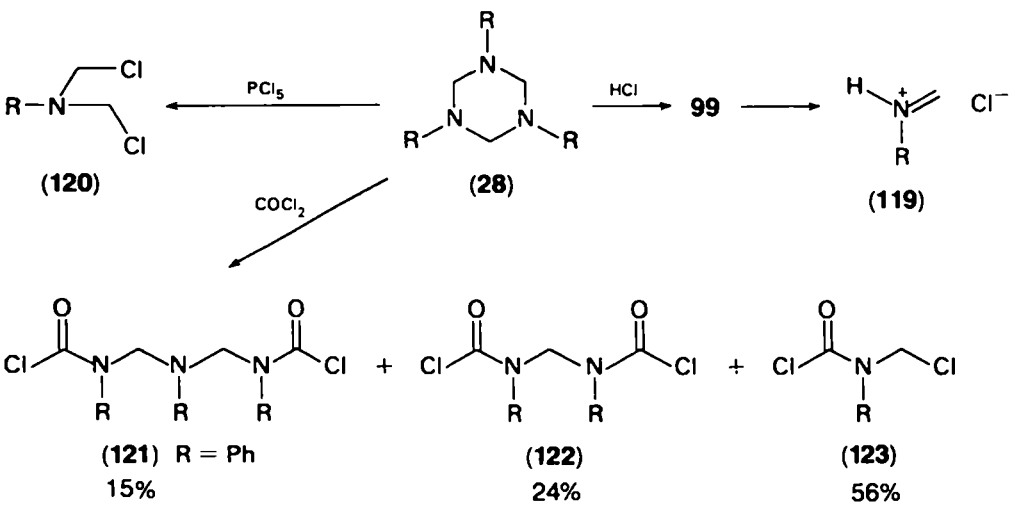


(59)

(**44**) (**118**)

R^1 = H, Pr
R = alkyl

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[229] [for a similar reaction with hexahydrotriazine **56** (n = 3) see Reference 26]. Reactions with phosphorus pentachloride[116] yield bis(chloromethyl)alkylamine **120** and cleavage with excess phosgen affords compounds **121**–**123**[260] (equation 60).

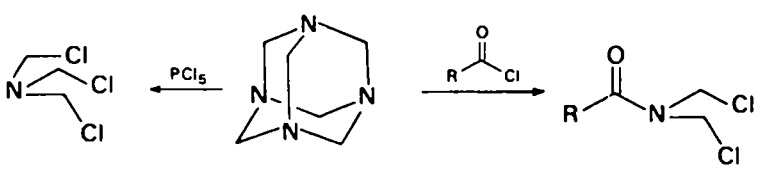


(60)

(**120**) (**28**) (**119**)

(**121**) R = Ph 15% (**122**) 24% (**123**) 56%

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



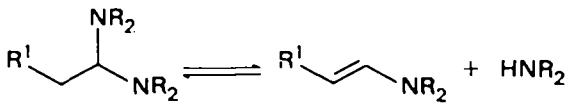
(61)

(**125**) (**59**) (**124**)

IV. FORMATION OF ENAMINES

A. The Aminal–Enamine Equilibrium

Equilibrium (62) has long been known for acetaldehyde aminals **19** ($R^1 = H$)[70,195]. On distillation, 1,1-dimorpholinoethane dissociates into morpholinoethylene (**126**)



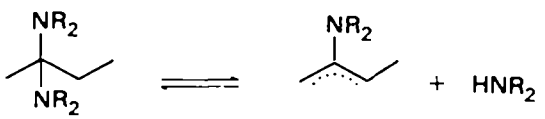
(62)

(19) **(126)**

R^1 = H, NR_2 = 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[70,111].

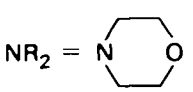
The next higher aminal homologue (**19**; R^1 = Me; NR_2 = morpholino) partly dissociates into enamine and amine on dissolution in $CDCl_3$. The same composition **19/126** = 1 at 37°C is obtained from an equimolecular mixture of the enamine **126** and morpholine[239].

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[10].



(63)

(127)

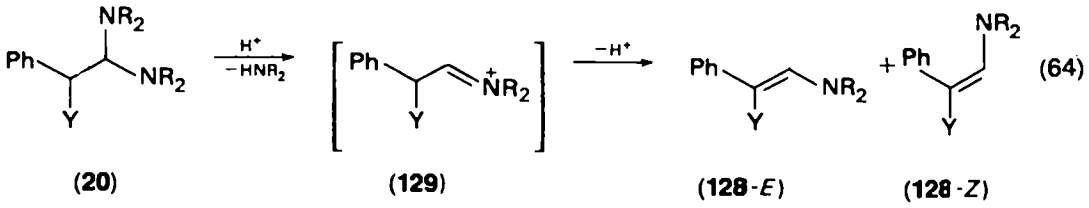


Except for these few cases (see also Section IV.E), the dissociation equilibrium is almost always completely shifted toward the corresponding enamine.

B. Kinetics of the Dissociation into Enamine

The dissociation of aminal **20** into enamines **128**-*Z* and **128**-*E* has been studied. The dissociation rate (ν) is very sensitive to the nature of the solvent: $\nu(CDCl_3) > \nu(C_6D_6) \gg \nu(NEt_3)$. In DMSO, dissociation is accelerated by traces of hydrogen chloride and strongly retarded by addition of potassium *t*-butylate. In $CDCl_3$, the dissociation is first order with respect to aminal. The rate constant increases with the size of Y (Y = Me, $k = 4.3 \times 10^{-4}\ s^{-1}$; Y = C_6H_{11}, $k = 16.7 \times 10^{-4}\ s^{-1}$, in $CDCl_3$ at 37°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**[86,239] (equation 64).



(64)

(20) (129) (128-*E*) (128-*Z*)

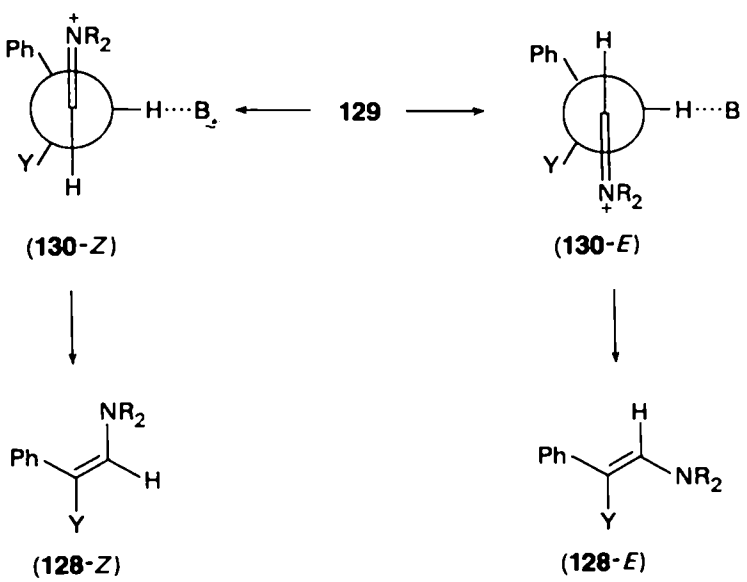
Y = Me, Et, *i*-Pr, C_6H_{11}; NR_2 = 

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.[86]

	Z	*E*
Equilibrium at 37°C	16	84
Aminal heating and distillation	64	36
Aminal dissociation in $CDCl_3$, CCl_4 or NEt_3 at 37°C	80	20

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%)[86] (equation 65).



(65)

(130-*Z*) (130-*E*)

(128-*Z*) (128-*E*)

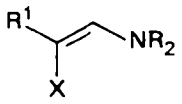
B = any base such as aminal, enamine, morpholine, always present in the medium

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[86].

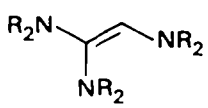
D. Enamines from Functional and Cyclic Aminals

α-Haloaminals **21** are transformed by heating into β-haloenamines **131**[94,99] of exclusive or predominant *Z* configuration[125,222].

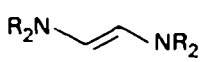
Aminals **15** and **22** (R^1 = H) yield by distillation triaminoethylenes **132**[112,172] and *E*-1,2-diaminoethylenes **133**[83,96,129].



(131)

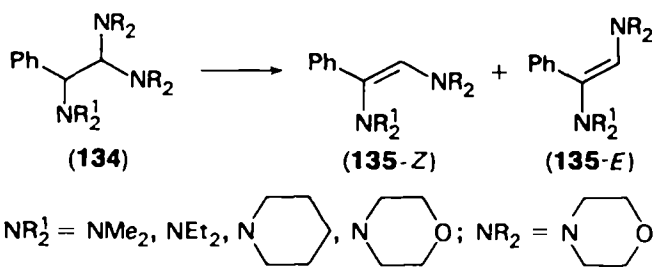


(132)



(133)

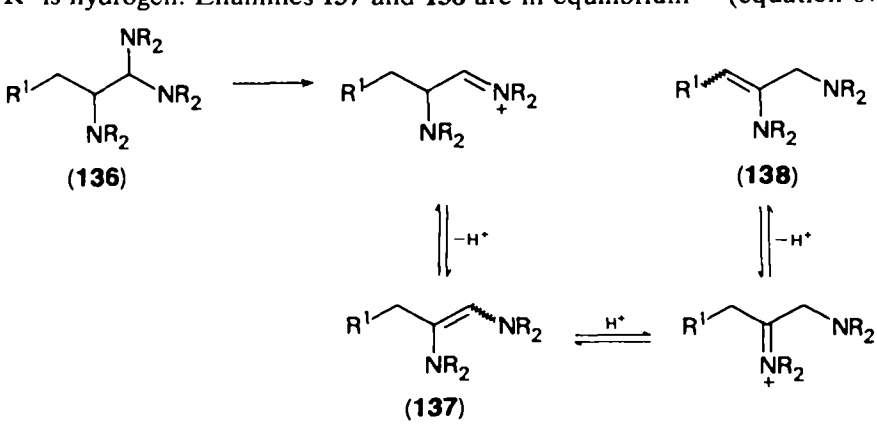
Dissociation (66) of α-aminoaminals **134** with different NR_2^1 groups has been studied in $CDCl_3$. In the kinetic product, the enamine **135**-*Z* (Ph and NR_2 in the *trans* position) is predominant and its ratio varies only slightly with the size of NR_2^1 [61% (NMe_2) to 70% (NEt_2)]. For these compounds, transition states such as **130** (Y = NR_2^1) are insufficient, because they take in consideration only the size of Y[239].



(134) **(135-*Z*)** **(135-*E*)** (66)

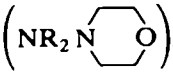
NR_2^1 = NMe_2, NEt_2, N⟨ ⟩, N⟨ ⟩O; NR_2 = N⟨ ⟩O

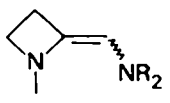
α-Aminoaminals **136** containing a β-H atom could lead to enamines **137** or **138**, thus presenting in addition to the configurational isomerism a double-bond positional isomerism. The ratio **137/138** is 3 when R^1 is a methyl group and 4 when R^1 is hydrogen. Enamines **137** and **138** are in equilibrium[104] (equation 67).



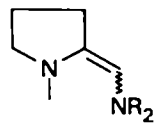
(136) **(138)** **(137)** (67)

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[91,103] and enamines **143** and **144** with an endocyclic double bond[208] have been characterized. Both types of double bonds are present in enamine **141**

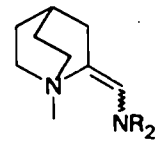
 , the endocyclic isomer **141b** representing 80% of the mixture[103]. The structural differences between five- and six-membered ring aminoenamines **140** and **141** are in agreement with the Brown Rule[56] and with other studies on five- and six-membered heterocyclic enamines[62,66b,193]. An equilibrium between endocyclic and exocyclic structures is always detected by deuteration even if only one structure is apparent[208,239].



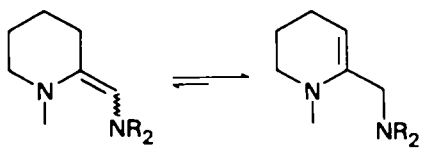
(139)



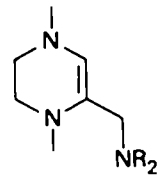
(140)



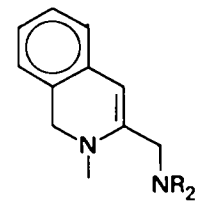
(142)



(141a) **(141b)**

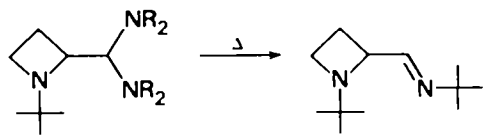


(143)



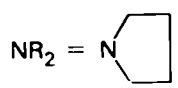
(144)

The particular behaviour of aminal **145** underlines the unstability of the four-membered heterocycle. Heating affords imine **146** isolated with 28% yield[89] (equation 68). The same product was characterized by decomposition of animal **145** in $CDCl_3$.



(68)

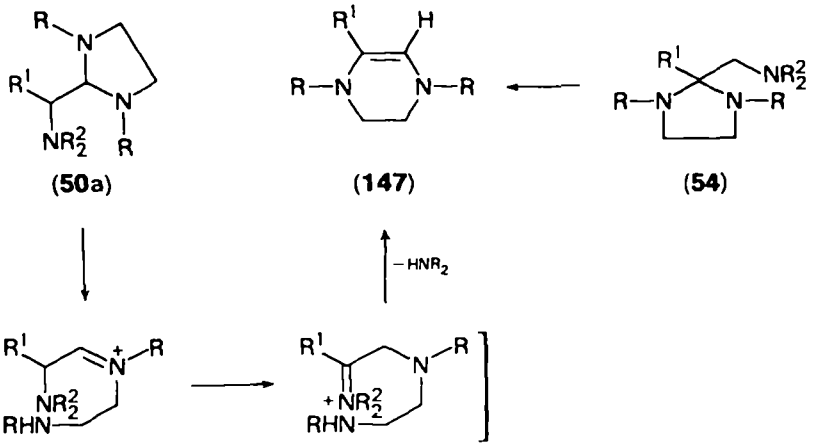
(145) **(146)**

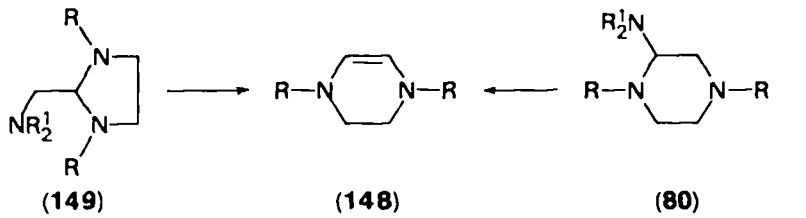


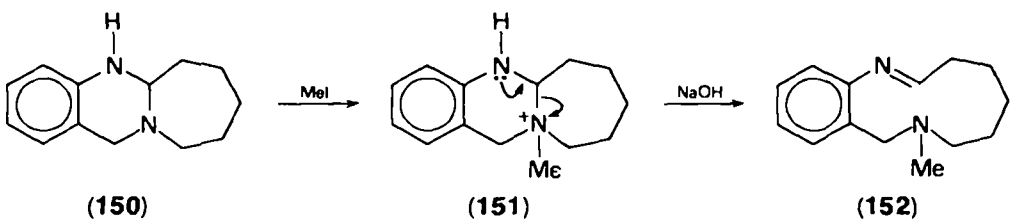
Imidazolidines **44** and hexahydropyrimidines **45** can be distilled without decomposition. Imidazolidines **50a** and **54** are transformed by heating into 1,2,4-trisubstituted tetrahydropyrazines **147**. An internal transamination via open-chain iminium compounds is a plausible scheme[93] (equation 69).

Tetrahydropiperazine **148** has been prepared either from imidazolidine **149**[239] or from hexahydropiperazine **80**[130] (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 substraction of a proton leading to imine **152** in equilibrium with the corresponding enamine[57] (equation 71).

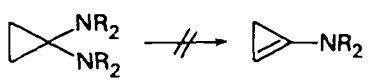


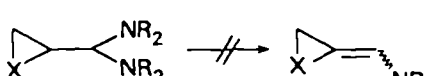




E. Aminals Non-transformable into Enamines

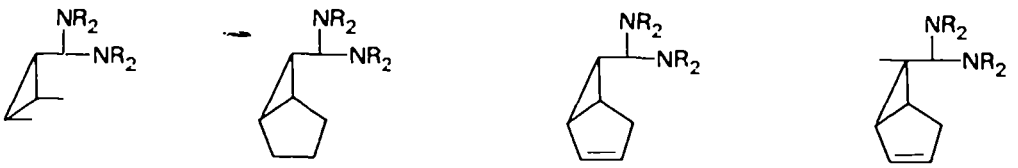
Cyclopropanone aminals **32**, cyclopropylcarbaminals[53,67,145-147,228] and azacyclopropylcarbaminals **153**[269,270] are not transformed by distillation or by prolonged heating into the expected enamines (equations 72 and 73).





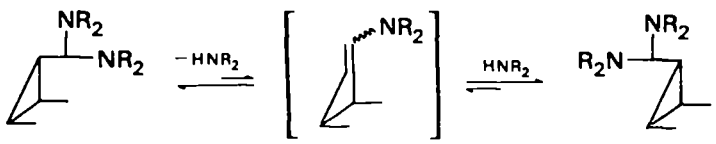
X = CHR^2, NR^2

endo-Cyclopropylaminals such as **154**, **155** and **156** (NR_2 = ) undergo an



(154) **(155)** **(156)** **(157)**

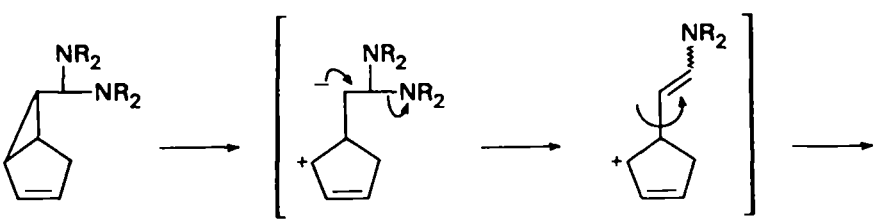
easy isomerization into the *exo* isomers. This isomerization sometimes occurs during the isolation of the aminal. It is catalysed by benzoic acid and is complete on distillation. It is considered to occur via a cyclopropylidene amine such as **158** with which the *endo* and *exo* aminals are in equilibrium[146,228]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



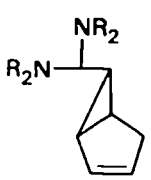
(74)

(154) **(158)**

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 allyl cation but cannot give an enamine such as **158**, does not undergo the *endo* ⇌ *exo* isomerization[145].



(156) **(159)**

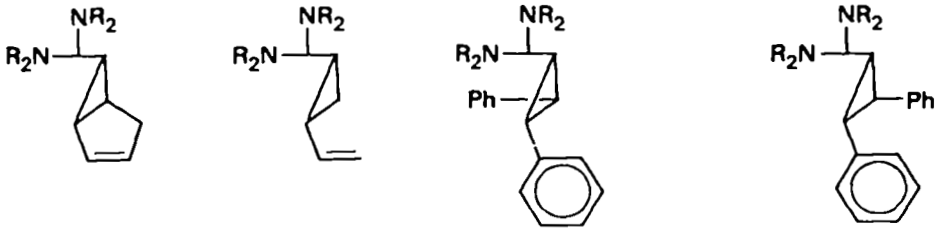


(75)

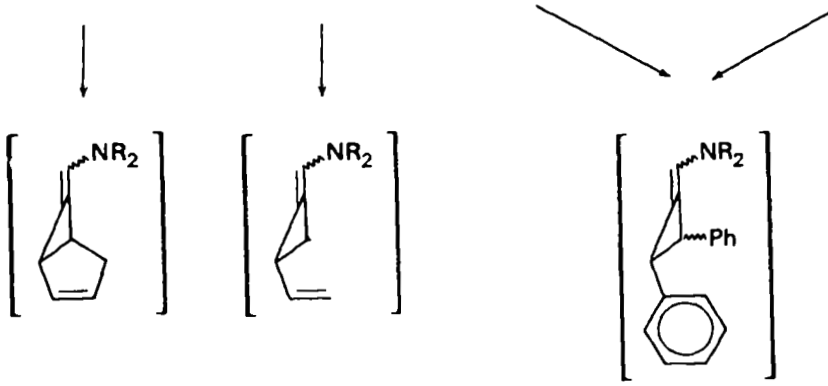
(160)

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).

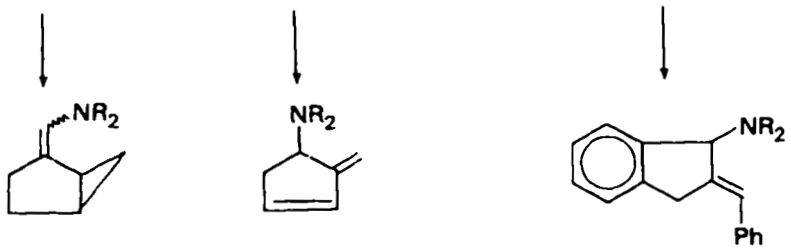
Aziridinoaminals **167** are recovered unchanged after heating at 200°C[269], whereas aminal **168** is transformed into a pyrrole[270] (equation 77).



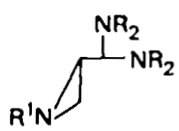
(160) (161) (162) (163)



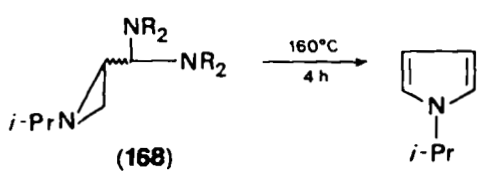
(76)



(164) (165) (166)



(167)



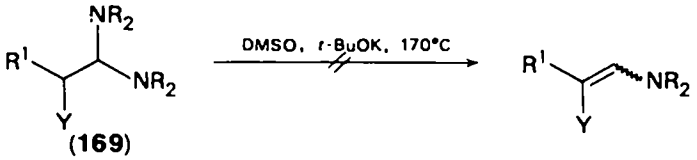
(77)

(168)

NR_2 = N⟨ ⟩ ; R^1 = *i*-Pr, *t*-Bu

F. Stability of Aminals in Strongly Basic Media

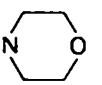
Aminals **169** and aminoimidazolidine **50** (X = NEt_2, R^1 = Et, R = Me) are stable in DMSO in the presence of potassium *t*-butylate, even after two hours at 170°C, while they are totally transformed into enamines in the absence of this base (equation 78).

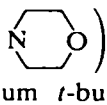


(78)

(169)

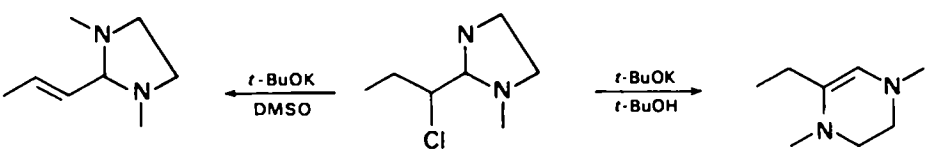
R^1 = Me Ph Ph Ph

Y = H H Me  NR_2 = 

Similarly aminoaminal **169** $\left(R^1 = Ph,\ Y = NR_2 = \text{  }\right)$ is unchanged after some hours of reflux in DMF containing potassium *t*-butylate, or in ether, tetrahydrofurane or dioxane containing lithium aluminium hydride[93,239].

This result suggests that decomposition of aminals into enamines does not occur when the formation of iminium ions is impossible. Therefore, an E_1 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*-butylate. 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).



(79)

(172) **(170)** **(171)**

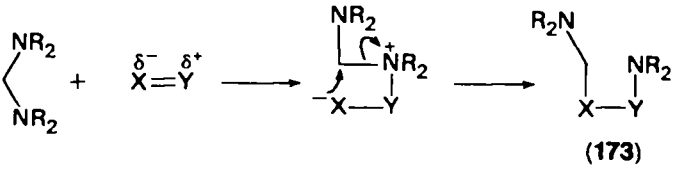
V. REACTIONS

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).

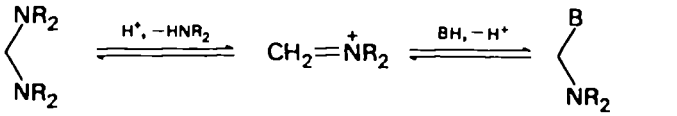
A. Reactions with Heteroatom Nucleophilic Reagents

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

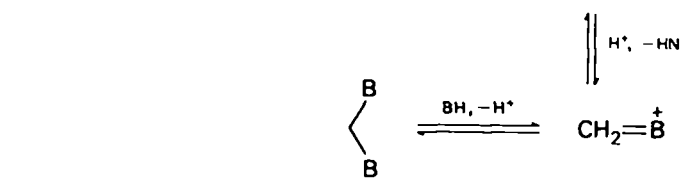


(80)

(173)



(174)



(81)

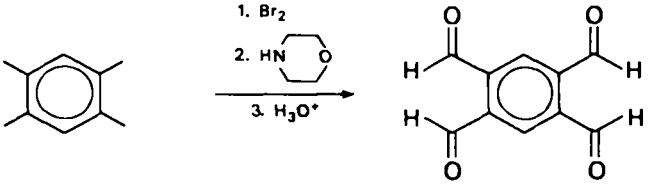
(175)

1. Water

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

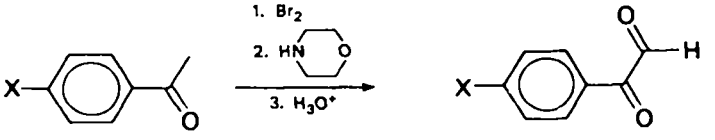
Polyformylbenzenes (**176**) and *para*-substituted phenylglyoxals (**177**) have been advantageously prepared from polymethylbenzenes[159,161,164,166,167,241] (equation 82) and *para*-substituted acetophenones[160,262] (equation 83) via aminals. In some cases, isolation of the aminal is not necessary, 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



(82)

(176)



(83)

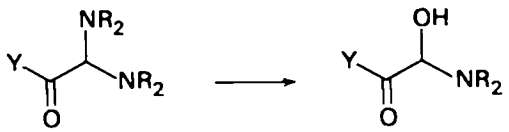
(177)

X = Me, CN, CO_2H, F, Cl, Br

equivalents of *p*-toluenesulphonic acid monohydrate in acetone and methylene chloride. The diamine salt is removed by filtration and the aldehyde by aqueous extraction[2].

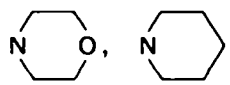
Hydrolysis of aminals with $H_2{}^{18}O$ represents a useful method for the preparation of ^{18}O-carbonyl compounds[248].

Monosubstitution products **179** have been obtained by partial hydrolysis of α-ketoaminals **178**[49,127,128,217,218] (equation 84).

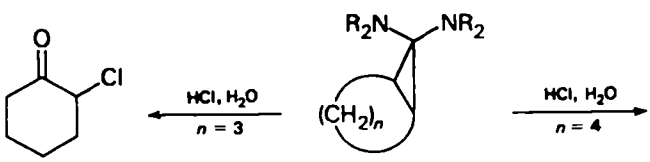


(84)

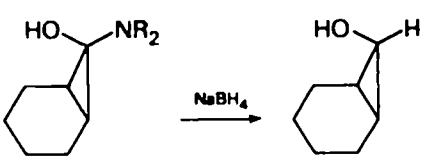
(178) **(179)**

Y = NR_2, Ph ; NR_2 = 

The cyclopropanone aminal **38** (NR_2 =) on treatment with hydrochloric acid affords the hemiaminal **180** which permits a convenient synthesis of endonorcaranol **181** (equation 85). Under similar conditions, **37** () gives 2-chlorocyclohexanone[250,251]. The unexpected formation of the *exo*-amine **180** from **38** is probably the result of a thermodynamically controlled isomerization[263]. The isomeric *endo*-amine **182** can be prepared from the fluorosulphonate **40** in basic medium (equation 86). In the presence of traces of acid, it undergoes rapid

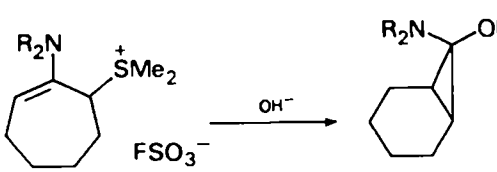


(37) *n* = 3
(38) *n* = 4



(85)

(180) **(181)**

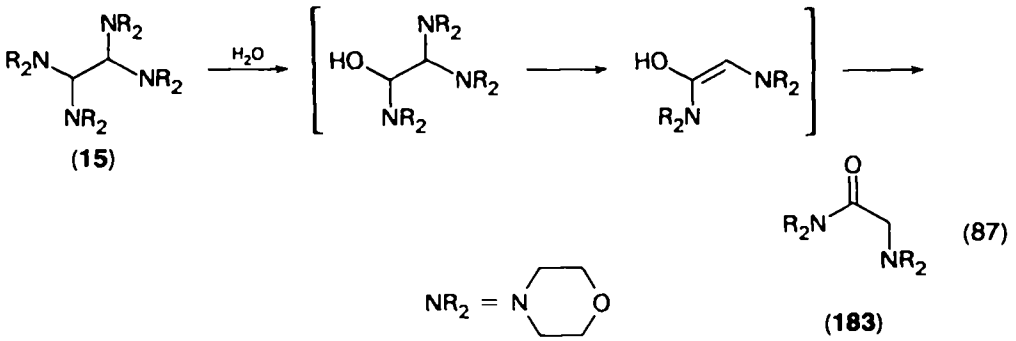


(86)

(40) **(182)**

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 ^{1}H-NMR an AA'XX' signal while an *endo* morpholino group shows an ABXY system[263].

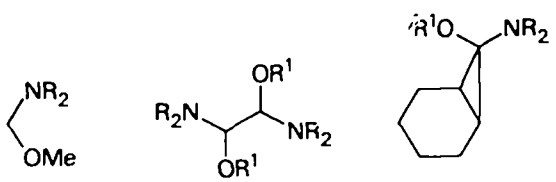
The specific hydrolysis of tetramorpholinoethane (**15**; NR_2 = N⟨CH$_2$CH$_2$⟩O) into the aminoamide **183**, according to equation (87), must be noted[113].



(15) (183) (87)

2. Alcohols

Monosubstitution products **184–186** have been obtained by successively adding acetyl chloride, triethylamine and methanol to aminal **5**[34], by heating tetramorpholinoethane (**15**; NR_2 = N⟨CH$_2$CH$_2$⟩O) in alcohols[112] or by reaction of methanol or ethanol with cyclopropanone aminal **38**[263,273].



(184) (185) (186)

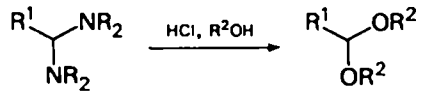
R^1 = Me, Et, Pr

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[163,217,218].

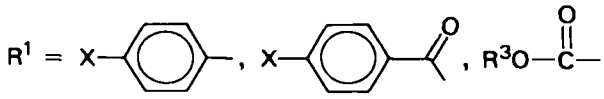
Solvolysis by methanol of α-ketoaminals such as **17a** is complex. Ketals **188** and **189** have been detected. Nevertheless, it has been possible to determine experimental conditions yielding exclusively acetal **187** (equation 89). Direct acetalization of phenylglyoxal by methanol has given, in the best case, an equal mixture of the ketal **188** and the starting material[218].

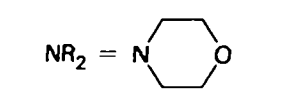
3. Thiols

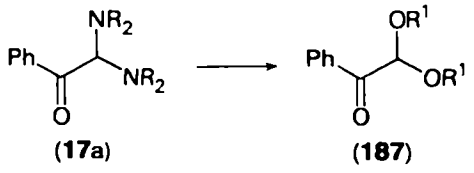
Mono- and di-substitution products **190** and **191** have been obtained by reaction of thiols with aminals in the presence of acetyl chloride, hydrogen chloride or



(88)

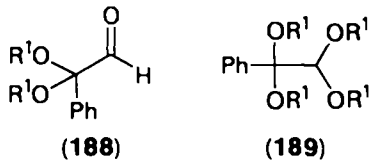






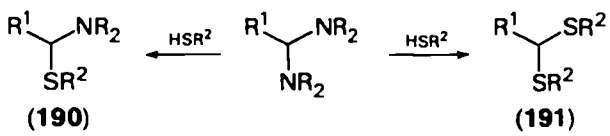
(89)

(17a) (187)



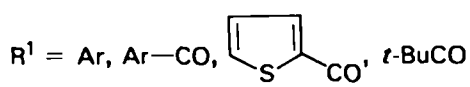
(188) (189)

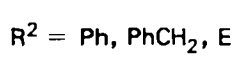
sulphuric acid[34,181,182,184] (equation 90). The reaction is rapid and the yields are often in excess of 80%. The method is useful for the preparation of α-ketothioacetals which are difficult to obtain.



(90)

(190) (191)



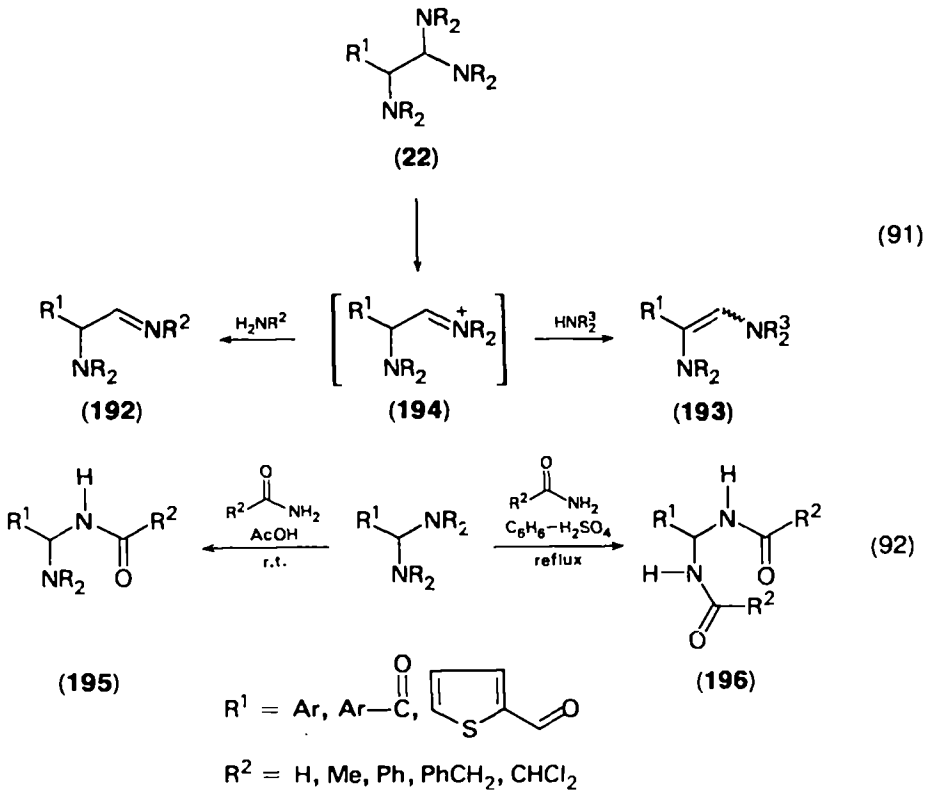


4. Amines

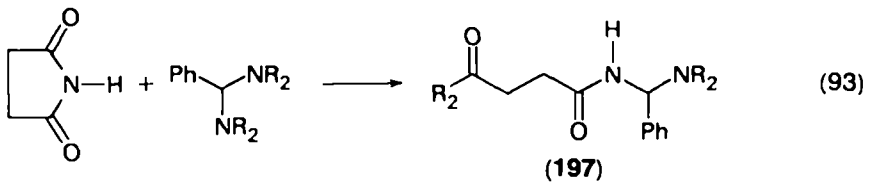
Reaction of α-aminoaminals **22** with primary and secondary amines leads to α-amino imines **192** and enediamines **193** (equation 91). The amine exchange occurs on the aminal carbon involving an α-aminoaldiminium cation **194**[98,102].

5. Amides

A variety of monosubstitution compounds **195** and amidals (*N,N*-diacylaminals) **196** have been prepared by reaction of aminals with amides[183,185,238] (equation 92).



Reaction with succinimide results in rupture of the succinimide ring with formation of amide **197**[238] (equation 93).



B. Reactions with Carbon Nucleophilic Reagents

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

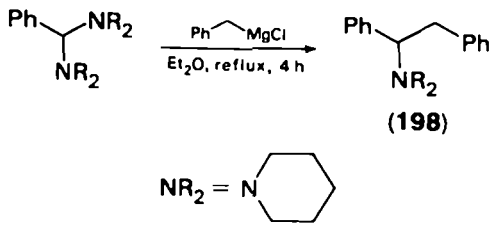
1. *Grignard reagents*

Grignard reagents react very slowly with aminals leading to a tertiary amine such as **198** isolated in low yield[122] (equation 94).

2. *Diazoalkanes*

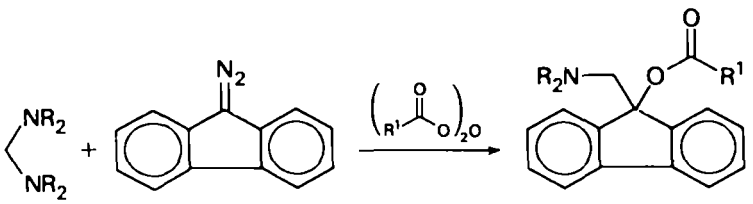
Reaction of aminals **5** with diazofluorene in the presence of carboxylic anhydrides yields *O*-acylethanolamines **199**[235] (equation 95).

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



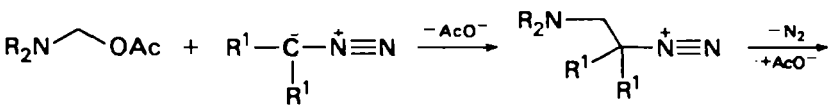
(94)

(198)

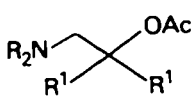


(95)

(5) (199)



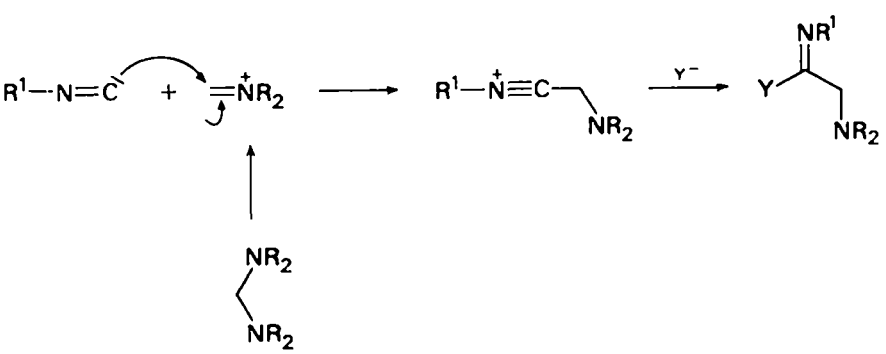
(200)



(96)

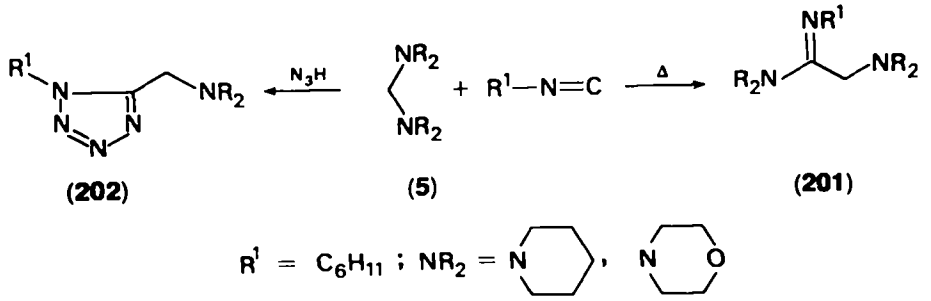
3. *Isonitriles*

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).



(97)

Reaction of aminal **5** with an isonitrile yields an aminoacetamidine **201**[285]. In the presence of hydrazoic acid, a tetrazole derivative **202** is obtained[258] (equation 98).



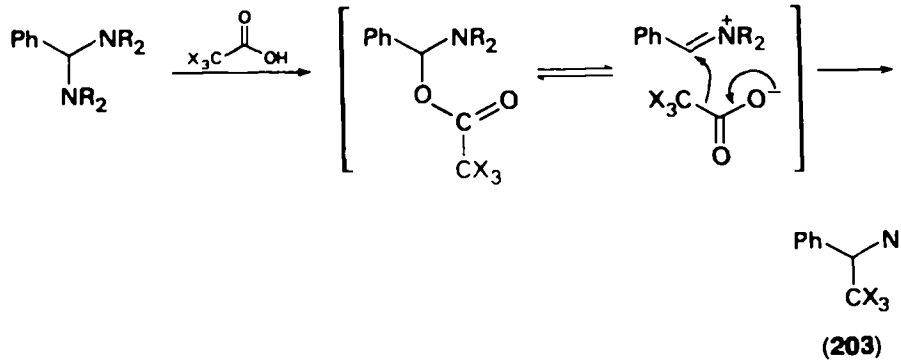
(98)

(202) (5) (201)

$R^1 = C_6H_{11}$; NR_2 =

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 **203**[192] (equation 99).

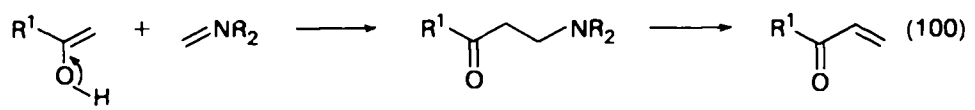


(99)

(203)

5. C—H acidic compounds

The acid-catalysed Mannich reaction is believed to involve an iminium cation intermediate[69] 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[25]. The condensation product can be transformed into an α-ethylenic carbonyl compound by amine elimination (equation 100).

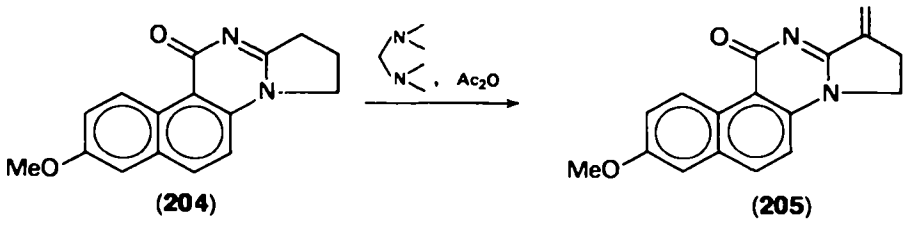


(100)

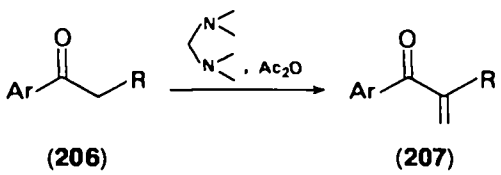
Instead of aldehydes and amines, this reaction may be carried out with the corresponding aminals which give iminium cations easily under acidic conditions[187].

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[78,252] (equations 101 and 102).

Reaction of phenylacetone with aminal **10** yields a labile intermediate **208** which upon elimination provides the ethylenic ketone **209**[71] (equation 103).

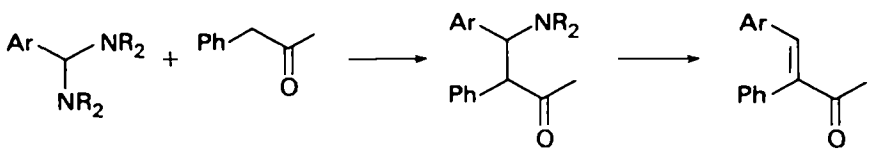


(204) (205) (101)



(206) (207) (102)

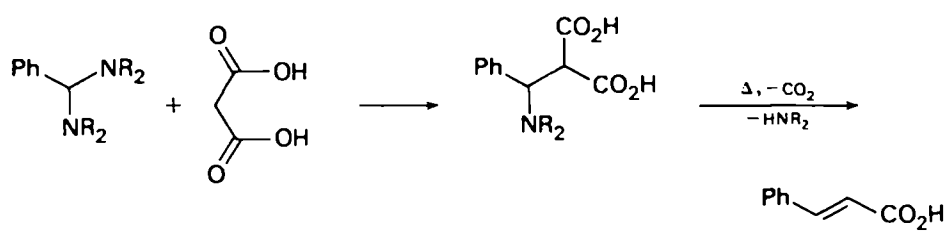
R = Ar, Et



(10) (208) (209) (103)

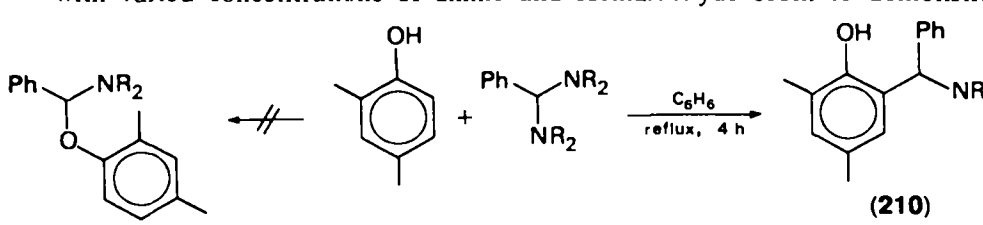
NR_2 = N

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].



(104)

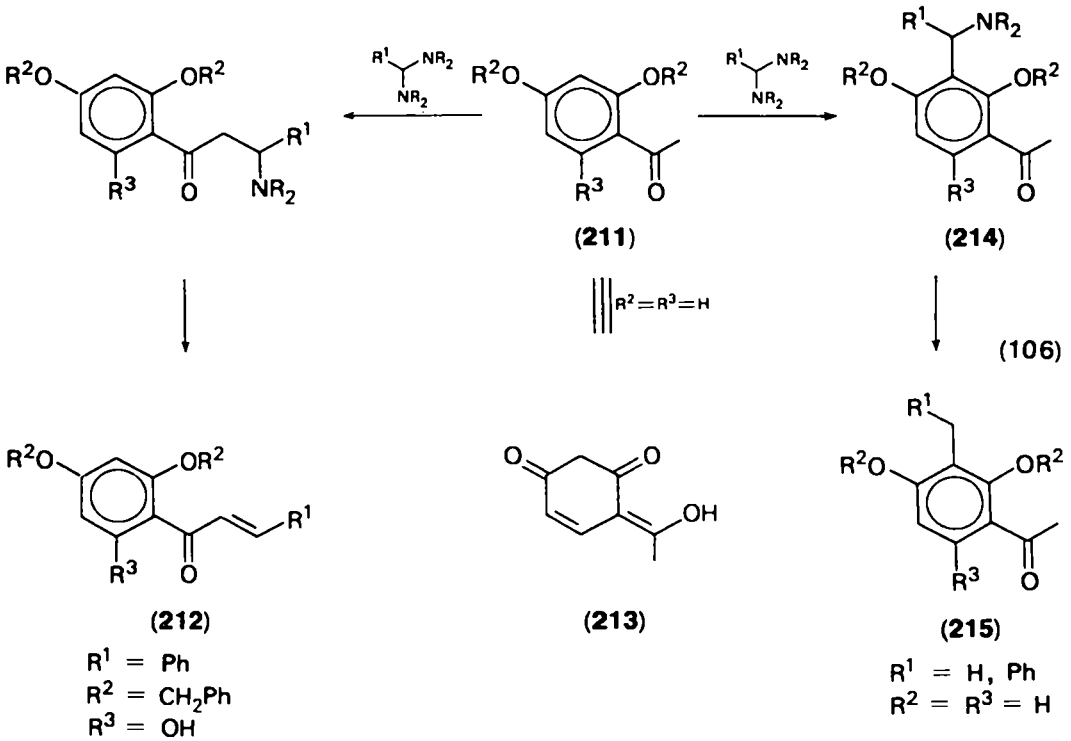
Aminals aminoalkylate the aromatic ring of phenols[34], yielding substituted phenols such as **210**[209] (equation 105). In basic solutions (pH ~ 9), kinetic studies with varied concentrations of amine and formaldehyde seem to demonstrate the



(210) (105)

intermediary role of an aminal, thus ruling out an iminium cation[59]. The different behaviour of phenols and alcohols must be underlined.

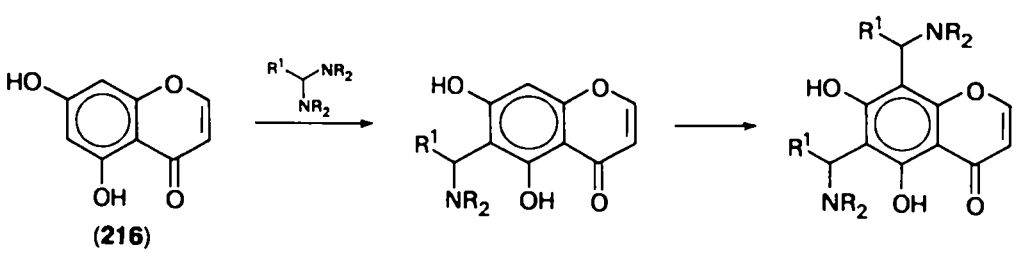
With acetophenones such as **211**, aminoalkylation can occur either on the aromatic ring or on the methyl group (equation 106). When the two hydroxyl



(106)

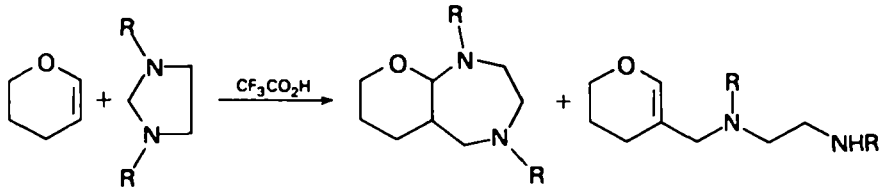
groups are protected, the reaction takes place exclusively on the methyl group giving the chalcone **212**. When the two hydroxy groups are free, a regiospecific aminoalkylation of the nucleus occurs, due to the tautomeric structure **213**. Since the benzylic amino group of compound **214** can be removed by reduction, this method offers a selective route to *C*-methyl- or *C*-benzyl-acetophenone **215**[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[155–157] (equation 107).



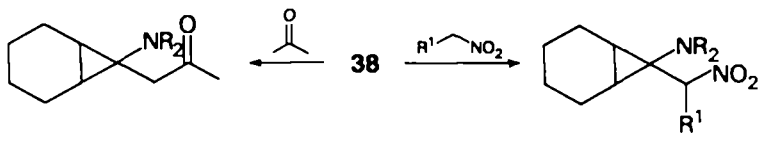
(107)

The condensation of imidazolidines **44a** with dihydropyrane proceeds similarly, yielding an perhydrodiazepine **217** and a secondary amine **218**[126] (equation 108).



(44a) (217) (218) (108)

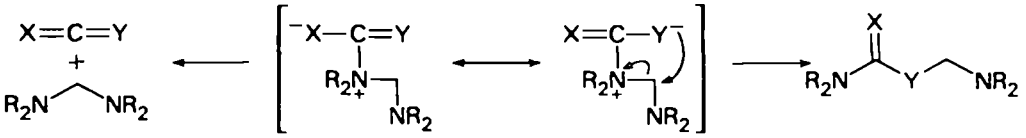
The cyclopropanone aminal **38** readily undergoes reaction with ketones (acetone, methyl ethyl ketone, cyclopentanone) in the presence of an aqueous buffer of pH 5.5, to form addition products such as **219**. **38** also reacts with nitromethane or nitroethane[188] in the presence of methyl iodide (used to generate a cyclopropyliminium intermediate) leading to the nitro compound **220**[273,274] (equation 109).



(219) (220) (109)

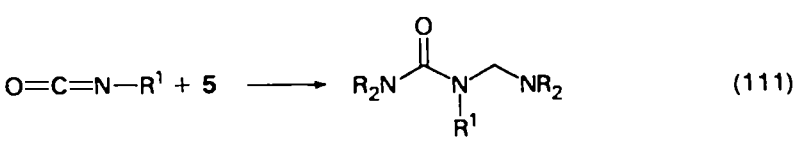
C. Reactions with Heterocumulenes

Aminals **5** react with heterocumulenes X=C=Y with formation of a 1:1 adduct (equation 110).

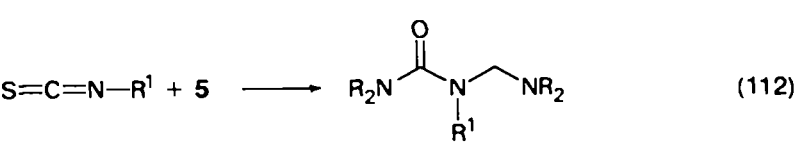


(5) (110)

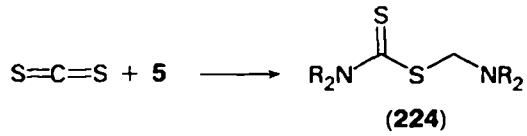
Addition products of this type (**222–226**) have been obtained with isocyanates (equation 111), isothiocyanates (equation 112)[43,259], carbon disulphide[80,177,259] (equation 113), ketene (equation 114)[105,214] and ketene imines (equation 115)[43]. Generally, reaction occurs even at room temperature in the absence of a catalyst.



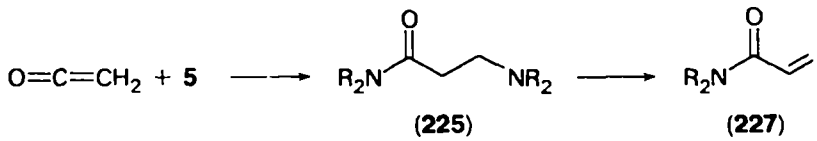
(222) (111)



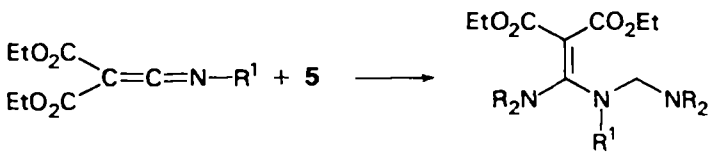
(223) (112)



(224) (113)



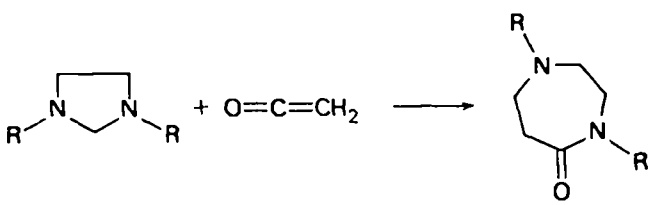
(225) (227) (114)



(221) (226) (115)

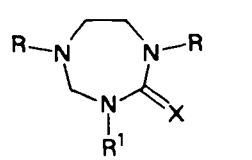
Compounds **222–224** are thermolabile and are cleaved into the starting materials on heating to 100°C[259]. The β-aminoamide **225** eliminates amine forming an α-unsaturated amide **227**[105].

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[43].



(**44a**) (**228**) (116)

R = *n*-Bu, $PhCH_2$



(**229**)

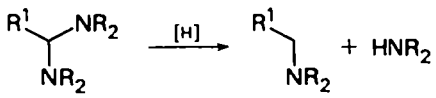
X = O, S, $C(CO_2Et)_2$

R^1 = Ar

R = *n*-Bu, $PhCH_2$

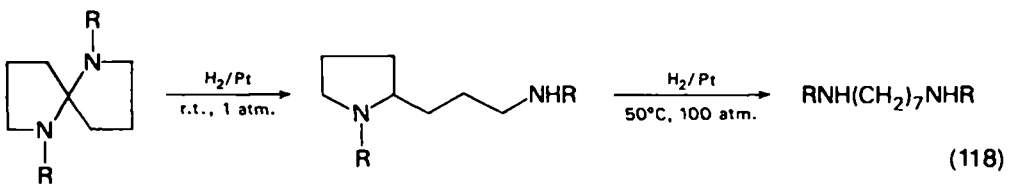
D. Reduction

Aminals are cleaved and reduced into both tertiary and secondary amines by catalytic hydrogenation, formic acid, or metal hydrides (equation 117).



(117)

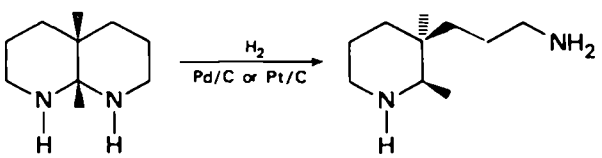
Reduction of open-chain and cyclic aminals occurs by hydrogenation in the presence of platinium, palladium or Raney nickel[174,286]. Splitting of the C—N bond of the spiroaminal **81a** is easy, whereas more drastic conditions are required for the cleavage of the pyrrolidino ring[174] (equation 118).



(118)

(81a)

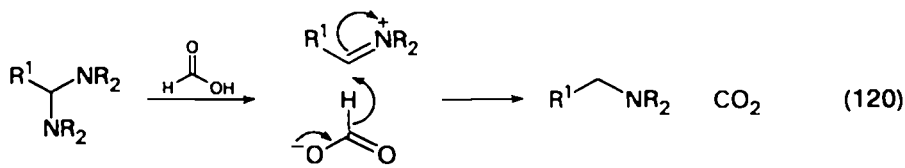
Cis- and *trans*-3(γ-aminopropyl)piperidines **231** are formed by reduction of decahydronaphthyridines **230**. The *cis* isomer is largely predominant. The stereoselectivity is influenced by the catalyst used (Pt or Pd)[286] (equation 119).



(119)

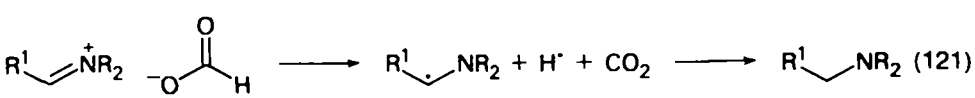
(230) **(231)**

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[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

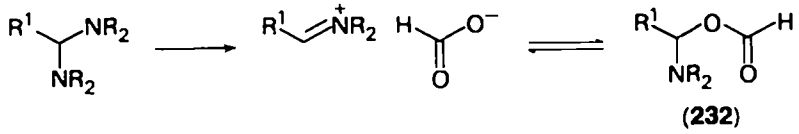


(120)

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[191] (equation 122).

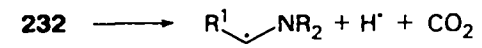


(121)

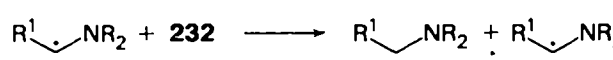


(122a)

(232)

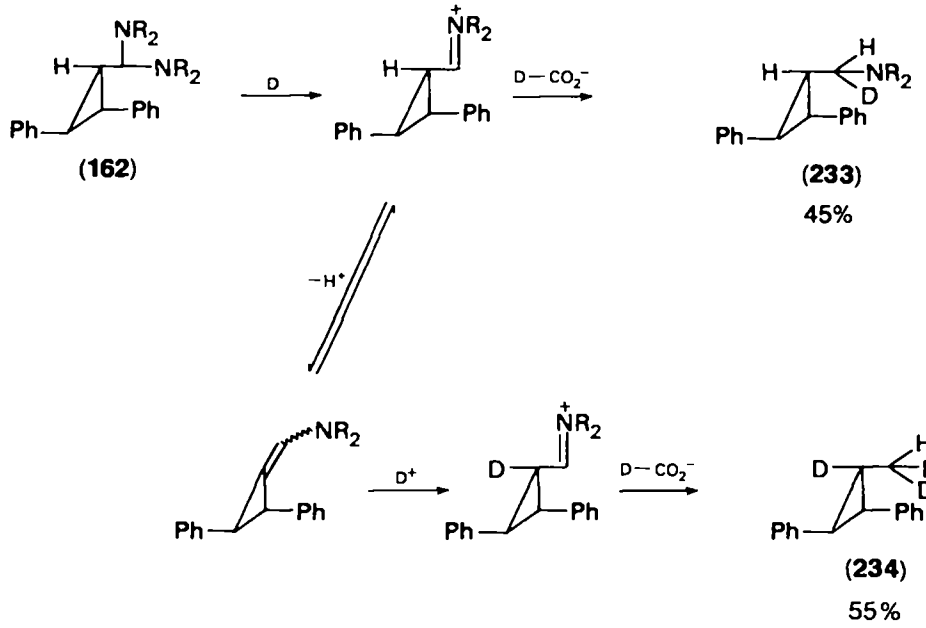


(122b)



(122c)

The reduction of cyclopropylcarbaminal **162** by formic acid-d_2 yields a monodeuterioamine **233** and a bideuterioamine **234** (equation 123) suggesting an equilibrium between the iminium cation and the not nonisolated cyclopropylidene amine (Section IV.E)[147].

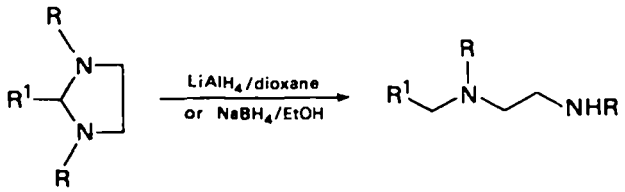


(123)

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 reflux[103,279] (equation 124). The chloroimidazolidine **50** is transformed into piperazine **236** by these reagents[103] (equation 125). The proposed mechanism is shown in equation (126).

1,2,3-Trisubstituted hexahydropyrimidines **45** (R^1 = Me) are similarly cleaved by these two reducing agents. However, 1,3-disubstituted hexahydropyrimidines **45** (R^1 = H) are not affected under the same conditions[279]. Spiroaminoaminals **81a**[174] ($R^1 = R^2$ = H) and α-aminoaminals **22** (R^1 = H, Ph)[83,93] are recovered unchanged following treatment by lithium aluminium hydride, while cyclopropylcarbaminals are reduced[67].

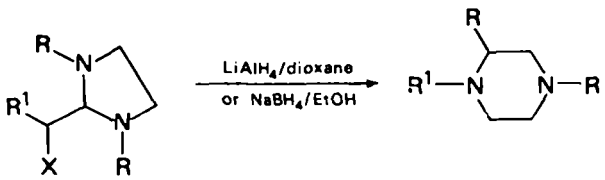
Imidazolidines **44** are also cleaved to the diamines **235** by reduction with borane–tetrahydrofurane[213].



(124)

(44) (235)

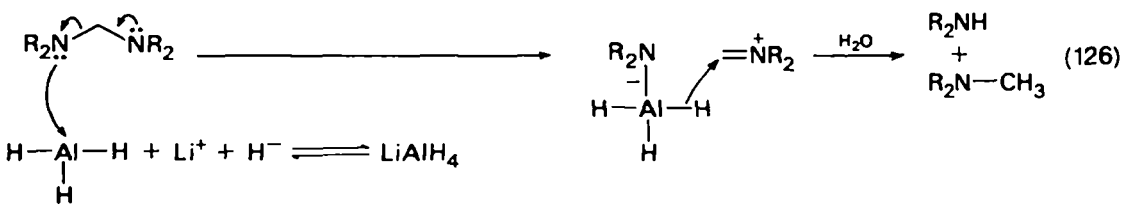
R^1 = H, Me, Et—CH(N O)



(125)

(50) (236)

R^1 = Et, X = Cl



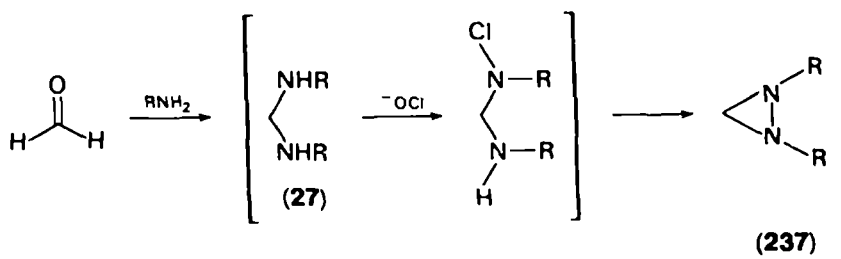
(126)

The reduction of aminals **27** with zinc in the presence of sodium hydroxide has been reported[120].

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[215,221b] (equation 127). This reaction also occurs with the hexahydrotriazine

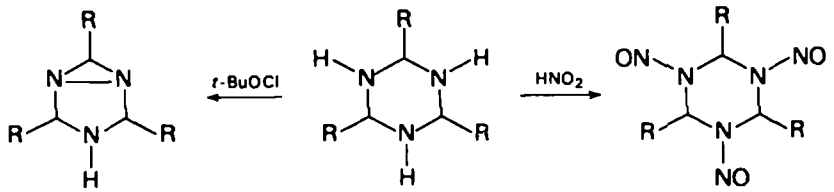


(127)

(237)

R = *n*-Bu

58[210] (equation 128). The hexahydrotriazine **58** reacts with nitrous acid to provide a fair yield of the trinitroso derivative **238**[210] (equation 128).

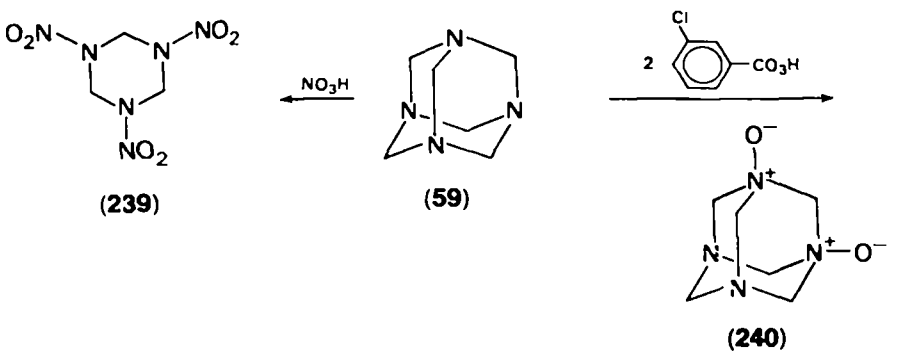


(128)

(58) **(238)**

R = Me

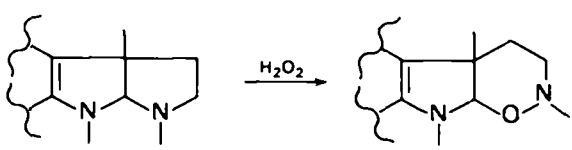
The nitration of hexamethylenetetramine **59** leads to the high-explosive cyclotrimethylenetrinitroamine **239**[5]. *N*-Oxide aminals such as **240** have only been isolated from rigid systems such as polyazaadamantanes. Mono-, di- or tri-*N*-oxides are obtained by reaction of hexamethylenetetramine **59** with 3-chloroperbenzoic acid, depending on structural type and molar ratio between the reactants[170] (equation 129).



(129)

(239) **(59)** **(240)**

In other cases, the *N*-oxides are unstable and rearrange into oxazines such as **241** and **243** obtained from the aminals **1**[144,223] and **242**[171] (equations 130 and 131).



(130)

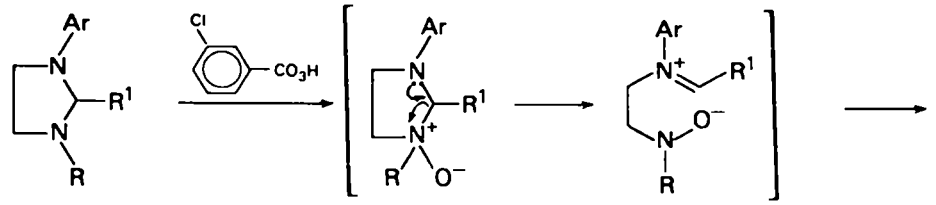
(1) **(241)**

Triazines **28** are transformed into oxaziranes **244** by action of peracetic acid, via oxidation of formaldehyde imine[109] (equation 132).

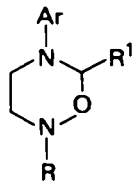
2. *With modification of the oxidation number of the aminal carbon atom*

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[225].

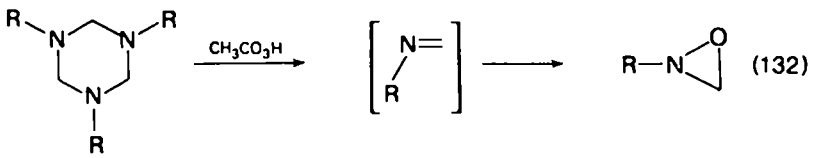
Dehydrogenation also occurs with potassium permanganate, peracetic acid in aqueous solutions[151], quinones, ethyl azodicarboxylate[226], mercuric



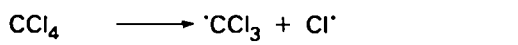
(242)



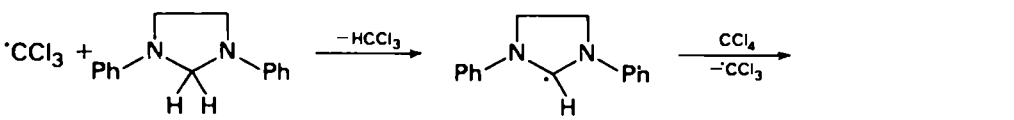
(243) (131)

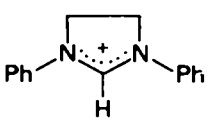


(28) (244) (132)

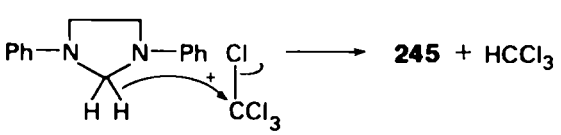


(133a)





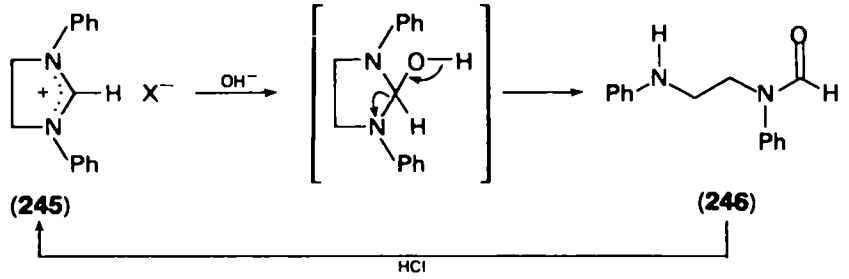
(245) (133b)



(134)

ethylenediaminetetracetate[201,202], and dimethyl sulphoxide in the presence of zinc chloride[126]. In some cases *N*-monoformyldiamine **246** is isolated, which can yield the imidazolidinium salt **245** after acidic treatment[151,226] (equation 135).

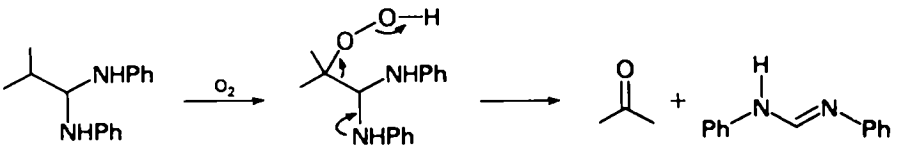
Dehydrogenation of 2-substituted 1,3-diphenylimidazolidines **44** is more difficult, but is effected with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone[226] and with mercuric ethylenediaminetetracetate[201,202].



(135)

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[233].

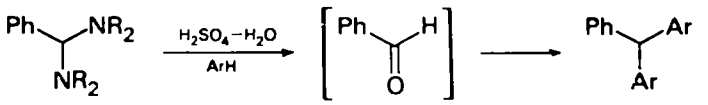


(136)

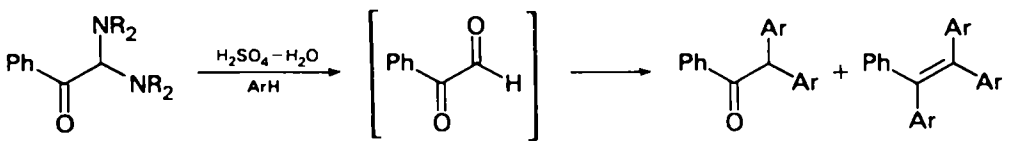
VI. AMINALS AS POTENTIAL AND PROTECTED CARBONYL COMPOUNDS

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[204,219] (equations 137 and 138).

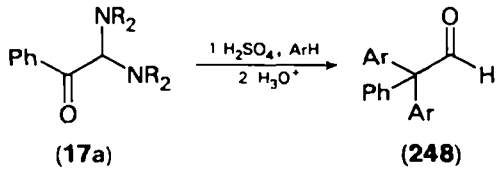


(137)



(138)

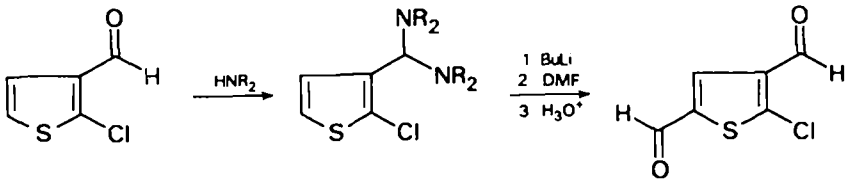
In even more strongly acidic media such as anhydrous sulphuric acid, the aminal function does not react with aromatic compounds. This lack of reactivity is probably due to the protonation of both amino groups. This property permits the preparation of triarylacetaldehydes **248** from the α-ketoaminal **17a**[219] with good yields (equation 139).



(17a) (248) (139)

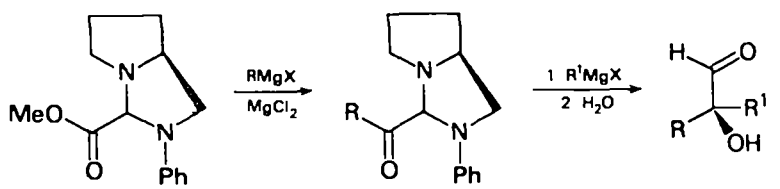
Ar = MeO-C6H4-

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[64] (equation 140).



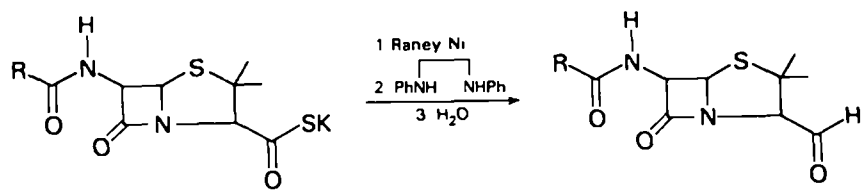
(140)

α-Hydroxy aldehydes **251** have been prepared in high optical yields by the reaction of α-ketoaminals **250** with Grignard reagents and hydrolysis of the resulting hydroxyaminal. α-Ketoaminals **250** have been obtained by treatment of the methoxycarbonylaminal **249** with Grignard reagents in the presence of magnesium chloride[206,207] (equation 141).



(249) (250) (251) (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[2,123,131] (equation 142). Penicillin aldehydes have been synthesized under these conditions[123].



(142)

Reduction of *p*-isopropylbenzaldehyde into the 2,5-dihydro derivative has been effected by metal ammonia after conversion into the 1,3-dimethylimidazolidine derivative[13].

Aminals have also been used to trap labile aldehydes. Thus, α-amino aldehydes have been isolated from reaction mixtures as crystallized aminals **22**, in order to avoid their transformation into the more stable isomeric ω-aminoketones[84,90,95].

VII. REFERENCES

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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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[1-11] and spectroscopy[12,13] 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[14] 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[2-5] and a recent review[1], 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

$$RNO_2 + 6\,H^+ + 6\,e \longrightarrow RNH_2 + 2\,H_2O \qquad (1)$$

acid[4,5]. The resulting primary amine can then be detected[4,5]. Nitroso, azoxy or azo compounds give the same results.

With a neutral reducing agent[5] or with zinc dust and acetic acid in alcohol[4] nitro compounds are reduced to hydroxylamines (equation 2), which can be detected by

$$RNO_2 + 4\,H^+ + 4\,e \longrightarrow RNHOH + H_2O \qquad (2)$$

Tollen's reagent or by the ferric hydroxamate test[4]. Under the same conditions azoxy and azo compounds are reduced to hydrazo and hydrazine derivatives respectively, which also respond positively to Tollen's test. However, only hydroxylamines give the ferric hydroxamate test[4]. 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 Tollen'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[3-5] (equation 3). Not all nitroparaffins give a positive response, whereas a positive test is given also by other oxidizing compounds.

$$RNO_2 + 6\,Fe(OH)_2 + 4\,H_2O \longrightarrow RNH_2 + 6\,Fe(OH)_3 \quad (3)$$
(green) (brown)

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 $Na_3[Fe(CN)_5NH_3]$ (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 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

$$ArNO + 4\,H^+ + 6\,e \xrightarrow{Sn,\ HCl} ArNH_2 + H_2O \quad (4)$$

$$ArNO + 2\,H^+ + 2\,e \xrightarrow{Zn,\ CaCl_2} ArNHOH \quad (5)$$

$$R_2NNO + 4\,H^+ + 4\,e \longrightarrow R_2NNH_2 + H_2O \quad (6)$$

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.

$$R_2N{-}NO + HN_3 \longrightarrow R_2NH + N_2 + N_2O \quad (7)$$

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].

$$R_2NNO + H_2O \longrightarrow R_2NH + HNO_2 \quad (8)$$

Nitroso compounds can be distinguished from nitro compounds by their reaction with $[Fe(CN)_5NH_3]^{-3}$ or $[Fe(CN)_5H_2O]^{-3}$. A colour develops upon the exchange of NH_3 or H_2O for the nitroso compound[1,2] (equation 9). Aromatic amines or hydrazines will also give a positive test.

$$Na_3[Fe(CN)_5NH_3] + RNO \longrightarrow NH_3 + Na_3[Fe(CN)_5RNO] \quad (9)$$

Nitroso compounds give a positive Liebermann test (red colouration upon heating in conc. H_2SO_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 indeces 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[12] 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 (ν_s) in the region of 1300–1700 cm^{-1}, and the asymmetric stretching (ν_{as}) in the region of 1500–1600 cm^{-1}. Generally primary and secondary nitro derivatives absorb at slightly higher frequencies than the tertiary derivatives, as seen in Table 2. α-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 NO_2 vibrations toward lower frequencies[17]. Coplanar aromatic nitro groups generally have their ν_{as} vibration in the region of 1520–1550 cm^{-1}. Strongly electron-withdrawing groups in the *para* position or bulky groups in the *ortho* position cause an increase in the ν_{as} frequency. Electron-releasing groups lower the ν_{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 1. The fundamental infrared and Raman frequencies of nitromethane[12]

Description	Infrared[a] (cm^{-1})	Raman[b] (cm^{-1})
NO_2 asym. stretching (ν_{as})	1586	1562
NO_2 sym. stretching (ν_s)	1377	1377.3
C—N stretching	918	918.8
NO_2 sym. bending	658	656.5
NO_2 rocking	605	608
	477	481

[a] Vapour.
[b] Liquid.

TABLE 2. Infrared frequencies of aliphatic nitro compounds[16]

Nitro derivative	ν_{as} (cm^{-1})	ν_s (cm^{-1})
Primary	1550 ± 2	1379 ± 3
Secondary	1550 ± 2	1357
Tertiary	1536 ± 2	1348 ± 3

decrease in frequency in polar solvents has been recorded for *para*-substituted nitrobenzenes[19].

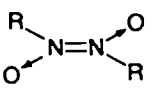
The infrared spectra of nitro derivatives have been recently reviewed[20]. Several papers dealing with various aspects of the infrared[21–24] and Raman[25,26] spectra of nitro compounds have appeared recently.

2. Nitroso compounds[13]

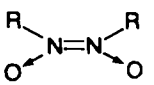
Owing to possibilities of dimerization and geometrical isomerism in nitroso compounds, their characteristic frequencies vary with temperature and concentration.

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^{-1}, whereas in the nitrosobenzene monomer it appears at 1506 cm^{-1}. Generally aliphatic *C*-nitroso compounds show the free N=O stretching vibration in the region of 1538–1621 cm^{-1}, while in aromatic *C*-nitroso compounds it appears at 1485–1515 cm^{-1}. 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_2 group increases this frequency.

The C—N stretching vibration appears in these compounds around 1100 cm^{-1}, and the C—N=O bending in the region of 400–460 cm^{-1}. The absorption frequencies of the *cis* and *trans* dimers of *C*-nitroso compounds are given in Table 3.



Trans dimer



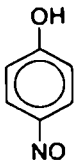
Cis dimer

The *trans* dimers generally show high-intensity bands in the region 1180–1300 cm^{-1}, 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.

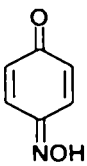
TABLE 3. Infrared characteristic frequencies of *cis* and *trans* dimers of *C*-nitroso compounds[13]

R	*Trans* dimer	*Cis* dimer
Aliphatic	Single band in the region 1176–1290 cm^{-1}	Two bands in the regions 1323–1344 and 1330–1420 cm^{-1}
Aromatic	Single band in the region 1253–1299 cm^{-1}	Two bands in the regions 1389–1397 and 1409 cm^{-1}

The infrared spectra of some nitroso derivatives are indicative of oxime formation. According to infrared spectroscopic evidence, *p*-nitrosophenol (**1**) is present in the quinoid oxime structure **2**.



(1)



(2)

N-Nitrosamines in the monomeric state show the N=O stretching frequency in the region 1430–1530 cm^{-1}, whereas dimers absorb around 1300 cm^{-1}. The N=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—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—N stretching of these compounds is assigned to a band in the region 1160–1200 cm^{-1}, and the N—N=O deformation mode to a band around 660 cm^{-1}.

The infrared spectra of nitroso derivatives have been reviewed recently[27].

C. Electronic Spectroscopy

The electronic spectra of nitro and nitroso compounds have been extensively reviewed[12,13]. A brief summary is presented here.

1. *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 ($\log \varepsilon = 1.3$), while the band due to the $\pi \rightarrow \pi^*$ transition appears at 210 nm ($\log \varepsilon = 4.2$). 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 ($\varepsilon = 8500$) (probably corresponds to the 203 nm band of benzene), and at 290 nm ($\varepsilon = 1500$) (corresponding to the forbidden $\pi \rightarrow \pi^*$ transition of benzene, around 260 nm). *para*-Substituted nitrobenzenes exhibit a bathochromic shift relative to nitrobenzene when substituted with an electron-donating substituent. The absorption spectra of *ortho*-substituted benzenes are governed by electronic and steric effects of the substituents. Substituents in the *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 ($\varepsilon \sim 20{,}000$) while those of α,β-unsaturated derivatives absorb at 380 nm ($\varepsilon \sim 25{,}000$).

Several papers dealing with the interpretation of electronic spectra of

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 $\varepsilon \sim 5000$ ($\pi \rightarrow \pi^*$ transition), at 270–290 nm with $\varepsilon \sim 80$ ($n \rightarrow \pi^*$ oxygen lone-pair transition) and at 630–790 nm with $\varepsilon \sim 1$–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 ($\varepsilon \sim 11{,}890$), 280 nm ($\varepsilon \sim 10{,}330$), 301–350 nm ($\varepsilon \sim 5200$) and at 680–760 nm ($\varepsilon \sim 40$–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 ($\varepsilon \sim 1000$). The change in absorption is expressed by the change in colour from blue to yellow. The wavelength of absorption is lower in the *cis* dimer than in its *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].

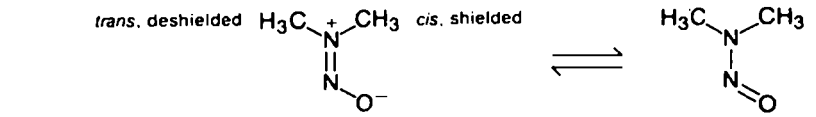
D. Nuclear Magnetic Resonance

1. Proton NMR

The ^{1}H-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 nitromethone is $\delta = 4.28$ ppm. The effect of the nitro group on the ^{1}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: $\delta_{ortho} = 0.92$, $\delta_{meta} = 0.25$ and $\delta_{para} = 0.38$ ppm[33].

N-Nitrosamines have been studied by ^{1}H-NMR spectroscopy with respect to hindered rotation about the N—N bond. Generally, protons within two bonds removed from the nitroso group and *cis* to it are shielded, and protons *trans* to the nitroso group are deshielded in *N*-nitrosodialkylamines. The resonance structure **3** accounts for these findings. *C*-Nitroso compounds exist as *cis* and *trans* dimers having distinguishable ^{1}H-NMR spectra.

Several papers dealing with the structure and barriers to hindered rotation in *N*-nitrosamines have appeared recently[34–38].



(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 NO_2 group on the ^{13}C chemical shifts of the aliphatic chain, relative to the parent alkane is as following:

$$O_2N\text{—}C(1)\text{—}C(2)$$
$$\delta = \quad 64.5 \quad 4.7 \text{ ppm}$$

The ^{13}C chemical shifts of the carbons of nitrosobenzene are[33]: $\delta_{(1)} = 148.3$, $\delta_{(2)} = 123.4$, $\delta_{(3)} = 129.5$ and $\delta_{(4)} = 134.7$ ppm.

N-Nitrosamines and *N*-nitrosoanilines have been studied by ^{13}C-NMR spectroscopy with respect to their structure, *cis–trans* isomerism and the effect of the N—NO group on ^{13}C chemical shifts[39,40]. 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 ^{13}C 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[40].

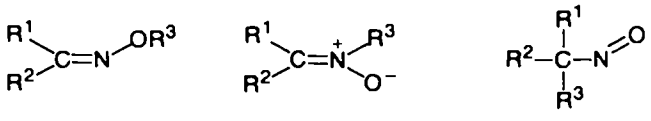
3. Nitrogen-14 NMR

The ^{14}N-NMR spectra of nitroalkanes, nitroaromatic compounds as well as various nitroso compounds have been extensively reviewed[12,41–43].

Nitromethane serves as a standard for ^{14}N-NMR chemical shifts. Generally the ^{14}N-NMR resonances of nitro compounds appear at higher fields with increasing electronegativity of the group R in $R\text{—}NO_2$. ^{14}N resonance signals of nitroaromatic compounds occur at higher fields than those of nitroalkanes. The ^{14}N chemical shift of nitrobenzene is 8 ppm (from CH_3NO_2)[41]. Studies of aromatic nitro compounds have indicated little effect on the chemical shifts due to the π-electron conjugation between the substituents[44].

A double bond exerts a general shielding effect on the ^{14}N 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[45]. High-field ^{14}N 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[45]. The ^{14}N chemical shifts of several nitroalkanes have been calculated according to the Pople MO theory and compared with experimental values[46].

The mutually isomeric structures of oximes (**4**), nitrones (**5**) and nitroso compounds (**6**) may be differentiated on the basis of their ^{14}N chemical shifts[47]: for



(**4**) (**5**) (**6**)

oximes 0 to 50 ppm, for nitrones 70 to 110 ppm and for nitroso compounds −400 to −550 ppm (referred to CH_3NO_2 or NO_3^- on the screening constant scale). The tautomeric equilibria present in oxime–nitroso systems may thus be easily observed by means of ^{14}N-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 π-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 σ and σ_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

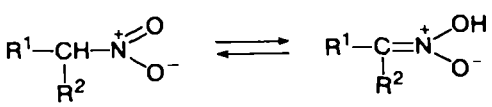
1. *Nitro compounds*

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 tritable as acid



(7)

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[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—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)[53]. The same method is also suitable for the microdetermination of aromatic

$$Ph{-}NO_2 + 6\,Fe^{+2} + 6\,H^+ \longrightarrow Ph{-}NH_2 + 6\,Fe^{+3} + 2\,H_2O \quad (10)$$

$$Ph{-}NO_2 + 6\,Fe(OH)_2 + 4\,H_2O \longrightarrow Ph{-}NH_2 + 6\,Fe(OH)_3 \quad (11)$$

$$Ph{-}NO + 4\,Fe^{+2} + 4\,H^+ \longrightarrow Ph{-}NH_2 + 4\,Fe^{+3} + H_2O \quad (12)$$

$$Ph{-}NO + 4\,Fe(OH)_2 + 3\,H_2O \longrightarrow Ph{-}NH_2 + 4\,Fe(OH)_3 \quad (13)$$

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}–SCN^- complex[53].

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[54]. 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 $Hg_2(NO_3)_2$.

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[55]. 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

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[56]. *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 $AgNO_3$ using a silver sulphide or silver cyanide selective electrode.

Nitro and nitroso compounds have been determined by reduction with a known excess of Ti^{+3} solution and thermometric titration of the excess with Fe^{+3} solution[57]. 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[58]. The method allows determination of nitrophenols, some dinitro- and trinitro-phenols and various halogenated nitrophenols.

A microdetermination of nitro compounds based on reduction with $TiCl_3$ in dimethylformamide solution and subsequent titration of the water formed in the reaction has been described[59]. The $TiCl_3$ is generated from $TiCl_4$ in dimethylformamide by electrolysis with an Hg cathode. The water is determined by Karl Fischer titration.

B. The Modified Kjeldahl Method[1,6,9,11]

Nitro and nitroso compounds can be determined by reduction and decomposition to ammonia, and determination of the latter by the Kjeldahl[52,60] method (equation 14). The method is completely nonselective and can be specific only when other nitrogenous species are absent.

$$RNO_2 \xrightarrow{[H]} RNH_2 \xrightarrow{H_2SO_4} (NH_4)_2SO_4 \xrightarrow{NaOH} NH_3 \qquad (14)$$

C. Gasometric Methods[1,6,9,11]

Nitro and nitroso functions attached to an amino liberate NO on treatment with Hg in H_2SO_4[6,9,11]. Aliphatic and aromatic nitro compounds can be decomposed to nitrite or nitrate which liberate NO on treatment with the same reagent[1]. 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[61]. 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 HNO_3–HCl. The N_2O 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[1,6,9,11]

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[62]. The nitroso aromatic derivatives were determined in the presence of their parent nitro analogues by titration with Ti^{+3}, which was generated coulometrically from Ti^{+4} in an aqueous EDTA solution. A subsequent coulometric titration with Cr^{+2} 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^{+3} has been described by Mitev and coworkers[63]. Both the nitro and the nitroso groups were found to react quantitatively with Ti^{+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[64], the polarographic determination of some aromatic nitro derivatives in corresponding amines[65] and the simultaneous polarographic determination of *N*-unsubstituted and *N*-substituted nitroazoles[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[67].

E. Spectroscopic Methods[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[1,9]. *m*-Dinitro aromatics can be determined colorimetrically via their reaction with diethylamine in dimethyl sulphoxide[1]. Aromatic nitro compounds can also be determined colorimetrically after their conversion to the corresponding amines[1].

2. Nitroso compounds

C-Nitroso compounds form coloured solutions in some organic solvents and can thus be measured directly[1]. One colorimetric method for determining these compounds is based on their conversion to the coloured azoxy derivative[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 μg amounts[68]. The sample was used to oxidize Fe^{+2} in alkaline solution to Fe^{+3}, and the latter was determined photometrically after reaction with KSCN.

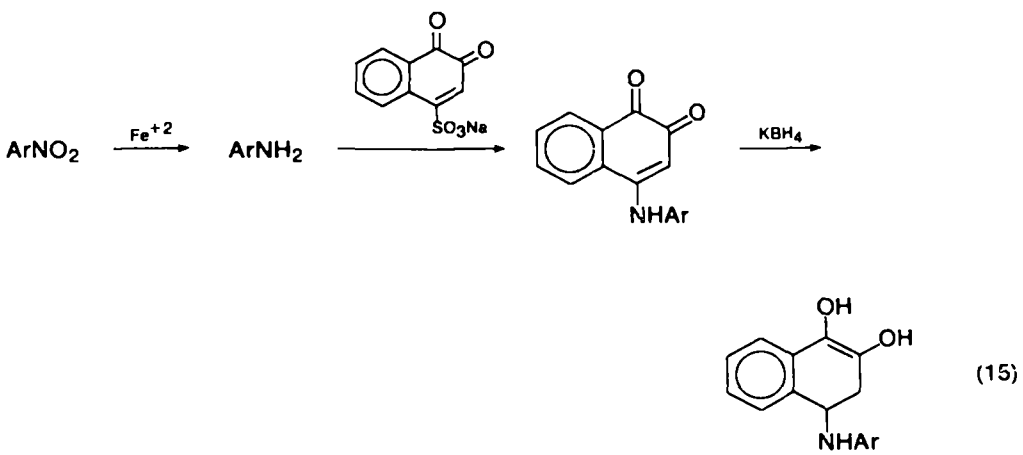
$LiAlH_4$ in tetrahydrofuran has been used to reduce aromatic nitro compounds to yield coloured azo compounds, which were determined spectrophotometrically[69]. The method enables analysis in μg quantities within 2.5%. $NaBH_4$ in ethanol has been used for a specific spectrophotometric determination of *meta* di- and tri-nitro aromatic compounds[70]. The coloured products of the reaction were measured at 520–530 nm. The method enables the determination of μg amounts within 2%.

Zinc in the presence of NH_4Cl has been used as the reducing agent to convert aromatic nitro compounds to arylhydroxylamines, which form violet complexes with Fe^{+3} and acetyl chloride[71]. 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 formamdine–sulphinic acid, and subsequent spectrophotometric determination of the Schiff bases formed was by condensation of the resulting amines with *p*-dimethylaminobenzaldehyde[72].

A separate spectrophotometric determination of the three isomeric nitrophenols[73] and simultaneous determination of nitropyrazoles[74] have been described.

An automatic colorimetric analysis of *N*-nitroso compounds, based on their cleavage by UV irradiation followed by determination of the released nitrite has been described[75]. The nitrite was determined using its diazotization reaction with sulphanilic acid. The coupling of the product with *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 fluorimetrically[76].



(15)

F. Gravimetric Determination[1,6,9,11]

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 literature[1,6,11].

G. Other Methods of Determination

Aromatic nitro compounds can be determined indirectly by reduction to the amine stage and subsequent determination of the latter[1]. Primary and secondary aliphatic nitroso compounds rearrange readily to the corresponding oximes and are most conveniently determined as such[1].

IV. DETECTION AND DETERMINATION BY CHROMATOGRAPHIC METHODS

Nitro and nitroso compounds rearrange and decompose relatively easily on heating or by contact with chromatographic supports[1]. 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*[77].

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[78] 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[79]. 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[80]. Fusion reaction GC including its application to nitro compounds has been reviewed by Whitlock and Siggia[81]. The effect of the dipole moment of nitroaromatic hydrocarbons on their retention in gas-liquid chromatography, has been the subject of a recent work[82].

B. Liquid Chromatography (LC)[83,84]

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 technqiue has been used for the separation and qualitative analysis of various nitroaromatics and other constituents of explosive formulations[85]. Toluene, *p*-nitrotoluene, 2,4-dinitrotoluene and 2,4,6-trinitrotoluene were separated on Corasil II within 15 minutes, using 60% hexane/40% CH_2Cl_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[86]. 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_2Cl_2/80% cyclohexane, by one group[87], and on Microbondapack C18 with a mobile phase of 67.5 methanol in water by another group[88].

β-Nitroso-α-naphthol and its isomer α-nitroso-β-naphthol have been separated by ligand exchange chromatography[89], 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.

C. Paper and Thin-layer Chromatography[90]

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[91,92] and given experimental verification. The moldel 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[93], alumina[94], Florisil and magnesium silicate[95,96], 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[97] 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[98] have developed a method for the detection and separation of sixteen nitropesticides. The compounds were separated on silica TLC plates, and then converted with $TiCl_3$ 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[99]. The method is generally applicable to aromatic nitro compounds. The determination is based on TLC separation, subsequent reduction of the nitro group with $SnCl_2$, 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[100] 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[101]. 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-naphthyl)ethylenediamine is superior to β-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[102], or with an acetone solution of tetraethylammonium hydroxide (10% aqueous solution), 1:1 by volume[103].

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[104].

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[105–110], 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[111–115]. The detection is based on the decomposition of the *N*-nitroso compound into a nitrosyl radical (·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 ·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[115,116] and with HPLC[117,118], 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[110].

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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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[331] and the Hoffmann elimination[186] 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)[31].

$$\begin{aligned} ROH + X^- &\rightleftharpoons RX + OH^- \\ ROR^1 + X^- &\rightleftharpoons RX + OR^{1-} \\ RNH_2 + X^- &\rightleftharpoons RX + NH_2^- \end{aligned} \qquad (1)$$

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].

$$ROH + R^1SO_2Cl \longrightarrow ROS(=O)R^1(=O) + HCl \qquad (2)$$

(**1**)

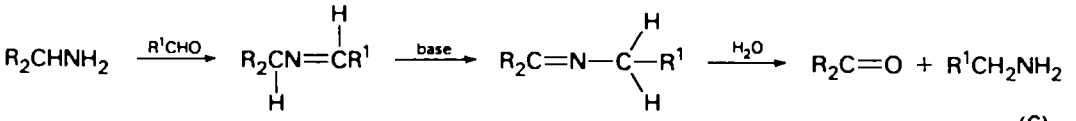
$$RNH_2 + 2\,R^1SO_2Cl \xrightarrow{(base)} R{-}N(SO_2R^1)_2 + 2\,HCl \qquad (3)$$

(**2**)

(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).

$$R_2CH{-}OH \xrightarrow{[O]} R_2C{=}O \underset{H^+}{\overset{R^1NH_2}{\rightleftharpoons}} R_2C{=}NR^1 \qquad (4)$$

$$R_2CH{-}NH_2 \xrightarrow{[O]} R_2C{=}NH \xrightarrow{H_2O} R_2C{=}O + NH_3 \qquad (5)$$



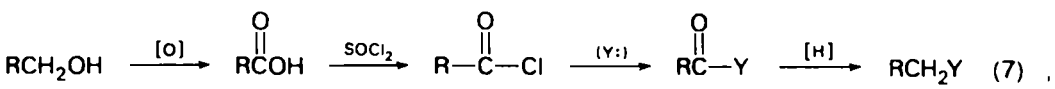
(6)

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).

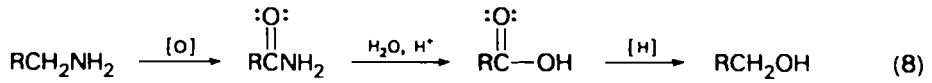
Another example of α-activation with respect to dehydroxylation of alcohols involves one of the oldest and most common synthetic procedures in organic chemistry – namely the conversion of a primary alcohol into some activated carboxylic acid derivative (equation 7). Thus, for example, alcohols may be



(7)

converted to a variety of amines by this procedure, without the complications of eliminations, rearrangements, etc.

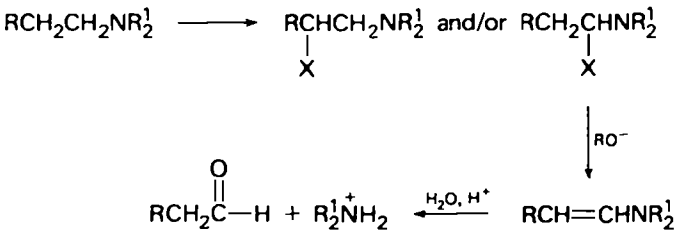
Similarly, oxidizing reagents which might convert amines to amides would lead to kinetic weakening of the carbon–nitrogen bond with analogous synthetic utility (equation 8). No reagents, however, are currently known which accomplish this



(8)

conversion in good yield, although oxidations of primary carbinamines 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).

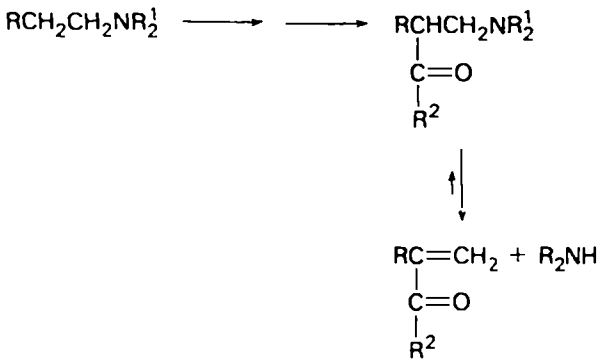
Yet another activation for deamination via the α-position would involve the conversion of a saturated amine to an enamine (equation 9), since the enamine is readily hydrolysed to the corresponding carbonyl compound. Such procedures are modifications of the procedures summarized in equation (6), and would appear to be a very promising approach for innovations in the field (see also Sections IV.F and IV.C).



(9)

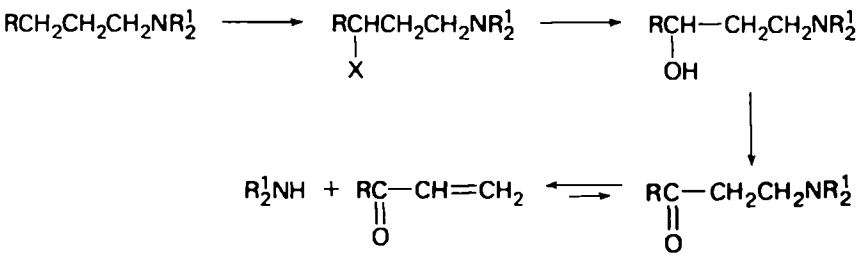
(b) Activation at the β-position: The reaction scheme described in equation (9) might also be considered as an example of initial activation at the β-position.

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).



(10)

(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.



(11)

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

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 carbinamines 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[394], emphasizing nitrogen gas leaving groups, in the earlier volume in this series and one by Wulfman[424], covering aspects of aromatic deaminations, in a recent volume in this series. Other reviews have discussed yet other aspects of gaseous nitrogen leaving groups[88,231,264,297,298,429]. 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[220]. 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 NH_2^- 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)[331] and trialkylamine[186] 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[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_as 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[31,32,34]. All these anions, with the exception of the last two, have since been

TABLE 1. pK_as of the conjugate acids of several observed or potential leaving groups in deamination

Leaving group	pK_a of the conjugate acid of leaving group	Reference
NH_2^-	>35	316
RNH^-	>35	316
$:NH_3$; RNH_2	~9–11	316
R_2NH; R_3N	~9–11	316
Aziridine	8.0	316
$R-\overset{\overset{O}{\|}}{C}-NR^-$	~16	316, 87
Acetamide	~−1	316
Amidine	~12	316
Urea	1.0	316
N-Phenylurea	−2.0	316
Succinimide anion	~10.5	421
Phthalimide anion	~7	421
Saccharin anion	~2	384
N-Phenylbenzenesulphonamide anion	8.65	104
p-Aminobenzenesulphonamide anion	10.6	207
N,N-Di(*p*-toluene)sulphonimide anion	1.70	104
N,N-Di(benzene)sulphonimide anion	1.45	104
N,N-Di(*p*-nitrobenzene)sulphonimide anion	0.30	104
N,N-Disulphonimides	$\ll 1$	–
Uracil anion	9.45	261
Barbituric acid anion	~4	421
Purine	2.6	316
Pyrimidine	1.3	316
Pyrrole	0.4	316
Pyridine	5.3	316
2-Chloropyridine	0.7	316
$ArNH_2$	~4	316
Diphenylamine	0.9	316
o-Nitroaniline	0.3	316
2,4-Dinitroaniline	−4.5	316
2,4,6-Trinitroaniline	−9.4	316

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[27,210,224]. Table 1 lists the pK_as 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.

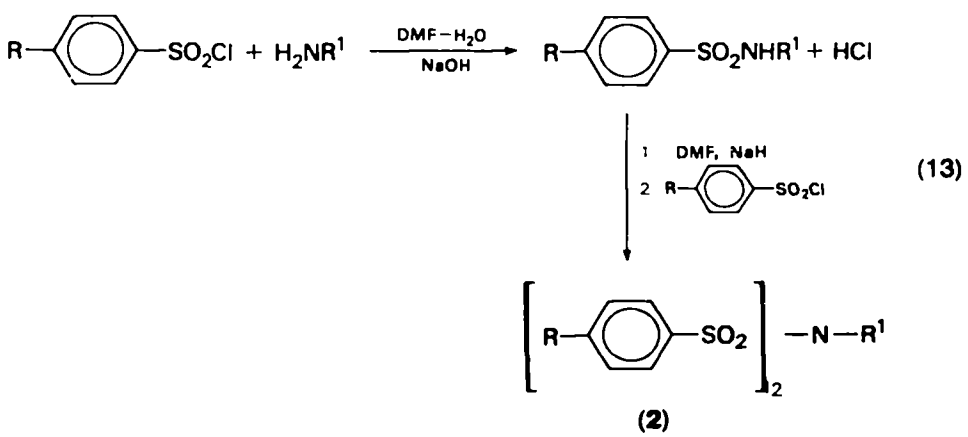
A. *N,N*-Diarylsulphonimide Anion (3) Leaving Groups

As predicted from the pK_as 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[109,110,112,113].

$$\underset{\textbf{(2)}}{R{-}N(SO_2R^1)_2} + Y^- \longrightarrow RY + \underset{\textbf{(3)}}{\bar{:}\ddot{N}(SO_2R^1)_2} \quad (+ \text{alkenes}) \qquad (12)$$

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



(13)

(2)

primary and secondary carbinamines[110,112,113]. More recently, Bartsch[29] 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 aryl-sulphonamides[110,113,199,200]. In an effort to obtain these difficult cases. Hutchins and his research group[200] introduced a variety of modifications, including one

originally devised by Pan and Fletcher[322] employing thallium salts, without any success. A few other procedures for disulphonimide synthesis have been reported[2,174,234,347b,370]. Finally a technique for synthesizing polymeric diarylsulphonimides has been described[295], as has one for *o*-benzenedisulphonimides[182,198].

Some chemical and physical properties of a large number of disulphonimides have been reported, including IR and PMR properties[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[100,101,110,113,156,199,200].

2. Scope of the reaction with respect to R, R^1 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[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[7,109,112–114,436]. Fair-to-good yields of 3,5-dinitrobenzoates have also been obtained[101,102]. Other substitutions have been observed with the homocysteine thiolate anion, azide, mercaptide, tosylate, triphenylphosphine and aniline[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 hydrolyses 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[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[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[111–113].

TABLE 2. Sample conditions and yields for selected deaminations with various disulphonimides

R	R^1	Y	Solvent	Temp., time	Products, yield	References
n-Hexyl	*p*-Nitrobenzene	KI	DMF	95–105°C, 2–4 h	1-Iodohexane, 85–90%	109, 112, 113, 439
n-Hexyl	*p*-Nitrobenzene	LiCl	DMF	100°C, 2 h	1-Chlorohexane, 93.5%	112, 113, 439
dl-2-Heptyl	*p*-Nitrobenzene	LiBr	DMF	25°C, 7 days	2-Bromoheptane, 73.7%	112, 113, 439
l-2-Octyl	*p*-Nitrobenzene	LiCl	DMF	43°C, 1 day	*l*-2-Octyl chloride 87%	112, 113, 439
Benzyl	*p*-Nitrobenzene	NaN_3	DMSO	70°C, 40 h	Benzyl azide, 56.5%	112, 113, 439
2-Phenylethyl	*p*-Nitrobenzene	LiCl	DMF	60°C, 1 day	2-Phenylethyl chloride, 46.3%	112, 113, 439
n-Hexyl	*p*-Toluene	Aniline	DMF	Reflux, 3 days	*n*-Hexylaniline, 75.5%	109, 112, 113, 439
Cyclohexyl	*p*-Toluene	Aniline	DMF	145°C, 72 h	*N*-Cyclohexylaniline, 34.6%	109, 112, 113, 439
Cyclohexyl	*m*-Nitrobenzene	LiCl	DMF	68°C, 7 days	Cyclohexyl chloride, ~7–12%	36
Cyclohexyl	*p*-Nitrobenzene	KI	DMF	90°C, 41 h	Cyclohexene, 90.3%	112, 113, 439
n-Hexyl	*p*-Toluene	KI + CH_3COO^-	HMPA	115°C, 1 day	*n*-Hexyl acetate, 100%	7
n-Hexyl	*p*-Toluene	NaSH	DMF	60°C, 17 h	1-Hexanethiol, 24.7%	112, 113, 439
Cyclohexyl	*p*-Nitrobenzene	Lithium 3,5-dinitrobenzoate	DMF	107°C, 24 h	Cyclohexyl 3,5-dinitrobenzoate, ~12%; cyclohexene, 60%	101, 102, 439
n-Dodecyl	*p*-Nitrobenzene	Lithium 3,5-dinitrobenzoate	DMF	140°C, 24 h	*n*-Dodecyl 3,5-dinitrobenzoate, 60%	101, 102, 439
n-Hexyl	*p*-Nitrobenzene	Lithium tosylate	DMF	Reflux, 1 h	*n*-Hexyl tosylate, 18.5%	101, 102, 439
n-Decyl	*p*-Toluene	$NaBH_4$	HMPA	175°C, 8 h	*n*-Decane, 91%	200

TABLE 2. *continued*

R	R^1	Y	Solvent	Temp., time	Products, yield	References
Cyclooctyl	*p*-Nitrobenzene	Neat	Pyrolysis	200°C, 30 min	*cis*-Cyclooctene, >91%	101, 103, 439
1,2-Diphenylethyl	*p*-Nitrobenzene	Neat	Pyrolysis	200°C, 25 min	*trans*-Stilbene, 99%	101, 103, 439
n-Dodecyl	*p*-Nitrobenzene	Lithium tosylate	DMF	Reflux, 18 h	*n*-Dodecyl formate, 57%; *n*-Dodecanol, 25%	101, 102, 439
n-Hexyl	*p*-Toluene	HI	H_2O–HI–DMF	125°C, 94 h	1-Hexanol, 60.3%; 1-hexyl formate	111, 113, 439
Benzyl	CF_3	CN^-	HMPA	R.t.	Benzyl cyanide, 80%	157
n-Hexyl	CF_3	$^-CH(CO_2Et)_2$	HMPA	R.t.	*n*-Hexyldiethyl malonate, 57%	157
Methyl	'Mixed' *p*-toluene and *p*-nitrobenzene	$^-CH(CO_2Et)_2$	HMPA	R.t.	Methyl diethyl-malonate, 60%	388
n-Hexyl	*p*-Toluene	PhS^-	DMF	150°C, 1.5 h	*n*-Hexyl phenyl sulphide, 68%	436
n-Hexyl	*p*-Toluene	$PhSe^-$	DMF	150°C, 1.5 h	*n*-Hexyl phenyl selenide, 96%	436
Benzyl	*p*-Toluene	Ph_3P, LiI	AcOH	Reflux, 24 h	$PhCH_2PPh_3$, 53%	436
n-Hexyl	CF_3	NaI	CH_3CN	25°C, 2 h	1-Iodohexane, 76%	112, 113, 439

$$\underset{\textbf{(2)}}{R\ddot{N}(SO_2Ar)_2} + HX \rightleftharpoons \underset{\textbf{(2a)}}{R-\overset{H}{\overset{|}{\overset{+}{N}}}(SO_2Ar)_2\ X^-} \qquad (14)$$

$$X^- + R-\overset{H}{\overset{|}{\overset{+}{N}}}(SO_2Ar)_2 \rightleftharpoons R-X + \underset{\textbf{(3a)}}{HN(SO_2Ar)_2}$$

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*-hexyl)-*N*,*N*-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 'Aal2' amide hydrolysis mechanism[111–113,204].

$$\underset{\textbf{(2)}}{R-N(SO_2Ar)_2} + HI \rightleftharpoons \underset{\textbf{(2a)}}{R-\overset{H}{\overset{|}{\overset{+}{N}}}(SO_2Ar)_2\ I^-}$$

$$I^- + \textbf{2a} \rightleftharpoons RI + \underset{\textbf{(3a)}}{H-N(SO_2Ar)_2} \qquad (15)$$

$$RI + H_2O \rightleftharpoons [ROH_2^+]\ I^- \overset{base}{\rightleftharpoons} ROH$$

$$ROH + \underset{\text{(from DMF hydrolysis)}}{HCOOH} \overset{H^+}{\rightleftharpoons} ROOCH + H_2O$$

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 alkylamine 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*-(cyclohexyl)-*N*,*N*-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*-*t*-butyldiarylsulphonimides (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][30,113].

Disulphonimides (**2**) derived from secondary carbinamines 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 carboxamides. This reaction is stereoselective. For example, *N*-cyclooctyl-*N*,*N*-di(*p*-nitrobenzene)sulphonimide gives over 91% *cis*-cyclooctene when pyrolysed at 175°C, and the corresponding 1,2-diphenylethyl derivative gives 99% *trans*-stilbene at 200°C. The analogous primary carbinamine derivatives do not give this reaction[101,103]. *N*-Cyclohexyl-*N*,*N*-di(*p*-nitrobenzene)sulphonimide gives cyclohexene in 70% yield when refluxed in pure DMF[111,113].

Small amounts of mostly Saytzeff alkenes are obtained with some nucleophiles[113]. Finally, alkenes are obtained in 22–88% yields as unwanted by-products during oxidations with DMSO–$NaHCO_3$ (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 configuration[112,113]. 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 inversion[12,278], and Townsend and Theis[388] 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 coworkers[30] 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 S_N 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 $-N(SO_2-)_2$ portion of the leaving group. The steric bulk of the $-N(SO_2-)_2$ group is also suggested by the difficulties encountered in all attempted preparations of disulphonimides derived from hindered alkylamines[110,113,200]. Nonetheless, the small amounts of alkene obtained with less bulky and less basic nucleophiles were the Saytzeff oriented alkenes[113].

B. *N*-Alkyl-*N*,*N*-di(trifluoromethane)sulphonimide 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 groups[112,113,156,157,180,181]. 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)

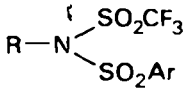
The triflimides **2b** may be prepared via the same procedure as other disulphonimides[110,113]. However, trifluoromethanesulphonyl chloride is handled with considerable difficulty and the trifluoromethanesulphonic anhydride is used instead (equation 16). In many cases yields are not as good as the yields obtained in the preparations of diarylsulphonimides (**2**)[69,110,112,113,156,157,163,180].

$$2\ RNH_2 + (CF_3SO_2)_2O \longrightarrow RNHSO_2CF_3 + R\overset{+}{N}H_3\bar{O}_3SCF_3 \qquad (16)$$

$$RNHSO_2CF_3 \xrightarrow[2.\ (CF_3SO_2)_2O]{1.\ NaH} RN(SO_2CF_3)_2 + CF_3SO_3^-\ Na^+$$

(2b)

While most diarylsulphonimides (2) are crystalline solids, most triflimides (**2b**) are liquids[110,113,156,180]. Finally, crystalline mixed aryl-'trifyl'-sulphonimides (**2c**) have been prepared[158,388].



(2c)

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(*p*-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[112,113]. 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 alkylations and nitrile formations. Thus, Glass and Swedo have alkylated malonic ester anions in poor-to-good yields using alkyl

$$RN(SO_2CF_3)_2 + NaCH(CO_2Et)_2 \xrightarrow{HMPA} RCH(CO_2Et)_2 + Na^+\ \bar{N}\ (SO_2CF_3)_2 \qquad (17)$$

11–51%

triflimides in HMPA (equation 17)[156,157]. Müller and Phuong have obtained somewhat better alkylation yields using lithium dimethyl cuprate and lithium diphenylcuprate (equation 18)[307,436]. Most recently, Townsend and Theis have alkylated potassium salts of various malonic esters with the mixed disulphonimides **2c** in 19

$$R{-}N(SO_2CF_3)_2 + R^1_2CuLi \longrightarrow R{-}R^1 + :\bar{\bar{N}}(SO_2CF_3)_2 \quad (18)$$

12–73%

to 60% yields[388]. Another type of carbon–carbon bond formation, nitrile formation, has been achieved by reacting these triflimides with cyanide in HMPA[156].

Other types of deamination utilizing triflimides have been reported. Thus, Hendrickson and his group[180] have obtained indirect evidence for the synthesis of the *t*-amine derivative, *N*-(*t*-butyl)-*N*,*N*-di(trifluoromethane)sulphonimide, by observing quantitative isobutylene formation during its attempted preparation at −78°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[113]. Hendrickson and coworkers have reported the only example of a successful substitution of disulphonimides with alkoxides[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[156,158] and Hendrickson and coworkers[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[178,179,192].

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*-hexyl)-*N*,*N*-di(benzene)-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 ρ 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[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[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[156,157] and the $NaBH_4$ reductions of Hutchins[199,200]. In fact in some cases the HMPA may itself act as a nucleophile to form intermediate salts (**4**) with the HMPA[156].

$$ROP^{+}(NMe_2)_3\ \bar{N}(SO_2CF_3)_2$$

(4)

Anselmi[10] and Glass[156] caution that other reported substitutions in HMPA may involve similar solvent participation. However, the work of Arigoni[12] and Townsend and Theis[388] 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[110]. Unlike tosylates and most other good leaving groups mast sulphonimides are not solvolysed by nucleophilic solvents, and they may even be recrystallized from them[110,113]. DMSO, however, may act as a nucleophile in oxidative deaminations (see Section IV.I)[100,101,138].

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 $-N(SO_2\overline{)}_2$ portion of the leaving group equals or surpasses the trimethylammonium ion in its steric requirements (see Section II.A.5)[30,200]. When less bulky and less basic nucleophiles initiate the eliminations, however, Saytzeff orientation predominates[113].

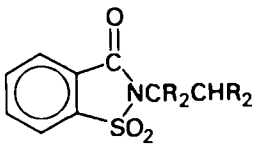
4. *Carbon–nitrogen vs. sulphur–nitrogen bond cleavage*

Under most conditions, strongly basic nucleophiles react with disulphonimides to give primarily sulphur–nitrogen bond cleavages[100,101,110,113,199]. Exceptions to this rule include the $NaBH_4$ reductions in HMPA[199,200], alkylations in HMPA[156,157], alkylations with organocuprates[307], nitrile formations in HMPA[156], sulphide and selenide formations in DMF[436] and one case of alkoxide formation[180].

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[436,437]. 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

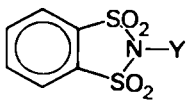
The first imide investigated as an activating group for the deamination of amines was saccharin. Unfortunately, nonbasic nucleophiles did not react at all with *N*-alkylsaccharins (5), while basic nucleophiles (i.e. hydroxide anion) react with



(5)

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 sp^2 system β to the nitrogen, as with *N*-2-phenylethylsaccharin), alkenes are formed upon heating with potassium hydroxide pellets[32,34,339,340].

Shortly after the very limited activating effect of saccharin was reported, the *o*-benzenedisulphonimide (**6**) activating group was observed to have an even weaker



(**6**)

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[182].

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[174].

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[34]. Similarly arylaminomethylsuccinimides have been shown to give alkyl carbon–nitrogen bond cleavage upon treatment with $NaBH_4$ in DMSO[209] (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[34]. Similarly, benzenesulphonamides derived from tertiary carbinamines and benzylic amines give S_Ni and E1-type products during acid-catalysed hydrolysis[59].

The trifluoromethanesulphonyl group is a more potent activator than arylsulphonyl groups towards deaminations. Thus, *N*-acyltrifluoromethanesulphonamides (**7**) have been observed to act as excellent acylating agents (equation 19)[181] Although this acylation process is not a true deamination due to the formation of **7**

$$ROH + R^1CON(Ph)SO_2CF_3 \longrightarrow ROCOR^1 + \bar{N}(Ph)SO_2CF_3 \qquad (19)$$

(**7**)

from acyl halides and triflamides[181], 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[31,394]. Thus

N-alkylamides have been pyrolysed with and without acid catalysts to give alkenes[89,116]. 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[35,143,144,411].

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)[160,276,277]. A related reaction involves the degradation of tertiary amines with phenyl chloroformate and related reagents. (equation 20b)[160,184,249,293].

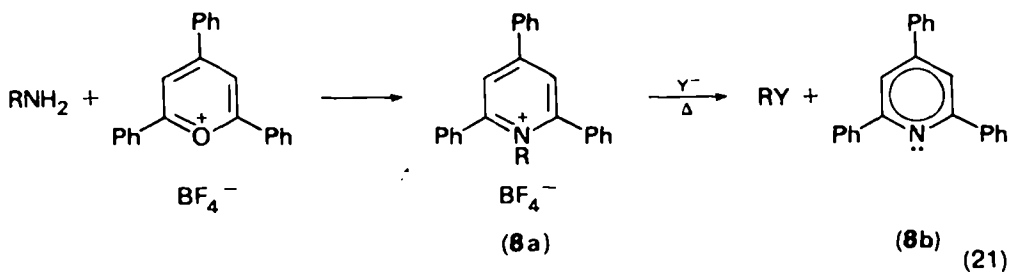
$$PhCH_2NMe_2 + (MeCO)_2O \longrightarrow PhCH_2O_2CMe + Me_2NCOMe \quad (20a)$$

$$R_3N + ClCOOPh \longrightarrow RCl + R_2NCOOPh \quad (20b)$$

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)[27,210–215,217,220–222,381,426,433]. Although Ziegler and Fries[426]



(21)

were the first to report an example of this reaction, Susan and Balaban[381] 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, sulphinate 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[220] (see also Sections III.C, III.F, and IV.K).

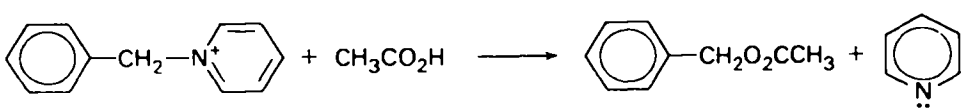
Katritzky and coworkers[220,433] have also mentioned some preliminary results which indicate that this method should be subtly selective in deaminating polyfunctional natural products which contain one or more amino groups under conditions which may be mild enough to be termed 'pseudophysiological conditions' (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

N-Substituent	Nucleophile	Product	Yield (%)	Reference
Methyl	Acetate	Methyl acetate	65	212
n-Butyl	Benzoate	*n*-Butyl benzoate	85	212
2-Butyl	I^-	2-Iodobutane	83	213, 220
Cyclohexyl	I^-	Cyclohexene	66	213, 220
		Cyclohexyl iodide	20	
Phenyl	I^-	Iodobenzene	75	213, 220
3-Hydroxypropyl	Br^-	3-Bromo-1-propanol	72	214
Benzyl	Cl^-	Benzyl chloride	50	214, 220
Benzyl	Piperidine	Benzylpiperidine	85	27
n-Heptyl	F^-	1-Fluoroheptane	82	216
n-Hexyl	NO_3^-	*n*-Hexyl nitrate	68	220
Benzyl	β-Napthoxide	Benzyl β-naphthyl ether	71	220
Methyl	SCN^-	Methyl thiocyanate	95	217, 220
Phenyl	SCN^-	Phenyl thiocyanate	98	220, 221
n-Butyl	Xanthate	*n*-Butyl xanthate	80	217, 220
n-Hexyl	Succinimide	*n*-Hexyl succinimide	65	220, 222
n-Butyl	Anion of 2-nitropropane	*C*-alkylated product	73	220
2-Phenylethyl	Base	Styrene		220

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



(**9**)

47%

(22)

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*

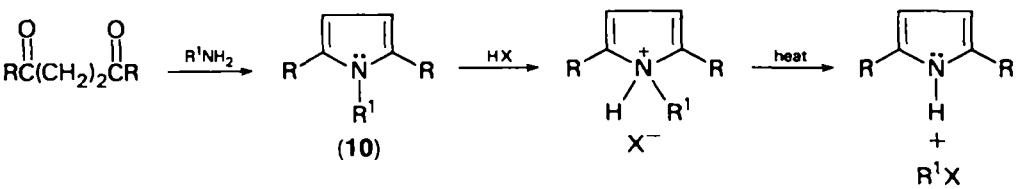
An important synthetic feature of this reaction is an apparently useful new procedure for converting arylamines into iodides and thiocyanates[213,221]. None of the other modern activating techniques such as the ones using disulphonimides have so far been shown to be useful for the deamination of arylamines.

4. Mechanistic considerations

Susan and Balaban[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[212] proposes a charge-transfer complex promoted $S_{RN}1$ mechanism. Some kinetic mechanistic data are discussed in the review by Katritzky[220].

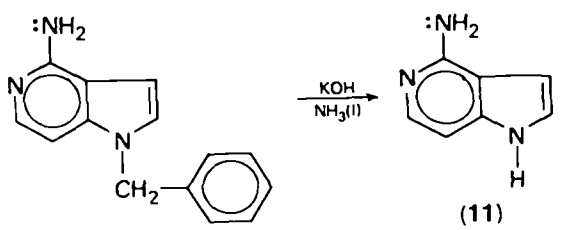
H. Pyrrole Derivatives as Potential Leaving Groups

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 α-position than the nitrogen for many pyrroles.



(23)

Nonetheless, there is an example of the related azaindole **(11)** acting as a leaving group (equation 24)[133]. In this reaction, the authors were only concerned with the azaindole leaving group, and, thus did not characterize the benzyl-derived product.



(24)

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[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 amines as leaving groups

The Hofmann *trans* (or *anti* or antarafacial) elimination is represented by equation (25a)[186,187]. This reaction and the competing substitution pathway have been reviewed previously and will not be discussed further[31,91,116,394]. A variety of related

$$R_2CHCR_2^1\overset{+}{N}Me_3\ OH^- \xrightarrow{heat} R_2C{=}CR_2^1 + H_2O + NMe_3 \qquad (25a)$$

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[31,165,272,394]. More recent examples involve the pyrolyses of quaternary ammonium halides to give alkyl halides (equation 25b)[235a,235b,254], and the pyrolyses of quaternary ammonium salts with acetate ions in aprotic solvents[419].

$$R_4N^+\ X^- \xrightarrow{heat} R_3N + RX \qquad (25b)$$

2. *Dialkylhydroxylamines* (13) *as leaving groups*

Wernick and Wolffenstein[393] 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)[90,91]. This *cis* (*syn*, suprafacial) elimination has also been reviewed and will not be discussed further[91,116,394].

$$\underset{\displaystyle O^-}{\overset{\displaystyle +}{R_2N}}CH_2CH_2R^1 \longrightarrow R_2NOH + CH_2{=}CHR^1 \qquad (26)$$

(**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 β to the leaving ammonia or amine group (see Section I). Thus, Mannich bases (**14**) may undergo elimination and/or substitution at the carbon–nitrogen bond under basic or acidic conditions (equations 27–29)[34,58,74,75,96,190,258,387,394]. Tramontini's discussion[387] 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

$$\underset{(\mathbf{14})}{RC(=O)CH_2CH_2NR_2^1} \xrightarrow[\text{or } H^+]{NaOH} RC(=O)CH{=}CH_2 + R_2^1NH \qquad (27)$$

$$\underset{(\mathbf{14})}{RC(=O)CH_2CH_2NR_2^1} + Y \xrightarrow[\text{source}]{H^+} RC(=O)CH_2CH_2Y + R_2^1NH \qquad (28)$$

$$\underset{(\mathbf{14})}{RC(=O)CH_2CH_2NR_2^1} + R_2^2NH \underset{}{\overset{HOH}{\rightleftharpoons}} RC(=O)CH_2CH_2NR_2^2 + R_2^1NH \qquad (29)$$

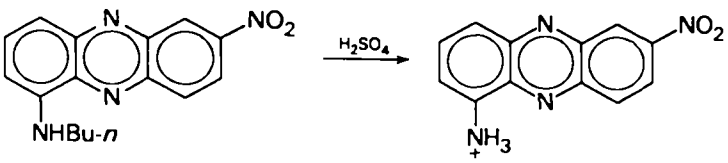
syntheses and degradations of a variety of alkaloids and other natural products[45,317,387,389].

Activated amines, such as *N*-benzylic tertiary amines, readily undergo reductive deaminations (see also Section III)[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.

$$ArNR_2 + HBr \longrightarrow RBr + ArNHR \qquad (30a)$$

$$ArNHR + HBr \longrightarrow RBr + ArNH_2 \qquad (30b)$$



(30c)

Even amines which are totally unactivated deaminate with the loss of ammonia when conditions are severe enough (equations 31–33)[139,241,269,270,385].

$$CH_3CH_2NH_2 + HBr \xrightarrow[\text{gas phase}]{500-540^\circ C} CH_2{=}CH_2 + NH_3 + HBr \qquad (31)$$

$$(CH_3)_3CNH_2 + HBr \xrightarrow[\text{gas phase}]{395-460^\circ C} CH_2{=}C(CH_3)_2 + NH_3 + HBr \qquad (32)$$

$$CH_3(CH_2)_3NH_2 + HBr \xrightarrow[\text{heat}]{Al_2O_3} CH_3CH_2CH{=}CH_2 + NH_3 \qquad (33)$$

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[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)[17,267,282] (see also Sections V.A.2 and V.B).

$$RCH_2CH(NH_2)COOH \xrightarrow{\text{enzyme}} RCH{=}CHCOOH + NH_3 \qquad (34)$$

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)[1,17]. While most amino acids pyrolytically decompose with CO_2 evolution, aspartate decomposes with loss of ammonia (equation 35). The kinetics of this

$$^-O_2CCH_2CH(\overset{+}{N}H_3)CO_2^- \rightleftharpoons {}^-O_2CCH{=}CHCO_2^- + NH_3 + H^+ \qquad (35)$$

reaction have been used to estimate the minimum concentration of ammonium ion on prebiotic earth[1,17].

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[31,88,147,194,228,231,264,294,297,298,341,364,379,394,427–429] 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*[324].

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

$$\mathrm{RNH_2} \xrightarrow[\mathrm{HX}]{\mathrm{NO_2^-}} \begin{pmatrix} \mathrm{NO} \\ | \\ \mathrm{R{-}NH} \end{pmatrix} \longrightarrow (\mathrm{R{-}N{=}NOH}) \longrightarrow \begin{matrix} \mathrm{RX + ROH} \\ + \ \mathrm{RNO_2 + H_2O} \\ + \ \text{mixed alkenes} \\ + \ \mathrm{N_2} \end{matrix} \qquad (36)$$

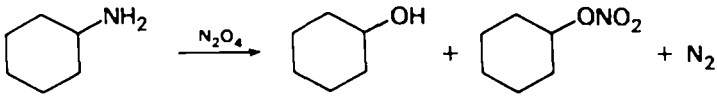
featured nitrosation in water. These almost always led to complex mixtures of products which usually included rearranged R groups as well as the promiscuous variety of functionalities. More recently nonaqueous protic and aprotic conditions have been utilized along with a variety of modifications employed in the generation of nitrosating agents[231,297,298,341,390,394]. 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[39,147–149] and Bakke[18–20]. More recently, Doyle and coworkers[129] 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)[129]. Similarly, the research groups of

$$\mathrm{TiCl_4 + 4\ RONO \longrightarrow Ti(OR)_4 + 4\ NOCl}$$

$$\mathrm{RNH_2} \xrightarrow[\mathrm{DMF}]{\mathrm{NOCl}} \mathrm{RCl + ROH + RO_2CH + N_2} \qquad (37)$$

Wudl[422,423], Barton[28] and White[404] have greatly advanced the utility of dinitrogen tetroxide as a synthetically useful nitrosating agent. For example, Barton and Narang[28] have converted cyclohexylamine to a cyclohexanol–cyclohexyl nitrate mixture in 81–89% yield, and 3β-aminocholestane to the corresponding alcohol–nitrate ester mixture in 87% yield, by treating the amines with dinitrogen tetroxide in the presence

of a tertiary amine of stronger base strength (amidine) than the reactant amine in ether at −78°C (equation 38).



(38)

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)[205]. Alkyl nitrites as nitrosating agents had earlier been reported by the groups of Cadogan, Friedman and Curtin[39,70,71,99,149,208].

$$RNH_2 + R^1COOH \xrightarrow{i\text{-AmONO}} R^1COOR + N_2 \qquad (39)$$

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[297,301,303,304], significant stereochemical control may be exereted, even though no claims are made for improved yields of products. For example, the stereochemistry of the 2-aminooctane 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[231,232] 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[231–233].

b. Decompositions of diazoalkanes (**15**). Since one of the many procedures for generating diazoalkanes (**15**) 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[394].

$$\underset{\textbf{(15)}}{R_2C{=}N_2} \overset{H^+}{\rightleftharpoons} \underset{\textbf{(15a)}}{[R_2CHN_2^+]} \xrightarrow{X^-} \text{various substitution and elimination products} + N_2 \qquad (40)$$

Diazoalkanes, and their possible participation in the various mechanisms involving nitrogen leaving groups, have been much discussed, and, thus, will not be considered further here[18–20,76,88,118,136,147,231,294,297,324,380,394,428]. 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*[171]. Also, a section of Wulfman's chapter in the same volume deals with alkyldiazonium ions[424].

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°

$$RNH_2 \xrightarrow{R^1COCl} RNHCR^1 \xrightarrow{\text{nitrosation}} \underset{\textbf{(16)}}{R{-}N(NO){-}CR^1} \quad (41)$$

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

$$\underset{\textbf{(16)}}{R{-}N(NO){-}CR^1} \begin{cases} \xrightarrow{(a)} ROOCR^1 + N_2 \\ \xrightarrow{(b)} \text{alkenes} + R^1COOH + N_2 \end{cases} \quad (42)$$

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[195,196] and White and coworkers[394,395,397–401]. The many fascinating mechanistic subtleties have been mainly elucidated by White and his research group[248,394,396,399,400,402,403,407–410].

Nitrosocarbamates, nitrososulphonamides, nitrosohydrazones, nitrosohydroxylamines and the corresponding *N*-nitro derivatives behave in an analogous fashion[264,297,394,396,416] (see also Section II.M).

The very highly mutagenic and carcimogenic properties of nitrosoamides and related compounds will be briefly discussed in Section V.C.

Nitrosoamide deaminations have been extensively reviewed[31,264,297,394].

The photochemistry of nitrosoamides and other properties of nitrosoamides have also been discussed[79].

d. Decompositions of triazenes (**17**). Triazenes (**17**) are easily prepared in one step (equation 43). They readily deaminate under acidic conditions (equation 44).

$$RNH_2 + ArN_2^+ \longrightarrow \underset{\textbf{(17)}}{RNHN{=}NAr} \quad (43)$$

$$\underset{\textbf{(17)}}{RNHN{=}NAr} + HX \longrightarrow RX + \text{alkenes} + ArNH_2 + N_2 \quad (44)$$

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[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 beonds with the production of nitrogen as leaving group, involves the treatment of alkane diazotates (**18**) with acids (equation 45)[298,300].

Alkane diazotates are formed by treating *N*-nitrosocarbamates (**19a**) with strong base (equation 46).[167,298,300,306]

$$RN{=}NO^- \xrightarrow{H^+}$$

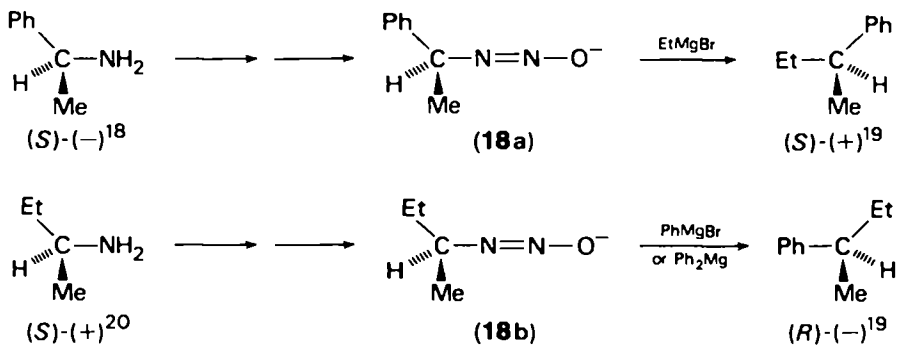
(18)

$$[R{-}N{=}N{-}OH] \longrightarrow \begin{matrix}\text{substitution and}\\ \text{elimination products}\end{matrix} + RN_2 + N_2 + H_2O \qquad (45)$$

$$\underset{\textbf{(19a)}}{R{-}\overset{\displaystyle NO}{\overset{|}{N}}COOR^1} \xrightarrow{R^2O^-\ K^+} \underset{\textbf{(18)}}{R{-}N{=}N{-}O^-\ K^+} \qquad (46)$$

Alkane diazotates (**18**) are the conjugate bases of the unstable R—N=N—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 R group is primary[298].

Another interesting aspect of alkane diazotates is that they apparently give extensive amounts of S_N2 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[298,299]. Complete inversion is not observed, due to the competing internal return process. Perhaps the synthetically most promising of these S_N2 displacements is the reaction of 1-phenylethyldiazotate (**18a**) with Grignard reagents to give the corresponding 2-phenylbutane with 70% inversion (equation 47)[298,299]. The overall yield, however, of 2-phenylbutane is only 25%[299].



(47)

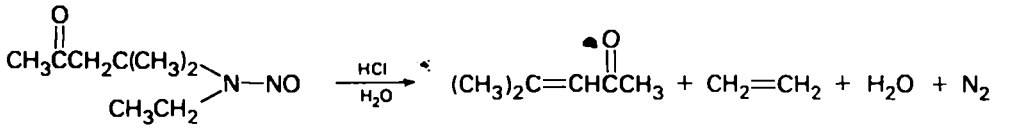
White and coworkers have generated diazotate intermediates, from nitrosoamide precursors, in their studies on enzyme active-site inhibition and labelling. The diazotates generate carbonium ions which alkylate the enzyme (see Section V.B.2)[415].

Most of the work on diazotates has been reported by Moss and his group. Moss has also extensively reviewed the subject[297,298].

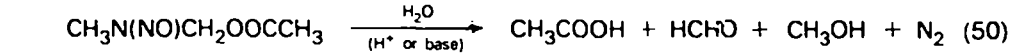
f. Nitrosations of secondary amines. When secondary amines are nitrosated under a variety of conditions, *N,N*-dialkyl-*N*-nitrosamines (**19b**) are produced (equation 48)[9,146,390].

$$\underset{}{R_2NH} \xrightarrow{\text{nitrosation}} \underset{\textbf{(19b)}}{R_2NNO} \qquad (48)$$

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)[146,344]. Nitrosamine **19d** is believed to be similar to oxidized nitrosamine metabolites[229,268,287,344,417].



(**19c**) (49)



(**19d**) (50)

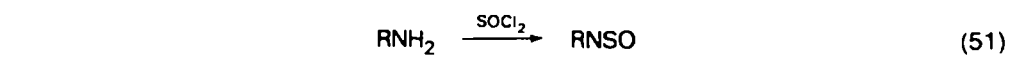
Stereochemical effects on *N*-nitrosamine chemistry have also been surveyed[268].

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[146], and most recently in an ACS symposium report[9].

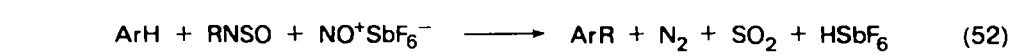
Finally, certain aspects of nitrosamine chemistry are discussed in the chapter by Challis in this volume.

g. Alkylsulphinylamines (**20**). Alkylsulphinylamines (**20**) may be prepared from primary amines and $SOCl_2$ (equation 51)[319].



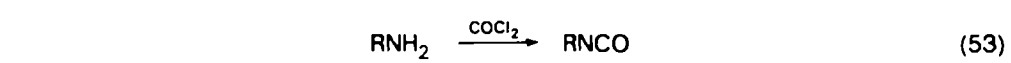
(**20**) (51)

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)[319].



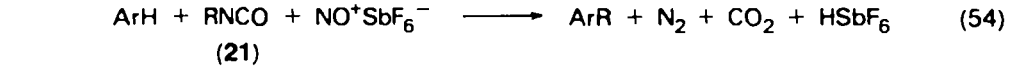
(**20**) (52)

h. Alkyl isocyanates (**21**). Alkyl isocyanates (**21**) may be formed from primary amines by treatment with $COCl_2$ (equation 53)[319].



(**21**) (53)

Isocyanates (**21**) behave similarly to sulphinylamines (**20**) when treated with certain nitrosating reagents (equation 54)[319].



(**21**) (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).

$$ArNH_2 \xrightarrow{HNO_2} ArN_2^+ \xrightarrow[X\cdot]{X^- \text{ or}} ArX + N_2 \qquad (55)$$

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[44]. The fascinating story of the mechanisms of aromatic dediazoniation is worth whole review articles, and such articles have been excellently written by Zollinger[427,429]. 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[424].

a. 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, N_3, Br, Cl, I, F (via BF_4^-), CN, NO_2, 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[427,429].

Factors affecting yields in Sandmeyer reactions have been discussed[123].

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[41,95,338,343,382]. Furthermore, the process of diazotization has also been reviewed[76,352].

b. One-pot aromatic deaminations. Most aromatic deaminations involve two separate synthetic steps. Recently, however, one-step procedures utilizing alkyl nitrites and copper (II) halides have been reported (equation 56)[123]. 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[53,313].

$$2\,ArNH_2 + 2\,RONO + CuX_2 \longrightarrow 2\,ArX + 2\,ROH + CuO + H_2O + N_2 \qquad (56)$$

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]

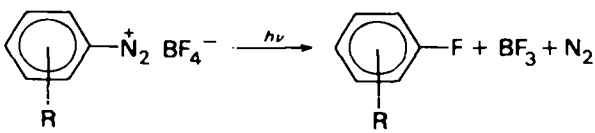
$$\left.\begin{array}{l} t\text{-BuSNO} \\ \text{or} \\ t\text{-BuSNO}_2 \end{array}\right\} + ArNH_2 + CuX_2 \xrightarrow[0-25°C]{CH_3CN} ArX + N_2 + (t\text{-Bu})_2S_3 + (t\text{-Bu})_2S_2 \qquad (57)$$

A one-pot Meerwein arylation of alkenes using alkyl nitrites and copper (II) halides has similarly been developed (equation 58)[124].

$$ArNH_2 + H_2C{=}CHY \xrightarrow[CuCl_2]{RONO} ArCH_2\underset{Cl}{\underset{|}{C}}HY + N_2 \qquad (58)$$

Analogous displacements of the aryl amino group with hydrogen have been reported and will be briefly discussed under 'reductive deaminations' (Section III)[71,125,220,223].

c. Photochemcical dediazoniation and the photorearrangements of diazoketones. The photochemistry of diazonium ions has been reviewed by Ando[8], and by Dinaburg[119]. Two representative examples of photodediazoniation are given in equations (59a) and (59b)[8,24,253,335,363,425]. When the anions in these photochemical deaminations are derived from Lewis acids, as in equation (59a), the Lewis acid

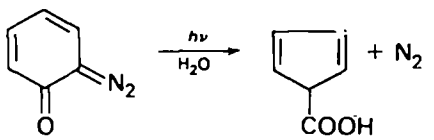


(59a)

$$ArN_2^+ \xrightarrow[h\nu]{C_2H_5OH} ArH + ArCH_2CH_2OH + ArOCH_3 + Ar\underset{CH_3}{\underset{|}{C}}HOH + N_2 \qquad (59b)$$

is released as a by-product. This method of generating Lewis acids *in situ* has found much application in industrial polymer chemistry (see Section II.K.2.e)[24,335].

Aryl-1,2-diazooxides ('*o*-quinone diazides') (**22**), give Arndt–Eistert-type ring-contractions on photolysis (equation 60)[363]. This reaction has also been found to be useful to industrial chemists (see Section II.K.2.e).

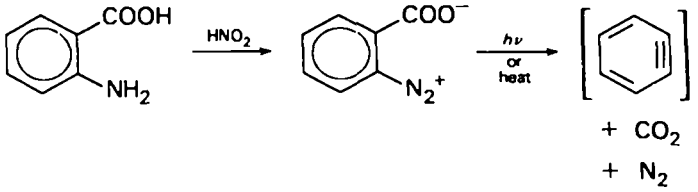


(60)

(**22**)

d. 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)[148,161,266,374,375,424].

e. 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



(61)

processes[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[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[335].

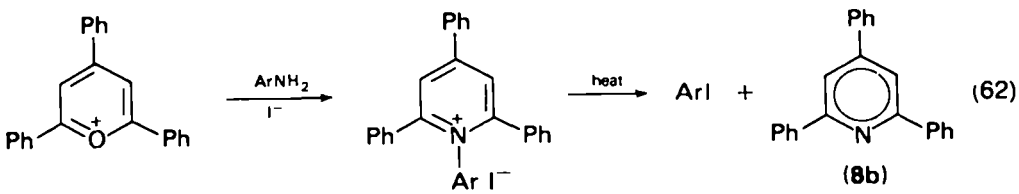
L. Miscellaneous Leaving Groups in Aromatic Deaminations

1. *Photochemical deaminations of aromatic amines*

Whereas photochemical dealkylation of amines is commonly observed, photochemical dearylation of arylamines is a rarely observed process[355,365]. An example of the latter involves the photodegradation of certain quarternary amine salts with easily oxidizable counterions such as iodide[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)[213,221]. A variant on **8b** has recently been found to give better yields[221].

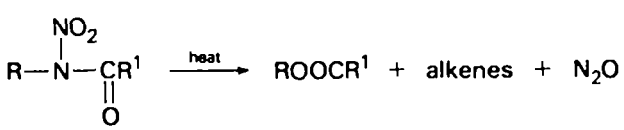


(62)

M. Dinitrogen Oxide (N_2O) 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 N_2O being expelled instead of nitrogen (equation 63)[411,416] (see also Section II.K.1.c).

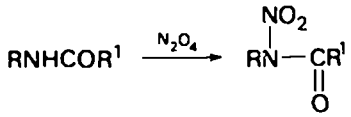


(**23**) (63)

White and Field[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 carbonium 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].

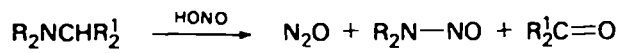


(64)

(**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).

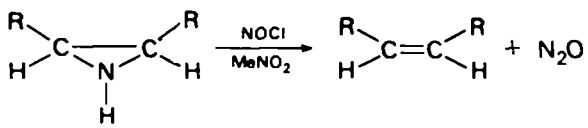


(65)

(**19**)

3. *The reaction of aziridines* (**24**) *with certain nitrosating agents*

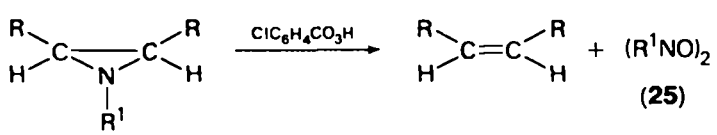
Aziridines (**24**) react with nitrosating agents such as nitrosyl chloride or methyl nitrite to give alkenes and N_2O (equation 66). The reactions are completely stereospecific with retention of configuration[68,80,130,345,347a,394].



(66)

(**24**)

A related reaction involves treating certain aziridines (**24a**) with *m*-chloroperbenzoic acid. Alkenes with retention of stereochemistry are again produced, but the leaving group in this case is the nitroso dimer (**25**) instead of N_2O (equation 67a)[173,321].



(67a)

(**24a**) (**25**)

N. Nitrile Leaving Group

The von Braun degradation which involves the heating of secondary or tertiary amides with PCl_5 or PBr_5, expels nitrile leaving groups (equations 67b and 67c)[31,50,54,55,327,391,394].

$$ArCONR_2 \xrightarrow[\Delta]{PX_5} RX + ArCX{=}NR \xrightarrow{\Delta} ArCN + RX \qquad (67b)$$

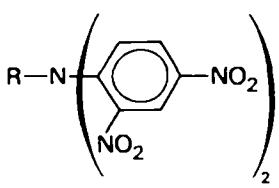
$$ArCONHR \xrightarrow{PCl_5} \underset{\displaystyle Cl}{ArC{=}NR} \xrightarrow{\Delta} ArCN + RCl \qquad (67c)$$

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 heterocyclics such as pyrrole and the barbiturates might be good leaving groups. Other candidates may be suggested by perusing pK_a 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 N_2O are well known and have already been discussed.

$$\underset{\textbf{(23)}}{RC(=O)-N(NO_2)-R} + Y^- \longrightarrow \underset{\textbf{(26)}}{[R-C(=O)-\ddot{N}-NO_2]^-} + RY \qquad (68)$$

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 *N*,*N*-di(2,4-nitrophenyl)alkylamines (**27**) with a variety of nucleophiles gave no evidence for carbon–nitrogen bond cleavage[113,114].



(27)

P. *N*-Containing Leaving Groups Compared with Other Leaving Groups

It has already been mentioned that aryl disulphonimides (**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[31,154,394].

As in the previous section, reductive deaminations are organized according to leaving group.

A. Sulphonimide Anion (3) Leaving Groups

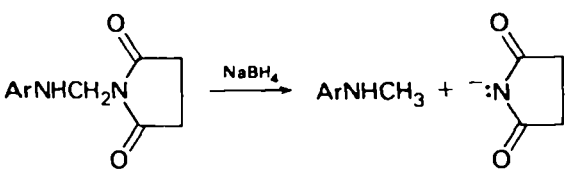
Hutchins and coworkers have recently reported that hydride (from BH_4^-) may displace diarylsulphonimide anions and triflimides (3) (equation 69)[199,200]. Yields in

$$\underset{\textbf{(2)}}{RN(SO_2R^1)_2} \xrightarrow[HMPA]{BH_4^-} RH + \underset{\textbf{(3)}}{^-N(SO_2R^1)_2} \qquad (69)$$

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[156,200].

B. Succinimide Leaving Group (28b)

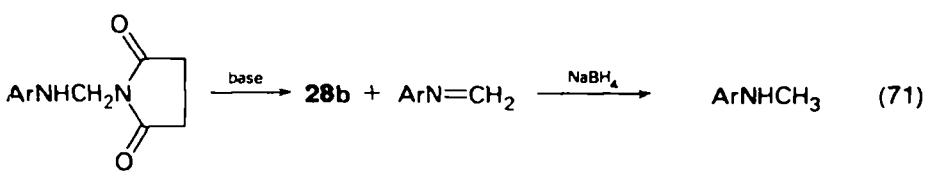
In the course of developing a new monomethylation procedure for aromatic amines, Kadin[209] has found that certain succinimides derived from Mannich bases (28a) may be reductively deaminated with $NaBH_4$ (equation 70). Functionalities



(70)

(28a) (28b)

such as ester, nitrile, or amide do not interfere with the reaction. Circumstantial evidence suggests the mechanism shown in equation (71) for this reduction[209].

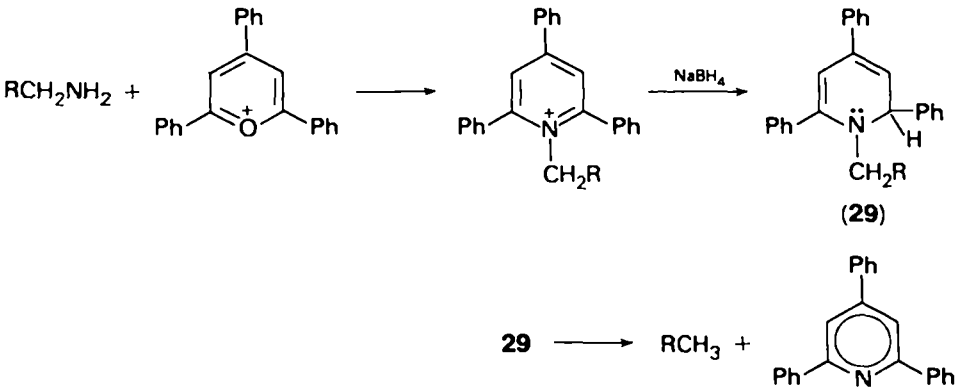


(71)

(28a)

C. Pyridine-derived Leaving Groups (8b)

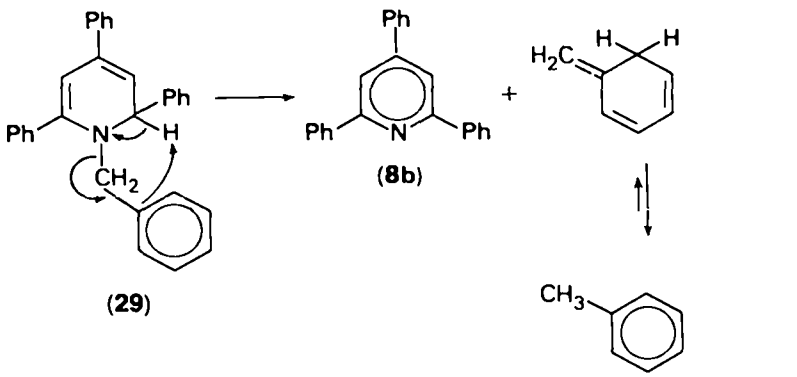
Katritzky and coworkers have reported a novel procedure for reducing benzyl-, allyl- and heteroarylmethyl-amines via substituted dihydropyridines (29) (equation



(72)

72). Yields are generally very good[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[52,215].

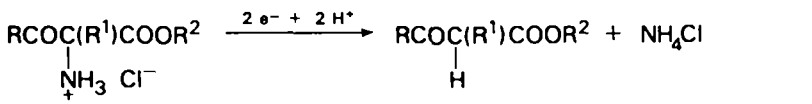


(73)

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[31,154,273,387,394]. Furthermore, certain enamines have been reduced via AlH_3 or diborane to the corresponding alkene[94,262,292].

Electrolytic reductions are also known and have been briefly reviewed[394]. A more recent example involves the electrolytic reduction of α-acylamino acid esters to the corresponding β-keto esters in good yields (equation 74)[280].



(74)

Hutchins and group have developed a synthesis of tertiary amines derived from aniline (**30**), using $NaBH_4$ as the reducing agent. Yields are good (71–79%) (equation 75)[200].

$$\mathrm{PhNHR} \xrightarrow[(CH_3)_2SO,\ 2,6\text{-lutidine}]{CH_3I} \mathrm{PhN^{+}(CH_3)_2\ I^{-}} \quad (\mathbf{30}) \xrightarrow{NaBH_4} \mathrm{PhNCH_3} \quad (+\ CH_4) \qquad (75)$$

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].

$$\mathrm{RNH_2 + HNF_2} \longrightarrow \underset{(\mathbf{31})}{[\mathrm{R{-}N{=}NH}]} \longrightarrow \mathrm{RH + N_2} \qquad (76)$$

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)[98,314,315,394]. Similar reductions are observed when alkylhydrazines are oxidized to alkyldiimides[98].

$$\mathrm{RNH_2} \xrightarrow{ArSO_2Cl} \mathrm{RNHSO_2Ar} \xrightarrow[NH_2X]{OH^-,} \mathrm{RH + ArSO_3H + N_2} \qquad (77)$$

$$\mathrm{X = OSO_3H\ or\ Cl}$$

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)[122]. This procedure is also believed to proceed via a diimide intermediate.

$$\mathrm{RNH_2} \xrightarrow[OH^-,\ 0°C]{NH_2OSO_3H} \mathrm{RH + SO_4^{=} + N_2} \qquad (78)$$

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 acic[122].

Trace amounts of cupric ion give a reaction which appears to be a disproportionation (equation 79).

$$\mathrm{PhCH_2NH_2} \xrightarrow[OH^-,\ Cu^{+2}]{NH_2OSO_3H} \mathrm{PhCHO + PhCH{=}NCH_2Ph + PhCH_2CH_2Ph} \qquad (79)$$

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.

$$\mathrm{RCOCHN_2 + 2\ HI} \longrightarrow \mathrm{RCOCH_3 + N_2 + I_2} \qquad (80)$$

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].

$$ArNH_2 \xrightarrow[2\ H_3PO_2]{1\ HNO_2} ArH + N_2 \qquad (81a)$$

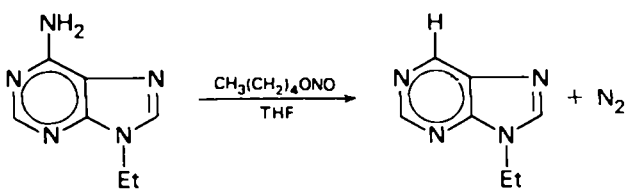
In newer one-pot procedures, the arylamines are treated with alkyl nitrites in solvents such as ethers or DMF[71,125]. In the modification by Doyle and coworkers[125], yields are generally good (equation 81b).

$$ArNH_2 + RONO \longrightarrow ArH + ROH + N_2 + H_2O \qquad (81b)$$

Doyle and coworkers[125] have obtained evidence for a free-radical mechanism for this reaction (equation 82).

$$\begin{aligned} &ArNH_2 + RONO \longrightarrow ArN{=}NOR + H_2O \\ &ArN{=}NOR \longrightarrow ArN_2^{\cdot} + RO\cdot \\ &ArN_2^{\cdot} \longrightarrow Ar\cdot + N_2 \\ &Solvent + Ar\cdot \longrightarrow ArH + Solvent\cdot \end{aligned} \qquad (82)$$

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].



(83a)

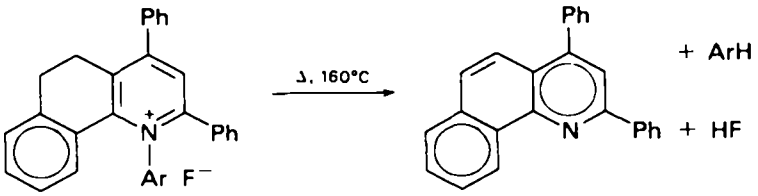
This procedure has been used to synthesize the antibiotic, nebularine and other nucleosides[308a]. Nair and Richardson have also found that Cl, Br and I may replace nitrogen using this procedure[308b].

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



(83b)

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[63,275]. 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[31,76,78,84,108,368,394].

Since a recent comprehensive review by Chow and coauthors[78] on amine oxidations which proceed via nonaromatic aminium 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.

$$RCH_2NH_2 \xrightarrow{-2\,H\cdot} RHC{=}NH \xrightarrow{H_2O} RHC{=}O + NH_3 \qquad (84)$$

$$R_2CHNHR^1 \xrightarrow{-2\,H\cdot} R_2C{=}NR^1 \xrightarrow{H_2O} R_2C{=}O + R^1NH_2 \qquad (85)$$

$$RCH_2NH_2 \xrightarrow{-4\,H\cdot} RC{\equiv}N \xrightarrow{H_2O} RCOOH + NH_3 \qquad (86)$$

A representative list of inorganic oxidizing reagents used in these types of dehydrogenation includes: Ag(II)[14,16], Ag_2CO_3[141], $KMnO_4$[334,353,354], MnO_2[333], NiO_2[21], $Pb(OAc)_4$[359], chromic oxide[31], copper chromite–nickel–K_3PO_4[289], mercuric oxide[175], $Hg(OAc)_2$[259], potassium peroxydisulphate[191], IF_5[371], other peroxides[108,185], $NaNH_2$–NH_3[169], Ni, Pt, Cr[108], Pd[22,31], S[342], Se[73], ruthenium and other transition metals[117], chromic acid[38,153], $FeCl_3$[38], silver oxide[153], $S_2O_8^{-2}/Ag^{+1}$[15]. Not all these reagents work in all cases, and in those cases where they do work, yields are often

poor[31,108]. Of the above, the Ag(II) 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 amminium radical intermediates[78]) (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[134], various derivatives of formic acid[281], derivatives of diaminomethane[281], *o'*-bromoanisole[42,108,296], *t*-butyl peroxide[202], quinones[177], nitrosobenzene[383], and photochemically with benzophenone (see next topic)[81–84,106]. 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[11,394].

$$ArCH_2NH_2 + [CH_2{=}NH] \longrightarrow ArCH{=}NH + CH_3NH_2 \qquad (87)$$

A procedure has also been developed for oxidizing enamines to α-acetoxyketones with thallium triacetate[243,292].

A number of oxidizing agents may oxidize primary amines and/or hydroxylamines to oximes[31,108].

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[31,356]. Some of these reactions proceed via transamination mechanisms which will be discussed later (Section IV.F).

$$R{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}COOH \xrightarrow{[O]} RCH{=}NH + CO_2 \xrightarrow{H_2O} RCH{=}O + NH_3 \qquad (88)$$

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

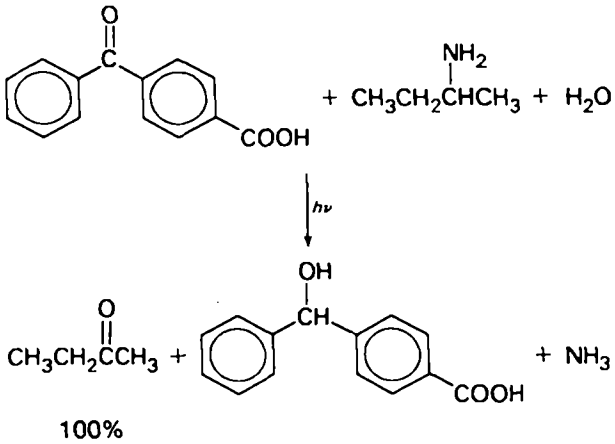
A reaction well known to photochemists, but surprisingly neglected by synthetic chemists, involves the photodehydrogenation of amines by benzophenone and related compounds (equation 89)[81,82,84]. By this technique, both aldehydes and ketones may be obtained simply and in good yield.

$$2\,RR^1CHNH_2 + Ph_2C{=}O \xrightarrow{h\nu} Ph_2C(OH)C(OH)Ph_2 + RR^1C{=}NCHRR^1$$

$$RR^1C{=}NCHRR^1 \xrightarrow{H_2O} RCR^1 + RR^1CHNH_2 \qquad (89)$$
$$\qquad\qquad\qquad\qquad\qquad\quad \|$$
$$\qquad\qquad\qquad\qquad\qquad\quad O$$

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)[83,84,85,106].

The products and mechanisms of these reactions are different in aqueous media from those observed under anhydrous conditions. Many interesting aspects as well



(90)

as the mechanisms of these and related reactions have been investigated by Cohen and coworkers and reviewed by Cohen, Parola and Parsons[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 α-amino acids, as Cohen and Ojanpera[86] have reported that methionine can be oxidatively deaminated to the corresponding aldehyde (equation 91).

$$CH_3SCH_2CH_2CH(NH_2)CO_2^- \xrightarrow[\text{4-carboxybenzophenone}]{h\nu,\ H_2O} CH_3SCH_2CH_2CHO + CO_2 + NH_3 \quad (91)$$

Other varieties of photochemical amine oxidations involving amminium ion radical intermediates from *N*-haloamines have been reviewed[78].

Yet another interesting photooxidation is apparently more limited in scope. Hyatt[203] has reported that salts of certain amines are converted to aldehydes or ketones by a Norrish type II photolysis (equation 92).

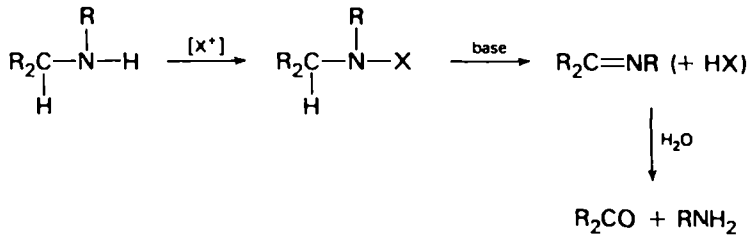
$$R_2CHNH_2CH_2COPh \xrightarrow{h\nu} R_2C{=}O + PhCOCH_3 \quad (92)$$

The photochemistry of nitrosoamides is rather complex; among the many products isolated have been aldehydes, amides and *N*-arylimines[79].

Nonoxidative photochemical dealkylations are also known[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).



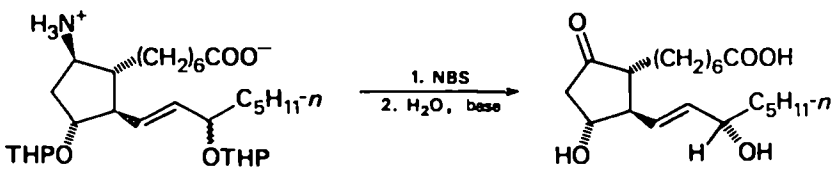
(93)

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[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_2[115], *N*-bromosuccinimide[135,177], *t*-butyl hypochlorite[13,60,170,260], hypochlorous acid[43] and NaOCl with phase-transfer catalysts[251].

Deaminations via *N*-haloamines are sometimes called the 'Ruschig reaction'[346b]. Labler and Sorm[244], and Bachmann, Cava and Dreiding[13] have successfully applied this reaction to a variety of systems.

Corey and coworkers[92] have used this type of oxidative deamination as a key step in their syntheses of prostaglandins of the E_1 and F_1 series (equation 94). The overall yield of ketone in this process is 25%.



(94)

Amino acids give a Strecker-type oxidative decarboxylation with hypohalites[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)[329].

$$(CF_3)_2NH \xrightarrow[\Delta]{KF} CF_3N{=}CF_2 \quad (+ HF) \qquad (95)$$

2. *Sulphonic acids as leaving groups – oxidations with sulphonyl peroxides* (32)

Sulphonyl peroxides (**32**) oxidize primary and secondary amines to the corresponding aldehydes and ketones in 37–96% yield (equation 96). This reaction

$$RCH_2NHR^1 + (p\text{-}NO_2C_6H_4SO_3)_2 \longrightarrow RCH{=}NR^1 + 2\ p\text{-}NO_2C_6H_4SO_3H \qquad (96)$$

(**32**)

R^1 = H or alkyl

was reported by Hoffman[185] who proposed the mechanistic sequence shown in equation (97).

$$R^1CH_2NHR + (ArSO_3)_2 \longrightarrow R^1CH_2\overset{+}{N}(OSO_2Ar)HR + ArSO_3^-$$

(32)

$$\longrightarrow R^1CH_2NR + ArSO_3H \qquad (97)$$

$$R^1CH_2NR \longrightarrow R^1CH{=}NR + ArSO_3H$$

$Ar = p\text{-}O_2NC_6H_4^-$

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^1 is hydrogen[312,325,326,366].

$$RCH_2NSO_2Ar \xrightarrow{base} RCH{=}NR^1 + ArSO_3^- \qquad (98)$$

(**33**)

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)[158]. The details of this mechanism have also been discussed by Glass and Hoy[158].

$$PhCH_2N(SO_2Ar)_2 \xrightarrow{^-OCMe_3} PhCH{=}NSO_2Ar \qquad (99)$$

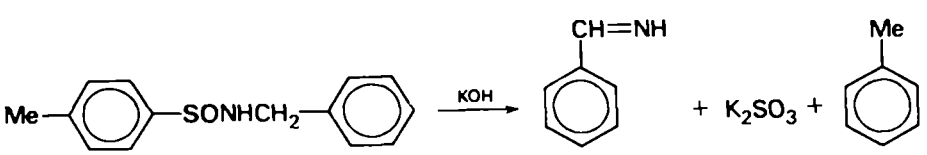
(**2**) (**35**)

$Ar = p$-tolyl

$$PhCH{=}NSO_2Ar \xrightarrow{CN^-} PhC{\equiv}N + ArSO_2^- \qquad (100)$$

(**35**) (**34**)

The following reaction is probably related to the reactions in this section (equation 101)[189].



(101)

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].

$$\underset{\text{NHPh}}{\text{PhCHCH(COMe)}_2} \xrightarrow{\Delta} \text{PhCH=NPh} + \underset{\textbf{(36)}}{\text{CH}_2\text{(COMe)}_2} \qquad (102)$$

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].

$$\underset{\textbf{(37)}}{\text{CF}_3(\text{CF}_2)_3\text{NF}_2} \xrightarrow{\text{ferrocene}} \text{CF}_3(\text{CF}_2)_2\text{CF=NF} + (2\text{F}) \qquad (103)$$

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_5[371], Br_2[188], Ni and other catalysts[328,348], 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)[126,127].

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].

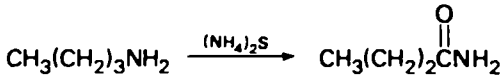
$$(\text{C}_4\text{H}_9)_2\text{NH} \xrightarrow[\text{Cr oxide}]{\text{NH}_3,\ \text{Zn and}} 2\ \text{C}_3\text{H}_7\text{CN} \qquad (104)$$

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].

$$\text{RCH}_2\text{NH}_2 \xrightarrow[\text{OH}^-]{\text{KMnO}_4} \text{RCOO}^- + (\text{NH}_3) \qquad (105)$$

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[140]. 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).

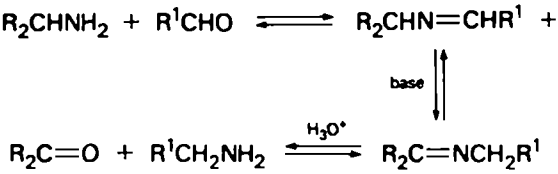


(106)

Some secondary and tertiary amines have been oxidized to amides via a variety of reagents[153,431,432].

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.



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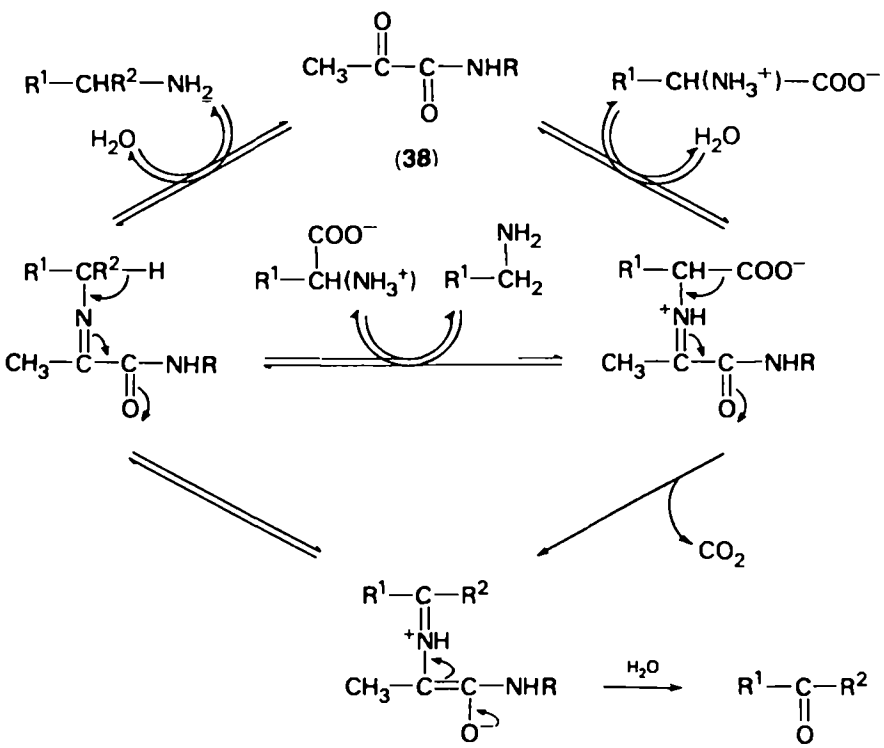
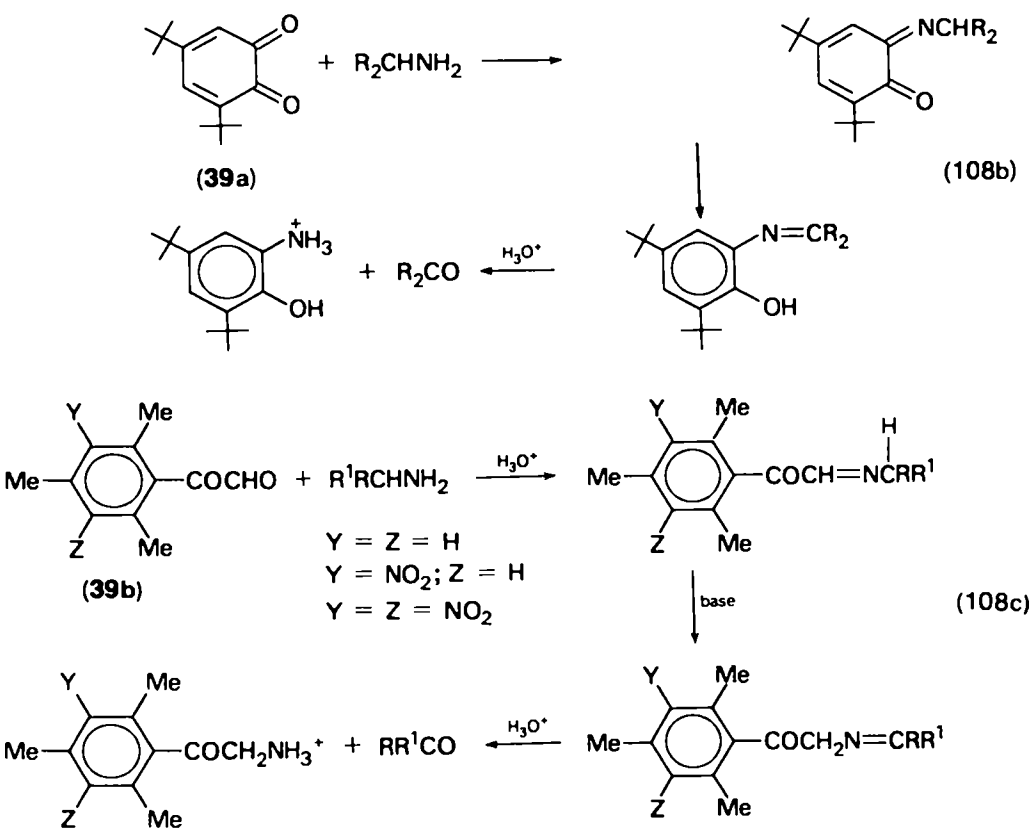


(108a)

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 residue[336]. Also, Owen and Young[320] 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].

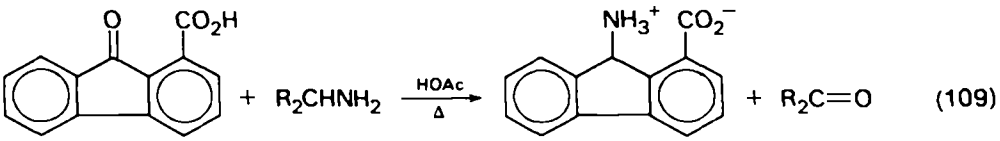
Corey and Achiwa[93] have developed an elegant transamination scheme which utilizes highly hindered conjugated carbonyl compounds for imine formation, followed by facile prototropic interconversion. The isomerized imines are then hydrolysed in mostly good yields. Thus, 3,5-di-*t*-butyl-1,2-benzoquinone (**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 coworkers[14,16] observed for direct Ag(II) picolinate oxidations.



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[434] have reported yet another transamination system analogous to the Corey–Achiwa system.

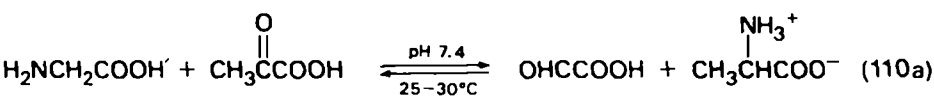
Most recently Panetta and Dixit[323] have reported the deamination of simple aliphatic and cycloalkylamines, as well as L-glutamic acid and L-alanine, to the corresponding carbonyl compounds utilizing 9-fluorenone-1-carboxylic acid (**39c**) as the transaminating oxidizing agent (equation 109). The L-amino acids in turn convert **39c** to the corresponding amine with some asymmetric induction.



(**39c**)

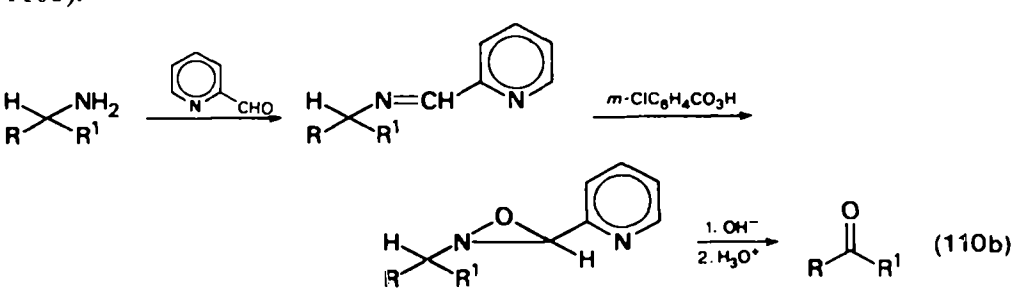
Amino acids and other amines are oxidized by ninhydrin. The mechanism again most probably involves transamination[151,283,356]. Those cases (i.e. α-amino acids) which give simultaneous CO_2 loss and deamination are called Strecker degradations[283,378]. Besides ninhydrin and pyridoxal other transaminating reagents capable of effecting Strecker degradations are alloxan and *p*-nitrosalicylaldehyde[93,283,356,378]. Yields of amine to carbonyl compound conversion are poor for amines other than amino acids[305].

Transaminations involving such systems as pyruvic acid and glycine have also been reported (equation 110a)[309].



2. *Transamination oxidations via imines and oxaziridines* (**40**)

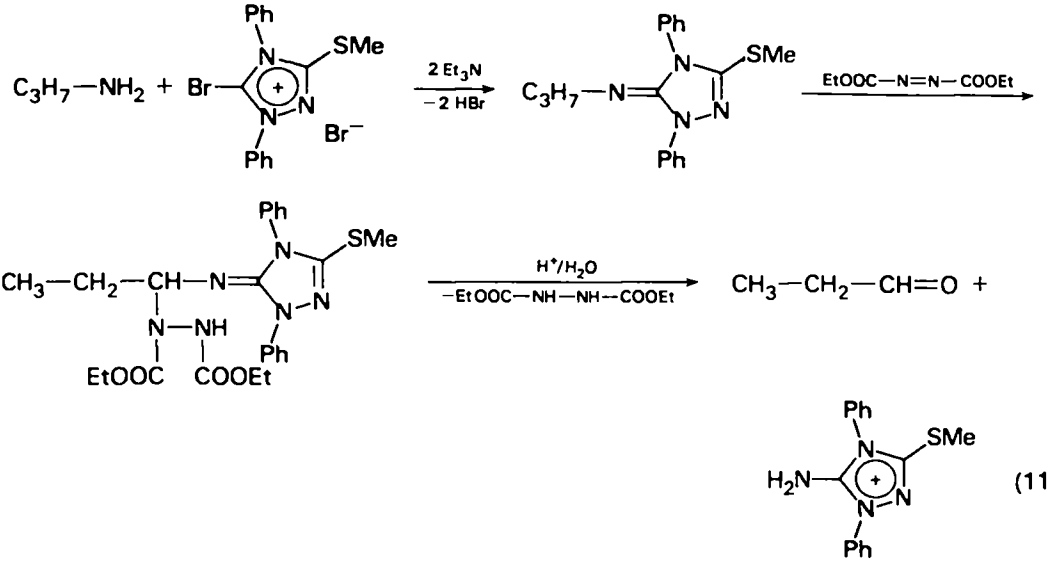
Dinizio and Watt[120] have devised a novel transamination procedure for converting a variety of amines to ketones in 42–77% yield. The procedure consists of the initial condensation of the amine with 2-pyridinecarboxyaldehyde to form the aldimine. *m*-Chloroperoxybenzoic acid then oxidizes the aldimine to the oxaziridine (**40**), after which base followed by acid gives the ketone via another imine (equation 110b).



(**40**)

G. Primary Amines to Aldehydes via Triazoles

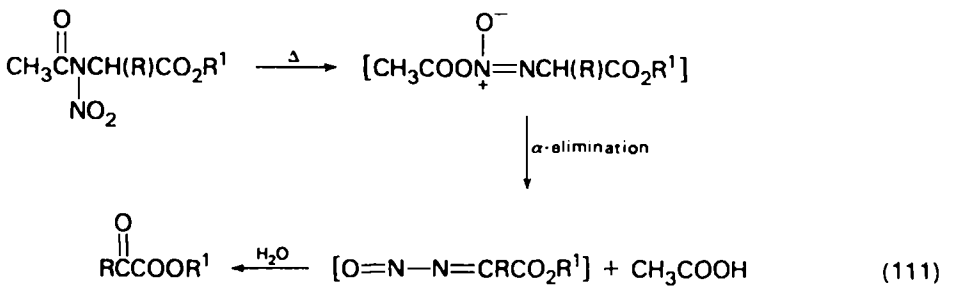
Doleschall[435] has reported a procedure wherein primary carbinamines have been converted to aldehydes in good yields via triazole activation (equation 110c).



(110c)

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)[35,411]. The mechanism of this reaction possibly involves a nitrosoimine intermediate (**41**).



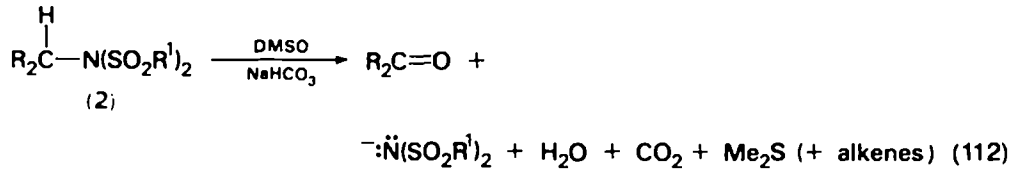
(111)

(**41**)

J. Dimethyl sulphoxide (DMSO) Oxidations of Disulphonimides (2) (Disulphonimide Anion Leaving Groups)

All the oxidations considered up to now most probably proceed via imine or nitrile intermediates. DMSO-mediated oxidations of disulphonimides (**2**), however, most probably do not proceed via imine intermediates at all.

A typical DMSO oxidation of **2** is summarized in equation (112)[100,101]. As suggested by the equation, this oxidation only proceeds on sulphonimides derived

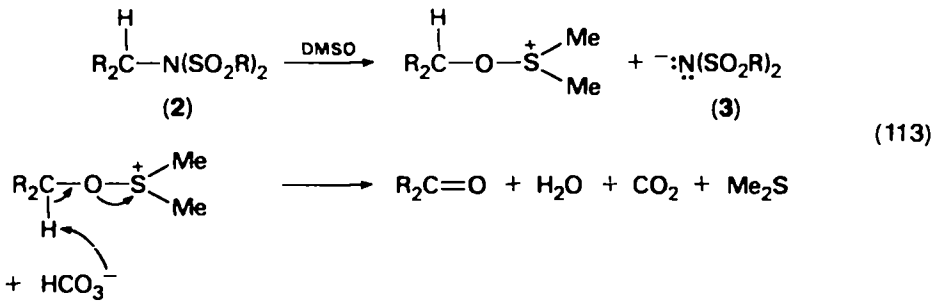


(2)

$$^{-}:\ddot{N}(SO_2R^1)_2 + H_2O + CO_2 + Me_2S\ (+\ \text{alkenes}) \quad (112)$$

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



(2) (3) (113)

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 oxidations[138]. Bosworth and Magnus[51] 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 group[218–220]. A variation on this reaction involves the treatment of 1-benzyl-2,4,6-triphenylpyridiniums with $K_2Cr_2O_7$ to give benzaldehyde[224] (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

$$RCH_2NH_2 + 2\ CuX + R^1ONO \longrightarrow RCHX_2 + 2\ CuX + N_2 \quad (114)$$

$$RCH_2CH_2NH_2 \cdot CuX_2 + (CuX_i \cdot NO)_2 \xrightarrow[25°C]{CH_3CN} RCH_2CHX_2 + RCH_2CN + RCH_2CH_2X + RCH_2CH_2OH \quad (115)$$

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[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[126] suggest that the geminal dihalide is produced by reaction of a diazoalkane intermediate and copper (II) chloride, by analogy to the previously reported[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[146,172,360,361,394].

$$R_2NCHR_2^1 \xrightarrow{HONO} R_2^1C{=}O + R_2NO + H_2O + H_2O \quad (116)$$

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.[197,346a,361]. These and similar oxidations have been reviewed[78,108,394].

Examples of oxidations of cyclic tertiary amines to iminium salts utilizing mercuric acetate have found application in the study of alkaloids[47,259].

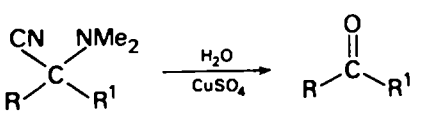
Oxidation of certain secondary and tertiary amines to amides have been reported[153,431,432].

Substituted diaminomethanes may be degraded via iminium salts utilizing chlorine or acyl halides (equation 117)[48,49]. This reaction is related to the von Braun amide reaction (Section II.N).

$$(R_2N)_2CH_2 + R^1COCl \longrightarrow \underset{Cl^-}{R_2\overset{+}{N}{=}CH_2} + R_2NCOR^1 \quad (117)$$

A complex novel method involves treating a tertiary amine with 2-nitropropane and H_2O_2–$CuCl$[145].

A procedure has been reported for obtaining aldehydes or ketones from α-dialkylaminonitriles (**42**) (equation 118)[66]. Yields range from 65 to 94%.



(118)

(**42**)

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

$$(CH_3)_2NCH(CH_3)CH_2CH_3 \xrightarrow[h\nu]{\text{benzophenone}} H_2CO + CH_3NHCH(CH_3)CH_2CH_3 \quad (119)$$

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.

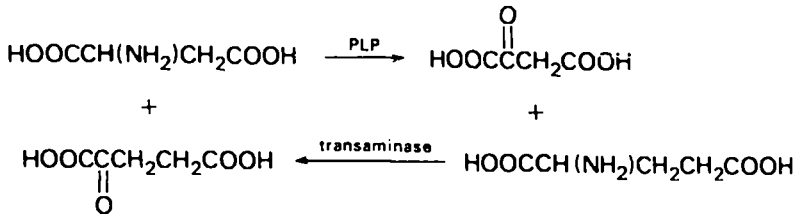
Deaminations and related processes comprise vast areas of study in the voluminous life science field, and, thus, only selected examples of such deaminations will be outlined here.

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[26,57,255,283,284].

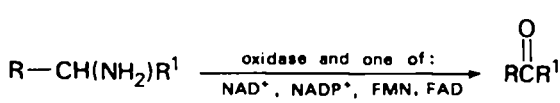
The most common deamination mechanism in cells is the transamination wherein α-ketoglutarate (or another keto acid) is the ultimate recipient of NH_3 via pyridoxal phosphate (PLP) (equation 120)[225]. The mechanisms of these reactions involving



(120)

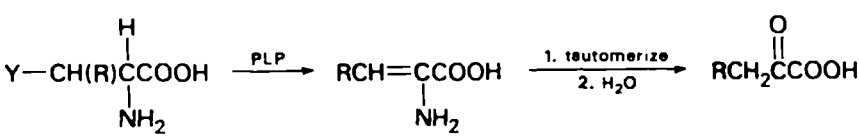
Schiff bases derived from pyridoxal phosphate have been discussed[26,57,255,283,284]. Over 50 pyridoxal-requiring transaminase enzymes have already been reported[57,283,284,350]. Although the transamination mechanism is most important for amino acids, other amines may oxidatively deaminate by this mechanism. Prosthetic groups in place of or in addition to pyridoxal may be at least partly involved in some transaminases[320].

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[26,255,284].



(121)

Amines which have a leaving group β to the amino group may be converted to the carbonyl group by elimination to form the enamine, followed by tautomerization and hydrolysis (equation 122)[26,284]. These deaminations also

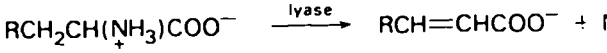


(122)

require pyridoxal. However, these conversions are not true oxidative deaminations, since the carbon β 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), H_2S (from cysteine), propanethial *S*-oxide, the onion lachrymatory factor [from *trans*-(+)-(l-propenyl)-L-cysteine sulphoxide], and indole (from tryptophan).[26,46,283].

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 α,β-unsaturated acids (equation 123)[107,283]. Amino acids which may



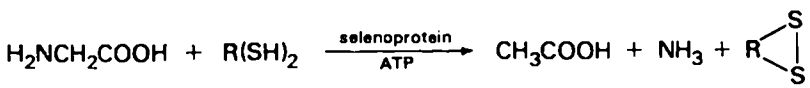
(123)

deaminate by this route include phenylalanine (to *trans*-cinnamic acid), tyrosine (to *p*-coumarate), histidine (to urocanic acid), aspartic acid (to fumarate) and

β-hydroxyaspartate (to oxaloacetate)[236,267,282,283]. These deaminations are most commonly observed in plants and certain 'lower' organisms. Mechanisms have been proposed[121,166].

3. A reductive deamination

Reductive biological deaminations are very rare. However, one remarkable example in *Clostridium sticklandii* involves the reduction of glycine to acetate with the aid of a dithiol, ATP and a selenoprotein (equation 124)[367].



(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[285]. Also, many of the newer transamination schemes described in Section IV.F, such as the Corey–Achiwa transaminations[93], and the recent use of 9-fluorenone-1-carboxylic acid as a transaminating agent[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.

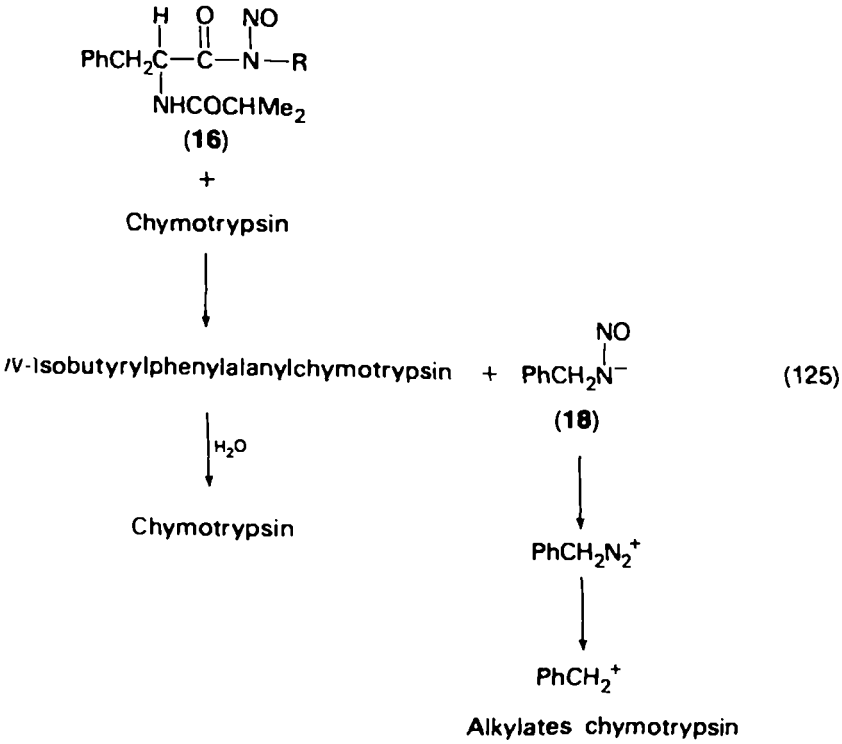
Analogies to the biochemical deaminations of α-substituted amino acids are worth considering for enamine preparations as well as for the conversions of amines to carbonyls.

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 *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

(especially oxygen) at the active site (equation 125)[405,406,414,415]. Analogous inhibitors have been called 'suicide-type' inhibitors[25].

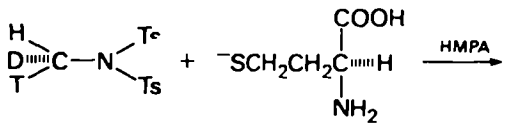


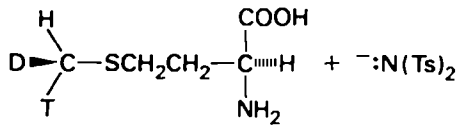
In addition to inhibiting the enzyme's active site, these alkylating agents provide a valuable tool for the mapping of active sites. The preferential points of attack are apparently the oxygens of imidate anions derived from the peptide bonds. The alkylated imidates can then be hydrolysed at pH 5 into 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





(126)

(43)

course of the enzymatic *C*-methylation of indole pyruvate during the biosynthesis of the antibiotic indolymcin.

Townsend and Theis[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. *Deaminations of amino sugars*

The deamination of amino sugars is a well-explored area which has been reviewed[418]. A discussion of the specific use of the Corey–Achiwa method for deaminating aminodeoxy sugars has also appeared[257].

5. *'Pseudophysiological' deaminations via pyridinium salts*

Katritzky and coworkers[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 *in vitro* deamination technique and enzyme-active sites (see also Section II.G).

C. 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 *N*-nitroso and related compounds, some of which have been shown to be the most powerful mutagens yet discovered. However, while the dangers of *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, *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. *Nitrosamines, nitrosoamides and related compounds*

N,N-Dialkyl-*N*-nitrosoamines, *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[5,6,9,62,132,137,271,291,311,420]. 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[9].

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[386]. Evidence has been presented for the formation of triazenes from the treatment of diamines, polyamines and amine derivatives with nitrous acid *in vivo* and *in vitro*[386].

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[279].

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

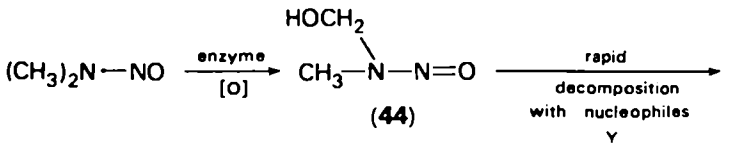
Lists of teratogens, including many amines and amine derivatives, have been published[286,358].

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 *N*,*N*-dialkylnitrosamines are good examples of indirect mutagens. These do not normally undergo deamination *in vitro* (see Section II.K.1.f). However, indirect evidence has been obtained to show that they are enzymatically oxidized *in vivo* to *C*-hydroxy compounds (**44**). It is these metabolites (**44**) which then, most likely, rapidly decompose to carbonium ions which alkylate nucleophilic portions of enzymes and/or nucleic acids (equation 127)[9,229,287,344].

Tertiary amines may also be mutagenic agents in the presence of nitrosating agents, since they react with nitrous acid to give *N*,*N*-dialkylnitrosamines (see Sections II.M.2 and IV.M).



$$CH_3Y\ (+\ N_2\ +\ CH_2O\ +\ OH^-) \quad (127)$$

Triazenes are probably direct-acting mutagens and carcinogens, as only acid is required to convert them into labile nitrogen-emitting alkylating agents[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*-toluenesulphonamide 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*-nitrosotoluenesulphonamide is now recommended as the reagent to use for generating diazomethane in the laboratory[131].

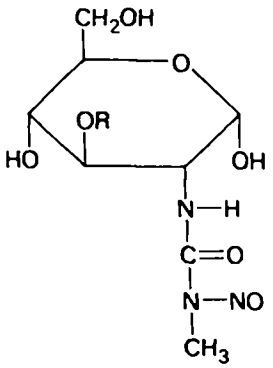
N-Nitroamides probably behave in an analogous manner expelling dinitrogen oxide instead of nitrogen.

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, nitrates 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. Nitrates 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 pH($\sim$1–3) of gastric juice is below the optimum pH 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 putrification) 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].



(**45**)

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 identifiying 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[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[430]. Finally, Meyers and Meyers[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 *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.

VI. REFERENCES

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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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 α-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[10]. The description of the first recording circular dichrograph[12] led to a rapid development in this field and the commercial availability of instruments

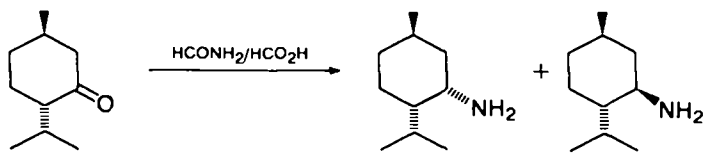
capable of routine CD measurements in the visible and near ultraviolet spectral regions, 185–600 nm[11,13].

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[19], 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

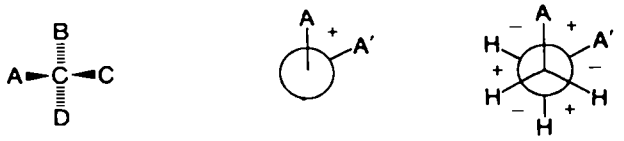


(1) (2) (3)

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

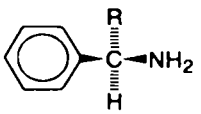
Brewster[9] concluded that two contributions, atomic and conformational asymmetry, in general make up the rotatory power (with sodium D light) of a chiral substance. The atomic asymmetry contribution for absolute configuration **4** is dextrorotatory when the polarizability of the substituent attachment atoms decreases in the order A > B > C > D. Brewster also tabulated the rotational



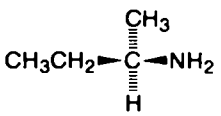
(4) (5) (6)

ranking of a number of common substituents[9], including deuterium[24], 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[9].

With the attachment atom polarizability sequence decreasing in the order phenyl > methyl (alkyl) > amino > hydrogen[9], (*R*)-α-phenylethylamine [(*R*)-**7**] and (*R*)-α-phenylneopentylamine[25] [(*R*)-**8**], having only atomic asymmetry, are correctly predicted to be dextrorotatory. On the other hand (*R*)-2-aminobutane[9] [(*R*)-**9**] has

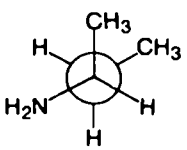


[(*R*)-**7**] R = CH_3
[(*R*)-**8**] R = $C(CH_3)_3$

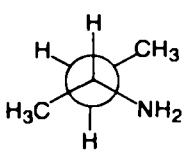


[(*R*)-**9**]

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**[9], the molecular rotation of (*R*)-**9** is calculated as +3°[9].



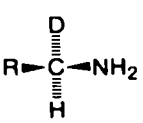
(10)



(11)

Experimentally the molecular rotation of (*R*)-**9** is −5°[9] and thus the conformational asymmetry rule fails to predict even the correct sign for the rotatory power of this amine and for similar methylalkylcarbinamines[9].

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[24] [(*R*)-**12**] and (+)-1-amino-2,2-dimethylpropane-1-d[26]



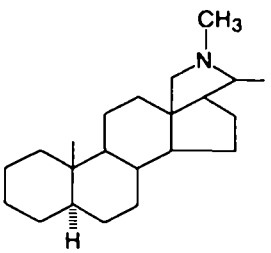
[(*R*)-**12**] R = CH_3
[(*R*)-**13**] R = $C(CH_3)_3$
[(*R*)-**14**] R = C_6H_5
[(*R*)-**15**] R = $CH_2CH_2CH_3$

[(*R*)-**13**]. When the laevorotation of (*R*)-benzylamine-α-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 α 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].

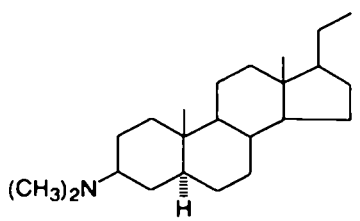
C. Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD)

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



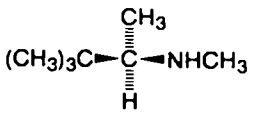
(16)



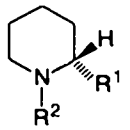
(17)

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*)-α-pipecoline [(*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],



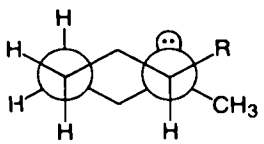
[(*R*)-**18**]



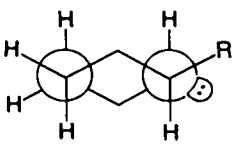
[(*S*)-**19**] $R^1 = CH_3$, $R^2 = H$

[(*S*)-**20**] $R^1 = R^2 = CH_3$

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**, $R = CH_3$] 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**),



(**21**)

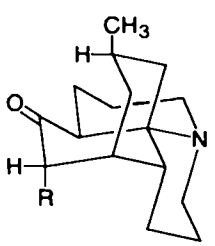


(**22**)

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[37].

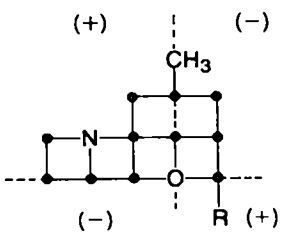
2. *Amino group influence on other chromophores*

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



(**23**) R = H

(**24**) R = Br



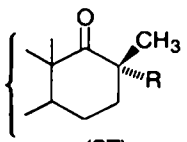
(**25**) R = H

(**26**) R = Br

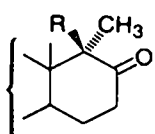
interaction of an ammonium group β to a carbonyl group was detected in the ORD spectrum. Lycopodine (**23**)[38] in methanol shows, as anticipated by application of the octant diagram[39] **25**, a positive Cotton effect associated with the carbonyl $n \rightarrow \pi^*$ transition at about 300 nm. In fact the absolute configuration of **23** was first established on this basis[40]. 6α-Bromolycopodine hydrobromide (**24**·HBr) in methanol also shows a positive Cotton effect at about 300 nm[38], but with an intensity less than that of **23** and thus substantially less than that expected by application of the α-haloketone rule[41], 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 dissignate (antioctant) contribution[42] to the Cotton effect[38]. In agreement with this conclusion, lycopodine methiodide and lycopodine perchlorate in methanol also show negative Cotton effects at about 300 nm[38], and a solution of lycopodine in acetic acid also exhibits a negative Cotton effect[38]. As predicted by the α-haloketone rule, 6α-bromolycopodine (**24**) in methanol shows a stronger positive Cotton effect than does lycopodine (**23**) itself[38].

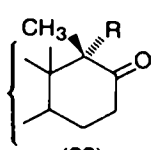
When the ORD curves of a number of α-amino-D-homoketo steroids and their salts (**27a–d**, **27g**, **28a–d** and **29a–f**) were compared with the corresponding ketols (**27h**, **28h** and **29h**), good correlations were found except with salts **29b** and **29d**[43]. The unusual ORD spectra for **29b** and **29d** were explained by the presence of the positively charged nitrogen atom which makes a dissignate contribution to the Cotton effect. The reduced magnitude, as compared to that of 17-keto steroids, of



(**27**)



(**28**)

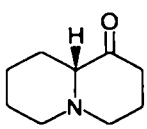


(**29**)

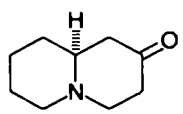
(**a**) R = NH_2
(**b**) R = $\overset{+}{N}H_3\bar{C}l$
(**c**) R = $NHCH_3$
(**d**) R = $\overset{+}{N}H_2(CH_3)\bar{C}l$
(**e**) R = $N(CH_3)_2$
(**f**) R = $\overset{+}{N}H(CH_3)_2\bar{C}l$
(**g**) R = $\overset{+}{N}(CH_3)_3\bar{I}$
(**h**) R = OH

the positive Cotton effect associated with the $n \rightarrow \pi^*$ transition of 16β-amino-17-keto steroid hydrochlorides was also explained on the basis of an antioctant contribution of the ammonium group[44].

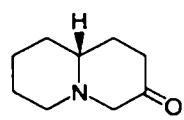
Application of the octant rule[41] for the establishment of the absolute configuration of a series of oxoquinolizidines (**30–32**), each showing a strong CD



[(*R*)-**30**]



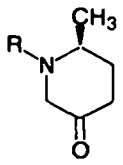
[(*S*)-**31**]



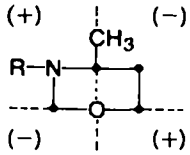
[(*R*)-**32**]

maximum at about 300 nm, leads to the incorrect configurational assignment for (−)-30[45,46]. The latter's configuration was independently established as (*R*)-**30** by synthesis[47], and its CD could only be explained on the basis of a strong antioctant contribution of the nitrogen atom[47]. Similar results are encountered in the CD study of six-membered heterocyclic saturated ketones [(*S*)-**33**], all having the hetero group predominantly in the upper-left-rear sector of the octant projection **34** but showing small negative Cotton effects centred at 305 nm in all solvents investigated[48].

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[49]. This interaction is



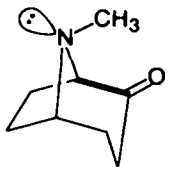
[(*S*)-**33**]



(**34**)

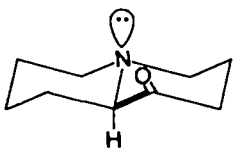
R = CH_3, CH_2CH_3 or $COCH_3$

reflected in both the UV and CD spectra. Octant (consignate[42]) behaviour with respect to the $n \rightarrow \pi^*$ carbonyl transition is to be expected of an α-amino group when the lone pair of electrons on the nitrogen atom is *trans* diaxial to the C_α—CO bond (**35**) or of a β-amino group, as in lycopodine (**23**), when the lone pair is *trans*

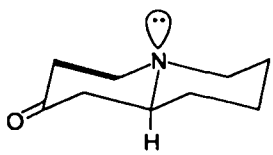


(**35**)

diaxial to the C_α—C_β bond. Antioctant (dissignate[42]) behaviour of an α- or β-amino group is observed when the lone pair on nitrogen is *cis* to the C_α—CO (**36**) or C_α—C_β bond (**37**), respectively. For β-aminocyclohexanones, antioctant behaviour

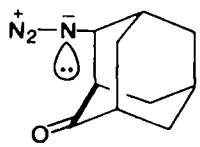


(**36**)



(**37**)

will also apply when the C_β—N bond is axial (i.e. *cis*) to the C_α—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.

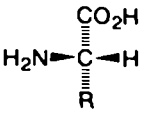


(**38**)

Verification of this analysis has appeared[50], and the CD spectra displayed by chiral acyclic α-(*N*,*N*-dialkylamino)ketones[51] and β-aminoketones[52] and their salts can be interpreted using this analysis. This also appears to be true for chiral α-trimethylammonio aldehydes as well[53].

b. Carboxyl chromophore. Since the first observation of the complete Cotton effect at about 210 nm associated with the carboxyl chromophore of α-amino acids[54], their ORD and CD have been extensively studied. Included in the CD

studies were surveys of the more common[55,56] and less common[57] α-amino acids. These studies have shown that these acids with the L configuration (L-**39**), which is



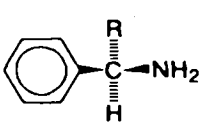
(L-**39**)

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 α- or β-aryl[56,58,59], sulphide, disulphide[55,57,60,61] or seleno[61] 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**, R = CH_3) (zwitterionic and nonzwitterionic forms), L-alanine cation and L-alanine anion as a function of the angle between the $C_\alpha COO$ and the $CC_\alpha N$ (C = carboxylate carbon atom) planes have been calculated by a semiempirical quantum-mechanical method[62]. 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 α-amino acids[63].

c. Benzene chromophore. In chiral benzene-ring-containing compounds, the benzene chromophore gives rise to observable Cotton effects associated with the benzene ^1L_b and ^1L_a $\pi \rightarrow \pi^*$ transitions at about 260 and 210 nm, respectively[64].

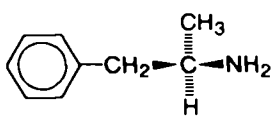
In the ORD spectra of (*R*)-α-phenylalkylamines, (*R*)-**7**, (*R*)-**8** and (*R*)-α-phenyl-*n*-propylamine [(*R*)-**40**] (Figure 1), and (*R*)-α-benzylethylamine



[(*R*)-**7**] R = CH_3

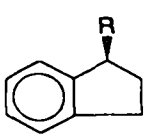
[(*R*)-**8**] R = $C(CH_3)_3$

[(*R*)-**40**] R = CH_2CH_3



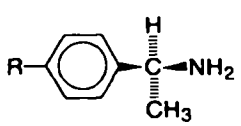
[(*R*)-**41**)]

[(*R*)-**41**] display multiple, negative Cotton effects[65] associated with the totally symmetric vibrational progression of the ^1L_b benzene transition[66]. For (*S*)-1-aminoindane [(*S*)-**42**] these Cotton effects are also negative[67]. In the ORD spectrum of these amines, the ^1L_b Cotton effects are superimposed on strong background curves which are the long-wavelength wings of transitions below 240 nm[65]. These short-wavelength contributions far override in intensity its rotatory



[(*S*)-**42**] R = NH_2

[(*S*)-**44**] R = CH_3



[(*S*)-**43**] R = CH_3, OCH_3, Br or Cl

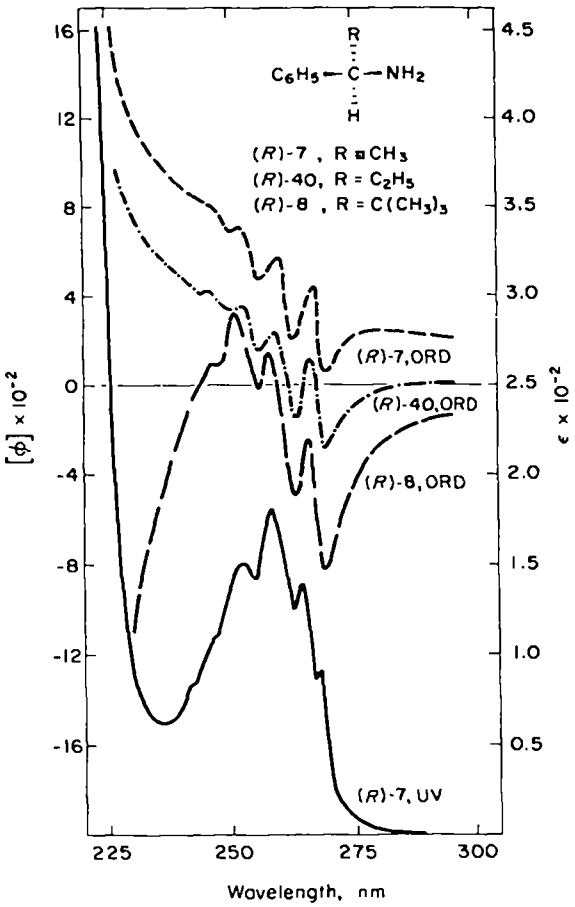


FIGURE 1. Ultraviolet absorption (UV) spectrum of (*R*)-α-phenylethylamine [(*R*)-**7**] in absolute ethanol and the ORD spectra of (*R*)-α-phenylethylamine [(*R*)-**7**], (*R*)-α-phenyl-*n*-propylamine [(*R*)-**40**] and (*R*)-α-phenylneopentylamine [(*R*)-**8**] in methanol. Adapted from H. E. Smith, M. E. Warren, Jr. and L. I. Katzin, *Tetrahedron*, **24**, 1327 (1968) by permission of Pergamon Press.

contribution at 240–270 nm and in general give the sign to the rotatory power at the sodium D line (589 nm). For (*R*)-α-phenylethylamine [(*R*)-**7**] and (*R*)-α-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*)-α-phenylneopentylamine [(*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 ^1L_b Cotton effects of α- and β-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[68]. For the *para*-substituted derivatives of (*S*)-α-phenylethylamine [(*S*)-**43**] and their respective hydrochloride salts, the ^1L_b transition moment becomes larger, and the negative-signed contribution of the coupled oscillator mechanism becomes dominant[68]. Thus the ^1L_b Cotton effects of (*S*)-**43** and its salts are opposite in sign (negative) to those of (*S*)-α-phenylethylamine [(*S*)-**7**] and its salt[69].

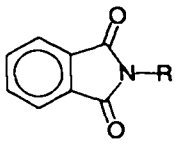
The negative Cotton effect at about 215 nm in the CD spectrum of (*S*)-1-methylindane[67] [(*S*)-**44**] is clearly due to the ^1L_a benzene transition. The shorter wavelength and the larger moment of the ^1L_a transition, as compared to those of the ^1L_b transition, suggest the dominance of the coupled oscillator mechanism for generation of this Cotton effect, and as predicted by the coupled oscillator mechanism, this Cotton effect is negative[67]. For (*S*)-1-aminoindane [(*S*)-**42**], the positive CD maximum in this same spectral region is due to the coupling of the benzene ^1L_a transition with the $n \rightarrow \sigma^*$ transition of the amino group at about 210 nm. Protonation of the amino group eliminates its $n \rightarrow \sigma^*$ transition and (*S*)-1-aminoindane hydrochloride [(*S*)-**42**·HCl] displays a negative Cotton effect near 215 nm[67]. 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[69].

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)[65]. The curve for the hydrochloride salt of (*R*)-α-phenylethylamine [(*R*)-**7**·HCl] and (*R*)-α-phenylneopentylamine [(*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[65].

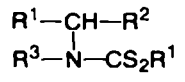
3. *Chromophoric derivatives*

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[32] (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[70] 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**)[70,71], the dithiocarbamate derivatives of primary and secondary amines and of α-amino acids



(**45**)

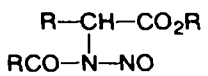


(**46**)

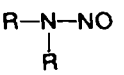
R^2 = alkyl or carboxyl

R^3 = H or alkyl

(**46**)[70,72] and the *N*-nitroso derivatives of *N*-acyl-α-amino acid esters[73] (**47**) and of secondary amines[74] (**48**). The *N*-phthaloyl and *N*-dithiocarbamate derivatives are



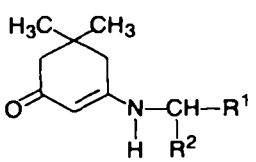
(**47**)



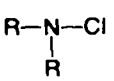
(**48**)

easily prepared, but only for the latter has a sector rule been formulated for the interpretation of the CD spectra[72]. The preparation of *N*-nitroso compounds is somewhat cumbersome, and the derivatives are sometimes unstable[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[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[76]. Significant among these for chiral amines are the dimedonyl derivatives of primary amines and of α-amino acid esters[77] (**49**), the *N*-chloro derivatives of secondary amines[78] (**50**) and the Schiff base, *N*-benzylidene (**51**) and *N*-salicylidene (**52**),



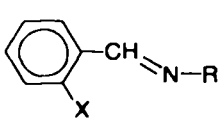
(**49**)



(**50**)

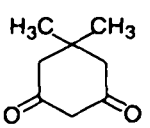
R^1 = alkyl, aryl or alkoxycarbonyl

derivatives of primary amines[79,80]. Reaction of an amine or α-amino acid ester with dimedone (**53**) to form **49** requires heat but the condensation appears to be almost



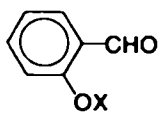
(**51**) X = H

(**52**) X = OH



(**53**)

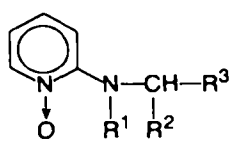
quantitative[77]. The requirement of a free base or an α-amino acid ester, an amine salt or zwitterion being unreactive, is inconvenient when dealing with milligram quantities of amine. Further, since the sign of the Cotton effect in the CD spectra depends on both the configuration and the conformational 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 α-amino acid[80]. The absolute



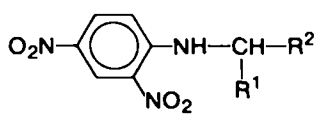
(54) X = H
(55) X = Na

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 α-amino acids[81] and chiral primary and secondary amines (**56**)[82],



(56)

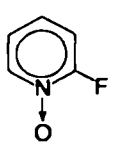


(57)

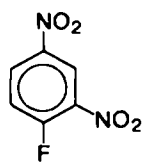
R^1 = H or alkyl
R^3 = carboxyl, alkyl or aryl

R^2 = alkyl or carboxyl

including heterocyclic amines[78,83], and the *N*-2,4-dinitrophenyl derivatives of α-amino acids[84,85] and chiral primary amines (**57**)[86]. 2-Fluoropyridine *N*-oxide (**58**) reacts slowly at room temperature with an α-amino acid or a primary or secondary



(58)

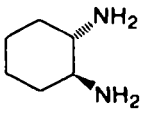


(59)

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 α-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 α-amino acids

found as components of peptide antibiotics[84]. 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[87], and the configuration of (*S*)-*trans*-1,2-cyclohexanediamine [(*S*)-**60**] was established on this basis[87].

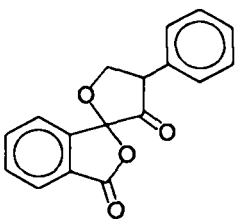


[(*S*)-**60**]

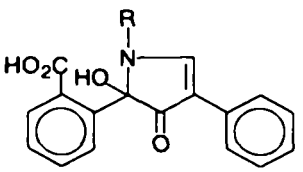
b. Derivatives formed in situ. As a matter of convenience and when the amount of chiral amine is extremely small, it is possible to form chromophoric derivatives of chiral amines suitable for ORD and CD studies in the reaction medium. A number of such studies of metal chelates of α-amino acids and peptides have been reported[88,89]. As an extension of this technique, when a chiral, vicinal amino alcohol is added to a solution of di(acetylacetonato)nickel(II)[90] [$Ni(acac)_2$] or tris(dipivalomethanato)praseodymium(III)[91] [$Pr(dpm)_3$] 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[92], 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 disuccinimidatodiisopropylaminecopper(II) [$Cu(su)_2(ip)_2$] or disuccinimidato-dipyridinecopper(II) [$Cu(su)_2(py)_2$] 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[93,94]. 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



(**61**)

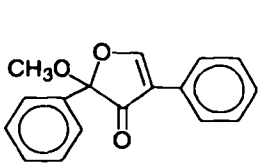


(**62**)

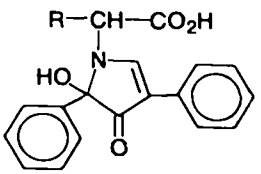
chiral primary amines[95]. Secondary amine, including cyclic amine[96], derivatives can also be formed *in situ* for CD measurements[96]. Configurational assignments for primary and secondary amines using these derivatives, however, can be made only

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[95,96].

2-Methoxy-2,4-diphenyl-3(2*H*)-furanone (MDPF) (**63**) reacts with α-amino acids to form chromophoric derivatives **64** which for a substantial variety of α-amino



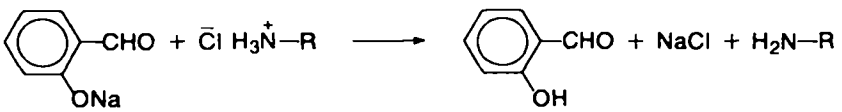
(**63**)



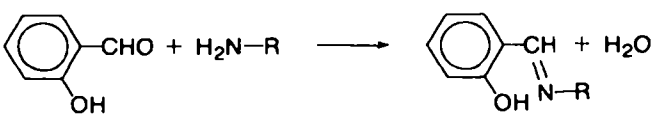
(**64**)

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[97].

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[80].



(**55**)



(**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[80]. Application of the salicylidenimino chirality rule[79] (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[80] and terpene[98] and steroidal amines[99].

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)[100,101], designated as bands I, II and III, respectively (Figure 2), which are assigned to transitions of the intramolecularly hydrogen-bonded salicylidenimino chromophore (**65**)[102]. In polar solvents such as dioxane,

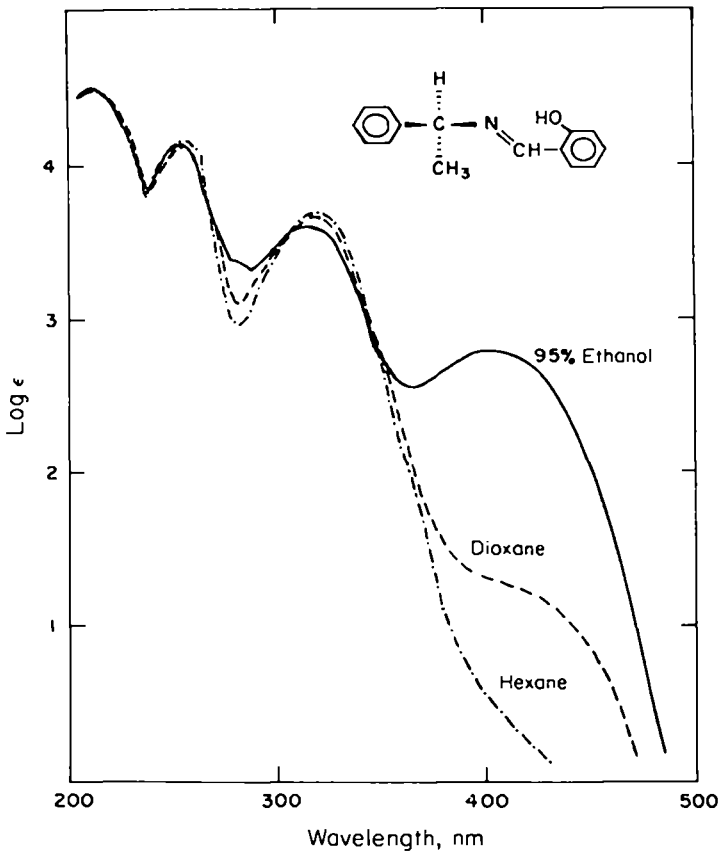
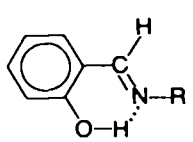
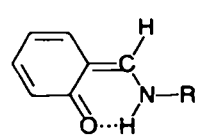


FIGURE 2. Electronic absorption (*EA*) spectra of (*S*)-*N*-salicylidene-α-phenylethylamine in various solvents. Adapted from H. E. Smith, S. L. Cook and M. E. Warren, Jr., *J. Org. Chem.*, **29**, 2265 (1964) by permission of the American Chemical Society.

methanol and ethanol, a broad band at about 400 nm (log ε_{max} 1.32–1.89 in dioxane and 3.06–3.08 in methanol and ethanol) and a shoulder near 280 nm (log ε_{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



(65)



(66)

of a quinoid tautomer (**66**) in the polar solvent[102]. 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[79].

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[80]. 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[101] and CNDO/S calculations on the azomethine and conjugated azomethine chromophore[103], 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*)-α-(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[101].

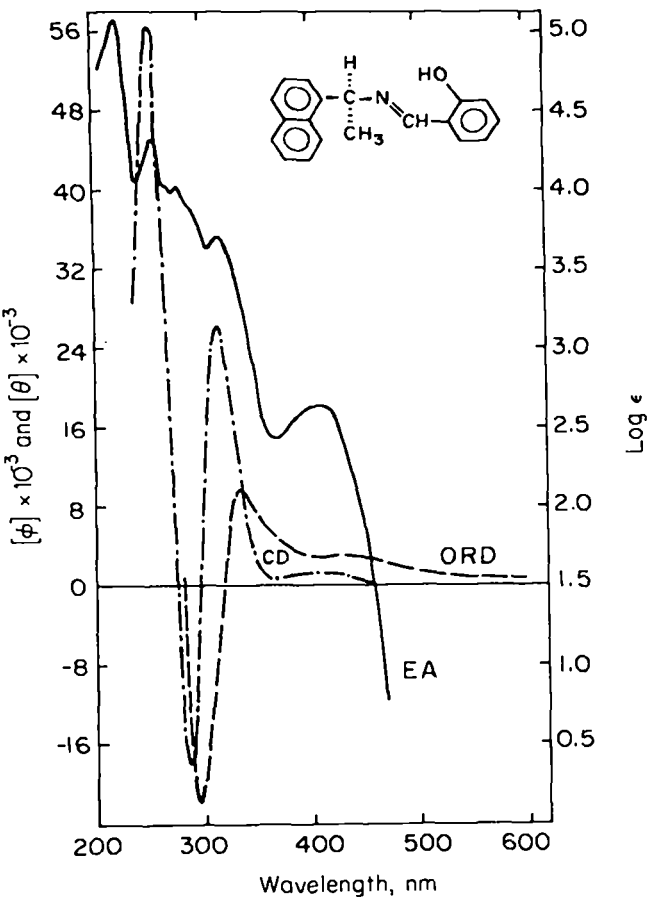
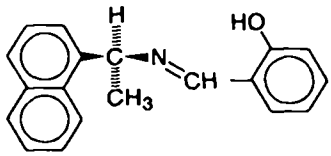
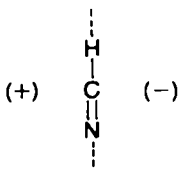


FIGURE 3. Electronic absorption (EA) spectrum in absolute ethanol, optical rotatory dispersion (ORD) spectrum in 95% ethanol, and circular dichroism (CD) spectrum in absolute ethanol of (*S*)-*N*-salicylidene-α-(1-naphthyl)ethylamine [(*S*)-**67**]. Adapted from H. E. Smith and R. Records, *Tetrahedron*, **22**, 813 (1966) by permission of Pergamon Press.



[(*S*)-**67**]

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 salicylideniminq chromophore using a planar sector rule (**68**)[79]. The distribution of groups with

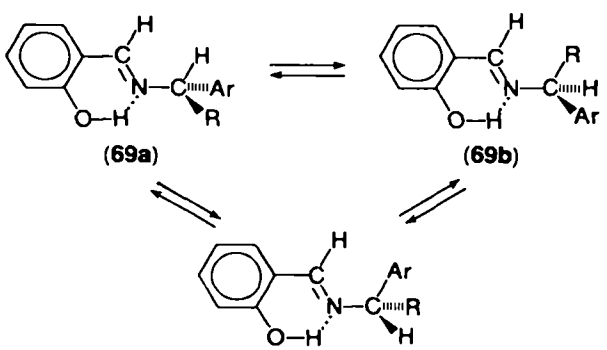


(Viewed from the chromophore to the chiral centre)

(68)

respect to the chromophore depends on the preferred conformation of the salicylidenimino group about its attachment bond to the chiral centre and the absolute configuration of the chiral centre to which the chromophore is attached[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 salicylidenimino 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

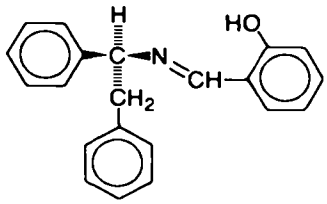


(69a) **(69b)**

(69c)

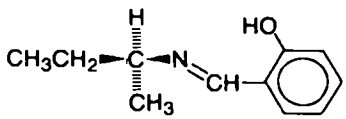
of lowest energy whether the R group is larger or smaller in effective bulk size than the Ar group. With structure and configuration **69** (Ar = 1-naphthyl, phenyl, benzyl, substituted benzyl, 2- or 4-pyridyl, 2-thienyl, 2-thienylmethyl, 2-furanyl or 4-imidazolylmethyl group, R = alkyl, carboxylate, 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, alkoxycarbonyl or alkoxycarbonylmethyl group[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-α,β-diphenylethylamine [(*S*)-**70**][106], the perturbing effect of the α-phenyl group being essentially cancelled by the α-benzyl group.

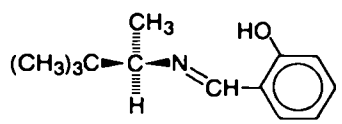


[(*S*)-**70**]

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



[(*S*)-**71**]

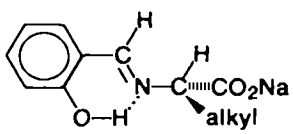


[(*R*)-**72**]

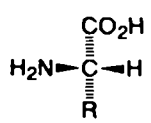
observed[79]. Since both (*S*)-**71** and (*R*)-**72** have preferred conformations similar to **69a**, and the rotatory perturbation by an ethyl group and by a *t*-butyl group is larger than that of a methyl group, the same planar sector rule for the salicylidenimino chromophore (**68**) also predicts the sign of the observed Cotton effects, positive for (*S*)-**71** and negative for (*R*)-**72**[79].

Assuming a similar preferred conformation of the salicylidenimino 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[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[108], these derivatives also showing positive Cotton effects for bands I and II.

An aliphatic L-α-amino acid derivative with a preferred conformation (L-**73**) similar to **69a** always shows positive Cotton effects for bands I and II[80]. Thus in the CD spectrum of the derivative L-**73** (alkyl = CH_3) formed by condensation of



(L-**73**)



(L-**74**) R = CH_3
(L-**75**) R = CH_3SCH_2

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 → π* transition of the salicylidenimino chromophore[101].

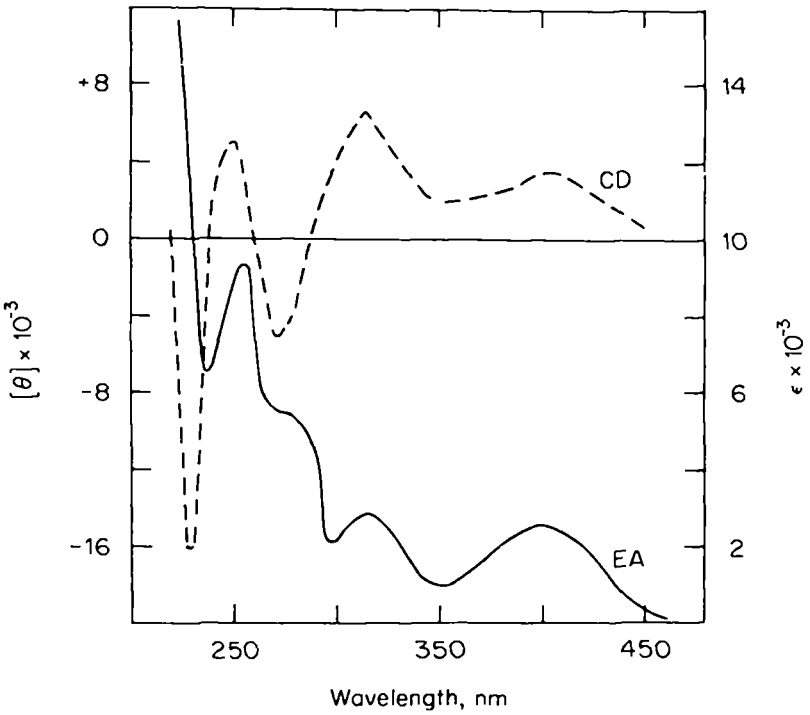
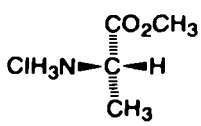


FIGURE 4. Electronic absorption (EA) and circular dichroism (CD) spectra of L-alanine (L-**74**) with a 15% molar excess of sodium salicylaldehyde (**55**) in methanol. Reproduced with permission from H. E. Smith, E. P. Burrows, M. J. Marks, R. D. Lynch and F.-M. Chen, *J. Amer. Chem. Soc.*, **99**, 707 (1977). Copyright by the American Chemical Society.

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*-methylcysteine (L-**75**) derivative is opposite that of the L-alanine (L-**74**) derivative, and no CD maximum near 275 nm was detected[80]. A couplet structure for band II in the derivative of L-**75** also arises from a sulphide transition in this spectral region[80].

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

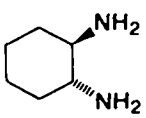


(L-**76**)

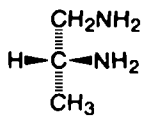
bands I and II are predicted to be positive on the basis of a preferred conformation similar to L-**73** and a stronger influence on the chromophore by an alkoxycarbonyl group than by an alkyl group. For the few aliphatic α-amino acid ester derivatives studied, band I is positive, but the CD band near 265 nm is negative[80]. Although

this latter band has been assigned to transition II of the salicylidenimino chromophore[80], it in fact may be due to the $n \rightarrow \pi^*$ transition of the salicylidenimino group[101].

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*-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[79]. Using the exciton splitting in the CD spectra of the *N,N'*-disalicylidene derivatives of (*R*)-*trans*-1,2-cyclohexanediamine [(*R*)-**60**] and (*R*)-1,2-propanediamine[79] [(*R*)-**77**] and CNDO/S calcu-



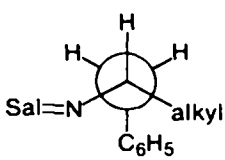
[(*R*)-**60**]



[(*R*)-**77**]

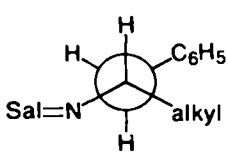
lations[103], the transition moment directions for the salicylidenimino chromophore were determined[103]. The Cotton effects associated with the transitions near 315 (band I) and 255 nm (band II) are the result of coupling of these respective moments, both approximately along the attachment bond of the salicylidenimino group, with transition moments in the other groups attached to the chiral centre. For β-phenylalkylamine derivatives the important transition moments are those of the ^1L_a and $^1B_{a,b}$ transitions of the benzene group, and the effective direction of these moments is along the phenyl group attachment bond. The $^1B_{a,b}$ 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*-salicylidene-β-phenylalkylamine are shown as **78a–78c**. For each particular



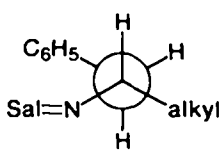
(−)

(78a)



(~0)

(78b)



(+)

(78c)

Sal = salicylidene

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 anticolinearity 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 β-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 α- and β-arylalkylamines[79], 1-alkyl-2-propynylamines[108], 1-alkyl-2-propenylamines[108] and α-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 salicylidenimino chromophore with those of $\pi \rightarrow \pi^*$ transitions of the aryl, ethynyl, ethenyl and carboxylate groups.

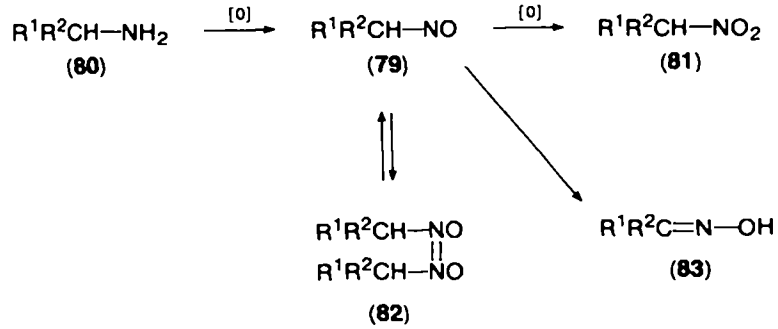
The Cotton effects associated with bands I and II in spectra of chiral *N*-salicylidenealkylamines also arise by the coupled oscillator mechanism[98]. Since the polarizability of a carbon–hydrogen bond is small compared with that of a carbon–carbon bond[98], only the latter near the chromophore attachment 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

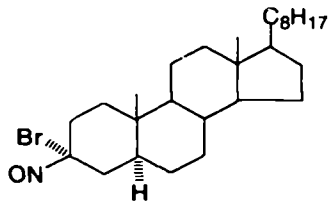
1. C-Nitroso compounds

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.

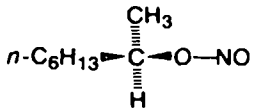
Treatment of a chiral ketoxime with *N*-bromosuccinimide in cold pyridine–ethanol gives the α-bromo-*C*-nitroso compound[110]. For a series of monoterpene and steroidal oximes only 5α-cholestan-3-one oxime yielded a stable, crystalline monomeric derivative (**84**). The reaction leading to **84** and the other α-halo derivatives is such that the halogen atom occupies an axial position[110]. All chiral α-halo-*C*-nitroso compounds are extremely unstable and even **84** could not be obtained in analytical purity[110].



(84)

2. O-Nitroso compounds, nitrite esters

Although chiral nitrites are produced in the reaction of silver nitrite with chiral bromides[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°C[113,114]. Although (*R*)-2-octyl nitrite [(*R*)-**85**] can be purified by distillation at reduced

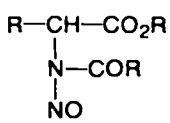


[(*R*)-**85**]

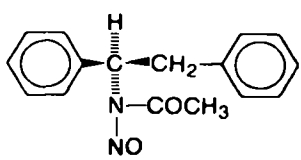
pressure[112] and some steroidal nitrites may be recrystallized in the usual way[113], other steroidal nitrites are reported as recrystallized only at room temperature[114]. Dioxane solutions of nitrite esters used for spectroscopic measurements should be stabilized by the addition of 0.2% pyridine[114].

3. N-Nitroso compounds

a. N-Nitrosoamides. The *N*-nitroso derivatives of primary amines are unstable but the *N*-nitroso-*N*-acyl-α-amino acid esters (**86**) are easily prepared using nitrogen



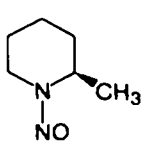
(**86**)



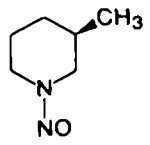
[(*R*)-**87**]

tetroxide (N_2O_4) in carbon tetrachloride in the presence of sodium acetate[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[73,115–117].

b. Nitrosamines. The *N*-nitroso derivatives of chiral secondary amines may be prepared by treatment of the amine with nitrous acid[117,118] (sodium nitrite in hydrochloric acid[117] or acetic acid[74]). These nitrosamines are frequently oils[117,118], but sometimes they can be distilled at reduced pressure[74]. Thus the *N*-nitroso derivatives of steroidal alkaloids[74,119], (*R*)-α-pipecoline[74] [(*R*)-**88**] and (*R*)-β-pipecoline[120] [(*R*)-**89**], and other chiral secondary amines[117,120–122] have been prepared. It is to be recognized that chiral nitrosamines occur as conformational diastereomers and

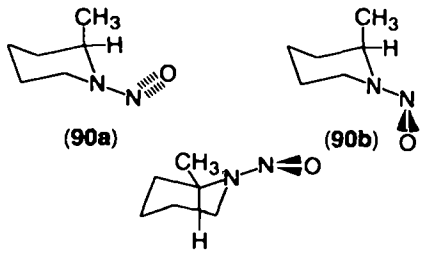


[(*R*)-**88**]



[(*R*)-**89**]

that (*R*)-**88** exists in carbon tetrachloride essentially in three conformations, **90a–c**, 27% **90a**, at least 37% **90b** and the rest **90c**[123]. Crystalline L-*N*-nitrosoproline is



(**90a**) (**90b**) (**90c**)

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°C[124]. The diastereomers

(L-**91a**) (L-**91b**)

L-**91a** and L-**91b** have been separated by column chromatography at low temperature[125].

B. Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD)

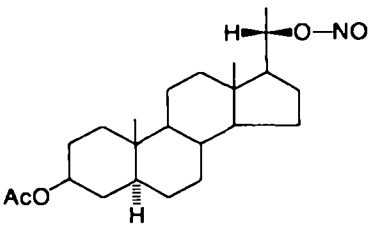
1. *C-Nitroso compounds*

The *C*-nitroso chromophore shows an n → π* transition at 680 nm[126], and in the few ORD[73] and CD[110] 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 amines[110], 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 intensities[110].

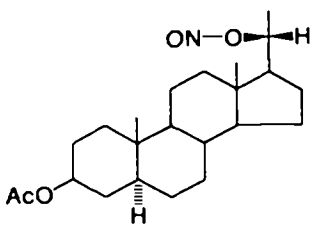
Circular dichroism measurements[110] with chiral α-bromo-*C*-nitroso compounds such as **84** indicate that the n → π* transition[127] near 650 nm is optically active, but again, the instability of the compounds precludes the observation of spectra with reproducible intensities[110].

2. O-*Nitroso compounds, nitrite esters*

The earliest circular dichroism studies with chiral nitrite esters are those of Elkins and Kuhn[128]. These compounds, showing an $n \rightarrow \pi^*$ transition with much vibrational fine structure centred at about 360 nm[127,128], also show multiple Cotton effects in the same region[128–130]. Thus 5α-pregnan-3β,20α- (**92**) and 5α-pregnan-3β,20β-diol 3-acetate 20-nitrite (**93**) show oppositely signed, multiple Cotton effects



(**92**)

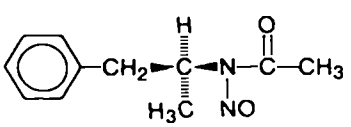


(**93**)

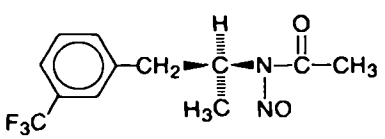
in this spectral region[130], and the *O*-nitroso group has been suggested as a chromophoric derivative for chiral alcohols[130]. The conformational mobility of the nitrite group about its attachment bond to the chiral centre makes the interpretation of the Cotton effect in terms of a sector rule difficult. Reported spectra, for the most part of nitrite esters of steroidal alcohols[129,130], 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[73,131] which in ORD and CD studies is found to be optically active[73,115–117]. The derivatives most extensively studied are those of the *N*-acetyl- and *N*-benzoyl-α-amino acid esters[73] and α- and β-phenylalkylamines[115–117]. 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 (+)-norfenflur-



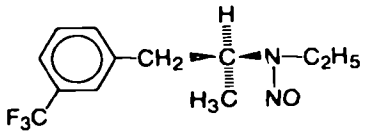
[(*S*)-**94**]



[(*S*)-**95**]

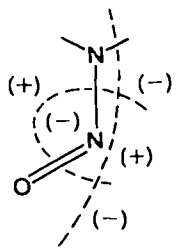
amine [(*S*)-**95**] show identical ORD and CD curves in isooctane[117], supporting the assignment of the *S* configuration to (+)-norfenfluramines[117].

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[117]. 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[74,119]. Considering the sign of



[(*S*)-**96**]

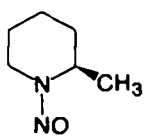
the Cotton effects in these spectra and the symmetry of the chromophore, a sector rule (**97**) was proposed for the nitrosamino chromophore[74]. As discussed for



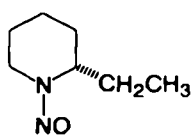
(Signs refer to upper sectors)

(**97**)

(*R*)-*N*-nitroso-α-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

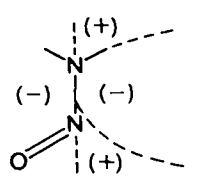


[(*R*)-**88**]



[(*S*)-**98**]

to a chiral nitrosamine requires that all conformers that possibly could make a contribution to the Cotton effect be considered[122]. However, a careful analysis of the three lowest energy conformers of (*R*)-**88**[122], and the CD spectra of other more conformationally rigid nitrosamines, suggests that the sector signs in **97** should be reversed[124,132]. More recently a different sector rule for the nitrosamino chromophore (**99**) was suggested[75]. Successful application of this rule to *N*-nitroso deriva-

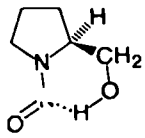


(Signs refer to upper sectors)

(**99**)

tives of α-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[75].

It is to be noted that there is sometimes an additional difficulty in the interpretation of the Cotton effects for chiral nitrosamines[75]. (*S*)-*N*-Nitrosoprolinol [(*S*)-**100**] in methanol, shown by IR and NMR measurements to occur in a fixed *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



[(*S*)-**100**]

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[75].

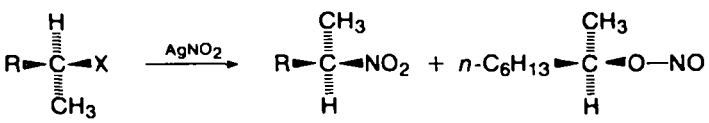
Quantum-mechanical calculations also suggest that a clear-cut sector rule cannot be applied to the nitrosamino chromophore[133]. The calculated results for chiral alkyl-substituted *N*-nitrosopiperidines reflect the extreme sensitivity of the $n \rightarrow \pi^*$ rotatory strength to the position of 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

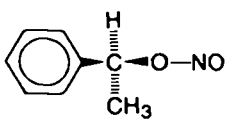


[(*S*)-**101**] R = C_6H_{13}-*n*, X = Br
[(*S*)-**103**] R = C_6H_5, X = Cl

[(*R*)-**102**] R = C_6H_{13}-*n*
[(*R*)-**104**] R = C_6H_5

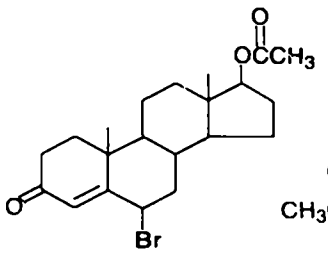
[(*R*)-**85**]

nitrite [(*R*)-**85**], both with complete or almost complete inversion of configuration[112]. In contrast, the same reaction using (*S*)-α-phenylethyl chloride [(*S*)-**103**] leads to (*R*)-α-phenylnitroethane [(*R*)-**104**] and also to (*S*)-α-phenylethyl nitrite [(*S*)-**105**], both of these compounds being far from optically pure. A direct displace-



[(*S*)-**105**]

ment of this type was unsuccessful with 6β-bromotestosterone acetate (**106**), but direct nitration with fuming nitric acid of 5-androstene-3,17-diol diacetate (**107**) and related steroids (**108** and **109**) gives the corresponding vinyl nitro steroids



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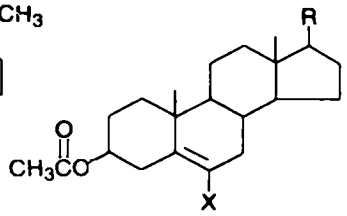
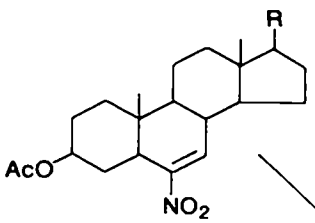
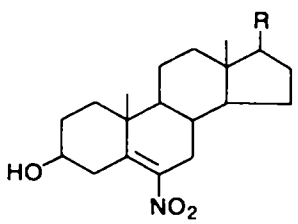


(107) R = $OCOCH_3$, X = H
(108) R = $COCH_3$, X = H
(109) R = C_8H_{17}, X = H
(110) R = $OCOCH_3$, X = NO_2
(111) R = $COCH_3$, X = NO_2
(112) R = C_8H_{17}, X = NO_2



(110) R = $OCOCH_3$
(111) R = $COCH_3$

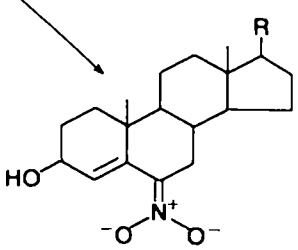
$HClO_4/CH_3OH$



(113) R = OH
(114) R = $COCH_3$

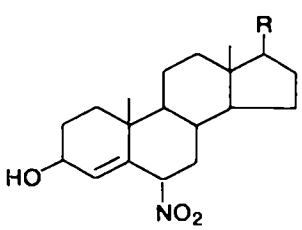
OH^-

OH^-



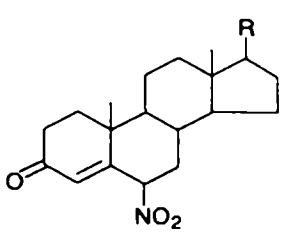
(115) R = OH
(116) R = $COCH_3$

H^+



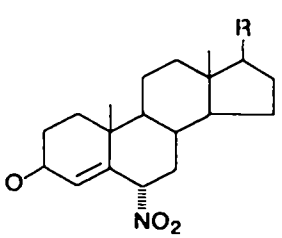
(117) R = OH
(118) R = $COCH_3$

[O]



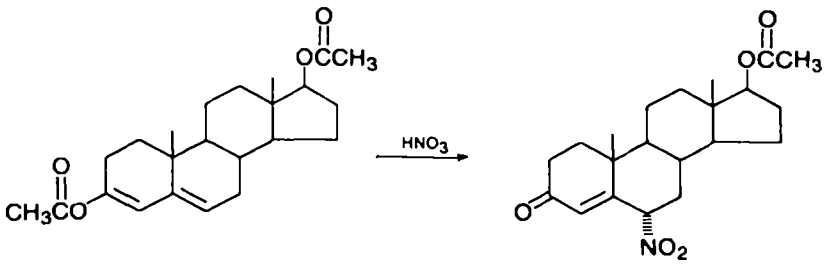
(119) R = OH
(120) R = $COCH_3$

OH^-



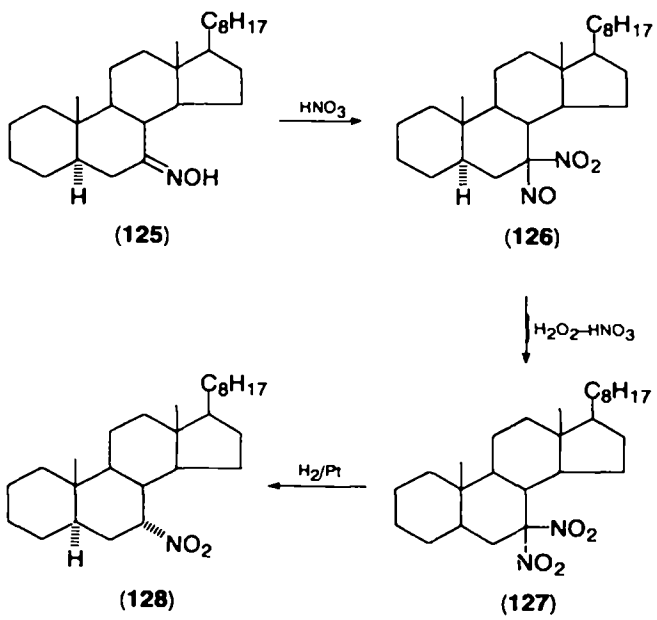
(121) R = OH
(122) R = $COCH_3$

(**110–112**)[134]. 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[135]. 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**)[136].



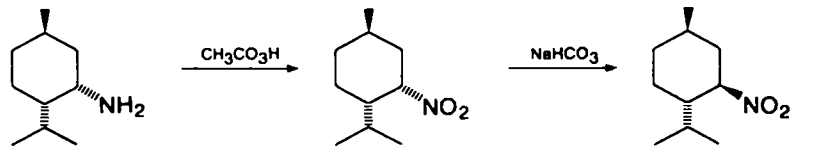
(**124**) (**123**)

Oxidative reactions for the formation of *C*-nitro compounds employ either an oxime[137,138] or a primary amine[139,140]. A very successful method for the preparation of steroidal nitro compounds[138] 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-cholestane (**128**), the configuration at C-7 is controlled by the stereochemical features in **127**.



(**125**) (**126**) (**128**) (**127**)

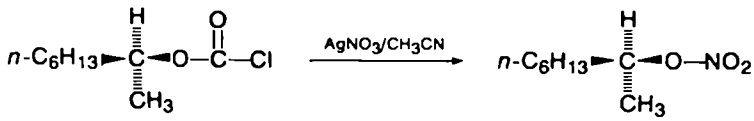
Oxidation of an amine using peracetic acid (Emmons oxidation[139]) preserves the chirality at the centre to which the amino group is attached. Thus oxidation of (+)-neomenthylamine [(+)-**2**] gives (1*R*,3*S*,4*S*]-3-nitro-*p*-menthane [(1*R*,3*S*,4*S*)-**129**], which on treatment with a catalytic amount of sodium bicarbonate in boiling ethanol is isomerized to (1*R*,3*R*,4*S*)-3-nitro-*p*-menthane [(1*R*,3*R*,4*S*)-**130**][141].



[(+)-**2**] [(1*R*, 3*S*, 4*S*)-**129**] [(1*R*, 3*R*, 4*S*)-**130**]

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° to 0°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

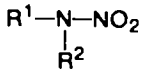


[(*S*)-**131**] [(*S*)-**132**]

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.

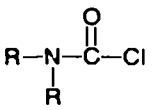
3. N-*Nitro compounds, nitramines*

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]. Anal-

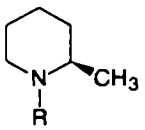


(**133**) R^1 = alkyl or aryl, R^2 = H
(**134**) R^1 = R^2 = alkyl or aryl

ogous 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*)-*N*-nitroso-α-pipecoline [(*R*)-**88**] was converted to (*R*)-*N*-nitro-α-pipecoline [(*R*)-**136**][149].



(135)



[(*R*)-**88**] R = NO
[(*R*)-**136**] R = NO_2

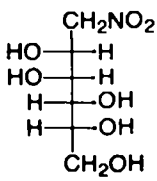
B. Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD)

1. C-*Nitro compounds*

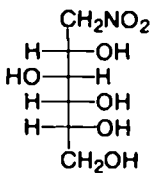
An early review of the ORD of chiral *C*-nitro compounds[151] has been augmented by extensive ORD[114,140,152] and CD measurements[114,153,154] of a substantial number of *C*-nitro steroids and ORD measurements of 1-nitro-1-deoxy monosaccharide derivatives[155,156].

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[39] 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].



(D-**137**)

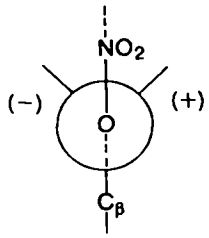


(D-**138**)

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 α-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.

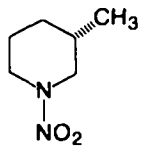
For the nitrate esters of other chiral alcohols, including those of steroidal alcohols[142,143], monoterpene alcohols[143] and α-hydroxy acids[143], three optically active absorption bands, at 270, 230 and 200–210 nm, are observed. Using conformational analysis based on X-ray and spectrographic data, 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 application 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 symmetry plane[143].



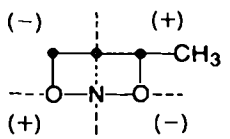
(139)

3. N-*Nitro compounds, nitramines*

The CD spectra of chiral nitramines[148,149], showing a strong absorption band near 240 nm, also reveals an optically active, forbidden transition near 270 nm[148], the position agreeing with the energy of an $n \rightarrow \pi^*$ transition predicted by semi-empirical calculations[133]. The planar arrangement of the nitramino chromophore (C_{2v} symmetry) suggests an octant rule[148], similar to that for chiral ketones[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[39]. Thus, (*S*)-*N*-nitro-β-pipecoline [(*S*)-**140**] with

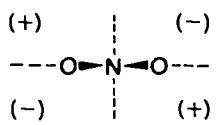


[(*S*)-**140**]



(141)

its methyl group preferably in an equatorial conformation is, on the basis of octant projection **141**, predicted to show, in agreement with experiment, a positive Cotton effect near 270 nm[148]. As is suggested by quantum-mechanical calculations on chiral nitramines[133], more recent CD measurements[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-α-pipecoline [(*R*)-**136**], the methyl group in (*R*)-**136** preferably in an axial conformation. On the other hand, a quadrant rule (**142**)



(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[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 α-alkyl-substituted *N*-nitropiperidines[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[133].

V. ACKNOWLEDGEMENTS

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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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[1] 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):

$$AB \longrightarrow \dot{A} + \dot{B} \qquad (1)$$

when the reverse reaction, a radical combination reaction (2):

$$\dot{A} + \dot{B} \longrightarrow AB \qquad (2)$$

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 $\Delta U^{\ominus}(T)$, which will be given by:

$$\Delta U^{\ominus}(\bar{T}) = E_1 - E_2 = \Delta H_1^{\ominus}(\bar{T}) - \Delta nR\bar{T}$$

where $\Delta H_1^{\ominus}(\bar{T})$ is the enthalpy change during reaction (1) at the mean reaction temperature $\bar{T}$, and Δn is the change in the number of moles during reaction (1). Hence, for the case where E_2 is equal to zero:

$$\Delta H_1(\bar{T}) = E_1 + \Delta nR\bar{T}$$

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 $\bar{T}$. Hence:

$$\Delta H_1^{\ominus}(298) = E_1 + \Delta nR\bar{T} + \overline{\Delta C_p}(298 - T) \qquad (A)$$

where $\overline{\Delta C_p}$ is the mean change between the heat capacities of the products and

reactant over the temperature range 298 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, $\Delta H_1^{\ominus}(298)$ may be equated with the dissociation energy of the bond broken in the reaction, D(A—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 ±1 kcal/mol; the $\Delta nR\overline{T}$ term, for Δn equal to one, ranges from 0.6 to 3.0 kcal/mol between 298 and 1500 K. Thus the assumption that D(A—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—B) may be obtained in other cases, especially where the mean reaction temperature is high. Knowledge of the heats of formation of the radicals Ȧ and Ḃ and the reactant AB allows calculation of D(A—B) from the thermochemistry:

$$D(\text{A—B}) = \Delta H_f^{\ominus}(\dot{\text{A}}) + \Delta H_f^{\ominus}(\dot{\text{B}}) - \Delta H_f^{\ominus}(\text{AB}) \qquad \text{(B)}$$

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—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 $-[\Delta G^{\ominus}(T) - \Delta H^{\ominus}(298)]/T$ and $\Delta H^{\ominus}(T) - \Delta H^{\ominus}(298)$, 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 J. A decision had also to be reached regarding the notation for standard states. McGlashan[5] recommends use of the symbol $^{\ominus}$ to represent standard states and we have adopted this convention. We have denoted the standard heat of formation as $\Delta H_f^{\ominus}$, as this seems more satisfactory than $\Delta_f H^{\ominus}$. For standard heats of sublimation and vaporization we have used $\Delta H_s^{\ominus}$ and $\Delta H_v^{\ominus}$.

II. NITRO COMPOUNDS

A. Nitroalkanes

Stull, Westrum and Sinke[3] and Cox and Pilcher[4] list thermochemical data on several nitroalkanes and, more recently, Shaw[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[4] and Stull, Westrum and Sinke[3] for the heat of formation of liquid nitromethane is the unpublished National Bureau of Standards value of -27.03 ± 0.15 kcal/mol quoted by McCullough and coworkers[7]. On the basis of a value of 9.17 ± 0.01 kcal/mol for the heat of vaporization of nitromethane[7] a value of $\Delta H_f^\ominus$ for gaseous nitromethane of -17.86 ± 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[8] determined the heat of combustion of nitromethane from which a value of $\Delta H_f^\ominus$ for gaseous nitromethane of -19.3 ± 0.3 kcal/mol was obtained. Lebedeva and Ryadnenko[9] obtained a value of $\Delta H_f^\ominus$ for liquid nitromethane of -26.9 ± 0.1 kcal/mol giving $\Delta H_f^\ominus$ equal to -17.73 ± 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[8] also measured the heat of combustion of dinitromethane, from which they obtained a value of -25.2 ± 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[10] to -18.6 kcal/mol[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[12] who obtained $\Delta H_f^\ominus = -11.5 \pm 0.5$ kcal/mol for the solid, $\Delta H_f^\ominus = -7.0 \pm 0.4$ kcal/mol for the liquid and -0.2 ± 0.5 kcal/mol for gaseous trinitromethane.

The value selected by Cox and Pilcher[4] for the heat of formation of liquid tetranitromethane is that of $+8.9 \pm 0.7$ kcal/mol obtained by Gardner and Grigger[13]. Using the value of 9.7 kcal/mol for the heat of vaporization of tetranitromethane obtained by Edwards[14] a value of 18.6 ± 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[15]. Using a semimicrocalorimeter they obtained $\Delta H_f^\ominus$ equal to 9.2 ± 0.4 kcal/mol for liquid tetranitromethane. With $\Delta H_v^\ominus$ equal to 10.5 ± 0.1 kcal/mol they obtained a value of 19.7 ± 0.5 kcal/mol for the heat of formation of gaseous tetranitromethane, in agreement within experimental error with the results of Gardner and Grigger[13].

The heat of formation of fluorodinitromethane was determined by Pepekin and coworkers[16]. They found that the heat of formation of liquid fluorodinitromethane was -66.5 ± 0.6 kcal/mol. They obtained the heat of vaporization of the compound and thus found a value of -56.1 ± 0.8 kcal/mol for the heat of formation of gaseous fluorodinitromethane.

TABLE 1. Preferred values of heats of formation of nitro derivatives of methane

Compound	State	$\Delta H_f^\ominus$ (kcal/mol)	Reference
Nitromethane	l	−27.0 ± 0.15	7, 9[a]
	g	−17.8 ± 0.15	7, 9[a]
Dinitromethane	l	−25.2 ± 0.2	8
	g	−14.2[b]	8
Trinitromethane	s	−11.5 ± 0.5	12
	l	−7.9 ± 0.4	12
	g	−0.2 ± 0.5	12
Tetranitromethane	l	9.0 ± 0.4	13, 15[c]
	g	19.2 ± 0.6	13, 15[c]
Fluorodinitromethane	l	−66.5 ± 0.6	16
	g	−56.1 ± 0.8	16

[a]Mean of the values of Lebedeva and Ryadnenko[9] and the unpublished National Bureau of Standards value[7].
[b]$\Delta H_v^\ominus$ was estimated by analogy with other nitro compounds.
[c]Mean of the values obtained by Gardner and Grigger[13] and Lebedev and coworkers[15].

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, $S^\ominus(298)$ has been determined to be 65.73 cal/(mol K)[17] and $C_p^\ominus(298)$ = 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)

	Solid				Liquid				Gas			
Compound	ΔH_f° (exp.)	Reference	ΔH_f° (g.a.r.)	ΔH_f° (exp.) − ΔH_f° (g.a.r.)	ΔH_f° (exp.)	Reference	ΔH_f° (g.a.r.)	ΔH_f° (exp) − ΔH_f° (g.a.r.)	ΔH_f° (exp.)	Reference	ΔH_f° (g.a.r.)	ΔH_f° (exp) − ΔH_f° (g.a.r.)
1-Nitroalkanes												
Nitroethane					−34.3	3	−33.6	−0.7	−24.2	3	−24.6	+0.4
					−34.4	9	−33.6	−0.8				
1-Nitropropane					−40.2	3	−39.7	−0.5	−29.8	3	−29.5	−0.3
					−40.0	9	−39.7	−0.3				
1-Nitrobutane					−46.0	3	−45.8	−0.2	−34.4	3	−34.4	0.0
1-Nitropentane					−51.5	9	−51.9	+0.4			−39.3	
2-Nitroalkanes												
2-Nitropropane					−43.3	3	−44.4	+1.1	−33.5	3	−34.0	+0.5
2-Nitrobutane					−49.6	3	−48.5	−1.1	−39.1	3	−38.9	−0.2
2-Nitrodecane					−84.0	9	−85.1	+1.1			−68.3	
1,1-Dinitroalkanes												
1,1-Dinitroethane					−35.4	18	−35.6	+0.2			−20.1	
1,1-Dinitropropane					−39.0	18	−39.7	+0.7	−25.8	4	−25.8	[0][a]
1,1-Dinitropentane					−51.9	18	−51.9	0.0			−35.6	
1,1,1-Fluorodinitroalkanes												
1,1,1-Fluorodinitroethane					−67.3	19	−71.8	+4.5	−57.0	20	−57.0	[0][a]
1,1,1-Fluorodinitropropane					−80.4	19	−75.9	−4.5			−61.9	
α,ω-*Dinitroalkanes*												
1,2-Dinitroethane	−42.7	18	−44.4	+1.7	−39.7	18	−44.0	+4.3			−28.8	
	−43.9	3	−44.4	+0.5	−40.9	3[b]	−44.0	+3.1				

1,3-Dinotropropane			−51.3		−49.5	18	−50.1	+0.6			−33.7	
1,4-Dinitrobutane	−59.6	18	−58.1	−1.5	−56.8	18	−56.2	−0.6			−38.6	
Primary–secondary nitroalkanes												
1,2-Dinitropropane							−52.8				−38.2	
2,2-Dinitroalkanes												
2,2-Dinitropropane	−46.0	18	−46.5	+0.5	−43.3	18	−43.5	+0.2	−30.4	11	−30.4	[0][a]
2,2,3,3-Tetranitrobutane	−43.6	18	−42.7	−0.9	−40.1	18	−39.8	−0.3			−27.2	
1,1,1-Trinitroalkanes												
1,1,1-Trinitroethane	−26.9	18	−26.8	−0.1	−23.2	18	−24.6	+1.4			−11.6	
Hexanitroethane	28.6	19	20.8	+7.8			22.0					
	20.0	21	20.8	−0.8					36.9	21	36.9	[0][a]
1,1,1-Trinitropropane					−28.1	19	−26.7	−1.4			−16.6	
1,1,1,3-Tetranitropropane	−38.6	19	−38.7	+0.1			−36.6				−20.8	
1,1,1,4-Tetranitrobutane	−45.4	18	−45.5	+0.1	−42.8	18	−42.7	−0.1			−25.6	
1,1,1,3,5,5,5-Heptanitro-pentane	−36.7	18	−49.9	+13.2	−33.7	18	−47.4	+13.7			−26.3	
Tertiary nitroalkanes												
2-Methyl-2-nitropropane	−54.9	22	−55.6	+0.7	−51.9	22	−52.5	+0.6	−42.2	22	−42.2	[0][a]
2,3-Dimethyl-2,3-dinitro-butane	−74.5	18	−73.0	−1.5	−71.0	18	−69.8	−1.2			−64.0	
2-Methyl-2,3,3-trinitro-pentane	−70.0	3	−64.7	−5.3								
Phenyl-substituted nitroalkanes												
Dinitrophenylmethane	−9.9	23							8.3	23	8.3	[0][a]
2,2,2-Trinitro-1-phenyl-ethane	−4.4	23							15.7	23	15.7	[0][a]
Fluorodinitrophenylmethane					−56.5	23			−44.2	23	−44.2	[0][a]

[a] 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.

[b] 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]

Group	$\Delta H_f^\ominus$ (solid)	$\Delta H_f^\ominus$ (liquid)	$\Delta H_f^\ominus$ (gas)
$C-(C)(H)_2(NO_2)$	−22.2	−22.0	−14.4
$C-(C)_2(H)(NO_2)$	−21	−21.2	−13.6
$C-(C)_3(NO_2)$	−16.2	−17.7	−11.6
$C-(C)(H)(NO_2)_2$		−24.0	−10.7
$C-(C_b)(H)(NO_2)_2$			−13.7
$C-(C)(F)(NO_2)_2$		−60.2	−46.8
$C-(C_b)(F)(NO_2)_2$			−66.2
$C-(C)_2(NO_2)_2$	−20.2	−20.3	−10.0
$C-(C)(NO_2)_3$	−13.6	−13.0	−1.45
$C-(C)(H)_3$	−13.15	−11.6	−10.2
$C-(C)_2(H)_2$	−6.85	−6.1	−4.9
$C_B-(C)$			5.51
$C_B-(H)$			3.3
Gauche interactions			
Alkyl–alkyl	2	2	0
Alkyl–NO_2	2	2	0
NO_2–NO_2	8	8	6.6

[a]Based on the review by Shaw[6].

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[19], 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 $\Delta H_f^\ominus$, $S^\ominus$ (298) and $C_p^\ominus$ 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]

Compound	$\Delta H_f^\ominus$ kcal/mol	$S^\ominus$ (298) cal/(mol K)	$C_p^\ominus$ [cal(mol K)] 298 K	500 K	800 K	1000 K
Nitromethane	−17.8	65.73	13.70	19.56	25.56	28.17
Nitroethane	−24.2	75.39	18.69	27.92	36.81	40.67
1-Nitropropane	−29.8	85.00	24.41	36.24	47.96	53.06
2-Nitropropane	−33.5	83.10	24.26	36.52	48.22	53.24
1-Nitrobutane	−34.4	94.28	29.85	44.48	59.03	65.39
2-Nitrobutane	−39.1	91.62	29.51	44.61	59.44	65.96

[a]Values taken from Stull, Westrum and Sinke[3].

methane 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:

$$RNO_2 \longrightarrow \dot{R} + NO_2 \quad (3)$$

$$\dot{R} + NO_2 \longrightarrow RNO_2 \quad (4)$$

D(C—N) may be calculated from the thermochemistry, using:

$$\Delta H^{\ominus}(298) = D(C—N) = \Delta H_f^{\ominus}(\dot{R}, g) + \Delta H_f^{\ominus}(NO_2, g) - \Delta H_f(RNO_2, g)$$

and knowing the heats of formation of the alkyl radical (from group additivity or published values), of nitrogen dioxide (7.91 ± 0.2 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 ± 0.15 kcal/mol, and using a value of -17.8 ± 0.15 kcal/mol for the heat of formation of nitromethane, D(C—N) is calculated to be 60.8 ± 0.3 kcal/mol. Values of D(C—N) for various mononitroalkanes are listed in Table 5.

If the activation energy for reaction (3) is known, the relationship discussed in the introduction:

$$D(C—N) = \Delta H^{\ominus}(298) = E_3 - E_4 + R\overline{T} + \overline{\Delta C}_p^{\ominus}(298 - \overline{T})$$

may be used to derive the bond dissociation energy. This may be simplified to:

$$D(C—N) = E_3 + R\overline{T} + \overline{\Delta C}_p^{\ominus}(298 - \overline{T}) \quad (C)$$

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	$E_1 + R\overline{T}$	$\Delta H^{\ominus}(298) = D$(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 ± 1.4 kcal/mol.
[b]Mean D(C—N) (kinetic) = 58.4 ± 2.0 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[26]; for nitrogen dioxide the heat capacity is tabulated[24], 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 ± 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 $\overline{\Delta C}_p^\circ(298 - \overline{T})$ 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 ±1 kcal/mol. We therefore make the approximation that $\Delta H(T)$ is equal to $\Delta H^\circ(298)$ 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	$E_1 + R\overline{T} \sim D$(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
Tetranitromethane	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 $\overline{\Delta C}_p^\circ(298 - \overline{T}) \sim 0$.
[b]No experimental details available for these unpublished results so we assume $\overline{T}$ = 235°C as in Reference 28.

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 $CH_3CH_2\dot{C}HNO_2$ radical an approximate value for the heat of formation may be arrived at by considering the process:

$$CH_3CH_2CH_2NO_2 \longrightarrow CH_3CH_2\dot{C}HNO_2 + \dot{H}$$

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 $\Delta H_f^{\ominus}(\dot{H})$ equal to 52.1 kcal/mol, we find that $\Delta H_f^{\ominus}(CH_3CH_2\dot{C}HNO_2)$ is 16.1 kcal/mol. Hence, with $\Delta H_f^{\ominus}$ 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 $\Delta H_f^{\ominus}(CH_3\dot{C}NO_2CH_3)$ 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 7. C—N bond dissociation energies for halonitroalkanes and halopolynitroalkanes (kcal/mol)

Compound	E_1	$E_1 + R\overline{T} \sim D$(C—N) (kinetic)[a]	Reference
Mononitro compounds			
Nitromethane	58.5	59.5	27
Trichloronitromethane	37.67	38.5	37
Dinitro compounds			
1,1-Dinitroethane	47.1	48.1	28
Fluorodinitromethane	48.5	49.5	32
Difluorodinitromethane	47.4	48.4	38
Chlorodinitromethane	40.6	41.5	32
Dichlorodinitromethane	34.3	35.1	34
1,1,1-Fluorodinitroethane	47.7	48.6	38
Trinitro compounds			
Trinitromethane	42.4	43.1	32
Fluorotrinitromethane	41.9	42.8	38
Chlorotrinitromethane	36.4	37.2	34
Bromotrinitromethane	36.2	37.0	34
Iodotrinitromethane	34.4	35.2	34
Hexanitroethane	35.8	36.6	34
1,2-Difluorotetranitroethane	42.2	43.0	38
Fluoropentanitroethane	36.5	37.3	38

[a]No information on heat capacities available so we assume $\Delta C_p(298 - \overline{T}) \sim 0$.

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 than 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[4] and by Stull, Westrum and Sinke[3]. Shaw[39] 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[39] 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[3]. Nitroaromatic amines are also included in Table 8.

TABLE 8. Heats of formation of some aromatic nitro compounds

Formula	Name	State	$\Delta H_f^\ominus$ (kcal/mol)	Reference
$C_6H_3N_3O_6$	1,3,5-Trinitrobenzene	s	−8.9 ± 0.3	40
		l	−4.9 ± 0.4	40
$C_6H_4N_2O_4$	*m*-Dinitrobenzene	s	−6.5 ± 0.1	40
		l	−1.6 ± 0.2	40
$C_6H_4N_2O_4$	*o*-Dinitrobenzene	s	−0.4 ± 0.15	40
		l	+5.1 ± 0.25	40
$C_6H_4N_2O_4$	*p*-Dinitrobenzene	s	−9.2 ± 0.1	40
		l	−1.2 ± 0.4	40
$C_6H_5NO_2$	Nitrobenzene	l	+2.32 ± 0.10	41
		g	+15.72 ± 0.10	41
$C_6H_5N_5O_6$	1,3-Diamino-2,4,6-trinitro-benzene	s	−23.4 ± 0.8	42
$C_6H_6N_2O_2$	*m*-Nitroaniline	s	−9.2 ± 0.1	43
		l	−3.5 ± 0.3	43
		g	+16.3 ± 1.8[a]	44

TABLE 8. *continued*

Formula	Name	State	$\Delta H_f^{\ominus}$ (kcal/mol)	Reference
$C_6H_6N_2O_2$	*o*-Nitroaniline	s	−6.3 ± 0.1	43
		l	−2.3 ± 0.3	43
$C_6H_6N_2O_2$	*p*-Nitroaniline	s	−10.3 ± 0.2	43
		l	−5.2 ± 0.4	43
		g	+14.2 ± 0.4[a]	44
$C_6H_6N_6O_6$	1,3,5-Triamino-2,4,6-trinitro-benzene	s	−33.4 ± 1.2	42
$C_7H_4N_2O_6$	3,5-Dinitrobenzoic acid	s	−103.4 ± 0.1	40
		l	−98.0 ± 0.3	40
$C_7H_5NO_4$	*m*-Nitrobenzoic acid	s	−98.9 ± 0.1	40
		l	−94.3 ± 0.4	40
$C_7H_5NO_4$	*o*-Nitrobenzoic acid	s	−95.3 ± 0.15	40
		l	−90.6 ± 0.45	40
$C_7H_5NO_4$	*p*-Nitrobenzoic acid	s	−102.1 ± 0.2	40
		l	−93.8 ± 0.5	40
$C_7H_5N_3O_6$	2,4,6-Trinitrotoluene	s	−15.1 ± 1.2	42
		s	−19.25 ± 0.74	45
		g	+5.75 ± 0.84	45
		g	+7.7 ± 0.8[a]	46
$C_7H_6N_2O_4$	2,4-Dinitrotoluene	s	−15.38 ± 0.74	45
		g	+8.42 ± 0.80	45
		g	+5.8 ± 0.7[a]	46
$C_7H_7NO_2$	*p*-Nitrotoluene	s	−11.52 ± 0.72	45
		g	+7.38 ± 0.94	45
$C_{10}H_4N_4O_8$	1,4,5,6-Tetranitro-naphthalene	s	+11.3 ± 2.0	42
$C_{12}H_4N_6O_{12}$	2,2′,4,4′,6,6′-Hexanitro-biphenyl	s	+16.3 ± 2.0	42
$C_{12}H_4N_8O_{12}$	2,2′,4,4′,6,6′-Hexanitro-azobenzene	s	+69.2 ± 1.3	42
		s	+61.087 ± 0.26	47
$C_{12}H_6N_8O_{12}$	3,3′-Diamino-2,2′,4,4′,6,6′-hexanitrobiphenyl	s	−3.6 ± 2.9	42
$C_{13}H_5N_5O_{11}$	2,2′,4,4′,6-Pentanitrobenzo-phenone	s	−27.4 ± 1.2	42
$C_{14}H_6N_6O_{12}$	2,2′,4,4′,6,6′-Hexanitrostilbene	s	+16.2 ± 2.5	42
		s	ΔH_s = 43.01 kcal/mol at 183°C	48
$C_{18}H_5N_9O_{18}$	2,2′,2″,4,4′,4″,6,6′,6″-Nona-nitroterphenyl	s	+31.6 ± 2.6	42
$C_{18}H_6N_8O_{16}$	2,2″,4,4′,4″,6,6′,6″-Octanitro-*m*-terphenyl	s	+22.6 ± 4.4	42
$C_{24}H_6N_{12}O_{24}$	2,2′,2″,2‴,4,4′,4″,4‴,6′,6′, 6″,6‴-Dodecanitroquater-phenyl	s	+50.9 ± 2.4	42
$C_{24}H_6N_{14}O_{24}$	Azobis(2,2′,4,4′,6,6′-hexanitro-biphenyl)	s	+114.8 ± 1.9	42
$C_{24}H_6N_{16}O_{24}$	2,2′,2″,2‴,4,4′,4″,4‴,6,6′, 6″,6‴-Dodecanitro-3,3′-bis(phenylazo)-biphenyl	s	+189.2 ± 2.6	42

[a]Standard enthalpy of sublimation was measured by these workers. Values of $\Delta H_f^{\ominus}$ (g) are based on the values given by Cox and Pilcher[4] for $\Delta H_f^{\ominus}$ (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 ± 0.45 kcal/mol for the heat of formation of the solid compound[4], 1.5 kcal/mol lower than the more recent value of Lebedeva and coworkers[40], for which experimental details are not easily available. For *m*-dinitrobenzene, Cox and Pilcher[4] corrected results by Badoche[49] to obtain a value of -8.1 ± 0.6 for the heat of formation of the solid, lower by 1.6 kcal/mol than the value of Lebedeva and coworkers[40]. Stull, Westrum and Sinke[3] list heats of formation for *o*- and *p*-dinitrobenzene of 2.7 and -9.05 kcal/mol, given by Kharasch[50]. The more recent values by Lebedeva and coworkers[40] 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[51] of 2.7 kcal/mol, which compares well with the value of Lebedeva and coworkers[41] of 2.32 ± 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[4] list heats of formation of -6.29 ± 0.77, -6.8 ± 1.5 and -9.91 ± 0.17 kcal/mol respectively, compared with the values of -6.3 ± 0.1, -9.2 ± 0.1 and -10.3 ± 0.2 kcal/mol obtained by Lebedeva and coworkers[43]: 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[3] 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[50], written in 1929. These values are not very far removed from the results of Lebedeva and coworkers[40] of -95.3 ± 0.15, -98.9 ± 0.1 and -102.1 ± 0.2 kcal/mol respectively. These latter, more recent, values will probably be more reliable. For 2,4,6-trinitrotoluene, Cox and Pilcher[4] select a value of -16.03 ± 0.65 kcal/mol for the heat of formation of the solid, which agrees within experimental error with the value of -15.1 ± 1.2 kcal/mol obtained by Rouse[42]. The value of -19.25 ± 0.74 kcal/mol obtained by Lenchitz and coworkers[45] 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[4] for 2,4,6-trinitrotoluene is 28.3 ± 1.0 kcal/mol. Lenchitz and Velicky[56] found ΔH_s° equal to 25.0 ± 0.4 kcal/mol, using a Knudsen effusion cell, while Pella[46] obtained a value of 23.7 ± 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[52], is probably too high[56]. The heat of formation of gaseous 2,4,6-trinitrotoluene is selected here to be 7.7 ± 0.8 kcal/mol[46], bearing in mind the relative precision of the various determinations. For solid 2,4-dinitrotoluene Cox and Pilcher[4] select a heat of formation of -17.10 ± 0.65 kcal/mol. Lenchitz and coworkers[45] measured the heat of combustion of the solid compound and hence obtained a value of -15.38 ± 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[56] of 23.8 ± 0.3 kcal/mol for 2,4-dinitrotoluene is in good agreement with the value of -22.9 ± 0.3 kcal/mol obtained by Pella[46]. Using the value selected by Cox and Pilcher for the heat of formation of the solid, and using a mean value of 23.3 ± 0.3 kcal/mol for its heat of sublimation we arrive at a value of 6.2 ± 0.7 kcal/mol for the heat of formation of gaseous 2,4-dinitrotoluene. For *p*-nitrotoluene Stull, Westrum and Sinke[3] list a value by Kharasch[50] of -8.9 for the heat of formation of the solid. The more recent value by Lenchitz and coworkers of -11.52 ± 0.72 kcal/mol is more reliable. For 2,2′,4,4′,6,6′-hexanitroazobenzene the result of Rouse[42] differs considerably from that of Baroody and Carpenter[47].

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[42], 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:

$$D(\text{C—N}) = \Delta H_f^{\ominus}(\text{C}_6\text{H}_5^{\bullet}, \text{g}) + \Delta H_f^{\ominus}(\text{NO}_2, \text{g}) - \Delta H_f^{\ominus}(\text{C}_6\text{H}_5\text{NO}_2, \text{g})$$

Using heats of formation of 78.5, 7.91 and 15.72 kcal/mol for the phenyl radical[26], nitrogen dioxide[24] and nitrobenzene[41] 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):

$$\text{C}_6\text{H}_5\text{NO}_2 \longrightarrow \text{C}_6\text{H}_5^{\bullet} + \text{NO}_2 \qquad (5)$$

by the expression

$$D(\text{C—N}) = E_5 + R\bar{T} + \overline{\Delta C}_p^{\ominus}(298 - \bar{T})$$

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 $\Delta H_5(720)$. If we assume that $\overline{\Delta C}_p(298 - \bar{T})$ is negligibly small, then $\Delta H_5(720)$ may be taken to be approximately equal to $\Delta H_5^{\ominus}(298)$. 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 ±1 kcal/mol, if no correction is made for NH_2—R or RNH—R *gauche* interactions. For the diamines, agreement is best for the unbranched compounds, again not correcting for *gauche* interactions. In each case the estimated $\Delta H_f^\ominus$ is higher, by ~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 $\Delta H_f^\ominus$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 $\Delta H_f^\ominus$ for the groups $C(N)(F)_3$, $C(N)(H)_2(C_B)$ and $N(C_B)_3$ of −161 2, −5.83 and 30.1 kcal/mol respectively.

For the standard entropies, agreement between observed and estimated values is better than ±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-, *s*-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 9. Thermochemical properties of gaseous amines obtained experimentally and estimated by group additivity rules (g.a.r.)

Compound	σ[a]	ΔH_f° (kcal/mol)				S° (298) [cal/(mol K)]				C_p° (298) [cal/(mol K)]			
		ΔH_f° (obs.)	Ref.	ΔH_f° (g.a.r.)	ΔH_f° (obs.) – ΔH_f° (g.a.r.)	S° (298) (obs.)	Ref.	S° (298) (g.a.r.)	S° (obs.) – S° (g.a.r.)	C_p° (298) (obs.)	Ref.	C_p° (298) (g.a.r.)	C_p° (obs.) – C_p° (g.a.r.)
Perfluoroaminomethane		−169.0	57	−169.0	[0][b]								
Ethylamine	3	−11.35	4	−11.9	0.55	68.03	58	67.74	0.29	17.36	58	17.16	0.2
Ethylenediamine	2	−4.07	59	−3.6	−0.47	76.92	60	77.64	−0.72				
Cyclopropylamine		18.42	61	17.3	1.12								
Propylamine	3	−16.77	62	−16.83	0.06	77.9	63	77.16	0.74	21.8	63	22.66	−0.86
						77.7	64	77.16	0.54				
Isopropylamine	3^2	−20.02	62	−20.56	0.54	74.7	63	74.46	0.23	22.6	63	22.77	−0.17
1,2-Propanediamine	2 optical isomers $\sigma = 3$	−12.81	59	−12.28	−0.53	86.07	60	87.12	−1.05				
Cyclobutylamine		9.8	65	10.95	−1.15								
2-Methyl-1-aminopropane		−23.57	59	−23.86	0.29								
2-Methyl-2-aminopropane	3^4	−28.9	62	−28.64	−0.26	78.3	63	78.1	0.2	28.8	63	28.64	0.10
1,2-Butanediamine		−17.68	59	−17.23	−0.45								
2-Methyl-1,2-propanediamine	3^2	−21.57	59	−20.36	−1.21	88.34	60	91.57	−3.28				
Cyclopentylamine		−13.13	65	−13.9	0.77								
Cyclohexylamine		−25.07	66	−25.15	0.08								
Dipropylamine		−27.43	67	−27.86	0.43								
Diisopropylamine		−34.44	67	−35.32	0.88								
Diethyl(2-hydroxyethyl)amine		−74.0	69	−61.94	−12.06								
Benzylamine		20.98	68	20.98	[0][c]								
Dibutylamine		−37.77	67	37.76	−0.01								
Diisobutylamine		−42.84	67	−41.92	−0.92								
Triphenylamine		78.1	70	78.1	[0][d]								

[a] σ is the symmetry of the molecule which is required in calculating S° (298). $R \ln \sigma$ is subtracted from the group additivity value of S° (298).

[b] From this value of the heat of formation of perfluoroaminomethane we may derive a value of ΔH_f° 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 ΔH_f° for the group $C(N)(H)_2(C_B)$ 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 ΔH_f° for the group $N(C_B)_3$ of 30.1 kcal/mol, on the assumption that there is no steric destabilization in the molecule.

TABLE 10. Recent thermochemical results for amines

Formula	Name	State	ΔH_f° (kcal/mol)	Reference	S° (298) [cal/(mol K)]	Reference	C_p° (298) [cal/(mol K)]	Reference
CF_5N	Difluoroaminotrifluoromethane	g	−169.0 ± 0.6	57				
C_2H_7N	Ethylamine	g			68.03	58	17.36	58
$C_2H_8N_2$	Ethylenediamine	l	−15.06 ± 0.13	59				
		g	−4.07 ± 0.14	59	76.92	60		
C_3H_7N	Cyclopropylamine	l	10.95 ± 0.12	61				
		g	18.42 ± 0.16	61				
C_3H_9N	Propylamine	l	−24.26 ± 0.09	62				
		g	−16.77 ± 0.13	62	77.9 ± 0.2	63	21.8	63
C_3H_9N	Isopropylamine	l	−26.83 ± 0.16	62				
		g	−20.02 ± 0.19	62	74.7 ± 0.2	63	22.6	63
$C_3H_{10}N_2$	1,2-Propanediamine	l	−23.38 ± 0.10	59				
		g	−12.81 ± 0.11	59	86.07 ± 0.2	60		
$C_4H_5F_2N_5O_8$	Bis(2-fluoro-2,2-dinitroethyl)amine	s	−126.952 ± 0.49	71				
C_4H_9N	Cyclobutylamine	l	1.34 ± 0.14	65				
		g	9.8 ± 0.1[a]	65				
$C_4H_{11}N$	2-Methyl-1-aminopropane	l	−31.68 ± 0.12	59				
		g	−23.57 ± 0.13	59				
$C_4H_{11}N$	2-Methyl-2-aminopropane	l	−36.00 ± 0.12	62				
		g	−28.90 ± 0.15	62	78.3 ± 0.2	63	28.8	63
$C_4H_{12}N_2$	1,2-Butanediamine	l	−28.74 ± 0.19	59				
		g	−17.68 ± 0.20	59				
$C_4H_{12}N_2$	2-Methyl-1,2-propanediamine	l	−32.00 ± 0.16	59				
		g	−21.57 ± 0.17	59	88.34 ± 0.21	60		
$C_5H_{11}N$	Cyclopentylamine	l	−22.74 ± 0.20	65				
		g	−13.13 ± 0.22	65				
$C_6F_{13}N$	Perfluorotriethylamine	l	−746.6	72				
C_6H_7N	Dipropargylamine	l	102.7 ± 1.0	74				
$C_6H_{12}N_4$	Hexamethylenetetramine	s	29.65 ± 0.18	75				
		g	47.6 ± 0.7	75				

$C_6H_{13}N$	Cyclohexylamine	l	−35.3 ± 0.3	66
		g	25.1 ± 0.3	66
$C_6H_{14}ClN$	Cyclohexylamine hydrochloride	s	−97.6 ± 0.4	66
$C_6H_{14}N_2O$	2-(Diethylamino)ethanamide	s	−84.0 ± 1.3	69
$C_6H_{15}N$	Dipropylamine	l	−37.33 ± 0.10	67
		g	−27.43	67
$C_6H_{15}N$	Diisopropylamine	l	−42.64 ± 0.01	67
		g	−34.44	67
$C_6H_{15}NO$	Diethyl(2-hydroxyethyl)amine	g	−74.0 ± 0.13	69
$C_7H_7NO_2$	*m*-Aminobenzoic acid	s	−99.74 ± 0.39	76
		g	−69.15 ± 0.86	76
$C_7H_7NO_2$	*o*-Aminobenzoic acid	s	−95.87 ± 0.29	76
		g	−70.80 ± 0.38	76
$C_7H_7NO_2$	*p*-Aminobenzoic acid	s	−97.99 ± 0.41	76
		g	−70.24 ± 0.98	76
C_7H_9N	Benzylamine	l	8.18 ± 0.41	68
		g	20.98 ± 0.65[b]	68
$C_8H_{19}N$	Dibutylamine	l	−49.27 ± 0.09	67
		g	−37.77	67
$C_8H_{19}N$	Diisobutylamine	l	−52.24 ± 0.11	67
		g	−42.84	67
C_9H_9N	Tripropargylamine	l	160.4 ± 1.4	74
$C_9H_{13}N$	Dipropargylpropylamine	l	90.1 ± 0.5	74
$C_9H_{17}N$	Dipropylpropargylamine	l	20.1 ± 0.6	74
$C_9H_{18}N_2$	Diethyl(1-cyanobutyl)amine	l	−14.8 ± 0.2	69
$C_{10}H_{21}NO_2$	Ethyl 2-(diethylamino)butanoate	l	−134.3 ± 0.15	69
$C_{12}F_{27}N$	Perfluorotributylamine	l	−1328	72
		g	−1313.6	77, 72
$C_{18}H_{15}N$	Triphenylamine	s	56.1 ± 0.8	70
		g	78.1 ± 1.0	70

[a]Based on estimated enthalpy of vaporization calculated as the mean of the values of ΔH_v° for cyclopropyl- and cyclopentyl-amines.
[b]ΔH_v° was obtained from early boiling-temperature data (see Ref. 68).

compounds. For the *trans* isomer of ethylamine*, Petrov and Vvedenskii[58] calculated thermodynamic functions from published vibrational frequencies. Their values for C_p° and S° do not differ significantly from those listed by Stull, Westrum and Sinke[3]. For propylamine, Stull, Westrum and Sinke list thermodynamic functions based upon a substitution constant; the values listed by Scott[63] are based upon vibrational assignments of molecular spectra together with calorimetric determinations of ΔH_f° and S°[62]. 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[3], a value considerably higher than that of −97.99 kcal/mol obtained by Nabavian and coworkers[76]. For benzylamine the only other value of the heat of formation in the liquid state is the value listed by Kharasch[50] in 1929 of 2.0 kcal/mol; the more recent value of 8.18 kcal/mol obtained by Carson and coworkers[68] is preferred. Kharasch[50] 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[67]. Lastly, for the heat of formation of solid triphenylamine an early value of 58.7 kcal/mol is quoted by Stull, Westrum and Sinke[3], in fair agreement with the value of 56.1 kcal/mol obtained by Steele[70]. 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[2] 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[78–81]. Benson and O'Neal[82] 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[83–85]. Tsang[86] 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[83–85] and by Tsang[86] 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

Reaction	E (kcal/mol)	Ref.	$\Delta H^\circ(\bar{T})$ (kcal/mol)	ΔH° (298 K) = D(C—N) (kcal/mol)
$C_6H_5CH_2NH_2 \rightarrow C_6H_5\dot{C}H_2 + \dot{N}H_2$	71.9	83	74.2	73.1
$C_6H_5CH_2NHCH_3 \rightarrow C_6H_5\dot{C}H_2 + \dot{N}HCH_3$	68.7	83	70.9	70.9
$C_6H_5CH_2N(CH_3)_2 \rightarrow C_6H_5\dot{C}H_2 + N(CH_3)_2$	60.9	83	62.8	63.1
$C_6H_5CH_2CH_2NH_2 \rightarrow C_6H_5\dot{C}H_2 + \dot{C}H_2NH_2$	63.9	84	66.1	65.5
$C_6H_5NHCH_3 \rightarrow C_6H_5\dot{N}H + \dot{C}H_3$	66.7	85	68.9	68.9
$C_6H_5N(CH_3)_2 \rightarrow C_6H_5\dot{N}CH_3 + \dot{C}H_3$	64.7	85	66.8	66.6
$t\text{-}C_5H_{11}NH_2 \rightarrow t\text{-}C_5H_{11}^{\cdot} + \dot{N}H_2$	78.9	86	81.0	81.5
$CH_3NH_2 \rightarrow \dot{C}H_3 + \dot{N}H_2$	83.8	86	85.9	83.0
$C_2H_5NH_2 \rightarrow C_2H_5^{\cdot} + \dot{N}H_2$	80.7	86	82.8	82.8
$i\text{-}C_3H_7NH_2 \rightarrow i\text{-}C_3H_7^{\cdot} + \dot{N}H_2$	80.7	86	82.8	82.8
$t\text{-}C_4H_9NH_2 \rightarrow t\text{-}C_4H_9^{\cdot} + \dot{N}H_2$	80.1	86	82.2	82.5
$C_6H_5CH_2NH_2 \rightarrow C_6H_5\dot{C}H_2 + \dot{N}H_2$	70.5	86	72.6	71.6

results using the relationship:

$$E = \Delta H^{\ominus}(\bar{T}) + R\bar{T}$$

$$\Delta H^{\ominus}(298) = D(\text{C—N}) = \Delta H^{\ominus}(\bar{T}) + \overline{\Delta C}_p(298 - \bar{T})$$

Values of $\overline{\Delta C}_p^{\ominus}$ 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, $\dot{N}H_2$, 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 $\dot{N}H_2$ 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 benzylamine[83], knowing the heats of formation of benzylamine and the benzyl radical. A recent determination of the heat of formation of benzylamine[68] which used early vapour-pressure results to obtain the heat of vaporization of the compound, yielded $\Delta H_f^{\ominus}$ 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[87] obtained an activation energy of 69.1 kcal/mol

(1100 K) for the reaction

$$C_6H_5CH_2CH(CH_3)_2 \longrightarrow C_6H_5\dot{C}H_2 + \dot{C}H(CH_3)_2$$

Hence $\Delta H(1100) = 71.3$ kcal/mol and $\overline{\Delta C}_p^{\ominus} = -0.48$ cal/(mol K), whence $\Delta H_f^{\ominus}$ (benzyl) = 48.9 kcal/mol. The heat of formation of the benzyl radical obtained by Walsh and coworkers[88], of 45 kcal/mol, was based on a study of reactions (6) and (7):

$$I^{\cdot} + C_6H_5CH_3 \longrightarrow C_6H_5\dot{C}H_2 + HI \quad (6)$$

$$C_6H_5\dot{C}H_2 + HI \longrightarrow I^{\cdot} + C_6H_5CH_3 \quad (7)$$

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 ± 1.0 kcal/mol the heat of formation of the benzyl radical was calculated to be 44.9 kcal/mol, assuming that $\overline{\Delta C}_p^{\ominus} = 0$ 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[89] and of Szwarc[90]. Esteban and coworkers[89] used the aniline carrier technique to examine the decomposition of ethylbenzene and (in more detail) *n*-propylbenzene. For the second of these reactions:

$$C_6H_5CH_2CH_2CH_3 \longrightarrow C_6H_5\dot{C}H_2 + \dot{C}H_2CH_3 \quad (8)$$

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 $\Delta H_f^{\ominus}$ (benzyl) = 44.5 kcal/mol. The result of Esteban and coworkers may now be used to calculate $\Delta H_f^{\ominus}$ (benzyl) using:

$$\Delta H^{\ominus}(T) = E_8 + RT$$

$$\Delta H^{\ominus}(298) = \Delta H^{\ominus}(T) + \overline{\Delta C}_p \Delta T$$

and using more recent thermochemical data. From their result, $\Delta H_8^{\ominus}(930) = 70.7$ kcal/mol. Group additivity gives $\overline{\Delta C}_p^{\ominus} = -0.8$ cal/(mol K) and hence $\Delta H_8^{\ominus}(298) = 71.2$ kcal/mol. Using $\Delta H_f^{\ominus}$ (*n*-propylbenzene) = 1.87 kcal/mol[1] and $\Delta H_f^{\ominus}(C_2H_5^{\cdot}) = 26.5$ kcal/mol[26] we arrive at $\Delta H_f^{\ominus}$ (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 ± 1.5 kcal/mol for the heat of formation of the benzyl radical, the mean of the values derived from the results of Tsang[87] and Esteban and coworkers[89]. 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[83] yield a value of 46.4 ± 2.0 kcal/mol for the heat of formation of the amino radical.

Tsang's[86] study of the shock-tube decomposition of *t*-amylamine leads to $D(C{-}N) = 81.5$ 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[86] 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:

$$t\text{-}C_5H_{11}NH_2 \longrightarrow t\text{-}C_5H_{11}^{\cdot} + \dot{N}H_2 \quad (9)$$

$$t\text{-}C_5H_{11}CH_3 \longrightarrow t\text{-}C_5H_{11}^{\cdot} + \dot{C}H_3 \quad (10)$$

and assumed that for these reactions

$$E_9 - E_{10} = \Delta H_f^{\ominus}(\dot{N}H_2) - \Delta H_f^{\ominus}(\dot{C}H_3) - [\Delta H_f^{\ominus}(t\text{-}C_5H_{11}NH_2) - \Delta H_f^{\ominus}(t\text{-}C_5H_{11}CH_3)] \quad (D)$$

whence

$$78.9 - 81.5 = \Delta H_f^{\ominus}(\dot{N}H_2) - \Delta H_f^{\ominus}(\dot{C}H_3) - (33.9 + 44.75)$$

giving $\Delta H_f^{\ominus}(\dot{N}H_2)$ 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 $\Delta H_f^{\ominus}(\dot{N}H_2)$ 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):

$$NH_2^- + H_2 \longrightarrow H^- + NH_3 \quad (11)$$

the equilibrium constant has been measured by Bohme and coworkers[91]. From their result a value of $\Delta H_{11}^{\ominus}(298)$ for the reaction of -3.2 ± 0.3 kcal/mol was obtained. Using the measured electron affinities of the hydrogen atom and the amino radical $D(NH_2—H)$ was calculated to be 107.4 ± 1.1 kcal/mol, and hence a value of 44.3 ± 1.1 kcal/mol for $\Delta H_f^{\ominus}(\dot{N}H_2)$ was obtained. The activation energy for the reaction (12):

$$O + NH_3 \longrightarrow \dot{N}H_2 + \dot{O}H \quad (12)$$

was measured over the temperature range 361–677 K by Kurylo and coworkers[92]. They found $E_{12} = 6.6 \pm 0.1$ kcal/mol. Assuming zero activation energy for the reverse of this process $\Delta H_{12}(520)$ is calculated to be 7.6 kcal/mol, which yields $\Delta H_{12}^{\ominus}(298) = 7.4$ kcal/mol, when heat capacity corrections are made[26]. Thus the heat of formation of the amino radical is calculated to be 46.6 ± 0.4 kcal/mol.

Franklin and Sharma[93] measured the appearance potential of the methyl ion for the process (13):

$$CH_3NH_2 \longrightarrow CH_3^+ + \dot{N}H_2 + e^- \quad (13)$$

After making a correction for excess energy they obtained $\Delta H_f^{\ominus}(\dot{N}H_2) = 41$ 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[94] they obtained $\Delta H_f^{\ominus}(\dot{N}H_2) = 46$ 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 $\Delta H_f^{\ominus}(\dot{N}H_2)$. What does seem clear, however, is that the value of this quantity quoted by JANAF[24] 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[83] 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, *n*-propylbenzene would help to clear up this uncertainty. The value of $\Delta H_f^{\ominus}(\dot{N}H_2)$ of 46.6 ± 0.4 kcal/mol which results from the study by Kurylo and coworkers[92] 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[83]. 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 $\Delta H_f^{\ominus}(\dot{N}H_2)$, 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, $CH_3\dot{N}H$, 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):

$$(CH_3)_2NH \longrightarrow CH_3^+ + CH_3\dot{N}H + e^- \qquad (14)$$

corrected for excess energy.

Golden and coworkers' value of 68.7 kcal/mol for the activation energy for the reaction (15)[83]:

$$C_6H_5CH_2NHCH_3 \longrightarrow C_6H_5\dot{C}H_2 + CH_3\dot{N}H \qquad (15)$$

leads to $\Delta H_{15}^{\ominus}(1100\ K) = 70.9$ kcal/mol. With $\overline{\Delta C}_p = 0$ cal/(mol K), $\Delta H_{15}^{\ominus}(298) = 70.9$ kcal/mol, and so using ΔH_f (benzyl) = 47.7 kcal/mol and ΔH_f (*N*-methylbenzylamine) = 21.5 kcal/mol (by group additivity), we obtain $\Delta H_f^{\ominus}(CH_3\dot{N}H) = 44.7 \pm 2.0$ 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):

$$(CH_3)_3N \longrightarrow CH_3^+ + (CH_3)_2\dot{N} + e^- \qquad (16)$$

to deduce $\Delta H_f^{\ominus}$ 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 $\Delta H_{17}^{\ominus}(298) = 63.1$ kcal/mol for the process (17):

$$C_6H_5CH_2N(CH_3)_2 \longrightarrow C_6H_5\dot{C}H_2 + \dot{N}(CH_3)_2 \qquad (17)$$

together with $\Delta H_f^{\ominus}$ (*N*,*N*-dimethylbenzylamine) = 26.25 kcal/mol (by group additivity) and $\Delta H_f^{\ominus}$ (benzyl) = 47.7 kcal/mol, lead to $\Delta H_f^{\ominus}[\dot{N}(CH_3)_2] = 41.6 \pm 2.0$ 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, $\dot{C}H_2NH_2$, 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):

$$C_2H_5NH_2 \longrightarrow CH_3^+ + \dot{C}H_2NH_2 + e^- \qquad (18)$$

and hence derived $\Delta H_f^{\ominus}(\dot{C}H_2NH_2) = 43$ kcal/mol. In a VLPP study, Colussi and Benson[84] obtained a value of 63.9 kcal/mol for the high-pressure activation energy

for the reaction (19):

$$C_6H_5CH_2CH_2NH_2 \longrightarrow C_6H_5\dot{C}H_2 + \dot{C}H_2NH_2 \quad (19)$$

over the temperature range 960–1245 K. Hence $\Delta H^{\ominus}_{19}(1100\ K) = 66.1$ kcal/mol, and making a heat capacity correction of $\overline{\Delta C}_p = 0.7$ cal/(deg mol), $\Delta H_{19}(298) = 65.5$ kcal/mol. Then using heats of formation of 2-phenylethylamine and the benzyl radical of 15.5[84] and 47.7 kcal/mol respectively we obtain $\Delta H^{\ominus}_f(\dot{C}H_2NH_2) = 33.3 \pm 2.0$ 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[84], who used $\Delta H^{\ominus}_f$(benzyl) = 44.2 kcal/mol, now believed to be too low, to obtain $\Delta H^{\ominus}_f(\dot{C}H_2NH_2) = 37.0$ 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 $\Delta H^{\ominus}_f(\dot{C}H_2NH_2) = 33.3 \pm 2.0$ kcal/mol we obtain D(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 Sharma[93] measured appearance potentials for the processes (20) and (21):

$$(C_2H_5)_2NH \longrightarrow CH_3^+ + \dot{C}H_2N(C_2H_5)H + e^- \quad (20)$$

$$(C_2H_5)_3N \longrightarrow CH_3^+ + \dot{C}H_2N(C_2H_5)_2 + e^- \quad (21)$$

from which they obtained heats of formation of 37 and 23 kcal/mol for the $\dot{C}H_2N(C_2H_5)H$ and $\dot{C}H_2N(C_2H_5)_2$ radicals respectively, but they do not consider these values to be very satisfactory. A rough group additivity calculation using the approximation that $\dot{C}$ is equivalent to C and that N is equivalent to 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 Benson[85] obtained high pressure activation energies for the reactions (22) and (23):

$$C_6H_5NHCH_3 \longrightarrow C_6H_5\dot{N}H + \dot{C}H_3 \quad (22)$$

$$C_6H_5N(CH_3)_2 \longrightarrow C_6H_5\dot{N}CH_3 + \dot{C}H_3 \quad (23)$$

of 66.7 and 64.7 kcal/mol respectively, giving $\Delta H_{22}(1100\ K) = 68.9$ kcal/mol for the first of these reactions and $\Delta H_{23}(1070\ K) = 66.8$ kcal/mol for the second. No heat capacity correction is needed for the first reaction[50], so $\Delta H^{\ominus}_{22}(298) = 68.9$ kcal/mol. Using $\Delta H^{\ominus}_f$ (N-methylaniline) = 20.4 kcal/mol[3] and $\Delta H^{\ominus}_f(\dot{C}H_3) = 35.1$ 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 $\Delta H^{\ominus}_f(CH_3) = 34.3$ 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 $\overline{\Delta C}_p^\ominus$ = 0.25 cal/(mol K) and thus $\Delta H_{23}^\ominus(298)$ = 66.6 kcal/mol. Using $\Delta H_f^\ominus$-(*N,N*-dimethylaniline) = 20.1 kcal/mol[3] and $\Delta H_f^\ominus(\dot{C}H_3)$ = 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 $\Delta H_f^\ominus$ (*N*-methylanilino) = 53.2 ± 2.0 kcal/mol, using the earlier value of $\Delta H_f^\ominus(\dot{C}H_3)$ and making a different correction for $\overline{\Delta C}_p^\ominus$.

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 $\Delta H_f^\ominus$ (*N*-methylaniline) = 20.4 kcal/mol[3], D(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[86] 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 $\dot{N}H_2$ 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 12. Heats of formation of amino radicals

Radical	$\Delta H_f^\ominus$ (kcal/mol)
$\dot{N}H_2$	46.6 ± 2.0
$CH_3\dot{N}H$	44.7 ± 2.0
$(CH_3)_2\dot{N}$	41.6 ± 2.0
$\dot{C}H_2NH_2$	33.3 ± 2.0
$C_6H_5\dot{N}H$	54.2 ± 2.0
$C_6H_5\dot{N}CH_3$	51.6 ± 2.0

TABLE 13. C—N bond dissociation energies in amines obtained from kinetic studies and calculated from the thermochemistry

Reaction	D(C—N)(thermochemical) (kcal/mol)	E (kcal/mol)	D(C—N)(kinetic) (kcal/mol)	Reference
Primary amines				
$CH_3NH_2 \rightarrow \dot{C}H_3 + \dot{N}H_2$	87.2	83.8	83.0	86
$C_2H_5NH_2 \rightarrow C_2H_5^{\cdot} + \dot{N}H_2$	84.4	80.7	82.8	86
n-$C_3H_7NH_2 \rightarrow n$-$C_3H_7^{\cdot} + \dot{N}H_2$	84.4			
i-$C_3H_7NH_2 \rightarrow i$-$C_3H_7^{\cdot} + \dot{N}H_2$	84.2	80.7	82.8	86
c-$C_3H_5NH_2 \rightarrow c$-$C_3H_5^{\cdot} + \dot{N}H_2$	94.2 ± 6[a]			
n-$C_4H_9NH_2 \rightarrow n$-$C_4H_9^{\cdot} + \dot{N}H_2$	85.4			
t-$C_4H_9NH_2 \rightarrow t$-$C_4H_9^{\cdot} + \dot{N}H_2$	83.9	80.1	82.5	86
c-$C_4H_7NH_2 \rightarrow c$-$C_4H_7^{\cdot} + \dot{N}H_2$	87.8[b]			
t-$C_5H_{11}NH_2 \rightarrow t$-$C_5H_{11}^{\cdot} + \dot{N}H_2$	83.0	78.9	81.5	86
c-$C_5H_9NH_2 \rightarrow c$-$C_5H_{11}^{\cdot} + \dot{N}H_2$	83.7			
n-$C_5H_{11}NH_2 \rightarrow n$-$C_5H_{11}^{\cdot} + \dot{N}H_2$	84.2			
c-$C_6H_{11}NH_2 \rightarrow c$-$C_6H_{11}^{\cdot} + \dot{N}H_2$	84.4			
$C_6H_5NH_2 \rightarrow C_6H_5^{\cdot} + \dot{N}H_2$	104.3			
$C_6H_5CH_2NH_2 \rightarrow C_6H_5CH_2^{\cdot} + \dot{N}H_2$	73.2	70.5	71.6	86
	73.2	71.9	73.1	83

TABLE 13. *continued*

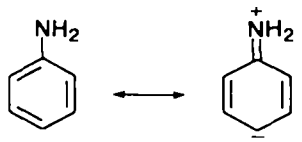
Reaction	D(C—N)(thermochemical) (kcal/mol)	E (kcal/mol)	D(C—N)(kinetic) (kcal/mol)	Reference
Secondary amines				
$(CH_3)_2NH \rightarrow \dot{C}H_3 + CH_3\dot{N}H$	84.5			
$(C_2H_5)_2NH \rightarrow C_2H_5^{\cdot} + C_2H_5\dot{N}H$	82.6[c]			
$(C_3H_7)_2NH \rightarrow C_3H_7^{\cdot} + C_3H_7\dot{N}H$	82.0[c]			
$(i\text{-}C_3H_7)_2NH \rightarrow i\text{-}C_3H_7^{\cdot} + i\text{-}C_3H_7\dot{N}H$	82.3[c]			
$(n\text{-}C_4H_9)_2NH \rightarrow n\text{-}C_4H_9^{\cdot} + n\text{-}C_4H_9\dot{N}H$	81.5[c]			
$(i\text{-}C_4H_9)_2NH \rightarrow i\text{-}C_4H_9^{\cdot} + i\text{-}C_4H_9\dot{N}H$	81.4[c]			
$(i\text{-}C_4H_9)(n\text{-}C_4H_9)NH \rightarrow i\text{-}C_4H_9^{\cdot} + n\text{-}C_4H_9\dot{N}H$	82.2[c]			
$\rightarrow n\text{-}C_4H_9^{\cdot} + i\text{-}C_4H_9\dot{N}H$	81.9[c]			
$C_6H_5CH_2NHCH_3 \rightarrow C_6H_5\dot{C}H_2 + \dot{N}HCH_3$	70.9[d]	68.7	70.9	83
$C_6H_5NHCH_3 \rightarrow C_6H_5\dot{N}H + \dot{C}H_3$	68.9[d]	66.7	68.9	85
$\rightarrow C_6H_5^{\cdot} + \dot{N}HCH_3$	102.8			
$(C_6H_5)_2NH \rightarrow C_6H_5^{\cdot} + C_6H_5\dot{N}H$	78.5			
Tertiary amines				
$(CH_3)_3N \rightarrow (CH_3)_2\dot{N} + \dot{C}H_3$	82.4			
$(C_2H_5)_3N \rightarrow (C_2H_5)_2\dot{N} + C_2H_5^{\cdot}$	79.2			
$C_6H_5CH_2N(CH_3)_2 \rightarrow C_6H_5\dot{C}H_2 + \dot{N}(CH_3)_2$	63.1[d]	60.9	63.1	83
$C_6H_5N(CH_3)_2 \rightarrow C_6H_5\dot{N}CH_3 + \dot{C}H_3$	66.6[d]	64.7	66.6	85
$\rightarrow C_6H_5^{\cdot} + \dot{N}(CH_3)_2$	100.0			

[a]Using ΔH_f° (cyclopropyl) = 66 ± 6 listed by Benson[26], a value of 94.2 kcal/mol is obtained for the C—N bond dissociation energy; using ΔH_f° (cyclopropyl) = 55.2 kcal/mol calculated by group additivity, with a strain energy of 27.6 kcal/mol[26] the resulting D(C—N) is 83.4 kcal/mol.
[b]Using ΔH_f° (cyclobutyl) = 51 kcal/mol, listed by Benson[26], a value of 87.8 kcal/mol is obtained; using ΔH_f° (cyclobutyl) = 48.8 kcal/mol calculated by group additivity, with a strain energy of 26.2 kcal/mol[26] the resulting D(C—N) is 85.6 kcal/mol.
[c]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).
[d]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 teriary 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:



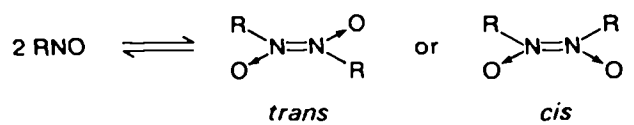
Likewise, in *N*-methylaniline and *N,N*-dimethylaniline the aryl carbon–nitrogen bond is strengthened by this resonance. In all these cases fission of the (strengthened) aryl C—N bond is made less favourable by the fact that the phenyl radical, which is incapable of stabilization by resonance, is formed. 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:



trans *cis*

(2) the reactivity of primary and secondary nitrosoalkanes towards isomerization to the oxime, e.g.:

At the time of the reviews by Cox and Pilcher[4] and Stull, Westrum and Sinke[3] there had been no determination of the heat of formation of any gaseous monomeric nitroso compound. Stull, Westrum and Sinke[3] list a value for the heat of formation of solid nitrosobenzene of −7.0 kcal/mol. Evans, Fairbrother and Skinner[96] 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 ± 1 kcal/mol. For the *trans* dimer of nitrosocyclohexane they obtained an approximate value of 57.7 ± 8 kcal/mol for the solid. Médard and Thomas[97] obtained the heat of formation of solid *p*-nitrosodiphenylamine in a bomb calorimetry experiment: they found a value of 50.93 ± 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 ΔH°_{24} for the reaction

$$(RNO)_2 \longrightarrow 2\,RNO \tag{24}$$

or (*b*) by obtaining a value for the C—N bond strength of the nitroso compound either from the kinetics of the decomposition:

$$RNO \longrightarrow \dot{R} + \dot{N}O \tag{25}$$

or from electron impact studies which yield the C—N bond dissociation energy, whence:

$$\Delta H^{\circ}_f(RNO) = \Delta H^{\circ}_f(\dot{R}) + \Delta H^{\circ}_f(NO) - D(C{-}N)$$

Thus Benson and coworkers[1] 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 Milne[98] carried out a bomb calorimetric study on the *trans* dimer of nitrosomethane, from which they obtained a value of +0.2 ± 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 ± 1 kcal/mol. Using the enthalpy change for the equilibrium (26):

$$trans\text{-}(CH_3NO)_2 \rightleftharpoons 2\,CH_3NO \tag{26}$$

obtained by Christie and coworkers[99], they estimated a value of 16.7 ± 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:

$$\begin{aligned}\Delta H^{\circ}_{25} = D(C{-}N) &= \Delta H^{\circ}_f(\dot{C}H_3) + \Delta H^{\circ}_f(NO) - \Delta H^{\circ}_f(CH_3NO)\\ &= 35.1 + 21.6 - 16.7\\ &= 40.0 \pm 0.8\ \text{kcal/mol}\end{aligned}$$

Pepekin and coworkers[100] carried out a calorimetric study on dimeric 2-methyl-2-nitrosopropane and nitrosobenzene. For the first of these 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 ± 0.4 kcal/mol. Coupled with a value of 18.2 ± 0.2 kcal/mol for the heat of sublimation of the compound, this yielded a value of -31.9 ± 0.6 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 kcal/mol for the enthapy change for the reaction (27):

$$(t\text{-}C_4H_9NO)_2 \longrightarrow 2\,t\text{-}C_4H_9NO \qquad (27)$$

on the basis of the result of Batt and coworkers[101], who studied the decomposition of the *trans* dimer of 2-methyl-1-nitrosopropane. They obtained an activation energy of 25.6 kcal/mol for the reaction (28):

$$(i\text{-}C_4H_9NO)_2 \longrightarrow 2\,i\text{-}C_4H_9NO \qquad (28)$$

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):

$$(i\text{-}C_4H_9NO)_2 \rightleftharpoons 2\,i\text{-}C_4H_9NO \qquad (29)$$

$$2\,i\text{-}C_4H_9NO \longrightarrow (i\text{-}C_4H_9NO)_2 \qquad (30)$$

but we may estimate a value of 4.6 ± 1.0 kcal/mol for the enthalpy of the dimerization reaction by analogy with the nitrosomethane equilibrium[99]. Thus

$$\Delta H^{\ominus}_{29} = E_{28} - E_{30} + R\bar{T} = 25.6 - 4.6 + 0.8$$
$$= 21.8 \pm 1.0 \text{ kcal/mol at } 385 \text{ K}$$

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 ± 1.6 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 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 ± 2 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 ± 0.2 kcal/mol), a value of -28.0 ± 1.2 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 ± 1.0 kcal/mol), the heat of formation of the gaseous monomeric compound is estimated to be -3.1 ± 2.2 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 ± 2.2 kcal/mol.

Pepekin and coworkers carried out seven combustion experiments on dimeric nitrosobenzene from which they calculated a value of 57.7 ± 0.5 kcal/mol for the heat of formation of the solid compound[100]. They determined the heat of

sublimation to be 20.8 ± 0.2 kcal/mol from which they calculated the heat of formation of the gaseous dimer to be 78.5 ± 0.7 kcal/mol. No information exists on the equilibrium constant for the equilibrium (31):

$$(C_6H_5NO)_2 \rightleftharpoons 2\,C_6H_5NO \qquad (31)$$

Pepekin's group assume a value of 24.5 kcal/mol for the enthalpy of the process (32):

$$(C_6H_5NO)_2 \longrightarrow 2\,C_6H_5NO \qquad (32)$$

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 ± 2.0 kcal/mol. Hence the C—N bond dissociation energy may be calculated to be 48.6 ± 2.0 kcal/mol, using a value of 78.5 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:

$$(RNO)_2 \longrightarrow 2\,RNO$$

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

$$D(\text{R—NO}) = AP[(R^+) \text{ or } (NO^+)] - IP(\dot{R})$$

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):

$$RNO \longrightarrow \dot{R} + NO \qquad (25)$$

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

Compound	D(R—NO) (kcal/mol)	Reference
i-C_3H_7NO	36.5 ± 3	102
t-C_4H_9NO	34 ± 3; 46 ± 3[a]	102
t-$C_5H_{11}NO$	36 ± 3	102
C_6H_5NO	41 ± 3	102
CF_3NO	31 ± 3	103
CCl_3NO	32 ± 3	103
C_6F_5NO	62 ± 5[b]	103

[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 $\Delta H^{\ominus}_{33}(0)$ for the process

$$CF_3NO \longrightarrow \dot{C}F_3 + NO \qquad (33)$$

was equal to 42 ± 2 kcal/mol. At 800 K they quote a value of 41.5 ± kcal/mol for $\Delta H^{\ominus}_{33}$. After making heat capacity corrections, using $F_3CCH{=}CH_2$ as a model compound and making corrections for the loss of the vibrations of three hydrogen atoms, a value of $\Delta H^{\ominus}_{33}(298)$ 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):

$$t\text{-}C_4H_9NO \longrightarrow t\text{-}C_4H_9^{\bullet} + NO \qquad (34)$$

$$t\text{-}C_4H_9^{\bullet} + NO \longrightarrow t\text{-}C_4H_9NO \qquad (35)$$

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, Kaseel, Marcus) calculation which yielded a high-pressure activation energy of 36.0 ± 1.0 kcal/mol for reaction (34) at 600 K. Hence $\Delta H^{\ominus}_{34}(600)$ = 37.2 ± 1.0 kcal/mol. They were also able to obtain the enthalpy change during reaction (34) using the relationship:

$$\ln K = \frac{-\Delta H^{\ominus}}{RT} + \frac{\Delta S^{\ominus}}{R}$$

from which they found $\Delta H^{\ominus}_{34}(600)$ = 38.5 ± 1.5 kcal/mol. They selected an average value of these two results and obtained $\Delta H^{\ominus}_{34}(600)$ = 38.0 ± 1.5 kcal/mol. After

heat capacity corrections, using the isoelectronic t-$C_4H_9CH{=}CH_2$ as a model compound and correcting for the loss of vibration of the three hydrogen atoms, they obtained a value of 39.5 ± 1.5 kcal/mol for $\Delta H^{\ominus}_{34}(298)$, and hence D(C—N) for 2-methyl-2-nitrosopropane is 39.5 ± 1.5 kcal/mol. If the heat of formation of the t-butyl radical is taken to be 10.5 kcal/mol[26] a value of −7.5 ± 1.5 kcal/mol for the heat of formation of 2-methyl-2-nitrosopropane is obtained, 2.5 kcal/mol lower than the value derived from the results of Pepekin and coworkers[100].

In a further VLPP study, Choo and coworkers[108] 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):

$$C_6H_5NO \longrightarrow C_6H_5^{\cdot} + NO \qquad (36)$$

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 ± 1.0 kcal/mol. Assuming zero activation energy for the reverse of this reaction, $\Delta H^{\ominus}_{36}(700)$ is calculated to be 50.4 ± 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 $\Delta H^{\ominus}_{36}(298)$ = 51.5 ± 1.0 kcal/mol, which is the C—N bond dissociation energy of nitrosobenzene. Using $\Delta H^{\ominus}_f(C_6H_5^{\cdot})$ = 78.5 kcal/mol[26] we obtain $\Delta H^{\ominus}_f$(nitrosobenzene, g) = 48.6 ± 1 kcal/mol, which is not far removed from the result of Pepekin's group[100] which yielded $\Delta H^{\ominus}_f$(nitrosobenzene, g) = 51.5 ± 2.0 kcal/mol).

For pentafluoronitrosobenzene[108] the unimolecular rate constants for the reaction (37) (698–943 K):

$$C_6F_5NO \longrightarrow C_6F_5^{\cdot} + NO \qquad (37)$$

were subjected to RRKM calculations which yielded a value of 48.0 ± 1.0 kcal/mol for the high-pressure activation energy for this reaction at 700 K. Thus $\Delta H^{\ominus}_{37}(700)$ = 49.4 ± 1.0 kcal/mol and $\Delta H^{\ominus}_{37}(298)$ = 50.5 ± 1.0 kcal/mol, after heat capacity corrections. Using $\Delta H^{\ominus}_f(C_6F_5^{\cdot})$ = −130.9 ± 2 kcal/mol[108], the heat of formation of pentafluoronitrosobenzene was calculated to be −160 ± 3 kcal/mol.

D. The C—N Bond Dissociation Energy and Heats of Formation

The values of the heats of formation of gaseous nitroso compounds and C—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 C-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[1] had derived group values for nitroso compounds based upon a 'judicious guess' that for secondary nitrosoalkanes D(C—N) was equal to 37 kcal/mol, with D(C—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(C—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 ± 1.5 to 42.8 ± 2.0 kcal/mol. It is therefore concluded that the C—N bond dissociation energy in nitrosoalkanes is 40 ± 2 kcal/mol,

TABLE 15. Thermochemical properties of *C*-nitroso compounds

Compound	ΔH_f° (kcal/mol)	Method	D(C—N) (kcal/mol)	Reference
Nitrosomethane	16.7 ± 0.8	Calorimetry + equilibrium constant	40.0 ± 0.8	98
Trifluoronitrosomethane	−122 ± 4	Electron impact	31 ± 3	103
Trifluoronitrosomethane	−133.7 ± 3	Shock wave	42.8 ± 2	106
Trichloronitrosomethane	8 ± 4	Electron impact	32 ± 3	103
2-Nitrosopropane	2.7 ± 3	Electron impact	36.5 ± 3	102
2-Methyl-1-nitrosopropane	−3.1 ± 2.2	Calorimetry + equilibrium constant	38.4 ± 2.2	100
2-Methyl-2-nitrosopropane	−5.0 ± 1.6	Calorimetry + equilibrium constant	35 ± 2	100
2-Methyl-2-nitrosopropane	−4 ± 3; −16 ± 3[a]	Electron impact	34 ± 3; 46 ± 3	102
2-Methyl-2-nitrosopropane	−9.5 ± 1.5	VLPP	39.5 ± 1.5	107
2-Methyl-2-nitrosobutane	−10.9 ± 3	Electron impact	36 ± 3	102
Nitrosobenzene	51.5 ± 2	Calorimetry + equilibrium constant	48.6 ± 2.0	100
Nitrosobenzene	59.1 ± 3	Electron impact	41 ± 3	102
Nitrosobenzene	48.6 ± 1	VLPP	51.5 ± 1.0	108
Pentafluoronitrosobenzene	−171 ± 7	Electron impact	62 ± 5	103
Pentafluoronitrosobenzene	−160 ± 3	VLPP	50.5 ± 1.0	108

[a]See Table 14, footnote a.

independent of R. On the basis of this conclusion, and group values for nitrosoalkanes obtained by Benson and coworkers[1] may be amended: we select $\Delta H_f^{\ominus}[C(H)_2(C)(NO)]$ = 17.7 kcal/mol, $\Delta H_f^{\ominus}[(C(H)(C)_2(NO)]$ = 19.6 kcal/mol and $\Delta H_f^{\ominus}[C(C)_3(NO)]$ = 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[108] of 51.5 ± 1.0 and 50.5 ± 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[108] estimate the heat of formation of the $C_B(NO)$ group to be 31.6 kcal/mol on the basis of their results.

V. ALKYL NITRITES

A. Methyl Nitrite

1. Heat of formation

A flame calorimetric study of methyl nitrite by Geiseler and Thierfelder[109] yielded $\Delta H_f^{\ominus}$(methyl nitrite, g) = −16.8 ± 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[110] used the equilibrium constant for:

$$CH_3OH + NOCl \rightleftharpoons CH_3ONO + HCl$$

obtained by Leermakers and Ramsperger[111] together with unpublished results on an enthalpy of hydrolysis[112] to obtain a value of −14.93 ± 0.26 kcal/mol for the heat of formation of methyl nitrite. Ray and Gershon[113] also used the enthalpy of the above reaction and obtained $\Delta H_f^{\ominus}$(methyl nitrite, g) = −15.64 ± 0.20 kcal/mol.

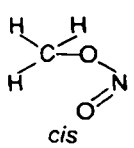
Silverwood and Thomas[114] examined the reaction between methanol and nitrogen dioxide:

$$CH_3OH + 2\,NO_2 \rightleftharpoons CH_3ONO + HNO_3$$

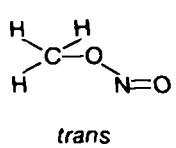
Values of the equilibrium constant yielded a value of 15.9 ± 0.1 kcal/mol for the enthalpy change for the above reaction and hence $\Delta H_f^{\ominus}$(methyl nitrite,g) = −16.05 ± 0.2 kcal/mol. This value is preferred.

2. Standard entropy

The value of the standard entropy of methyl nitrite is an important quantity since group values for values of $S^{\ominus}(298)$ for the higher nitrites depend upon this value. Equilibrium studies have yielded values in the range 64.2[111] to 71.5 ± 0.9[110] cal/(mol K). Silverwood and Thomas[114] obtained a value of $S^{\ominus}(298)$ for methyl nitrite of 69.7 ± 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[110]. It is known[73] that alkyl nitrites exist in two isomeric forms, *cis* and *trans*:



cis



trans

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 $S^{\ominus}(298)$ to be 74.1 ± 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 ~7.8 kcal/mol. A subsequent proton magnetic resonance study[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[116]. There is also a barrier to rotation of the methyl group in the *cis* isomer (the more stable isomer) of ~2.1 kcal/mol[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[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[114].

Stull, Westrum and Sinke[3] list thermodynamic functions for methyl nitrite.

B. Higher Alkyl Nitrites

For ethyl nitrite, Rossini and coworkers[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[120] quote an unpublished result of Baldrey, Lotzgesell and Style of $\Delta H_f^{\ominus}$ = −24.2 kcal/mol for gaseous ethyl nitrite. This latter value is preferred. Gray and Williams[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[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 ± 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[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 $\Delta H_f^{\ominus}$ for gaseous *i*-propyl nitrite was −31.9 ± 1.0 kcal/mol. Batt and coworkers[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 ± 1.0, −36.1 ± 1.0, − 36.5 ± 1.0 and −41.0 ± 1.0 kcal/mol for gaseous *n*-butyl, *i*-butyl, *s*-butyl and *t*-butyl nitrites. Lastly, Islam[122] obtained a value of −53.8 for the heat of formation of liquid *t*-pentyl nitrite by bomb calorimetry from which, with $\Delta H^{\ominus}$ = 7.98 kcal/mol, a value of −45.8 ± 0.8 kcal/mol for the heat of formation of gaseous *t*-pentyl nitrite was obtained.

Benson and coworkers[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)

Compound	ΔH_f° (exp.)	ΔH_f°(g.a.r.)[a]	ΔH_f° (corr.) (*gauche*)	ΔH_f° (exp.) − ΔH_f° (calc., corr.)	ΔH_f° (corr., g.a.r.)[b]	Δ[c]	Reference
CH_3ONO	−16.05	−16.0	−16.0	−0.05	−15.7	−0.35	114
C_2H_5ONO	−24.2	−24.2	−24.2	0.0	−23.9	−0.3	120
n-C_3H_7ONO	−28.4	−29.1	−29.1	+0.7	−28.8	+0.4	121
i-C_3H_7ONO	−31.9	−33.5	−32.7	+0.8	−32.4	+0.5	121
n-C_4H_9ONO	−34.8	−34.1	−34.1	−0.7	−33.8	−1.0	121
i-C_4H_9ONO	−36.1	−36.3	−36.3	+0.2	−36.0	−0.1	121
s-C_4H_9ONO	−36.5	−38.4	−37.6	+1.1	−37.3	+0.8	121
t-C_4H_9ONO	−41.0	−43.1	−41.5	+0.5	−41.2	+0.2	121
t-$C_5H_{11}ONO$	−45.8	−48.0	−46.4	+0.6	−46.1	+0.3	122

[a] Using ΔH_f° [O(NO)(C)] = −5.9 kcal/mol.
[b] Using ΔH_f° [O(NO)(C)] = −5.6 kcal/mol.
[c] $\Delta = \Delta H_f^\circ$(exp.) − ΔH_f°(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 $\Delta H_f^\ominus$ 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 $\Delta H_f^\ominus$[O(NO)(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:

$$D(\text{RO–NO}) = \Delta H_f^\ominus(\text{R}\dot{\text{O}}) + \Delta H_f^\ominus(\text{NO}) - \Delta H_f^\ominus(\text{RONO})$$

The heats of formation of the alkoxy radicals may be derived from the thermochemistry of the decomposition of the dialkyl peroxides:

$$\text{ROOR} \longrightarrow 2\,\text{R}\dot{\text{O}} \qquad (38)$$

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(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]:

$$\text{RONO} \longrightarrow \text{R}\dot{\text{O}} + \text{NO} \qquad (39)$$

TABLE 17. Heats of formation of alkoxy radicals (kcal/mol)

Radical	ΔH_f° (g.a.r.)	E	Reference	$E + R\overline{T}$	ΔH° (298)	ΔH_f° (ROOR)	Reference	ΔH_f° (RȮ)
$CH_3\dot{O}$	—	37.0	123	37.8	38.0	−30.0	128	4.0
$C_2H_5\dot{O}$	−4.1	37.3	124	38.1	38.3	−46.1	128	−3.9
$C_3H_7\dot{O}$	−9.03	37.2	82	38.0	38.2	−55.5	g.a.r.	−8.6
i-$C_3H_7\dot{O}$	−12.6	37.1	124	37.9	38.1	−64.2	g.a.r.	−13.0
$C_4H_9\dot{O}$	−14.0							
i-$C_4H_9\dot{O}$	−16.2							
s-$C_4H_9\dot{O}$	−17.5	36.4	125	37.2	37.4	−74.1	g.a.r.	−18.3
t-$C_4H_9\dot{O}$	−21.7	37.4	126	38.2	38.4	−81.5	128	−21.6
t-$C_5H_{11}\dot{O}$	−26.9	36.4	127	37.0	37.2	−93.3	g.a.r.	−28.1

TABLE 18. Values of RO—NO bond dissociation energies of alkyl nitrites (kcal/mol)

Compound	D(RO—NO) (thermochemical)[a]	E	$E + R\bar{T}$	$\Delta H^\circ_{298} = D$(RO—NO) (kinetic)[b]	Reference
CH_3ONO	41.7	41.2	42.1	42.1	129
C_2H_5ONO	41.9	41.8	42.2	42.2	130
C_3H_7ONO	41.4				
i-C_3H_7ONO	40.5	41.0	41.8	41.8	131
C_4H_9ONO	42.4	41.0[c]	42.3	42.3	132
i-C_4H_9ONO	41.5				
s-C_4H_9ONO	40.6	40.3	41.2	41.2	133
t-C_4H_9ONO	41.0	40.3	41.1	41.1	134
t-C_5H_9ONO	40.5	40.3	41.1	41.1	135

[a]Mean D(RO—NO) (thermochemical) = 41.3 ± 0.7 kcal/mol.
[b]Mean D(RO—NO) (kinetic) = 41.6 ± 0.6 kcal/mol.
[c]Assumed E_∞ = 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 $\Delta\bar{C}^\circ_p(298 - \bar{T})$ 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_∞ on the basis that E_∞ 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:

$$\dot{R}O + NO \longrightarrow RONO \qquad (40)$$

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 nitrites is 41.5 ± 1 kcal/mol. It is interesting to note that there is a slight decrease in D(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

TABLE 19. Thermochemical properties of gaseous alkyl nitrates[a]

Compound	ΔH_f° (g) (kcal/mol)	S° (298) [cal/(mol K)]	C_p° [cal/(mol K)]			
			300	500	800	1000
CH_3ONO_2	−28.8	72.15	18.34	24.95	31.47	34.19
$C_2H_5ONO_2$	−36.8	83.25	(23.36	33.31	42.72	46.69)[b]
$C_3H_7ONO_2$	−41.6	(92.1	29.1	41.63	53.87	59.08)[b]
i-$C_3H_7ONO_2$	−45.65	(89.20	28.95	41.91	54.13	59.26)[b]
$C_3H_5(ONO_2)_3$	−64.7 ± 1.2[c]					

[a]Values taken from Stull, Westrum and Sinke[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:

$$D(\text{RO–NO}_2) = \Delta H_f^\circ(\text{NO}_2) + \Delta H_f^\circ(\text{R}\dot{\text{O}}) - \Delta H_f^\circ(\text{RONO}_2)$$

Bond dissociation energies calculated in this way, using the heats of formation of the alkoxy radicals listed in Table 17, and $\Delta H_f^\circ(NO_2)$ = 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)

Compound	D(RO—NO_2) (thermochem.)[a]	E	$E + R\bar{T}$	ΔH° (298) = D(RO—NO_2) (kinetic)[b]	Reference
CH_3ONO_2	40.7	39.5	40.5	40.9	138
		40.0	40.9	41.2	139
$C_2H_5ONO_2$	40.8	39.9	40.8	41.0	140
		38	38.9	39.1	141
		39.3	40.2	40.4	142
$C_3H_7ONO_2$	40.5	40.0	40.5	40.5	143
i-$C_3H_7ONO_2$	40.9	38.1	38.9	40.0	139

[a]Mean D(RO—NO_2)(thermochem.) = 40.7 ± 0.2 kcal/mol.
[b]Mean D(RO—NO_2)(kinetic) = 40.4 ± 1.3 kcal/mol.

TABLE 21. Activation energies (kcal/mol) obtained for RO—NO_2 bond breaking in dinitrates and trinitrates[144]

Compound	E	$E + R\overline{T}$
Ethylene glycol dinitrate	39	39.7
Trimethylene glycol dinitrate	38.1	38.8
Propylene glycol dinitrate	37.4	38.1
Nitroglycerine	40.3	41.0
Trimethylol nitromethane trinitrate	36.3	37.0

reaction (41):

$$RONO_2 \longrightarrow R\dot{O} + NO_2 \qquad (41)$$

may be converted to bond dissociation energies as before. In making the heat capacity corrections, the values of $C_p^{\ominus}$ derived by Stull, Westrum and Sinke[3] 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(RO—NO_2) is equal to 40.7 ± 0.2 kcal/mol independent of R.

Phillips[144] carried out a series of studies on dinitrates and trinitrates and the activation energies he obtained for the RO—NO_2 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 $\Delta H°(298)$. 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—NO_2 bond dissociation energies at 298 K. It appears that for these compounds the RO—NO_2 bond dissociation energy is virtually the same as in the mononitrates.

VII. CONCLUSIONS

Since the reviews of Stull, Westrum and Sinke[3] and Cox and Pilcher[4] 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 coworkers[1,26]: 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

TABLE 22. New or amended group values for the estimation of heats of formation of nitrogen-containing compounds in the gas phase (kcal/mol)

Group	ΔH_f°
$C-(C)_3(NO_2)$	−11.6
$C-(C)(H)(NO_2)_2$	−10.7
$C-(C_B)(H)(NO_2)_2$	−13.7
$C-(C)(F)(NO_2)_2$	−46.8
$C-(C_B)(F)(NO_2)_2$	−66.2
$C-(C)_2(NO_2)_2$	−10.0
$C-(C)(NO_2)_3$	−1.45
$C-(N)(F)_3$	−161.2
$C-(N)(H)_2(C_B)$	−5.83
$N-(C_B)_3$	30.1
$C-(H)_2(C)(NO)$	17.7
$C-(H)(C)_2(NO)$	19.6
$C-(C)_3(NO)$	20.6
$O-(NO)(C)$	−5.6
Gauche interactions	
Alkyl–alkyl	0
Alkyl–NO_2	0
NO_2–NO_2	6.6
Alkyl–ONO	0.8
Alkyl–NH_2	0
Alkyl–NHR	0

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[6]. 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 $C_p^\circ(298)$ 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[1]. This is not the only system, however: for example, a new method has recently been devised by Yoneda[145], based upon an earlier method of Anderson, Beyer and Watson[146]. 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[1], 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

$$D = E + R\overline{T} + \overline{\Delta C}_p^\circ(298 - \overline{T})$$

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

Bond	Bond dissociation energy (kcal/mol)
H—NO_2	~78[a]
R—NO_2	59.4 ± 1.4
Ph—NO_2	71
H—NH_2	109.7
R—NH_2	84.2 ± 1.3
R—NHR	82 ± 1
R—NR_2	79 ± 1
Ph—NH_2	104.3
Ph—NHR	102.8
Ph—NR_2	100.0
H—NO	49.9
R—NO	40 ± 2
Ph—NO	51.5 ± 1.0
HO—NO	49.6
RO—NO	41.5 ± 1.0
HO—NO_2	49.4
RO—NO_2	40.7 ± 0.2

[a]Based on an approximate value of 18 kcal/mol for ΔH_f° (HNO_2) (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

$$\dot{R} + NO_2 \rightarrow RNO_2$$
$$\dot{R} + \dot{N}H_2 \rightarrow RNH_2$$

may have small activation energies when R is larger than ethyl. We list in Table 23 the values of D(C—N) and D(RO—N) for the compounds considered in this review together with D(H—N) or D(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.

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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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 α-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[52], 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 α-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, 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[211] (equation 1). Its reactions with secondary and especially tertiary

$$HOCl + 2NaClO_2 \longrightarrow 2ClO_2 + NaCl + NaOH \qquad (1)$$

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[78,82,154,156,157,257,262,263]. Aqueous chlorine dioxide is easily measured spectrophotometrically (λ_{max} 358.3 nm, ε 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[118]. 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[78,82,154,156,157,262,263].

Oxidative dealkylation is typically seen in reactions of chlorine dioxide with tertiary and secondary nonaromatic amines; reactivity is in the order $R_3N > R_2NH > RNH_2$, with RNH_2 relatively unreactive[156,262,263]. 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[156]. The first such reaction to be studied was the conversion of triethylamine

by aqueous chlorine dioxide to diethylamine and acetaldehyde[262], as shown in reaction (2). Addition of chlorite ion at constant pH and a constant excess of amine

$$ClO_2 + Et_3N: \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ClO_2^- + Et_3N^+\cdot \xrightarrow{-H^+} Et_2\ddot{N}-\dot{C}(H)-Me \xrightarrow[k_2]{ClO_2}$$

(1)

$$ClO_2^- + Et_2\overset{+}{N}=C(H)-Me \xrightarrow{H_2O} Et_2NH + MeCHO + H^+ \qquad (2)$$

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

$$2ClO_2 + Et_3N: \longrightarrow \text{products} \qquad (3)$$

both chlorine dioxide and amine. The kinetic rate law[156] was of the form:

$$\frac{-d[ClO_2]}{dt} = \frac{2\,k_1k_2[Et_3N:]\,[ClO_2]}{(k_{-1}[ClO_2^-] + k_2)} \qquad (4)$$

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 (1) 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[263]. The Brønsted plot gave an equation (corrected for a factor of 2 not accounted for in the original reference) of

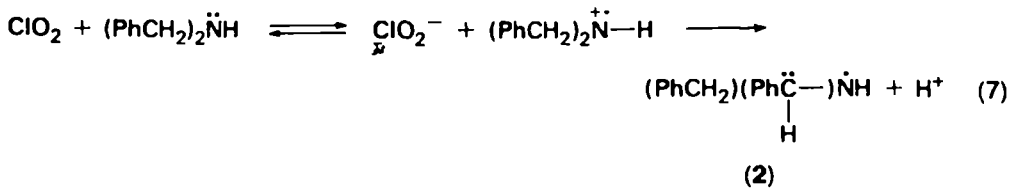
$$\log k_1 = 2.598 + 0.812\,pK_a \qquad (5)$$

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

$$\log k_1 = 4.15 - 0.924\,\sigma \qquad (6)$$

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[156]. 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



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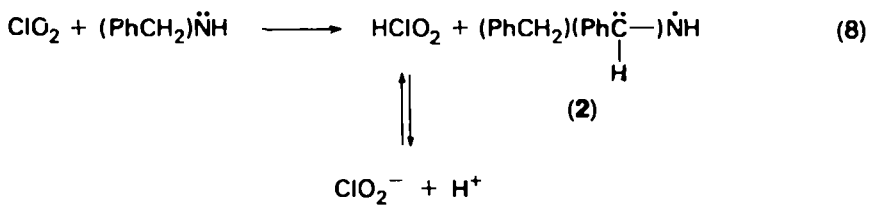
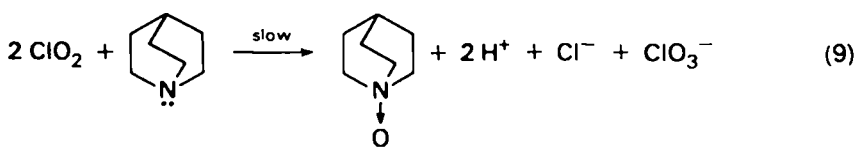


(8)

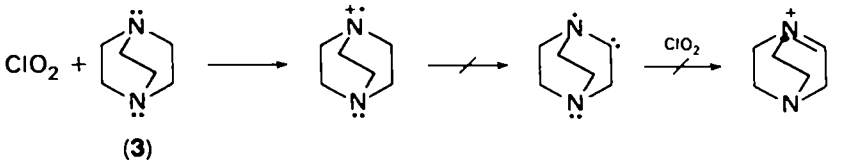
pH or because the abstraction of a hydrogen atom by chlorine dioxide is by nature not reversible. The electron abstraction reaction for benzyl-*t*-butylamine showed a kinetic deuterium isotope effect of 1.8, whereas the hydrogen abstraction reaction gave a value of 4.97. Thus, the duality of the mechanisms 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 sp^2-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). A limited kinetic study of this reaction indicated the probability of a complex chain mechanism not involving aminium radicals[84b,118].



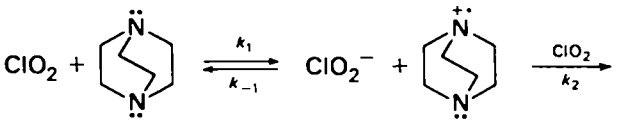
(9)

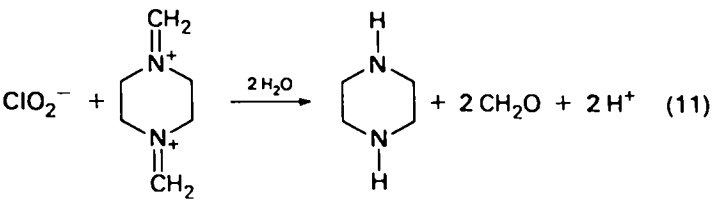
It had been surmised that the very similar compound, triethylenediamine (**3**), should behave like quinuclidine. In one sense, this was certainly not so. The rate constant for the initial step of the reaction with chlorine dioxide, i.e. to form an aminium radical, was about 50 times that predicted on the basis of the Taft σ^* 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 (λ_{max} 465 nm, ε 2,104 ± 231) and its electron spin resonance (ESR) spectrum measured[259,261], 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



(10)

(3)





(11)

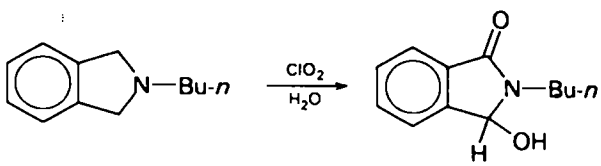
was observed, i.e. oxidative fragmentation[82] (reaction 11). The kinetic rate law for reaction (11) in the presence of added chlorite ion was[261]:

$$\frac{-d[ClO_2]}{dt} = \frac{2\,k_1k_2[ClO_2]^2[\mathbf{3}]}{k_{-1}[ClO_2^-]} \tag{12}$$

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 β-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].



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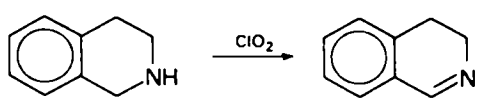

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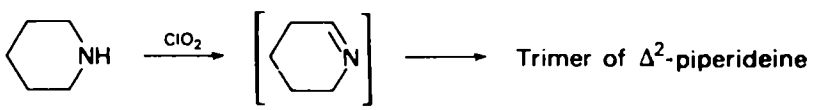


(15)

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[55], 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 σ^* values of the amines and the redox potentials of the oxidants[154]:

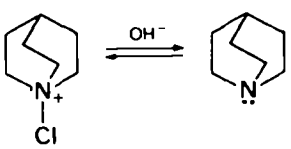
$$\log k_1 = -7.84\,E^0 - 5.31\,IP + 3.85 \tag{16}$$

or

$$\log k_1 = -7.64\,E^0 - 4.78\Sigma\sigma^* - 3.47 \tag{17}$$

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[91] 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[91]. *N*-Chloroquinuclidinium ion (**4**) is exceptional; it can be hydrolysed to quinuclidine but does not undergo oxidative decomposition[144] (equation 18).



(18)

(**4**)

Crane and coworkers[62] reported that amines containing the β-chloroethyl group underwent both α- and β-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 α- or β-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)[294]. The 'product' **7** remained undefined because reaction (20) could be interpreted as either abstraction of an α-proton from **6** by **5** (reaction 24) to give **8**, or electrophilic attack by **6** on the α-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)

$$\underset{\textbf{(5)}}{R_2(R^1CH_2)N\!:} + HOCl \longrightarrow \underset{\textbf{(6)}}{R_2(R^1CH_2)\overset{+}{N}\!-\!Cl} \tag{19}$$

$$R_2(R^1CH_2)\overset{+}{N}—Cl + \mathbf{5} \longrightarrow \mathbf{5} + \text{'product'} \quad (20)$$

(7)

$$\mathbf{7} \xrightarrow[H_2O]{} R_2NH + R^1CHO \quad (21)$$

$$R_2NH + HOCl \longrightarrow R_2NCl \quad (22)$$

$$R_2NH + R_2(R^1CH_2)\overset{+}{N}—Cl \longrightarrow R_2NCl + R_2(R^1CH_2)NH^+ \quad (23)$$

$$\mathbf{6} + \mathbf{5} \longrightarrow R_2\overset{+}{N}—\underset{\underset{\cdot\cdot}{}}{\overset{H}{C}}—R^1 \longrightarrow R_2\overset{+}{N}=CH_2 + Cl^- \quad (24)$$

$$\begin{matrix} & & & H & \\ & & & | & \\ & & & C & \\ & & & | & \\ & & & Cl & \end{matrix}$$

(8)

$$\mathbf{6} + \mathbf{5} \longrightarrow R_2N—\overset{H}{\underset{Cl}{C}}—R^1 + H^+ \quad (25)$$

(9)

is more attractive than (25), Taraszka[294] 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.

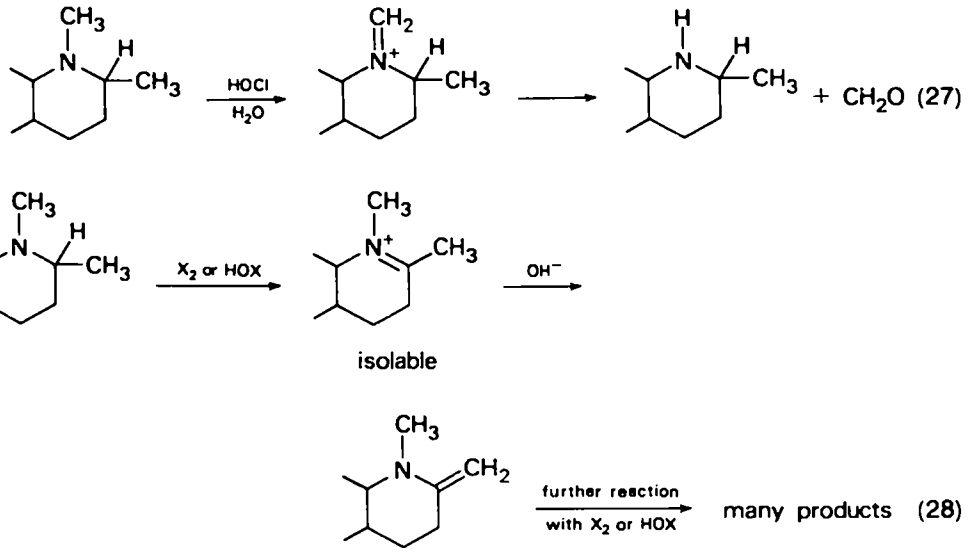
Differences from the foregoing are seen with Br_2. Lee and Srinivasan[183], in studies on dimethylbenzylamines, confirmed speculation by Deno and Fruit[87] to the effect that Br_2 attacks the nitrogen electron pair in concert with general base attack on an α-hydrogen (reaction 26). Both Br_2[183] and HOCl[263] show preferred benzyl

$$ArCH(H)—\overset{\cdot\cdot}{N}Me_2 \xrightarrow{\text{slow}} ArCH=\overset{+}{N}Me_2 + 2\,Br^- + BH^+ \xrightarrow[H_2O]{\text{fast}} ArCHO + HNMe_2 \quad (26)$$

(Br—Br; B)

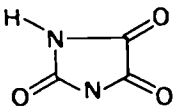
cleavage of dimethylbenzylamines, whereas ClO_2 cleavage is proportional to the number of α-hydrogens[263]. Moreover, Br_2 attack favours ring oxidation of *N*-methylpyrrolidine and *N*-methylpiperidine, in contrast to a greater tendency towards *N*-methyl oxidations by HOCl[87] and ClO_2[118], thus, Deno and Fruit[87] concluded that the Br_2 reaction is not promising for *N*-demethylation of alkaloids, unlike HOCl. The pronounced selectivity for ring oxidation over demethylation by Br_2 was demonstrated by studies on the alkaloids nicotine[88] and conanine[243,244]. Even with HOCl, less methyl cleavage (though still significant) than ring oxidation was seen with conanine[244]. The studies by Picot and Luschini on reactions of alkaline Br_2 and I_2 and sodium hypochlorite with conanine and related alkaloids provide examples of the diversity of possible reactions[244]. 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).

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[89,151].

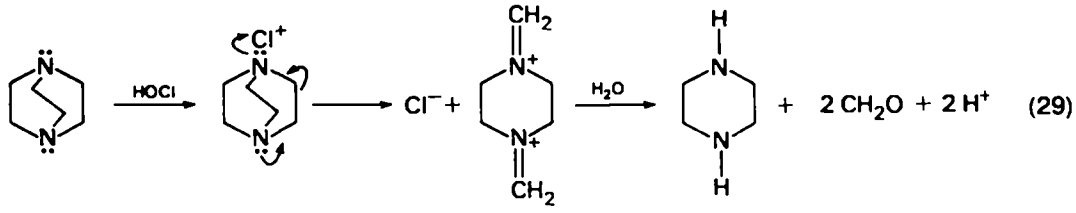
Purine and pyrimidine bases also undergo sequential halogenation reactions. Initially, *N*- and *C*-halogenated intermediates are formed, which are often quite stable[83,84a,153,240,295]. However, when the reaction mixtures stand for a long time, especially in the continued presence of excess active 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[85] and chloroform at higher pH[217]; acetic acid, trichloracetic acid and isobutyramidinium ion, along with a little chloroform, result from HOCl attack on 2-isopropyl-4-methyl-6-pyrimidinol[83,84a]. Guanine, adenine and xanthine slowly form parabanic acid (**10**), whereas caffeine and theophylline produce *N,N'*-dimethylparabanic acid when treated with the same reagent[153].



(**10**)

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**[217]. 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[217].

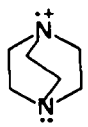
In addition to such oxidative dealkylations or ring oxidations as were shown previously, 1,2-diamines can undergo oxidative fragmentation. An outstanding example is reaction (29)[259]. The intermediate, **11**, also appears to undergo reversible homolysis, as discussed later. Perchloryl fluoride is another oxidant capable of



(29)

(3) (11) (12)

converting **3** to **12**[111]. Consensus seems to favour two-electron pathways in these oxidations[40,87,183,294]; in particular, evidence for this is the fact that light has no effect on the bromination reaction[87,183]. 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[150] and by the easily observed formation of the red aminium radical intermediate **13** when triethylenediamine reacts with HOCl[259,261]. Moreover, one-electron transfer to give aminium ion intermediates was implicated in the amine-catalysed bromination of olefins by *N*-bromosuccinimide[74] and in amine oxidations by 1-chlorobenzotriazole[205].



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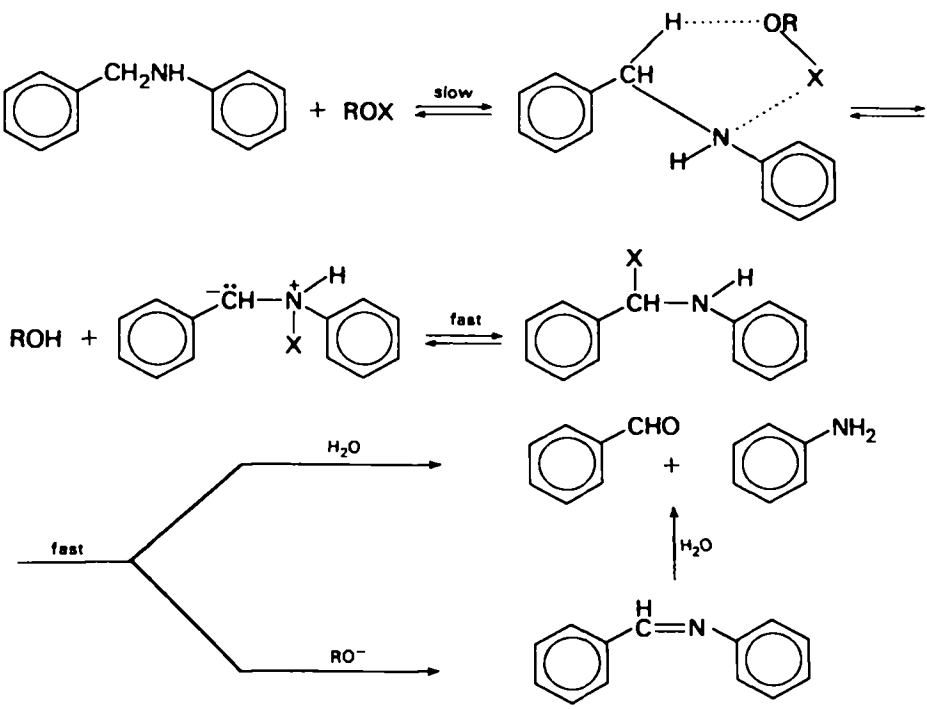
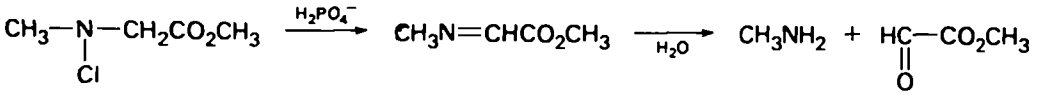


(30)

Product and kinetic studies by Ogata and Nagura[229] 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).

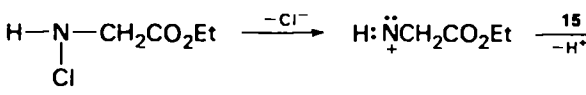
At pH 7, HCl elimination from **14** is general base-catalysed[164] (reaction 31).



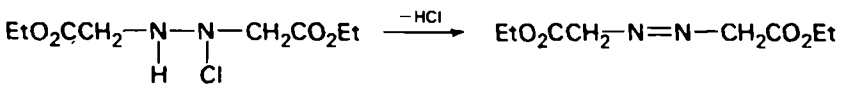
(31)

(14)

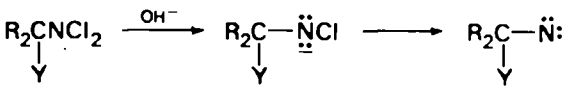
A slight change from structure **14** gives a compound **15**, whose decomposition is unaffected by general base[164]. The nitrenium ion pathway suggested by Kaminski and coworkers[164] (equation 32) borrows from the nitrene mechanism proposed by Pinchuk and coworkers[245] (equations 33 and 34).



(15)

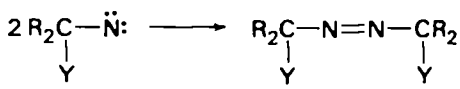


(32)



(33)

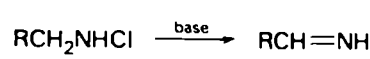
$Y = CN, PO(OEt)_2$ or CO_2Me



(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[13,45,90,134,175,198,267]. Here, the initial step could well be attack of base on an α-hydrogen, e.g. equations (35)–(37).

(35)

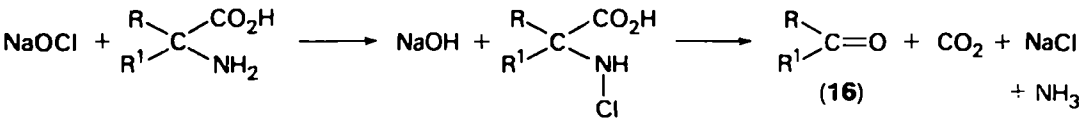


(36)

(37)

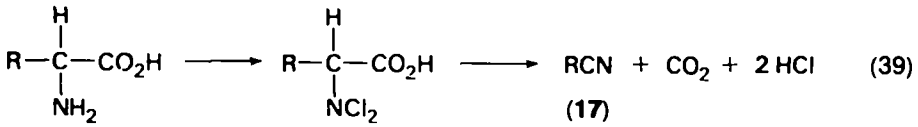
Although a number of mono- and di-chloroamines and bromoamines have been prepared, pure or in aqueous solution, they are not very stable; this seems to be especially true of the bromoamines[175,216]. Excess bromine in pH 6 buffer converted dipropylamine to a mixture of pyruvic and propionic acids; propylamine gave propionic acid as the sole product, even with equimolar Br_2[87].

In the literature of amine halogenation, the reactions of amino acids and peptides occupy a special place. As early as 1909, Langheld[181] reported the oxidative decarboxylation of α-amino acids at neutral pH (reaction 38). Dakin showed that



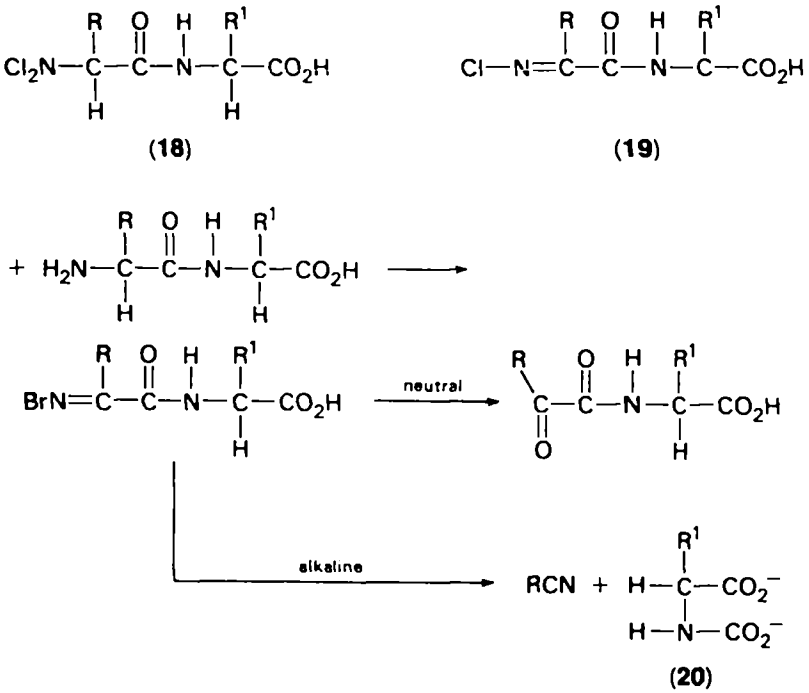
(38)

chlorosulphonamides could also act as the chlorinating agents[70], and later that two moles of sodium hypochlorite[70], or chlorosulphonamide[71] produced nitriles (reaction 39). Hypobromite oxidations gave the same types of decarboxylation products



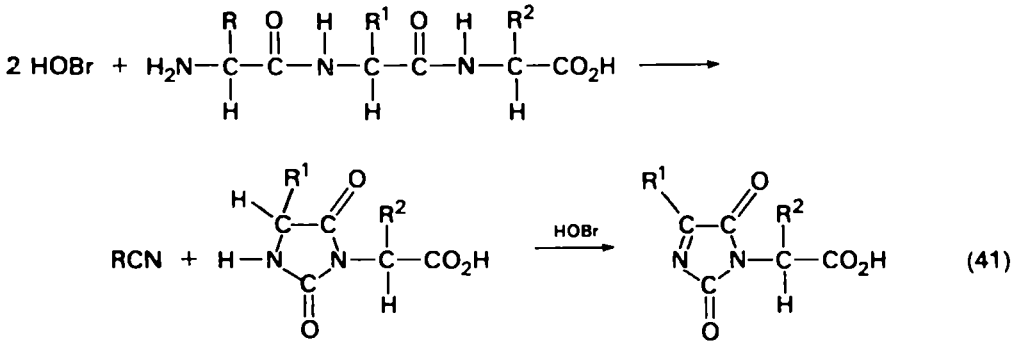
(39)

(**16** or **17**)[106,117]. *N,N*-Dichloropeptides (**18**), which decomposed on standing to *N*-chloroimides (**19**), were isolated on treatment of dipeptides with hypochlorous acid[242]. Goldschmidt and coworkers[117] elaborated on the bromination of dipeptides as shown in reaction (40).



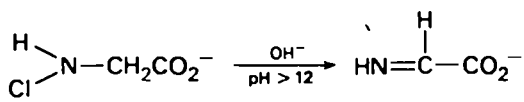
(40)

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 dehydrohydantoin were obtained[115,116] (reaction 41).



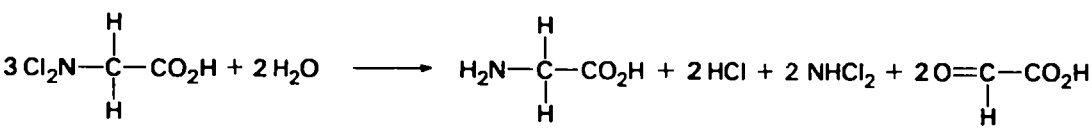
(41)

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 iminoacetate 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

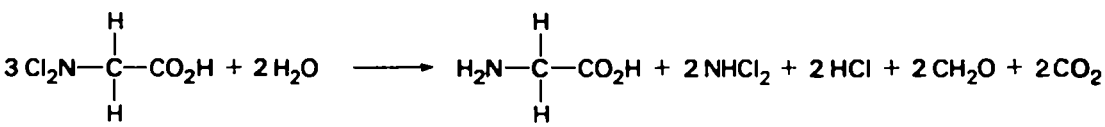


(42)

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

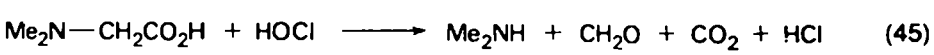


(43)



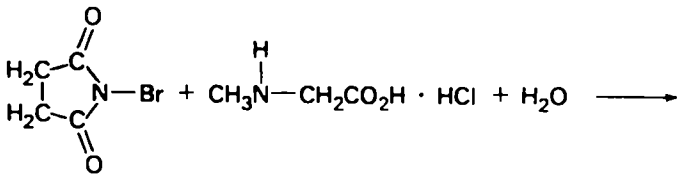
(44)

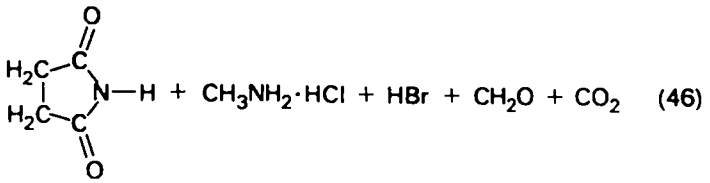
oxidation of *N,N*-dimethylglycine with one mole of hypochlorous acid in the pH range 1.5–6.3 showed maximum decarboxylation at pH 1.5 (reaction 45).



(45)

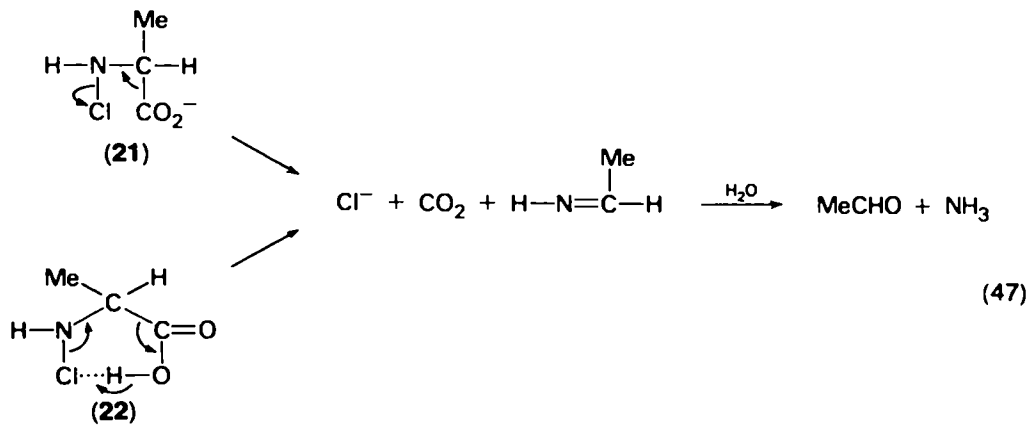
N-Methylglycine, when treated with *N*-bromosuccinimide under acidic conditions, also yielded formaldehyde[271] (reaction 46). The decomposition rate of *N*-chloro-*N*-methylglycine was shown to be independent of buffer concentration at pH 7[164].



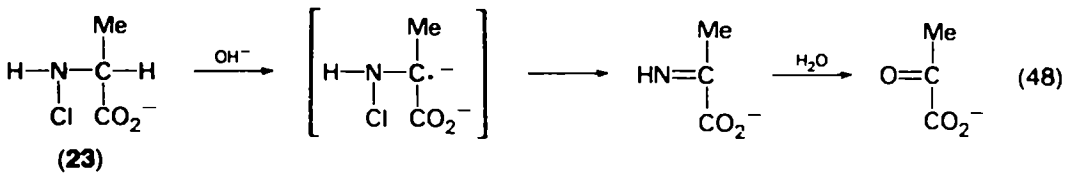


(46)

Among recent studies on the mechanism of such amino acid oxidations, that of Stanbro and Smith[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[105] (reaction 47). Although Fox and Bullock[105] explained the higher pH formation of pyruvic acid by a carbanion intermediate (equation 48), Stanbro and

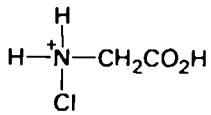


(47)



(48)

Smith[286] found that the kinetics did not justify such a mechanism. The scheme of Stanbro and Smith[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



(24)

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 Smith[284], Weil and Morris[303,304], Culver[66], Friend[107], Higuchi and coworkers[144], Kaminski and coworkers[165], Higuchi and Hasegawa[143], Pitman and coworkers[246], Hussain and coworkers[158], Gray[119], Gray and coworkers[120] and Margerum and coworkers[210]. Particularly significant has been the development of values and correlations for chlorine potential, $-\log_{10}K_{cp}$, where:

$$K_{cp} = \frac{[R_2NH][HOCl]}{[R_2NCl]} \text{ or } \frac{[R_3N][HOCl]}{[R_3NCl^+]} \tag{49}$$

Although chlorine transfer could occur via hydrolysis to HOCl, Hussain and coworkers[158] and Margerum and collaborators[210] 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 acid[216], but the evidence so far is fragmentary.

IV. POTASSIUM FERRICYANIDE

Lindsay Smith's group[6,7,8,203,204] 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–water[55].

The ferricyanide oxidation mechanisms (equations 50–53) parallel corresponding chlorine dioxide mechanisms in many details (see equation 2). One notable

$$RCH_2\ddot{N}R_2^1 + Fe(CN)_6^{-3} \longrightarrow RCH_2\overset{+}{\ddot{N}}R_2^1 + Fe(CN)_6^{-4} \tag{50}$$

$$RCH_2\overset{+}{\ddot{N}}R_2^1 \longrightarrow R\dot{C}H-\ddot{N}R_2^1 + H^+ \tag{51}$$

$$R\dot{C}H-\ddot{N}R_2^1 + Fe(CN)_6^{-3} \longrightarrow RCH=\overset{+}{N}R_2^1 + Fe(CN)_6^{-4} \tag{52}$$

$$RCH=\overset{+}{N}R_2^1 + H_2O \longrightarrow \left[\begin{array}{l} RCH-NR_2^1 \\ \quad | \\ \quad OH \end{array}\right] \longrightarrow RCHO + R_2^1NH \tag{53}$$

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[6]; this stands in contrast to the large effect of ferrocyanide at pH 8.8[154]. Other important characteristics of these reactions include:

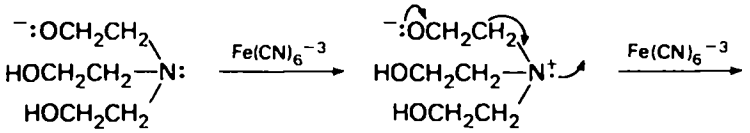
(1) Stoichiometry of the dealkylation (2 moles of oxidant per mole of tertiary amine)[6,7].
(2) First order, each, in oxidant and amine[6,7,203,204].
(3) Rate control by electron density on nitrogen (very small α-deuterium isotope effect)[203].
(4) Product control by acidity of the α-protons, with associated preference for demethylation[6].
(5) α-Deuterium isotope effect on the nature of the products ($k_H/k_D = 3.6$)[203].
(6) Lack of any effect by molecular oxygen[7].
(7) Formamide formation from *N*-methyl when oxidant is in excess, presumably via the carbinolamine[6].
(8) Values of ρ^* and ρ[6,7] similar to those for chlorine dioxide[155,263].
(9) Large cation salt effects[6].
(10) Clear indication that aminium ions are intermediates[8].
(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)[203,204].

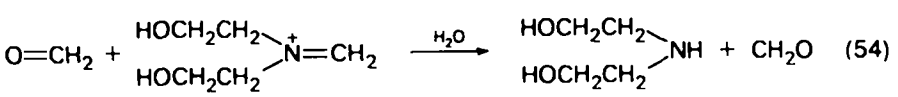
The inductive effect of amino or hydroxy groups in the β-position reduces reactivity somewhat; this effect falls off with increasing distance along a chain[204]. The reactivity is increased, however, when a strong base causes a β-hydroxyl or β-oxo (in the enol form) to ionize[204,280].

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[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[203]. This readier 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[55,206].

Like chlorine dioxide[82], ferricyanide causes oxidative fragmentation of triethanolamine to formaldehyde[280]. For the alkaline medium used, one can write reaction (54).

Haynes and Hewgill[130–132] have described oxidation of three substituted anilines (compounds **25**, **26** and **27**) by ferricyanide ion. In each instance, the corresponding





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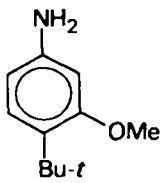

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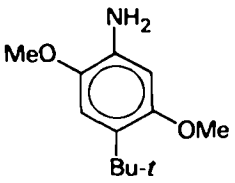
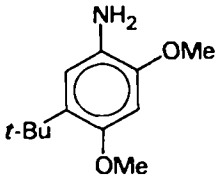


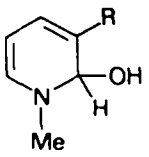
(26)



(27)

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.

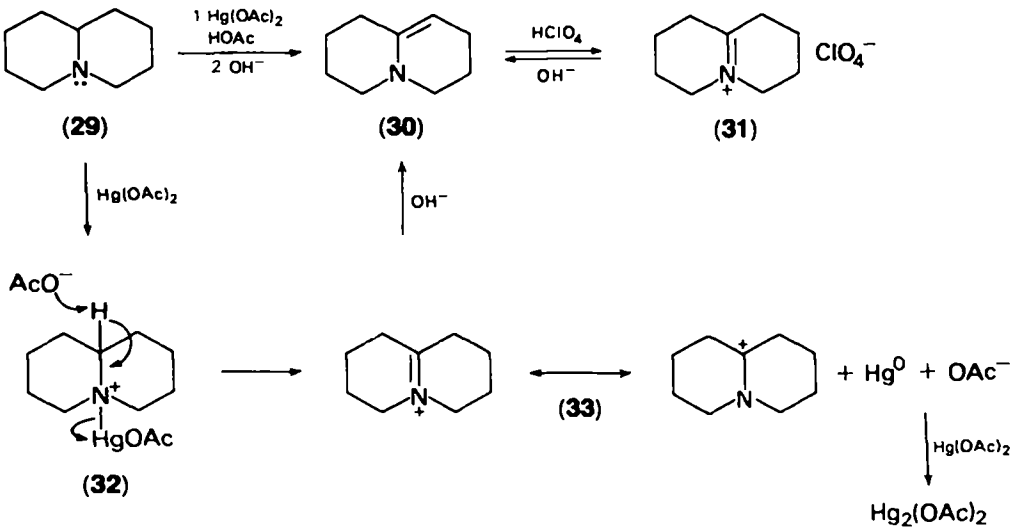


(28)

V. MERCURIC ACETATE

Prior to the extensive studies of Leonard and coworkers more than two decades ago[129,186–189,192–197], 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 α-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 π-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 α-H removal is tertiary > secondary > primary.

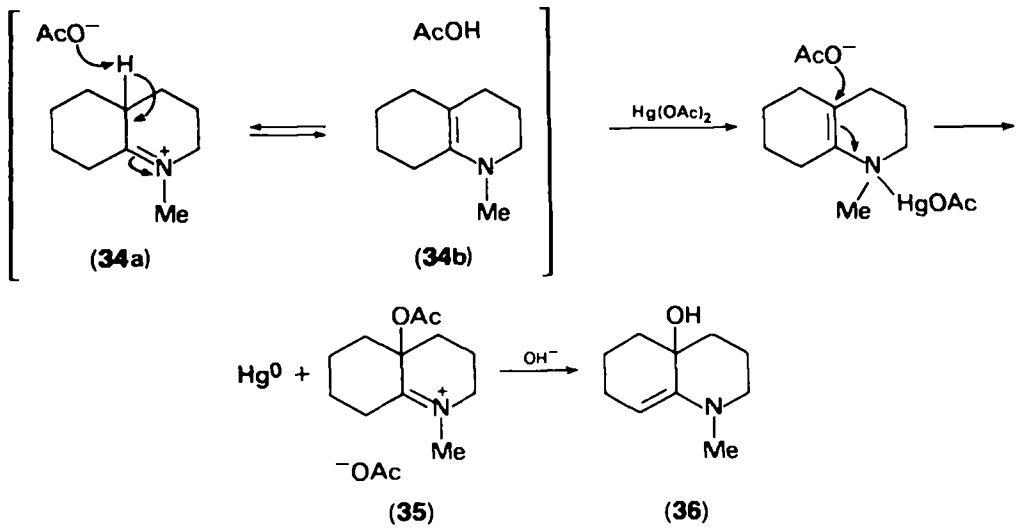
In cases where a tertiary carbon is present β as well as α to nitrogen, the oxidation may take a different course, a combined dehydrogenation and hydroxylation leading to carbinolamines[193,196]. The example of 1-methyldecahydroquinoline[196] is illustrative (Scheme 2). A prior equilibrium between **34a** and the corresponding base **34b** is interrupted by formation of a mercurated π-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 Hg^0, 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



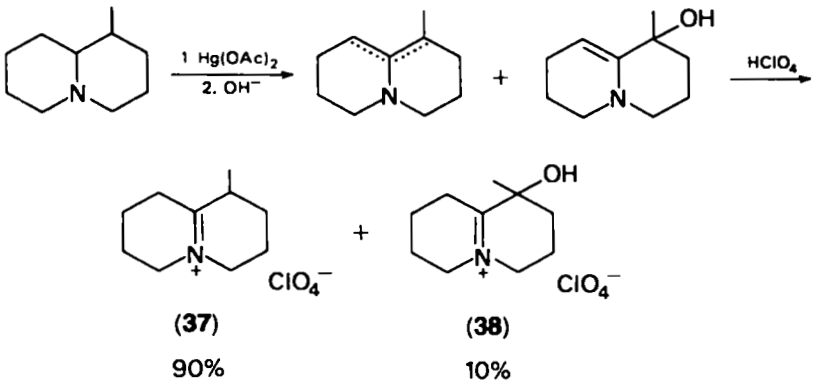
SCHEME 1

obtained on oxidation of 4-methylquinolizidine (Scheme 3)[193]. However, in the case of bicyclic pyrrolidine **39**[121] and in two cases of decahydroquinoline derivatives where the β-carbon was tetrasubstituted (**40** and **41**)[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[187] and -pyrrolidines[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

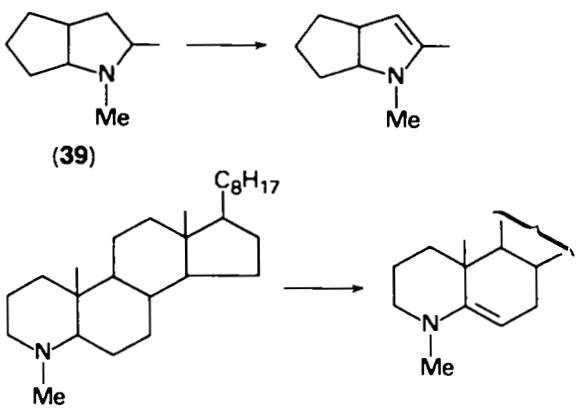


SCHEME 2



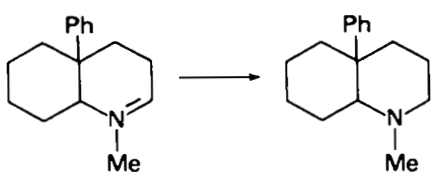
(37) 90% **(38)** 10%

SCHEME 3

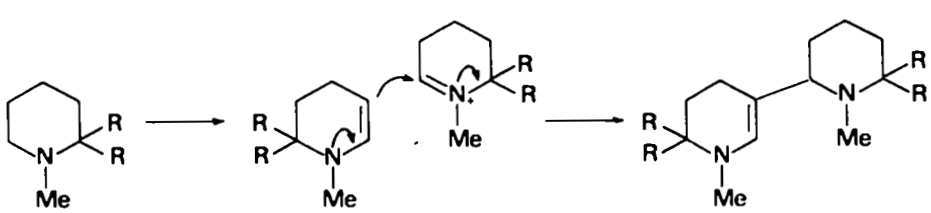


(39)

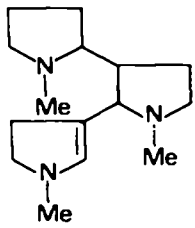
(40)



(41)

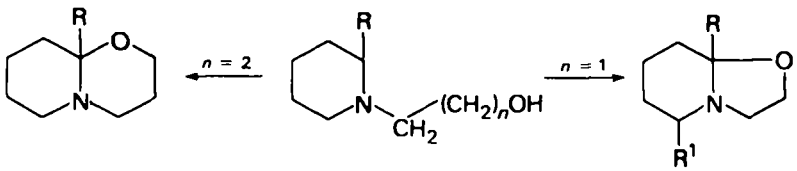


SCHEME 4



(42)

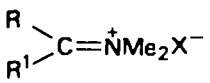
trimer (42) were found. These oxidations provide synthetically useful routes to substituted Δ^2-tetrahydroanabasines and, after treatment of the pyrrolidine products with ethyl acetoacetate, substituted hygrines. While cyclic secondary amines were inert to Leonard's conditions, Bonnett and coworkers[41] 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[190] (Scheme 5). The reagent is also effective in aromatization of certain *N*-heterocyclic systems, notably bisbenzylisoquinoline alkaloids[171] and 2-dehydroisoemetine[113].



$n = 2,1$

SCHEME 5

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[187]. As for noncyclic secondary amines, one report[235] cites low and variable yields of carbonyl compounds.

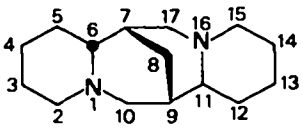


(43)

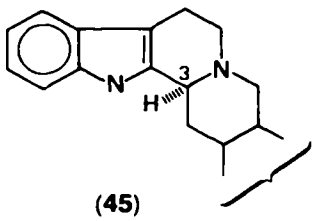
(a) $R, R^1 = C_5H_{10}$

(b) $R = Ph, R^1 = H$

Experiments by Leonard and by others have served to define the steric requirements for the dehydrogenation reaction, and the results strongly substantiate the proposed[188,194] 4-centre elimination mechanism requiring *trans* coplanarity of the α-H and the N—Hg bond. Sparteine (**44**), with two nonequivalent bridgehead tertiary α-hydrogens (C-6 hydrogen axial–axial to the adjoining rings and C-11 hydrogen equatorial–axial) was shown[197] to lose the former hydrogen more readily. Further, in the yohimbine–reserpine series, alkaloids bearing an axial (α) hydrogen at C-3 (shown in **45**) are more readily oxidized than their β C-3 epimers[306],

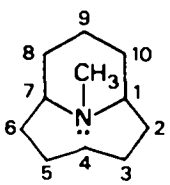


(44)

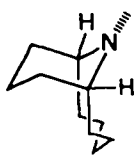


(45)

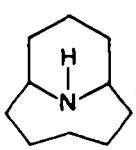
although the possibility of epimerization of the less stable β-epimer may present a complication[94,308]. Finally, the synthesis and oxidation of 11-methyl-11-azabicyclo-[5.3.1]hendecane (**46a**)[188] proved conclusively the requirement for elimination of a proton in *trans* diaxial relationship to 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 *syn* or *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 *trans*



(46a)

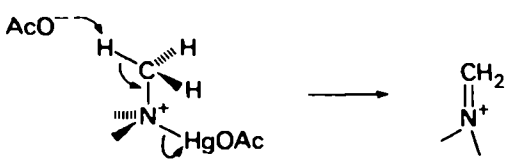


(46b)



(47)

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 CO_2 [188].

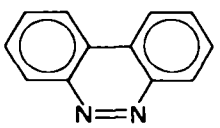


SCHEME 6

VI. MANGANESE SPECIES

A. Manganese Dioxide

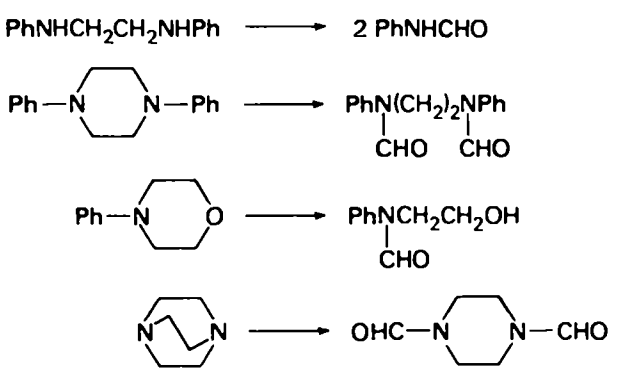
Primary aliphatic amines, e.g. ethylamine[27] and benzylamine[142], were oxidized in moderate yields to the corresponding carbonyl compounds, and spectal evidence for an imine precursor was reported[142]. Primary aromatic amines, including *o*- and *p*-phenylenediamines, on the other hand, gave good 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 benzylidineanilines (**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].



(**48**)

$ArCH_2NHAr^1 \longrightarrow ArCH{=}NAr^1$

(**49**) (**50**)

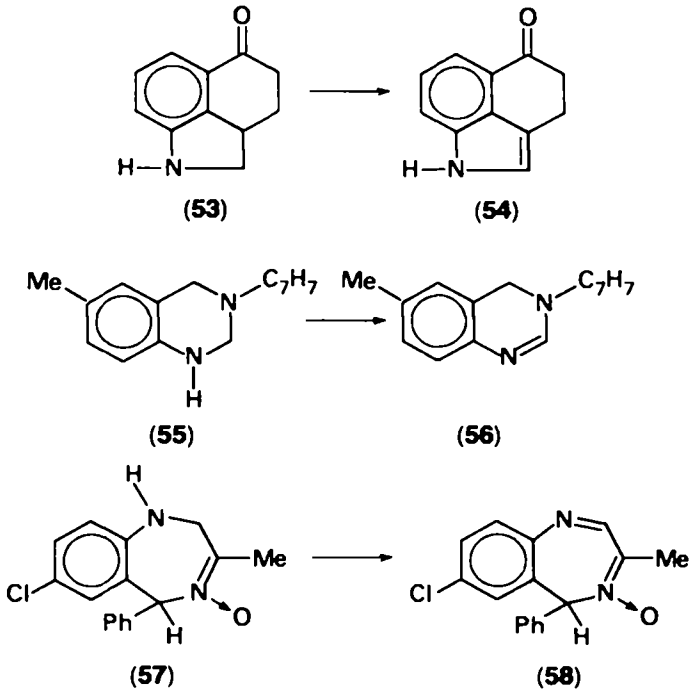


SCHEME 7

A series of tri-*N*-alkylamines R_3N where R = *n*-C_3H_7 through *n*-C_7H_{15} gave the respective formamides $R_2N{-}CHO$ in yields improving with increase in chain length (27–54%)[136]. Variation of conditions for $(n\text{-}C_4H_9)_3N$ 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].

(**51**) (**52**)

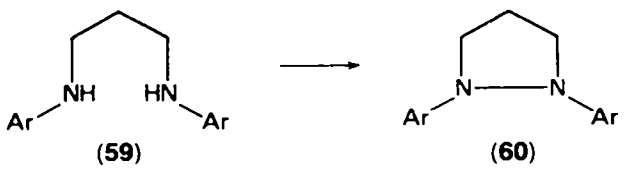
Manganese dioxide has found some synthetic utility in selective dehydrogenation of certain heteroaromatic systems (Scheme 8). Tricyclic ketone **53**, which readily



SCHEME 8

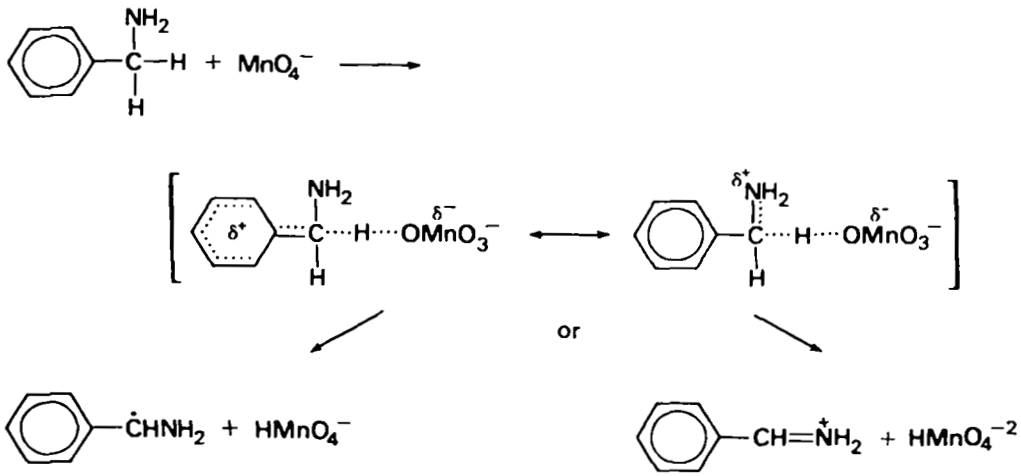
aromatizes to a naphthalene system or undergoes oxidative polymerization, gave a 64% yield of indole **54** on treatment with MnO_2 in CH_2Cl_2 at room temperature[161]. Similarly, tetrahydroquinazoline **55** gave the dihydro derivative **56**[93], and dihydrobenzodiazepine oxide **57** was dehydrogenated without loss of the labile *N*-oxide[98].

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[73]. For additional examples the reader is referred to an earlier review[215].



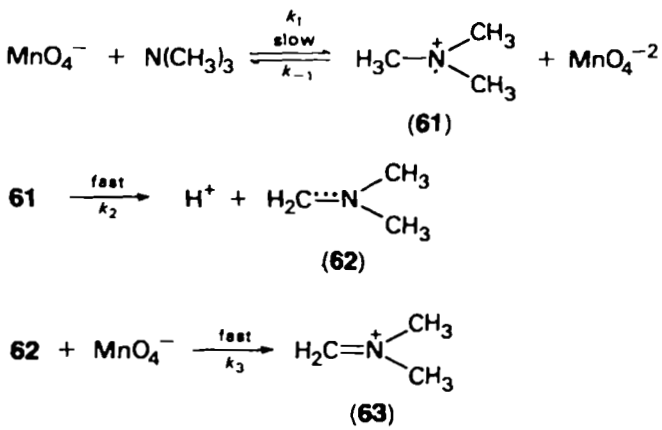
B. Potassium Permanganate

Neutral[274,275] or alkaline[302] 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[260] 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[302] 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



SCHEME 9

abstraction[302], or electron abstraction from nitrogen[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 aminium 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: $3\,MnO_4^{-2} + 2\,H_2O \rightarrow 2\,MnO_4^- + MnO_2 + 4\,OH^-$. 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 aminium cation radicals from chlorine dioxide[156]. The relative rates

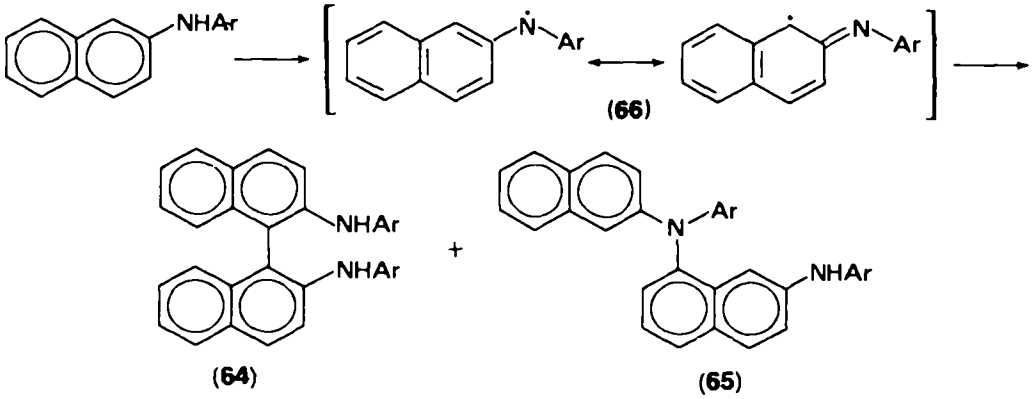


SCHEME 10

for oxidation in buffered permanganate of triethylamine, diethylamine and ethylamine were 31, 0.9 and 0.08, respectively[260]. This order of reactivity conforms to that observed for chlorine dioxide[263] and ferricyanide[6], where involvement of aminium cation radicals has been demonstrated independently, and is opposite to that inferred from earlier data for permanganate[179]. In summary, in view of these observations and other considerations[260], 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[252] have reported a modification of their earlier procedure[274,275], 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[310,311], has been clarified by Bridger and coworkers more than 60 years later[43,44]. 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 **66**[43]. The observed ρ of −0.68 suggests that transfer of hydrogen to permanganate in a single step is most probable in formation of the latter.

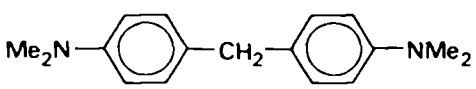


SCHEME 11

C. Manganic Acetate

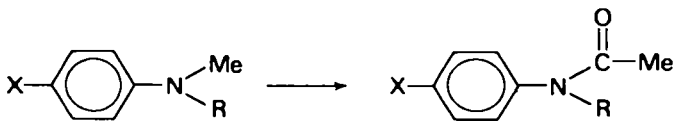
Oxidation of *N,N*-dialkylanilines, the only amine substrates so far investigated for Mn(III) species, evidently follows different courses under different experimental conditions. In addition to polymeric material, the only product isolated from oxidation of *N,N*-dimethylaniline with two molar equivalents of $Mn(OAc)_3$ in acetic acid in the presence of air was **67**, derived by condensation of a formaldehyde unit with the substrate[5].

On the other hand, under conditions where *N,N*-dialkylanilines are known to



(67)

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.



(68) **(69)**

TABLE 1. Percentage yields of substituted *N*-phenyl-*N*-alkylacetamides **69**

	Para substituent			
R	H	OMe	NO_2	Cl
Me	58	55	36	72
Et	61	69	43	67
n-Bu	83	50	33	53

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[108,110]. 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

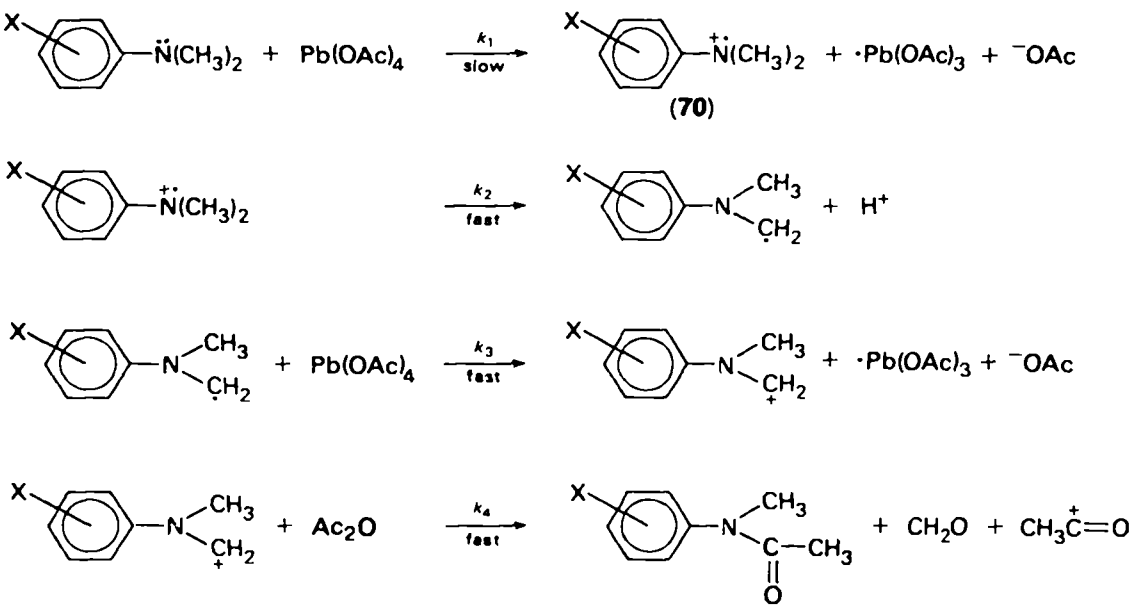
A series of primary aliphatic amines as well as benzylamine have been oxidized to nitriles in 40–60% yields with two molar equivalents of $Pb(OAc)_4$ (LTA) in refluxing benzene[289]. Isolation of benzaldehyde (in addition to benzonitrile in 59% yield) constituted evidence for an intermediate imine, and 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-dicyanobutadienes 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

(24%), along with smaller amounts of *N*-benzylidene-α-acetoxybenzylamine (14%) and *N*-benzylidenebenzylamine (6%)[289].

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 $CHCl_3$/acetic anhydride[109,255]. 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 **70**, followed by rapid proton loss and a second (rapid) electron transfer, has been proposed[108,110]. 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[226]. Furthermore, the ρ value (-2.4 ± 0.5) found[110] for ring-substituted dimethylanilines is indicative of a high degree of positive charge on nitrogen in the transition state.

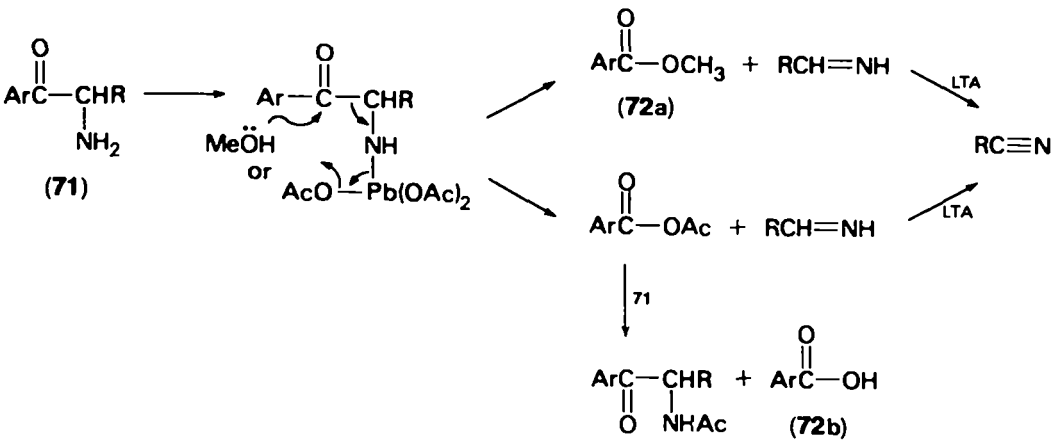


SCHEME 12

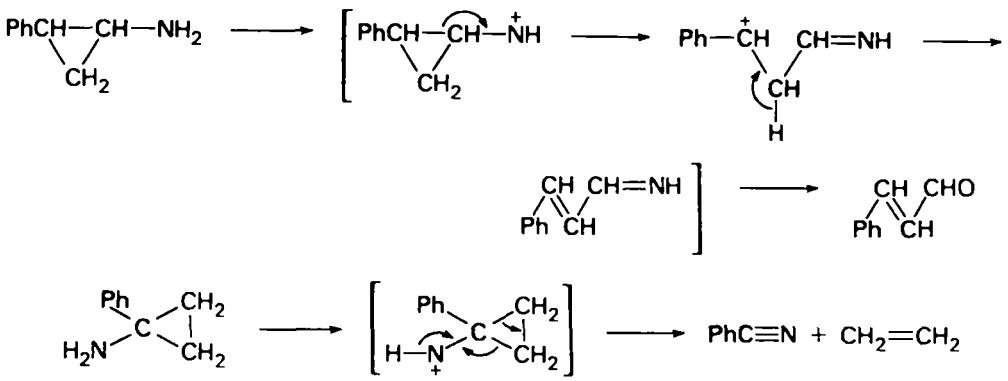
Primary and secondary 1,2-amino alcohols undergo carbon–carbon cleavage to aldehydes and imines, the latter generally being further oxidized to nitriles[63], while tertiary 1,2-amino alcohols are cleaved at carbon–nitrogen to secondary amines and α-hydroxycarbonyl compounds[191].

Baumgarten and coworkers[33] have studied the oxidative cleavage of a series of α-aminoketones (**71**) by LTA in CH_2Cl_2 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



SCHEME 13

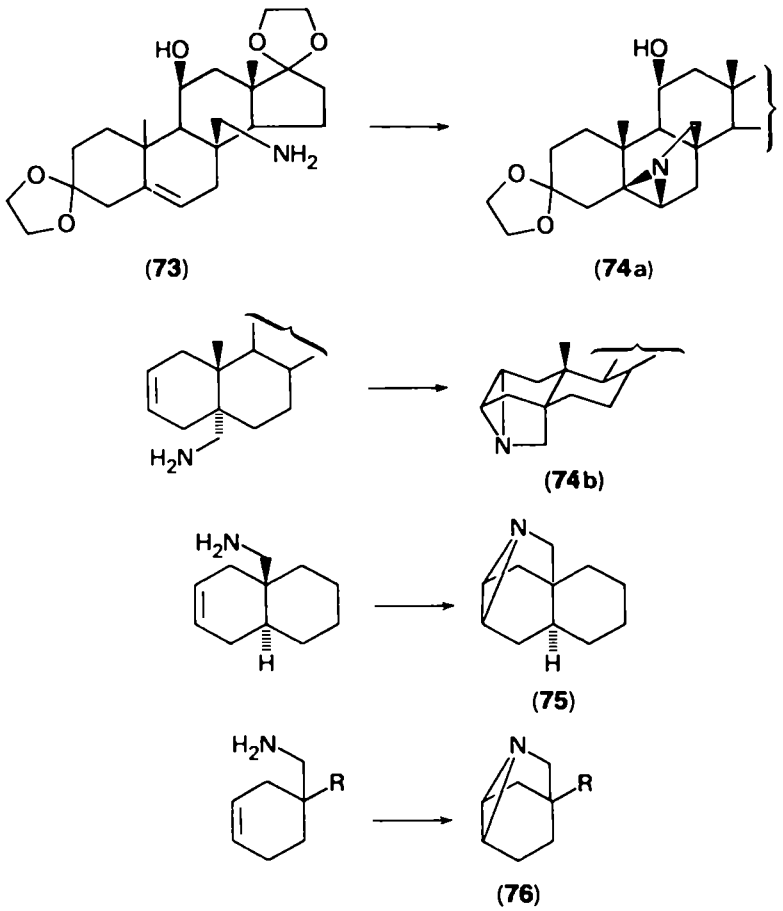


SCHEME 14

same conditions, 1-phenylcyclopropylamine gave benzonitrile (69%) and ethylene[145a]. 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)[145a].

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)[218]. 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[124]. However, on treatment with one equivalent of LTA in CH_2Cl_2 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**[99] (Scheme 16). Thus, reserpiline (**80**) was



(a) R = H
(b) R = Me

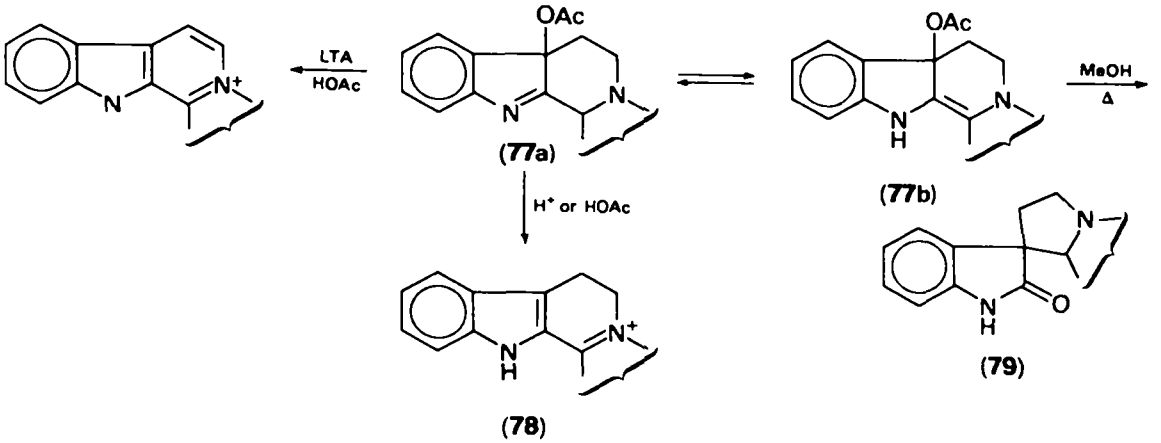
SCHEME 15

rearranged to carapanaubine (**81**). In contrast, certain ajmaline derivatives (**82**) were found to yield 2-hydroxy compounds (**83**) that underwent demethylation on further treatment with LTA[32].

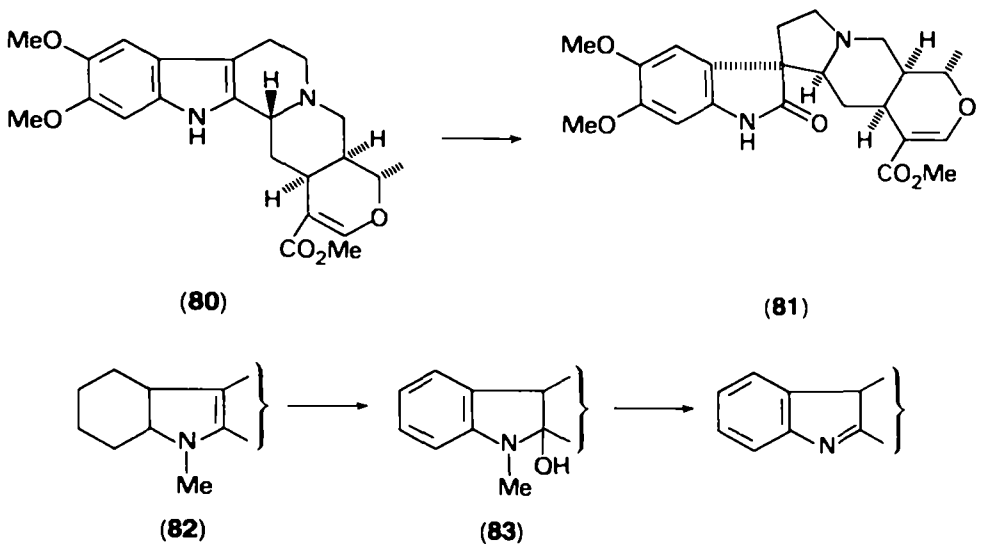
VIII. OTHER METALS

A. Copper

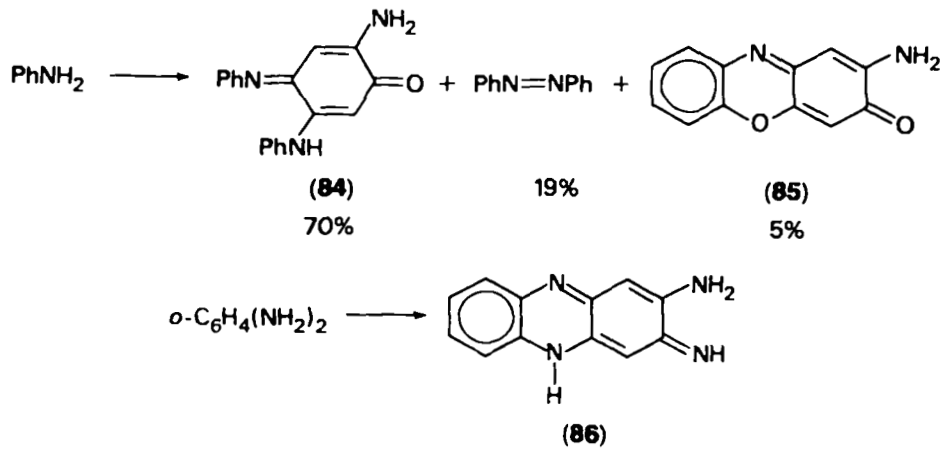
Aliphatic amines, with the exception of α-aminoketones, are generally inert to Cu(II). The latter are oxidized to dicarbonyl compounds by Cu(II) in alkaline solution[160]. Aromatic amines are oxidized by Cu(II) in hydroxylic solvents in the presence of O_2 to complex mixtures (Scheme 17). Aniline gave 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].



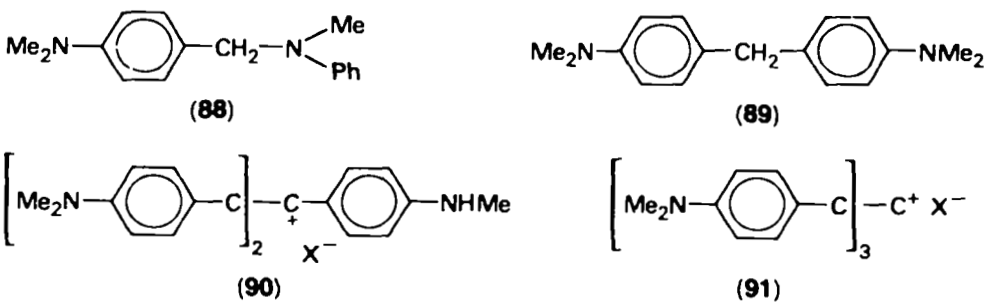
SCHEME 16



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[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).

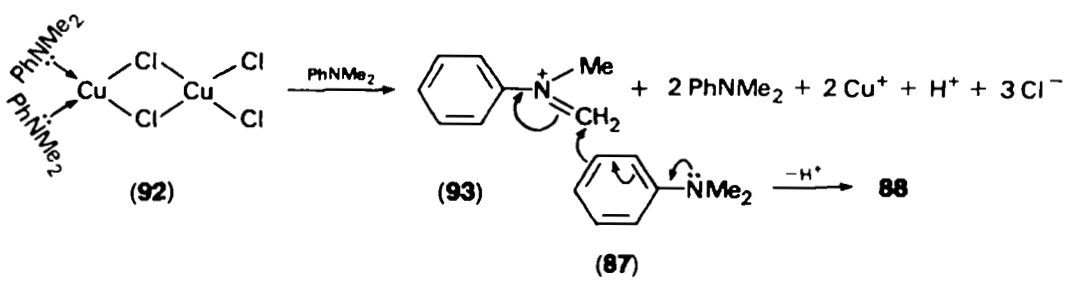


SCHEME 17

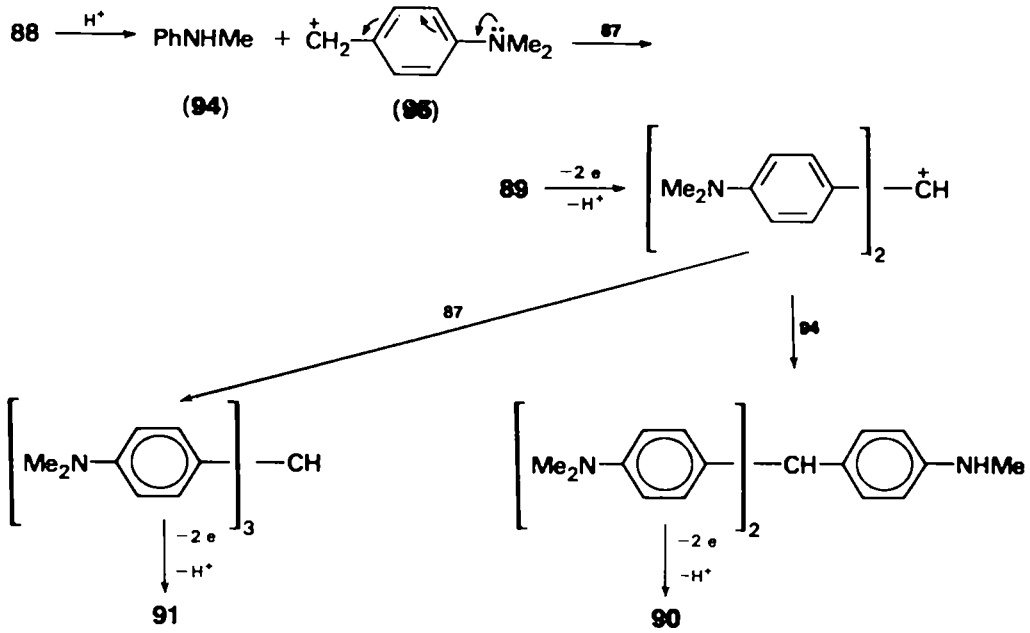


Further sequential two-electron transfers lead to the violet dyes **90** and **91** as shown in Scheme 19.

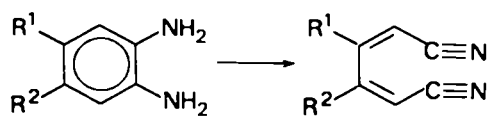
Cuprous chloride in pyridine in the presence of O_2 was used to oxidize substituted benzylamines to the corresponding benzonitriles[163] and was found to be the reagent of choice for conversion of *o*-phenylenediamines (**96**) to *Z*,*Z*-1,4-dicyanobutadienes (**97**)[162]. Yields were 62–96% in the unsubstituted case and for electron-donating substituents. Similarly, *o*-cyano-*Z*-cinnamonitrile (**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



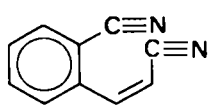
SCHEME 18



SCHEME 19



(96) (97)



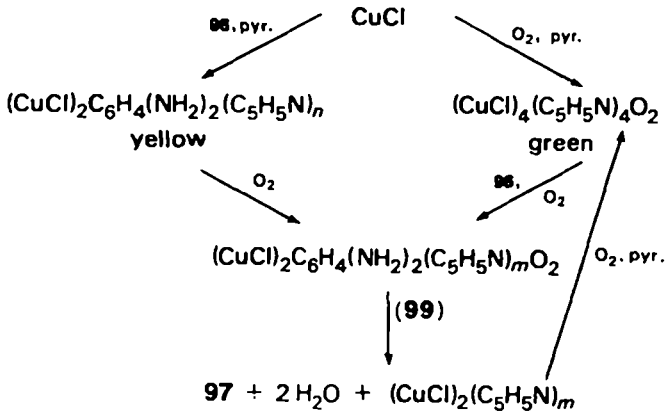
(98)

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[200]. The role of the catalyst is yet unclear.

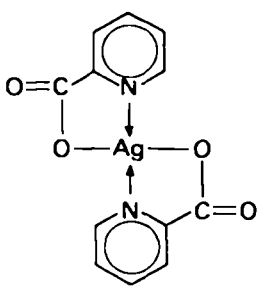
B. Silver

Argentic oxidants will be treated here as three general classes that differ significantly in methods of preparation and properties as oxidants. Silver persulphate,



SCHEME 20

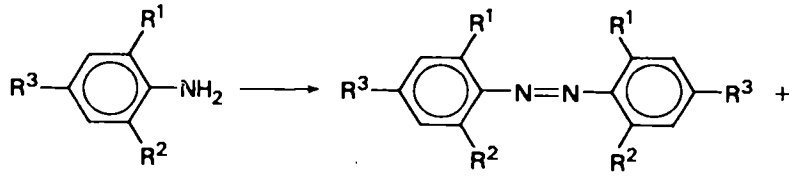
prepared *in situ* by addition of sodium persulphate to a catalytic amount of aqueous alkaline silver nitrate solution containing the amine, is a useful reagent for the conversion of low molecular weight primary amines to carbonyl compounds (60–95% yields)[15], and the intermediate aldimines (but not 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[16]. Intermediacy of Ag(III) in persulphate oxidations has been suggested[11], but the mechanistic picture is unclear. Alternatively, argentic ion may be isolated as the red solid picolinate **100** prepared by persulphate treatment of an alkaline solution of



(100)

silver nitrate and picolinic acid. With this reagent, primary amines were found, in contrast to earlier observation[14], 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[185]. Water[14,185], 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[53], 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[56]. The products appeared similar to those of

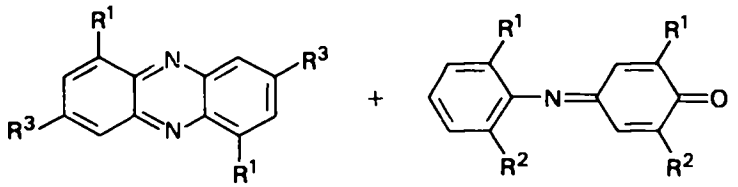


(101)

(a) $R^1 = R^2 = R^3 = Me$
(b) $R^1 = R^2 = Me$, $R^3 = H$
(c) $R^1 = R^3 = Me$, $R^2 = H$
(d) $R^1 = R^2 = R^3 = Ph$
(e) $R^1 = R^2 = H$, $R^3 = Cl$

(102)

(a) 75%
(b) 35%
(c) 30%
(d) 95%
(e) 35%



(103)

(c) 25%
(e) 8%

(104)

(b) 10%

SCHEME 21

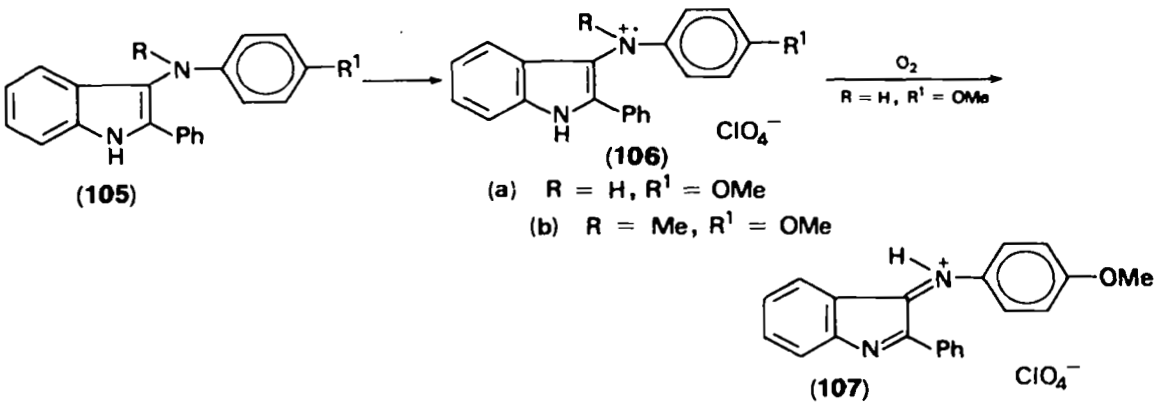
Ag(II) picolinate for amines having α-hydrogen, and in addition *t*-butylamine was oxidized to a 2:1 mixture of *t*-butyl alcohol and 2-methyl-2-nitropropene. Certain ring-substituted anilines were converted to the respective azobenzenes in 15–59% yields on treatment with AgO in organic media (benzene or ether)[235] (Scheme 21).

Oxidation of ring-substituted anilines (**101a–e**) by Ag_2CO_3/celite, reported by two French groups[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**, **103e**, **104b**) resulting from C—N couplings of the initial radical were also isolated[133].

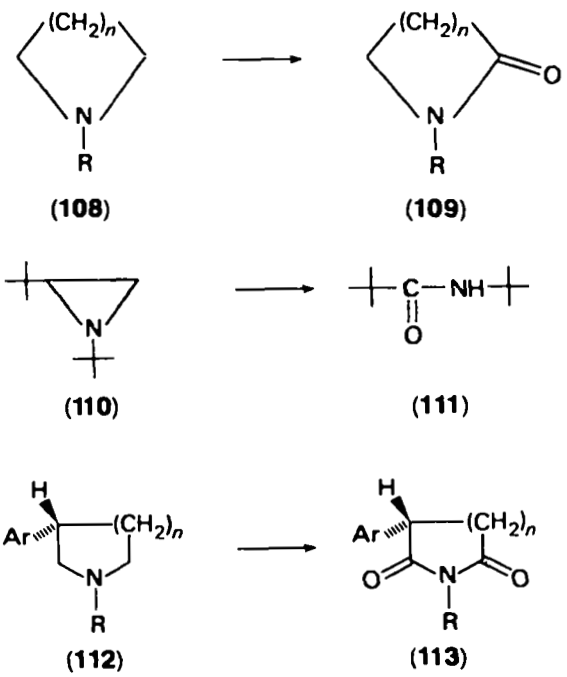
Treatment of a number of substituted *N*-phenylaminoindoles (**105**, R = H or Me) with silver(I) perchlorate in acetonitrile gave rise to aminium radical cations (**106**), some of which (R^1 = OMe or NMe_2) were sufficiently stable to be isolated and characterized[47]. Aminium perchlorate **106a** in acetonitrile was further oxidized to iminium perchlorate **107** by molecular oxygen (Scheme 22)[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[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[35].



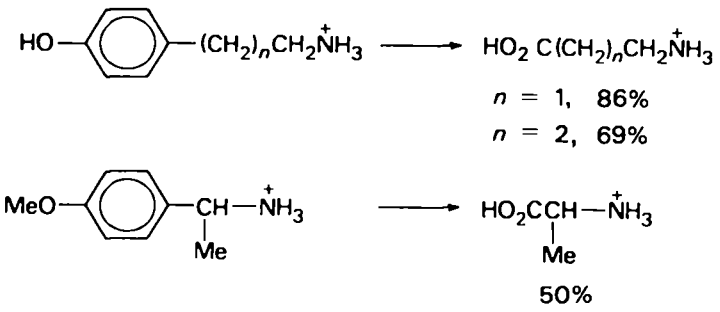
SCHEME 22



A ruthenium tetroxide–sodium periodate reagent has been employed to oxidize arylalkylamines with electron-donating substituents to amino acids (Scheme 23)[10]. 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[221], but was a poor choice for conversion of *o*-phenylenediamines (**96**) to dinitriles (**97**)[220]. Tetraarylhydrazines were obtained in moderate yields from diarylamines[112].

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-



SCHEME 23

tially inert[277]. 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 a benzylic 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-dihydroisoquinoline from 1,2,3,4-tetrahydroisoquinoline[9]. Tertiary amines were not oxidized.

A comparison of oxidations of eight primary amines to carbonyl compounds with $PdCl_2$ and $AuCl_3$ in water was made, and in five cases $AuCl_3$ at pH 4.5–6 gave higher yields[176]. Exceptions were cyclopentylamine and α-methylbenzylamine (each requiring addition of 10% Pd on charcoal to the $PdCl_2$) and cycloheptylamine. Indoline underwent Pd-promoted dehydrogenation to indole in 83% yield.

In the course of investigation of UF_6 as a selective oxidant for organic compounds, five *N,N*-dimethylalkylamines were oxidized to the respective carbonyl compounds (16–70% yields)[234]. A two-electron pathway via an iminium ion intermediate was suggested.

A number of examples of metal-catalysed O_2 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[77,258]. 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 $CuCl_2$, Cu_2Cl_2, $CuBr_2$, Cu_2I_2, $FeCl_3$, $NiCl_2$, $CoBr_2$, $CoCl_2$, AgCl, $AuCl_3$, $ZnCl_2$, $HgCl_2$, $MnCl_2$, $ReCl_3$, $PdCl_2$ and $PtCl_2$, anhydrous or hydrated[269]. Although the synthesis of *N,N*-dimethylformamide from trimethylamine was studied in greatest detail, other examples, such as *N*-formylpiperidine from *N*-methylpiperidine 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 $RuCl_3$ in toluene catalysed conversion of RCH_2NH_2 to RCN and $RCONH_2$, and RR^1CHNH_2 to $RR^1C{=}O$ and $RR^1C{=}NH$[293].

IX. PEROXY SPECIES

A. Hydroperoxides – Peroxy Acids and Hydrogen Peroxide

The peracid oxidant of choice for conversion of primary aliphatic amines RCH_2NH_2 or R_2CHNH_2 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 $KMnO_4$ oxidation of tertiary carbinamines[174], it is worth noting that in one case (*t*-$BuNH_2$) sodium tungstate-catalysed H_2O_2 oxidation gave only a somewhat lower yield (70%)[290] compared to $KMnO_4$ (83%)[174].

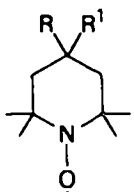
Of various peracid oxidants employed for conversion of secondary amines to stable nitroxyl free radicals[207,266], the most generally useful appear to be MCPBA and sodium tungstate-catalysed H_2O_2 in methanol/acetonitrile[251]. The yields for some substituted piperidines (Table 2) show a dramatic improvement in comparison with aqueous sodium tungstate-catalysed H_2O_2 for the less water-soluble compounds[251].

Progress has been made recently in synthetic methodology for oxidation of polynitroanilines 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 tetranitrobenzenes and pentanitrobenzene, the oxidant of choice was nearly anhydrous peroxydisulphuric acid (78–95% yields)[227]. For oxidation of pentanitroaniline a new reagent, peroxytrifluoromethanesulphonic acid, gave hexanitrobenzene in 90% yield[228], compared to 58% obtained with peroxydisulphuric acid[227].

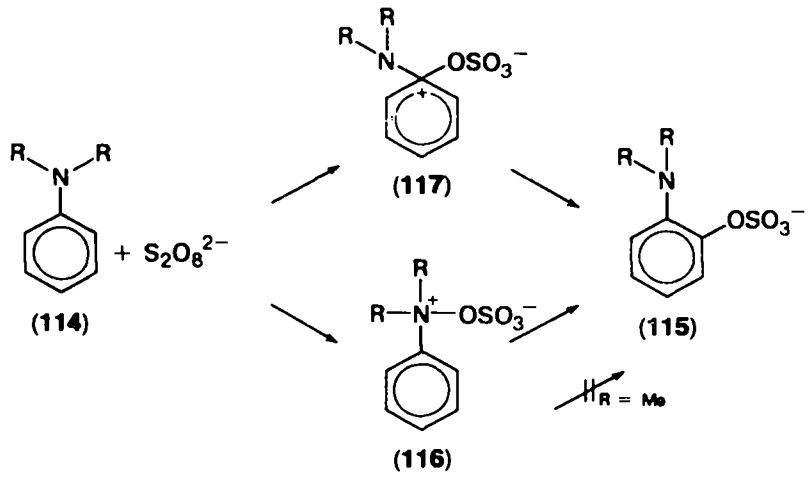
Oxidation of 2-aminopyridines to the corresponding nitropyridines (60–68%) with Caro's acid has been reported[312], but later work[57,140] indicates that further oxidation to *N*-oxides as major products may present a complication. Hindered aromatic amines have been oxidized to nitroso compounds with 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



		Yields (%) in		
R	R^1	H_2O/aq.	H_2O/MeOH/MeCN	MCPBA
O	O	50	86	85
H	OH	80	85	86
H	CO_2Me	15	84	84
H	CO_2Bu-*t*	10	88	83



(a) R = Me

SCHEME 24

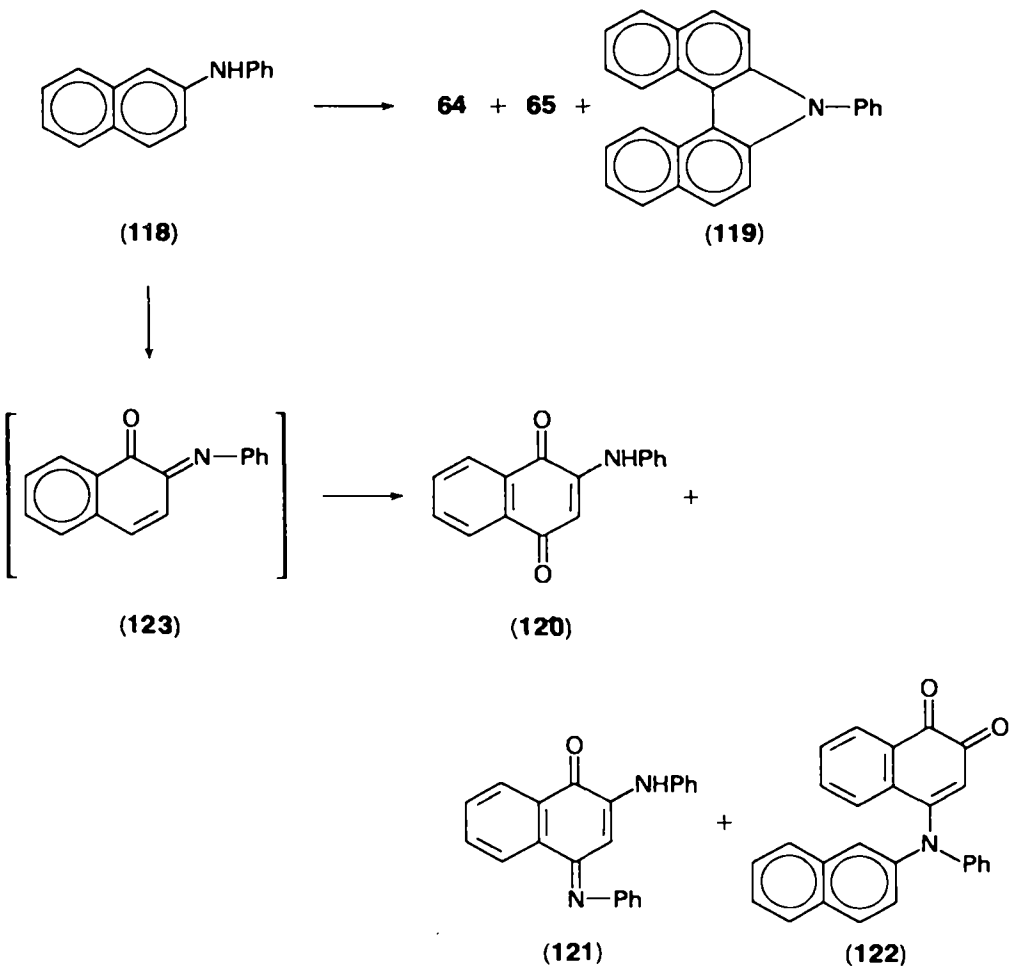
N-phenylaniline with peroxymonophosphoric acid[230] has shown a rate-determining nucleophilic attack of neutral amine on peracid oxygen similar to that well established for other peracid oxidations of primary amines[247].

Behrman and Behrman[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 *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 *ortho* carbon for tertiary amines as well as for primary. Rather, the reaction is now viewed as proceeding by *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*-benzoquinonediimines 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

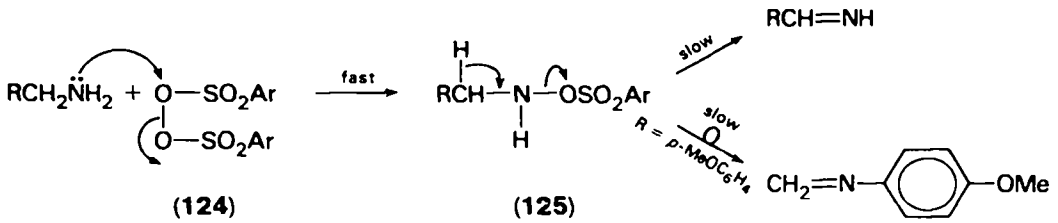


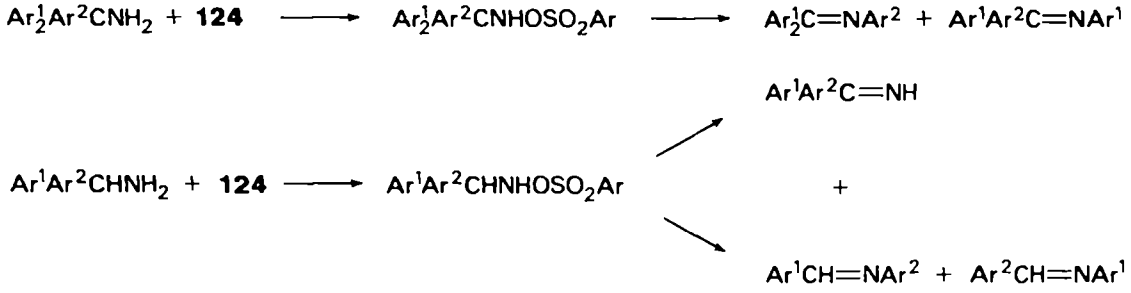
SCHEME 25

coworkers (Scheme 25)[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[141]. Since then, the course of oxidation of amines by diarylsulphonyl peroxides (**124**) has been studied comprehensively by Hoffman and coworkers[145b,146-149], and detailed pictures of the mechanisms of competing elimination and rearrangement processes have been well documented. Primary and





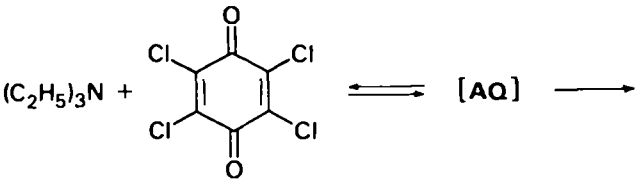
SCHEME 26

secondary alkyl- and alkylaryl-amines (substituted benzylamines) having α-hydrogen gave as major products carbonyl compounds resulting from hydrolysis of the intermediate imine[145b]. An exception was *p*-methoxybenzylamine in which rearrangement (40%) competed favourably with elimination (12%)[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[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)[81] is followed by rate-determining elimination to imine[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[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[148].

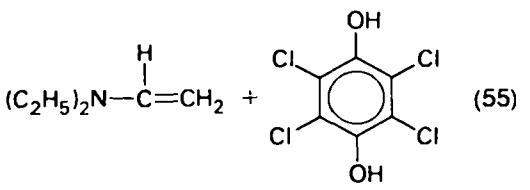
X. QUINONES

Henbest and coworkers investigated the oxidation of aliphatic tertiary amines in benzene by a variety of quinones[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[48] (reactions 55 and 56).

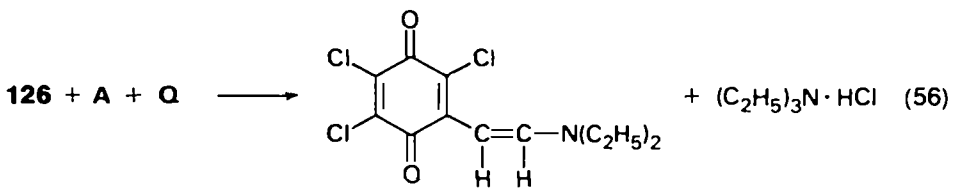


(A) (Q)



(55)

(126)

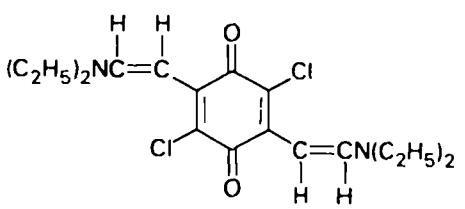


(56)

(127)

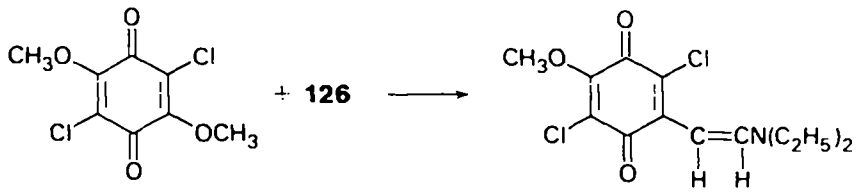
blue

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[48]. Other oxidants can perform the oxidizing function, for example, benzoyl peroxide, 3,3′,5,5′-tetrachlorodiphenoquinone or *N*-bromosuccinimide[49]. When triethylamine is oxidized by benzoyl peroxide in the presence of **127**, a purple product, **128**, is formed[48].



(128)

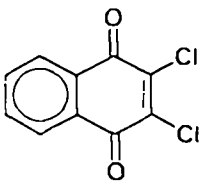
Triethylamine forms a complex with **129**, but **129** lacks the oxidation potential to dehydrogenate the amine in the dark (although it does so under strong illumination[48]); when benzoyl peroxide is added, however, **130** forms easily, owing to



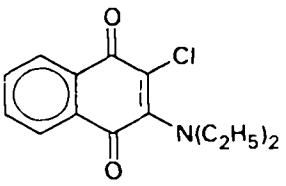
(129) (130)

reaction 57[49]. Thus, formation of a blue conjugate from **129** in the presence of a suitable amine and an oxidant is evidence of an enamine intermediate.

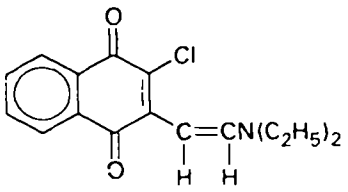
Diethylamine also reacts with quinones, but the vinyl group formed by oxidation can transfer to a molecule of unoxidized diethylamine to form **126**. For example, the products of **131** and diethylamine included **132** and **133**, and under appropriate conditions **134** and **135** could be obtained[135].



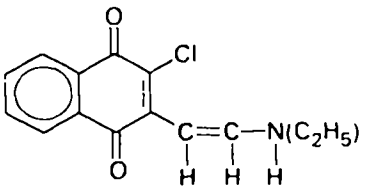
(131)



(132)



(133)



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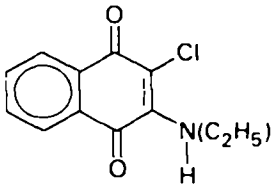
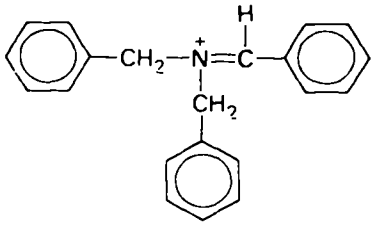


(135)

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[48].

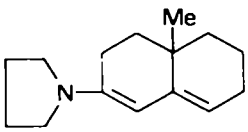


(136)

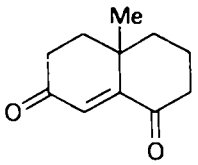
Bromanil reacts substantially as chloranil; iodanil seems to react much more slowly, owing to steric factors[48].

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[208].

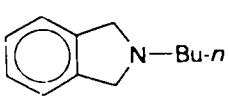


(137)



(138)

N-Alkylisoindolines are especially subject to autoxidation. Kochi and Singleton[172] studied the effect of 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*-butylphthalimidine (**141**), *N*-*n*-butylphthalimide (**142**) and, to a lesser extent, *N*-*n*-butyl-3-hydroxyphthalimide (**143**).



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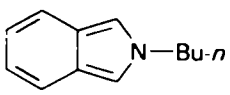
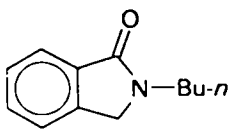


(140)



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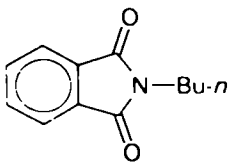

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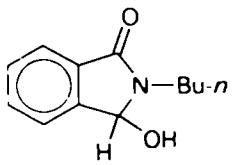
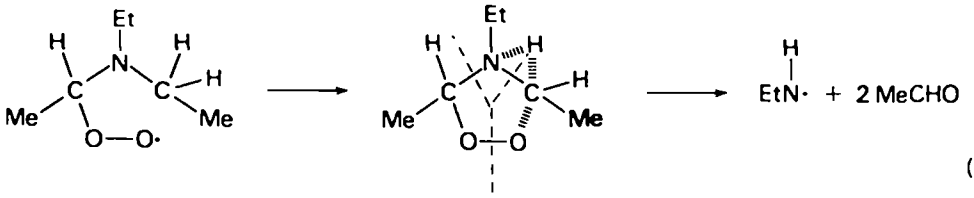


(143)

Under more severe conditions than the foregoing, a study[80] was made of the reaction kinetics of 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[64] and trimethylamine[65] 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[64]. 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.



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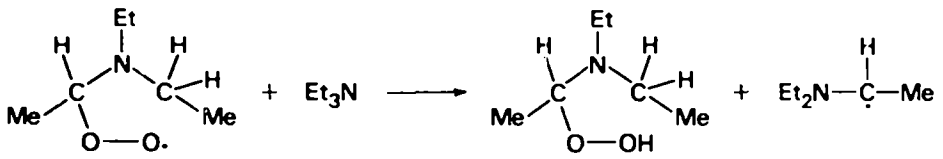


(59)

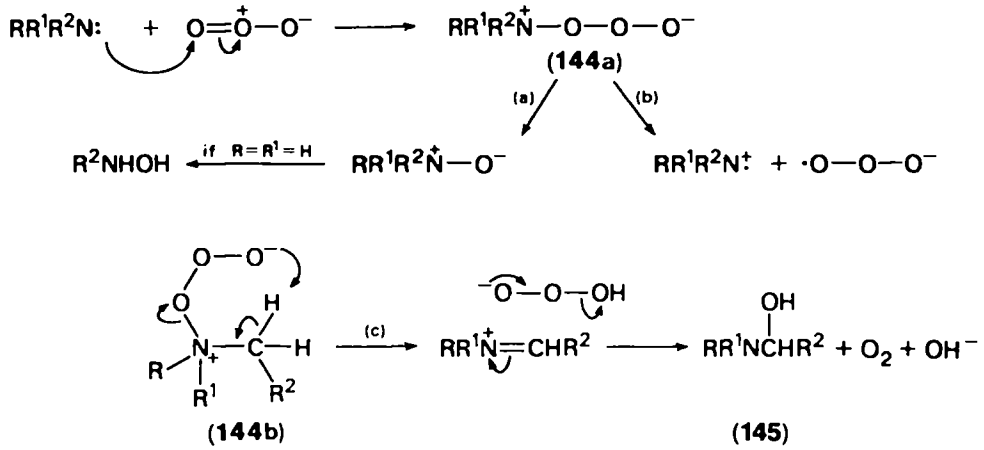
The reaction of trimethylamine with oxygen was rapid even at 165°C, but did not go to completion; at initial pressures of 100 mm in each reactant, 75% of the initial amine and 65% of the oxygen were unconsumed when reaction ceased. Small amounts of formaldehyde, dimethylamine and nitrogen were found 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 methylamine were reported as CH_4, NH_3, ·OH, H_2O, H_2 and O_2.

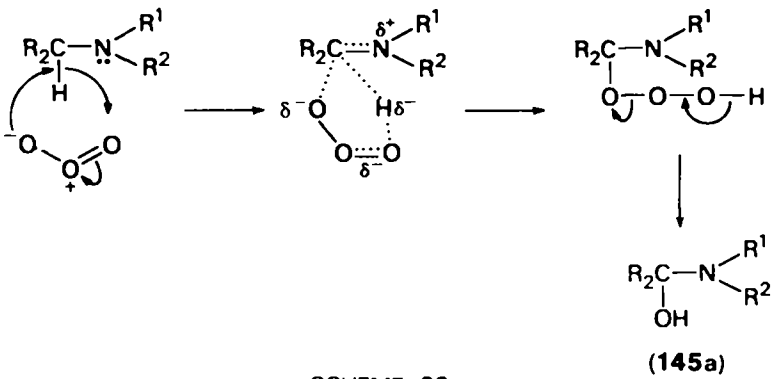
XII. OZONE

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 α-hydroxyamine **145**, which yields α-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

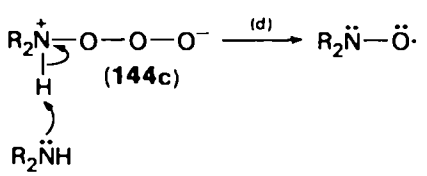


SCHEME 27



SCHEME 28

145[24,26]. 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[22]. 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



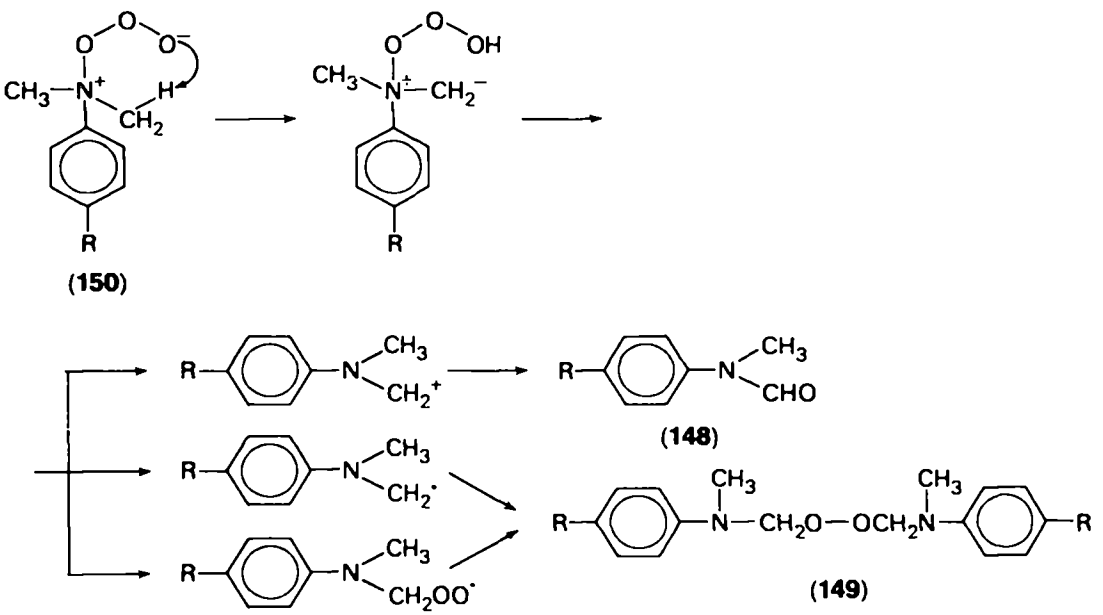
SCHEME 29

(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[21]; similar mixtures of products from pathways a and b were obtained from *t*-butylamine[19]. In contrast, products of pathways c (*N*-*n*-butylidene-*n*-butylamine, **146**, and nitrone **147** from di-*n*-butylamine,

(146) **(147)**

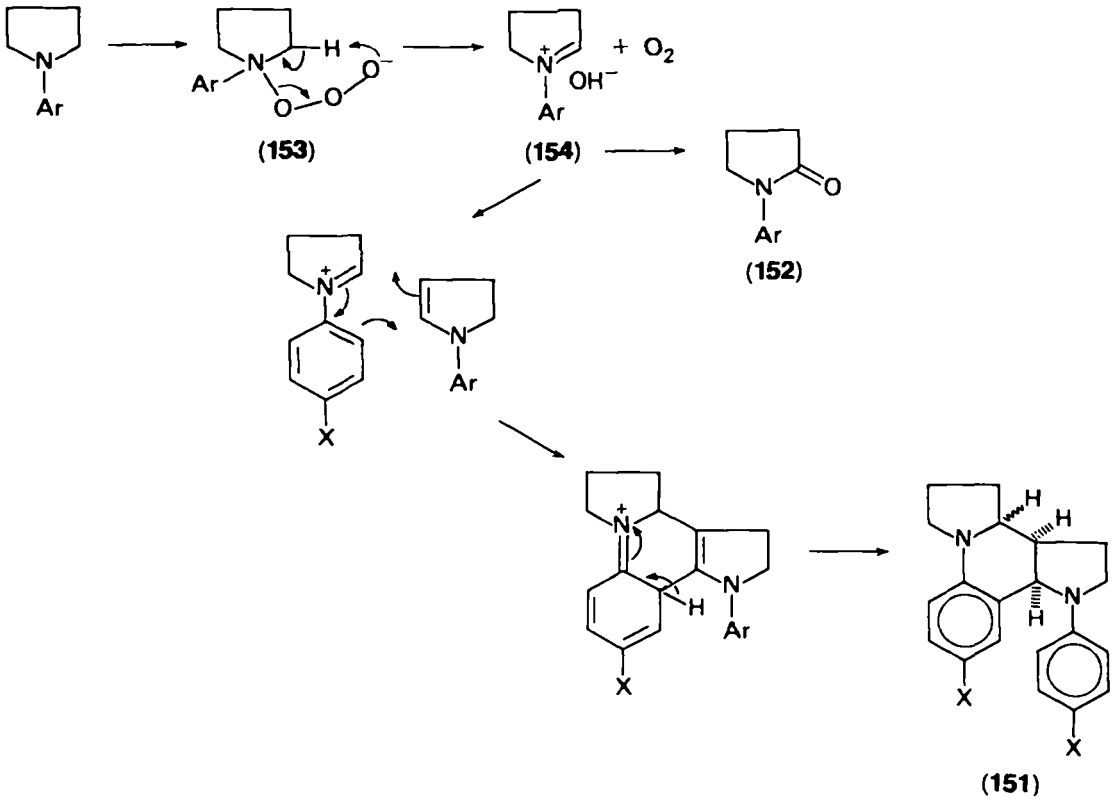
and acetone from di-*i*-propylamine) and d (ammonium salts from di-*i*-propylamine and di-*t*-butylamine) predominated for secondary amines[22,26]. In addition, 2-nitropropane and 2-methyl-2-nitropropane, isolated in significant amounts from ozonation of the latter two amines, were shown to be derived from oxidation of the respective nitroxides[20]. The presence of nitroxides as important intermediates in ozonation of secondary amines had been demonstrated earlier by Russian workers[253]. 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*,*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



(150) **(148)** **(149)**

SCHEME 30



SCHEME 31

the initial ozone adduct **150** relative to an aliphatic counterpart, resulting in proton abstraction from the N—CH_3 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**)[168]. The initial adduct **153** was envisioned to undergo proton abstraction and loss of O_2, followed by dimerization or further oxidation of the resulting iminium species (**154**) (Scheme 31).

XIII. ELECTROCHEMISTRY

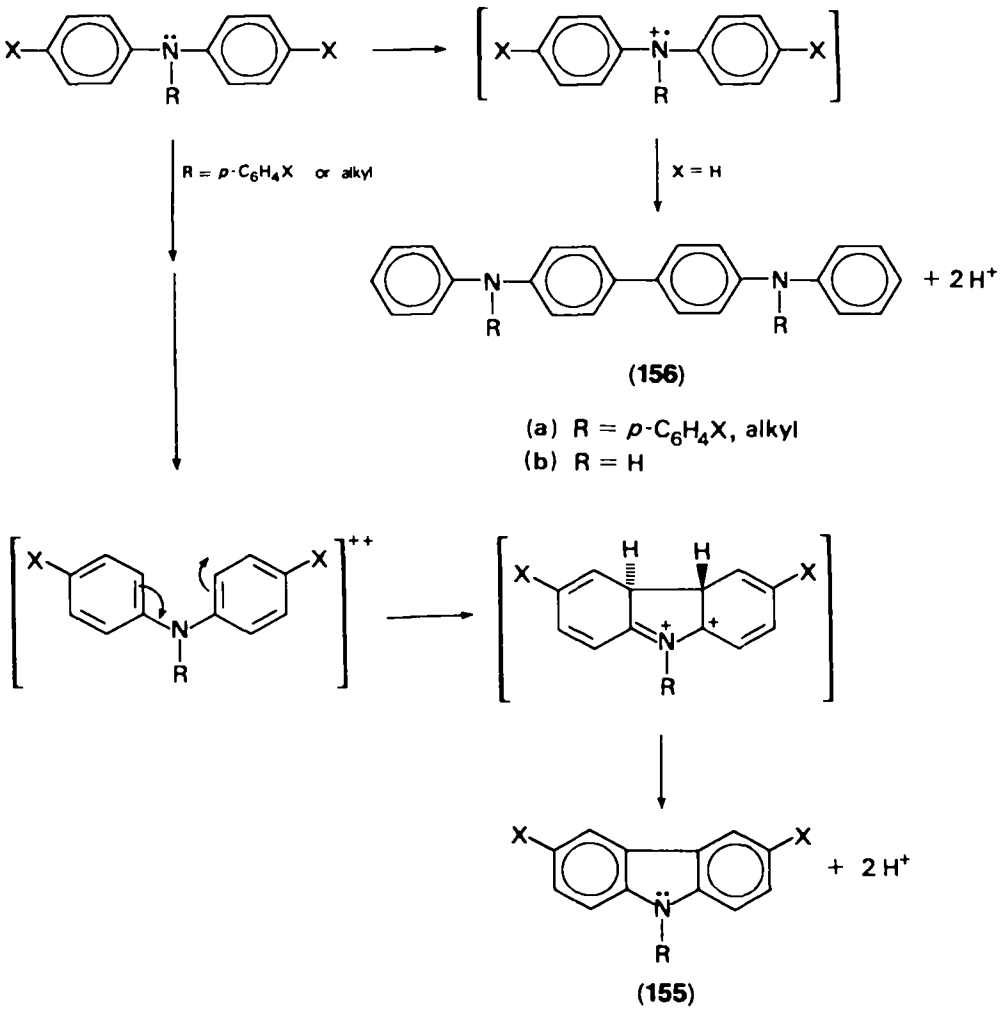
A. 'Inert' Electrodes: Platinum, Glassy Carbon, Lead Dioxide

Electrochemical oxidations of aromatic amines and amino acids have long been studied, and are detailed in four recent reviews[54,238,265,282]. Thus, this discussion is limited to a few papers in the former category that were not reviewed or were published subsequently. Nelsen and coworkers[224] have measured free energies of formation of cation radical (E_1^0) and dication (E_2^0) 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

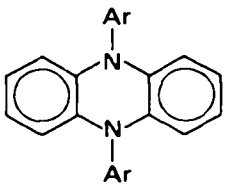
correlation of downfield shifts in ^{13}C-NMR of the two carbons bonded to nitrogen with decreased conjugation of the nitrogen lone pairs with the ring was made.

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).

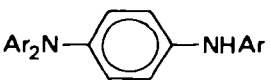
Anodic oxidation of secondary *p*-substituted diphenylamines showed that the



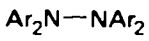
SCHEME 32



(157)



(158)



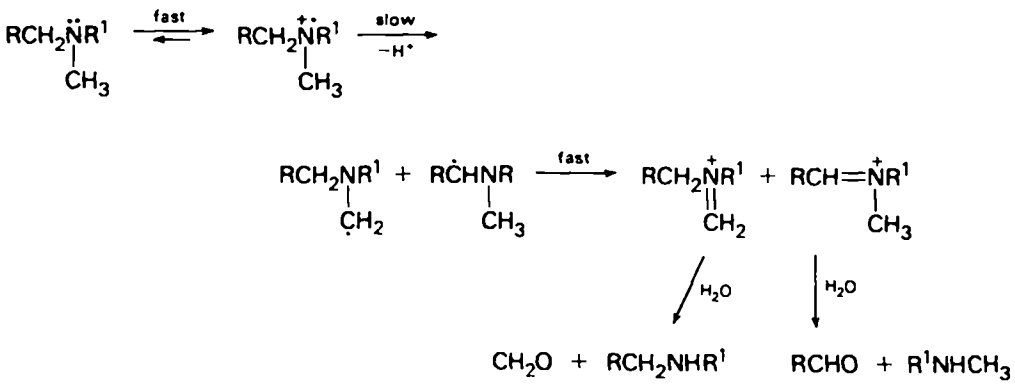
(159)

SCHEME 33

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 (Ar_2N^+) is believed to be an intermediate in the formation of types **157** and **158**[51,273].

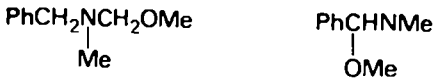
The overall process in anodic oxidation of tertiary alkylamines in acetonitrile or in aqueous alkaline solutions is oxidative dealkylation to carbonyl compounds and secondary amines[54]. The latter also undergo similar dealkylation[301]. In methanol, however, α-methoxylation may be a predominant process[305]. 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 α-C—H bond, resembling the aminium cation radical more than the α-amino radical[201].

The complex course of α-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



SCHEME 34

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

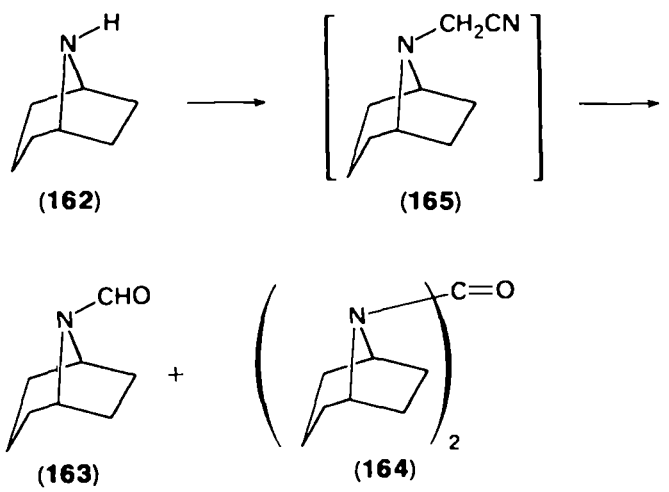


(160) **(161)**

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 CH_2, 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[279].

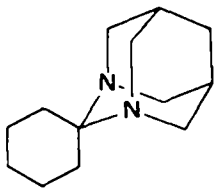
In the case of nortropane (**162**), the α-protons are considered to lie nearly perpendicular to the charge-bearing orbital in the radical cation, and α-deprotonation becomes an unimportant process. The products isolated on anodic oxidation in acetonitrile (**163** and **164**, Scheme 35) were believed to arise from adduct **165** formed by coupling of nortropyl radical and solvent-derived $\cdot CH_2CN$[182].

Geometrical factors influencing the stability (longevity) of nonaromatic aminium radical cations have been extensively investigated by Nelsen and coworkers using cyclic voltammetry[223] and photoelectron spectroscopy[222]. 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-σ_{cc} interactions, i.e. through-bond rather than through-space interactions. A later study by Lindsay Smith and Masheder[202] 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

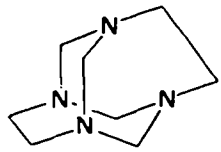


(162) **(165)** **(163)** **(164)**

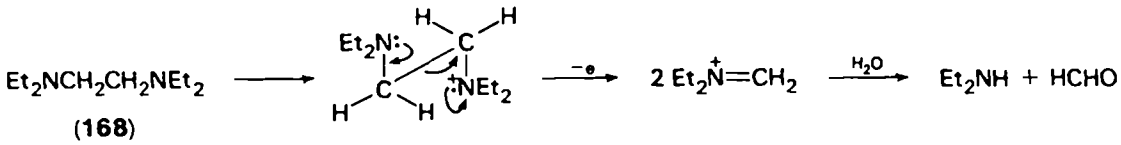
SCHEME 35



(166)



(167)



(168)

SCHEME 36

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'*-dimethylhexahydropyrimidine < *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 (**168**) 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[202]. Thus, the oxidation proceeded via Grob fragmentation (Scheme 36), which has the same stereochemical requirement as a through-bond interaction[122].

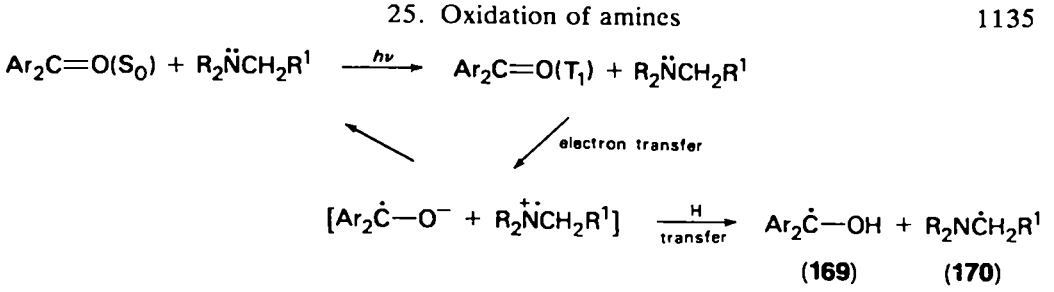
B. 'Active' Electrodes: Silver, Copper, Nickel, Cobalt

Oxidations of amines have been observed at oxide-covered silver, copper, nickel and cobalt anodes in aqueous alkaline solution[4,102,125–127]. Both products and processes appear to be similar in the cases investigated. Primary amines with α-hydrogen gave exclusively nitriles[4] or mixtures of nitriles and aldehydes, and *t*-butylamine gave a mixture of nitro compound, alcohol and olefin[127]. Secondary amines reacted more slowly, giving *N*-alkyl cleavage products[126], 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[102]. A primary isotope effect was observed for oxidation of CD_3OH at a nickel electrode[102], 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[61]. Substantial evidence has



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**[60]. 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].

$$Ar_2C{=}O(S_0) + R_2N\dot{C}HR^1 \xrightarrow{\text{if R = H}} RN{=}CHR^1 + Ar_2\dot{C}{-}OH \qquad (60)$$

$$Ar_2C{=}O(S_0) + R_2N\dot{C}HR^1 \longrightarrow R_2\overset{+}{N}{=}CHR^1 + Ar_2\dot{C}{-}O^- \qquad (61)$$

$$Ar_2C{=}O(S_0) + R_2N\dot{C}HR^1 \xrightarrow{\text{if } R^1 = CH_3} R_2NCH{=}CH_2 + Ar_2\dot{C}{-}OH \qquad (62)$$

$$Ar_2C{=}O(S_0) + R_2N\dot{C}HR^1 \longrightarrow Ar_2\dot{C}{-}O{-}CHR^1NR_2 \qquad (63)$$

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

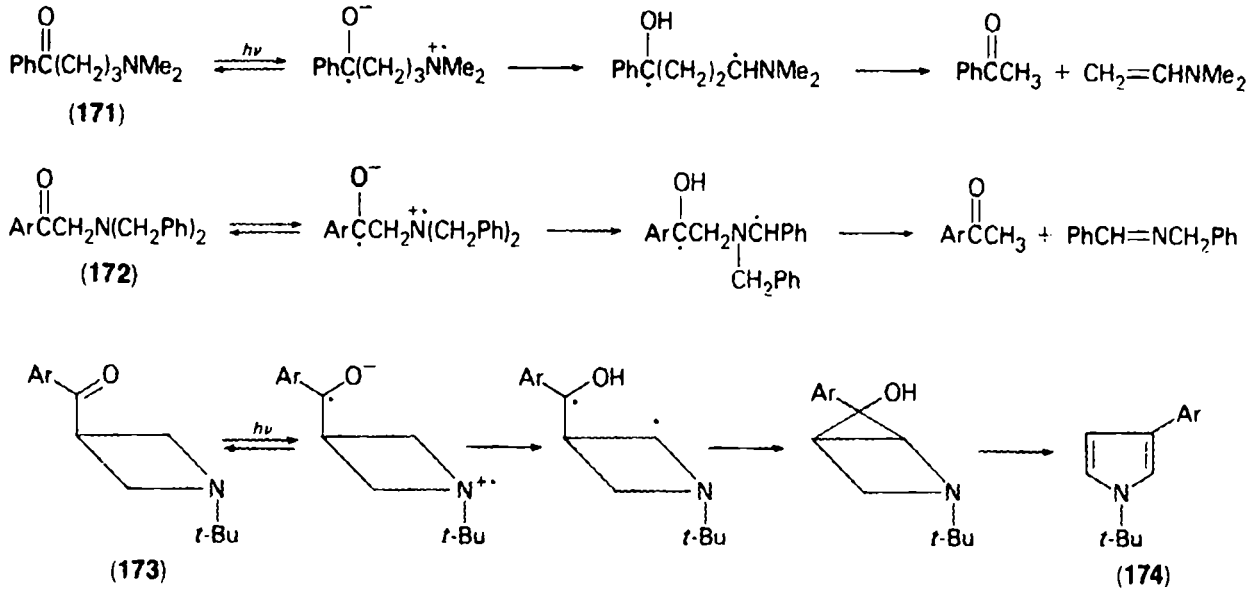
$$Ar_2\dot{C}{-}OH + Ar_2\dot{C}{-}O^- \longrightarrow Ar_2CHOH + Ar_2C{=}O \qquad (64)$$

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_2NMe and *i*-Pr_2NEt) were deprotonated highly selectively to the less stable α-amino radicals, while in less hindered cases (Et_2NMe, Me_2NEt and *i*-$PrNMe_2$), deprotonation was relatively nonselective. In extremely hindered cases (*i*-Pr_3N and **3**) there was no reaction.

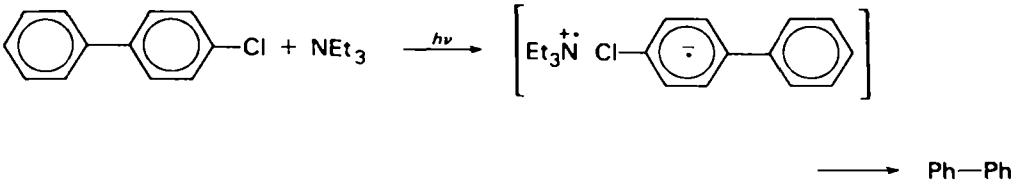
Photochemical cleavage reactions of arylaminoketones **171**[298] and **172**[237] have been shown to proceed via an initial fast intramolecular charge-transfer process (Scheme 38) characterized by low quantum yields and high chemical yields. Photochemical conversion of 3-aroylazetidines (**173**) to 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].

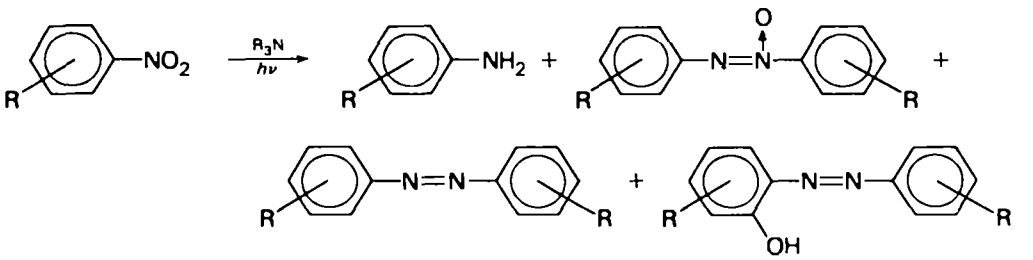
Photoreductions of a number of aromatic nitro compounds by diethyl- and triethyl-amine gave mixtures of up to as many as four of the products shown (Scheme 40)[28]. A mechanism involving initial hydrogen abstraction, rather than electron



SCHEME 38



SCHEME 39



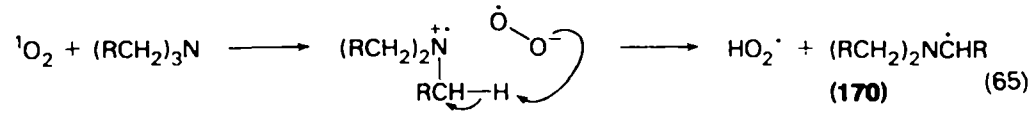
SCHEME 40

transfer, by a nitro compound π–π^* 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) β-oxidation of *N*-alkylidene groups to give hydroperoxides that led to formamides or α-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[75,76]. 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

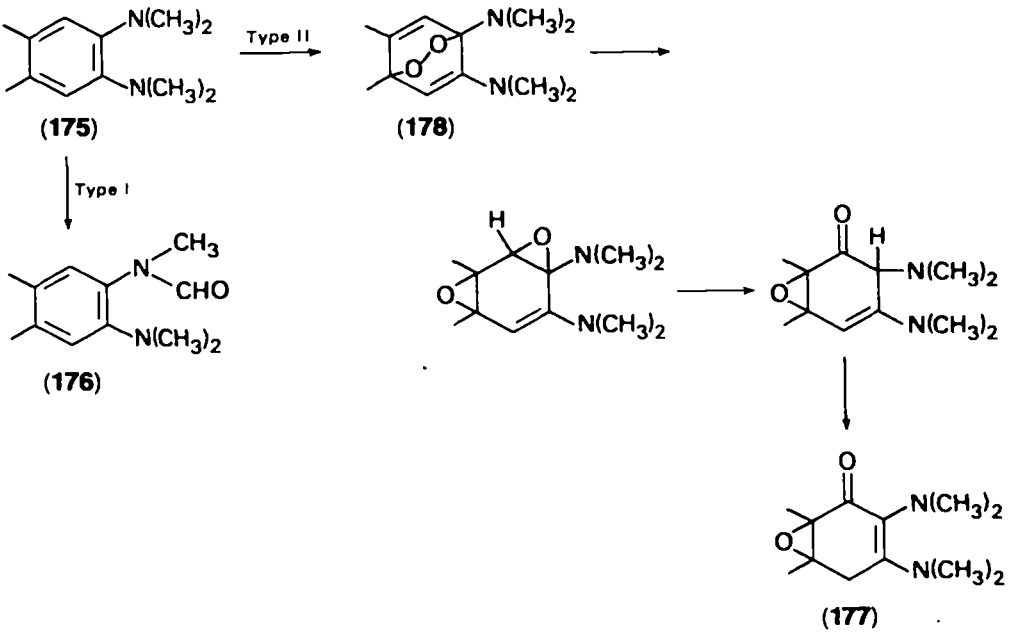


(65)

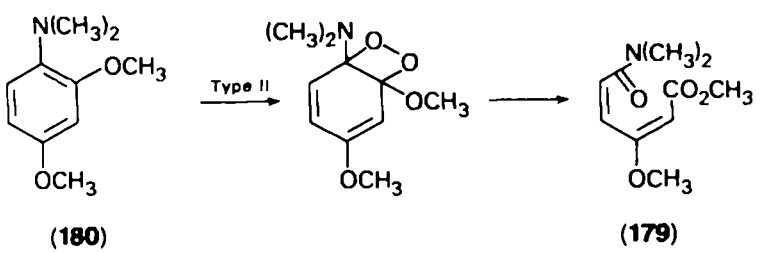
scheme to separate the contribution of singlet oxygen from other processes, Davidson and Trethewey[75,76] have shown that in the case of triethylamine the two processes are operative simultaneously.

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[268]. 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).

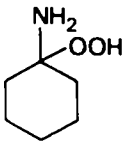
Dye-sensitized photooxidation of cyclohexylamine and dicyclohexylamine in organic media gave the respective hydroperoxides **181** and **182** as primary products (50% isolated yield in each case)[128]. Further treatment of **181** and **182** with the respective amines, or prolonged oxidations, gave complex mixtures of nonphoto-derived products. In contrast, on irradiation of O_2-saturated cyclohexylamine (neat)



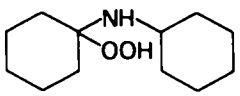
SCHEME 41



SCHEME 42



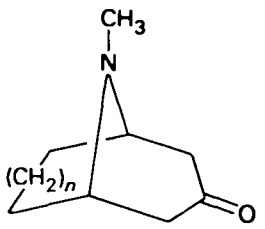
(181)



(182)

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



(183)

(a) $n = 0$

(b) $n = 1$

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

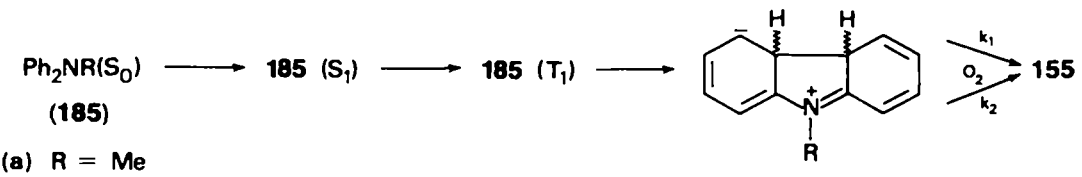
Oxidations of amines in polyhalomethane solvents have been studied under a variety of conditions and may involve thermal, photochemical or meta-ion-catalysed processes[209]. Thus, a variety of mechanistic pathways are possible, and this discussion is limited to two examples illustrative of electron-transfer 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.

(184)

(a) R = H
(b) R = Me
(c) R = Ph

$$\mathbf{184}\ (S_1) + CHCl_3 \longrightarrow A^{\cdot+} + Cl^- + \dot{C}HCl_2 \qquad (66)$$



(185)

(a) R = Me
(b) R = Ph

(186)

SCHEME 43

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 CCl_4, however, the intramolecular triplet pathway was suppressed and intermolecular electron-transfer processes were favoured, leading to complex mixtures of products[315].

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 ($R_3N^{+\cdot}$) were formed; in neutral and alkaline media only aminoalkyl radicals (R_2NCH_2) were found[225]. Radicals of the type $R\dot{C}(NH_2)-CO_2H$ and $R\dot{C}(NH_2)-CO_2^-$ 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)[55].

$$Me_3\overset{+}{N}H + \cdot OH \longrightarrow Me_3N^{+\cdot} + H_2O \qquad (67a)$$

$$RCH_2-\ddot{N}R_2 + \cdot OH \longrightarrow R\dot{C}H_2-\ddot{N}R_2 \longleftrightarrow RC\ddot{H}-\overset{+}{\ddot{N}}R_2 \qquad (67b)$$

Aminoalkyl radicals were also generated on room-temperature irradiation of aliphatic amines in adamantane matrices[313]. 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 ($R_2CH—\dot{N}H$) that isomerized to aminoalkyl radicals ($R_2\dot{C}—NH_2$) on warming[299]. Dimethylamine under these conditions gave mixtures of radicals $(CH_3)_2\dot{N}$ and $\dot{C}H_2NHCH_3$, and trimethylamine gave aminoalkyl radical $\dot{C}H_2N(CH_3)_2$ 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 $(CH_3)_3N^{\cdot+}$ was observed[300]. In contrast, ultraviolet irradiation of methyl-, dimethyl- and trimethylamine 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].

$$CCl_4^{\cdot+} + A: \longrightarrow CCl_4 + A^{\cdot+} \qquad (68)$$

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 $H^{\cdot}$ from amine (equation 69). The finding of *N,N,N′,N′*-tetramethylmethylenediamine (**187**) (but

$$RNH\dot{C}HR^1 + RNHCH_2R^1 \longrightarrow R\dot{N}CH_2R^1 + RNHCH_2R^1 \qquad (69)$$

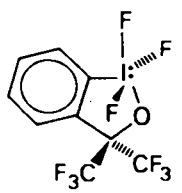
$Me_2NCH_2NMe_2$

(187)

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 ($Me_3C\dot{N}H$)[281]. In certain symmetrical cases, the initial α-alkylamino radicals were trapped by *N*-phenylmaleimide[96].

XVI. MISCELLANEOUS OXIDATIONS

Treatment of primary amines with IF_5 gave nitriles (or, in the absence of α-hydrogen, 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.



(188)

Three primary amines (diphenylamine, 9-fluorenylamine and 2-adamantylamine) were oxidized to the respective ketones in 97–100% yields by diphenylselenic anhydride[68] and diphenylselenyl chloride[69], but the reagents lacked general synthetic utility[69]. Peroxyacetyl nitrate gave high yields of acetamides from primary amines[307]. 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[103]. Quinones and quinoneimines were obtained from aromatic amines and potassium nitrosodisulphonate (Fremy's salt)[317].

A reinvestigation of the reaction of benzylamines with nitrosobenzene, which was reported earlier[291] to give azoxybenzenes and aldehydes derived from the amine, failed to detect the latter product[180]. Rather, azoxybenzene and substituted imines, the latter shown to arise from amine exchange with the initial amine, were the products isolated.

Benzylammonium salts [$PhCH(R)\dot{N}R_3^1X^-$], on prolonged heating with dimethyl sulphoxide, underwent oxidation to carbonyl compounds (PhCOR) and, in some instances, elimination to olefins. Evidence was presented for an ionic pathway[296].

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
Edited by Saul Patai

CHAPTER **26**

N-Nitrosamines and *N*-nitrosoimines

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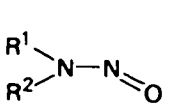
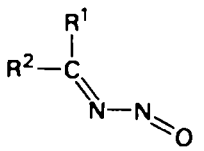
I. INTRODUCTION

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.



(**1**)



(**2**)

Primary aromatic *N*-nitrosamines (**1**, R^1 = H, R^2 = aryl) are tautomeric with aryl diazohydroxides (ArN=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 = 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 = 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 = 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 π-electron system of the nitroso

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.

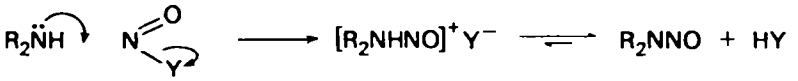
N-Nitrosamines have been known since the last century but they attracted little interest until the 1960s when it was found that many were powerful carcinogens. This stimulated interest in both their chemical and biological properties. The present review deals mainly with advances made in *N*-nitrosamine 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:

N-Nitrosodimethylamine	NDMA
N-Nitrosodi-*n*-butylamine	NDBA
N-Nitrosodiisobutylamine	ND*i*-BA
N-Nitrosoethylmethylamine	NEMA
N-Nitrosopyrrolidine	NPYR
N-Nitrosopiperidine	NPIP
N-Nitrosomorpholine	NMOR
Mononitrosopiperazine	M-NPZ
Dinitrosopiperazine	D-NPZ
N-Nitrosoproline	NPRO
N-Nitrososarcosine	NSAR
N-Nitrosohydroxyproline	NHPRO
N-Nitrosopipecolic acid	NPIC
N-Nitrosohydroxypyrrolidine	NHPYR
N-Nitrosonornicotine	NNN
N-Nitrosodiethanolamine	NDELA

II. FORMATION OF *N*-NITROSAMINES

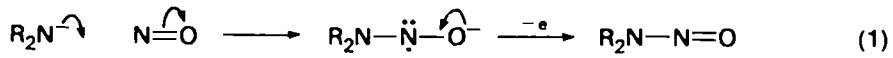
N-Nitrosamines are usually obtained by N—N bond formation between an amino compound and the NO function. The most common method involves interaction of a secondary amine (R_2NH) with an NO^+ entity. Free NO^+ (nitrosonium ion) can



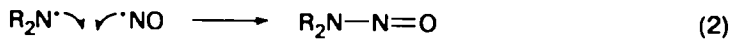
SCHEME 1. Nitrosation of secondary amines by Y—NO reagents.

be obtained only in strong acids or as solid salts (e.g. $NO^+BF_4^-$). It is readily available, however, from labile nitrosating agents of the type Y—NO (where Y is either a stable anion such as Cl^- or NO_2^-, or a neutral molecule such as ROH or R_2NH) which can be regarded as carriers of NO^+. These reactions involve nucleophilic (S_N2) displacement at the nitroso nitrogen atom by the secondary amine as in Scheme 1. Neither nitrous acid itself (HO—NO) nor nitrite ion (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 (Y—NO) is N_2O_3 formed from two molecules of HNO_2 (Section II.A.1). Otherwise, photolysis of gaseous 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 NO^+ include the conjugate acids of alkyl nitrites and *N*-nitrosamines (e.g. Y—NO, where Y = ROH or R_2NH) and gaseous reagents such as nitrosyl chloride (NOCl), dinitrogen trioxide (N_2O_3) and dinitrogen tetraoxide (N_2O_4). These reactions are discussed in Sections II.C and II.B, respectively.

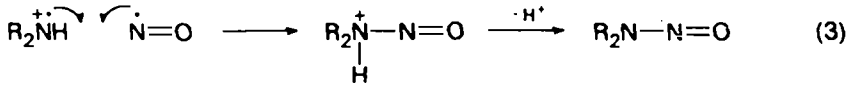
There is also good evidence that *N*-nitrosamines can be obtained from the interaction of secondary amines with several organic nitroso and nitro compounds under thermal conditions. These reactions, as discussed in Section II.C, probably involve nitrogen oxide (e.g. N_2O_3 and N_2O_4) intermediates. Formation of *N*-nitrosamines from nitric oxide (NO) is less common, but in principle it may occur with amine anions (R_2N^-, equation 1), or when oxidants generate either amino radicals ($R_2N^{\bullet}$, equation 2) or amino radical cations ($R_2\dot{N}H$, equation 3) from secondary amines (Section II.B.5).



(1)



(2)



(3)

Amino compounds other than secondary amines can also generate *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 *in situ* to generate nitrosating agents (Section II.E).

Because of widespread concern about the carcinogenic properties of many *N*-nitrosamines (Section IV) methods of inhibiting their formation are discussed in Section II.A.3.

A. Nitrosation of Secondary Amines by Aqueous HNO_2

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[1,9]. Neither HNO_2 nor NO_2^- 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 preequilibrium 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 N_2O_3. 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 HNO_2 to either N_2 or NO or bind the NO^+ group irreversibly.

$$NO_2^- \overset{H_3O^+}{\rightleftharpoons} HO{-}N{=}O \overset{H_3O^+}{\rightleftharpoons} H_2\overset{+}{O}{-}N{=}O \overset{Y^-}{\rightleftharpoons} Y{-}N{=}O + H_2O$$

$$Y^- = NO_2^-,\ Cl^-,\ SCN^-,\ \text{etc.}$$

$$R_2NH_2^+ \underset{H_3O^+}{\rightleftharpoons} R_2NH + Y{-}NO \xrightarrow{\text{slow}} R_2N{-}NO + HY$$

SCHEME 2. General mechanism for the nitrosation of secondary amines in aqueous HNO_2.

1. *Mechanisms and reactivities*

N-Nitrosamine formation from secondary alkyl and heterocylic amines and $NaNO_2$ in aqueous buffers at pH 2–5 has been widely examined[4]. The reaction rates approximate to equation (4) where the $[HNO_2]^2$ term shows that the nitrosating agent is N_2O_3 (nitrous anhydride) formed in equilibrium with HNO_2 (equation 5). Thus the mechanism in Scheme 2 applies with $Y^- = NO_2^-$. For the

$$\text{rate} = k_3[R_2NH][HNO_2]^2 \tag{4}$$

$$2\,HNO_2 \rightleftharpoons N_2O_3 + H_2O \tag{5}$$

more basic amines ($pK_a > 5$), the rates of these reactions calculated from the gross amounts of amine and nitrite salt added (rate $= \bar{k}_3$[amine][nitrite]^2) have a characteristic pH dependence with a maximum value at ca. pH 3.4 (Figure 1)[10]. This reflects the counteracting effects of acidity, which increases the amount of HNO_2 (pK_a 3.4) but decreases the amount of unprotonated amine[11]. The level of observed rates over the whole pH range, however, is dependent on the amine basicity (pK_a) which determines the proportion of unprotonated amine available for reaction. Data in Table 1 from the review by Mirvish[4] show clearly that: (1) *N*-nitrosamines form most rapidly (i.e. largest $\bar{k}_3$ values) from the least basic amines, and (2) amines of widely different basicities have surprisingly similar reactivities (k_3 values) towards N_2O_3. The second observation suggests that the rate is governed by factors (possibly diffusion through the solvent) other than the case of amine attack on N_2O_3. This conclusion has important ramifications in explaining the effect of catalysts (see Section II.A.2), and implies that evidence[12] for steric retardation of *N*-nitrosamine formation needs to be reexamined. Mirvish[4] formulated a

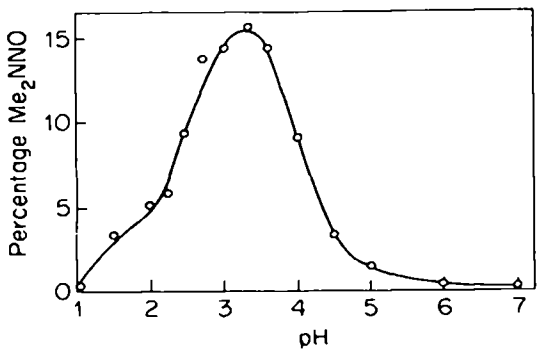


FIGURE 1. Variation in the yield of Me_2NNO with pH after 3 h for reaction of 0.02M Me_2NH with 0.1M $NaNO_2$ at 25°C. Reproduced from Reference 10 by permission of the author.

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])

Amine	pK_a	Optimum pH	$\bar{k}_3$[b] ($l^2\ mol^{-2}\ s^{-1}$)	$10^{-5}\ k_3$[c] ($l^2\ mol^{-2}\ s^{-1}$)
Pyrrolidine	11.27	3.0	0.0053	21
Piperidine	11.2	3.0	0.00045	1.4
Dimethylamine	10.72	3.4	0.0017	1.5
N-Methylbenzylamine	9.54	3.0	0.013	0.92
Proline		2.5	0.037	1.4
Morpholine	8.7	3.4	0.42	2.3
N-Nitrosopiperazine	6.8	3.0	6.7	0.83
Piperazinium ion	5.57	3.0	83	0.62
N-Methylaniline[a]	4.85		250	18

[a]At 0°C and pH 1.
[b]Calculated from the experimental data using gross concentrations of reactants (i.e. rate = $\bar{k}_3$[amine][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.

$$\log \bar{k}_3 = 7.8 - pk_{amine} \qquad (6)$$

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_2O_3.

Many weakly basic compounds (e.g. some aromatic amines) are too unreactive to combine readily with N_2O_3[1,4,13]. At about pH 2, however, they react by another pathway which follows equation (7) and is attributed to a direct reaction of the

$$\text{rate} = k_3 [R^1R^2NH] [HNO_2] [H_3O^+] \quad (7)$$

$$RArNH_2^+ \underset{H_3O^+}{\rightleftharpoons} RArNH + NO^+(H_2O) \xrightarrow{\text{slow}} RArNNO + H_3O^+$$

SCHEME 3. Acid-catalysed nitrosation of weakly basic amines by aqueous HNO_2.

neutral substrate with either H_2ONO^+ 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*

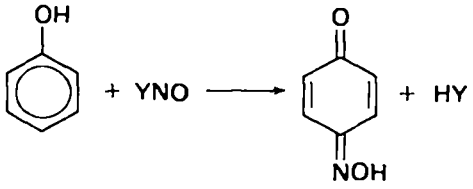
In the presence of anionic (Y^-) or nucleophilic (HY) entities, HNO_2 forms additional YNO reagents (Scheme 2). These accelerate nitrosation principally by increasing the concentration of NO^+ carriers[14], but most are potentially more reactive than N_2O_3. It should be noted, too, that the strength 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

$$\text{rate} = k_4 [R_2NH] [HNO_2] [H_3O^+] [Y^-] \quad (8)$$

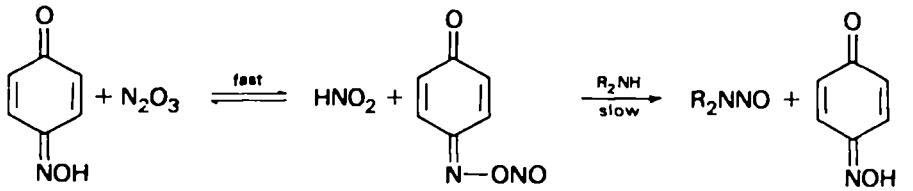
I^- have attracted attention because of their possible *in vivo* relevance[11,15]. Salivary SCN^- levels are known to be enhanced for smokers and I^- is present in gastric secretion. For strongly basic substrates such as morpholine, 2.5 mM KSCN shifts the maximum rate of nitrosation from pH 3.4 to 2.3 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_2O_3) to be consistent with previous conclusions (see above) that morpholine may react with N_2O_3 on encounter. Much stronger SCN^- catalysis is observed for less basic substrates such as *N*-methylaniline 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_2O_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 HNO_2 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*-nitrosodimethylamine at pH 4 is strongly



(9)

(3)



(10)

(4)

catalysed by thioureas, possibly via an *S*-nitroso adduct (**5**) which could be a powerful reagent (equation 11)[20].

$$(H_2N)_2C{=}S + N_2O_3 \rightleftharpoons [(H_2N)_2C{=}S{-}NO]^+NO_2^- \xrightarrow{Me_2NH}$$

(5)

$$Me_2NNO + (H_2N)_2C{=}S + HNO_2 \quad (11)$$

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[21]. Catalysis by microorganisms under similar conditions has been explained by an analogous hydrophobic interaction between the amine and cellular constituents[22].

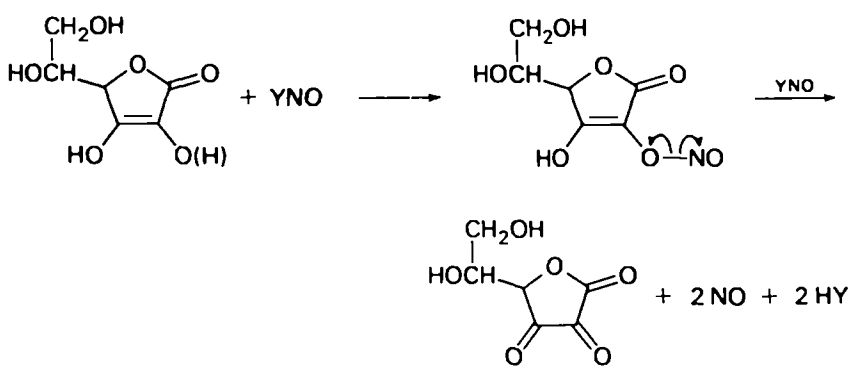
3. *Inhibition of* N-*nitrosamine formation*

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.

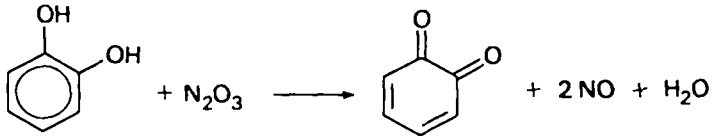
Reduction to N_2 takes place with ammonia, primary amines, hydrazine, urea, sulphamic acid and its salts, hydroxylamine and azides. Ammonia is a poor inhibitor, however, because of extensive protonation at low pH. A similar reser-

vation applies to primary amines (unless aromatic) and alkylation reactions concurrent with deamination produce small amounts of secondary amines and, ultimately, *N*-nitrosamines[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[24]. Hydroxylamines[25], hydrazoic acid (azide)[26] and hydrazine[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 $N_3H > NH_2SO_3H > PhNH_2 > NH_2OH > CO(NH_2)_2$[28]. It must be remembered, however, that the order will be different at lower acidity.

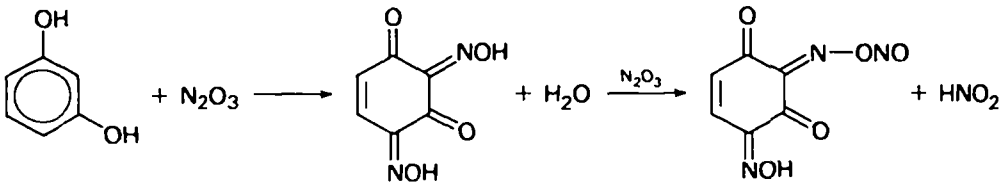
A wider range of compounds reduce HNO_2 to NO under mildly acidic conditions. In this category are sulphur dioxide and bisulphite ion, ascorbic acid, tocopherols, gallic acid, thiols, several dihydroxyphenols and some other well-established synthetic and natural 'antioxidants'. Their inhibition of *N*-nitrosamine and *N*-nitrosamide formation both *in vitro* and *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[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[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 α-tocopherol may be superior[30,31]. Other recent work[32] has cleared up confusing results concerning the effect of polyhydroxylated phenols on *N*-nitrosamine formation. In particular, Pignatelli and her colleagues[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[33] and gallic acid[34] are incorrect because of artifactual formation during work-up. The inhibition again relates to reduction of the nitrosating agent (e.g. N_2O_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_2O_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



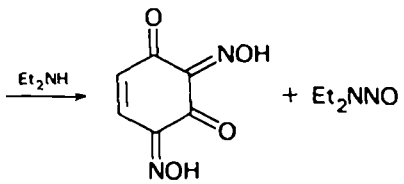
SCHEME 4. Reduction of Y—NO to NO by ascorbic acid.



(12)



(6)



(13)

oxidation of NO back to NO_2 and subsequent formation of N_2O_3 ($NO + NO_2 \rightleftharpoons N_2O_3$) quickly restores nitrosating capability. This effect has been noted for the formation of *N*-nitrosomorpholine in the presence of ascorbic acid[35].

Inhibition by irreversible binding of the NO^+ group seems less effective than the reductive methods discussed above. An early suggestion[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 *N*-nitrosamine formation. It has been reported, however, that pyrrole inhibits the formation of *N*-nitrosomorpholine[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 *N*-nitroso compounds. These are nitrogen dioxide (NO_2), dinitrogen tetraoxide (N_2O_4), dinitrogen trioxide (N_2O_3) 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 NO_2 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 *N*-nitrosamine formation is much faster and more extensive than with aqueous HNO_2.

1. Nitrosation by gaseous nitrosyl chloride (NOCl)

Nitrosation reactions employing nitrite salts in HCl involve NOCl generated *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(NOCl) ca. 7.8×10^{-8} atm. at 25°C[41]] than either N_2O_3 or N_2O_4 (equation 14)

$$2\,NOCl \rightleftharpoons 2\,NO + Cl_2 \qquad (14)$$

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 N_2O_3 and N_2O_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 *in situ*[43].

2. *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 N_2O_3 [$K_p(N_2O_3)$ = 1.91 atm. at 25°C[44]] and N_2O_4 [$K_p(N_2O_4)$ = 0.15 atm. at 25°C[44]] 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°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 NO_2 (equation 17) and NO, itself, is a poor reagent. NO_2 may dimerize to N_2O_4 (equation 16) or combine with NO to give N_2O_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.

$$N_2O_3 \rightleftharpoons NO + NO_2 \qquad (15)$$

$$N_2O_4 \rightleftharpoons 2\,NO_2 \qquad (16)$$

$$2\,NO + O_2 \longrightarrow 2\,NO_2 \qquad (17)$$

In organic solvents secondary amines react with gaseous N_2O_3 to give high yields of *N*-nitrosamine[13,48] whereas N_2O_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 Spincer and their colleagues[51,52] have shown that NO by itself is unreactive, whereas equimolar mixtures of NO and NO_2 (i.e. N_2O_3) lead to rapid formation of *N*-nitrosamines. Also, low concentrations of diethylamine and

NO_2 form *N*-nitrosodiethylamine rapidly at ambient temperatures[53,54]. Other work designed to mimic atmospheric conditions shows that moist gases containing dimethylamine and diethylamine, NO, NO_2 and HNO_2 (at concentrations of 0.5 to 2 ppm) produce a mixture of *N*-nitroso- and *N*-nitro-amines[55,56]. *N*-Nitrosamine formation under these conditions has been attributed[57] to free-radical processes arising from photodissociation of HNO_2, where activation of the amine by production of an amino radical facilitates reaction with nitric oxide (equation 18).

$$HONO \xrightarrow{h\nu} NO^{\cdot} + HO^{\cdot} \xrightarrow{R_2NH} H_2O + R_2N^{\cdot} \xrightarrow{NO} R_2NNO \qquad (18)$$

3. *Nitrosation by dinitrogen trioxide and dinitrogen tetraoxide gases in aqueous media*

Nitrosation by gaseous N_2O_3 and N_2O_4 in aqueous solution is a recent development probably because both were expected to undergo rapid hydrolysis at pH >5 to innocuous NO_2^- (equations 19 and 20). Hydrolysis does occur, but less rapidly

$$N_2O_3 + 2\,HO^- \longrightarrow 2\,NO_2^- + H_2O \qquad (19)$$

$$N_2O_4 + 2\,HO^- \longrightarrow NO_2^- + NO_3^- + H_2O \qquad (20)$$

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[13]. With N_2O_4, small amounts of *N*-nitramine form concurrently[50]. Only the unprotonated substrates react, but product yields are not strongly dependent on substrate basicity (pK_a) except for very feebly basic compounds ($pK_a < 1$). Analysis of these data suggests that N_2O_3 and N_2O_4 react about 2000 times more rapidly with most amines than with H_2O and that N_2O_3 formed by recombination of NO and NO_2 is more reactive than the reagent produced by dehydration of HNO_2 (equation 5).

TABLE 2. Nitrosation of amino compounds by gaseous N_2O_3 and N_2O_4 in aqueous 0.1 M NaOH at 25°C[13]

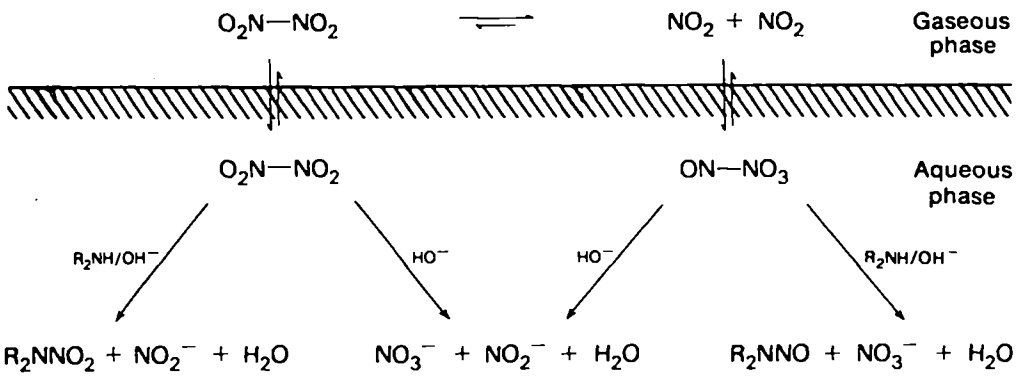
Amine	pK_a	% Nitrosation[a]	
		N_2O_4	N_2O_3
Piperidine	11.12	39(0)[b]	65(0)[b]
Morpholine	8.33	19	52
N-Methylpiperazine	9.8, 5.11	33(44)[b]	39(45)[b]
Aniline	4.65	27	45
N-Methyl-4-nitroaniline	1.19	16	27
4-Nitroaniline	0.99	24(38)[b]	29(31)[b]
Diphenylamine	0.78	6	
3,5-Dinitroaniline	0.35	14	
2-Nitroaniline	−0.3	11	
2-Chloro-4-nitroaniline	−1.0	13	13
2,4-Dinitroaniline	−4.53	0	
N-Butylacetamide	−0.29	0	

[a] Based on [amine].
[b] 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** ⇌ **8** and **9** ⇌ **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.

(**7**) (**8**) (**9**) (**10**)

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].



SCHEME 5. Nitrosation of amines in aqueous solution by N_2O_4.

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 β-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.

$$ROH + YNO \xrightarrow{HO^-} RONO + Y^- + H_2O \quad (21)$$

EtONO) are poor nitrosating agents in the absence of acids (see Section II.C.3). Other alcohols which bear an electron-withdrawing group β 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), β-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 β-substituent renders it reactive towards amines under nonacidic conditions (Scheme 6). This conclusion is supported by independent measurements showing that 2-ethoxyethyl nitrite ($EtOCH_2CH_2ONO$) effects the nitrosation of

TABLE 3. Effect of β-substituted alcohols on the nitrosation of piperidine by NOCl in 0.1M NaOH at 25°C[59]

[Alcohol] (M)	10^4[*N*-Nitrosopiperidine] (M)[a]	$t_{1/2}$(min)[b]
None	7.0	<1
0.05 D-Glucose	11.6	2.0
0.25 D-Glucose[c]	20	3.0
0.05 D-Mannose	12.2	4.1
0.05 D-Galactose	11.4	2.2
0.05 Sucrose	18	2.3
Table sugar (0.86 g/5 ml)	18.5	2.3
Milk (1.5 ml/5 ml)	10	4.0
0.26 Ethylene glycol	17.8	25
0.05 Triethanolamine	12.1	19
0.05 Diethanolamine	3.75	24
0.05 *N*-Nitrosodiethanolamine	17.5	4.0
0.05 *N*-Nitrosodiethanolamine[c]	4.9	3.5
0.05 Choline chloride	10.0	3.0
0.25 2,2,2-Trifluoroethanol	17.0	1.2
0.25 2-Fluoroethanol	16	8.0

[a]Maximum yield for reaction of 2×10^{-3}M piperidine with 1.14×10^{-2}M NOCl.
[b]Time to obtain 50% of the maximum yield.
[c]Using 10^{-2}M N_2O_4 in place of NOCl.

$$XCH_2CH_2OH + YNO \xrightarrow{HO^-} XCH_2CH_2ONO + Y^- + H_2O$$

(11)

X = OH, NH_2, etc;
Y = Cl, ONO, ONO_2

$\xrightarrow{R_2NH}$

$$R_2NNO + XCH_2CH_2OH$$

SCHEME 6. Catalysis of nitrosyl gas nitrosation of amines by β-hydroxyalkyl compounds.

piperidine and morpholine in 0.1 M NaOH, and of the *N*-methylpiperazinium ion in phosphate buffer at pH 6.85[60]. 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 (pK_a 8.33) is about 100 times less reactive than piperidine (pK_a 11.12) towards 2-ethoxyethyl nitrite.[60]

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 N_2O_3 and N_2O_4 form *N*-nitrosamines in blood and plasma[63] and these reactions are likely to be mediated by carbohydrates. Further, they suggest the pathway by which *N*-nitroso compounds may form from gaseous NO_x pollutants in the presence of common materials such as glycerine and alkanolamines. Triethanolamine, for example, has been recommended for both the removal[64] and estimation[65] of NO_2 in studies of atmospheric pollution.

5. *Catalysed nitrosation by nitric oxide*

Early work by Drago and Paulik[66] established that secondary amines react with excess NO in EtOH to give first *N*-nitrosamines and then ammonium salts ($R_2NN_2O_2^-$ $R_2NH_2^+$). Subsequently, Brackman and Smit[67] showed that the *N*-nitrosamine formation was catalysed by $CuCl_2$ and proposed a complex mechanism involving several redox processes. Related reactions were the subject of innumerable patents[68].

Under anaerobic conditions, the reaction of NO with heterocyclic amines is either catalysed or promoted by ZnI_2, $ZnBr_2$, CuCl, $CuCl_2$, $Fe(NO_3)_2$, $AgNO_3$, $AgClO_4$, $CoSO_4$, $SnCl_2$, $NiCl_2$, $CdCl_2$, $HgCl_2$ and $Hg(OAc)_2$ [69]. Some of these reactions are retarded by H_2O, and all are inhibited by added acids. The mechanisms by which several occur are now understood. For $AgNO_3$ and $AgClO_4$, 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 ($R_2\dot{N}H$) which combines directly with NO to produce the *N*-nitrosamine as shown in Scheme 7[70]. Other work[71] 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 O_2 (cf. equation 17), two of the best promoters for nitrosation by NO are I_2 and HI. With I_2, quantitative yields of *N*-nitrosamine are obtained from heterocyclic amines in EtOH at 25°C in ca. 20 min[72]. 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,

$$Ag^{I} + 4\,R_2NH \rightleftharpoons Ag^{0} + Ag^{II}(R_2NH)_4$$

(12)

$$R_2NNO + R_2NH_2^+ + 2\,R_2NH + Ag^{I} \xleftarrow{NO} Ag^{I}(R_2\dot{N}H)(R_2NH)_3$$

SCHEME 7. Silver salt catalysis of nitrosation of amines by NO.

$$NO + 1/2\,I_2 \rightleftharpoons NOI \overset{EtOH}{\rightleftharpoons} EtONO + HI$$

$$\downarrow 2R_2NH$$

$$R_2NNO + R_2NH_2^+\ I^-$$

SCHEME 8. Iodine catalysis of amine nitrosation by NO.

it is surprising that *N*-nitrosamine formation is also promoted by HI. The explanation lies in the discovery that HI is reduced to I_2 by NO in organic solvents (equation 22). This effectively reduces the acidity of the reaction solutions by converting HI (strong acid) to H_2O (weak acid). The formation of *N*-nitrosamines then

$$2\,HI + 2\,NO \longrightarrow N_2O + H_2O + I_2 \qquad (22)$$

proceeds via the reaction of NO with I_2 as described in Scheme 8[73]. Rapid *N*-nitrosamine formation in the presence of metal iodides and bromides (e.g. ZnI_2 and $ZnBr_2$) proceeds similarly following solvolysis of the salt to HI or HBr (e.g. equation 23)[73].

$$ZnI_2 + 2\,EtOH \longrightarrow Zn(OEt)_2 + 2\,HI \qquad (23)$$

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 I_2, 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.

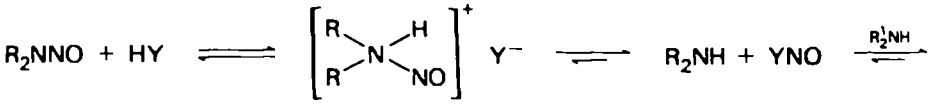
C. Nitrosation of Secondary Amines by Organic Nitroso and Nitro Compounds

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*

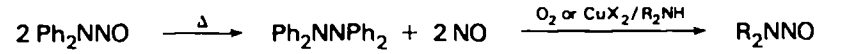
Denitrosation by aqueous acid[74], thermally as in the TEA® Analyzer[75] and photochemically[76], implies that *all* *N*-nitrosamines are potential nitrosating agents under the appropriate conditions. Interaction with other amines leading to new *N*-nitrosamines (often termed transnitrosation) is only 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 Ph_2NNO > PhMeNNO > *N*-nitrosopiperazine > *N*-nitrosomorpholine > *N*-nitrosopiperidine in line with decreasing bond strength[77,78]. The reactions tend to be sluggish because the amino substrates are extremely protonated, but catalysis by anions and nucleophiles ($I^- \approx$ thiourea > SCN^- > Br^- > Cl^-) has been demon-



$$R_2NNO + HY \rightleftharpoons \left[\begin{matrix} R \\ R \end{matrix}\!\!>\!N\!-\!\begin{matrix} H \\ NO \end{matrix}\right]^+ Y^- \rightleftharpoons R_2NH + YNO \xrightarrow{R^1_2NH} R^1_2NNO + HY \quad (24)$$

strated[79]. This implies that release of YNO is involved (equation 24) so the scope and limitations of these reactions can be assessed from direct investigations of nitrosation using HNO_2. Under certain conditions (e.g. in EtOH or with excess Y^-) protonation of the *N*-nitrosamine appears to become rate-limiting for *N*-nitrosodiphenylamine and *N*-nitroso-*N*-methylaniline[80]. The conditions under which these transnitrosations occur are not too dissimilar from those in the stomach. It follows that many noncarcinogenic materials (e.g. *N*-nitrosodiphenylamine, *N*-nitrosoamino acids) may produce carcinogenic compounds by reacting with secondary amines *in vivo*[81]. Transnitrosation can also be effected in non-aqueous solvents by heating the more labile *N*-nitrosamines (e.g. *N*-nitrosocarbazole, *N*-nitrosodiphenylamine) with another secondary amine[82,83]. Temperatures in the region of 50–80°C are usually required. Unpublished work[84] shows that these reactions proceed via release of NO, which requires either oxidation to NO_2 ($\rightleftharpoons N_2O_4$), or catalysis by metal salts (see Section II.B.5) to react with another amine (equation 25). Aromatic *N*-nitrosamines find industrial application as antioxidants and retardants. It is conceivable

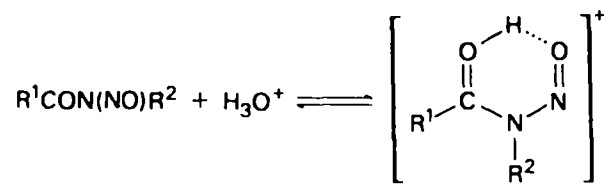


$$2\,Ph_2NNO \xrightarrow{\Delta} Ph_2NNPh_2 + 2\,NO \xrightarrow{O_2 \text{ or } CuX_2/R_2NH} R_2NNO \quad (25)$$

that thermal reactions similar to equation (25) may explain, for example, the detection of *N*-nitrosomorpholine in some rubber factories[85].

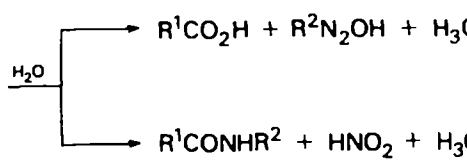
2. *Nitrosation by N-nitrosamides and related compounds*

N-Nitrosamides[86,87], *N*-methyl-*N*-nitroso-*p*-toluenesulphonamide[88] and *N*-nitrosoureas[78,89] have been shown to undergo denitrosation and (sometimes) concurrent deamination in mildly acidic conditions (pH <4) as in equation (26). Usually H^+ transfer to form the conjugate acid intermediate (e.g. **13**) is rate-limiting. In



$$R^1CON(NO)R^2 + H_3O^+ \rightleftharpoons \left[\begin{matrix} O \\ \| \\ R^1\!-\!C \end{matrix}\!\!>\!N\!-\!\begin{matrix} H\cdots O \\ \| \\ N \end{matrix}\!\!>\!C\!-\!R^1\right]^+$$

(13)



$$\xrightarrow{H_2O} \begin{cases} R^1CO_2H + R^2N_2OH + H_3O^+ \\ R^1CONHR^2 + HNO_2 + H_3O^+ \end{cases} \quad (26)$$

principle, this could result in transnitrosation to another amino substrate, but, thus far, the reaction has been demonstrated only for *N*-nitrosoureas and *N*-nitrosomethylurethane[78]. Above pH 4, deamination is dominant for most compounds.

Further, homolytic fission of the N—N(=O) bond has not been reported (other than in the TEA® 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].

$$R^1CON(NO)R^2 \xrightarrow{\Delta} [R^1\overset{\overset{O}{\|}}{C}-ON{=}NR^2] \longrightarrow R^1CO_2R^2 + N_2 \quad (27)$$

(**14**)

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[91], 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

$$R^1ONO + HY \rightleftharpoons \underset{(15)}{[R^1\overset{\overset{H}{|}}{O}NO]^+} \begin{cases} \xrightarrow{Y^-} R^1OH + YNO \\ \xrightarrow{R^2_2NH} R^2_2NNO \end{cases} \quad (28)$$

acidium ion (H_2ONO^+). Simple nitrite esters undergo homolytic fission both thermally[6] and photolytically[92] to generate alkoxy radicals ($RO^\bullet$) 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).

$$2\,R^1ONO \xrightarrow{\Delta \text{ or } h\nu} 2\,R^1O^\bullet + 2\,NO \xrightarrow{O_2} N_2O_4 \xrightarrow{R^2_2NH} R^2_2NNO + HNO_3 \quad (29)$$

As discussed in Section II.B.4, nitrite esters bearing electron-withdrawing β-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

$$XCH_2CH_2ONO + R_2NH \longrightarrow XCH_2CH_2OH + R_2NNO \quad (30)$$

($EtOCH_2CH_2ONO$) reacts with both piperidine and morpholine in 0.1 M NaOH and with the *N*-methylpiperazinium ion at pH 6.85 to give significant yields of the corresponding *N*-nitrosamines in ca. 30 min[60]. Base-catalysed hydrolysis of $EtOCH_2CH_2ONO$ competes with the *N*-nitrosation, but piperidine and morpholine react 320 and 3.7 times faster, respectively, than HO^-. Related reactions have been reported for β-phenethyl nitrite in aqueous dioxan[93] and nitrite esters derived from a variety of vicinal diols, β-alkanolamines and carbohydrates[59,61]. 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[94] 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[94] suggest that release of NO followed by oxidation to NO_2 ($\rightleftharpoons N_2O_4$) 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 [$C(NO_2)_4$] are relevant; it converts *N*,*N*-dimethylaniline to *N*-methyl-*N*-nitroso-aniline on heating in pyridine[97] yet effects the nitration of phenols in aqueous solution at pH 8 and 25°C[98]. The nitration is considered to involve charge-transfer intermediates[99] 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[100]. 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_2O_4, which then effects nitrosation. For bronopol (2-bromo-2-nitropropane-1,3-diol), an alternative pathway involving formaldehyde and NO_2^- has been suggested[101], 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[102] and by UV photolysis at ambient temperature in the solid state[103]. The thermolysis is considered to involve radicals produced by breakage of the N—N bond[102], 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[104], 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)[1]. 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)[23]. The kinetic characteristics

$$\underset{\textbf{(16)}}{R\overset{+}{N}{\equiv}N\ Y^-} + RNH_2 \longrightarrow HY + N_2 + R_2NH \xrightarrow{YNO} R_2NNO + HY \qquad (31)$$

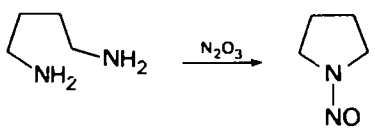
of the initial deamination (including catalysis and inhibition) should be similar to *N*-nitrosamine formation, but yields of *N*-nitrosamines obtained from primary amines are very low because the intermediate **16** reacts by several competitive

$$RNH_2 + YNO \rightleftharpoons HY + RNHN{=}O \longrightarrow RN{=}N{-}OH + HY$$

$$RN{=}N{-}OH + HY \longrightarrow \underset{\textbf{(16)}}{R\overset{+}{N}{\equiv}N\ Y^-} + H_2O \longrightarrow \text{Olefins, RY, etc.}$$

SCHEME 9. Nitrosation of primary aliphatic amines.

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 HNO_2 in an aqueous slurry compared to 0.01% *N*-nitroso-di-*n*-butylamine from *n*-butylamine under similar conditions[105].

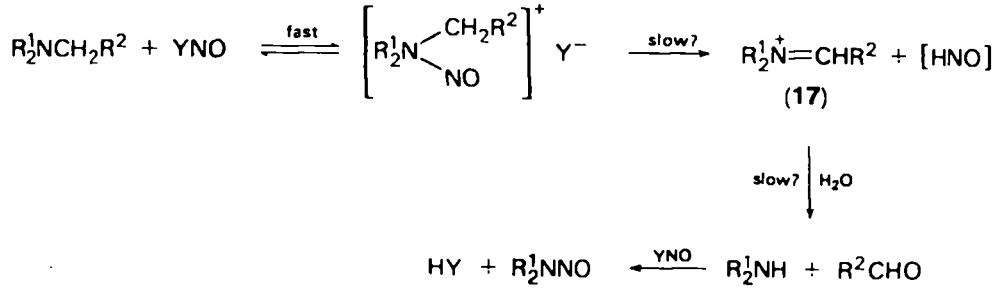


(32)

2. Tertiary amines

Early work on the interaction of tertiary amines with acidified nitrite has been reviewed[106], but these reactions have attracted further attention because of *N*-nitrosamine formation[107–110]. 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 NO_2^-. The hydrolysis hypothesis is supported by recent identification of secondary amines[111] as co-products to aldehydes, N_2O ($2\,HNO \rightarrow N_2O + H_2O$) and *N*-nitrosamines[108,112]. An alternative pathway involving electron transfer rather than *N*-nitrosation to form **17** has been proposed[113] and this could be favoured for aromatic amines.

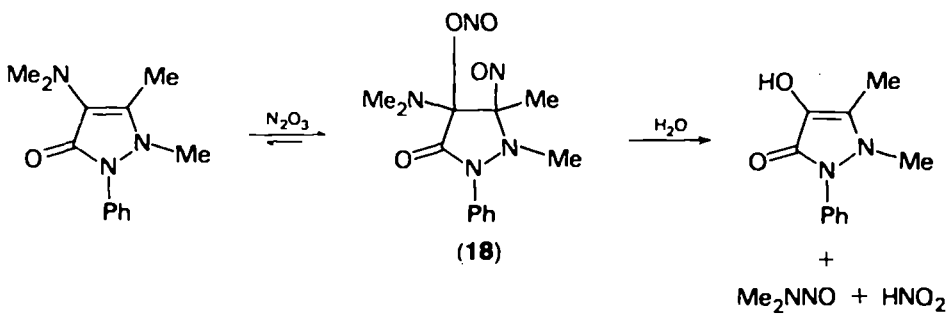
Usually quite stringent conditions (50–100°C) are required for tertiary alkylamines and it has been estimated that these compounds are ca. 10,000 times less reactive than comparable secondary amines[4]. This implies that either formation or hydrolysis of **17** is rate-limiting (Scheme 10). Most investigations (e.g. References



SCHEME 10. Nitrosation of tertiary amines.

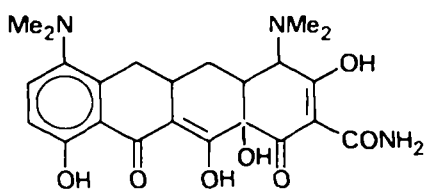
109 and 110) find maximum rates with HNO_2 at pH 3–3.4 (as for secondary amines) but there is considerable disagreement as to the kinetic dependence on $[HNO_2]$ (cf. References 110, 111 and 114). This may relate to different experimental conditions or to inadequate attention to concurrent thermal decomposition 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



(33)

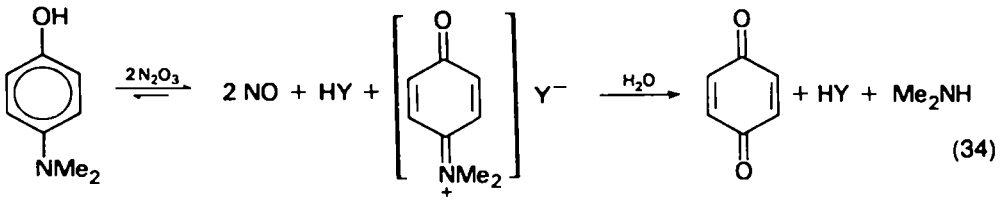
have been discussed[116] and may be required to explain strong SCN^- catalysis[117]. A pathway similar to equation (33) would apply to oxytetracycline. For minocycline (**19**), rapid *N*-nitrosodimethylamine formation probably relates to the presence of



(**19**)

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 HNO_2 at pH 3 and 25°C (equation 34)[118]. The interaction of other aromatic



(34)

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 $NaNO_2$ 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 4. Yields of *N*-nitrosodimethylamine after reaction of amino compounds for 4 h with a five-fold excess of NO_2^- at pH 5.6 and 78°C[119]

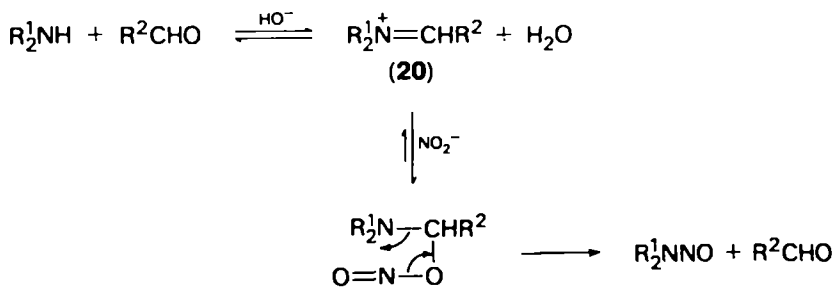
Amino substrate	Yield of Me_2NNO (%)
Me_2NH	9.6
Me_3N	0.9
Me_4N^+	0.6
$Me_2NCH_2CH_2OH$	1.6
$Me_3NCH_2CH_2OH$	0.0002

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^- [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[116]. This type of reaction may also explain the unexpected formation of *N*-nitrosamines from secondary amines and solid $NaNO_2$ in halogenated solvents (e.g. CH_2Cl_2)[124] and small amounts of *N*-nitrosodiethanolamine in cosmetics containing the bacteriocide 2-bromo-2-nitropropane-1,3-diol(bronopol) which decomposes to release NO_2^- and formaldehyde[101].

$NaNO_2$ has also been shown to produce *N*-nitrosamines from secondary amines at pH 11 in the presence of ferrocyanide ion[125] and in 2,2′-bipyridine in the presence of cupric nitrate[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 $Cu^{II}(bipyr)(ONO)_2$, 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.



SCHEME 11. Formation of *N*-nitrosamines from nitrite ion, carbonyl compounds and amines.

Recent work demonstrates that *N*-nitrosamines form rapidly from neutral aqueous $NaNO_2$ and heterocyclic amines both on γ-irradiation[59] and on UV photolysis[127]. It seems probable that HO radicals and solvated electrons generated from H_2O convert NO_2^- to NO_2 and NO. These combine to form N_2O_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[128,129].

Other recent work reveals that *N*-nitrosamines are readily formed when neutral aqueous solutions of $NaNO_3$ and secondary amines are exposed either to γ-radiation[59] or to UV photolysis[127]. The highest yields apply to experiments with excess $NaNO_3$. These reactions are thought to result from reduction of NO_3^- to NO_2, which then dimerizes to form the N_2O_4 reagent. This conclusion is supported by the concurrent formation of *N*-nitramines[59,127].

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 amides[130] 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 amides[130]. 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 $R^1C^-HN(R^2)NO$, 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

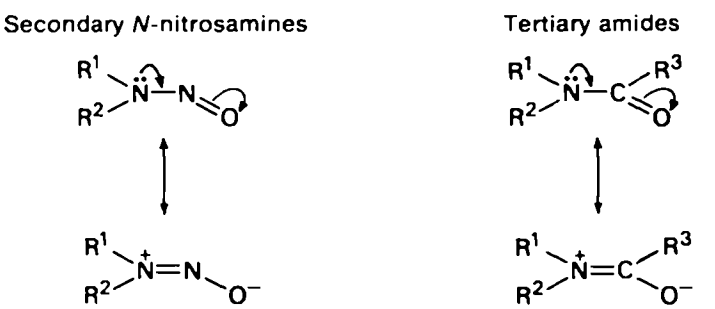
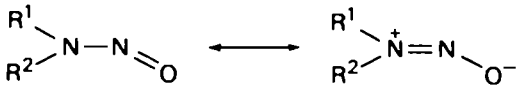


FIGURE 2. Comparison of resonance structures of secondary *N*-nitrosamines and tertiary amides.

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[130] the structure and stereochemistry of *N*-nitrosamines should reflect extensive delocalization of the amino nitrogen lone-pair electrons into the π-system of the N=O group. This is borne out by the limited evidence available. Thus an electron diffraction study[131] of gaseous *N*-nitrosodimethylamine (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=N (125 pm) and N—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



(21) **(22)**

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[132], which are significantly larger than those for tertiary amides (3.75 D)[130]. *N*-Nitrosodiphenylamine, however, has a lower dipole moment (3.39 D)[133] implying reduced charge development arising from competitive delocalization of the amino lone-pair electrons into the aromatic nucleus. Condensed-phase infrared spectra of *N*-nitrosamine[134] 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})[6]. This is further evidence of intermediate bond order for the N=O group in *N*-nitrosamines.

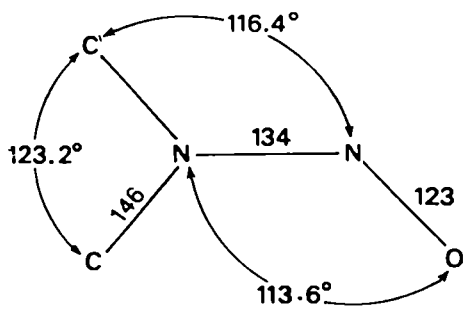


FIGURE 3. Structure of *N*-nitrosodimethylamine from electron diffraction data[131]. (Bond lengths in pm.)

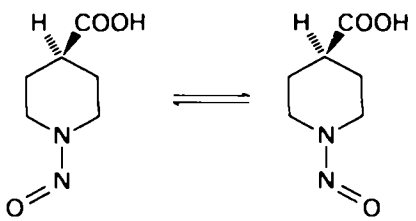
*Unambiguous bond lengths for N=O are not available, the best being in nitric oxide (115 pm) and nitrosyl chloride (114 pm).

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**

(23) **(24)**

($R^1 \neq R^2$). Good evidence to this effect is the observation of nonequivalent signals in the ^{1}H-NMR spectra of symmetrical *N*-nitrosamines ($R^1 = R^2$). For example, *N*-nitrosodimethylamine shows two CH_3 signals separated by 19 ppm and their temperature dependence gives a rotational barrier ($\Delta G^{\neq}$) 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 ($\Delta G^{\neq}$ 79.9 kJ mol^{-1})[138] is consistent with a decreased N—N double-bond character. Another investigation of heterocyclic *N*-nitrosamines[139] shows that α-substitution also lowers the rotational barriers ($\Delta G^{\neq}$ 77–92 kJ mol^{-1}). In general, however, the barriers to rotation in *N*-nitrosamines are slightly higher than those for *N,N*-dimethylamides ($\Delta G^{\neq}$ ca. 75 kJ mol^{-1}) and considerably lower than for ethylene ($\Delta G^{\neq}$ 167 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 ($t_{1/2}$ ca. 1–2 h in solution at 36°C), (*E*) and (*Z*) isomers have rarely been separated, except for **23**, **24** (R^1 = $PhCH_2$, R^2 = 2,6-$Me_2C_6H_4$) by thin-layer chromatography[141] and for the chiral *N*-nitrosamine (**25**) by crystallization with an



(25)

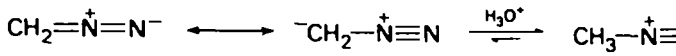
optically pure amine[142]. Separation of (*E*) and (*Z*) isomers of α-*N*-nitrosamino acids is easier and can be accomplished by either t.l.c.[143] or h.p.l.c.[144].

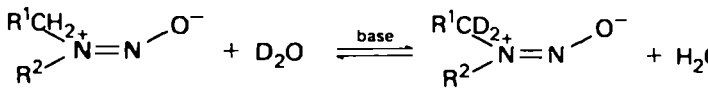
Both UV and mass spectra of *N*-nitrosamines have characteristic features of diagnostic value. Their UV spectra have two bands in the region of 230–240 nm ($\log\varepsilon$ ca. 4) or 330–370 nm ($\log\varepsilon$ ca. 2)[8,145,146]. The first is assigned to a $\pi \rightarrow \pi^*$ transition and is 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 α-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 α-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].

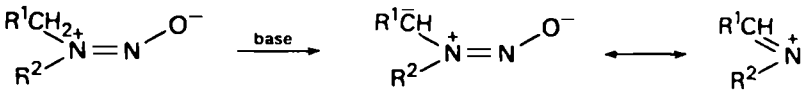
B. Acid–Base, Hydrogen-bonding and Complexing Properties

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 α-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:





(35)



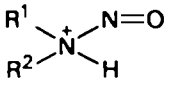
(36)

(**26**) (**27**)

although the *N*-nitrosamines are significantly weaker acids. The lability of the α-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 *syn*- and *anti*-α-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 $pK_a = -0.62$ 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

(**28**)



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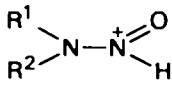


(30)

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 $HSO_3F{\cdot}SbF_5$ ('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_5 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

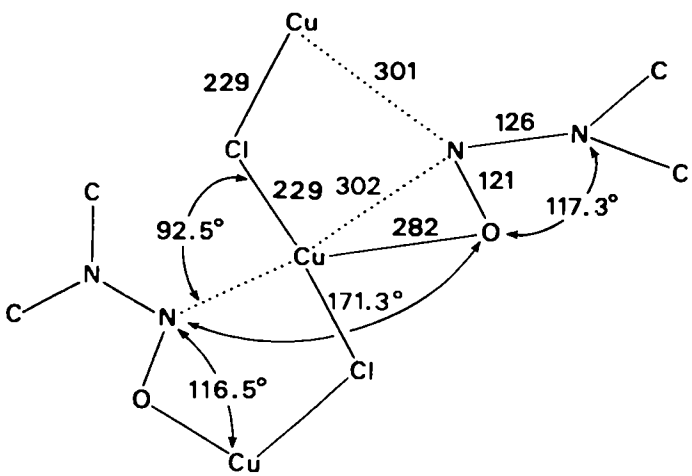
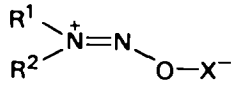


FIGURE 4. Structure of the 1:1 complex between *N*-nitrosodimethylamine and $CuCl_2$. (From X-ray diffraction data[160]; bond lengths in pm.)

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[157] 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.

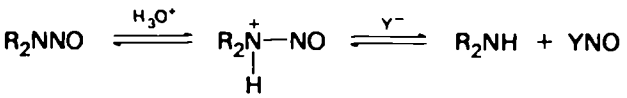


(**31**)

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**)



(37)

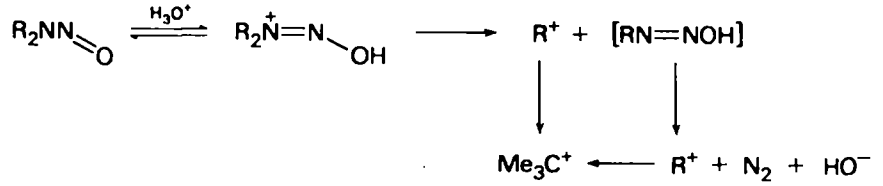
(**29**)

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).

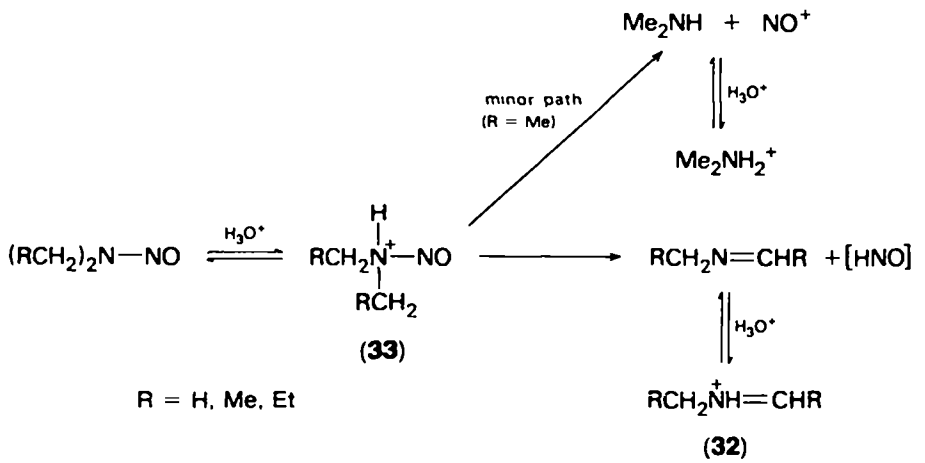
1. Reactions with anhydrous acids

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_2ClF plus 'magic acid' ($HSO_3F{\cdot}SbF_5$) catalyst with the evolution of N_2 and a carbocation. The latter undergoes condensation and



R = *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu

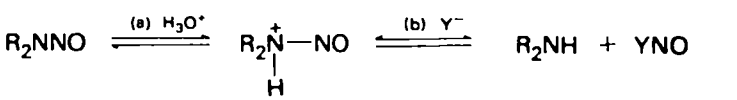
SCHEME 12. Decomposition of *N*-nitrosoalkylamines in $HSO_3F{\cdot}SbF_5$.



SCHEME 13. Decomposition of *N*-nitrosodialkylamines in H_2SO_4 or HSO_3F.

fragmentation to form ultimately the *t*-butyl carbocation as the principal identifiable product (Scheme 12). In $FHSO_3$ or 100% H_2SO_4 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 procedure[161], for example, a 5–10% solution of HBr in glacial acetic acid added to the



(38)

N-nitrosamine in an organic solvent releases NOBr which can be estimated by an 'NO chemiluminescence' detector. Related procedures employ either NaI plus H_3PO_4[162] or gaseous HCl[74,163] 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[80] have examined the denitrosation of aryl-*N*-nitrosamines by HCl in ethanol. The reaction rate follows equation (39), and the absence of catalysis by

$$\text{rate} = k_2[N\text{-Nitrosamine}][HCl] \tag{39}$$

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 HNO_2 (equation 40) does occur in aqueous acid

$$R_2NNO + H_2O \overset{H_3O^+}{\rightleftharpoons} R_2NH + HNO_2 \tag{40}$$

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[8,74]; 50–80% H_2SO_4, 40% H_3PO_4, formic and acetic acids are all largely ineffective[74].

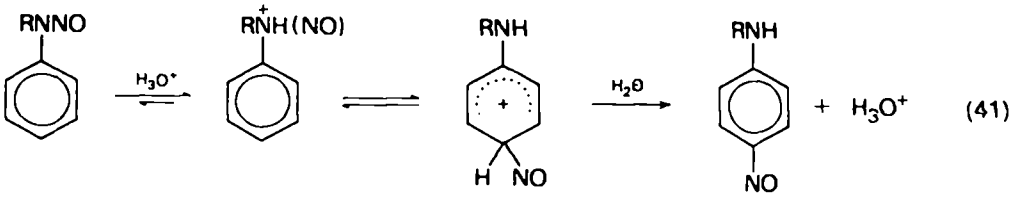
The mechanism of hydrolysis has been specifically examined for aryl-*N*-nitrosamines only[79,88,164], but indirect information for alkyl analogues is available from transnitrosation studies (see below). Because the hydrolysis is reversible, it is advantageous to remove HNO_2 by means of a 'trap' such as HN_3, 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*-nitrosoanilines in 0.5–3 M acid show a first-order dependence on $[Y^-]$, and the efficacy of various nucleophiles decreases in the order $I^- > SC(NH_2)_2 > SCN^- > Br^- > Cl^- >> H_2O$. 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 of ^{18}O exchange between *N*-nitrosamines and aqueous acids[165].

$$R_2NNO \overset{H_3O^+}{\rightleftharpoons} R_2\overset{+}{\underset{|}{N}}\underset{H}{}—NO \overset{Y^-}{\rightleftharpoons} R_2NH + YNO \overset{H_2O}{\rightleftharpoons} HNO_2 + HY$$

$$Y^- = Cl^-,\ Br^-,\ SCN^-,\ H_2O \text{ etc.}$$

SCHEME 14. Acid-catalysed hydrolysis of *N*-nitrosamines.

In concentrated aqueous acids (2–5 M), the hydrolysis of aryl-*N*-nitrosamines 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.

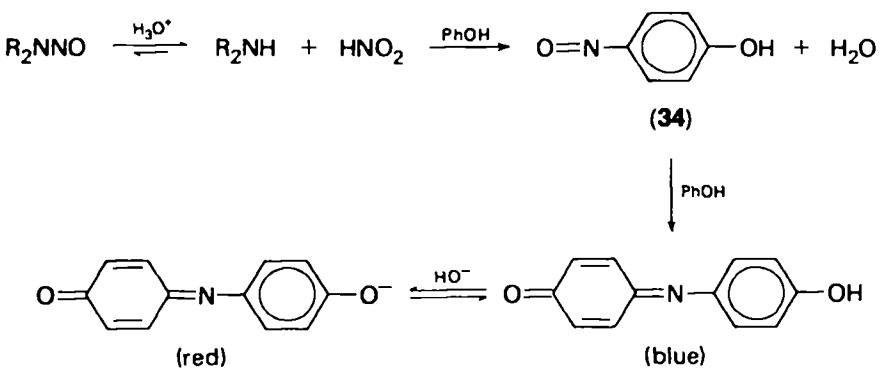


(41)

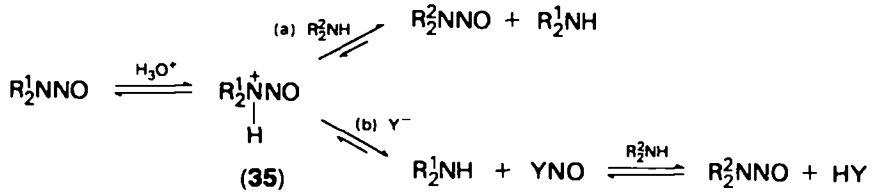
Treatment of *N*-nitrosamines with aqueous acid in the presence of nucleophilic organic materials such as phenols or amines often results in the formation of new nitrosated products. These reactions are often described as 'transnitrosations'. With phenol, transnitrosation provides a spot test for *N*-nitrosamines, well-known as the Lieberman reaction[166] (Scheme 15). Here *p*-nitrosophenol (**34**) (probably produced from HNO_2 obtained by hydrolysis of the *N*-nitrosamine) 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*-nitrosamine (equation 42) (see also Section

$$R^1_2NNO + R^2_2NH \overset{H_3O^+}{\rightleftharpoons} R^2_2NNO + R^1_2NH \qquad (42)$$

II.C.1). As for hydrolysis these reactions are reversible and, in order to obtain an appreciable amount of product, the reagent *N*-nitrosamine must have a weaker N—N bond than that of the product *N*-nitrosamine. This condition is met when aryl-*N*-nitrosamines 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*-nitrosamine (**35**) with the amine substrate (path a) or intermediate formation of an inorganic nitrosating agent (YNO) from an external nucleophile such as Cl^-, Br^- or 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 0.1M HCl or $HClO_4$[77,82], but indirect transnitrosation (path b) is implicit in the



SCHEME 15. Lieberman's spot test for *N*-nitrosamines.



SCHEME 16. Transnitrosation of amines by *N*-nitrosamines.

strong SCN^- catalysis observed for reactions of *N*-nitrosomorpholines and *N*-nitrosopiperazines[78,167].

Other nucleophiles such as HN_3, NH_2OH, 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

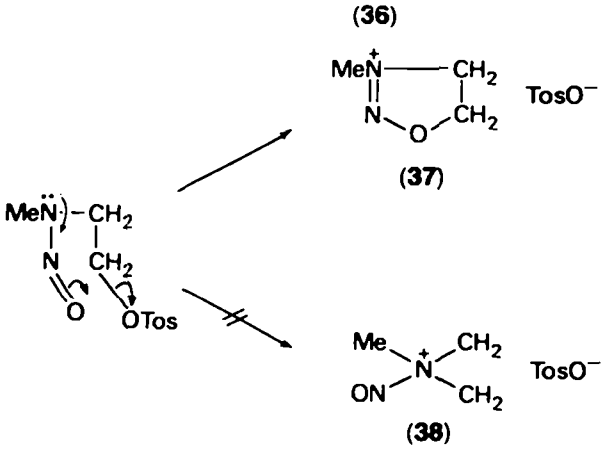
Again, by analogy with tertiary amides, the most basic atom in *N*-nitrosoamines, i.e., the oxygen should also be the most nucleophilic. This is borne out in practice for reaction with alkylating agents (equation 43) where the usual product is the salt **36**. Less is known about acylating agents but it is probable that they react similarly.

$$R_2^1N{-}NO + R^2X \longrightarrow \underset{\textbf{(36)}}{R_2^1\overset{+}{N}{=}N\!\!\begin{array}{l}\diagup\\\diagdown\end{array}\!\!\begin{array}{l}X^-\\OR^2\end{array}} \qquad (43)$$

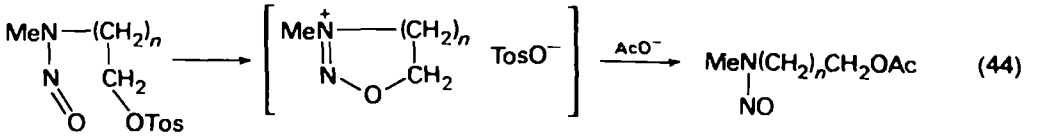
1. Alkylation

N-Nitrosamines react under mild conditions with powerful alkylating agents such as triethyloxonium tetrafluoroborate[168], triethyloxonium 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 acetolysis of β- and γ-(tosyloxy)-*N*-nitrosamines in acetic acid and sodium acetate (equation 44).



SCHEME 17. Intramolecular alkylation of *N*-nitrosamines.



(44)

n = 1 or 2

2. Acylation

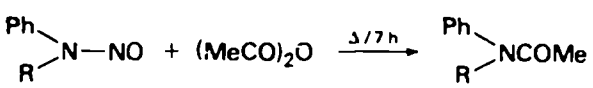
It is reasonable to suppose that acylation of *N*-nitrosamines proceeds by an analogous route to alkylation whereby reaction at the nitroso oxygen atom gives an *O*-acyl intermediate (**39**) (equation 45). However, as with tertiary amides, this intermediate is expected to be considerably more labile than its *O*-alkyl counterpart (**36**) and evidence for its existence is therefore indirect (see below).

(45)

(**39**)

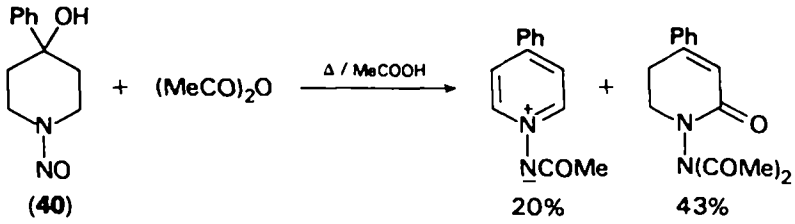
X = Cl, OCOR, etc.

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-



(46)

R = alkyl



(47)

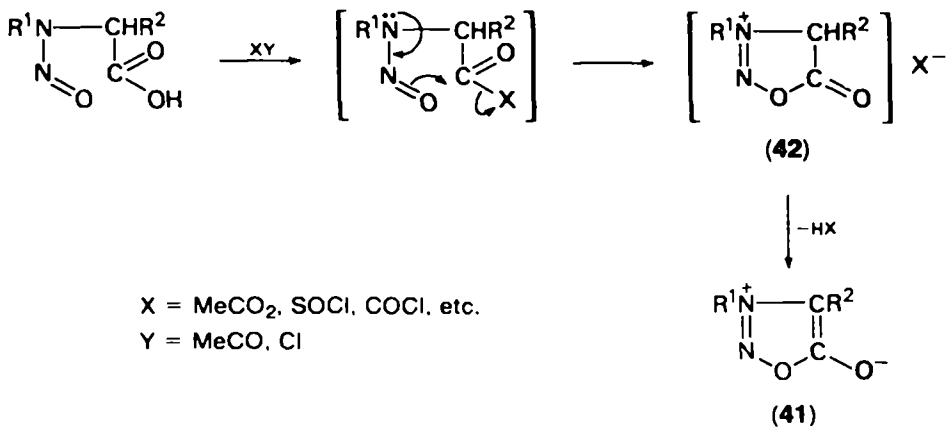
$$R_2NNO + (C_3F_7CO)_2O \xrightarrow{\text{pyridine}} R_2NN(COC_3F_7)_2 \qquad (48)$$

R = alkyl

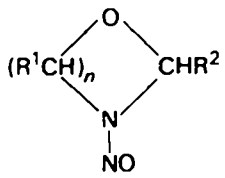
piperidine (**40**) with acetic anhydride in acetic acid[174] (equation 47) and using the more reactive heptafluorobutyric anhydride in pyridine at room temperature to acylate *N*-nitrosodialkylamines[175] (equation 48).

In contrast, much information is available about intramolecular acylations resulting in the formation of mesoionic sydnones (**41**) (Scheme 18)[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.

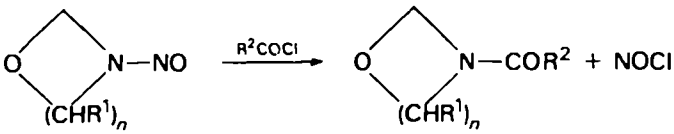
Another interesting study[178] concerns the reactions of reactive acid chlorides (e.g. phosgene, ethyl chloroformate, chloroacetyl chloride, dichloroacetyl chloride, chlorocarbonyl isocyanate, *p*-toluenesulphonyl chloride and oxalyl chloride) with *N*-nitroso derivatives of substituted 1,3-oxazolidines 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 sydnones 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.



SCHEME 18. Intramolecular acylation of *N*-nitrosamines to give sydnones.

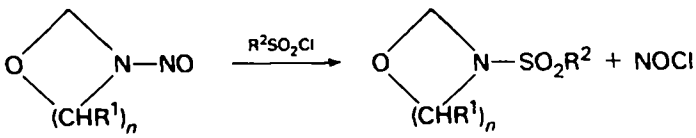


(43)



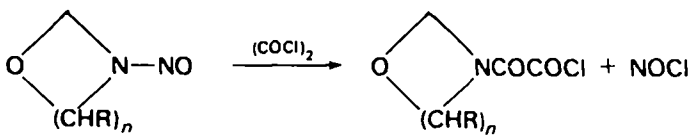
(49)

R^2 = Cl, EtO, R^2CCl, NCO
n = 2,3



(50)

n = 2,.3



(51)

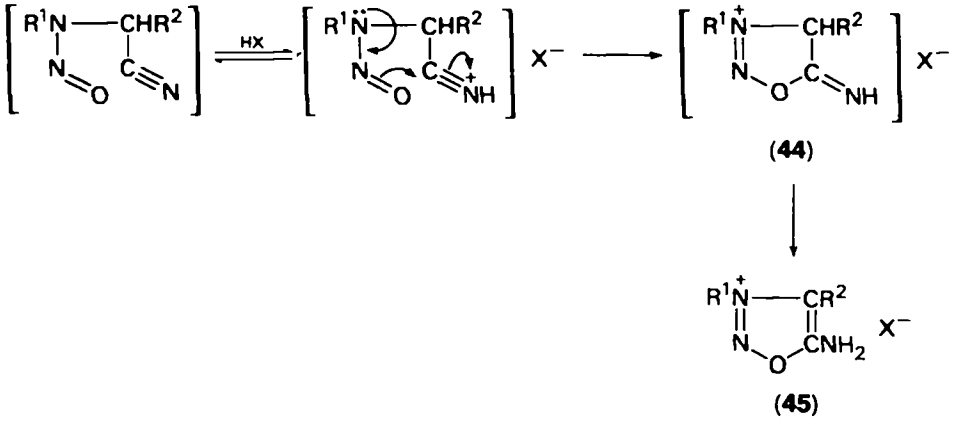
n = 2, 3

3. *Reaction with other electrophiles*

N-Nitrosamines have recently been reported to react with other electrophiles such as molecular halogens[74] and phosphorus oxychloride[171], 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-amino-acetonitriles to give sydnone imines (**44**)[176,177], 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-methylaminopropio-nitrile) undergoes denitrosation rather than cyclization to the larger six-membered ring in methanolic HCl[163], (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)[179].

E. Reaction With Organometallic Reagents

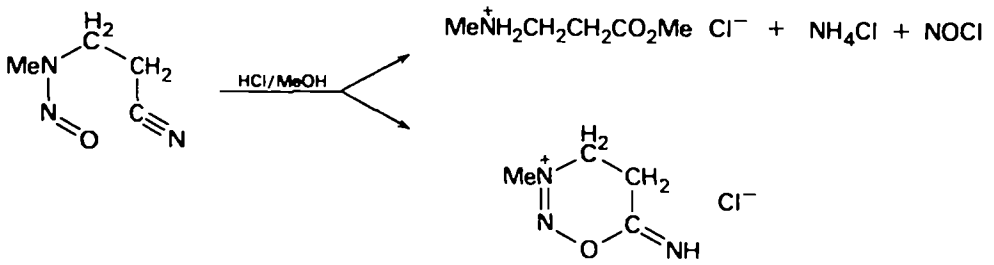
In contrast to the hydroxide ion (Section III.C.2), Grignard and alkyl- or phenyl-lithium reagents are sufficiently powerful nucleophiles to add across the N=O



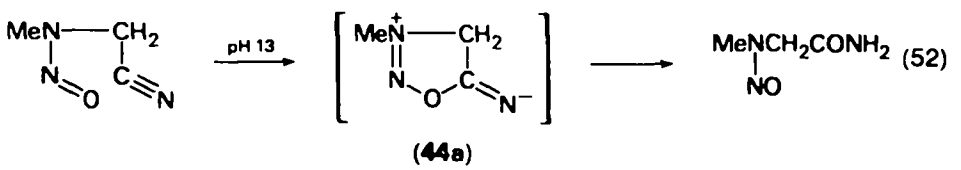
(44)

(45)

SCHEME 19. Formation of sydnone imines from cyclization of *N*-alkyl-*N*-nitroso-α-aminoacetonitriles.

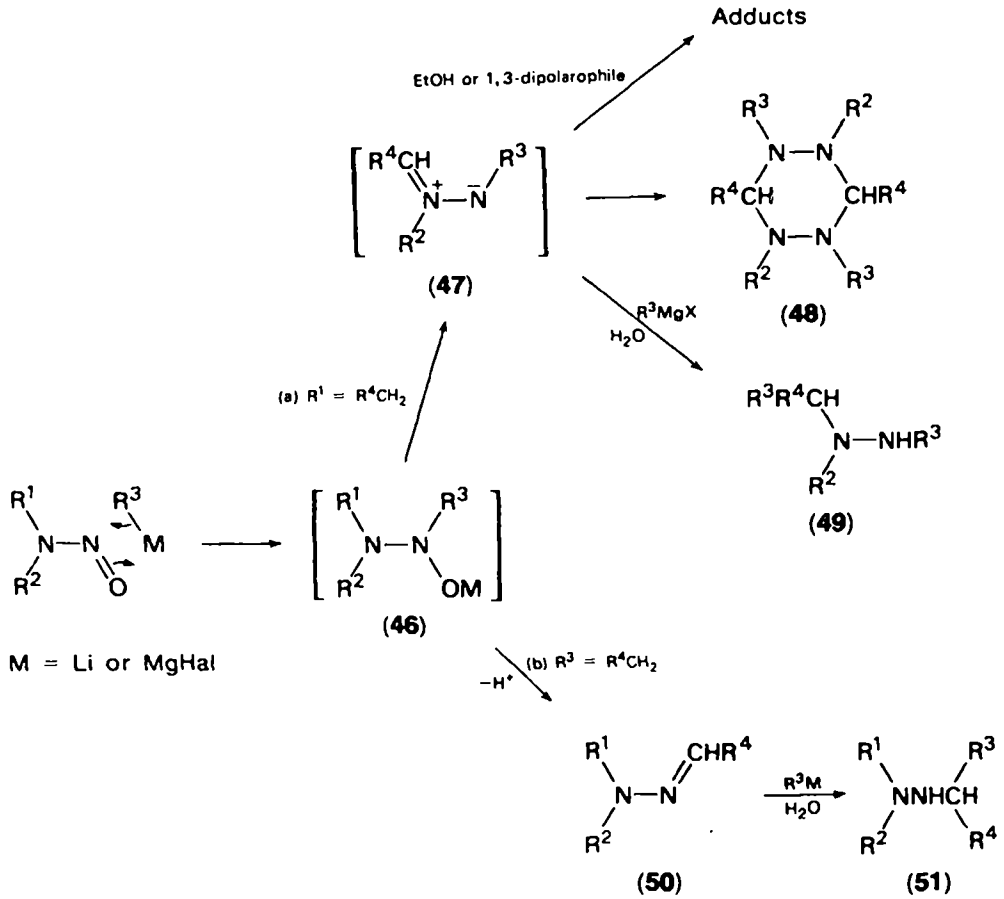


SCHEME 20. Denitrosation of *N*-nitroso-3-methylaminopropionitrile.



(44a)

group of *N*-nitrosamines. Unfortunately, they also abstract a proton from the α-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—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 α-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.

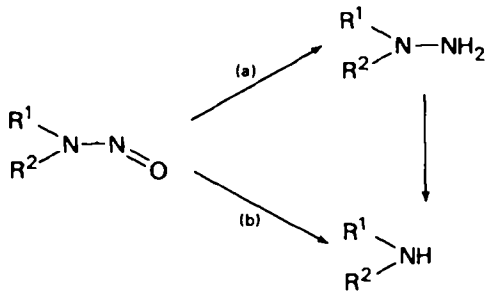
reagent to give a trialkylhydrazine (**49**)[183]. Alternatively, loss of H^+ from the α-carbon of R^3 produces the hydrazone **50** which on reaction with further organometallic reagent gives the trialkylhydrazine **51**[184]. The structure of **51** differs from **49** obtained via the azomethine imine 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[185] (equation 53). The mechanism of these transformations has not been established, but formation of biphenyl implies a radical pathway.

$$R_2NNO + PhCu \longrightarrow R_2NH + Ph_2NH + Ph_2NOH + PhOH + Ph{-}Ph \quad (53)$$

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

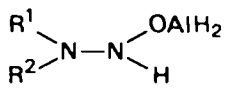


(a) $LiAlH_4$ or electrochemical
(b) H_2/RaNi or HCl/CuCl

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



(52)

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

$$R_2N{-}NO \xrightarrow{M} R_2N{-}\dot{N}{-}O^- M^+ \xrightarrow{M} R_2N^- M^+ + [MNO] \longrightarrow R_2NH \quad (54)$$

(53)

M = Li, K

pentacarbonyl[197], aryl azides[198a] or phenacyl bromides in the presence of silver hexafluoroantimonate[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

$$(PhCH_2)_2NNO \xrightarrow{Na_2S_2O_4/HO^-} \left[(PhCH_2)_2\overset{+}{N}{=}\bar{N} \leftrightarrow (PhCH_2)_2N{-}\underset{\cdot\cdot}{N}: \right] \longrightarrow (PhCH_2)_2 + N_2 \quad (55)$$

(54)

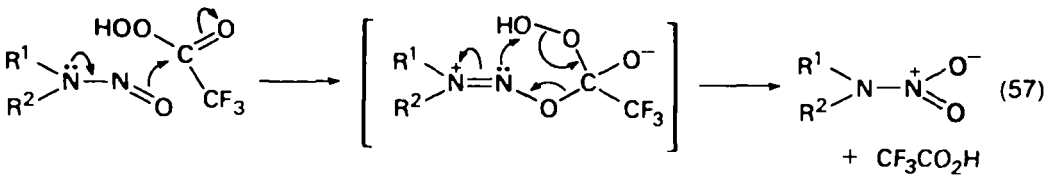
coworkers[196], but any reagent capable of producing the intermediate nitrene **54** also gives these products. Other *N*-nitrosamines are reduced by alkaline sodium dithionite to the corresponding hydrazine[196], and iron pentacarbonyl produces parent amines in high yield from *N*-nitroso derivatives of diphenylamine, *N*-phenylbenzylamine, *N*-methylaniline and carbazole[199]. These reactions probably proceed via nitrenes similar to **54** but the exact mechanism remains in dispute[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[200], using peroxytrifluoroacetic acid

$$\begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!N{-}N{=}O \xrightarrow{[O]} \begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!N{-}\overset{+}{N}\!\begin{matrix} O^- \\ =O \end{matrix} \quad (56)$$

prepared *in situ* from trifluoroacetic anhydride and 90% H_2O_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



(57)

on prolonged treatment with *t*-amyl hydroperoxide in the presence of $MoCl_5$[201]. The readily available 2-butanone peroxide is also effective but the yields of *N*-nitramine are only moderate[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 α-hydroperoxy-*N*-nitrosoalkylamines can be obtained by

treatment of the lithium salts of *N*-nitrosodialkylamines with oxygen[203] is particularly interesting and has an analogy in the oxidation of enolate ions[204]. Further, treatment of *N*-nitrosoalkylamines with the Undenfriend hydroxylating mixture (ascorbic acid, ferrous iron, EDTA and molecular oxygen) produces γ-hydroxy and γ-keto derivatives and, possibly, very unstable α-substituted analogues[205,206].

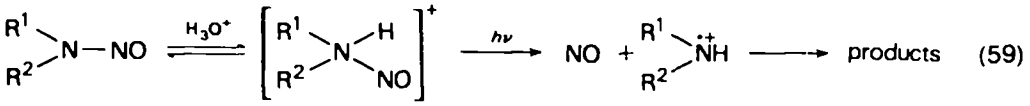
H. Homolysis of the N—N(O) Bond

Molar N—N(O) bond enthalpies are of the order of 217–225 kJ mol^{-1} for heterocyclic and aliphatic *N*-nitrosoamines, but only 46 kJ mol^{-1} for *N*-nitrosodiphenylamine[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^{-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

$$R_2NNO \xrightarrow{\Delta \text{ or } h\nu} NO + R_2N^{\bullet} \longrightarrow \text{Products} \qquad (58)$$

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*-nitrosamines under certain conditions[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.

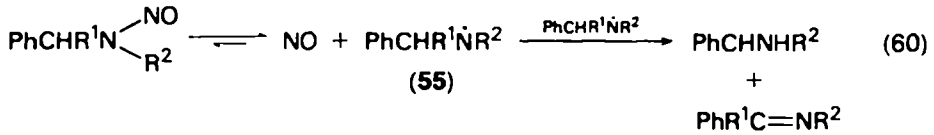


(59)

1. *Thermolysis*

All *N*-nitrosamines 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_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_2[209] and in the vapour phase at 325°C[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



(60)

reactions for *N*-nitrosodiarylamines have been investigated by Welzel[211] in solvent chlorobenzene under nitrogen (to prevent oxidation of NO to NO_2). The production of various arylamine products can be ascribed to reactions of the diarylamino radical (**56**) formed by homolysis of the N—N(O) bond (equation 61). For

$$Ar_2N{-}NO \xrightarrow{\Delta} NO + Ar_2\dot{N} \longrightarrow \text{products} \qquad (61)$$

(56)

Ar = Ph, 2-naphthyl

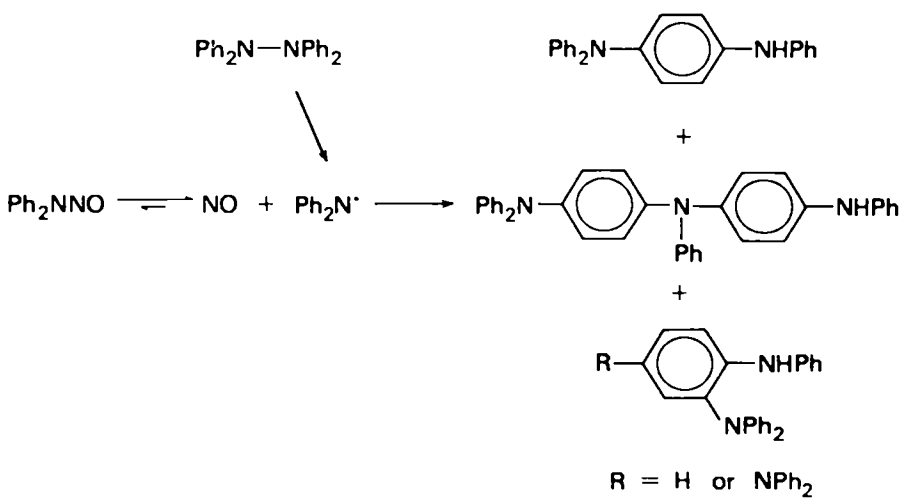
instance, the products obtained from thermolysis of *N*-nitrosodiphenylamine are the same as those obtained from thermolysis of tetraphenylhydrazine (also expected to give the diphenylamino radical) as outlined in Scheme 23.

When similar reactions are carried out in polar solvents under oxygen, N—N(O) bond cleavage again occurs but NO_2 produced by oxidation of the NO results in the formation of nitroaromatic products[212] (equation 62).

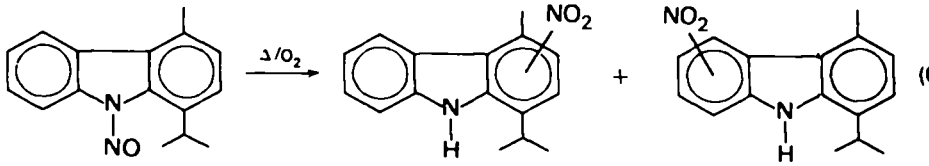
Measurement of NO released by thermolysis is the basis of the TEA® procedure for *N*-nitrosamine analysis[207]. The *N*-nitrosamine is heated in the gas phase at ca. 300°C in the presence of catalysts, and the NO evolved reacts with ozone to form NO_2 in an electronically excited state. Light emitted when NO_2^* 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[82,213] (equation 63). The mechanism



SCHEME 23. Formation and reactions of the diphenylamino radical.



(62)

$$Ph_2NNO + R^1R^2NH \longrightarrow Ph_2NH + R^1R^2NNO \quad (63)$$

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[82]. The observation of ESR spectra may indicate a free-radical pathway but reaction via N_2O_3 (following partial oxidation of NO to NO_2) has not been excluded[82]. *N*-Nitroso-3-nitrocarbazole also converts *N*-methylaniline to its *N*-nitroso derivative[214].

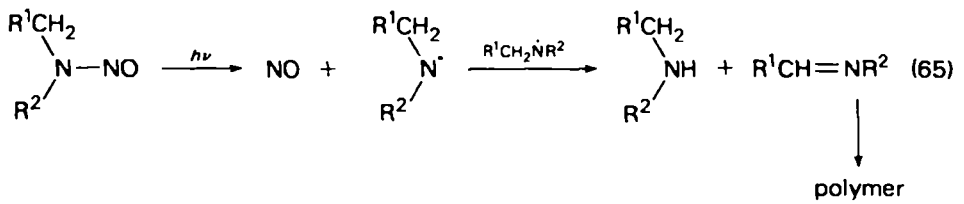
N-Nitrosodiphenylamine and its 4-substituted derivatives also react with compounds such as 1,2,3,4-tetrachloropentadiene[215] or deoxybenzoin[216], containing an active methylene group, to form an oxime (e.g. equation 64). Reaction rates are

$$Ph_2NNO + PhCOCH_2Ph \xrightarrow{80°C/1/2\ h} Ph_2NH + PhCOCPh{=}NOH \quad (64)$$

slowest for aromatic *N*-nitrosamines bearing electron-donating 4-substituents[216] 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[217] showed that photolysis of neutral *N*-nitroso-diethyl- and -dimethyl-amines 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(O) 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



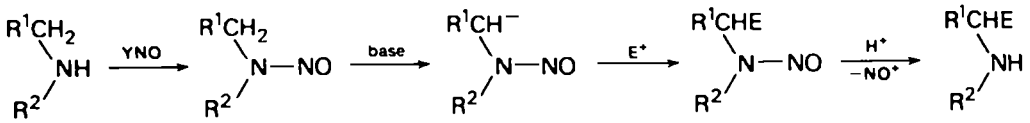
(65)

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[218], but the products were not identified. Photolysis of *N*-nitrosodibenzylamine, either neat or in hydrocarbon solvents, gives equal proportions of dibenzylamine and *N*-benzylidenebenzylamine[210], 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[219], probably as a result of oxidation of NO to NO_2.

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[76] 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[150] 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[150] coined the term 'Umpolung'

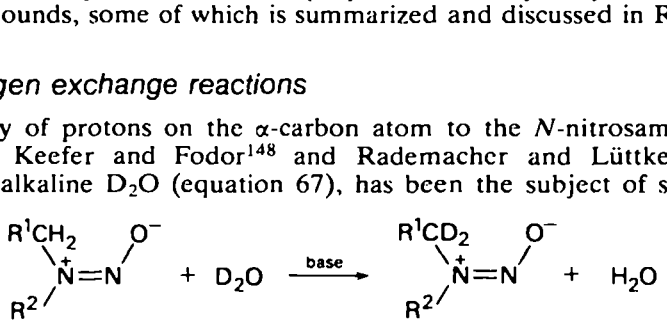


(66)

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.

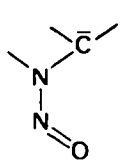
1. α-Hydrogen exchange reactions

The lability of protons on the α-carbon atom to the *N*-nitrosamino group, first reported by Keefer and Fodor[148] and Rademacher and Lüttke[149] from facile exchange in alkaline D_2O (equation 67), has been the subject of some discussion.



(67)

Originally, this lability was attributed[148] 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[151] to conclude that delocalization involving structure **59** was of overriding importance. Fraser and Ng[151] studied the rigid *N*-nitrosodibenzazepine derivative (**60**), where relative hydrogen exchange rates with respect to **61** lie in the order H_a (*syn–axial*) > H_b (*syn–equatorial*) > H_c (*anti–axial*) > H_d (*anti–equatorial*). The axial hydrogen atoms exchange more readily than the equatorial hydrogen atoms by a factor of 100 ($H_a > H_b$ and $H_c > H_d$) whereas the *syn* hydrogen atoms exchange faster than the *anti* hydrogen atoms by a factor of 1000 ($H_a > H_c$ and $H_b > H_d$). 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.



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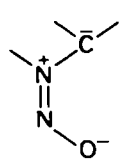

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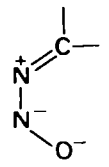

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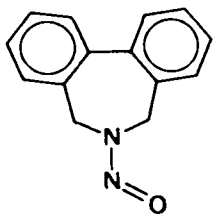
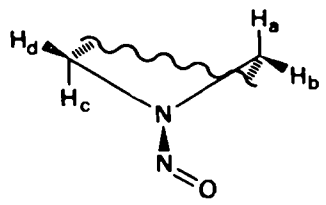
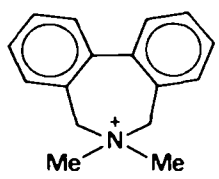


(60)

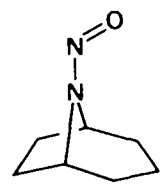


(61)

Further, Fraser and Ng[151] 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).



(62)



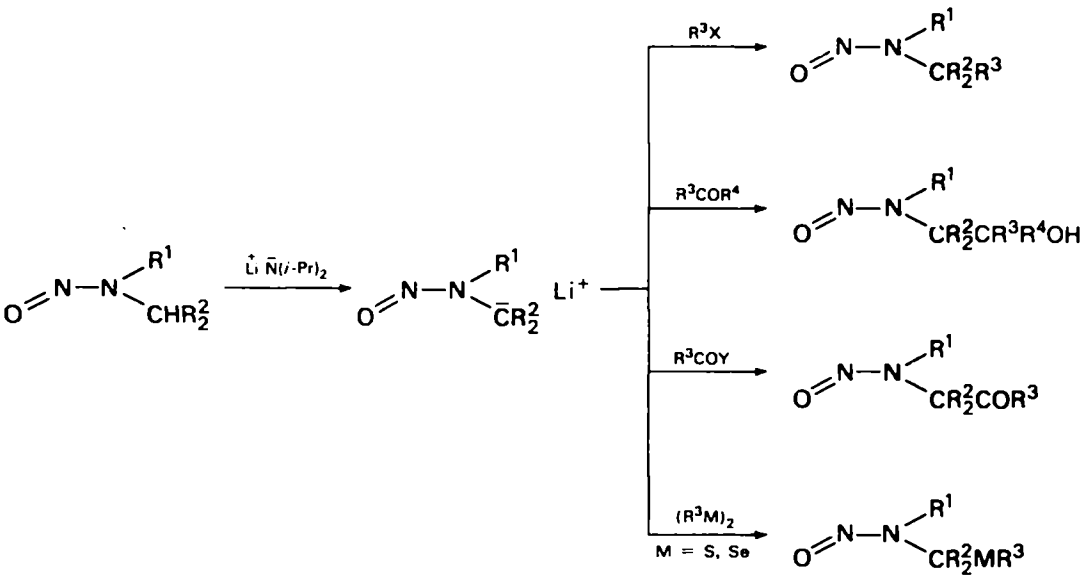
(63)

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 α-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_2O has been demonstrated[222]. Nonetheless, the labilization of hydrogen at the α-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 α-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.

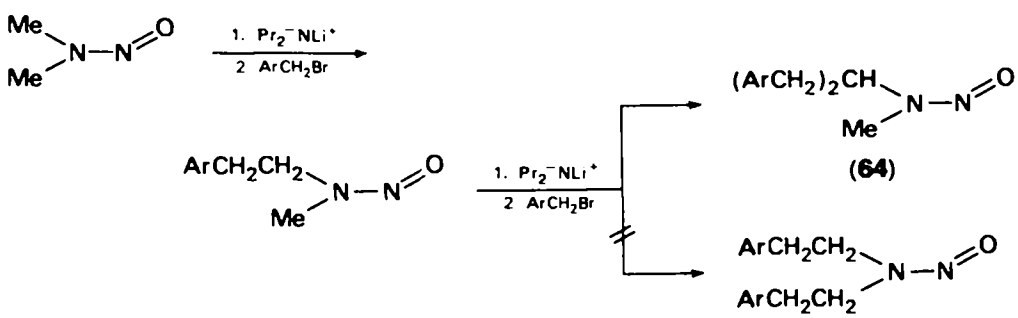
2. Preparation

The most important method for the synthesis of α-substituted *N*-nitrosamines is that of electrophilic substitution of the α-carbanion intermediate, usually generated using lithium diisopropylamide as base. The reactions have been widely reported



SCHEME 24. Preparation of α-substituted *N*-nitrosamines via an α-carbanion.

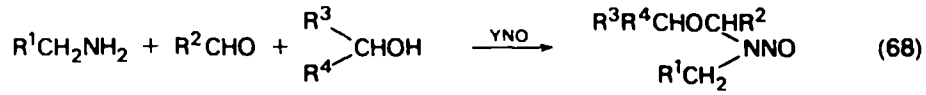
and a compilation of the products and yields obtained under various reaction conditions is given in Beak and Reitz's review[223]. The carbanions readily undergo electrophilic substitutions such as alkylation, hydroxyalkylation, acylation and thioalkylation as outlined in Scheme 24, and recently, reactions with methyl chloroformate[224] and oxygen[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[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 *syn* substitutions (Scheme 25). Subsequently, a preference for *syn–axial* substitutions has been demonstrated with *N*-nitrosopiperidines[226,227]. The carbanion from 4-phenyl-*N*-nitrosopiperidine, for example, gives yields of 76, 79 and 72% on



SCHEME 25. Regioselective alkylation of the α-*syn* carbanion of *N*-nitrosodimethylamine.

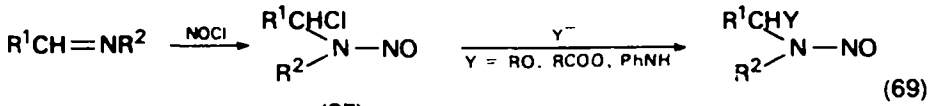
reaction with CO_2, methyl iodide and benzophenone, respectively, and < 1% of the corresponding equatorial products[226].

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 acids[228] or -α-amino aldehydes[229]. 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[230] (equation 68) presumably by way of a Mannich-type condensation. A modification



(68)

of this method employing acetic acid in place of the alcohol gives the α-acetoxy-*N*-nitrosamine[231]. 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-unsaturated derivatives by rearrangement of allylic isomers, elimination of β-tosylates or oxidative elimination of α-phenylselenyl derivatives (e.g. equations 70–72)[233].



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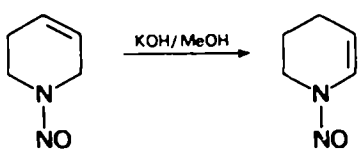

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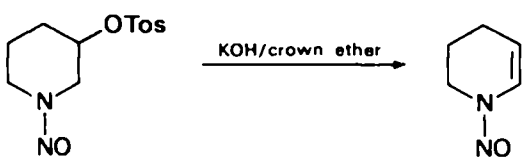

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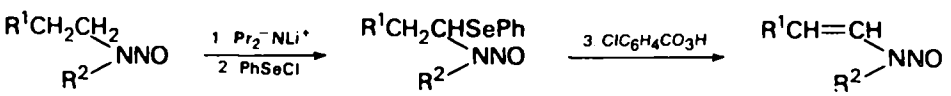
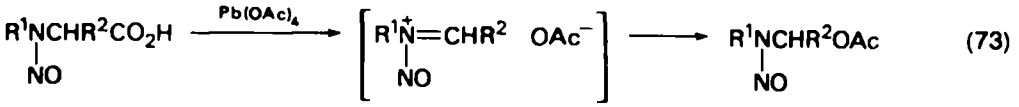


(72)

3. *Reactions*

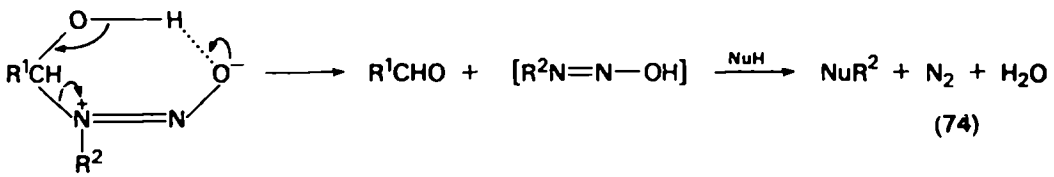
Cyclisation of the α-carboxy and α-cyano derivatives of *N*-nitrosamines to give sydnones and sydnone imines, respectively, has already been mentioned (Section III.D). The α-carboxy derivatives can also be decarboxylated to the parent *N*-nitrosamine by heating either alone or as the sodium salt in solution[234]. On heating the α-carboxy derivatives with lead tetraacetate, the intermediate *N*-nitroso-iminium ion is trapped to give an α-acetoxy derivative (equation 73) in varying



(73)

yield (depending on the structure of the *N*-nitrosamine), along with other products[235].

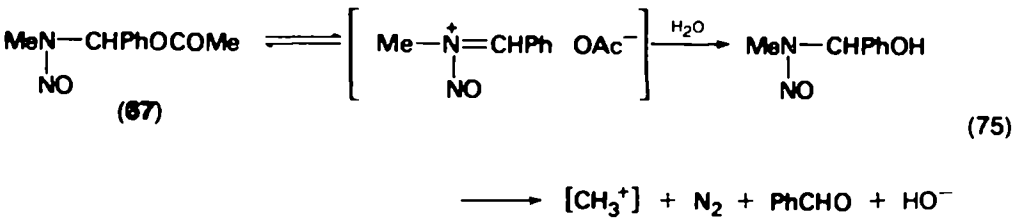
The most widely examined reactions of these compounds concern the production and decomposition of α-hydroxy-*N*-nitrosamines (**66**), the putative metabolites obtained by microsomal activation. These α-hydroxy-*N*-nitrosamines appear to be very unstable and thus far they have been isolated in only one 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 C—N bond fission (equation 74), leading to the generation of an alkylating agent. Useful precursors to the α-hydroxy-*N*-nitrosamines are the α-acetoxy



(74)

(**66**)

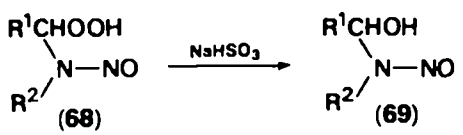
derivatives and studies on their hydrolysis, reaction with amines and conversion to α-hydroperoxy derivatives have all been reported. Hydrolysis with conventional reagents under mild conditions is usually difficult but hog liver esterase has proved efficacious[231,236,237]. The products commonly found are attributable to the formation and decomposition of an α-hydroxy-*N*-nitrosamine. An unusually labile α-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



(**67**)

(75)

stabilizing benzylic function. α-Acetoxy compounds react very readily with *n*-propylamine to give *N*-*n*-propylacetamide in good yields, the facility of the reaction being attributed to the inductive effect of the nitrosamino group[237]. Treatment of the α-acetoxy or α-methoxy compounds with hydrogen peroxide in acetic acid provides the very interesting α-hydroperoxides (**68**)[203]. One of these compounds has been



(**68**) (**69**)

(76)

deoxygenated using sodium bisulphite (equation 76) to give first reported isolation of an α-hydroxy-*N*-nitrosamine (**69**; R^1 = *n*-Pr, R^2 = Me)[203].

IV. BIOLOGICAL PROPERTIES OF *N*-NITROSAMINES

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[145,238–240] and aspects of their teratogenicity[241] and mutagenicity[242] 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[243] and in biological fluids such as blood[244], faeces[245] and urine[246], they can be metabolized by cultured human tissue[247–249] and they are systemic carcinogens, inducing tumours in certain organs regardless of the route of administration[238–240].

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[250] in the 1930s showed that *N*-nitrosodimethylamine induced pronounced liver damage. This finding was later confirmed by Barnes and Magee[251] and is now known to be the main acute biological action of most dialkyl- and heterocyclic *N*-nitrosamines. Subsequently, Magee and Barnes[252], along with many others[145,238–240], 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[145,238–240] 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 symmetrical dialkyl-*N*-nitrosamines are liver carcinogens, whereas unsymmetrical dialkyl and heterocyclic compounds tend to attack the oesophagus and nasal cavity, respectively[145]. Other target organs include the trachea, lung, urinary bladder and kidney[145,238–240].

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[145,238–240]. With male B-D rats, for example, the mean tumorogenic dose for *N*-nitrosodiethylamine is ca. 6×10^{-3} mol/kg body weight whereas that for *N*-nitrosodiethanolamine is ca. 1 mol/kg body weight[145]. Further, carcinogenic action results both from single, relatively large doses[253] and from long-term chronic exposure to lower doses[145,254]. Wishnok and his colleagues[255] have suggested that the potency of *N*-nitrosamines be expressed as $\log(1/D_{50})$ [where D_{50} = 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

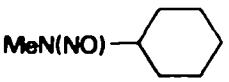
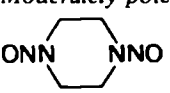
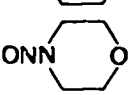
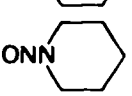
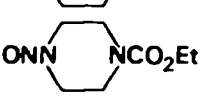
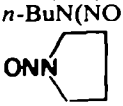
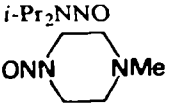
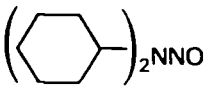
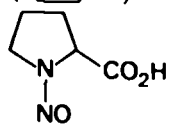
N-Nitrosamine	$\log(1/D_{50})^a$
Highly potent: log (1/D$_{50}$) > 3	
MeN(NO)CH_2CH_2Cl	3.2
Et_2NNO	3.2
MeN(NO)CH_2Ph	3.1
MeN(NO)CH_2CH_2Ph	3.0
Potent: log (1/D$_{50}$) 2.0 to 3.0	
	3.0
MeN(NO)$CH{=}CH_2$	2.9
EtN(NO)$CH{=}CH_2$	2.6
MeN(NO)C_5H_{11}-*n*	2.6
MeN(NO)Et	2.3
Me_2NNO	2.3
MeN(NO)CH_2CN	2.2
EtN(NO)Bu-*n*	2.1
MeN(NO)$CH_2CH{=}CH_2$	2.1
n-Pr_2NNO	2.05
Moderately potent: log (1/D$_{50}$) 1.0 to 2.0	
	1.95
	1.95
	1.9
	1.9
n-Bu_2NNO	1.6
MeN(NO)Ph	1.6
MeN(NO)C_7H_{15}-*n*	1.5
EtN(NO)Pr-*i*	1.5
n-BuN(NO)$(CH_2)_4OH$	1.5
	1.4
n-BuN(NO)C_5H_{11}-*n*	1.0
Weakly potent: log (1/D$_{50}$) < 1	
i-Pr_2NNO	1.0
	0.95
$(AcOCH_2CH_2)_2NNO$	0.7
$(n\text{-}C_5H_{11})_2NNO$	0.6

TABLE 5. (*continued*)

N-Nitrosamine	$\log(1/D_{50})^a$
$EtN(NO)CH_2CH_2OH$	0.2
$(HOCH_2CH_2)_2NNO$	0.05
Probably noncarcinogenic	
Ph_2NNO	—
$(PhCH_2)_2NNO$	—
	—
	—
$(HO_2CCH_2)_2NNO$	—

$^aD_{50}$ = mean total carcinogenic dose, expressed in mol/kg body weight, for production of tumours in 50% of the test animals.

cyclic *N*-nitrosamines[256,257] and highly substituted dialkyl or aromatic compounds without hydrogen on the α-carbon atom (e.g. *t*-Bu_2NNO, Ph_2NNO) are non-carcinogenic[145]. Nonetheless, these compounds should be handled with considerable care because transnitrosation *in vivo* may generate other, carcinogenic *N*-nitrosamines[81]. Substituents β to the nitrosamino group, irrespective of their electronic properties, generally increase the potency of heterocyclic *N*-nitrosamines[257,258]. With one or two exceptions, there is no simple explanation for the α- and β-substituent effects. Several investigations, however, have shown that α-deuteriated *N*-nitrosamines are less carcinogenic than regular analogues[259,260] and this difference has been regarded as evidence that α-hydrogen abstraction is kinetically important in the metabolic activation of *N*-nitrosamines. In an interesting extension of this work, Lijinsky and Reuber[261] have shown that the deuteriated metabolite, itself, is a more potent carcinogen.

Attempts have been made recently to develop structure–activity relationships for *N*-nitrosamines[262]. Wishnok and his colleagues[255] find that the carcinogenic potency of acyclic compounds correlates reasonably well with a linear combination of their hexane–water partition coefficients and Taft (σ^*) substituent parameters. The significance of the correlation coefficients for each term, however, is far from clear. Earlier, Wishnok and Archer[263] demonstrated that the carcinogenic potency of acyclic *N*-nitrosamines is inversely related to the number of carbon atoms, but Lijinsky[264] 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 gestation[241,265,266]. 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 micro-organisms (bacteria) and in some higher systems such as insects. For bacterial tests

in vitro (e.g. Ames test), enzymatic activation by pretreatment with liver homogenates or microsomal fractions is necessary and even then some *N*-nitrosamines give a weak response[267–269]. Both the results and limitations of these tests have been reviewed[270,271], and recent studies show that it is advantageous to activate *N*-nitrosamines with liver extracts from hamsters rather than rats[272]. Bacterial tests using whole animals as the activating agent ('host-mediated assay') have also been described[273] and those based on intrahepatic procedures appear to be particularly sensitive[274,275]. *N*-Nitrosamines also produce mutations in the insect Drosophila[276], where the enzyme-mediated reactions necessary for their biological activation presumably occur. Certain *N*-nitrosamines bearing labile α-substituents, particularly the α-acetoxy compounds, are mutagenic *in vitro* without microsomal activation[277]. This supports the hypothesis, discussed further in Section IV.C, that the biologically active metabolite is an α-hydroxy derivative.

Correlation between carcinogenic and mutagenic action has been critically assessed, but for simple *N*-nitrosamines no systematic relationship is apparent[269,271,278,279]. It has been shown, however, that bacterial mutagenesis is subject to an α-deuterium isotope effect similar to that observed for carcinogenesis[280,281].

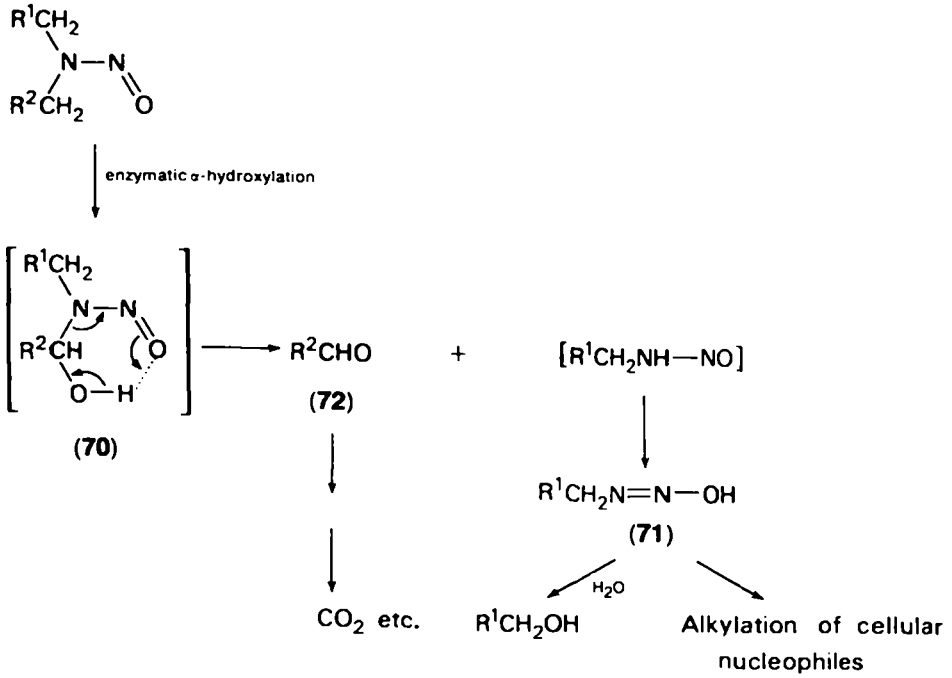
C. Metabolism

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[282,283].

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 evenly[238,284], whereas complete metabolism to $^{14}CO_2$ usually takes several hours or even days depending on the compound's structure[238,285]. Further, the labelled *N*-nitrosamines or their metabolites persist in organs susceptible to tumour formation[286,287].

Early work by Magee and Vandekar[288] 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[247], colon[248] and oesophagus[249], 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[289,290].

Although neither the enzyme system nor the mechanism of activation of *N*-nitrosamines has been explicitly defined, much evidence points to an oxidative dealkylation[145,238] (Scheme 26) mediated by a cytochrome P-450 dependent mixed-function oxidase[291,292]. Gangolli and his colleagues[293,294], 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[295] and Kroege-Koepke and Michejda[296] demonstrate that *N*-nitrosodimethylamine is demethylated

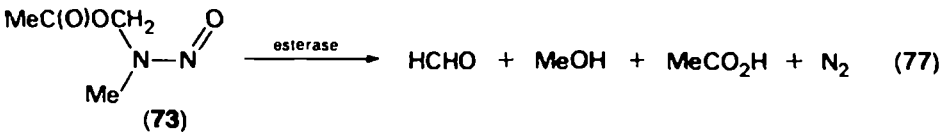


SCHEME 26. Proposed pathway for the metabolic decomposition of *N*-nitrosamines.

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[297] 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[298]. 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 (**70**) decomposes by spontaneous C—N bond cleavage to yield the reactive diazohydroxide metabolite (**71**) 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 CO_2[242,299]. A substantial body of evidence has accumulated in support of this pathway, particularly for *N*-nitrosodimethylamine. Thus HCHO[300], MeOH[301–302] and high (ca. 70%) yields of nitrogen[303] (contrary to earlier reports)[304] 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[305] 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*[239] and an intact CD_3 group is transferred to guanine bases of hepatic nucleic acids following the administration of hexadeuterio-*N*-nitrosodimethylamine to rats[306]. Further indirect support for Scheme 26 comes from

observations that the α-acetoxy derivative **73** hydrolyses to a mixture of HCHO, MeOH, $MeCO_2H$ and nitrogen[231] (equation 77), is mutagenic towards bacteria

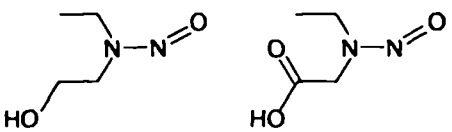


(73) (77)

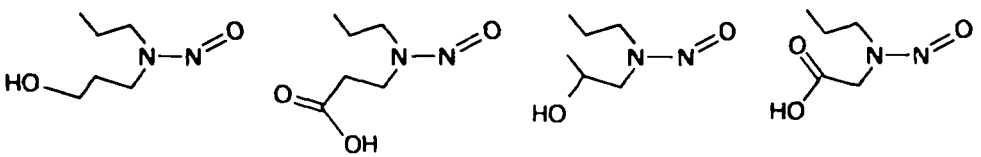
without metabolic activation[307,308], and is both a DNA-methylating agent[309] and a carcinogen in the rat[308,310], with a different organ specificity from *N*-nitrosodimethylamine itself[310].

TABLE 6. Urinary metabolites from the administration of symmetrical *N*-nitrosodialkylamines to rats

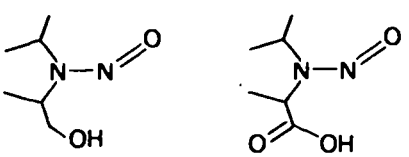
From Et_2NNO



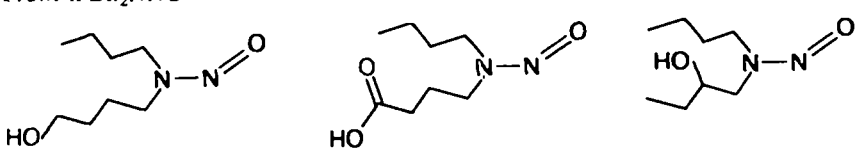
From n-Pr_2NNO



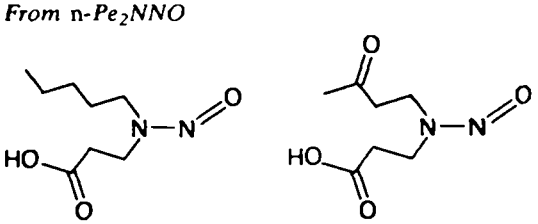
From i-Pr_2NNO



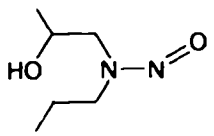
From n-Bu_2NNO



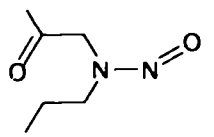
From n-Pe_2NNO



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]



(**74**)

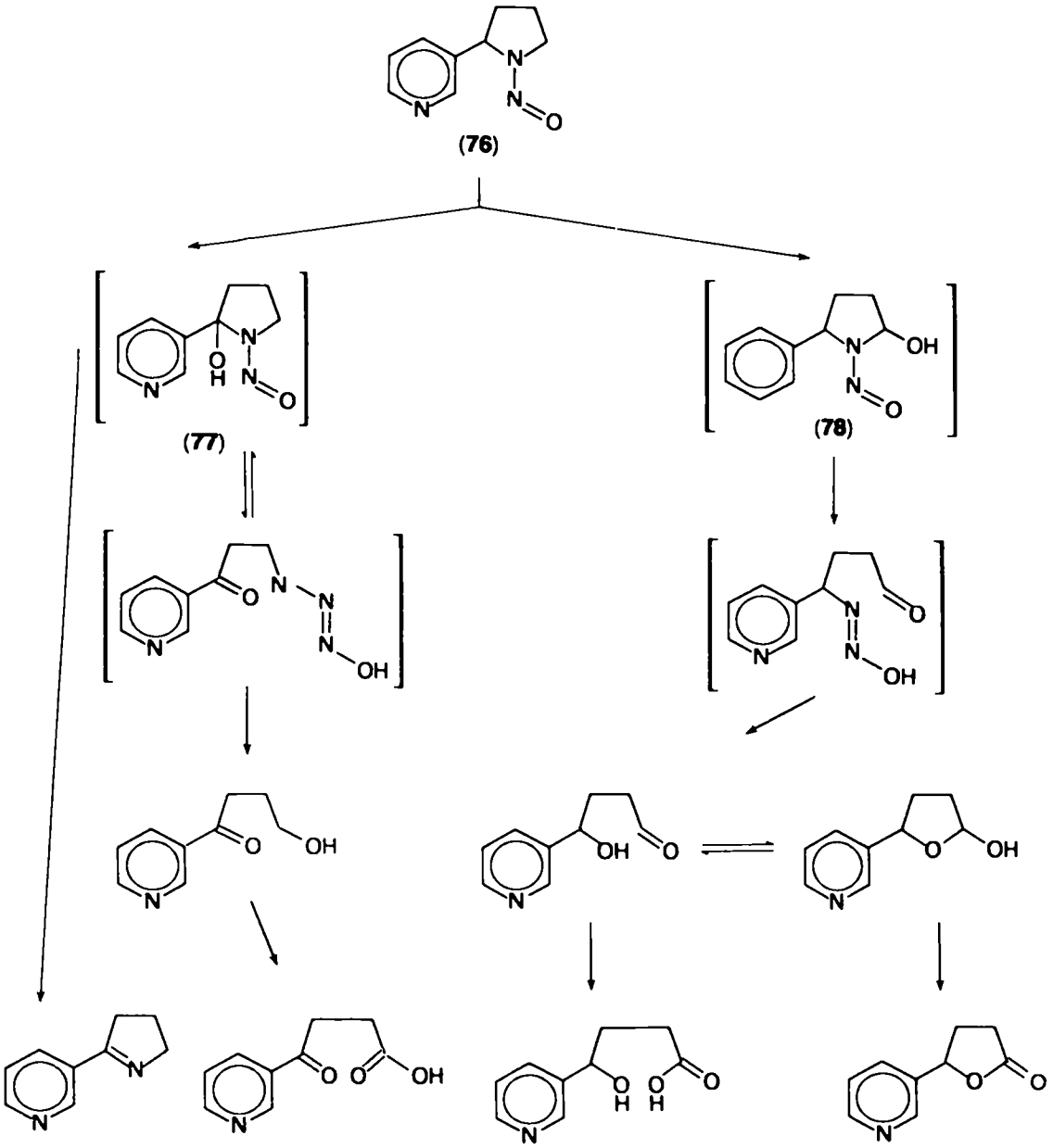


(**75**)

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 β-oxidation to an *N*-nitrosomethylalkylamine, which acts as the methylating agent after activation by the established α-oxidative process (Scheme 26). Other, more recent, work[316,317] lends support to this hypothesis.

Enzymatic hydroxylation at either the α- or β-carbon atom is also observed for several heterocyclic compounds. The most complete evidence for α-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**) ε-caprolactam (**80**) and ε-aminocaproic acid (**81**) from *N*-nitrosohexamethyleneimine[323,324] (Scheme 28). Krüger and Bertram[325], however, have shown that *N*-nitroso-3-hydroxypyrrolidine (i.e. β-oxidation product) is a urinary metabolite of *N*-nitrosopyrrolidine administered to rats. Other examples of *in vivo* β-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*-nitrosodiethanolamine (**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].

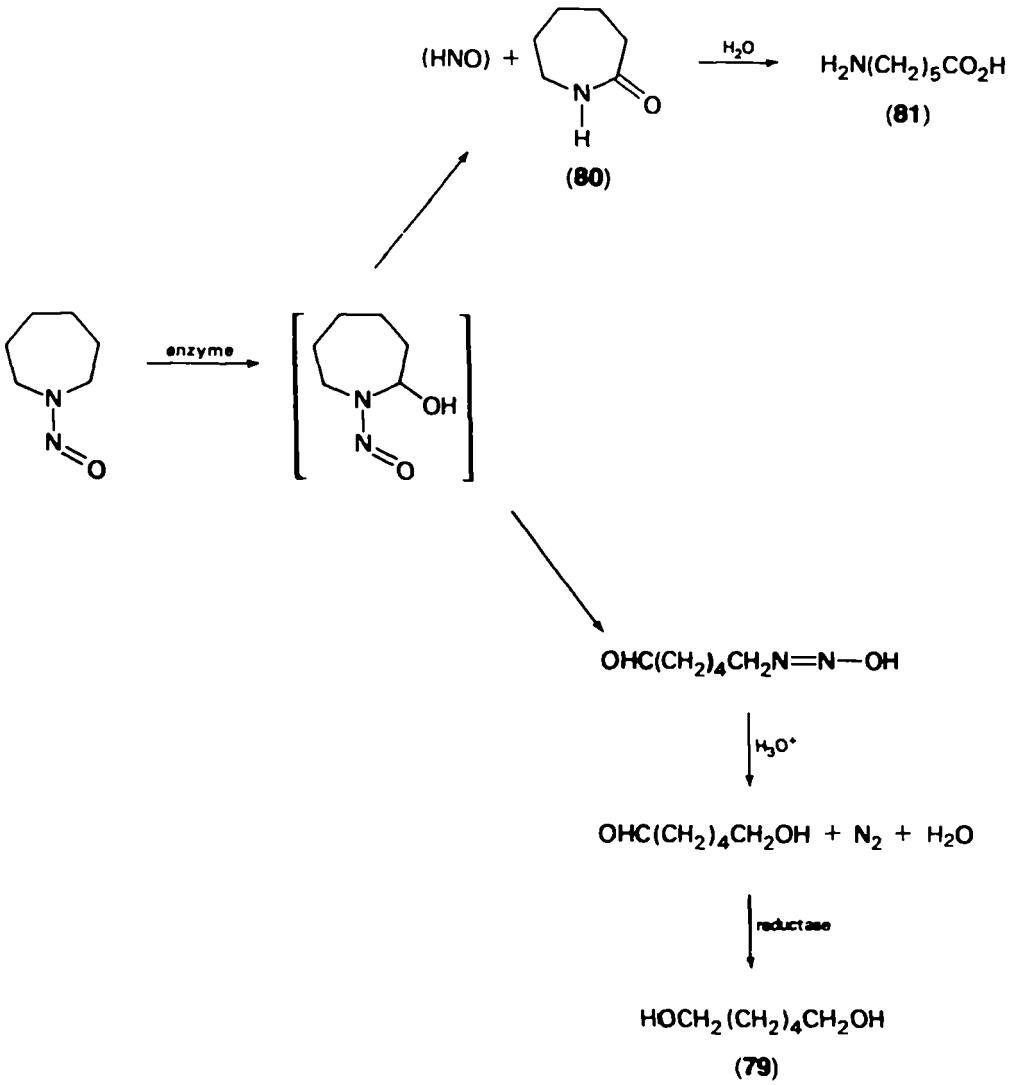
There has been considerable speculation about the structure of the metabolic alkylating agent (so-called 'ultimate carcinogen') that interacts with cellular constituents. Recent work, however, points towards the diazohydroxide (**71**) rather



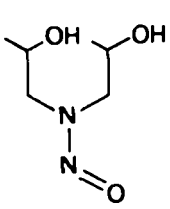
SCHEME 27. Pathways for product formation in the metabolic degradation of *N*-nitrosonornicotine.

N-nitrosonornicotine.

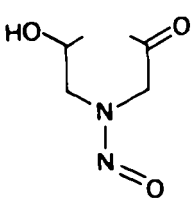
than the diazoalkane (**85**) or the unstable carbocation (**86**) (equation 78). The diazoalkane is firmly discounted by observations that both CD_3 and C_2D_5 substituents transfer intact to the guanine bases of nucleic acids when $(CD_3)_2NNO$[306] and $(C_2D_5)_2NNO$[330] are incubated with rat-liver slices. *A priori*, reaction via the carbo-



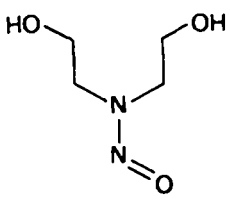
SCHEME 28. Proposed pathways involving α-hydroxylation for the metabolism of *N*-nitrosohexamethyleneimine in rats.



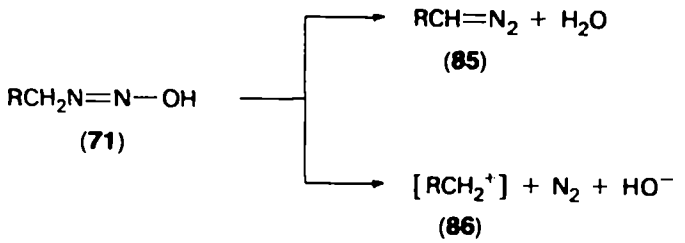
(82)



(83)



(84)



(78)

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[331], but products bearing the rearranged alkyl group are obtained when the same reaction is carried out with liver microsomes *in vitro*[332]. The origin of this difference requires clarification. Affirmative evidence in favour of the diazohydroxide metabolite is that hydrolyses of chiral **87** and **88** proceed with similar

(87) **(88)**

stereochemical consequences for the 1-phenylethanol product[333]. Further, the observation that **88** but not **87** inhibits the hog-liver esterase used in their hydrolysis leads Gold and Linder[333] to conclude that α-hydroxy-*N*-nitrosamines may be transportable metabolites of *N*-nitrosodialkylamines.

D. Interactions with Cellular Constituents

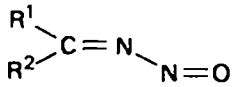
The idea that *N*-nitrosamines exert their adverse biological properties via the alkylation of cellular constituents is widely accepted and evidence for it has been critically reviewed[239,283]. Attention has focused on the interaction with DNA because it is considered to be the critical cellular target for the induction of tumours[239,282]. It has also been shown, however, that *N*-nitrosamines alkylate the nuclear proteins of rat liver and kidney. Administration of [^{14}C-1]-labelled *N*-nitrosodimethylamine, for example, produces labelled *S*-methylcysteine, 1-methylhistidine, 3-methylhistidine and ε-*N*-methyllysine in the liver histones[334].

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}C-1]- *N*-nitrosodimethylamine to rats[283]. Most alkylation seems to occur at the N-7 position of DNA guanine, but recent studies, summarized in an excellent review by Pegg[335], 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[336,337], which varies in activity from tissue to tissue and is lowest in organs most susceptible to tumour formation[335]. There is also evidence to suggest that this enzyme system can be both inhibited by exposure to large doses of *N*-nitrosodimethylamine[336,338] and stimulated by continuous exposure to low doses[339].

V. *N*-NITROSOIMINES

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*-nitrosoaldimines (**89**; R^1 = alkyl, R^2 = H) are known, and



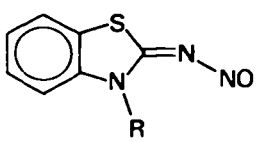
(**89**)

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

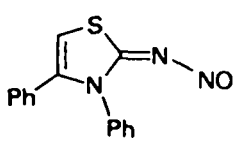
N-Nitrosoketimines are usually prepared by nitrosation using regular reagents such as acidified sodium nitrite or gaseous NOCl of either the parent ketimine or an organometallic derivative.

The most stable *N*-nitrosoketimines (e.g. **90–93**), derived from imino-substituted

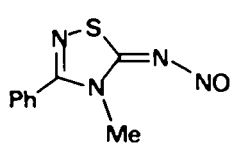


(**90**)

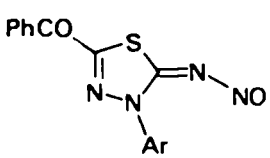
R = Me, Et, Ph



(**91**)

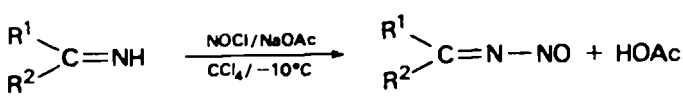


(**92**)



(**93**)

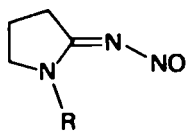
dihydrothiazoles and the corresponding thiadiazoles, are conveniently prepared by direct nitrosation of the substrate with aqueous sodium nitrite in glacial acetic acid[340–342]. For less stable *N*-nitrosoimines, the use of either gaseous nitrosyl chloride plus a base such as triethylamine or sodium acetate in an inert solvent at ca. −20°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 α-nitrogen



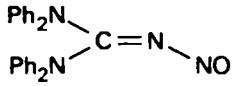
(79)

R^1 = aryl
R^2 = aryl, *i*-Pr, *t*-Bu

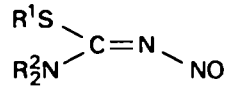
atoms. For example, 2-iminopyrrolidines give *N*-nitroso derivatives (**94**) in the presence of triethylamine[344] and 1,1,3,3-tetrasubstituted guanidines give *N*-nitroso derivatives such as **95** in the presence of sodium acetate[345]. The related *S*-alkylthioureas can be converted to *N*-nitroso derivatives (**96**) (which decompose spontaneously) by isopentyl nitrite[346].



(**94**)



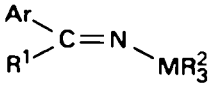
(**95**)



(**96**)

R = 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.



(**97**)

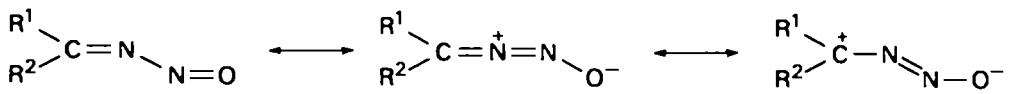
R^1 = alkyl, aryl

R^2 = Me, Et, Ph

M = Si, Sn, Pb

B. Properties

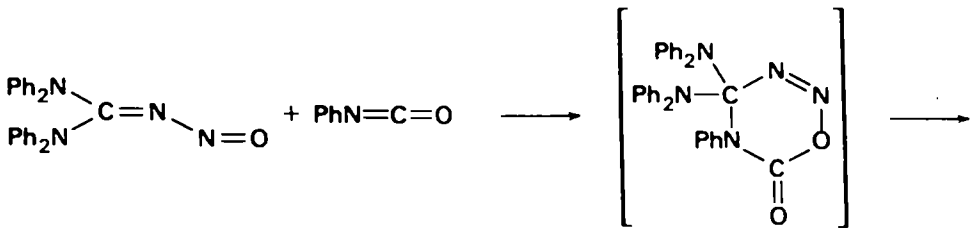
N-Nitrosoketimines are highly coloured oils or crystals of red, orange and purple hue. Major contributing resonance structures are **98**, the 1,3-dipolar ion **99** and the 1,4-dipolar ion **100**. The 1,4-dipolar ion is thought to be more important than **99**



(**98**) (**99**) (**100**)

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}



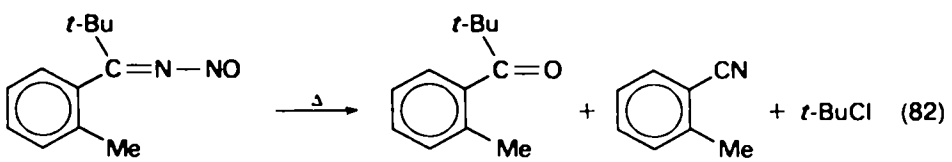
$$Ph_2N(Ph_2N)C{=}N{-}N{=}O + PhN{=}C{=}O \longrightarrow \left[\begin{array}{c} Ph_2N \\ Ph_2N{-}C \\ PhN \end{array}\!\!\begin{array}{c} N \\ \| \\ N \\ O \\ C \\ \| \\ O \end{array}\right] \longrightarrow Ph_2N(Ph_2N)C{=}NPh + N_2 + CO_2 \quad (80)$$

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 ε ca. 4) and 423–454 nm (log ε 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

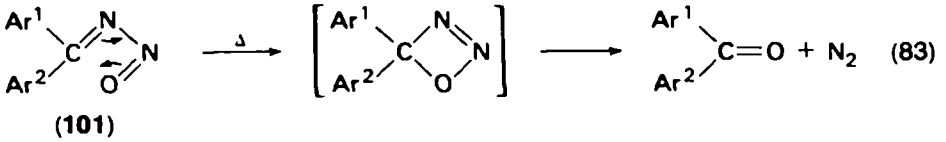
$$R^1(R^2)C{=}N{-}NO \xrightarrow{\Delta} R^1(R^2)C{=}O + N_2 \quad (81)$$



$$t\text{-Bu}(Me)C_6H_3C{=}N{-}NO \xrightarrow{\Delta} t\text{-Bu}(Me)C_6H_3C{=}O + NC(Me)C_6H_3 + t\text{-BuCl} \quad (82)$$

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-$NO_2C_6H_4$) and is decreased by electron-donating 4-substituted phenyl groups. Stabilities range from 6–8 weeks at room temperature (**89**; R^1 = *t*-Bu, R^2 = 2-MeC_6H_4) to a few minutes at −10°C (**89**; R^1 = 4-$MeOC_6H_4$, R^2 = 2-$MeOC_6H_4$)[343]. *N*-Nitrosoimines bearing heteroatoms (N or S) adjacent to the imino carbon atom are also labile (e.g. **94**, R = C_6H_{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*-



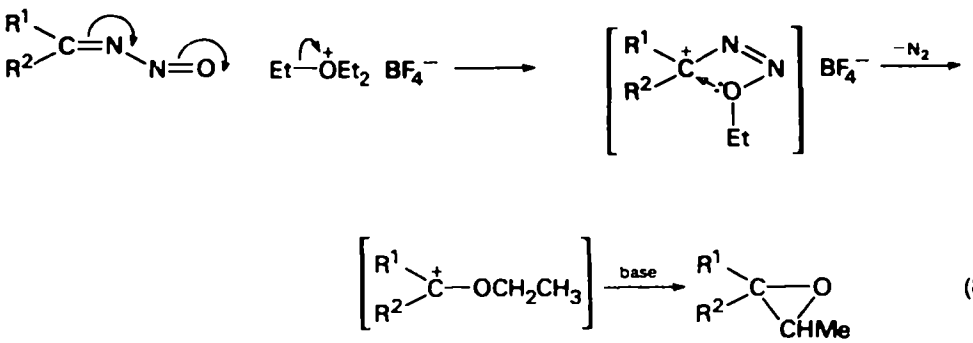
(101)

(83)

Ar^1 = 4-MeC_6H_4

Ar^2 = 2-MeC_6H_4

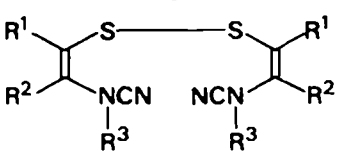
nitrosoketimines, the only other reaction studied thus far is that with triethyloxonium tetrafluoroborate to give substituted propylene oxide and nitrogen[343]. A plausible mechanism, outlined in equation (84), involves initial alkylation of the



(84)

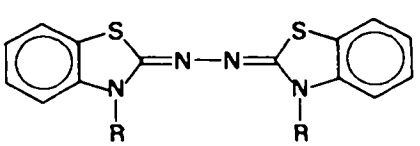
nucleophilic nitroso oxygen atom followed sequentially by intramolecular rearrangement with elimination of nitrogen and then loss of H^+ to give the propylene oxide.

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[348]. For example, photolysis of **90** or **91** produces the disulphide **102** and nitric

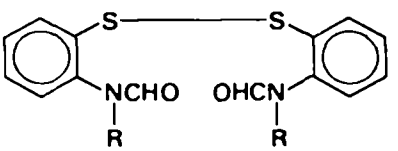


(102)

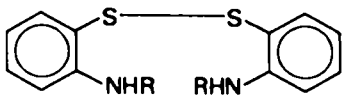
oxide[340,342], implying homolysis of the N—N(O) bond (as in photolysis of *N*-nitrosamines, Section III.H), followed by radical rearrangement and recombination. Treatment of **90** with nucleophilic reagents such as lithium aluminium hydride[349], organolithium[350] and Grignard reagents[351–353], however, 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**[349], possibly through initial attack by hydride ion at both the imino carbon atom and the nitroso nitrogen atom. With organometallic



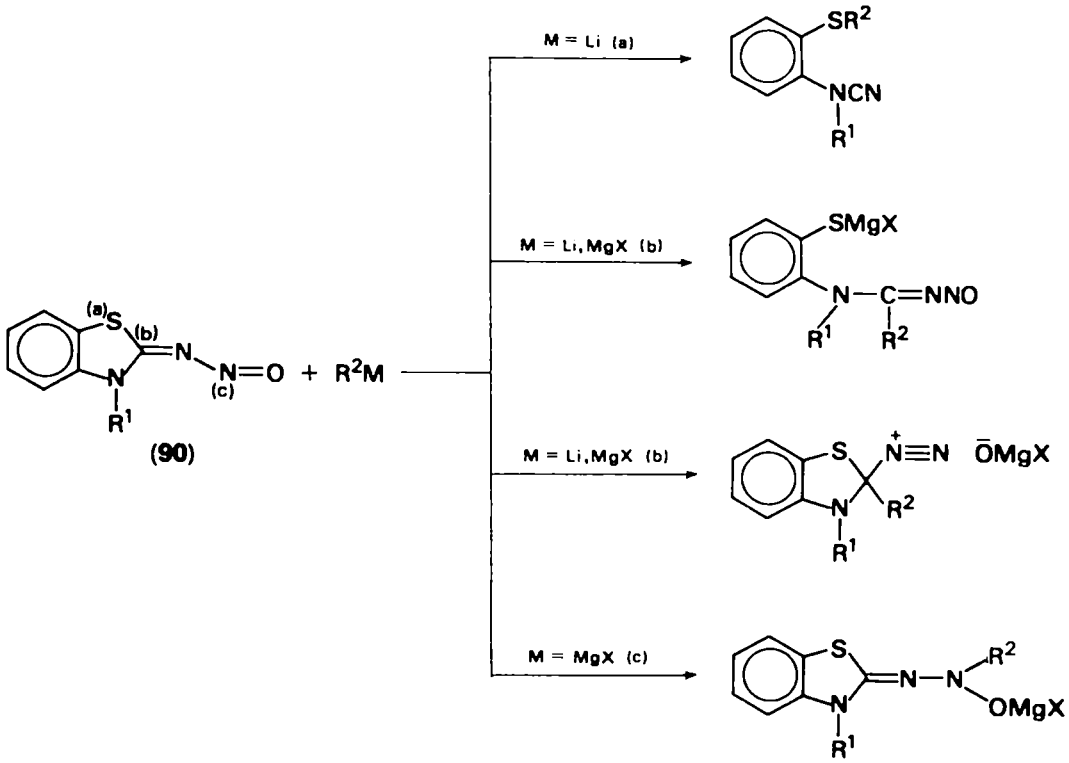
(103)



(104)



(105)



(90)

SCHEME 29. Probable intermediates from the reaction of **90** with organometallic reagents.

reagents, a multitude of products is obtained from **90** but Inamoto and his colleagues[348,354] 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[348], but reasons for the high specificity of the different nucleophilic reagents need confirmation.

VI. ACKNOWLEDGEMENTS

It is a great pleasure to acknowledge the imaginative hard work of many former colleagues and the helpful suggestions of many friends that have stimulated our interest in chemistry of *N*-nitrosamines. Also, we thank the Cancer Research Campaign, the Science Research Council, the Ministry of Agriculture, Fisheries and

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **27**

The role of Meisenheimer or σ-complexes in nitroarene–base interactions

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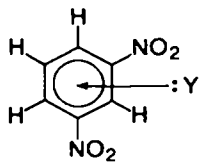
I. INTRODUCTION AND SCOPE

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 α-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.



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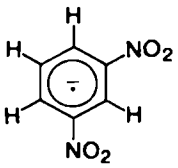

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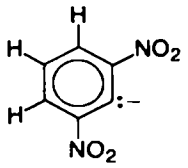

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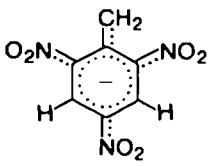

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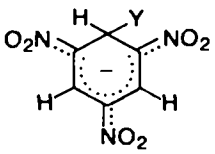


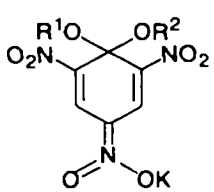
(5)

Donor–acceptor complexes will not be considered in the present account. A monograph[1] published in 1970 was devoted largely to that topic and such species are also featured in a recent edited work[2]. 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[3]. 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 σ-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[4–7]. However, definitive formulations were made independently and almost concurrently by Jackson[8,9] and by Meisenheimer[10], 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



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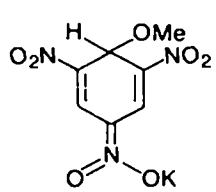


(7)

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 σ-complexes, or simply σ-complexes, which is the terminology adopted in this account.

σ-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 σ-complexes appeared[11]. Over the next five years no less than seven other reviews were published dealing wholly or partly with this topic[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 σ-complexes, and the methods currently used for their investigation, we shall describe some of the important σ-complexes that have been synthesized during the past decade. This will be followed by consideration of nitroarene–base systems where σ-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 σ-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[19,20] essentially confirmed the formulation of Jackson[9] and Meisenheimer[10], when written in current form (i.e. $=NO_2^-$ 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 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[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[21].

The ^{1}H-NMR spectra of typical σ-complexes generally provide definitive evidence of their structure. This can be illustrated for the case of the methoxide adduct of TNB as follows[22,23] [chemical shifts are given in ppm relative to tetramethylsilane for a solution of TNB·OMe^- K^+ in $(CD_3)_2SO$]. The C-3,5 protons appear as a doublet at δ 8.48 (J = 1 Hz), the C-1 proton appears at δ 6.17 as a triplet (J = 1 Hz), and the methoxyl protons appear as a singlet at δ 3.22. In comparison with TNB which displays a single resonance at δ 9.20, the moderate upfield shift of the sp^2 hydrogens in the TNB·OMe^- complex is in accord

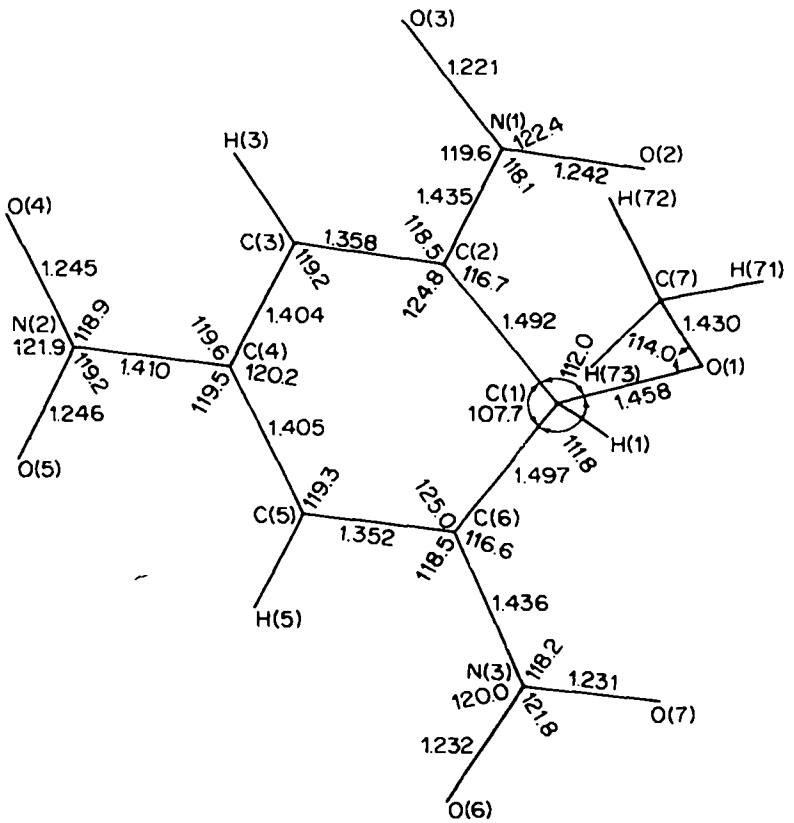
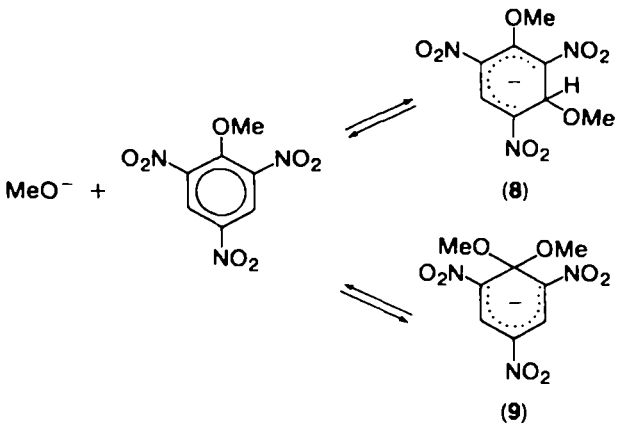


FIGURE 1. Bond distances and angles involving heavy atoms for the 1,3,5-trinitrobenzene–potassium methoxide σ-complex. Reproduced by permission of the International Union of Crystallography from R. Destro, C. M. Gramaccioli and M. Simonetta, *Acta Cryst.*, **B35**, 733 (1979).

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 sp^2 to sp^3, 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[24]. 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[25–30], though some exceptions have been noted[31,32].

^{13}C-NMR spectroscopy has been applied recently to the study of σ-complexes[33,34], and ^{3}H-NMR as well[35]. An important development is the application of flow NMR spectroscopy to nitroarene–base interactions[36], as this method yields structural information in chemically reacting systems. Use of this method is described in Section III.A.



SCHEME 1

Electron absorption spectroscopy has been used extremely widely in the investigation of σ-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 (ϵ_1 = 31,200, ϵ_2 = 21,000 l mol^{-1} 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 σ-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 σ-complexes. Equilibrium constants for σ-complex formation typically show very large increases in such media[40]. For example, in formation of the TNB·OH⁻ σ-complex, K_{eq} increases from 3 l mol^{-1} in pure water to ca. 10^4 l mol^{-1} in 70 vol % DMF[40b]. Similarly, for the TNB·OMe⁻ σ-complex, K_{eq} increases from 15 l mol^{-1} in methanol to 10^4 l mol^{-1} in 40 vol % DMSO[41]. It has been shown that increasing the dipolar aprotic component increases primarily the rate of the forward, σ-complex formation process, while the rate of the reverse,

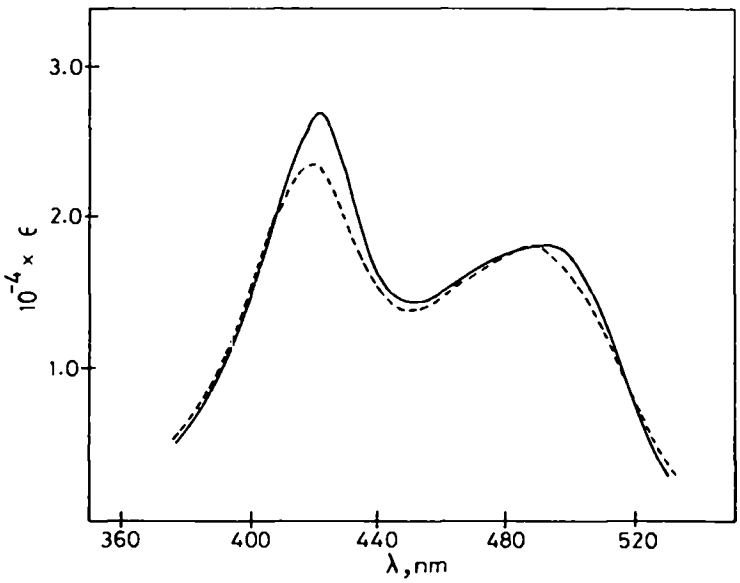


FIGURE 2. Absorption spectra of 2,4,6-trinitroanisole–methoxide ion σ-complexes in 96% DMSO–4% methanol; —— 1,1-complex, ---- 1,3-complex. Reprinted with permission from C. F. Bernasconi and M. C. Muller, *J. Amer. Chem. Soc.*, **100**, 5530 (1978). Copyright by the American Chemical Society.

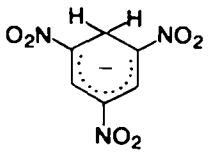
σ-complex decomposition process, is relatively unaffected[38,39b]. These medium effects can be attributed largely to desolvation of the anionic reagent in the dipolar aprotic media, though stabilization of the σ-complex relative to the parent nitroarene may also be a contributing factor[38–42].

C. Hydride Ion Adducts

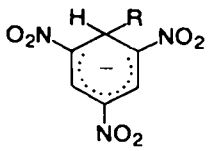
In 1970, Taylor described the preparation of the prototype anionic σ-complex of TNB, namely the product of hydride ion addition to the ring, **10**[43a]. This complex was readily obtained, as the tetramethylammonium salt, on addition of TNB to a stirred dispersion of Me_4N^+ BH_4^- in MeCN. The purple product (m.p. 131–132°C) has a typical UV–visible spectrum – λ_{max} 478 nm (ϵ 3.1×10^4 l mol^{-1} cm^{-1}) and 585 nm (ϵ 1.5×10^4 l mol^{-1} cm^{-1}), in MeCN. The NMR spectrum consists of two triplets, the C-3,5 protons appearing at δ 8.26 ($J \sim 0.5$ Hz) and the C-1 protons at δ 3.88 ($J \sim 0.5$ Hz). Complex **10** was also obtained by H^- transfer to TNB from 1-propyl-1,4-dehydronicotinamide[44] as well as from dehydro derivatives of other nitrogen heterocycles[45].

It is interesting that the decomposition of complex **10** is accelerated by a factor of ca. 10^4 by bovine serum albumin (BSA) in the pH range 7–10[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[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



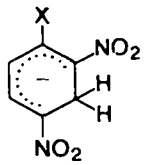
(10)



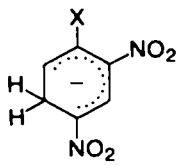
(11)

tetralkylboron salts were used in the reaction with TNB[43b]. 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 $NaBH_4$ in DMSO medium[48]. 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.



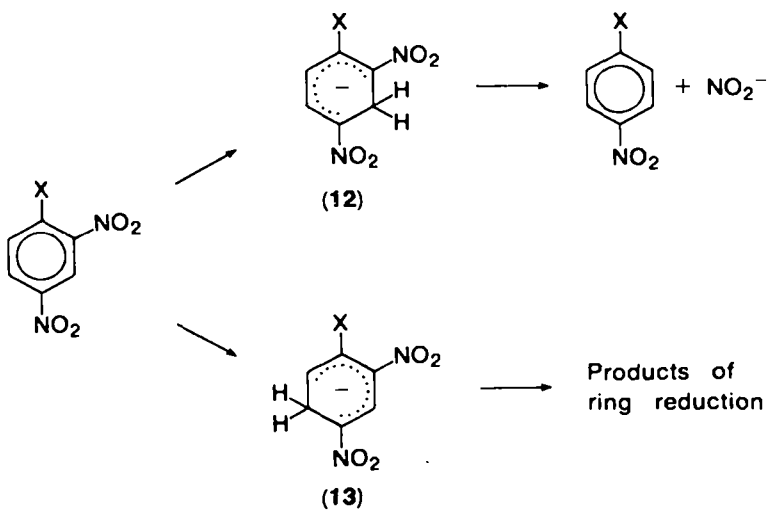
(12)



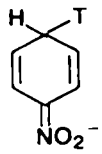
(13)

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 NO_2^- by H^- in the anionic species **12**. This pathway was confirmed by various hydrogen isotope labelling experiments[48].

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



SCHEME 2



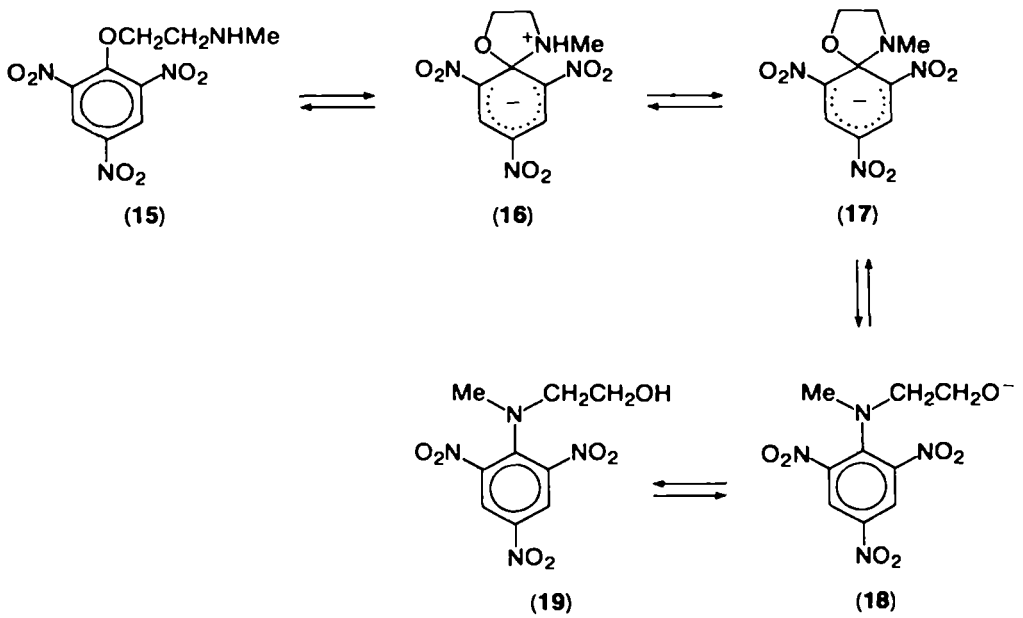
(14)

between nitrobenzene and tritium-labelled sodium borohydride in DMSO solution[49].

D. Spiro Complexes

There has been a gread 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[50–52].

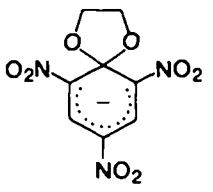
An example of an in-depth study is illustrated in Scheme 3 which depicts the rearrangement of *N*-methyl-β-aminoethyl picryl ether (**15**) into *N*-methyl-*N*-β-hydroxyethylpicramide (**19**) through the action of base. The overall conversion



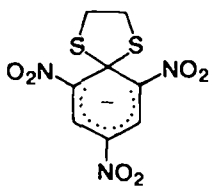
SCHEME 3

15 → **19** is rapid, requiring study by a combined stopped-flow temperature-jump method; this has shown that the reaction occurs in two stages[53]. 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[54–60], giving considerable insight into mechanisms of spiro complex formation and decomposition as well as into S_NAr processes in general (see below).

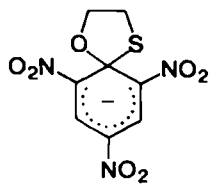
Spiro complexes of various structural types have been characterized by spectroscopic techniques including NMR, having been prepared either as stable compounds or *in situ* by the action of base on the appropriate open-chain derivative. A partial listing of such spiro complexes is given below together with the appropriate references.



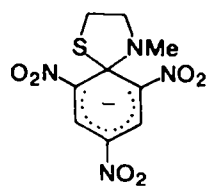
(**20**)[61–63]



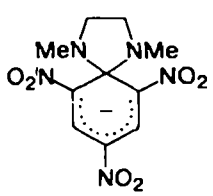
(**21**)[64,65]



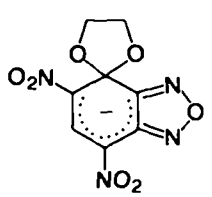
(**22**)[66]



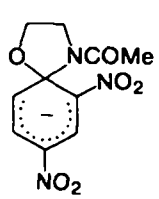
(**23**)[67]



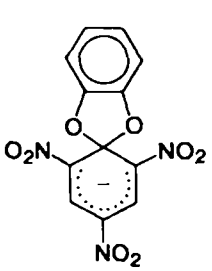
(**24**)[54,68]



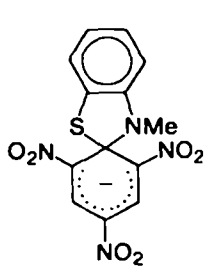
(**25**)[60]



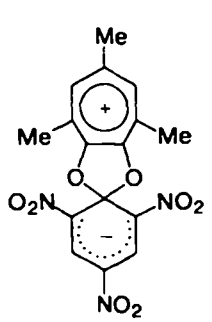
(**26**)[59]



(**27**)[66]



(**28**)[66]

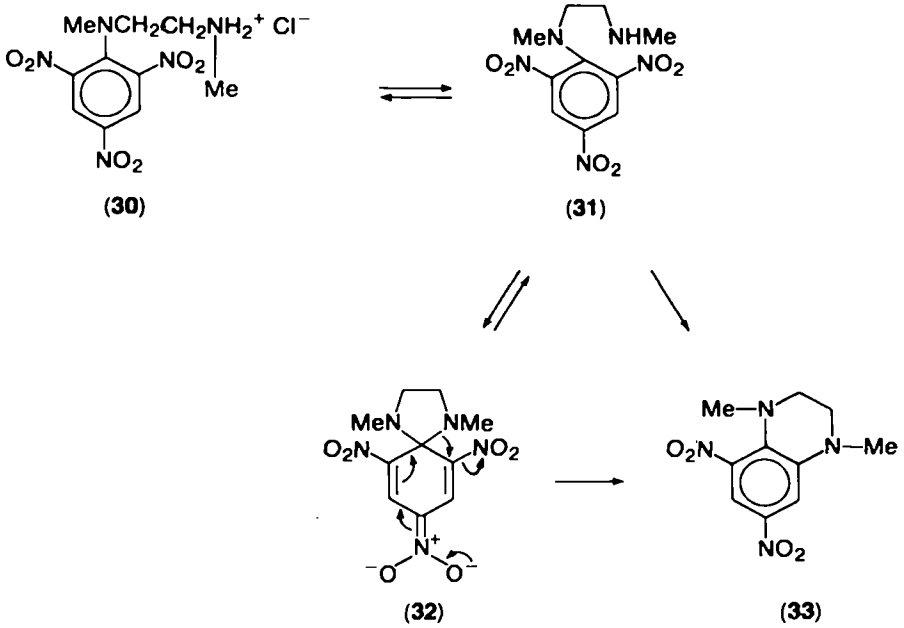


(**29**)[69]

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[70].

Competitive processes involving spiro complex formation, and concurrent intramolecular displacement of a nitro group, have been observed in several cases[64–68]. For example, in the reaction of *N,N'*-dimethyl-*N*-picrylethylenediamine hydrochloride (**30**) with Et_3N, there is rapid conversion to spiro complex **32**, followed by slow formation of **33**, the product of intramolecular NO_2 displacement[68]. Some possible mechanisms are given in Scheme 4. Displacement of NO_2 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 NO_2^- by H^- found in hydride σ-complexes[48] (see above).

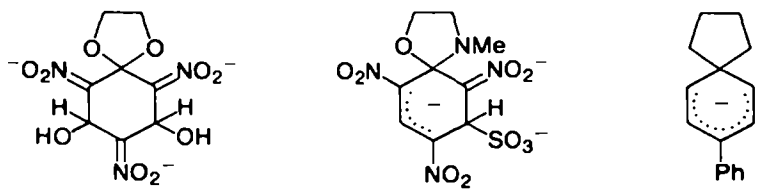
Reaction of spiro complexes with nucleophiles has been reported in a few cases, yielding adducts such as **34**[70b] and **35**[71]. The prototype spiro complex **36** containing



(30) (31) (32) (33)

SCHEME 4

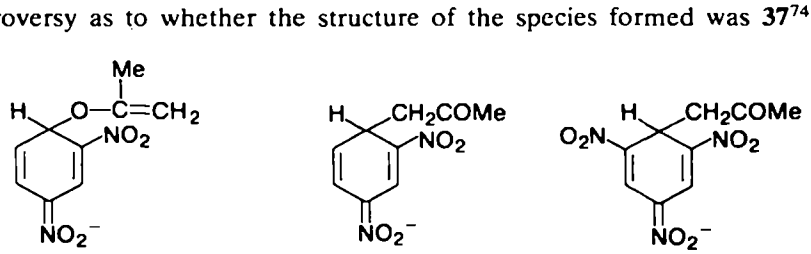
no NO_2 groups to stabilize negative charge has been prepared by reaction of 4-(4-chlorobutyl)biphenyl with lithium at $-70°C$[72].



(34) (35) (36)

E. Ambident Nucleophiles in σ-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[73]. After a period of controversy as to whether the structure of the species formed was **37**[74] or **38**[75],

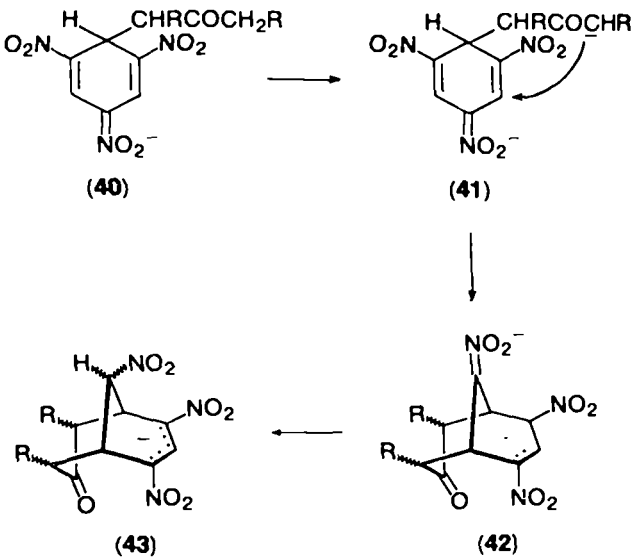


(37) (38) (39)

the latter was proved unambiguously by NMR[76]. 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 **39**[77].

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[78].

Acetonate adducts such as **39**, and the analogues **40** (R = Me, Ph, CO_2Me etc.), have been found to undergo very interesting and useful cyclization processes in basic media[78–84]. 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**.

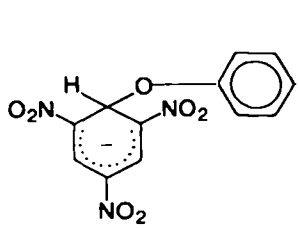


SCHEME 5

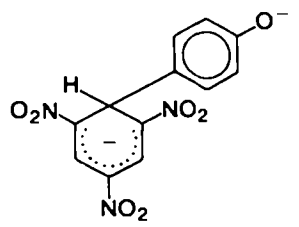
A variety of bicyclic and tricyclic products (the latter formed via a second internal nucleophilic addition) have been obtained in this manner, affording a number of products of biological significance, e.g. potential narcotic antagonists[84–86]. In no instance was cyclization found to occur via the enolate oxygen.

The reaction of phenoxide ion with picryl chloride has been the normal method of preparing phenyl picryl ether[87]. In accord with nucleophilic attack by phenoxy oxygen, Shein and Byval'kevich reported[88] that PhOK reacts with TNB in DMSO solution to yield the complex **44**. However, Buncel and Webb found[89] 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[90] 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

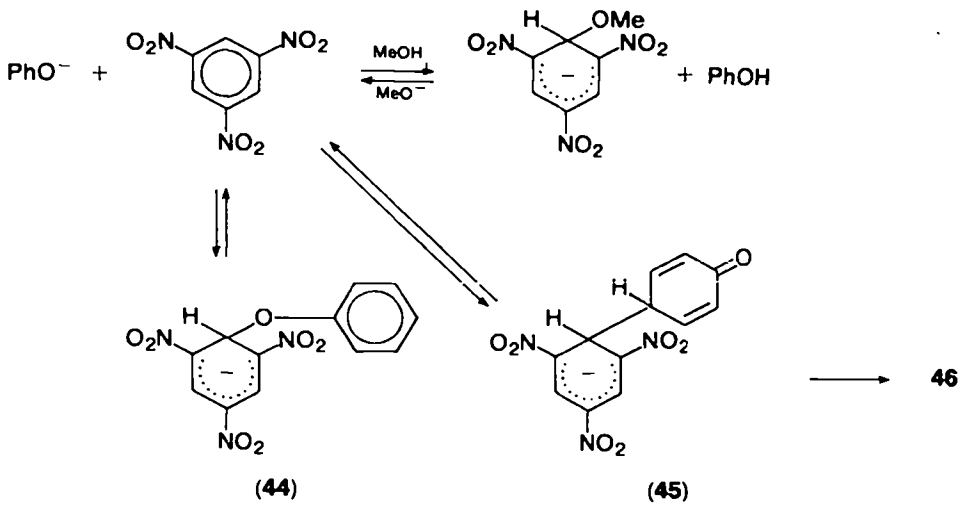


(44)



(46)

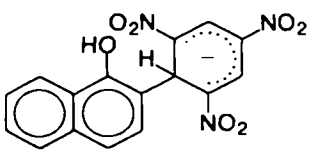
dilute acid readily permits its isolation and characterization[91]. In moderately concentrated acid, protonation in a nitro group occurs giving rise to a nitronic acid[92].



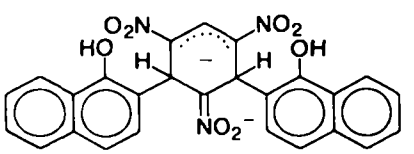
(44) (45)

SCHEME 6

Spectroscopic evidence has been presented of initial oxygen attack in the reaction of TNB[93] and TNA[94] with phenoxide, and of TNB with 2,4,6-trimethylphenoxide[95]. However, in the reaction of TNB with 1-naphthoxide only the 1:1 and 2:1 carbon-bonded adducts **47** and **48** were observed[96].

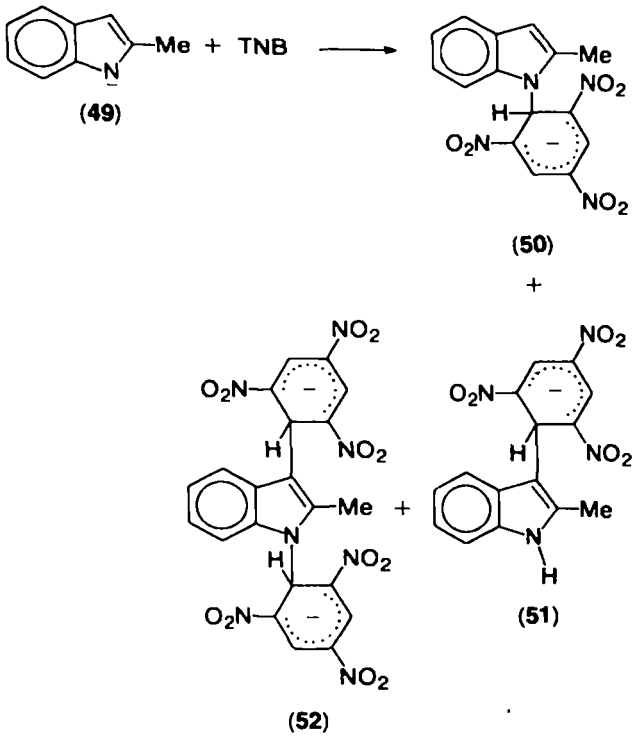


(47)



(48)

Another instance of ambident reactivity towards arenes has been reported recently, concerning indolyl anions[97]. 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.

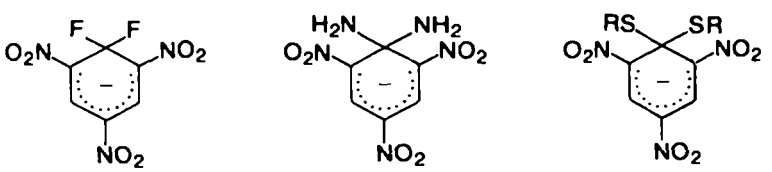


SCHEME 7

F. Other σ-Complexes

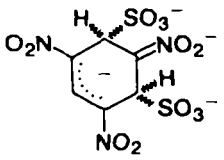
It is important to emphasize the great diversity in σ-complex structural types that have been characterized over the past two decades. In this section a brief selection is made of some of these unusual complexes.

The *gem*-difluoro adduct **53** is readily obtained by reaction of picryl fluoride with potassium fluoride/18-crown-6 ether in acetonitrile[98]. The *gem*-diamino and -di(alkylthio) adducts **54**[99] and **55**[100] are likewise obtained from the parent nitroarenes and the respective anions.



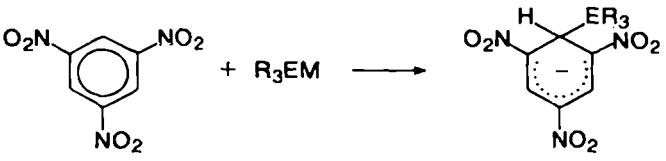
Both the *cis* and *trans* forms of the 2:1 sulphite adduct of TNB, **56**, have been characterized[101–103]. The evidence includes NMR, absorption spectroscopy, reaction rates and equilibrium properties.

The scope of nitroarene σ-complexes has been extended through addition to TNB of organometallic compounds of the type R_3EM where R = alkyl, E = Si, Ge,



(56)

Sn and M = Li, K (equation 1)[104]. σ-Complexes have also been obtained from reaction of TNB with organophosphorus compounds[105].

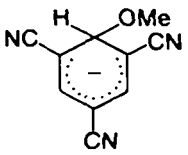


(1)

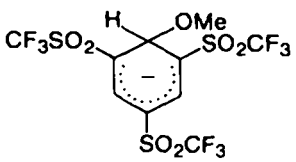
(57)

E = Si, Ge, Sn

Electron-withdrawing groups other than NO_2 can serve to stabilize, to varying extents, the negative charge on anionic σ-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].

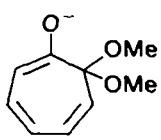


(58)



(59)

σ-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.

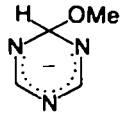


(60)

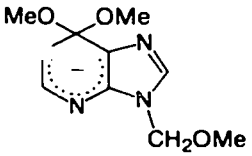
σ-Complexes of heteroaromatic compounds have been extensively investigated. Indeed, this area has developed into a field of study in its own right[110]. Some of the heterocyclics which have been found to give rise to σ-complexes on reaction with anionic reagents are pyrrole[111], thiophene[112–116], selenophene[115], pyridine[117,118],

pyrimidine[119], triazene[120,121] benzofurazan and benzofuroxan[122–126] and various purine derivatives[127,128].

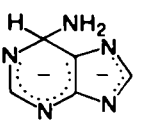
In the case of the heterocycles containing only one heteroatom, such as pyridine and thiophene, the presence of at least one strongly electron-withdrawing substituent such as nitro is required in order for stable σ-complexes to be formed. However, when several heteroatoms are present, as in triazene and purine, then σ-complexes can be observed without the necessity of further electron withdrawing substituents. Examples of complexes of this type are **61**[120], **62**[127] and **63**[128].



(61)



(62)



(63)

A number of σ-complexes in the heterocyclic series are of biological interest. For example, σ-complexes have been implicated in the observed antileukaemic activity of nitrobenzofurazan and furoxan derivatives[129]. As well, a number of molecular rearrangements that occur through the action of nucleophiles with heterocyclic derivatives have been shown to occur via σ-complex intermediates[130,131].

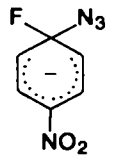
III. COMPETITIVE PROCESSES INVOLVING σ-COMPLEXES

A. Nucleophilic Displacement versus σ-Complex Formation

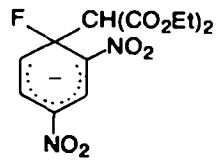
For many years interest in σ-complexes had focused on their role in aromatic nucleophilic substitution (S_NAr) processes. This situation came about largely as a result of the appearance in 1951 of two comprehensive reviews concerned with S_NAr processes[132,133], both pointing to an addition–elimination mechanism for activated aromatic substrates, in contrast to the concerted mechanism accepted for bimolecular nucleophilic substitution at saturated carbon centres. The Jackson–Meisenheimer σ-complex thus served as the model of the adduct formed in S_NAr processes. A number of kinetic studies during the 1950s and 60s of the structure–reactivity type[134,135] were interpreted on this basis. Particularly interesting was the observation of base catalysis in S_NAr processes involving amines as nucleophiles, providing kinetic evidence for a reaction intermediate[136–140]. Studies of the latter type are still continuing[141–144].

However, difficulties arose in obtaining unambiguous spectroscopic evidence for the formation of σ-complexes as *bona fide* intermediates in S_NAr processes. A claim that a spectrally detectable coloured species (λ_{max} 397 nm) corresponding to structure **64** was formed in the reaction of 1-fluoro-4-nitrobenzene with azide ion in DMF[145] was subsequently withdrawn[146]. The reaction of 1-chloro-2,4-dinitrobenzene with hydroxide ion in aqueous medium does not give rise to a spectrally detectable intermediate[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_3N, and which was earlier assigned as corresponding to structure **65**[148], was subsequently reassigned as corresponding to the final reaction products[149a]. However, at very short reaction times (<0.2 s), the

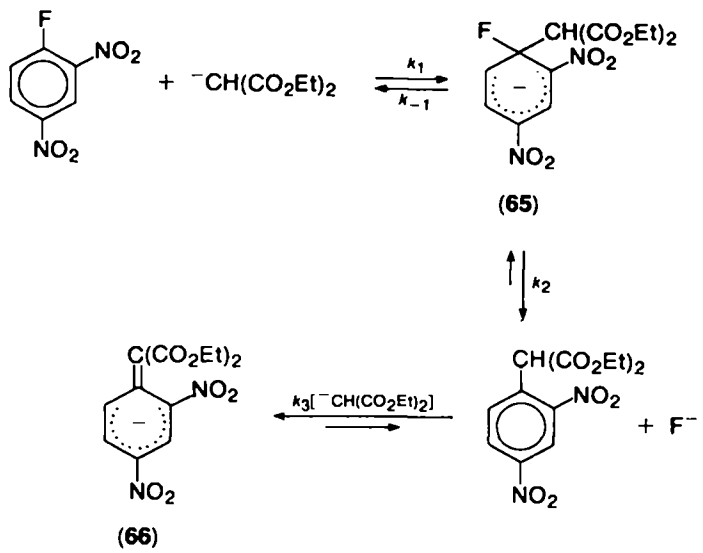


(64)



(65)

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_{-1} and k_2 being derived from the kinetic data[149b]. The final reaction product is the anion of diethyl 2,4-dinitrophenylmalonate, **66**.

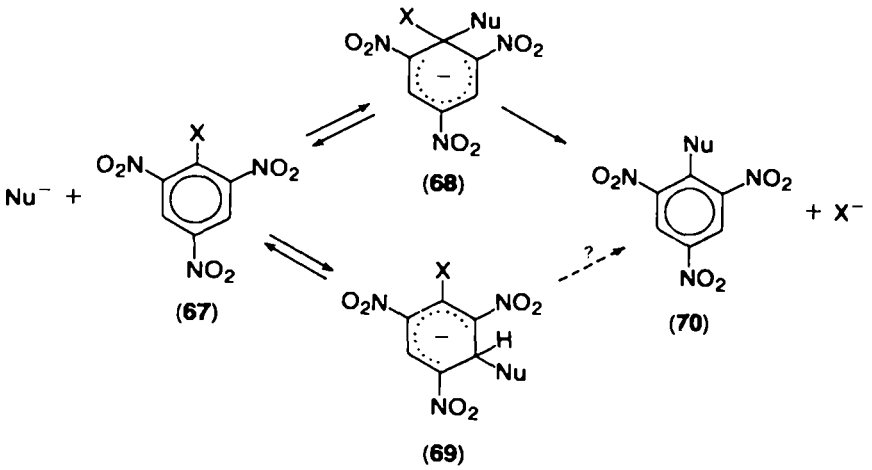


SCHEME 8

Coloured solutions are generally obtained in S_NAr 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)[150]. 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**[151].

A careful kinetic study of the reaction of picryl chloride with MeONa–MeOH followed by stopped-flow and UV–visible spectroscopy showed that *two* distinct



SCHEME 9

processes could be discerned[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^-, **9**. This product is formed via the sequence of reactions shown in Scheme **10**[152]. It is

$$\mathbf{67} + MeO^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{69} \quad (X = Cl, Nu = OMe)$$

$$\mathbf{67} + MeO^- \xrightarrow{k_2} \mathbf{68} \quad (X = Cl, Nu = OMe)$$

$$\mathbf{68} \xrightarrow{fast} \mathbf{70} \quad (Nu = OMe) + Cl^-$$

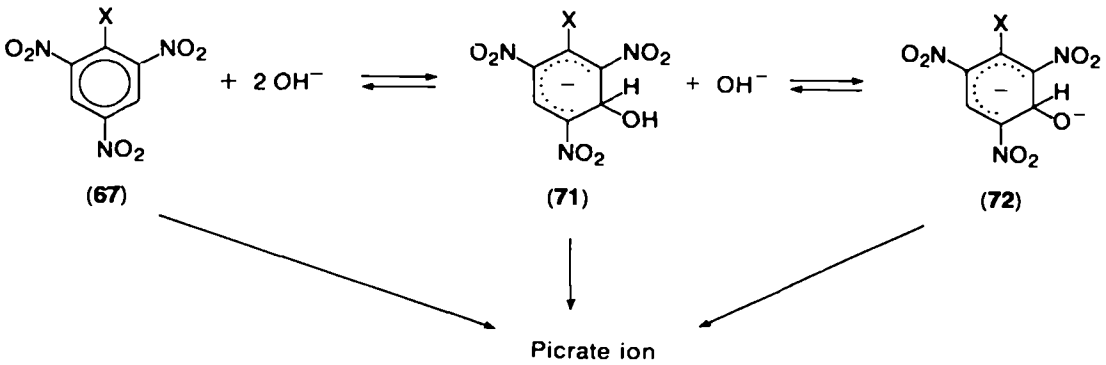
$$\mathbf{70} + MeO^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathbf{9}$$

SCHEME 10

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 ^{1}H-NMR, pertaining to the reaction of 2,4,6-trinitroanisole with MeO^- in DMSO–MeOH[24], as noted previously.

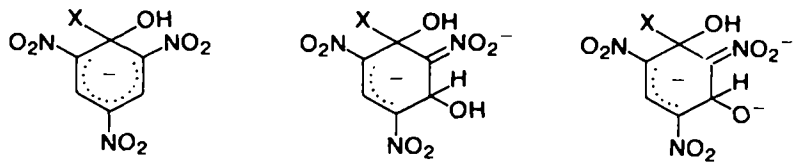
An extensive study[147] of the alkaline hydrolysis of 1-X-2,4,6-trinitrobenzene derivatives (X = Cl, NO_2, OMe) by stopped-flow spectroscopy has confirmed the rapid formation of the 3-hydroxy adduct as the first coloured species obtained in these systems. The kinetic results, however, provide strong evidence for the occurrence of nucleophilic substitution of X^- 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[147].

Picrate ion, which is the final product in each case, is formed by attack of OH^- 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



SCHEME 11

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.

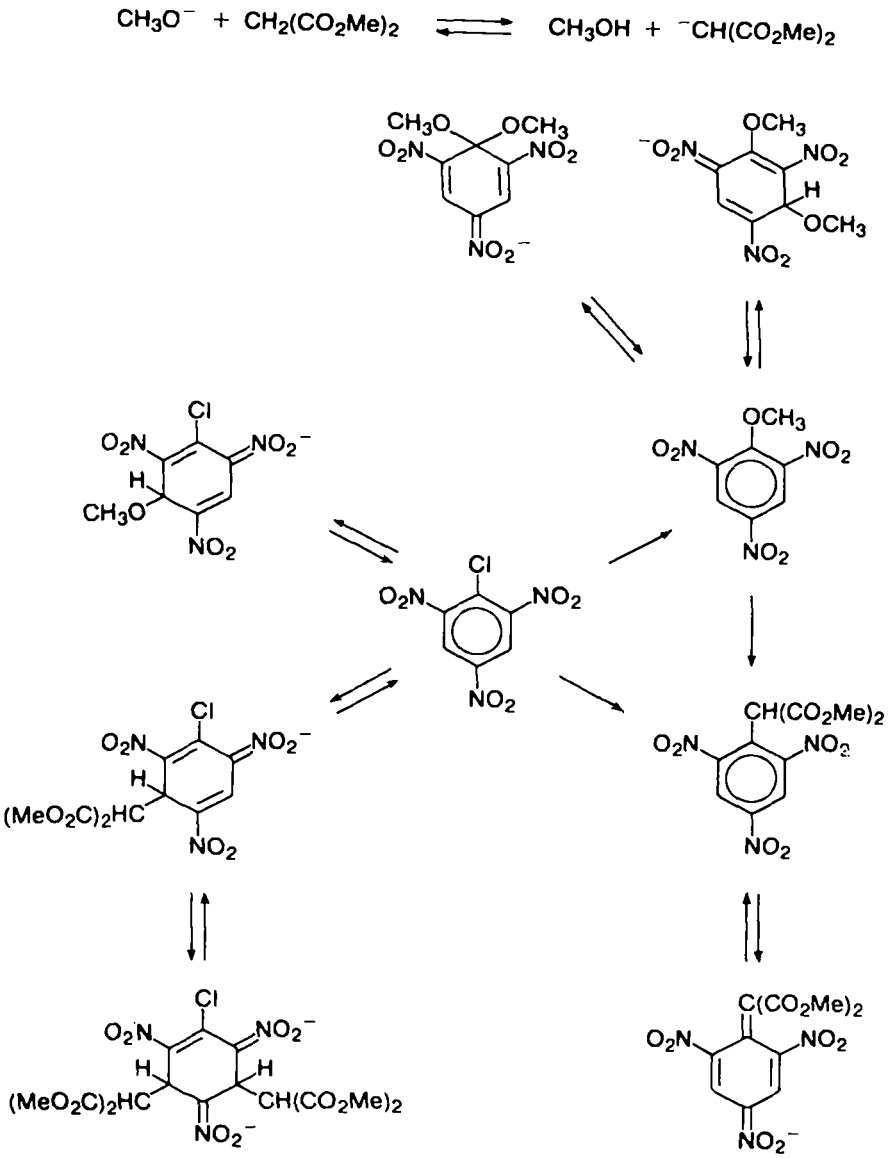


(73) (74) (75)

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 **65**[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].

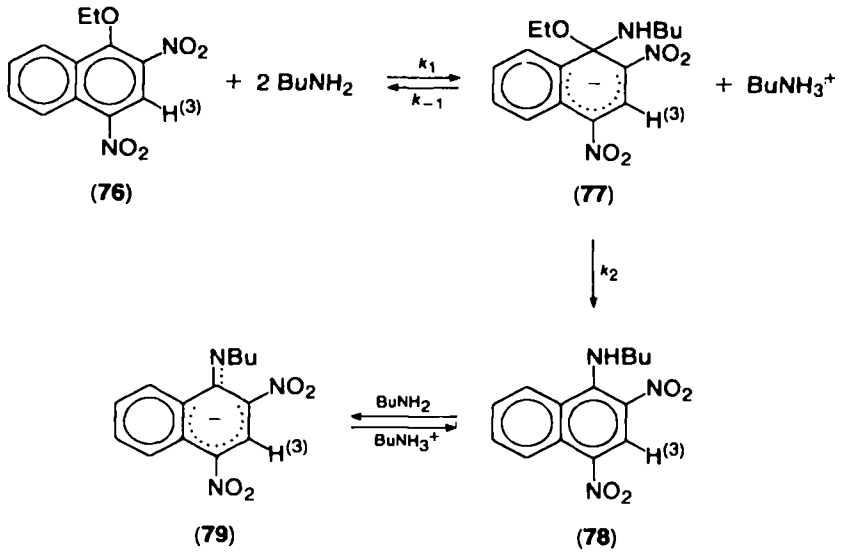
In view of these different interpretations, an approach by some other method is clearly desirable. Pertinent evidence has been obtained by the flow NMR method developed by Fyfe and his coworkers[36,158–161]. The flow NMR method allows high-resolution spectra of reliable intensities to be measured in 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.



SCHEME 12

In S_NAr 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[158]. This reaction had previously been studied by Orvik and Bunnett[162] 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[158] are in complete accord with the formulations in Scheme 13, including the structure assigned to the transient



SCHEME 13

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[11–18].

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 3[158], 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 S_NAr 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 reported[70,163–167], and

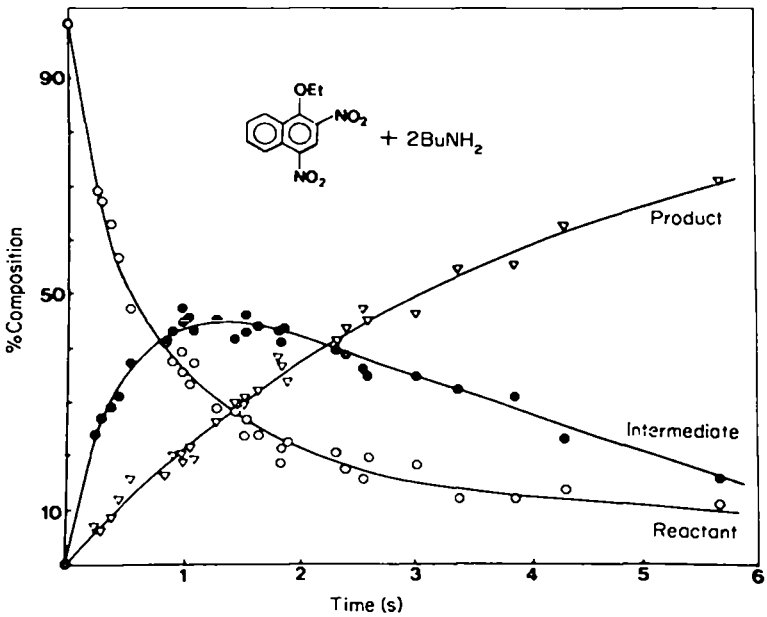
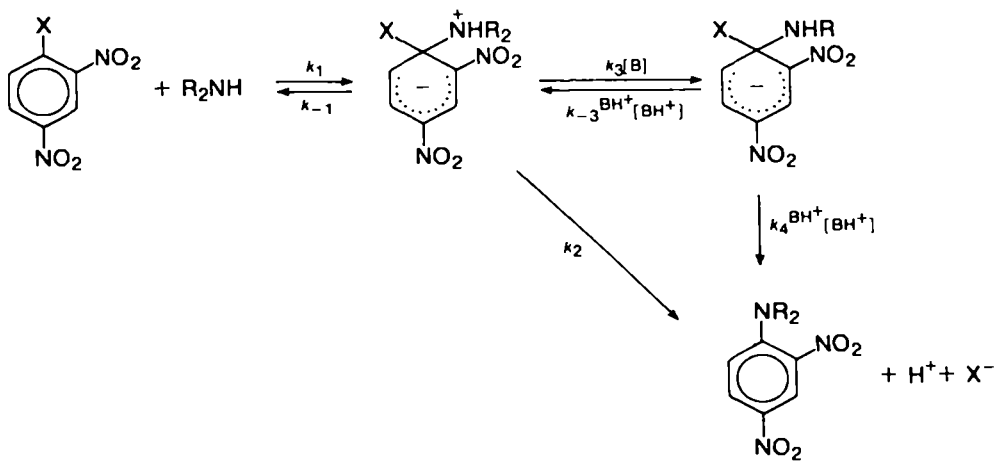
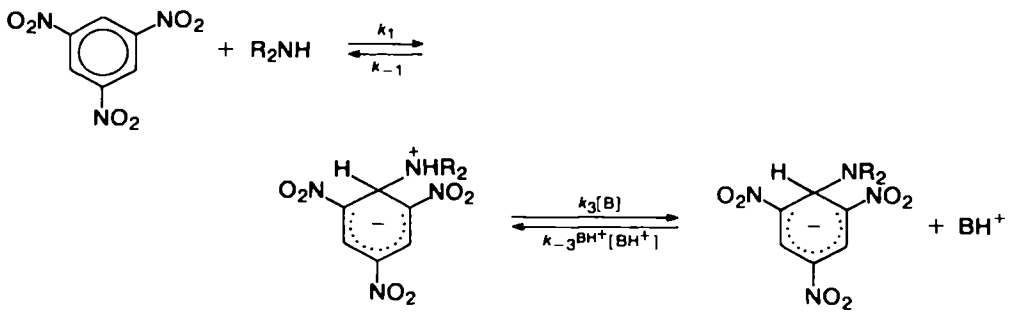


FIGURE 3. Percentage composition of the reaction mixture during the reaction of 0.20 M 1-ethoxy-2,4-dinitronaphthalene (75% DMSO–25% MeOH) with *n*-butylamine (0.4 M in 75% DMSO–25% MeOH) at 0°C, from measurement of the relative intensities of the singlet low-field absorptions assigned to the H-3 protons 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)



SCHEME 14



SCHEME 15

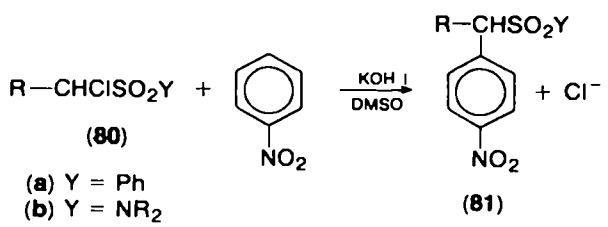
have demonstrated that kinetic investigations involving σ-complexes, in which no displaceable group is present, provide very useful insight into S_NAr processes which do involve displaceable groups. The detailed kinetic arguments are outside the scope of the chapter and the interested reader is referred to the original references.

Other aspects of S_NAr processes which have received attention recently and which intimately involve σ-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

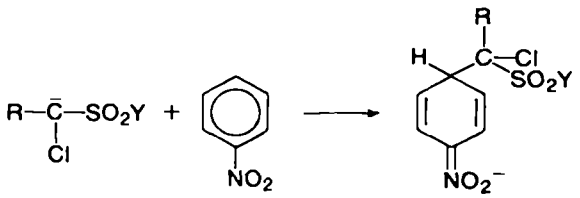
Displacement of hydride ion from a nitroarene through nucleophilic displacement is generally considered as an energetically prohibitive process. This, indeed, is the basis of the formation of stable σ-complexes of compounds containing no readily displaceable leaving group, as exemplified by the stable 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

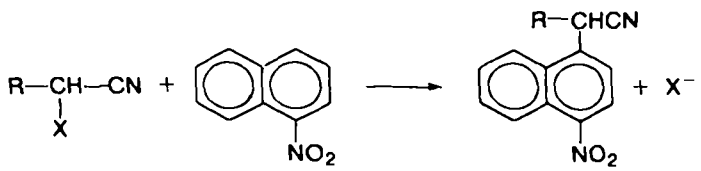


(2)

form the σ-complex **82**. Expulsion of chloride from **82**, with concurrent migration of hydride to the α-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].

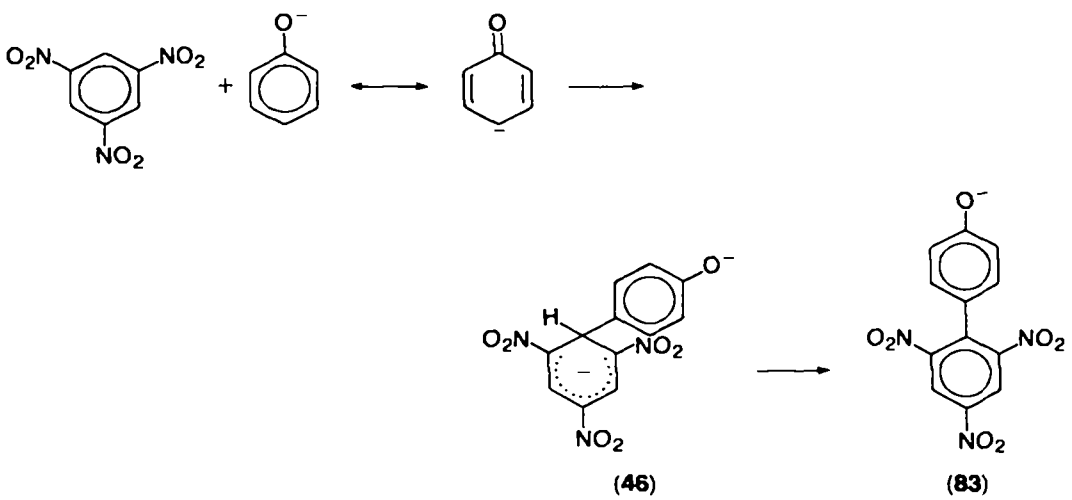


(82)



X = Cl, MeS, PhS

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[91]. The carbon-bonded phenoxide adduct **46** can be readily oxidized by reagents such as benzoquinone to yield the diphenyl derivative **83** (Scheme 16)[181].

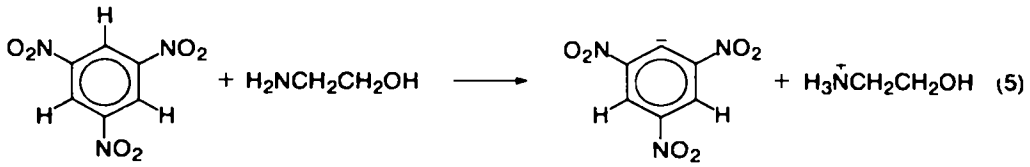


SCHEME 16

C. Aromatic Proton Abstraction versus σ-Complex Formation

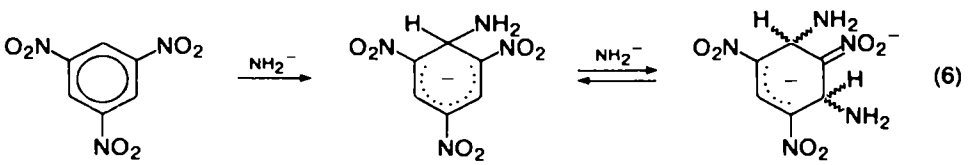
In 1940, Lewis and Seaborg[182] advanced the possibility of ionization of an aryl hydrogen in a polynitroarene, through action of base, in order to account for the conducting properties of solutions in liquid ammonia. The observed cryoscopic properties of TNB in 2-aminoethanol were similarly explained according to equation (5) by Baliah and Ramakrishnan[183].

However, Wheland and coworkers[184] suggested that the conductivity of solutions of 1,3-dinitrobenzene (DNB) in liquid ammonia was a result of σ-complex



(5)

formation by NH_2^-, 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



(6)

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_2O 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_2O at room temperature[189]. However, complete exchange occurred when TNB (0.5M) was treated with NaOD (0.01M) in DMF–D_2O (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_2O–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_2O–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[195]. 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%).

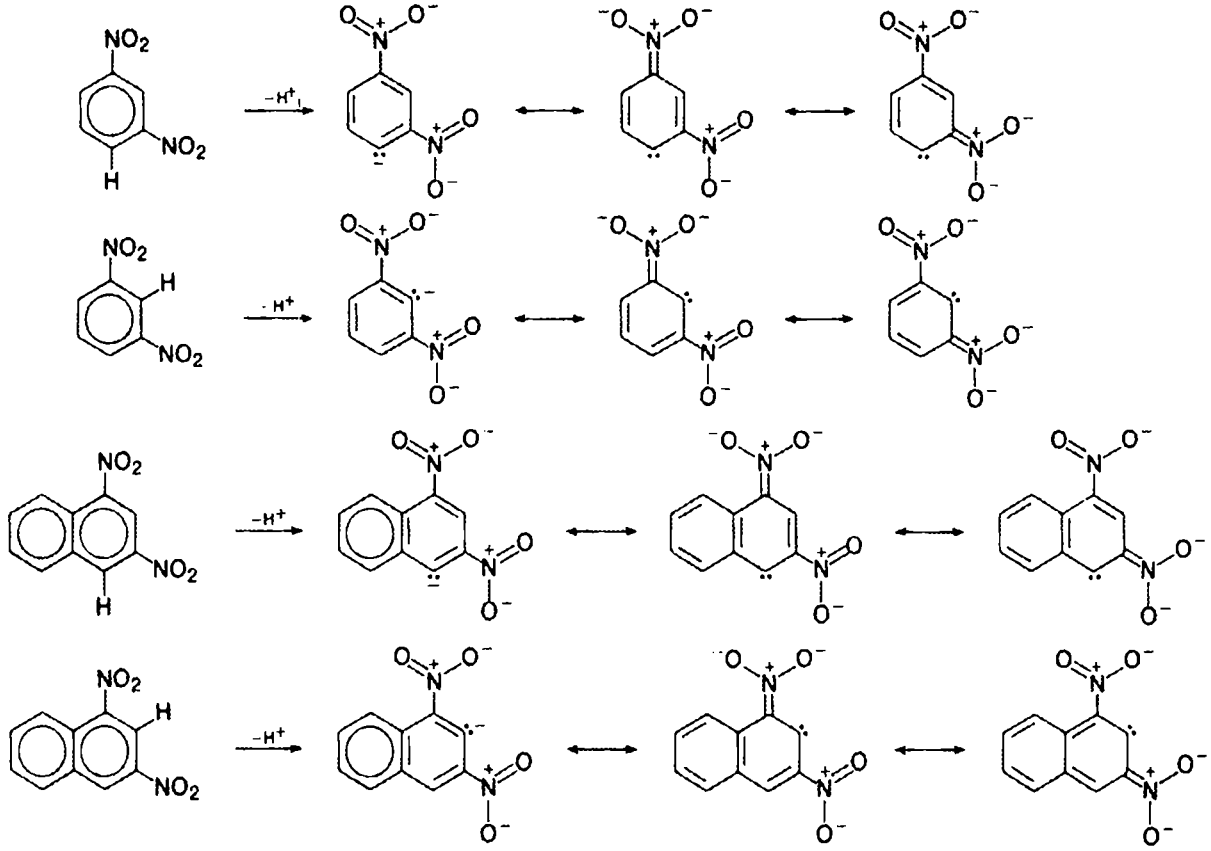
An explanation of this contrasting behaviour can be proposed when one considers the possibility of stabilization of the nitroaryl carbanions through resonance structures entailing carbenoid delocalization. Thus, as shown in Scheme 17, for the carbanions derived from DNB, two carbenoid structures can 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[196–197], 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_2O–DMF system described above. What is the relationship between carbanion formation, leading to isotopic exchange, and σ-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[183]. However, the unambiguous characterization of σ-complexes via their spectral properties (see above) has shown unambiguously that σ-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 σ-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[188]. The plots of log k vs. H_-, and of log ε 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 σ-complex formation, for the case of TNB in the NaOD–D_2O–DMF system[198]. In this case σ-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[199] of the concurrent exchange and σ-complex formation processes in DNB in the NaOD–D_2O–DMF system has in fact revealed the behaviour anticipated in the earlier work with TNB[198]. The kinetic data for exchange now do



SCHEME 17

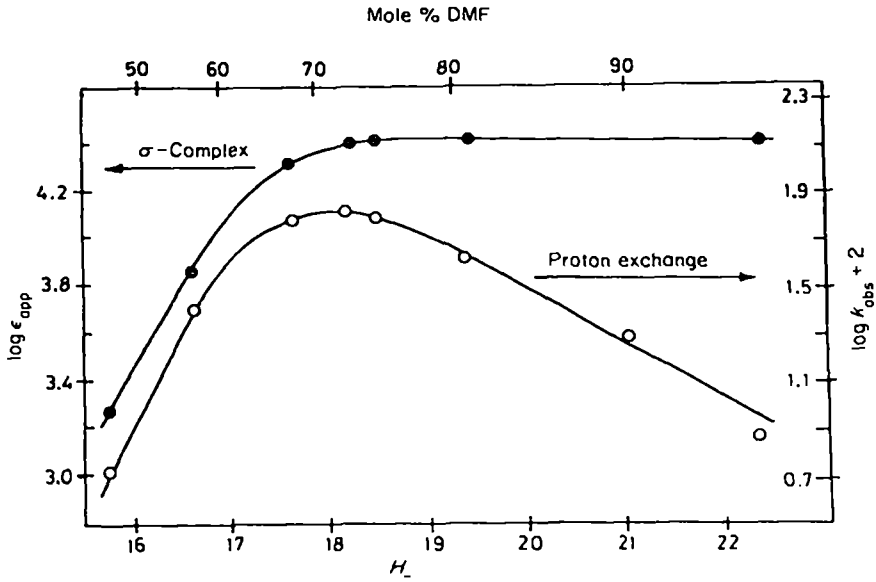


FIGURE 4. Competition between hydrogen exchange and σ-complex formation for 1,3-dinitrobenzene in the NaOD–D_2O–DMF system.

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

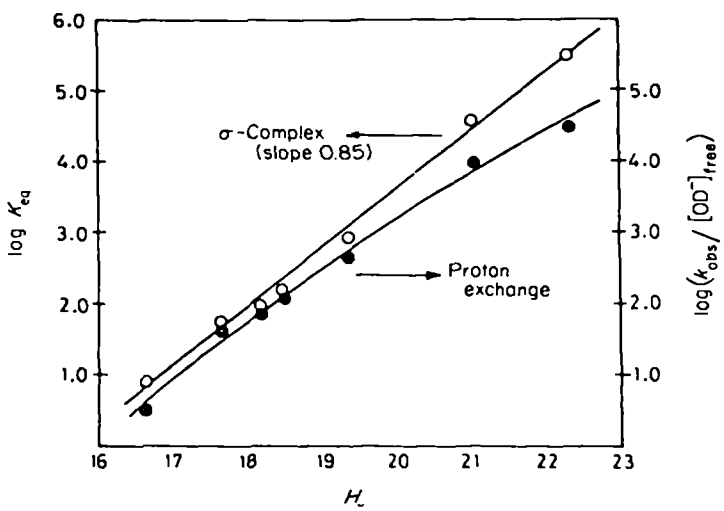
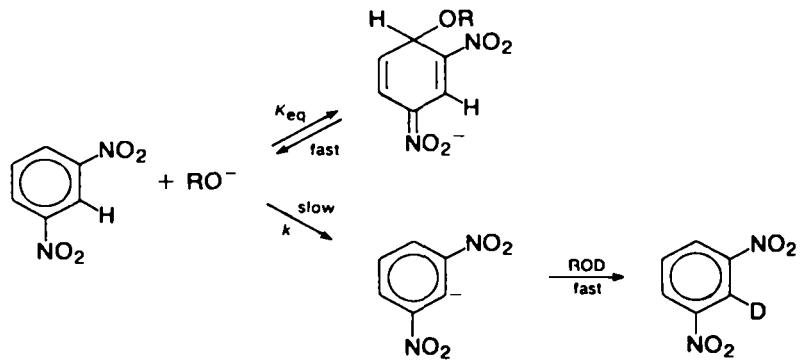


FIGURE 5. Dependence of hydrogen exchange and σ-complex formation on solution basicity for 1,3-dinitrobenzene in the NaOD–D_2 O–DMF system.

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 case in the NaOD–D_2O–DMF system (0.5M DNB, 0.004M NaOD)[199]. From the K_{eq} values for σ-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_-[20], 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 σ-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.

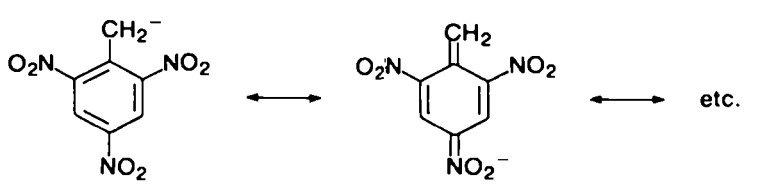
The sum of the evidence points to isotopic exchange occurring via the aryl carbanion intermediate and the involvement of the σ-complex in a side-equilibrium as an unreactive species. This is illustrated in Scheme 18.



SCHEME 18

D. Benzylic Proton Abstraction versus σ-Complex Formation

In the interaction of nitrobenzylic compounds with bases, σ-complex formation can potentially compete with α-hydrogen abstraction. The latter possibility arises from increased acidity of α-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:

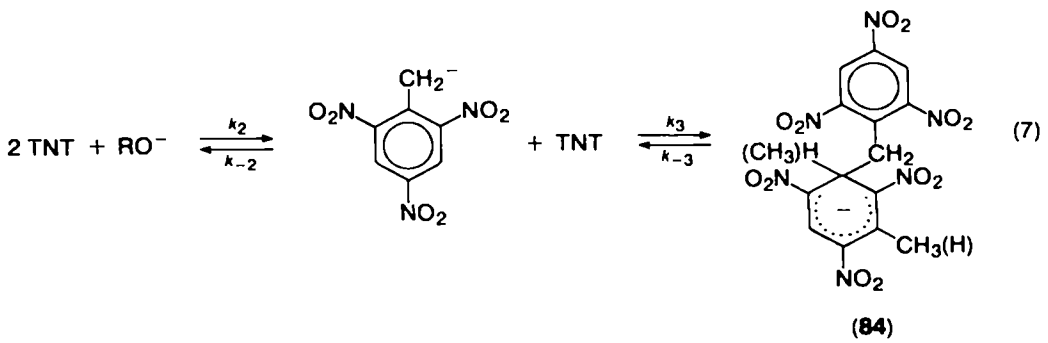


Formation of the TNT^- anion from TNT under alkaline conditions is implicated in the reported isolation of 2,2′,4,4′,6,6′-hexanitrobibenzyl[200] and 2,2′,4,4′,6,6′-hexanitrostilbene[201], the latter having the properties of a thermally stable explosive with possible application in space research[202]. Another kind of evidence for the intervention of TNT^- in TNT–base systems derives from the observation of

hydrogen–deuterium exchange, as in the pyridine–D_2O[203], NaOD–D_2O–DMF[204] or NaOD–D_2O–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.

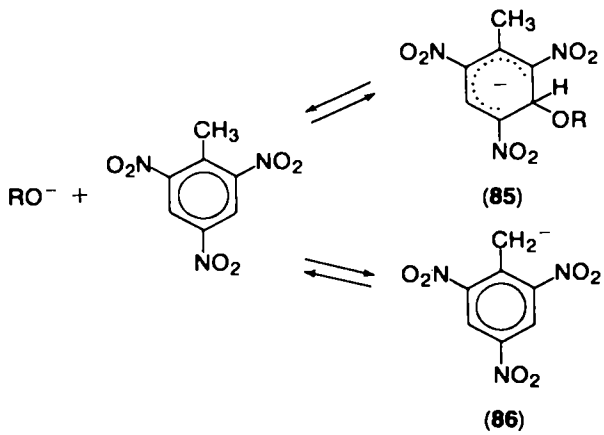
With TNT in excess of base, in a medium of 50% dioxan–50% water or in methanolic or ethanolic media containing the respective lyate ions, the processes that have been identified are shown in equation (7)[206]. The TNT^- anion generated in the first step reacts with another mole of TNT to yield the Janovsky type σ-complex **84**. Rate constants for the various processes could be determined using



(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.

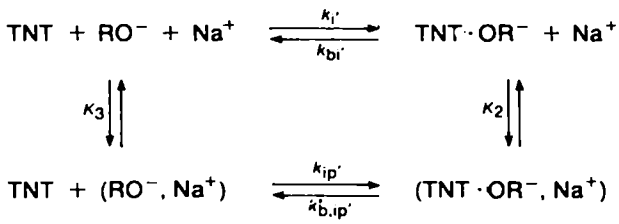
In a series of studies by stopped-flow techniques involving TNT and TNT-d_3 with EtO^-, *i*-PrO^- and *t*-BuO^- in the respective alcohols, with alkoxide in large excess, the concurrent formation of a σ-complex and the TNT^- anion was proved unequivocally[207–209]. A gradation of behaviour as a function 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 **87** and **88** applicable to σ-complex formation and TNT^- anion formation respectively. It is seen that in the



SCHEME 19

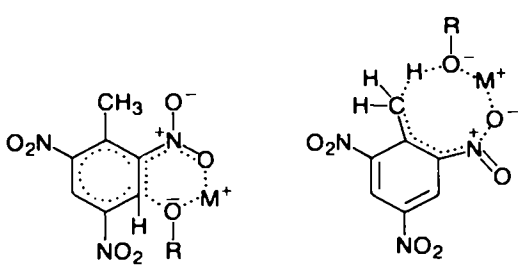
former case the metal cation stabilizes the incipient negative charge on the aromatic ring in a favourable six-membered transition state, unlike the latter case.

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



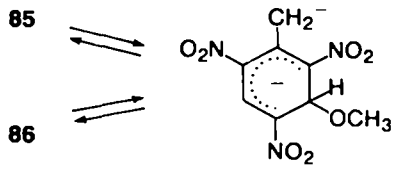
SCHEME 20

7–8 at 25°C[207–209], use of 1,1′,3,3′-tetramethylguanidine as base in DMF solvent led to a KIE of 16.9 at 20°C and 24.3 at 0°C, 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[211] that whereas reaction between equimolar proportions of TNT and MeO^- in 87.5% DMSO–12.5% MeOH led to the formation of a σ-complex and of TNT^-, 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

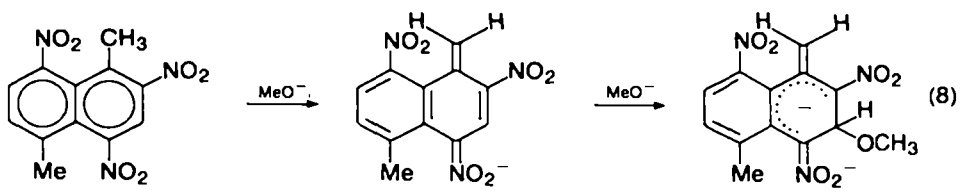


(89)

SCHEME 21

that in this study[211] the presence of free radicals was also detected, although these could not be structurally identified.

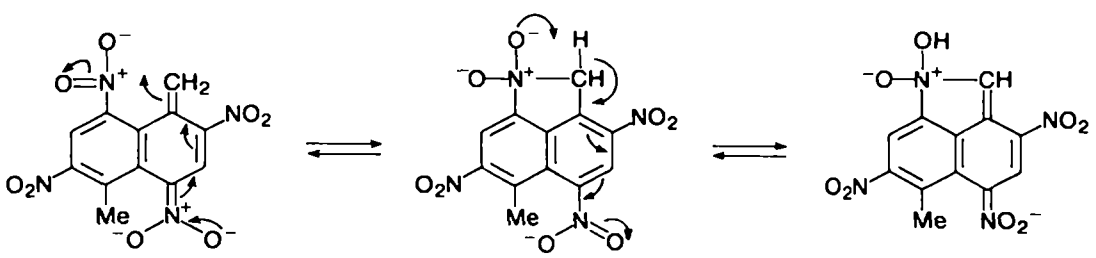
An NMR study of nitromethylnaphthalene compounds has yielded interesting results[212]. 1,5-Dimethyl-2,4,8-trinitronaphthalene (**90**) on reaction with one mole of methoxide in DMSO solution is reported to yield initially the deprotonated species **91**. Addition of further methoxide yields the dianionic species **92**, in analogy with the TNT system (equation 8).



(8)

(90) (91) (92)

1,5-Dimethyl-2,4,6,8-tetranitronaphthalene yielded two σ-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].



(93) (94)

SCHEME 22

IV. ACKNOWLEDGEMENTS

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **28**

Uses of isotopically labelled amino, quaternary ammonium and nitro compounds

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I. THEORY OF KINETIC ISOTOPE 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 monographs[1–4] have detailed discussion dealing with heavy-atom and primary and secondary hydrogen–deuterium kinetic isotope effects. The recent monograph by Melander and Saunders[4] 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 treatment[5–7], based on Eyring and coworkers' absolute rate theory[8], 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.

The expression for the rate constant 'k' of the reaction according to these assumptions may be expressed by equation (1),

$$k = \frac{\bar{k}T\kappa K^{\neq}}{h} \tag{1}$$

where $\bar{k}$ is the Boltzmann constant, T is the absolute temperature, h is Planck's constant, κ is the so-called transmission coefficient and $K^{\neq}$ 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, κ 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[9]. Using equation (2) with a knowledge of the potential energy surface, $K^{\neq}$ may be calculated using the methods of statistical mechanics, since:

$$K^{\neq} = \frac{Q^{\neq}}{Q_A Q_B} \tag{2}$$

where the Qs are the complete partition functions for reactants A, B, . . ., etc. and $Q^{\neq}$ 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 $Q^{\neq}$ and therefore of $K^{\neq}$. 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:

$$\mathrm{A + B + C \ldots} \rightleftharpoons \left[\begin{matrix}\text{Transition}\\ \text{state}\end{matrix}\right]^{\neq} \rightleftharpoons \text{Products} \tag{3}$$

$$\frac{k_1}{k_2} = \frac{\kappa_1}{\kappa_2} \cdot \frac{Q_1^{\neq}}{Q_2^{\neq}} \cdot \frac{Q_{A2}}{Q_{A1}} \cdot \frac{Q_{B2}}{Q_{B1}} \cdot \frac{Q_{C2}}{Q_{C1}}$$

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[10] expressed the partition functions in terms of the vibrational frequences 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 Ms are the molecular weights, the Is are the moments of inertia about the three principal axes of the n-atom molecules and the νs are the fundamental vibrational frequencies of the molecules in wave numbers.

$$\frac{Q_2}{Q_1} = \frac{S_1}{S_2}\left(\frac{I_{A_2}I_{B_2}I_{C_2}}{I_{A_1}I_{B_1}I_{C_1}}\right)^{1/2}\left(\frac{M_2}{M_1}\right)^{3/2}\pi_i^{3n-6}\exp\left[\frac{(\nu_{1_i}-\nu_{2_i})hc}{2\bar{k}T}\right]\left[\frac{1-\exp(-hc\nu_{1_i}/\bar{k}T)}{1-\exp(-hc\nu_{2_i}/\bar{k}T)}\right] \tag{4}$$

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[11] 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[12], 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 frequently 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),

$$\frac{k_H}{k_D} = \exp[(-hc/2kT)(\nu_H - \nu_D)] \tag{5}$$

where ν_H and ν_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.

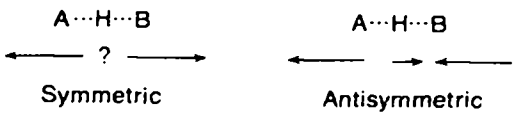
For reactions involving a proton transfer from one molecule to another, however, the situation is more complex. Westheimer[13] and Melander[1] have independently pointed out that, because bond formation and breaking are occurring concurrently,

new stretching vibrations in the transition state which are not present in the reactants must be considered.

They considered the reaction:

$$AH + B \longrightarrow [A\cdots H\cdots B] \longrightarrow A + HB \qquad (6)$$

where [A · · · H · · · 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:



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:

$$\frac{k_H}{k_D} = \exp\{(-hc/2\bar{k}T)[(\nu_H - \nu_D) - \Delta\nu_s]\} \qquad (7)$$

where $\Delta\nu_s$ 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

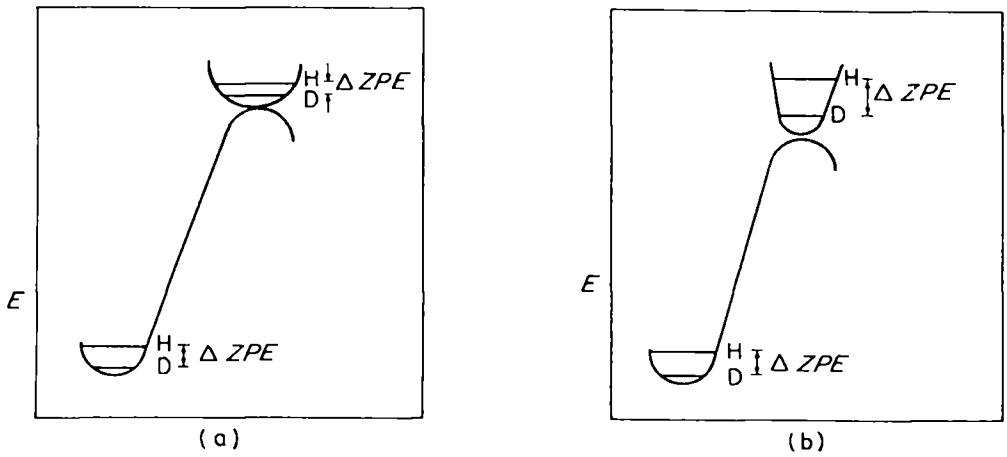


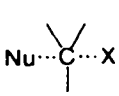
FIGURE 1. (a) Reaction where Δ *ZPE*(reactant) is greater than Δ *ZPE*(transition state) and $k_H/k_D > 1$. (b) Reaction where Δ *ZPE* (reactant) is less than Δ *ZPE* (transition state) and $k_H/k_D < 1$.

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 (Δ *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 α- or reacting carbon. The generally accepted view originally proposed by Streitwieser and coworkers[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, $(k_H/k_D)_\alpha$, 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[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 α-carbon–hydrogen bonds. This leads to an increased force constant at the S_N2

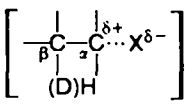


(1)

transition state, **1** (see Figure 1b). In fact, small or inverse isotope effects, $(k_H/k_D)_{\alpha D} = 0.95–1.04$, are observed for the S_N2 reactions of primary substrates[18].

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 $(k_H/k_D)_\beta$ 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



(2)

CD_3 group increases from about 1.03 for ethyl compounds, which undoubtedly react by an S_N2 mechanism, to approximately 1.37 for a *t*-butyl compound, which reacts by a limiting S_N1 mechanism[19]. A wealth of experimental evidence[20] indicates that these isotope effects are primarily, if not completely, a result of hyperconjugative electron release from the C_β—H bonds[21]. Other studies by Shiner and coworkers[22,23] have demonstrated that the magnitude of these isotope effects vary with the dihedral angle between the C_β—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_β—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 smally 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 Thornton[24] 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

$$2\,OD^- + H_2O \overset{K_B}{\rightleftharpoons} 2\,OH^- + D_2O \qquad (8)$$

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^-

$$OD^- + \tfrac{1}{2}H_2O \overset{K}{\rightleftharpoons} HO^- + \tfrac{1}{2}D_2O \qquad (9)$$

and OH^-. Since OD^- is the stronger base, $K = K_B^{1/2} = k^{OD^-}/k^{OH^-} > 1$. 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).

$$2\,H_2O \overset{K_H}{\rightleftharpoons} OH^- + H_3O^+ \quad (10)$$

$$2\,D_2O \overset{K_D}{\rightleftharpoons} OD^- + D_3O^+ \quad (11)$$

$$2\,D_3O^+ + 3\,H_2O \overset{L}{\rightleftharpoons} 2\,H_3O^+ + 3\,D_2O \quad (12)$$

From equations (10) and (11) it is seen that:

$$\frac{K_H}{K_D} = \frac{[OH^-][H_3O^+]}{[H_2O]^2} \cdot \frac{[D_2O]^2}{[D_3O^+][OD^-]} \quad (13)$$

In fact K_H/K_D is the equilibrium constant, K_{eq}, for the exchange reaction (14):

$$2\,H_2O + OD^- + D_3O^+ \overset{K_{eq}}{\rightleftharpoons} 2\,D_2O + OH^- + H_3O^+ \quad (14)$$

From equations (14), (13), (12) and (8) it is evident that:

$$K_B = K_{eq}^2/L \quad (15)$$

Since the equilibrium constants K_{eq} and L can be measured, $k^{OD^-}/k^{OH^-} = K_B^{1/2}$ can be calculated[23] 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^{OD^-}/k^{OH^-}, will occur when the proton is completely transferred from H_2O to 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^{OD^-}/k^{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[25–30]. This section will deal briefly with two of these theoretical studies.

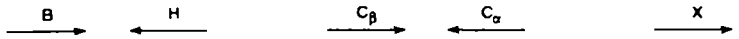
Thornton[28] considered the influence of substituents on the motion along the reaction coordinate, designated as 'parallel' motion (vibration), and on the normal modes of vibration, or 'perpendicular' vibrations, of the transition states.

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:



where B is the base and X is the leaving group. An electron-withdrawing substituent at C_β will weaken the C_β—H bond and thus make the motion which extends this bond easier. It will also make compression of the C_β—C_α 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_β—C_α 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_β will shorten the C_β—H bond. Electron-releasing substituents on the the other hand will lengthen the C—H bond in the transition state. The B—H and C_α—X bonds will follow along in the direction of coordinate motion set by the C_β—H bond, i.e. the B—H bond is lengthened and the C_α—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_β—H and C_α—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_α, and C_β move more relative to X; a more product-like transition state will have relatively more carbanion character at C_β than carbonium ion character at C_α, that is, it becomes more Elcb-like.

Thornton and Winey[29] 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[26] 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[31] and applied to reactions involving the cleavage of a single bond. Now the same principles are applied to concerted 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^-,

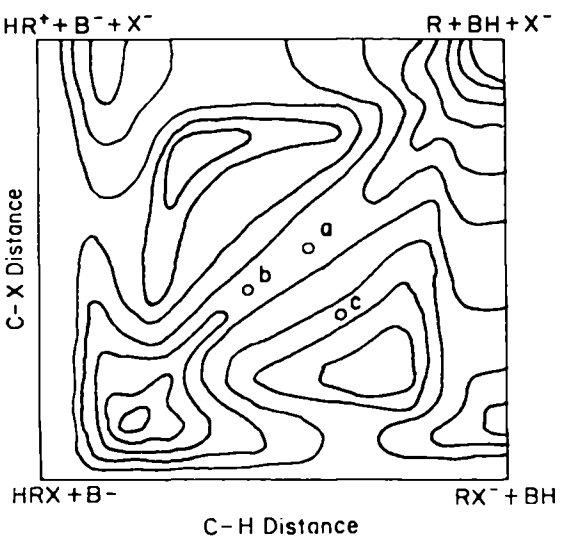


FIGURE 2. Potential energy diagram for concerted β-elimination reactions.

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 C_β—H and shorter C_α—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 QUARTERNARY 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

$$R_3N + R{-}X \longrightarrow R{-}\overset{+}{N}R_3\ X^- \tag{16}$$

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.

$$R{-}\overset{+}{N}R_3 + X^- \longrightarrow R{-}X + NR_3 \tag{17}$$

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 α-carbon and in the α-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-α-d_2)amine and methyl *p*-bromobenzenesulphonate. 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-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[39,46] and by Kaplan and Thornton[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_N2 reactions. Brown and McDonald[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[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_as 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_N2 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 1. Secondary hydrogen-deuterium kinetic isotope effects for the Menschutkin reaction between substituted pyridines and alkyl iodides in nitrobenzene

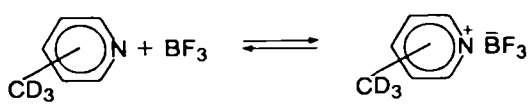
Pyridine	Substrate	Temp (°C)	k_H/k_D[a]
4-Methyl-d_3-	CH_3I	25	0.999
3-Methyl-d_3-	CH_3I	25	0.991
2-Methyl-d_3-	CH_3I	25	0.971
2,6-Dimethyl-d_6-	CH_3I	25	0.913
4-Deutero-	CH_3I	25	0.988
2,3,4,5,6-Pentadeutero-	CH_3I	25	0.970
2-Methyl-d_3-	C_2H_5I	75	0.965
2,6-Dimethyl-d_6-	C_2H_5I	75	0.933[b]
2-Methyl-d_3-	$(CH_3)_2CHI$	100	0.945[c]

[a]The isotope effects are accurate to ±1%.
[b]This isotope effect is accurate to ±2%.
[c]This isotope effect is accurate to ±3%.

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[40] came to the same conclusion. These workers found a large inverse secondary hydrogen–deuterium kinetic isotope effect (k_H/k_D = 0.883 ± 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.

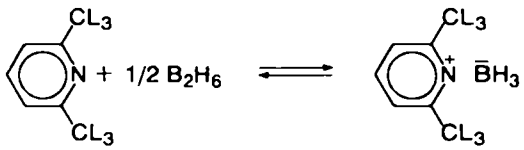
The steric origin for the inverse secondary hydrogen–deuterium kinetic isotope effects in the Menschutkin reaction was also substantiated by the isotope effects on the enthalpies of reaction ($\Delta H_H^{\neq} - \Delta H_D^{\neq}$) for the formation of the acid–base complex between methyl-d_3-substituted pyridines and boron trifluoride in nitrobenzene (equation 18)[46].



(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-dimethyl-pyridine 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

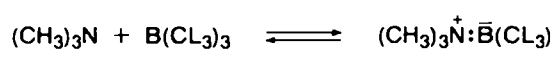
isotope effect is observed in the 2-methylpyridine reaction, is only consistent with a steric isotope effect. This is because 4-methyl- and 2-methyl-pyridine have the same pK_a[39] and therefore the same inductive effect. Secondly, there was no isotope effect in the reaction between 2,6-dimethylpyridine and diborane (equation 19). An



(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 sterically 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



(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[38] 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-dimethyl-pyridine 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 α-carbon–nucleophile and α-carbon–leaving-group transition-state bond lengths)

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 MacLean[38] 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 $T(\Delta S_D^{\neq} - \Delta S_H^{\neq}) = 75$ cal/mol at 300 K than on the enthalpy of activation term $(\Delta H_D^{\neq} - \Delta H_H^{\neq}) = -2$ 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 $\Delta H^{\neq}$ 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[41] 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[40] 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. $(\Delta H_D^{\neq} - \Delta H_H^{\neq})$ was equal to -134 cal/mol whereas $T(\Delta S_D^{\neq} - \Delta S_H^{\neq})$ 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[42] 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[47].

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[45]. 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[43,48,49]. The latter effect leads to lower energy C_α—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 S_N2 reactions has been reported by Westaway and Ali[50].

Unlike the secondary alpha deuterium kinetic isotope effects, the secondary beta hydrogen–deuterium kinetic isotope effects for the reactions of ethyl-β-d_3, propyl-β-d_2 and isopropyl-β-d_6 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[43,48,49]. It is worth noting that the secondary beta hydrogen–deuterium kinetic isotope effect is significantly smaller when the substrate is isopropyl iodide (k_H/k_D 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[50].

Finally, the secondary gamma hydrogen–deuterium kinetic isotope effect in the reaction between propyl-γ-d_3 bromide and pyridine was too small to measure. The actual isotope effect was k_H/k_D = 0.995 or 0.9985 per γ-D.

Finally, Vitullo, Grabowski and Sridharan[51] 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[36] measured the primary nitrogen (entering-group) kinetic

TABLE 2. Primary nitrogen kinetic isotope effects in the Menschutkin reactions of tertiary amines and alkyl halides in benzene

Amine	Substrate	k^{14}/k^{15}	Temperature (°C)
$(C_2H_5)_3N$	CH_3I	1.0009 ± 0.0005	8
$(CH_3)_3N$	CH_3CH_2Br	0.9994 ± 0.0006	6
		0.9991 ± 0.0007	25
$(C_2H_5)_3N$	CH_3CH_2I	1.0007 ± 0.0006	6
		1.0015 ± 0.0006	25
		1.0017 ± 0.0006	56.8
		1.0020 ± 0.0006	78.2

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 show 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:

$$\frac{k^{14}}{k^{15}} = \left(\frac{\mu_{15}^{\neq}}{\mu_{14}^{\neq}}\right)^{\frac{1}{2}} \left[1 + \sum_{i}^{3n-6} G(u_i)\Delta u_i - \sum_{i}^{3n-7} G(u_i^{\neq})\Delta u_i^{\neq}\right] \tag{21}$$

where $\mu_{14}^{\neq}$ and $\mu_{15}^{\neq}$ are the effective masses of the transition state containing the C—^{14}N and C—^{15}N bonds, respectively. The $\Sigma_i^{3n-6}\Delta G(u_i)\Delta u_i$ term gives the difference in the vibrational energies of the ^{14}N and ^{15}N bonds in the reactants. The $\Sigma^{3n-7}\Delta G(u_i^{\neq})\Delta u_i^{\neq}$ term is the corresponding term for the ^{14}N and ^{15}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 C—N bonds in the free amine (there is no bond between the α-carbon of the alkyl halide and the nitrogen of the amine). In the transition state however, the α-carbon–nitrogen bond has partially formed and changing the isotope will also affect the vibrational frequencies of the partially formed $C_\alpha \cdots N^+$ bond. As a result, the $\Sigma_i^{3n-7}G(u_i^{\neq})\Delta u_i^{\neq}$ term will be larger than the $\Sigma_i^{3n-6}G(u_i)\Delta u_i$ 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 $\Sigma_i^{3n-7}G(u_i^{\neq})\Delta u_i^{\neq}$ 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 α-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 α-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[43] and Ballistreri and coworkers[54] in the Menschutkin reaction and by Westaway and Ali in the reverse of the Menschutkin reaction[50]. 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[35] 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 ± 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 $C_\alpha \cdots Cl$ 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.

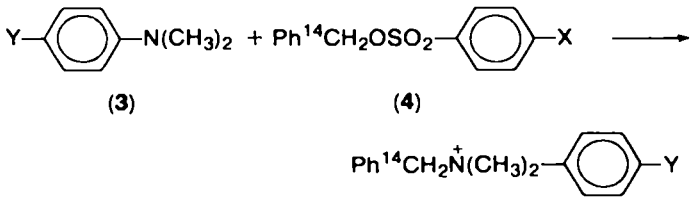
These results are opposed to the earlier results of Swain and Hershey[34], who found a larger chlorine kinetic isotope effect and concluded that the transition state was later or more product-like when a less sterically hindered amine was used as the nucleophile in the Menschutkin reaction. The chlorine isotope effect (k^{35}/k^{37}) was only 1.00640 ± 0.00009 in the more sterically crowded Menschutkin reaction between triethylamine and methyl chloride whereas a larger isotope effect of 1.00709 ± 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[55] 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 istope effect.

4. *Carbon kinetic isotope effects*

Yamataka and Ando[33,56] 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

acetone at 35 and 45°C (equation 22).



(3) (4)

(22)

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°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 ρ values observed when the *para* substituent in the incoming nucleophile is changed for each leaving group. In fact, the Hammett ρ values obtained by substitution in the nucleophile decrease as a more electron-withdrawing substituent is placed in the leaving group, i.e. the ρ 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 $X = m\text{-}NO_2$. Since a larger ρ value is indicative of a transition state with a more complete nucleophile–α-carbon bond[50], it would appear that the transition states with electron-withdrawing substituents 'X' have longer nucleophile–α-carbon bonds and are more reactant-like, whereas the

TABLE 3. Carbon-14 kinetic isotope effects[a] in the Menschutkin reactions between *para*-substituted *N,N*-dimethylanilines (**3**) and benzyl *para*-substituted benzenesulphonates (**4**) in acetone at 45°C

	X				
Y	*p*-CH_3O	*p*-CH_3	H	*p*-Cl	*m*-NO_2
p-CH_3O	—	1.148	1.140	1.142	—
p-CH_3	1.147	1.156	1.162	1.149	1.119
H	—	—	1.135	1.143	1.158
p-Br	—	—	—	1.139	—
m-NO_2	—	—	—	—	1.127

[a]The error limits range from ±0.001 to ±0.008. Most of the errors are ±0.002 and ±0.003.

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[31], Thornton's reacting bond rule[28] and the More O'Ferrall-type of energy surface as applied to S_N2 reactions[50].

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[43] and by Westaway and Ali[50], 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 Hoeg[32] and Buist and Bender[57] 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[58] 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

benzyldimethylphenylammonium ion and bromide ion in chloroform and acetone (equation 23).

$$PhCL_2—\overset{+}{N}(CH_3)_2Ph\ Br^- \longrightarrow PhCL_2Br + (CH_3)_2NPh \quad (23)$$

$$L = H, D$$

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 S_N2 reaction was thought to be 1.04 per α-D[18], and because the corresponding 1-phenylethyldimethylphenylammonium bromide reacted 22 times faster than the benzyl compound[59], 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.

$$3\ PhCH_2\overset{+}{N}(CH_3)_2Ph\ Br^- \rightleftharpoons [(PhCH_2\overset{+}{N}(CH_3)_2Ph)_2\ Br^-]^+ + [PhCH_2\overset{+}{N}(CH_3)_2Ph\ Br_2^-]^-$$

$$[(PhCH_2\overset{+}{N}(CH_3)_2Ph)_2\ Br^-]^+ \xrightarrow{slow} \left[\begin{array}{l} PhC\overset{+}{H}_2\ (CH_3)_2NPh \\ Br^- \\ PhCH_2(CH_3)_2\overset{+}{N}Ph \end{array}\right] \xrightarrow{fast} \begin{array}{l} (CH_3)_2NPh \\ + \\ PhCH_2Br \\ + \\ PhCH_2\overset{+}{N}(CH_3)_2Ph \end{array} \quad (24)$$

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 S_N2 reaction (equation 25).

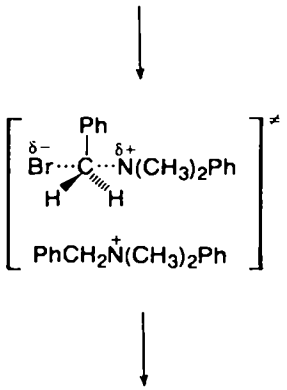
$$PhS^- + PhCH_2\overset{+}{N}(CH_3)_2Ph \longrightarrow \left[PhS^{\delta-}\cdots\overset{\overset{Ph}{|}}{\underset{H\quad H}{C}}\cdots N^{\delta+}(CH_3)_2Ph\right]^{\neq} \longrightarrow$$

$$PhSCH_2Ph + (CH_3)_2NPh \quad (25)$$

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 S_N2 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)[16].

$$[(PhCH_2\overset{+}{N}(CH_3)_2Ph)_2Br^-]^+$$



(26)

$$PhCH_2Br + (CH_3)_2NPh + PhCH_2\overset{+}{N}(CH_3)_2Ph$$

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[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 α-deuterium or 1.42 per 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 α-deuterium or 1.30 per CD_2 group[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 benzyldimethylphenylammonium ion to yield a benzyl carbonium ion and dimethylaniline. This occurs because the C_α—H and C_α—D bonds in the substrate are in a very crowded environment and the C_α—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 C_α—H and C_α—D out-of-plane bending vibrations will be much larger for the benzyldimethylphenylammonium 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[58] and by Westaway and Ali[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 thiophen-oxide ion reaction is unexpectedly large because the extreme crowding around

the C_α—H bonds is reduced in going to the S_N2 transition state[16], because the $C_\alpha \cdots N^+$ 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_α—H bonds. Other work[16,50] has shown that the $S \cdots C_\alpha$ 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[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.

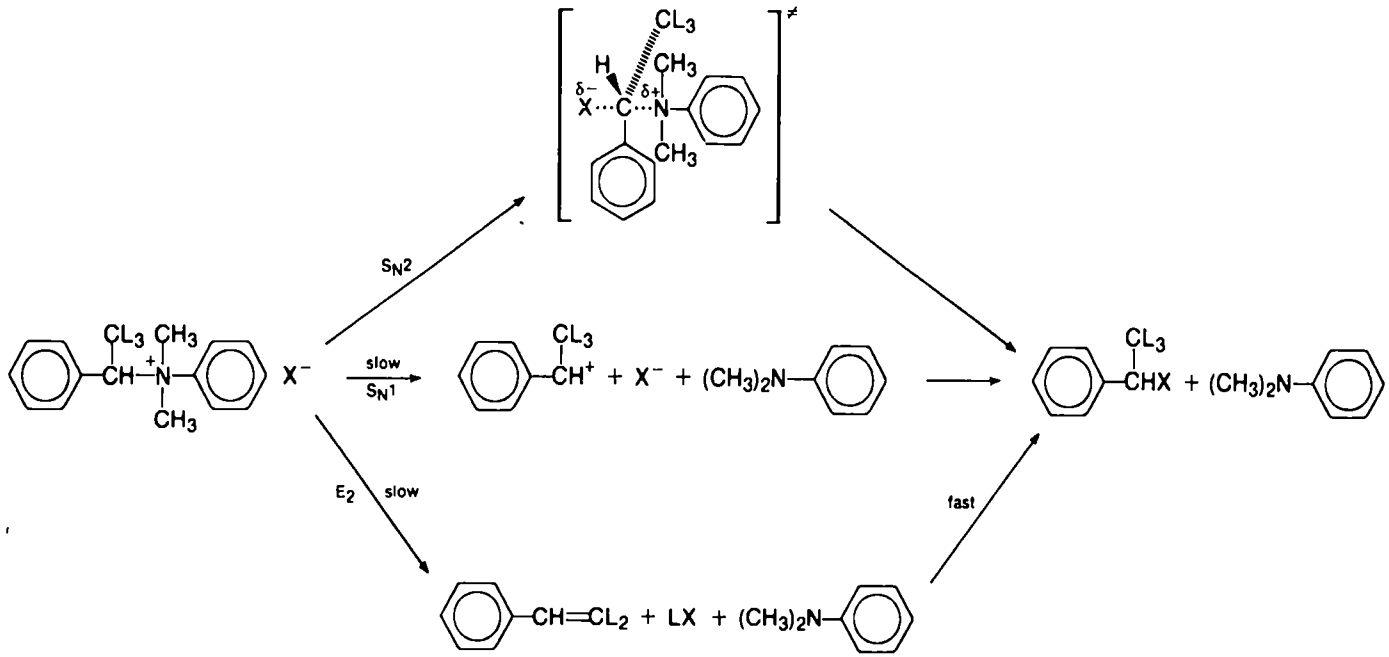
If the actual substitution reaction between the benzyldimethylphenylammonium ion and bromide ion in chloroform and acetone occurs by way of an S_N2 mechanism and the 1-phenylethyl compound reacts by the same mechanism, it is surprising that the 1-phenylethyldimethylphenylammonium ion reacts with bromide ion in chloroform (equation 27) 22.5 times faster than the

$$\begin{array}{l} \mathrm{CH_3} \\ | \\ \mathrm{PhCH\overset{+}{N}(CH_3)_2PhBr^-} \end{array} \xrightarrow{\mathrm{CHCl_3}} \begin{array}{l} \mathrm{CH_3} \\ | \\ \mathrm{PhCHBr} \end{array} + (\mathrm{CH_3})_2\mathrm{NPh} \qquad (27)$$

benzyldimethylphenylammonium ion[61]. Westaway and Joly[49] have used secondary alpha and beta hydrogen–deuterium kinetic isotope effects to determine the mechanism of the nucleophilic substitution reaction between 1-phenylethyldimethylphenylammonium ion and bromide ion in chloroform.

The observed rate of the 1-phenylethyldimethylphenylammonium ion–bromide ion reaction could be faster than the rate of the benzyldimethylphenylammonium 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-phenylethyldimethylphenylammonium bromide reacting by an S_N1 mechanism which is faster than the S_N2 reaction of benzyldimethylphenylammonium bromide; (*iii*) the 1-phenylethyl compound reacting by an S_N2 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 β-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_N1 or an S_N2 mechanism on the other hand, a secondary beta hydrogen–deuterium kinetic isotope effect would be observed. An S_N1 reaction would have a secondary beta deuterium kinetic isotope effect of between 1.2 and 2.5 whereas an S_N2 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


CL3
H
CH3
δ−
X···C···N
δ+
CH3
≠
SN2
CL3 CH3
CH N
CH3
X−
slow
SN1
CL3
CH+ + X− + (CH3)2N
CL3
CHX + (CH3)2N
E2
slow
fast
CH=CL2 + LX + (CH3)2N

L = H, D

SCHEME 1

proceed by the elimination–addition pathway the isotope effect should be at least 1.3.

The observed secondary beta hydrogen–deuterium kinetic isotope effect for this reaction was 1.144 ± 0.0095 per β-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[62] 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 β-CD_3 group. Since the leaving group is nearly removed or has been removed from the α-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 β-CD_3 is smaller than the expected value of 1.2 per β-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[63] found that the isotope effect was 1.13 per β-CD_3 group for the S_N2 ethanolysis of isopropyl *p*-bromobenzenesulphonate. Although the magnitude of the isotope effect in the 1-phenylethyldimethylphenylammonium 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 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 $(k_H/k_D)_\alpha = 1.178 \pm 0.006$ at 25°C was found. Several studies have shown that adding a methyl group to the α-carbon increases the secondary alpha hydrogen–deuterium kinetic isotope effect by approximately four per cent for an S_N2 reaction[61]. 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 $(k_H/k_D)_\alpha = 1.16$. 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 $(k_H/k_D)_\alpha = (1.19 \times 1.04)^{0.75} = 1.18$[61]. 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-phenylethyldimethylphenylammonium bromide because the substrate is extremely crowded in the region around the C_α—H(D) bond and the out-of-plane C_α—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-phenylethyldimethylphenylammonium 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-phenylethyldimethylphenylammonium ion and iodide ion under the same conditions used for the bromide ion reaction (equation 28).

$$PhCH(CH_3)\overset{+}{N}(CH_3)_2Ph\ I^- \xrightarrow[25°C]{CHCl_3} PhCHI(CH_3) + (CH_3)_2NPh \qquad (28)$$

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-phenylethyldimethylphenylammonium iodide reacted by an S_Ni 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 4. The secondary alpha and secondary beta hydrogen–deuterium kinetic isotope effects for the reactions between 1-phenylethyldimethylphenylammonium ion and halide ions at 25°C in chloroform

Halide ion	$(k_H/k_D)_\alpha$	$(k_H/k_D)_\beta$
Br	1.178 ± 0.006	1.144 ± 0.0095
I	1.187 ± 0.005	1.169 ± 0.0125

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-phenylethyldimethylphenylammonium halides in chloroform occurs in two steps. The first step is the preequilibrium 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-phenylethyldimethylphenylammonium ion (it reacts 23 times faster than the benzyldimethylphenylammonium ion) is attributed to the greater steric crowding that exists in the 1-phenylethyldimethylphenylammonium ion. Other work[49,65] shows that the

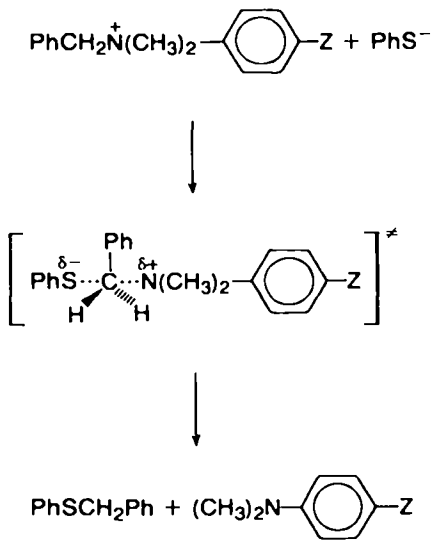
α-carbon–nucleophile and α-carbon–leaving-group transition-state bonds are significantly longer in the 1-phenylethyl compound than they are in the corresponding reaction of the benzyl compound. As a result, the relief of steric crowding in going to the transition state is much greater for the 1-phenylethyl 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 C_α—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[66], 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 S_N2 reaction of a quaternary ammonium salt effects the structure of the transition state. Westaway and Ali[50] have measured the secondary alpha hydrogen–deuterium and the primary nitrogen (leaving-group) kinetic isotope effects in the S_N2 reactions between *para*-substituted phenylbenzyldimethylammonium 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 $C_\alpha \cdots N^+$ 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[50] 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 $C_\alpha \cdots N^+$ 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 $C_\alpha \cdots N^+$ bond is slightly longer in the transition state when a more electron-withdrawing substituent is present in the leaving group.



(29)

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_α—H(D) out-of-plane bending vibrations in the substrate because the point of structural change occurs too far away (six bonds) from the α-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_α—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 α-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_α—H bending vibrations and a large isotope effect[50]. In fact, this idea is supported by experimental[48] as well as two different theoretical calculations[67,68].

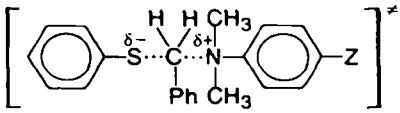
Applying this criterion to the data presented in Table 5 indicates that the longest $^-S\cdots N^+$ distance in the transition state is observed when the *para* substituent is

TABLE 5. The secondary alpha hydrogen–deuterium and primary nitrogen kinetic isotope effects in the S_N2 reactions between thiophenoxide ion and *para*-substituted phenylbenzyldimethylammonium ions in DMF at 0°C

Para substituent	$(k_H/k_D)_\alpha$[a]	k^{14}/k^{15}[a]
OCH_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[a]



Para substituent (Z) on the leaving group	k^{14}/k^{15}	Relative C_α—N bond length in transition state	$(k_H/k_D)_\alpha$	Relative S—N distance in transition state	Relative transition-state structure
OCH_3	1.0197	C·····N	1.207	S·····N	S·····C·····N
H	1.0200	C·····N	1.179	S·····N	S·····C·····N
Cl	1.0202	C·····N	1.151	S···N	S··C·····N

[a]The relative lengths of the sulphur–α-carbon transition-state bonds have been confirmed by measuring the Hammett ρ values obtained by changing the substituent in the thiophenoxide ion.

methoxy (the poorest leaving group) and that the shortest $^-S\cdots N^+$ 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 α-carbon–leaving-group ($C_\alpha\cdots N^+$) bond and a much shorter nucleophile–α-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.

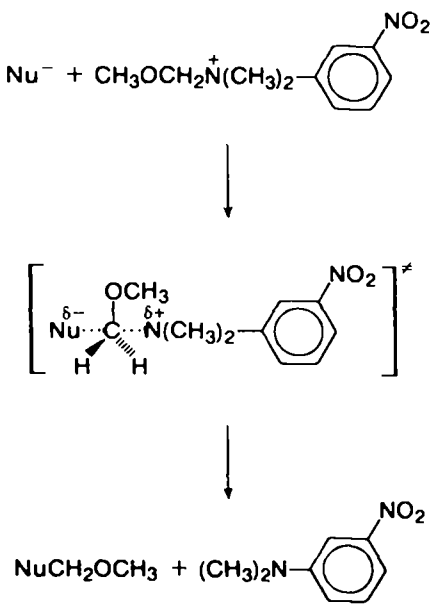
The results found in this study can be compared with the substituent effects predicted for S_N2 reactions with a better leaving group by Thornton's reacting bond rule[28] and the More O'Ferrall-type energy surface for S_N2 reactions[69,50]. Both Thornton's rules and the More O'Ferrall-type energy surface predict that changing to a better leaving group should lead to a transition state with a much longer α-carbon–nucleophile ($S\cdots C_\alpha$) bond and a slightly longer α-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[29].) 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[50].

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 α-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 α-carbon, the shortest nucleophile–α-carbon ($S\cdots C_\alpha$) bond would be expected in the transition state with the most electron-withdrawing substituent.

TABLE 7. Secondary alpha hydrogen–deuterium kinetic isotope effects and rate constants for the S_N2 reactions of various nucleophiles with the *N*-methoxymethyl-*N*,*N*-dimethyl-*m*-nitroanilinium ion in water at 25°C

Nucleophile	$(k_H/k_D)_\alpha$ per D	$10^5 k_2$(l mol^{-1} s^{-1})
I^-	1.18	278
Br^-	1.16	85.9
$HOCH_2CH_2S^-$	1.14	751
$CH_3O_2CCH_2S^-$	1.14	1140
Cl^-	1.13	39.6
H_2O	1.11	0.434
$CH_3(CH_2)_2NH_2$	1.08	196
$NC(CH_2)_2NH_2$	1.07	78.4
CN^-	1.08	52
PhO^-	1.08	237
OH^-	1.07	90.6
AcO^-	1.07	24
F^-	0.99	14.1

Recently, Knier and Jencks[70] have reported the secondary alpha hydrogen–deuterium kinetic isotope effects for the S_N2 reactions between several different nucleophiles and the *N*-methoxymethyl-*N*,*N*-dimethyl-*m*-nitroanilinium ion (equation 30). Their results are given in Table 7.



(30)

These results are interesting for several reasons. The most striking feature is that these isotope effects are extremely large for S_N2 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 α-D originally predicted for S_N2 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 α-D)[16,50] or by Ko and Leffek (1.10 and 1.12 per α-D[58]) for the S_N2

reactions of the closely related benzyldimethylanilinium 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 $CH_3(CH_2)_2NH_2$ and $NC(CH_2)_2NH_2$ and identical isotope effects are observed for the nucleophiles $HOCH_2CH_2S^-$ and $CH_3O_2CCH_2S^-$.

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_α—H bonds in the transition state than in the reactants. This suggests that these transition states are very loose, i.e. have long α-carbon–nucleophile and α-carbon–leaving group bonds. The long α-carbon–leaving-group bond is required because the approaching nucleophile increase the steric crowding around the α-carbon. The large reduction in the steric crowding at the C_α—H bonds must, therefore, result from a substantial increase in the α-carbon–leaving-group bond, i.e. moving the large bulky leaving group away from the C_α—H bonds.

Although there is insufficient information to *prove* whether the α-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_H/k_D = 1.14 per α-D) are significantly larger than those reported for the S_N2 reaction between thiophenoxide ion and benzyldimethylanilinium ion (k_H/k_D = 1.09 per α-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 α-carbon–nucleophile and the α-carbon–leaving-group bonds are long in the transition state of the thiophenoxide ion–benzyldimethylanilinium ion reaction. The much larger isotope effect for the methoxymethyl compound suggests that both the α-carbon–nucleophile and α-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 α-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 S_N2 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 C_α—H bonds is not altered significantly in going from the reactant to the transition state. This requires much more steric crowding around the C_α—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 C_α—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 Jencks[70] 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, $k(H_2O)/k(D_2O)$, 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 S_N2 reactions of methyl substrates and are significantly smaller than the solvent isotope effects of 1.2 to 1.4 reported for S_N1 reactions[74]. These results confirm that the nucleophilic substitution reactions of the methoxymethyl compounds proceed via an S_N2 mechanism and illustrate that the solvent isotope effects for the S_N2 reactions of anilinium ions are normal.

C. Substituent Effects on the Geometry of S_N2 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 S_N2 transition state[28]. The second method, which is an extension[69] 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 geomety[50,69].

Recently, Westaway and Ali[50] published a study describing how changes in the leaving group altered the geometry of the S_N2 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

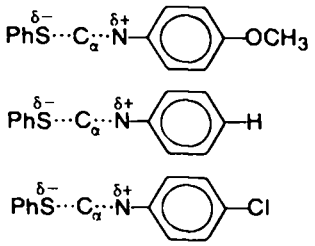
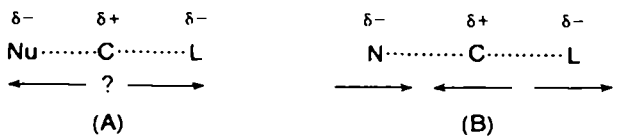


FIGURE 3. Relative transition-state structures for the S_N2 reactions of *para*-substituted phenylbenzyldimethylammonium ions with thiophenoxide ion.

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:



Adding a more electron-withdrawing 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-withdrawing substituent would have a longer nucleophile–α-carbon and α-carbon–leaving-group bond. For the parallel vibration, B, a more electron-withdrawing substituent will make an increase in the vibration easier and the transition state should have a longer nucleophile–α-carbon and a shorter α-carbon–leaving-group bond. Whether one assumes that the parallel effect is more important[28] or that the parallel and perpendicular effects are equally important[29], Thornton's theory predicts a longer $S\cdots C_\alpha$ bond in the transition state with a better leaving group. The change in the $C_\alpha\cdots N^+$ bond, on the other hand, is less certain. If the parallel effect is greater, a shorter $C_\alpha\cdots N^+$ bond would be expected, whereas there should be almost no change in the $C_\alpha\cdots N^+$ bond if the parallel and perpendicular effects are equally important. An examination of the relative transition-state structure in Figure 3 indicates that the $S\cdots C_\alpha$ bond is significantly shorter and that the $C_\alpha\cdots N^+$ bond is slightly longer in the transition state with a more electron-withdrawing substituent in the leaving group. The reacting bond rule predicts correctly that the $S\cdots C_\alpha$ bond will change more than the $C_\alpha\cdots N^+$ bond. Moreover, the observed change in the $C_\alpha\cdots N^+$ bond is described if the perpendicular effect is slightly more important than the parallel effect. Obviously, the change in the $S\cdots C_\alpha$ bond cannot be accommodated by Thornton's theory since the theory predicts a longer $S\cdots C_\alpha$ bond and a shorter $S\cdots C_\alpha$ 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

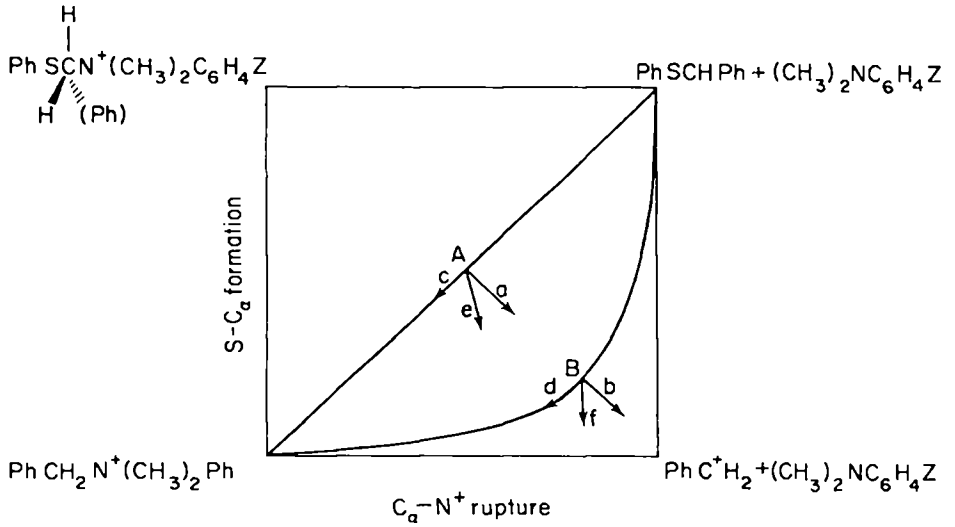


FIGURE 4. Transition-state map for the various possible substitution mechanisms of benzyldimethylanilinium ions with thiophenoxide ion.

the transition state on the energy surface. Both the S···C_α and C_α···N^+ bonds are long (weak) in the transition state. The means that the bond order at the α-carbon, n_{C_α}, given by the sum of the S···C_α and C_α···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 $n_{C_\alpha} = 1.00$[69]) or in the lower right-hand part of the energy surface where n_{C_α} 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···C_α and C_α···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···C_α and a shorter C_α···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···C_α bond and a slightly longer C_α···N^+ bond (the perpendicular effect is slightly more important). A transition state with a longer S···C_α bond and a slightly shorter C_α···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···C_α bond whether the transition state is at A or B and the C_α···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···C_α bond) will change more than the closer C_α···N^+ bond. It also suggests correctly that the C_α···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 $S\cdots C_\alpha$ bond incorrectly. A shorter $S\cdots C_\alpha$ bond is observed in the transition state with a better leaving group whereas a longer $S\cdots C_\alpha$ 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[75] who studied the carbonyl elimination reaction of benzyl nitrate to give benzaldehyde. Subsequently, Bourns and Smith[76] 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.

$$PhCH_2CH_2\overset{+}{N}(CH_3)_3 + EtO^- \longrightarrow PhCH{=}CH_2 + N(CH_3)_3 \qquad (31)$$

1. *Deuterium exchange at the β-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

$$PhCH_2CH_2\overset{+}{N}(CH_3)_3 + EtO^- \longrightarrow \left[\begin{array}{l} \overset{+}{N}(CH_3)_3 \\ Ph{-}CH{=}CH_2 \\ \vdots \\ H \\ \vdots \\ {}^-OEt \end{array}\right] \qquad (32)$$

[T.S.]

products

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

$$PhCH_2CH_2\overset{+}{N}(CH_3)_3 + EtO^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Ph\bar{C}HCH_2\overset{+}{N}(CH_3)_3 + EtOH \qquad (33)$$

$$\downarrow k_3$$

$$PhCH{=}CH_2 + N(CH_3)_3$$

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 0.1M 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, $Ph\bar{C}H{-}CH_2{-}\overset{+}{N}(CH_3)_3$, 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:

$$\text{Rate of reaction} = \frac{k_1 k_3[\text{substrate}][EtO^-]}{k_2[EtOH] + k_3}$$

If $k_3 \gg k_2$[EtOH] then:

$$\text{Rate of reaction} = k_1\,[\text{substrate}]\,[EtO^-]$$

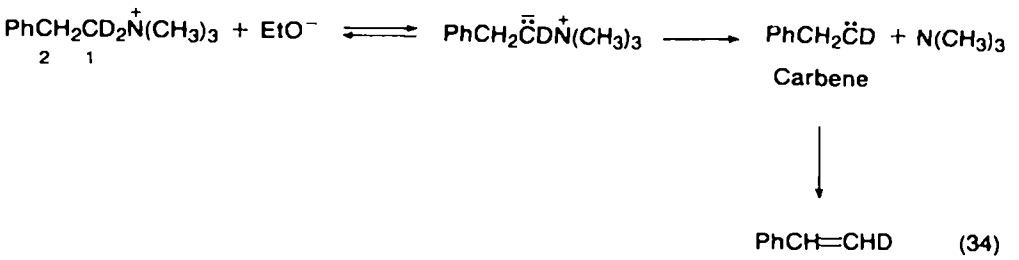
Consequently, the slow (rate-determining) step for the carbanion mechanism where $k_3 \gg k_2$, as well as for the concerted process, involves rupture of the carbon–hydrogen bond at the transition state. A primary hydrogen–deuterium kinetic isotope effect therefore, is expected and in fact, Saunders and Edison[77] found a value of $k_H/k_D = 3$ 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, $[(k^{14}/k^{15}) - 1]100$, 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 $[(k^{14}/k^{15}) - 1]100 = 1.33$ 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[76].

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



(34)

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-d_2 bromide and it was found that no significant exchange occurs at the α-position. Consequently, the zwitterion, $PhCH_2\ddot{C}D\dot{N}(CH_3)_3$, 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-d_2 and 2-phenylethyltrimethylammonium-2,2-d_2 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 $-CH_2Br$ 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[76].

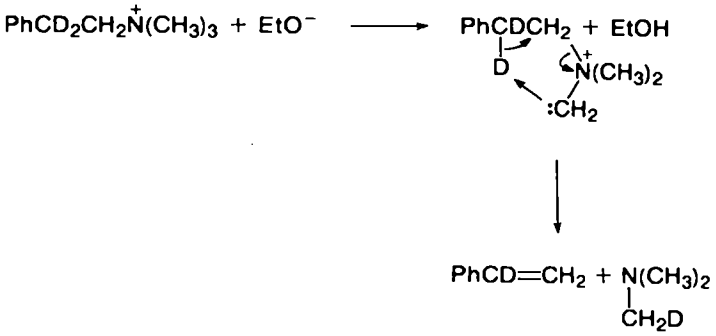
TABLE 8. A comparison of the number (N_1) of hydrogen atoms per molecule found (by NMR analysis) on the terminal carbon of styrene dibromide with the number predicted for the β- and α-elimination processes (N_2 and N_3 respectively)

Reactant	N_1	N_2	N_3
$PhCD_2CH_2\dot{N}(CH_3)_3$	2.04	2	1
$PhCH_2CD_2\dot{N}(CH_3)_3$	0.00	0	1

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.

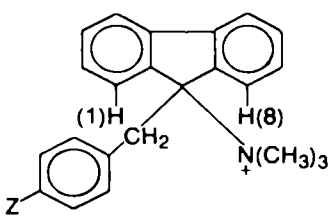


(35)

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[76].

B. A Hydrogen–Deuterium Kinetic Isotope Effect Study of the Reaction of 9-(*ortho*-Substituted-benzyl)-fluorenyl-9-trimethylammonium Ions in Ethanol

The reaction of several 9-(4-substituted-benzyl)fluorenyl-9-trimethylammonium ions (**5**) with ethoxide ion has been investigated[78,79] in order to determine the effect of substituents on transition-state geometry. The results, which will be discussed in



(5)

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[80] 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^{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 (alkene)/k^S(ether) ratio (equation 36) calculated from the ratio of products together with the hydrogen–deuterium kinetic isotope effects, k_H^{obs}/k_D^{obs}, and k_H^E/k_D^E are included.

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

Ortho substituent	$10^5 k^{obs}(s^{-1})$	% Alkene	$(k^E/k^S)^a$	$(k_H^E/k_D^E)^b$	k_H^{obs}/k_D^{obs}
2-Methyl	2.35	56.2	1.28	1.54	1.22
2-Methyl-β,β-d_2	1.92	42.8	0.748		
2,4-Dimethyl	2.85	56.8	1.31	1.76	1.16
2,4-Dimethyl-β,β-d_2	2.45	40.1	0.669		
2,6-Dichloro	9.60	28.6	0.401	2.10	1.45
2,6-Dichloro-β,β-d_2	6.60	14.7	0.172		
2,6-Dimethyl-	268	28.8	0.404	2.78	2.35
2,6-Dimethyl-β,β-d_2	114	11.6	0.131		
2,4,6-Trimethyl	248	25.4	0.340		

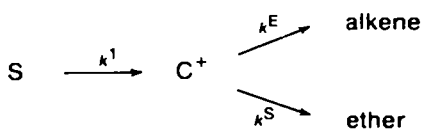
[a]See text and equation (36).
[b]Calculated with the assumption that $k_H^S/k_D^S = 0.9$.

The Elcb, 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[81] 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



(36)

then it can be shown that the observed rate constant for alkene formation is given by:

$$k^{obs} = k^{I}k^{E}/(k^{E} + k^{S})$$

If $k^{E} > k^{S}$, then:

$$k_H^{obs}/k_D^{obs} \simeq k_H^{I}/k_D^{I}$$

and the observed isotope effects will mainly be secondary β-deuterium isotope effects, i.e. when $k^{E}/k^{S} = 1.28$ then $k_H^{obs}/k_D^{obs} = 1.22$ for the 2-methyl substrate. However, when $k^{E} < k^{S}$ and if $k_H^{S}/k_D^{S} \simeq 1$, then:

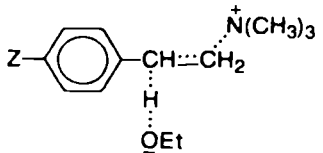
$$k_H^{obs}/k_D^{obs} \simeq (k_H^{I}/k_D^{I})(k_H^{E}/k_D^{E}).$$

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 $k_H^{obs}/k_D^{obs} = 2.35$ for the 2,6-dimethyl salt. The isotope effects for loss of hydrogen from the carbocation (k_H^{E}/k_D^{E}) 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 *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[82] initiated a study concerning the effect of substituents on the nature of the E2 transition state for the reaction of a series of *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 C_β—H and C_α—N^+ bond rupture at the E2 transition state (**6**)



(**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 *para* substituent. Although the effects for the *p*-H or *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.

TABLE 10. Isotope effects found for the E2 reaction of 2-arylethyltrimethylammonium ions $[ZC_6H_4CH_2CH_2N(CH_3)_3]$ with sodium ethoxide in ethanol at 40°C

Para substituent 'Z'	$[(k^{14}/k^{15}) - 1]100$	k_H/k_D
OCH_3	1.37 ± 0.09[a]	2.64 ± 0.05[b]
H	1.33 ± 0.02	3.23 ± 0.06
Cl	1.14 ± 0.09	3.48 ± 0.07
CF_3	0.88 ± 0.06	4.16 ± 0.07

[a]The limits shown are standard deviations.
[b]Ratio of 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.

$[(k^{14}/k^{15}) - 1]100$ is 1.33 and 0.88 for the *p*-H and *p*-CF_3 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 Steffa and Thornton[24] who determined the secondary isotope effect, k^{OD^-}/k^{OH^-}, for the reaction of several quaternary ammonium ions at 80°C. The secondary isotope effects, k^{OD^-}/k^{OH^-}, and the primary β-deuterium isotope effect, k_H/k_D, 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, k^{OD^-}/k^{OH^-}, 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 k^{OD^-}/k^{OH^-} values, result in an increase in the k_H/k_D 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

Substrate	(k^{OD^-}/k^{OH^-})[a]	(k_H/k_D)[b]
$PhCH_2CH_2\dot{N}(CH_3)_3$	1.79	3.23
p-$ClC_6H_4CH_2CH_2\dot{N}(CH_3)_3$	1.73	3.48
$PhCH_2CH_2\dot{N}(CH_3)_2Ph$	1.62	4.50[c]

[a]Reference 24.
[b]Measured with ethoxide ion in ethanol at 40°C.
[c]Reference 83.

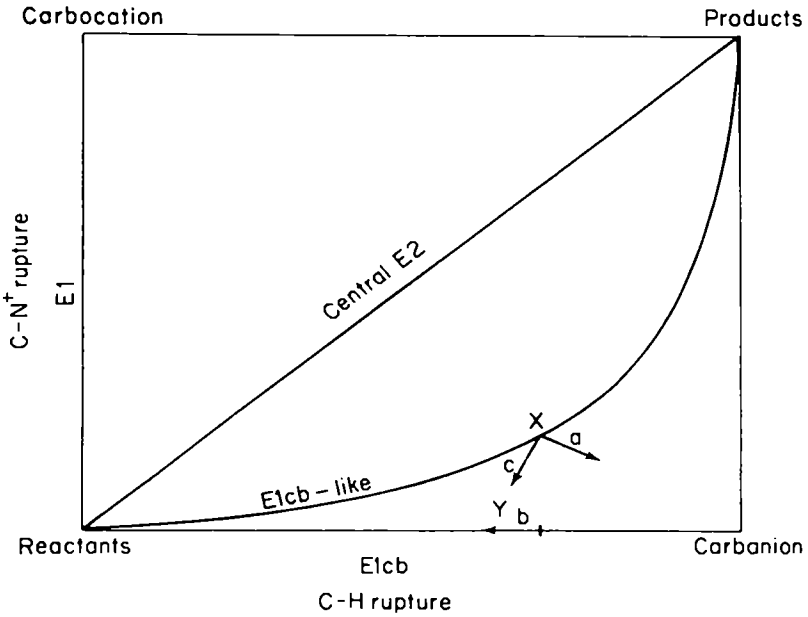


FIGURE 5. Transition-state map for the various elimination mechanisms of 2-arylethylammonium salts with ethoxide ion.

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 β-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.

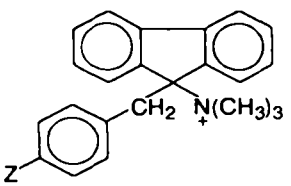
A consideration of the More O'Ferrall potential energy diagram (Figure 2, Section I.B) can also accomodate the isotope effect results. The energy diagram can be represented schematically, (Figure 5), in terms of the various mechanisms for elimination.

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 ρ 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-trimethylammonium ions (**5**) with sodium ethoxide in ethanol has recently been investigated[78,79]. The mechanism was shown to be the normal concerted E2 process



(**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 12. Deuterium and nitrogen isotope effects for reaction of 9-(4-substituted-benzyl)-fluorenyl-9-trimethylammonium ions (**5**) with sodium ethoxide in ethanol

Substituent 'Z'	k_H/k_D (60°C)	$[(k^{14}/k^{15}) - 1]100$ (70°C)
OCH_3	5.91 ± 0.09[a]	0.80 ± 0.03[b]
CH_3	5.75 ± 0.10	0.91 ± 0.09
H	5.61 ± 0.08	0.92 ± 0.04
F	—	0.95 ± 0.03
Cl	5.34 ± 0.08	—
Br	5.10 ± 0.07	—
CF_3	4.15 ± 0.12	1.24 ± 0.07

[a]Ratio of 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.
[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 π-system of the phenyl ring. This is consistent with the observation of a small value of ρ (+1.33) for the reaction of **5**.

Assuming that ρ does not provide a measure of the degree of 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* 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 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[29] 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

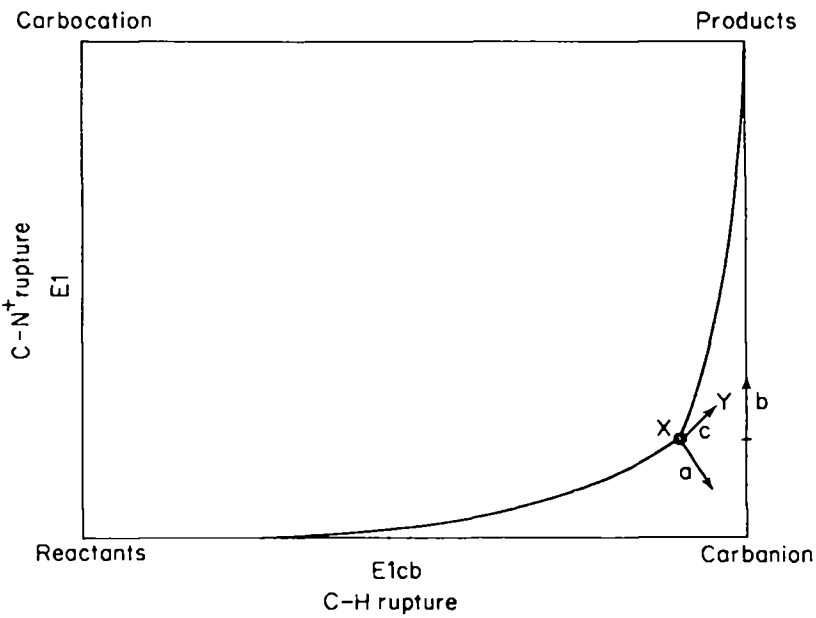


FIGURE 6. Transition-state map for the various elimination mechanisms of the 9-(4-substituted-benzyl)fluorenyl-9-trimethylammonium ions.

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 Elcb-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-Phenylethyldimethylanilinium 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-phenylethyldimethylanilinium salts with ethoxide in ethanol at 40°C (equation 37).

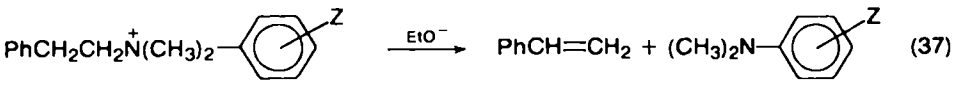
The nitrogen isotope effect results show that an electron-withdrawing group in the aniline ring leads to an increased magnitude of the leaving-group isotope effect. Consequently, the extent of carbon–nitrogen bond rupture is greater for the more electron-withdrawing substituents, i.e. the 'better' the leaving group.

The authors, after a consideration of the k^{OD^-}/k^{OH^-} values of Steffa and

TABLE 13. Primary hydrogen–deuterium and nitrogen isotope effects for the reaction of $PhCH_2CH_2\overset{+}{N}(CH_3)_2C_6H_4Z$ ions with sodium ethoxide in ethanol at 40°C

Substituent 'Z'	k_H/k_D	$[(k^{14}/k^{15}) - 1]100$
p-OCH_3	4.70 ± 0.06[a]	1.19 ± 0.07[b]
p-CH_3	4.61 ± 0.04	1.13 ± 0.06
H	4.50 ± 0.04	1.12 ± 0.08
p-Cl	4.53 ± 0.09	1.30 ± 0.07
m-CF_3	5.00 ± 0.07	1.32 ± 0.06
p-CF_3	5.39 ± 0.07	—

[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.



(37)

Thornton[24], and the variation of the primary k_H/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 $k_H/k_D = 4.50$ and a smaller Hammett ρ 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_H/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[84] 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_H/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_H/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

Leaving groups	$k_2 \times 10^4$ (1 mol^{-1} s^{-1})	k_H/k_D	pK_a
Triethylamine	2.99 ± 0.03	2.82	11.01
Quinuclidine	1.12 ± 0.08	2.47	10.58
N-Methylpyrrolidine	2.29 ± 0.05	2.80	10.32
N-Methylpiperidine	4.06 ± 0.04	2.96	10.08
Trimethylamine	5.27 ± 0.05	3.02	9.81
N,N-Dimethylbenzylamine	11.23 ± 0.09	3.31	9.02
N-Methylmorpholine	18.09 ± 0.01	3.19	7.40
N-Methyl-*N*-ethylaniline	54.30 ± 0.03	4.50	6.00
N,N-Dimethylaniline	70.90 ± 0.03	4.50	5.15

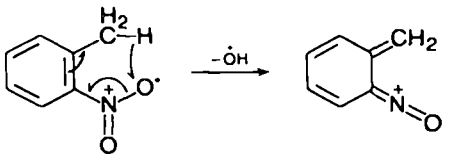
Consequently, considering that the proton is more than one-half transferred at the transition state, the conclusion is reached, in agreement with Bourns, that the better the leaving group the less the degree of C—H bond weakening at the transition state.

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*

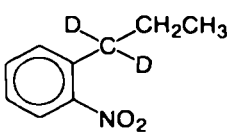
The loss of ·OH is observed from the molecular ion of *o*-nitrotoluene whereas there is no observed loss of ·OH from the molecular ions of the *meta* and *para* isomers. A cyclic mechanism (equation 38) has been proposed to account for these



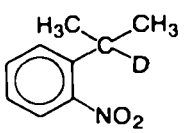
(38)

results. Recently[85] it was found that α-d_3-*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[85] examined the spectra of α,α-d_2-*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



(7)



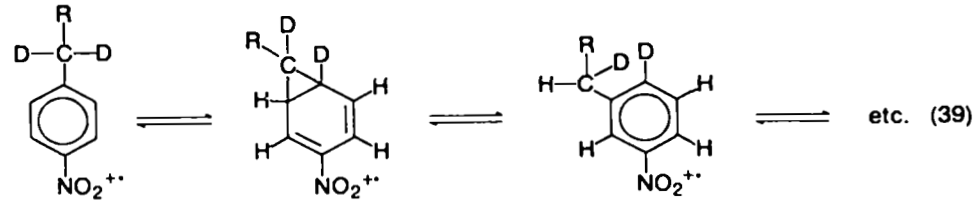
(8)

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*-alkylnitrobenzenes also lost ·OH from the molecular ion in contrast to the behaviour of the isomeric nitrotoluenes. For example, the mass spectrum of *n*-propylnitrobenzene 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

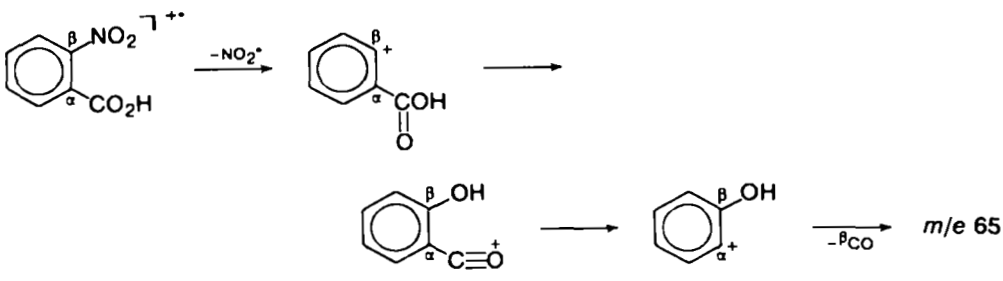
hydroxyl group be lost. On this basis, the observed extent of loss of ·OH from the three isomers seems reasonable as no rearrangement is necessary for loss of ·OH from the *ortho* isomer and the *meta* isomer can rearrange to the *ortho* compound more easily than the *para* substrate. A general mechanism to account for the rearrangement is shown in equation (39).



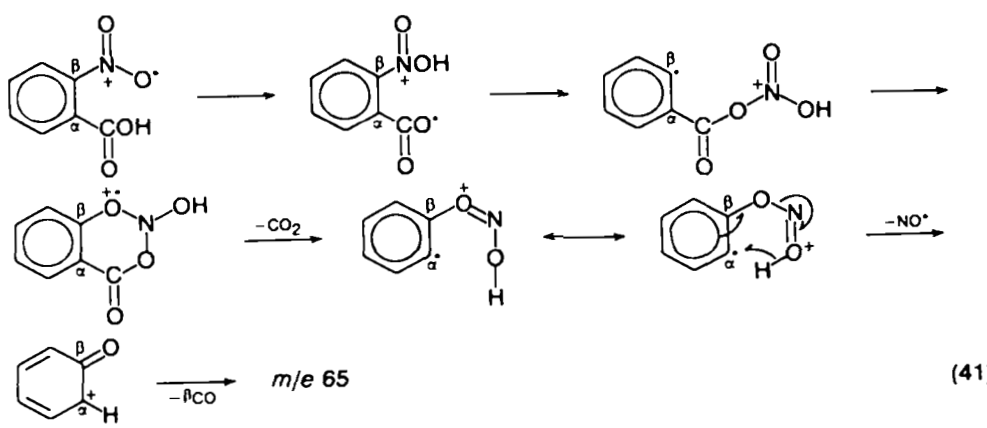
etc. (39)

2. *Carbon-13 and oxygen-18 labelling*

Benoit and Holmes[86] investigated the mechanism for the formation of the *m/e* 93 ion from the molecular ion of *o*-nitrobenzoic acid. On the basis of labelling experiments they suggested two mechanisms (equations 40 and 41).

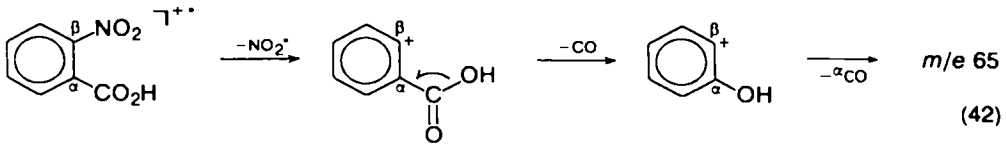


(40)



(41)

Djerassi and coworkers[87] suggested two alternate pathways (equations 42 and 43), which are consistent with the data of Benoit and Holmes[86]. It is seen that the $^{\beta}CO$ is lost in the mechanisms shown in equations (40) and (41) while for mechanisms (42) and (43) the $^{\alpha}CO$ is lost.



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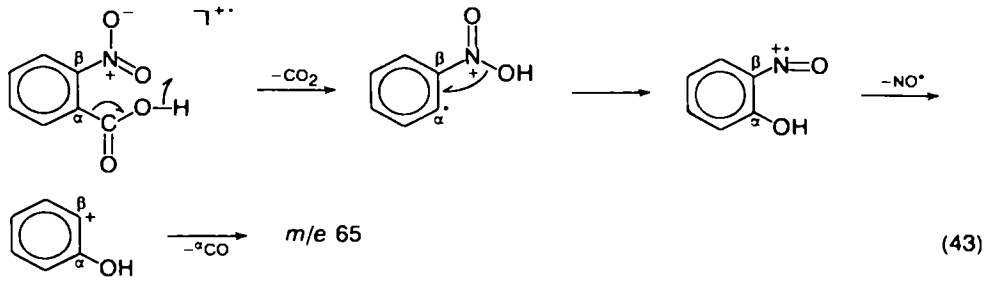
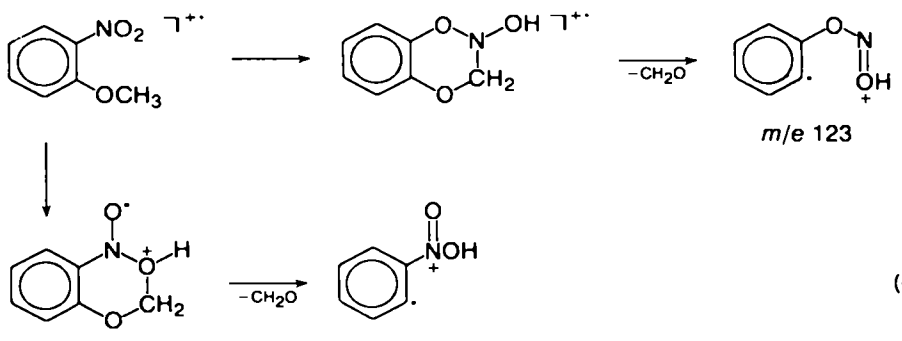


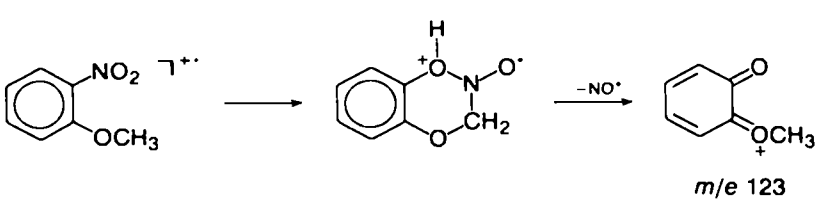
(43)

Djerassi's group[87] prepared the substrate with ^{13}C at the ring carbon to which the carboxyl group is attached, i.e. the α-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[86] 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_2O loss (equation 44) and the remainder comes from NO· expulsion (equation 45).



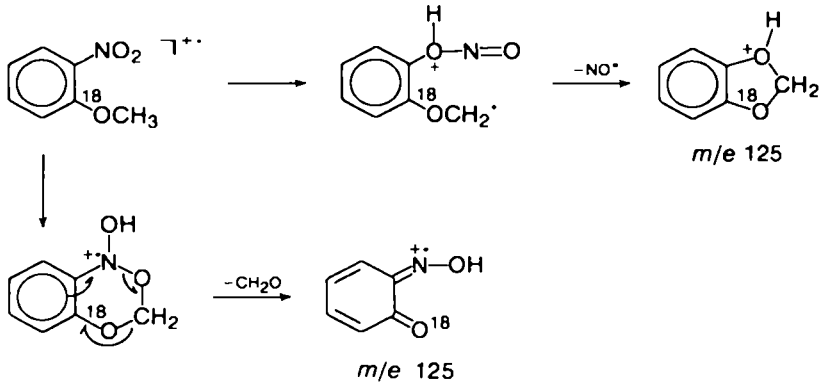
(44)



(45)

In order to gain further information concerning the two proposed mechanisms, Djerassi[87] 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).



(46)

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[88] using carbon-13 and nitrogen-15 labelling.

When the mass spectra of the 2-, 3- and 4-cyanopyridines labelled with ^{15}N in the cyano group were examined, it was found that the retention of the label in the $[M - HCN]^{+\cdot}$ ions was 64–66%. Thus the neutral HCN lost from $M^{+\cdot}$ 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 $M^{+\cdot}$, the mass spectra of 2-, 3- and 4-cyanopyridines labelled with ^{13}C in the cyano group were determined. It was found that the percentage retention of ^{13}C in the $[M - CN]^{+\cdot}$ ions was very similar to the corresponding ^{15}N retention, i.e. 67% for 2-^{13}CN- pyridine, 69% for 3-^{13}CN-pyridine and 66% for 4-^{13}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}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}C retention was due to the loss of the positional identity of the ring-carbons prior to the loss of HCN.

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Subject Index