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SOME SUBSTITUTION REACTIONS OF ARYL SULFIDES AND ARYL ETHERS WITH ALIPHATIC AMINES IN DMSO: THE MECHANISM OF BASE CATALYSIS

by

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A thesis submitted for the degree of Doctor Of Philosophy in the
Department of Chemistry, University of Durham
April 1995

For my mother

DECLARATION

The material in this thesis is the result of research carried out in the Department of Chemistry, University of Durham, between October 1991 and September 1994. It has not been submitted for any other degree and is the authors own work, except where acknowledged by reference.

STATMENT OF COPYRIGHT

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SOME SUBSTITUTION REACTIONS OF ARYL SULFIDES AND ARYL ETHERS WITH ALIPHATIC AMINES IN DMSO: THE MECHANISM OF BASE CATALYSIS

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ABSTRACT

The reactions of several nitro-aromatic substrates with the aliphatic amines, n-butylamine, pyrrolidine and piperidine in DMSO have been studied.

Reaction of the amines with trinitroaromatic compounds, such as ethyl thiopicrate, phenyl thiopicrate and phenyl 2,4,6-trinitrophenyl ether, was shown to occur in two well separated processes. A rapid reaction, occuring at an unsubstituted ring position, resulted in the formation of a σ-adduct;this was followed by a slower substitution reaction, resulting in the displacement of the 1-substituent to give the amino-substituted compound.

Kinetic results show that in the formation of the 3-adduct, the rate determining step changes from nucleophilic attack by amine with n-butylamine to proton transfer from the zwitterionic intermediate with piperidine; with pyrrolidine the proton transfer step is partially rate limiting.

The substitution reaction involving n-butylamine is not base catalysed indicating nucleophilic attack, the k_1 step, is rate determining. However, the reactions with pyrrolidine and piperidine are subject to general base catalysis showing proton transfer is involved in the slow step. The rate limiting step is thought to be the proton transfer from the zwitterionic intermediate to base.

A single substitution reaction was seen for the reaction of the less activated 1-substituted 2,4-dinitrophenyl and 1-substituted 2,4-dinitronaphthyl compounds. The rate limiting step again changes from nucleophilic attack with n-butylamine to proton transfer with pyrrolidine and piperidine. The uncatalysed, k_2, pathway was detected during the reaction of the 1-substituted 2,4-dinitrophenyl compounds. Those were the least activated substrates studied and as the effectiveness of the base catalysed step relative to the uncatalysed decomposition of the intermediate decreases with decreasing activation of the substrate, detection of the uncatalysed step became possible.

Kinetic and equilibrium studies were also made on the reaction of morpholine with several phenyl ethers. Results were compared with those for piperidine with the same substrates, the values of the kinetic and equilibrium constants were as expected considering morpholine has the same steric requirements as piperidine but is considerably less basic.

CONTENTS

CHAPTER 1

Introduction

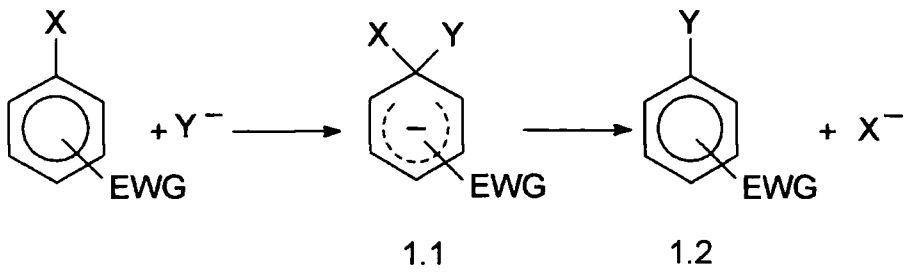
Introduction

1.1 Nucleophilic Aromatic Substitution

Nucleophilic displacements at an unsubstituted aromatic ring do not usually occur as the hydride ion is a poor leaving group.[1] If however there is a suitable leaving group on the ring then nucleophilic aromatic substitution may take place by one of the following mechanisms:

1.1.1 S_NAr

If an aromatic ring contains strongly electron-withdrawing groups and a good leaving group, nucleophilic displacement can occur under mild conditions.

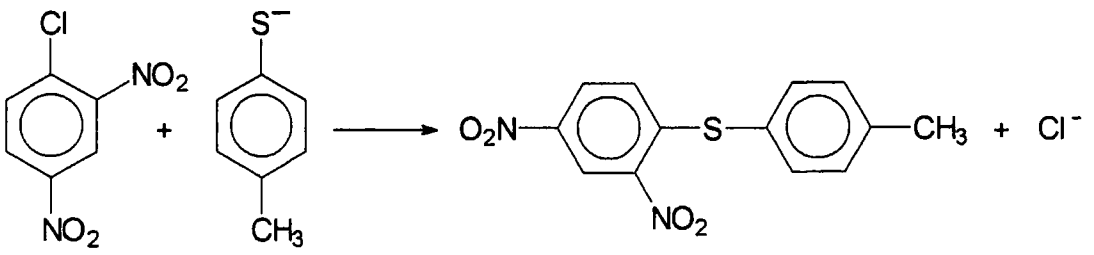


1.1 1.2

equation 1.1

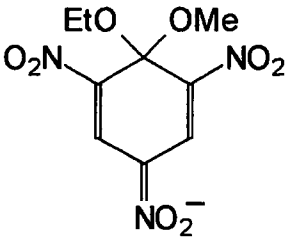
X = Good leaving group or nucleofuge, e.g. Cl
Y = Anionic or neutral nucleophile, e.g. RO^-, RNH_2.
EWG = One or more electron-withdrawing groups, e.g. NO_2.

The Addition-Elimination mechanism for nucleophilic substitution is analogous to the mechanism of electrophilic aromatic substitution in that a charged intermediate is produced. In nucleophilic substitution, the intermediate is negatively charged and reaction is generally favoured by electron-withdrawing groups. An example[2] is shown in equation 1.2. In electrophilic substitution, where positive charge is usually created in the ring, reaction is favoured by electron-releasing groups.



equation 1.2

The S_NAr mechanism for nucleophilic aromatic substitution occurs in two steps. The first step involves addition of the nucleophile to the aromatic ring to form an intermediate anion, σ-complex, which then decomposes to give the substitution product. There is a great deal of evidence for this mechanism, including the isolation of the intermediate σ-complexes. Initial work was by Jackson[3] and Meisenheimer[4] at the turn of the century leading to the name, Meisenheimer complexes. Structure 1.3 was proposed for the structure of a coloured species, resulting from the reaction of 1-ethoxy 2,4,6,-trinitrobenzene with methoxide.[4]

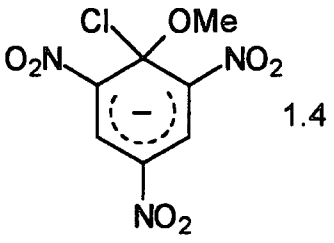


1.3

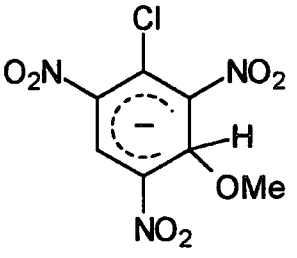
Following this, structures of many other σ-complexes were determined by NMR spectroscopy and by x-ray crystallography.[5-12] The majority of these studies have involved attack of the nucleophile at an unsubstituted ring position (X=H) so that further reaction of 1.1 is unfavourable. Other studies have involved symmetrical adducts where the leaving group is the same as the nucleophile, i.e. X=Y=OMe.

The stability of σ-complexes is enhanced by the use of protic-dipolar aprotic cosolvent systems i.e. H_2O-DMSO, ROH-DMSO. The use of DMSO as a cosolvent has allowed a much wider range of adducts to be studied and has yielded information on the kinetics of the formation and decomposition of the Meisenheimer complexes, and hence the mechanism of S_NAr reactions.[5-14] In DMSO, intermediates, 1.1, on the substitution pathway may be directly observed. Although UV/Visible spectra provide useful information, further evidence is usually required to prove the structure of an intermediate. Thus work on the UV/Visible spectra of the reaction of picryl chloride with methoxide suggested species 1.4 was formed.[15] However, the observable species

was later proved by NMR to be 1.5. In general NMR is a more diagnostic technique to determine the structure of intermediates than UV/Visible spectroscopy.

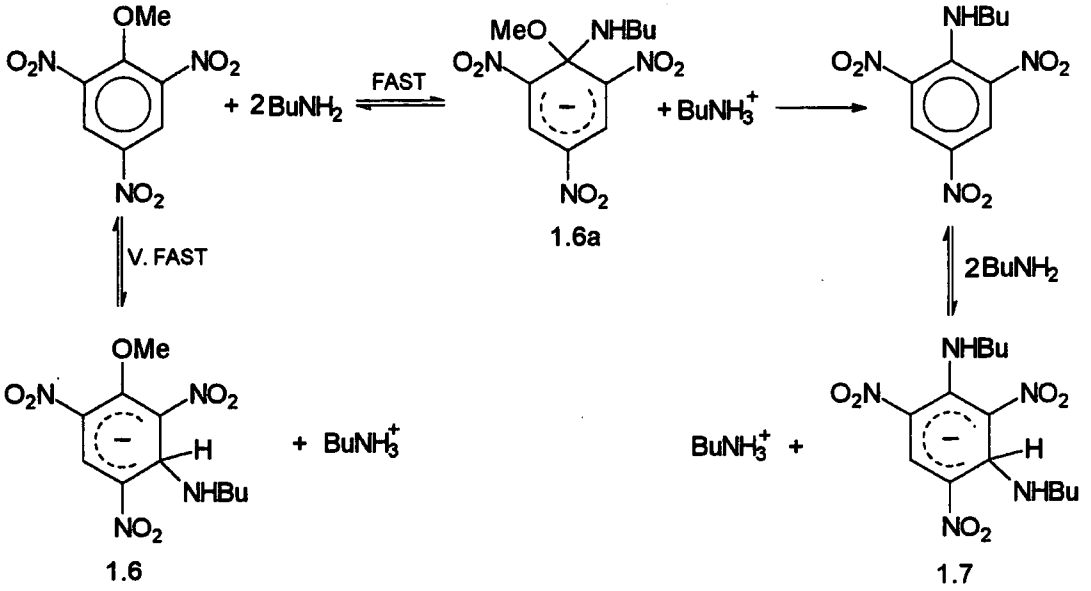


1.4



1.5

The reaction of 2,4,6-trinitroanisole (TNA) with butylamine has been studied by low temperature flow NMR studies.[22,23] The most rapid reaction involves attack at the 3-position to give 1.6. However, the intermediate on the substitution pathway, 1.6a, may be observed. N-butyl picramide, the substitution product, is found in the presence of excess amine, to be in equilibrium with its 3-adduct, 1.7, and with the conjugate base formed by transfer of the side-chain proton.

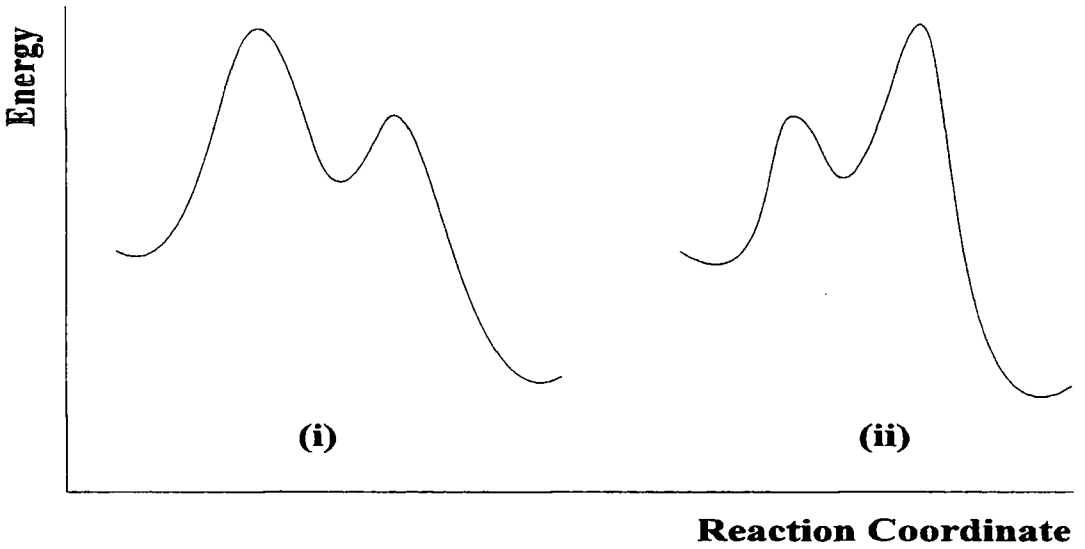


Scheme 1.1

In general, reactivity in S_NAr reactions, is found to vary with nucleophile, leaving group and solvent.

With anionic nucleophiles, the reaction proceeds as in equation 1.1. Either the formation or decomposition of the Meisenheimer complex, 1.1, may be rate limiting, depending on the energy of the two transition states.

Figure 1.1. Reaction coordinates for reactions involving an intermediate such as in equation 1.1.

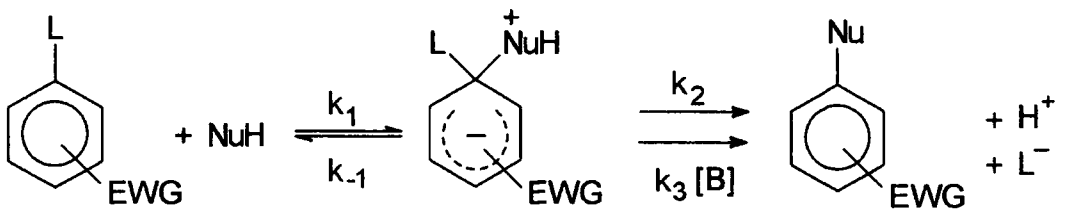


The energy diagram shows:

i). Rate limiting formation of the intermediate and

ii). Rate limiting decomposition of the intermediate, 1.1.

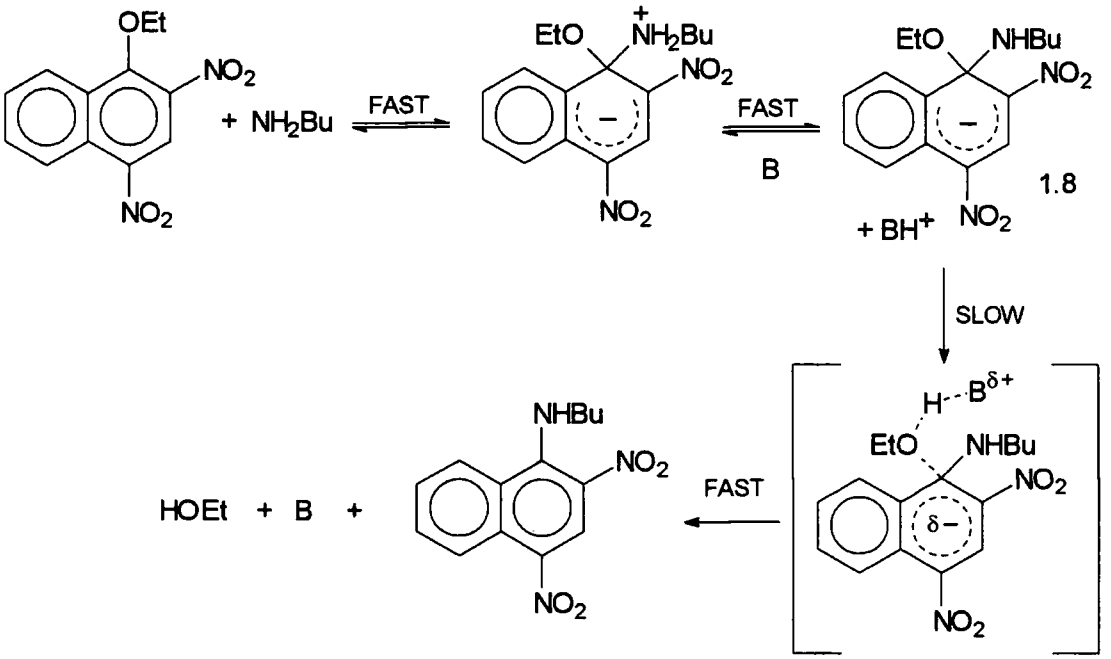
When the reaction involves a neutral nucleophile e.g. water, alcohol or amines, the mechanism can be represented by equation 1.4.



equation 1.4

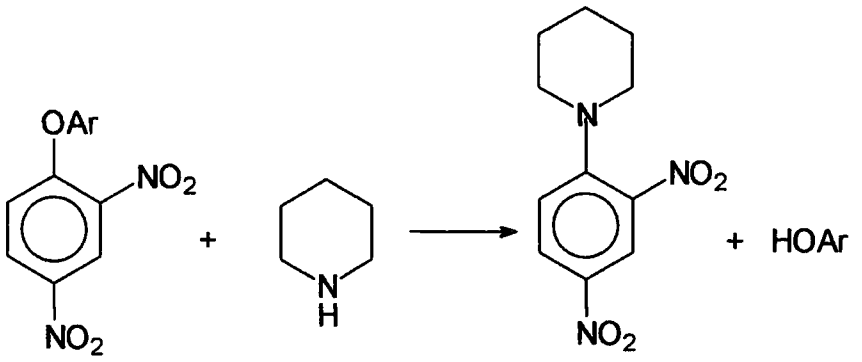
The σ-adduct formed here is zwitterionic and contains a proton which can be removed by a base (e.g. the nucleophile). Therefore conversion of 1.11 to products can occur via an uncatalysed pathway, k_2, or via a base catalysed pathway, k_3.

Bunnett and Orvik made a study by UV/Visible spectroscopy of the reaction of 1-ethoxy-2,4-dinitronaphthalene with butylamine in DMSO. They found that the intermediate on the substitution pathway, 1.8, was observable spectroscopically. They observed that the rate of decomposition of the intermediate was equal to the rate of appearance of the butylamino-substituted product. The reaction involves specific base-general acid catalysis, with the rate determining step being proton transfer from the conjugate acid, BH^+, to the intermediate. This is illustrated in scheme 1.2. It will be seen later in this thesis that in other situations the rate determining proton transfer may be from the initially formed zwitterion to base.

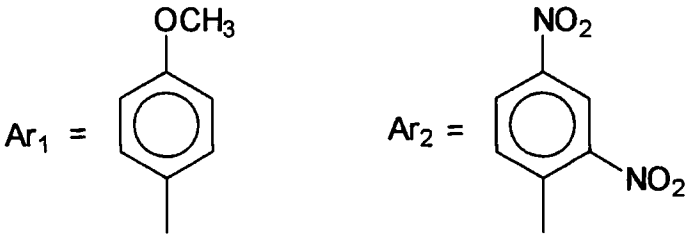


Scheme 1.2

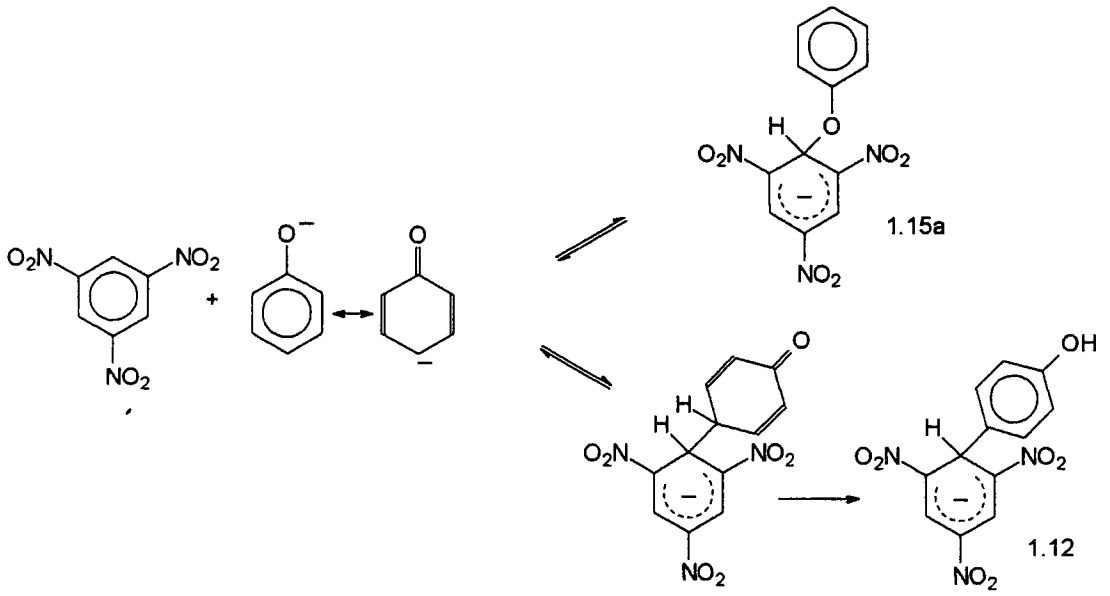
Similarly, in protic solvents, base catalysis may result either from rate limiting proton transfer from zwitterion to base, or from the conjugate acid of the base to the leaving group. It has been found that the occurrence of base catalysis may depend on the nature of the leaving group. Thus study of the reaction shown in equation 1.3 in aqueous dioxane has shown that with the relatively poor leaving group, Ar_1, base catalysis is observed, but with the better leaving group, Ar_2, added base has little effect.



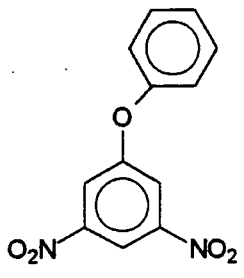
equation 1.3



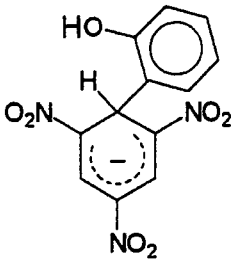
The ambident reactivity of the phenoxide anion towards TNB has been reported by means of a novel reaction system (CD_3CN-glyme d10) which allows the investigation of species formed at low temperature.[24] NMR studies using this solvent system allowed definite observation of both the O- and C-bonded phenoxide σ-complex adducts, confirming the formation of the former through kinetic control and of the latter through thermodynamic control.



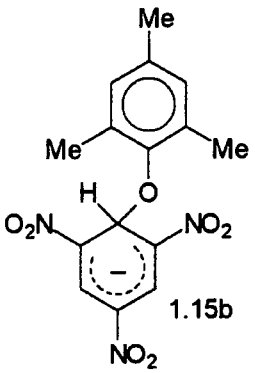
Carbon attack via the para-position to produce 1.12 was found to be kinetically more favourable than formation of the ortho-carbon adduct, 1.14, or the diaryl ether, 1.13. Formation of 1.13 may be rationalised in terms of an addition-elimination mechanism, involving nitro-group displacement[25].



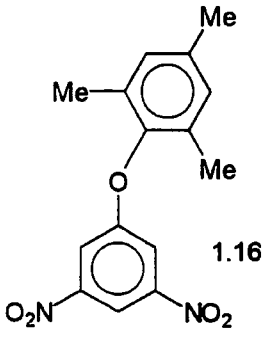
1.13



1.14



1.15b

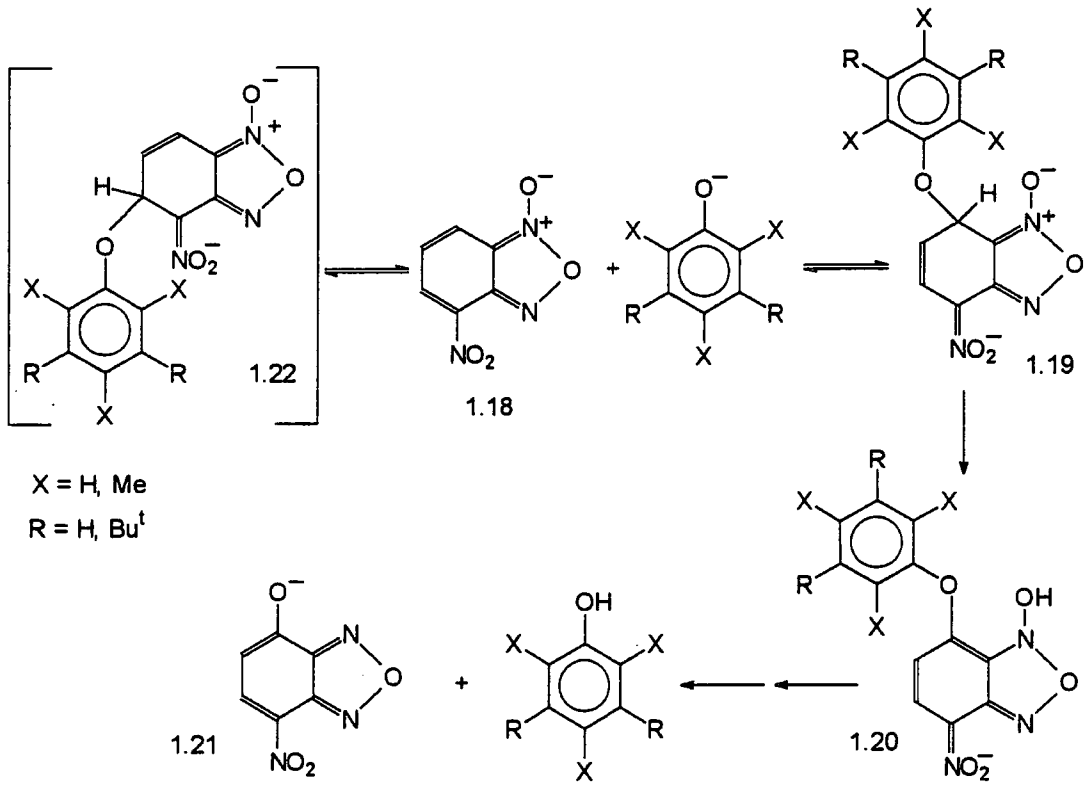


1.16

In the reaction of TNB with 2,4,6-trimethylphenoxide ion, where formation of the C-bonded σ-adduct is not possible, formation of the O-bonded adduct, 1.15b, is followed by NO_2 group displacement, to give 1.16.

For the reaction of 2,4,6-trimethylphenoxide ion with 2,4,6-trinitroanisole, a kinetic preference for C-1 attack was seen, however the adduct formed by attack at the 3-position was seen to be thermodynamically more stable.[26] This is a direct contrast to the more usual isomerisation pathway for alkoxide ions, where the 3-adduct is kinetically preferred and the 1-adduct is thermodynamically preferred. Stereoelectronic stabilisation of the 3-adduct through interaction of the antiperiplanar lone pairs with the requisite C-O acceptor bond is thought to be a major factor in the regioselectivity of the C-1 versus C-3 attack.

The reactions of several aryloxide nucleophiles with 4-nitrobenzofuroxan, 1.18, have also been studied, see scheme 1.3.



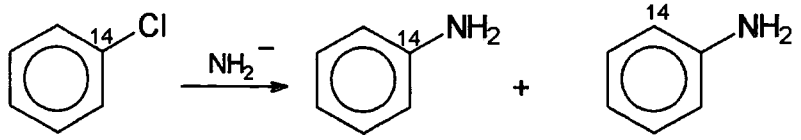
scheme 1.3

With the phenoxide ion the initial attack occurs at the 7-position to give 1.19, followed by transfer of the sp^3 bound proton of the C-7 phenoxide. A series of steps shown in scheme 1.3 eventually yields the nitrobenzofurazan derivative, 1.21. This contrasts with the reaction of 1.18 with methoxide ion, where the C-5 adduct is kinetically preferred while the C-7 adduct is thermodynamically more stable. No C-5 adduct of phenoxide is observed in the above system. A similar reaction sequence was found with 3,5-di-tert-butylphenoxide and 2,4,6-trimethylphenoxide ions. However, reaction with 2,6-di-tert-butylphenoxide ion, where O-attack is sterically blocked, attachment through carbon at the 7-position is observed[27].

1.1.2 The Benzyne mechanism

Some aromatic nucleophilic substitutions have been seen to occur on aryl halides that have no activating groups, also the incoming group does not always occupy the position of the leaving group.

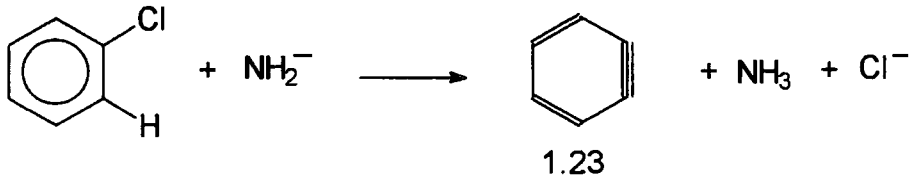
The reaction of potassium amide with 1-^{14}C-chlorobenzene was found to yield almost equal amounts of aniline labelled in the 1-position and the 2-position, as shown in equation 1.5.



equation 1.5

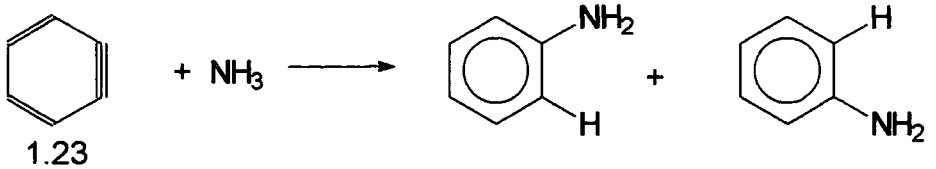
This provides evidence for substitution by an elimination-addition mechanism in which the highly strained benzyne intermediate is formed.[28-30]

Step 1:



1.23

Step 2:



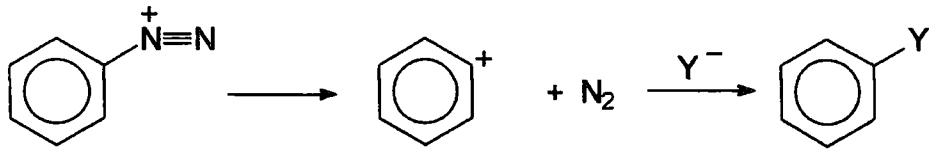
1.23

The symmetrical benzyne, 1.23, can be attacked by the ammonia molecule at either of two positions, which explains why half of the radioactive aniline was labelled at the 2-position.

Comparison of the rates of formation of the aniline from bromobenzene and bromobenzene-^{2}d gives $k_H/ k_D = 5.5$, thus the proton is removed from the substrate in the rate determining step.[29] Fluorobenzene-^{2}d exchanges its deuterium with solvent a million times faster than deuterobenzene, but no aniline is formed.[31] Apparently, when the halogen is weakly electron-withdrawing but a good leaving group, hydrogen abstraction is the slow step; when the halogen is strongly electron-withdrawing but unreactive as a leaving group, its expulsion is the slow step.

1.1.3 Nucleophilic Substitution on Aromatic Diazonium Compounds.

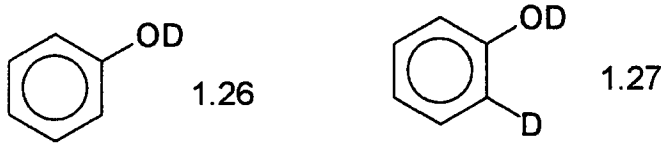
Another mechanism of nucleophilic substitution, specific for substitution on aromatic diazonium compounds is shown in equation 1.6.



1.24 1.25

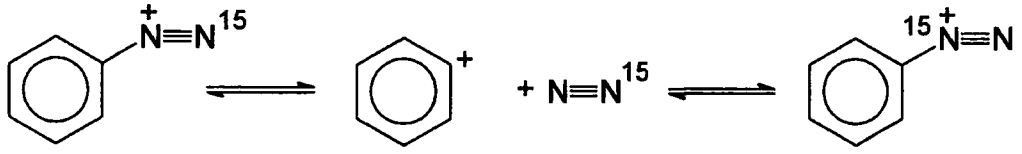
equation 1.6

There is good evidence that the intermediate is as shown, 1.25.[32-35] Species 1.24 reacts with D_2O to give only species 1.26, none of species 1.27 was formed. Hence the benzyne mechanism is excluded.



1.26 1.27

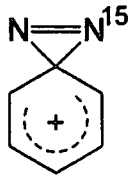
H_2O and D_2O react at about the same rate and so there can be no involvement of the nucleophile in the rate determining step.[32]



1.28 1.25

equation 1.7

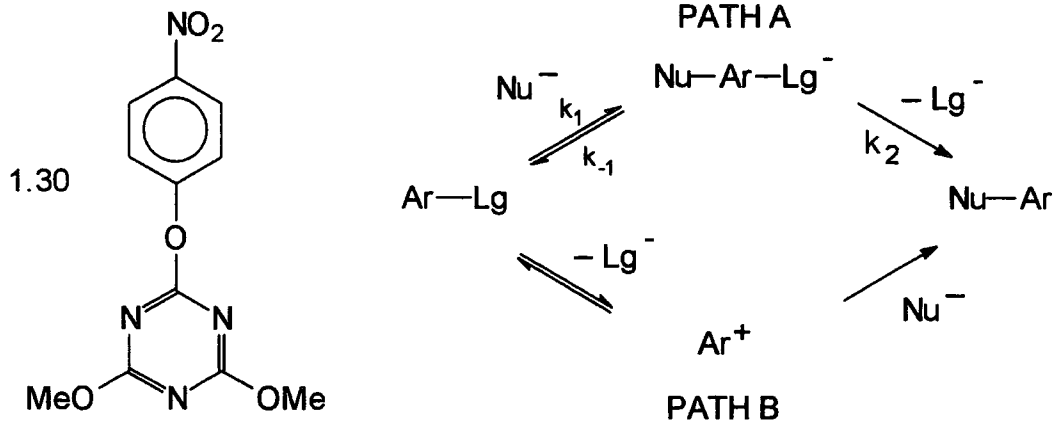
When the starting material is selectively labelled with ^{15}N, the rearrangement shown in equation 1.7 occurs. This takes place through dissociation-reassociation and not through the transition state 1.29. This was shown by the scrambling of nitrogen from 1.28 in 300 atmospheres of unlabelled nitrogen, 2.5% of unlabelled nitrogen was seen to be incorporated into the diazonium cation.[35]



1.29

1.1.4 A Single Step Mechanism for Nucleophilic Aromatic Substitution.

Recent work has been published suggesting that displacement by a series of substituted phenolate ions of the 4-nitrophenolate ion from 2-(4-nitrophenoxy)-4,6-dimethoxy-1,3,5-triazene, 1.30, proceeds via a single step mechanism rather than a two step mechanism involving an intermediate.[36] Evidence for the concerted mechanism comes from an absence of curvature in the Bronsted dependence for displacement by nucleophiles with pKa values well above and well below that of the leaving group. The stepwise mechanism would be predicted to have a change in rate limiting step at Δ pK = 0, where the forward, k_2, and reverse, k_{-1}, rate constants would be identical.



scheme 1.4

Generally, nucleophilic aromatic substitutions occur by one of the mechanisms shown in scheme 1.4. Either addition then elimination, path A, or elimination followed by addition, path B, occurs. This suggests that such conditions may exist, by suitable manipulation of the structures of solvent, nucleophile, leaving group and aromatic nucleus, to favour a concerted mechanism. The example given above is thought to occur by this mechanism.

1.1.5 Radical Mechanisms

Recently there has been increased interest in the nucleophilic substitution reactions that occur through a chain process with radicals and radical anions as intermediates. Two proposals for the propagation step involve fragmentation of the radical intermediate anion of the substrate to give a radical which reacts with the nucleophile (the $S_{RN}1$ mechanism), or the reaction of the radical anion with the nucleophile to give the substitution product (the $S_{RN}2$ mechanism).

The $S_{RN}1$ mechanism is a chain mechanism involving both radicals and radical anions as intermediates, as in scheme 1.5.

Initiation step: $RX \xrightarrow{e.t.} (RX)^{\cdot -}$

$(RX)^{\cdot -} \longrightarrow R^{\cdot} + X^{-}$ equation 1.8

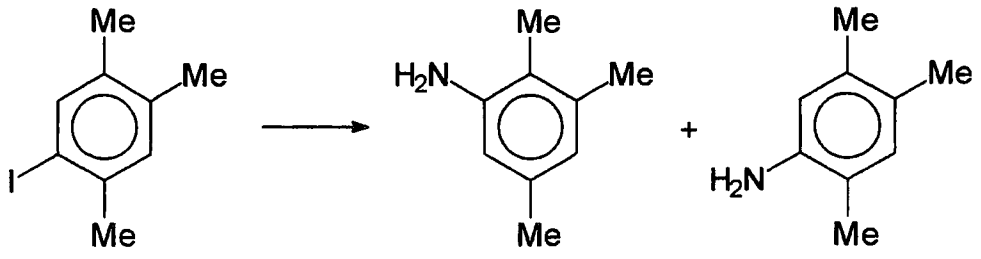
$R^{\cdot} + Nu^{-} \longrightarrow (RNu)^{\cdot -}$ equation 1.9

$(RNu)^{\cdot -} + RX \longrightarrow RNu + (RX)^{\cdot -}$ equation 1.10

scheme 1.5

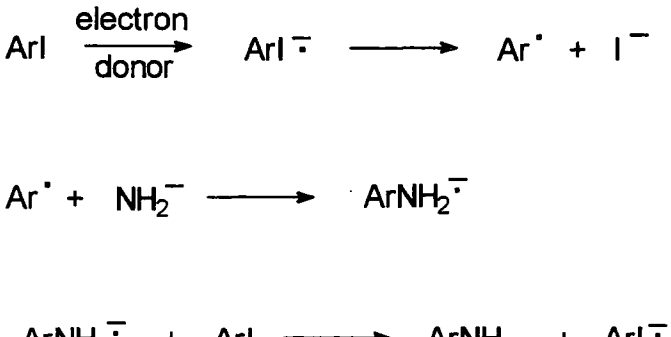
In the propagation cycle, the fragmentation of the radical anion of the substrate to give a radical and the anion of the nucleofugal group, equation 1.8, was proposed. This radical couples with the nucleophile to give a radical anion of the product, equation 1.9, which is followed by an electron transfer to the substrate, RX, which continues the chain process, equation 1.10.

The $S_{RN}1$ mechanism for aromatic systems was first proposed by Bunnett[37] in 1970. Reactions studied include the reaction of 5-iodo-1,2,4-trimethylbennzene, 1.31, which when treated with KNH_2 in liquid ammonia forms 1.32 and 1.33 in the ratio 0.63:1, as shown in equation 1.11.[38]



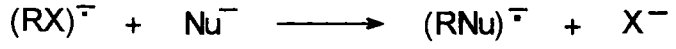
equation 1.11

Reaction of the 6-iodo isomer gave 1.32 and 1.33 in the ratio 5.9:1 and hence the benzyne mechanism cannot be occurring. Instead the $S_{RN}1$ mechanism was proposed, electrons were provided from potassium in ammonia, scheme 1.6.



scheme 1.6

In the $S_{RN}2$ mechanism, it is proposed that the radical anion $RX^{-}\cdot$ does not fragment, instead it reacts with the nucleophile to give the radical anion of the substitution product and the anion of the leaving group, equation 1.12. This is followed by electron transfer to the substrate, as in equation 1.10.

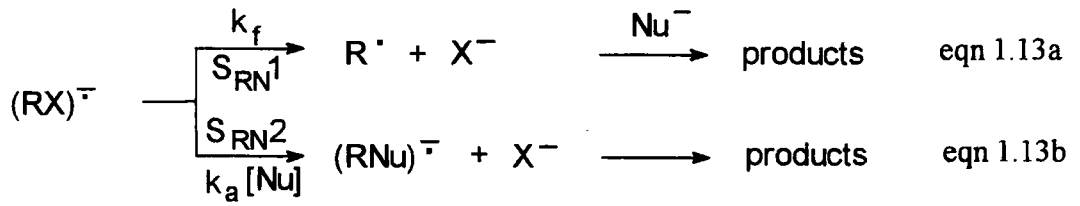


equation 1.12

Both mechanisms require the same initiation step, that is the formation of the radical anion intermediate ($RX^{-}\cdot$). This can occur by several methods including:- photostimulation, reaction with electrons from dissolution of alkali metals in liquid ammonia, reaction with electrons from a cathode or from a sodium amalgam.

Arguments against the general applicability of the $S_{RN}2$ mechanism include incompatibility with experimental observations or violation of quantum-mechanical principles.[39]

Once the radical anion, $RX^{-\cdot}$, is formed it may either fragment ($S_{RN}1$ mechanism, equation 1.13a), or react with the nucleophile ($S_{RN}2$ mechanism, equation 1.13b), as in scheme 1.7.



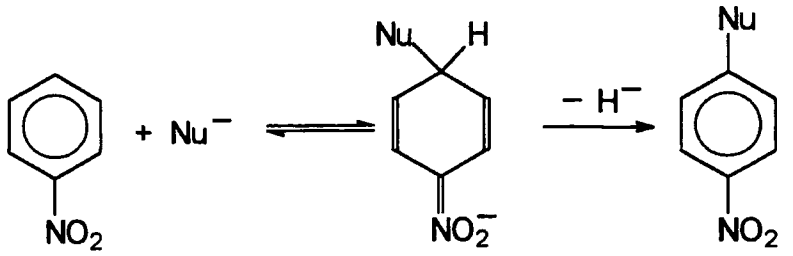
Scheme 1.7

Generally it is thought that the reaction of radical anions with nucleophiles cannot compete kinetically with their fragmentation.[40] For example, in the reaction of haloarenes, the rate constant of fragmentation of their radical anions is in the order of 10^4 s^{-1}. Hence the reaction of the radical anions with nucleophiles is thought to be too slow to compete with this process.

However for reactions involving relatively stable radical anions, which may fragment slowly, the $S_{RN}2$ mechanism may operate. Possible examples include the photo- or electro-stimulated reactions of pentafluoronitrobenzene with nucleophiles involving fluoride displacement[41] or the displacement of a nitro group in 4-nitrobenzephenone and 4-nitrobenzonitrile.[42]

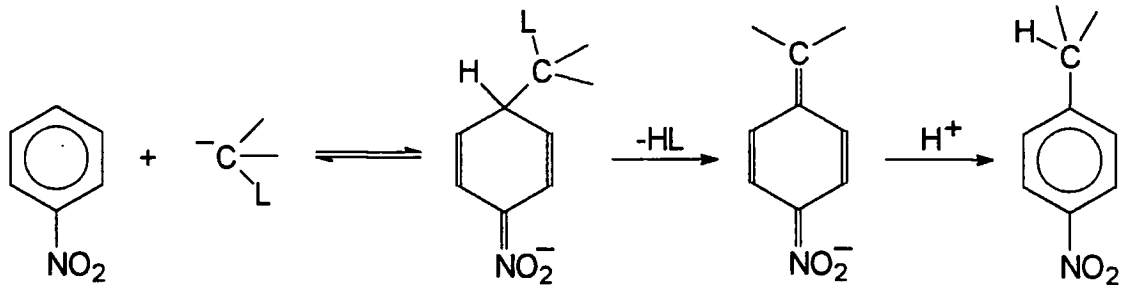
1.1.6 Vicarious Nucleophilic Substitution.

As mentioned previously, nucleophilic substitution of a hydrogen on an electron deficient aromatic via the S_NAr mechanism is not a common process as the hydride ion has a very low stability and is therefore a poor leaving group.[9,10,13,21] However, reactions are known where an aromatic hydrogen atom is replaced by the attacking nucleophile. As with general S_NAr reactions, they usually occur by addition of the nucleophile to form σ-complex type intermediates. These intermediates then decompose via 'oxidation' pathways and so formally achieve nucleophilic aromatic substitution of hydrogen in an aromatic ring, see equation 1.6.



equation 1.14

Alternatively, rearomatisation of the intermediate can occur via a series of chemical transformations not involving an oxidation step. An example of this is Vicarious Nucleophilic Substitution where the driving force for rearomatisation of the intermediate is the elimination of a nucleofugal group initially present at the reaction centre of the incoming nucleophile.[6,43,44] Equation 1.15 shows the reaction of nitrobenzene with a carbanionic nucleophile bearing a leaving group at the anionic carbon atom. Formation of the σ-adduct is followed by base catalysed elimination of HL followed by protonation to yield the re-aromatised product.[44]

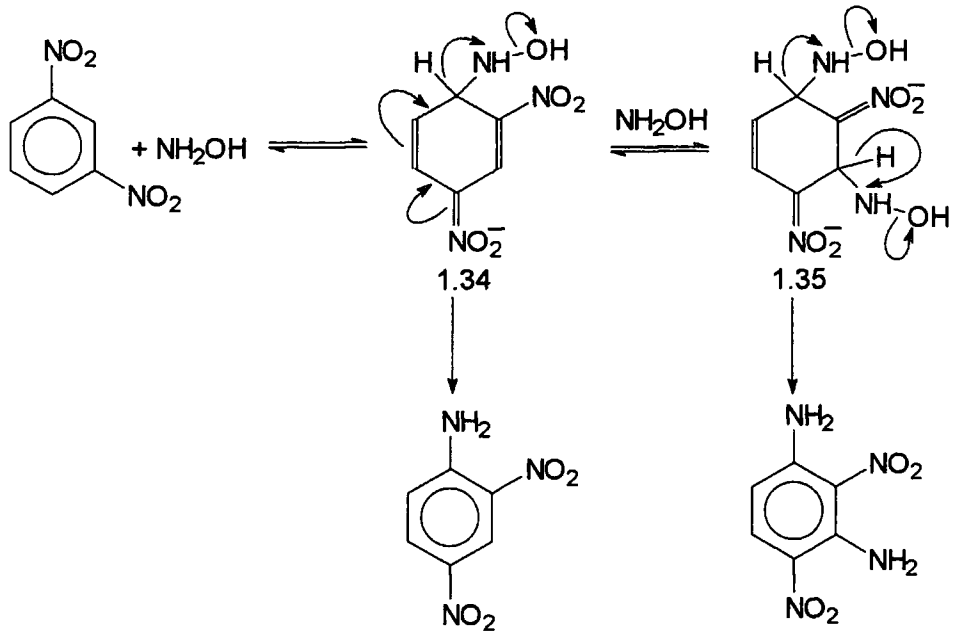


L = Cl, Br, CH_3O, C_6H_5O, C_6H_5S, $(CH_3)_2NC(S)S$

equation 1.15

A further example of this type of reaction is that between m-dinitrobenzene and hydroxylamine, as shown in scheme 1.8.[21,45,46] Departure of the hydrogen atoms in 1.34 and 1.35 is assisted by the departure of the hydroxy group of the NHOH addend; i.e. the hydroxy group acts as a vicarious leaving group in the overall process which formally accomplishes nucleophilic aromatic substitution of a hydride anion.

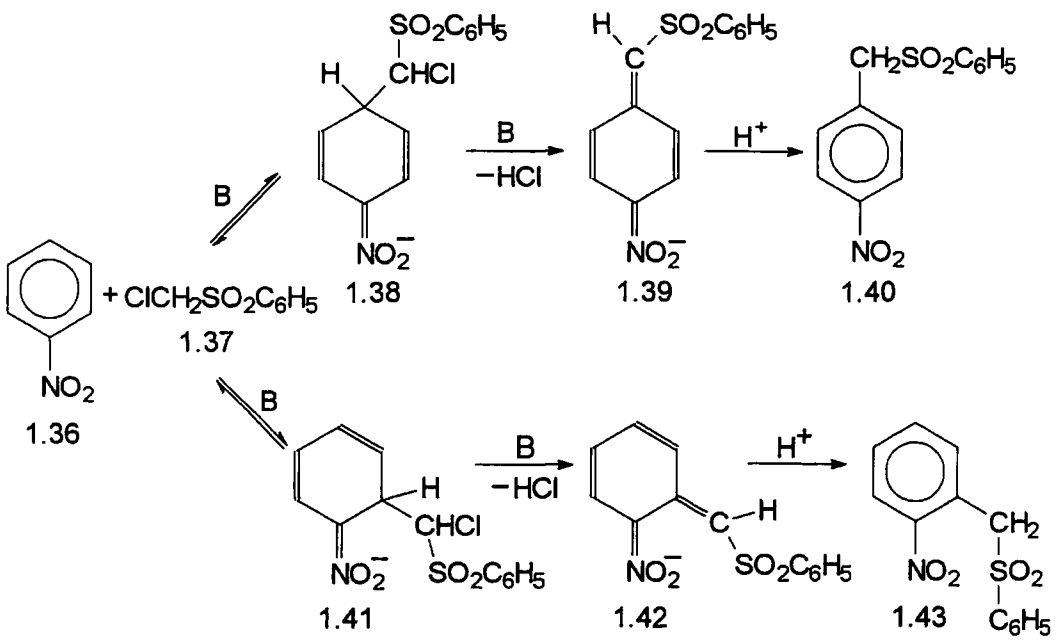
A study of meta-dinitrobenzene and d_4-m-dinitrobenzene revealed that the leaving hydrogen does migrate to the amino group during the reaction, although the exact method of rearomatisation is still unknown.



scheme 1.8

Makosza and co-workers have developed VS_NArH reactions involving carbanionic nucleophiles. They found carbanions containing leaving groups at the carbanion centre react rapidly with nitroarenes, replacing the hydrogen atom para- or ortho- to the nitro group with the carbanion moiety.[47,48]

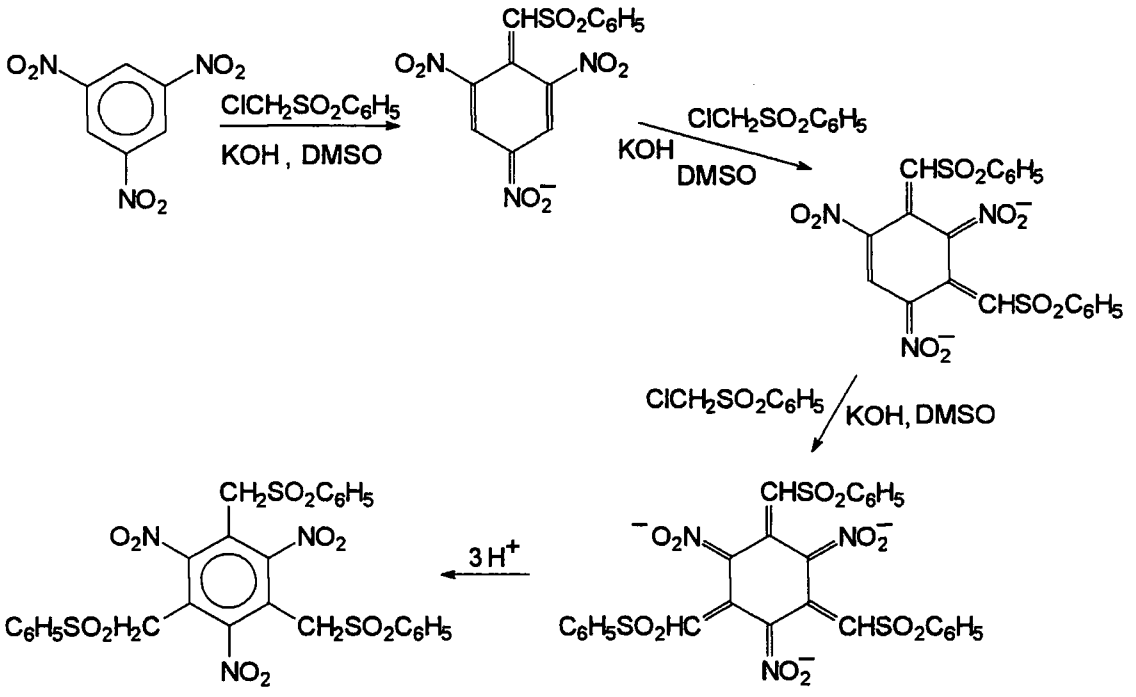
This behaviour can be seen in scheme 1.9, for the reaction of nitrobenzene, 1.36, with the carbanion of chloromethyl phenyl sulfone, 1.37, in the presence of a strong base (KOH, NaOH, t- BuOK) in DMSO.[44,48,49]



scheme 1.9

The reaction proceeds via competitive nucleophilic addition of the carbanions to the two activated positions ortho- and para- to the nitro group, forming adducts 1.38 and 1.41. This is followed by departure of the hydrogen bonded to the sp^3 carbon and the chloride ion in a base-induced β-elimination step. This elimination gives highly stabilised nitrobenzyl carbanions, 1.39 and 1.42, which are protonated to give the final products, 1.40 and 1.43.[43,49]

Strong delocalisation of the negative charge onto the nitro groups reduces the electrophilic character and therefore the susceptibility to nucleophilic attack of the ring. Introduction of a second or third nitro group into the aromatic ring activates the system and hence compensates for the above. This accommodation of the negative charge, conjugated with the ring by the second nitro group creates a possibility of disubstituted and even trisubstituted derivatives, as in scheme 1.10.[50]

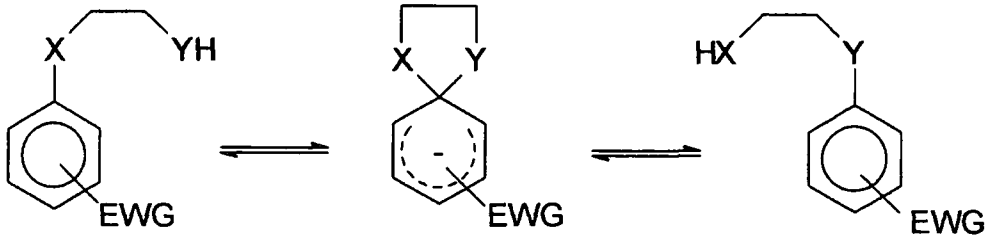


scheme 1.10

In the above scheme, 1.10, introduction of the first, second and third substituents occurs at different rates.

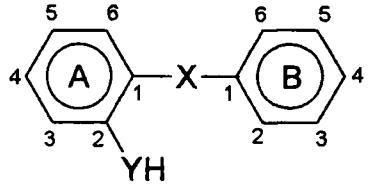
1.2 The Smiles Rearrangement

Smiles rearrangements of activated aromatic substrates are typical intramolecular S_NAr reactions[51-55]. The reaction proceeds via nucleophilic attack of the carbon atom attached to the side chain connecting X and Y, which may be saturated or part of an aromatic system, but must contain an atom with a lone pair of electrons, i.e. a nucleophile. X and Y represent various combinations of heteratoms (O, S, NR). In most cases the displacement is by Y^- rather than by YH and so the presence of a strong base is required. However, when YH is an amino group (NH_2 or NHR), a base may or may not be required for reaction to proceed.



1.50

Ring substituents will exert both an electronic and steric effect, and the influence of these effects on the rearrangement will depend on which ring they are placed on and also the position these groups occupy[53].

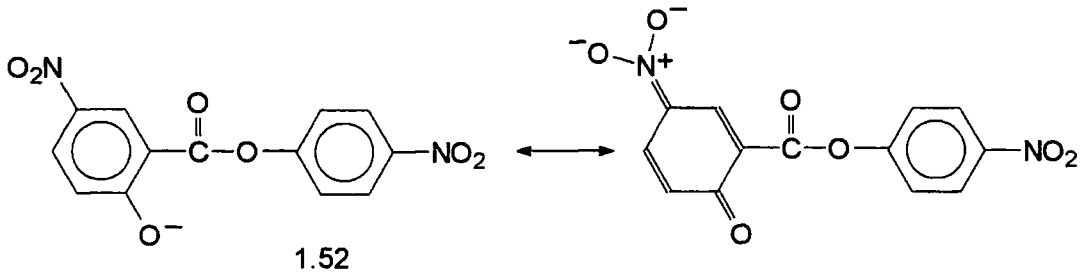


1.51

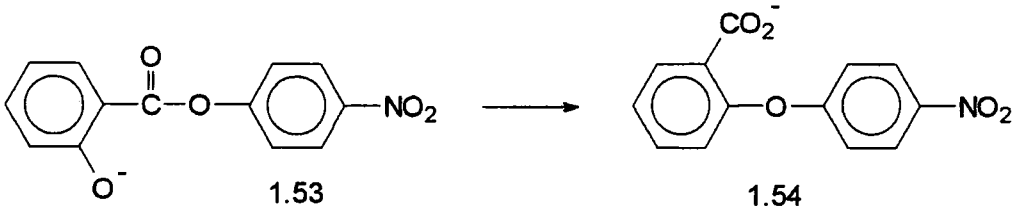
In the general representation above, 1.51, an electron-withdrawing substituent in the 2- or 4-position of ring B will enhance whereas an electron donating group will hinder the nucleophilic attack of Y^- at the 1-position. For this reason, many rearrangements are carried out in components which have a 2- or 4-nitro substituent in ring B, (the nitro group being an especially efficient electron withdrawing group).

Electron withdrawing groups in the 4- and 6-position of ring A will facilitate the acceptance of a negative charge by X and so assist the displacement reaction. These groups, by their inductive effects, may also facilitate proton removal from YH, and this will also assist rearrangement. A similar situation arises with electron withdrawing groups in the 3- and 5-position of ring A. These will assist proton removal from YH and may also help in electron withdrawal from the C-X bond. However, if conjugation of a

group in the 3- or 5-position of ring A with the negative charge on Y^- is large enough, Y^- may be too weakly nucleophilic to carry out the displacement reaction.
Thus, the rearrangement of 1.52 does not take place on boiling with aqueous sodium hydroxide, while 1.53 rearranges readily to 1.54 at low temperatures.[58]

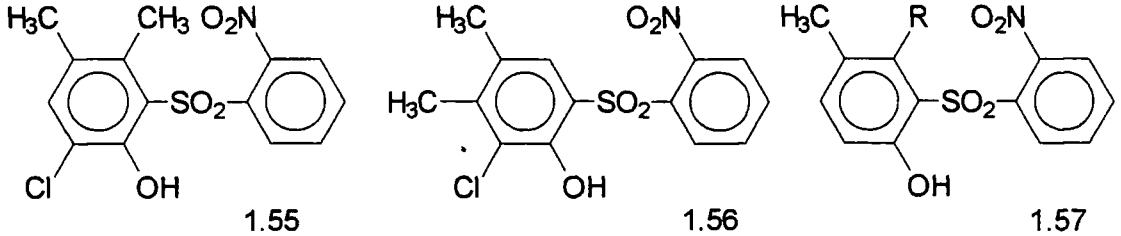


1.52



1.53 1.54

Steric effects can also arise during the Smiles rearrangement of an aromatic molecule, 1.51, where YH is say OH or NH_2, because during the rearrangement the planes of the two rings would be at right angles to one another. This can be seen in the reaction of sulfones, where rearrangement is influenced not only by the relative configurations that the two rings may adopt, but also by the control which the two oxygen atoms of the sulfone group can exercise over the positions of the rings. For example, a substituent in the 6-position of ring A accelerates rearrangement in comparison with similar sulfones having a hydrogen atom in that position.



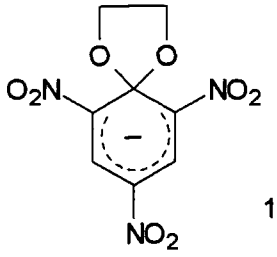
1.55 1.56 1.57

Thus the rate of rearrangement of 1.55 in aqueous sodium hydroxide was faster than that of 1.56,[59] even though the electronic characters of the two rings are about the same. Further, the rate of rearrangement of the sulfone 1.57 (R=H), in an aqueous dioxan solution of sodium hydroxide, was increased 500,000 fold by placing a methyl-, chloro-, bromo-substituent in the 6-position.[56] In these cases, the inductive effects of the halogens are the opposite to that of methyl, yet similar rate increases were observed.

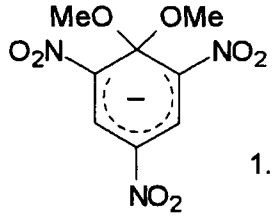
In general, the rearrangement goes through the formation of an intermediate spiro complex, 1.50. The stability of such complexes tends to parallel both the electron deficiency of the C-1 carbon and the stability of the corresponding non-spiro cyclic Meisenheimer complexes and can be seen to be:-

2.4-dinitrophenyl << 2.4-dinitronapthyl << 2,4,6-trinitrophenyl.

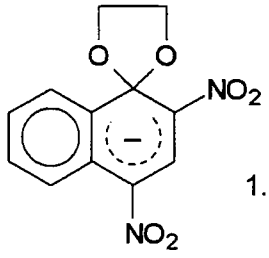
The leaving group ability of intra- versus inter-molecular groups can be studied with respect to molecules 1.58 and 1.59.[61, 62] The spiro complex, 1.58, has a much greater stability, but decomposes much faster than its' 1,1-dimethoxy analogue, 1.59. Thus the ring opening of 1.58 occurs about 82 times faster than MeO^- departure from the 1,1-complex of TNA.[62,63]



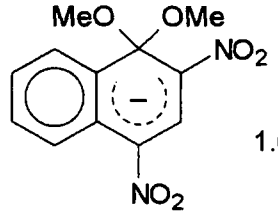
1.58



1.59



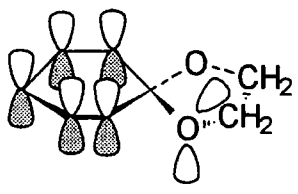
1.60

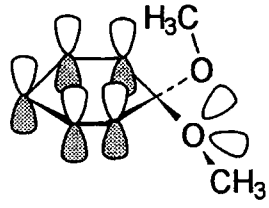


1.61

In the case of 1.60, ring opening is approximately 1500 times faster than methoxy group loss from the naphthyl complex 1.61. The three factors believed to contribute to these changes are:

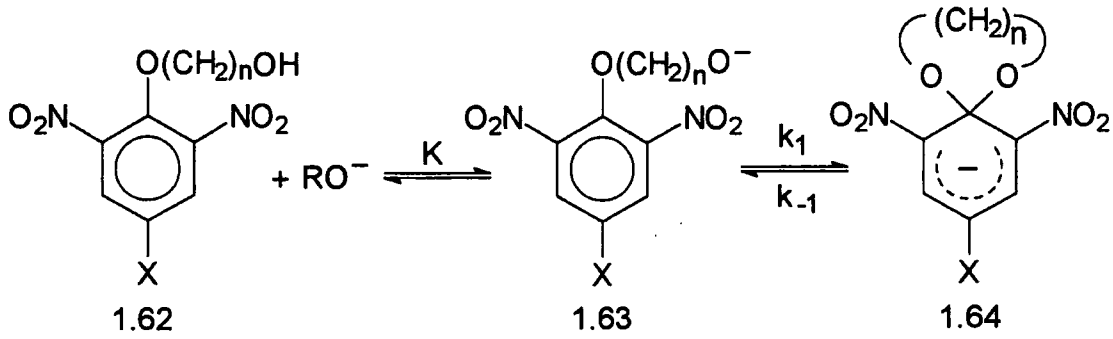
1) Relief of steric strain upon complex decomposition
2) Difference in the basicity of the respective leaving groups
3) p-π overlap of the lone pairs of the non-leaving oxygen with the aromatic π-system.





(Enhanced stabilisation of the transition state of the spiro complex due to p-π overlap of one of the lone pairs of the non-reacting oxygen with the aromatic π-system, which is not possible for the transition state in the dimethoxy reaction.)

Depending on the system under study and experimental conditions, the proton transfer may be fast or rate determining. Equation 1.20 is representative of the cyclisation of suitably ring activated 1-(n-hydroxyalkoxy)arenes and heteroarenes (n=2, 3, 4) [61,62-70]. The reaction consists of a rapid proton transfer from the alcohol side chain to the base (HO^-, RO^-), followed by a slow internal cyclisation of the formed anion 1.63 to give the spiro complex 1.64.



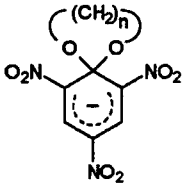
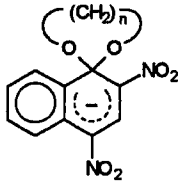
1.62 1.63 1.64

X = NO_2, SO_2, CF_3, Cl

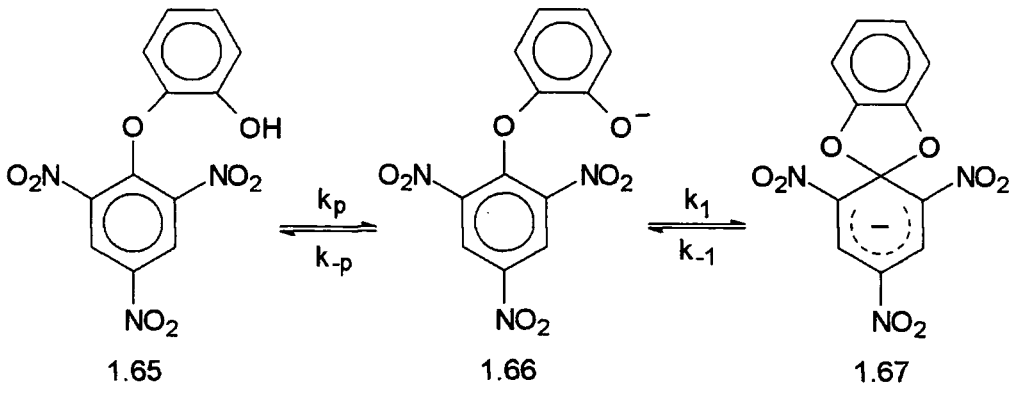
n = 2, 3, 4

equation 1.20

Table 1.1. Rate and equilibrium constants for some dioxolan spiro complexes in water at 25°C.[61,67] (where $K_1 = k_1/k_{-1}$)

	n	Kk_1/ l mol^{-1} s^{-1}	k_{-1}/ s^{-1}	KK_1/ l mol^{-1}
 1.15	2	7.25×10^5	0.045	1.6×10^7
	3	19.5	0.87	22.6
	4	≤ 10		≤ 1
	2	9×10^4	2.3	3×10^4
	3	1.7	0.85	2
	4	0.6	0.64	0.9

From the table it can be seen that the spiro complex stability strongly decreases with increasing size of the spiro ring, primarily because of a decrease in the rate constant of complex formation, k_1.[60, 67-69]

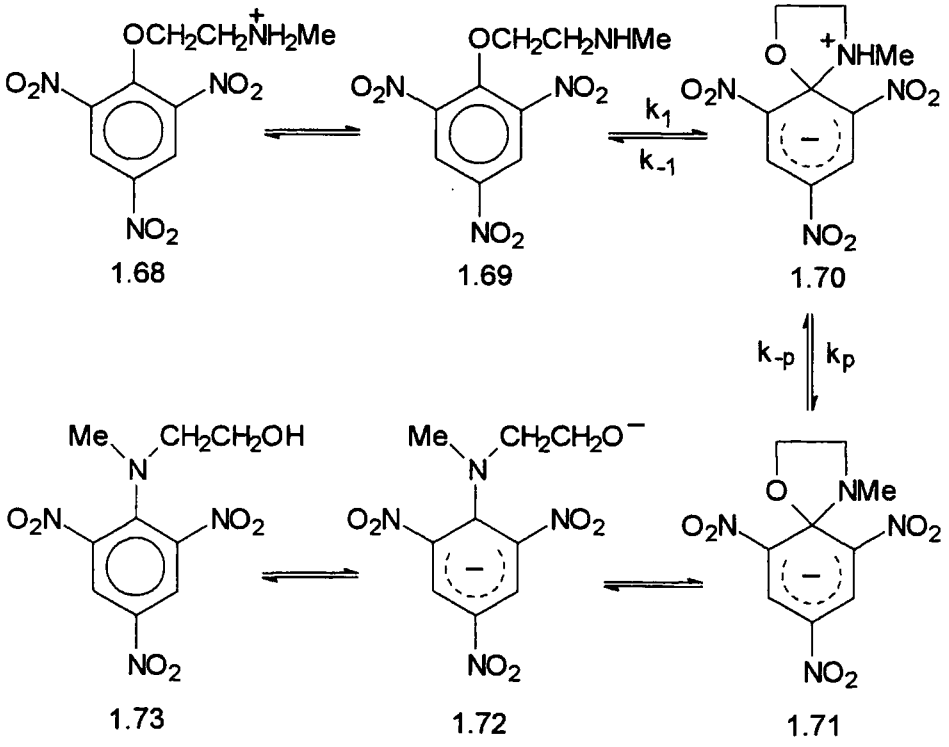


1.65 1.66 1.67

equation 1.21

Using the temperature jump technique and buffered solutions, the cyclisation of catechol 2,4,6-trinitrophenylether, 1.65, into 1.67 has been studied in 50 % DMSO/50 % water.[71] This system is the first reported case of the general reaction where proton transfer may be the rate limiting step. Rate determining proton transfer implies that $k_1 > k_{-p}$. This condition results from the very rapid cyclisation of 1.66, with $k_1 \approx 10^9$ s^{-1}, and the relatively slow protonation by the solvent of the acidic phenolate ion.

Kinetic analysis of the picryl system, described in scheme 1.20 shows that conversion of the ether, 1.68, into the picramide derivative, 1.73, occurs in two distinct stages in aqueous solution.



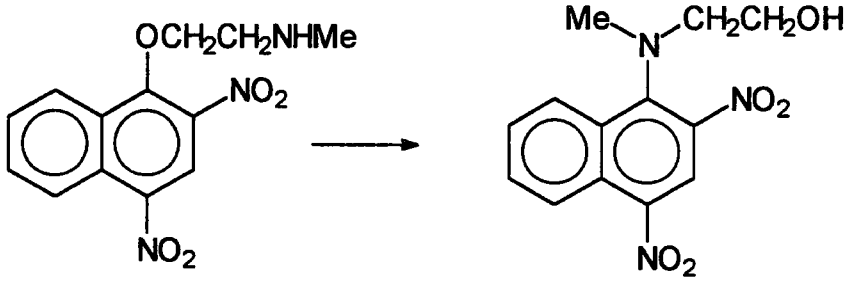
1.68 1.69 1.70

1.73 1.72 1.71

scheme 1.20

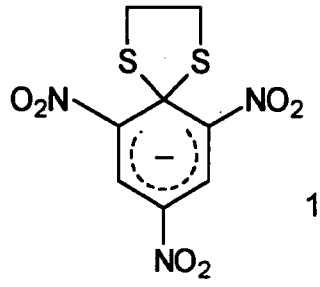
The first is very rapid, involving equilibrium deprotonation of 1.68 followed by intramolecular nucleophilic attack by the NHMe group to form the zwitterion 1.70, which is then deprotonated to form the anionic complex 1.71. The second stage is relatively slow and involves the conversion of 1.71 into 1.73 by three concurrent routes:
1) Breaking of the C-O bond in 1.71, followed by rapid protonation of the negative oxygen of 1.72, (the reverse of cyclisation in equation 1.20). (1.71 ⇔ 1.72 ⇔ 1.73).
2) General acid catalysed C-O bond breaking in 1.71, which leads directly to 1.73 presumably via a concerted process. (1.71 + BH ⇔1.73 + B).
3) Direct conversion of 1.70 into 1.73 via a concerted intramolecularly acid catalysed leaving group departure.

Similar results were obtained in the conversion of the naphthyl ether 1.74 into the naphthylamine 1.75.[72]



1.74 1.75

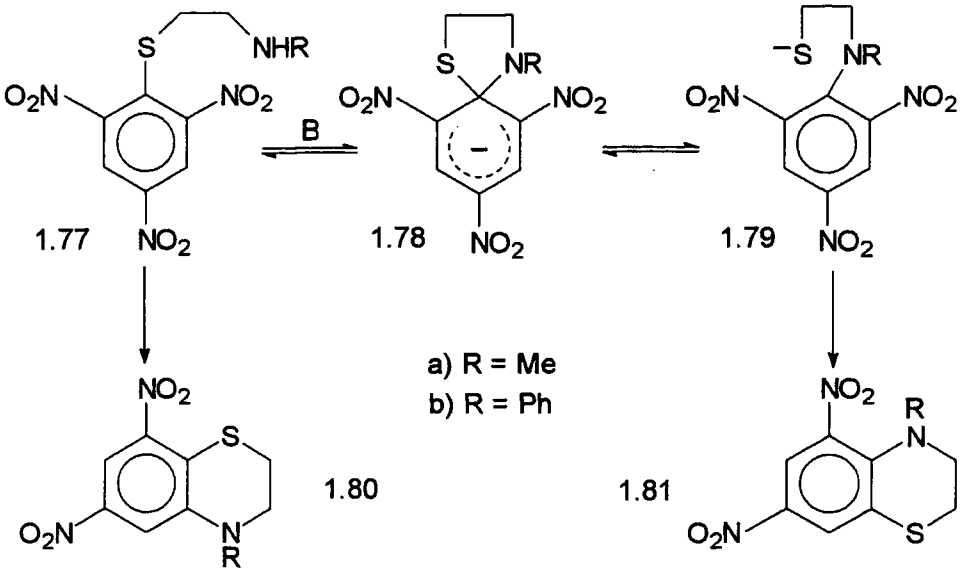
Scheme 1.20 also holds for the formation of dithiolan spiro complexes from various 2-mercaptoethyl thioethers.[73, 74] Complexes such as 1.76 have a high stability and due to the low basicity of sulfur, a "soft base" compared to oxygen, the opening of the spiro ring is remarkably insensitive to hard acids but highly sensitive to "soft acids" such as mercuric Hg^{2+} ions.



1.76

Several systems have been studied containing nitrogen and sulfur heteroatoms, some of these will be discussed in the following section.

Cyclisation of 1-(β-N-R-aminoethylthio)-2, 4, 6-trinitrobenzene, 1.77a, occurs in basic media to form 6,8- and/or 5,7-dinitro-4-methyl-2,3-dihydro-1,4-thiazenes.[75] The ratio of these isomers is largely dependent on the strength of the base and the nature of the solvent.



scheme 1.21

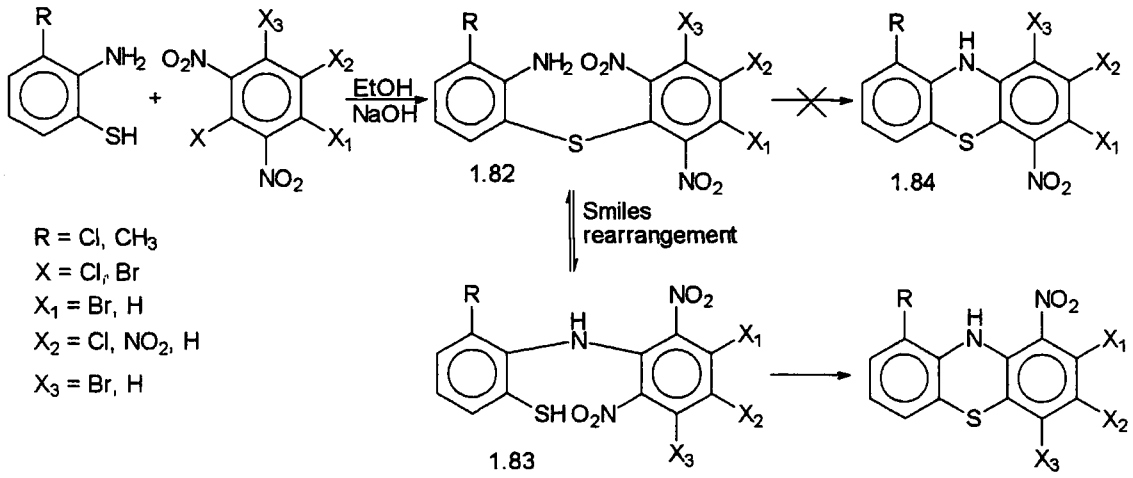
This suggests a mechanism as in scheme 1.21, involving partial rearrangement of 1.77a to the sulfide 1.79 via the spiro adduct 1.78a. Intramolecular substitution of an ortho nitro group in each picryl moiety occurs, giving 1.80a and 1.81a respectively. The results in table 1.2 show that the use of strong bases in dipolar aprotic solvents such as HMPA or DMF allows the formation of the direct substitution product 1.80. The use of weak bases such as pyridine gives the rearranged product 1.81 in all solvents.

Table 1.2. The ratio of isomers 180a:181a and the total yield (%) on the nucleophilic cyclisation of 1.77a.HCl

base\solvent	HMPA	DMF	t-BuOH	MeOH	C_6H_6	THF
t-BuOK	-	100:0(86)	86:14(16)	-	25:75(40)	0:100(32)
NEt3	68:32(13)	67:33(80)	30:70(19)	24:76(20)	-	-
Pyridine	-	0:100(53)	0:100(44)	4:96(82)	0:100(2)	0:100(17)

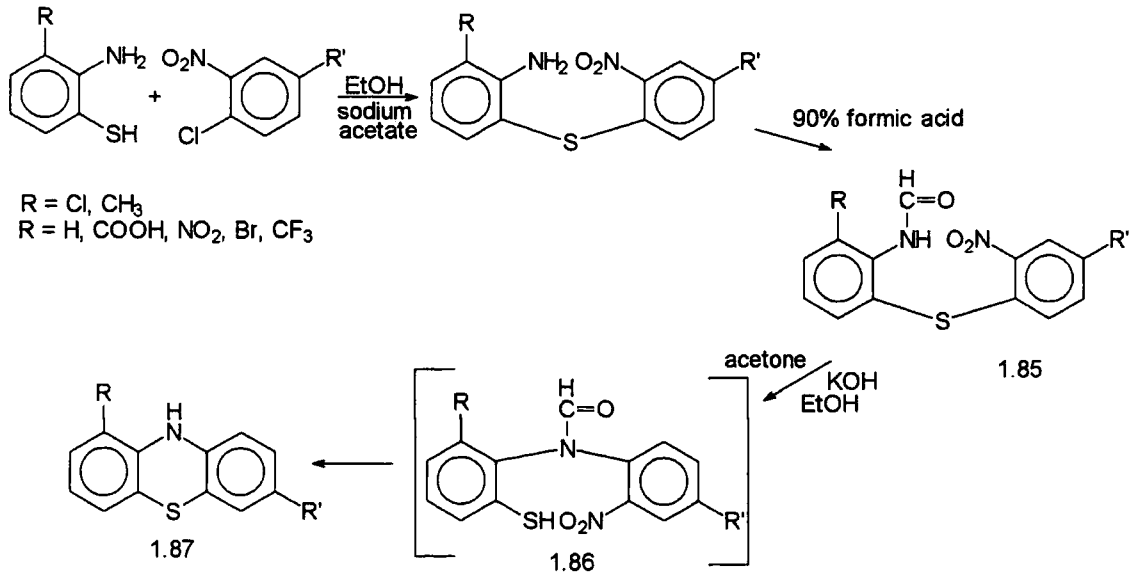
The cyclisation of 1-(β-N-phenylaminoethylthio)-2,4,6-trinitrobenzene, 1.77b, almost entirely goes with Smiles rearrangement and the formation of 5,7-dinitro-4-phenyl-2,3-dihydrobenzo-1,4-thiazene 1.81b. A mixture of isomers 181b:180b of 95:5 is only formed on heating in pyridine.

Smiles rearrangements are a key step in most reaction schemes leading to phenothiazenes.[76,77]



scheme 1.22

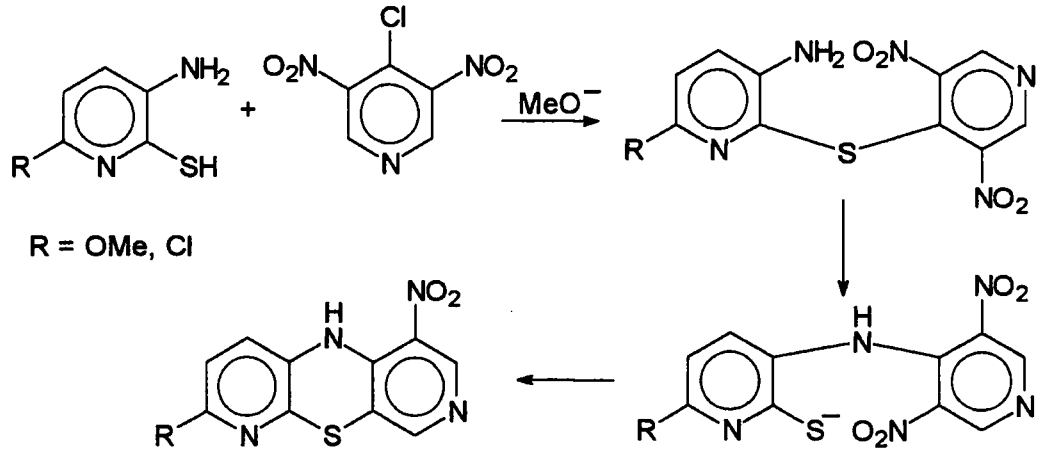
Substituted 2-aminobenzenethiols were condensed with reactive o-halonitrobenzenes (2,4,6-trinitrochloro-, 1,4-dichloro-, 2,6-dinitro-, 2,4,6-tribromo-benzenes) in ethanolic sodium hydroxide to give the corresponding phenothiazenes via the Smiles rearrangement, which occurs in situ,[76] as in scheme 1.22. The reaction involves rapid Smiles rearrangement of the sulfide intermediate 1.82 and then cyclisation of the amide, 1.83. No appreciable amount of the isomeric nitrophenothiazenes, 1.84, was found.



scheme 1.23

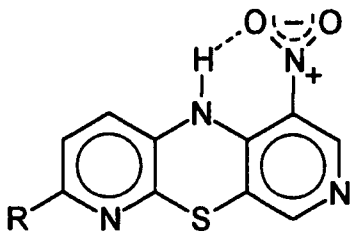
Similarly, 1-chloro/methyl-7-substituted phenothiazenes, 1.87, were prepared by a Smiles rearrangement of 3-chloro/methyl-2-formamido-2'-nitro-4'-substituted diphenyl sulfide, 1.85, in alcoholic potassium hydroxide.[77] The formyl derivatives were prepared by the formylation of diphenyl sulfides obtained by condensation of 2-amino-3-chloro/methyl thiophenol with substituted ortho-halonitrobenzenes in ethanolic sodium acetate, scheme 1.23. This indicates that rearrangement of 1.85 to 1.86 occurs prior to cyclisation.

3,6-Diazaphenothiazenes can be synthesised by a route involving condensation of the appropriate 3-amino-2-mercaptopyridine (R=OMe,Cl) with 3,5-dinitro-4-chloropyridine in the presence of excess base via a Smiles rearrangement and then cyclisation, as in scheme 1.24.[78]



scheme 1.24

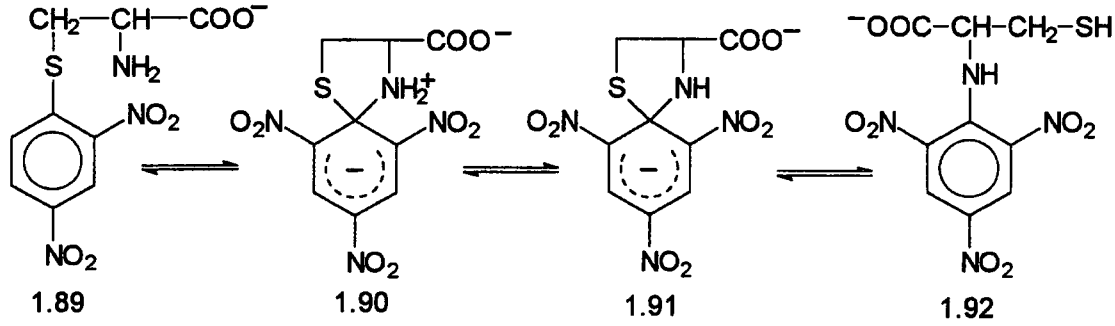
In the product, the proximity of the N-10 proton to the nitro group makes it possible that a 6-membered chelate of high stability can be formed through strong N-H-O hydrogen bonding, 1.88.[79,80]



1.88

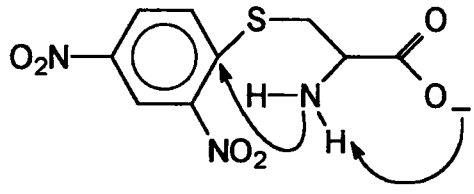
The base catalysed rearrangement of S-(2,4-dinitrophenyl) cysteine, 1.89, into 1.92 occurs under mild conditions, scheme 1.25.[81] In methanol the rearrangement of 1.89 into 1.92 goes almost to completion. Changing the medium to DMF or DMSO greatly

increases the rate of rearrangement of 1.89, and occurs even in the absence of base, giving a ratio of 5.0:4.7. In DMF the intermediate 1.91 may be observed spectroscopically in the presence of a strong base e.g. DBU, which is capable of ionising the SH group of 1.92, the reverse reaction becomes effective i.e. causing a time-dependent N → S Smiles rearrangement, giving a final ratio of 1.89:1.92 of 9:1.



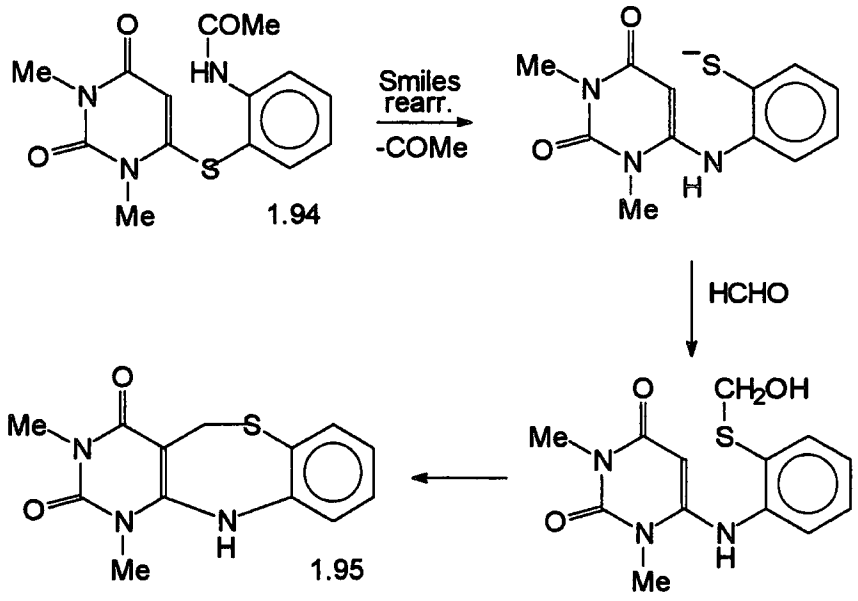
scheme 1.25

The two isomers (1.89, 1.92), were found to have stabilities differing by no more than 2 kcalmol^{-1} under the conditions employed. Presumably, this intrinsically small difference between the two isomers is responsible for the ready change in the relative properties depending on the medium. An important point to note is that the neighbouring carboxyl group in 1.89 plays an essential role in the rearrangement, probably abstracting a proton intramolecularly to give the intermediate 1.91 via 1.93.



1.93

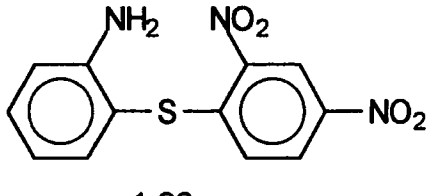
The pyrimido-1,5-benzothiazepine, 1.95, was obtained in high yield by treating the N-acetyl derivative, 1.94, with methanolic caustic alkali in the presence of formaldehyde, then without isolating the intermediate acidifying the reaction mixture, scheme 1.26.[82]



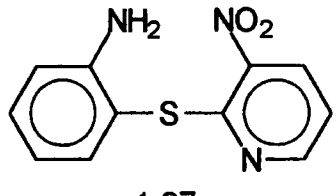
scheme 1.26

The rate coefficients for the rearrangement of the 2-aminophenyl sulfides 1.96 and 1.97 in excess base have been reported.[83] The results are consistent with the reaction pathway shown in scheme 1.27. In DMSO-water and DMSO-t-butyl alcohol, the spiro Meisenheimer intermediate is effectively the initial state.

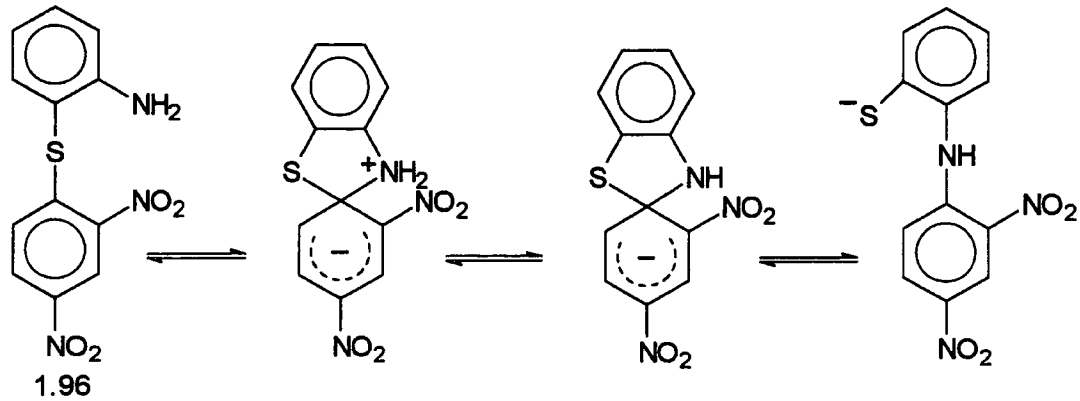
The excess base present has two functions; firstly, to ionise the product to drive the reaction to completion and secondly, to catalyse the formation of the complex by removal of the proton from the zwitterionic intermediate.



1.96



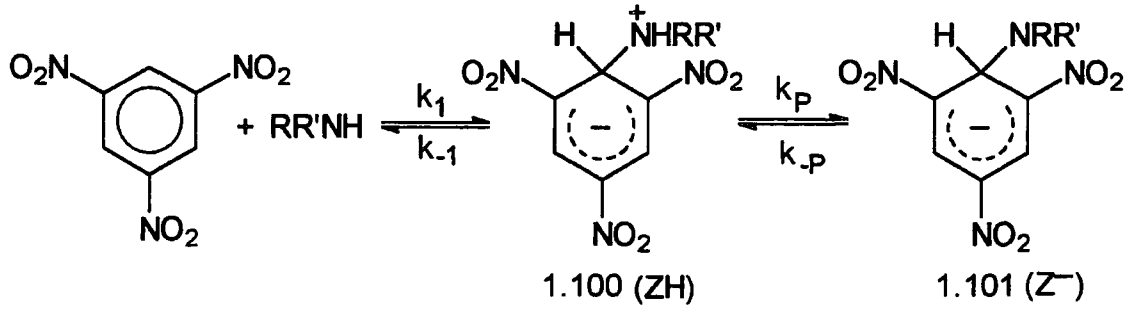
1.97



scheme 1.27

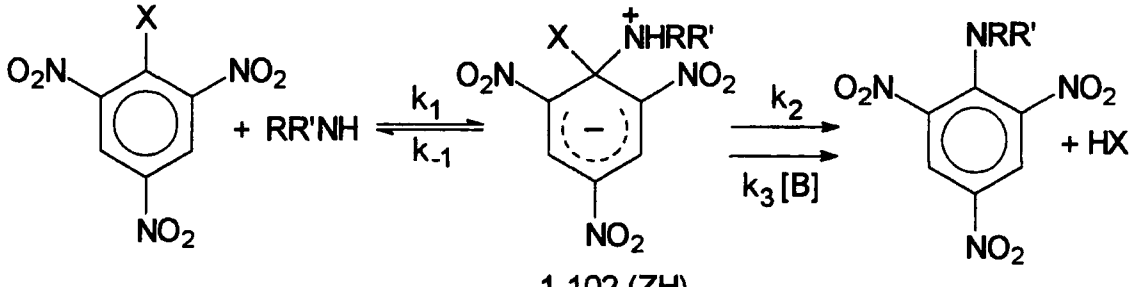
1.3 Reaction With Amines

The reaction of amines (primary, secondary, aliphatic, alicyclic and aromatic) at an unsubstituted ring position of an aromatic substrate has been shown to occur in two steps as shown in equation 1.30.[84-85]



equation 1.30

The first step involves addition of the amine to the aromatic substrate to form a zwitterion, ZH, which then loses an alkylammonium proton to give the anionic σ-adduct 1.101 (Z^-). The mechanism of equation 1.30, in which k_p refers to the deprotonation of ZH by a general base (amine, Z^-, solvent) and k_{-p} refers to the reprotonation of Z^- by a general acid ($RR'NH_2^+$ ions, ZH, solvent), has been investigated in detail in aqueous solvent and DMSO for various systems.[86-90] Depending on the system under study, the proton transfer step is found to be rapid (2,2,2-trifluoroethylamine)[88], rate determining over the entire range of amine concentrations (piperidine)[87] or only at low amine concentrations (benzylamine, butylamine)[87] for the reaction with 1,3,5-trinitrobenzene in DMSO. In contrast, for the reaction of TNB with 2,2,2-trifluoroethylamine in acetonitrile, the proton transfer step is found to be rate limiting.[88] This is explained in terms of the much lower ability of acetonitrile, relative to DMSO, to solvate ionic species. The zwitterion, ZH, would therefore decompose very rapidly in acetonitrile, hence $k_{-1}^{CH_3CN} >> k_{-1}^{DMSO}$, accounting for $k_{-1} >> k_p$.



equation 1.31

Reaction at a substituted ring position occurs via a two step mechanism, equation 1.31, first proposed by Bunnett.[13] The first step involves amine addition to the aromatic

substrate, giving a zwitterionic intermediate, 1.102 (ZH), which contains a labile proton which can be removed by base. The intermediate can be converted to products either spontaneously (k_2) or by base catalysis ($k_3[B]$). The uncatalysed step generally involves intramolecular proton transfer from nitrogen to the leaving group,[17,84,91] and can be represented by the energy profile shown in figure 1.1 (ii). The base catalysed step, $k_3[B]$, may involve rate limiting proton transfer from the zwitterion (ZH), or rapid interconversion of ZH into its deprotonated form, Z^-, followed by general acid-catalysed leaving group departure (the SB-GA mechanism). The former process generally applies in protic solvents, while in aprotic solvents, where leaving group expulsion is more difficult, there is evidence for the latter mechanism. The incidence and efficiency of base catalysis depends on the identity of the amine, the leaving group, the base and the solvent.[21,91-95] In general, base catalysis is more often observed with secondary than with primary amines, with poor leaving groups and in less polar solvents.[91]

With activated substrates the $k_3[B]$ step is usually found to be favoured relative to the k_2 step. Hence addition of base to the reaction mixture in some cases should considerably affect the relative rates of product formation versus reversion to reactants of the intermediate, and hence affect the overall rate-controlling step. The base may be the amine used as the nucleophile or another base added specifically to the reaction mixture.[10,84,85,91]

Studies performed on this system use a rate expression of the form :

$$\frac{\text{rate}}{[ArX][RR'NH]} = k_A = \frac{k_1k_2 + k_1k_3[B]}{k_{-1} + k_2 + k_3[B]} \qquad \text{eqn 1.32}$$

Where k_A is the measured second order rate constant obtained by applying the steady state approximation to the reaction at a given concentration of base. Three main areas of interest occur:

i) $k_2 + k_3[B] >> k_{-1}$

In this case, the formation of the intermediate is rate limiting, and equation 1.32 reduces to equation 1.33:

$$k_A = k_1 \qquad \text{eqn 1.33}$$

and hence no base catalysis will be observable (the energy profile will be as in figure 1.1 (i)).

ii) $k_2 + k_3[B] << k_{-1}$

This corresponds to a rapidly established pre-equilibrium, followed by decomposition of the zwitterion in the rate determining step. In this case equation 1.32 reduces to equation 1.34:

$$k_A = \frac{k_1 k_2 + k_1 k_3[B]}{k_{-1}} \qquad \text{eqn 1.34}$$

This predicts base catalysis with a linear dependence of k_A on base concentration

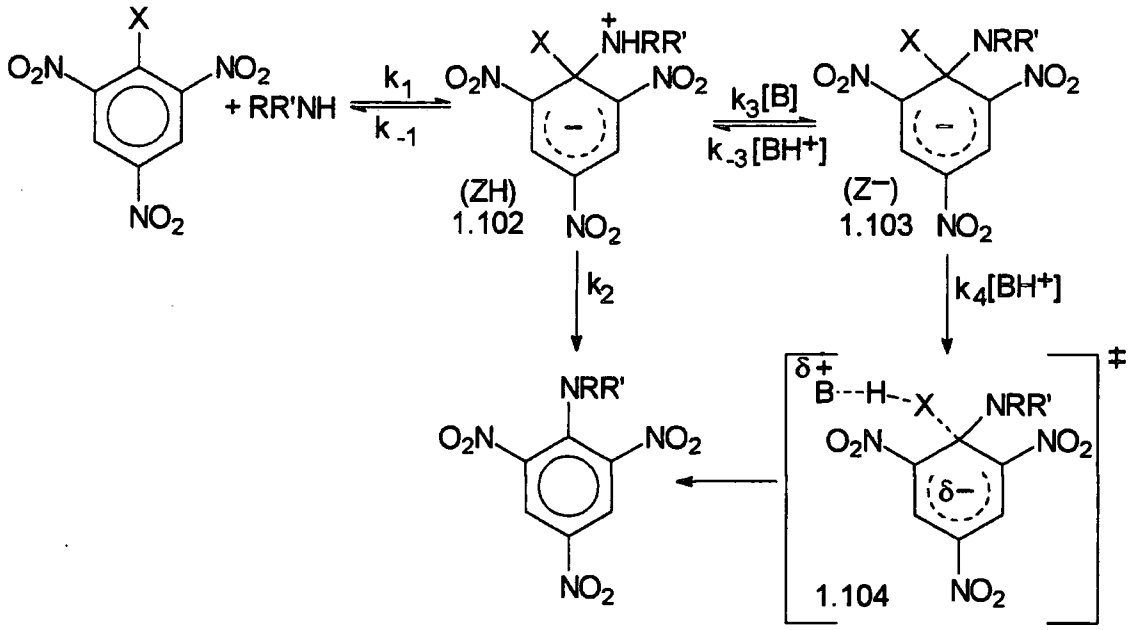
iii) $k_2 + k_3[B] \approx k_{-1}$

In this intermediate case, base catalysis may also be observed at low base concentrations but will diminish at higher base concentrations. The measured rate constant will show a characteristic curvilinear dependence on base concentration, going from approximately linear dependence to zero dependence.

All three cases have been observed in kinetic studies of the reactions in equation 1.31.

In order to observe base catalysis, the condition $k_2 + k_3[B] \leq k_{-1}$ must apply. Considering the effect of the leaving group, the above condition is more likely to apply with poor leaving groups such as F and OR than with good or moderately good leaving groups, such as Cl,Br and I.

The understanding of how the base catalysis occurs in reactions in which the decomposition of the zwitterionic intermediate is, at least partially, rate limiting has improved considerably over recent years.[10,17,84,85,97,98] Two mechanisms, the specific base- general acid (SB-GA) mechanism and the rate limiting proton transfer (RLPT) mechanism will be discussed along with several examples of each. Both can be represented by scheme 1.30, where the effect of the base is to deprotonate the zwitterion, 1.102 (ZH), yielding the anionic σ-complex, 1.103 (Z^-), which subsequently decomposes to products. The uncatalysed decomposition step, k_2, often contributes negligibly to the overall process.



scheme 1.30

1.3.1 The Specific Base-General Acid Mechanism.

The SB-GA mechanism involves a rapid equilibrium deprotonation of the zwitterionic complex, 1.102 (ZH), followed by rate limiting, general acid catalysed leaving group departure from the anionic σ-complex, 1.103 (Z^-), via the concerted transition state 1.104. The reaction can be expressed by the equation 1.35, where k_4 is the rate coefficient for acid catalysed expulsion of the leaving grouup from 1.103 and K_3 is the equilibrium constant for the conversion of 1.102 into 1.103.

$$k_A = \frac{k_1k_2 + k_1k_4K_3[B]}{k_{-1} + k_2 + k_4K_3[B]} \qquad \text{eqn 1.35}$$

The SB-GA mechanism, advanced in the 1960s[99-101], became generally accepted in 1970 after a study of the reaction of 2,4-dinitro-1-naphthylethyl ether, 1.105, with n-butylamine and t-butylamine in DMSO.[17] This was the first study of an S_NAr process in which the formation and decomposition of a Meisenheimer complex, 1.107, were separately observable. Independent confirmation was subsequently obtained through a ^1H flow NMR study in which the formation and disappearance of 1.106 as a function of time could be followed directly.[102,103] (See figure 1.2).

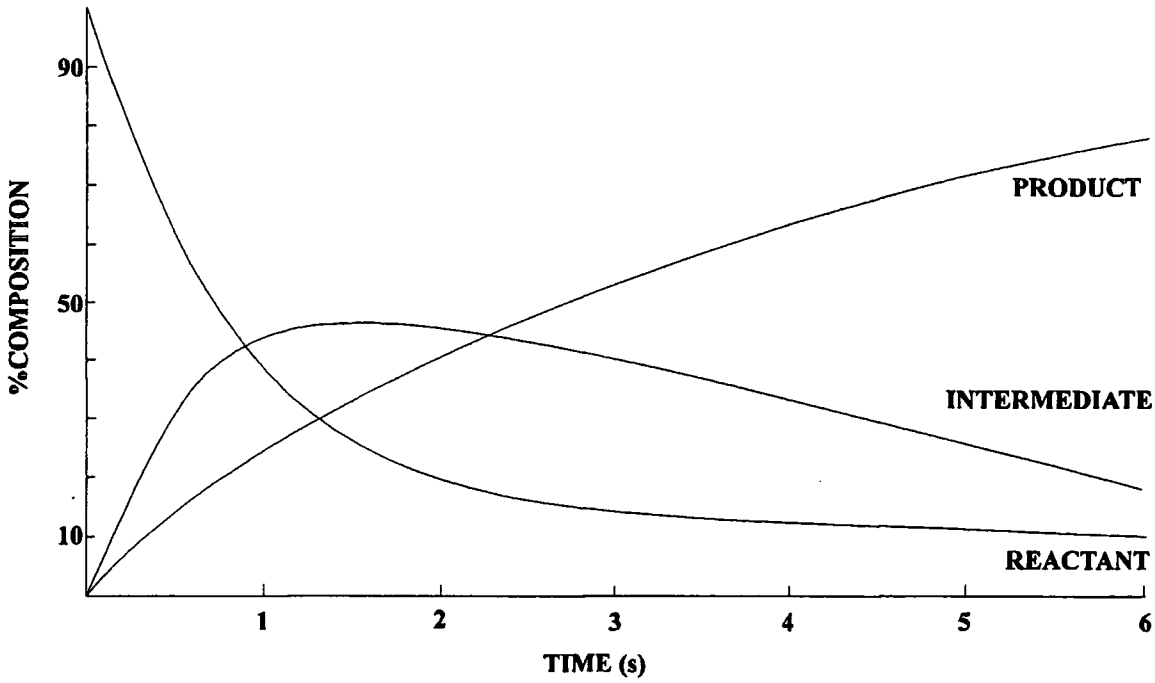
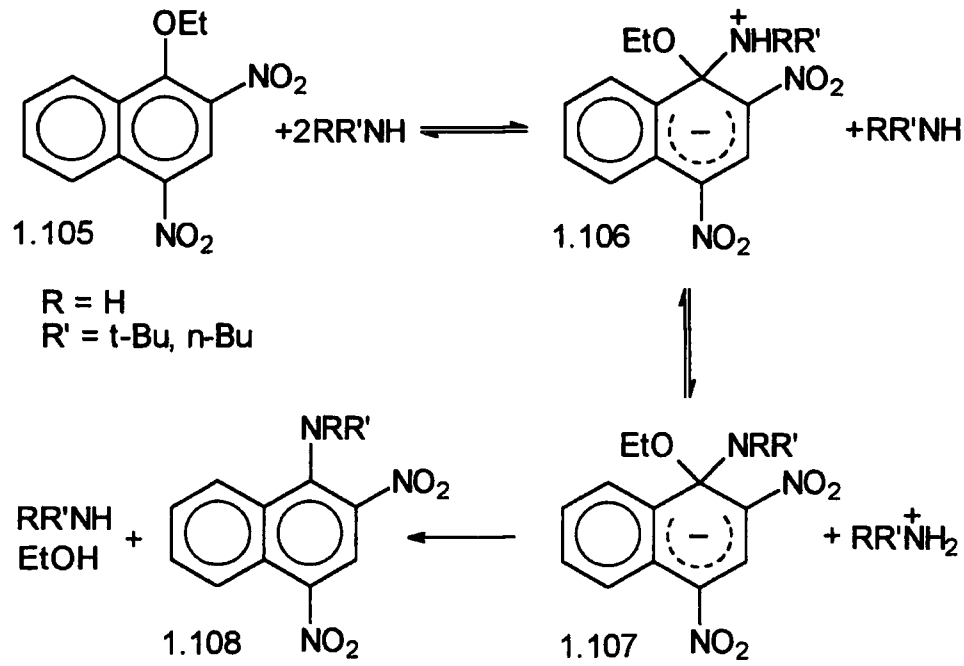


Figure 1.2 Percentage composition of the reaction mixture during the reaction of 1-ethoxy-2,4-dinitronapthalene (0.2 mol dm^{-3}) with n-butylamine in 75% DMSO/25% methanol at 0°C.



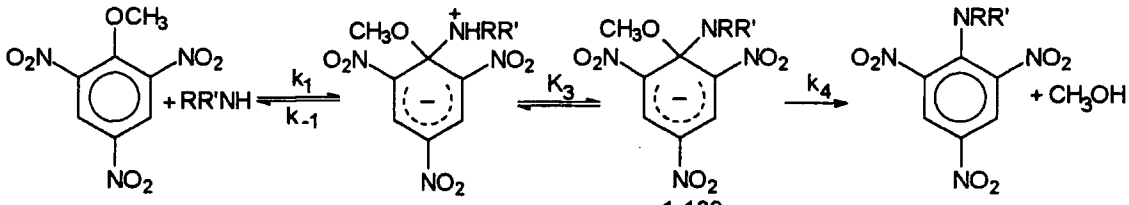
scheme 1.31

The first stage being addition of the amine to give 1.106 which is in rapid equilibrium with its conjugate base 1.107. The second stage being transformation of this anionic species to the product, 1.108, which was first order in ammonium ions but independent

of amine concentration, this being consistent with the SB-GA mechanism. The product was seen to be in equilbrium with an anionic species formed by loss of the amino proton which is known to be relatively acidic in DMSO.

Further evidence for the SB-GA mechanism has been provided for the reaction of several other systens studied:

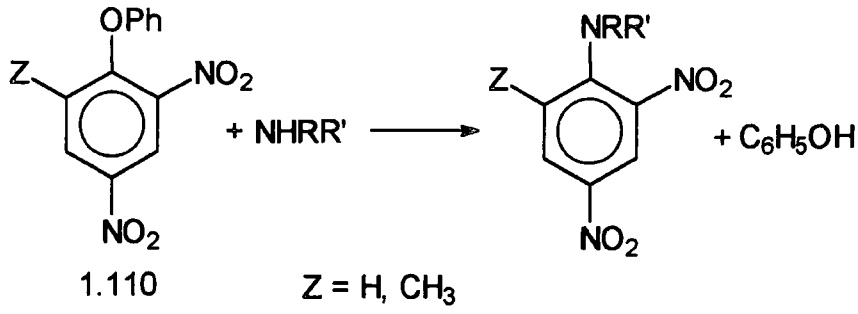
The reactions of 1-ethoxy-2,4-dinitronaphthalene with piperidine and pyrrolidine in DMSO were seen to occur in two separate stages, [97,98] involving formation of the adduct 1.107 and then the product 1.108. No conversion of the product to an anionic species could occur with the secondary amines. The rate constants for nucleophilic attack on species 1.105 show that pyrrolidine is more reactive than piperidine by a factor of 2.7, a similar value to that found for other similar systems. However, in the second stage of the reaction, the rate constant for pyrrolidine is approximately 11000 times greater than for piperidine.[97,104] This huge difference between systems, which appear so similar, is judged to arise from steric interactions forced by differences in conformation between the amino moieties in the intermediate σ-adducts as they release the nucleofuge. Hence, for these reactions general acid catalysis of slow nucleofuge departure has been demonstrated.



equation 1.36

Similarly, in the reaction of 2,4,6-trinitroanisole with piperidine and pyrrolidine,[105,106] the general acid-catalysed decomposition of the pyrrolidino intermediate, 1.109, is considerably faster than that of the piperidino analogue. Evidence for the SB-GA mechanism has also been obtained in other solvents such as acetone, acetonitrile[107,108] and aqueous dioxane.[97] An example in the latter solvent is shown in equation 1.37. Thus the reaction between 2,4-dinitrophenyl phenyl ether and 2,4-dinitro-6-methyl phenyl phenyl ether, 1.110, with piperidine and pyrrolidine was studied[98] in 60% dioxane / 40% water. All four amino-dephenoxylation reactions were catalysed by sodium hydroxide and the rate of base-catalysed transformation of the intermediate adduct to products is an order of magnitude greater for pyrrolidine than piperidine. Although this reactivity difference is less than in the naphthyl systems, the trend occurs in the same

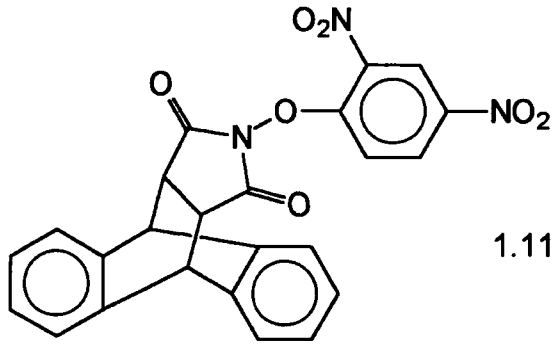
direction and can be explained in a similar way, i.e. destabilisation of the transition state for general acid-catalysed expulsion of the phenoxy group in the piperidino system.



1.110 Z = H, CH_3

equation 1.37

The reaction of 2,3-(9,10-dihydroanthracene-endo-9,10-diyl)-N-(2,4-dinitrophenoxy) succinimide, 1.111, with piperidine was studied in several solvents.[109] The second order rate coefficient increased with increasing piperidine concentration in all solvent systems studied except methanol. The observed base catalysis in acetonitrile, ethyl acetate, benzene and dioxane was explained in terms of rate limiting nucleofuge detachment. For the case with methanol, the formation of the intermediate is rate determining due to its high hydrogen bond donating property which facilitates expulsion of the nucleofuge.



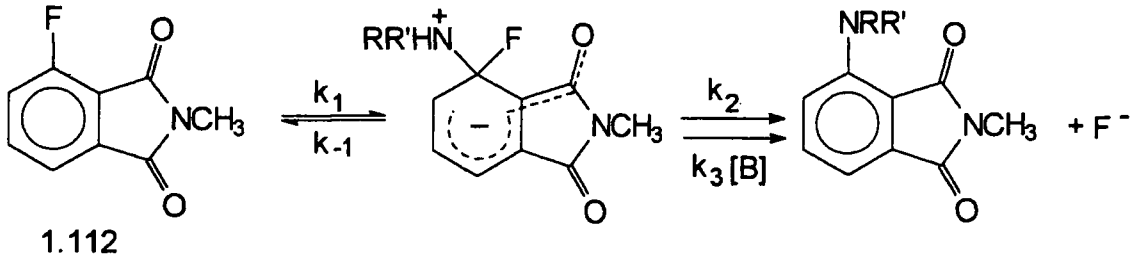
1.111

Base catalysis was not observed in the reaction of 1-fluoro-2,4-dinitrobenzene with piperidine in acetonitrile.[110] In the above reaction of the succinimide, 1.111, base catalysis was observed in the same solvent; here the substrate contained a bulky, sterically rigid nucleofuge. This reflects the importance of the nature of the nucleofuge in influencing the rate determining step in nucleophilic substitution reactions.

For the reaction of oxime ethers with primary amines (n-propyl, n-butyl, n-pentyl and n-hexylamine) in DMSO, DMF and MeCN,[111] the observed second order rate constants were found to exhibit a curvilinear dependence on amine. The reaction of piperidine in DMSO was found to follow a wholly catalysed pathway. No catalysis was observed for the reactions of n-butylamine in methanol and a 1:1 mixture of methanol / acetonitrile.

As with the succinamide, 1.111, the participation of the hydrogen bond donor solvent molecule in the intermediate is believed to account for the absence of base catalysis in these solvents.

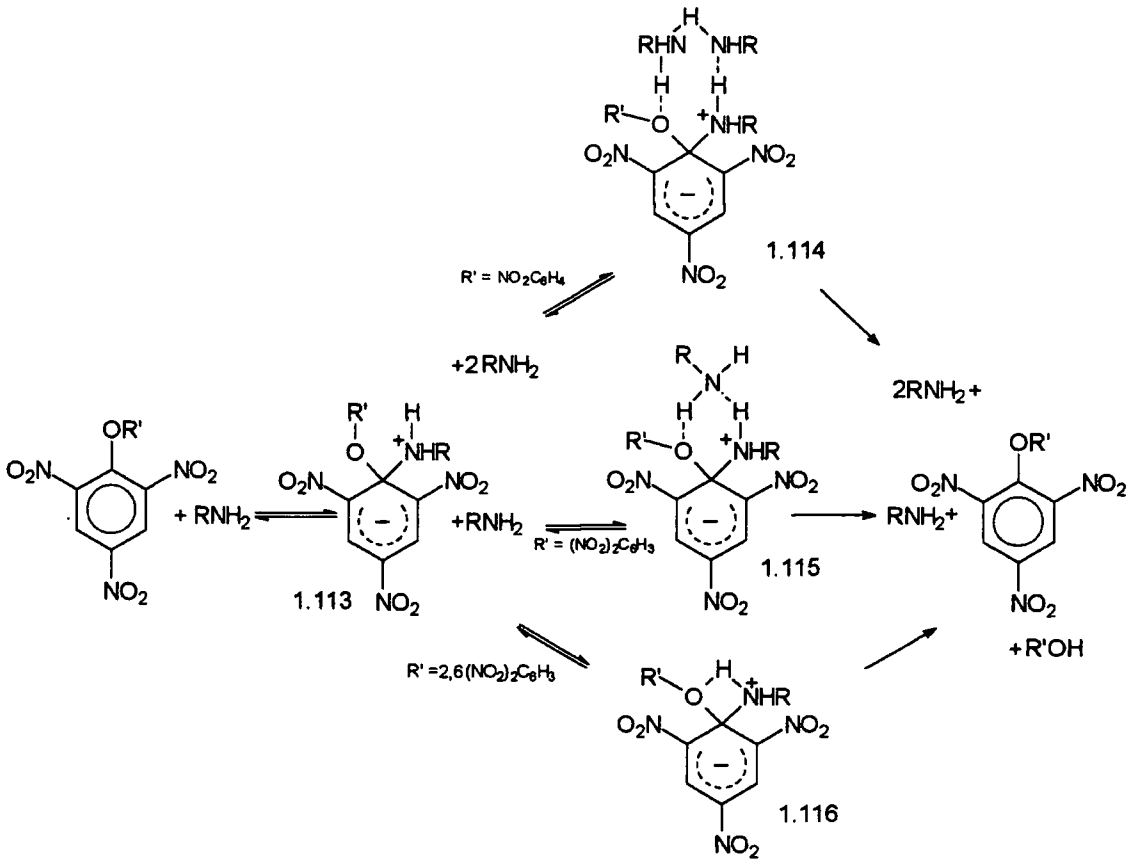
Base catalysis observed in the reaction of 3-fluoro-N-methylphthalimide, 1.112, with secondary amines in acetonitrile and benzene is also thought to involve the SB-GA mechanism,[112] as shown in equation 1.38. Base catalysis was observed for piperidine, pyrrolidine and morpholine in benzene and for piperidine and pyrrolidine in acetonitrile. This apparent base catalysis may be attributed to removal of a fluoride ion by the secondary amine acting as a hydrogen bond donor, rather than as a proton acceptor. This establishes the cyclic imide moiety as an activating group for the S_NAr mechanism in anhydrous aprotic media.



equation 1.38

The absence of base catalysis with morpholine in acetonitrile is attributable to its weaker basicity (also slower rates of reaction). Reaction rates were faster in acetonitrile than benzene, this being due to the greater solvating ability of the polar solvent enhancing the rate of departure of both the proton and the fluoride ion.

In non-polar aprotic solvents like toluene or benzene, modifications of the Bunnett mechanism have been suggested to account for the inability of these solvents to stabilise ionic species.[113-124] Most of these proposals assume that decomposition of the intermediate proceeds via a cyclic transition state, [113,114] such as 1.114. For example, the reactions of X-phenyl-2,4,6-trinitrophenyl ethers with aniline were found to be base catalysed.[113] Catalysis of the mono-nitro substituted ether involves two aniline molecules and proceeds at a temperature independent rate whereas the dinitro-substituted ethers involve one amine molecule and proceed at a temperature dependent rate. These results were interpreted in terms of a cyclic mechanism, involving four, six and eight membered rings in the transition state.



scheme 1.32

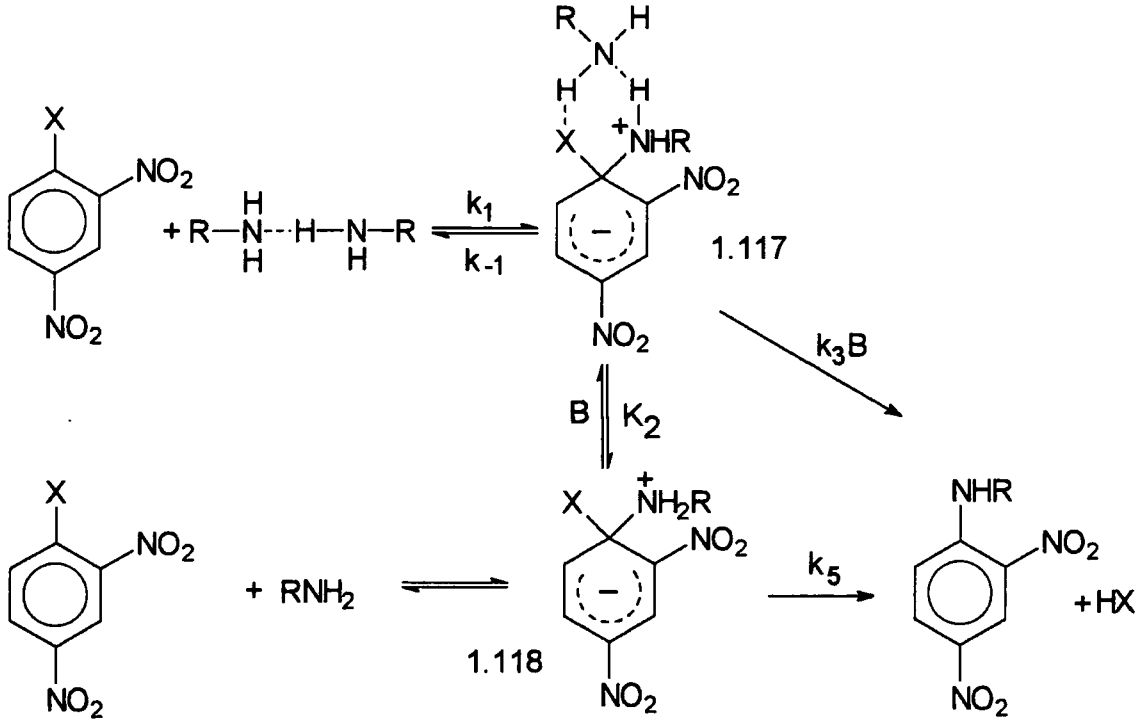
In non-polar aprotic solvents like benzene, nucleophilic aromatic substitution involving primary amines and substrates with fairly poor leaving groups may proceed by a catalysed path through a cyclic transition involving an 8-membered ring, 1.114. This is formed by intermolecular hydrogen bonding between the zwitterionic intermediate, 1.113, and two amine molecules acting bifunctionally, one as a proton donor to the leaving group (electrophilic catalysis) and the other as a proton acceptor from the positively charged nitrogen of the zwitterion (base catalysis). With a slightly better leaving group, the reaction still goes through a catalysed path, but now the cyclic transition state involves a six-membered ring, 1.115, formed by similar intermolecular hydrogen bonding between the zwitterionic intermediate and only one amine molecule, acting bifunctionally.

With a fairly good leaving group, however, the reaction is not likely to be base catalysed, and will proceed through a cyclic transition state involving a four-membered ring, 1.116, formed only by the zwitterionic intermediate, 1.113, through intramolecular hydrogen bonding.

These three types are exemplified by the reactions of 3-nitro, 3,4-dinitro and 2,6-dinitrophenyl-2,4,6-trinitrophenyl ethers respectively, in which the phenoxide portion becomes a progressively better leaving group due to the increasing activating effects of

the nitro groups in the respective positions of the phenoxide components of the ether. The fact that the phenoxide group of the 2,6-dinitro substituted phenyl ether is a fairly good leaving group is partly attributable to the steric compressions in the intermediate complex, 1.113,[91,100] when this ether is the substrate, thus facilitating conversion to products.

Another possibility in these solvents is the so called dimer mechanism. Here it is postulated that the initial attack of a dimer of the amine gives the cyclic intermediate, 1.117.[115-122] The reactions of 2,4- and 2,6-dinitroanisoles with cyclohexylamine in benzene and in cyclohexane were found to have an overall reaction rate of third order with respect to amine concentration and an inverse temperature effect was found for the reaction of 2,6-dinitroanisole in cyclohexane.[115,116] Both of these experimental findings were explained in a scheme involving dimer amine molecules.



scheme 1.33

The cyclic intermediate is formed straightforwardly in an addition step through the dimer of the amine which exists in aprotic solvents due to equation 1.39.

$$2\,NH_2R \rightleftharpoons RNH_2\text{-----}NH_2R \qquad \text{eqn 1.39}$$

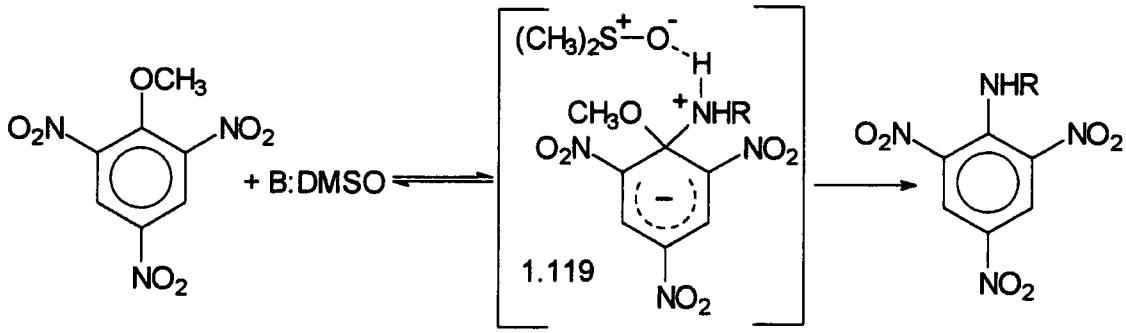
Intermediate 1.117, formed in the first step, is in a mobile equilibrium with a second, classical intermediate, 1.118, and either of these can react and go on to form the ultimate

products. In the cyclic intermediate proposed, 1.117, the second molecule of amine acts as a proton donor to the leaving group as well as a proton acceptor from the positively charged nitrogen atom of the zwitterion, thus stabilising the dipolar transition state that otherwise should be quite unstable in benzene. The proposed mechanism does not preclude attack by the monomer, which would straightforwardly form intermediate 1.118, proposed in the usual two step mechanism.

Amine dimers have been proposed to be involved in other reactions,[115-122] for example the buylaminolysis of p-nitrophenolacetate in chlorobenzene,[121] and of nitro-substituted 4-nitrophenyl benzoates and cinnamates.[119,120]

The reaction of 2,6-dinitroanisole with cyclohexylamine was also studied in toluene-DMSO mixtures.[123] in mixtures low in DMSO content, third order kinetics with respect to amine were observed and again explained by way of the dimer mechanism. A catalytic effect of DMSO observed, was explained by association of DMSO with the amine (mixed dimer) in a solute-solvent hydrogen bond interaction. At higher DMSO contents, behaviour typical of amine catalysis was found which is related to considerable additional stabilisation of the intermediate complex through solvation by DMSO.

Since it has been shown that association with DMSO reduces amine self-association,[124] it has been proposed that the catalytic effect of DMSO is due to participation in the first step of the reaction, forming a 'mixed dimer' with the amine molecules and producing the intermediate complex, 1.119.



equation 1.40

The mixed dimer will have the structure shown, 1.119. This kind of coordination of the amine proton should produce greater nucleophilicity of the amine owing to the greater electron density on the nitrogen atom,[125] and therefore explains the catalytic effect of DMSO.

Kinetic isotope effects (KIE's) have been shown to be important as 'mechanistic tools' yielding information on the rate determining step.[126] The $^{18}F/^{19}F$ KIE for the reaction of piperidine with 2,4-dinitrofluorobenzene in THF has been measured,[127] and was suggestive of substantial C-F bond breaking in the rate determining step. This gives

support to the earlier mechanistic conclusion by Nudelman[110] based on a study of the dependence of reaction rates on amine concentration in different solvents.

1.3.2 Rate Limiting Proton Transfer

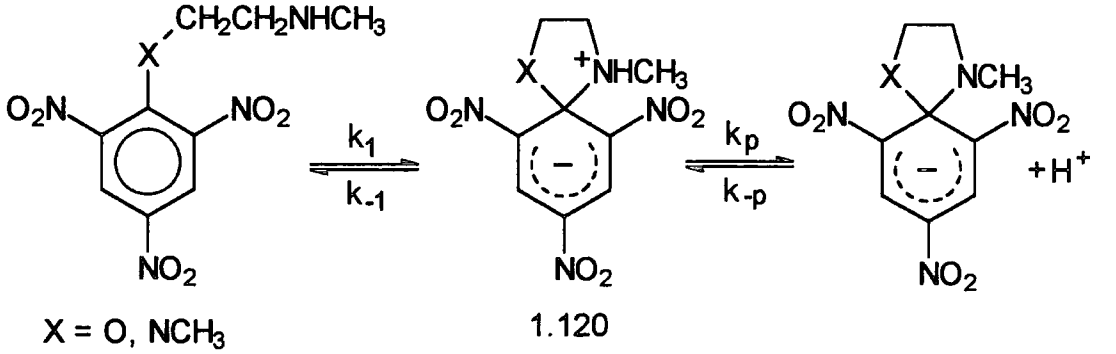
In the RLPT mechanism, the zwitterionic intermediate, ZH (formed by nucleophilic attack of the amine), undergoes rate limiting, base induced deprotonation, followed by rapid uncatalysed or acid catalysed leaving group departure.

This mechanism was first proposed by Bunnett and Randall[128] in 1958. It was initially rejected when it was shown that proton transfer between "normal" (O, N) acids generally proceeds at a rate which is close to diffusion controlled.[129] However, it has now been established that diffusion controlled proton transfer steps can become rate limiting.[130,131] This can occur in a multi-step process where the species undergoing deprotonation is present in a highly unfavourable equilibrium, or where reversion of this process is extremely rapid.[104] The general reaction can be expressed by equation 1.41.

$$ArL + RR'NH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ZH \underset{k_{-p}}{\overset{k_p}{\rightleftharpoons}} Z^- \xrightarrow{k_4} P \qquad \text{eqn 1.41}$$

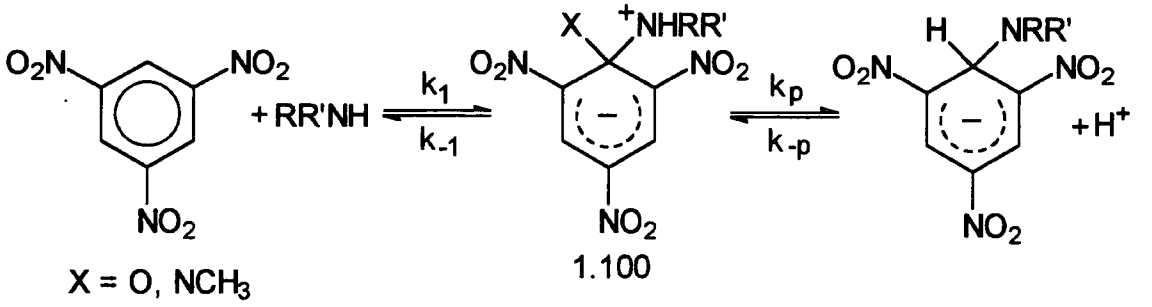
Where k_p refers to the deprotonation of ZH by the base, k_{-p} refers to protonation of Z^- by an acid and k_4 to the leaving group departure, either unassisted or catalysed by general acids. In order for the deprotonation of ZH to be the overall rate limiting step, according to equation 1.41 $k_4 >> k_{-p}$ and $k_{-1} >(>) k_p$. No base catalysis would be observed if the first but not the second condition were met.[84,85,100]

Most of the evidence for the RLPT mechanism in S_NAr systems has come from studies of the formation and decomposition of stable Meisenheimer complexes.[72,86,87,90,132-136] Temperature jump studies on reactions such as in equations 1.42 and 1.43 have revealed that amine departure from zwitterionic complexes such as 1.120 and 1.100. is remarkably fast. As a consequence, deprotonation of 1.120 and 1.100, although thermodynamically favoured and therefore essentially diffusion controlled, becomes rate limiting ($k_p << k_{-1}$) or partially so ($k_p < k_{-1}$) at low pH and low buffer concentrations.[84,85]



X = O, NCH_3 1.120

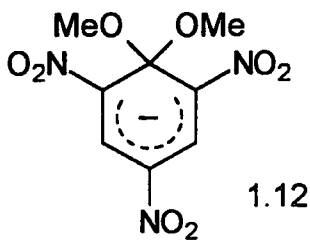
equation 1.42



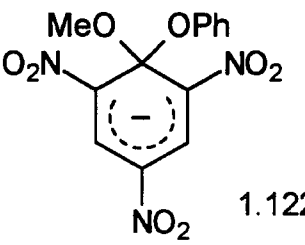
X = O, NCH_3 1.100

equation 1.43

Extrapolation of k_{-1} values determined for typical S_NAr systems such as the less activated 2,4-dinitrobenzene derivatives suggests values of 10^7 to 10^8 for k_{-1}. Hence, for these derivatives and even more for mono-nitro derivatives, the relationship $k_{-p} < k_{-1}$ will hold under typical base catalysis conditions, i.e. high base concentrations.[84,85] Other results have concluded that the other condition $k_4 >> k_{-p}$ is probably met in many cases. Studies of the reactions in equations 1.42 and 1.43 indicate that the basicity of the amino moieties in anionic adducts such as 1.120 and 1.100 is much less than the basicity of the parent amine ($\Delta pK \geq 2$), therefore the k_{-p} step refers to a thermodynamically unfavourable proton transfer under typical conditions and hence has a low rate constant.[86,132,133] This implies that $k_4 >> k_{-p}$ will hold for all reactions involving good leaving groups. Values of k_4 were found to be high by extrapolation of k_4 values for the spontaneous or solvent assisted departure of alkoxide and phenoxide ion departure from complexes such as 1.121 and 1.122 in aqueous solution.[84]

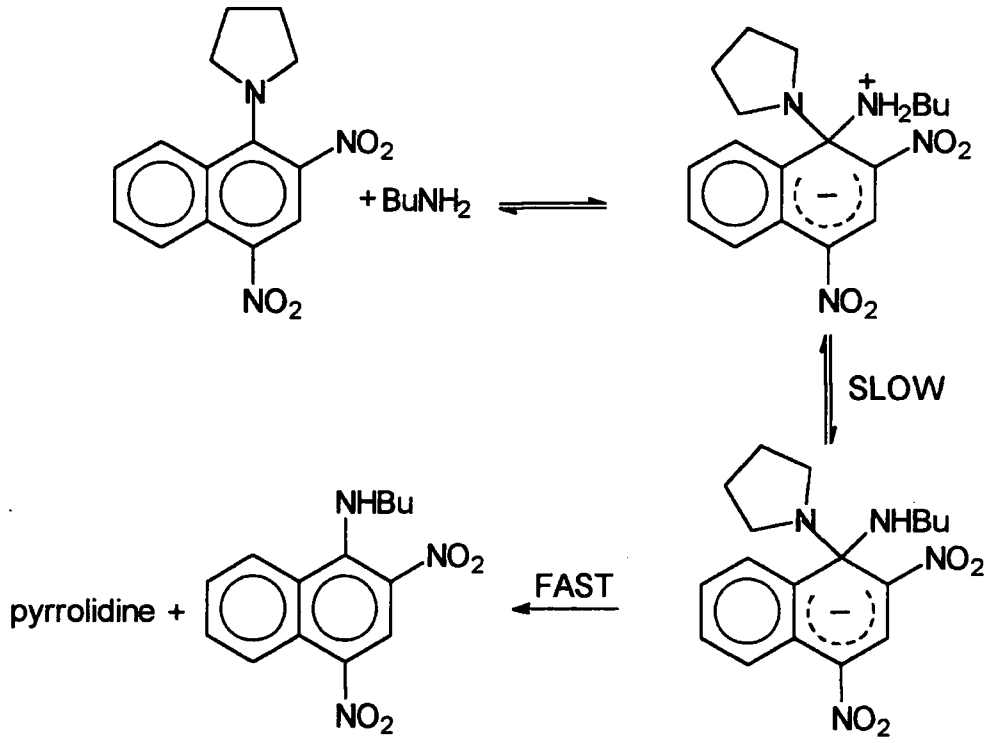


1.121



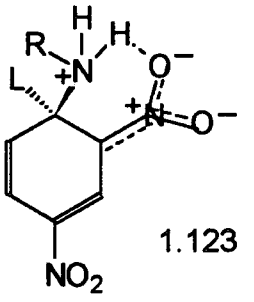
1.122

The SB-GA mechanism has gained general acceptance for reactions in DMSO, particularly since Orvik and Bunnett[17] studied the reaction of 1-ethoxy-2,4-dinitronapthalene with n-butylamine and t-butylamine in DMSO. They showed the reaction consisted of two stages, rapid formation of 1.107 and rate determining butylammonium ion catalysed ethoxy group expulsion to give 1.108, (see scheme 1.31). However, in amine-amine exchange reactions Sekiguchi et al.[137] have suggested that proton transfer may occur in the rate determining step. The nucleophilic substitution reaction of butylamine with 1-pyrrolidino-2,4-dinitronapthalene in DMSO was shown to be subject to general base catalysis. Evidence was presented showing this to be a consequence of rate limiting deprotonation of the zwitterionic intermediate complex.

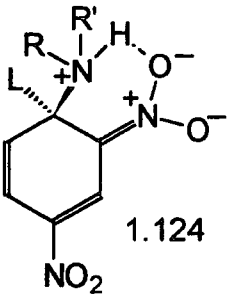


scheme 1.34

There is a greater tendency of substrates containing an ortho nitro group to undergo base catalysed reactions with secondary amines than with primary amines of the same basicity. This has been explained[91,138] in terms of stabilisation of the zwitterionic intermediates of ortho-nitro derivatives through intra-molecular hydrogen bonding between an ammonio proton and the ortho-nitro group.[139] Such stabilisation would be expected to reduce the k_{-1} value for reversion to reactants by the same extent for primary and secondary amines, as both structures 1.123 and 1.124 require initial breaking of the hydrogen bond.



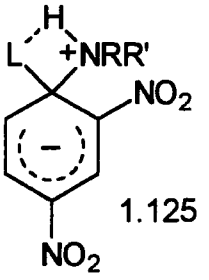
1.123



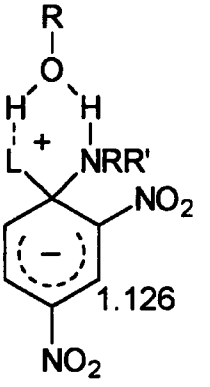
1.124

In contrast, the effect on the expulsion of the leaving group will be different; as the hydrogen bond must be broken when the nucleophile is the secondary amine, but not when it is a primary one. This will result in a greater reduction of the ($k_2 + k_3[B]$)/ k_{-1} ratio for secondary amines compared to primary ones.

In particular, there may be a large influence on k_2, involving the spontaneous decomposition of the zwitterion, commonly viewed as involving an intramolecular transfer of the ammonio proton to the leaving group, either via the transition state, 1.125, in aprotic solvents like benzene or the transition state, 1.126, in hydroxylic solvents.[99]



1.125



1.126

With primary amines, there is a non-hydrogen bonded proton available, so the possibility for spontaneous decomposition is not much affected by the hydrogen bonding. With secondary amines, the one proton available is tied up in a hydrogen bond, thus reducing its susceptibility to spontaneous decomposition and hence decreasing the ratio k_2/k_{-1} for secondary amines compared with that for primary amines.

If a second nitro group is introduced at the 4-position, a large proportion of the negative charge on the intermediate is accommodated on this group. As it is well known that a nitro group has a much greater stabilising effect on Meisenheimer complexes in a 4- rather than a 2-position. The strength of the hydrogen bonds is therefore reduced and so the condition $k_{-1} >> k_2$ holds .

The presence of two ortho nitro groups in a 2,6-substrate allows the possibility of hydrogen bonding both ammonio hydrogen atoms in the complex formed by reaction

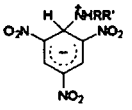
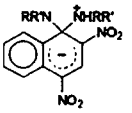
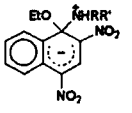
with primary amines, but also increases congestion at the reaction centre. This inhibits a bimolecular SB-GA like mechanism of the uncatalysed mode of decomposition of the intermediate when primary amines are the nucleophiles and instead favours unimolecular decomposition via an internally hydrogen bonded transition state.

Bernasconi[91] has also shown that the effect of the hydrogen bond between the ortho-nitro group and ammonio proton is greater on k_{-1} than k_2, and the discrepancy between the two is magnified when the hydrogen bond is strong. DMSO is much more basic than acetonitrile and can form quite strong hydrogen bonds with the ammonio proton. Thus intramolecular hydrogen bonding is more effective in acetonitrile giving an increase in k_2/k_{-1} compared to DMSO. The reaction of 2-phenoxy-3,5-dinitropyridine with aniline is not catalysed in DMSO, but is catalysed in acetonitrile.[140] Similar behaviour has been observed in the reaction of 2,4-dinitroanisole with butylamine,[141] 2,4,6-trinitrophenyl phenyl ether with aniline [114,141] and 1-fluoro-2,4-dinitrobenzene with aniline.[142] In all cases these changes when primary amines are the nucleophiles correspond to a change in the condition $k_{-1}/k_2 << 1$ in DMSO to $k_{-1}/k_2 >> 1$ in acetonitrile.[140]

Congestion at the reaction centre can be increased by introducing any substituent at the 6-position of the substrate. For example, a 6-bromine atom will have an activating electronic effect and a rate reducing steric effect. The reaction of 1-bromo-2-fluoro-3,5-dinitrobenzene and 2-methylaniline, resulting in the displacement of the fluorine atom is not base catalysed[143] (reaction of 1-fluoro-2,4-dinitrobenzene and 2-methylaniline is base catalysed). Thus the introduction of a 6-bromo substituent to 1-fluoro-2,4-dinitrobenzene has caused the mechanism of its reaction with 2-methylaniline to revert to a rate determining formation of the intermediate. As increasing the steric requirements of the intermediate favours its rate limiting decomposition to products, the present results therefore suggests the probable existence of an additional factor due to the electronic effect of the bromine atom, which overcomes the steric effects in this reaction. As conjugative effects are more effective from the 4-position and inductive effects greater from the 2-position,[9] the activating effect of a bromo substituent would be expected to be greater when it is in the 2- than the 4- position.

The effect of other ortho substituents such as methyl and aza groups on the mechanism of aromatic nucleophilic substitution reactions in dipolar aprotic solvents has been studied.[140] (The activating power of a nitro group in aromatic nucleophilic substitution is known to be greater than that of an aza group and its bulk comparable to that of a methyl group.[144])

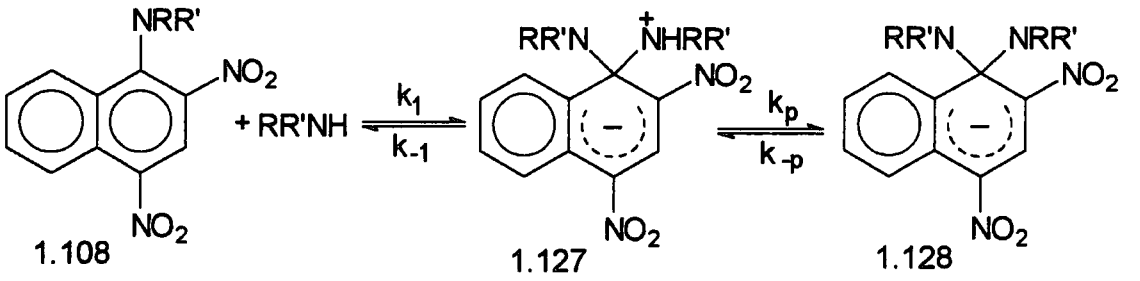
Table 1.3 Rate and equilibrium data for the formation and decomposition of zwitterionic amino complexes in aqueous dioxane and DMSO solutions and DMSO at 25°C.

substrate	R R'	solvent	k_1/ $dm^3mol^{-1}s^{-1}$	k_{-1}/ s^{-1}	K/ dm^3mol^{-1}
	CH_3 H	10% dioxane in water	160	1.5×10^5	1.07×10^{-3}
	n-C_4H_9 H	10% dioxane	123	1.5×10^5	8.2×10^{-4}
	n-C_4H_9 H	DMSO	4.5×10^4	2×10^4	2
	pyrrolidine	10% dioxane	8.1×10^3	1.5×10^6	5.8×10^{-3}
	piperidine	10% dioxane	3×10^3	2.1×10^6	1.43×10^{-3}
	piperidine	DMSO	$> 6 \times 10^4$	$> 7 \times 10^3$	9
	n-C_4H_9 H	DMSO	3.1×10^{-4}	0.095	3.26×10^{-3}
	pyrrolidine	DMSO	2.1×10^{-3}	0.38	5.52×10^{-3}
	piperidine	DMSO	v. low		
	n-C_4H_9 H	DMSO	31.8	5.9	5.4
	t-C_4H_9 H	DMSO	0.58	490	1.02×10^{-3}
	pyrrolidine	DMSO	650	1.89×10^4	3.44×10^{-2}
	piperidine	DMSO	240	1.54×10^4	1.55×10^{-2}

Values of the equilibrium constant, K, give a measure of the thermodynamic affinity of the nucleophile for the electrophilic carbon centre, a quantity commonly known as the carbon basicity of the nucleophile. On the other hand, the values of the rate constant k_1 measure nucleophilicity of the incoming nucleophile, while those of k_{-1} measure its leaving group ability, its nucleofugality.

As can be seen in table 1.3, addition at an unsubstituted ring position of primary amines such as butylamine, or secondary amines such as pyrrolidine and piperidine, to give zwitterionic complexes, ZH, occurs very rapidly in aqueous or DMSO solutions.[86,87] The values for k_1 can be seen to follow the familiar pattern found in S_NAr reactions, with the more basic secondary amines being more reactive than primary amines. The k_{-1} values, measuring the susceptibility of the zwitterion to spontaneous decomposition, are

also very high and so the situation required for having a rate limiting deprotonation step in equation 1.30, i.e. $k_{-1} >> k_p$, is met under some experimental conditions.[120-122] The high values for k_{-1} imply that the corresponding equilibrium constants for zwitterion formation are relatively low. These rate constants, k_{-1}, for amine expulsion are found to be higher with secondary than primary amines.[84-86] This is unexpected on the basis of pKa values, but is consistent with other observations and has been attributed to greater steric strain in the zwitterion, ZH, when secondary amines are involved.[87] This effect partly compensates for the higher k_1 values for these amines with TNB, so that the stabilities of the zwitterions are all of the same order of magnitude. Going from aqueous solvents to DMSO causes a 10^3-fold increase in K for the zwitterion formation in the reaction between TNB and n-butylamine and piperidine.[87] As generally found for other 1,1-Meisenheimer complexes, this increase reflects increases in values of k_1 and decreases in k_{-1}.



where RR' = piperidine, pyrrolidine or N-methyl-butylamino

equation 1.44

The naphthalene zwitterionic σ-complexes, 1.127, which result from amine addition at an amino substituted carbon, form much more slowly than the TNB analogues in DMSO, and nucleophilic addition is the rate limiting step in equation 1.44. The changes in k_1 on going from equation 1.30 to equation 1.44 are too great to be accounted for only on the basis of lower activation of the 2,4-dinitronaphthyl system. Also the low k_1 values for formation of 1.127 are coupled with low k_{-1} values.

These differences between the reactions of equations 1.30 and 1.44 can be explained in the same way as has been used to account for the differences in the reactivities of alkoxide ions with TNB and trinitroanisole; i.e. the contrasting behaviour between alkoxy and gem-dialkoxy complexes.[73,145,146] The major effects determining the rate and equilibrium parameters in equation 1.44 are thought to be:-

i) ground state stabilisation through resonance interaction involving the amino group in the parent naphthalenes, 1.108,

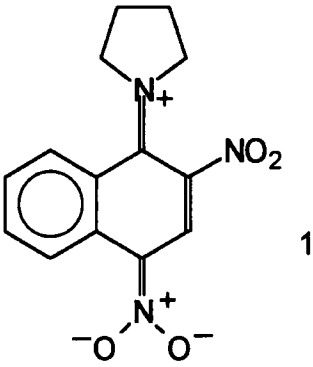
ii) steric hindrance to the approach of the amine reagent to the substituted amino carbon and,

iii) relief of steric strain on complex formation.

It can be seen in the table 1.3, that there is a large difference in the value of rate constants, k_1, for attack by pyrrolidine and piperidine at the C-1 of 1.108 to form zwitterions, 1.127. Pyrrolidine is thought to be about 400 times more reactive than piperidine, although in the latter case reliable rate and equilibrium measurements for the formation of 1.128 could not be obtained. The two amines exhibit similar rates of nucleophilic attack on numerous other aromatic sites,[86,97,98] and so the great difference in the present case is judged to arise from the influence of the amino group present in 1.108 rather than from the attacking nucleophile. The problem does not appear to arise in the reaction of N-methyl-butylamine with the corresponding naphthalene compound. In this reaction, the k_1 value for piperidine is approximately a seventh of that for the pyrrolidine reaction, this decrease can be attributed to steric factors in the attacking nucleophile.

The characteristic of the piperidino group in 1.108 which retards nucleophilic attack on C-1 is probably concerned with the transition state stereoelectronic requirements which oblige conformations which can only be attained at the expense of steric compressions.[91] These factors which raise the energy of the transition state are thought to be similar in origin to those responsible for the very slow expulsion of ethoxide from the adduct 1.107 (NRR' = piperidino) during the reaction of piperidine with 2,4-dinitronaphthyl ethyl ether.[97]

The rate constant, k_1, for attack of pyrrolidine at C-1 of 1.108 is lower than that for attack at the C-1 of 2.4-dinitro-1-naphthyl ethyl ether by a factor of 3×10^5. The lesser reactivity of 1.108 probably stems from a mesomeric interaction between the amino nitrogen and the nitro groups, involving contributions from structures such as 1.129. Such mesomerism reduces the enthalpy of 1.108 and therefore increases the enthalpy of activation to the transition state where such interaction is much reduced.[91]



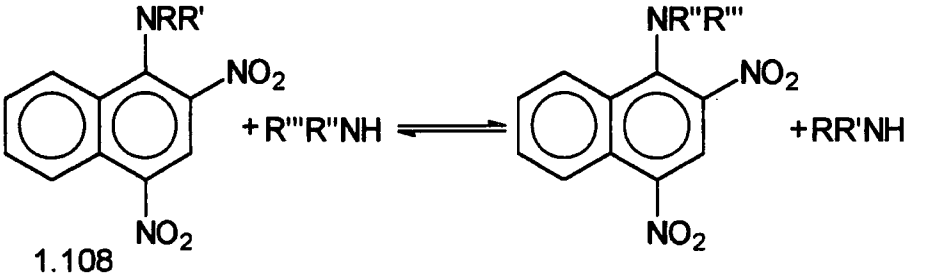
1.129

Values of the rate constant, k_1, for nucleophilic attack at the 1-position of 2,4-dinitro 1-naphthyl ethyl ether are comsiderably lower than values for attack at an unsubstituted ring position of TNB. Pyrrolidine is more reactive than piperidine by a factor of 2.7, n-butylamine is an order of magnitude less reactive while t-butylamine is two orders of magnitude less reactive than its straight chain isomer. This order of amine reactivity

resembles the order of overall reactivity in S_NAr reactions in which formation of the σ-adduct is rate determining.[9]

The overall equilibrium constant, K_1, for formation of the σ-adduct 1.107 (see scheme 1.31) has the highest value for n-butylamine , is about a hundred-fold less and similar for pyrrolidine and piperidine and nearly a hundred-fold lower for t-butylamine. These differences probably reflect the steric crowding in the adducts 1.107, which are severe for t-butylamine, considerable for piperidine, a little less for pyrrolidine and substantially less for n-butylamine. The substituted ammonium ion catalyses the expulsion of the ethoxide ion from the σ-complex intermediate, 1.107, with rate constant k_4. For the pyrrolidine system, k_4 is approximately 11000 times greater than for piperidine. In view of the similarity of the stage one reactivity, the stage two differences are probably due to differences in transition state energies (that for piperidine being higher), as explained previously.

Amino groups are generally not regarded as good leaving groups in activated aromatic substitution reactions.[9] However, dialkylamino groups such as dimethyl, diethyl, N-methylbutylamino, piperidine and pyrrolidine of 1-substituted 2,4-dinitronapthalenes are very easily replaced by primary amines and pyrrolidine at room temperature in DMSO, as shown in equation 1.45.

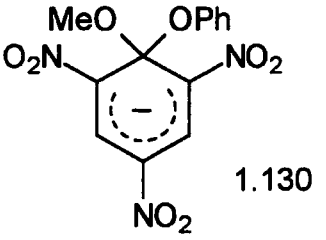


equation 1.45

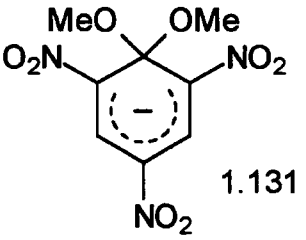
Nucleophilic secondary amines, other than pyrrolidine, eg.dimethyl, diethyl, diisopropylamine and piperidine showed extremely low reactivity. Similar reactivity orders were found in the reaction of 1-dimethylamino-2,4-bis(trifluoro-acetyl) naphthalene with various amines in acetonitrile.[48] Such discrepancy in reactivity between piperidine and pyrrolidine has often been observed in S_NAr reactions.[73,84,91,97,98,136]

In the amine-amine exchange reactions of 1.108 it is found that primary amines will replace secondary amino functions although the reverse reactions do not occur. There seems to be little correspondence with the pK_a value of the amines involved. However,

Bernasconi and Muller[148] showed that phenoxide ion departure from 1.130 is approximately 10^7 times faster than methoxide loss from 1.131. They suggested that in the alkoxyl or aryloxyl group departure from complexes or intermediates, an RO group of lower pKa generally leaves faster.[130] This principle does not seem to hold with amine leaving groups which is believed to depend mainly on the size and conformation of the amino groups attached, eg. the more bulky 1-alkylamino group of 1.108, such as piperidino, is easily replaced with another less bulky alkylamine, such as methylamine in a higher yield. The substitution of the methylamino group of 1.108 with ethylamine occurs only in low yield.[149]

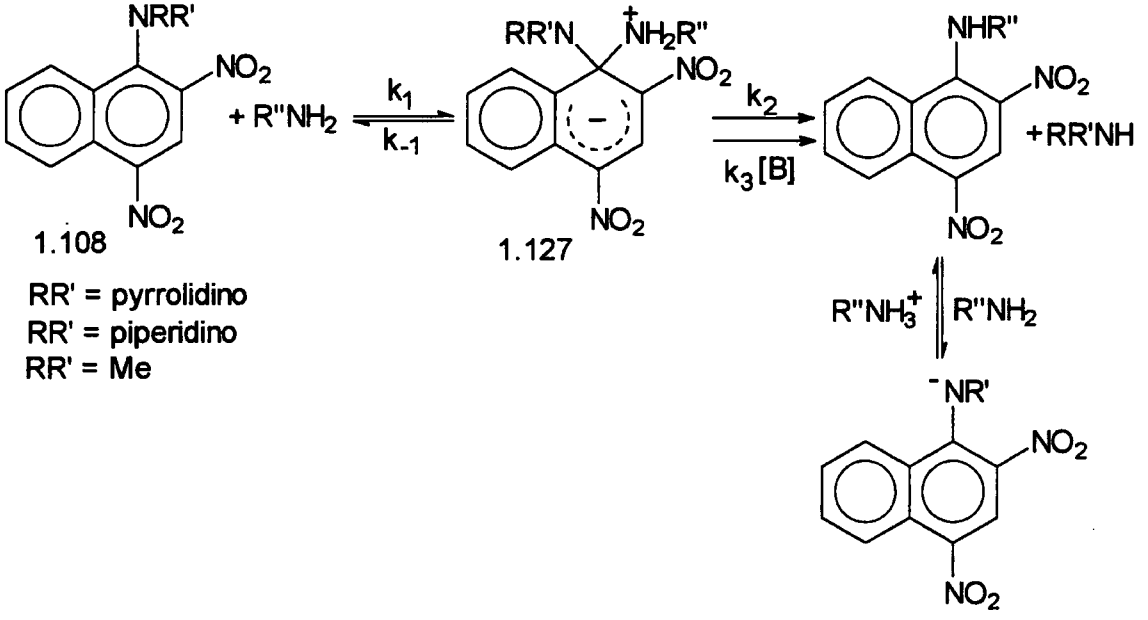


1.130



1.131

The reaction of butylamine with 1-pyrrolidino-2,4-dinitronaphthalene in DMSO was found to be subject to catalysis by both butylamine and DABCO, whereas the reaction of the same amine with 1-piperidino- or 1-dimethylamino-2,4-dinitronapthalene was not subject to any base catalysis,[137] (see scheme 1.35). The following explanation has been suggested.



1.108

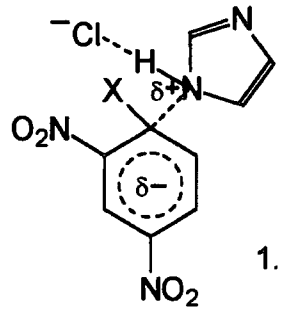
RR' = pyrrolidino
RR' = piperidino
RR' = Me

1.127

scheme 1.35

The reaction of 1.108 (NRR' = C_4H_8) proceeds via general base catalysis, with rate limiting deprotonation of 1.127 by base and then spontaneous detachment of the pyrolidine group, (proton transfer mechanism). Butylamine is able to approach the C-1 of the piperidino and 1-dimethylamino compounds less easily than with the 1-pyrrolidino compound because of the steric interference of the α-CH_2 groups of the piperidino ring or the CH_3 groups of the dimethylamino group. These effects could render the free energy for the transition state in the k_1 step remarkably high, resulting in a great reduction in k_{-1} and in turn the k_2/k_{-1} value could become higher than one, hence base catalysis is not observed. The high value of k_{-1} reflects the difficulty of rotating bulky groups back into the ring plane.

The reactions of imidazole with 1-chloro- and 1-fluoro-2,4-dinitrobenzene were found to be uncatalysed in DMSO. In acetonitrile there is catalysis by tetraethylammonium chloride which may be rationalised by stabilisation by the chloride ion of the transition state for the formation of the intermediate.[151]



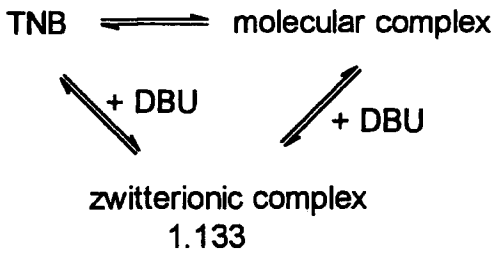
1.132

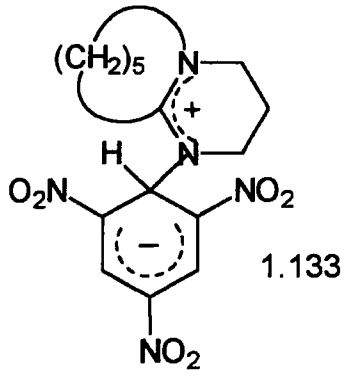
In both of the above solvents, amine attack is rate limiting. In benzene, the reactions with imidazole are catalysed by the nucleophile, tetrabutylammonium chloride and weakly by pyridine. This catalysis has been explained in terms of the reactions taking place via molecular complexes formed from the reactants and catalysts.

The concept of the reaction of imidazole with 1-halogeno-2,4-dinitrobenzene in benzene taking place via reactions involving complexes is not new. It was used by Pietra and del Cima[152] to explain their observations of the catalysis of the reaction of imidazole with 1-fluoro-2,4-dinitrobenzene by imidazole and quinuclidine in benzene. Forliani[92,94] also reported the catalysis, as being due to the interaction between the substrate and catalyst in a rapidly achieved pre-equilibrium, preceding the substitution process, where the catalyst could be either the nucleophile or the base.

For example, in the reaction between TNB and 1,8-diazabicyclo [5.4.0]-undec-7-ene in toluene,[153,154] kinetic data showed autocatalytic behaviour. Inspection of the reaction mixture at time zero indicated the presence of an equilibrium preceding the attack of the nucleophile affording a molecular complex (substrate-nucleophile) which explained the observed kinetic features. In solvents of low polarity, the substrate-catalyst molecular complex is assumed to be more reactive than 'free' substrate (complexed or solvated).

Consequently the observed second order dependence on amine concentration may arise from the presence of a pre-equilibrium, involving a further molecule of the amine (or catalyst) in the transition state. The nature of the complex is not known fully, but the main interaction is thought to be a donor-acceptor type, due to the structure of the reagents. The proposed reaction scheme is shown in scheme 1.36.





1.133

scheme 1.36

Thus the catalytic behaviour observed in apolar solvents may in some cases be due to substrate-catalyst interaction rather than by catalysis of leaving group departure. It is worth noting that in polar solvents, such as DMSO, the substrate will be well solvated so that molecular interactions with additives are unlikely.

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CHAPTER 2

Experimental

Experimental

2.1 Chemicals used

2.1.1 Solvents

Dimethyl sulfoxide (DMSO): Commercial sample (99+%), was used as supplied.

Dioxan: Commercial sample (99+%, ACS Reagent), was used as supplied.

Deuterated solvents:

Dimethyl sulfoxide-d_6: Commercial sample of isotopic purity 99.9% in 1 cm^3 glass phials, were used as supplied.

2.1.2 Nucleophiles

n-Butylamine: Commercial reagents, (98%, >99%), were used as supplied.

Pyrrolidine:Commercial sample (99%), was used as supplied.

Piperidine: Commercial sample (99%), was used as supplied.

Morpholine: Commercial sample (99+%, ACS Reagent), was used as supplied.

2-Aminoethanethiol: Commercial sample, was used as supplied.

Sodium hydroxide: Sodium hydroxide solutions were either prepared by dissolving analytical grade sodium hydroxide pellets in distilled water or were diluted from AnalaR stock solutions.

1,4-Diazabicyclo [2,2,2] octane (DABCO): Reagent grade (98%), used as supplied.

2.1.3 Added Salts

n-Butylammonium Perchlorate: Prepared in DMSO from amine and perchloric acid; the pH value of the solution was measured and if necessary, small quantities of acid or base were added until the theoretically calculated pH was obtained. The salt solution prepared contained less than 0.1% of free acid or free amine.

Pyrrolidinium perchlorate: Prepared in an analagous way to butylammonium perchlorate, using pyrrolidine and perchloric acid.

Pyrrolidinium chloride: Prepared from an anhydrous commercial sample of HCl in ether and pyrrolidine. The solution of HCl was cooled in ice, pyrrolidine dissolved in ethanol was added to the above with stirring. The white precipitate immediately falling out of solution was dried under vacuum and stored in a dessicator.

Piperidinium chloride: A commercial sample (99%), was used as supplied.

Morpholinium perchlorate: Prepared in an analagous way to butylammonium perchlorate, using morpholine and perchloric acid.

Tetraethylammonium perchlorate: Commercial sample (> 99%), used as supplied.

Sodium Chloride: Used to maintain ionic strength, was a commercial sample, used as supplied.

2.1.4 Aromatic Compounds

Ethyl thiopicrate: was a prepared sample available from previous work.[1]

1-Butylammonium 2,4-dinitrobenzene: Available from previous work.[2]

2,4,6-Trinitrophenetole: was a prepared sample available from previous work.[3]

Phenyl 2,4-dinitrophenyl sulfide: was a prepared sample available from previous work.[4]

The following samples were all commercial samples of the highest available purity and were used without further purification:

1,3,5-trinitrobenzene
Picryl chloride (1-chloro-2,4,6-trinitrobenzene)
1-chloro-2,4-dinitronaphthalene
1-chloro-2,4-dinitrobenzene
1-chloro-2,6-dinitro 4-trifluoromethylbenzene
2,4-dinitrophenyl phenyl ether

The following compounds were all prepared in the present work. Details of their preparation are outlined in the relevant chapters:

1-piperidino-2,4,6-trinitrobenzene
1-pyrrolidino-2,4,6-trinitrobenzene
1-butylamino-2,4,6-trinitrobenzene
4'-R-phenyl 2,4,6-trinitrophenyl sulfides (R = H, Me, Br, NO_2)
phenyl 2,4-dinitronaphthyl sulfide
phenyl 2,6-dinitro-4-trifluoromethylphenyl sulfide
1-pyrrolidino-2,6-dinitro 4-trifluoromethyl benzene
1-piperidino-2,6-dinitro 4-trifluoromethylbenzene
phenyl 2,4,6-trinitrophenyl ether
phenyl 2,4-dinitronaphthyl ether

2.2 Measurement Techniques

2.2.1 UV/ Visible Spectra

All UV/Visible spectra were recorded using 1 cm silica cells on a Perkin-Elmer Lambda 2 spectrophotometer. The Lambda 2 instrument was also used for kinetic measurements of slow reactions ($t_{1/2} > 1$ min.).

All kinetic measurements were made under first order conditions by keeping the base concentration well in excess of the substrate concentrations. Rate coefficients were determined by following a change in absorbance at an appropriate wavelength and are quoted as the mean of at least five separate measurements and are precise to ±5%. All measurements were made at 25°C.

Derivation of first order rate constant

For the first order reaction $X \xrightarrow{k_{obs}} Y$

The rate of formation of Y is given by $\frac{d[Y]}{dt} = k_{obs}[X]$

The reaction can be followed by measuring an increase in absorbance. If we assume species X does not absorb, then any absorbance measured is due to species Y.

Abs_t = absorbance at time t

Abs_∞ = absorbance at time ∞, i.e. completion of reaction.

$$\frac{d(Abs)}{dt} = k_{obs}(Abs_\infty - Abs_t)$$

$$\therefore \quad \int_{Abs_0}^{Abs_t} \frac{d(Abs)}{(Abs_\infty - Abs_t)} = \int_0^t k_{obs}\,dt$$

$$\Rightarrow \quad \left[\ln(Abs_\infty - Abs_t)\right]_{Abs_0}^{Abs_t} = -k_{obs}[t]_0^t$$

$$\Rightarrow \quad \ln\left(\frac{Abs_\infty - Abs_t}{Abs_\infty - Abs_0}\right) = -k_{obs}t$$

2.2.2 Stopped-Flow Spectrophotometry

This was the main technique used for kinetic measurements in this work. The instruments used were Hi-Tech SF-3L and Applied Photophysics SX.17MV spectrophotometers. Figure 2.1 gives a schematic representation of the apparatus. All stopped-flow measurements were made at 25°C.

The two solutions A and B which undergo reaction are placed in the two reservoirs from which they flow into two identical syringes. A single piston drives both syringes together so that an equal volume of each reactant is mixed at point X before passing into a thermostatted 2mm quartz cell at point Y. Fast flow throughout the mixing chamber is required to ensure adequate mixing before significant reaction has occurred. This flow must be halted very rapidly in order to avoid simply observing incompletely mixed reactants. This cessation of flow is achieved by making the spent reaction solution drive a movable piston (stopping syringe) which is brought up against an external stop and simultaneously operates a micro switch. The latter triggers a recording device which causes monitoring of the reaction at point Y. This is done by passing a beam of monochromatic light of the appropriate wavelengh through the cell. The reaction within the cell causes and increase or decrease in the transmitted light which is fed through a photomultiplier and displayed on an oscilloscope screen from which voltage changes can be read off.

Changes in voltage can be related to absorbance values using equation 2.1 where V_0 is the applied voltage (typically 6-8 volts) and ΔV is the change in voltage (usually less than 1 volt but up to 2 volts).

$$\text{Abs} = \log_{10}\frac{I_0}{I} = \log_{10}\left(\frac{V_0}{V_0 - \Delta V}\right) \qquad \text{eqn 2.1}$$

i.e. $\Delta V = V_\infty - V_c$

where:

V_∞ = absorbance at the completion of a fast reaction, i.e. maximum voltage in the presence of the absorbing species

V_c = voltage in the absence of the absorbing species

The instrument was also used to calculate absorbance values and spectral shapes of species formed very rapidly.

The stopped flow apparatus is connected to a microcomputer which is used to calculate rate coefficients.

During reaction in the stopped flow apparatus, a steady flow must first be established which is then rapidly brought to a halt; after which subsequent concentration changes are measured in real time.

The limits for this method are:-

$$1 \text{ ms} < t_{½} < 100 \text{ s}$$

The lower limit is set by the time taken for the solutions to mix and actually reach the observation point. The upper limit is set by the electronics used, as fluctuations can alter the trace for slower reactions.

Hence, the rate constants which can be measured by this method are:-

$$10^{3} \text{ s}^{-1} > k > 10^{-2} \text{ s}^{-1}.$$

2.2.3 ^{1}H NMR Spectroscopy

^{1}H NMR spectra were measured on a Brucker AC250 (250 MHz), a Varian XL200 or a Varian 400 MHz instrument. All chemical shifts were measured relative to DMSO (2.50 ppm) using fully deuterated DMSO.

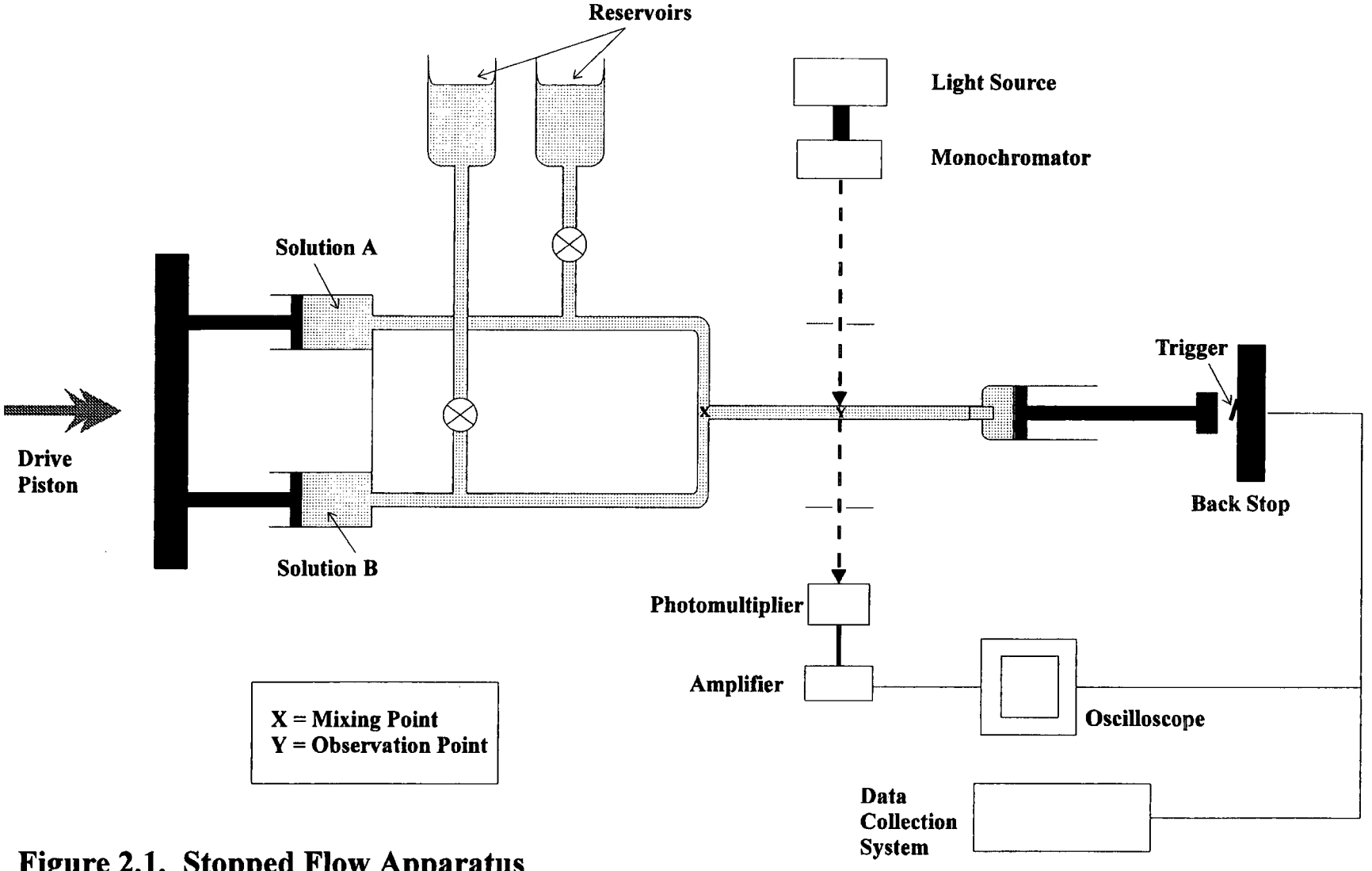
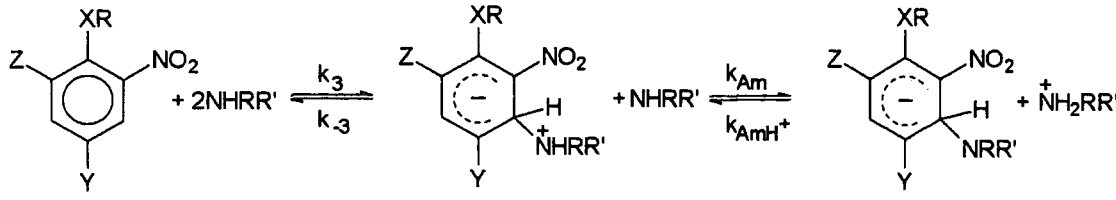


Figure 2.1. Stopped Flow Apparatus

2.3 Derivation of Equations Used

2.3.1 Rate Expressions for Attack at an Unsubstituted Ring Position

i) Attack at an unsubstituted ring position of a nitro-activated aromatic ring to form a 3-adduct, 2.3, in a system containing added amine salt.



2.1 2.2 2.3

X = O, S
Y = NO_2, CF_3
Z = H, NO_2

Assuming the solvent plays no or very little part in the reaction, i.e. in the protonation, k_{Am}, step or in the deprotonation, k_{AmH^+} step; equation 2.1 applies to the above system.

$$\frac{d[2.3]}{dt} = k_{Am}[2.2][Am] - k_{AmH^+}[AmH^+][2.3] \qquad \text{eqn 2.1}$$

Assuming the zwitterion, 2.2, can be treated as a steady state intermediate, then $\frac{d[2.2]}{dt} = 0$.

$$\therefore \frac{d[2.2]}{dt} = k_3[2.1][Am] + k_{AmH^+}[AmH^+][2.3] - k_{-3}[2.2] - k_{Am}[2.2][Am] = 0$$

Rearranging:

$$[2.2] = \frac{k_3[2.1][Am] + k_{AmH^+}[AmH^+][2.3]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 2.2}$$

Substituting equation 2.2 into equation 2.1.

$$\frac{d[2.3]}{dt} = k_{Am}[Am]\left(\frac{k_3[2.1][Am] + k_{AmH^+}[AmH^+][2.3]}{k_{-3} + k_{Am}[Am]}\right) - k_{AmH^+}[AmH^+][2.3]$$

$$\Rightarrow \frac{d[2.3]}{dt} = \left(\frac{k_3 k_{Am}[2.1][Am]^2 + k_{AmH^+} k_{-3}[AmH^+][2.3]}{k_{-3} + k_{Am}[Am]} \right)$$

$$- k_{AmH^+}[AmH^+][2.3]\left(\frac{k_{-3} + k_{Am}[Am]}{k_{-3} + k_{Am}[Am]} \right)$$

$$\Rightarrow \frac{d[2.3]}{dt} = \left(\frac{k_3 k_{Am}[2.1][Am]^2 + k_{AmH^+} k_{-3}[AmH^+][2.3]}{k_{-3} + k_{Am}[Am]} \right) \qquad \text{eqn 2.3}$$

The initial concentration of the substrate, 2.1, can be represented as $[2.1]_0$ and can be related to the concentration of species formed during the reaction by equation 2.4.

$$[2.1]_0 = [2.1] + [2.2] + [2.3] \qquad \text{eqn 2.4}$$

Species [2.2] is treated as a steady state intermediate and hence [2.2] = 0. Rearranging equation 2.4 gives equation 2.5.

$$[2.1] = [2.1]_0 - [2.3] \qquad \text{eqn 2.5}$$

Substituting equation 2.5 into equation 2.3 gives equation 2.6.

$$\therefore 0 = \frac{k_3 k_{Am}[2.1]_0[Am]^2 - k_3 k_{Am}[2.3]_e[Am]^2 - k_{-3} k_{AmH^+}[2.3]_e[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 2.6}$$

At equilibrium, $\frac{d[2.3]}{dt} = 0$ and $[2.3] = [2.3]_e$, hence equation 2.6 becomes equation 2.7.

$$\therefore 0 = \frac{k_3 k_{Am}[2.1]_0[Am]^2 - k_3 k_{Am}[2.3]_e[Am]^2 - k_{-3} k_{AmH^+}[2.3]_e[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 2.7}$$

Subtracting equation 2.7 from 2.6 gives equation 2.8.

$$\frac{d[2.3]}{dt} = \frac{\left(k_3 k_{Am}[Am]^2 + k_{-3} k_{AmH^+}[AmH^+]\right)\left([2.3]_e - [2.3]\right)}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 2.8}$$

Relating the concentration to absorbance:

The parent species, 2.1, is assumed not to absorb at the wavelength used to measure the reaction. The zwitterion, 2.2, is a steady state intermediate and so is assumed to have a very small concentration, hence if it did absorb at the wavelength used, its contribution would be negligible. Therefore any absorbance is due to the 3-adduct, 2.3, only.

$$Abs = \varepsilon_{2.3}[2.3] \qquad \text{eqn 2.9}$$

At equilibrium:

$$Abs_e = \varepsilon_{2.3}[2.3]_e \qquad \text{eqn 2.10}$$

Subtracting equation 2.9 from 2.10 gives equation 2.11.

$$Abs_e - Abs = \varepsilon_{2.3}([2.3]_e - [2.3]) \qquad \text{eqn 2.11}$$

Differentiating equation 2.9 gives equation 2.12.

$$\frac{d(Abs)}{dt} = \varepsilon_{2.3}\frac{d[2.3]}{dt} \qquad \text{eqn 2.12}$$

Substituting into equation 2.12 for $\varepsilon_{2.3}$ from equation 2.11, gives equation 2.13.

$$\frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} = \frac{1}{[2.3]_e - [2.3]} \times \frac{d[2.3]}{dt} \qquad \text{eqn 2.13}$$

The observed rate constant, k_{obs}, is defined by equation 2.14.

$$k_{obs} = \frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} \qquad \text{eqn 2.14}$$

Hence, from equations 2.13 and 2.14, equation 2.15 is obtained.

$$k_{obs} = \frac{1}{[2.3]_e - [2.3]} \times \frac{d[2.3]}{dt} \qquad \text{eqn 2.15}$$

Combining equations 2.8 and 2.15 gives the expression used in the following chapters, (equation 2.16).

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2 + k_{-3}k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 2.16}$$

ii) Attack at the 3-position of a nitro-activated aromatic ring, 2.1, to form a 3-adduct, 2.3, in a system containing no added amine salt.

In all cases measurements were made with the concentration of amine in large excess over the parent concentration. In the absence of added ammonium salt, measurements were made with sufficient excess of amine to ensure > 95% conversion of reactant to adduct, giving equation 2.17.

$$\ln \frac{Abs_e}{Abs_e - Abs} = k_{obs} t \qquad \text{eqn 2.17}$$

This equation is in the form of a first order rate equation and hence $k_{obs} = k_f$, where k_f is the forward rate constant.

For the formation of the 3-adduct, it has been shown previously, as equation 2.16, that:

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2 + k_{-3} k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 2.16}$$

With no added amine salt, $[AmH^+] \approx 0$, giving equation 2.18.

$$\therefore \quad k_{obs} = k_f = \frac{k_3 k_{Am}[Am]^2}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 2.18}$$

2.3.2 Equilibrium constants

$$2.1 + 2Am \underset{k_{-x}}{\overset{k_x}{\rightleftharpoons}} Z + Am \underset{k_{AmH^+}}{\overset{k_{Am}}{\rightleftharpoons}} A + AmH^+$$

Z = Zwitterion

A = Adduct

X = 3 or 1, depending on whether the 3-adduct or the 1-adduct is formed.

The overall equilibrium constant for the equilibrium shown above can be defined as equation 2.19.

$$K_{c,x} = \frac{[A][AmH^+]}{[2.1][Am]^2} \qquad \text{eqn 2.19}$$

At equilibrium, the rate of the forward and reverse reactions is equal, hence equation 2.20 applies.

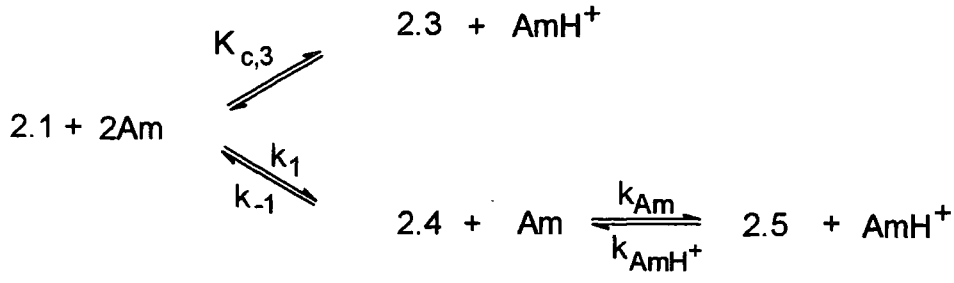
$$k_x k_{Am}[2.1][Am]^2 = k_{-x} k_{AmH^+}[A][AmH^+] \qquad \text{eqn 2.20}$$

Substituting equation 2.20 into equation 2.19 gives equation 2.21

$$K_{c,3} = \frac{k_x k_{Am}}{k_{-x} k_{AmH^+}} \qquad \text{eqn 2.21}$$

2.3.3 Rate expressions for attack at a substituted ring position

i) Attack at a substituted ring position to give the substitution product involving a rate limiting proton transfer (from the zwitterion to base) mechanism, in a reaction system involving attack at the 3-position.



Formation of the 3-adduct, 2,3, is rapid, whereas the formation of the 1-adduct, 2.5, is slower. Assuming the solvent plays no or very little part in the reaction, equation 2.22 applies.

$$\frac{d[2.5]}{dt} = k_{Am}[2.4][Am] - k_{AmH^+}[2.5][AmH^+] \qquad \text{eqn 2.22}$$

Assuming the zwitterion, 2.4, can be treated as a steady state intermediate, $\frac{d[2.4]}{dt} = 0$.

$$\frac{d[2.4]}{dt} = k_1[2.1][Am] + k_{AmH^+}[2.5][AmH^+] - k_{-1}[2.4] - k_{Am}[2.4][Am] = 0$$

Rearranging gives equation 2.23.

$$[2.4] = \frac{k_1[2.1][Am] + k_{AmH^+}[2.5][AmH^+]}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 2.23}$$

Substituting equation 2.23 into equation 2.22 gives equation 2.24.

$$\frac{d[2.5]}{dt} = k_{Am}[Am]\left(\frac{k_1[2.1][Am] + k_{AmH^+}[2.5][AmH^+]}{k_{-1} + k_{Am}[Am]}\right) - k_{AmH^+}[2.5][AmH^+]$$

eqn 2.24

Rearranging gives equation 2.25.

$$\frac{d[2.5]}{dt} = \frac{k_1 k_{Am}[2.1][Am]^2 - k_{-1}k_{AmH^+}[2.5][AmH^+]}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 2.25}$$

The initial concentration of substrate, $[2.1]_0$, can be related to the concentration of species formed during the reaction by equation 2.26.

$$[2.1]_o = [2.1] + [2.3] + [2.5] \qquad \text{eqn 2.26}$$

As shown previously in section 2.3.2, the overall equilibrium constant for formation of the 3-adduct is defined by equation 2.19.

$$K_{c,x} = \frac{[A][AmH^+]}{[2.1][Am]^2} \qquad \text{eqn 2.19}$$

Rearranging this and inserting in equation 2.26 for [2.3] gives equation 2.27.

$$[2.1]_o = [2.1] + K_{c,3}[2.1]\frac{[Am]^2}{[AmH^+]} + [2.5] \qquad \text{eqn 2.27}$$

Rearranging gives equation 2.28.

$$[2.1] = \frac{[2.1]_o - [2.5]}{1 + K_{c,3}\dfrac{[Am]^2}{[AmH^+]}} \qquad \text{eqn 2.28}$$

Substituting equation 2.28 into equation 2.25 gives equation 2.29.

$$\frac{d[2.5]}{dt} = \frac{k_1 k_{Am}[Am]^2([2.1]_o - [2.5])}{\left(1 + K_{c,3}\dfrac{[Am]^2}{[AmH^+]}\right)(k_{-1} + k_{Am}[Am])} - \frac{k_{-1}k_{AmH^+}[2.5][AmH^+]}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 2.29}$$

At equilibrium, $\frac{d[2.5]}{dt} = 0$, giving equation 2.30.

$$0 = \frac{k_1 k_{Am}[Am]^2([2.1]_o - [2.5]_e)}{\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)(k_{-1} + k_{Am}[Am])} - \frac{k_{-1}k_{AmH^+}[2.5]_e[AmH^+]}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 2.30}$$

Subtracting equation 2.30 from 2.29 gives equation 2.31.

$$\frac{d[2.5]}{dt} = \left[\frac{k_1 k_{Am}[Am]^2}{\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)(k_{-1} + k_{Am}[Am])} + \frac{k_{-1}k_{AmH^+}[AmH^+]}{k_{-1} + k_{Am}[Am]}\right]([2.5]_e - [2.5])$$

eqn 2.31

The observed rate constant , k_{obs}, is defined by equation 2.14

$$k_{obs} = \frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} \qquad \text{eqn 2.14}$$

In the above reaction, the only absorbing species are 2.3 and 2.5, hence they can be related to absorbance by equation 2.32.

$$Abs = \varepsilon_{2.3}[2.3] + \varepsilon_{2.5}[2.5] \qquad \text{eqn 2.32}$$

Substituting equation 2.26 into equation 2.32 gives equation 2.33.

$$Abs = \varepsilon_{2.3}([2.1]_o - [2.1] - [2.5]) + \varepsilon_{2.5}[2.5] \qquad \text{eqn 2.33}$$

Rearranging equation 2.28 gives equation 2.34.

$$[2.1]K_{c,3}\frac{[Am]^2}{[AmH^+]} = [2.1]_o - [2.1] - [2.5] \qquad \text{eqn 2.34}$$

Substituting equation 2.34 into equation 2.33 gives equation 2.35.

$$Abs = \varepsilon_{2.5}[2.5] + \varepsilon_{2.3}\left([2.1]K_{c,3}\frac{[Am]^2}{[AmH^+]}\right) \qquad \text{eqn 2.35}$$

Substituting equation 2.28 into equation 2.35 gives equation 2.36.

$$Abs = \varepsilon_{2.5}[2.5] + \varepsilon_{2.3}\left(\frac{[2.1]_o - [2.5]}{1 + K_{c,3}\dfrac{[Am]^2}{[AmH^+]}} \times K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)$$

$$Abs = \varepsilon_{2.5}[2.5] + \varepsilon_{2.3}\left(\frac{K_{c,3}[Am]^2([2.1]_o - [2.5])}{[AmH^+] + K_{c,3}[Am]^2}\right) \qquad \text{eqn 2.36}$$

If we let:

$$X = \varepsilon_{2.5} - \frac{\varepsilon_{2.3}K_{c,3}[Am]^2}{[AmH^+] + K_{c,3}[Am]^2}$$

$$Y = \frac{\varepsilon_{2.3}[2.1]_o K_{c,3}[Am]^2}{[AmH^+] + K_{c,3}[Am]^2}$$

Then equation 2.36 becomes equation 2.37.

$$Abs = [2.5]X + Y \qquad \text{eqn 2.37}$$

At equilibrium this becomes equation 2.38.

$$Abs_e = [2.5]_e X + Y \qquad \text{eqn 2.38}$$

Differentiating equation 2.37 gives equation 2.39.

$$\frac{d(Abs)}{dt} = \frac{d[2.5]}{dt}X \qquad \text{eqn 2.39}$$

Subtracting equation 2.37 from equation 2.38 gives equation 2.40.

$$Abs_e - Abs = ([2.5]_e - [2.5])X \qquad \text{eqn 2.40}$$

Combining equations 2.39 and 2.40 gives equation 2.41.

$$\frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} = \frac{1}{[2.5]_e - [2.5]} \times \frac{d[2.5]}{dt} \qquad \text{eqn 2.41}$$

Combining equations 2.14, 2.31 and 2.41 gives equation 2.42.

$$\frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} = k_{obs} = \frac{d[2.5]}{dt} \times \frac{1}{[2.5]_e[2.5]}$$

$$\Rightarrow k_{obs} = \frac{k_1 k_{Am}[Am]^2}{\left(k_{-1} + k_{Am}[Am]\right)\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)} + \frac{k_{-1}k_{AmH^+}[AmH^+]}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 2.42}$$

ii) Attack at a substituted ring position involving a rate limiting proton transfer between the zwitterion and base, in a system with no rapid attack at the 3-position.

$$2.1 + 2Am \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2.4 + Am \underset{k_{AmH^+}}{\overset{k_{Am}}{\rightleftharpoons}} 2.5 + AmH^+$$

The initial concentration of the substrate, $[2.1]_o$, can be expressed by the expression 2.43.

$$[2.1]_o = [2.1] + [2.5] \qquad \text{eqn 2.43}$$

Substituting equation 2.43 into equation 2.25, derived previously, gives equation 2.44.

$$\frac{d[2.5]}{dt} = \frac{k_1 k_{Am}[Am]^2([2.1]_o - [2.5])}{(k_{-1} + k_{Am}[Am])} - \frac{k_{-1}k_{AmH^+}[2.5][AmH^+]}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 2.44}$$

At equilibrium, $\frac{d[2.5]}{dt} = 0$, giving equation 2.45.

$$0 = \frac{k_1 k_{Am}[Am]^2([2.1]_o - [2.5]_e)}{(k_{-1} + k_{Am}[Am])} - \frac{k_{-1}k_{AmH^+}[2.5]_e[AmH^+]}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 2.45}$$

Subtracting equation 2.45 from 2.44 gives equation 2.46.

$$\frac{d[2.5]}{dt} = \left[\frac{k_1 k_{Am}[Am]^2}{(k_{-1} + k_{Am}[Am])} + \frac{k_{-1} k_{AmH^+}[AmH^+]}{k_{-1} + k_{Am}[Am]} \right] ([2.5]_e - [2.5]) \qquad \text{eqn 2.46}$$

The observed rate constant , k_{obs}, is defined by equation 2.14

$$k_{obs} = \frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} \qquad \text{eqn 2.14}$$

In the above reaction, the only absorbing species is 2.5, hence it can be related to absorbance by equation 2.47.

$$Abs = \varepsilon_{2.5}[2.5] \qquad \text{eqn 2.47}$$

At equilibrium equation 2.48 applies.

$$Abs_e = \varepsilon_{2.5}[2.5]_e \qquad \text{eqn 2.48}$$

Subtracting equation 2.47 from 2.48 gives equation 2.49.

$$Abs_e - Abs = \varepsilon_{2.5}([2.5]_e - [2.5]) \qquad \text{eqn 2.49}$$

Differentiating equation 2.47 gives equation 2.50.

$$\frac{d(Abs)}{dt} = \frac{d[2.5]}{dt} \varepsilon_{2.5} \qquad \text{eqn 2.50}$$

Substituting equation 2.49 into equation 2.50, gives equation 2.41.

$$\frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} = \frac{1}{[2.5]_e - [2.5]} \times \frac{d[2.5]}{dt} \qquad \text{eqn 2.41}$$

Combining equations 2.14, 2.41 and 2.46 gives equation 2.51.

$$k_{obs} = \frac{k_1 k_{Am}[Am]^2 + k_{-1} k_{AmH^+}[AmH^+]}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 2.51}$$

iii) Attack at a substituted ring position involving rate limiting leaving group departure from the 1-adduct, to give the N-substituted picramide.

$$2.1 + 2Am \rightleftharpoons 2.5 + AmH^+ \xrightarrow{k_4} 2.6 + Am + L$$

The reaction can be followed by measuring the formation of 2.6, as in equation 2.52.

$$\frac{d[2.6]}{dt} = k_4[2.5][AmH^+] \qquad \text{eqn 2.52}$$

The initial concentration of the substrate, $[2.1]_0$, can be expressed by the expression 2.53.

$$[2.1]_0 = [2.1] + [2.5] + [2.6] \qquad \text{eqn 2.53}$$

As derived previously, the equilibrium constant, $K_{c,1}$, can be expressed by equation 2.19.

$$K_{c,1} = \frac{[2.5][AmH^+]}{[2.1][Am]^2} \qquad \text{eqn 2.19}$$

Substituting equation 2.19 in equation 2.53 gives equation 2.54.

$$[2.1]_o = [2.5]\left(1 + \frac{[AmH^+]}{K_{c,1}[Am]^2}\right) + [2.6] \qquad \text{eqn 2.54}$$

Rearranging gives equation 2.55.

$$[2.5] = \left([2.1]_o - [2.6]\right)\left(\frac{K_{c,1}[Am]^2}{K_{c,1}[Am]^2 + [AmH^+]}\right) \qquad \text{eqn 2.55}$$

Substituting equation 2.55 into equation 2.52 gives equation 2.56.

$$\frac{d[2.6]}{dt} = \left([2.1]_o - [2.6]\right)\left(\frac{k_4 K_{c,1}[Am]^2[AmH^+]}{K_{c,1}[Am]^2 + [AmH^+]}\right) \qquad \text{eqn 2.56}$$

At equilibrium, $\frac{d[2.6]}{dt} = 0$, giving equation 2.57.

$$0 = \left([2.1]_o - [2.6]_e\right)\left(\frac{k_4 K_{c,1}[Am]^2[AmH^+]}{K_{c,1}[Am]^2 + [AmH^+]}\right) \qquad \text{eqn 2.57}$$

Subtracting equation 2.57 from equation 2.56 gives equation 2.58.

$$\frac{d[2.6]}{dt} = \left([2.6]_e - [2.6]\right)\left(\frac{k_4 K_{c,1}[Am]^2[AmH^+]}{K_{c,1}[Am]^2[AmH^+]}\right) \qquad \text{eqn 2.58}$$

Species 2.6 is the only compound absorbing at the wavelength used to study the reaction, hence equation 2.59 applies.

$$Abs = \varepsilon_{2.6}[2.6] \qquad \text{eqn 2.59}$$

At equilibrium, equation 2.60 applies.

$$Abs_e = \varepsilon_{2.6}[2.6] \qquad \text{eqn 2.60}$$

Subtracting equation 2.59 from equation 2.60 gives equation 2.61.

$$Abs_e - Abs = \varepsilon_{2.6}\left([2.6]_e - [2.6]\right) \qquad \text{eqn 2.61}$$

Differentiating equation 2.59 gives equation 2.62.

$$\frac{d(Abs)}{dt} = \varepsilon_{2.6}\frac{d[2.6]}{dt} \qquad \text{eqn 2.62}$$

Combining equations 2.61 and 2.62 gives equation 2.63.

$$\frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} = \frac{d[2.6]}{dt} \times \frac{1}{[2.6]_e - [2.6]} \qquad \text{eqn 2.63}$$

The observed rate constant, k_{obs}, can be defined by equation 2.14.

$$k_{obs} = \frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} \qquad \text{eqn 2.14}$$

Combining equations 2.58, 2.63 and 2.14 gives:

$$\frac{d(Abs)}{dt} \times \frac{1}{Abs_e - Abs} = k_{obs} = \frac{d[2.6]}{dt} \times \frac{1}{[2.6]_e - [2.6]}$$

$$\Rightarrow \qquad k_{obs} = \frac{k_4 K_{c,1}[Am]^2[AmH^+]}{K_{c,1}[Am]^2 + [AmH^+]}.$$

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2. M. R. Crampton and P.M. Wilson, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1859.
3. A. Cooney and M. R. Crampton, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1793.
4. R. A. Chamberlin, M. R. Crampton and R. L. Knight, *J. Chem. Res.*, 1993, (S) 444, (M) 2986.

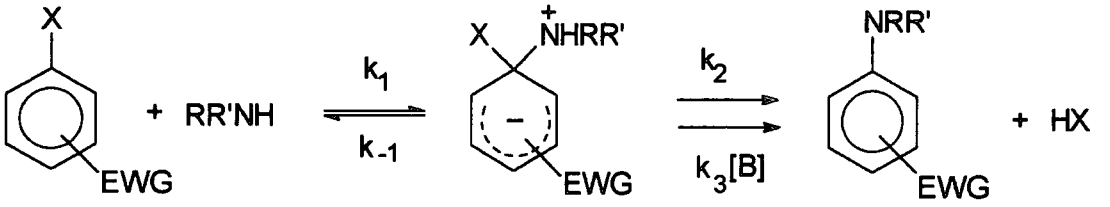
CHAPTER 3

The Reactions Of Ethyl Thiopicrate With Aliphatic Amines (Piperidine, Pyrrolidine And n-Butylamine) In Dimethyl Sulphoxide

The Reaction of Ethyl Thiopicrate with Aliphatic Amines (Piperidine, Pyrrolidine, Butylamine) in Dimethyl Sulfoxide

3.1 Introduction

Nucleophilic attack at a substituted ring position usually results in substitution and the accepted mechanism[1-3] for the reaction with amine nucleophiles is shown in scheme 3.1.

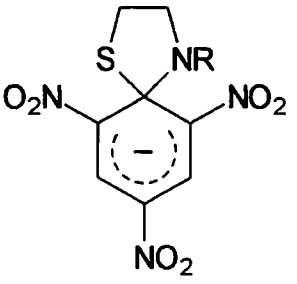


scheme 3.1

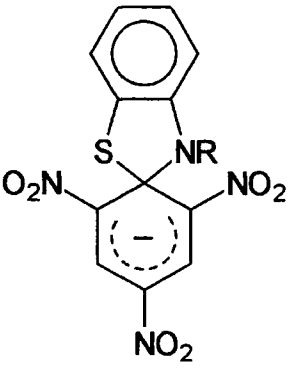
The base catalysed pathway may involve rate-limiting proton transfer from the zwitterionic intermediate to base, or general acid catalysis of the leaving group expulsion from an anionic intermediate, in rapid equilibrium with the zwitterion. The latter pathway, the SB-GA mechanism, has been shown to be generally applicable to reactions involving displacement of alkoxy groups by amines in DMSO. Orvik and Bunnett[3] were the first to report the observation of both the formation and decomposition (acid catalysed conversion to substitution products) of the Meisenheimer complexes; as separate processes.

Several examples of the Smiles rearrangement involving intramolecular displacements of thiolate groups by amines have been reported[4,5]. Spiro adducts 3.1 and 3.2 (R = Me, Ph) have been characterised spectroscopically[6,7]. Nevertheless, few examples of intermolecular displacements of thiolate groups by amines have been reported. However, Bunnett and Bernasconi[8,9] studied the reaction of 2,4-dinitrophenyl sulfide with piperidine. They found that, although there was no evidence for catalysis by piperidine itself, the reaction showed mild catalysis by hydroxide. This indicates base catalysis showing that conversion of the zwitterionic intermediate to products is rate determining.

It is known that for σ-adduct formation[10], intrinsic barriers, in the Marcus sense, for reactions of sulfur bases are considerably lower than for the reactions of oxygen bases. Hence thiolate groups might be expected to be relatively good leaving groups in substitution reactions.



3.1



3.2

Kinetic and NMR measurements were made for the reaction of ethyl thiopicrate (ETP) with aliphatic amines in dimethyl sulfoxide (DMSO). Butylamine was chosen as an example of a primary amine, and piperidine and pyrrolidine as secondary amines. With piperidine, there is evidence for steric and stereochemical effects during substitution[9-14], causing a high energy barrier when the piperidino group is twisted either into or out of the ring plane in ortho-substituted benzene derivatives.

3.2 Experimental

1-Butylamino-2,4,6-trinitrobenzene: was prepared as a yellow crystalline solid by reacting butylamine with a solution of picryl chloride in methanol.(literature melting point 80.5-81.5°C, actual melting point 72-74°C)[15].

1-Pyrrolidino-2,4,6-trinitrobenzene: prepared as above, by reacting pyrrolidine with a solution of picryl chloride in methanol Yellow crystalline solid.(literature melting point 189.5-191°C, actual melting point 194-196°C)[15].

1-Piperidino-2,4,6-trinitrobenzene: prepared as above, by reacting piperidine with a solution of picryl chloride in methanol. Yellow crystalline solid.(literature melting point 104.5-105.5 °C, actual melting point 95-97°C)[15].

A preparative reaction was carried out involving the reaction of ethyl thiopicrate (0.5g) with a fourfold excess of piperidine in DMSO. The mixture was allowed to stand for four hours and then poured onto crushed ice. The yellow-orange precipitate was collected, dried and the ^{1}H NMR spectrum was recorded in [$^{2}H_6$] DMSO, see figure 3.1.

^1H NMR spectra were recorded with the parent nitro-compound 0.1 moldm^{-3} in [$^2H_6$] DMSO. Spectra were recorded as soon as possible after amine addition and any subsequent changes followed with time. The NMR data are collected in table 3.1.

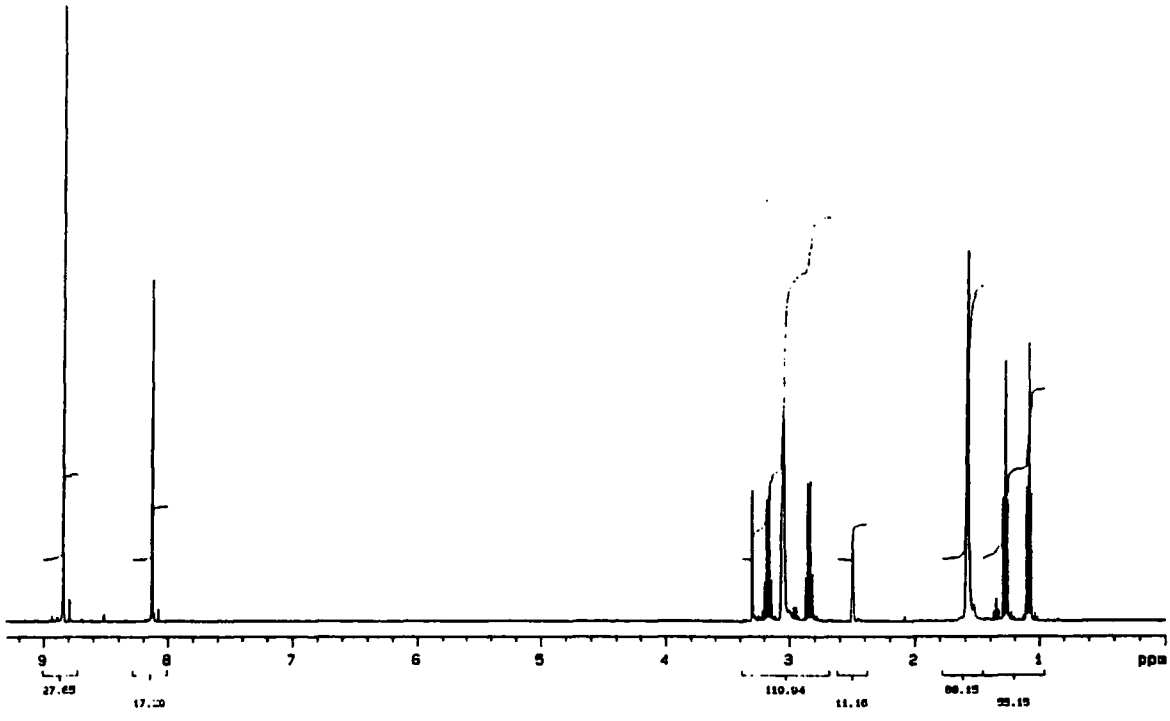
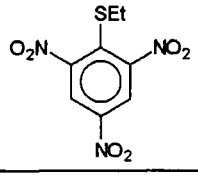
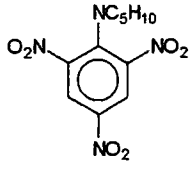
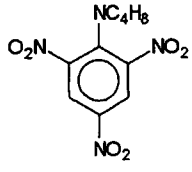
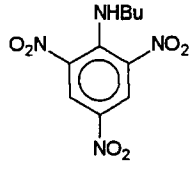
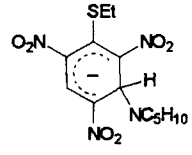
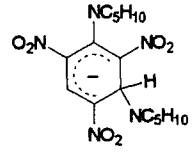
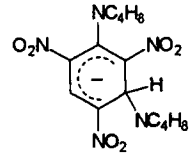
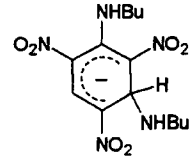
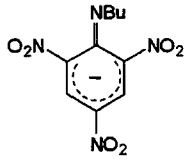
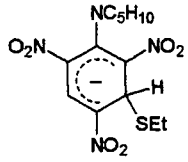
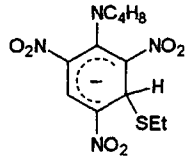
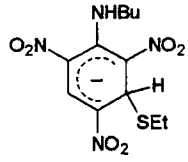
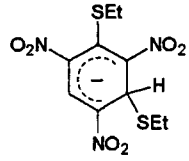
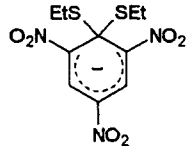
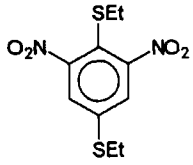


figure 3.1. The ^1H NMR spectrum of the product formed during the reaction of ethyl thiopicrate and piperidine in DMSO.

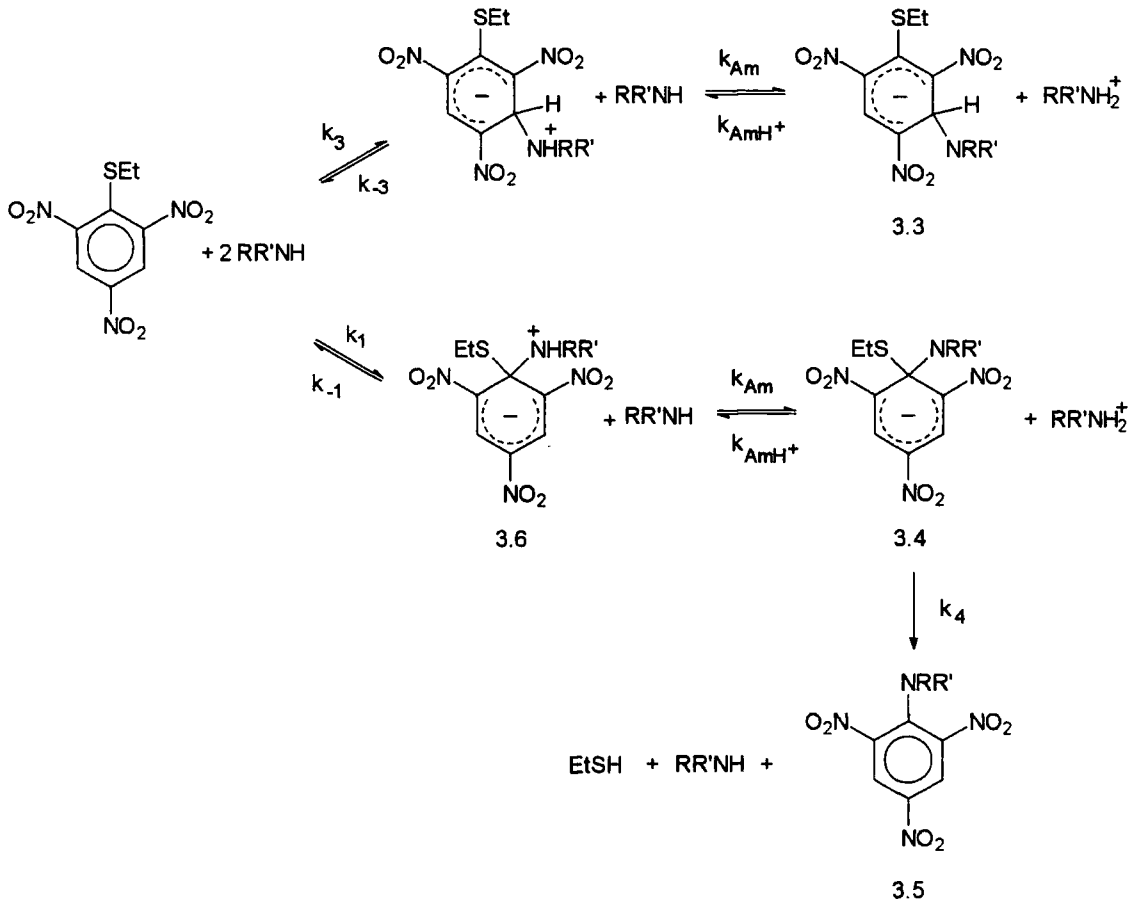
Table 3.1. ^1H NMR data, (δ values).

Structure	Ring	Ethylthio[a]		NRR'
		CH_2	CH_3	
	9.11	2.93	1.12	-
 3.5	8.85			3.05,1.58
 3.5	8.84			3.27,1.95
 3.5	8.94			8.80(NH),3.03,1.63,1.30,0.86
 3.3	8.45,5.68	2.9	1.1	
 3.11	8.45,5.55			Not measured
 3.11	8.35,5.89			3.38,1.92
 3.11	8.36,5.60			(2.6,2.3)[b],1.6,1.2,0.8

	8.36			
 3.10	8.31,6.09	2.6	1.1	Not measured
 3.10	8.27,6.07	2.46	1.14	(3.7,3.3)[b],1.92
 3.10	8.35,6.00	2.47	1.12	(2.7,2.5)[b],1.6,1.3,0.9
 3.13	8.31,5.99			
 3.12	8.36			
 3.14	8.13	2.83 3.16	1.07 1.26	

a) Coupling J = 7 Hz was observed between methylene and methyl hydrogens.

b) Non-equivalent methylene hydrogens, α to nitrogen.



Scheme 3.2

3.3 Results

UV/Visible measurements of the reactions between ETP and amines in DMSO showed the presence of two well separated processes, as in scheme 3.2. With each amine, a rapid reaction was observed, giving species with λ_{max} 450-460nm and 510-520nm (shoulder). In the case of piperidine, NMR evidence suggests that this species is adduct 3.3 (NRR' = NC_5H_{10}), see figure 3.2. With butylamine and pyrrolidine these initial species proved to be too transient for NMR measurements. However, nucleophilic attack at an unsubstituted position of 1-substituted-2,4,6-trinitrobenzenes is known to be considerably faster than reaction at the 1-position[15-16]. Therefore, the fast reaction products are thought to be those, 3.3, resulting from attack at the 3- position.

At completion of the second, slower reaction, UV/visible spectra obtained indicate that the amines have displaced the ethylthio group to give the N-substituted picramide derivatives, 3.5. The final spectra obtained with pyrrolidine and butylamine were identical to the N-pyrrolidino-2,4,6-trinitrobenzene and N-butylamino-2,4,6-trinitrobenzene respectively (see figures 3.3 and 3.4) in solutions containing the same amine concentration. The reaction products were shown to be in rapid equilibrium with

species formed by amine addition (or loss of a side chain proton in the case of butylamine).

Adducts of type 3.4 are not observable kinetically or spectroscopically. With piperidine, the second reaction was found to be inconveniently slow for kinetic measurements.

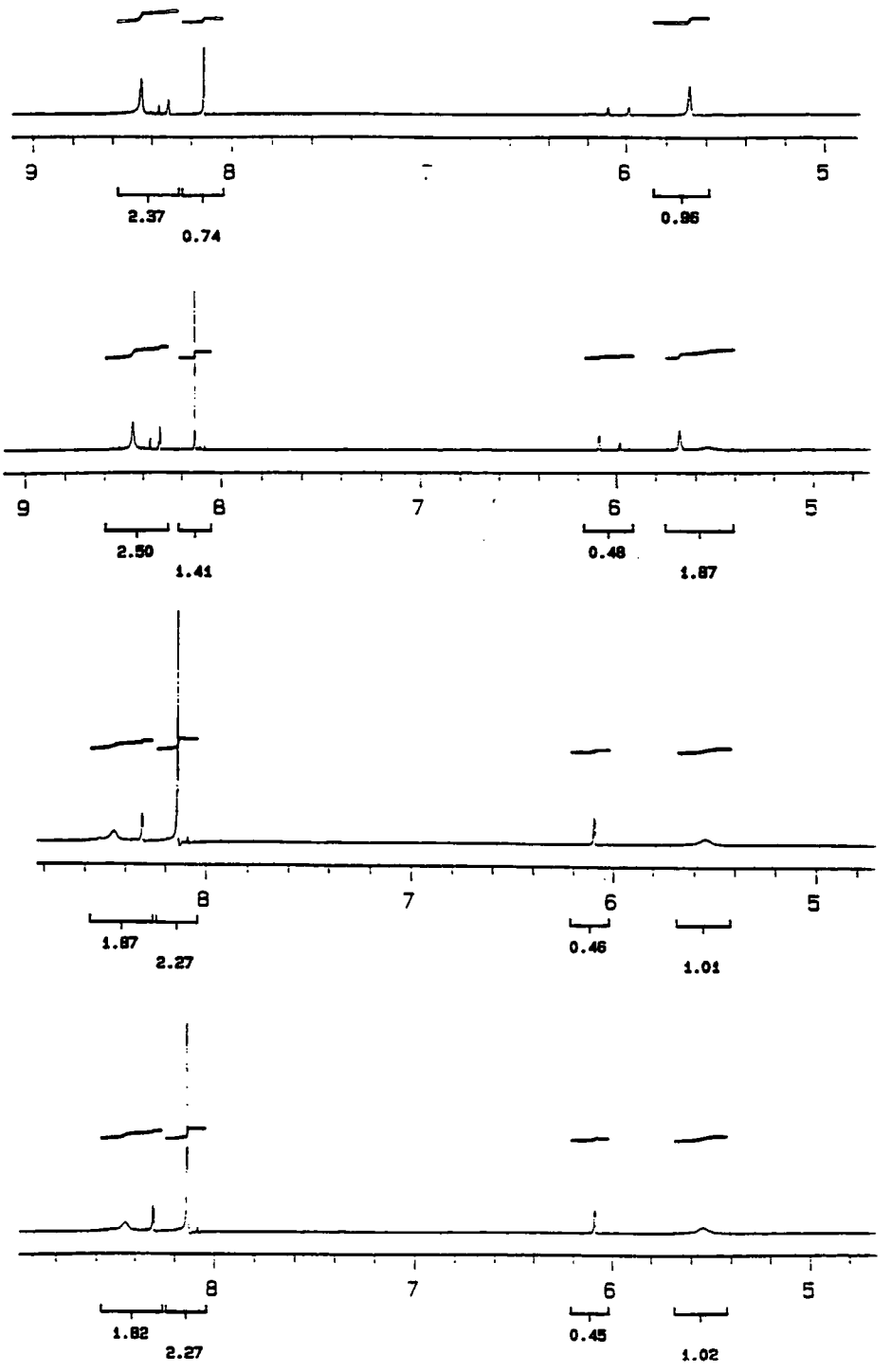


figure 3.2. The ^{1}H NMR spectra of the reaction occuring between ethyl thiopicrate and piperidine, recorded as soon as possible after mixing, after ten minutes, after one hour and after two hours.

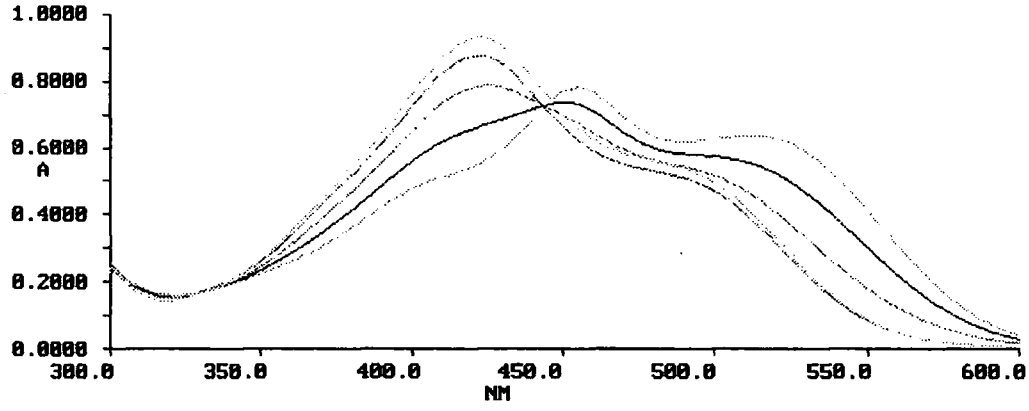


figure 3.3. The UV/ Visible spectra of the reaction between ethyl thiopicrate and pyrrolidine, showing the fast reaction product (peak 450nm and shoulder 510nm) and its conversion to the final, slower reaction product (peak 420nm). The spectrum of the final reaction product being identical to that of the separately prepared compound in the presence of pyrrolidine.

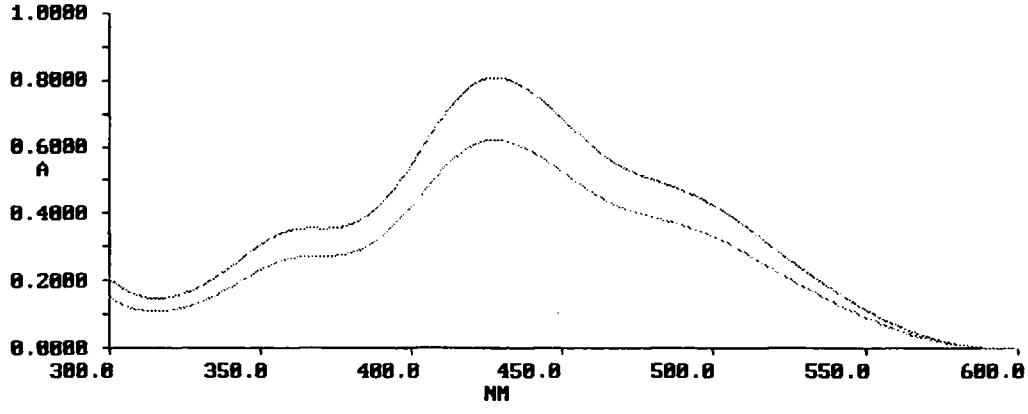


figure 3.4. The UV/ Visible spectrum of the final reaction product formed between ethyl thiopicrate and butylamine and that of the separately prepared amino-compound in the presence of amine.

3.3.1 Kinetic Analysis:

Rate constants were all measured under first order conditions. For reactions involving buffers (amine plus amine salt), the buffer components were in large excess of the parent concentration ($2x10^{-5}$ mol dm^{-3}). For reactions in the absence of added amine salt, a sufficient excess of amine was used to ensure conversion to adduct was > 95% at equilibrium.

Under these conditions, equation 3.1 applies.

$$\ln\left(\frac{Abs_{\infty}}{Abs_{\infty} - Abs}\right) = k_{obs}t \qquad \text{eqn 3.1}$$

The zwitterions formed are treated as steady-state intermediates and so the general rate expression for the reaction to produce the 3-adducts, 3.3, is equation 3.2.

$$k_{fast} = \frac{k_3 k_{Am}[Am]^2 + k_{-3}k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 3.2}$$

With no salt added, where the reverse reaction becomes negligible, this reduces to equation 3.3.

$$k_{fast} = \frac{k_3 k_{Am}[Am]^2}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn3.3}$$

The equilibrium constant, $K_{c,3}$, for conversion of ethyl thiopicrate into the 3-adduct, 3.3, is defined by equation 3.4.

$$K_{c,3} = \frac{[3.3][AmH^+]}{[ETP][Am]^2} \qquad \text{eqn 3.4}$$

This can be related to absorbance values in the following form, equation 3.5.

$$K_{c,3} = \frac{Abs}{Abs_{\infty} - Abs} x \frac{[AmH^+]}{[Am]^2} \qquad \text{eqn 3.5}$$

This equilibrium constant, $K_{c,3}$, can be related to rate coefficients by equation 3.6.

$$K_{c,3} = \frac{k_3}{k_{-3}} x \frac{k_{Am}}{k_{AmH^+}} \qquad \text{eqn 3.6}$$

The reactions involving substitution of the ethylthio group were considerably slower than those giving the 3-adducts, and so the processes could be measured consecutively. The formation of the final products, 3.5, could occur by two different pathways, either:

i) Rate determining formation of 3.4, followed by rapid loss of the ethylthio group,or

ii) A rapid equilibrium to give 3.4, followed by rate determining loss of the ethylthio group.

Allowing for the rapid reversible reaction to give the 3-adduct, 3.3, the two rate equations for (i) and (ii) can be expressed as equations 3.7 and 3.8 respectively.

$$k_{slow} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} x \frac{1}{1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}} \qquad \text{eqn 3.7}$$

$$k_{slow} = \frac{k_4 K_{c,1}[Am]^2}{1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}} \qquad \text{eqn 3.8.}$$

The equilibrium constant, $K_{c,1}$, refers to the formation of the 1-adduct, 3.4, from ethyl thiopicrate.

It is more convenient to define a modified rate coefficient k'slow, as in equation 3.9.

$$k'_{slow} = k_{slow}\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right) \qquad \text{eqn 3.9}$$

Equation 3.7 and 3.8 can thus be written as equations 3.10 and 3.11.

$$k'_{slow} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 3.10}$$

$$k'_{slow} = k_4 K_{c,1}[Am]^2 \qquad \text{eqn 3.11}$$

3.3.2 Reaction with butylamine

Results for attack at the 3- position, measured as a colour forming process at 530nm, are in table 3.2.

In the absence of added butylammonium perchlorate, values of k_{fast}, relating to the formation of the 3-adduct, 3.3, increase linearly with amine concentration. This indicates $k_{Am}[Am] >> k_{-3}$ and thus equation. 3.2 can be reduced to equation 3.12.

$$k_{fast} = k_3[Am] + \left(\frac{k_{-3}k_{AmH^+}}{k_{Am}} x \frac{[AmH^+]}{[Am]} \right) \qquad \text{eqn.3.12}$$

In the absence of added salt, a value for k_3 of 800 $dm^3mol^{-1}s^{-1}$ can be obtained, hence using equation 3.12, a value of 71 s^{-1} is obtained for $k_{-3}k_{AmH^+}/k_{Am}$. Combination of these values in equation 3.6 gives a value for $K_{c,3}$ of 11 dm^3mol^{-1}, which is in agreement with those obtained using absorbance values at completion of the rapid reaction using equation 3.5.

Results for attack at the 1-position, measured at 540nm, are in table 3.3. Values calculated for k'_{slow}, from equation 3.9 using $K_{c,3}$ = 11 dm^3mol^{-1}, are linear in amine concentration. This indicates $k_{Am}[Am] >> k_{-1}$, leading to equation 3.13.

$$k'_{slow} = k_1[Am] \qquad \text{eqn.3.13}$$

Hence, a value of 8 $dm^3mol^{-1}s^{-1}$ is obtained, giving values of k_{calc} (obtained using equations 3.9 and 3.13) which agree well with those determined experimentally.

These results show that in the formation of the 3-adduct, 3.3, initial attack by the amine is rate-determining, and proton transfer occurs rapidly. Also, in the substitution reaction, the results show rate-determining attack by the amine at the 1-position, followed by rapid proton transfer and rapid loss of the ethylthio group.

Table 3.2. Kinetic and equilibrium data for the rapid reaction involving attack at the 3-position of ethyl thiopicrate by butylamine in DMSO at 25°C.

$[BuNH_2]$/ moldm^{-3}	$[BuNH_3^+ClO_4^-]$/ moldm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	Abs[b]	$K_{c,3}$[c]/ dm^{3}mol^{-1}
0.01	-	7.8	8.0	-	-
0.02	-	15	16	-	-
0.04	-	31	32	-	-
0.07	-	60	56	-	-
0.10	-	80	80	0.025	-
0.01	0.01	-	-	0.0031	14
0.02	0.01	55	52	0.0068	9
0.03	0.01	45	48	0.0106	8
0.04	0.01	49	50	0.0138	8
0.05	0.01	56	54	0.0179	10

a) Calculated from equation 3.12 using k_3 800 dm^{3}mol^{-1}s^{-1}, $k_{-3}k_{AmH^+}/k_{Am}$ 71 s^{-1}

b) Absorbance measured, at 530nm, at completion of the rapid colour-forming reaction.

c) Calculated using equation 3.5 with $Abs_\infty = 0.025$.

Table 3.3. Kinetic data for the reaction of butylamine at the 1-position of ethyl thiopicrate in DMSO at 25°C.

$[BuNH_2]$/ moldm^{-3}	$[BuNH_3^+ClO_4^-]$/ moldm^{-3}	k_{slow}/ s^{-1}	k'_{slow} s^{-1}	k_{calc}[a] /s^{-1}
0.005	0.01	0.037	0.038	0.039
0.01	0.01	0.069	0.077	0.070
0.02	0.01	0.112	0.161	0.116
0.03	0.01	0.142	0.283	0.138
0.04	0.01	0.150	0.414	0.143
0.05	0.01	0.124	0.465	0.114

a) Calculated using k_1 8 dm^{3}mol^{-1}s^{-1} and $Abs_\infty = 0.025$.

3.3.3 Reaction with pyrrolidine

Results for attack at the 3-position, leading to 3.3 (NRR' = NC_4H_8) are in table 3.4.
Data obtained in the absence of added pyrrolidinium perchlorate show the dependence of k_{fast} on amine concentration is between one and two, indicating that proton transfer is partially rate limiting. Values of k_3 9000 $dm^3mol^{-1}s^{-1}$ and k_3k_{Am}/ k_{-3} 40 dm^3mol^{-1} can be obtained from a plot of $[Am]/k_{obs}$ vs 1/[Am] using equation 3.3, hence a value of k_{AmH^+} 5500 $dm^3mol^{-1}s^{-1}$ can be obtained from equation 3.6. Values calculated using the above gave a good fit with experimental data, both with and without added pyrrolidinium perchlorate. Using the above in equation 3.6 leads to a value for $K_{c,3}$ of 65 ± 10 dm^3mol^{-1}, a value in fairly good agreement with that obtained from absorbance data, 55 ± 10 dm^3mol^{-1}.
Data for the slower reaction, leading to substitution are in table 3.5. Values of k'_{slow}, calculated from equation 3.9 with $K_{c,3}$ 60 dm^3mol^{-1}, show an almost squared dependence on amine concentration (see final column in table 3.5). Values of k'_{slow} depend strongly on the value of $K_{c,3}$, so the slight decrease in values of $k'_{slow}/ [Am]^2$ with increasing amine concentration is not experimentally secure. The results show that the proton transfer is completely or largely rate determining in the slower reaction.

Table 3.4. Kinetic and equilibrium data for the formation of 3.4 (NRR' = NC_4H_8) from ethyl thiopicrate and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ moldm^{-3}	[pyrrolidinium perchlorate]/ moldm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	Abs[b]	$K_{c,3}$[c]/ dm^{3}mol^{-1}
0.006	-	12	11	-	-
0.008	-	19	18	-	-
0.010	-	26	26	-	-
0.015	-	51	51	-	-
0.0175	-	61	65	-	-
0.025	-	109	112	-	-
0.03	-	148	147	0.051	-
0.035	-	190	184	0.051	-
0.005	0.01	56	53	0.006	53
0.010	0.01	63	65	0.017	51
0.015	0.01	83	85	0.027	50
0.020	0.01	107	110	0.037	69

a) Calculated using equation. 3.2 with k_3 9000 dm^{3}mol^{-1}s^{-1}, k_{Am}/k_{-3} 40 dm^{3}mol^{-1} and k_{AmH^+} 5500 dm^{3}mol^{-1}s^{-1}

b) Absorbance values measured at 434nm at completion of the fast reaction.

c) Calculated using equation. 3.5 with $Abs_\infty = 0.051$.

Table 3.5. Kinetic data for the reaction of pyrrolidine at the 1-position of ethyl thiopicrate in DMSO at 25°C.

[pyrrolidine]/ moldm^{-3}	[pyrrolidinium perchlorate]/ moldm^{-3}	k_{slow} /10^{-3}s^{-1}	k'_{slow}[a] / 10^{-3}s^{-1}	$\frac{k'_{slow}}{[Am]^2}$
0.01	0.01	4.0	6.4	64
0.02	0.01	7.9	27	67
0.03	0.01	8.7	56	62
0.04	0.01	9.1	9.6	60
0.05	0.01	9.4	150	60
0.06	0.01	8.9	200	56

a) Calculated using equation.3.9 with $K_{c,3}$ 60 dm^{3}mol^{-1}.

3.3.4 Reaction with piperidine

Results for the rapid reaction, producing the 3-adduct, 3.3, (NRR' = NC_5H_{10}) are in table 3.6. In the absence of piperidinium chloride, values of k_{fast} show a squared dependence on the piperidine concentration. This indicates $k_{-3} >> k_{Am}[Am]$, showing that proton transfer is rate-determining in the formation of 3.3, reducing equation 3.2 to equation 3.14.

$$k_{fast} = \frac{k_3 k_{Am}}{k_{-3}}[Am]^2 + k_{AmH^+}[AmH^+] \qquad \text{eqn. 3.14}$$

Using equation 3.14 in the absence of added salt, a value of $\frac{k_3 k_{Am}}{k_{-3}}$ 1.5×10^4 $dm^6mol^{-2}s^{-1}$is obtained and hence with added salt a value of k_{AmH^+} 500 $dm^3mol^{-1}s^{-1}$ is obtained. Using these values in equation 3.14 gives good agreement with experimental results obtained. Combination of these values gives $K_{c,3}$ 30 dm^3mol^{-1} which is in fairly good agreement with that obtained from absorbance data, 38 dm^3mol^{-1}.

There is some evidence[18] suggesting the nature of the counter ion may affect the rate and equilibrium constants obtained by association with the substituted ammonium ions. Values obtained using piperidinium perchlorate however gave $K_{c,3}$ 37 dm^3mol^{-1} and k_{AmH^+} 440 $dm^3mol^{-1}s^{-1}$, these are within experimental error of those obtained using the chloride salt. Data for reaction with added piperidinium perchlorate are in table 3.7.

Table 3.6. Kinetic and equilibrium data for the rapid reaction between ethyl thiopicrate and piperidine in DMSO at 25°C, (using piperidinium chloride).

[Piperidine] /moldm^{-3}	[Piperidinium chloride]/ moldm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	Abs[b]	$K_{c,3}$[c]/ dm^{3}mol^{-1}
0.010	-	1.68	1.5	-	-
0.015	-	3.26	3.4	-	-
0.020	-	5.9	6.0	-	-
0.025	-	9.5	9.4	-	-
0.030	-	14	14	-	-
0.040	-	24	24	0.068	-
0.050	-	38	38	0.068	-
0.006	0.01	5.4	5.5	0.009	42
0.008	0.01	6.1	6.0	0.014	40
0.010	0.01	6.7	6.5	0.018	36
0.015	0.01	8.7	8.4	0.028	31
0.020	0.01	11.2	11.0	0.043	43
0.025	0.01	16.0	14.4	0.047	36
0.035	0.01	24	23	0.056	38
0.040	0.01	29	29	0.061	-
0.050	0.01	41	42	0.064	-

a) Calculated from equation 3.14 with k_3k_{Am}/ k_{-3} $1.5x10^4$ dm^{6}mol^{-2}s^{-1} and k_{AmH^+} 500 dm^{3}mol^{-1}s^{-1}.

b) Absorbance at 434nm.

c) Calculated using equation 3.5 with $Abs_\infty = 0.068$.

Table 3.7. Kinetic and equilibrium data for the rapid reaction between ethyl thiopicrate and piperidine in DMSO at 25°C, (using piperidinium perchlorate).

[Piperidine] /moldm^{-3}	[Piperidinium perchlorate]/ moldm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	Abs[b]	$K_{c,3}$[c]/ dm^3mol^{-1}
0.006	0.01	4.7	4.9	0.016	77
0.008	0.01	4.8	5.4	0.017	47
0.010	0.01	6.7	5.9	0.012	19
0.015	0.01	7.6	7.8	0.036	42
0.020	0.01	10.4	10.4	0.048	46
0.025	0.01	12.2	13.8	0.052	38
0.030	0.01	16.7	17.9	0.054	30
0.035	0.01	21	23	0.060	35
0.040	0.01	27	28	0.058	23
0.050	0.01	46	42	0.074	-

a) Calculated from equation 3.14 with k_3k_{Am}/ k_{-3} $1.5x10^4$ $dm^6mol^{-2}s^{-1}$ and k_{AmH^+} 440 $dm^3mol^{-1}s^{-1}$.

b) Absorbance at 434nm.

c) Calculated using equation 3.5 with $Abs_\infty = 0.074$.

3.4 Discussion

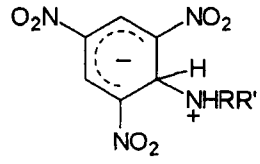
With all three amines used (in excess of ETP), the results are in accord with scheme 3.2, in which the initial rapid reversible attack at the 3-position is followed by a slower reaction at the 1-position leading to displacement of the ethylthio group.

3.4.1 Reaction at an Unsubstituted Ring Position

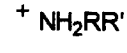
The kinetic results show the rate determining step for formation of the 3-adducts, 3.3, changes from attack by the amine in the case of butylamine, to proton transfer in the case of piperidine, with pyrrolidine showing intermediate behaviour.

Attack is occurring at an unsubstituted ring position and hence there is little steric hindrance to nucleophilic attack. Values of k_3, which increase in the order butylamine < piperidine < pyrrolidine therefore reflect the relative basicities of the amines. Values of the equilibrium constant, $K_{c,3}$, are also in the same order. The major difference in values on changing amines occurs with the rate constants for proton transfer. The value of k_{AmH^+} decreases by an order of magnitude going from butylamine to pyrrolidine and again by a order of magnitude from pyrrolidine to piperidine. This is probably due to increasing steric hindrance to approach of the reagents in the proton transfer step, i.e. from the substituted ammonium ion to adduct 3.3. This factor will also influence the value for the proton transfer from the zwitterionic intermediate to the amine, k_{Am}. This will be the major effect in decreasing the k_{Am}/k_{-3} values in the order butylamine > pyrrolidine > piperidine. Hence the change in rate determining step from amine attack with butylamine to proton transfer with piperidine is due to the slower rate of proton transfer in the latter case.

Values of the rate and equilibrium constants can be compared with those of 2,4,6-trinitrophenetole, TNP, and 1,3,5-trinitrobenzene, TNB, see table 3.8. Values of k_{AmH^+}, for a given amine, are independent of the nature of the nitro-compound. This is due to the fact that as reaction is occurring at an unsubstituted ring position, any steric effects at the reaction centre will be similar for all substrates. Previously[19,20], it has been shown that for trinitro-activated substrates the ratio k_{Am}/ k_{AmH^+} will have a value of ca. 500, which will not vary greatly with changes in aromatic compounds or amines; reflecting instead the higher acidity of the zwitterionic adducts over the ammonium ions. The higher acidities of zwitterions, 3.7, compared to the parent ammonium ions, 3.8, is due to the fact that the trinitro-substituted benzene ring, even though negatively charged, is electron withdrawing relative to hydrogen.[21,22]



3.7



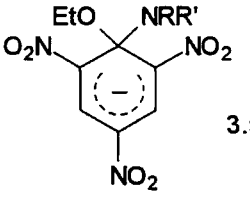
3.8

Values of k_{Am}/ k_{-3} can also be seen not to vary greatly with changes in structure of the nitro- compound. As k_{Am} is not expected to vary with changes in aromatic substrate for a given amine, k_{-3} must also not vary. Hence, for attack by the amine at the unsubstituted position of the ring, the transition state is likely to be product like.

For a given amine, values of the rate constant for initial attack by the amine, k_3, are almost two orders of magnitude smaller for ETP than for TNB. This is due to the steric effect exerted by the 1-substituent which results in the twisting from the ring plane of the 2- and 6- nitro groups, thus reducing their electron withdrawing ability[23]. This effect can be seen to be slightly larger for ETP than for TNP.

3.4.2 Reaction At A Substituted Ring Position

The reactions of TNP and ETP show much larger difference for attack at the 1- position than for attack at the 3-position. Structures analagous to 3.4 (i.e. 3.9) were observable intermediates in the reaction of TNP[18], therefore the kinetics of their formation and decomposition could be obtained. Such intermediates (3.4) were not observable in any of the reactions of ETP studied.



3.9

Attack at the 1- position of ETP by butylamine shows a first order dependence on amine, indicating that nucleophilic attack by the amine is rate determining. Using the mechanism as in scheme 3.2, substitution must then occur by rate determining amine attack, followed by rapid proton transfer and rapid loss of the ethylthio group. This would agree with the low intrinsic barrier expected for the loss of thiolate[8]. An alternative mechanism would involve spontaneous decomposition of the zwitterion 3.6 to products without the formation of anion 3.4. This, however, is unlikely as it would involve proton transfer to sulfur which is known to have a low afininty for protons[25] and also to be a poor hydrogen-bond acceptor[26].

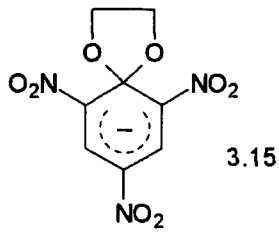
The value of k_1 for nucleophilic attack by butylamine at the 1-positiom of ETP is 8 $dm^3mol^{-1}s^{-1}$. This value is considerably lower than the value of 250 $dm^3mol^{-1}s^{-1}$ found[18] for attack by butylamine at the 1-position of TNP. This decrease is thought to result from the greater steric bulk of the ethylthio group compared with the ethoxy

group. Also the lower electronegativity of sulfur relative to oxygen will decrease the positive charge of the 1-position and hence tend to reduce the rate of nucleophilic attack. In the substitution reaction of ETP and pyrrolidine, the kinetic data show that proton transfer is rate limiting, or at least largely rate limiting. Two possibilities exist for the rate limiting step:

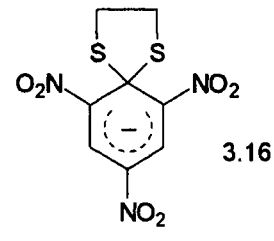
i) Proton transfer from the zwitterionic intermediate, 3.6 (NRR' = NC_4H_8) to pyrrolidine is the slow step, followed by rapid expulsion of the ethylthio group. Using equation 3.10 leads to K_1k_{Am} = 60 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-1} < 5 dm^3 mol^{-1}. (This value is smaller than the corresponding value for attack at the 3-position i.e. k_{Am}/k_{-3} (40 dm^3 mol^{-1}). This would be expected however, due to greater steric hindrance for proton transfer from the adduct, resulting from attack at the 1-position, hence reducing k_{Am}).

ii) k_4 is rate determining, involving proton transfer from the pyrrolidinium ions to the ionic adduct 3.4. Using equation 3.11 leads to $k_4K_{c,1}$ = 60 dm^6 mol^{-2} s^{-1}.

The former explanation is preferred, that is rate determining proton transfer from the zwitterion 3.6 to amine, followed by rapid expulsion of the ethanethiolate ion from 3.4. This is due to the failure to observe 3.4, which we would expect to be able to observe if k_4 was the rate determing step. The failure to observe the 1,1-adduct, 3.4, may be explained if it were considerably less stable than the 1,3-adduct, 3.3, i.e. $K_{c,3}$ >> $K_{c,1}$. Usually the 1,1-adduct are more thermodynamically stable than their 1,3-adducts due to the relief in steric strain once the 1-substituent is rotated out of the ring plane during adduct formation[17]. Adduct 3.4 may be thought to be sterically disfavoured due to the two bulky groups at the 1-position, although spiro-intermediates of a similar nature i.e. 3.1 and 3.2 were observed by spectroscopy. The lower intrinsic barrier expected for loss of the thiolate group should lead to its rapid expulsion from 3.4. Also, if k_4 were rate determining, then proton transfer from the pyrrolidinium ion to the sulfur of 3.4 would be involved in the slow step. The low proton affinity for thiolate groups renders unlikely general acid catalysis for their expulsion. Comparing this with ring opening of spiro adducts, that of the dioxolan adduct 3.15 is acid catalysed, that of the dithiolan adduct, 3.16, however is not catalysed.



3.15



3.16

The fact that base catalysis is observed for reaction with pyrrolidine but not for butylamine is explicable in terms of the slower rate of proton transfer with the secondary amine.

Reaction with piperidine was considerably slower than that of pyrrolidine, no kinetic measurements were made on the substitution reaction. Through NMR measurements, it was shown that substitution of the ethylthio group did occur, although no build up of species 3.4 was detected. Again there are two possibilities for the rate determining step, both agreeing with the lower rate of substitution by piperidine over pyrrolidine. The value of k_{Am} would be expected to be lower for piperidine due to its greater steric requirements compared to pyrrolidine. This can be seen by comparison with reaction at the 3- position which indicates that proton transfer is an order of magnitude smaller for reaction with piperidine than with pyrrolidine. Hence if proton transfer from zwitterion to amine was rate determining, this would explain the slowness of the substitution by piperidine. Alternatively, loss of the ethylthio group, catalysed by piperidinium ions, could be rate limiting. Movement of the piperidino group into the ring plane has been shown to have greater steric requirements than for the pyrrolidino group; hence k_4 would be expected to have a lower value for piperidine. This situation would only occur however if the 1,1-adduct, 3.4, had a lower thermodynamic stability than its 1,3-isomer, 3.3, as intermediate 3.4 is not observed.[9- 13] Again the former explanation is the more likely.

Table 3.8 Reaction of ethyl thiopicrate, trinitrophenetole and trinitrobenzene with amines in DMSO at 25°C.

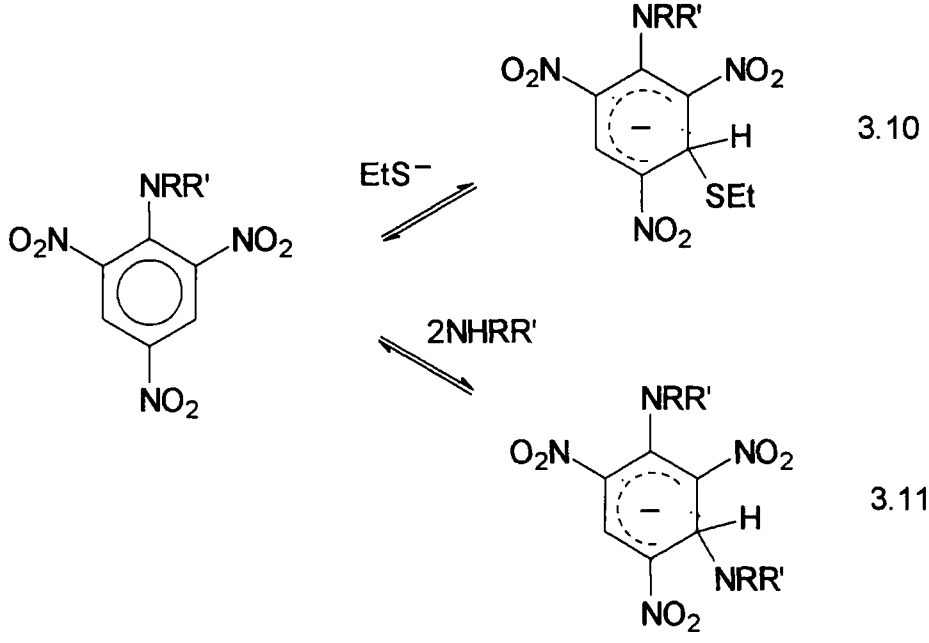
substrate	amine	k_3/ $dm^3mol^{-1}s^{-1}$	$K_{c,3}$/ dm^3mol^{-1}	$\frac{k_{-3}k_{AmH^+}}{k_{Am}}$ /s^{-1}	k_{AmH^+} / $dm^3mol^{-1}s^{-1}$	$\frac{k_{Am}}{k_{-3}}$ /dm^3mol^{-1}
ETP	piperidine	> 5000	35	> 170	500	< 3
	pyrrolidine	9000	60	150	5500	40
	butylamine	800	11	71	> 3.6 x 10^4	> 500
TNP	piperidine	> 9000	27	> 320	1600	< 5
	pyrrolidine	-	-	-	-	-
	butylamine	3200	15	210	> 4.2 x 10^4	> 200
TNB	piperidine	> 2 x 10^5	2140	> 900	280	< 10
	pyrrolidine	7.5 x 10^5	3500	210	3000	14
	butylamine	4500	1000	45	6 x 10^4	1200

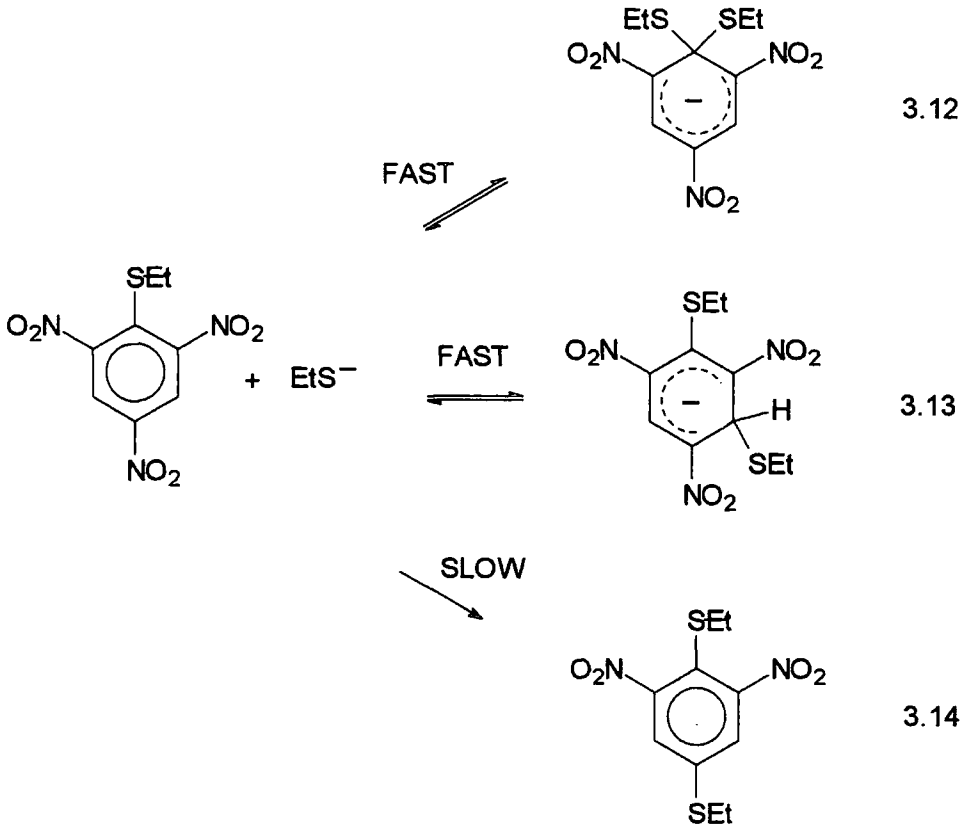
3.5 ^{1}H NMR Measurements

NMR spectra were recorded with ETP (0.1 moldm^{-3}) and amines (0.05-0.6 moldm^{-3}), data are in table 3.1. The substrate concentration was relatively high and therefore allowed the detection of further reactions of the displaced ethanethiolate groups. An equilibrium as shown in equation 3.15 resulted in the formation of a sulfur nucleophile which could attack the substrate in competition with the amine present.

$$EtSH + Am \Leftrightarrow EtS^- + AmH^+ \qquad \text{eqn 3.15}$$

Products were observed for attack by the ethanethiolate ions, both on unreacted ethylthiopicrate and also the substitution products, N-amino 2,4,6-trinitrobenzenes, 3.5. The reaction of ETP with excess piperidine initially showed the formation of the 3-adduct, 3.3 (NRR' = NC_5H_{10}), with ring proton bands at δ 5.68 and 8.45. With time these bands decreased and others increased due to attack of the ethanethiolate ions on unreacted ETP and on the N-piperidino-2,4,6-trinitrobenzene and also due to attack of the amine on the substitution product, 3.5. Bands due to the ring hydrogens of species 3.10 at δ 6.09 and 8.31, and those due to species 3.11 at δ 5.55 and 8.45 appeared during the reaction, due to attack on the substitution products formed. Comparison of the NMR bands obtained with previous work carried out on the ETP/ethanethiolate ion system,[8] showed the presence of 3.12 and 3.13, i.e. adducts resulting from attack of the ions at the 1- and 3- position of ETP, with bands at δ 8.36, and δ 5.99 and 8.31 respectively. A slower reaction was observed, resulting in species 3.14, by displacement of the 4- nitro group of ETP.





Eventually the spectrum showed bands due to the presence of 3.10, 3.11 and 3.14. This agrees with results obtained from an NMR spectrum of a solid formed during a preparative reaction (see experimental), which showed bands due to species 3.14 and N-piperidino-2,4,6-trinitrobenzene, 3.5.

NMR spectra obtained from the reaction of ETP with butylamine and with pyrrolidine, indicate displacement of the ethylthio group to give species 3.5 (NRR' = NC_4H_{10} and NC_4H_8 respectively). Bands due to species 3.3, i.e. due to attack at the 3-position, were not observed, probably due to these species being too transient. The final spectra showed species 3.10 with butylamine and species 3.11 and 3.14 with pyrrolidine to be the major compounds present.

The spectrum of adduct 3.10, NRR' = NC_4H_8, showed two bands at δ 3.3 and 3.7 due to the ring- hydrogens α to nitrogen. The non- equivalence of these hydrogens results from the asymmetry introduced by the nucleophilic attack at the 3- position and indicates that rotation about the N to ring C bond in the adduct is slow. Related asymmetry was observed in the methylene groups α to nitrogen in the adducts 3.10 and 3.11, NRR' = NHBu, which gave two multiplets.

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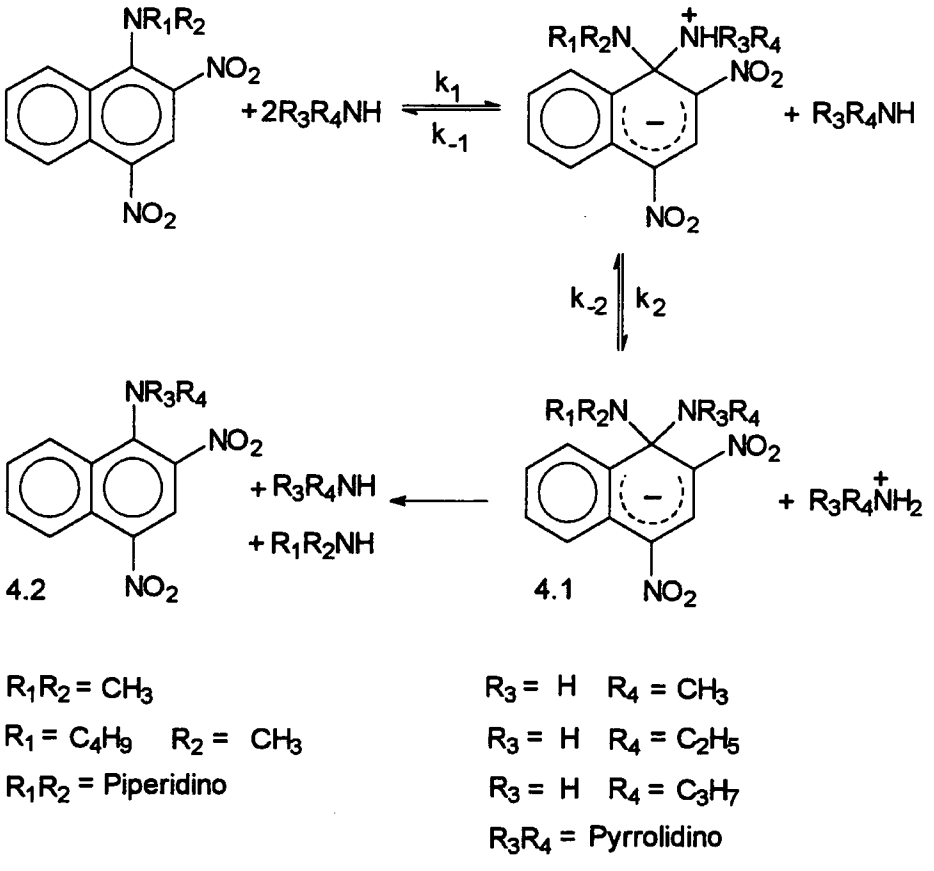
CHAPTER 4

Reactions Of N-Substituted Picramides With Amines In Dmso

Reactions of N-Substituted Picramides with Amines in DMSO.

4.1 Introduction

Several studies have been reported of amine-amine exchange reactions occurring at an aromatic carbon atom in a system activated by electron-withdrawing groups. Such reactions have been seen to occur with compounds such as 2,4-dinitronaphthylamine[1-3],.2,4-dinitroaniline[4] and 2,4,6,-trinitroaniline[4].



$R_1R_2 = CH_3$

$R_1 = C_4H_9$ $R_2 = CH_3$

R_1R_2 = Piperidino

$R_3 = H$ $R_4 = CH_3$

$R_3 = H$ $R_4 = C_2H_5$

$R_3 = H$ $R_4 = C_3H_7$

R_3R_4 = Pyrrolidino

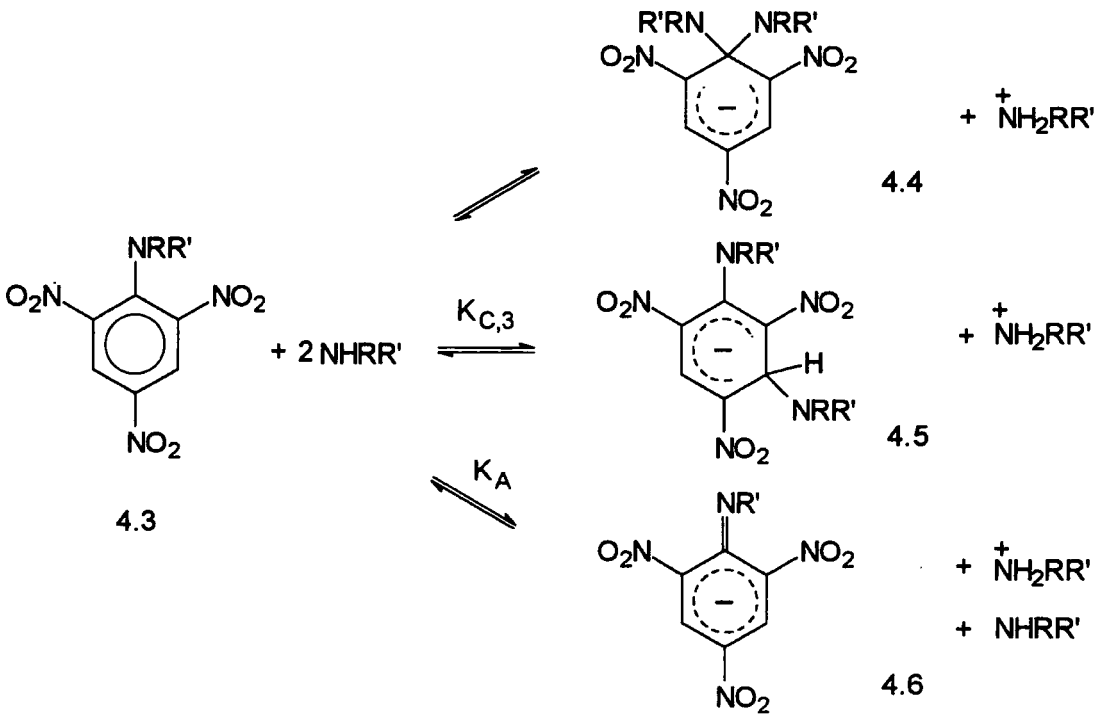
Scheme 4.1

These reactions are thought to proceed as shown in scheme 4.1, via intermediates such as 4.1, to give substitution products 4.2.

Various dialkyl groups such as dimethyl and N-methylbutylamino were seen to undergo facile amine-amine exchange reactions upon addition of primary amines at room temperature in DMSO. Secondary amines other than pyrrolidine showed extremely low nucleophilic reactivity; presumably due to increased steric effects. For example, the greater reactivity of pyrrolidine than of piperidine as a nucleophile has been attributed to

a stereoelectronic effect in which the lone pair of electrons of the entering pyrrolidino group may assume an anti-periplanar configuration to the ring carbon to nitrogen band of the leaving amino moiety[1-4]. Such a configuration is less accesible with piperidine.
The observation of base catalysis varies with the amino groups involved;if the ratio $k_2:k_1 > 1$ then base catalysis will not be observed, but when $k_2:k_1 < 1$ the reaction will be subject to base catalysis. The reaction of butylamine with 1-pyrrolidino-2,4,6-dinitronaphthalene in DMSO was found to be subject to base catalysis by butylamine and DABCO; whereas the reaction of the same amine with 1-piperidino- or 1-dimethylamino-dinitronapthalene was not subject to any catalysis[5]. Butylamine is able to approach the C-1 of the 1-pyrrolidino compound more easily than with the 1-piperidino or 1-dimethylamino compounds because in the latter cases of the steric interference of the α-CH_2 groups of the piperidino ring or the CH_3 groups of the dimethylamino group. These steric effects could render the free energy activation for the transition state in the first step much higher, resulting in a concomitant reduction in k_{-1} and hence increasing the k_2 / k_{-1} ratio to a value larger than one.

The products of the reactions of ethyl thiopicrate with amines are N-substituted picramides. It was thought to be of interest to study their reactions with the corresponding amines. The reactions of 1-butylamino- , 1-pyrrolidino- and 1-piperidino-2,4,6-trinitrobenzenes with their respective parent amines have been studied in DMSO. The possible reactions are shown in scheme 4.2.



Scheme 4.2

These involve: attack at the 1-position to give σ-adduct 4.4, attack at the 3-position to give 4.5 and in the case of butylamine only, transfer of a side-chain proton to give the conjugate base 4.6. Kinetic and equilibrium data were obtained and the different modes of reaction compared.

4.2 Experimental

4.2.1 Preparative Reactions

N-Substituted-2,4,6-trinitroanilines: prepared by reacting a fourfold excess of the appropriate amine with a warmed solution of picryl chloride in methanol. The yellow crystals of the required product were separated from the red solution obtained. Melting points were in good agreement with literature data.[3,4].

4.2.2 ^{1}H NMR Spectra

^{1}H NMR spectra were recorded using a Bruker 250 MHz instrument or a Varian 400 MHz instrument with [$^{2}H_{6}$] DMSO as a solvent. The concentration of the parent nitro-compound was 0.1 mol dm^{-3}. Spectra were recorded as soon as possible after addition of the amines and any changes with time were followed. The NMR data are collected in table 4.1. ^{1}H NMR spectra of the 1-butylamino-, 1-pyrrolidino-and 1-piperidino compounds in DMSO are shown in figures 4.1, 4.2 and 4.3 respectively.

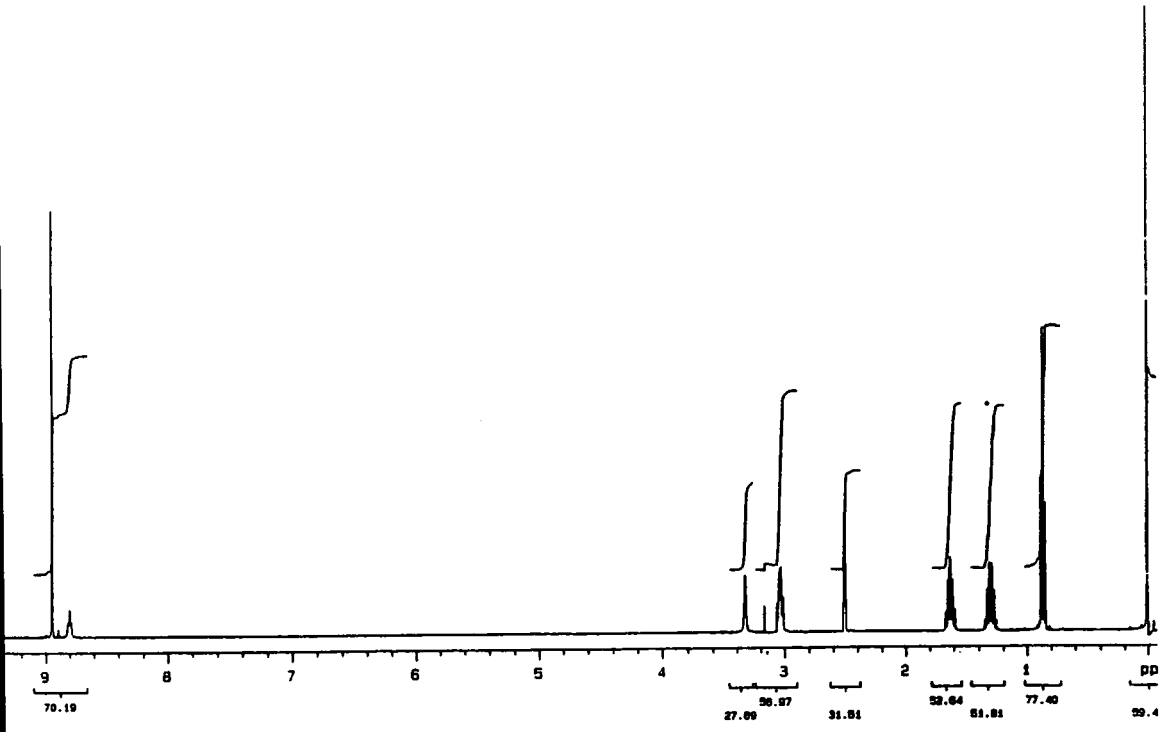


Figure 4.1. The ^{1}H NMR spectrum of 1-butylamino 2,4,6-trinitrobenzene.

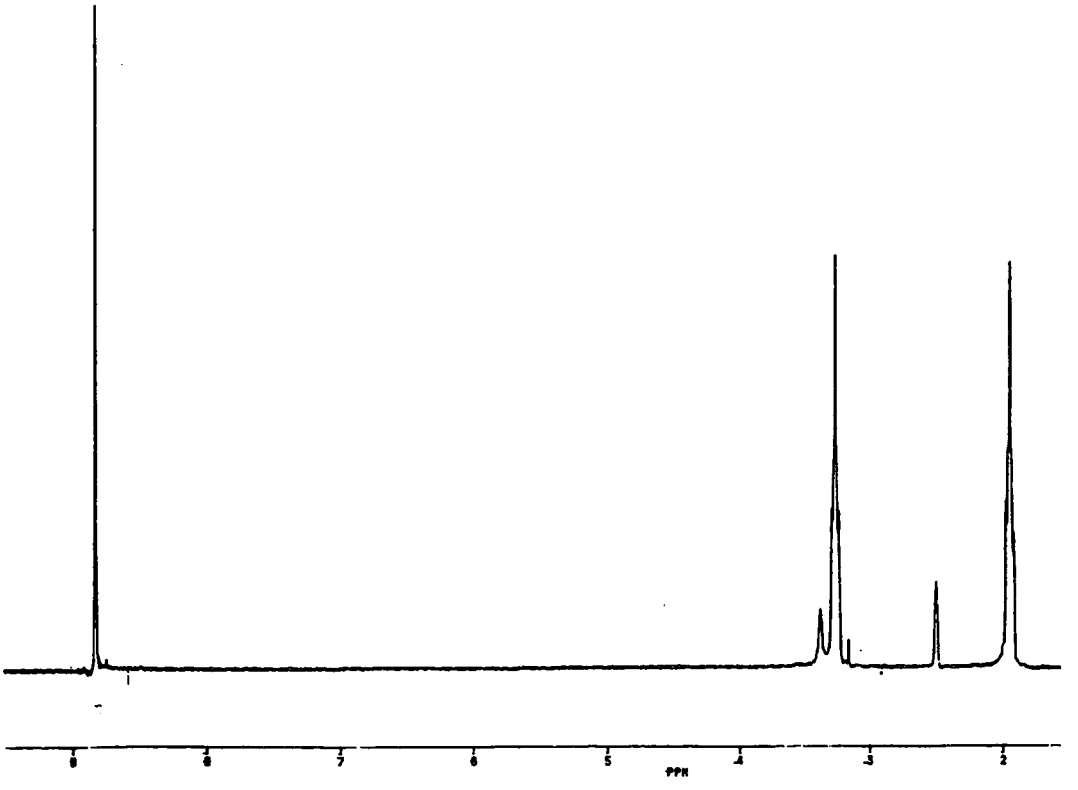


Figure 4.2. The ^{1}H NMR spectrum of 1-pyrrolidino 2,4,6-trinitrobenzene.

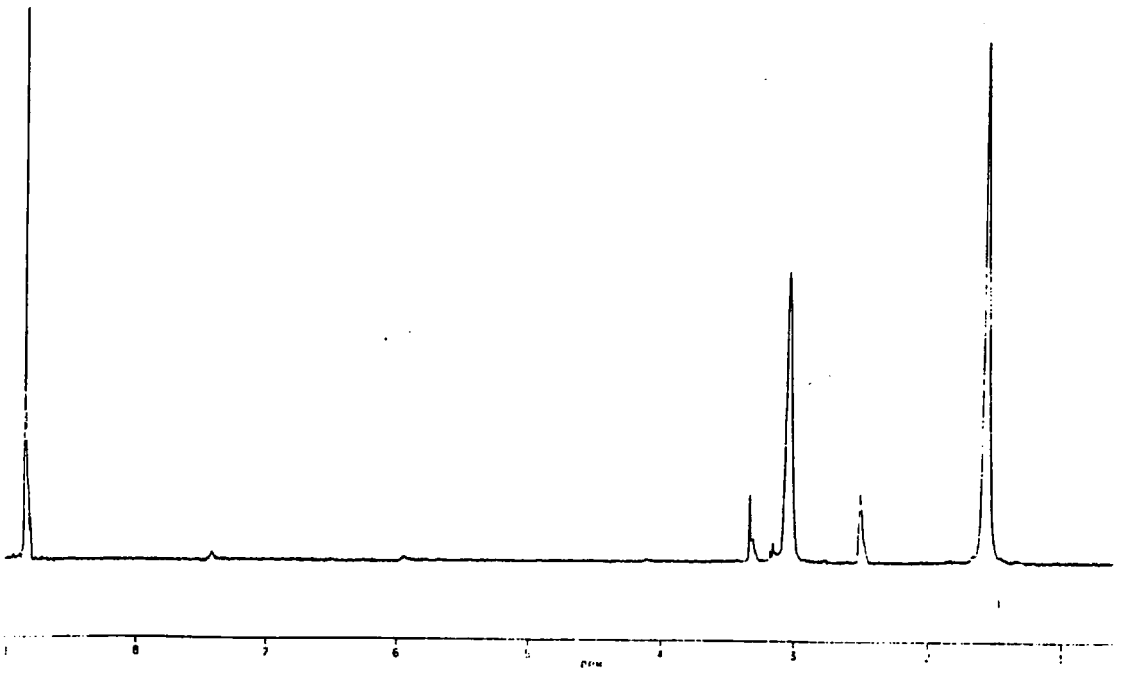
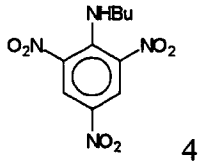
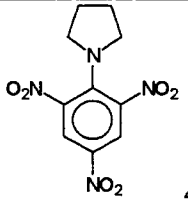
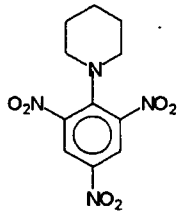
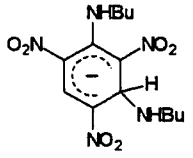
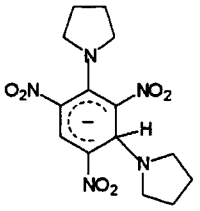
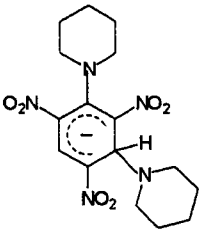
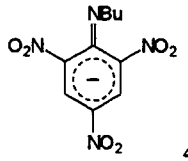


Figure 4.3. The ^{1}H NMR spectrum of 1-piperidino 2,4,6-trinitrobenzene.

Table 4.1 Spectroscopic data for the 1-amino-2,4,6-trinitrobenzene compounds and their adducts formed on reaction with amines in DMSO, (δ values).

Structure	^{1}H NMR Ring	^{1}H NMR NRR'	UV/Vis Max. / nm
 4.3	8.94	8.80 (NH), 3.03, 1.63, 1.30, 0.86	350
 4.3	8.84	3.27, 1.95	370
 4.3	8.85	3.05, 1.58	394
 4.5	8.36, 5.60	(2.6, 2.3)[a], 1.6, 1.2, 0.8	424, 500 (sh.)
 4.5	8.35, 5.89	3.38, 1.92	420, 480
 4.5	8.45, 5.55	N/M	420, 485
 4.6	8.36	N/M	444, 500 (sh.)

a) Non-equivalent methylene hydrogens.

4.3 Results

4.3.1 NMR

^1H NMR measurements of the parent molecules, 4.3, 0.1 mol dm^{-3} in [$^2H_6$] DMSO, show bands at δ 8.94, 8.84, 8.85 for the ring hydrogens of the butylamino-, pyrrolidino- and piperidino- compounds, as seen in figures 4.1, 4.2 and 4.3. NMR data are in table 4.1.

The data for 1-piperidino-2,4,6-trinitrobenzene in the presence of piperidine show two bands of equal intensity at δ 8.45 and 5.55 due to the ring protons of the 3-adduct, 4.5 (NRR' = NC_5H_{10}). The bands are broad indicating that exchange between the amine and adduct is relatively fast. No bands were seen which would correspond to the 1-adduct, 4.4 (NRR' = NC_5H_{10}) and from this we can say that the major interaction is that causing the 3-adduct, 4.5. Similarly for pyrrolidine, bands at δ 8.35 and 5.89 indicate formation of the 3-adduct, 4.5 (NRR' = NC_4H_8).

NMR studies of the reaction between 1-butylamino-2,4,6-trinitrobenzene and butylamine indicate the formation of two species, the amount of each depending on the ratio of parent to amine, as shown in figure 4.4. The spectra show bands at δ 8.36 and 5.60 due to the 3-adduct, 4.5 (NRR' = NHBu), but also a band at δ 8.36 due to 4.6 (NR' = NBu). Increasing the concentration of amine caused an increase in the bands due to 4.5 and a decrease in those for 4.6. This is due to the different stoichiometry of each interaction; the formation of 4.5 requiring two amine molecules while the formation of 4.6 requiring only one amine molecule. The two equilibrium constants $K_{c,3}$ and K_A, can be expressed by the following equations, 4.1 and 4.2 respectively.

$$K_{c,3} = \frac{[4.5][NH_2^+RR']}{[4.3][NHRR']^2} \qquad \text{eqn 4.1}$$

$$K_A = \frac{[4.6][NH_2^+RR']}{[4.3][NHRR']} \qquad \text{eqn 4.2}$$

Dividing the two equilibrium constants a ratio $K_A/K_{c.3}$ can be obtained, as in equation 4.3.

$$\frac{K_A}{K_{c,3}} = \frac{[4.6]}{[4.5]}[NHRR'] \qquad \text{eqn 4.3}$$

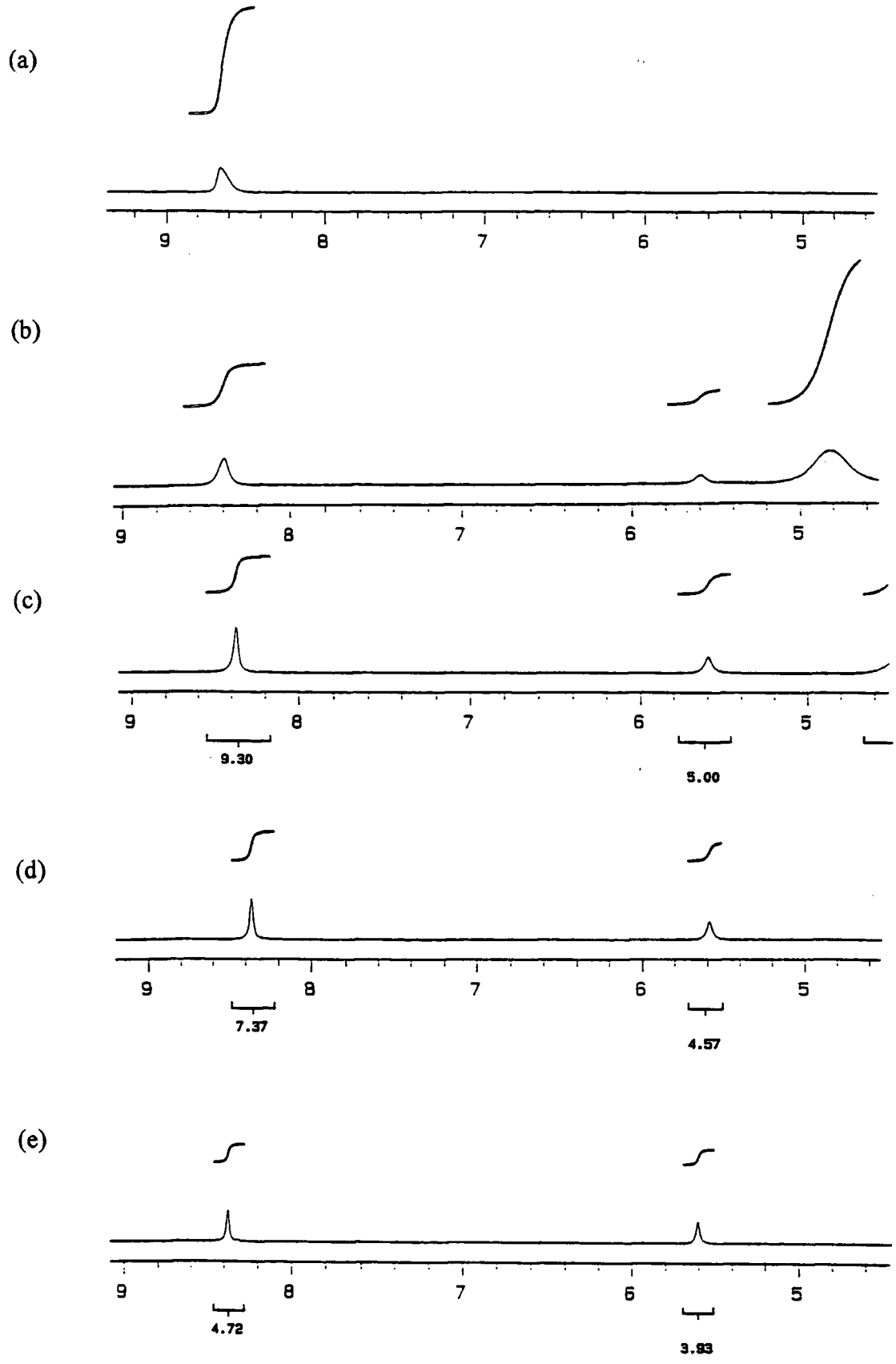


Figure 4.4. ^{1}H NMR spectra of the reaction product formed between 1-butylamino 2,4,6-trinitrobenzene and various concentrations of butylamine. The spectra show increasing amine concentration:- (a) 0.1 moldm^{-3}, (b) 0.2 moldm^{-3}, (c) 0.3 moldm^{-3}, (d) 0.4 moldm^{-3} and (e) 0.6 moldm^{-3}.

From the relative intensities of the ring proton signals, a value for the ratio $K_A/K_{c.3}$ can be obtained. Since the peak at δ 5.6 is due to 1 proton of the 3- adduct, species 4.5, and the peak at δ 8.36 is due to 1 proton of species 4.5 and two of species 4.6; the relative intensities for each proton can be calculated; i.e. by subtracting the intensity of the peak at δ 5.6 from that at δ 8.36, the intensity of the two protons of species 4.6 can be obtained.

e.g. With 0.2 mol dm^{-3} amine: Peak at δ 8.36ppm = 10.77 units

Peak at δ 5.6ppm = 3.51 units

$\therefore$ 1 proton of species 4.5 = 3.51 units

$$\Rightarrow \text{1 proton of species 4.6} = \frac{10.77 - 3.51}{2} = 3.63 \text{ units}$$

$$\text{Hence the ratio } \frac{[4.6]}{[4.5]} = \frac{3.63}{3.51} = 1.03$$

In all cases the concentration of parent used was 0.1 mol dm^{-3}, assuming complete conversion into 4.5 and 4.6 gives the equation:

$$[4.5] + [4.6] = 0.1$$

Hence, knowing the ratio of [4.6] / [4.5], each concentration can be determined separately,and then using equation 4.3 obtain a value of 0.055 dm^3 mol^{-1} for the ratio $K_A/K_{c.3}$. See table 4.2.

Table 4.2. ^1H NMR data used to calculate the ratio $K_A/K_{C,3}$

$[BuNH2]_{stoich}$ /moldm^{-3}	peak intensities δ δ 8.36 5.6	[4.6]/[4.5]	[4.6]	[4.5]	$[BuNH2]_{free}$[a] /mol dm^{-3}	$K_A/K_{C,3}$[b] /dm^{3}mol^{-1}
0.2	10.77 3.51	1.03	0.051	0.049	0.051	0.053
0.3	9.30 5.00	0.43	0.031	0.070	0.13	0.056
0.4	7.37 4.57	0.31	0.024	0.076	0.22	0.069
0.5	4.72 3.93	0.10	0.009	0.091	0.41	0.041

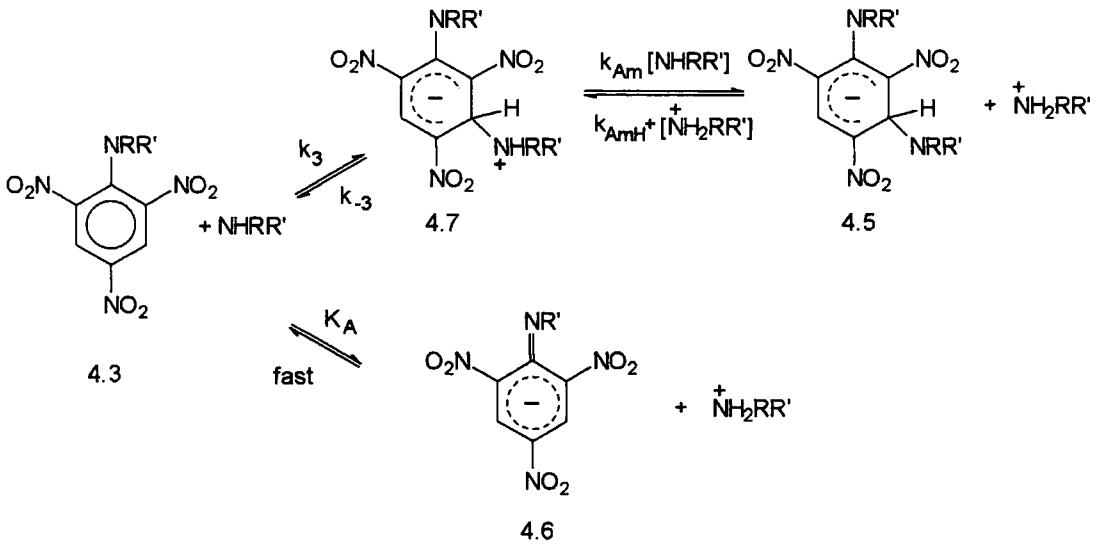
a) Calculated as $[BuNH2]_{stoich}$.-2[4.5]-[4.6]

b) Calculated using equation 4.3.

The above results give no evidence for the formation of the 1-adduct, 4.4. This species would be expected to have a band in the region δ 8.4 due to its two ring protons, about the same region as that for the anion, 4.6. However, a decrease is seen in the band at δ 8.4 relative to that of the 3-adduct, 4.5, with increasing amine concentration. This agrees with the formation of 4.6, requiring only one amine molecule, but not with the formation of 4.4 which would require two amine molecules and hence would be expected to behave similarly to the 3-adduct, 4.5. These results agree with NMR and UV/Visible data obtained previously for the reaction of 1-butylamino-2,4,6-trinitrobenzene, 4.3 (NRR' = NHBu) with butylamine[6,7].

4.4 Kinetic and Equilibrium Data

Through NMR data it seen that the parent compounds, 4.3, react with the respective amines giving the 3-adducts, 4.5, and in the case of butylamine by transfer of a side-chain proton to give 4.6. These results are interpreted by scheme 4.3, in which formation of the 3-adduct, 4.5, is likely to proceed via a zwitterionic intermediate 4.7.



scheme 4.3

UV/Visible spectroscopic data for the parent molecule, 4.3, and the various adducts formed by reaction with amines are given in table 4.1. Kinetic study by the stopped-flow method indicated that for each parent compound, 4.3, reacting with its respective amine there was a single rate process observable. The reaction products had λ_{max} = 420 nm

and 480-500 nm (sh) consistent with the formation of the 3-adducts, 4.5. In the case of butylamine, the observed process measurable was preceeded by a much faster process, too fast to measure, attributed to rapid equilibrium between the parent, 4.3, and conjugate base, 4.6.

4.4.1 Kinetic Analysis:

Rate constants were measured under first order conditions. For reactions involving buffers (amine plus amine salt), the buffer components were in large excess of the parent concentration (2×10^{-5} mol dm^{-3}). For the reactions in the absence of added salts, a sufficient excess of amine was used to ensure >95% conversion to adduct was achieved. Under these conditions, equation 4.4 applies:

$$\ln\left(\frac{Abs_{\infty}}{Abs_{\infty} - Abs}\right) = k_{obs}t \qquad \text{eqn 4.4}$$

It is assumed that the zwitterions formed may be treated as steady state intermediates, and so we obtain equation 4.5.

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2 + k_{-3}k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 4.5}$$

In the case of butylamine, where species 4.6 can be formed, equation 4.6 applies which allows for the initial equilibrium, K_A.

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2}{\left(k_{-3} + k_{Am}[Am]\right)\left(1 + K_A\frac{[Am]}{[AmH^+]}\right)} + \frac{k_{-3}k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 4.6}$$

4.4.2 Reaction with butylamine

UV/Visible spectroscopic data of the parent compound, 4.3 (NRR' = NHBu), the 3-adduct, 4.5, and the proton transfer anion, 4.6, are in table 4.1. Reactions involving low concentrations of amine, (< 0.005 moldm^{-3}), gave species 4.6 while species 4.5 was obtained at high concentrations of butylamine, (> 0.2 moldm^{-3}), as can be seen in figure 4.5.

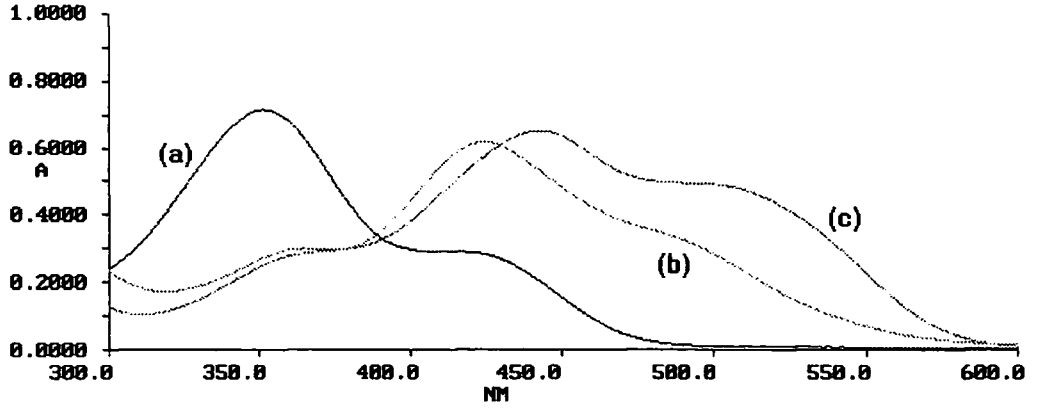


Figure 4.5. UV/Visible spectra showing (a) 1-butylamino 2,4,6-trinitrobenzene, (b) species 4.5 formed between 1-butylamino 2,4,6-trinitrobenzene and 0.1 moldm^{-3} butylamine and (c) species 4.6 formed during the reaction between 1-butylamino 2,4,6-trinitrobenzene and 0.002 moldm^{-3} butylamine.

From NMR data, the ratio $K_A/K_{C,3}$ could be obtained, 0.055 mol^{-1}dm^3, but not individual values. However, using abbsorbance values, K_A can be obtained and hence $K_{C,3}$ also. Absorbance values were measured at low amine concentrations ($\Leftrightarrow$ 0.003 mol dm^{-3}) where formation of species 4.6 will be the major process occurring, see table 4.3. The absorbance value with no added amine corresponding to parent, 4.3, and with added amine but no added salt i.e. full conversion to species 4.6, can be compared and hence used to calculate a value for K_A. Absorbance measurements were made at three different wavelengths and with the ionic strength maintained at 0.1 mol dm^{-3} by a neutral electrolyte, (tetraethylammonium perchlorate).

Table 4.3. Absorbance and equilibrium data for the formation of species 4.6 from 1-butylamino-2,4,6-trinitrobenzene in DMSO at 25°C[a].

[Butylamine] / moldm^{-3}	[Butylammonium perchlorate] / mol dm^{-3}	absorbances / nm			K_A		
		350	440	500	350[b]	440[c]	500[d]
0	0	0.586	0.176	0.000	-	-	-
0.003	0	0.229	0.630	0.472	-	-	-
0.003	0.015	0.444	0.356	0.184	3.3	3.3	3.2
0.003	0.010	0.424	0.430	0.256	2.8	4.2	4.0
0.003	0.020	0.467	0.330	0.155	3.3	3.4	3.3
0.002	0.010	0.458	0.354	0.186	2.8	3.2	3.3
0.002	0.006	0.412	0.386	0.223	2.9	2.6	2.7

a) Ionic strength maintained at 0.1 mol dm^{-3} with tetraethylammonium perchlorate.

b) Calculated as $\frac{0.586 - Abs}{Abs - 0.229} x \frac{[BuNH_3^+]}{[BuNH_2]}$

c) Calculated as $\frac{Abs - 0.176}{0.630 - Abs} x \frac{[BuNH_3^+]}{[BuNH_2]}$

d) Calculated as $\frac{Abs}{0.472 - Abs} x \frac{[BuNH_3^+]}{[BuNH_2]}$

The above results lead to a value of 3.2 ± 0.3 for K_A which is independent of the wavelength used. Using the value for the ratio $K_A / K_{C,3}$ of 0.055 mol^{-1}dm^3, allows the calculation of a value for $K_{C,3}$ of 58 dm^{3}mol^{-1}.

Rate constants for the process forming the 3-adduct, 4.3, are in table 4.4. Measurements were made on the stopped-flow apparatus at 410nm, with either 0.01 or 0.10 mol dm^{-3} butylammonium ions, with the ionic strength maintained at 0.1 moldm^{-3} in all cases.

Table 4.4. Data for the reaction of 1-butylamino-2,4,6-trinitrobenzene with butylamine to give the 3-adduct, 4.5, in DMSO at 25°C.

[butylamine] / moldm^{-3}	[Butylammonium perchlorate][a] / mol dm^{-3}	k_{obs}/ s^{-1}	k_{calc}[b]/ s^{-1}
0.06	0.01	34.0	35.7
0.08	0.01	31.9	32.0
0.10	0.01	29.6	30.2
0.15	0.01	28.3	27.3
0.20	0.01	26.0	26.0
0.04	0.10	380	350
0.07	0.10	300	280
0.10	0.10	270	260
0.20	0.10	250	235

a) Ionic strength maintained at 0.1 mol dm^{-3} with tetraethylammonium perchlorate.
b) Calculated using equation 4.7 with k_3 7000 dm^{3}mol^{-1}, $k_{-3}k_{AmH^+}/k_{Am}$ 90 s^{-1} and K_A 3.2.

When the condition $k_{Am}[Am] >> k_{-3}$ applies the equation relating to the formation of the 3-adduct, equation 4.6, can be reduced to equation 4.7. The results in table 4.4 correspond to this latter equation.

$$k_{obs} = \frac{k_3[Am]}{1 + K_A\dfrac{[Am]}{[AmH^+]}} + \frac{k_{-3}k_{AmH^+}[AmH^+]}{k_{Am}[Am]} \qquad \text{eqn 4.7}$$

The equilibrium constant for attack at the 3-position, $K_{C,3}$, can be expressed by the equation 4.8.

$$K_{C,3} = \frac{k_3 k_{Am}}{k_{-3}k_{AmH^+}} \qquad \text{eqn 4.8}$$

Since the values of $K_{C,3}$ and K_A are known and also since $k_{-3}k_{AmH^+}/k_{Am}$ is equivalent to $k_3/K_{C,3}$, a value for k_3 can be obtained directly from equation 4.7. The best fit is obtained with values k_3 = 7000 dm^{3}mol^{-1}, $k_{-3}k_{AmH^+}/k_{Am}$ = 90 s^{-1} and K_A = 3.2

These results show that in the formation of the 3-adduct, 4.5, nucleophilic attack by the amine is rate determining and this is followed by a rapid proton transfer step.

4.4.3 Reaction with pyrrolidine

A single colour forming reaction at 475nm was measured, which corresponds to the formation of the 3-adduct, 4.5. Data are in table 4.5.
Data obtained in the absence of added salt show an amine dependence of between one and two, indicating $k_{-3} \approx k_{Am}[Am]$. Hence, in the absence of added salt equation 4.5 reduces to equation 4.8.

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 4.8}$$

Dividing by the amine concentration and inverting this equation gives equation 4.9 and hence a plot of [Am] / k_{obs} vs. 1/ [Am] will have a slope of $k_{-3}/ k_3 k_{Am}$ and an intercept of $1/ k_3$; a linear plot gave values of $k_3 k_{Am}/ k_{-3}$ 5.2×10^5 $dm^6mol^{-2}s^{-1}$ and k_3 1.3×10^4 $dm^3mol^{-1}s^{-1}$, hence $k_{Am}/ k_{-3} = 40$ dm^3mol^{-1}.

$$\frac{[Am]}{k_{obs}} = \frac{k_{-3}}{k_3 k_{Am}} \cdot \frac{1}{[Am]} + \frac{1}{k_3} \qquad \text{eqn.4.9}$$

In the presence of added pyrrolidinium perchlorate (0.01 mol dm^{-3}), the observed rate constants were too fast to measure by the stopped-flow technique. Absorbance values were obtained however, allowing a value for $K_{C,3}$ of 3.6 dm^3mol^{-1} to be calculated.
Use of equation 4.10 allows the calculation of a value of 1.4×10^5 dm^3mol^{-1} for k_{AmH^+}.

$$K_{c,3} = \frac{k_3 k_{Am}}{k_{-3}} \times \frac{1}{k_{AmH^+}} \qquad \text{eqn 4.10}$$

Values calculated using the above gave a good fit with experimental data, both with and without added salt. The results show that in formation of 4.5 from the pyrrolidino compound, 4.3, the proton transfer step is partially rate limiting.

Table 4.5. Kinetic and equilibrium data for the reaction of 1-pyrrolidino-2,4,6-trinitrobenzene with pyrrolidine in DMSO at 25°C.

[pyrrolidine] /mol dm^{-3}	[pyrrolidinium perchlorate] / mol dm^{-3}	k_{obs} / s^{-1}	k_{calc}[a] / s^{-1}	Abs	$K_{c,3}$[b] / dm^3 mol^{-1}
0.010	-	38	37	-	-
0.015	-	72	73	-	-
0.020	-	105	115	-	-
0.025	-	167	163	-	-
0.030	-	219	213	0.296	-
0.010	0.01	>500	1040	-	-
0.020	0.01	>500	850	0.040	3.9
0.030	0.01	>500	850	0.080	4.1
0.040	0.01	>500	860	0.098	3.1
0.050	0.01	>500	900	0.131	3.2

a) Calculated from equation 4.5 with k_3k_{Am}/k_{-3} 5.2 x 10^5 $dm^6mol^{-2}s^{-1}$, k_{Am}/k_{-3} = 40 dm^3mol^{-1} and k_{AmH^+} 1.4 x 10^5 dm^3mol^{-1} .

b) Calculated using $\frac{Abs}{Abs_\infty - Abs} x \frac{[AmH^+]}{[Am]^2}$ where $Abs_\infty = 0.296$.

4.4.4 Reaction with piperidine

As with pyrrolidine, a single colour forming reaction at 475nm was measured, consistent with the formation of the 3-adduct 4.5 (NRR' = 5.10). Rate and equilibrium data are in table 4.6. In the absence of added salt, the measured rate constants show a squared dependence on amine concentration. Hence, the condition $k_{-3} >> k_{Am}[Am]$ applies and equation 4.5 can be reduced to equation 4.11.

$$k_{obs} = \frac{k_3k_{Am}}{k_{-3}}[Am]^2 + k_{AmH^+}[AmH^+] \qquad \text{eqn 4.11}$$

In the absence of added salt, a value of 2.5 x 10^5 $dm^6mol^{-2}s^{-1}$ was obtained for k_3k_{Am}/k_{-3}. From equation 4.11 it can be seen that at constant salt concentration the final term is constant. Data obtained with and without added salt yielded a value for k_{AmH^+} of 1.6 x 10^4 $dm^3mol^{-1}s^{-1}$. Combination of these values in equation 4.10 gave a value for $K_{C,3}$ of 16 dm^3mol^{-1}, which is in reasonable agreement with that obtained from absorbance data.

Values calculated using the above in equation 4.11 gave a good fit with those obtained experimentally. The above results imply that the rate determining step in the formation of the 3-adduct is the proton transfer step.

Table 4.6. Kinetic and equilibrium data for the formation of the 3-adduct 4.5 from 1-piperidino-2,4,6-trinitrobenzene, 4.3, with piperidine in DMSO at 25°C.

[piperidine] /mol dm^{-3}	[piperidinium chloride]/ mol dm^{-3}	k_{obs} / s^{-1}	k_{calc}[a]/ s^{-1}	Abs	$K_{c,3}$[b] / dm^3mol^{-1}
0.015	-	59	56	0.36	-
0.020	-	95	100	0.36	-
0.025	-	155	156	-	-
0.030	-	230	225	-	-
0.010	0.01	200	185	0.0564	19
0.015	0.01	211	216	-	-
0.020	0.01	250	260	0.167	22
0.030	0.01	-	-	0.226	19
0.040	0.01	-	-	0.28	22
0.050	0.01	-	-	0.307	23

a) Calculated from equation 4.11 with k_3k_{Am}/k_{-3} 2.5 x 10^5 $dm^6mol^{-2}s^{-1}$ and k_{AmH^+} = 1.6 x 10^4 $dm^3mol^{-1}s^{-1}$.

b) Calculated as $\frac{Abs}{Abs_\infty - Abs} x \frac{[AmH^+]}{[Am]^2}$ where $Abs_\infty = 0.36$.

4.5 Discussion

The results show that with both the piperidino and pyrrolidino compounds, the major reaction with their parent amines is attack at the 3-position to give adducts 4.5. With the butylamino compound there are two major reactions, attack at the 3-position and also transfer of the side chain proton to give 4.6. These two reactions have different stoichiometries, the former process requiring two amine molecules whereas the latter only requires one amine molecule. The extent of conversion to each adduct was seen to vary with amine concentration, the 3-adduct being favoured with higher amine concentrations, ($[BuNH_2] > 0.055 mol\ dm^{-3}$).

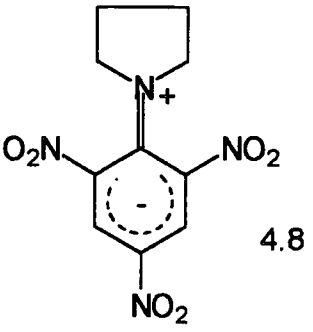
In the formation of the 3-adducts, 4.5, the rate determining step changes from nucleophilic attack by amine in the reaction of 1-butylamino-2,4,6-trinitrobenzene to proton transfer from the zwitterionic intermediate to amine in the case of the 1-piperidino compound. The reaction of amine with the pyrrolidino compound shows intermediate behaviour, that is the proton transfer step is partially rate limiting.

Values of the rate and equilibrium constants are collected in table 4.7 where they are compared with values for the reaction of amines at unsubstituted ring positions of 1,3,5-trinitrobenzene (TNB), trinitrophenetole (TNP) and ethylthiopicrate (ETP).

Changes in the value of the ratio k_{Am}/ k_{-3} reflect the change in rate limiting step with compounds 4.6, decreasing in the series butylamine > pyrrolidine > piperidine. This is likely to reflect changes in the value of k_{Am}, which will decrease with increasing steric requirements of the amines.[8-10] That is a piperidine molecule will be subject to more steric hindrance when approaching the zwitterion 4.7 (NRR' = NC_5H_{10}), to remove a proton than the butylamine molecule when approaching the less hindered zwitterion 4.7 (NRR' = NHBu).

For a given amine, the value of k_{Am}/ k_{-3} is largely independent of the nature of the substrate. This reflects the fact that reaction is occuring at an unsusbtituted ring position and as such the steric factors, at the reaction centre, will be the same in each case.

Generally, values of k_{AmH^+} are thought to behave in a similar manor to those above, k_{Am}/ k_{-3}. However, values of k_{AmH^+} for reactions of the piperidino and pyrrolidino compounds with piperidine and pyrrolidine respectively can be seen to be an order of magnitude larger than the corresponding values with other substrates. This may be due to decreases in acidity of the zwitterionic intermediates, 4.7, in which the planarity of the nitro groups is disrupted by the bulky 1-substituents and/or by electron donation as in species 4.8. As proton transfer from 4.7 to amine is thermodynamically favoured,[8] this decrease in acidity would be expected to exert a larger effect on the values of k_{AmH^+} than on k_{Am}.

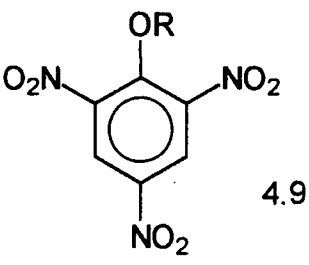


4.8

As can be seen from the above, both steric and electronic effects of the 1-substituents must be considered when discussing any results. As stated above, it is known that the presence of a 1-substituent will disrupt the planarity of the nitro groups at the 2- and 6-positions so that they cannot exert their maximum electron withdrawing effect.[11] Electron donation, as in species 4.8, may be a factor which stabilises the reactant more effectively than the anionic derivatives. Such delocalisation has been shown to be particularly important for pyrrolidino compounds.[2-4]

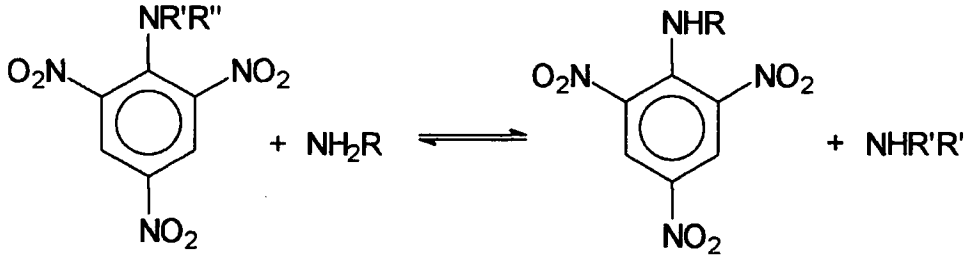
Values of $K_{C,3}$ can be seen to be considerably larger for the reaction of TNB than for substituted derivatives, this again can be attributed to the effect of the 1-substituent explained above. For TNB and ETP, these values of $K_{C,3}$ decrease in the order pyrrolidine > piperidine > butylamine, reflecting the relative basicities of the amines. However, in the reaction of 4.3 with amines, the order decreases as butylamine > piperidine > pyrrolidine, i.e. the opposite to that above. However in these cases the nature of the substrate, 4.3, is also changing with the change in amine. Hence the increased value for butylamine could be due to a decrease in steric requirements, as the primary amine at the 1-position will disrupt the planarity of the two nitro groups to a lesser extent tha the larger, more bulky secondary amines. In the case of pyrrolidine, the reactant could be stabilised as in 4.8 and hence would have a lower value of $K_{C,3}$ than piperidine even though it is less sterically hindered and as such would be expected to have a larger value. This effect would also decrease the value of k_3 for pyrrolidine which can again be seen to have a lower value than piperidine.

The reactions of picryl ethers, such as 4.9 with alkoxide groups are well known, forming 1-adducts which have a greater thermodynamic stability than those formed by attack at the 3-position.[12,13]



4.9

Attack at the 1-position to give adducts 4.4 was not observed, however, in the reaction of any of the amino compounds, 4.3. Failure to observe the pyrrolidino and piperidino adducts could be attributed to the large steric strain when two bulky secondary amine groups are attached to the same carbon atom. This however could not explain the failure to observe 1-adducts with butylamine. This could suggest that the 1,1-diamino adducts are intrinsically less stable than their 1,3-adducts. Unsymmetrical 1,1-diamino adducts have been observed however in other amine-amine exchange reactions.[1-5] The greater ability of primary amine nucleophiles to replace secondary amino groups than the reverse process has been attributed to steric and stereoelectronic effects associated with both the attack and departure of the amino groups.



equation 4.12

In the reaction shown in equation 4.12, the equilibrium will lie to the right in the presence of excess amine due to the greater ability of the product than the reactant to form anionic dreivatives.

Further stabilisation of the amino compounds, 4.3, occurs by the formation of the unreactive 3-adducts and in the case of butylamine only, by transfer of the side chain proton. This agrees with experimental results which show larger value for $K_{C,3}$ for the reaction of 4.3 with butylamine than piperidine or pyrrolidine.

A further point to note is that the equilibration process of the parent molecules, 4.3, with the amines derived from them are very rapid processes compared to nucleophilic substitution of ethyl thiopicrate with amines. Hence the processes described in this chapter occur after the rate determining steps in the substitution reactions described previously.

Table 4.7. Comparison of kinetic and equilibrium data for the reaction at an unsubstituted position of 1,3,5-trinitrobenzene (TNB), trinitrophenetole (TNP), ethylthiopipcrate (ETP) and the N-substituted picramides (4.3) in DMSO at 23 °C[a,b].

		Butylamine[c]	Pyrrolidine[d]	Piperidine[e]
k3 / $dm^3mol^{-1}s^{-1}$	TNB	45000	7.5×10^5	$> 2 \times 10^5$
	TNP	3200	-	$> 9 \times 10^3$
	ETP	800	9×10^3	$> 5 \times 10^3$
	4.6	7×10^3	1.3×10^4	$>8 \times 10^4$
$K_{C,3}$ /dm^3mol^{-1}	TNB	1000	3500	2140
	TNP	15	-	27
	ETP	11	60	35
	4.6	58	3.6	16
k_{Am}/k_{-3} / dm^3mol^{-1}	TNB	1200	14	< 10
	TNP	> 200	-	< 5
	ETP	> 500	40	< 3
	4.6	> 200	40	< 3
k_{AmH^+} / $dm^3mol^{-1}s^{-1}$	TNB	6×10^4	3000	280
	TNP	$> 4.2 \times 10^4$	-	1600
	ETP	$>3.6 \times 10^4$	5500	500
	4.6	$> 1.5 \times 10^4$	1.4×10^4	1.6×10^4

a) Results for TNB from refs. 8 and 9, for TNP from ref. 10 and for ETP from previous chapter,(chapter 3).

b) All data at ionic strength 0.01 mol dm^{-3}, except for 4.6, NRR' = NHBu, with butylamine where the ionic strength is 0.1 mol dm^{-3}.

c) Results are for the reaction of 4.6 (NRR' = NHBu) with butylamine.

d) Results are for the reaction of 4.6 ($NRR' = NC_4H_8$) with pyrrolidine.

e) Results are for the reaction of 4.6 ($NRR' = NC_5H_{10}$) with piperidine.

1. S. Sekiguchi, T. Horie and T. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1988, 698.
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11. C. M. Gramaccioli, R. Destro and M. Simmonetta, *Acta. Cryst., Ser. B*, 1968, **24**, 129.
12. E. Buncel, M. R. Crampton, M. J. Strauss and F. Terrier, *'Electron-Deficient Aromatic- and Heteroaromatic-base Interactions'*, Elsevier, Amsterdam, 1984.
13. F. Terrier, *'Nucleophilic Aromatic Displacement'*, VCH, New York, 1991.

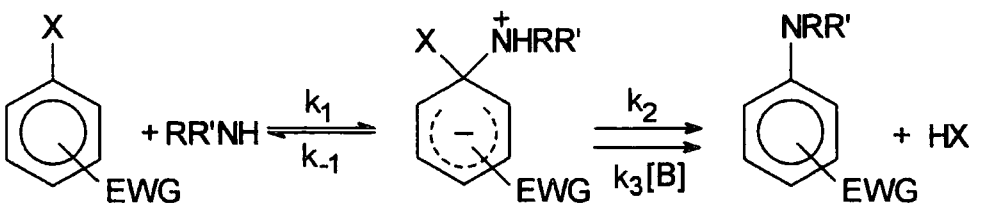
CHAPTER 5

The Reactions Of Some Phenyl Aryl Sulfides With Aliphatic Amines

The Reactions of some Phenyl Aryl Sulfides with Aliphatic Amines.

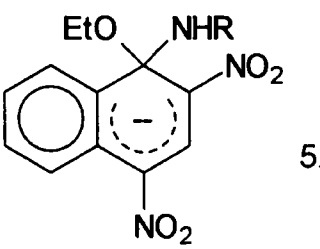
5.1 Introduction

Aromatic substitution reactions involving amines nucleophiles have provided much of the evidence for the S_NAr mechanism[1-4] , as shown in scheme 5.1.



scheme 5.1

The mechanism of base catalysis may occur by two different pathways.[5-10] One possibility is that proton transfer from the zwitterionic intermediate to base is rate limiting. Alternatively, the proton transfer from the zwitterion may be rapid to give an anionic adduct which loses its leaving group in a general acid catalysed step. The latter pathway, known as the SB-GA mechanism gained general acceptance for reactions in DMSO following a study by Orvik and Bunnett.[11] During the reaction of 1-ethoxy 2,4-dinitronaphthalene with aliphatic amines they observed both the formation and acid-catalysed decomposition of intermediates such as 5.1. Since then, many related intermediates have been observed, suggesting the SB-GA mechanism applies.[7,12-13]



5.1

However, recent work carried out on the amine-amine exchange reaction of butylamine with 1-pyrrolidino 2,4-dinitronaphthalene[14] suggested that the observed base catalysis was due to rate limiting proton transfer from the zwitterionic intermediate.

Kinetic and equilibrium studies were carried out on the reaction of several phenyl aryl sulfides, 5.2, with n-butylamine, pyrrolidine and piperidine in DMSO. Results were compared with those obtained using ethyl 2,4,6-trinitrophenyl sulfide, (see chapter 3), to compare the effect of changing the leaving group. Studies were also carried out on the reaction of the phenylthio derivatives of 2,4-dinitronaphthalene, 2,4-dinitrobenzene and 2,6-dinitro-4-trifluoromethylbenzene.

5.2 Experimental

Phenyl 2,4,6-trinitrophenyl sulfide, 5.2: Prepared by reacting thiophenol with a solution of picryl chloride in ethanol. Sodium acetate was added with stirring, producing yellow crystals of the required product.

4'-substituted phenyl 2,4,6-trinitrophenyl sulfides: Prepared as above, using the appropriate 4'-substituted thiophenol.

Phenyl 2,4-dinitronaphthyl sulfide, phenyl 2,6-dinitro-4-trifluoromethylphenyl sulfide and phenyl 2,4-dinitrophenyl sulfide: Prepared as above using the appropriate chloro compound and thiophenol.

Recrystallisation of the above from ethanol yielded products whose melting points were in good agreement with literature data, (with the exception of the 4'-nitro-phenyl 2,4,6-trinitrophenyl sulfide), see table 5.1.[15-18]

1-amino-2,4,6-trinitrobenzene compounds: See chapter 3 for details of their preparation.

1-pyrrolidino-2,4-dinitrobenzene: Available from previous work.[19]

1-piperidino- and 1-pyrrolidino-2,6-dinitro-4-trifluoromethylbenzenes: Prepared by adding an excess of amine to a warmed solution of the chloro compound in methanol.

^1H NMR data were recorded of the parent compounds in [$^2H_6$] DMSO using a Varian 200XL instrument. Data are in table 5.1. (see figures 5.1 to 5.4 for the ^1H NMR's of the 4'-substituted phenyl 2,4,6-trinitrophenyl sulfides).
^1H NMR spectra were also recorded of the reactions occurring between the parent compounds and amines. Figure 5.5 shows the reaction of 4'-methyl phenyl 2,4,6-trinitrophenyl sulfide with piperidine; figure 5.6 the reaction of 4'-nitro phenyl 2,4,6-trinitrophenyl sulfide with butylamine.

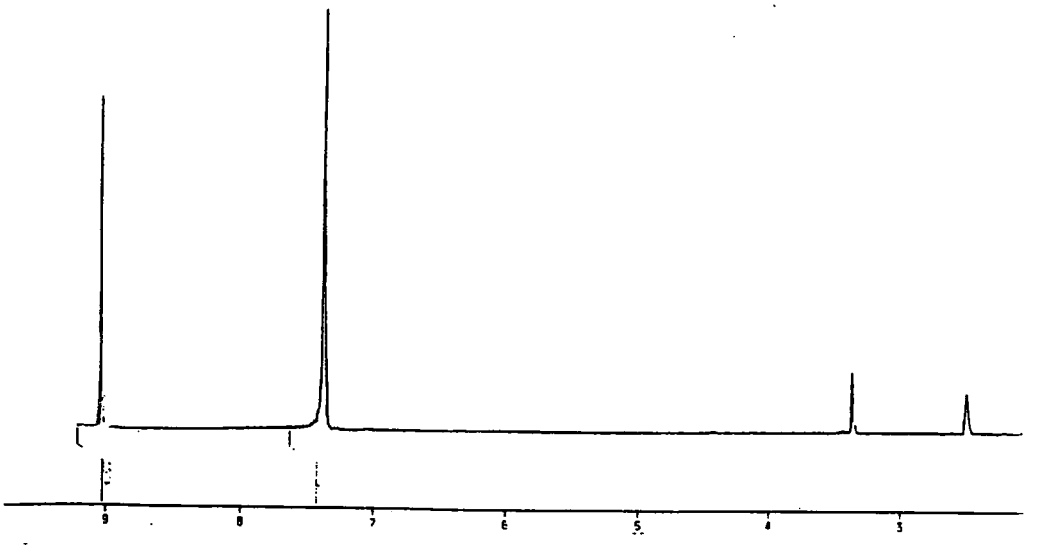


Figure 5.1. The ^{1}H NMR of 4'-methyl phenyl 2,4,6-trinitrophenyl sulfide in DMSO.

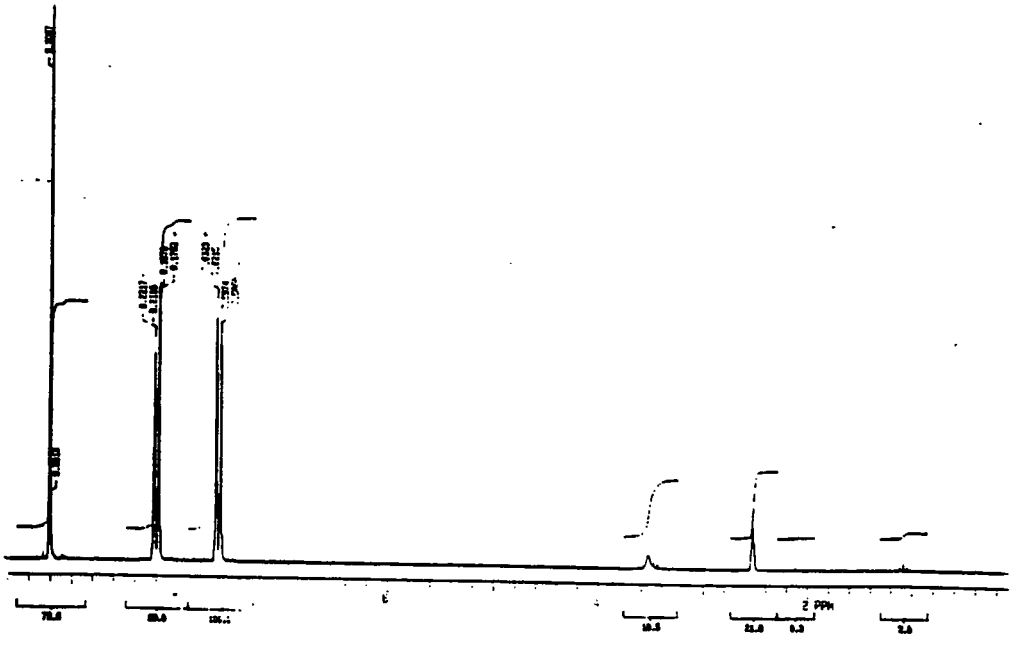


Figure 5.2. The ^{1}H NMR of 4'-nitro phenyl 2,4,6-trinitrophenyl sulfide in DMSO

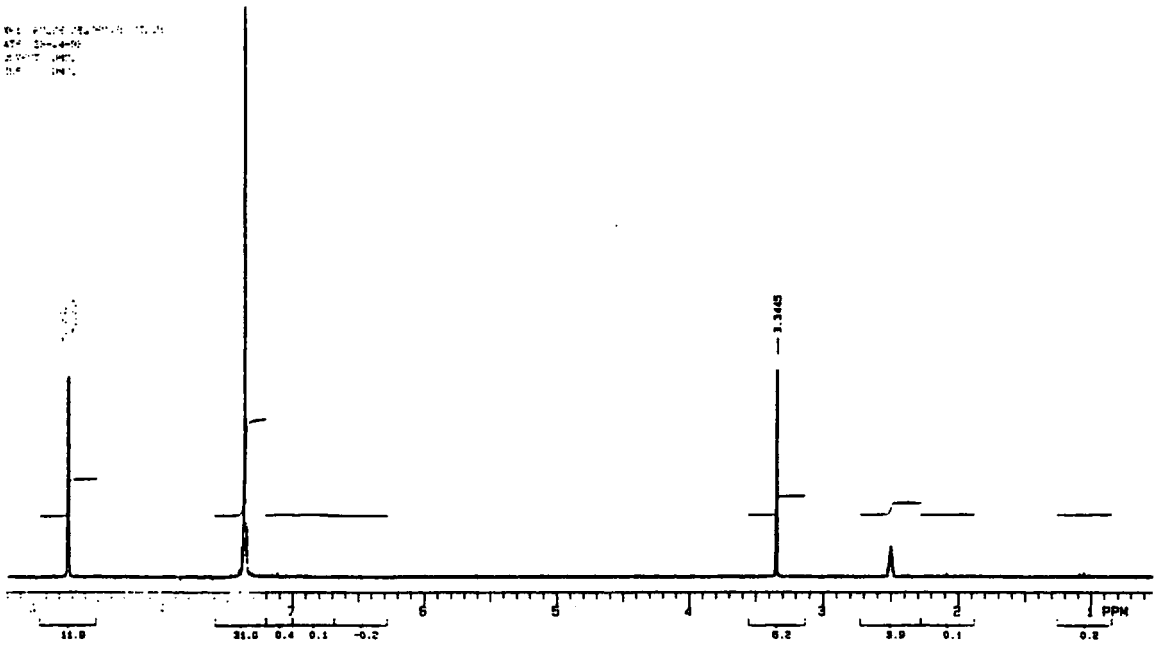


Figure 5.3. The ^{1}H NMR of phenyl 2,6-dinitro-4-trifluoromethylphenyl sulfide, 5.9, in DMSO.

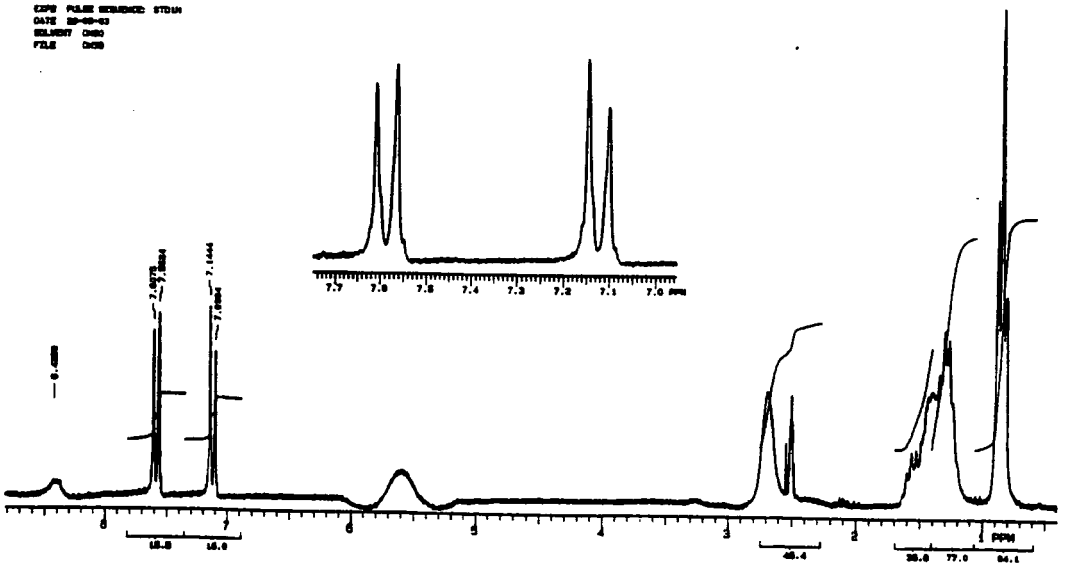


Figure 5.4. ^{1}H NMR spectra of the reaction occurring between 4'-nitro 2,4,6-trinitrophenyl sulfide and butylamine.

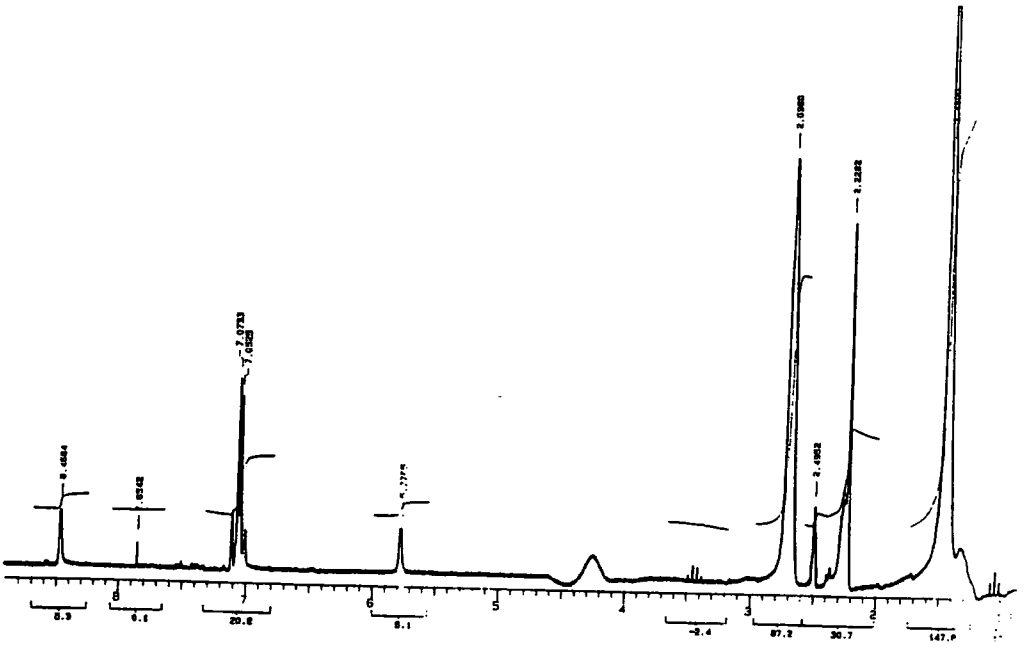


Figure 5.5. ^{1}H NMR spectra of the initial reaction occurring between 4'-methyl 2,4,6-trinitrophenyl sulfide and piperidine.

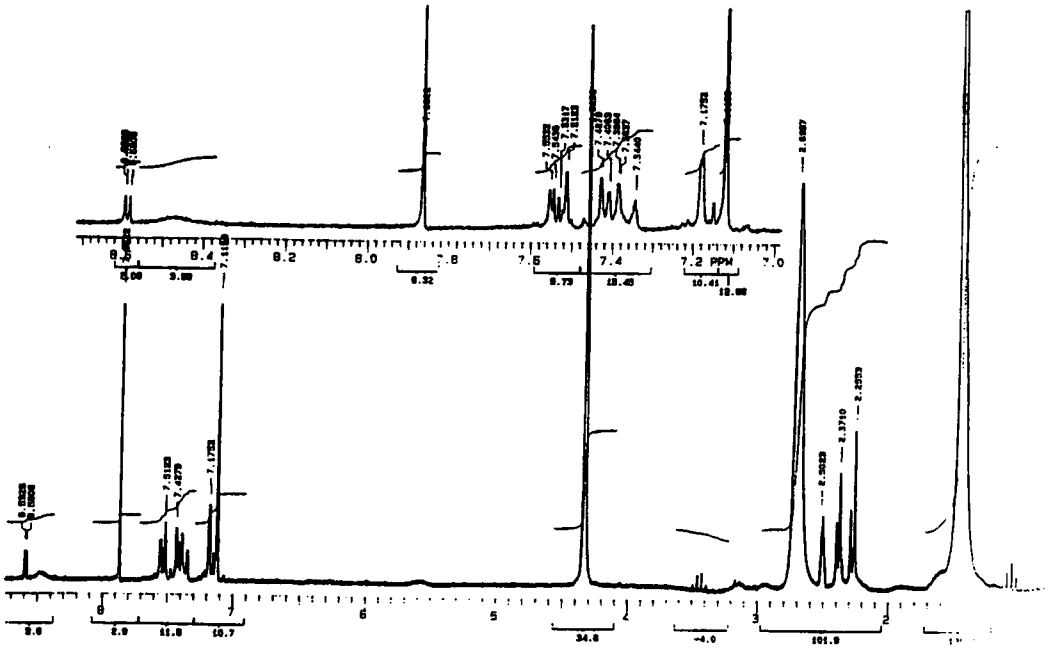
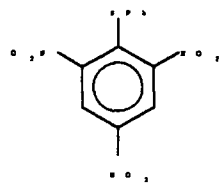
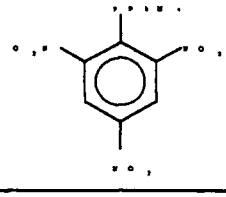
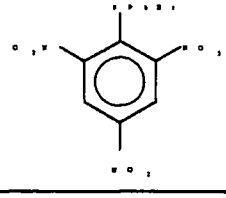
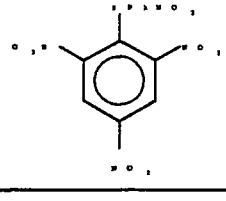
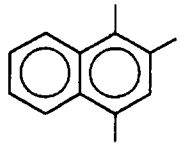
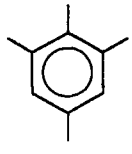
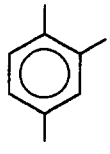
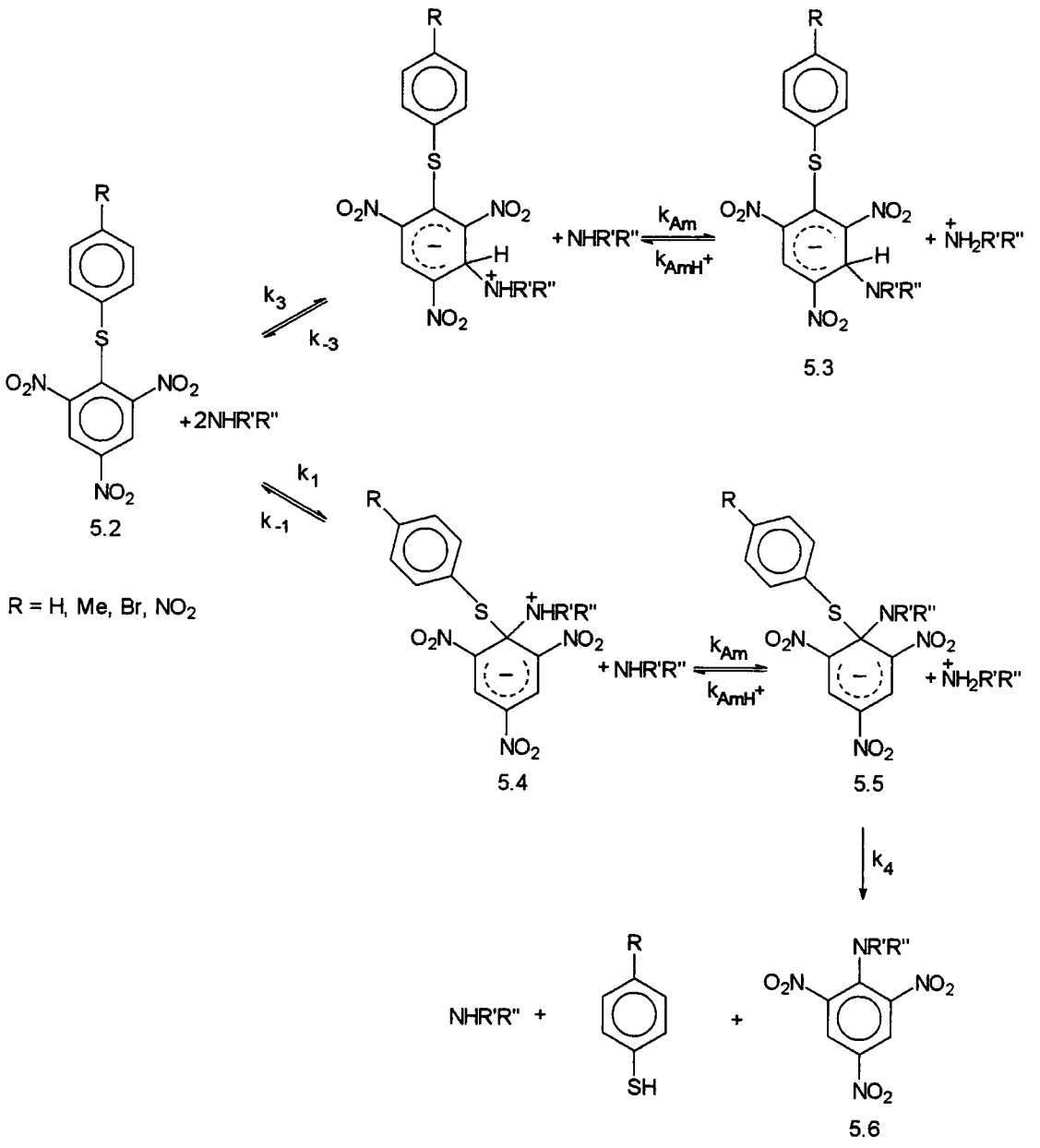


Figure 5.6. ^{1}H NMR spectra of the slower reaction occurring between 4'-methyl 2,4,6-trinitrophenyl sulfide and piperidine.

Table 5.1 Spectroscopic data for the parent phenyl sulfides in [$^2H_6$] DMSO.

Structure	^{1}H NMR (δ values)		λ_{max}/ nm (in DMSO).	M. Pt./ °C (Lit. M. Pt)
	Nitro ring	4' substituted ring		
	9.04	7.39	373	116-118 (120)
	9.01	7.29, 7.20	380	149-151 (154)
	9.06	7.57, 7.37	374	142-144 (152)
	9.21	8.20, 7.62	315	152-154 (257)
	8.93, 8.61(d), 8.40(d), 7.93(t), 7.25(t)	-	343	115-117 (117-118)
	8.71	7.34	350	100-102
			342	114-116 (119.5-120.5)

a) PhMe=C_6H_4Me, PhBr=C_6H_4, $PhNO_2$=$C_6H_4NO_2$


R
S
O_2N
NO_2
+2NHR'R"
k_3
k_{-3}
k_1
k_{-1}
5.2
R = H, Me, Br, NO_2
+NHR'R"
k_{Am}
k_{AmH^+}
H
$\overset{+}{N}HR'R"$
$\overset{+}{N}H_2R'R"$
NR'R"
5.3
5.4
5.5
k_4
NHR'R" +
SH
+
5.6

scheme 5.2

5.3 Results

5.3.1 4'-Phenyl 2,4,6-trinitrophenyl sulfides, (5.2).

UV/Visible measurements of the reaction of the substrates, 5.2, with amines in DMSO showed the presence of two processes well separated in time which are interpreted as scheme 5.2, (Figure 5.7 shows the UV/Visible spectra of the reaction between phenyl 2,4,6-trinitrophenyl sulfide and butylamine). A rapid equilibrium was observed forming the 3-adducts, 5.3, with λ_{max} = 455-465 nm and 520-530nm (shoulder). A second slower reaction led to the formation of N-substituted picramide derivatives, 5.6. The final spectra were seen to be identical to those of the N-picramide derivatives in the presence of amine. As seen in chapter 4, the reaction products are in rapid equilibrium with 3-adducts formed by further amine attack. In the case of the derivative from butylamine, the loss of a side chain proton can also occur. No build up of species 5.5 was observed during any of the reactions. With piperidine, the substitution reaction was found to be inconveniently slow for kinetic measurements.

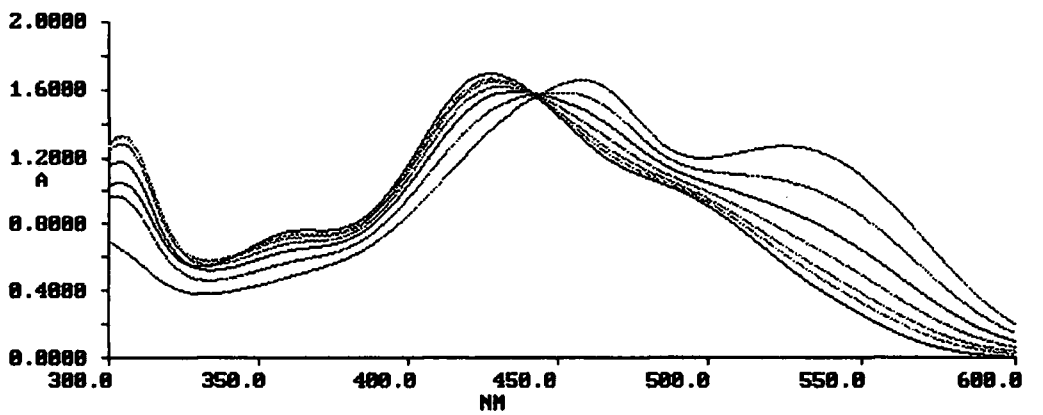


Figure 5.7. UV/ Visible spectra of the reaction between phenyl 2,4,6-trinitrophenyl sulfide and butylamine, showing the rapid process giving the 3-adduct, λ_{max} = 460nm (shoulder 525nm); followed by the substitution reaction to give the N-butylamino-2,4,6-trinitrobenzene, λ_{max} = 428nm (shoulder 500nm).

Kinetic analysis:

Rate constants were all measured under first order conditions. For reactions involving buffers (amine plus amine salt) the buffer components were in large excess of the substrate concentration (1-5 x 10^{-5} mol dm^{-3}). For reactions in the absence of added salt, a sufficient excess of amine was used to ensure >95% conversion.
Zwitterions formed are treated as steady state intermediates, thus the general rate expression for attack at the 3-position can be stated as in equation 5.1.

$$k_{fast} = \frac{k_3 k_{Am}[Am]^2 + k_{-3} k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 5.1}$$

The equilibrium constant for attack at the 3-position to give adduct 5.3 is defined as in equation 5.2 which can be related to absorbance values as in equation 5.3 and to separate rate constants by equation 5.4.

$$K_{C,3} = \frac{[5.3]}{[5.2]} x \frac{[AmH^+]}{[Am]^2} \qquad \text{eqn 5.2}$$

$$K_{C,3} = \frac{Abs}{Abs_\infty - Abs} x \frac{[AmH^+]}{[Am]^2} \qquad \text{eqn 5.3}$$

$$K_{C,3} = \frac{k_3}{k_{-3}} x \frac{k_{Am}}{k_{AmH^+}} \qquad \text{eqn 5.4}$$

The slower reaction giving the substituted products, 5.6, can be expressed by equation 5.5, allowing for the rapid equilibrium giving the 3-adduct and also assuming the k_4 step, i.e. leaving group departure, is not rate limiting.

$$k_{slow} = \frac{k_1 k_{Am}[Am]^2}{(k_{-1} + k_{Am}[Am])\left(1 + K_{C,3}\frac{[Am]^2}{[AmH^+]}\right)} \qquad \text{eqn 5.5}$$

It is more convenient to define a modified rate constant k'_{slow} (as in equation 5.6) which allows equation 5.5 to be reduced to equation 5.7.

$$k'_{slow} = k_{slow}\left(1 + K_{C,3}\frac{[Am]^2}{[AmH^+]}\right) \qquad \text{eqn 5.6}$$

$$k'_{slow} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 5.7}$$

An alternative pathway would involve the direct conversion of the zwitterion, 5.4, into 5.6. The results obtained however, indicate that this process does not contribute greatly to the overall process.

5.3.2 Phenyl 2,4,6-trinitrophenyl sulfide

Reaction with butylamine

Kinetic and equilibrium results for attack at the 3-position are recorded in table 5.2; data were measured at 540nm.

In the absence of added salt, values of k_{fast} can be seen to increase linearly with amine concentration. This indicates $k_{Am}[Am] >> k_{-3}$ and so equation 5.1 can be reduced to equation 5.8.

$$k_{fast} = k_3[Am] + \left(\frac{k_{-3} k_{AmH^+}}{k_{Am}} x \frac{[AmH^+]}{[Am]} \right) \qquad \text{eqn 5.8}$$

In the absence of added salt, when the reverse reaction becomes negligible, a value for k_3 of 1500 $dm^3\ mol^{-1}s^{-1}$ can be obtained. The data in the presence of added salt yield a value of 45 s^{-1} for $k_{-3}k_{AmH^+}/\ k_{Am}$. Combination of these values in equation 5.4 leads to a value for $K_{C,3}$ of 33 $dm^3\ mol^{-1}$, which is in reasonable agreement with those, 27 $dm^3\ mol^{-1}$, obtained from absorbance values. Values calculated using k_3 1500 $dm^3\ mol^{-1}s^{-1}$ and $k_{-3}k_{AmH^+}/\ k_{Am}$ 45 s^{-1} in equation 5.8 are in good agreeement with those obtained experimentally.

Data for attack at the 1-position are in table 5.3. Values for k'_{slow}, calculated using equation 5.6, are linear in amine concentration. This indicates $k_{Am}[Am] >> k_{-1}$ and hence equation 5.7 can be reduced to equation 5.9.

$$k'_{slow} = k_1[Am] \qquad \text{eqn 5.9}$$

Hence a value for k_1 of 33 dm^3 mol^{-1} is obtained. Values calculated using k_1 33 dm^3 mol^{-1} and $K_{C,3}$ 33 dm^3 mol^{-1} in equations 5.9 and 5.6 are in very good agreement with experimental values.

These results indicate that during the formation of the 3-adduct, 5.3, the initial amine attack is rate determining. Also, in the substitution process, amine attack is rate determining and is followed by rapid proton transfer and loss of the phenyl thio group.

Table 5.2 Kinetic and equilibrium data for the rapid reaction of phenyl 2,4,6-trinitrophenyl sulfide with butylamine to give the 3-adduct, 5.3, in DMSO at 25°C.

[Butylamine] / mol dm^{-3}	[Butylammonium perchlorate] /mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]	Abs	$K_{c,3}$[b]/ dm^3mol^{-1}
0.01	-	14.5	15	-	-
0.02	-	31	30	-	-
0.03	-	46	45	-	-
0.04	-	61	60	-	-
0.05	-	72	75	0.07	-
0.008	0.01	-	-	0.013	35
0.01	0.01	57	60	0.011	19
0.02	0.01	54	53	0.041	35
0.03	0.01	60	60	0.046	21
0.04	0.01	71	71	0.051	17
0.05	0.01	84	84	0.061	27

a) Calculated using equation 5.8 with k_3 1500 dm^3 $mol^{-1}s^{-1}$ and $k_{-3}k_{AmH^+}/k_{Am}$ 45 s^{-1}.

b) Calculated with $Abs_\infty = 0.07$ using equation 5.3.

Table 5.3 Kinetic data for the slower reaction of phenyl 2,4,6-trinitrophenyl sulfide with butylamine to give the substitution product, 5.6, in DMSO at 25°C.

[Butylamine] / mol dm^{-3}	[Butylammonium perchlorate] / mol dm^{-3}	k_{slow}/ s^{-1}	k'_{slow}[a]/ s^{-1}	k_{calc}[b]
0.008	0.01	0.22	0.27	0.22
0.01	0.01	0.26	0.35	0.25
0.02	0.01	0.25	0.58	0.28
0.03	0.01	0.25	0.99	0.25
0.04	0.01	0.21	1.32	0.21
0.05	0.01	0.18	1.67	0.18

a) Calculated using equation 5.6 with $K_{c,3} = 33$ dm^3 mol^{-1}.

b) Calculated using $k_1 = 33$ dm^3 mol^{-1} and $K_{c,3} = 33$ dm^3 mol^{-1} in the expression .

$$\frac{k_1[Am]}{\left(1+K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)}.$$

Reaction with pyrrolidine

Data, measured at 540 nm, for attack at the 3-position of 5.2 to give the 3-adduct, 5.3, are in table 5.4.

In the absence of added salt, values of k_{fast} obtained, show the amine dependence is between one and two, indicating that proton transfer is partially rate limiting. In the absence of salt the term for the forward reaction in equation 5.1 will dominate and rearrangement gives equation 5.10.

$$\frac{[Am]}{k_{obs}} = \left(\frac{k_{-3}}{k_3 k_{Am}} x \frac{1}{[Am]}\right) + \frac{1}{k_3} \qquad \text{eqn 5.10}$$

Hence, a plot of [Am]/ k_{obs} against 1/ [Am] allows the determination of values of k_3 1.25 x 10^4 dm^3 $mol^{-1}s^{-1}$ and k_3k_{Am}/ k_{-3} 2.8 x 10^5. Data obtained in the presence of salt lead to a value for k_{AmH^+} 2.6 x 10^3 dm^3 $mol^{-1}s^{-1}$. Using these values in equation 5.1 gives a good fit with experimental data.

Substitution of these values in equation 5.4 leads to a value for the equilibrium constant $K_{C,3}$ of 108 dm^3 mol^{-1}. This value agrees well with that, 104 dm^3 mol^{-1}, obtained from absorbance data.

Data for the slower reaction, leading to the substitution product, 5.6, measured at 540 nm, are in table 5.5. Values of k'_{slow}, calculated from equation 5.6 with $K_{C,3} = 108$ dm^3 mol^{-1}, show a squared dependence on amine concentration. This indicates $k_{-1} >> k_{Am}[Am]$, reducing equation 5.7 to equation 5.11, and hence giving a value for K_1k_{Am} of 250 dm^6 mol^{-2}s^{-1}.

$$k'_{slow} = \frac{k_1 k_{Am}}{k_{-1}}[Am]^2 \qquad \text{eqn 5.11}$$

These results indicate that proton transfer from the zwitterion, 5.4, to amine is the rate determining step in the substitution reaction.

Table 5.4 Kinetic and equilibrium data for the reaction between phenyl 2,4,6-trinitrophenyl sulfide and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ mol dm^{-3}	[pyrrolidinium perchlorate]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	Abs	$K_{c,3}$[b]/ dm^3 mol^{-1}
0.006	-	8.8	8.9	-	-
0.008	-	15	15	-	-
0.010	-	22.5	23	-	-
0.015	-	48	47	-	-
0.020	-	76	77	-	-
0.030	-	152	151	-	-
0.006	0.01	32	32	0.021	133
0.008	0.01	36	37	0.026	104
0.010	0.01	44	44	0.029	81
0.015	0.01	67	67	0.044	93
0.020	0.01	96	95	0.053	110

a) Calculated using equation 5.1 with the values k_3 1.25 x 10^4 dm^3 mol^{-1}s^{-1}, k_{Am}/k_{-3} 22.6 dm^3 mol^{-1}, k_{AmH^+} 2.6 x 10^3 dm^3 mol^{-1}s^{-1}.

b) Calculated using equation 5.3 with $Abs_\infty = 0.065$.

Table 5.5 Kinetic data for the substitution reaction between phenyl 2,4,6-trinitrophenyl sulfide and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ $dm^3\ mol^{-1}$	[pyrrolidinium perchlorate]/ $dm^3\ mol^{-1}$	k_{slow}/ $10^{-2}\ s^{-1}$	k_{calc}/ $10^{-2}\ s^{-1}$	k'_{slow}[a]/ $10^{-2}\ s^{-1}$	$k'_{slow}/[Am]^2$/ $dm^6\ mol^{-2}s^{-1}$
0.008	0.01	0.94	0.95	1.59	250
0.01	0.01	1.25	1.21	2.60	250
0.03	0.01	2.15	2.10	23.0	260
0.04	0.01	2.12	2.19	38	240
0.05	0.01	2.08	2.23	59	240

a) calculated from equation 5.6 with $K_{c,3} = 108\ dm^3\ mol^{-1}$.

Reaction with piperidine

Kinetic and equilibrium results for the reaction producing the 3-adduct, 5.3, measured at 540 nm are in table 5.6.

Values of k_{fast} obtained in the absence of added salt show a squared dependence on the piperidine concentration, indicating $k_{-3} >> k_{Am}[Am]$. Hence. proton transfer must be the rate limiting step in the formation of the 3-adduct, 5.3 NRR' = NC_5H_{10}, and we can reduce equation 5.1 to equation 5.12.

$$k_{fast} = \frac{k_3 k_{Am}}{k_{-3}}[Am]^2 + k_{AmH^+}[AmH^+] \qquad \text{eqn 5.12}$$

In the absence of added salt, using equation 5.12, a value of $1.9 \times 10^4\ dm^6\ mol^{-2}s^{-1}$ is obtained for $k_3k_{Am}/\ k_{-3}$. Data with added salt yield a value of k_{AmH^+} 450 $dm^3\ mol^{-1}s^{-1}$. Combination of these values in equation 5.4 gives $K_{c,3}$ a value of 48 $dm^3\ mol^{-1}$, which is in acceptable agreement with that obtained from absorbance data, 49 $dm^3\ mol^{-1}$.

Values of $k_3k_{Am}/\ k_{-3}$ $1.9 \times 10^4\ dm^6\ mol^{-2}s^{-1}$ and k_{AmH^+} 450 $dm^3\ mol^{-1}s^{-1}$ in equation 5.12 give good agreement with experimentally determined results.

Table 5.6 Kinetic and equilibrium data form the reaction of phenyl 2,4,6-trinitrophenyl sulfide and piperidine in DMSO at 25°C.

[piperidine]/ mol dm^{-3}	[piperidinium chloride]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]	Abs	$K_{c,3}$/ dm^3 mol^{-1}
0.01	-	2.1	1.9	-	-
0.02	-	7.4	7.6	-	-
0.025	-	11	12	-	-
0.03	-	16	17	-	-
0.04	-	28	30	-	-
0.05	-	50	48	0.053	-
0.008	0.01	6.3	5.7	0.014	56
0.01	0.01	6.6	6.4	0.017	47
0.02	0.01	12	12	-	-
0.03	0.01	22	22	0.044	54
0.04	0.01	35	35	0.047	49
0.05	0.01	53	52	0.048	39

a) Calculated using equation 5.12 and the values k_3k_{Am}/ k_{-3} 1.9 x 10^4 dm^6 mol^{-2} s^{-1} and k_{AmH^+} 450 dm^3 $mol^{-1}s^{-1}$.

b) Calculated using equation 5.3 with $Abs_\infty = 0.053$.

5.3.3 4'-Substituted phenyl 2,4,6-trinitrophenyl sulfides

These compounds were found to behave similarly to the unsubstituted phenyl sulfide, 5.2, (R = H). Hence, calculations for these compounds were carried out as described for the phenyl 2,4,6-trinitrophenyl sulfide, giving values summarised in tables 5.22 to 5.24. Data for these compounds are contained in tables 5.7 to 5.21.

Table 5.7 Kinetic and equilibrium data for the rapid reaction of 4'-methyl phenyl 2,4,6-trinitrophenyl sulfide with butylamine in DMSO at 25°C.

[Butylamine]/ mol dm^{-3}	[Butylammonium perchlorate]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]	Abs	$K_{c,3}$[b]/ dm^3 mol^{-1}
0.01	-	15	14	-	-
0.02	-	26	27	-	-
0.03	-	40	41	-	-
0.04	-	52	54	-	-
0.05	-	70	68	0.043	-
0.01	0.01	-	-	0.007	19
0.02	0.01	69	71	0.018	18
0.03	0.01	71	70	0.029	23
0.04	0.01	73	76	0.033	21
0.05	0.01	88	85	0.034	15

a) Calculated using equation 5.8 with k_3 1350 dm^3 $mol^{-1}s^{-1}$ and $k_{-3}k_{AmH^+}/ k_{Am}$ 88 s^{-1}.
b) Calculated with Abs_∞ = 0.043 using equation 5.3.

Table 5.8 Kinetic data for the slower reaction of 4'-methyl phenyl 2,4,6-trinitro phenyl sulfide with butylamine to give the substitution product, 5.6, in DMSO at 25°C.

[Butylamine] / mol dm^{-3}	[Butylammonium perchlorate] / mol dm^{-3}	k_{slow}/ s^{-1}	k'_{slow}[a]/ s^{-1}	k_{calc}[b]
0.01	0.01	0.25	0.29	0.24
0.03	0.01	0.30	0.76	0.33
0.04	0.01	0.30	1.12	0.30
0.05	0.01	0.27	1.42	0.27

a) Calculated using equation 5.6 with $K_{c,3}$ = 17 dm^3 mol^{-1}.

b) Calculated using k_1 = 28 dm^3 mol^{-1} and $K_{c,3}$ = 17 dm^3 mol^{-1} in the expression

$$\frac{k_1[Am]}{\left(1+K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)}.$$

Table 5.9 Kinetic and equilibrium data for the rapid reaction between 4'-methyl phenyl 2,4,6-trinitrophenyl sulfide and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ mol dm^{-3}	[pyrrolidinium perchlorate]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	Abs	$K_{c,3}$[b]/ dm^3 mol^{-1}
0.008	-	13.9	14.4	-	-
0.010	-	21.5	21.6	-	-
0.015	-	43	44	-	-
0.020	-	72	72	-	-
0.03	-	134	139	-	-
0.050	-	-	-	0.085	-
0.006	0.01	39	39	0.017	69
0.008	0.01	43	44	0.026	69
0.010	0.01	50	50	0.034	67
0.015	0.01	69	69	0.048	58
0.020	0.01	96	95	-	-

a) Calculated using equation 5.1 with the values k_3 1.08 x 10^4 dm^3 $mol^{-1}s^{-1}$, k_{Am}/k_{-3} 25 dm^3 mol^{-1}, k_{AmH^+} 3.5 x 10^3 dm^3 $mol^{-1}s^{-1}$.

b) Calculated using equation 5.3 with Abs_∞ = 0.085.

Table 5.10 Kinetic data for the substitution reaction between 4'-methyl phenyl 2,4,6-trinitrophenyl sulfide and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ $dm^3\ mol^{-1}$	[pyrrolidinium perchlorate]/ $dm^3\ mol^{-1}$	k_{slow}/ $10^{-2}\ s^{-1}$	k_{calc}/ $10^{-2}\ s^{-1}$	k'_{slow}[a]/ $10^{-2}\ s^{-1}$	$k'_{slow}/[Am]^2$/ $dm^6\ mol^{-2}s^{-1}$
0.01	0.01	1.3	1.1	2.3	230
0.02	0.01	2.05	1.9	8.2	210
0.03	0.01	1.99	2.1	15.4	170
0.04	0.01	2.01	2.2	26	165
0.05	0.01	1.85	2.3	37	150

a) calculated from equation 5.6 with $K_{c,3} = 75\ dm^3\ mol^{-1}$.

Table 5.11 Kinetic and equilibrium data form the reaction of 4'-methyl phenyl 2,4,6-trinitrophenyl sulfide and piperidine in DMSO at 25°C, measured at 540nm.

[piperidine]/ $mol\ dm^{-3}$	[piperidinium chloride]/ $mol\ dm^{-3}$	k_{fast}/s^{-1}	k_{calc}[a]	Abs	$K_{c,3}$/ $dm^3\ mol^{-1}$
0.01	-	1.6	1.5	-	-
0.02	-	6.0	5.8	-	-
0.03	-	13	13	-	-
0.04	-	23	23	-	-
0.05	-	37	37	0.073	-
0.008	0.01	4.3	4.3	0.016	44
0.01	0.01	4.9	4.9	0.022	43
0.02	0.01	9.2	9.2	0.044	38
0.03	0.01	17	17	0.058	43
0.04	0.01	26	27	0.061	32
0.05	0.01	37	40	0.066	38

a) Calculated using equation 5.12 and the values $k_3k_{Am}/\ k_{-3}$ $1.46 \times 10^4\ dm^6\ mol^{-2}\ s^{-1}$ and k_{AmH^+} $340\ dm^3\ mol^{-1}s^{-1}$.

b) Calculated using equation 5.3 with $Abs_\infty = 0.073$.

Table 5.12 Kinetic and equilibrium data for the rapid reaction of 4'-bromo phenyl 2,4,6-trinitrophenyl sulfide with butylamine in DMSO at 25°C.

[Butylamine] / mol dm^{-3}	[Butylammonium perchlorate]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]	Abs	$K_{c,3}$[b]/ dm^3 mol^{-1}
0.01	-	20	20	-	-
0.02	-	40	40	-	-
0.03	-	59	60	-	-
0.04	-	78	80	-	-
0.05	-	108	100	0.133	-
0.01	0.01	56	55	0.051	62
0.02	0.01	60	58	0.097	67
0.03	0.01	71	72	0.111	56
0.04	0.01	91	89	0.117	46
0.05	0.01	110	107	0.122	44

a) Calculated using equation 5.8 with k_3 2000 dm^3 $mol^{-1}s^{-1}$ and $k_{-3}k_{AmH^+}/k_{Am}$ 35 s^{-1}.

b) Calculated with $Abs_\infty = 0.133$ using equation 5.3.

Table 5.13 Kinetic data for the slower reaction of 4'-bromo phenyl 2,4,6-trinitro phenyl sulfide with butylamine to give the substitution product, 5.6, in DMSO at 25°C.

[Butylamine] / mol dm^{-3}	[Butylammonium perchlorate] / mol dm^{-3}	k_{slow}/ s^{-1}	k'_{slow}[a]/ s^{-1}	k_{calc}[b]
0.02	0.01	0.22	0.72	0.22
0.03	0.01	0.18	1.10	0.18
0.04	0.01	0.14	1.42	0.14
0.05	0.01	0.12	1.83	0.12

a) Calculated using equation 5.6 with $K_{c,3} = 57$ dm^3 mol^{-1}.

b) Calculated using $k_1 = 36$ dm^3 mol^{-1} and $K_{c,3} = 57$ dm^3 mol^{-1} in the expression $\frac{k_1[Am]}{\left(1+K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)}$.

Table 5.14 Kinetic and equilibrium data for the rapid reaction between 4'-bromo phenyl 2,4,6-trinitrophenyl sulfide and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ mol dm^{-3}	[pyrrolidinium perchlorate]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	Abs	$K_{c,3}$[b]/ dm^3 mol^{-1}
0.006	-	14.2	14.7	-	-
0.008	-	26	25	-	-
0.010	-	38	38	-	-
0.015	-	78	77	-	-
0.020	-	130	125	-	-
0.030	-	-	-	0.132	-
0.006	0.01	39	40	0.060	230
0.008	0.01	48	49	0.075	200
0.010	0.01	60	61	0.085	180
0.015	0.01	103	98	0.111	230
0.020	0.01	-	-	0.116	180

a) Calculated using equation 5.1 with the values k_3 1.9 x 10^4 dm^3 $mol^{-1}s^{-1}$, k_{Am}/ k_{-3} 25 dm^3 mol^{-1}, k_{AmH^+} 2.9 x 10^3 dm^3 $mol^{-1}s^{-1}$.

b) Calculated using equation 5.3 with $Abs_\infty = 0.132$.

Table 5.15 Kinetic data for the substitution reaction between 4'-bromo phenyl 2,4,6-trinitrophenyl sulfide and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ dm^3 mol^{-1}	[pyrrolidinium perchlorate]/ dm^3 mol^{-1}	k_{slow}/ 10^{-2} s^{-1}	k_{calc}/ 10^{-2} s^{-1}	k'_{slow}[a]/ 10^{-2} s^{-1}	$k'_{slow}/[Am]^2$/ dm^6 $mol^{-2}s^{-1}$
0.01	0.01	1.33	1.5	3.5	350
0.02	0.01	2.2	2.2	16	400
0.03	0.01	2.5	2.35	38	430
0.04	0.01	2.4	2.4	64	400
0.05	0.01	2.4	2.4	99	400

a) calculated from equation 5.6 with $K_{c,3}$ = 160 dm^3 mol^{-1}.

Table 5.16 Kinetic and equilibrium data form the reaction of 4'-bromo-phenyl 2,4,6-trinitrophenyl sulfide and piperidine in DMSO at 25°C, measured at 540nm.

[piperidine]/ mol dm^{-3}	[piperidinium chloride]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]	Abs	$K_{c,3}$/ dm^3 mol^{-1}
0.01	-	2.9	2.6	-	-
0.02	-	10.6	10.4	-	-
0.03	-	23	23	-	-
0.04	-	41	42	-	-
0.05	-	60	65	0.075	-
0.004	0.01	2.5	2.7	0.014	140
0.006	0.01	3.3	3.2	0.023	120
0.008	0.01	3.9	4.0	0.034	130
0.01	0.01	5.0	4.9	0.037	100
0.02	0.01	12.8	12.9	0.060	100
0.03	0.01	26	25	-	-
0.04	0.01	44	43	-	-
0.05	0.01	63	62	-	-

a) Calculated using equation 5.12 and the values k_3k_{Am}/ k_{-3} 2.6 x 10^4 dm^6 mol^{-2} s^{-1} and k_{AmH^+} 230 dm^3 $mol^{-1}s^{-1}$.

b) Calculated using equation 5.3 with $Abs_\infty = 0.075$.

Table 5.17 Kinetic and equilibrium data for the rapid reaction of 4'-nitro phenyl 2,4,6-trinitrophenyl sulfide with butylamine in DMSO at 25°C.

[Butylamine] / mol dm^{-3}	[Butylamminium perchlorate] / mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]	Abs	$K_{c,3}$[b]/ dm^3mol^{-1}
0.008	-	20	20	-	-
001	-	25	25	-	-
0.02	-	50	50	-	-
0.03	-	75	75	-	-
0.05	-	-	-	0.064	-
0.004	0.01	30	32	0.018	245
0.006	0.01	29	30	0.029	230
0.008	0.01	32	31	0.040	260
0.01	0.01	33	34	0.045	237

a) Calculated using equation 5.8 with k_3 2500 dm^3 $mol^{-1}s^{-1}$ and $k_{-3}k_{AmH^+}/ k_{Am}$ 9 s^{-1}.

b) Calculated with $Abs_\infty = 0.064$ using equation 5.3.

Table 5.18 Kinetic data for the slower reaction of 4'-nitro phenyl 2,4,6-trinitro phenyl sulfide with butylamine to give the substitution product, 5.6, in DMSO at 25°C.

$[BuNH_2]$/ mol dm^{-3}	$[BuNH_3^+ClO_4^-]$/ mol dm^{-3}	k_{slow}/ s^{-1}	k'_{slow}[a]/ s^{-1}	k_{calc}[b]
0.004	0.01	0.12	0.17	0.12
0.006	0.01	0.12	0.23	0.13
0.008	0.01	0.13	0.35	0.13
0.010	0.01	0.13	0.47	0.12

a) Calculated using equation 5.6 with $K_{c,3} = 260$ dm^3 mol^{-1}.

b) Calculated using $k_1 = 43$ dm^3 mol^{-1} and $K_{c,3} = 260$ dm^3 mol^{-1} in the expression

$$\frac{k_1[Am]}{\left(1+K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)}.$$

Table 5.19 Kinetic and equilibrium data for the rapid reaction between 4'-nitro phenyl 2,4,6-trinitrophenyl sulfide and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ mol dm^{-3}	[pyrrolidinium perchlorate]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	Abs	$K_{c,3}$[b]/ dm^3mol^{-1}
0.006	-	24	24	-	-
0.008	-	42	41	-	-
0.010	-	62	61	-	-
0.015	-	130	120	-	-
0.020	-	190	200	-	-
0.004	0.01	18	18	0.037	1101
0.006	0.01	31	31	0.047	1187
0.008	0.01	48	47	0.051	1138
0.010	0.01	66	67	0.056	-
0.015	0.01	135	128	0.058	-

a) Calculated using equation 5.1 with the values k_3 2.6 x 10^4 dm^3 $mol^{-1}s^{-1}$, k_{Am}/ k_{-3} 31 dm^3 mol^{-1}, k_{AmH^+} 750 dm^3 $mol^{-1}s^{-1}$.

b) Calculated using equation 5.3 with $Abs_\infty = 0.058$.

Table 5.20 Kinetic data for the substitution reaction between 4'-nitro phenyl 2,4,6-trinitrophenyl sulfide and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ dm^3 mol^{-1}	[pyrrolidinium perchlorate]/ dm^3 mol^{-1}	k_{slow}/ 10^{-3} s^{-1}	k_{calc}/ 10^{-3} s^{-1}	k'_{slow}[a]/ 10^{-2} s^{-1}	$k'_{slow}/[Am]^2$/ dm^6 $mol^{-2}s^{-1}$
0.01	0.01	1.9	1.6	2.3	230
0.02	0.01	1.6	1.7	7.2	180
0.03	0.01	1.7	1.75	17	190
0.04	0.01	1.5	1.75	26.6	170
0.05	0.01	1.5	1.75	41.4	170

a) calculated from equation 5.6 with $K_{c,3}$ = 1140 dm^3 mol^{-1}.

Table 5.21 Kinetic and equilibrium data form the reaction of 4'-nitro phenyl 2,4,6-trinitrophenyl sulfide and piperidine in DMSO at 25°C, measured at 540nm.

[piperidine]/ mol dm^{-3}	[piperidinium chloride]/ mol dm^{-3}	k_{fast}/ s^{-1}	k_{calc}[a]	Abs	$K_{c,3}$/ dm^3 mol^{-1}
0.008	-	3.2	3.0	-	-
0.010	-	4.7	4.6	-	-
0.020	-	20	18	-	-
0.030	-	48	42	-	-
0.040	-	75	74	-	-
0.050	-	115	115	-	-
0.004	0.01	1.6	1.6	-	-
0.005	0.01	2.2	2.1	0.038	630
0.006	0.01	2.6	2.6	0.042	580
0.008	0.01	3.8	3.9	0.048	540
0.010	0.01	5.6	5.5	0.051	460
0.05	0.01	-	-	0.062	-

a) Calculated using equation 5.12 and the values k_3k_{Am}/ k_{-3} 4.6 x 10^4 dm^6 mol^{-2} s^{-1} and k_{AmH^+} 90 dm^3 $mol^{-1}s^{-1}$.

b) Calculated using equation 5.3 with $Abs_\infty = 0.062$.

Summary tables of the kinetic and equilibrium data for the reactions of the 4'-substituted phenyl 2,4,6-trinitrophenyl sulfides with amines in DMSO at 25°C.

Table 5.22 Summary of kinetic and equilibrium data for the reactions of 4'-substituted phenyl 2,4,6-trinitrophenyl sulfides with butylamine in DMSO at 25°C.

	R = Me	R = Br	$R = NO_2$
k_3/ dm^3 $mol^{-1}s^{-1}$	1350	2000	2500
$k_{-3}k_{AmH^+}/ k_{Am}$/ s^{-1}	88	35	9
$K_{C,3}$/ dm^3 mol^{-1}	17	57	260
k_1/ dm^3 mol^{-1}	28	36	43

Table 5.23 Summary of kinetic and equilibrium data for the reactions of 4'-substituted phenyl 2,4,6-trinitrophenyl sulfides with pyrrolidine in DMSO at 25°C.

	R = Me	R = Br	$R = NO_2$
k_3/ $dm^3\ mol^{-1}s^{-1}$	1.08×10^4	1.9×10^4	2.6×10^4
$k_{Am}/\ k_{-3}/\ s^{-1}$	25	25	31
k_{AmH^+}/ $dm^3\ mol^{-1}s^{-1}$	3.5×10^3	2.9×10^3	750
$K_{C,3}$/ dm^3mol^{-1}	75	160	1140
K_1k_{Am}/ $dm^6mol^{-2}s^{-1}$	210	400	180

Table 5.24 Summary of kinetic and equilibrium data for the reactions of 4'-substituted phenyl 2,4,6-trinitrophenyl sulfides with piperidine in DMSO at 25°C.

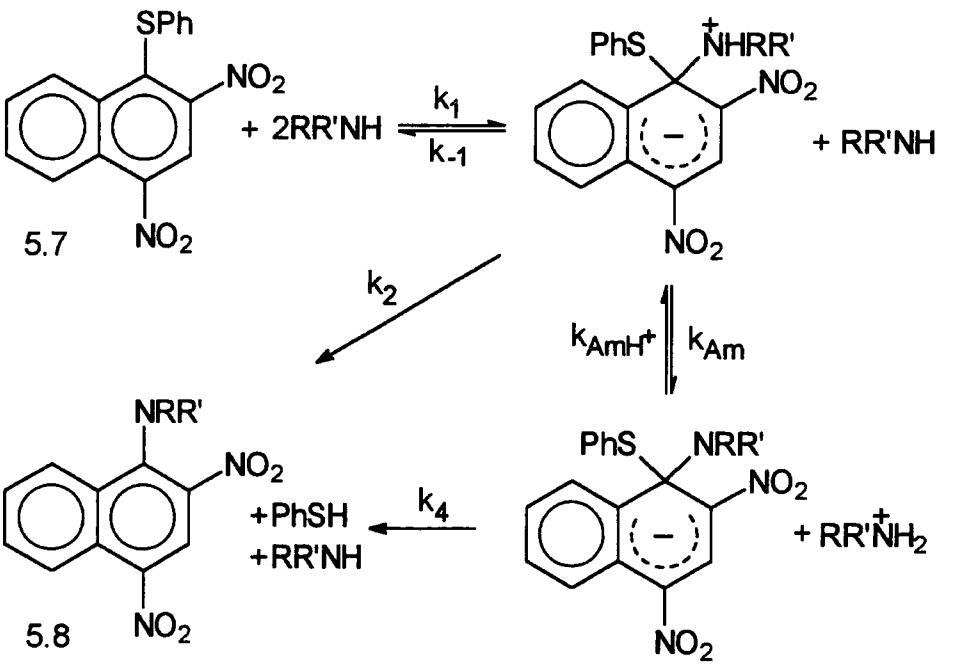
	R = Me	R = Br	$R = NO_2$
$k_3k_{Am}/\ k_{-3}/\ dm^6\ mol^{-2}s^{-1}$	1.46×10^4	2.6×10^4	4.6×10^4
k_{AmH^+}/ $mol^{-1}s^{-1}$	340	230	90
$K_{C,3}$/ dm^3mol^{-1}	43	120	510

5.3.4 Phenyl 2,4-dinitronaphthyl sulfide

UV/Visible measurements made with phenyl 2,4-dinitronaphthyl sulfide, 5.7, (2.5×10^{-5} mol dm^{-3}) and amines, showed a single process resulting quantitatively in the formation of the substitution compound, 5.8, as shown in scheme 5.3. The rate expression for this process, involving attack at the 1-position, is equation 5.13.

$$k_{obs} = \frac{k_1k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 5.13}$$

The final spectra in all cases were found to be identical to those of the separately prepared compounds in the presence of amines in DMSO. Further slower reactions of the substitution product, 5.8, with amines were observed, agreeing with other work.[20]



scheme 5.3

Reaction with butylamine

A reaction was seen to take place giving a species with λ_{max} at 523 nm and 391 nm. This reaction was measured by stopped flow spectrophotometry at 525 nm; data are in table 5.25.

In the absence of added salt, values of k_{fast} were found to increase linearly with amine concentration, indicating that nucleophilic attack was rate limiting. Hence it can be said $k_{Am}[Am] >> k_{-1}$ and so equation 5.13 can be reduced to equation 5.14. A value for k_1 of 0.46 $dm^3\ mol^{-1}s^{-1}$ is obtained.

$$k_{obs} = k_1[Am] \qquad \text{eqn 5.14}$$

The reaction also was carried out in the presence of added salt (butylammonium perchlorate); the rate constants obtained were found to be unaffected by this addition of salt.

Table 5.25 Kinetic data for the reaction of phenyl 2,4-dinitronapthyl sulfide, 5.7, with butylamine in DMSO at 25°C.

[Butylamine] / mol dm^{-3}	[Butylammonium perchlorate] / mol dm^{-3}	k_{obs}/ s^{-1}	k_{calc}	k_{obs}/[Am] / $dm^3\ mol^{-1}s^{-1}$
0.05	-	0.023	0.023	0.46
0.06	-	0.027	0.028	0.45
0.08	-	0.037	0.037	0.46
0.09	-	0.041	0.041	0.46
0.10	-	0.046	0.046	0.46
0.05	0.01	0.022	0.023	0.44
0.10	0.01	0.045	0.046	0.45

a) Calculated using equation 5.14 with $k_1 = 0.46\ dm^3\ mol^{-1}s^{-1}$.

Reaction with pyrrolidine

The reaction with pyrrolidine, which gave a species with λ_{max} at 439nm, was measured on the stopped flow apparatus at 440 nm; data are in table 5.26. An almost squared dependence on amine concentration was found in the absence of added salt.
If it is considered that the uncatalysed step, k_2, may be contributing to the overall process, equation 5.15 is obtained.

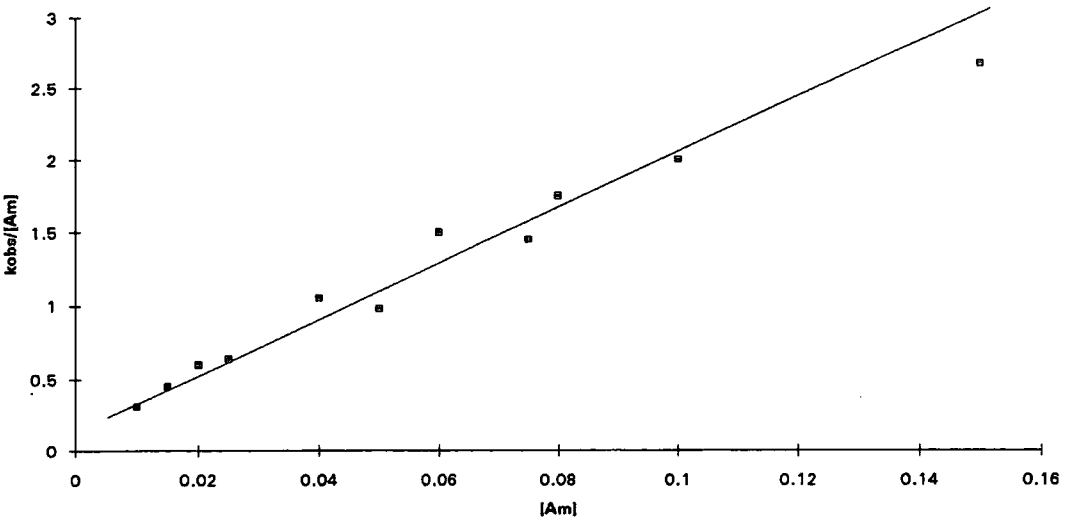
$$k_{obs} = \frac{k_1[Am](k_2 + k_{Am}[Am])}{k_{-1} + k_2 + k_{Am}[Am]} \qquad \text{eqn 5.15}$$

The squared amine dependence indicates that $k_{-1} >> k_2 + k_{Am}[Am]$ and hence equation 5.15 reduces to equation 5.16, after rearrangement.

$$\frac{k_{obs}}{[Am]} = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_{Am}}{k_{-1}}[Am] \qquad \text{eqn 5.16}$$

Therefore a plot of k_{obs}/ [Am] against [Am] will tell us if the uncatalysed, k_2, step is important. The graph appears to have an intercept close to zero, and hence the uncatalysed pathway is unimportant.

Graph 5.1 A graph showing the reaction between phenyl 2,4-dinitronaphthyl sulfide and pyrrolidine



Values of k_{obs} / $[Am]^2$ are seen to have a value of appproximately 30 for low amine concentrations, this value however starts to decrease with increasing amine concentration, see table 5.25. At low amine concentrations, the condition $k_{-1} >> k_{Am}[Am]$ can be applied to equation 5.13, giving equation 5.17. Hence k_1k_{Am}/ k_{-1} can be seen to have a value of 30 $dm^6\ mol^{-2}s^{-1}$.

$$k_{obs} = \frac{k_1 k_{Am}}{k_{-1}}[Am]^2 \qquad \text{eqn 5.17}$$

As amine concentration increases, the value of $k_{Am}[Am]$ will also increase and hence the condition above ($k_{-1} >> k_{Am}[Am]$) will not hold and so the observed decreases in the value for k_{obs} / $[Am]^2$ are observed. Dividing through equation 5.13 by k_{-1} gives equation 5.18, allowing us to calculate a value for k_{Am}/ k_{-1} at high amine concentration and hence a value of 6 $dm^3\ mol^{-1}s^{-1}$ for k_1, (see table 5.27).

$$k_{obs} = \frac{K_1 k_{Am}[Am]^2}{1 + \frac{k_{Am}}{k_{-1}}[Am]} \qquad \text{eqn 5.18}$$

Rate constants were not affected by the addition of 0.01 mol dm^{-3} pyrrolidinium perchlorate. However the addition of DABCO, where equation 5.19 applies, did cause an increase in values of observed rate constants.

$$k_{obs} = \frac{k_1[Am](k_{Am}[Am] + k_{DABCO}[DABCO])}{k_{-1} + k_{Am}[Am] + k_{DABCO}[DABCO]} \qquad \text{eqn 5.19}$$

Allowing for the condition $k_{-1} >> k_{Am}[Am] + k_{DABCO}[DABCO]$ gives equation 5.20. From this we see a plot of $k_{obs}/ [Am]$ against DABCO concentration will have a slope of K_1k_{DABCO} and an intercept of $K_1k_{Am}[Am]$, giving K_1k_{DABCO} = 5 $dm^6\ mol^{-2}s^{-1}$ and K_1k_{Am} = 30 $dm^6\ mol^{-2}s^{-1}$.

$$\frac{k_{obs}}{[Am]} = K_1(k_{Am}[Am] + k_{DABCO}[DABCO]) \qquad \text{eqn 5.20}$$

Substituting these values back into equations 5.13 and 5.19 gave a good fit with experimental values.

Table 5.26 Kinetic data for the reaction of phenyl 2,4-dinitronaphthyl sulfide, 5.7, with pyrrolidine in DMSO at 25°C, measured at 440 nm.

[pyrrolidine]/ mol dm^{-3}	[pyrrolidinium perchlorate]/ mol dm^{-3}	[DABCO]/ mol dm^{-3}	k_{obs}/ s^{-1}	$k_{obs}/[Am]^2$ / $dm^6mol^{-2}s^{-1}$	k_{calc}[a]/ s^{-1}
0.010	-	-	0.0031	31	0.0029
0.015	-	-	0.0067	30	0.0063
0.020	-	-	0.012	30	0.011
0.025	-	-	0.016	26	0.017
0.040	-	-	0.042	26	0.040
0.050	-	-	0.049	20	0.060
0.060	-	-	0.090	25	0.083
0.075	-	-	0.109	19	0.120
0.080	-	-	0.140	22	0.140
0.10	-	-	0.200	20	0.20
0.15	-	-	0.400	18	0.39
0.025	0.01	-	0.014	-	0.017
0.05	0.01	-	0.060	-	0.060
0.075	0.01	-	0.120	-	0.12
0.10	0.01	-	0.210	-	0.20
0.025	-	-	0.017	-	0.018
0.025	-	0.025	0.021	-	0.022
0.025	-	0.050	0.024	-	0.025
0.025	-	0.075	0.027	-	0.028
0.025	-	0.100	0.029	-	0.031

a) calculated using equations 5.13 and 5.19 with the values K_1k_{Am} = 30 dm^6 $mol^{-2}s^{-1}$, k_{Am}/ k_{-1} = 5 dm^3 mol^{-1}, k_1 = 6 dm^3 $mol^{-1}s^{-1}$, K_1k_{DABCO} = 5 dm^6 $mol^{-2}s^{-1}$ and k_{DABCO}/ k_{-1} = 0.8 dm^3 mol^{-1}.

Table 5.27 Summary of data for the reaction of pyrrolidine at the 1-position of phenyl 2,4-dinitronapthyl sulfide.

[pyrrolidine]/ mol dm^{-3}	k_{obs}/ s^{-1}	k_{Am}/ k_{-1} a/ mol dm^{-3}
0.075	0.109	7.3
0.08	0.142	4.4
0.10	0.200	5
0.15	0.400	4.6

a) Calculated using equation 5.18 with $K_1k_{Am} = 30$ dm^6 $mol^{-2}s^{-1}$.

Reaction with piperidine

The reaction to give the substitution product, 5.8, was measured at 420 nm; data are in table 5.28. Figure 5.8 shows the reaction between phenyl 2,4-dinitronaphthyl sulfide and piperidine.

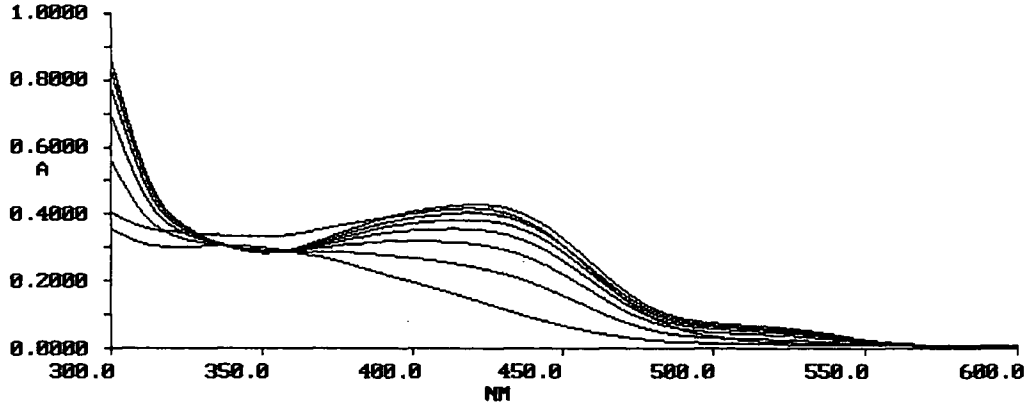


Figure 5.8. UV/Visible spectra of the reaction between phenyl 2,4-dinitronaphthyl sulfide and piperidine.

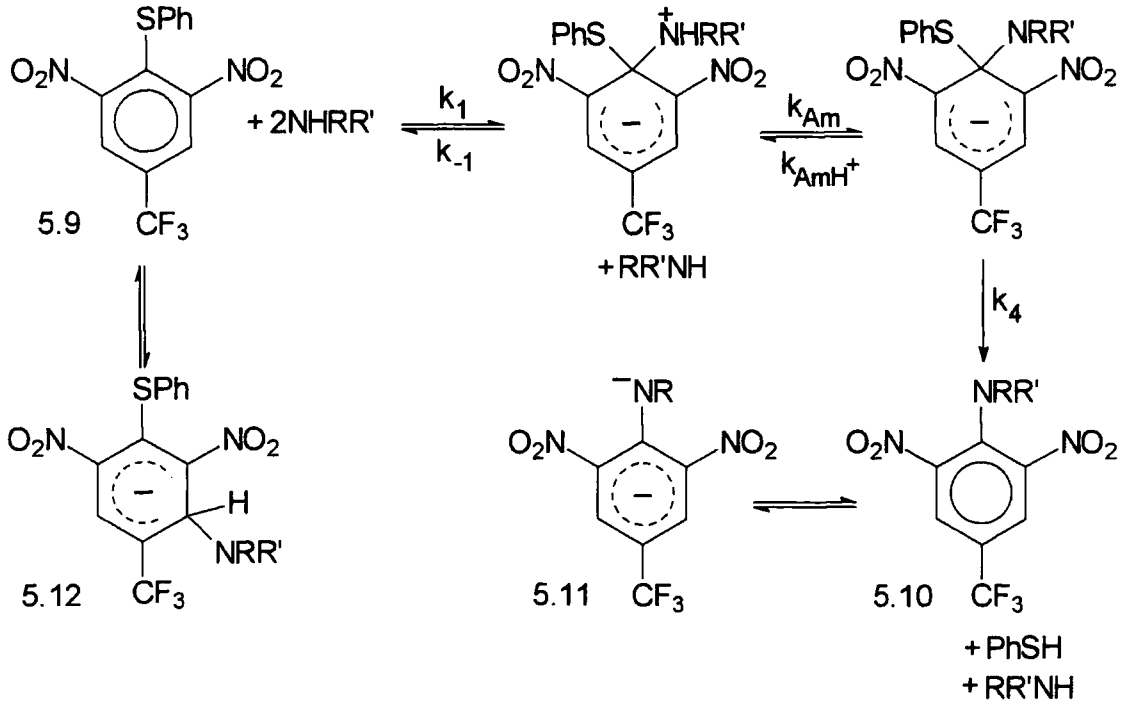
In the absence of added salt, a squared dependence on amine concentration was observed, indicating that the proton transfer step, k_{Am}, is rate determining in the substitution process. Hence, using the condition $k_{-1} >> k_{Am}[Am]$ in equation 5.13 gives equation 5.17. Application of this equation gives a value of 0.40 $dm^6\ mol^{-2}s^{-1}$ for $k_1k_{Am}/\ k_{-1}$.

Table 5.28 Kinetic data for the reaction of phenyl 2,4-dinitrophenyl sulfide with piperidine in DMSO at 25°C, measured at 420 nm.

[piperidine]/ mol dm^{-3}	[piperidinium chloride] / mol dm^{-3}	k_{obs}/ $10^{-3}\ s^{-1}$	$k_{obs}/\ [Am]^2$ / $dm^3mol^{-1}s^{-1}$
0.05	-	1.04	0.41
0.06	-	1.47	0.41
0.07	-	2.06	0.42
0.08	-	2.51	0.39
0.09	-	3.20	0.40
0.10	-	3.40	0.34
0.04	0.01	0.75	0.47
0.06	0.01	1.59	0.44
0.08	0.01	2.66	0.42
0.10	0.01	3.73	0.37

5.3.5 Phenyl 2,6-dinitro-4-trifluoromethylphenyl sulfide, 5.9

Spectrophotometric measurements were made with the parent, 5.9, (2.5 or 5.0 x 10^{-5} mol dm^{-3}) in DMSO with amines. The substitution reaction was seen to take place as in scheme 5.4. The final spectra agreed well with those of separately prepared compounds in the presence of amine.



scheme 5.4

Reaction with butylamine

A reaction was seen to take place giving the substituted product, N-n-butylamino-2,4-dinitro-4-trifluoromethylphenyl sulfide, 5.10, with λ_{max} = 428 nm, as shown in figure 5.9. In the presence of excess amine, this substitution product was found to be in equilibrium with its anion, 5.11, formed by transfer of the side chain proton, λ_{max} = 440nm.

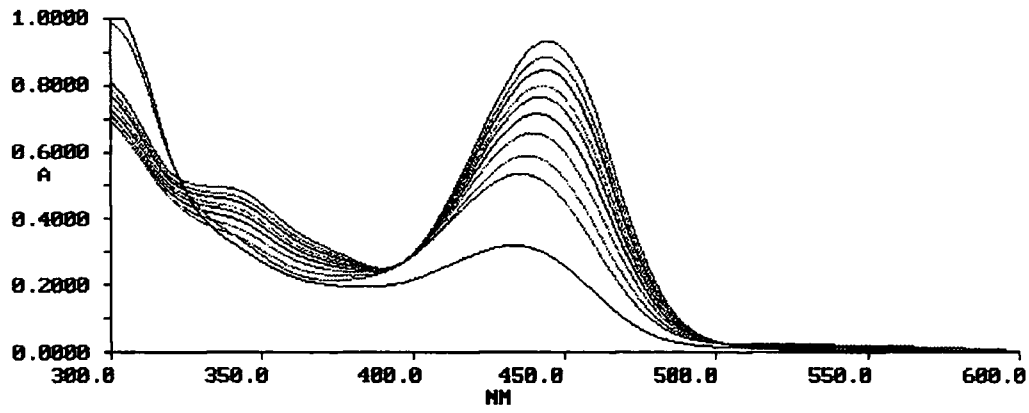


Figure 5.9. UV/Visible spectra of the reaction between phenyl 2,6-dinitro-4-trifluoromethylphenyl sulfide and butylamine.

Values of the observed rate constants were seen to increase linearly with amine concentration. Hence, as with the naphthyl compound, 5.7, k_{Am} [Am] >> k_{-1} and the initial attack by the amine must be rate limiting. Using equation 5.14 gives a value for k_1 of 0.48 $dm^3\ mol^{-1}s^{-1}$. Data are in table 5.29.

Table 5.29. Kinetic data for the reaction of phenyl 2,6-dinitro-4-trifluoromethylphenyl sulfide, 5.9, with butylamine in DMSO at 25°C, measured at 440nm.

$[BuNH_2]$/ mol dm^{-3}	k_{obs}/ s^{-1}	k_{obs}/[Am]/ $dm^3\ mol^{-1}s^{-1}$
0.02	0.010	0.50
0.04	0.020	0.51
0.06	0.030	0.50
0.08	0.037	0.46
0.10	0.044	0.44
0.15	0.065	0.43
0.20	0.083	0.42

Reaction with pyrrolidine

Reaction of the phenyl sulfide, 5.9, with pyrrolidine resulted in the initial formation of the 3-adduct, 5.12, λ_{max} = 360nm and 521nm. This was followed by the slower substitution reaction yielding the N-pyrrolidino-2,6-dinitro-4-trifluoromethylphenyl sulfide, 5.10, λ_{max} = 419nm. Pyrrolidinium perchlorate (0.01 mol dm^{-3}) was added to supress the initial attack at the 3-position by driving the equilibrium to the left. At high pyrrolidine concentrations, the substitution product, 5.10, was in rapid equilibrium with its 3-adduct, λ_{max} = 424nm.

The reaction of 5.9 to give the substitution product, 5.10, was measured at 519nm; data are in table 5.30. A squared dependence on amine was observed, indicating that proton transfer is rate determining. Hence using equation 5.17, a value for k_1k_{Am}/ k_{-1} of 0.18 dm^6 $mol^{-2}s^{-1}$ can be obtained.

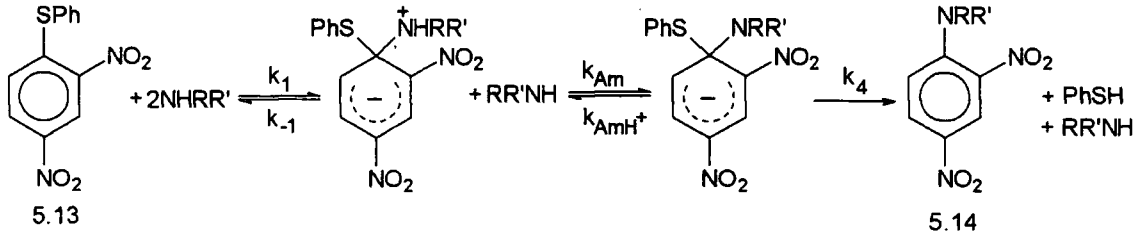
Table 5.30. Kinetic data for the reaction of phenyl 2,6-dinitro-4-trifluoromethylphenyl sulfide, 5.9, with pyrrrolidine in DMSO at 25°C, measured at 519nm.

[pyrrolidine]/ mol dm^{-3}	[pyrrolidinium perchlorate]/ mol dm^{-3}	k_{obs}/ 10^{-4} s^{-1}	$k_{obs}/[Am]^2$/ dm^6 $mol^{-2}s^{-1}$
0.006	0.01	6.7	0.19
0.08	0.01	11.8	0.18
0.10	0.01	18.8	0.19
0.15	0.01	40.1	0.18

No measurements were made with piperidine.

5.3.6 Phenyl 2,4-dinitrophenyl sulfide

Spectroscopic measurements were made of the reaction between phenyl 2,4-dinitrophenyl sulfide, 5.13, (5 x 10^{-5} mol dm^{-3}) with amines in DMSO. A single reaction was seen to occur, as in scheme 5.5 to give the substitution products, 5.14. Spectra of the final products were found to be identical to those obtained using a separately prepared sample in the presence of amine in DMSO.



5.13 5.14

scheme 5.5

Reaction with butylamine

A single reaction was seen to take place giving the substitution product N-butylamino-2,4-dinitrobenzene, 5.14, λ_{max} = 363nm and 430nm (sh); data are in table 5.31.
A linear increase in amine concentration was seen for the observed rate constants, indicating that initial amine attack is rate determining. Using equation 5.14 gives a value of 5.6 dm^3 $mol^{-1}s^{-1}$ for k_1.

Table 5.31 Kinetic data for the reaction of phenyl 2,4-dinitrophenyl sulfide, 5.13, with butylamine in DMSO at 25°C, measured at 385nm.

$[BuNH_2]$/ mol dm^{-3}	k_{obs}/ 10^{-5} s^{-1}	k_{obs}/[Am]/ 10^{-4} dm^3 $mol^{-1}s^{-1}$
0.05	2.56	5.1
0.10	5.99	6.0
0.15	8.36	5.6
0.20	11.20	5.6
0.25	13.40	5.4

Reaction with pyrrolidine

The reaction of phenyl 2,4-dinitrophenyl sulfide with pyrrolidine to give the pyrrolidino-substituted compound, 5.14, as shown in figure 5.10, was measured at 385nm. Data are in table 5.32. As expected the presence of added pyrrolidinium chloride did not affect the values of rate constants. However the substitution was catalysed by added DABCO.

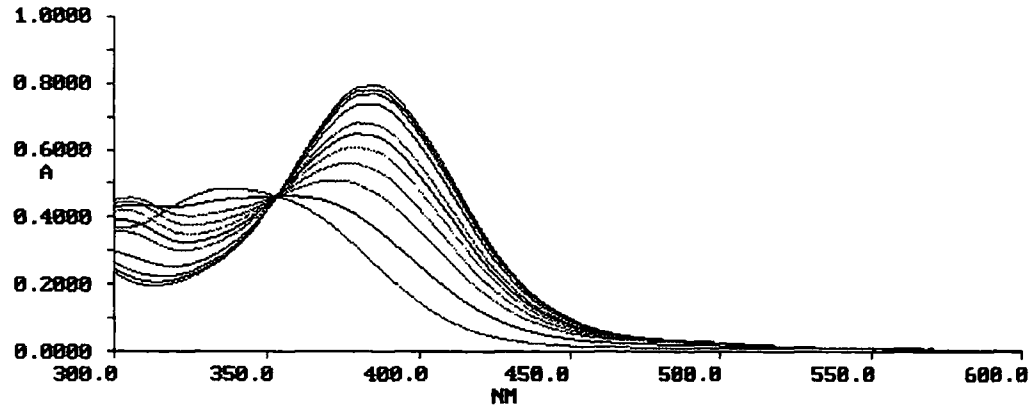


Figure 5.10. UV/Visible spectra of the reaction between phenyl 2,4-dinitrophenyl sulfide and pyrrolidine.

In this case it was not possible to fit the data using equation 5.13. There is evidence for the direct conversion of the zwitterion to product via the k_2 step. If the condition, $k_{-1} >> k_2 + k_{Am}[Am]$, is applied then the appropriate rate expression, allowing for the catalysis by DABCO, is equation 5.21.

$$k_{obs} = \left(K_1k_2 + K_1k_{Am}[Am] + K_1k_{DABCO}[DABCO]\right)[Am] \qquad \text{eqn 5.21}$$

There is an excellent fit with data calculated with $K_1k_2 = 2.7 \times 10^{-3}$ s^{-1}, $K_1k_{Am} = 1.0 \times 10^{-2}$ dm^3 mol^{-1} s^{-1} and $K_1k_{DABCO} = 5.0 \times 10^{-3}$ s^{-1}.

Bernasconi has noted that the effectiveness of the base catalysed step relative to the uncatalysed decomposition of the intermediate decreases as the activation in the substrate decreases. The 2,4-dinitrophenyl derivative is the least activated substrate used and allows the detection of the uncatalysed decomposition pathway, the k_2 step.

Table 5.32 Kinetic data for the reaction of phenyl 2,4-dinitrophenyl sulfide, 5.13, with pyrrolidine in DMSO at 25°C, measured at 385nm.

[pyrrolidine]/ mol dm^{-3}	[Pyrrolidinium chloride]/ mol dm^{-3}	[DABCO]/ mol dm^{-3}	k_{obs}/ x 10^{-4} s^{-1}	k_{calc}[a]/ x 10^{-4} s^{-1}
0.01	-	-	0.28	0.28
0.02	-	-	0.59	0.58
0.03	-	-	0.92	0.90
0.04	-	-	1.28	1.24
0.05	-	-	1.60	1.6
0.10	-	-	3.9	3.7
0.15	-	-	6.4	6.3
0.20	-	-	9.4	9.4
0.25	-	-	13.1	13.0
0.05	0.01	-	1.6	1.6
0.10	0.01	-	3.7	3.7
0.20	0.01	-	9.3	9.4
0.25	0.01	-	12.7	13.0
0.05	-	-	1.61	1.6
0.05	-	0.10	1.94	1.9
0.05	-	0.20	2.21	2.1
0.05	-	0.30	2.42	2.4

a) Calculated from equation 5.21 with K_1k_2 = 2.7 x 10^{-3} s^{-1}, K_1k_{Am} = 1.0 x 10^{-2} dm^{-3} mol^{-1} s^{-1} and K_1k_{DABCO} = 5.0 x 10^{-3} s^{-1}.

5.4 Discussion

Kinetic and equilibrium data are collected in tables 5.33 to 5.35 for all compounds reported in this chapter and also for ethyl thiopicrate (ethyl 2,4,6-trinitrophenyl sulfide).

Table 5.33 Summary of data for the reaction of the compounds studied with butylamine.

compound	k_3/ mol $dm^{-3}s^{-1}$	$k_{-3}k_{AmH^+}/k_{Am}$ / s^{-1}	$K_{c,3}$/ dm^3 mol^{-1}	k_1/ dm^3 mol^{-1}
ETP	800	71	11	8
5.2(R = H)	1500	45	33	33
5.2(R = Me)	1350	88	17	28
5.2(R = Br)	2000	35	57	36
5.2(R = NO_2)	2500	9	260	43
5.7	-	-	-	0.46
5.9	-	-	-	0.48
5.13	-	-	-	5.6×10^{-4}

Table 5.34 Summary of data for the reaction of the compounds studied with pyrrolidine.

compound	k_3/ dm^3 $mol^{-1}s^{-1}$	k_{Am}/k_{-3}/ dm^3 mol^{-1}	k_{AmH^+}/ dm^3 mol^{-1}	$K_{c,3}$/ dm^3 mol^{-1}	K_1k_{Am}/ dm^6 $mol^{-2}s^{-1}$
ETP	9000	40	5500	60	60
5.2(R = H)	1.25×10^4	22	2.6×10^3	108	250
5.2(R = Me)	1.08×10^4	25	3.5×10^3	75	210
5.2(R = Br)	1.9×10^4	25	2.9×10^3	160	400
5.2(R = NO_2)	2.6×10^4	31	750	1140	180
5.7	-	-	-	-	30
5.9	-	-	-	-	0.18
5.13	-	-	-	-	0.01

Table 5.35 Summary of data for the reaction of the compounds studied with piperidine.

compound	k_3k_{Am}/k_{-3}/ $dm^6\ mol^{-2}s^{-1}$	k_{AmH^+}/ $dm^3\ mol^{-1}$	$K_{c,3}$/ $dm^3\ mol^{-1}$
ETP	1.5×10^4	500	35
5.2(R = H)	1.9×10^4	450	48
5.2(R = Me)	1.46×10^4	340	43
5.2(R = Br)	2.6×10^4	230	120
5.2(R = NO_2)	4.6×10^4	90	510
5.7	-	-	0.40

5.4.1 Reaction at an unsubstituted ring position

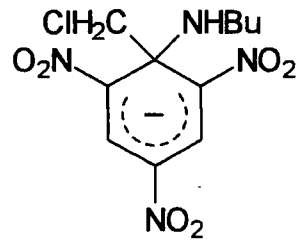
The kinetic results show that in the formation of the 3-adducts, 5.3, from the 4'-substituted 2,4,6-trinitrophenyl sulfides, 5.2, the rate determining step changes from nucleophilic attack with butylamine, (k_3), to proton transfer, (k_{Am}), with piperidine. Pyrrolidine shows intermediate behaviour, i.e. partially rate limiting proton transfer. The change in rate limiting step is due to changes in the ratio $k_{Am}[Am]/ k_{-3}$; as this ratio decreases (< 1) then proton transfer will become rate limiting. The main factor to consider is the value of k_{Am}, which will change with the nature of the reacting amine.

Values of k_{Am} and k_{AmH^+} have been seen to be largely independent of the nature of the substrate for any given amine. This is due to the fact that the reaction is occurring at an unsubstituted ring position and hence the steric effects at the reaction centre will be quite similar for all trinitrophenyl compounds studied.

The ratio k_{Am}/ k_{AmH^+} for trinitro-activated substrates is thought to have a value of approximately 500, not varying greatly with the nature of the amine or aromatic substrate[21,22]; this reflects the higher acidity of the zwittterions over the corresponding ammonium ions.

For the reaction of 1,3,5-trinitrobenzene, values of k_{Am} have been seen to decrease in the order n-butylamine > pyrrolidine > piperidine.[21, 23] Hence, we would expect both values of k_{Am} and k_{AmH^+} for the formation of the 3-adducts from species 5.2 to decrease in the order n-butylamine > pyrrolidine > piperidine. This is confirmed by the data in table 5.33, where values of k_{AmH^+} can be seen to be larger for pyrrolidine than piperidine by a factor of 10. This can be explained by the steric hindrance to approach of the amine for proton transfer, which will increase on going from a primary amine like butylamine to a more bulky secondary amine such as pyrrolidine and be even greater still for piperidine.

This steric hindrance would be expected to be even greater for proton transfer from an addduct formed by attack at a substituted ring position due to the subsituent already present. For example, the value of k_{Am} in the formation of species 5.15, from n-butylamine and 2,4,6-trinitrobenzyl chloride, is three orders of magnitude smaller than the corresponding value for attack at an unsubstituted position.



5.15

Values of $K_{c,3}$ can be seen to decrease in the order pyrrolidine > piperidine > butylamine for each substrate, which reflects the relative basicities of the amines. Similarly, values of k_3 are an order of magnitude larger for pyrrolidine than for butylamine.

The phenyl thio groups are thought to play a significant role in the delocalisation of the negative charge in the 3-adduct. Comparing the ethyl and phenyl thio compounds, values of both k_3 and $K_{c,3}$ are seen to be lower for the former compound. This is thought to be due to the poorer electron-withdrawing ability of the SEt group relative to the SPh group. The 4-substituents of the phenyl ring cause k_3 to increase with their increasing electron-withdrawing capability, while the values of k_{AmH}^+ decrease and k_{Am}/ k_{-3} show little variation with changes in substrate.

A Hammett plot, figure 5.11, of the values of $K_{c,3}$ has slope ρ, of 1.2. In view of the remoteness of the substituents from the reaction centre, this is a surprisingly large value and indicates that the phenylthio groups play a significant role in delocalising the negative charge in the adduct.

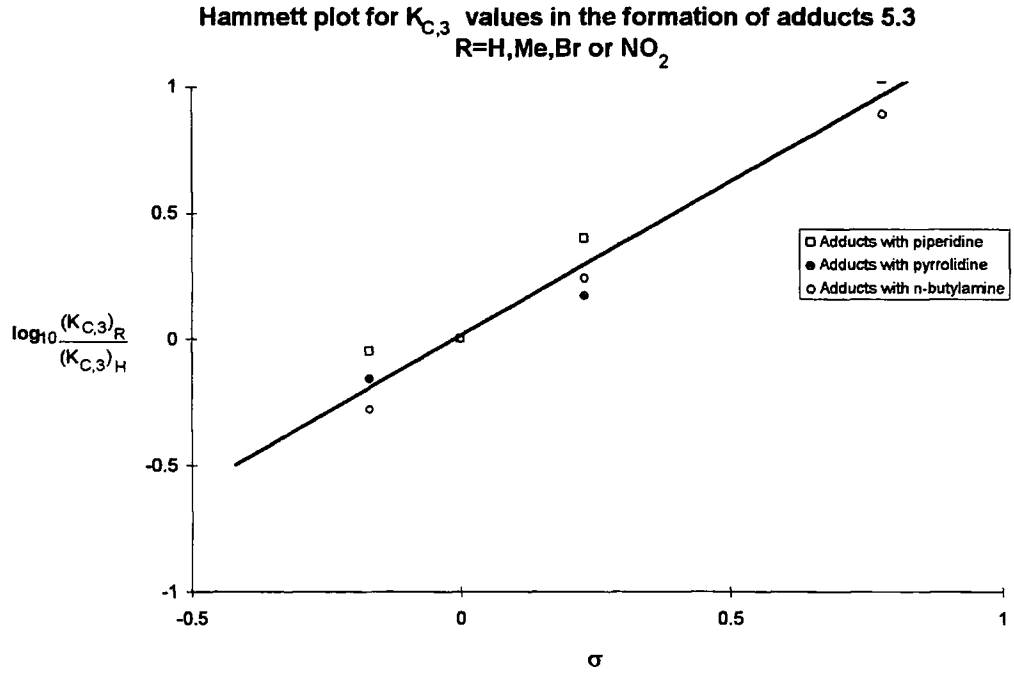


Figure 5.11. A Hammett plot for the formation of the 3-adducts formed during the reaction of the 4'-substituted phenyl 2.4.6-trinitrophenyl sulfides with amines.

5.4.2 Reaction at the substituted position

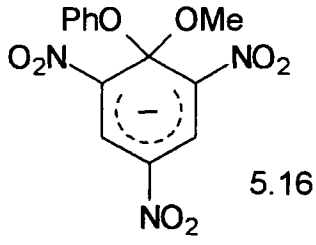
In all cases reaction at the 1-position resulted in substitution of the phenylthio group by the amino group. No intermediates on the reaction pathway were observable spectroscopically.

When the nucleophile was butylamine, the reactions were all found to be first order in amine concentration. This shows that the nucleophilic attack by the amine is the rate determining step, and hence proton transfer and loss of the phenylthio group must both occur rapidly. This is thought to be due to high values of k_{Am} and low values of k_{-1}. This may be due to the steric interactions in the zwitterion, 5.4, being lower for the primary amine than with the other secondary amines.

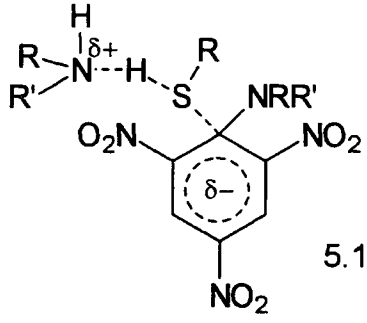
Values of k_1 for the 4'-substituted phenyl compounds, 5.2, show little variation with changes in the 4'-R group, indicating that they exert only a very small electronic effect.

Reactions involving pyrrolidine as the nucleophile were seen to be base catalysed. Data are summarised in table 5.34. This could be due to either rate limiting proton transfer from the zwitterionic intermediates to base, k_{Am}; or general acid catalysed expulsion of the phenylthio group, the k_4 step i.e. the SB-GA mechanism.

If the latter case applied, then values quoted for K_1k_{Am} would in fact be values of $k_4K_{c,1}$, where $K_{c,1}$ refers to the overall equilibrium for attack at the 1-position, i.e. 5.2 $\Leftrightarrow$ 5.5. As this term now includes k_4, which involves the loss of the phenyl thio group, a strong dependence on the leaving group ability of this substituent would be expected. For example, phenoxide departure is found to be 10^6 times faster than methoxide departure from adduct 5.16.[24] Hence we would expect the phenylthio group to have a much higher value of k_4 than the ethyl thio group.



5.16

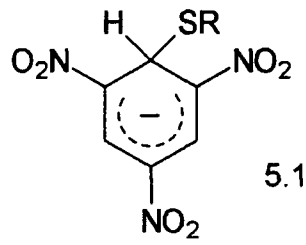


5.17

A correlation between leaving group ability and acid strength is expected.[4] Thiophenol is four orders of magnitude more acidic than ethanethiol; agreeing with the above.

The transition state would involve proton transfer to the sulfur as well as the breaking of the C-S bond, as in 5.17, however, but a dependence on the structure of the leaving group would still be expected for k_4. A further argument against the transition state, 5.17,comes from consideration of pK_a values, in water pK_a of the pyrrolidinium ion is 11.2 and thiophenol 6.5.[26] These values are not likely to become any more similar in DMSO, and hence the transition state, 5.17, represents a proton transfer in an unfavourable thermodynamic direction, hence there is no driving force for this to occur.

Also, rate determining acid catalysed expulsion of the leaving group would require the condition $k_{AmH^+} > k_4$, evidence suggests that this is unlikely to apply. Intrinsic barriers, in the Marcus sense, are known to be lower for sulfur bases reacting with aromatic systems, than for oxygen bases,[27] which implies thiolate expulsion will occur at a faster rate than alkoxide expulsion. The rate constant for uncatalysed expulsion of the thiophenoxide from adduct 5.18 has been shown[28] to have a value in excess of 10^3 s^{-1}. Hence, k_4 would have to have a value larger than this for the expulsion to be acid catalysed.



5.18

For reaction at an unsubstituted position, values of k_{AmH^+} have been shown to be approximately 10^3 dm^3 $mol^{-1}s^{-1}$ (see table 5.34). For reaction at a substituted ring position, greater steric hinndrance would occur, causing a decrease in k_{AmH^+} and so the value of k_{AmH^+} will be less than 10^3, while k_4 must be greater than 10^3, hence $k_4 >> k_{AmH^+}$.

A strong dependence on the nature of the leaving group was not observed and so it seeems unlikely that the k_4 step is rate determining. A more likely explanation is that the proton transfer from the zwitterion to base is rate determining. The results in table 5.34 indicate that values of K_1k_{Am} show only a small dependence on the changing 4'-substituent in compounds 5.2. Values of k_{Am} will not be expected to vary with these compounds as proton transfer is in a thermodynamically preferred direction and so any steric factors will cause more of an effect than electronic ones. Hence values of K_1 will also be fairly constant and show relatively little dependence on the 4'-substituent.
Changing the 1-substituent from SEt to SPh causes a small increase of 60 to 250 dm^6 $mol^{-2}s^{-1}$. This agrees with the above in that k_{Am} will show little variation, while K_1 will increase slightly due to electronic factors. With most of the compounds studied, the experimentally determined value was K_1k_{Am}, although with 5.7, separate values for k_1 and k_{Am}/ k_{-1} could be determined.
Values of k_1 for the substitution reaction with butylamine are known and in general, values of the rate constants for nucleophilic attack by butylamine are a factor of approximately 10 smaller than for pyrrolidine. This can be seen to be true for attack at the 3-position (see tables 5.33 and 5.34) and also for attack at the 1-position in species 5.7,

$$\text{i.e. } \frac{k_1(\text{pyrrolidine})}{k_1(\text{butylamine})} = \frac{6}{0.46}$$

If this assumption is made for the other substrates, then values shown in table 5.36 are obtained.

Table 5.36. Summary of data obtained for reaction at the 1-position with pyrrolidine.

Compound	K_1k_{Am}/ $dm^6\ mol^{-2}s^{-1}$	k_1[a]/ $dm^3\ mol^{-1}s^{-1}$	k_{Am}/k_{-1}[b]/ $mol\ dm^{-3}$
ETP	60	(80)	(0.8)
5.2 (R = H)	250	(330)	(0.8)
5.2 (R = Me)	210	(280)	(0.8)
5.2 (R = Br)	400	(360)	(1.1)
5.2 ($R = NO_2$)	180	(430)	(0.42)
5.7	30	6	5
5.9	0.18	(5)	(0.04)
5.13	0.01	5.6×10^{-3}	1.7

a) Values in brackets calculated assuming the ratio k_1(pyrrolidine)/ k_1(butylamine) has a value of 10.

b) Calculated as K_1k_{Am}/ k_1.

Values for the ethyl and all of the substituted phenyl compounds are almost constant. This is due to the fact that the steric situation at the 1-position is similar in all cases, leading to similar values of k_{Am}. Also, the activation in the trinitro substituted ring will be about the same causing the values of k_{-1} not to vary.

With the naphthyl compound, 5.7, a higher value of k_{Am}/ k_{-1} is observed. The ring activation in the naphthyl system will be less than in the picryl system and so the value of k_{-1} would be expected to be larger for 5.7 than for 5.2. However, the steric hindrance to proton transfer in the naphthyl system will be less than in the picryl system as there is no 6-nitro group. Hence a larger value of k_{Am} will be expected with the naphthyl system, this being the major factor causing an increase in the value of k_{Am}/k_{-1}.

Similarly with the 2,4-dinitro compound, which would have even less ring activation than the naphthyl system, hence a larger value of k_{-1} would be obtained. However the considerable reduction in steric hindrance to proton transfer due to the absence of a substituent at the 6-position will cause a larger value of k_{Am}, hence overall causing the increase in the k_{Am}/ k_{-1} ratio.

With species 5.9, which has a 4-trifluoromethyl group, a lower value of k_{Am}/ k_{-1} is observed. The steric situation in species 5.9 will be similar to that for the trinitro compounds, however the ring activation will be decreased relative to the trinitro compound due to the CF_3 group and hence a larger value of k_{-1} would be expected. This overall leads to the decrease in the value of k_{Am}/ k_{-1}.

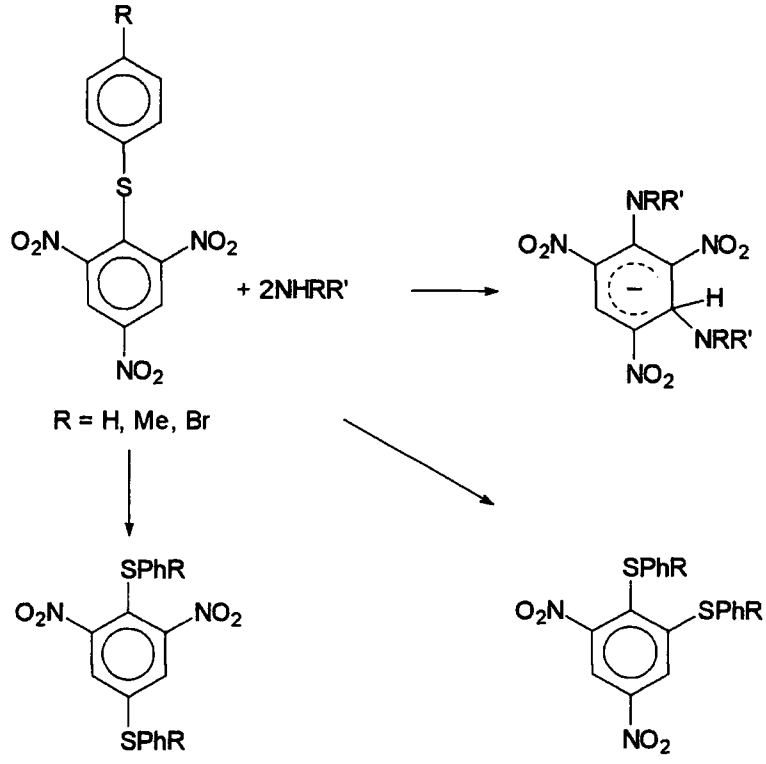
For the reaction of phenyl 2,4-dinitronaphthyl sulfide with pyrrolidine, catalysis by DABCO but not by added pyrrolidinium ions was observed. This suggests general base catalysis and so the reaction cannot have a mechanism involving a rapid equilibrium of the substrate with its anionic adduct followed by slow uncatalysed loss of the phenylthio group. Instead the likely mechanism is that involving rate limiting proton transfer. This is substantiated by the fact that pyrrolidine is seen to be a better catalyst than DABCO, with $k_{pyrr}/ k_{DABCO} = 4$, as found in other systems involving rate limiting proton transfer where k_{Am}/ k_{DABCO} is in the range 2-5.[14, 22, 23]
A similar situation was found with the phenyl 2,4-dinitrophenyl sulfide which has a ratio of k_{pyrr}/ k_{DABCO} of 2, a little lower than usually found.

Reaction with piperidine was generally found to be inconveniently slow for kinetic measurements or was found not to yield the expected substitution products. The reaction of phenyl 2,4-dinitronaphthyl sulfide, 5.7, was measured however and rate constants were seen to have a squared dependence on amine concentration. This indicates that proton transfer is rate determining with a value of 0.40 $dm^6\ mol^{-2}s^{-1}$ for K_1k_{Am}. This value is 75 times smaller than that found for pyrrolidine, which can be accounted for by a reduction in k_{Am} due to the more sterically hindered piperidine and also a reduction in K_1 as piperidine is less nucleophilic.[21, 23, 7, 13, 25]

5.5 ^{1}H NMR results

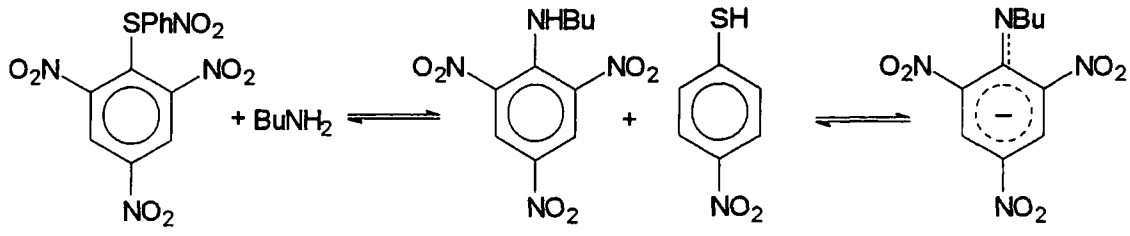
NMR results were recorded with the phenylthio compound (0.1 mol dm^{-3}) and amines (0.1 -0.4 mol dm^{-3}). Data are in table 5.1 and table 5.37.

As with ethyl thiopicrate (see chapter 3), the substrate concentration was fairly high and hence allowed the detection of further reactions of the displaced thiolate groups.



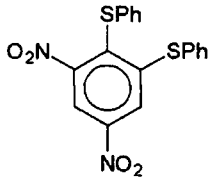
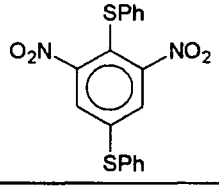
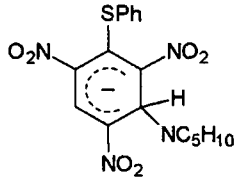
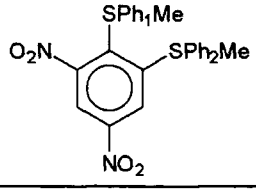
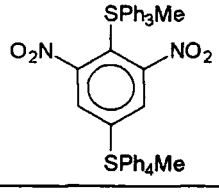
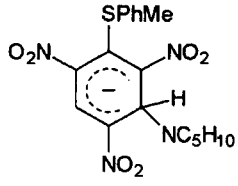
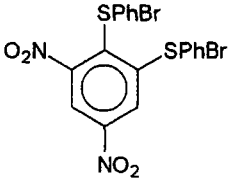
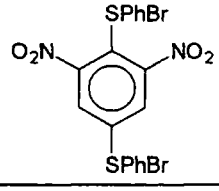
scheme 5.6

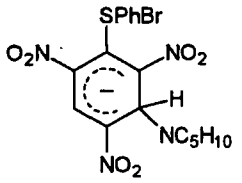
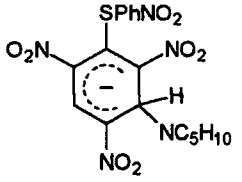
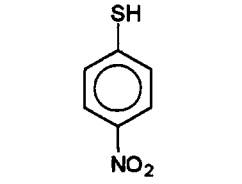
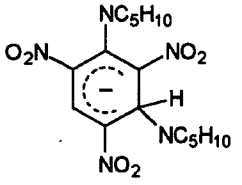
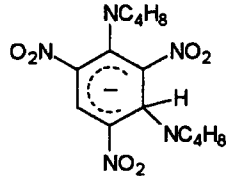
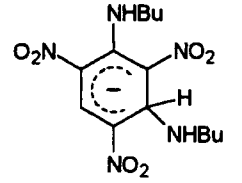
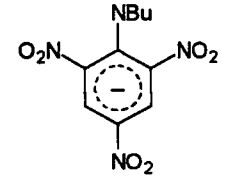
Products were observed for attack of the thiolate groups on both the ortho and para positions of the parent compounds. This was not observed for reaction with the 4-nitro compound, in which the displaced thiolate group is less nucleophilic than the other substrates used, due to the electron withdrawing nitro group. Hence the fast reaction with the amine to give the 1-substituted product occurs in preference to attack by the 4-nitro thiophenoxide ion. In the case of butylamine, the amino-substituted product loses a side-chain proton in an equilibrium to give species 5.19.



5.19

Table 5.37 ^{1}H NMR data for the reactions of 4'-substituted phenyl 2,4,6-trinitrophenyl sulfides with amines in [$^{2}H_6$] DMSO.

Structure	Nitro ring	4'-substituted ring	4'-substituent
	8.64, 7.64		
	7.95		
	8.50, 5.79	7.22	
	8.58, 7.54	7.17[1] 7.38, 7.40[2]	2.28 2.39
	7.86	7.11[3], 7.42, 7.51[2]	2.21 2.37
	8.47, 5.78	7.05, 7.07	2.23
	8.68, 7.62	7.77,7.50[1] 7.18, 7.52[2]	
	8.05	7.74,7.57[3] 7.18, 7.52[2]	

	8.51, 5.80	7.42, 7.19	
	8.57, 5.83	8.10, 7.43	
		7.18, 7.60	
	8.49, 5.53		
	8.45, 6.05		
	8.36, 5.58		
	8.42		

1) Ortho and para to the nitro groups.

2 and 4) Meta to the nitro groups.

3) Ortho to the nitro groups.

4) PhMe=C_6H_4Me, PhBr=C_6H_4Br, $PhNO_2$=$C_6H_4NO_2$

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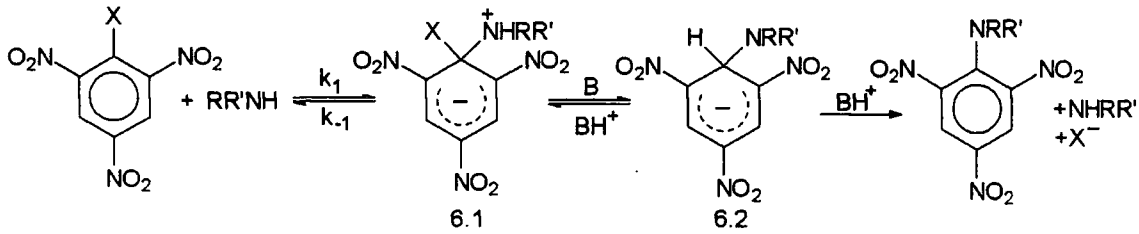
CHAPTER 6

Kinetics Of The Reactions Of Phenyl Ethers With Aliphatic Amines

Kinetics of the Reactions of Phenyl Ethers with Aliphatic Amines

6.1 Introduction

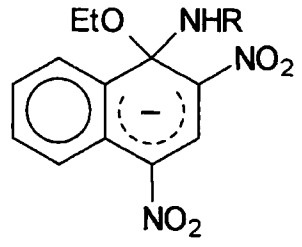
Nucleophilic Aromatic Substitution reactions involving amine nucleophiles are often found to be subject to base catalysis.[1-3]



6.1 6.2

The mechanism of base catalysis is the subject of much discussion.[4-7] The base catalysed pathway may involve rate limiting proton transfer from the zwitterionic intermediate, 6.1, to base followed by rapid expulsion of the leaving group from 6.2. Alternatively, this proton transfer may occur in a rapid equilibrium between the zwitterion and anion, after which the leaving group is lost in a general acid-catalysed step.

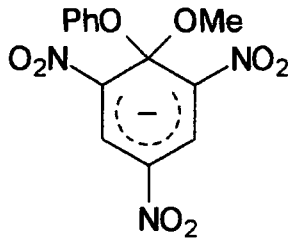
The latter mechanism, known as the SB-GA mechanism, gained general acceptance for reactions occuring in DMSO after a study carried out by Orvik and Bunnett.[8] They showed that in the reaction of 1-ethoxy-2,4-dinitronaphthalene with amines, anionic σ-adducts, such as 6.3 were observable intermediates. The formation and acid-catalysed decomposition of these intermediates were observed as separate steps. Related intermediates have been observed during the reaction of several other ring activated alkyl aryl ethers giving further evidence for the SB-GA mechanism.[9-14]



6.3

In earlier chapters of this thesis evidence has been presented that substitutions of alkylthio- and phenylthio-groups by amines involve rate determining proton transfer from the zwitterionic intermediates to base. It was thought to be of interest to make measurements with phenyl ethers to compare their behaviour with alkyl ethers. The pK_a values of phenols are considerably lower than those of alcohols, so that phenoxide ions

are weaker bases than alkoxide ions. Hence phenoxide ions are likely to be better leaving groups than alkoxide ions. For example Bernasconi and Muller[15] have shown that phenoxide departure from the adduct 6.3b is 10^6 times faster than methoxide departure. Hence it is possible that the mechanisms of base catalysis in the reactions of phenyl ethers and alkyl ethers will differ.



6.3b

Kinetic and equilibrium measurements were made on the reactions of phenyl 2,4,6-trinitrophenyl ether, 6.4, phenyl 2,4-dinitronaphthyl ether, 6.10, and phenyl 2,4-dinitrophenyl ether, 6.14, with three aliphatic amines in DMSO. Two secondary amines were used, piperidine and pyrrolidine and one primary amine, n-butylamine.

6.2 Experimental

6.2.1 Preparative Reactions

Phenyl 2,4,6-trinitrophenylether: Prepared by dissolving sodium hydroxide into a solution of phenol in water. On warming to approximately 40°C, picryl chloride was added and stirred for a further 30 minutes. Water was added to remove any picric acid present. The solid was recrystallised from an ethanol:toluene mixture (actual melting point 148-150°C, Literature melting point 153°C[16]).

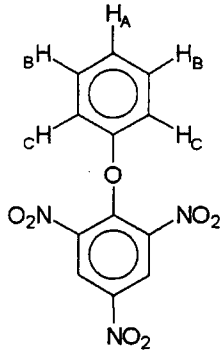
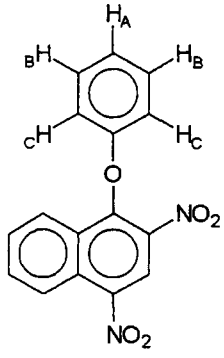
Phenyl 2,4-dinitronaphthyl ether: Prepared as above, by dissolving sodium hydroxide in a phenol solution, adding 1-chloro 2,4-dinitronaphthalene to the warmed solution and stirring for several hours. Water was added and the solid obtained recrystallised form ethanol. (Actual melting point 178-180 °C, Literature melting point 183.5°C[17]).

Phenyl 2,4-dinitrophenyl ether: Reagent grade (95%).

6.2.2 ^{1}H NMR

^{1}H NMR spectra were recorded with the parent nitro compound 0.1 mol dm^{-3} in [$^2H_6$] DMSO, data are in table 6.1 (δ values). Figure 6.1 shows phenyl 2,4,6-trinitrophenyl ether and figure 6.2 shows phenyl 2,4-dinitronaphthyl ether.

Table 6.1 ^{1}H NMR data for the parent phenyl ether compounds, phenyl 2,4,6-trinitrophenyl ether and phenyl 2,4-dinitronaphthyl ether.

Substrate	Nitro ring	Phenyl ether ring
	9.25	H_A = 7.19(t of t) H_B = 7.39(t) H_C = 7.04(d)
	8.99(s), 8.57(d), 8.26 (d), 8.07 (t), 6.88 (t)	H_A = 7.14 (t) H_B = 7.37(t) H_C = 7.00(d)

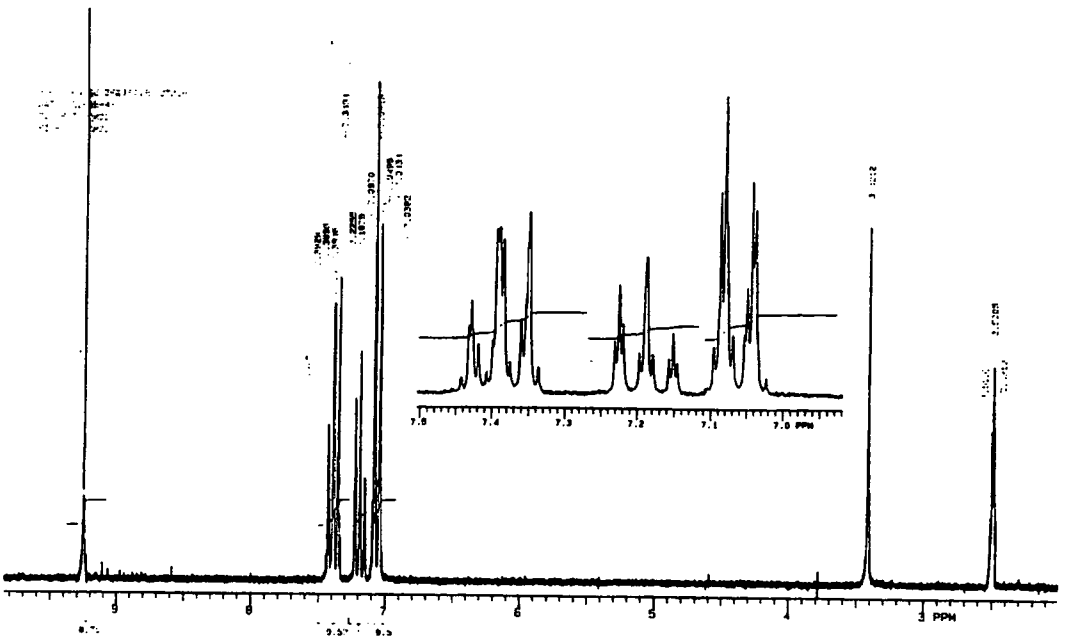


Figure 6.1. The ^{1}H NMR spectrum of phenyl 2,4,6-trinitrophenyl ether.

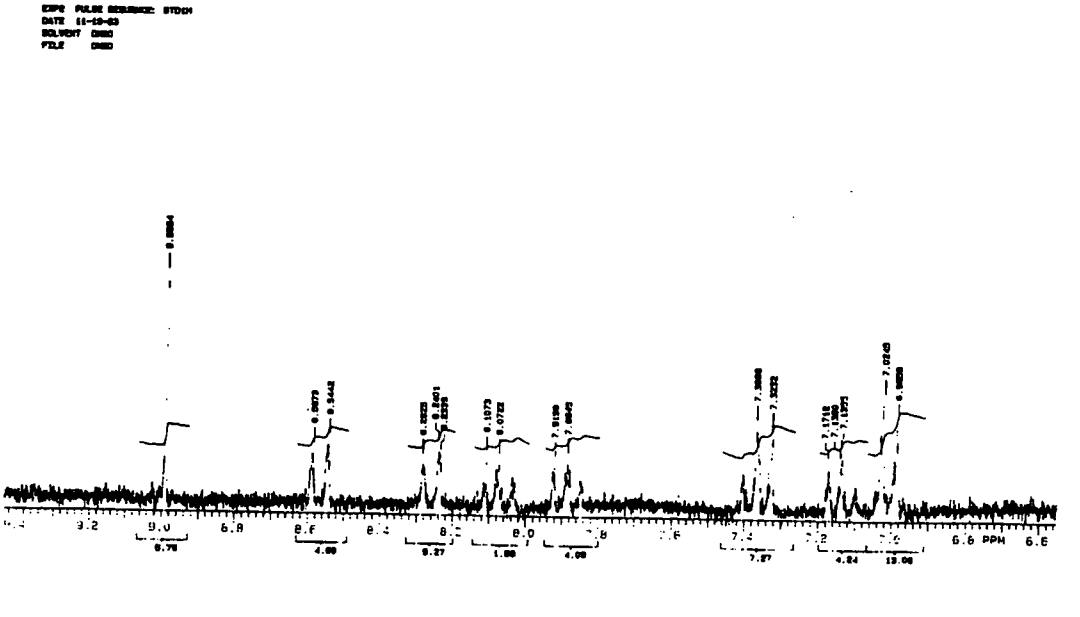
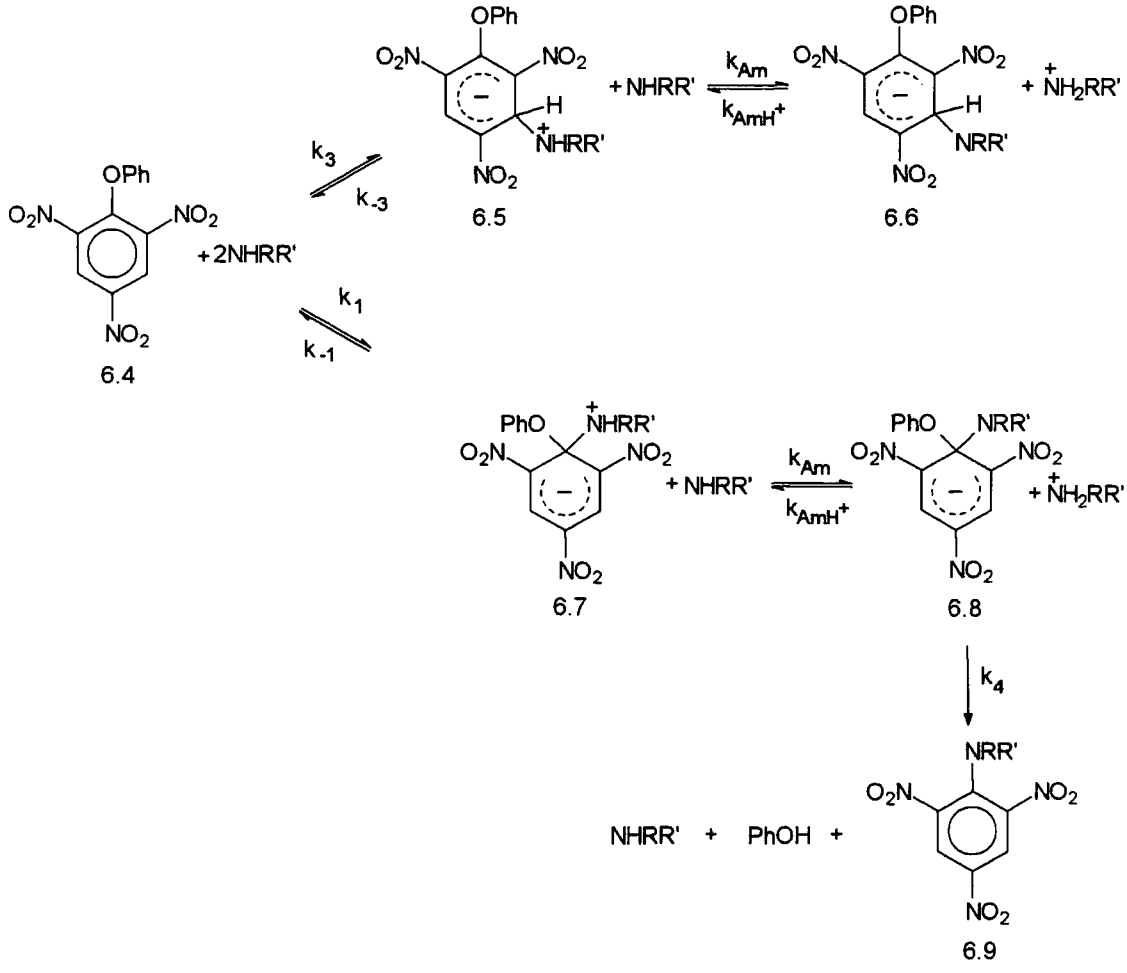


Figure 6.2. The ^{1}H NMR spectrum of phenyl 2,4-dinitronaphthyl ether.

6.3 Results for the reactions of phenyl 2,4,6-trinitrophenyl ether

UV/ visible measurements made with the parent compounds and amines in DMSO showed the presence of two processes interpreted in scheme 6.1. Nucleophilic attack at an unsubstituted ring position is known to occur considerably faster than attack at a substituted ring position.[1, 17, 18] Therefore the rapid reaction is thought to give the 3-adduct, 6.6, with λ_{max} = 425-435 nm. The slower reaction is therefore the substitution reaction resulting from attack at the 1-position of 6.4, giving the N-substituted picramides, 6.9, with λ_{max} = 422-423 nm.

No intermediates along the reaction pathway were observable with any of the compounds studied.



scheme 6.1

6.3.1 Kinetic analysis

Rate constants were all measured under first order conditions. For reactions involving buffers (amine plus amine salt), the buffer components were in large excess of the parent concentration (2.5×10^{-5} moldm^{-3}). For reactions in the absence of added amine salt, a sufficient excess of amine was used to ensure > 95% conversion to adduct at equilibrium. Under these conditions, equation 6.1 applies;

$$\ln\left(\frac{Abs_\infty}{Abs_\infty - Abs}\right) = k_{obs}t \qquad \text{eqn 6.1}$$

The zwitterions formed are treated as steady state intermediates, and so the general rate expression for the reaction to produce the 3-adducts, 6.6, is equation 6.2.

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2 + k_{-3}k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 6.2}$$

With no added salt, the reverse reaction becomes negligible and this reduces equation 6.2 to equation 6.3.

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 6.3}$$

The overall equilibrium constant, $K_{c,3}$, for reaction of phenyl 2,4,6-trinitrophenyl ether, 6.4, into its 3-adduct, 6.6, is defined by equation 6.4.

$$K_{c,3} = \frac{[6.3][AmH^+]}{[6.1][Am]^2} \qquad \text{eqn 6.4}$$

This can be related to the absorbance values by equation 6.5.

$$K_{c,3} = \frac{Abs}{Abs_\infty - Abs} \cdot \frac{[AmH^+]}{[Am]^2} \qquad \text{eqn 6.5}$$

The equilibrium constant, $K_{c,3}$, can also be expressed by the separate rate coefficients, as in equation 6.6.

$$K_{c,3} = \frac{k_3 k_{Am}}{k_{-3}k_{AmH^+}} \qquad \text{eqn 6.6}$$

Assuming the substitution reaction occurs by rate limiting proton transfer and then rapid loss of the phenyl ether group, the rate expression is equation 6.7.

$$k_{slow} = \frac{k_1 k_{Am}[Am]^2}{(k_{-1} + k_{Am}[Am])\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)} \qquad \text{eqn 6.7}$$

It is more convenient to express a modified rate coefficient k'_{slow}, as in equation 6.8. equation 6.7 can therefore be expressed as equation 6.9.

$$k'_{slow} = k_{slow}\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right) \qquad \text{eqn 6.8}$$

$$k'_{slow} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 6.9}$$

6.3.2 Reaction with butylamine

The results for attack at the 3-position, measured at 430 nm, are in table 6.2.
In the absence of added butylammonium perchlorate values of k_{fast}, relating to the formation of the 3-adduct, 6.6, can be seen to increase linearly with amine concentration. This indicates $k_{Am}[Am] >> k_{-3}$, hence equation 6.3 reduces to equation 6.10 and a value of 8000 $dm^3mol^{-1}s^{-1}$ can be obtained for k_3.With added salt a value of 40 s^{-1} for $k_{-3}k_{AmH^+}/ k_{Am}$ can be obtained using equation 6.10

$$k_{obs} = k_3[Am] + \frac{k_{-3}k_{AmH^+}[AmH^+]}{k_{Am}[Am]} \qquad \text{eqn 6.10}$$

Combination of the above values in equation 6.6 leads to a value of 200 dm^3mol^{-1} for $K_{c,3}$, which is similar to that, 230 dm^3mol^{-1}, obtained using absorbance values in equation 6.5.
Results for the slow substitution reaction are recorded in table 6.3. Assuming a linear amine dependence, hence the condition $k_{Am}[Am] >> k_{-1}$, the slow reaction can be expressed by equation 6.11.

$$k_{slow} = \frac{k_1[Am]}{1 + K_{c,3}\dfrac{[Am]^2}{[AmH^+]}} \qquad \text{eqn 6.11}$$

At low amine concentrations $1 >> K_{c,3}\,[Am]^2/\,[AmH^+]$ allowing the determination of a value of 410 $dm^3mol^{-1}s^{-1}$ for k_1. Using this value and a value of 210 dm^3mol^{-1} for $K_{c,3}$, a good fit is obtained with equation 6.11 over the entire concentration range.

Thus in both the reactions involving σ-adduct formation at the 3-position and substitution at the 1-position, the rate determining step is nucleophilic attack by the butylamine molecule. The proton transfer step is, in each case, rapid

Table 6.2 Kinetic and equilibrium data for the rapid reaction between phenyl 2,4,6-trinitrophenyl ether and butylamine in DMSO at 25°C.

$[BuNH_2]$/ $moldm^{-3}$	$[BuNH_3^+]$/ $moldm^{-3}$	k_{fast}/ s^{-1}	Abs[a]	$K_{c,3}$/[b] dm^3mol^{-1}	k_{calc}/ [c] s^{-1}
0.006	-	45	-	-	48
0.008	-	63	-	-	64
0.010	-	76	-	-	80
0.015	-	120	-	-	120
0.020	-	160	-	-	160
0.003	0.01	149	0.023	263	157
0.004	0.005	83	0.045	188	82
0.004	0.01	149	0.039	301	132
0.005	0.01	104	0.046	249	120
0.006	0.01	108	0.052	212	115
0.008	0.01	119	-	-	114
0.01	0.01	112	0.083	224	120
0.02	0.01	206	0.104	-	180
0.03	0.01	350	0.110	-	253
0.04	0.01	460	0.112	-	330
0.05	0.01	500	0.115	-	408

a) Measured at 430 nm.

b) Calculated using equation 6.5 with $Abs_\infty = 0.120$.

c) Calculated using equation 6.10 with $k_3 = 8000$ dm^3mol^{-1} and $k_{-3}k_{AmH^+}/k_{Am} = 40$ s^{-1}.

Table 6.3 Kinetic data for the reaction between phenyl 2,4,6-trinitrophenyl ether and butylamine in DMSO at 25°C, measured at 430 nm.

$[BuNH_2]$/ moldm^{-3}	$[BuNH_3^+]$/ moldm^{-3}	k_{slow}/ s^{-1}	k_{calc}[a]
0.0006	0.01	0.24	0.24
0.0008	0.01	0.33	0.33
0.001	0.01	0.41	0.40
0.002	0.01	0.78	0.76
0.006	0.01	1.40	1.40
0.008	0.01	1.46	1.40
0.010	0.01	1.33	1.32
0.020	0.01	0.86	0.87
0.030	0.01	0.61	0.62
0.040	0.01	0.44	0.47
0.050	0.01	0.39	0.38
0.003	0.01	1.12	1.04
0.004	0.01	1.35	1.23
0.005	0.01	1.47	1.39
0.004	0.005	1.03	0.98

a) Calculated from equation 6.11 with k_1 410 dm^{3}mol^{-1}s^{-1} and $K_{c,3}$ 210 dm^{3}mol^{-1}.

6.3.3 Reaction with pyrrolidine

Results for attack by the amine at the 3-position of the phenyl 2,4,6-trinitrophenyl ether to give the 3-adduct, 6.6, measured at 430 nm, are in table 6.4.

In the absence of any added pyrrolidinium perchlorate, a squared dependence on amine concentration is found, hence the condition $k_{Am}[Am] << k_{-3}$ applies and equation 6.2 reduces to equation 6.12.

$$k_{obs} = \frac{k_3 k_{Am}}{k_{-3}}[Am]^2 + k_{AmH^+}[AmH^+] \qquad \text{eqn 6.12}$$

From the data in table 6.4 a value of 3.5 x 10^5 dm^{6}mol^{-2}s^{-1} is obtained for k_3k_{Am}/ k_{-3} in the absence of added salt. With added pyrrolidinium perchlorate, a value of 2800

$dm^3mol^{-1}s^{-1}$ is obtained for k_{AmH^+}. Using the above values in equation 6.6 leads to a value of 1250 dm^3mol^{-1} for $K_{c,3}$.

Data for the slower reaction are in table 6.5. They show that the rate constant goes through a maximum value as the amine concentration is increased. The results indicate that proton transfer is partially rate limiting in the substitution pathway. The results are accomodated by equation 6.7 using the values K_1k_{Am} 2 x 10^5 $dm^6mol^{-2}s^{-1}$, k_{Am}/k_{-1} 20 dm^3mol^{-1} and $K_{c,3}$ 1100 dm^3mol^{-1}.

Table 6.4 Kinetic and equilibrium data for the formation of the 3-adduct, 6.6, from the reaction between phenyl 2,4,6-trinitrophenyl ether and pyrrolidine in DMSO at 25°C.

[pyrrolidine] / $moldm^{-3}$	[pyrrolidinium perchlorate/ $moldm^{-3}$	k_{fast}/ s^{-1}	k_{calc}[a]/ s^{-1}	k_{fast}/ [pyrr]^2/ $10^5dm^6mol^{-2}s^{-1}$	k_{AmH^+}/ $dm^3mol^{-1}s^{-1}$
0.007	-	1.68	1.71	34	-
0.001	-	3.22	3.5	32	-
0.0015	-	8.60	7.9	38	-
0.002	-	15.1	14	38	-
0.003	-	32.2	32	36	-
0.004	-	54.9	56	34	-
0.005	-	84.3	87	34	-
0.006	-	116	126	32	-
0.001	0.01	31.3	31.5	-	2780
0.002	0.01	43.2	42	-	2920
0.003	0.01	58.2	59.5	-	2670
0.004	0.01	85	84	-	2900
0.005	0.01	109	116	-	-

a) Calculated using equation 6.12 with the values

Table 6.5 Kinetic data for the substitution reaction between phenyl 2,4,6-trinitrophenyl ether and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ moldm^{-3}	[pyrrolidinium perchlorate]/ moldm^{-3}	k_{slow}/ s^{-1}	k'_{slow}[a]	k_{slow}[b]
0.001	0.01	0.135	0.136	0.17
0.002	0.01	0.314	0.45	0.27
0.003	0.01	0.70	1.39	0.85
0.004	0.01	0.94	2.59	1.07
0.005	0.01	1.11	4.2	1.21
0.01	0.01	1.40	16.8	1.40
0.02	0.01	1.49	67	1.27
0.03	0.01	1.24	124	1.13
0.04	0.01	1.07	190	1.01
0.05	0.01	0.97	268	0.91

a) Calculated using equation 6.8 with $K_{c,3}$ = 1100 dm^{3}mol^{-1}.

b) Calculated from equation 6.7 with K_1k_{Am} 2 x 10^5 dm^{6}mol^{-2}s^{-1}, k_{Am}/k_{-1} 20 dm^{3}mol^{-1} and $K_{c,3}$ 1100 dm^{3}mol^{-1}.

6.3.4 Reaction with piperidine

Data for attack at the 3-position of phenyl 2,4,6-trinitrophenyl ether to give the 3-adduct, 6.6 (NRR' = NC_5H_{10}), are in table 6.6. Figure 6.3 shows the change in absorbance during the reaction of phenyl 2,4,6-trinitrophenyl ether and piperidine.

In the absence of added piperidinium chloride, values of the rate constant show a squared dependence on amine concentration, indicating $k_{-3} >> k_{Am}[Am]$, and hence equation 6.2 reduces to equation 6.12.

$$k_{obs} = \frac{k_3k_{Am}}{k_{-3}}[Am]^2 + k_{AmH^+}[AmH^+] \qquad \text{eqn 6.12}$$

In the absence of added salt, a value of 1.7 x 10^5 dm^{6}mol^{-2}s^{-1} for k_3k_{Am}/k_{-3} is obtained using equation 6.12. Hence, with added piperidinium chloride, a value of k_{AmH^+} of 400 dm^{3}mol^{-1}s^{-1} can be obtained. Combining these values in equation 6.6 gives a value of 400 dm^{3}mol^{-1} for $K_{c,3}$.Using absorbance values in equation 6.5 gives a value of 300 dm^{3}mol^{-1} for $K_{c,3}$, a slightly lower value than that obtained from the rate coefficients.

Values calculated with $k_3k_{Am}/ k_{-3} = 1.7 \times 10^5$ $dm^6mol^{-2}s^{-1}$ and $k_{AmH}{}^+ = 400$ dm^3mol^{-1} in equation 6.12 are in reasonable agreement with experimental data.

Data for attack at the 1-position, resulting in the substitution products, are in table 6.7. Values of k'_{slow}, calculated using equation 6.8 with $K_{c,3} = 300$ dm^3mol^{-1}, show a squared dependence on amine concentration. Hence, $k_{-1} >> k_{Am}[Am]$ and so equation 6.9 reduces to equation 6.13, allowing a value of 2600 $dm^6mol^{-2}s^{-1}$ to be calculated for K_1k_{Am}.

$$k'_{slow} = K_1k_{Am}[Am]^2 \qquad \text{eqn 6.13}$$

Table 6.6 Kinetic and equilibrium data for the rapid reaction between phenyl 2,4,6-trinitrophenyl ether and piperidine to give the 3-adduct in DMSO at 25°C.

[piperidine] / $moldm^{-3}$	[piperidinium chloride]/ $moldm^{-3}$	k_{fast}/ s^{-1}	Abs[a]	$K_{c,3}$[b]/ dm^3mol^{-1}	k_{calc}[c]/ s^{-1}
0.006	-	6.21	-	-	6.1
0.008	-	12.0	-	-	10.9
0.010	-	15.7	-	-	17
0.020	-	61.0	-	-	68
0.030	-	151	-	-	153
0.004	0.01	6.53	0.042	340	6.7
0.006	0.01	8.57	0.061	290	10.1
0.008	0.01	15.1	0.077	280	14.9
0.010	0.01	19.7	0.090	300	21
0.020	0.01	66.7	0.110	280	72
0.050	0.01	-	0.144	-	-

a) Absorbance measured at 430 nm.

b) Calculated using equation 6.5 with $Abs_\infty = 0.12$.

c) Calculated using equation 6.12 with $K_3k_{Am} = 1.7 \times 10^5$ $dm^6mol^{-2}s^{-1}$ and $k_{AmH}{}^+ = 400$ $dm^3mol^{-1}s^{-1}$.

Table 6.7 Kinetic data for the substitution reaction between phenyl 2,4,6-trinitrophenyl ether and piperidine in DMSO at 25°C, measured at 430 nm.

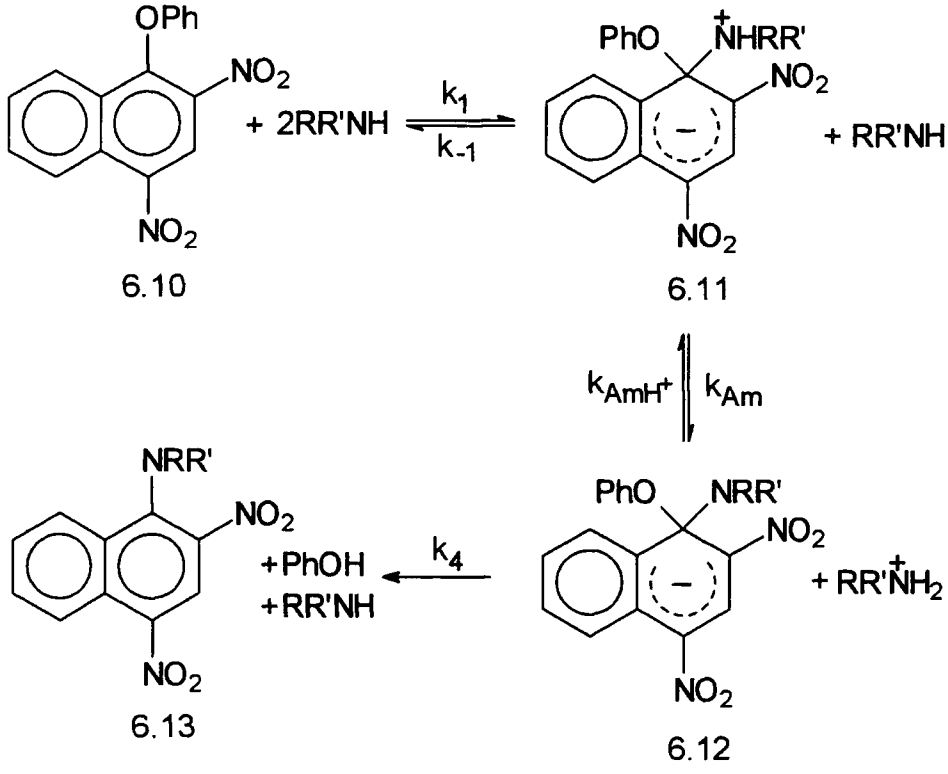
[piperidine]/ moldm^{-3}	[piperidinium chloride]/ moldm^{-3}	k_{slow}/ s^{-1}	k'_{slow}	k'_{slow}/ [Am]^2
0.004	0.01	0.0247	0.037	2310
0.006	0.01	0.0371	0.077	2140
0.008	0.01	0.0619	0.181	2830
0.010	0.01	0.0577	0.231	2310
0.020	0.01	0.0701	0.911	2280
0.002	0.0	0.0117	0.0131	3280
0.003	10.01	0.0211	0.0268	2980
0.004	0.01	0.0294	0.0435	2720
0.005	0.01	0.0376	0.0658	2630

6.4 Results for the reactions of phenyl 2,4-dinitronaphthyl ether

UV/ visible measurements of the reaction between phenyl 2,4-dinitronaphthyl ether, 6.10, and amines in DMSO showed a single process resulting in the formation of the substituted compound 6.13, as shown in scheme 6.2. This process involving attack at the 1-position can be represented by equation 6.14.

$$k_{obs} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 6.14}$$

In all cases, the final spectra were found to be identical to those of the separately prepared compounds in the presence of amines.



scheme 6.2

6.4.1 Reaction with butylamine

The reaction of phenyl 2,4-dinitronaphthyl ether, 6.7, with butylamine resulted in the amino substituted compound with λ_{max} = 392 and 524 nm. This reaction was measured at 525 nm with a parent concentration of 2.5 x 10^{-5} moldm^{-3}. Data are in table 6.8.
Values of the observed rate constant can be seen to increase linearly with amine concentration, indicating that nucleophilic attack by the amine is rate limiting, hence $k_{Am}[Am] >> k_{-1}$ and equation 6.14 reduces to equation 6.15.

$$k_{obs} = k_1[Am] \qquad \text{eqn 6.15}$$

Hence a value of 31 dm^{3}mol^{-1}s^{-1} can be obtained for k_1 from equation 6.15. Values of k_{calc}, obtained usng equation 6.15 with the above value give a good fit with experimental data.

Table 6.8. Kinetic data for the substitution reaction between phenyl 2,4-dinitronaphthyl ether, 6.7, and butylamine in DMSO at 25°C, measured at 525 nm.

[Butylamine]/ moldm^{-3}	k_{obs}/ s^{-1}	k_{obs}/ [Am]	k_{calc}[a]/ s^{-1}
0.01	0.31	31	0.31
0.02	0.62	31	0.62
0.03	0.90	30	0.93
0.04	1.2	31	1.24
0.05	1.5	30	1.55

a) Calculated using equation 6.15 with k_1 = 31 dm^{3}mol^{-1}s^{-1}.

6.4.2 Reaction with pyrrolidine

The reaction of phenyl 2,4-dinitronaphthyl ether with pyrrolidine gave the N-pyrrolidino substitution product, 6.10, with λ_{max} = 438 nm. This reaction was measured at 440 nm with a parent concentration of 2.5 x 10^{-5} moldm^{-3}. Data are in table 6.9.
Values of the rate constant show a dependence on amine concentration between the powers of one and two; indicating that proton transfer is partially rate limiting. Rearranging equation 6.14 gives equation 6.16.

$$\frac{[Am]}{k_{obs}} = \frac{k_{-1}}{k_1 k_{Am}[Am]} + \frac{1}{k_1} \qquad \text{eqn 6.16}$$

From a plot of [Am]/ k_{obs} against 1/ [Am], values of k_1 = 590 dm^{3}mol^{-1}s^{-1}, K_1k_{Am} = 2.4 x 10^4 dm^{6}mol^{-2}s^{-1} and k_{Am}/ k_{-1} = 41 dm^{3}mol^{-1} are obtained. Values of k_{calc}, obtained using the above values in equation 6.14 are in good agreement with those obtained experimentally.

Table 6.9 Kinetic data for the substitution reaction between phenyl 2,4-dinitronaphthyl ether and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ moldm^{-3}	k_{obs}/ s^{-1}	k_{obs}/ [Am]	k_{calc}[a]/ s^{-1}
0.002	0.076	38	0.088
0.004	0.33	83	0.330
0.006	0.68	114	0.690
0.008	1.03	130	1.10
0.01	1.85	185	1.7
0.02	5.39	269	5.3
0.03	10.0	334	9.7
0.04	14.6	366	14.5
0.05	19.7	394	19.7
0.07	28.0	400	30
0.10	43.0	430	47

a) Calculated using equation 6.14 with the values k_1 = 590 dm^{3}mol^{-1}s^{-1} and k_{Am}/ k_{-1} = 41 dm^{3}mol^{-1}.

6.4.3 Reaction with piperidine

The reaction between phenyl 2,4-dinitronaphthyl ether and piperidine occurs to give the amino substituted compound, 6.10, which has a λ_{max} = 421 nm. This reaction was measured at 420 nm with a parent concentration of 2.5 x 10^{-5} moldm^{-3}, data are in table 6.10.

Values of the observed rate constant can be seen to have a squared dependence on amine concentration, hence $k_{-1} >> k_{Am}[Am]$ and equation 6.14 reduces to equation 6.17. Hence a value of 580 dm^{6}mol^{-2}s^{-1} is obtained for K_1k_{Am}.

$$k_{obs} = \frac{k_1 k_{Am}}{k_{-1}}[Am]^2 \qquad \text{eqn 6.17}$$

The reaction was carried out with added DABCO; data are in table 6.10. The overall equation for the reaction with added DABCO can be expressed as equation 6.18.

$$k_{obs} = \frac{k_1[Am](k_{Am}[Am] + k_{DABCO}[DABCO])}{k_{-1} + k_{Am}[Am] + k_{DABCO}[DABCO]} \qquad \text{eqn 6.18}$$

Applying the condition $k_{-1} >> k_{Am}[Am] + k_{DABCO}[DABCO]$, equation 6.18 reduces to equation 6.19. From a plot of k_{obs}/ [Am] against amine concentration, values of K_1k_{Am} = 500 dm^{6}mol^{-2}s^{-1} and K_1k_{DABCO} = 86 dm^{6}mol^{-2}s^{-1} can be obtained.

$$k_{obs} = K_1[Am](k_{Am}[Am] + k_{DABCO}[DABCO]) \qquad \text{eqn 6.19}$$

Values of k_{calc} obtained with equations 6.17 and 6.19 and the values K_1k_{Am} = 540 dm^{6}mol^{-2}s^{-1} and K_1k_{DABCO} = 86 dm^{6}mol^{-2}s^{-1} are in reasonable agreement with experimental values.

Table 6.10 Kinetic data for the substitution reaction between phenyl 2,4-dinitronaphthyl ether and piperidine in DMSO at 25°C.

[piperidine]/ moldm^{-3}	[piperidinium chloride]/ moldm^{-3}	[DABCO]/ moldm^{-3}	k_{obs}/ s^{-1}	k_{obs}/ [Am]^2	k_{calc}[a]/ s^{-1}
0.01	-	-	0.061	610	0.054
0.02	-	-	0.228	570	0.22
0.03	-	-	0.519	577	0.49
0.04	-	-	0.942	589	0.86
0.05	-	-	1.45	580	1.35
0.01	0.01	-	0.054	539	0.054
0.02	0.01	-	0.219	547	0.22
0.03	0.01	-	0.494	549	0.49
0.04	0.01	-	0.836	523	0.86
0.05	0.01	-	1.34	537	1.35
0.02	-	0	0.218	-	□0.22
0.02	-	0.05	□0.281	-	0.30
0.02	-	0.10	0.348	-	0.39
0.02	-	0.15	0.477	-	0.47
0.02	-	0.20	0.542	-	0.56

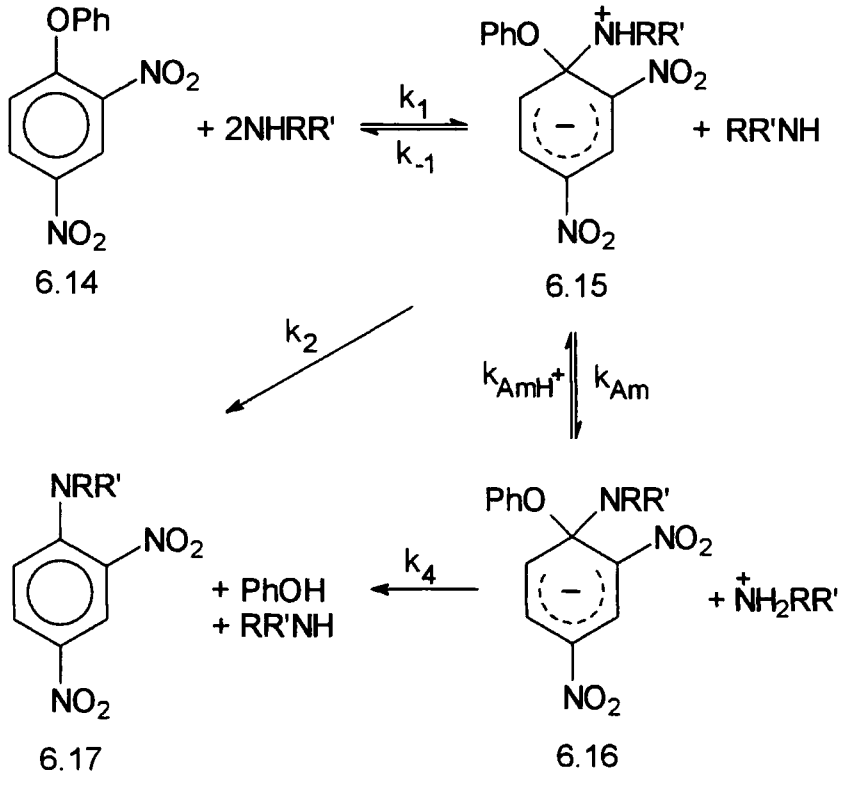
a) Calculated using equations 6.17 and 6.19 with the values K_1k_{Am} = 540 dm^{6}mol^{-2}s^{-1} and K_1k_{DABCO} = 86 dm^{6}mol^{-2}s^{-1}.

6.5 Reactions of phenyl 2,4-dinitrophenyl ether

UV/Visible measurements made on the reaction between phenyl 2,4-dinitrophenyl ether, 6.11, and amines in DMSO showed the presence of a single process resulting in formation of the substitution product, 6.14.

Possible pathways for the conversion are shown in scheme 6.3. Assuming that the only kinetically significant processes are the initial nucleophilic attack and the proton transfer step from the zwitterion to amine leads to equation 6.14

$$k_{obs} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 6.14}$$



scheme 6.3

6.5.1 Reaction with butylamine

The reaction between phenyl 2,4-dinitrophenyl ether, 6.14, and butylamine occurs to give the substitution product, 6.17 (NRR' = NC_4H_9), λ_{max} = 363 nm, as can be seen in figure 6.4. The reaction was measured at 363 nm with the parent 5 x 10^{-5} $moldm^{-3}$; data are in table 6.11.

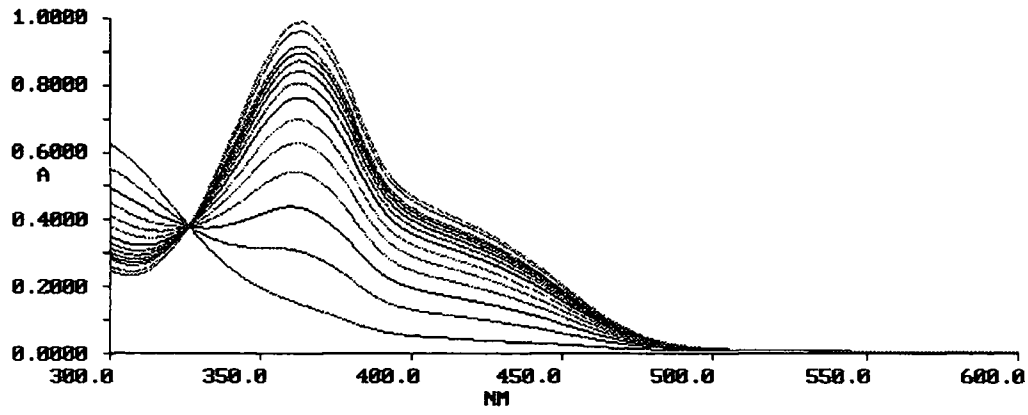


Figure 6.4. UV/ Visible spectra showing the reaction between phenyl 2,4-dinitrophenyl ether and butylamine.

Values of the observed rate constant show a linear dependence on amine concentration, hence $k_{Am}[Am] >> k_{-1}$ and equation 6.14 can be reduced to equation 6.15. Using this equation, a value of 4.2 x 10^{-2} $dm^3mol^{-1}s^{-1}$ can be obtained for k_1.

$$k_{obs} = k_1[Am] \qquad \text{eqn 6.15}$$

Table 6.11 Kinetic data for the reaction of phenyl 2,4-dinitrophenyl ether with butylamine in DMSO at 25°C.

[butylamine]/ $moldm^{-3}$	k_{obs}/ 10^{-4} s^{-1}	k_{obs}/[Am] / 10^{-2} $dm^3mol^{-1}s^{-1}$
0.01	4.2	4.2
0.02	8.3	4.2
0.03	12.6	4.2
0.04	16.7	4.2
0.05	20	4.0

6.5.2 Reaction with pyrrolidine

The reaction between phenyl 2,4-dinitrophenyl ether and pyrrolidine occurs to give the N-substituted product, 6.17 (NRR' = NC_4H_8), λ_{max} = 386 nm. This reaction was measured at 383 nm with a parent concentration of 5 x 10^{-5} moldm^{-3}; data are in table 6.12.

Values of the observed rate constant can be seen to have a dependence on amine concentration of between one and two. Rearranging equation 6.14 gives equation 6.16, and hence from a plot of [Am]/ k_{obs} against 1/ [Am], approximate values of k_1 = 1.1 dm^{3}mol^{-1}s^{-1} and K_1k_{Am} = 50 dm^{6}mol^{-2}s^{-1}.were obtained.

$$\frac{[Am]}{k_{obs}} = \frac{k_{-1}}{k_1 k_{Am}[Am]} + \frac{1}{k_1} \qquad \text{eqn 6.16}$$

The reaction was carried out with added DABCO, in which case equation 6.18 applies.

$$k_{obs} = \frac{k_1[Am](k_{Am}[Am] + k_{DABCO}[DABCO])}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 6.18}$$

Rearranging equation 6.18 gives equation 6.20, from which a value of k_{DABCO}/ k_{-1} can be calculated. Manipulation of the values obtained was carried out to obtain a best fit; the values obtained were: K_1k_{Am} = 43 dm^{6}mol^{-2}s^{-1}, k_1 = 1.15 dm^{3}mol^{-1}s^{-1}, k_{Am}/ k_{-1} = 37 dm^{3}mol^{-1}, K_1k_{DABCO} = 4 dm^{6}mol^{-2}s^{-1} and k_{DABCO}/ k_{-1} = 3.5 dm^{3}mol^{-1}.

$$k_{obs} = \frac{K_1k_{Am}[Am]^2 + K_1k_{DABCO}[DABCO][Am]}{1 + \frac{k_{Am}}{k_{-1}}[Am] + \frac{k_{DABCO}}{k_{-1}}[DABCO]} \qquad \text{eqn 6.20}$$

Values of k_{calc} obtained by using the above values in equations 6.16 and 6.20 gave a good fit with experimental values.

Table 6.12 Kinetic data for the substitution reaction between phenyl 2,4-dinitrophenyl ether and pyrrolidine in DMSO at 25°C.

[pyrrolidine]/ moldm^{-3}	[DABCO]/ moldm^{-3}	k_{obs}/ 10^{-3} s^{-1}	k_{calc}[a]/ 10^{-3} s^{-1}
0.001	-	0.06	0.04
0.002	-	0.20	0.16
0.0025	-	0.30	0.25
0.003	-	0.45	0.35
0.005	-	1.08	1.2
0.075	-	2.4	1.9
0.010	-	3.6	3.2
0.020	-	10	9.9
0.030	-	19	18
0.040	-	28	28
0.050	-	37	38
0.02	0.05	11	11
0.02	0.10	12.5	12.1
0.02	0.15	13	12.9
0.02	0.20	13	13.6

a0 Calculated using equations 6.16 and 6.20 with the values K_1k_{Am} = 43 dm^{6}mol^{-2}s^{-1}, K_1k_{DABCO} = 4 dm^{6}mol^{-2}s^{-1} and k_1 = 1.15 dm^{3}mol^{-1}s^{-1}.

6.5.3 Reaction with piperidine

The reaction between phenyl 2,4-dinitrophenyl ether and piperidine to give the substitution product, 6.17 (NRR' = NC_5H_{10}), λ_{max} = 392 nm, can be seen in figure 6.5. The reaction was measured at that wavelength with the parent concentration 2.5 x 10^{-5} $moldm^{-3}$. Data are in table 6.12.

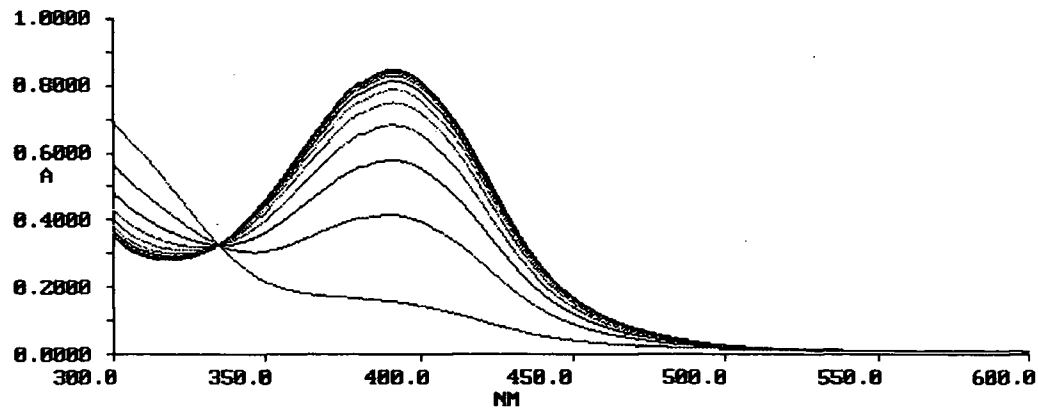


Figure 6.5. UV/Visible spectra showing the reaction between phenyl 2,4-dinitrophenyl ether and piperidine.

The plot of k_{obs}/ [Am] against amine concentration was found to have an intercept and so the uncatalysed, k_2, step must be considered. This can be expressed by the equation 6.21.

$$k_{obs} = \frac{k_1[Am](k_2 + k_{Am}[Am])}{k_{-1} + k_2 + k_{Am}[Am]} \qquad \text{eqn 6.21}$$

At the lower amine concentrations this plot was linear, implying that $k_{-1} >> k_2+k_{Am}[Am]$, so that equation 6.21 reduces to equation 6.22. From the plot of k_{obs} /[Am] against amine concentration, values of K_1k_{Am} = 0.8 $dm^6mol^{-2}s^{-1}$ and K_1 k_2 = 5 x 10^{-3} $dm^3mol^{-1}s^{-1}$ are obtained.

$$\frac{k_{obs}}{[Am]} = K_1k_2 + K_1k_{Am}[Am] \qquad \text{eqn 6.22}$$

With higher amine concentrations, k_{-1} is no longer much greater than $k_{Am}[Am]$, which implies $k_{-1} + k_{Am}[Am] >> k_2$, hence equation 6.21 becomes equation 6.23. With 0.1 moldm^{-3}, the value of $k_{obs}/ [Am]$ is 0.075. The values of K_1k_2 and K_1k_{Am} are known and so inserting these values into equation 6.22 gives:

$$0.075 = \frac{k_{obs}}{[Am]} = \frac{K_1k_2 + K_1k_{Am}[Am]}{1 + \frac{k_{Am}}{k_{-1}}[Am]}$$

$$\Rightarrow \qquad 0.075 = \frac{k_{obs}}{[Am]} = \frac{0.085}{1 + \frac{k_{Am}}{k_{-1}}[Am]}$$

Hence a value of k_{Am}/ k_{-1} = 1.3 dm^{3}mol^{-1} can be calculated.

The reaction with piperidine was carried out with added DABCO,where equation 6.23 applies, data are in table 6.12.

$$k_{obs} = \frac{k_1[Am](k_2 + k_{Am}[Am] + k_{DABCO}[DABCO])}{k_{-1} + k_{Am}[Am] + k_{DABCO}[DABCO]} \qquad \text{eqn 6.23}$$

At the base concentrations used, the condition $k_{-1} >> k_{Am}[Am] + k_{DABCO}[DABCO]$ applies thus reducing equation 6.23 to equation 6.24. Hence a plot of $k_{obs}/ [Am]$ against [DABCO] allows a value of K_1k_{DABCO} = 0.11 dm^{6}mol^{-2}s^{-1} to be obtained.

$$\frac{k_{obs}}{[Am]} = K_1k_2 + K_1k_{Am}[Am] + K_1k_{DABCO}[DABCO] \qquad \text{eqn 6.24}$$

Values of k_{calc} obtained using equations 6.22 and 6.24 with the values K_1k_2 = 5 x 10^{-3} dm^{3}mol^{-1}s^{-1}, K_1k_{Am} = 0.8 dm^{6}mol^{-2}s^{-1} and K_1k_{DABCO} = 0.11 dm^{6}mol^{-2}s^{-1}.

Table 6.12 Kinetic data for the reaction between phenyl 2,4-dinitrophenyl ether and piperidine in DMSO at 25°C.

[piperidine]/ moldm^{-3}	[DABCO] / moldm^{-3}	k_{obs} / 10^{-4} s^{-1}	k_{calc}[a]/ 10^{-4} s^{-1}
0.01	-	1.3	1.3
0.02	-	4.2	4.2
0.03	-	8.1	8.7
0.04	-	15	15
0.05	-	22	23
0.10	-	75	85
0.02	0	4.4	4.2
0.02	0.05	5.6	5.3
0.02	0.10	6.5	6.4
0.02	0.15	7.6	7.5
0.02	0.20	8.7	8.6

a) Calculated using equations 6.22 and 6.44 with the values $K_1k_2 = 5 \times 10^{-3}$ dm^{3}mol^{-1}s^{-1}, $K_1k_{Am} = 0.8$ dm^{6}mol^{-2}s^{-1} and $K_1k_{DABCO} = 0.11$ dm^{6}mol^{-2}s^{-1}.

6.6 Discussion

The reaction of phenyl 2,4,6-trinitrophenyl ether with all three amines used showed the presence of two processes, a rapid reaction corresponding to attack at the 3-position; followed by a slower reaction, corresponding to the substitution of the phenoxy group. The reaction of both the phenyl 2,4-dinitronaphthyl ether and the phenyl 2,4-dinitrophenyl ether with the amines showed the presence of one process, the substitution reaction. Data is summarised in tables 6.13 and 6.14.

6.6.1 Reaction at an unsubstituted ring position

The results show that for the reaction of butylamine with phenyl 2,4,6-trinitrophenyl ether, the rate determining step is the nucleophilic attack by the amine, however with pyrrrolidine and piperidine the rate determining step changes to proton transfer. The change in rate limiting step is due to a change in the ratio $k_{Am}[Am]/ k_{-3}$, proton transfer becoming rate limiting when the ratio has a value less than one. It is expected that the value of k_{Am} will show the greatest change with changing amine

Values of k_{Am} and k_{AmH^+} have been shown to be largely independent of the nature of the substrate for any given amine, this is largely due to the fact that reaction is occurring at an unsubstituted ring position and hence any steric effects will be similar at the reaction centre for all trinitrophenyl compounds. The ratio of k_{Am}/ k_{AmH^+} has been shown[19,20] to have a value of approximately 500 for trinitro-activated substrates, the value not varying greatly with changes in aromatic substrate or amine. This is due to the higher acidity of the zwitterions over the corrseponding ammonium ions.
Values of k_{Am} have been seen[19,21] to decrease in the order butylamine > pyrrolidine > piperidine, hence values of k_{Am} and k_{AmH^+} would be expected to occur in the same order for the phenylether compounds studied. This order is explained by the increasing steric hindrance to approach of the amine going from a primary to a secondary amine, pyrrolidine, increasing further for the more sterically hindered piperidine. Data in table 6.15 show that the value of k_{AmH^+} for reaction with pyrrolidine is much larger than that for piperidine.
Values of $K_{c,3}$ decrease in the order pyrrolidine > piperidine > butylamine, this reflects the relative basicities of the three amines as steric effects do not create a large influence as attack is occuring at an unsubstituted ring position. Values of k_3 would be expected to show the same trends.

6.6.2 Reaction at a substituted ring position

As observed with other activated aromatic compounds, attack at a substituted ring position occurs with a much lower rate constant than attack at an unsubstituted ring position. During the reaction of the ethyl trinitrophenyl ether and ethyl 2,4-dinitronaphthyl ether, intermediates such as 6.18 could be observed and hence the kinetics of their formation and acid catalysed decomposition measured. Such intermediates were not observable with any of the compounds studied.
The reaction of butylamine at a substituted ring position was shown to be first order in amine concentration, indicating that nucleophilic attack by the amine was rate determining. This being followed by rapid proton transfer and loss of the phenoxy group. This is thought to be due to high values of k_{Am} and low values of k_{-1}, possibly caused by lower steric interactions in the zwitterion with the primary amine, rather than with a secondary amine.

The reactions of pyrrolidine at a substituted ring position were base catalysed. This could be due to either rate limiting proton transfer from the zwitterion to base or general acid catalysed expulsion of the leaving group, the SB-GA mechanism. If the latter case applied then values quoted for K_1k_{Am} would in fact represent $K_{c,1}k_{Am}$. The former explanation is preferred for several reasons, one of those being the failure to observe intermediates such as 6.8. If reaction with phenyl 2,4,6-trinitrophenyl ether is compared with the corresponding ethoxy compound, see table 6.13, the experimentally determined values with the phenoxy compound can be seen to have better agreement with values of K_1k_{Am} than with values of $K_{c,1}k_4$.
Thus the value of K_1k_{Am} for reaction of the ethyl ether with pyrrolidine is 1×10^5 $dm^6mol^{-2}s^{-1}$ while the corresponding value of $K_{c,1}k_4$ is 48 $dm^6mol^{-2}s^{-1}$. For reaction of the phenyl ether only one value is experimentally accesible and its magnitude 1.8×10^5 $dm^6mol^{-2}s^{-1}$ indicates that this is more likely to correspond to K_1k_{Am} than to $K_{c,1}k_4$. The value of k_1 is expected to be somewhat larger for the phenyl than for the ethyl ether due to its larger inductive effect, while values of k_{Am} are likely to be similar. Hence it is likely that the measured process corresponds to rate determining proton transfer from the zwitterion to base.

Table 6.13 Comparison of the data for the reaction of amines with phenyl 2,4,6-trinitrophenyl ether and ethyl 2,4,6-trinitrophenyl ether.

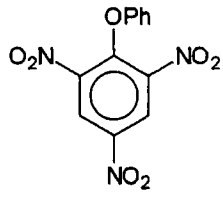
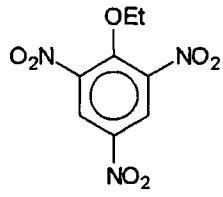
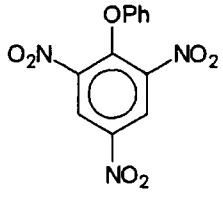
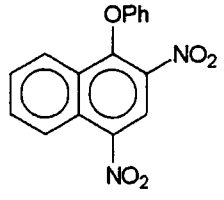
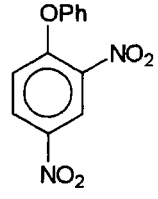
		
K_1k_{Am}(pyrrolidine)	1.8×10^5	1×10^5
K_1k_{Am}(piperidine)	3×10^3	5.6×10^3
$K_{c,1}k_4$(pyrrolidine)	-	480
k_1(butylamine)	400	250

Table 6.14 Summary of the kinetic data for the reaction of phenyl 2,4,6-trinitrophenyl ether, phenyl 2,4-dinitrophenyl ether and phenyl 2,4-dinitronaphthyl ether with amines in DMSO.

				
Butylamine	k_1	410	31	4.2×10^{-2}
Pyrrolidine	K_1k_{Am}	2×10^5	2.4×10^4	43
	k_1	1×10^4	590	1.15
	k_{Am}/k_1	20	41	37
	K_1k_{DABCO}			4
Piperidine	K_1k_{Am}	2600	540	0.8
	K_1k_{DABCO}		86	0.11
	K_1k_2			5×10^{-3}

The data in table 6.14 shows that the values of K_1k_{Am} for pyrrolidine are a factor of approximately 50 greater than values for piperidine. This can be accounted for by a factor of approximately 20 in the value of k_{Am} with the less sterically hindered pyrrolidine and a factor of 2-3 in the value of K_1 with the more nucleophilic amine.
The uncatalysed, k_2, pathway was detected during the reaction of phenyl 2,4-dinitrophenyl ether with piperidine. Generally it is found that the effectiveness of the base catalysed step relative to the uncatalysed decomposition of the intermediate decreases as the activation of the substrate decreases. The dinitrophenyl compound was the least activated substrate studied and hence detection of the uncatalysed step became possible.

In the case of pyrrolidine proton transfer is partially rate limiting in the substitution reaction. Values shown in table 6.14 can be calculated for k_{Am}/k_{-1}. Values of k_{Am}/ k_{-1} are similar for all three compounds studied. The naphthyl compound would have less ring activation than the trinitrophenyl compound and hence a larger value of k_{-1} is expected. However, steric hindrance to proton transfer from the zwitterion would be reduced as the second aromatic ring would cause less steric hindrance than the 6-nitro group and hence a larger value of k_{Am} is expected. The two differing factors seemed to cancel each other out, giving a similar value to the trinitrophenyl compound.
The phenyl 2,4-dinitrophenyl ether would again have less ring activationand hence a larger k_{-1} value . However, even less steric hindrance to proton transfer would occur, due to the lack of 6-substituent giving a larger value of k_{Am}. Overall the 3 compounds having rather similar values of the ratio k_{Am}/ k_{-1}.

6.7.Comparison of data for phenyl ethers and phenyl sulfides

Data are compared in tables 6.15 to 6.17 for reaction of n-butylamine, pyrrolidine and piperidine with phenyl ethers and phenyl sulfides. The data are compatible with two major effects:- i) the greater steric effect of the phenylthio group and ii) the greater inductive effect of the phenoxy group.
In the picryl compounds, where attack may occur at an unsubstituted ring position, values of $K_{c,3}$ are greater for reaction of the phenyl ethers by a factor of 8-10. Values of k_3 are similarly enhanced. This is attributable to the greater size of the phenylthio group which will be expected to result in an increase in the degree of rotation from the ring-plane of the nitro groups at the 2- and 6- positions. The greater inductive effect of the phenoxy group, relayed to the 3- position, will also favour attack on the phenyl ether. Values of k_{AmH^+}, the rate constants for proton transfer, are virtually identical for a given amine reflecting the similar steric situation at the 3- position in the two classes of compound.

For reaction at the 1- position, values of K_1k_{Am} are ca. 1000 times larger for attack on the phenyl ethers. For reaction at the 1- position, steric and electronic effects will be maximised. The results provide evidence for the greater steric effect of the phenylthio group and the greater electronic effect of the phenoxy group. The major effect in the product K_1k_{Am} is likely to be in the value of K_1. Values of k_1 are between ten and one hundred times smaller for reaction with the phenyl sulphides, and it is likely that values of k_{-1} will be larger for the sulphur compounds.

Hence values of the ratio k_{Am}/k_{-1} for the reactions with pyrrolidine are ca. ten times smaller for the phenyl sulphide. The major factor here is likely to be variation in the k_{-1} values, since values of k_{Am} will probably not vary much with structure.

Table 6.15. Comparison of kinetic and equilibrium data for the reactions of phenyl ethers and phenyl sulfides with butylamine.

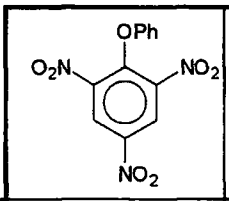
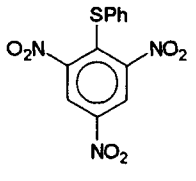
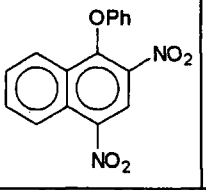
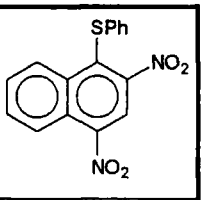
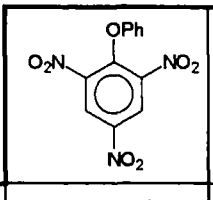
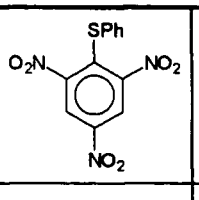
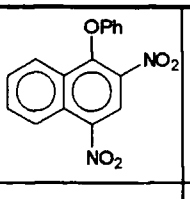
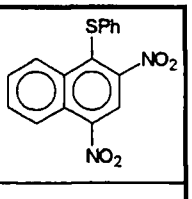
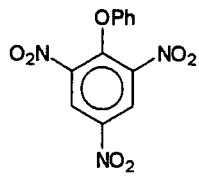
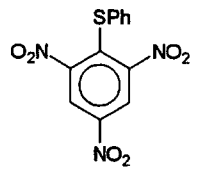
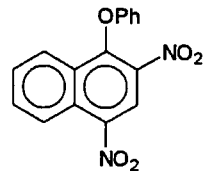
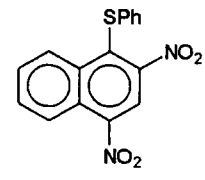
				
k_3/ $dm^3mol^{-1}s^{-1}$	8000	1500	-	-
$K_{c,3}$/ dm^3mol^{-1}	210	33	-	-
k_1/ $dm^3mol^{-1}s^{-1}$	410	33	31	0.46

Table 6.16. Comparison of kinetic and equilibrium data for the reactions of phenyl ethers and phenyl sulfides with pyrrolidine.

				
k_3/ $dm^3mol^{-1}s^{-1}$	(8×10^4)	12500	-	-
$K_{c,3}$/ dm^3mol^{-1}	1100	108	-	-
$k_{Am}/k_{-3}/dm^3mol^{-1}$	(38)	22		
k_{AmH^+}[a]/$dm^3mol^{-1}s^{-1}$	2800	2600		
K_1k_{Am}/ $dm^6mol^{-2}s^{-1}$	2×10^5	250	2.4×10^4	30
k_1/ $dm^3mol^{-1}s^{-1}$	1×10^4	(330)	590	6
k_{Am}/k_{-1}	20	(0.8)	41	5

a) Refers to attack at the 3-position.

Table 6.17. Comparison of kinetic and equilibrium data for the reactions of phenyl ethers and phenyl sulfides with piperidine.

				
$K_{c,3}$/ dm^3mol^{-1}	400	48	-	-
k_{AmH^+}[a]/ $dm^3mol^{-1}s^{-1}$	400	400	-	-
K_1k_{Am}/ $dm^6mol^{-2}s^{-1}$	2600	N. M.	500	0.4

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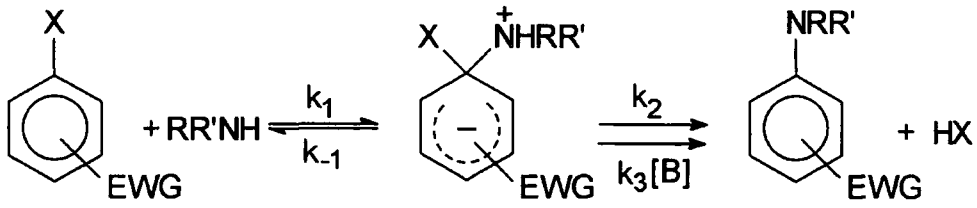
CHAPTER 7

The Reaction Of Morpholine With Several Phenyl Ethers

The Reaction of Morpholine with Several Phenyl Ethers

7.1 Introduction

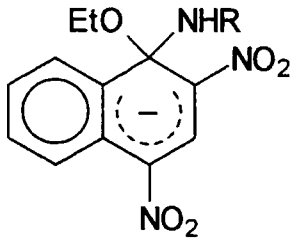
Nucleophilic attack by amines at a substituted ring position usually results in substitution[1-3], the accepted mechanism for this process is shown in scheme 7.1.



scheme 7.1

The base catalysed step may occur via rate determining proton transfer from the zwitterion to the base followed by rapid loss of the leaving group; or via a rapidly established equilibrium between the zwitterion and anion followed by rate determining acid catalysed leaving group expulsion, the SB-GA mechanism.[4-7]

The latter mechanism became generally accepted for the displacement of alkoxy groups by amines in DMSO after a study carried out by Orvik and Bunnett.[8] They were able to observe both the formation and acid catalysed decomposition of the intermediate, 7.1.



7.1

Since then many more studies on similar reactions have observed related intermedates, giving more evidence for the SB-GA mechanism.[4, 9-11]

However, more recently Sekiguchi and co-workers[12] suggested the base catalysis observed during the reaction of butylamine with 1-pyrrolidino 2,4-dinitronaphthalene was due to rate limiting proton transfer.

Morpholine is considerably less basic than piperidine; pK_a values in water are morpholine 8.33, piperidine 11.12. However, the steric requirements should be similar. Hirst and coworkers have shown recently that some substitution reactions involving morpholine are subject to base catalysis whereas the corresponding reactions with piperidine are not. It was thus thought to be of interest to compare the behaviour of morpholine with other cyclic secondary amines.

Kinetic and equilibrium studies were made on the reaction of morpholine with 1,3,5-trinitrobenzene, phenyl 2,4,6-trinitrophenyl ether, phenyl 2,4-dinitronaphthyl ether and phenyl 2,4-dinitrophenyl ether in DMSO.

7.2 Experimental

1,3,5-trinitrobenzene:- Used as supplied.

phenyl 2,4,6-trinitrophenyl ether:- Prepared as described in chapter 6.

phenyl 2,4-dinitronaphthyl ether:- Prepared as described in chapter 6.

phenyl 2,4-dinitrophenyl ether:- Used as supplied.

7.3 Results

7.3.1 Reaction with 1,3,5-trinitrobenzene

UV/Visible measurements of the reaction between morpholine and 1,3,5-trinitrobenzene show the presence of a single process resulting in a species with λ_{max} = 447 and 530 nm. By analogy with the reaction of other amines, this will be the adduct formed by attack at an unsubstituted ring position, as shown in scheme 7.2. The reaction was measured at 445 nm with a parent concentration of 5 x 10^{-5} moldm^{-3}, data are in table 7.1. The rate equation can be expressed by equation 7.1.

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 7.1}$$

Values of the observed rate constant show a squared dependence on morpholine concentration, hence $k_{-3} >> k_{Am}$ [Am] and equation 7.1 reduces to equation 7.2. From a plot of k_{obs}/ [Am] against amine concentration a value for K_3k_{Am} of 8.5 x 10^3 $dm^6mol^{-2}s^{-1}$ was obtained.

$$\frac{k_{obs}}{[Am]} = K_3k_{Am}[Am] \qquad \text{eqn 7.2}$$

The reaction was also carried out with added DABCO; data are in table 7.1. The overall expression for reaction with added DABCO is equation 7.3.

$$k_{obs} = \frac{k_3[Am](k_{Am}[Am] + k_{DABCO}[DABCO])}{k_{-3} + k_{Am}[Am] + k_{DABCO}[DABCO]} \qquad \text{eqn 7.3}$$

Applying the condition $k_{-3} >> k_{Am}[Am]+k_{DABCO}[DABCO]$ equation 7.3 reduces to equation 7.4. Hence from a plot of k_{obs} /[Am] against amine concentration values of K_3k_{Am} = 8.5 x 10^3 $dm^6mol^{-2}s^{-1}$ and K_3k_{DABCO} = 5 x 10^3 $dm^6mol^{-2}s^{-1}$ could be obtained.

$$\frac{k_{obs}}{[Am]} = K_3k_{Am}[Am] + K_3k_{DABCO}[DABCO] \qquad \text{eqn 7.4}$$

The reaction was also carried out with added morpholinium perchlorate in which case the expression for the reaction occurring is equation 7.5.

$$k_{obs} = \frac{k_3k_{Am}[Am]^2}{k_{-3} + k_{Am}[Am]} + \frac{k_{-3}k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 7.5}$$

Allowing for the condition $k_{-3} >> k_{Am}[Am]$, equation 7.6 can be obtained and hence a value for k_{AmH^+} of 400 $dm^3mol^{-1}s^{-1}$.

$$k_{obs} = K_3k_{Am}[Am]^2 + k_{AmH^+}[AmH^+] \qquad \text{eqn 7.6}$$

The equilibrium constant, $K_{c,3}$, can be expressed by equation 7.7 and using the values calculated above , K_3k_{Am} = 8500 $dm^6mol^{-2}s^{-1}$ and k_{AmH^+} = 400 $dm^3mol^{-1}s^{-1}$, gives a value of 21 dm^3mol^{-1}.

$$K_{c,3} = \frac{k_3k_{Am}}{k_{-3}k_{AmH^+}} \qquad \text{eqn 7.7}$$

Alternatively the equilibrium constant, $K_{c,3}$, can be calculated using absorbance values in equation 7.8, giving a value of 26 dm^3mol^{-1} (see table 7.2), which is in reasonable agreement with the value obtained above.

$$K_{c,3} = \frac{Abs}{Abs_\infty - Abs} \times \frac{[AmH^+]}{[Am]^2} \qquad \text{eqn 7.8}$$

Values of k_{calc}, obtained using equations 7.2, 7.4 and 7.8 with the values K_3k_{Am} = 8500 $dm^6mol^{-2}s^{-1}$, K_3k_{DABCO} = 5000 $dm^6mol^{-2}s^{-1}$ and k_{AmH^+} = 400 $dm^3mol^{-1}s^{-1}$, are in reasonable agreement with those obtained experimentally.

Table 7.1 Kinetic data for the reaction between 1,3,5-trinitrobenzene and morpholine in DMSO at 25°C.

[morpholine]/ $moldm^{-3}$	[DABCO]/ $moldm^{-3}$	[morpholinium perchlorate]/ $moldm^{-3}$	k_{obs}/ s^{-1}	k_{calc}[a]/ s^{-1}
0.03	-	-	7.9	7.7
0.04	-	-	14.3	13.6
0.05	-	-	20	21
0.06	-	-	30	31
0.07	-	-	40	41
0.08	-	-	55	54
0.09	-	-	66	69
0.10	-	-	81	85
0.02	0	-	3.4	3.4
0.02	0.05	-	8.0	8.4
0.02	0.10	-	13.2	13.4
0.02	0.15	-	18	18
0.02	0.20	-	24	23
0.01	-	0.01	4.7	4.8
0.02	-	0.01	7.8	7.4
0.03	-	0.01	12.2	11.7
0.04	-	0.01	17.8	17.6
0.05	-	0.01	25	25
0.06	-	0.01	34	34
0.10	-	0.01	82	89

a) Calculated using equation 7.2, 7.4 and 7.8 with the values K_3k_{Am} = 8500 $dm^6mol^{-2}s^{-1}$, K_3k_{DABCO} = 5000 $dm^6mol^{-2}s^{-1}$ and k_{AmH^+} = 400 $dm^3mol^{-1}s^{-1}$.

Table 7.2 Kinetic and equilibrium data for the reaction between 1,3,5-trinitrobenzene and morpholine in DMSO at 25°C.

[morpholine] / moldm^{-3}	[morpholinium perchlorate]/ moldm^{-3}	k_{obs}/ s^{-1}	Abs[a]	$K_{c,3}$[b]/ dm^{3}mol^{-1}
0.02	0.01	5.9	0.084	26.3
0.02	0.02	8.2	0.061	30.8
0.02	0.03	11.7	0.049	33.1
0.04	0.01	16	0.118	17.6
0.04	0.02	19	0.107	25.2
0.04	0.03	22	0.094	26.7

a) Measured at 445 nm.

b) Calculated using equation 7.8 with the $Abs_{\infty} = 0.16$.

7.3.2 Reaction with phenyl 2,4,6-trinitrophenyl ether

Uv/ visible measurements made on the reaction between phenyl 2,4,6-trinitrophenyl ether and morpholine showed the presence of two reactions, an initial fast reaction giving a species with λ_{max} = 432 and 500 nm followed by a slower reaction giving a species with λ_{max} = 418 and 480 nm, as shown in figure 7.1. Reaction at an unsubstituted ring position is known to occur at a faster rate than attack at a substituted ring position[1, 6, 9, 13] and hence the rapid reaction is believed to be the attack at the 3-position and the slower reaction, substitution of the phenyl ether group. The final spectrum obtained was found to be identical to that of a separately prepared sample of the substitution product (N-morpholino 2,4,6-trinitrobenzene) in the presence of morpholine in DMSO. A further, much slower reaction was seen to occur as found with other amines.

The rapid reaction was measured at 435 nm with a parent concentration of 2.5 x 10^{-5} moldm^{-3}, data are in table 7.3. The rate expression for attack at the 3-position is equation 7.9.

$$k_{obs} = \frac{k_3 k_{Am}[Am]^2 + k_{-3} k_{AmH^+}[AmH^+]}{k_{-3} + k_{Am}[Am]} \qquad \text{eqn 7.9}$$

In the absence of added salt, the rate constants for attack at the 3-position show a squared dependence on amine concentration, hence $k_{-3} >> k_{Am}[Am]$ and so equation 7.9 reduces to equation 7.10, from which a value of 2450 $dm^6mol^{-2}s^{-1}$ is obtained for K_3k_{Am}.

$$k_{obs} = K_3k_{Am}[Am]^2 \qquad \text{eqn 7.10}$$

With added morpholinium perchlorate, equation 7.11 applies and hence a value for k_{AmH^+} of 600 $dm^3mol^{-1}s^{-1}$ is obtained.

$$k_{obs} = K_3k_{Am}[Am]^2 + k_{AmH^+}[AmH^+] \qquad \text{eqn 7.11}$$

A value for the equilibrium constant, $K_{c,3}$, can be obtained using the above values in equation 7.12, giving a value of 4.1 dm^3mol^{-1}.

$$K_{c,3} = \frac{k_3k_{Am}}{k_{-3}k_{AmH^+}} \qquad \text{eqn 7.12}$$

The equilibrium constant can also be obtained from absorbance values in equation 7.13, giving a value of 5 dm^3mol^{-1} ,which is in reacsonable agreement with that obtained above.

$$K_{c,3} = \frac{Abs}{Abs_\infty - Abs} \times \frac{[AmH^+]}{[Am]^2} \qquad \text{eqn 7.13}$$

Values of k_{calc} obtained usng equations 7.10 and 7.11 with the values K_3k_{Am} = 2450 $dm^6mol^{-2}s^{-1}$ and k_{AmH^+} = 600 $dm^3mol^{-1}s^{-1}$. are in good agreement with experimental data.

Table 7.3 Kinetic and equilibrium data for the reaction between phenyl 2,4,6-trinitrophenyl ether and morpholine in DMSO at 25°C.

[morpholine]/ moldm^{-3}	[morpholinium perchlorate]/ moldm^{-3}	k_{obs}/ s^{-1}	Abs[a]	$K_{c,3}$[b]/ dm^{3}mol^{-1}	k_{calc}[c]/ s^{-1}
0.02	-	1.07	-	-	0.98
0.03	-	2.24	-	-	2.21
0.04	-	3.86	-	-	3.92
0.05	-	6.01	-	-	6.12
0.01	0.01	6.02	0.006	5.2	6.2
0.02	0.01	6.70	0.023	5.9	7.0
0.03	0.01	8.0	0.037	4.9	8.2
0.04	0.01	9.8	0.052	4.7	9.9
0.05	0.01	12.7	0.064	4.5	12.1
0.10	0.01	29	0.099	4.5	30.5
0.10	-	-	0.121	-	-

a) Measured at 435 nm.

b) Calculated using equation 7.13 with $Abs_\infty = 0.121$.

c) Calculated using equations 7.10 and 7.11 with the values $K_3k_{Am} = 2450$ dm^{6}mol^{-2}s^{-1} and $k_{AmH^+} = 600$ dm^{3}mol^{-1}s^{-1}.

The slower reaction was measured at 370 nm with a parent concentration of 5 x 10^{-5}moldm^{-3}, data are in table 7.4. The rate constant for the slower reaction can be expressed by equation 7.14, allowing for the rapid formation of the 3-adduct.

$$k_{slow} = \frac{k_1 k_{Am}[Am]^2}{(k_{-1} + k_{Am}[Am])\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right)} \qquad \text{eqn 7.14}$$

It is more convenient however to define a modified rate constant, k'_{slow} (equation 7.15), which reduces equation 7.14 to equation 7.16.

$$k'_{slow} = k_{slow}\left(1 + K_{c,3}\frac{[Am]^2}{[AmH^+]}\right) \qquad \text{eqn 7.15}$$

$$k'_{slow} = \frac{k_1 k_{Am}[Am]^2}{k_{-1} + k_{Am}[Am]} \qquad \text{eqn 7.16}$$

Values of k'_{slow} , calculated using equation 7.15 assuming $K_{c,3}$ =4.1 dm^3mol^{-1}, show a squared dependence on amine concentration, hence $k_{-1} >> k_{Am}[Am]$ and equation 7.16 reduces to equation 7.17. From this equation a value for K_1k_{Am} of 75 $dm^6mol^{-2}s^{-1}$ can be obtained.

$$k'_{slow} = K_1 k_{Am}[Am]^2 \qquad \text{eqn 7.17}$$

Values of k_{calc} obtained using equations 7.15 and 7.17 with the values $K_{c,3}$ = 4.1 dm^3mol^{-1} and K_1k_{Am} = 75 $dm^6mol^{-2}s^{-1}$ are in good agreement with those obtained experimentally.

Table 7.4 Kinetic data for the substitution reaction between phenyl 2,4,6-trinitrophenyl ether and morpholine in DMSO at 25°C.

[morpholine]/ $moldm^{-3}$	[morpholinium perchlorate]/ $moldm^{-3}$	k_{slow}/ 10^{-3} s^{-1}	k'_{slow}[a]	$k'_{slow}/[Am]^2$ / 10^{-3}	k_{calc}[b]/ 10^{-3} s^{-1}
0.002	0.01	0.52	0.52	130	0.3
0.004	0.01	1.4	1.4	87	1.2
0.006	0.01	2.7	2.7	76	2.7
0.008	0.01	5.2	5.3	83	4.7
0.01	0.01	7.0	7.2	73	7.2
0.015	0.01	13	14	63	15
0.02	0.01	21	24	60	26

a) Calculated using equation 7.15 with a value for $K_{c,3}$ = 4.1 dm^3mol^{-1}.

b) Calculated using equations 7.15 and 7.17 with the values $K_{c,3}$ = 4.1 dm^3mol^{-1} and K_1k_{Am} = 75 $dm^6mol^{-2}s^{-1}$.

7.3.3 Reaction with phenyl 2,4-dinitronaphthyl ether

Uv/ visible measurements showed the presence of a single process occurring to give the substitution product with λ_{max} = 409 nm. This reaction was measured at 410 nm with a parent concentration of 5 x 10^{-5} mol dm^{-3}, data are in table 7.5.

The values of the observed rate constant show a squared dependence on amine concentration, therefore $k_{-1} >> k_{Am}[Am]$. Equation 7.1 therefore becomes equation 7.2 and a value of 11 $dm^6mol^{-2}s^{-1}$ is obtained for K_1k_{Am}.

$$\frac{k_{obs}}{[Am]} = K_1 k_{Am}[Am] \qquad \text{eqn 7.2}$$

The reaction was carried out in the presence of added DABCO where equation 7.4 was found to apply. A plot of k_{obs}/ [Am] against DABCO concentration allows values of K_1k_{Am} = 10 $dm^6mol^{-2}s^{-1}$ and K_1k_{DABCO} = 5 $dm^6mol^{-2}s^{-1}$ to be obtained.

$$\frac{k_{obs}}{[Am]} = K_1 k_{Am}[Am] + K_1 k_{DABCO}[DABCO] \qquad \text{eqn 7.4}$$

The reaction was also carried out with added morpholinium perchlorate, where the values obtained were similar to those in the absence of added salt. Values calculated using equations 7.2 and 7.4 gave a reasonable fit with experimental data.

Table 7.5 Kinetic data for the reaction between phenyl 2,4-dinitronaphthyl ether and morpholine in DMSO at 25°C.

[morpholine]/ moldm^{-3}	[morpholinium perchlorate]/ moldm^{-3}	[DABCO]/ moldm^{-3}	k_{obs}/ 10^{-3} s^{-1}	k_{calc}/ $10^{-3}s^{-1}$
0.01	-	-	1.19	1.1
0.02	-	-	4.4	4.4
0.03	-	-	9.9	9.9
0.04	-	-	17	17.6
0.05	-	-	26	27
0.02	-	0	4.44	4.4
0.02	-	0.05	8.55	9.4
0.02	-	0.10	12.6	14
0.02	-	0.15	17.5	19
0.02	-	0.20	23.3	24
0.02	0.01	-	5.33	4.4
0.03	0.01	-	10.9	9.9
0.04	0.01	-	20	17.6
0.05	0.01	-	30	27

7.3.4 Reaction with phenyl 2,4-dinitrophenyl ether

Uv/ visible measurements made of the reaction between phenyl 2,4-dinitrophenyl ether and morpholine showed the presence of a single process giving a species with λ_{max} = 386 nm, as can be seen in figure 7.1. This process, giving the substitution product, was measured at 385 nm with a parent concentration of 5 x 10^{-5} moldm^{-3}, data are recorded in table 7.6.

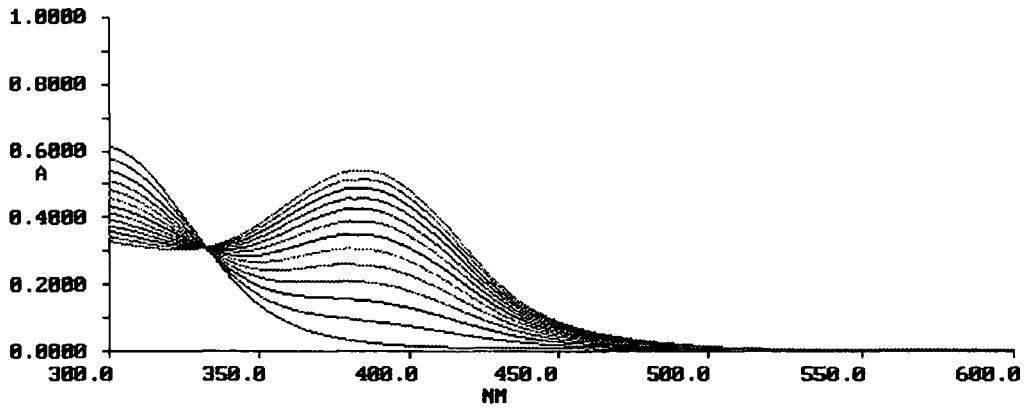


Figure 7.1. UV/Visible spectra showing the reaction between phenyl 2,4-dinitrophenyl ether and morpholine, resulting in a species with λ_{max} = 385nm.

A plot of k_{obs}/ [Am] against amine concentration is linear with an intercept indicating that the uncatalysed, k_2, step must be contributing to the overall process, hence equation 7.18 applies.

$$k_{obs} = \frac{k_1[Am](k_2 + k_{Am}[Am])}{k_{-1} + k_2 + k_{Am}[Am]} \qquad \text{eqn 7.18}$$

The linearity of the above plot indicates that the condition $k_{-1} >> k_{Am}[Am]$ applies and equation 7.19 can be obtained. From a plot of k_{obs}/ [Am] against amine concentration values of K_1k_{Am} = 1.3 x 10^{-2} dm^{6}mol^{-2}s^{-1} and K_1k_2 = 4.5 x 10^{-4} s^{-1} are obtained.

$$\frac{k_{obs}}{[Am]} = K_1k_2 + K_1k_{Am}[Am] \qquad \text{eqn 7.19}$$

The reaction was also measured with added DABCO, allowing for the condition $k_{-1} >> k_{Am}[Am]$, equation 7.20 applies. Hence a plot of k_{obs}/ [Am] against amine concentration gives a value for K_1k_{DABCO} of 7.7 x 10^{-3} dm^{6}mol^{-2}s^{-1}.

$$\frac{k_{obs}}{[Am]} = K_1k_2 + K_1k_{Am}[Am] + K_1k_{DABCO}[DABCO] \quad \text{eqn 7.20}$$

Values of k_{calc} obtained using equations 7.19 and 7.20 with the values obtained above are in good agreement with experimental values.

Table 7.6 Kinetic data for the reaction between phenyl 2,4-dinitrophenyl ether and morpholine in DMSO at 25°C.

[morpholine]/ moldm^{-3}	[DABCO]/ moldm^{-3}	k_{obs}/ 10^{-4} s^{-1}	k_{calc}[a]/ 10^{-4} s^{-1}
0.05	-	0.43	0.55
0.075	-	1.03	1.06
0.10	-	1.67	1.75
0.15	-	3.67	3.6
0.20	-	6.04	6.1
0.25	-	8.75	9.2
0.01	0	1.69	1.75
0.01	0.05	2.19	2.14
0.01	0.10	2.52	2.52
0.01	0.15	2.76	2.90
0.01	0.20	3.47	3.34
0.01	0.25	3.68	3.68

a) Calculated from equations 77.19 and 7.20 with the values K_1k_{Am} = 1.3 x 10^{-2} dm^{6}mol^{-2}s^{-1}, K_1k_2 = 4.5 x 10^{-4} s^{-1} and K_1k_{DABCO} = 7.7 x 10^{-3} dm^{6}mol^{-2} s^{-1}.

7.4 Discussion

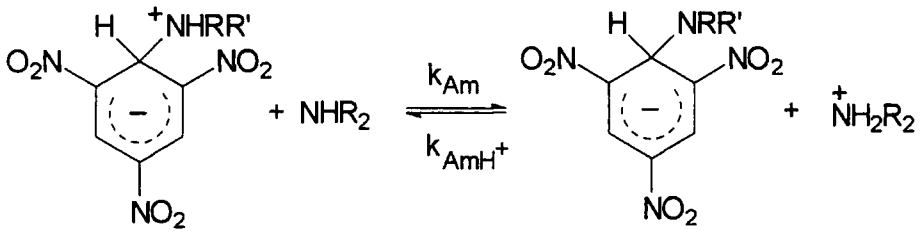
Reaction of morpholine with the phenyl 2,4-dinitronaphthyl ether and phenyl 2,4-dinitrophenyl ether reaction was only seen to occur at the substituted ring position, however with the more activated phenyl 2,4,6-trinitrophenyl ether reaction was seen to occur at both the unsubstituted and substituted ring positions,

7.4.1 Reaction at an unsubstituted ring position

Data for the reaction of morpholine at unsubstituted ring position of 1,3,5-trinitrobenzene and phenyl 2,4,6-trinitrophenyl ether are compared in table 7.7 with data for reaction of piperidine and pyrrolidine.

Values of $K_{c,3}$ for both substrates decrease in the order pyrrolidine > piperidine >> morpholine reflecting the relative basicities of the three amines. However, values of k_{AmH^+}, the rate constant for reprotonation of the anionic products by substituted ammonium ions, are similar for morpholine and piperidine and a factor of ca. 10 larger for pyrrolidine. It has been argued previously that these values largely reflect steric hindrance to proton transfer, which decreases from piperidine to pyrrolidine. Since piperidine and morpholine are both six-membered cyclic amines it is reasonable that steric effects here should be similar leading to similar values for k_{AmH^+}.

Values for k_{Am} for proton transfer from the zwitterion to amine are also likely to be similar for reactions of morpholine and piperidine. Thus, values of K for the proton transfer reaction in equation 7.21 are likely to show little variation with the nature of the amine; the acidifying effect of the trinitroaryl ring being constant. Hence if values of k_{AmH^+} are similar for two amines, values of k_{Am} will also be similar. The factor of ca. 100 in values of K_3k_{Am} favouring piperidine over morpholine is, then, due to an increased value of K_3.



eqn 7.21

$$K = \frac{k_{Am}}{k_{AmH^+}} = \frac{K_a(\text{Zwitterion})}{K_a(^+NH_2R_2)}$$

eqn 7.22

Hence the higher overall equilibrium constant, $K_{c,3}$, for reactions of piperidine relative to morpholine will be attributed to the higher equilibrium constant, K_3, for nucleophilic attack to yield the zwitterion.

Comparing data for reactions of 1,3,5-trinitrobenzene and phenyl 2,4,6-trinitrophenyl ether it can be seen that values of rate constants for the proton transfer step are similar, reflecting the similar steric situation when attack occurs at an unsubstituted ring position. However, values of $K_{c,3}$, and K_3 favour 1,3,5-trinitrobenzene by a factor of ca. 5 which varies little with the nature of the amine. There is likely to be a balance of factors here. The steric effect of the phenoxy group at the 1- position will result in rotation of the nitro groups at the 3- and 6- positions from the ring plane. This will cause a reduction in their electron withdrawing capability and hence will tend to reduce $K_{c,3}$. However, the inductive effect of the phenoxy group will favour attack at the 3- position and partially compensate for the unfavourable steric effect.

Table 7.7 Summary of kinetic and equilibrium data for the reaction at unsubstituted ring-positions of 1,3,5-trinitrobenzene (TNB)[a] and phenyl 2,4,6-trinitrophenyl ether (PTPE).

		TNB	PTPE
Reaction with morpholine	K_3k_{Am}/ $dm^6mol^{-2}s^{-1}$	8500	2450
	k_{AmH^+}/ $dm^3mol^{-1}s^{-1}$	400	600
	$K_{c,3}$/ dm^3mol^{-1}	21	4.1
Reaction with piperidine	K_3k_{Am}/ $dm^6mol^{-2}s^{-1}$	6×10^5	1.7×10^5
	k_{AmH^+}/ $dm^3mol^{-1}s^{-1}$	280	400
	$K_{c,3}$/ dm^3mol^{-1}	2140	300
Reaction with pyrrolidine	K_3k_{Am}/ $dm^6mol^{-2}s^{-1}$	1.05×10^7	3.5×10^6
	k_{AmH^+}/ $dm^3mol^{-1}s^{-1}$	3000	2800
	$K_{c,3}$/ dm^3mol^{-1}	3500	1250

a). Data for reaction of morpholine and piperidine with TNB from ref. 16.

7.4.2 Reaction at a substituted ring position

For phenyl 2,4,6-trinitrophenyl ether, phenyl 2,4-dinitrophenyl ether and phenyl 2,4-dinitronaphthyl ether nucleophilic attack at the 1- position yielded the corresponding 1-morpholino derivatives. No intermediate in the reaction pathway were observed. In each case, the substitution reaction is precisely second order in morpholine, and base catalysis by DABCO is observed. Hence reaction involves general base catalysis with rate-limiting proton transfer. The results are compared in table 7.8 with those for reaction of the three substrates with piperidine.

Table 7.8 Summary of the kinetic data for attack at the 1-position of 1,3,5-trinitrobenzene, phenyl 2,4,6-trinitrophenyl ether, phenyl 2.4-dinitrophenyl ether and phenyl 2,4-dinitronaphthyl ether

Substrate	Amine	K_1k_{Am}/ $dm^6mol^{-2}s^{-1}$	K_1k_{DABCO}/ $dm^6mol^{-2}s^{-1}$	K_1k_2/ s^{-1}
tnb	morpholine	8500	5000	-
	piperidine	6×10^5	1.3×10^5	-
p246tnpe	morpholine	75	-	-
	piperidine	2600	-	-
p24dnne	morpholine	11	5	-
	piperidine	540	86	-
p24dnpe	morpholine	1.3×10^{-2}	7.7×10^{-3}	4.5×10^{-4}
	piperidine	0.8	0.11	5×10^{-3}

The data are readily accounted for assuming that the rate limiting proton transfer is from the zwitterion to base. In this case the observed rate constants correspond to the parameter K_1k_{Am}. The values are ca. 50 times smaller for morpholine than for piperidine. Since the two amines are expected to have similar steric requirements values of k_{Am}, the rate constant for proton transfer, are likely to be similar for the two amines. However, the greater basicity of piperidine will lead to a very much higher value of K_1, just as values of K_3 for reaction at the 3- position are higher for reaction with piperidine. It was noted by Bernasconi that as the activation in the substrate decreases the effectiveness of the base catalysed step relative to the uncatalysed decomposition of the intermediate decreases. The phenyl 2,4-dinitrophenyl ether is the least activated of the substrates studied and hence allows the detection of the uncatalysed pathway, k_2.
Studies of other systems involving rate limiting proton transfer found the ratio k_{Am}/k_{DABCO} to have a value in the range 2-5. The value obtained for k_{Am}/k_{DABCO} for attack by morpholine on 1,3,5-trinitrobenzene is 1.7. Here it is known that proton transfer from the zwitterion is rate limiting. Values for k_{Am}/k_{DABCO} are 1.7 for the

phenyl 2,4-dinitrophenyl ether and 2.2 for the phenyl 2,4-dinitronaphthyl ether. The similarity of these three values suggests that in the latter two cases proton transfer from the zwitterion is rate limiting. The fact that values of the ratio k_{Am}/k_{DABCO} are rather similar for reactions involving morpholine and piperidine indicate that steric effects rather than basicity effects are dominant in determining values of the rate constants for proton transfer.

Values of K_1k_{Am} decrease on going from the trinitro derivative, to the dinitronaphthyl derivative, to the dinitrophenyl derivative. The proton transfer step will be subject to decreasing steric hindrance in this series and hence values of k_{Am} will be expected to increase. However, the decreasing activation in the aromatic ring will lead to decreases in the K_1 values which will be the dominant effect.

These results suggest a reason why base catalysis is more likely to be observed in reactions of morpholine than of other amines such as piperidine.

Values of k_{Am} will be similar for the two amines. However values of K_1 will be smaller for morpholine. Smaller values of K_1 ($= k_1/k_{-1}$) are likely to be associated with larger values of k_{-1}. Hence for morpholine the condition necessary to achieve base catalysis, $k_{-1} > k_{Am}[Am]$, is more likely to be achieved.

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CHAPTER 8

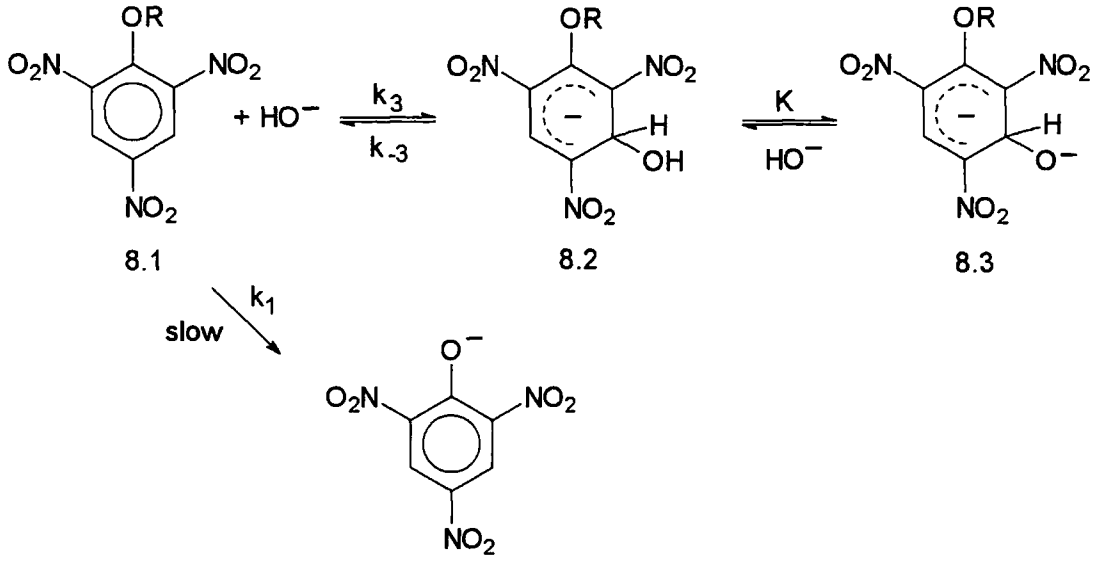
Kinetic Studies Of The Reactions Of 2,4,6-Trinitrophenyl Ethers With Hydroxide Ions

Kinetic studies of the reactions of 2,4,6-trinitrophenyl ethers with hydroxide ions.

8.1 Introduction

The reaction of 1-substituted 2,4,6-trinitrophenyl ethers with nucleophiles can occur via attack at the 3-position to give anionic σ-adducts, or at the 1-position, resulting in substitution.

Rate and equilibrium constants for the reaction of hydroxide ions with 1,3,5-trinitrobenzene, ethyl picrate and phenyl picrate were measured. With 1,3,5-trinitrobenzene, only attack at an unsubstituted ring position is possible, whereas with the ethers attack can also occur at the unsubstituted position. Comparison with previous work[1] indicates that reactions seen correspond to those shown in scheme 8.1.



scheme 8.1

Thus there is evidence for rapid reaction of the unsubstituted 3-position to give an adduct which may transfer an hydroxyl proton to give an dianionic species.

Due to the insolubility in water of the substrates used, all measurements were made in 20:80 DMSO:water (v/ v). The ionic strength was kept at 0.5 mol dm^{-3} with sodium chloride. This value is lower than that used for related systems[1,2] where a higher value of K was obtained. This would be expected, as the value of K (an equilibrium between two anions yielding a dianion) would be expected to increase with increasing ionic strength.

Also, values were obtained in a solvent mixture of 20:80 DMSO:water, whereas previous measurements were obtained only in water. DMSO is known[2-7] to solvate

delocalised anions well, but to be inferior to water in solvating localised negative charges. Hence DMSO would be better at solvating 8.2 than 8.3, causing a decrease in the value of K (and an increase in K_3).

8.2 Experimental

Ethyl picrate was available from previous work
Phenyl picrate was available from previous work, see chapter6, section 2.

8.3 Results

With both ethyl and phenyl picrates, a rapid reaction was seen, followed by another slower reaction. By comparison with other systems[1,5,8], where attack at an unsubstituted ring position has been shown to occur at a faster rate than reaction at a substituted ring position. The rapid reaction is thought to be attack at an unsubstituted position, while the slower reaction is the substitution reaction
Also, it is known that in the presence of base, the hydroxyl group of adducts such as 8.2 is sufficiently acidic to ionise and give 8.3. This proton transfer will be a rapid equilibrium.
The UV/Visible spectrum at completion of the slower reaction corresponded precisely to that of the picrate ion.

8.3.1 Kinetic Analysis

The hydroxide ions were in large excess over the substrate concentration, hence first order kinetics were observed. The relevant rate expressions for the fast and slow reactions are given in equations 8.1 and 8.2.

$$k_{fast} = k_3[HO^-] + \frac{k_{-3}}{1+K[HO^-]} \qquad \text{eqn 8.1}$$

$$k_{slow} = \frac{k_1[HO^-]}{1+K_3[HO^-](1+K[HO^-])} \qquad \text{eqn 8.2}$$

8.3.2 Reaction with 1,3,5-trinitrobenzene

The rapid reaction between 1,3,5-trinitrobenzene and hydroxide ions was measured on the stopped-flow apparatus at 480 nm, with the parent concentration 2 x 10^{-5} moldm^{-3}. Data are in table 8.1.

The rate constant for the reaction can be expressed by equation 8.1, hence from a plot of k_{obs} against hydroxide concentration a value of 93 dm^{3}mol^{-1}s^{-1} for k_3 can be obtained from the slope at high hydroxide concentrations. K is known to have a value of approximately 3 dm^{3}mol^{-1} by comparison with other systems, and so a value of k_{-3} can be estimated using equation 8.1. The best fit was found with k_{-3} = 3.2 s^{-1} and K = 3 dm^{3}mol^{-1}.

Since nitro group displacement is a very slow reaction in TNB, no slow reaction was observed on the stopped-flow time-scale.

Table 8.1 Kinetic and equilibrium data for the reaction between 1,3,5-trinitrobenzene and hydroxide ions in 20:80 DMSO:water at 25°C, measured at 480 nm.[a]

[Sodium Hydroxide]/ moldm^{-3}	k_{fast}/ s^{-1}	k_{calc}[b]/ s^{-1}
0.02	5.12	4.9
0.04	6.57	6.5
0.07	8.87	9.1
0.10	10.9	11.8
0.15	15.7	16.1
0.20	19.8	20.6
0.30	29.6	29.6
0.40	39.5	38.7
0.50	48.9	47.8

a) Ionic strength maintained at 0.5 moldm^{-3} with sodium chloride.

b) Calculated using equation 8.1 with the values k_3= 93 dm^{3}mol^{-1}s^{-1}, k_{-3} = 3.2 s^{-1} and K = 3 dm^{3}mol^{-1}.

8.3.3 Reaction with ethyl picrate

The rapid reaction between ethyl picrate and hydroxide ions was measured at 480nm, the slower substitution reaction was measured as either a fading reaction at 480 nm or a colour forming reaction at 400 nm. The parent concentration was 2 x 10^{-5}moldm^{-3}; data are in table 8.2.

The rate equation for the rapid reaction is equation 8.1. A value for k_3 of 16 dm^{3}mol^{-1}s^{-1} was obtained from the slope of a plot of k_{fast} against hydroxide concentration at high concentrations. By calculation, the best fit could be obtained using the values K = 2 dm^{3}mol^{-1} and k_{-3} = 2.9 s^{-1}.

The slower reaction is expressed by equation 8.2. Using the values K = 2 dm^{3}mol^{-1} and K_3 = 55 dm^{3}mol^{-1} allows a value of 1.6 dm^{3}mol^{-1}s^{-1} to be calculated for k_1.

Table 8.2 Kinetic and equilibrium data for the rapid and slower reactions between ethyl picrate and hydroxide ions in 20:80 DMSO:water (v/v) at 25°C.[a]

[Sodium hydroxide]/ moldm^{-3}	k_{fast}/ s^{-1}	k_{calc}[b]/ s^{-1}	k_{slow}/ s^{-1}	k_{calc}[c]/ s^{-1}
0.02	3.12	3.1	0.024	0.028
0.04	3.26	3.3	0.047	0.051
0.07	3.66	3.7	-	
0.10	3.98	4.0	0.091	0.096
0.15	4.47	4.6	0.12	0.12
0.20	5.07	5.3	0.13	0.13
0.30	6.78	6.6	0.14	0.13
0.40	8.13	8.0	0.14	0.13
0.50	10.26	9.5	0.13	0.12

a) Ionic strength maintained at 0.5 moldm^{-3} with sodium chloride.

b) Calculated using equation 8.1 with the values k_3 = 16 dm^{3}mol^{-1}s^{-1}, k_{-3} = 2.9 s^{-1} and K = 2 dm^{3}mol^{-1}.

c) Calculated using equation 8.2 with k_1 = 1.6 dm^{3}mol^{-1}s^{-1}, K_3 = 5.5 dm^3 mol^{-1} and K = 2 dm^{3}mol^{-1}.

8.3.4 Reaction with phenyl picrate

Both the rapid and slower reactions were measured at 480 nm, the rapid reaction being colour forming, the slower being colour fading. The parent concentration was 2 x 10^{-5} moldm^{-3}, data are in table 8.3.

The rate equation for the rapid reaction is equation 8.1. A value of 50 dm^{3}mol^{-1}s^{-1} was obtained for k_3 from a plot of k_{obs} against hydroxide concentration at high concentrations. The best fit in equation 8.1 was obtained with K = 5 dm^{3}mol^{-1} and k_{-3} = 1.1 s^{-1}.

The slower reaction is expressed by equation 8.2; substituting in values of K = 5 dm^{3}mol^{-1} and K_3 = 42 dm^{3}mol^{-1}, allows a value of 2.4 dm^{3}mol^{-1} to be calculated for k_1.

Table 8.3 Kinetic and equilibrium data for the rapid and slower reactions between phenyl picrate and hydroxide ions in 20:80 DMSO: Water at 25°C.[a]

[Sodium hydroxide] / moldm^{-3}	k_{fast}/ s^{-1}	k_{calc}[b]/ s^{-1}	k_{slow}/ s^{-1}	k_{calc}[c]/ s^{-1}
0.005	1.40	1.4	-	-
0.01	1.72	1.6	-	-
0.015	1.78	1.9	-	-
0.02	2.06	2.1	0.025	0.025
0.04	2.90	3.0	0.032	0.032
0.07	4.19	4.4	0.034	0.034
0.10	5.58	5.8	0.035	0.033
0.15	7.87	8.2	0.030	0.030
0.20	10.4	10.6	0.028	0.027
0.30	16.0	15.5	0.022	0.022
0.40	21.7	20.4	0.018	0.019
0.50	28.7	25.5	0.016	0.016

a) Ionic strength maintained at 0.5 moldm^{-3} with sodium chloride.

b) Calculated using equation 8.1 with the values k_3 = 50 dm^{3}mol^{-1}s^{-1}, k_{-3} = 1.2 s^{-1} and K = 5 dm^{3}mol^{-1}.

c) Calculated using equation 8.2 with k_1 = 2.4 dm^{3}mol^{-1}s^{-1}, K_3 = 42 dm^3 mol^{-1} and K = 5 dm^{3}mol^{-1}.

8.4 Discussion

Rate and equilibrium constants for the three compounds studied are summarised in table 8.4.

Table 8.4 Summary of the kinetic and equilibrium data for the rapid and slower reactions between 1,3,5-trinitrobenzene, ethyl picrate and phenyl picrate with hydroxide ions in 20:80 DMSO:water (v/v) at 25°C.

	TNB	Ethyl picrate	Phenyl picrate
k_3/ $dm^3mol^{-1}s^{-1}$	93	16	50
k_{-3}/ s^{-1}	3.2	2.9	1.2
K_3/ dm^3mol^{-1}	29	5.5	42
K/ dm^3mol^{-1}	3	2	5
k_1/ $dm^3mol^{-1}s^{-1}$	-	1.6	2.4

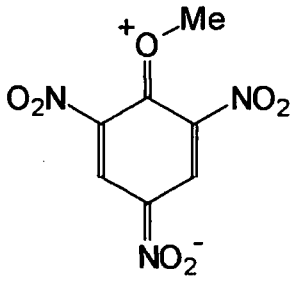
8.4.1 Attack at an unsubstituted ring position

The presence of a bulky group at the 1-position is known to result in the rotation from the ring plane of the nitro groups at the 2- and 6-positions.[1,5] This causes a decrease in their electron withdrawing effect, which is at a maximum when they are coplanar with the aromatic ring. This would be expected to cause a decrease in the value of K_3, as seen with ethyl picrate. The phenyl picrate has a value even larger than TNB, presumably this is caused by the favourable electronic effect outweighing the unfavourable steric effect.

8.4.2 Attack at a substituted ring position

When observing attack at a substituted ring position, both the electronegativity of the 1-substituent and also its steric bulk must be considered.

Values for attack at the 1-position, k_1, can be seen to be lower than values obtained for the attack at the 3-position, k_3, by orders of approximately 10-20. This may be caused by an increase in the F-strain associated with the approach of the hydroxide ions.[9,10]



8.4

When discussing the F-strain, the stereochemistry at the 1-position of these substrates should be considered. It is thought that the methoxy substituent in 2,4,6-trinitroanisole can exist in the form 8.4, where the methoxy group is coplanar with the aromatic ring.[11,12] However the x-ray structure of the ethoxy compound shows that the ring plane and the ethoxy plane are at an angle of 88° to one another[13], and the 2- and 6-nitro groups suffer severe twisting from the ring plane. By comparison with other systems,[14] the phenoxy group is also thought to be perpendicular to the nitro-substituted ring. Hence changing from an ethyl to a phenyl group would be expected to have a relatively small effect on the coplanarity of the nitro groups and also on the F-strain associated with the approach of the hydroxide group to the 1-position, as observed.

Comparing the two ether componds with the corresponding thioether compounds[15], values of k_1 can be seen to decrease in the order OPh > OEt > SPh > SEt. Oxygen has a greater electronegativity than sulfur, causing the ring carbon to be more δ+, i.e. more prone to nucleophilic attack and hence the observed decrease in going from oxygen to sulfur would be expected. The inductive effects, however, are known[16,17] to decrease in the order OPh > SPh > OEt > SEt. The decrease in the value of k_1 for the SPh group relative to the OEt group may be due to the greater steric bulk of the phenylthio group, resulting in greater F-strain. This greater steric bulk of the thioethers over the ethers results in both an increase in the F-strain for these compounds, and also an increase in the disruption of planarity of the ortho-nitro groups in the aromatic ring.

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CHAPTER 9

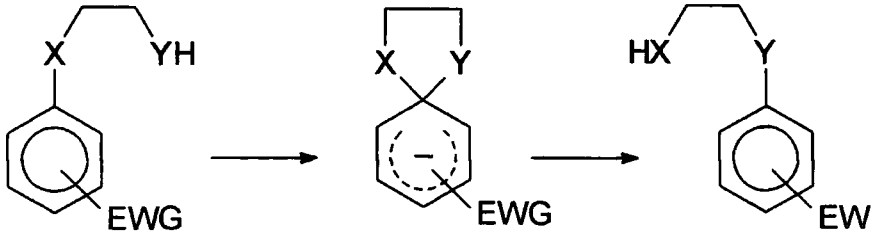
The Reaction Of 2,6-Dinitrochlorobenzene With 2-Aminoethanethiol Hydrochloride In The Presence Of Base

The Reaction of 2,6-dinitrochlorobezene with 2-aminoethanethiol hydrochloride in the presence of base.

9.1 Introduction

The Smiles Rearrangement is an intramolecular rearangement of an activated aromatic substrate,[1-3] as shown in equation 9.1 The reaction proceeds via nucleophilic attack by the Y atom attached to the side chain connecting X and Y. This carbon chain may be either saturated or part of an aromatic system. Usually the displacement is by Y^- rather than by YH and hence the presence of a strong base is required. However, if YH is an amino group, a base may or may not be required.

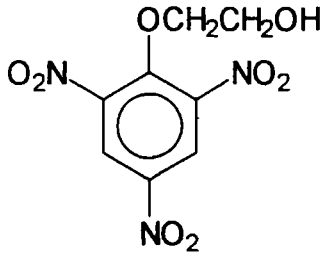
An unsymmetrical intermediate spiro Meisenheimer complexes, 9.1, may be formed along the reaction pathway.



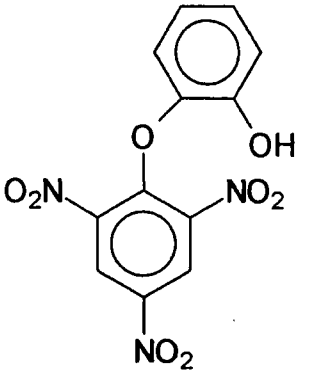
9.1

equation 9.1

During formation of the spiro complex, the rate determining step may be nucleophilic attack or proton transfer depending on the experimental conditions used and the system under study. For example, cyclisation of 9.2 consists of a rapid proton transfer from the alcohol side chain to the base, followed by slow internal cyclisation to form the spiro complex.[4] However, during the reaction of 9.3, proton transfer is rate determining.[5]

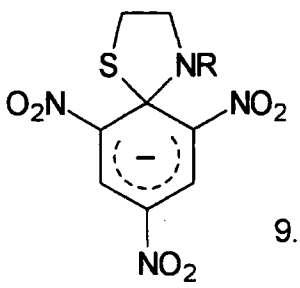


9.2

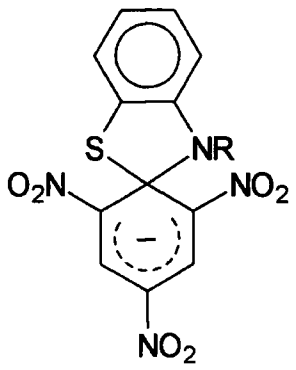


9.3

Several examples of the Smiles Rearrangement involving intramolecular displacement of the thiolate group by amines have been reported,[6,7] including the spectroscopic characterisation of spiro adducts 9.4 and 9.5.[8,9]



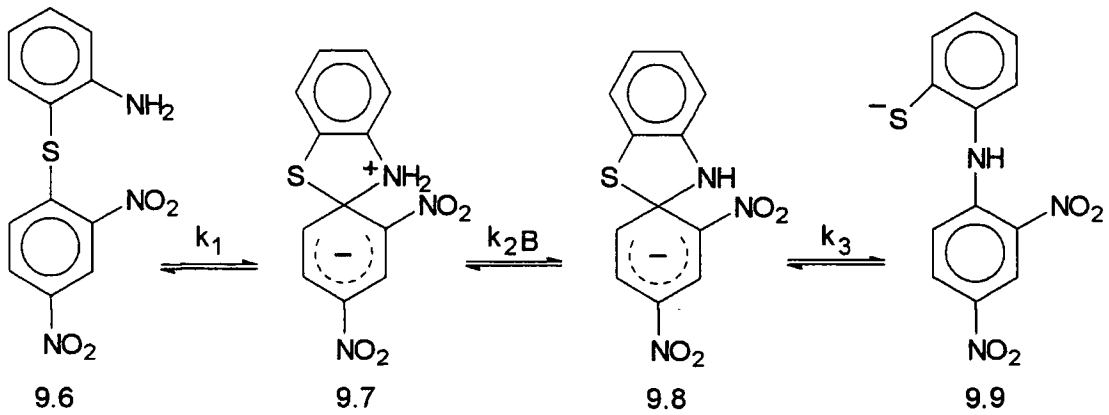
9.4



9.5

R = Me, P

The Smiles Rearrangement of 2-amino-2',4'-dinitrodiphenyl sulfide, 9.6, was studied in several solvent systems.[6] The proposed reaction scheme is shown in scheme 9.1, although steps k_1 and k_2 may be concerted to give 9.8 directly. The rate determining step was found to be k_3 with species 9.8 being effectively the 'initial' state.



9.6 9.7 9.8 9.9

scheme 9.1

9.2 Experimental

A preparative reaction was carried out to attempt to synthesise 1-(2-aminoethylthio) - 2,4,6-trinitrobenzene:
2-aminoethanethiol hydrochloride was dissolved in ethanol, and a sodium hydroxide solution was added to neutralise the initial solution. This was then mixed with a solution of picryl chloride in ethanol, which had been warmed to approximately 40°C. A solution of sodium acetate was added with stirring, the mixture was warmed to approximately 50 °C for ten minutes and then poured onto crushed ice. The red/orange precipitate formed was collected and recrystallised from benzene. ^1H NMR spectra were recorded in [$^2H_6$] DMSO, see table 9.1.

Table 9.1 ^1H NMR data for the product of the reaction between picryl chloride and 2-aminoethanethiol in the presence of base.

δ values	Due to:
8.90	Ring
8.72	NH
3.32	CH_2
3.15	CH_2
2.77	SH

Analysis of the NMR data indicated that the reaction product was bonded through the nitrogen and not through the sulfur as had been hoped. The position of the amino proton resonance is characteristic of an NH conjugated with an electron deficient aromatic ring. Hence, the product formed was 1-(2-mercaptoethylamino)-2,4,6-trinitrobenzene. It is possible that attack via the sulfur occured initially and the product rapidly rearranged to give the nitrogen bonded product.

9.3 Results

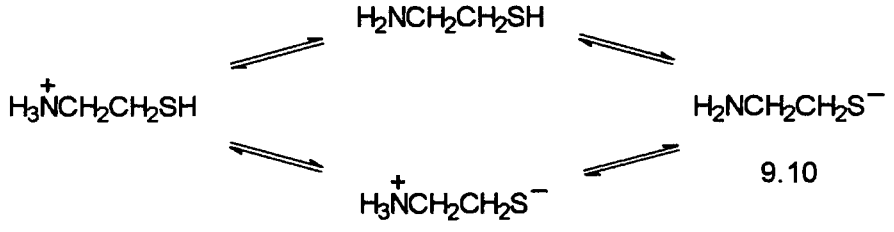
The reaction between 2,4-dinitrochlorobenzene and 2-aminoethanethiol in the presence of sodium hydroxide was studied in water. A rapid reaction was observed giving a species with λ_{max} = ~345 nm, followed by a slower reaction forming a product with λ_{max} = ~370 nm.
The rapid reaction is attributed to nucleophilic attack to give the S-bonded product, and the slower reaction to rearrangement to the N-bonded species.
The 2-aminoethanethiol hydrochloride requires two equivalents of base for each one of thiol, due to the fact that protons can be removed from both the thiol and amino groups.

$$HSCH_2CH_2CH_3 \overset{K_A}{\rightleftharpoons} {}^{-}SCH_2CH_2CH_3 + H^+ \qquad pK_A = 10.6$$

$$H_3\overset{+}{N}CH_2CH_2CH_3 \overset{K_A}{\rightleftharpoons} H_2NCH_2CH_2CH_3 + H^+ \qquad pK_A = 10.7$$

Two pK_A values can be seen to be very similar, hence loss of the proton bonded to the sulfur would occcur as readily as loss of a proton bonded to nitrogen, i.e. a zwitterion is just as likely to occur as a neutral species.

With excess base however, both protons can be removed to give the anionic species shown below,9.10, hence attack is more likely to occur through the sulfur atom.



9.10

9.3.1 The rapid reaction

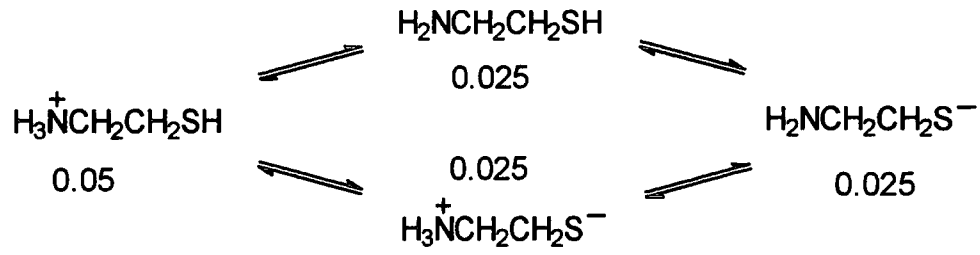
The rapid reaction, corrreponding to initial attack by 1-aminoethanethiol on the dinitrochlorobenzene, was measured using the stopped flow apparatus at 425 nm, with the parent concentration 2.5 x 10^{-5} $moldm^{-3}$. Data are in table 9.2.

Table 9.2 Kinetic data for the reaction of 2-aminoethanethiol with dinitrochlorobenzene in water at 25°C.

$[H_3{}^+NCH_2CH_2SH]$/ $moldm^{-3}$	$[NaOH]_{stoich.}$ /$moldm^{-3}$	$[H_2NCH_2CH_2S^-]^a$ /$moldm^{-3}$	$[NaOH]_{excess}$ a/$moldm^{-3}$	k_{obs} / s^{-1}
0.025	0.100	0.025	0.050	0.0667
0.050	0.100	0.050	0	0.1007
0.075	0.175	0.075	0.025	0.1541
0.050	0.175	0.050	0.075	0.1043
0.050	0.075	0.025[b]	0	0.0741

a) Calculated assuming two equivalents of base were required to produce one of $^-SCH_2CH_2NH_2$.

b) Insufficient base is present to convert all of the $^+H_3NCH_2CH_2SH$ to $H_2NCH_2CH_2S^-$.



The 0.05 mol dm^{-3} salt is converted equally into the zwitterion and neutral species shown, using 0.05 mol dm^{-3} of the sodium hydroxide. The remaining 0.025 mol dm^{-3} base can therefore only produce 0.025 mol dm^{-3} of the anionic species from the two intermediates shown, i.e. the zwitterion and the neutral species.

The data are consistent with rate determining nucleophilic attack by the anion, as shown in scheme 9.1.

$$k_{obs} = k\left[{}^{-}SCH_2CH_2NH_2\right] \qquad \text{eqn 9.1}$$

Hence from the slope of the plot of k_{obs} against the anion concentration, a value of 2.1 dm^3 mol^{-1} s^{-1} is obtained for the rate constant for nucleophilic attack of the dinitrochlorobenzene.

9.3.2 The slower reaction

The slower reaction corresponding to the rearrangement of the 1- (2-aminoethylthio) - 2,4,6-trinitrobenzene, was measured, again at 425 nm, with 1 x 10^{-5} $moldm^{-3}$ dinitrochlorobenzene and 0.05 $moldm^{-3}$ 1-aminoethanethiol hydrochloride. Data are in table 9.3.

Table 9.3 Kinetic data for the slower, rearrangement, reaction between dinitrochlorobenzene and 1-aminoethanethiol hydrochloride in the presence of base at 25 °C.

$[H_3^+NCH_2CH_2SH]$ / moldm^{-3}	$[NaOH]_{stoich.}$/ moldm^{-3}	$[NaOH]_{free}$[a]/ moldm^{-3}	k_{slow}/ x 10^{-3} s^{-1}
0.05	0.050	0	1.55
0.05	0.075	0	1.74
0.05	0.100	0	1.70
0.05	0.150	0.05	1.73
0.05	0.200	0.10	1.80

a) Calculated assuming two equivalents of base are required for each one equivalent of 2-aminoethanethiol hydrochloride.

Average rate constant = 1.7 x 10^{-3} s^{-1}.

The observed rate constant can be seen to show little variation with changing base concentration.

The slower reaction was also measured with a fixed hydroxide concentration (0.2 moldm^{-3}), and varying salt concentration, with the dinitrochlorobenzene 4 x 10^{-5} mol dm^{-3}. Data are in table 9.4.

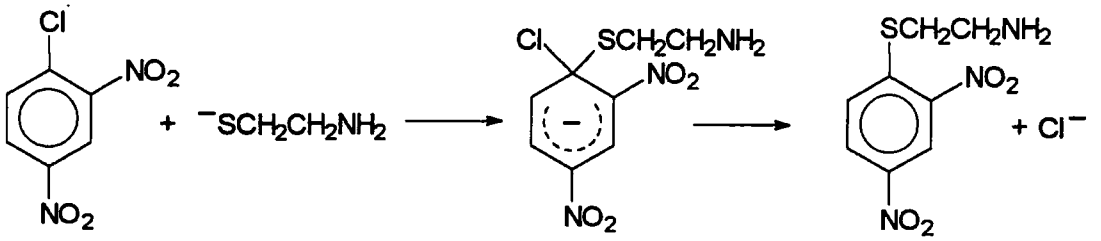
Table 9.4 Kinetic data for the reaction between dinitrochlorobenzene and 2-aminoethanethiol in the presence of base at 25°C.

$[H_3^+NCH_2CH_2SH]$/ moldm^{-3}	k_{slow}/ x 10^{-3} s^{-1}
0.01	1.9
0.02	1.9
0.03	1.9
0.04	1.6
0.05	1.8

The observed rate constants can be seen to show no variation with the changes in salt concentration.

9.4 Discussion

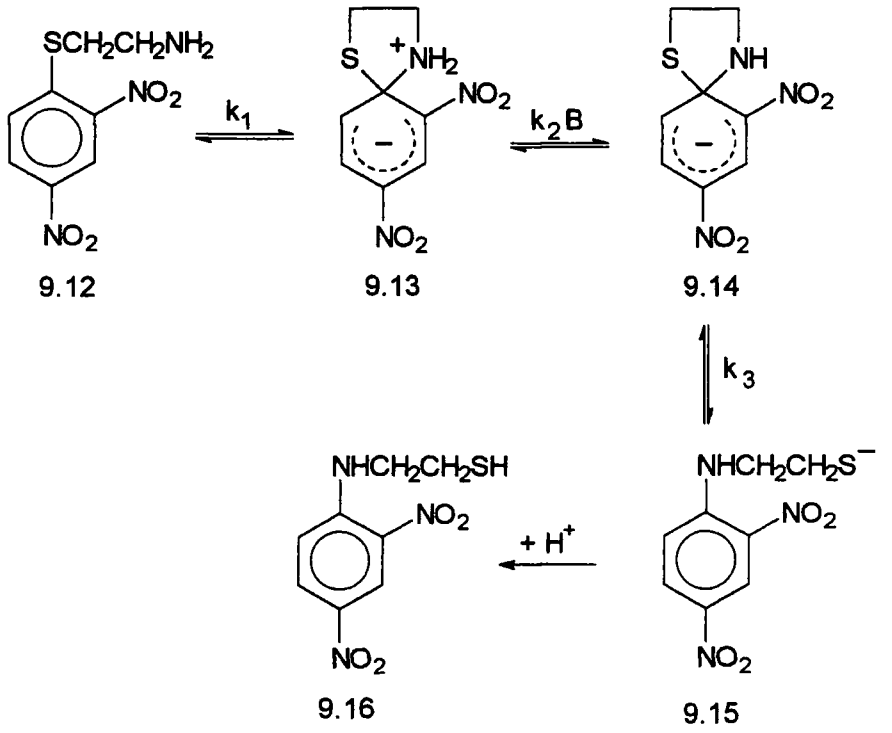
With excess sodium hydroxide present, the 2-aminoethanethiol is converted into the anionic species: $H_2NCH_2CH_2S^-$. Given the high nucleophilicity of sulfur, the reaction is most likely to occur through the sulfur atom, i.e.



9.11

Once the intermediate, 9.11, is formed, loss of chloride, a good leaving group, will occur rapidly to give the product.

The slower reaction is therefore likely to be the conversion of the sulfur bonded species to the nitrogen bonded species. This process was seen to be independent of the salt concentration and hence it must be intra- rather than inter-molecular. Hence, this would be likely to occur via the Smiles Rearrangement with a spiro intermediate: involving intramolecular nucleophilic attack by the amino group. This could occur via the mechanism shown in scheme 9.2

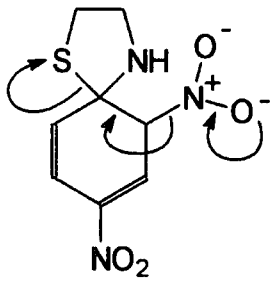


scheme 9.2

The reaction has been shown to be independent of the base concentration and hence proton transfer, the k_2 step, cannot be rate determining. This is further supported by the fact that no build up of species 9.13 or 9.14 is seen.

If the cleavage of the C-S bond were rate limiting, we would expect to see a build up of species 9.14. This is not observed and hence carbon-sulfur bond breaking cannot be rate determining.

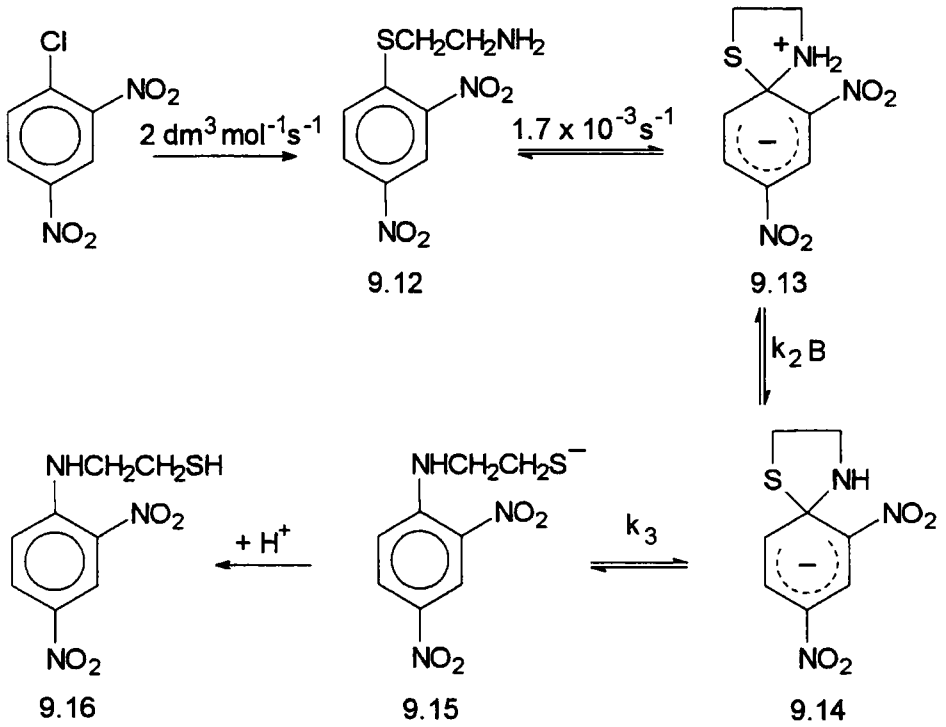
The mechanism of ring opening can be represented as in 9.17, where the negative charge is shown localised on the nitro group rather than the more usual way of showing the negative charge delocalised in the ring.



9.17

Hence, it is likely that step 1, the nucleophilic attack, is rate determining. This agrees with experimental results in that no base dependence is observed in the overall reaction.

Hence, in the reaction scheme 9.3, the rate constants can be shown:



scheme 9.3

This result may be compared with those obtained for the 2-amino-2',4'-dinitrophenyl sulfide, 9.6, where the intermediate 9.8 was observable and the k_3 step was found to be rate limiting.

One major difference in the two studies is the solvent system used. The present work was carried out in water whereas studies with 9.6 were in media containing DMSO. The latter solvent is known to stabilise anionic σ-adducts and this may account for the observation of the adduct 9.8.

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APPENDIX

Colloquia, Lectures and Seminars from Invited Speakers

APPENDIX

COLLOQUIA, LECTURES AND SEMINARS FROM INVITED SPEAKERS

COURSES ATTENDED

- o Chemistry Department induction courses;
- o Physical Organic Chemistry, 6 lectures;
- o Terpenes and Steroids, 6 lectures,
- o Enzyme Chemistry, 6 lectures.

LECTURES (* denotes attendance)

1991

Sept. 17 — Prof. R. D. Fischer, University of Hamburg, Germany
Organo-f-element Systems to Organo-Main-Group Polymers

October 17 — Dr. J. A. Salthouse, University of Manchester
Son et Lumiere - a Demonstration Lecture*

October 31 — Dr. R. Keeley, Metropolitan Police Forensic Science
Modern Forensic Science*

Nov. 6 — Prof. B. F. G. Johnson, Edinburgh University
Cluster-Surface Analogies

Nov. 7 — Dr. A. R. Butler, University of St. Andrews
Traditional Chinese Herbal Drugs: a Different Way of Treating Disease*

Nov. 13 — Prof. D. Gani, University of St. Andrews
The Chemistry of PLP-dependent Enzymes*

Nov. 20 — Dr. R. M. O'Ferral, University College, Dublin
Some Acid-catalyzed Rearrangements in Organic Chemistry*

Nov. 28 — Prof. I. M. Ward, IRC in Polymer Science, University of Leeds
The Science and Technology of Orientated Polymers

Dec. 4 — Prof. R. Grigg, Leeds University
Palladium-catalyzed Cyclization and Ion Capture Processes*

Dec. 5 — Dr. W. D. Cooper, Shell Research
Colloid Science, Theory and Practice*

Dec. 5 — Prof. A. L. Smith, ex Unilever
Soap, Detergents and Black Puddings

1992

January 22 — Dr. K. D. M Harris, University of St. Andrews
Understanding the Properties of Solid Inclusion Compounds*

January 29	Dr. A. Holmes, Cambridge University Cycloaddition Reactions in the Service of the Synthesis of Piperidine and Indolizidine Natural Products*
January 30	Dr. M. Anderson, Shell Research Recent Advances in the Safe and Selective Chemical Control of Insect Pests
February 12	Prof. D. E. Fenton, Sheffield University Polynuclear Complexes of Molecular Clefts as Models for Copper Biosites
February 13	Dr. J. Saunders, Glaxo Group Research Molecular Modelling in Drug Discovery
February 19	Prof. E. J. Thomas, Manchester University Applications of Organostannanes to Organic Synthesis
February 20	Prof. E. Vogel, University of Cologne Porphyrins, Molecules of Interdisciplinary Interest
February 25	Prof. J. F. Nixon, University of Sussex Phosphalkynes, New Building Blocks in Inorganic and Organometallic Chemistry
March 5	Dr. N. C. Billingham, University of Sussex Degradable Plastic - Myth or Magic
March 11	Dr. S. E. Thomas, Imperial College Recent Advances in Organoiron Chemistry*
March 12	Dr. R. A. Hann, ICI Imagedata Electronic Photography - An Image of the Future
March 18	Dr. H. Maskill, Newcastle University Concerted or Step-wise Fragmentation in a Deamination-type Reaction*
April 7	D. M. Knight, University of Durham Interpreting Experiments: the Beginning of Electrochemistry
May 6	Prof. T. Marder, University of Waterloo Metal-catalyzed Alkene Hydroboration
May 6	Dr. J. C. Gehret, Ciba-Geigy Some Aspects of Industrial Agrochemical Research
October 15	Dr M. Glazer & Dr. S. Tarling, Oxford University & Birbeck College, London It Pays to be British! - The Chemist's Role as an Expert Witness in Patent Litigation
October 20	Dr. H. E. Bryndza, Du Pont Central Research Synthesis, Reactions and Thermochemistry of Metal (Alkyl) Cyanide Complexes and Their Impact on Olefin Hydrocyanation Catalysis
October 22	Prof. A. Davies, University College London The Behaviour of Hydrogen as a Pseudometal*
October 28	Dr. J. K . Cockcroft, University of Durham Recent Developments in Powder Diffraction
October 29	Dr. J. Emsley, Imperial College, London The Shocking History of Phosphorus

Nov. 4	Dr. T. P. Kee, University of Leeds Synthesis and Co-ordination Chemistry of Silylated Phosphites
Nov. 5	Dr. C. J. Ludman, University of Durham Explosions, A Demonstration Lecture*
Nov. 11	Prof. D. Robins, Glasgow University Pyrrolizidine Alkaloids : Biological Activity, Biosynthesis and Benefits*
Nov. 12	Prof. M. R. Truter, University College, London Luck and Logic in Host - Guest Chemistry
Nov. 18	Dr. R. Nix, Queen Mary College, London Characterisation of Heterogeneous Catalysts
Nov. 25	Prof. Y. Vallee. University of Caen Reactive Thiocarbonyl Compounds
Nov. 25	Prof. L. D. Quin, University of Massachusetts, Amherst Fragmentation of Phosphorous Heterocycles as a Route to Phosphoryl Species with Uncommon Bonding
Nov. 26	Dr. D. Humber, Glaxo, Greenford AIDS - The Development of a Novel Series of Inhibitors of HIV
Dec. 2	Prof. A. F. Hegarty, University College, Dublin Highly Reactive Enols Stabilised by Steric Protection*
Dec. 2	Dr. R. A. Aitken, University of St. Andrews The Versatile Cycloaddition Chemistry of $Bu_3P.CS_2$*
Dec. 3	Prof. P. Edwards, Birmingham University The SCI Lecture - What is Metal?
Dec. 9	Dr. A. N. Burgess, ICI Runcorn The Structure of Perfluorinated Ionomer Membranes

1993

January 20	Dr. D. C. Clary, University of Cambridge Energy Flow in Chemical Reactions
January 21	Prof. L. Hall, Cambridge NMR - Window to the Human Body
January 27	Dr. W. Kerr, University of Strathclyde Development of the Pauson-Khand Annulation Reaction : Organocobalt Mediated Synthesis of Natural and Unnatural Products*
January 28	Prof. J. Mann, University of Reading Murder, Magic and Medicine*
February 3	Prof. S. M. Roberts, University of Exeter Enzymes in Organic Synthesis

February 10	Dr. D. Gillies, University of Surrey NMR and Molecular Motion in Solution
February 11	Prof. S. Knox, Bristol University *The Tilden Lecture* Organic Chemistry at Polynuclear Metal Centres
February 17	Dr. R. W. Kemmitt, University of Leicester Oxatrimethylenemethane Metal Complexes
February 18	Dr. I. Fraser, ICI Wilton Reactive Processing of Composite Materials
February 22	Prof. D. M. Grant, University of Utah Single Crystals, Molecular Structure, and Chemical-Shift Anisotropy
February 24	Prof. C. J. M. Stirling, University of Sheffield Chemistry on the Flat-Reactivity of Ordered Systems*
March 10	Dr. P. K. Baker, University College of North Wales, Bangor Chemistry of Highly Versatile 7-Coordinate Complexes
March 11	Dr. R. A. Y. Jones, University of East Anglia The Chemistry of Wine Making
March 17	Dr. R. J. K. Taylor, University of East Anglia Adventures in Natural Product Synthesis*
March 24	Prof. I. O. Sutherland, University of Liverpool Chromogenic Reagents for Cations*
May 13	Prof. J. A. Pople, Carnegie-Mellon University, Pittsburgh, USA Applications of Molecular Orbital Theory*
May 21	Prof. L. Weber, University of Bielefeld Metallo-phospha Alkenes as Synthons in Organometallic Chemistry
June 1	Prof. J. P. Konopelski, University of California, Santa Cruz Synthetic Adventures with Enantiomerically Pure Acetals
June 2	Prof. F. Ciardelli, University of Pisa Chiral Discrimination in the Stereospecific Polymerisation of Alpha Olefins
June 7	Prof. R. S. Stein, University of Massachusetts Scattering Studies of Crystalline and Liquid Crystalline Polymers
June 16	Prof. A. K. Covington, University of Newcastle Use of Ion Selective Electrodes as Detectors in Ion Chromatography
June 17	Prof. O. F. Nielsen, H. C. _rsted Institute, University of Copenhagen Low-Frequency IR - and Raman Studies of Hydrogen Bonded Liquids
Sept. 13	Prof. Dr. A.D. Schlüter, Freie Universität Berlin, Germany Synthesis and Characterisation of Molecular Rods and Ribbons
Sept. 13	Dr. K.J. Wynne, Office of Naval Research, Washington, USA Polymer Surface Design for Minimal Adhesion

Sept. 14	Prof. J.M. DeSimone, University of North Carolina, Chapel Hill, USA Homogeneous and Heterogeneous Polymerisations in Environmentally Responsible Carbon Dioxide
Sept. 28	Prof. H. Ila, North Eastern Hill University, India Synthetic Strategies for Cyclopentanoids via Oxoketene Dithioacetals
October 4	Prof. F.J. Feher, University of California, Irvine, USA Bridging the Gap between Surfaces and Solution with Sessilquioxanes
October 14	Dr. P. Hubberstey, University of Nottingham Alkali Metals: Alchemist's Nightmare, Biochemist's Puzzle and Technologist's Dream
October 20	Dr. P. Quayle, University of Manchester Aspects of Aqueous ROMP Chemistry*
October 21	Prof. R. Adams, University of South Carolina, USA Chemistry of Metal Carbonyl Cluster Complexes : Development of Cluster Based Alkyne Hydrogenation Catalysts*
October 27	Dr. R.A.L. Jones, Cavendish Laboratory, Cambridge Perambulating Polymers*
Nov. 10	Prof. M.N.R. Ashfold, University of Bristol High Resolution Photofragment Translational Spectroscopy : A New Way to Watch Photodissociation
Nov. 17	Dr. A. Parker, Rutherford Appleton Laboratory, Didcot Applications of Time Resolved Resonance Raman Spectroscopy to Chemical and Biochemical Problems
Nov. 24	Dr. P.G. Bruce, University of St. Andrews Structure and Properties of Inorganic Solids and Polymers
Nov. 25	Dr. R.P. Wayne, University of Oxford The Origin and Evolution of the Atmosphere
Dec. 1	Prof. M.A. McKervey, Queen's University, Belfast Synthesis and Applications of Chemically Modified Calixarenes*
Dec. 8	Prof. O. Meth-Cohn, University of Sunderland Friedel's Folly Revisited - A Super Way to Fused Pyridines*
Dec. 16	Prof. R.F. Hudson, University of Kent Close Encounters of the Second Kind

1994

January 26	Prof. J. Evans, University of Southampton Shining Light on Catalysts
February 2	Dr. A. Masters, University of Manchester Modelling Water Without Using Pair Potentials*
February 9	Prof. D. Young, University of Sussex Chemical and Biological Studies on the Coenzyme Tetrahydrofolic Acid*

February 16	Prof. K.H. Theopold, University of Delaware, USA Paramagnetic Chromium Alkyls : Synthesis and Reactivity
February 23	Prof. P.M. Maitlis, University of Sheffield Across the Border : From Homogeneous to Heterogeneous Catalysis
March 2	Dr. C. Hunter, University of Sheffield Noncovalent Interactions between Aromatic Molecules*
March 9	Prof. F. Wilkinson, Loughborough University of Technology Nanosecond and Picosecond Laser Flash Photolysis
March 10	Prof. S.V. Ley, University of Cambridge New Methods for Organic Synthesis*
March 25	Dr. J. Dilworth, University of Essex Technetium and Rhenium Compounds with Applications as Imaging Agents
April 28	Prof. R. J. Gillespie, McMaster University, Canada The Molecular Structure of some Metal Fluorides and Oxofluorides: Apparent Exceptions to the VSEPR Model.
May 12	Prof. D. A. Humphreys, McMaster University, Canada Bringing Knowledge to Life