NITRITE ACTIVATION BY ORGANIC ANHYDRIDES

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ABSTRACT

The reaction of nitrite ion with some heterocumulene organic anhydrides is investigated with reference to the activation of the nitrite as a nitrosating agent.

Nitrite ion reacts with aromatic isocyanates in organic solvents to give good yields of 1,3-diaryltriazenes. Reaction occurs via nucleophilic attack of nitrite ion on the isocyanate, and rearrangement of the intermediate to give an N-nitroso species. Loss of carbon dioxide gives an aromatic diazotate which reacts with further isocyanate to yield the 1,3-diaryltriazene. Independent reaction of the isolated diazotate is demonstrated.

Alkyl isocyanates were less reactive. Reaction with nitrite ion in the presence of dibutyl tin diacetate, a Lewis acid, gives deamination products.

Aromatic carbodiimides react analogously giving diazotates and hence 1,3-diaryl triazenes. For unsymmetrical carbodiimides the selectivity of the nitrosation is discussed.

Isothiocyanates gave only small amounts of nitrosation. Evidence indicated that S-nitrosation predominates.

The reactions provide a novel route to nitrosation products from nitrite ion under mild non-acidic conditions.
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CHAPTER 1

INTRODUCTION AND REVIEW
1.1 INTRODUCTION

Considerable interest continues to be shown in the formation of N-nitroso compounds due to their implication in cancer induction. Indeed the in vivo formation of N-nitroso compounds has been proposed to be the cause of gastric cancer.

Nitrosation reactions are normally carried out under acidic conditions, in the presence of nitrous acid. The nitrous acid is itself unreactive but is in equilibrium with a range of reactive species. Some are listed in Scheme 1, in order of increasing reactivity.

\[
\begin{align*}
\text{ON - NO}_2 & \quad \text{nitrous anhydride} \\
\text{ON - Cl} & \quad \text{nitrous chloride} \\
\text{ON - OH}^+ & \quad \text{nitrous acidium ion} \\
\text{ON}^+ & \quad \text{nitrousonium ion}
\end{align*}
\]

SCHEME 1

All of these reagents are electrophilic. They effect nitrosation by delivering the NO\(^+\) entity to a suitable nucleophile, such as an amino substrate.

Past reviews fully describe the mechanistic and kinetic details of N-nitrosation in aqueous solution. Methods for carrying out nitrosation reactions under non-acidic conditions are relatively few. They include the use of the gaseous nitrogen oxides and certain alkyl nitrites in aqueous alkali solution.

Nitrite ion itself cannot bring about nitrosation. However, there is some current interest in methods of activating nitrite as a nitrosating agent under mild conditions. One route is by reaction of nitrite ion with organic anhydrides. Our work concerns the reaction of nitrite with the heterocumulene anhydrides.

The following review covers methods for nitrosation under non-acidic conditions and relevant aspects of the chemistry of the heterocumulene anhydrides; the isocyanates, isothiocyanates, carbodiimides and N-sulphinyl amines.
1.2 NITROSATION UNDER NON-ACIDIC CONDITIONS

1.2.1 Nitrosation by Alkyl Nitrites

Alkyl nitrites (RONO) are often employed as a source of nitrous acid. The simple alkyl nitrites such as amyl nitrite are normally activated by an acid catalyst, promoting cleavage of the O-NO bond. (Scheme 2)

\[ \text{H}_3\text{O}^+ + \text{RNH}_2 \rightarrow \text{H}_2\text{O} + \text{RO} - \text{NO} \rightarrow \text{ROH} + \text{R}_2\text{NNO} + \text{H}_3\text{O}^+ \]

SCHEME 2

Hydrolysis under acidic and neutral conditions was found to be faster than in aqueous alkali. Cleavage of the O-NO bond was demonstrated to occur during hydrolysis of optically active alkyl nitrites, with retention of configuration.

Recent work has been carried out on the hydrolysis and aminolysis of β-phenethyl nitrite, by Oae and co-workers. Alkaline hydrolysis gave the corresponding alcohol and was found to be accelerated by triethylamines. Secondary amines were nitrosated in alkaline conditions in quantitative yield. Good kinetic behaviour was observed and the second order rate constants were determined.

The base catalysed hydrolysis was studied in detail and compared with hydrolysis of carboxylic esters. The carboxylic esters reacted more rapidly. The alkyl nitrites showed larger polar effects in the leaving alkoxide group, smaller steric effects, and unlike the esters gave no oxygen exchange with the medium during hydrolysis. It was argued that these results implied a concerted displacement for alkyl nitrite hydrolysis (Equation 1) rather than the addition-elimination mechanism that has been established for base catalysed hydrolysis of carboxylic esters.

\[ \text{RONO} + \text{HO}^- \rightarrow \text{RO}^- + \text{HONO} \]

A similar concerted mechanism was proposed for reaction with amines under basic conditions in aqueous dioxan. A solvent isotope effect \((k_H/k_D)\) of around 2 was found for aminolysis, implying that proton transfer to the alkoxide occurs in the rate-limiting step. A transition
state was proposed where OH bond formation is synchronous with O-N bond fission and N-N bond formation (Scheme 3).

The Brønsted plots for the aminolysis were scattered. Reasonable correlation was obtained for

\[
\text{RO-NO} + R_1 R_2 \text{NH} \rightarrow \begin{array}{c}
\text{H} \\
\text{R} \\
\text{O} \end{array} \\
\begin{array}{c}
\delta^- \\
\delta^- \\
\downarrow \text{N} \\
\text{O} \end{array} \\
\text{ROH} + R_1 R_2 \text{NNO}
\]

SCHEME 3

amines of similar structure, giving a $\rho$ value of 0.58 for aliphatic secondary amines. However the points for ammonia, and the primary and tertiary amines deviated from the line. A good correlation was obtained between log $k$ and the vertical ionization potentials of the amines. The lower the potential the faster the reaction.

Similar results have been obtained for the reactions of $\beta$-ethoxy ethanol, for both hydrolysis and aminolysis in aqueous alkali.\(^{13,14,15}\)

1.2.2 Nitrosation by Gaseous Nitrogen Oxides

The nitrosation of amines in neutral and alkaline solution with gaseous dinitrogen trioxide ($N_2O_3$) and dinitrogen tetroxide ($N_2O_4$) has been reported by Challis and Kyropoulos.\(^{16,17}\)

Secondary amines such as pyridine and morpholine produced the N-nitroso compounds, whereas aniline and its derivatives were diazotised. The yields of diazotisation were 1.5 - 2% with respect to $N_2O_4$, at aniline concentrations of $10^{-3}$ to $10^{-4}$ mol dm$^{-3}$, and the reactions were very fast. The extent of nitrosation had little dependency on the basicity implying the reactions were diffusion or encounter-controlled. Thus the reaction with the amine is in competition with the hydrolysis of the $N_2O_4$ by water. In the gas phase the $N_2O_4$ is substantially dissociated into $NO_2$ radicals, but in solution there is less dissociation, and $NO_2$ radicals may combine to give the reactive metastable isomer ONONO$_2$ (Scheme 4). Evidence suggests this to be
predominant as a nitrosating agent in solution, reacting with the amine on encounter. Radical coupling to give ONONO$_2$ or the diffusion of N$_2$O$_4$ into the aqueous phase would have to be the rate limiting step. A similar mechanism can be proposed for the reaction of N$_2$O$_3$.

Preparatively gaseous N$_2$O$_3$ has been used to produce N-nitroso compounds$^{18}$, and to deaminate primary amines$^{19}$ in organic solvents.

![Scheme 4]

Nitrosation products have also been isolated from reactions of N$_2$O$_4$ in carbon tetrachloride.$^{20,21}$ Kinetics of the diazotisation of aniline with N$_2$O$_4$ in acetonitrile, ethyl acetate and mixtures of these solvents, have been measured.$^{22}$ The reaction was first order in N$_2$O$_4$ and zero order in aniline, and the rate limiting step was proposed to be formation of the nitrousonium ion (Scheme 5). Gaseous N$_2$O$_4$ has also been used to produce N-nitrosamides$^{23}$ by reaction with amides in dichloromethane in the presence of sodium acetate at low temperature (-20°C).

![Scheme 5]
Nitric oxide (NO) reacts with amines to form N-nitrosamines, although it appears not to be the nitrosating agent. The presence of air or other catalysts was required, and nitrogen dioxide or other species were assumed to bring about reaction. For example in the presence of iodine, nitrosyl iodide (NOI) was found to be the nitrosating agent. With silver ions present it was believed that the amine was oxidised to a cation radical and this reacted directly with the nitric oxide. (Scheme 6).

\[
\text{Ag}^+ \quad \text{R}_2\text{NH} \quad \text{NO} \quad \text{R}_2\text{N-NO} + \text{H}^+ \\
\text{SCHEME 6}
\]

1.2.3 Nitrosation by Transition Metal Nitrosyl Complexes

A number of transition metal nitrosyl complexes have been shown to act as nitrosating agents under non-acidic conditions. For example nitric oxide forms a complex with copper (II) salts. This copper nitrosyl complex was a powerful nitrosating agent in alkaline media, and organic solvents giving quantitative yields of nitrosamines from reaction with secondary amines. (Scheme 7).

\[
\text{Cu}^{\text{II}} + \text{NO} \rightarrow \text{Cu}^{\text{II}}\text{NO} \\
\text{Cu}^{\text{II}}\text{NO} + \text{R}_2\text{NH} \rightarrow \text{Cu}^{\text{I}} + \text{H}^+ + \text{R}_2\text{NNO} \\
\text{SCHEME 7}
\]

The nitroprusside anion (1) nitrosated ketones such as acetone and acetophenone, under basic conditions to produce oximes. Similarly reaction with secondary amines gave N-nitrosamines, and with primary amines deamination products were obtained. The deaminations could be carried out at pH's up to 12.7, although at higher pH the nitroprusside ion is destroyed. Deamination produced predominantly alcohols with small amounts of alkene, and in the presence of air, traces of oxidised products. For example cyclohexylamine gave 120% cyclohexanol, 9% cyclohexene and 3% cyclohexanone. Predominant formation of the alcohol is expected in the basic conditions.
employed.

The mechanism proposed (Scheme 8) involved attack of the amine on the nitrosyl complex. Aromatic amines were unreactive, probably because of their lower basicity. The new complex (2) could then react with another molecule of amine to release the nitroso compound.

\[
[\text{Fe(CN)}_5 \text{NO}]^{2-} + \text{RNH}_2 \xrightarrow{} [\text{RNH}_2\text{NOFe(CN)}_5]^{2-}
\]

(1)

\[
[\text{RNH}_2\text{NOFe(CN)}_5]^{2-} + \text{RNH}_2 \rightarrow \text{RNHNO} + \text{H}^+ + [\text{RNH}_2\text{Fe(CN)}_5]^{2-}
\]

\[
\text{RNHNO} \xrightarrow{\text{H}_2\text{O}} \text{RN}_2^+
\]

\[
\text{RN}_2^+ \rightarrow \text{R}^+ \rightarrow \text{PRODUCTS}
\]

SCHEME 8

A second possibility was loss of water from the complex (2), to give a complexed diazonium ion (3) which then fragments by reaction with further amine (Scheme 9).

\[
[\text{RNH}_2\text{NOFe(CN)}_5]^{2-} \xrightarrow{} [\text{RN}_2\text{Fe(CN)}_5]^{2-} + \text{H}_2\text{O}
\]

(2)

(3)

\[
[\text{RN}_2\text{Fe(CN)}_5]^{2-} + \text{RNH}_2 \rightarrow \text{RN}_2^+ + [\text{RNH}_2\text{Fe(CN)}_5]^{2-}
\]

SCHEME 9

Nitrosation has also been observed from ruthenium nitrosyl complexes,\textsuperscript{32} and from nitrosyl haems, formed from reaction of nitric oxide and haems.\textsuperscript{33, 34}
1.3 NITRITE ACTIVATION

1.3.1 Photolysis

Aqueous solutions of nitrite have been shown to produce nitrogen oxides on photolysis. \(^{35,36,37}\) The mechanism is not fully understood, but nitrite salts produce \(\text{N}_2\text{O}_3\). Nitrate salts produce both \(\text{N}_2\text{O}_3\) and \(\text{N}_2\text{O}_4\). Both these nitrogen oxides are known to be powerful nitrosating agents under acidic, neutral and alkaline conditions. \(^{16,17}\) Thus nitroso compounds should be produced by photolysis of nitrite in the presence of amines. However N-nitrosamines are also decomposed by photolysis, particularly under acidic conditions. \(^{38}\) Therefore the amount of N-nitrosamine formed will depend on the conditions and relative quantum yields of the two photochemical processes.

Challis and Li \(^{39}\) found the formation of N-nitrosamines from heterocyclic amines under mild conditions. When 0.1M sodium nitrite in water at 25°C was photolysed in the presence of \(5 \times 10^{-3}\) M morpholine, after 300 minutes the concentration of N-nitrosomorpholine produced was \(3.43 \times 10^{-3}\) M. Therefore the yield of N-nitrosamine was 69%. In the presence of added nitrate salt the N-nitrosamine was observed to readily decompose on photolysis. \(^5\)

So nitrite ion can be activated by photolysis to produce reactive nitrosating agents under non-acidic conditions.

1.3.2 Radiolysis

Similar reactions to those from photolysis were also observed on \(\gamma\)-irradiation of nitrite solutions. Radical intermediates such as NO\(^+\) and NO\(^-\) are known to be produced on radiolysis of aqueous solutions of nitrite. \(^{40,41}\) These radicals can then combine to form \(\text{N}_2\text{O}_3\).

Quantitative formation of N-nitrosamines from morpholine and N-methyl piperazine was obtained \(^{42}\) on radiolysis of \(2 \times 10^{-3}\) M amine in 0.1 M aqueous sodium nitrite for 60 mins at 1 Mrad Hr. \(^{-1}\) The highest yields were obtained using excess nitrite. The excess salt attenuated the concurrent radiolytic decomposition of the product. This effect was proposed to be due to preferential trapping by the nitrite ion of the hydroxyl radicals and solvated electrons produced on \(\gamma\)-radiolysis. The N-nitrosamines were thought to be formed from \(\text{N}_2\text{O}_3\) (Scheme 10).
Evidence included the relative indifference of product yields to the
structure and basicity of the amine, and the inhibitory effect of added
acid and sodium azide. Sodium azide converts most nitrosating agents
to nitrogen and nitrous oxide ($N_2O$).

\[
2 \text{NO}_2^- + \text{H}_2\text{O} \xrightarrow{\gamma} \text{N}_2\text{O}_3^- + 2 \text{HO}^- \\
\text{N}_2\text{O}_3^- + \text{R}_2\text{NH} \xrightarrow{} \text{R}_2\text{NNO} + \text{H}_2\text{O} + \text{NO}_2^-
\]

SCHEME 10

Radiolysis of nitrate solutions containing amines, gives both the
N-nitrosamines and N-nitroamines, arising from formation of $N_2O_4$.

Thus nitrosation reactions can be brought about by radiolysis of
nitrite solutions, producing reactive nitrosating agents, under non-acidic
conditions.

1.3.3 Reaction with Acetic Anhydride

In their studies of the solvolysis of acetic anhydride, Lees and
Saville observed the reaction to be markedly catalysed by nitrite ion.
The reaction was carried out in 50% aqueous acetone at $25^\circ\text{C}$ and the rate
equation was determined (Equation 2)

\[
\text{RATE} = \left[ k_{\text{H}} + k_1 [\text{AcO}^-] + k_2 [\text{NO}_2^-] \right] [\text{Ac}_2\text{O}] - 2
\]

The reaction was first order in acetic anhydride, and showed
first order terms in acetate and nitrite. The rate coefficients were
determined as; $k_{\text{H}} = 0.0110 \text{ min}^{-1}$ for uncatalysed hydrolysis,
$k_1 = 0.0986 \text{ mol}^{-1} \text{ dm}^3 \text{ min}^{-1}$ for the acetate catalysed reaction and
$k_2 = (9.15 \pm 0.26) \text{ mol}^{-1} \text{ dm}^3 \text{ min}^{-1}$ for the nitrite catalysed reaction.

Determination of the nitrite concentration at the end of the reaction
confirmed that it was not consumed and was indeed acting as a catalyst.

Two explanations could be proposed for the action of nitrite.

i) Nitrite was acting as a general base catalyst (Scheme 11). If this
were so, then the rate of the acetate and nitrite catalysed processes
should be similar, as they have similar $pK_a$'s of 4.75 and 3.4
respectively. In fact acetate should be the better base, whereas
experimentally the acetate term was 100 times less than the nitrite term. This was therefore an unsatisfactory explanation.

\[
\begin{align*}
\text{CH}_3\text{C}O\text{O}_2^- &\rightarrow \text{CH}_3\text{CO}_2^- + \text{CH}_3\text{CO}_2\text{H} + \text{HNO}_2 \\
\text{CH}_3\text{C}O\text{H} &\rightarrow \text{CH}_3\text{CO}_2^- + \text{CH}_3\text{CO}_2\text{H} + \text{HNO}_2
\end{align*}
\]

SCHEME 11

ii) Nitrite acts as a nucleophile, attacking the anhydride in a bimolecular rate determining step giving an intermediate that rapidly decomposes to give acetic acid and nitrite (Scheme 12).

\[
\begin{align*}
\text{NO}_2^- + \text{Ac}_2\text{O} &\xrightarrow{\text{slow}} \text{[INTERMEDIATE]} \xrightarrow{\text{fast}} \text{H}_2\text{O} \rightarrow \text{NO}_2^- + 2\text{AcOH} \\
\end{align*}
\]

SCHEME 12

The second explanation was favoured by Lees and Saville. They proposed that the intermediate was an acyl nitrite (4) formed by nucleophilic attack of the nitrite ion via oxygen (Scheme 13).

\[
\begin{align*}
\text{CH}_3\text{C}O\text{H} &\rightarrow \text{[INTERMEDIATE]} \xrightarrow{\text{fast}} \text{H}_2\text{O} \rightarrow \text{CH}_3\text{CO}_2^- + \text{CH}_3\text{C}O\text{H} \\
\end{align*}
\]

SCHEME 13

Evidence for the structure of the intermediate was obtained from reactions carried out in the presence of excess of 6-naphthylamine (5). This led to the formation of an azo-dye, namely 4-amino-1,1'-azonaphthalene (6) (Equation 3).

\[
\begin{align*}
\text{NH}_2 &\xrightarrow{\text{Ac}_2\text{O/NO}_2^-} \text{50% aq. Acetone} \\
\end{align*}
\]

(5) (6)
The amounts of the dye produced, which were determined spectrophotometrically, corresponded with the calculated fraction of the intermediate (4), that could be produced if its hydrolysis were avoided. The rate of formation of the dye was also consistent with formation of the intermediate. With a large excess of \( \gamma \)-naphthylamine almost quantitative formation of (6) was obtained.

It was proposed that the acetyl nitrite was indeed formed, and acted as a nitrosating agent to diazotise the amine (Scheme 14). So reaction of nitrite ion with acetic anhydride in 50% aqueous acetone, activated the nitrite ion as a nitrosating agent, under mild non-acidic conditions.

\[
\begin{align*}
\text{CH}_3\text{CO} & \quad + \quad \text{RNH}_2 \\
\text{O} & \quad \text{NO} \\
\text{O} & \quad \text{NO}
\end{align*}
\]

\[(4)\]

\text{SCHEME 14}

Similar reaction was also observed with ethyl chloroformate, various 4-substituted benzoylchlorides, and succinic and butyric anhydrides. 43

1.3.4  Reaction with Iminium Cations

Keefer and Roller 44 observed catalysis of N-nitrosamine formation by formaldehyde at pH 6-11. Aqueous nitrite is known not to react with amines at pH \( \geq 7.5 \). A range of secondary amines were easily nitrosated in alkaline formaldehyde solution. Yields of N-nitrosamine were low, being less than 1% at pH \( \geq 6 \). Chloral was also a catalyst although acetone and 2,2-dimethylpropionaldehyde were unreactive. Other groups have observed the phenomenon. 45 Tannenbaum and co-workers 46 found pyridoxal and benzaldehydes to also act as catalysts, as did malondialdehyde. 47

A mechanism was proposed to account for these observations (Scheme 15). This involved formation of the iminium cation (7) from reaction of the amine with the aldehyde. This species is highly reactive toward nucleophiles and could be attacked by nitrite ion as shown, to give the adduct (8). Rearrangement of the nitroso group, from oxygen
to nitrogen, and collapse of the intermediate, produces the N-nitrosamine and regenerates the aldehyde.

\[
R_1R_2NH + O = CHR \quad \xrightarrow{HO^-} \quad R_1R_2N = CHR \quad (7)
\]

\[
R_1R_2N + HO^- \quad \xrightarrow{OH^-} \quad R_1R_2N-O = CHR \quad (8)
\]

\[
R_1R_2N-N=O + RCH=O
\]

**SCHEME 15**

Keefer and Roller\textsuperscript{44,48} found that reaction of the iminium cation from dimethylamine and formaldehyde, with silver nitrite in anhydrous acetonitrile, produced a quantitative yield of the N-nitrosamine.

Recently detailed kinetic studies of the system have been carried out.\textsuperscript{49,50} The various equilibria between the amine and formaldehyde, in its hydrated form (9) were taken into account (Scheme 16). The initial rate of nitrosation of morpholine \((r_o)\) obeyed equation 3, where the iminium cation concentration was proportional to the concentration of protonated carbinolamine (10).

\[
r_o = kK_5[NO_2^-]_o [R_2N^+HCH_2OH]_o \quad - 3
\]

(10)
\[
R_2NH + H_2C(OH)_2 \xrightleftharpoons{K_1} R_2N-CH_2OH \xrightarrow{K_3} R_2NCH_2NHR_2
\]
\[
R_2NH^+ + H_2C(OH)_2 \xrightarrow{K_2} R_2NHCH_2OH \xrightarrow{K_4} R_2NCH_2NHR_2^+
\]

\[K_{a1}, K_{a2}, K_{a3}, K_5\]

\[
R_2N\equiv CH_2
\]

**Scheme 16**
The equilibrium constants for formation of the neutral and cationic carbinolamine, $K_1$ and $K_2$, were observed to be more dependent on the steric accessibility of the nitrogen atom than on the polar character of the amine. This was in agreement with the order of yields of N-nitrosamine from various amines, found by Keefer and Roller. The yields varied in the order, pyrrolidine $\approx$ piperidine $\approx$ dimethylamine $\approx$ diethylamine $\approx$ di-$n$-propylamine $\gg$ diisopropylamine. They were also dependent on steric effects due to the aldehyde alkyl group explaining why 2,2-dimethylpropion-aldehyde was not a catalyst. The rate limiting step could be either reaction of the nitrite ion with the iminium cation, or decomposition of the adduct formed from them.
1.4 THE REACTIONS OF HETEROCUMULENES

1.4.1 Isocyanates

The organic isocyanates (11) are formally the anhydrides of the carbamic acids (12). They have a heterocumulene structure, containing the unsaturated, linear \(-N=C=O\) group.

\[
\begin{align*}
R - N &= C = O \\
(11) \\
R - NH - &
\end{align*}
\]

They are a very reactive class of compounds being very highly susceptible to nucleophilic attack. The attack takes place at the electron deficient acyl carbon atom of the heterocumulene structure.

The chemistry of the isocyanates has been extensively studied due to their industrial importance. In 1974 world production reached \(10^5\) tons per annum. \(^{51}\) Of this, 90% was accounted for by two compounds; toluene di-isocyanate and diphenylmethane di-isocyanate, both very important as monomers in the polymer industry.

A number of excellent reviews already exist, \(^{52,53,54,55}\) so only relevant and recent developments will be discussed here.

Isocyanates react with most nucleophiles. Reaction with alcohols gives urethanes, with amines gives ureas, and with thiols gives thiourethanes. The reactions of isocyanates with nucleophiles are summarised in Scheme 17. Isocyanates are readily hydrolysed by water giving, after loss of \(CO_2\), an amine which reacts further to give the urea.
The catalysis of many of these reactions by a variety of Lewis acids has been studied. Among the most effective are compounds of tin (IV).

The isocyanates readily dimerize and trimerize and often form these compounds as side products.

The reaction with acetic acid is well known giving the initial adduct (13) which reacts further (Scheme 18). Aliphatic isocyanates give the N-acetyl compound (14) as the product after rearrangement and loss of CO₂. Aromatic isocyanates give a second anhydride (15) which loses CO₂ to give the urea (16).
Reaction of aryl isocyanates with 4-nitrophenol in the presence of potassium carbonate gives the urethane (17) which on heating extrudes CO₂ giving the amine (18) (Scheme 19).

Few reactions of isocyanates are carried out in aqueous solution. Both aliphatic and aromatic isocyanates however react with aqueous bisulphite solutions to give stable, water soluble adducts in high yields (Scheme 20). The adducts (19) will then react with benzylamine to give the urea and regenerate the bisulphite. Thus the bisulphite ion is sufficiently nucleophilic to compete with hydrolysis despite the large
excess of water.

\[
\text{R-} \text{N} = \text{C} = \text{O} + \text{HSO}_3^- \rightarrow \text{R-NH} = \text{C} = \text{NHR} + \text{H}_2\text{O} + \text{PhCH}_2\text{NH}_2 \rightarrow \text{R-NH} + \text{NHCH}_2\text{Ph} + \text{HSO}_3^-
\]

(19)

**SCHEME 20**

Nucleophilic acylation of isocyanates by reaction with acyl lithium reagents has been demonstrated\(^6\)\(^1\) (Scheme 21), giving direct attack of the organolithium reagent as a side reaction. The reaction of isocyanates with other organometallic species is well known.\(^6\)\(^2\)

**SCHEME 21**

An interesting reaction of isocyanates is that with peroxo compounds. At low temperature reaction of equimolar quantities of isocyanate and peroxide gave peroxycarbamates\(^6\)\(^3\),\(^6\)\(^4\) (20). These are unstable and decompose with loss of CO\(_2\) to give azo and/or hydrazo compounds\(^6\)\(^5\),\(^6\)\(^6\) (Scheme 22). A patent was issued for commercial production of azo compounds by reaction of ethereal hydrogen peroxide and isocyanates\(^6\)\(^7\). An analytical procedure was developed using the colorimetric reaction of phenyl isocyanates and peroxides under basic conditions.\(^6\)\(^8\) The coloured product formed was not an azo compound, but thought to be nitrosobenzene (21), formed from oxidation of the radical (22).
Very little work has been done on the nitration of isocyanates. Reaction of phenyl isocyanate with $\text{N}_2\text{O}_4$ in chloroform was found to give high yields of benzene diazonium nitrate (13) (Scheme 23).

\begin{equation}
\text{PhNCO} + \text{N}_2\text{O}_4 \xrightarrow{\text{CHCl}_3} \text{PhN}_2^+\text{NO}_3^- + \text{CO}_2
\end{equation}

\textbf{SCHEME 23}

Olah and co-workers examined the reaction of isocyanates with nitrosonium salts. This gave the carbonium ion (Scheme 24) which was identified by n.m.r.

\begin{equation}
\text{R}^- \text{N} = \text{C} = \text{O} + \text{NO}^+\text{X}^- \xrightarrow{\text{MeNO}_2} \text{R}^+\text{X}^- + \text{N}_2 + \text{CO}_2
\end{equation}

\textbf{SCHEME 24}

Carrying out the reaction in the presence of an aromatic compound resulted in alkylation of the aromatic ring. The reaction must take place via attack of the nitrosonium ion on the isocyanate, then rearrangement and fragmentation (Scheme 25). A similar mechanism must take place in the reaction with $\text{N}_2\text{O}_4$.

\begin{equation}
\text{R}^- \text{N} = \text{C} = \text{O} + \text{NO}^+\text{X}^- \xrightarrow{\text{X}^-} \text{R}^- \text{N} = \text{C} = \text{O} \xrightarrow{\text{X}^-} \text{R}^+ + \text{N}_2 + \text{CO}_2
\end{equation}

\textbf{SCHEME 25}

The other important class of isocyanate reactions are the 1,2-
cycloadditions across the $C = N$ bond. These will not be discussed in detail here. However one recent example involves the denitrosation of $N$-nitrosamines by $N$-chlorosulphonyl isocyanate\(^\text{71}\) (Scheme 25). This was thought to involve cycloaddition, then fragmentation of the 4-membered ring to give $CO_2$ and the $N$-chlorosulphonyl triazene (23) which hydrolysies to the amine under the reaction conditions. High yields of amine were obtained.

\[
\begin{align*}
\text{R}_1 \text{N} - \text{N} = \text{O} & \xrightarrow{\text{Et}_2\text{O}} \text{R}_1 \text{N} - \text{N} = \text{O} \\
\text{ClSO}_2 - \text{N} = \text{C} = \text{O} & \xrightarrow{\text{H}_2\text{O}} \text{ClSO}_2 - \text{N} = \text{C} = \text{O} \\
\text{R}_1 \text{N} - \text{N} = \text{NH} & \xrightarrow{\text{H}^+} \text{R}_1 \text{N} - \text{N} = \text{NH} \\
\text{R}_1 \text{NH} & \xrightarrow{\text{H}^+} \text{R}_1 \text{NH} \\
\text{R}_2 & \\
\text{R}_2
\end{align*}
\]

**SCHEME 25**

1.4.2 **Isothiocyanates**

The isothiocyanates (24) are the thio analogues of the isocyanates, and the anhydrides of the thiocarbamic acids (25).

\[
\begin{align*}
\text{R} - \text{N} = \text{C} = \text{S} & \\
\text{R} - \text{NH} & \xrightarrow{\text{OH}} \\
(24) & \\
(25)
\end{align*}
\]

They exhibit similar properties to the isocyanates but are less reactive. Isothiocyanates are attacked by a wide range of nucleophiles\(^\text{72}\) including alcohols, amines and thiols. Reaction with carboxylic acids gives amides (Scheme 27) but high temperatures ($> 130^\circ\text{C}$) are required.
Isothiocyanates are stable to water, often being purified by steam distillation. No tendency for dimerization and trimerization has been observed.

Adducts are formed from reaction of isothiocyanates with aqueous bisulphite solution. Organolithium reagents undergo nucleophilic addition to isothiocyanates. Using acyllithium reagents Seyferth and Hui observed interesting behaviour of the anions formed (Scheme 28).

The intermediate (26) could be trapped by acid to give the thiocarbonyl compound (27) via N-protonation. Trapping with methyl iodide, however produces the imine (28) as a result of S-alkylation. This is rationalised by the HSAB theory, as the harder electrophile (H+) reacts on the harder atom (N) of the ambident anion (26) and the softer electrophile (MeI) at the softer sulphur atom.

Recent studies often concern the more reactive classes of isothiocyanates such as the acyl (29), sulphonyl (30), and phosphoryl (31) derivatives, which are commonly used in synthesis.
Only one study on the nitrosation of isothiocyanates appears to have been done. Olah and co-workers\(^\.signal{70}\) found that alkyl and acyl isothiocyanates reacted with NO\(^+\) salts in nitromethane to give deamination, in a similar fashion to the isothiocyanates, (Scheme 29).

\[
\text{Scheme 29}
\]

\[
R - N = C = S + NO^+ \text{SbF}_6^- \xrightarrow{\text{MeNO}} R^+ \text{SbF}_6^- + N_2 + \text{COS}
\]

1.4.3 Carbodiimides

The carbodiimides (32) are the anhydrides of the ureas (33). They have a heterocumulene structure with a central electron deficient carbon atom and are readily attacked by nucleophiles.

\[
\text{(32)} \quad \text{(33)}
\]

Carbodiimides are less reactive than isocyanates but more reactive than isothiocyanates.

The chemistry of carbodiimides has been widely reviewed.\(^\signal{75,76}\) It is well known that carbodiimides react with a wide range of nucleophiles, such as amines, thiols, hydroxylamine etc. They readily hydrolyse to the parent urea. Alcohols are usually inert toward carbodiimides unless a suitable catalyst, such as Cu\(_2\)Cl\(_2\) or CuCl\(_2\), is present. Even reaction with alkoxydes requires high temperature. Carbodiimides dimerize as do isocyanates, and may polymerize on heating.

One of the most important reactions of carbodiimides is with carboxylic acids. It gives highly reactive mixed anhydrides which are used as reagents in bond making processes, such as the synthesis of peptides and phosphate esters. Dicyclohexylcarbodiimide (DCC) is usually used. For example Scheme 30 shows the use of DCC in peptide formation, where the mixed anhydride (34) is formed and reacted with a protected amino acid (35) to give the dipeptide (36).
SCHEME 30

The two problems with this reaction are competing rearrangement of the anhydride by an O —► N acyl shift giving (37), and the difficulty of removing the dicyclohexyl urea (38) side product. These difficulties are overcome by employing polymer supported unsymmetrically disubstituted carbodiimides \(^{80}\): the polymer support ensures freedom from urea and the differential electron density reduces the ease of the acyl shift.

Carbodiimides are also used to promote ylide formation between dimethyl sulphoxide (DMSO) and hydroxy compounds in the Pfitzner-Moffat oxidation of alcohols \(^{81}\) (Scheme 31). Nucleophilic attack of DMSO on the carbodiimide gives the reactive anhydride (39).
Reaction of carbodiimides and hydrogen peroxide has been used to produce oxidising agents. Rebek and co-workers\textsuperscript{82} found reaction of various dehydrating agents such as activated ureas, cyanates and ortho esters reacted with hydrogen peroxide to give epoxidising agents. DCC failed in this respect unless acetic or trifluoro acetic acid was added, and this was thought to produce a peracid as the epoxidising agent. Using a more reactive carbodiimide however, with a benzoyl substituent, epoxidation of alkenes was obtained by reaction with hydrogen peroxide and carbodiimide in THF. The epoxide was also decomposed under the reaction conditions, for example reaction with cyclohexene gave 41% epoxide but only 25% recovered alkene. Reaction of hydrogen peroxide was thought to form an intermediate (40) (Scheme 32).

\[
\begin{align*}
\text{N} \begin{array}{c} \text{N} \\ \text{N} \end{array} + \text{H}_2\text{O}_2 & \rightarrow \text{O} \end{align*}
\]

\[
\text{R}_1 \quad \text{R}_2 \equiv \text{PhC} - \quad \text{R}_2 \equiv \text{t Bu} -
\]

**SCHEME 32**

Other workers\textsuperscript{83} have observed epoxidation of pyrene and phenanthrene by a mixture of diisopropylcarbodiimide, acetic acid and hydrogen peroxide, presumably by formation of a peracid (Scheme 33)
The unreactive carbodiimides may either not react with hydrogen peroxide, or if reaction occurs then the unstable anion formed may trap out the peroxide internally giving an N-hydroxy compound (41) and consequently no epoxidation of alkenes (Scheme 34).

\[
\begin{align*}
&\text{R} - \text{N} &\text{C} = \text{N} &\text{R}^1 \quad \text{R} - \text{N} &\text{C}^\ominus &\text{N} &\text{R}^1 \quad \text{H}^+ \\
&\text{O} &\text{O} &\text{O} &\text{O} &\text{OH} &\text{O} \\
&\text{H} & & & & & \\
\end{align*}
\]

(41)

SCHEME 34

1.4.4 N-Sulphinyl Amines

The N-sulphinyl amines (42) have not been much studied.\(^{84,85}\) They are easily prepared by the action of thionyl chloride on amines (Scheme 35), the aliphatic derivatives being least stable.

\[
\text{RNH}_2 + \text{SOCl}_2 \quad \longrightarrow \quad \text{RN} = \text{S} = \text{O} + 2\text{HCl}
\]

(42)

SCHEME 35

They are attacked by nucleophiles but are less reactive than the other heterocumulenes. Indeed they do not possess the same type of structure. The -NSO group is non-linear, and gives cis and trans isomers.\(^{86,87}\) (Scheme 36)

\[
\begin{align*}
&\text{Ph} &\text{S} &\text{Ph} \\
&\text{Ph} &\text{S} &\text{Ph} \\
&\text{Ph} &\text{S} &\text{Ph} \\
&\text{Ph} &\text{S} &\text{Ph} \\
\end{align*}
\]

SCHEME 36

They do not have the typical i.r. absorbance of heterocumulene structures at around 2200 cm\(^{-1}\), but have an i.r. spectra very similar to that of SO\(_2\), suggesting a similar non-linear structure.

N-sulphinyl amines react with water to give the parent amine and SO\(_2\). Alcoholsysis also gives the amine, as the initial adduct is unstable and decomposes. Amines and thiols react as do Grignard reagents and organolithium reagents.
Olah found that N-sulphinyl amines reacted with nitrosonium salts in nitromethane to give carbonium ions (Scheme 37).

\[
\begin{align*}
R - N = S = O & + \text{NO}^+ \text{SbF}_6^- \rightarrow R^+ \text{SbF}_6^- + N_2 + SO_2 \\
R &= (\text{CH}_3)_3C-, (\text{C}_6\text{H}_5)_3C-, \text{C}_6\text{H}_5\text{CO}
\end{align*}
\]

SCHEME 37

Aromatic derivatives reacted with nitrosonium salts in ethylene dichloride to give diazonium salts (Scheme 38).

\[
\begin{align*}
R - N = S = O & + \text{NO}^+ X^- \rightarrow RN^+_2 X^- + SO_2 \\
X &= \text{ClO}_4^-, \text{SbCl}_6^- \\
R &= \text{NO}_2\text{Cl}, \text{Cl}, \text{NO}_2
\end{align*}
\]

SCHEME 38
1.5 CONCLUSION

These examples show that nitrite ion can be activated to produce nitrosation reactions, by both physical and chemical means. Nitrite activation offers methods of producing nitrosation reactions under mild, non-acidic conditions.

Reactions of this type may be important for two reasons. Firstly, they give possible routes for the formation of carcinogenic materials in the environment. Photolysis of nitrite ion to produce nitroso compounds may be important with respect to the storage of foods containing nitrite. An example is the storage of bacon in see-through packs in fluorescent lit cabinets. Nitrosation catalysed by formaldehyde also has environmental importance, as formaldehyde is used as a germicide and fungicide for plants and vegetables and in combination with nitrite as a fish preservative.

Secondly these mild methods of nitrosation may be useful in synthesis. Deamination usually occurs under acidic conditions, which may be unacceptable for multifunctional compounds.

The chemical methods of activation both involved reaction of nitrite ion with anhydrides. The high reactivity of the heterocumulene anhydrides to nucleophilic addition has been discussed. These are therefore ideal substrates for reaction with nitrite ion.

The work described in this thesis is directed towards examining the reaction of nitrite ion with these organic anhydrides and to investigate the possibility of activation of the nitrite ion to give nitrosation reactions under mild conditions.
CHAPTER 2

REACTION OF NITRITE ION WITH AROMATIC ISOCYANATES
2.1 INTRODUCTION

The isocyanates are the most reactive class of anhydrides examined and the particularly high reactivity of the aromatic compounds relates to electron withdrawal by the aromatic group, increasing the electron deficiency at the isocyanate group.

Reaction of isocyanates with acetic acid is well known (see Section 1.4.1). The pKa of acetic acid is 4.75, and similar to that of nitrous acid, which is 3.4. Thus some reaction should be expected between the organic isocyanates and nitrite ion, especially with the more reactive aromatic compounds. These reactions are reported in this chapter.

2.2 HETEROGENOUS REACTION

The first evidence for attack by nitrite ion on the isocyanate came from a simple heterogenous reaction. Stirring a mixture of solid sodium nitrite and liquid phenyl isocyanate produced a solid mass after five hours at room temperature. The product contained unchanged sodium nitrite and a greater than 91% yield of the trimer of phenyl isocyanate (Scheme 39). Stirring phenyl isocyanate in the absence of sodium nitrite gave only small amounts of trimer with most of the isocyanate unreacted.

Sodium nitrite was acting as a catalyst for the trimerization. Dissolution of a small amount of nitrite in the isocyanate results in nucleophilic attack of the nitrite on the isocyanate (Scheme 39). An anionic intermediate (43) is produced and in the presence of such a large excess of isocyanate it attacks a second molecule. The dimeric anion (44) produced can either cyclise via a four-membered transition state to give the dimer (45), observed as an impurity, or attack a third isocyanate molecule to give (46). Finally (46) cyclises via a more favoured 6-membered transition state to give the trimer (47) and regenerate nitrite ion.

A range of other nucleophiles are known to catalyse this reaction, including triethylamine, sodium methoxide, potassium acetate and sodium carbonate. Evidence therefore implied that nitrite did indeed attack phenyl isocyanate. At this stage it was not known whether nitrite was acting as
SCHEME 39
an oxygen-centred nucleophile as depicted in scheme 39, or as a nitrogen-centred nucleophile.

More interesting reactions required the minimization of the trimerization reaction, because having been used as an initial probe for reaction it was now undesirable.

2.3 REACTION UNDER AQUEOUS CONDITIONS

Isocyanates are very susceptible to hydrolysis and it is generally inadvisable to use them under aqueous conditions.

However one reaction was attempted between phenyl isocyanate and aqueous sodium nitrite. The reaction was fairly heterogenous due to the low solubility of phenyl isocyanate in water. As expected hydrolysis to give the diphenylurea (48) was the major reaction (Scheme 40). However two yellow compounds were observed by tlc examination, but in small amounts and they were not further identified.

![Scheme 40](image)

These two reactions produced three important observations.

1. Nitrite did indeed attack phenyl isocyanate.
2. Aqueous conditions had to be avoided due to hydrolysis of the isocyanate.
3. Large excess of isocyanate produced mainly trimer.

2.4 REACTION OF PHENYL ISOCYANATE IN ORGANIC SOLVENTS

2.4.1 Toluene

In order to carry out reactions in organic solvents it was desirable to solubilize the salt. A potential answer was the use of crown ethers.
Reaction was carried out in toluene using 18-crown-6 and sodium nitrite. With phenyl isocyanate a complex reaction apparently ensued giving a highly coloured solution. Products included the isocyanate dimer and trimer, some hydrolysis and some very polar material. Also obtained was 1,3-diphenyltriazene (49) in 6% yield.

\[
\text{Ph-N = N-NH-Ph} \\
(49)
\]

Attempts were made to optimize the yield of the triazene. By slow addition of the phenyl isocyanate to the nitrite solution at -3°C, a yield of 22% was achieved. No further improvement could be made.

It appeared that poor solubility of the nitrite was the problem. The crown ether was acting mainly as a phase transfer catalyst, taking the nitrite into solution as the reaction proceeded. Even excess 18-crown-6 would not dissolve all the nitrite at once. This led to the presence of nitrite with excess isocyanate and extensive trimerization. So the best yield was obtained by slow addition of isocyanate to the nitrite solution.

### 2.4.2 Acetonitrile

Another potential method of solubilizing the nitrite ion was to prepare the tetraethylammonium salt. Mixing equimolar quantities of silver nitrite and tetraethylammonium bromide in acetonitrile, precipitated silver bromide and then removal of the solvent at reduced pressure gave the tetraethylammonium nitrite (TEAN) (Scheme 41). Recrystallization gave further purification.

\[
\text{AgNO}_2 + \text{Et}_4\text{NBr} \xrightarrow{\text{MeCN}} \text{Et}_4\text{NNO}_2 + \text{AgBr} \\
(\text{TEAN})
\]

SCHEME 41

TEAN was soluble in a range of polar organic solvents. Silver nitrite itself was only slightly soluble in acetonitrile.

Reactions were first carried out in acetonitrile, and under these conditions phenyl isocyanate reacted with nitrite ion to give 1,3-diphenyltriazene in 15-16% yield.
2.5 REACTION OF 4-NITROPHENYL ISOCYANATE IN ACETONITRILE

A more reactive substrate was used to optimize the yield of triazene. The 4-nitrophenyl derivative is more reactive due to the electron withdrawing effect of the nitro group. Reaction of TEAN with a two-fold excess of 4-nitrophenyl isocyanate in acetonitrile at 0°C gave instantaneous formation of a deep purple solution. Protic work-up and column chromatography gave a 65% yield of 1,3-bis (4-nitrophenyl) triazene (50).

\[
\begin{align*}
\text{NO}_2\text{C} & \text{N} \equiv \text{N}\text{NH} \text{NO}_2 \\
\text{(50)}
\end{align*}
\]

Thus formation of the triazene appeared to be the major reaction pathway. A reasonable mechanism can be proposed for the transformation (Scheme 42). Initially nucleophilic attack of the nitrite ion on the acyl carbon atom of the isocyanate moiety produces the anion (51). Nitrite ion attacks as an oxygen centred nucleophile, the harder of the two potential sites, on the relatively hard carbon atom of the heterocumulene system. The anionic intermediate (51) must rearrange by means of migration of the nitroso group from oxygen to nitrogen to give (52). Facile loss of carbon dioxide then produces the diazotate (53), which in the presence of further isocyanate will itself react to give the second anionic adduct (54). Again this adduct can rearrange by means of migration of the 4-nitrophenyl diazo group from oxygen to nitrogen to give (55). A second loss of carbon dioxide produces the anion of the triazene (56). This anion (56) is very stable due to the extensive delocalization of the negative charge over both aromatic rings. Anion (56) is the deep purple species observed in solution. Finally protic work-up gives the triazene.

The 4-nitro group has a major effect on the reaction and produces a higher yield of triazene. Firstly the conjugative effect of the nitro group stabilizes all of the anionic intermediates, in particular the diazotate (53). Secondly, electron withdrawal by the nitro group increases reactivity of the acyl carbon atom which leads to more efficient trapping of the diazotate to give the triazene. Thirdly, the triazene anion (56) is, itself, highly stabilized.
Scheme 42

\[
\text{Et}_4\text{N}^+\text{O} = \text{N} = \text{N} \xrightarrow{\text{MeCN/0°C}} \text{NO}_2\text{N} = \text{C} = \text{O}
\]

(51)

\[
\text{NO}_2\text{N} = \text{N} = \text{N} = \text{O} \xrightarrow{-\text{CO}_2} \text{NO}_2\text{N} = \text{C} = \text{O}
\]

(52)

(53)

\[
\text{NO}_2\text{N} = \text{N} = \text{C} = \text{O} \xrightarrow{-\text{CO}_2} \text{NO}_2\text{N} = \text{N} = \text{N} = \text{N} = \text{O}
\]

(54)

(55)

(56)

(50)
The reaction of Scheme 42 is remarkable insofar as nitrosation has been brought about under very mild conditions using nitrite ion in an organic solvent at 0°C. The nitrosation occurs in an intramolecular fashion after the nitrite ion has been activated to a nitrosating agent by the initial reaction with the anhydride.

The yield of triazene was then optimized. The excess of isocyanate was varied and the yield of triazene measured using reverse phase hplc. Concentrations were determined by comparison with standard solutions of the authentic 1,3-bis(4-nitrophenyl) triazene prepared by another method.94

The results are given in Table 1, and show a maximum yield of 85% with a ten-fold excess of the isocyanate over nitrite ion. The yield increases with the excess of isocyanate, presumably because of more efficient trapping of the diazotate ion. However there is an optimum because with very large amounts of isocyanate, trimerization becomes significant. This explains the decreased triazene yield with greater than 10-fold excess.

Reaction at higher temperature (37°C) showed a reduced yield, probably because of the instability of the diazotate intermediate.

<table>
<thead>
<tr>
<th>RATIO</th>
<th>RNCO</th>
<th>NO₂⁻</th>
<th>TRIAZENE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>10⁻³</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>10⁻³</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>10⁻³</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>10⁻³</td>
<td>84</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>10⁻³</td>
<td>85 ± 2</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
<td>10⁻³</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>10⁻³</td>
<td>23</td>
</tr>
</tbody>
</table>

a - [TEAN] = 2.5 x 10⁻³ mol dm⁻³
b - Average of three reactions
c - At 37°C
2.6 EVIDENCE FOR PROPOSED MECHANISM

The mechanism proposed for the formation of the triazene required verification and confirmatory evidence was therefore sought.

2.6.1 Evolution of Carbon Dioxide

In the reaction outlined in Scheme 42, two moles of carbon dioxide are released for every mole of triazene formed. No obvious evolution of gas i.e. bubbles, is observed, but when nitrogen is bubbled through the reaction solution the effluent gases turn lime water turbid.

2.6.2 Detection of Diazotate

According to Scheme 42, the diazotate intermediate should be obtained for reactions with excess nitrite ion over isocyanate. The diazotate was therefore trapped and the yield determined.

The method of analysis for the diazotate involved dilution of the reaction solution into aqueous 0.1N borax (pH 9) containing excess 2-naphthol-3,6-disulphonic acid (57, R-Salt). This caused hydrolysis of the diazotate to the diazonium ion, which was trapped by the R-Salt to give an orange azo-dye (58) (Scheme 43).

\[
\begin{align*}
\text{NO}_2 & \quad \text{N=N-} \quad \text{O} \quad \text{pH9} \\
\text{H}_2\text{O/HO} & \quad \text{NO}_2 \quad \text{N=N} \quad \text{N}_2 \\
\text{SCHEME 43} & \\
& \quad \text{OH} \quad \text{S} \text{O}_3^{-} \quad \text{R-Salt} \quad \text{R-Salt} \quad \text{OH} \quad \text{S} \text{O}_3^{-}
\end{align*}
\]

The yield of azo dye and therefore of diazotate was determined spectrophotometrically. The assay was calibrated using solutions of the diazonium ion formed in situ by treating the corresponding amine with nitrous acid.

Using this method the 4-nitrophenyl diazotate was detected in a maximum yield of 72% with a 50-fold excess of nitrite ion (Table 2). The yield was observed to increase with the excess of nitrite ion as this minimized competing dimerization, trimerization and further reactions of the diazotate.

The results confirm that the diazotate is an intermediate in the formation of triazene.
TABLE 2: Yields of Diazotate from reaction of excess TEAN with 4-nitrophenylisocyanate\(^a\) in acetonitrile at 0\(^\circ\)C

<table>
<thead>
<tr>
<th>RATIO ([\text{TEAN}] / [\text{RNCO}])</th>
<th>DIAZOTATE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>19</td>
<td>60</td>
</tr>
<tr>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>50</td>
<td>72</td>
</tr>
</tbody>
</table>

\(a\) \([\text{RNCO}]\) ca. 4 \times 10^{-3} \text{ mol dm}^{-3}

2.6.3 Reaction of Diazotate with Isocyanate

The 4-nitrophenyldiazotate is the most stable of the aromatic diazotates due to its high level of conjugation (Scheme 44). This allows the preparation and isolation of the sodium salt as a crystalline solid. The isolated diazotate was therefore reacted with the isocyanate in order to independently demonstrate the second step of the reaction in Scheme 42. A best yield of 85% was obtained with a 20-fold excess of isocyanate (Table 3).

![Scheme 44](image)

**SCHEME 44**

TABLE 3: Yields of triazene from reaction of excess 4-nitrophenyl isocyanate with sodium 4-nitrophenyl diazotate\(^a\) in acetonitrile at 0\(^\circ\)C

<table>
<thead>
<tr>
<th>RATIO ([\text{RNCO}] / [\text{DIAZOTATE}])</th>
<th>TRIAZENE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>70 (\pm) 5(^b)</td>
</tr>
<tr>
<td>20</td>
<td>85 (\pm) 5(^b)</td>
</tr>
<tr>
<td>30</td>
<td>80</td>
</tr>
</tbody>
</table>

\(a\) \([\text{DIAZOTATE}]\) = 2.5 \times 10^{-3} \text{ mol dm}^{-3}

\(b\) - average of 3 runs
The large excess required suggests that reactivity of the diazotate towards 4-nitrophenyl isocyanate is less than expected. This may be due however to the use of the sodium salt of the diazotate rather than the tetraethylammonium salt for the reaction of nitrite ion with the isocyanate. The sodium salt of the diazotate is not readily soluble and probably not highly dissociated in acetonitrile and consequently it may appear to be less reactive. The tetraethylammonium salt of the diazotate was difficult to prepare due to its hygroscopic nature.

In conclusion all the above evidence supports the mechanism outlined in Scheme 42. A kinetic study might have given added evidence and identified the rate determining step, but the reactions are too fast even at 0°C for simple rate measurements.

2.7 VARIATION OF SOLVENT

Preliminary experiments with phenyl isocyanate indicated that similar products were obtained from reaction with TEAN in a range of solvents i.e. acetonitrile, acetone and dichloromethane. A more detailed study of solvent effects was therefore made with 4-nitrophenyl isocyanate.

2.7.1 Tetrahydrofuran (THF)

TEAN is virtually insoluble in THF, so the tetrabutylammonium salt was prepared by the same method and used. Reaction of nitrite ion with a 5-fold excess of 4-nitrophenyl isocyanate in THF at 0°C gave a 58% yield of triazene as determined by hplc.

2.7.2 Dimethyl sulfoxide (DMSO)

The use of DMSO as solvent enables sodium nitrite to be used as it is readily soluble. Initial reactions gave very poor yields of the triazene. This was found to be due to reaction of the isocyanate with the DMSO95,96,97 The solvent is sufficiently nucleophilic to attack the isocyanate giving an intermediate (59) which ultimately yields dimers, trimers and two other products (60) and (61) containing a solvent molecule (Scheme 45).

Reactions were therefore carried out with a solution of 4-nitrophenyl isocyanate in a small amount of acetonitrile (5 ml) and adding this to a solution of sodium nitrite (10 mg) in DMSO (10 ml) at 0°C. An 80% yield of triazene was achieved with a 10-fold excess of isocyanate. Under
\[ \text{DIMERS and TRIMERS} \]

\[ (59) \]

\[ (60) \]

\[ (61) \]

SCHEME 45
identical conditions the sodium diazotate reacted with the isocyanate to
give a 64% yield of triazene.

So the reaction is not special to the TEAN-Acetonitrile system and
may be carried out in other solvents with varying degrees of success.

2.8 VARIATION OF ISOCYANATE STRUCTURE

2.8.1 Phenyl Isocyanate

When good yields of triazene were obtained from 4-nitrophnyl
isocyanate, the reaction of the phenyl derivative was re-examined. Using
the hplc assay, the yield of 1,3-diphenyl triazene was optimized
(Table 4) and found to be 90\+5\% with a 30-fold excess of isocyanate over
nitrite. The greater excess required reflects the lower reactivity of
the phenyl isocyanate and therefore the less efficient trapping of the
diazone. Increase in the reaction temperature reduced the yield of
triazene probably because of the instability of the phenyl diazotate. A
similar effect was noted for the 4-nitrophnyl isocyanate (Table 1).

<table>
<thead>
<tr>
<th>RATIO $\frac{[\text{RNCO}]}{[\text{NO}_2^-]}$</th>
<th>TRIAZENE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>43, 46</td>
</tr>
<tr>
<td>20</td>
<td>54</td>
</tr>
<tr>
<td>$20^b$</td>
<td>17</td>
</tr>
<tr>
<td>25</td>
<td>57</td>
</tr>
<tr>
<td>30</td>
<td>$90^+5^c$</td>
</tr>
<tr>
<td>53</td>
<td>59</td>
</tr>
</tbody>
</table>

a - $[\text{NO}_2^-] = 2-5 \times 10^{-3}$ mol dm$^{-3}$
b - At 25°C
c - Average of 4 runs

The reaction in water was therefore re-examined. Reaction of
0.46 M phenyl isocyanate and 1.0 M sodium nitrite at room temperature
gave a 2% yield of triazene. With excess isocyanate ($[\text{PhNCO}] = 0.46$ M)
and a deficiency of nitrite ([NO$_2^-$] = 0.073 M) the yield was 8%. So the nitrite ion will compete with water for the isocyanate to give measurable amounts of triazene.

2.8.2 Other 4-substituted Phenyl Isocyanates

Several 4-substituted phenyl isocyanates were examined to probe the effect of substituents on the reaction. The corresponding 1,3-diaryl-triazenes were prepared by a literature method$^{94}$ and used as standards for the hplc assay.

4-Methylphenyl isocyanate gave an optimum yield of (60 ± 3)% in acetonitrile at 0°C, with a 30-fold excess of isocyanate (Table 5). Cooling the reaction to -40°C decreased the yield. 4-Chlorophenyl isocyanate gave an optimum yield of 65 ± 5% with a 20-fold excess of substrate under the same conditions (Table 6). The best temperature for these reactions appeared to be 0°C and so further optimization reactions were carried out at this temperature.

4-Trifluoromethylphenyl isocyanate gave a best yield of 63±10% with a ten-fold excess of substrate, and the 4-methoxyphenyl isocyanate gave an optimum of 20% with a 50-fold excess of substrate. These data are summarized in Table 7.

<p>| TABLE 5: Yields of Triazene from reaction of excess 4-Methylphenyl isocyanate with TEAN$^a$ in Acetonitrile at 0°C |</p>
<table>
<thead>
<tr>
<th>RATIO $\frac{[\text{RNCO}]}{[\text{NO}_2^-]}$</th>
<th>TRIAZENE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>30</td>
<td>63, 57</td>
</tr>
<tr>
<td>30$^b$</td>
<td>28</td>
</tr>
<tr>
<td>60</td>
<td>23</td>
</tr>
</tbody>
</table>

$^a$ [NO$_2^-$] = 2.5 x 10$^{-3}$ mol dm$^{-3}$

$^b$ Done at -40°C
TABLE 6: Yields of Triazene from reaction of excess 4-Chlorophenyl isocyanate and TEAN\textsuperscript{a} in Acetonitrile at 0\textdegree C

<table>
<thead>
<tr>
<th>RATIO [RNCO] ([\text{NO}_2^-])</th>
<th>TRIAZENE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (\times) 60 (\pm) 5</td>
<td></td>
</tr>
<tr>
<td>20 (\times) 65 (\pm) 5</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>30</td>
<td>47, 52</td>
</tr>
</tbody>
</table>

\(\text{a -}[\text{NO}_2^-] = 2-5 \times 10^{-3} \text{ mol dm}^{-3}\)

TABLE 7: Optimum Triazene yields for reaction of excess aromatic isocyanates and tetraethylammonium nitrite in acetonitrile at 0\textdegree C

\[
\begin{array}{c|c|c|c}
R & \text{N = C = O} & \text{RATIO [RNCO]} & \text{YIELD}^3 / \% & \sigma_R^- \\
\hline
\text{R = NO}_2 & 10 & 85 & +0.46 \\
\text{CF}_3 & 10 & 63 & +0.17 \\
\text{Cl} & 20 & 65 & -0.23 \\
\text{H} & 30 & 90 & 0 \\
\text{Me} & 30 & 60 & -0.11 \\
\text{MeO} & 50 & 20 & -0.45 \\
\end{array}
\]

\(\text{a -} \pm 5\%\)

2.8.3 Effect of substituents

The yields given in Table 7, show that formation of the 1,3-diaryl-triazene is favoured by electron withdrawing 4-substituents. The lowest yield is obtained with the electron donating 4-methoxy substituent.

Two effects probably contribute to the observed trend.

1. The electron withdrawing substituents (especially those with a greater resonance effect), stabilize the anionic intermediates, in particular the diazotate.
2. Electron withdrawing substituents increase the reactivity of the isocyanate moiety by increasing the electron deficiency of the acyl carbon atom. Thus the isocyanate will trap out the diazotate more effectively.

A moderate correlation exists between log (max. yield) and the $R^-$ substituent constants, $^{98}$ (Fig. 1) although the phenyl substrate gives a higher yield and the 4-chlorophenyl substrate a lower yield than expected. The correlation is perturbed by the fact that the optimum yields require different excesses of isocyanate over nitrite ion, due to the competing trimerization reaction. Substituent constants are normally used to correlate rates of reaction not product yields, and the inherent differences in the two types of measurement would be expected to result in a poorer correlation with product yields. The slope of the plot ($\rho = +0.55$) indicates that the reaction is favoured by electron withdrawal.

The diazotate yields exhibit similar behaviour to that observed for the triazenes. (Table 8). Thus the stability of the diazotate is of paramount importance to the success of the reaction.

**TABLE 8:** Yields of Diazotate from reaction of aromatic isocyanates with a 50-fold excess of TEAN in Acetonitrile at $0^\circ$C

<table>
<thead>
<tr>
<th>R =</th>
<th>DIAZOTATE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$</td>
<td>90</td>
</tr>
<tr>
<td>H</td>
<td>90</td>
</tr>
<tr>
<td>MeO</td>
<td>40</td>
</tr>
</tbody>
</table>

2.9 CONCLUDING REMARKS

It has been demonstrated that aromatic isocyanates will react with nitrite ion under mild conditions to give good yields of the 1,3-diaryl triazenes. Thus nitrosation is observed to take place as a result of the activation of the nitrite by its reaction with the anhydride. The reaction is similar to that observed when N-nitrosamines are produced from reaction of nitrite with iminium cations (see Section 1.3.4).

The reaction is a milder method for the formation of triazenes than the usual syntheses under acidic conditions. For compounds with electron withdrawing substituents, the yields are comparable to those of
FIG. 1  
Graph of log (maximum yield) versus $\sigma_R^-$ for Formation of 1, 3-Diaryltriazenes from Reaction of 4-Substituted Phenyl Isocyanates and Nitrite Ion in Acetonitrile at 0°C
previous syntheses, although purification is complicated by the by-products formed from the excess isocyanate on work-up.

It is interesting that the triazene anions formed do not react further with the isocyanates, although the reaction of protonated triazenes has been studied.\textsuperscript{99} Delocalization of the charge must result in greatly reduced nucleophilicity. Where there is less delocalization of negative charge, more triazene may be lost by further reaction. Thus the softer bases react less readily with the hard isocyanate centre. This gives another possible reason for the low yield obtained from 4-methoxyphenyl isocyanate.

The reaction also offers a mild synthesis of azo dyes. This is exemplified in the colorimetric test used to determine the diazotate yields. Reaction of excess nitrite ion with aromatic isocyanate gives an organic solution of the diazotate, which may be trapped with a range of aromatic compounds such as 2-naphthol-3,6-disulphonic acid, to give an azo compound. Usual methods of azo dye formation involve diazotization in concentrated acid solution. In industry disposal of the acid residues is a major problem. This method would give a route avoiding concentrated acid and for this reason could have commercial applications. Isocyanates are made in large quantities for the polymer industry, so the technology for their industrial scale production is well known.
CHAPTER 3

REACTION OF NITRITE ION WITH ALKYL ISOCYANATES
3.1 INTRODUCTION

Alkyl isocyanates react with nucleophiles but less readily than the aromatic analogues. They are sufficiently electron deficient, however to expect some reaction with nitrite ion.

3.2 CONSUMPTION OF NITRITE

Initial studies were carried out using cyclohexyl isocyanate. With an excess of the isocyanate over nitrite ion it was possible to observe the loss of nitrite ion by Shinn's method. 100

No significant consumption of nitrite, however was observed for reactions in acetonitrile at temperatures from 0 to 80°C. No reaction was observed in DMSO at room temperature, although nitrite was found to decompose in refluxing DMSO even without isocyanate present.

Thus it appeared that either cyclohexyl isocyanate was not reacting with nitrite ion or that the product was unstable. The anion (62) produced by attack of nitrite ion on the isocyanate (Equation 4) may collapse back to starting materials under the acidic conditions used in the Shinn's test, or react with further isocyanate to give trimers and regenerate the nitrite ion.

3.3 CATALYSIS BY DIBUTYLTIN DIACETATE

In order to promote reaction dibutyltin diacetate (DBTDA, Bu₂Sn(OAc)₂) was added to the reaction mixtures. DBTDA is a common catalyst for the reactions of isocyanates. 101 Addition of DBTDA increased the consumption of nitrite ion. As DBTDA was more soluble in DMSO reactions were carried out in this solvent, using sodium nitrite.

The consumption of nitrite ion depended on the concentration of DBTDA (Fig. 2), reaching a maximum of 90% with a 2.5 fold excess of catalyst.

Kinetic studies were carried out under pseudo first order conditions i.e. with excess unreacted isocyanate, using Shinn's method 100.
FIG. 2: PLOT OF NITRITE CONSUMPTION VERSUS AMOUNT OF DIBUTYLTINDIACETATE FOR REACTION OF CYCLOHEXYL ISOCYANATE AND SODIUM NITRITE IN DMSO AT 25°C.

Conditions: $[\text{NO}_2^-] = 7.25 \times 10^{-3} \text{ mol dm}^{-3}$

$[\text{RNCO}] = 0.10 \text{ mol dm}^{-3}$
FIG. 3: PLOT OF PSEUDO FIRST ORDER RATE CONSTANT VERSUS CYCLOHEXYL ISOCYANATE CONCENTRATION.
to measure the unreacted nitrite concentration. Good pseudo first order kinetics were observed and for constant DBTDA concentration the reaction was also first order in cyclohexyl isocyanate (Fig. 3). Thus the rate of reaction was described by equation 5, where

\[ k_2 = 3.6 \pm 0.07 \times 10^{-3} \text{ mol}^{-1} \text{ dm}^{3} \text{ S}^{-1}. \]

\[
\text{RATE} = k_2 \left[ \text{NO}_2^- \right] \left[ \text{RNCO} \right]
\]

The rate was also measured for several DBTDA concentrations (Table 9), and found to be independent of this factor.

This was unexpected because usually some dependence on the DBTDA is observed. For example, Entelis found a first order dependence on DBTDA for the reaction of methanol and 4-chlorophenyl isocyanate. The mechanism proposed involved initial formation of an alcohol-catalyst complex which resulted in activation of the hydroxyl group (Scheme 46).

\[
\begin{align*}
\text{CATALYST} + \text{ROH} & \xrightleftharpoons{} \text{CATALYST} \cdot \text{ROH} \\
\xrightarrow[\text{RNCO}]{\text{OR}} & \xrightarrow{} \text{RNH}
\end{align*}
\]

SCHEME 46

Subsequently evidence for the complexation of isocyanates by tin compounds was found and mechanisms were proposed involving rapid equilibrium formation of a complex between catalyst and isocyanate or alcohol, followed by slow bimolecular reaction with the other reagent. More recently, a mechanism has been proposed where the initial alcohol complex dissociates to give the charged species (63) followed by insertion of the isocyanate into the tin-oxygen bond (Scheme 47). The kinetic expression (Equation 6) showed the order with respect to catalyst was 0.5.

\[
\text{RATE} = k \left[ \text{DBTDA} \right]^{0.5} \left[ \text{MeOH} \right]^{0.5} \left[ \text{PhNCO} \right]
\]

The rate of the reaction of cyclohexyl isocyanate with nitrite ion shows no dependence on DBTDA, although the yield of product does. This implies that the DBTDA interacts with an intermediate formed after
TABLE 9: VARIATION OF PSEUDO FIRST ORDER RATE CONSTANT WITH DBTDA CONCENTRATION FOR REACTION OF CYCLOHEXYL ISOCYANATE AND SODIUM NITRITE$^a$
IN DMSO AT 25°C.

<table>
<thead>
<tr>
<th>[RNCO] / mol dm$^{-3}$</th>
<th>[DBTDA] / mol dm$^{-3}$</th>
<th>$k_o / 10^{-4}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.043</td>
<td>3.47</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0216</td>
<td>4.20</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0216</td>
<td>3.97</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0186</td>
<td>3.28</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0186</td>
<td>3.20</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0093</td>
<td>3.77</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0047</td>
<td>3.48</td>
</tr>
<tr>
<td>0.15</td>
<td>0.0216</td>
<td>5.78</td>
</tr>
<tr>
<td>0.15</td>
<td>0.0186</td>
<td>5.10</td>
</tr>
</tbody>
</table>

$^a$ - $[NO_2^-] = 7.25 \times 10^{-3}$ mol dm$^{-3}$

$^b$ - Average of rates with 0.1N isocyanate is $(3.62 \pm 0.37) \times 10^{-4}$ s$^{-1}$. Therefore all agree to within 10%
[Scheme 47]

\[
\begin{align*}
\text{PhNH}_2\text{COOH} & \quad \xrightarrow{\text{MeOH}} \quad \text{PhNCO} \\
\text{MeOH} & \quad \xrightarrow{\text{H}^+} \quad \text{SnOR}^' \\
\text{SnOR}^' & \quad \xrightarrow{\text{H}^+} \quad \text{SnOR}^' + \text{OMe} \\
\text{SnOR}^' + \text{OMe} & \quad \xrightarrow{\text{H}^+} \quad \text{SnOR}^' + \text{H}^+ \\
\end{align*}
\]
the rate limiting step, which is assumed to be attack of nitrite ion on the isocyanate. The effect must be stabilization of this intermediate promoting further reaction.

In its catalytic action with nucleophiles that contain NH or OH bonds DBTDA weakens these bonds and activates the nucleophile. However nitrite ion is ionic and this type of activation cannot be involved. Indeed formation of a charged complex similar to that with alcohols (63) gives a much bulkier and less reactive nucleophile than the nitrite ion itself. Thus stabilization of an intermediate is a more attractive explanation for the promotion by DBTDA in our reactions. This is discussed more fully in section 3.6.

3.4 PRODUCT ANALYSIS IN DMSO

The reaction of aromatic isocyanates with nitrite ion produced diazotates as intermediates. If alkyl diazotates were formed they would be much less stable and products of deamination would be expected.

Cyclohexyl isocyanate was chosen as a substrate because its deamination products (cyclohexene and cyclohexanol) are relatively involatile and therefore easier to detect. Accordingly reactions were carried out in DMSO and analysed for cyclohexene and cyclohexanol by glc. Aliquots were injected directly onto the gas chromatograph. So the reactions were carried out with excess nitrite ion to avoid injecting large amounts of unreacted isocyanate onto the column. Aqueous or methanolic work-up did not affect the product yields. Results are given in Table 10.
TABLE 10: PRODUCT ANALYSIS OF REACTIONS OF CYCLOHEXYL ISOXYANATE (0.125 mol dm$^{-3}$) AND SODIUM NITRITE (1.16 mol dm$^{-3}$) IN DMSO AT ROOM TEMPERATURE IN THE PRESENCE OF DBTDA.

<table>
<thead>
<tr>
<th>[DBTDA] / mol dm$^{-3}$</th>
<th>Cyclohexene Yield / %</th>
<th>Cyclohexanol Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>0.0186</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>0.186</td>
<td>11</td>
<td>27/30</td>
</tr>
<tr>
<td>0.373</td>
<td>13</td>
<td>29</td>
</tr>
</tbody>
</table>

The yields of both products increase with DBTDA concentration, reaching a maximum as expected from the nitrite consumption. Also small amounts of cyclohexene and cyclohexanol were obtained in the absence of catalyst. Greater than 40% deamination is observed but much of the product is unaccounted for.

3.5 PRODUCT ANALYSIS IN ACETONITRILE

For further work acetonitrile was used as the reaction solvent because its chromatographic behaviour simplified the product analysis.

Firstly, the reactions carried out in DMSO were repeated in acetonitrile (Table 11). Higher yields of cyclohexene (up to 22%) were observed, although the yields of cyclohexanol were similar to those in DMSO.

TABLE 11: YIELDS OF CYCLOHEXENE AND CYCLOHEXANOL FROM REACTION OF CYCLOHEXYL ISOXYANATE WITH EXCESS TEAN IN ACETONITRILE AT ROOM TEMPERATURE.

<table>
<thead>
<tr>
<th>[TEAN]$^a$/mol dm$^{-3}$</th>
<th>[DBTDA] / mol dm$^{-3}$</th>
<th>Cyclohexene /%</th>
<th>Cyclohexanol /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.13</td>
<td>0</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>0.12</td>
<td>0.011</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>0.125</td>
<td>0.034</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>0.12</td>
<td>0.075</td>
<td>22</td>
<td>34</td>
</tr>
</tbody>
</table>

$a - [RNCO] = 0.023$ mol dm$^{-3}$ in reactions
Again only ca. 50% of the starting material was accounted for. Identification of other products was resolved by g.c./m.s. These reactions were carried out with excess isocyanate to allow some correlation with the kinetic studies. The results are summarised in Table 12. Compounds were identified by comparison of both their mass spectra and gc retention times, with authentic compounds.

**Table 12: Products Identified by g.c./m.s.**

- **g.c. conditions:** BP15 silica capillary column, with He carrier gas (30 psi) and temperature from 60 to 100°C.

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>STRUCTURE</th>
<th>m / Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure1" /></td>
<td>Found: 82 (M⁺, 30%), 79 (12), 67 (83), 54 (100), &lt;br&gt;Authentic: 82 (M⁺, 39%), 79 (10), 67 (100), 54 (68), 41 (34)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure2" /></td>
<td>Found: 98 (M⁺, 40%), 82 (10), 69 (31), 55 (100), 42 (56), &lt;br&gt;Authentic: 98 (M⁺, 40%), 82 (12), 69 (30), 55 (100), 42 (60)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure3" /></td>
<td>Found: 82 (45%), 71 (20), 67 (29), 57 (100), 54 (10), &lt;br&gt;Authentic: 82 (50%), 71 (20), 67 (25), 57 (100), 54 (12), 44 (22)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure4" /></td>
<td>Found: 125 (M⁺, 14), 97 (74), 82 (81), 69 (55), 67 (100), 56 (55), 54 (62), &lt;br&gt;Authentic: - (unreacted starting material)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure5" /></td>
<td>Found: 100 (6), 99 (6), 82 (100), 67 (65), 61 (10), 57 (10), 54 (20), 43 (40), &lt;br&gt;Authentic: 100 (5%), 99 (5), 82 (95), 67 (50), 61 (10), 57 (22), 54 (20), 43 (100)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure6" /></td>
<td>Found: 141 (M⁺, 20%), 98 (18), 82 (5), 70 (8), 67 (9), 60 (100), 56 (91), 43 (62), &lt;br&gt;Authentic: 141 (M⁺, 20%), 98 (20), 82 (7), 70 (8), 67 (9), 60 (100), 56 (92), 43 (60)</td>
</tr>
</tbody>
</table>
They are listed in order of increasing retention time.

The formation of two deamination products; cyclohexene and cyclohexanol was confirmed. Two further deamination products found were cyclohexanone and cyclohexyl acetate. The acetate may arise by trapping of the carbonium ion with free acetate from the DBTDA, and cyclohexanone from oxidation of the alcohol. Unreacted isocyanate was also detected. N-acetyl cyclohexylamine was identified by mass spectrometry but not detected by normal glc analysis. This compound may be formed by reaction of cyclohexyl isocyanate with acetate and is therefore a consequence of the excess isocyanate.

The effect of reagent concentrations on the yields of the four major products was examined. Variation of the nitrite:isocyanate ratio using a constant 5-fold excess of DBTDA over nitrite ion (Table 13) shows the following features.

i) The yields of cyclohexanone and cyclohexanol are unaffected by changes in the nitrite:isocyanate ratio.

ii) The yields of cyclohexene and cyclohexyl acetate increase slightly with greater excess of isocyanate over nitrite ion. (The trend is clearer when the isocyanate concentration is increased (Table 13; runs 5-8), than when the nitrite concentration is reduced (Table 13; runs 1-4). This is due to greater accuracy in the analysis at higher concentrations).

iii) The total yield of all four products varies from 60 to 76%, the best being obtained with a high excess of isocyanate.

Variation of the DBTDA concentration (Table 14) showed the yields of all four products to be dependent on the excess of DBTDA.

i) The yield of cyclohexanone increases with increasing DBTDA concentration. None is observed at less than 2.5-fold excess of DBTDA.

ii) Above a 5-fold excess of DBTDA, the yield of cyclohexyl acetate is constant, but decreases when the excess is decreased, and is zero in the absence of DBTDA.

iii) The yields of cyclohexanol and cyclohexene show similar behaviour to that of the acetate. However small amounts of each are observed even when no DBTDA is used. The combined yield of 25% agrees with the 22% consumption of nitrite observed in the absence of DBTDA.
### TABLE 13: VARIATION OF PRODUCT YIELDS FOR REACTION OF CYCLOHEXYL ISOCYANATE AND TETRAETHYLAMMONIUM NITRITE IN ACETONITRILE AT ROOM TEMPERATURE.

<table>
<thead>
<tr>
<th>REACTION CONDITIONS</th>
<th>PRODUCT YIELDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>[RNCO] /mol dm⁻³</td>
<td>[NO₂⁻] /mol dm⁻³</td>
</tr>
<tr>
<td>1</td>
<td>0.235</td>
</tr>
<tr>
<td>2</td>
<td>0.235</td>
</tr>
<tr>
<td>3</td>
<td>0.235</td>
</tr>
<tr>
<td>4</td>
<td>0.235</td>
</tr>
<tr>
<td>5</td>
<td>0.470</td>
</tr>
<tr>
<td>6</td>
<td>0.235</td>
</tr>
<tr>
<td>7</td>
<td>0.117</td>
</tr>
<tr>
<td>8</td>
<td>0.060</td>
</tr>
</tbody>
</table>

a - RATIO [DBTA] / [NO₂⁻] = 5.3

### TABLE 13: VARIATION OF PRODUCT YIELDS FOR REACTION OF CYCLOHEXYL ISOCYANATE AND TETRAETHYLAMMONIUM NITRITE IN ACETONITRILE AT ROOM TEMPERATURE.
<table>
<thead>
<tr>
<th>REACTION CONDITIONS</th>
<th>PRODUCT YIELDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.235ᵇ</td>
<td>0.0115</td>
</tr>
<tr>
<td>0.235ᵇ</td>
<td>0.0115</td>
</tr>
<tr>
<td>0.235ᵇ</td>
<td>0.0115</td>
</tr>
<tr>
<td>0.235ᵇ</td>
<td>0.0115</td>
</tr>
<tr>
<td>0.28ᵃ</td>
<td>0.028</td>
</tr>
<tr>
<td>0.28ᵃ</td>
<td>0.028</td>
</tr>
<tr>
<td>0.235ᵇ</td>
<td>0.0115</td>
</tr>
<tr>
<td>0.28ᵃ</td>
<td>0.028</td>
</tr>
</tbody>
</table>

ⁿ - RATIO [RNCO] / [NO₂⁻] = 10
ᵇ - RATIO [RNCO] / [NO₂⁻] = 20

**TABLE 14: VARIATION OF PRODUCT YIELDS, FROM REACTION OF CYCLOHEXYL ISOCYANATE AND TEAN IN ACETONITRILE AT ROOM TEMPERATURE, WITH CHANGES IN DBTDA CONCENTRATION.**
3.6 **MECHANISM OF REACTION**

The yields of the deamination products obtained by reaction of cyclohexyl isocyanate and nitrite ion were compared with those from the deamination of cyclohexylamine. Under acidic conditions using nitrous acid, the major product is cyclohexanol with some cyclohexene and cyclohexyl nitrate. Some literature results are given in Table 15.

The most relevant comparison seems to be with deamination carried out under basic conditions, by coupling with diazotized sulphanilic acid and decomposition of the resulting triazene (Scheme 48). This reaction appears to give similar yields of cyclohexene and cyclohexanol to those from the reaction of cyclohexyl isocyanate and nitrite ion. The yield of alcohol from the triazene (67%) approximates to the combined yield of alcohol and acetate (44%) for isocyanate plus nitrite ion.

The deamination of cyclohexylamine using nitroprusside in basic conditions gave much greater amounts of alcohol and only small yields of alkene and ketone, reflecting the much higher pH (12.7) compared to the triazene method (pH 8) and the more efficient trapping of the carbonium ion by HO\(^-\). So the mild basic conditions of the triazene method gave the best comparison with the isocyanate/nitrite ion reaction.

Two important questions regarding the mechanism of the deamination of isocyanates by nitrite ion remain.
### TABLE 15: PRODUCT YIELDS FROM DEAMINATIONS OF CYCLOHEXYLAMINE

<table>
<thead>
<tr>
<th>METHOD</th>
<th>PRODUCT YIELDS / %</th>
<th>CYCLOHEXANOL</th>
<th>CYCLOHEXENE</th>
<th>CYCLOHEXANONE</th>
<th>OTHER PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NaNO₂ in 0.1N HClO₄</td>
<td>80%</td>
<td>6%</td>
<td>0</td>
<td>Cyclohexyl nitrite 12% Bicyclo[3.1.0]Hexane 2%</td>
<td></td>
</tr>
<tr>
<td>2. NaNO₂ in Acetic Acid (10%)</td>
<td>80</td>
<td>20</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3. Cross-coupling with Diazotized Sulphanilic Acid (Scheme 48)</td>
<td>67</td>
<td>27</td>
<td>6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4. Nitroprusside ion (^{31}) (Fe(CN)₅NO²⁻) at pH 12.7</td>
<td>120(^a)</td>
<td>9</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5. This work (RNCO + NO₂)</td>
<td>19</td>
<td>28</td>
<td>4</td>
<td>Cyclohexyl Acetate 25%</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Yield as calculated in Reference 10a
i) What is the role of the DBTDA, and
ii) does the diazonium ion or carbonium ion ever become free in solution?

The kinetic results discussed earlier imply that DBTDA stabilizes a reaction intermediate. The initial attack of nitrite ion should produce the anionic intermediate (64) which can then rearrange to the N-nitroso species (65) (Scheme 49). The Shinn's procedure to measure nitrite concentrations involves dilution of an aliquot of the reaction mixture into 5N hydrochloric acid. Under these conditions (64) would be expected to hydrolyse to give nitrite, whereas (65) would give the diazo compound and no nitrite ion. The formation of (65) consumes nitrite ion.

In the absence of DBTDA a small amount of nitrite ion is consumed and this may be explained by formation of an equilibrium mixture of (64) and (65). Hydrolysis of the two compounds during the Shinn's test is assumed to be more rapid than their interconversion, giving nitrite ion from (64) but none from (65). Thus the amount of nitrite consumed reflects the equilibrium concentration of (65). The anion (65) may be more stable than the diazotate formed by loss of carbon dioxide, due to its more extensive delocalization. Thus thermodynamic control prevents its decomposition. The delocalized aromatic diazoates are more stable and the driving force for loss of carbon dioxide from the aromatic urethane anion is therefore greater.
Complexation of (65) with DBTDA may give a species such as (66) (Scheme 50). Elimination of carbon dioxide then gives a complex of DBTDA and the diazotate attached via oxygen (67) or nitrogen (68). Elimination of nitrogen to give the carbonium ion must then occur, and this would seem to be easier from (67). The carbonium ion could be trapped before the species diffuse apart to give a cyclohexanol/DBTDA complex (69) which hydrolyses to the free cyclohexanol.

Similar trapping of the carbonium ion by acetate would give cyclohexyl acetate and tin oxide. It is not known if the DBTDA survives the reaction unchanged but the formation of an acetate product makes this unlikely. An intramolecular pathway for formation of cyclohexyl acetate is attractive because it is consistent with observations that the
SCHEME 50

\[
\begin{align*}
&\text{(65)} \\
\xrightarrow{\text{OBTDA}} &\xrightarrow{-\text{CO}_2} \\
&\xrightarrow{-\text{N}_2} \\
&\text{(67)} \\
&\xrightarrow{\text{HYDROLYSIS}} \\
&\text{OBTDA} + \text{OH} \\
&\xrightarrow{\text{a}} \\
&\xrightarrow{\text{b}}
\end{align*}
\]
yield did not increase with increasing excess of DBTDA, as would be expected if the carbonium ion were trapped by free acetate. Similarly, addition of a large excess of tetraethylammonium bromide gave no detectable cyclohexyl bromide, implying that no free carbonium ion was produced. Trapping by acetate could also occur at the same time as loss of nitrogen in a concerted reaction.

Formation of cyclohexene could then arise from further reaction of (69), with adjacent acetate groups acting as bases to remove the \( \alpha \)-proton (Scheme 51). The cyclohexanone arises from oxidation of the cyclohexanol by one of the tin species present.

![Scheme 51](image)

Formation of the deamination products proceeds without protic work-up, which is consistent with the mechanism proposed.

It is interesting that the cyclohexanol was not trapped by the excess isocyanate. This could indicate that pyrolysis of an intermediate on the gas chromatograph forms the alcohol, and it was not present in the reaction solution. However cyclohexanol only disappears slowly when added to a mixture of DBTDA and cyclohexyl isocyanate in acetonitrile. Thus cyclohexanol is probably present in the reaction solution because of low reactivity of the cyclohexyl isocyanate to nucleophiles.

### 3.7 KINETICS WITH \( \text{\textsuperscript{n}PROPYL AND \textsuperscript{t}BUTYL ISOCYANATE} \)

The relative reactivity of primary, secondary and tertiary isocyanates was examined via kinetic studies of the reaction of \( \text{\textsuperscript{n}PROPYL} \) and \( \text{\textsuperscript{t}BUTYL ISOCYANATE} \) with tetraethylammonium nitrite (TEAN) in acetonitrile at 25°C for comparison with cyclohexyl isocyanate.
Reactions were carried out under pseudo first order conditions with excess isocyanate and the loss of nitrite ion was measured by Shinn's method. The rate of reaction of cyclohexyl isocyanate was also measured in acetonitrile to compare with the value obtained in DMSO.

All three isocyanates gave overall second order kinetics (Equation 7).

\[
\text{RATE} = \frac{-d[\text{NO}_2^-]}{dt} = k_2 [\text{RNCO}] [\text{NO}_2^-]
\]

Cyclohexyl isocyanate gave \( k_2 = 13.4 \pm 0.25 \times 10^{-3} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1} \) at 25°C (Fig. 4), which was 3.7 times greater than in DMSO. This implies that the nitrite ion is a better nucleophile in acetonitrile than in DMSO, probably because of reduced solvation in the acetonitrile. The rate was independent of the DBTDA concentration.

\( \text{\(^n\)Propyl isocyanate gave } k_2 = 71.3 \pm 2.85 \times 10^{-3} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1} \) (Fig. 5), and the \( \text{\(^t\)butyl isocyanate } k_2 = 25.3 \pm 0.85 \times 10^{-5} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1} \) (Fig. 6) and in each case the rate was independent of the DBTDA concentration (Table 16).
FIG. 4: PLOT OF PSEUDO FIRST ORDER RATE CONSTANT VERSUS CYCLOHEXYL ISOCYANATE CONCENTRATION FOR REACTION WITH TEAN IN ACETONITRILE AT 25°C.

\[
\frac{k_0}{10^3 \text{ s}^{-1}}
\]

\[
\left[ \begin{array}{c}
N=C=O \\
\end{array} \right] / 10^4 \text{ mol dm}^{-3}
\]
FIG. 5  SECOND ORDER PLOT FOR $^n$PROPYL ISOCYANATE

$\frac{k_0}{10^{-3} \text{s}^{-1}}$ vs $[\text{PrNC}] / \text{mol dm}^{-3}$
FIG. 6. SECOND ORDER PLOT FOR $^t$BUTYL ISOCYANATE

$\frac{k_0}{10^{-5}}$ s$^{-1}$

$[t\text{BuNCO}]$/mol dm$^{-3}$

- 68 -
TABLE 16: VARIATION OF RATE OF REACTION OF ALKYL ISOCYANATES AND TEAN IN ACETONITRILE AT 
\((25 \pm 0.1)^{\circ}C\) WITH CHANGES IN DBTDA CONCENTRATION.

<table>
<thead>
<tr>
<th>R</th>
<th>([RNCO]^a/\text{mol dm}^{-3})</th>
<th>([\text{DBTDA}]/\text{mol dm}^{-3})</th>
<th>(k_2/10^{-3}\text{mol}^{-1}\text{dm}^{3}\text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n\text{Pr})</td>
<td>0.02(^a)</td>
<td>0.0075</td>
<td>69.3</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.02(^a)</td>
<td>0.0037</td>
<td>73</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.02(^a)</td>
<td>0.0018</td>
<td>71.5</td>
</tr>
<tr>
<td>(t\text{Bu})</td>
<td>0.25(^b)</td>
<td>0.039</td>
<td>0.29</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.25(^b)</td>
<td>0.020</td>
<td>0.27</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>0.10</td>
<td>0.039</td>
<td>12.8</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.10</td>
<td>0.020</td>
<td>14.1</td>
</tr>
</tbody>
</table>

\(a - [\text{TEAN}] = 1 \times 10^{-3}\text{mol dm}^{-3}\)

\(b - [\text{TEAN}] = 7.3 \times 10^{-3}\text{mol dm}^{-3}\)

\(c - [\text{TEAN}] = 2.0 \times 10^{-3}\text{mol dm}^{-3}\)

The primary alkyl isocyanate therefore reacted fastest and the tertiary slowest (Table 17). Increased substitution results in increasing electron donation into the isocyanate group and the rates reflect the subsequent reduction in the electrophilic character of the isocyanate moiety.

TABLE 17: SECOND ORDER RATE CONSTANTS FOR REACTION OF ALKYL ISOCYANATES AND TEAN IN ACETONITRILE AT \(25 \pm 0.1^{\circ}C\)

<table>
<thead>
<tr>
<th>R-N = C = O</th>
<th>(k_2/10^{-3}\text{mol}^{-1}\text{dm}^{3}\text{s}^{-1})</th>
<th>RELATIVE RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n\text{Propyl})</td>
<td>71.3</td>
<td>282</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>13.4</td>
<td>53</td>
</tr>
<tr>
<td>(t\text{Butyl})</td>
<td>0.25</td>
<td>1</td>
</tr>
</tbody>
</table>
A similar comparison of the reactivity of these three isocyanates to some other nucleophile could not be found in the literature. However, a comparison of the rates of reaction of the corresponding isothiocyanates to both hydroxide ion\(^{110}\) and \(\text{n}^\text{butylamine}^{111}\) have been measured (Table 18). The same trend is observed as in the reaction with nitrite ion. However, the isocyanate reaction appears to be more sensitive to electronic effects.

### Table 18: Relative Rates of Reaction of Some Alkyl Isothiocyanates with Hydroxide Ion\(^{110}\) and \(\text{n}^\text{Butylamine}^{111}\)

<table>
<thead>
<tr>
<th>R-N = C = S</th>
<th>(\text{HO}^-) Rel. (k_2)</th>
<th>(\text{n}^\text{BuNH}_2) Rel. (k_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{n}^\text{Propyl})</td>
<td>54</td>
<td>26</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>(\text{t}^\text{Butyl})</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### 3.8 Product Analysis with \(\text{n}^\text{Propyl}\) and \(\text{t}^\text{Butyl}\) Isocyanates

For the reaction of \(\text{t}^\text{butyl isocyanate}\) the yields of both \(\text{t}^\text{butyl acetate}\) and \(\text{t}^\text{butanol}\) were determined. A carbonyl compound cannot be formed in this case, and the alkene product, 2-methylprop-1-ene was too volatile to work with (b.p. = \(-6.9\,^\circ\text{C}\))\(^{112}\). The results in Table 19 show yields of \(\text{t}^\text{butanol}\) of ca. 30% with a greater than 2.5 fold excess of DBTDA. Only small amounts of acetate were obtained.

For \(\text{n}^\text{propyl isocyanate}\) the yields of both the alcohol and acetate were determined. The results in Table 20 show high yields of alcohol but only small yields of acetate.

### Table 20: Product Yields from Reaction of \(\text{n}^\text{PropylIso cyanate and Nitrite Ion in Acetonitrile at Room Temperature}

<table>
<thead>
<tr>
<th>([\text{RNCO}] / \text{mol dm}^{-3})</th>
<th>([\text{NO}_2^-] / \text{mol dm}^{-3})</th>
<th>([\text{DBTDA}] / \text{mol dm}^{-3})</th>
<th>(\text{n}^\text{PrOAc}/%)</th>
<th>(\text{n}^\text{PrOH}/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.28</td>
<td>0.061</td>
<td>0.28</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>0.28</td>
<td>0.058</td>
<td>0.28</td>
<td>9</td>
<td>71</td>
</tr>
</tbody>
</table>
### TABLE 19: PRODUCT YIELDS FROM REACTIONS OF $^t$BUTYL ISOCYANATE WITH NITRITE IN ACETONITRILE AT ROOM TEMPERATURE.

<table>
<thead>
<tr>
<th>REACTION CONDITIONS</th>
<th>PRODUCT YIELDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t\text{BuOH}$ Yield/ %</td>
</tr>
<tr>
<td>$[t\text{BuNCO}] / \text{mol dm}^{-3}$</td>
<td>$[\text{NO}_2^-] / \text{mol dm}^{-3}$</td>
</tr>
<tr>
<td>0.149</td>
<td>0.015</td>
</tr>
<tr>
<td>0.149</td>
<td>0.015</td>
</tr>
<tr>
<td>0.149</td>
<td>0.015</td>
</tr>
<tr>
<td>0.149</td>
<td>0.014</td>
</tr>
<tr>
<td>0.149</td>
<td>0.015</td>
</tr>
<tr>
<td>0.300</td>
<td>0.015</td>
</tr>
</tbody>
</table>
The relative yields can be rationalized by reference to the proposed mechanism. Thus the \( t \)-butyl derivative gives small yields of acetate because of steric hindrance to the intramolecular attack of acetate in the complex. This would fit with formation of the \( t \)-butyl acetate with concerted loss of nitrogen, so that an SN\(^2\) type attack of acetate is required (Scheme 52). The yield of the \( n \)-propyl acetate is slightly lower than the cyclohexyl derivative.

![Scheme 52](image)

Both the cyclohexyl and \( t \)-butyl derivatives give similar amounts of alcohol, but the \( n \)-propyl gives about twice as much. The \( n \)-propyl carbonium ion will be the least stable and may be rapidly trapped by the tin oxide species (Scheme 50). The yields are governed by the steric effects and electronic effects, with the cyclohexyl derivative giving a balance between the two.

An interesting phenomenon is the relative amounts of nitrite ion consumption in the absence of DBTDA. Under identical conditions the \( n \)-propyl, cyclohexyl and \( t \)-butyl isocyanates give 63, 22 and 1% nitrite consumption respectively. The equilibrium between the O-nitroso (70) and N-nitroso (71) species (Scheme 53) was proposed to account for this.

![Scheme 53](image)
Destabilization of the nitrogen anion form of (70) by increased substitution on the \( \alpha \)-carbon atom will result in a preponderance of the oxy-anion (72) and therefore reduce the amount of rearrangement of the nitroso group onto the nitrogen (Scheme 54).

![Scheme 54](image)

Thus there will be less of (71) with the \( \text{t} \)butyl derivative and more with the \( \text{n} \)propyl, and this is shown by the relative amounts of nitrite ion consumption.

3.9 CONCLUSION

It can be seen that reaction of alkyl isocyanates with nitrite ion in organic solvents at room temperature, in the presence of DBTDA gives rise to deamination products. The nitrite is activated as an intramolecular nitrosating agent by its reaction with isocyanate, in a similar fashion to that observed with the aromatic derivatives. This presents a mild method of deamination under non-acidic conditions. The range of Lewis acids that promote reaction was not examined. It would be interesting, however to see if compounds such as SnCl_4, BF_3 and AlCl_3 also react like the DBTDA, or whether this is just a property of the dialkyl tin (IV) diesters.
CHAPTER 4

REACTION OF NITRITE ION WITH CARBODIIMIDES
4.1 INTRODUCTION

The second most reactive class of heterocumulene anhydrides after the isocyanates are the carbodiimides. They react readily with carboxylic acids such as acetic acid, and reaction with nitrite ion should therefore be expected.

4.2 CHOICE OF SUBSTRATE

The carbodiimide (73) bearing 4-nitrophenyl and ethyl groups was thought to offer the best chance of reaction with nitrite ion bearing in mind the results of the study of the isocyanate reactions. The 4-nitrophenyl substituent should increase reactivity and stabilize the anionic intermediates, and the ethyl substituent should aid solubility in organic solvents.

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} = \text{C} = \text{N} \quad \text{CH}_2\text{CH}_3 \\
\text{(73)}
\end{align*}
\]

Synthesis of (73) was carried out in two steps (Scheme 55). Firstly the thiourea (74) was prepared in quantitative yield from ethylamine and 4-nitrophenyl isothiocyanate. The thiourea was then desulphurized with mercuric oxide to give (73) in 60% yield\(^{113}\).

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} = \text{C} = \text{S} \\
\text{CH}_3\text{CH}_2\text{NH}_2 & \quad \xrightarrow{\text{MeCN}} \quad \text{NO}_2 \quad \text{N} \quad \text{N} \quad \text{CH}_2\text{CH}_3 \\
\text{(73)}
\end{align*}
\]

SCHEME 55

4.3 FORMATION OF TRIAZENE

Reactions carried out with excess carbodiimide (73) and tetra-ethylammonium nitrite in acetonitrile at 0°C were very rapid. Shinn's tests\(^{100}\) showed complete consumption of nitrite ion and hplc analysis showed the formation of 1,3-bis(4-nitrophenyl) triazene.

Experiments to maximize the yield (Table 21) showed the best (33%) was achieved with a five-fold excess of carbodiimide over nitrite ion. With
larger excess the yield decreased probably as a result of extensive trimerization and polymerization of the carbodiimide.

4.4 REACTION MECHANISM

The reaction appeared to go in a similar fashion to the isocyanates. A mechanism can be proposed (Scheme 56) where the first step is nucleophilic attack of nitrite ion on the carbodiimide to give an anionic intermediate (75). Although two possible anions (75) and (76) could be formed, the most stable should be (75) where the negative charge is conjugated with the 4-nitrophenyl group. Migration of the nitroso group to the nitrogen anion gives the N-nitroso compound (77). This anion has no particular stabilization and will eliminate ethyl isocyanate to form the diazotate (53). The reaction is therefore the same as with 4-nitrophenyl isocyanate except that ethyl isocyanate is eliminated instead of CO₂.

**TABLE 21** YIELDS OF 1,3-BIS (4-NITROPHENYL)TRIAZENE FROM REACTION OF CARBODIIMIDE (73) WITH TEAN\(^a\) IN ACETONITRILE

<table>
<thead>
<tr>
<th>RATIO [\frac{[73]}{[\text{NO}_2^-]}]</th>
<th>TEMPERATURE / °C</th>
<th>TRIAZENE YIELD /(^+) 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>24.5</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>20.5</td>
</tr>
</tbody>
</table>

\[\text{[NO}_2^-\text{]} = 3.5 \times 10^{-3} \text{ mol dm}^{-3}\]

\[
\begin{array}{c}
\text{NO}_2\text{N} \equiv \text{N-CH}_2\text{CH}_3 \\
\text{O = N - O}
\end{array}
\]

(75)

\[
\begin{array}{c}
\text{NO}_2\text{N} \equiv \text{N-CH}_2\text{CH}_3 \\
\text{O - N = O}
\end{array}
\]

(76)
\[
\text{SCHMIE 55}
\]
The diazotate (53) can react with a second carbodiimide molecule again giving the more stable anion (78). Rearrangement gives (79) and loss of ethyl isocyanate, the triazene anion. Protic work-up gives the product (50).

The yields of triazene from the carbodiimide (73) are lower than those observed from 4-nitrophosphonyl isocyanate. To investigate this difference the yields of diazotate formed from reaction of the carbodiimide with excess nitrite ion were determined (Table 22). As the excess of nitrite ion increased, the yield of 4-nitrophosphonyl diazotate approached 100%. This shows that migration of the nitroso group was regiospecific towards the nitrogen atom attached to the aromatic ring. It also suggests that the lower yields of triazene relate to the lower nucleophilic reactivity of the intermediate compared with the nitrite ion. The aqueous pKₐ of the diazotate is ca. 9 compared to 3.4 for nitrite, so it should be a better nucleophile. A reversal of relative nucleophilicities is commonly observed in dipolar aprotic solvents such as acetonitrile. The smaller nitrite ion should be less solvated and therefore more reactive in acetonitrile relative to water. On the other hand, the larger organic diazotate ion is highly delocalized and maybe less susceptible to changes in solvation, so its nucleophilicity will be less changed. Consequently the nitrite ion may be more nucleophilic than the diazotate ion in acetonitrile.

TABLE 22

YIELDS OF 4-NITROPHENYL DIAZOTATE FROM REACTION OF CARBODIIMIDE (73) WITH EXCESS TEAN IN ACETONITRILE AT 0°C

<table>
<thead>
<tr>
<th>RATIO</th>
<th>[NO₂⁻]</th>
<th>DIAZOTATE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>85.4</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>88 + 6</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

a - Concentration = 1.3 - 5.3 x 10⁻⁴ mol dm⁻³
For example the pK\textsubscript{a}'s of phenol and its nitro derivatives all increase in acetonitrile relative to water (Table 23). The derivatives with more nitro groups have greater charge delocalization and their pK\textsubscript{a}'s are not increased as much in going from acetonitrile to water, as is phenol itself. Table 23 lists some other examples\textsuperscript{114}. Unfortunately no data was obtained for the pK\textsubscript{a} of nitrous acid in acetonitrile, although the inorganic acids listed i.e. nitric and hydrochloric acid both have a pK\textsubscript{a} of 8.9 in acetonitrile, and one would expect the pK\textsubscript{a} of nitrous acid to be higher than this.

**Table 23**

<table>
<thead>
<tr>
<th>Compound</th>
<th>(pK\textsubscript{a})\textsubscript{AN}</th>
<th>(pK\textsubscript{a})\textsubscript{W}</th>
<th>ΔpK\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td>26.6</td>
<td>10</td>
<td>16.6</td>
</tr>
<tr>
<td>2-Nitrophenol</td>
<td>22</td>
<td>7.23</td>
<td>14.8</td>
</tr>
<tr>
<td>4-Nitrophenol</td>
<td>20.7</td>
<td>7.15</td>
<td>13.5</td>
</tr>
<tr>
<td>2,4-Dinitrophenol</td>
<td>16</td>
<td>4.11</td>
<td>11.9</td>
</tr>
<tr>
<td>2,4,6-Trinitrophenol</td>
<td>11</td>
<td>0.71</td>
<td>10.3</td>
</tr>
<tr>
<td>HNO\textsubscript{3}</td>
<td>8.9</td>
<td>-1.4</td>
<td>10.3</td>
</tr>
<tr>
<td>HCl</td>
<td>8.9</td>
<td>-7.0</td>
<td>15.9</td>
</tr>
<tr>
<td>nBuNH\textsubscript{2}</td>
<td>18.26</td>
<td>10.59</td>
<td>7.67</td>
</tr>
<tr>
<td>PhCH\textsubscript{2}NH\textsubscript{2}</td>
<td>16.76</td>
<td>9.34</td>
<td>7.42</td>
</tr>
<tr>
<td>Benzoic Acid</td>
<td>20.7</td>
<td>4.20</td>
<td>16.5</td>
</tr>
<tr>
<td>4-Nitrobenzoic Acid</td>
<td>16.7</td>
<td>2.98</td>
<td>13.7</td>
</tr>
</tbody>
</table>

\(\text{(pK}_{a}\textsubscript{AN}) = \text{pK}_{a} \text{ in acetonitrile}\)

\(\text{(pK}_{a}\textsubscript{W}) = \text{Aqueous pK}_{a}\)

\(\Delta \text{pK}_{a} = \text{(pK}_{a}\textsubscript{AN}) - (\text{pK}_{a}\textsubscript{W})\)

To test this speculation the reactivity of the diazotate towards the carbodiimide (73) was independently examined. Reactions were carried out in DMSO, due to the greater solubility of the sodium diazotate salt in...
this solvent. Sodium nitrite reacted with a 10-fold excess of carbodiimide (73) at room temperature to give a 37% yield of triazene. The sodium salt of the 4-nitrophenyl diazotate reacted with (73) under the same conditions to give a 29% yield of triazene. Unfortunately these findings are ambiguous.

4.5 SELECTIVITY OF NITROSATION

The above findings show that nitrosation reactions can be carried out using nitrite ion and carbodiimide in an organic solvent at 0°C. The reaction is regiospecific as nitrosation occurs on only one of the two nitrogens to give a single N-nitroso urea anion (75). This relates to the preferential formation of the most stable anion and migration of the nitroso group solely to this position. Thus nitrosation proceeds at the least basic nitrogen atom of the parent urea.

In one reaction a small amount ( <10%) of the N-nitrosourea (80) was isolated and identified from its i.r. and n.m.r. spectra. The N-nitrosourea (81) was obtained in high yield, however, by electrophilic nitrosation of the parent urea. This arose because electrophilic nitrosation under acidic conditions proceeds at the most basic nitrogen atom. Thus the two reactions are complementary and give opposite regioisomers with high selectivity.

\[
\begin{align*}
\text{(80)} & \\
\text{(81)} & 
\end{align*}
\]

The formation of N-nitrosoureas from carbodiimides has not been exploited here as a synthetic method. However, if the anion (75) could be trapped efficiently, hitherto inaccessible N-nitrosoureas are readily available.
4.6 **REACTION OF DIPHENYL CARBODIIMIDE (82)**

The reaction of diphenyl carbodiimide (82) with nitrite ion was also examined. It seemed probable that after rearrangement the anion of N-nitrosodiphenyl urea (83) should be produced, which would then fragment to give a molecule of phenyl diazotate and a molecule of phenyl isocyanate (Scheme 56). These may recombine to give the 1,3-diphenyltriazene, or the diazotate could react with excess carbodiimide to give 1,3-diphenyltriazene. In any event a high yield of triazene was therefore anticipated.

![Scheme 56](image-url)
Reaction of excess diphenylcarbodiimide with nitrite ion in acetonitrile, however, gave very poor yields of the 1,3-diphenyltriazene. For example with a 10-fold excess of carbodiimide, the yield of triazene was only 5% at 0°C and 8% at room temperature. This surprising result required explanation.

Firstly it was necessary to discover whether the diazotate was being produced. So reactions were carried out with excess nitrite ion and the diazotate was trapped as an azo dye as before (see Chapter 2). With both a 30-fold and 60-fold excess of nitrite ion in acetonitrile at 0°C, a quantitative yield of phenyl diazotate was obtained. This result requires careful interpretation. If the anion (83) fragments in the reaction mixture in the presence of excess nitrite ion (Scheme 56) the isocyanate co-product should also react with nitrite ion to give diazotate. Thus the yield of diazotate based on substrate should be 200%. The observed yield of 100% implies that the anion (83) does not fragment until it is added to aqueous 0.1 N borax in the coupling reaction i.e. hydrolysis to the diazotate and isocyanate occurs. The diazotate then undergoes transformation to the diazonium ion, followed by coupling to give the azo dye.
Concurrently the isocyanate must rapidly hydrolyse to aniline (Scheme 57).

Thus the anion (83) from diphenylcarbodiimide appears to be more stable than that from 4-nitrophenylethylcarbodiimide presumably because of increased delocalisation of the negative charge.

Attempts to bring about decomposition of the anion, and to increase the yield of triazene by increasing the reaction temperature were successful. Thus using 10-fold excess of diphenylcarbodiimide over nitrite ion the yield of triazene was 16% after 3 hours at 40°C, and in refluxing acetonitrile (80°C) 44% after one hour and 70% after five hours.

Similar attempts to improve the yield of triazene from the carbodiimide (73) were unsuccessful.

4.7 CONCLUDING REMARKS

The findings demonstrate that nitrosation reactions can be readily brought about by the reaction of nitrite ion with aryl carbodiimides. On reaction the nitrite ion becomes activated as an intramolecular nitrosating agent.
For unsymmetrical carbodiimides nitrosation proceeds at the less basic nitrogen atom of the parent urea. That is, the most stable nitrogen anion is formed and migration of the nitroso group proceeds to this centre.

Further reaction is dependent on the stability of the anionic intermediate that is formed. It may remain stable in solution or fragment to diazotate and isocyanate. Subsequent reaction of the diazotate with further carbodiimide yields the 1,3-diaryltriazenes in an analogous manner to that of the isocyanates.
CHAPTER 5

REACTION OF NITRITE ION WITH AROMATIC ISOTHIOCYANATES
5.1 INTRODUCTION

Isothiocyanates are less reactive towards nucleophiles than the corresponding isocyanates. Aromatic isothiocyanates are about as reactive as the alkyl isocyanates, so some reaction with nitrite ion should be expected.

Isothiocyanates are commonly found in nature. They are present in many plants combined with a molecule of glucose to give a glucosinolate (84). After cell damage, the enzyme myrosinase releases the free isothiocyanate (Scheme 58). Isothiocyanates possess anti-microbial properties and their function is thought to be plant protection. The effect must be primarily curative as they are only released in damaged cells. The glucosinolates are also believed to act as a reserve of amino nitrogen and sulphur, as they occur in high levels in some parts of the plants including the seeds.

\[
\text{HO} \quad \text{N}^{-\text{OSO}_3^2} \\
\text{H} \quad \text{H} \\
\text{O} \quad \text{S} \quad \text{C} \quad \text{R} \\
\text{HO} \quad \text{OH} \quad \text{H} \quad \text{H} \\
\text{MYROSINASE} \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{GLUCOSE} \\
\quad \quad + \\
\text{R-C-S}^\ominus \quad \text{SO}_4^{2\ominus} \\
\quad \quad \quad \quad \quad \quad \text{N-OSO}_3^\ominus \\
\text{SCHEME 58}
\]

These compounds are found in many types of mustard, hence their old name, mustard oils. Their presence in the human diet, means the reaction with nitrite in the stomach could be important. This could either produce carcinogenic N-nitroso compounds or give a method for consumption of nitrite to prevent the formation of nitroso compounds by other means.
5.2 TRIAZENE FORMATION FROM 4-NITROPHENYLISOTHIOCYANATE

To ensure the best chance of reaction, the first substrate studied was 4-nitrophenylisothiocyanate (85). Using techniques developed in the study of the isocyanates, reactions were carried out with excess substrate over nitrite ion and analysed for 1,3-bis (4-nitrophenyl) triazene (Table 24). Reactions were carried out in acetonitrile with TEAN (tetraethylammonium nitrite).

Under a range of conditions only low yields of the expected triazene were obtained. In acetonitrile at 0°C, the best yield of 20% was obtained with a five fold excess of isothiocyanate over nitrite ion. The yield decreased with increasing temperature. In DMSO the optimum yield was 28%, at room temperature (Table 25). In acetonitrile a very poor yield was obtained using 18-crown-6 and sodium nitrite, and no triazene was obtained using silver nitrite.

**TABLE 24:** YIELDS OF 1,3-bis(4-NITROPHENYL) TRIAZENE FROM REACTION OF EXCESS 4-NITROPHENYLISOTHIOCYANATE WITH 4 x 10^-3 M TEAN IN ACETONITRILE.

<table>
<thead>
<tr>
<th>RATIO</th>
<th>[RNCS]</th>
<th>TEMPERATURE /°C</th>
<th>NITRITE SOURCE</th>
<th>TRIAZENE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.25</td>
<td>4 x 10^-3 M TEAN</td>
<td>0</td>
<td>Et_4N^+NO_2^-</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>4 x 10^-3 M TEAN</td>
<td>0</td>
<td>&quot;</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>4 x 10^-3 M TEAN</td>
<td>0</td>
<td>&quot;</td>
<td>20</td>
</tr>
<tr>
<td>35</td>
<td>4 x 10^-3 M TEAN</td>
<td>0</td>
<td>&quot;</td>
<td>13.5</td>
</tr>
<tr>
<td>10</td>
<td>4 x 10^-3 M TEAN</td>
<td>25</td>
<td>&quot;</td>
<td>18.5</td>
</tr>
<tr>
<td>10</td>
<td>4 x 10^-3 M TEAN</td>
<td>40</td>
<td>&quot;</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>4 x 10^-3 M TEAN</td>
<td>0</td>
<td>Et_4N^+NO_2^-</td>
<td>13.5</td>
</tr>
<tr>
<td>22</td>
<td>4 x 10^-3 M TEAN</td>
<td>0</td>
<td>NaNO_2/18-crown-6</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>4 x 10^-3 M TEAN</td>
<td>0</td>
<td>AgNO_2</td>
<td>0</td>
</tr>
</tbody>
</table>

a - with excess Et_4N^+Br^- present
TABLE 25: YIELDS OF TRIAZENE FROM REACTION OF EXCESS
4-NITROPHENYL ISOTHIOCYANATE WITH NITRITE
(4 x 10^{-3} mol dm^{-3}) IN DMSO AT ROOM TEMPERATURE

| RATIO \[
\frac{[RNCS]}{[NO_2^-]}\] | M$^{\ominus}$NO$_2$$^\ominus$ | TRIAZENE YIELD / % |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Na</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>Na</td>
<td>$28^+ - 2.5^a$</td>
</tr>
<tr>
<td>20</td>
<td>Na</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>Na</td>
<td>24.5$^b$</td>
</tr>
<tr>
<td>10</td>
<td>Na</td>
<td>29$^c$</td>
</tr>
<tr>
<td>10</td>
<td>Et$_4^+$N</td>
<td>31</td>
</tr>
</tbody>
</table>

a - Average of 3 runs
b - At 40°C
c - In presence of excess NaBr

The reaction was expected to go via a similar mechanism to that proposed for the isocyanates (Scheme 59) where carbonyl sulphide (COS) is expelled instead of carbon dioxide. This expectation was checked by carrying out reactions using sodium diazotate instead of nitrite (Table 26).

TABLE 26: YIELDS OF TRIAZENE FROM REACTION OF EXCESS
4-NITROPHENYLISOTHIOCYANATE WITH 4 x 10^{-3} mol dm^{-3} SODIUM 4-NITROPHENYL DIAZOTATE

| RATIO \[
\frac{[RNCS]}{[RN_2O^-]}\] | SOLVENT | TEMPERATURE / °C | TRIAZENE YIELD / % |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>MeCN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>&quot;</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>&quot;</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>MeCN$^a$</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>20</td>
<td>MeCN$^a$</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>25</td>
<td>28.5$^b$</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>40</td>
<td>31</td>
</tr>
</tbody>
</table>

a - With excess 18-crown-6
b - Average of two runs
SCHEME 59
Clearly, high yields of triazene were not obtained. Further, the reactions of sodium nitrite (Table 25) and sodium 4-nitrophenyl diazotate (Table 26) with 4-nitrophenyl isothiocyanate in DMSO gave very similar yields of triazene i.e. 28% and 28.5% respectively. Table 26 also shows that sodium diazotate alone gave virtually no triazene in acetonitrile but 6% in the presence of 18-crown-6 (cf. 4% from sodium nitrite in presence of 18-crown-6, Table 24). Finally TEAN gave the best yield of triazene (Table 25).

The apparently diverse results suggest reaction is dependent on the counter ion of the nitrite salt, and the solvent used.

5.3 DIAZOTATE FORMATION

To further investigate the reaction, the yields of diazotate formed when excess nitrite reacts with the isothiocyanate, were determined.

Table 27 shows that in acetonitrile the 4-nitrophenyl isothiocyanate was almost quantitatively converted to the diazotate by reaction with excess nitrite ion. In DMSO lower yields were obtained. This agrees with the above observation that similar yields of triazene apply to reactions of either the diazotate or the nitrite ion with 4-nitrophenyl isothiocyanate. Clearly nitrite ion gives quantitative yields of diazotate, but the diazotate doesn't give quantitative yields of triazene.

**TABLE 27:** YIELDS OF DIAZOTATE FROM REACTION OF 4-NITROPHENYL ISOTHIOCYANATE (5 x 10^{-3} mol dm^{-3}) WITH EXCESS NITRITE ION

<table>
<thead>
<tr>
<th>RATIO</th>
<th>([\text{NO}_2^-]/[\text{RNCO}])</th>
<th>SOLVENT</th>
<th>TEMPERATURE / °C</th>
<th>(\text{M}^+\text{NO}_2^-)</th>
<th>DIAZOTATE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>MeCN</td>
<td>0</td>
<td>(\text{Et}_4\text{N})</td>
<td>91 ± 0.5^a</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>&quot;</td>
<td>25</td>
<td>(\text{Et}_4\text{N})</td>
<td>87.5</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>DMSO</td>
<td>25</td>
<td>(\text{Et}_4\text{N})</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>&quot;</td>
<td>25</td>
<td>(\text{Et}_4\text{N})</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>&quot;</td>
<td>25</td>
<td>Na</td>
<td>74</td>
</tr>
<tr>
<td>50</td>
<td></td>
<td>&quot;</td>
<td>25</td>
<td>Na</td>
<td>75</td>
</tr>
</tbody>
</table>

^a - Average of three experiments
Reaction of nitrite ion with isothiocyanate does result in the formation of products of nitrosation. Activation of the nitrite ion as an intramolecular nitrosating agent was inferred by analogy with the reaction of isocyanates. Quantitative formation of diazotate is obtained although further reaction to give the 1,3-diaryltriazene gave poor yields.

5.4 REACTION OF PHENYL ISOTHIOCYANATE

5.4.1 Yields of Triazene

Reaction of nitrite ion with excess phenyl isothiocyanate under a range of conditions gave very poor yields of 1,3-diphenyltriazene (Table 28).

<table>
<thead>
<tr>
<th>RATIO [PhNCS]</th>
<th>TEMPERATURE / °C</th>
<th>TRIAZENE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>[NO₂⁻]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>1.0</td>
</tr>
<tr>
<td>20</td>
<td>25</td>
<td>1.2 / 1.0</td>
</tr>
<tr>
<td>40</td>
<td>25</td>
<td>2.7 / 1.6</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>1.0</td>
</tr>
</tbody>
</table>

5.4.2 Yields of Diazotate

Reaction of excess nitrite ion with phenyl isothiocyanate was observed to give low yields of phenyl diazotate. Between 5 and 7% diazotate were produced using from 5 to 50-fold excess of TEAN over phenyl isothiocyanate in acetonitrile at 0°C.

Although little reaction between phenyl isothiocyanate and nitrite is apparent from the triazene yields, analysis of reactions with excess isothiocyanate by Shinn's method, showed that the nitrite was consumed.
5.5 **KINETICS OF REACTION OF PHENYL ISOTHIOCYANATE**

Reactions of aromatic isothiocyanates are readily monitored by UV spectrophotometry, and many kinetic studies have been carried out in this way. The reaction of phenyl isothiocyanate and excess nitrite ion gave an orange/yellow solution. Thus reaction was readily studied by UV/visible spectrophotometry.

Figure 7, shows the change observed in the UV spectra of a reaction solution for an excess of nitrite ion over isothiocyanate during the course of the reaction. The absorbance due to the phenyl isothiocyanate at 266 and 276 nm, decreases smoothly with time. An absorbance at 420 nm appears and increases with time. Between these absorbances a good isosbestic point is observed which implies occurrence of a clean reaction with one mole of product absorbing at 420 nm, arising from every mole of starting material consumed.

Working under pseudo-first order conditions with excess nitrite ion, the kinetics of the reaction were examined in more detail. Good first order plots were obtained for both the loss of starting material and formation of product, as measured from the UV spectra. Both processes proceeded at the same rate.

Variation of the nitrite concentration showed the reaction to be first order with respect to nitrite ion (Fig. 8). Thus the reaction obeyed overall second order kinetics, (Equation 8) and at 25°C in acetonitrile, $k_2$ was $(0.378 \pm 0.007)$ mol$^{-1}$ dm$^3$ S$^{-1}$. Equation 8 implies that the rate determining step is the nucleophilic attack of nitrite ion on the phenyl isothiocyanate.

$$\text{RATE} = k_2 [\text{PhNCS}][\text{NO}_2^-]$$

For comparison literature data gives $k_2$ as $0.77$ mol$^{-1}$ dm$^3$ S$^{-1}$ for the reaction of phenyl isothiocyanate with $n$-butylamine in acetonitrile at 25°C. The aqueous $pK_a$ of $n$-butylamine is 10.59 compared to 3.4 for nitrite. Thus one would expect $n$-butylamine to be ca. $10^3 - 10^6$ times more nucleophilic in water than nitrite ion. The similar reactivity observed in MeCN is attributed to a solvent effect. Acetonitrile is a dipolar aprotic solvent in which anionic nucleophiles show increased...
FIG. 7: UV/VISIBLE SPECTRA OF REACTION OF PHENYL ISOTHIOCYANATE WITH EXCESS TEA IN ACetonitrile

\[
[RNCs] = \text{ca. } 1.2 \times 10^{-4} \text{ mol dm}^{-3}; [NO_2^-] = \text{ca. } 10 \times 10^{-4} \text{ mol dm}^{-3}.
\]
FIG. 8: PLOT OF PSEUDO FIRST ORDER RATE CONSTANT VERSUS NITRITE CONCENTRATION
nucleophilicity due to their lack of solvation (see Section 4.4).

A rough comparison was made of the nucleophilic reactivities of acetate and nitrite ions in DMSO. Thus, reaction of tetrabutylammonium acetate with phenyl isothiocyanate in DMSO at 25°C (the isothiocyanate monitored by UV as before) gave $k_2 = 0.05 \text{ mol}^{-1} \text{s}^{-1} \text{ dm}^3$. For tetraethylammonium nitrite in DMSO at 25°C, $k_2$ was $0.67 \text{ mol}^{-1} \text{s}^{-1} \text{ dm}^3$. The proximity of the solvent cut-off of DMSO (260 nm) to the isothiocyanate absorbance resulted in large errors. However the two anions give fairly similar rates of reaction and the findings for nitrite ion seem reasonable.

5.6 SPECTRAL BEHAVIOUR OF REACTION PRODUCTS

A key question is the identity of the product and with this in mind the behaviour of the product absorbance was investigated.

Addition of one equivalent of aqueous acid to the reaction solution resulted in loss of the product absorbance at 420 nm, and the appearance of a new absorbance at 288 nm (Fig. 9). Addition of one equivalent of base regenerated the original spectra with a slightly increased absorbance at 420 nm. Direct addition of base to the reaction solution produced a slight increase in absorbance at 420 nm. Thus the product absorbing at 420 nm appears to be an anion whose conjugate acid is relatively stable.

The spectra of the reaction solution remained unchanged for extended periods, implying the product was stable in the presence of excess nitrite ion. Addition of a range of electrophiles including dimethyl sulphate, acetyl chloride, chlorotrimethyl silane and ethyl bromide produced irreversible loss of the absorbance at 420 nm. The extinction coefficient of the product is ca. 10000 mol$^{-1}$ dm$^3$ cm$^{-1}$.

5.7 PROPOSED MECHANISM

The different behaviour of phenyl isothiocyanate and phenyl isocyanate requires examination. The lower reactivity of isothiocyanates might be expected to lead to lower yields and/or slower reaction but not to different products as apparently observed. Clearly substitution of S for O has a more dramatic effect than anticipated.

In the mechanism (Scheme 60) proposed for the formation of diazotates from isocyanates, the initial step produces an anion (86), which
FIG. 9: ACID/BASE BEHAVIOUR OF PRODUCT ABSORBANCE FROM REACTION OF PHENYL ISOTHIOCYANATE AND NITRITE ION.

a - Reaction Solution at infinity
b - Reaction Solution plus ONE equivalent of 5N HCl
c - Reaction Solution plus acid, plus one equivalent of 4N NaOH.

(Direct addition of base to reaction solution gives same spectra as C).
rearranges by migration of the nitroso group from O to N to give (87), followed by loss of CO$_2$ to give the diazotate. For the analogous anion formed from the isothiocyanate (88), two subsequent rearrangements are possible (Scheme 61). One involving migration of the nitroso group from O to N and loss of COS would give the diazotate as before. The other involving rearrangement of the nitroso group to the sulphur atom would give the S-nitroso anion (89). The S-nitroso anion (89) is postulated as the product absorbing at 420 nm.

Nitrosation at sulphur is a well known process and many S-nitroso compounds have been prepared and studied.$^{121}$ Indeed, thiols are observed to nitrosate faster than many NH compounds.

Application of the HSAB theory$^{122}$ to the rearrangement of the intermediate (88) suggests that NO$^+$, a soft (borderline) acid, should preferentially migrate to the softer sulphur atom rather than the harder N-atom. Also molecular orbital calculations have been carried out on the reaction of NO$^+$ with thiocyanate ion$^{123}$ (SCN$^-$).

\[
\text{Ph - N} = \overset{\cdots}{\text{C}} = \overset{\cdots}{\text{O}} \quad \xrightarrow{\text{O}} \quad \text{Ph - N} \quad \overset{\cdots}{\text{O}} \quad \xrightarrow{\text{Ph - N}} \quad \text{Ph-N}=\text{N-O}
\]

\[
\text{SCHM DIG RAME 60}
\]
Two structures are possible (Scheme 62). The product of S-nitrosation (90) was found to be 1.06 eV more stable than the N-nitroso compound (91). The system is analogous to the intermediate (89) and these calculations support preferential migration to the sulphur atom.

$$\text{NO}^+ + \text{S} = \text{C} = \text{N}^+ \rightarrow \text{NCS} - \text{NO} \text{ or SCN} - \text{NO}$$

(Scheme 62)

Most S-nitroso compounds are coloured. The S-nitrosothiols are yellow, red or sometimes green. For example benzyl thionitrite has absorbances at 350 (ε 1000 mol$^{-1}$ dm$^3$ cm$^{-1}$) and 560 nm (ε 26 mol$^{-1}$ dm$^3$ cm$^{-1}$). Nitrosation of thiourea (NH$_2$CSNH$_2$) in acid gives a species with a broad absorbance at 380 nm (ε 130 mol$^{-1}$ dm$^3$ cm$^{-1}$) and nitrosation in base with ethoxyethyl nitrite gives a product with λ max 418 nm (ε 330 mol$^{-1}$ dm$^3$ cm$^{-1}$). The nitroso species from
thiocyanate is blood red in acid solution with $\lambda_{\text{max}}$ 460 nm ($\epsilon \approx 100 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$). Significantly the absorbance at 420 nm is of a similar wavelength to those of other S-nitroso compounds, although it is more intense.

The stability of the product in weak acid also fits with the postulated S-nitroso structure. Protonation of the initial O-nitroso species (88) would certainly regenerate nitrite ion. However S-nitrosation differs from O-nitrosation in that it is relatively irreversible and denitrosation may only be effected at high acidity with steps taken to remove the free nitrous acid as it is formed. The product is observed not to regenerate nitrite ion in 5N hydrochloric acid (the conditions used in Shinn's method) and so consumption of nitrite by the isothiocyanate is observed. Further the UV experiments show the product is stable in weaker acid.

5.8 ISOLATION AND TRAPPING OF PRODUCTS

Reactions were carried out with equimolar quantities of phenyl isothiocyanate and nitrite ion to facilitate isolation and identification of products. The outcome was messy reaction mixtures from which the only identifiable product was 1,3-diphenyltriazene in 7% yield.

The work on the UV/Visible spectra suggested that trapping of the product with electrophiles was feasible. Attempts were therefore made to accomplish this on a preparative scale. These reactions were carried out with a 10% excess of nitrite ion to minimize the formation of nitrite by-products on addition of an electrophilic trapping agents.

Firstly chlorotrimethylsilane was used to silylate the anion. However, the addition of excess electrophile to the solution and removal of the solvent showed a mixture of at least 9 products by tlc examination. No evidence (nmr or ms) for any silylated products was obtained.

Secondly, dimethyl sulphate was employed to methylate the product. Again a mixture of ca. 10 products by tlc, was obtained. Three were isolated and identified. They were elemental sulphur, 4-phenylazophenol (92) and 2-nitrophenol (93) in yields of 22, 11, and 4% respectively. Identification was by mass spectrometry only.
Products (92) and (93) may be formed from phenyl diazonium ions. An aqueous work-up was used to remove excess dimethyl sulphate, and this would hydrolyse the diazotate, small amounts of which were detected in earlier reactions (Section 5.4.2). A possible mechanism is depicted in Scheme 63. The diazotate hydrolyses to diazonium ion and then to phenol. The phenol may couple with further diazonium ion to give (92) or react with nitrite in the presence of the acid produced on hydrolysis of the dimethyl sulphate to give (93).

\[
\begin{align*}
\text{Ph} - \text{N} &= \text{C} = \text{S} & \rightarrow & & \text{Ph} - \text{N} &= \text{N} - \text{O}^2 \\
\text{Ph} - \text{N} &= \text{S} \rightarrow & & \text{Ph} - \text{N} &= \text{N}_2 \\
\text{Ph} - \text{N} &= \text{O} \\
\text{Ph} - \text{N} &= \text{N} = \text{S} \\
\text{Ph} - \text{N} &= \text{N} = \text{O} \\
\end{align*}
\]

SCHEME 63

An alternative albeit more speculative intramolecular pathway can also be proposed for the formation of (93) (Scheme 64). This involves migration of the nitroso group into the ortho position of the benzene ring, and further rearrangement to give the ortho-nitrosophenol (94), which then gets oxidised to (93). Support for Scheme 64 is lack of 4-nitroso and 4-nitrophenols as co-products. These compounds are preferentially formed by intermolecular nitrosation/nitration of phenols.
The main conclusion however, was that no methylated products were obtained. Other electrophiles were also tested as trapping agents, i.e. ethyl bromide, acetyl chloride and trityl chloride, but all gave complex mixtures of products by tlc.

The results of the trapping experiments invite two explanations:
i) In all reactions the same product forms but decomposes on work-up,
ii) there is no major product as proposed in Scheme 61 but always a complex mixture.

In the light of the UV studies, the second explanation seems unlikely but these were carried out at much lower reactant concentrations than the preparative experiments. However reactions carried out with low reactant concentrations followed by quenching and concentration by freeze drying also showed a complex mixture of products by tlc.

Possible pathways for the decomposition of the S-nitroso anion (89) to various products can be envisaged. Nitrosothiols commonly decompose by homolysis of the S - N bond, to disulphides and nitric oxide (Scheme 65). A similar decomposition of the acyl S-nitroso compound (89) could produce several products via further reaction of the free radical intermediates.
\[ 2 \text{RS} \quad \overset{\text{N=O}}{\text{→}} \quad 2 \text{RS}^* \quad + \quad 2\text{NO} \quad \overset{\text{→}}{\text{→}} \quad \text{R} \quad - \quad \text{S} \quad - \quad \text{S} \quad - \quad \text{R} \]

SCHEME 65

An alternative explanation is extrusion of thionitrite ion (95) to give the isocyanate, followed by further reactions of the isocyanate (Scheme 66).

\[
\begin{array}{c}
\text{N} \quad \overset{\text{S}}{\text{C}} \quad \overset{\text{N=O}}{\text{→}} \\
\text{O} \\
\end{array}
\]

SCHEME 66

The thionitrite ion is not a very well known entity, although it has been identified by i.r. spectroscopy at low temperature in argon matrices. Thionitrite ion has also been proposed as an intermediate in the nitrosation of thioamides (Scheme 67).

\[
\text{Ph} \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{Ph} \quad \overset{\text{NOCl}}{\text{→}} \quad \text{Ph} \quad - \quad \text{N} \quad = \quad \text{C} \quad - \quad \text{Ph} \quad + \quad \text{HCl} \\
\overset{\text{0°C}}{\text{S}} \\
\overset{\text{S} \quad - \quad \text{N} \quad = \quad \text{O}}{\text{↓}} \\
4\text{NO} \quad + \quad 2\text{HCl} \quad + \quad 2\text{S} \quad \overset{\text{2 NOCl}}{\text{→}} \quad \text{HSNO} \quad + \quad \text{Ph} \quad - \quad \text{N} \quad = \quad \text{C} \quad - \quad \text{Ph} \\
\text{Cl} \\
\text{OR} \\
2 \text{HSNO} \quad \overset{\text{→}}{\text{→}} \quad \text{NO} \quad + \quad \frac{1}{2}\text{N}_2 \quad + \quad \text{H}_2\text{O} \quad + \quad 2\text{S} \\
\]

SCHEME 67

The decomposition of the thionitrous acid would then explain the presence of the elemental sulphur isolated in the trapping experiments.

A similar mechanism to Scheme 66, for the transformation of isothiocyanates to isocyanates has been proposed by Hudson (Scheme 68) This concerned reaction of an acyl isothiocyanate and an oxime, where rearrangement of an imine from oxygen to sulphur occurs followed by expulsion of the thio-oxime (96). The acyl isocyanate (97) then reacts further. The rearrangement was thought to involve radical intermediates because of the observation of strong C.I.D.N.P. \(^{13}\)C signals
Scheme 68
5.9 FURTHER SPECTRAL BEHAVIOUR

When reactions of excess phenyl isothiocyanate and nitrite ion were observed spectroscopically, the absorbance at 420 nm was observed to be reduced, and to decay with time. Presumably this arose from reaction of the anionic product (89) with the excess phenyl isothiocyanate as only this is available in the reaction mixture.

The 420 nm absorbance at the end of reaction i.e. the infinity of the kinetic run was also observed to increase with increasing nitrite ion concentration, for a constant isothiocyanate concentration (Table 29). The same effect was observed when excess tetraethylammonium bromide was added to the reaction solution i.e. the absorbance at 420 nm increased with tetraethylammonium bromide concentration but the rate of appearance of the 420 nm was unchanged (Table 30 and Fig. 10).

<table>
<thead>
<tr>
<th>$\left[\text{NO}_2^-\right]/10^{-4}$ mol dm$^{-3}$</th>
<th>$\text{OD}_\infty$</th>
<th>$k_0/10^{-4}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.77</td>
<td>0.65</td>
<td>2.58</td>
</tr>
<tr>
<td>8.66</td>
<td>0.77</td>
<td>3.985</td>
</tr>
<tr>
<td>11.54</td>
<td>0.93</td>
<td>4.59</td>
</tr>
<tr>
<td>23.26</td>
<td>1.05</td>
<td>8.395</td>
</tr>
</tbody>
</table>
TABLE 30: VARIATION OF 420 nm ABSORBANCE ($OD_\infty$) WITH BRO MIDE ION CONCENTRATION, FOR REACTION OF PHENYL ISO THIOCYANATE (1.16 x 10^{-4} mol dm^{-3}) AND TEAN (11.5 x 10^{-4} mol dm^{-3}) IN ACETONITRILE AT 25°C.

<table>
<thead>
<tr>
<th>$[Et_4N^+Br^-]/10^{-4}$ mol dm^{-3}</th>
<th>RATIO $\frac{[Br^-]}{[RNCS]}$</th>
<th>$OD_\infty$</th>
<th>$k / 10^{-4}$^-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>0.69</td>
<td>4.58</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
<td>0.71</td>
<td>4.46</td>
</tr>
<tr>
<td>11.5</td>
<td>10</td>
<td>0.78</td>
<td>4.63</td>
</tr>
<tr>
<td>11.5</td>
<td>10</td>
<td>0.795</td>
<td>4.75</td>
</tr>
<tr>
<td>23.0</td>
<td>20</td>
<td>0.815</td>
<td>4.47</td>
</tr>
<tr>
<td>45.7</td>
<td>40</td>
<td>0.829</td>
<td>4.32</td>
</tr>
<tr>
<td>100</td>
<td>86</td>
<td>0.97</td>
<td>4.32</td>
</tr>
<tr>
<td>200</td>
<td>172</td>
<td>1.01</td>
<td>4.33</td>
</tr>
<tr>
<td>250</td>
<td>216</td>
<td>1.08</td>
<td>4.32</td>
</tr>
<tr>
<td>300</td>
<td>260</td>
<td>0.99</td>
<td>4.39</td>
</tr>
<tr>
<td>400</td>
<td>345</td>
<td>0.975</td>
<td>4.38</td>
</tr>
</tbody>
</table>

FIG. 10: PLOT OF $OD_\infty$ VERSUS BRO MIDE ION CONCENTRATION FOR DATA IN TABLE 30
In the presence of excess tetraethylammonium bromide the absorbance was constant to $\pm$ 2% for different nitrite concentrations (Table 31). The data in Table 32 gave an average of $\varepsilon = 8385 \pm 665$ mol$^{-1}$ dm$^{3}$ cm$^{-1}$ for the 420 nm absorbance. A slight shift in the wavelength of the absorbance maximum of 420 to 408 nm was also observed as the ionic strength increased. A similar shift was apparent in the reactions with excess isothiocyanate.

Clearly the changes in the absorbance maximum are caused by changes in ionic strength an effect that has been observed for other absorbing anions and related to alteration of the physical properties of the solution.

Otherwise the changes in the 420 nm peak described above can only relate to inhibition of some competing reaction such as the hydrolysis of the phenyl isothiocyanate. Excess tetraethylammonium bromide would remove adventitious water by solvation. This explanation was checked by adding water to reactions in acetonitrile and the results are reported in Table 33. Evidently 0.3 % water decreases the 420 nm absorbance by 12% and 0.5% by 27%. Thus a relatively large amount of water (ca. 0.5%) is required to explain the absorbance changes and this is incompatible with the purification of the acetonitrile by distillation from calcium hydride.

The explanation could be simply that protonation of the product causes the reduction in absorbance. Indeed addition of base to the reaction mixture causes an increase in the absorbance at 420 nm. Thus changes in ionic strength may perturb the equilibrium between protonated and non-protonated forms of the product.
TABLE 31: VARIATION OF 420 nm ABSORBANCE ($\text{OD}_\infty$) WITH NITRITE ION CONCENTRATION, WITH CONSTANT PHENYL ISOTHIOCYANATE ($1.16 \times 10^{-4}$ mol dm$^{-3}$) AND EXCESS TETRAETHYL AMMONIUM BROMIDE ($250 \times 10^{-4}$ mol dm$^{-3}$) IN ACETONITRILE AT 25°C.

<table>
<thead>
<tr>
<th>[$\text{Et}_4\text{N}^+\text{NO}_2^-$] / $10^{-4}$ mol dm$^{-3}$</th>
<th>$\text{OD}_\infty$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.84</td>
<td>1.08</td>
</tr>
<tr>
<td>11.7</td>
<td>1.08</td>
</tr>
<tr>
<td>11.6</td>
<td>1.04</td>
</tr>
<tr>
<td>17.5</td>
<td>1.06</td>
</tr>
<tr>
<td>23.0</td>
<td>1.08</td>
</tr>
<tr>
<td>23.4</td>
<td>1.04</td>
</tr>
<tr>
<td>23.0</td>
<td>1.10</td>
</tr>
</tbody>
</table>

TABLE 32: VARIATION OF 420 nm ABSORBANCE ($\text{OD}_\infty$) WITH PHENYL ISOTHIOCYANATE CONCENTRATION WITH EXCESS TEAN AND TETRAETHYLAMMONIUM BROMIDE IN ACETONITRILE AT 25°C.

<table>
<thead>
<tr>
<th>[$\text{RNCS}$] / $10^{-4}$ mol dm$^{-3}$</th>
<th>[$\text{NO}_2^-$] / $10^{-3}$ mol dm$^{-3}$</th>
<th>[$\text{Br}^-$] / $10^{-3}$ mol dm$^{-3}$</th>
<th>$\text{OD}_\infty$</th>
<th>$\varepsilon$/mol$^{-1}$ dm$^3$ cm$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.147</td>
<td>1.176</td>
<td>3.13</td>
<td>0.114</td>
<td>7755</td>
</tr>
<tr>
<td>0.294</td>
<td>1.176</td>
<td>6.26</td>
<td>0.258</td>
<td>8775</td>
</tr>
<tr>
<td>0.294</td>
<td>2.35</td>
<td>6.26</td>
<td>0.242</td>
<td>8232</td>
</tr>
<tr>
<td>0.588</td>
<td>1.176</td>
<td>12.5</td>
<td>0.518</td>
<td>8810</td>
</tr>
<tr>
<td>0.588</td>
<td>2.35</td>
<td>12.5</td>
<td>0.514</td>
<td>8742</td>
</tr>
<tr>
<td>1.147</td>
<td>1.147</td>
<td>25.0</td>
<td>1.084</td>
<td>9451</td>
</tr>
<tr>
<td>5.96</td>
<td>1.19</td>
<td>123.4</td>
<td>4.62$^a$</td>
<td>7758</td>
</tr>
<tr>
<td>5.96</td>
<td>2.38</td>
<td>123.4</td>
<td>4.62$^a$</td>
<td>7557</td>
</tr>
</tbody>
</table>

a - Measured using 1 mm cells
### TABLE 33: EFFECT OF ADDITION OF WATER ON ABSORBANCE
AT 420 nm, WITH PHENYL ISOTHIOCYANATE
(1.152 x 10^{-4} mol dm^{-3}) IN ACETONITRILE AT 25°C.

<table>
<thead>
<tr>
<th>$\left[\text{Et}_4\text{N}^+\text{NO}_2^-\right]/10^{-4}\text{mol dm}^{-3}$</th>
<th>WATER CONTENT/ % v/v</th>
<th>OD_{\infty}</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.26</td>
<td>0</td>
<td>1.05</td>
</tr>
<tr>
<td>23.26</td>
<td>0.26</td>
<td>0.92</td>
</tr>
<tr>
<td>23.26</td>
<td>0.52</td>
<td>0.77</td>
</tr>
<tr>
<td>23.26</td>
<td>1.03</td>
<td>0.66</td>
</tr>
</tbody>
</table>

#### 5.10 ISO CYANATES AS REACTION PRODUCTS

The mechanism proposed by Hudson suggested that preferential formation of isocyanates from isothiocyanates by reaction with nitrite should be investigated.

The possibility exists that the formation of diazotates from isothiocyanates proceeds via isocyanate intermediates (Scheme 69). This pathway requires the consumption of two moles of nitrite per mole of isothiocyanate. To check this, reactions of both phenyl and 4-nitrophenyl isothiocyanate with a five fold excess of nitrite ion were assayed for nitrite consumed by hplc analysis and for diazotate by the R-salt method (see Chapter 2). Results in Table 34 show that exactly one equivalent of nitrite was consumed per mole of substrate, indicating diazotate was not formed via an isocyanate intermediate.

![Scheme 69](image_url)
TABLE 34: MEASUREMENT OF NITRITE ION CONSUMED BY REACTION OF AROMATIC ISOTHIOCYANATES WITH EXCESS TEAN IN ACETONITRILE AT 25°C

<table>
<thead>
<tr>
<th>SUBSTRATE</th>
<th>[RNCS] /mol dm⁻³</th>
<th>[NO₂⁻] (initial) /mol dm⁻³</th>
<th>[NO₂⁻] (final) /mol dm⁻³</th>
<th>No. EQUIVALENTS CONSUMED</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Nitrophenyl</td>
<td>0.002</td>
<td>0.01</td>
<td>0.0079</td>
<td>1.05</td>
</tr>
<tr>
<td>Phenyl</td>
<td>0.0002</td>
<td>0.001</td>
<td>0.0008</td>
<td>1.0</td>
</tr>
</tbody>
</table>

a - Diazotate Yield = 88%
b - Diazotate Yield = 5%

Analysis for the isocyanate was carried out by quenching the reaction mixture with methanol and using capillary gas chromatography to separate and quantify the urethane (98) from the thiourethane (99).

\[
\text{R - N} \quad \text{O} \\
\text{H} \quad \text{OMe}
\]

(98)

\[
\text{R - N} \quad \text{S} \\
\text{H} \quad \text{OMe}
\]

(99)

Initial reactions were carried out with an excess of nitrite ion over phenyl isothiocyanate followed by a methanol quench as indicated above. The reactions test whether the 420 nm product generates isocyanate. It was noted that addition of methanol slightly reduced the absorbance at 420 nm via protonation of the anion and addition of base restored the original absorbance. Therefore methanol does not react with the anion other than by protonation. Further, no urethane was evident in the reaction solutions under these conditions.

Additional reactions were carried out with an excess of the phenyl isothiocyanate over nitrite ion, conditions under which the 420 nm product is unstable. These results (Table 35) show that low yields of urethane were obtained initially, which increase substantially on prolonged contact with the methanol. The slow formation of the urethane was unexpected as reaction of methanol with phenyl isocyanate itself is instantaneous under the conditions used, and also as reported above, methanol does
not react with the 420 nm product, in the presence of excess nitrite ion.

This suggests that the isocyanate (and hence the urethane) must be from a secondary reaction of the excess isothiocyanate with the S-nitroso anion. A possible mechanism is shown in Scheme 70. The S-nitroso anion (100) attacks a second phenyl isothiocyanate molecule giving a dimeric anion (101). The anion (101) then cyclises to a four-membered ring (102) and eliminates thionitrite ion to give a neutral product (103). Compound (103) is then opened by nucleophilic attack of the methanol, followed by cleavage of the adduct (104) to give phenyl urethane (105) and regenerate phenyl isothiocyanate. An alternative mechanism is cyclisation via nitrogen to give a different four-membered ring (106). If intermediate (103), or (106) was formed rapidly, exposure to methanol would produce slow formation of the urethane.

**TABLE 35: URETHANE YIELDS FROM REACTION OF TEAN (0.006 mol dm\(^{-3}\)) AND PHENYL ISOThIOCYANATE (0.03 mol dm\(^{-3}\)) IN ACETONITRILE AFTER METHANOL QUENCH.**

<table>
<thead>
<tr>
<th>REACTION</th>
<th>TEMP / °C</th>
<th>URETHANE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 hr.</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>-</td>
</tr>
</tbody>
</table>

A similar study was carried out for the 4-nitrophenyl isothiocyanate. Again, reactions with excess nitrite ion (which is known to give quantitative yields of the diazotate), gave no urethane. With excess isothiocyanate, however, a 15% yield of the urethane was obtained. Unfortunately immediate removal of the methanol, meant that no increase in yield was observed. Thus the isocyanate must arise either from reaction of the diazotate with the isothiocyanate as in Scheme 71, or from reaction of the initial adduct of diazotate and isothiocyanate (107) with excess
\[
\text{Scheme 70}
\]
isothiocyanate in a similar fashion to that of Scheme 70. The thio analogue of the diazotate (108) would presumably decompose to give sulphur.

![Scheme 71](image)

In conclusion tentative evidence for a Hudson type pathway was obtained although it does not seem to be a major one for the reaction of nitrite ion with aromatic isothiocyanates.

5.11 EVIDENCE FROM I.R. AND N.M.R. SPECTROSCOPY

Difficulties in the isolation of the product of reaction of nitrite ion with phenyl isothiocyanate led to examination of the reaction solutions by spectroscopic methods.

i) I.R. Spectroscopy

The reaction was first examined by i.r. spectroscopy although absorption by the solvent acetonitrile, rendered all but the 1600 - 1800 cm\(^{-1}\) region opaque.

For a concentrated reaction solution with \([\text{PhNCS}] = 0.025\) and \([\text{TEAN}] = 0.068\) mol dm\(^{-3}\) at room temperature, two bands of equal intensity were observed in this region, at 1675 and 1650 cm\(^{-1}\). After ca. 1 hour both had disappeared.
The assignment of these bands was not obvious, but both are probably due to carbonyl groups. Of the two possible structures (89) and (109), one (109) is effectively a thiocarboxylate ion, which usually absorbs at 1525 cm\(^{-1}\), in solid state (kBr) spectra. The second species (89) is an anion of a urethane. Urethanes usually absorb at ca. 1650 and 1600 cm\(^{-1}\).

\[
\begin{align*}
\text{Ph - N} & \quad \text{S - N = O} \\
\mid & \\
\text{N} & \\
\end{align*}
\]

(109) \hspace{2cm} (89)

The observed i.r. spectra may imply a mixture of both compounds, although it would seem to favour the urethane-type structure (89). However, the assignments are speculative in the absence of data for comparable structures.

ii) N. M. R.

The \(^1\)H n.m.r. spectra of the reaction of phenyl isothiocyanate were uninformative showing only aromatic multiplets. To provide an internal standard the 4-methylphenyl isothiocyanate was used, reaction being carried out in \(d^3\)-acetonitrile. On reaction with excess nitrite ion the aromatic protons shifted 0.48 p.p.m. upfield and changed from a singlet to a double doublet, and the methyl group singlet shifted upfield by 0.14 p.p.m. (Fig. 10). There appeared to be only one product. The spectral changes were consistent with the formation of a nitrogen anion in conjugation with the aromatic ring (Scheme 72) be it the initial anion (110) or the S-nitroso compound (111).

\[
\begin{align*}
\text{Me} & \quad \text{N = C = S} \quad \text{NO}_2^- \\
\rightarrow & \\
\text{Me} & \quad \text{N = C = S} \quad \text{ONO} \\
\rightarrow & \\
\text{Me} & \quad \text{N = C = S} \quad \text{SNO} \\
\end{align*}
\]

SCHEME 72

In contrast, the 4-methylphenyl isocyanate on reaction with nitrite ion in \(d^3\)-acetonitrile showed a downfield shift of 0.25 p.p.m. and a change from a double doublet to a singlet for the aromatic protons and
FIG. 10: N.M.R. OF REACTION OF 4-METHYLPHENYLISOTHIOCYANATE

a) $\delta_H (90 \text{ MHz, CD}_3\text{CN})$ of $\text{MeN} = \text{C} = \text{S}$

7.18 (4H, s, ArH),
2.32 (3H, s, Ar-CH$_3$)

b) $\delta_H (90 \text{ MHz, CD}_3\text{CN})$ of Reaction of

$\text{MeN} = \text{C} = \text{S}$ and $\text{Et}_4\text{N}^+ \text{NO}_2^-$

$[\text{RNCS}] = 0.032 \text{ mol dm}^{-3}$

$[\text{NO}_2^-] = 0.044 \text{ mol dm}^{-3}$

Product

6.7 (4H, dd, ArH)
2.18 (3H, s, Ar-Me)

Et$_4$N$^+$

Solvent
the methyl group singlet shifted downfield by 0.09 p.p.m. (Fig. 11).

This is consistent with production of a more electron withdrawing substituent either the N-nitroso compound (112) or the diazotate (113) (Scheme 73).

\[
\begin{align*}
\text{Me} & \text{N} = \text{C} = \text{O} \rightarrow \text{Me} & \text{N} \rightarrow \text{O} \\
\text{NO}_2 & \rightarrow & \text{CO}_2
\end{align*}
\]

(112) (113)

SCHEME 73

The \(^1\)H n.m.r. spectra gave little direct evidence for the product structures. Further, no evidence for ring substitution as proposed in Scheme 64 was obtained.

More informative n.m.r. data was obtained from \(^{15}\)N n.m.r., which has been used previously to distinguish between S-nitroso and N-nitroso compounds.\(^{136, 137}\)

These experiments used tetraethylammonium nitrite, with the nitrite ion enriched at the 99 atom % \(^{15}\)N level. This was prepared from commercially available sodium nitrite - \(^{15}\)N. The reactions were carried out in \(^3\)-acetonitrile using excess nitrite ion (i.e. \([^{15}\text{NO}_2^- \text{Et}_4\text{N}^+]\) = 0.15 mol dm\(^{-3}\) and \([\text{PhNCS}]) = 0.10 \text{ mol dm}^{-3}\). The \(^{15}\)N n.m.r. spectra was measured at 250 MHz. Three lines were observed in the spectra at 697, 601 and 228 p.p.m. respectively, relative to \(^{15}\)NH\(^+\) as an external standard. The line at 228 p.p.m. was assigned to natural abundance \(^{15}\)N in the solvent. The line at 601 p.p.m. was assigned to unreacted nitrite ion, by comparison with a blank solution. Previous values obtained for the nitrite ion are 603 and 588 p.p.m., both in aqueous media.\(^{136, 137}\)

The third line was assigned to the reaction product, and it is consistent with an S-nitroso species. Table 36 shows the reported \(^{15}\)N chemical shifts for nitroso compounds. N-nitroso compounds are usually observed at \(\delta\) 500 to 550 p.p.m. and S-nitroso compounds at \(\delta\) 694 to 800 p.p.m. The nitrite ion and other O-nitroso compounds lie between the two. The resonance assigned to the product therefore occurs at the
FIG. 11: N.M.R. OF REACTION OF 4-METHYLPHENYL ISOCYANATE

$\delta_H (90 \text{ MHz, } \text{CD}_3\text{CN})$ of

$$\begin{align*}
\text{Me} & \quad \text{N} = \text{C} = \text{O} \\
\text{ArH}
\end{align*}$$

7.05 (4H, q, ArH)
2.30 (3H, s, Ar-CH$_3$)

$\delta_H (90 \text{ MHz, } \text{CD}_3\text{CN})$ of reaction mixture

$$\begin{align*}
[\text{Me} = \text{N} = \text{C} = \text{O}] &= 0.056 \text{ mol dm}^{-3} \\
[\text{NO}_2^-] &= 0.081 \text{ mol dm}^{-3}
\end{align*}$$

Product: 7.3 (4H, s, ArH)
2.39 (3H, s, Ar-Me)

Et$_4$N$^+$

H$_2$O

Solvent

ArH

CH$_3$
lower end of the range for S-nitroso compounds.

**TABLE 36:** $^{15}$N CHEMICAL SHIFTS OF SOME NITROSO COMPOUNDS

(δ IN p.p.m. relative to $^{15}$NH$_4^+$ as nitrate, downfield is positive).

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>REF.</th>
<th>SOLVENT</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhEtN - $^{15}$NO</td>
<td>137</td>
<td>(NEAT)</td>
<td>525.8, 522.7</td>
</tr>
<tr>
<td>MeN($^{15}$NO)CONH$_2$</td>
<td>137</td>
<td>EtOH</td>
<td>545</td>
</tr>
<tr>
<td>Ph$_2$N - $^{15}$NO</td>
<td>137</td>
<td>(NEAT)</td>
<td>554.4</td>
</tr>
<tr>
<td>Ph$_3$C-S- $^{15}$NO</td>
<td>137</td>
<td>CDCl$_3$</td>
<td>785.2</td>
</tr>
<tr>
<td>Et-S- $^{14}$NO</td>
<td>138$^a$</td>
<td>(NEAT)</td>
<td>764</td>
</tr>
<tr>
<td>CF$_3$-S- $^{14}$NO</td>
<td>138$^a$</td>
<td>(NEAT)</td>
<td>694</td>
</tr>
<tr>
<td>nC$_4$H$_9$O- $^{15}$NO</td>
<td>139</td>
<td>(NEAT)</td>
<td>572</td>
</tr>
<tr>
<td>4-Me$_2$NC$_6$H$_4$- $^{15}$NO</td>
<td>137</td>
<td>CDCl$_3$</td>
<td>783</td>
</tr>
</tbody>
</table>

a - Chemical shifts are independent of the nitrogen isotope observed.

Reaction of phenyl isocyanate under identical conditions gave no discernable peaks apart from that due to nitrite ion, implying that the N-nitroso products were too unstable to observe. More significantly no peak was observed at 697 p.p.m. as no S-nitroso product is possible in this case.

The data confirms rearrangement of the O-nitroso group to an S-nitroso group as proposed. No other nitrogen species are known to give $^{15}$N resonances in the same area as that attributed to an S-nitroso species. Overnight treatment with strong acid (HCl) destroyed the peak at 697 p.p.m., giving three peaks at 362, 355.4 and 354.2 p.p.m. The 601 peak also disappeared.

5.12 OTHER 4-SUBSTITUTED PHENYL ISOTHIOCYANATES

The reaction of nitrite with other 4-substituted phenyl isothiocyanates was briefly examined. The 4-methyl, 4-methoxy and 4-chloro analogues were used.
The reactions were monitored by UV spectrophotometry and all followed the second order rate equation (Equation 9) for loss of starting material. Second order plots (Figs. 12, 13 and 14) gave the values summarized in Table 37.

\[
\text{RATE} = k_2 [\text{RNCS}] [\text{NO}_2^-]
\]

**Table 37:** Second order rate constants for reactions of 4-substituted phenyl isothiocyanates with tetraethylammonium nitrite in acetonitrile at 25°C.

<table>
<thead>
<tr>
<th>(X)</th>
<th>(k_2/\text{mol}^{-1}\text{dm}^3\text{s}^{-1})</th>
<th>(\log k_2/k_H)</th>
<th>(\sigma_p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>0.097</td>
<td>-0.59</td>
<td>-0.27</td>
</tr>
<tr>
<td>Me</td>
<td>0.233</td>
<td>-0.21</td>
<td>-0.17</td>
</tr>
<tr>
<td>H</td>
<td>0.378</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cl</td>
<td>1.55</td>
<td>0.61</td>
<td>0.23</td>
</tr>
<tr>
<td>NO(_2^-)</td>
<td>(Too fast)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The \(k_2\) values correlate well with Hammett \(\sigma_{\text{para}}\) constants with \(\sigma = 2.26\) (Fig. 15). Thus as expected the reaction is facilitated by electron withdrawing substituents because increased electron deficiency at the acyl carbon atom of the isothiocyanate promotes nucleophilic attack.

Literature data of reactions of isothiocyanates with other nucleophiles show lower values of \(\sigma\) (Table 38) but all refer to reactions in protic media.

The reaction with nitrite ion in acetonitrile seems to be more sensitive to electronic effects. This probably reflects poor solvation of the anionic intermediate by the dipolar aprotic acetonitrile.

The UV/Visible spectra of the reaction solutions of the other 4-substituted phenyl isothiocyanates show loss of the isothiocyanate absorbance as before. They produce products that are less intensely absorbing than in the phenyl case. The 4-methyl (Fig. 16) and 4-chloro derivatives also show isobestic points but the 4-methoxy does not (Fig. 17). This may be due to lower stability of the anionic intermediate arising...
FIG. 12: PLOT OF $k_0$ VERSUS NITRITE CONCENTRATION FOR REACTION WITH 4-METHOXYPHENYL ISOThIOCYANATE
FIG. 13: PLOT OF $k_o$ VERSUS NITRITE CONCENTRATION FOR REACTION WITH 4-METHYL PHENYL ISOTHIOCYANATE
FIG. 14: PLOT OF $k_0$ VERSUS NITRITE CONCENTRATION FOR REACTION WITH 4-CHLOROPHENYL ISONIOTHIOCYANATE
FIG. 15: HAMMETT PLOT FOR REACTION OF 4-SUBSTITUTED
PHENYL ISOTHIOCYANATES WITH TETRACETYLAMMONIUM
NITRITE IN ACETONITRILE AT 25°C.
FIG. 16: UV SPECTRA OF REACTION OF 4-METHYLPHENYL ISOTHIOCYANATE WITH EXCESS TEAN IN ACETONITRILE AT 25°C
FIG. 17: UV SPECTRA OF REACTION SOLUTION, FOR REACTION OF 4-METHOXYPHENYL ISOThIOCYANATE AND EXCESS TEAN IN ACETONITRILE AT 25°C
from electron donation by the methoxy substituent.

The 4-methyl and 4-methoxy derivatives were found to give low yields of diazotate (6% and 9.5% respectively) for reaction with a 5-fold excess of nitrite ion in acetonitrile at 0°C. Thus they show similar behaviour to the phenyl isothiocyanate.

### TABLE 38: THE ϑ CONSTANTS OF THE HAMMETT PLOTS FOR REACTIONS OF 2, AND 4-SUBSTITUTED PHENYL ISOTHIOCYANATES AND VARIOUS NUCLEOPHILES

<table>
<thead>
<tr>
<th>Nucleophile (Solvent)</th>
<th>T/°C</th>
<th>No. of Compounds</th>
<th>ϑ</th>
<th>r</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO⁻ (aq)</td>
<td>30</td>
<td>13</td>
<td>1.68±0.17</td>
<td>0.95</td>
<td>142</td>
</tr>
<tr>
<td>HO⁻ (aq)</td>
<td>30</td>
<td>12</td>
<td>1.57±0.12</td>
<td>0.98</td>
<td>143</td>
</tr>
<tr>
<td>Glycine (aq)</td>
<td>25</td>
<td>27</td>
<td>0.94±0.05</td>
<td>0.96</td>
<td>144</td>
</tr>
<tr>
<td>nBuNH₂(MeOH)</td>
<td>30</td>
<td>5</td>
<td>1.13±0.08</td>
<td>0.99</td>
<td>145</td>
</tr>
<tr>
<td>HS⁻ (aq)</td>
<td>30</td>
<td>8</td>
<td>0.89±0.09</td>
<td>0.98</td>
<td>146</td>
</tr>
<tr>
<td>CH₃CH₂SH (aq)</td>
<td>25</td>
<td>5</td>
<td>0.536±0.07</td>
<td>0.97</td>
<td>147</td>
</tr>
<tr>
<td>NO₂⁻ (MeCN)</td>
<td>25</td>
<td>4</td>
<td>2.26±0.26</td>
<td>0.988</td>
<td>a</td>
</tr>
</tbody>
</table>

- This work

### 5.13 CONCLUDING REMARKS

Reaction between various aromatic isothiocyanates and nitrite ion has been demonstrated. The products appear to result from either N-nitrosation or S-nitrosation. Thus the nitrite ion has been activated as an intramolecular nitrosating agent by its reaction with the isothiocyanate.

The 4-nitrophenyl derivative gave mainly N-nitrosation whereas the phenyl derivative gave very little. The difference is related to the electron density at the nitrogen atom relative to the sulphur atom. Electron withdrawal by the 4-nitro group reduces electron density on the sulphur atom but increases that on nitrogen. So migration to the nitrogen anion becomes favoured relative to sulphur, despite its being the softer site. In the unsubstituted case lower electron withdrawal favours migration to the sulphur atom.
CHAPTER 6

REACTION OF NITRITE ION WITH ALKYL ISOTHIOCYANATES
6.1 INTRODUCTION

Alkyl isothiocyanates are less reactive than the aromatic analogues. Reactions with nucleophiles are known, however, and they were expected to react with nitrite ion. A brief study was undertaken to realise this expectation.

6.2 CONSUMPTION OF NITRITE

Reactions were carried out in acetonitrile at 25°C using an excess of isothiocyanate over nitrite ion. Using Shinn's method to monitor the nitrite, it was observed that cyclohexyl, ethyl and benzyl isothiocyanate all consumed substantial amounts of nitrite ion. Unlike the alkyl isocyanates, however, the presence of DBTDA (dibutyltin diacetate) was not required, and on addition it did not effect the reaction.

In acetonitrile with TEAN (tetracylammonium nitrite) a yellow solution was produced, which rapidly faded on exposure of the solution to air. Thus, the coloured product appears to oxidise readily, a property characteristic of S-nitroso compounds. On heating under reflux in acetonitrile, cyclohexyl isothiocyanate gave a green solution in the presence of excess nitrite ion. In DMSO, at room temperature, with sodium nitrite, cyclohexyl isothiocyanate gave an orange solution with \( \lambda_{\text{max}} 446 \text{ nm} \).

6.3 KINETICS OF REACTION

Rates of reaction were determined, as before by monitoring the loss of nitrite ion by Shinn's method. With excess cyclohexyl isothiocyanate about 60% nitrite ion was consumed in an initial rapid reaction from which good first order plots were obtained. Subsequently a slower reaction took place resulting in overall 90% nitrite consumption (Fig. 18). Similar behaviour was observed for the ethyl isothiocyanate (Fig. 19). The reactions were also first order in isothiocyanate (Figs. 20 and 21) and therefore followed equation 10.

\[
\text{RATE} = -\frac{d \left[ \text{NO}_2^- \right]}{dt} = k_2 [\text{RNCS}] \left[ \text{NO}_2^- \right]
\]
FIG. 18: PLOT OF NITRITE ION CONCENTRATION VERSUS TIME FOR REACTION OF CYCLOHEXYL ISOTHIOCYANATE (0.3 mol dm$^{-3}$) AND TEAN (7.25 x 10$^{-3}$ mol dm$^{-3}$) IN ACETONITRILE AT 25°C.
FIG. 19: PLOT OF NITRITE ION CONCENTRATION VERSUS TIME FOR REACTION OF ETHYL ISOTHIOCYANATE (0.15 mol dm$^{-3}$) AND TEAN (7.25 x 10$^{-3}$ mol$^{-1}$ dm$^{-3}$) IN ACETONITRILE AT 25°C.
FIG. 20: PLOT OF $k_0$ VERSUS CYCLOHEXYL ISOTHIOCYANATE CONCENTRATION FOR REACTION WITH TEAN IN ACETONITRILE AT $25 \pm 0.1\%$. 

![Graph showing a linear relationship between $k_0$ and [RNCS] in mol dm$^{-3}$]
FIG. 21: PLOT OF $k_0$ VERSUS ETHYL ISOThIOCYANATE CONCENTRATION FOR REACTION WITH TEAN IN ACETONITRILE AT $25 \pm 0.1^\circ C$. 

![Graph showing the plot of $k_0$ versus [EtNCS] with data points and a trend line.](image-url)
Cyclohexyl isothiocyanate gave \( k_2 = (2.71 \pm 0.3) \times 10^{-3} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1} \), and ethyl isothiocyanate gave \( k_2 = (5.0 \pm 0.5) \times 10^{-3} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1} \), both for reaction with TEAN in acetonitrile at 25 ± 0.1 °C. The ethyl compound reacts more rapidly because of less electron donation into the isothiocyanate moiety than in the cyclohexyl case. Therefore the acyl C-atom is more electrophilic. The ratio of \( k_2 \) for cyclohexyl:ethyl isothiocyanate of 1:1.85 is in good agreement with literature values of 1:1.73 and 1:2.16 for reactions of cyclohexyl and \( \text{^n} \)propyl isothiocyanate with aqueous hydroxide ion and \( \text{^n} \)butylamine respectively.\(^{110,111}\)

Reactions of both substrates with sodium nitrite in DMSO gave \( k_2 \) ca. 1.4 x 10\(^{-3}\) and 2.4 x 10\(^{-3}\) mol\(^{-1}\) dm\(^3\) s\(^{-1}\) for the cyclohexyl and ethyl isothiocyanates respectively.

6.4 **PRODUCT ANALYSIS**

Firstly the presence of deamination products was examined.Reaction of cyclohexyl isothiocyanate with sodium nitrite in DMSO at 25 °C, both with and without DBTDA gave very low yields of cyclohexene and cyclohexanol (Table 39).

The possibility of a Hudson type mechanism\(^{132}\) leading to the formation of an isocyanate was investigated. Reactions with excess cyclohexyl isothiocyanate over TEAN in acetonitrile, were carried out at three temperatures. Direct analysis for cyclohexyl isocyanate was carried out by capillary gc. The results in Table 40 show that moderate amounts of isocyanate were produced.

6.5 **PROPOSED REACTION MECHANISM**

Scheme 74 shows the proposed reaction mechanism which is analogous to that (Scheme 61) for aromatic isothiocyanates. Initial nucleophilic attack of nitrite ion on the isothiocyanate gives the anion (114) which can rearrange by migration of the nitroso group to an \( S \)-nitroso anion (115). Rearrangement to the \( S \)-nitroso anion should be more favoured for the alkyl isothiocyanates because the nitrogen anion will be destabilized by electron donation from the alkyl groups. So the charge will prefer to reside on the sulphur atom.
### TABLE 39: YIELDS OF DEAMINATION PRODUCTS\(^a\) FROM REACTION OF CYCLOHEXYL ISOTHIOCYANATE WITH SODIUM NITRITE IN DMSO AT ROOM TEMPERATURE

<table>
<thead>
<tr>
<th>[RNCS] / mol dm(^{-3})</th>
<th>[NO(_2^-)] / mol dm(^{-3})</th>
<th>[DBTDA] / mol dm(^{-3})</th>
<th>YIELD / %</th>
<th>YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.023</td>
<td>0.12</td>
<td>0.0343</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>0.023</td>
<td>0.114</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.125</td>
<td>1.16</td>
<td>0.186</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>0.125</td>
<td>1.16</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

\(a\)- Analyzed by gc as described in 9.3.3

### TABLE 40: YIELDS OF CYCLOHEXYL ISOXYANATE FROM REACTION OF CYCLOHEXYL ISOXYANATE WITH TEAN IN ACETONITRILE.

<table>
<thead>
<tr>
<th>[RNCS] / mol dm(^{-3})</th>
<th>[NO(_2^-)] / mol dm(^{-3})</th>
<th>TIME / hrs</th>
<th>TEMP / °C</th>
<th>ISOXYANATE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.060</td>
<td>6 \times 10^{-3}</td>
<td>12</td>
<td>25</td>
<td>8.5</td>
</tr>
<tr>
<td>0.060</td>
<td>6 \times 10^{-3}</td>
<td>12</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>0.055</td>
<td>5.5 \times 10^{-3}</td>
<td>4</td>
<td>80</td>
<td>37</td>
</tr>
</tbody>
</table>
Similarly the S-nitroso anion (115) will be less stable than its aromatic analogue. This may promote the fragmentation to give the isocyanate and thionitrite ion, in agreement with the substantial yields of isocyanate detected (Table 40). Further, the yield of isocyanate was observed to increase at higher temperatures.

![Chemical structure](image)

**SCHEME 74**

The S-nitroso anion is presumably the coloured species observed and which is extremely unstable to oxidation. The absorbance of the coloured species is not very intense with an extinction coefficient of ca. 100 \( \text{mol}^{-1} \text{dm}^3 \text{cm}^{-1} \).

Normally S-nitroso compounds are readily oxidised. Homolysis of the S-N bond occurs to give a sulphur radical and nitrogen oxide. The alkyl S-nitroso anions are much less stable than the aromatic analogues as one might expect and give a much less intense absorbance in their visible spectra probably due to their decreased conjugation.

The alkyl isothiocyanates behave differently to the alkyl isocyanates in two major respects. Firstly, they consume nitrite without the need for added DBTDA and secondly, they give only small amounts of deamination products. Both of these differences must relate to the presence of the sulphur atom and lend credence to the proposed mechanism. The consumption of nitrite relates to ready formation of the S-nitroso anion which is resistant to acid hydrolysis.
The kinetic studies revealed an initial fast reaction resulting in 60% nitrite consumption for cyclohexyl isothiocyanate and 80% for the ethyl. The remaining nitrite is then consumed in a slow reaction. These may be rationalized by Scheme 75. The rate determining step is nucleophilic attack by the nitrite ion on the isothiocyanate to give the anion (116). A rapid equilibrium exists between the O-nitroso anion (116) and the S-nitroso anion (117). For R = cyclohexyl a 40 : 60 ratio is observed and for R = ethyl a 20 : 80 ratio is found. If slow decomposition of (117) then occurs and the equilibrium between (116) (117) is perturbed, slow consumption of the remaining nitrite will result. This requires that the acid conditions used in the Shinn's test (5N HCl) causes hydrolysis of the O-nitroso compound to give nitrite which is detected, whereas the S-nitroso compound is either stable or hydrolyses without the formation of nitrite. A similar mechanism was proposed earlier (Section 3.6) for the alkyl isocyanates. The absence of significant deamination reflects rearrangement to an S-nitroso anion rather than an N-nitroso anion.

\[
\begin{align*}
R - N = C = S &\quad \xrightarrow{\text{slow}} \quad S - N = O \\
+ &\quad R . D . S. \\
NO_2^- &\quad \text{R - N} \\
(116) &\quad \text{ONO} \\
\end{align*}
\]

**SCHEME 75**

Under identical conditions in the presence of DBTDA cyclohexyl isothiocyanate reacted slower than cyclohexyl isocyanate (Table 41). It was five times slower in acetonitrile and three times slower in DMSO. This concurs with the known relative reactivities of isocyanates and isothiocyanates, the latter being less reactive to nucleophiles.
TABLE 41: RELATIVE REACTIVITIES OF CYCLOHEXYL ISOTHIOCYANATE AND ISOCYANATE TO NITRITE ION, IN THE PRESENCE OF DBTDA AT 25 ± 0.1°C.

<table>
<thead>
<tr>
<th>SUBSTRATE</th>
<th>SOLVENT</th>
<th>NITRITE SALT</th>
<th>$k_2/10^{-3}$ mol$^{-1}$ dm$^{-3}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNCO</td>
<td>MeCN</td>
<td>Et$_4$N$^+$</td>
<td>13.4</td>
</tr>
<tr>
<td>RNCS</td>
<td>MeCN</td>
<td>Et$_4$N$^+$</td>
<td>2.7</td>
</tr>
<tr>
<td>RNCO</td>
<td>DMSO</td>
<td>Na$^+$</td>
<td>3.6</td>
</tr>
<tr>
<td>RNCS</td>
<td>DMSO</td>
<td>Na$^+$</td>
<td>1.4</td>
</tr>
</tbody>
</table>

6.6 CONCLUDING REMARKS

This brief study of the reaction of alkyl isothiocyanates with nitrite ion shows that reaction does indeed occur with preferential formation of an S-nitroso compound. The nitrite ion is once more activated as an intramolecular nitrosating agent by reaction with the organic anhydride.

The findings suggest that reaction of nitrite ion with naturally occurring isothiocyanates is unlikely to produce carcinogenic compounds. The common isothiocyanates in plants are benzyl isothiocyanate, allyl isothiocyanate and other substituted benzyl isothiocyanates. As alkyl compounds, all are most likely to produce S-nitroso products. Their dietary significance may be inhibition of the formation of carcinogenic N-nitroso compounds by removal of nitrite. Their presence would then be beneficial to health rather than otherwise.
CHAPTER 7

REACTION OF NITRITE ION WITH N-SULPHINYL AMINES
7.1 INTRODUCTION

The previous sections show that nitrite ion reacts with isocyanates, carbodiimides and isothiocyanates. It was of interest to examine whether similar reactions proceed with N-sulphinyl amines. These compounds react with nucleophiles but are less reactive than the other compounds.

7.2 REACTION OF N-SULPHINYL-4-NITROANILINE

Initial studies were carried out with the 4-nitrophenyl derivative (118) as this should be the most reactive. Using methods developed for the isocyanates the reaction products were examined first.

Working with excess N-sulphinylamine over nitrite ion, the yields of 1,3-bis(4-nitrophenyl)triazene were determined. In principle this product could arise by a variation of the mechanism proposed for the reaction of isocyanates whereby evolution of SO$_2$ occurs instead of CO$_2$ (Scheme 76). The yields observed, however, were low (Table 42). The higher yield of triazene (13%) was for reaction at 40°C. The formation of triazene by reaction with 4-nitrophenyl diazotate was also examined and the final two entries in Table 42 show the yields for these reactions were also low.
\begin{align*}
\text{(118)} &\rightarrow \text{NO}_2\text{N} = \text{S} = \text{O} \\
\text{SCH E M E  76} &
\end{align*}
TABLE 42: YIELDS OF 1,3-BIS(4-NITROPHENYL)TRIAZENE FROM REACTION OF N-SULPHINYL-4-NITROANILINE AND TEAN (0.0185 mol dm$^{-3}$) IN ACETONITRILE

<table>
<thead>
<tr>
<th>RATIO $\frac{[RNSO]}{[NO_2^-]}$</th>
<th>TEMPERATURE / °C</th>
<th>YIELD OF TRIAZENE / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>25</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>43</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>100</td>
<td>40</td>
<td>9.5</td>
</tr>
<tr>
<td>19$^a$</td>
<td>25</td>
<td>4.5</td>
</tr>
<tr>
<td>40$^a$</td>
<td>40</td>
<td>7</td>
</tr>
</tbody>
</table>

$^a$ - Using Sodium 4-nitrophenyldiazotate instead of TEAN

Analysis by both Shinn's method$^{100}$ and by hplc showed that all the nitrite ion for the reactions in Table 42 was consumed. Also addition of acid or base on completion of reaction had no effect on the yield of triazene.

The reaction of N-sulphiny1-4-nitroaniline was then examined with excess nitrite ion and the yields of diazotate determined as before. (Table 43).

TABLE 43: YIELDS OF DIAZOTATE FROM REACTION OF N-SULPHINYL-4-NITROANILINE (2 x 10$^{-3}$ mol dm$^{-3}$) AND TEAN (0.1 mol dm$^{-3}$) IN ACETONITRILE

<table>
<thead>
<tr>
<th>TEMPERATURE / °C</th>
<th>YIELD OF DIAZOTATE$^a$ / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>40</td>
<td>8</td>
</tr>
</tbody>
</table>

$^a$ - Error $^\dagger$ 2%
Thus under a range of conditions only small amounts of triazene form, although all the nitrite ion is consumed.

7.3 REACTION OF N-SULPHINYLANILINE

N-Sulphinylaniline was also observed to react with nitrite ion. The UV spectra showed loss of the absorbance due to the N-sulphinylaniline at 312 nm on reaction with excess of nitrite ion (Fig. 22). The reactions showed good pseudo-first order behaviour for the plot of log (absorbance) versus time. Further, variation of the nitrite concentration showed the reaction to be first order in nitrite (Fig. 23) so the rate expression is given by equation 11.

\[
\text{RATE} = k_2 \left[\text{RNSO}\right] \left[\text{NO}_2^-\right]^{\text{-11}}
\]

At 25°C in acetonitrile, \(k_2 = (0.124 \pm 0.007) \text{ mol} \cdot \text{dm}^{-3} \cdot \text{s}^{-1}\). Thus N-sulphinylaniline reacts more slowly with nitrite ion than phenyl isothiocyanate as expected from their known relative reactivities.

With excess nitrite ion, yields of the diazotate from N-sulphinylaniline were also low (Table 44) and yields of 1,3-diphenyltriazene from reactions with excess N-sulphinylaniline were less than 5%.

<table>
<thead>
<tr>
<th>RATIO</th>
<th>DIAZOTATE YIELD / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>23.5</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>50</td>
<td>21</td>
</tr>
</tbody>
</table>

The reaction appears to give products other than those expected. A possible reason is that \(\text{SO}_2\) is not readily expelled from the N-nitroso intermediate (119) in Scheme 76. Attempts to detect \(\text{SO}_2\) using fuchsin \(148\), starch/iodide paper and acidified potassium dichromate \(148\) were unsuccessful.

Hydrolysis of N-sulphinylaniline in acetonitrile with 10% and 20% water at room temperature showed the expected quantitative formation.
FIG. 22: UV SPECTRA OF REACTION SOLUTION CONTAINING N-SULPHINYLAMLINE (1.15 x 10^{-5} \text{ mol dm}^{-3}) AND TEAN (18 x 10^{-4} \text{ mol dm}^{-3}) IN ACETONITRILE AT 25°C
FIG. 23: PLOT OF PSEUDO FIRST ORDER RATE CONSTANT VERSUS NITRITE ION CONCENTRATION FOR REACTION OF N-SULPHINYLAMILINE$^a$ AND TEAN IN ACETONITRILE AT 25 $\pm$ 0.1°C.

$[\text{NO}_2^-]/10^{-4}\text{mol dm}^{-3}$

$a - [\text{RNSO}] = 1.15 \times 10^{-5} \text{ mol dm}^{-3}$
of aniline by glc. Thus loss of \( \text{SO}_2 \) appeared to be facile. There seems to be no obvious reason why loss of \( \text{SO}_2 \) should be less facile on reaction with nitrite ion, so some other deviation must be occurring in the reaction pathway.

### 7.4 CONCLUDING REMARKS

Reaction of nitrite ion with N-sulphinyl-4-nitroaniline and N-sulphinylaniline produces only small amounts of obvious nitrosation products. Consumption of nitrite ion is observed which presumably generates the N-nitroso intermediate (120). This does not appear to lose \( \text{SO}_2 \) to give the diazotate even on addition of acid.

A possible alternative pathway for decomposition of the N-nitroso intermediate (120) is presented in Scheme 77. Instead of complete loss of \( \text{SO}_2 \) rearrangement (or fragmentation and rapid recombination) may give the intermediate (121).

\[
\begin{align*}
\text{Ar} - \text{N} = \text{S} = \text{O} & \quad \rightarrow \quad \text{Ar} - \text{N} - \text{S} - \text{O} \\
& \quad \rightarrow \quad \text{Ar} - \text{N} - \text{S} - \text{O} \\
& \quad \rightarrow \quad \text{Ar} - \text{N} = \text{N} - \text{O} - \text{S} - \text{O} \\
& \quad \rightarrow \quad \text{Ar} - \text{O} = \text{S} - \text{O} \\
& \quad \rightarrow \quad \text{Ar} - \text{SO}_2
\end{align*}
\]

SCHEME 77

Sulphur dioxide is more susceptible to nucleophilic attack than \( \text{CO}_2 \), so this step is feasible. Then loss of nitrogen might give the aryl sulphonylic acid (123) or the sulphate ester (122). Identification of the
reaction products as (122) or (123) would validate the postulated mechanism in Scheme 77.
CHAPTER 8

CONCLUSIONS
The work described in this thesis extends the principle of nitrite ion activation by organic anhydrides.

The reaction of nitrite ion with isocyanates and carbodiimides brings about activation of the nitrite ion as an intramolecular nitrosating agent and products of nitrosation. Isocyanates give 1,3-diaryltriazenes from the aromatic derivatives and deamination results from the reaction of the alkyl derivatives. Carbodiimides initially produce N-nitrosoureas which may further fragment. The isothiocyanates offer the opportunity of S-nitrosation and in consequence less N-nitrosation is observed and evidence supports the fact that S-nitroso products are also formed. The N-sulphinylamines give small amounts of products from N-nitrosation but most of the products remain unidentified.

In these reactions an initial condensation of the nitrite ion with the heterocumulene is activating and migration of the nitroso group occurs to the available nitrogen or sulphur atom. This is a further extension of the reaction type first observed between nitrite ion and iminium cations.

All these species produce intramolecular nitrosation. In order to nitrosate other molecules in the reaction mixture one must use an anhydride where there is no chance for intramolecular reaction, such as the acetic anhydride reaction of Lees and Saville. Heterocumulenes allow nitrosation and deamination reactions to proceed under remarkably mild conditions (i.e. at 0°C and in organic solvents). The potential of these reactions for synthetic chemistry has yet to be realised, but the work described in the Thesis establishes new methods for effecting nitrosation under non-acidic conditions.

Further applications of the reactions could be usefully examined and their scope further extended. Other organic anhydrides such as ketenes and ketene-imines, and the reactions of nitrite ion with the acyl chlorides briefly mentioned by Lees and Saville, warrant further investigation.
CHAPTER 9

EXPERIMENTAL
9.1 GENERAL AND INSTRUMENTATION

The physical properties of compounds were determined on the following instruments.

Infra-red spectra were measured on a Perkin-Elmer 298 grating spectrometer with polystyrene calibration. Proton n.m.r. spectra were measured on a Varian EM360A/60 MHz or a Jeol FX-90Q/90 MHz spectrometer with tetramethylsilane as internal standard. UV/Visible spectra were measured on a Pye-Unicam SP1800 or SP8-500, Cecil CE599, Perkin Elmer 124 or LKB 4050 spectrophotometer, calibrated with a holmium filter. Melting points were measured on a Gallenkamp hot-stage apparatus and were uncorrected. Mass spectra were provided by the departmental service using AEI MS-12 or VG 7070 instruments.

Commonly used solvents were purified as follows: Acetonitrile and light petroleum (b.p. 60-80\(^0\)) were redistilled off calcium hydride. DMSO was distilled off calcium hydride at reduced pressure. Dichloromethane was distilled off phosphorus pentoxide, and diethyl ether was sodium dried and redistilled under argon. THF was distilled off potassium under argon.

All other reagents were obtained commercially and purified by standard techniques\(^{149}\) when necessary. The isocyanates were all freshly distilled before use and stored under nitrogen to prevent hydrolysis.

9.2 AROMATIC ISOCYANATES

9.2.1 Heterogenous Reaction

Phenyl isocyanate (5 ml, 0.046 mols) was added to solid sodium nitrite (3g, 0.043 mols) and the reaction stirred for five hours at room temperature. Redistilled diethyl ether (30 ml) was added to the resulting pale brown solid. A white solid was filtered off, washed with water and dried under vacuum. This gave 1,3,5-triazine-2,4,6-trisphenyl cyanuric acid (the trimer of phenyl isocyanate) as a white solid (5 g, 91\%) m.p. 264-266\(^0\)C (Lit. 270\(^0\)C)\(^{91}\); \(\nu_{\text{max}}\) (nujol) 3070 w (Aromatic CH), 1715s, br (C = O), 1595 m, 1490s (Aromatic C = C), 755s, 690s cm\(^{-1}\) (Aromatic CH); m/z 357 (M\(^+\), 62%), 238 (5.5%, DIMER), 119 (100, Ph NCO\(^+\)), 91 (36, C\(_6\)H\(_5\)N\(^+\)), 77 (8, C\(_6\)H\(_5\)\(^+\)), 64 (17, C\(_5\)H\(_4\)\(^+\)), 51 (7, C\(_4\)H\(_3\)\(^+\)).
Removal of the solvent from the ether solution at reduced pressure gave a white solid (0.4 g) shown by mass spectrometry to be a mixture of phenyl isocyanate trimer, dimer, and 1,3-diphenylurea (M⁺, 212), the hydrolysis product.

9.2.2 Reaction in Aqueous Solution

Phenyl isocyanate (1 ml, 0.009 mols) was added to a stirred solution of aqueous sodium nitrite (1.0 mol dm⁻³, 20 ml). The solution gradually went yellow, darkening to red/brown as it was stirred overnight at room temperature. A brown solid (1.09 g) was filtered off. Recrystallization from ethanol gave 1,3-diphenylurea (0.88 g, 90%) m. p. 238-239°C (Lit. 150 239-240°C); v max (nujol) 3300 m (NH), 1640 s cm⁻¹ (C = O).

Traces of two other less polar products were observed by tlc but not identified.

Later re-examination found one product to be 1,3-diphenyltriazene and under the above reaction conditions it was obtained in 2% yield as measured by hplc analysis (see 9.2.12).

9.2.3 Reaction in Toluene

i) Initial Reaction

Phenyl isocyanate (0.4 ml, 3.36 mmols) was added to a solution of sodium nitrite (0.247 g, 3.58 mmols) and 18-crown-6 (1 g, 3.79 mmols) in sodium dried toluene. The solution was stirred at room temperature for 12 hours.

Unreacted sodium nitrite was filtered off from the resulting red/brown solution. Removal of the solvent at reduced pressure gave a red oil (1.53 g). Column chromatography on silica using light petroleum (b.p. 60-80°C) with ethyl acetate (0 to 50%) as eluant, gave six bands as well as baseline material. The two later bands were observed to be substantially 18-crown-6.

The second band was separated and identified as 1,3-diphenyltriazene giving identical spectral data to the authentic compound (see 9.2.4). This was obtained in 6% yield. No other products were identified.
ii) Attempted Optimization

The reaction conditions were varied in an attempt to optimize the yield of 1,3-diphenyltriazene. A crude colorimetric test was used to assay the yield of triazene, involving hydrolysis of the triazene in acid to give the diazonium ion which couples with excess NEDA (N-(1-naphthyl)ethylene diamine) to give a purple dye.

The procedure was as follows;

A sample of crude product mixture was weighed into a volumetric flask (50 ml). To this was added 10 ml of a 0.2 M solution of sulphamic acid in 1.0 M hydrochloric acid, in order to destroy the remaining nitrite. After 15 minutes a 1 ml aliquot of a 1% solution of NEDA hydrochloride was added and the solution made up to 50 ml with 1.0 M hydrochloric acid. After 24 hours the absorbance of the solution at 552 nm was measured. The test was calibrated with authentic 1,3-diphenyltriazene and the extinction coefficient found to be \(4829 + 265 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}\). From the absorbance the concentration and yield of triazene were determined.

The reactions used the following general procedure;

Sodium nitrite (0.076 g, 1.1 mmols) and 18-crown-6 (0.27 g, 1 mmol) were dissolved in toluene (75 ml) and stirred. Phenyl isocyanate (0.1 ml, 0.92 mmols) was added. After reaction the solvent was removed at reduced pressure and a sample of crude product mixture tested as described.

Results are shown in Table 45
TABLE 45: TRIAZENE YIELDS FROM REACTIONS OF PHENYL ISOCYANATE AND NITRITE ION IN TOLUENE
(CONDITIONS AS DESCRIBED IN 9.2.3)

<table>
<thead>
<tr>
<th>REACTION</th>
<th>CONDITIONS</th>
<th>TRIAZENE YIELD/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0°C for 4.75 hrs.</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>-3°C for 2 hrs.</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>-3°C. Isocyanate dissolved in toluene (100 ml) and added over 8 hrs.</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>-78°C. for 5.5 hrs. then warming to room temperature</td>
<td>18</td>
</tr>
</tbody>
</table>

9.2.4 Preparation of 1,3-Diphenyltriazene

A solution of redistilled aniline (6.98 g, 0.075 mols), concentrated HCl (11.5 ml, 0.134 mols) and ice (25 g) in water (38 ml) was stirred mechanically. To this was added a solution of sodium nitrite (2.73 g, 0.04 mols) in water (20 ml) over a period of 15 minutes. Stirring was continued for 15 mins. and then a solution of sodium acetate (10.55 g, 0.155 mols) in water (30 ml) was added over 5 mins.

The solution was stirred for 45 mins. and the solid filtered off, washed with water (150 ml) and air dried to give the crude product (5.06 g, 68.5%). The crude product was recrystallized from light petroleum (6 p. 60-80°C) to give pure 1,3-diphenyltriazene (4.56 g, 62%); m.p. 99-100°C (Lit. 99-100°C); \( \nu_{\text{max}} \) (nujol) 3200 w cm\(^{-1}\) (NH); \( \lambda_{\text{max}} \) (MeCN) 355 nm (\( \epsilon \) 20420 dm\(^3\) mol\(^{-1}\) cm\(^{-1}\)); \( \delta_{\text{H}} \) (60 MHz, CDCl\(_3\)) 7.25 m; m/z 197 (M\(^+\), 6%), 169 (4%, M\(^+\) - N\(_2\)), 168 (5, M\(^+\) - N\(_2\)H), 105 (34, C\(_6\)H\(_5\)N\(_2\)\(^+\)), 93 (14, C\(_6\)H\(_5\)NH\(_2\)\(^+\)), 77 (100, C\(_6\)H\(_5\)\(^+\)).

9.2.5 Preparation of Tetraethylammonium Nitrite

Silver nitrite (0.700 g, 4.55 mmols) was dissolved in acetonitrile (50 ml) and added to a solution of tetraethylammonium bromide (0.956 g, 4.55 mmols) in acetonitrile (50 ml). The precipitated silver bromide was removed by filtration through a pad of celite, and then removal of the solvent at reduced pressure gave tetraethylammonium...
nitrite as a white solid (0.8 g, 100%). The crude product was then recrystallized from acetonitrile-diethyl ether.

The material was shown to be pure by dissolving a sample in acetonitrile and measuring the nitrite concentration using Shinn's method\textsuperscript{100}. Tetraethylammonium nitrite was observed to be very hygroscopic, and was stored in sealed tubes in the freezer before use.

9.2.6 Reaction of Phenyl Isocyanate in Acetonitrile

Phenyl isocyanate (0.2 ml, 1.84 mmols) was added to a stirred solution of tetraethylammonium nitrite (TEAN) (0.355 g, 1.96 mmols) in acetonitrile (30 ml) cooled to 0°C. After an hour the solvent was removed at reduced pressure to give a red oily solid (0.72 g).

A sample (0.34 g) of the crude product was separated by column chromatography on alumina (neutral grade 1, 50 g) with light petroleum (b.p. 60-80°C) and ethyl acetate (0 to 100%) as eluant.

This gave two front running unidentified bands (0.0017 g and 0.0037 g), 1,3-diphenyltriazene (0.015 g, 17.5%) and a mixture of the isocyanate trimer and further triazene (0.046 g). The remainder was baseline material.

9.2.7 Reaction of 4-Nitrophenylisocyanate in Acetonitrile

Tetraethylammonium nitrite (0.087 g, 0.5 mmols) was dissolved in acetonitrile (30 ml) and the solution cooled to 0°C in an ice-bath. To this was added a solution of 4-nitrophenyl isocyanate (0.163 g, 1 mmol) in acetonitrile (50 ml). After 10 mins., 5N aqueous HCl (100 ml, 5 mmols) was added and the solution stirred for 30 mins. The solution was concentrated to approximately 2 ml, by removal of the solvent at reduced pressure. Diethyl ether (100 ml) was added, and the solution washed with water (2 x 20 ml) and dried (MgSO\textsubscript{4}). Removal of the solvent at reduced pressure gave the crude product mixture (0.16 g).

Column chromatography on neutral alumina with dichloromethane-ethyl acetate (4:1) as eluant gave 1,3-bis(4-nitrophenyl) triazene (0.093 g, 65%) observed to be identical with the authentic material (see 9.2.8).

9.2.8 Preparation of 1,3-bis(4-Nitrophenyl)Triazene\textsuperscript{94}

4-Nitroaniline (0.51 g, 3.73 mmols) was dissolved in dry, redistilled (off CaH\textsubscript{2}) nitromethane (40 ml) and stirred at room temperature. Then n-amyl nitrite (0.22 g, 1.88 mmols) was added and the reaction
stirred for 12 hours. Removal of the solvent at reduced pressure, and column chromatography of the residue on neutral alumina with dichloromethane-ethyl acetate (4:1) as eluant gave the triazene (0.32 g, 60%). Recrystallization from ethanol gave the pure material m.p. 230-233°C (decomp.) (Lit. 234°C (decomp)); νmax (nujol) 3370 w (NH), 1330 s cm⁻¹ (ArNO₂); λ max (MeCN) 395 nm; δH (90 MHz, d⁶-DMSO) 8.3 (2H, d, J 12.6 Hz, ArH), 7.7 (2H, d, J 12.6 Hz, ArH); m/z 287 (M⁺, 3%), 259 (1.4%, M⁺ - N₂), 150 (65, NO₂C₆H₄N₂⁺), 122 (100, NO₂C₆H₄⁺), 93 (31, C₆H₄O⁺), 75 (48, C₆H₃⁺), 64 (15.5, C₅H₄⁺).

9.2.9 Detection of Carbon Dioxide

TEAN (0.2 g, 1.13 mmols) was dissolved in acetonitrile (100 ml) and nitrogen bubbled through the solution, and the effluent gas then bubbled through lime water. To this was added phenyl isocyanate (25 μl, 0.23 mmols) and the solution left at room temperature. After 20 mins, the lime water was observed to go cloudy indicating the evolution of carbon dioxide. Blank reactions were carried out bubbling nitrogen through pure acetonitrile, phenyl isocyanate in acetonitrile and TEAN in acetonitrile, but none of these had any effect on the lime water.

9.2.10 Preparation of Sodium 4-Nitrophenyl Diazotate

4-Nitroaniline (1 g, 7.24 mmols) was dissolved in methanol (10 ml) saturated with HCl, and the solution stirred at 0°C. To this was added n-amyl nitrite (0.9 g, 7.7 mmols) dropwise keeping the temperature below 5°C. The solution was stirred at 0°C for five mins. and then for 10 mins. at room temperature. Diethyl ether was added to precipitate out the diazonium chloride which was filtered off and washed with ice cold ethanol-diethyl ether (1:1, 10 ml) and ice cold diethyl ether (30 ml).

The solid was dissolved in ice cold water (10 ml) and added to a mechanically stirred 18% aqueous sodium hydroxide solution (50 ml) at 30°C. The golden yellow precipitate of the diazotate was filtered off and recrystallized from absolute alcohol at 60°C to give golden yellow crystals of the sodium diazotate salt (0.93 g, 68%); m.p. 250-255°C (decomp); νmax (nujol) 1670 m, 1580 s and 1500 s (Aromatic C = C), 1330 s (ArNO₂), 850 m cm⁻¹ (Aromatic CH); λ max (MeCN) 402 nm; δH (90 MHz, CD₃CN) 8.12 (2H, d, ArH), 7.47 (2H, d, ArH); m/z (FAB, -ve ion)
166 (Å, 100%), 138 (15%, Å-N₂).

The purity of the diazotate was assessed by coupling solutions of it with 2-naphthol-3,6-disulphonic acid at pH9 in 0.1 N borax solution to give an azo dye (see Section 9.2.11). This showed the diazotate to be 98% pure.

9.2.11 Diazotate Determination

The concentration of diazotate in solution was measured by coupling the diazotate with 2-naphthol-3,6-disulphonic acid (R-salt). The concentration was determined by measurement of the absorbance due to the azo dye produced.

The test was calibrated using solutions of the corresponding diazonium ions as follows:

The substituted aniline (0.5 mmols) was dissolved in 0.1 N HCl (25 ml) with sodium nitrite (0.2 g, 3 mmols) and a trace of sodium bromide at 0°C. Aliquots (25 μl) were taken and added to a solution of R-salt (0.01 mol dm⁻³, 1 ml) in 0.1 N Borax and the solution made up to 10 ml with further 0.1 N borax. The absorbance was measured after one hour. A range of amine concentrations were used and the extinction coefficient determined.

Data are given for the compounds (Table 46) and the extinction coefficients were accurate to ± 5%.

**TABLE 46: SPECTRAL DATA FOR THE AZO DYES FORMED FROM R-SALT AND THE SUBSTITUTED ANILINES**

<table>
<thead>
<tr>
<th>R</th>
<th>λ_max/nm</th>
<th>ε/mol⁻¹ dm³ cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>490</td>
<td>31575</td>
</tr>
<tr>
<td>H</td>
<td>490</td>
<td>23530</td>
</tr>
<tr>
<td>MeO</td>
<td>508</td>
<td>22810</td>
</tr>
</tbody>
</table>

This protocol was used to determine yields of diazotate from reaction of isocyanate with excess nitrite ion. Aliquots of the reaction solution were taken and treated as above, left for 12 hours and then the absorbance measured and concentration calculated. The diazotate
solutions require longer reaction times due to the slow hydrolysis of the
diazotate ion at the pH employed. The dye was observed to be stable,
with no significant fading after 24 hours.

9.2.12 HPLC Analysis of 1,3-Diaryltriazenes

A modular hplc system was used consisting of a Cecil C5 515
double beam UV detector, a Beckman 1103 solvent delivery module and
a 20 µl injection loop. The UV detector was interfaced to a BBC
microcomputer and peak areas determined using integration software.

Reverse phase chromatography was used to separate the triazenes.
A 10µ ODs (250 x 4.6 mm) column was used with methanol-water mixtures
as eluant and a flow rate of 3.0 ml min⁻¹. The flow was monitored at
an appropriate wavelength for each triazene. The triazene concentrations
were determined by comparison of peak areas with those due to standard
triazene solutions. Details are given in Table 47.

TABLE 47: HPLC ANALYSIS OF TRIAZENES

<table>
<thead>
<tr>
<th>R</th>
<th>ELUANT (MeOH:H₂O)</th>
<th>RETENTION TIME/ MINS</th>
<th>λ  /nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>70:30</td>
<td>2.4</td>
<td>395</td>
</tr>
<tr>
<td>CF₃</td>
<td>75:25</td>
<td>2.7</td>
<td>350</td>
</tr>
<tr>
<td>H</td>
<td>70:30</td>
<td>2.0</td>
<td>355</td>
</tr>
<tr>
<td>Me</td>
<td>75:25</td>
<td>2.65</td>
<td>366</td>
</tr>
<tr>
<td>Cl</td>
<td>75:25</td>
<td>2.3</td>
<td>359</td>
</tr>
<tr>
<td>MeO</td>
<td>70:30</td>
<td>2.1</td>
<td>350</td>
</tr>
</tbody>
</table>

9.2.13 Optimization of Triazene Yields

This was achieved by running a series of small scale reactions
under a variety of conditions and measuring the yield of triazene using
the hplc assay described above. A typical reaction is as follows:
4-Nitrophenyl isocyanate (0.096 g, 0.588 mmols) was dissolved in acetonitrile (25 ml) and stirred in an ice bath. TEAN (10.4 mg, 0.059 mmols) was dissolved in acetonitrile (5 ml), the solution cooled to 0°C and then added to the isocyanate solution. Aliquots (1 ml) were withdrawn at intervals, diluted to 5 ml with methanol-water (70:30) and injected onto the hplc. Comparison of the peak area with that due to standard solutions of authentic 1,3-bis (4-nitrophenyl) triazene in acetonitrile, provided the triazene concentrations. All injections were carried out at least twice and an average taken.

Aliquots were taken over the first 20 mins. of reaction and the yields found to be constant with an average value of 82 ± 1.5% (Table 48), the error reflects the uncertainties in the sampling and hplc assay. The peak areas are themselves reproducible to ± 2% for repeat injections.

**TABLE 48:** RESULTS FROM TYPICAL OPTIMIZATION REACTION WITH 4-NITROPHENYL ISOCYANATE (0.0196 mol dm⁻³) AND TEAN (0.00196 mol dm⁻³) IN ACETONITRILE AT 0°C.

<table>
<thead>
<tr>
<th>TIME/MIN</th>
<th>TRIAZENE YIELD /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>81.5, 84</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>20</td>
<td>82.5</td>
</tr>
</tbody>
</table>

9.2.14 Preparación de 1,3-Diaryl Triazenes

i) 1,3-bis(4-Methylphenyl) Triazene

4-Methylaniline (0.4 g, 3.73 mmols) was dissolved in light petroleum (b.p. 60-80°C)-benzene (10:15, 15 ml) and stirred at room temperature. Amyl nitrite (0.22 g, 1.88 mmols) was added and the reaction stirred for 12 hours. Removal of the solvent at reduced pressure and column chromatography of the residue on neutral alumina with light petroleum (b.p. 60-80°C)-ethyl acetate (9:1) as eluant gave the triazene (0.3 g, 70%) m.p. 115-116°C (Lit. 94 116-118°C); νmax (nujol)
3200 w cm\(^{-1}\) (NH); \(\lambda\) max (MeCN) 366 nm; \(\delta\) H (90 MHz, d\(^6\)-DMSO) 7.3 (4H, d, ArH), 7.14 (4H, d, ArH), 2.35 (6H, s, Ar-CH\(_3\)).

**ii) 1,3-bis (4-Methoxyphenyl) Triazene**

4-Methoxyaniline (0.5 g, 4 mmols) was dissolved in light petroleum (b.p. 60-80\(^\circ\)) -benzene (10:15, 25 ml) and treated with \(\text{n} \) amyl nitrite (0.24 g, 2 mmols). After stirring for 12 hours the solvent was removed at reduced pressure, and column chromatography of the residue on neutral alumina with light petroleum (b.p. 60-80\(^\circ\)) -ethyl acetate (80:20) as eluant gave the triazene (0.12 g, 24%) m.p. 97-99\(^\circ\)C (Lit. 94-100\(^\circ\)) C; \(\nu\) max (nujol) 3160 w cm\(^{-1}\) (NH), 1250 s cm\(^{-1}\) (c-o); \(\lambda\) max (MeCN) 358 nm; \(\delta\) H (90 MHz, d\(^6\)-DMSO) 7.33 (4H, d, ArH), 6.87 (4H, d, ArH), 3.8 (6H, s, -OCH\(_3\)).

**iii) 1,3-bis (4-Chlorophenyl) Triazene**

4-Chloroaniline (3.6 g, 28.2 mmols) was dissolved in benzene-light petroleum (b.p. 60-80\(^\circ\)) (2:1, 75 ml) and treated with \(\text{n} \) amyl nitrite (1.65 g, 14 mmols). After stirring at room temperature for 12 hours, removal of the solvent at reduced pressure and column chromatography on neutral alumina with ethyl acetate-light petroleum (b.p. 60-80\(^\circ\)) (10:90) as eluant, gave the triazene (0.93 g, 25%) m.p. 127-129\(^\circ\)C (Lit. 128-130\(^\circ\)); \(\nu\) max 3200 w cm\(^{-1}\) (NH); \(\lambda\) max (MeCN) 359 nm; \(\delta\) H (90 MHz, d\(^6\)-DMSO) 7.42 (8H, m, ArH); m/z 265 (M\(^+\), 4%), 237 (1%, M\(^+\) - N\(_2\)), 139 (50, ClC\(_6\)H\(_4\)N\(_2\)\(^+\)), 111 (100, ClC\(_6\)H\(_4\)\(^+\)), 75 (16.5, C\(_6\)H\(_3\)\(^+\)).

**iv) 1,3-bis (4-Trifluoromethylphenyl) Triazene**

4-Trifluoromethylaniline (0.32 g, 2 mmols) was dissolved in benzene (15 ml) and \(\text{n} \) amyl nitrite (0.12 g, 1 mmol) added. After stirring at room temperature for 3 hours the solvent was removed at reduced pressure. Column chromatography on neutral alumina with ethyl acetate-light petroleum (b.p. 60-80\(^\circ\)) (1:9) gave the triazene (0.19 g, 57%) m.p. 117-119\(^\circ\)C (Lit. 154\(^\circ\)C); \(\nu\) max (nujol) 3190 w cm\(^{-1}\) (NH); \(\lambda\) max (MeCN) 352 nm; \(\delta\) H (90 MHz, d\(^6\)-DMSO) 7.78 (2H, d, ArH), 7.63 (2H, d, ArH); m/z 333 (M\(^+\) 2%), 314 (0.2% M\(^+\) - F), 173 (36, CF\(_3\)C\(_6\)H\(_4\)N\(_2\)\(^+\)), 145 (100, CF\(_3\)C\(_6\)H\(_4\)\(^+\)).
9.3 ALKYL ISOCYANATES

9.3.1 Nitrite Consumption Experiments

In these reactions the nitrite ion concentration was measured by Shinn's method.\(^\text{100}\) This involved addition of a 1% solution of sulphanilamide in 5 N HCl (2 ml) to an aliquot of reaction solution. The mixture was left for 30 seconds for diazotisation of the sulphanilamide to take place. Then a 0.1% aqueous solution of N-1-naphthyethylene diamine hydrochloride (2 ml) was added to produce a violet azo dye. This was allowed to develop for at least 20 mins. and the optical density at the absorption maximum at 541 nm measured. The extinction coefficient is 51 000 mol\(^{-1}\) dm\(^3\) cm\(^{-1}\) and so the nitrite concentration could be calculated.

A typical experiment to determine the nitrite consumption was carried out as follows:

TEAN (20 mg, 0.11 mmols) was dissolved in acetonitrile (20 ml) and DBTDA (dibutyl tin diacetate) (75 \(\mu\)l, 0.21 mmols) added. An aliquot (50 \(\mu\)l) was removed and tested by Shinn's method\(^\text{100}\), diluting the solution to 10 ml. Then cyclohexyl isocyanate (69 \(\mu\)l, 0.56 mmols) was added to the reaction solution, which was stirred for 24 hours at room temperature. After this time a further aliquot (50 \(\mu\)l) was removed and tested by Shinn's method\(^\text{100}\). From the initial and final nitrite concentrations the percentage of nitrite consumed was calculated.

9.3.2 Kinetic Studies

The rate of reaction of the alkyl isocyanates with nitrite ion was determined by monitoring the loss of nitrite by Shinn's method\(^\text{100}\). Reactions were carried out under pseudo-first order conditions with excess isocyanate.

A typical kinetic run was as follows:

A solution of sodium nitrite (0.25 g, 3.62 mmols) in DMSO (5 ml) was allowed to equilibrate at 25 \(\pm\) 0.1\(^\circ\) by immersion in a constant temperature water bath. DBTDA (50 \(\mu\)l, 0.186 mmols) and cyclohexyl isocyanate (192 \(\mu\)l, 1.5 mmols) were dissolved in DMSO (10 ml) and the solution also allowed to equilibrate at 25\(^\circ\)C for 10 mins. Reaction was
initiated by addition of an aliquot (0.1 ml) of the nitrite solution to the isocyanate solution.

Aliquots (25 μl) were withdrawn from the reaction solution with an autopipette that delivered volumes reproducible to better than ±5%. The aliquots were tested by Shinn's method \(^{100}\), making the solution up to 10 ml with distilled water. The absorbance of the solution at 541 nm was used directly as a measure of the nitrite concentration. The reaction was followed for the initial 2 or 3 half lives.

A pseudo first order plot of \(\ln (\text{OD}_t - \text{OD}_\infty)\) versus time, where \(\text{OD}_t\) is the absorbance at 541 nm at time \(t\) mins and \(\text{OD}_\infty\) the absorbance at infinity, was drawn. The best straight line was fitted to the data by regression analysis and from the gradient the value of the observed pseudo first order rate constant was determined.

The results of a typical kinetic run are given in Table 49 and a pseudo-first order plot in Fig. 24.
TABLE 49: RESULTS OF A TYPICAL KINETIC RUN FOR REACTION OF CYCLOHEXYL ISOCYANATE AND NITRITE ION.

CONDITIONS:  
- $[\text{RNCO}] = 0.15 \text{ mol dm}^{-3}$  
- $[\text{NaNO}_2] = 7.25 \times 10^{-3} \text{ mol dm}^{-3}$  
- $[\text{DBTDA}] = 0.0186 \text{ mol dm}^{-3}$  
- Solvent = DMSO; $T = 25 \pm 0.1^\circ \text{C}$

<table>
<thead>
<tr>
<th>TIME/MINS</th>
<th>$\text{OD}_{541}$</th>
<th>$\ln (\text{OD}<em>t - \text{OD}</em>\infty)$</th>
<th>$k_o/10^{-4} \text{ s}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.870</td>
<td>-0.261</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>0.760</td>
<td>-0.416</td>
<td>5.17</td>
</tr>
<tr>
<td>10</td>
<td>0.672</td>
<td>-0.559</td>
<td>4.77</td>
</tr>
<tr>
<td>15</td>
<td>0.600</td>
<td>-0.693</td>
<td>4.47</td>
</tr>
<tr>
<td>20</td>
<td>0.530</td>
<td>-0.844</td>
<td>5.03</td>
</tr>
<tr>
<td>25</td>
<td>0.480</td>
<td>-0.970</td>
<td>4.20</td>
</tr>
<tr>
<td>31</td>
<td>0.413</td>
<td>-1.162</td>
<td>5.33</td>
</tr>
<tr>
<td>35</td>
<td>0.372</td>
<td>-1.302</td>
<td>5.83</td>
</tr>
<tr>
<td>40</td>
<td>0.332</td>
<td>-1.461</td>
<td>5.30</td>
</tr>
<tr>
<td>45</td>
<td>0.295</td>
<td>-1.635</td>
<td>5.80</td>
</tr>
<tr>
<td>50</td>
<td>0.270</td>
<td>-1.77</td>
<td>4.50</td>
</tr>
<tr>
<td>60</td>
<td>0.221</td>
<td>-2.112</td>
<td>5.70</td>
</tr>
<tr>
<td>$\infty$</td>
<td>0.100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Average $k_o = (5.1 \pm 0.56) \times 10^{-4}$ $\text{s}^{-1}$

From Pseudo-First Order Plot (Fig. 24)  
$k_o = (5.1 \pm 0.1) \times 10^{-4}$ $\text{s}^{-1}$
FIG. 24: TYPICAL KINETIC RUN FOR REACTION OF CYCLOHEXYL ISOXYANATE AND NITRITE: PSEUDO-FIRST ORDER PLOT.
Runs were carried out with a range of isocyanate concentrations, and a second order plot drawn. This was linear implying reaction to be first order in cyclohexyl isocyanate, and from the gradient of this plot the second order rate constant ($k_2$) was determined (See Section 3.3).

The same protocol was used for the kinetic study of the reactions of cyclohexyl, $n$ propyl and $t$ butyl isocyanate with TEAN in acetonitrile at 25°C.

9.3.3 Product Analysis

The analysis of the deamination products from the reactions of the alkyl isocyanates were carried out by gas chromatography.

Some compounds were analysed by capillary gas chromatography using a Carlo Erba HRGC 4160 fitted with a 12 M BPO5 silica capillary column and with on column injection and an FID detector. Cyclohexyl acetate was analysed using an oven temperature of 60°C and a helium carrier gas pressure of 0.5 kg cm$^{-2}$, and gave a retention time of 6.2 mins. $t$ butyl acetate was analysed at a temperature of 40°C, with a helium carrier gas pressure of 0.4 kg cm$^{-2}$, and had a retention time of 1.4 mins. Injections of 0.3 µl were employed.

The remainder of the compounds were analysed using a Perkin Elmer F11 gas chromatograph fitted with an FID detector. Stainless steel columns (2 m x 1/8"), packed with an appropriate stationary phase, were employed. Injection volumes of 1 µl were used.

Details for particular compounds were as follows:

i) Cyclohexene in DMSO

The column was packed with Chromosorb 103 80-100 mesh, and used at 120°C with a carrier gas (N$_2$) pressure of 30 psi. The cyclohexene had a retention time of 3.7 minutes and DMSO, 19 minutes. This system gave broad peaks, and so peak areas were determined by cutting out and weighing the peaks from photocopied chromatograms. Cyclohexanol gave a broad peak at 17.7 mins., close to the solvent. The approximate concentrations determined from this agreed with those from the more efficient system described below.

ii) Cyclohexanol in DMSO

A column packed with 15% Carbowax 1500 on Chromosorb W 80/100
mesh was used. A temperature of 140°C and nitrogen carrier gas pressure of 30 psi were employed. The cyclohexanol and DMSO had retention times of 2.6 and 8 mins. respectively. The concentrations were determined using peak heights.

iii) Cyclohexanol and Cyclohexanone in Acetonitrile

Using a column packed with 15% Carbowax 1500 on Chromosorb W 80/100 mesh, an oven temperature of 140°C, and a nitrogen carrier gas pressure of 30 psi, the cyclohexanol and cyclohexanone had retention times of 2.6 and 2.95 minutes respectively.

iv) Cyclohexene in Acetonitrile

A Porapak Q 80-100 mesh column was used at 235°C with a nitrogen carrier gas pressure of 40 psi giving a retention time of 54 minutes for cyclohexene.

v) Butyl Alcohol

A column packed with SP1000 on Chromosorb 100-120 mesh was employed. The oven temperature was 50°C and carrier gas (N₂) pressure 30 psi, giving a retention time of 1.8 minutes. Concentrations were calculated using peak heights.

vi) n-Propyl alcohol and n-Propyl acetate

n-Propyl acetate was determined using a column packed with Porapak Q 80-100, at 205°C with a nitrogen carrier gas pressure of 40 psi. The retention time was 9.4 mins.

n-Propyl alcohol was analysed using the same system at a lower temperature of 170°C. The retention time was 5.5 mins.

In all analyses the concentrations were determined by comparison of the peak heights (or areas for broad peaks) due to standard solutions of the pure authentic compounds, with those obtained from reaction solutions. All samples were injected 2 or 3 times and an average taken. Peak heights (and areas) were reproducible to better than ±10%.

Reaction solutions for product analysis were all made up in 5 ml of the appropriate solvent, with the required amounts of nitrite (sodium nitrite in DMSO and TEAN in acetonitrile), isocyanate and DBTDA. After 24 hours at room temperature the solutions were analysed.

Acetonitrile solutions were injected directly onto the gas chromatograph.
DMSO solutions were generally diluted with 30% aqueous methanol and filtered prior to injection, however the work-up did not alter product yields.

9.3.4 Preparation of Acetates

i) Cyclohexyl Acetate

Cyclohexanol (10 ml, 0.096 mols) was dissolved in 50% pyridine-acetic anhydride (100 ml) with 4-dimethylamino pyridine (10 mg, 0.08 mmols) and stirred for 12 hours at room temperature. Water (150 ml) was added slowly and the solution extracted with diethyl ether (2 x 100 ml). The extracts were washed with 0.1 N hydrochloric (3 x 70 ml), dried (MgSO₄) and the solvent removed at reduced pressure to give the crude acetate (12 g, 85%). Distillation at reduced pressure gave the pure material; \( \eta^2_{D} 1.4396 \) (Lit. 1.4401); \( \nu_{\text{max}} \) (neat) 1740 s (C = O), 1240 s cm\(^{-1}\) (C - O); \( \delta_H \) (90 MHz, CDCl₃) 4.75 (1H, m, -CHOAc), 2.03 (3H, s, O-CH₃), 1.6 (10H, m, cyclohexyl protons).

ii) n-Propyl Acetate

This was prepared as described for the cyclohexyl acetate in 60% yield; \( \eta^2_{D} 1.3829 \) (Lit. 1.3842); \( \nu_{\text{max}} \) (neat) 1740 s (C = O), 1260 s cm\(^{-1}\) (C - O).

iii) t-Butyl Acetate

This was prepared by a literature method \(^{155}\) b.p. 96-98°C (Lit. 97-98°C); \( \eta^2_{D} 1.3852 \) (Lit. 1.3853); \( \nu_{\text{max}} \) (neat) 1730 s (C = O), 1250 s cm\(^{-1}\) (C - O); \( \delta_H \) (90 MHz, CDCl₃) 1.96 (3H, s, -OCH₃), 1.45 (9H, s, -C(CH₃)₃).

9.4 Carbodiimides

9.4.1 Preparation of Ethyl, 4-Nitrophenyl Carbodiimide

i) Preparation of 1-Ethyl-3(4-nitrophenyl)thiourea

4-Nitrophenyl isothiocyanate (1.84 g, 10 mmols) was dissolved in acetonitrile (75 ml) and ethylamine (5 ml, 77 mmols) added to the stirred solution at room temperature. After 10 minutes the solvent and excess amine were removed at reduced pressure to give the crude thiourea (2.14 g, 93%). Recrystallization from ethyl acetate yielded the pure material m.p. 155-156°C (Found: M⁺ 225.0577. C₉H₁₁N₃O₂S requires 225.057198); \( \nu_{\text{max}} \) (nujol) 3234 m cm\(^{-1}\) (NH); \( \delta_H \) (90 MHz, CD₃CN)
8.375 (1 H, s, br, ArNHCS-), 8.15 (2 H, d, ArH), 7.7 (2H, d, ArH), 6.925 (1H, s, br, CSNHCH₂CH₃), 3.6 (2H, m, -NHCH₂CH₃), 1.65 (3H, t, J 6.6Hz, NHCH₂CH₃); m/z 225 (M⁺, 100%), 192 (14%, M⁺ - HS), 180 (15, NO₂C₆H₅NCS⁺), 138 (90, M⁺ - CH₃CH₂NCS), 88 (34, CH₃CH₂NHCS⁺), 44 (43, CH₃CH₂NH⁻).

ii) Preparation of Carbodiimide

1-Ethyl-3(4-nitrophenyl)thiourea (0.75 g, 3.33 mmols) was dissolved in acetonitrile (75 ml) and stirred at room temperature. Mercuric oxide (1 g, 4.6 mmols), magnesium sulphate (0.5 g) and a trace of sulphur were added. The solution was stirred for 100 minutes, then further magnesium sulphate (2 g) added and the solvent removed at reduced pressure. The residue was taken up in acetonitrile (50 ml) and the solid filtered off. Removal of the solvent at reduced pressure gave the crude product as a yellow oil (0.5 g, 60%). Kugelrohr distillation gave the pure material b.p. 100°C/3 x 10⁻³ mm Hg (Found: C, 56.5; H, 5.1; N, 21.9. C₉H₉N₂O₂ requires C, 56.5; H, 4.75; N, 22.0); νmax (neat) 2141 s (N = C = N), 1340 s cm⁻¹ (ArNO₂); δH (90 MHz, CD₃CN) 8.13 (2H, d, ArH), 7.20 (2H, d, ArH), 3.55 (2H, q, J 7Hz, -N-CH₂CH₃), 1.34 (3H, t, J 7Hz, -NCH₂CH₃); m/z 191 (M⁺, 100%), 176 (25%, M⁺ -CH₃), 163 (26, M⁺ -C₂H₄), 133 (29, 163⁺ -NO), 117 (18, 163⁺ -NO₂), 90 (43, C₆H₄N⁺), 76 (13, C₆H₄⁺).

9.4.2 Preparation of Diphenylcarbodiimide

i) Preparation of 1,3-Diphenylthiourea

Phenyl isothiocyanate (2 g, 0.0148 mols) was dissolved in a solution of aniline (0.68 g, 7.4 mmols) in diethyl ether (20 ml). The solution was left at room temperature and diphenyl thiourea crystallized out. The product was filtered off, washed with diethyl ether and air dried (1.66 g, 100%) m.p. 154-155°C. (Lit. 156 154°C); νmax (nujol) 3200 s (NH), 1280 m (C = S), 760 s cm⁻¹ (ArH); δH (90 MHz, CDCl₃) 7.98 (2 H, s, br, NH), 7.38 (10H, m, ArH).

ii) Preparation of Diphenylcarbodiimide

Diphenyl thiourea (1.5 g, 6.7 mmols) was dissolved in acetonitrile (75 ml) and the solution stirred at room temperature. Mercuric oxide (2.17 g, 10 mmols), magnesium sulphate (1 g) and a catalytic amount of
sulphur (10 mg) were added, and the solution stirred for 1½ hours. Further magnesium sulphate (2 g) was added and the solvent removed at reduced pressure. The residue was taken up in acetonitrile (50 ml), filtered, and the solvent removed at reduced pressure to give the crude product as a colourless oil (1.17 g, 80%). The carbodiimide was then redistilled under vacuum b.p. 100°C/0.1 mm Hg (Lit. 155°C/0.2 mm Hg);

\[ \nu_{\text{max}} \text{ (neat)} = 2120 \text{ s}^{-1} \text{ (N = C = N)}; \delta H (90 \text{ MHz, CDCl}_3) = 7.2\]

(10 H, m, ArH); m/z 194 (M⁺, 100%), 91 (16%, C₆H₅N⁺), 77 (26, C₆H₅⁺), 51 (14, C₄H₃⁺).

9.4.3 Measurement of Triazene Yields

The yields of 1,3-bis (4-nitropheryl) triazene and 1,3-diphenyl-triazene were measured using the HPLC assay described in section 9.2.13.

A typical reaction is as follows;

Diphenylcarbodiimide (0.11 g, 0.58 mmols) was dissolved in acetonitrile (10 ml) and cooled to 0°C. A solution of TEAN (10.2 mg, 0.058 mmols) in acetonitrile (5 ml) was then added. After five minutes an aliquot (1 ml) was withdrawn and made up to 5 ml with 30% aqueous methanol. The concentration of triazene was then determined by hplc.

For both carbodiimides the reactions carried out on this scale were virtually instantaneous, however aliquots were taken between 5 and 20 minutes and an average yield taken. No significant change occurred over this time.

The eluant used to analyse the 1,3-bis(4-nitropheryl)triazene was changed from 30% water: 70% methanol to 35% water: 65% methanol to obtain better separation from the coloured hydrolysis products of the carbodiimide.

Measurement of diazotate yields were carried out using the protocol described in Section 9.2.12.

9.4.4 Isolation of Nitrosourea

The carbodiimide (73) (0.08 g, 0.42 mmols) was dissolved in acetonitrile (20 ml) and stirred at 0°C. TEAN (0.074 g, 0.42 mmols) was dissolved in acetonitrile (10 ml) and added to the stirred solution.

After 90 minutes at 0°C, 5 N Hydrochloric acid (83 μl, 0.42 mmols)
was added and the solution left for a further 10 minutes. The solution was concentrated to 10 ml by removal of the solvent at reduced pressure. Then dichloromethane (50 ml) was added, and the solution washed with water (30 ml) and dried (MgSO₄). Removal of the solvent at reduced pressure gave the crude product (0.072 g).

Column chromatography on neutral alumina (12 g) with dichloromethane as eluant gave a separated band (0.011 g) with the following data;

\[ \nu_{\text{max}} \text{(nujol)} \ 3412 \ \text{m (NH)}, \ 1700 \ \text{s (C = O)}, \ 1600 \ \text{s (Amide II)}, \ 1340 \ \text{s cm}^{-1} \ \text{(ArNO)} \]

\[ \delta H \ (90 \ \text{MHz, CD₃CN}) \text{ showed a mixture of two compounds.} \]

Major (60%): \[ 8.3 \ (2H, \text{d, ArH}), \ 7.68 \ (2H, \text{d, ArH}), \ 2.35 \ (2H, \text{m, NHCH₂CH₃}), \ 1.1 \ (3H, \text{t, NHCH₂CH₃}). \]

Minor (40%): \[ 8.1 \ (2H, \text{d, ArH}), \ 7.6 \ (2H, \text{d, ArH}), \ 3.2 \ (2H, \text{m, -NHCH₂CH₃}), \ 1.1 \ (3H, \text{t, NHCH₂CH₃}). \]

The data is consistent with (80) as the major product and (124) as the minor product.

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} & \quad \text{C} & \quad \text{NHCH₂CH₃} \\
\text{N} & \quad \text{O} & \quad \text{C} & \quad \text{NHCH₂CH₃}
\end{align*}
\]

(80)  (124)

9.4.5 Nitrosation of 1-ethyl-3(4-nitropheryl)urea

i) Preparation of Urea

4-Nitrophenyl isocyanate (1 g, 6.1 mmols) was dissolved in acetonitrile (50 ml) and ethylamine (5 ml, 76 mmols) added to the stirred solution. Removal of the solvent at reduced pressure gave the crude product (1.26 g, 99%); \[ \nu_{\text{max}} \text{(nujol)} \ 3300 \ \text{nm (NH)}, \ 1640 \ \text{s cm}^{-1} \ \text{(C = O)}; \]

\[ \delta H \ (90 \ \text{MHz, \text{d}^6 - DMSO}) \ 9.22 \ (1H, \text{s, ArNHCO}), \ 8.11 \ (2H, \text{d, ArH}), \ 7.6 \ (2H, \text{d, ArH}), \ 6.4 \ (1H, \text{t, CONHCH₂CH₃}), \ 3.12 \ (2H, \text{m, NHCH₂CH₃}), \ 1.1 \ (3H, \text{t, NHCH₂CH₃}). \]

\[ m/z \ 209 (M^+, \text{13%}), \ 179 (4\%, M^+ - \text{NO}), \ 138 (100, M^+ - \text{CH₃CH₂NCO}), \ 108 (40, 138^+ - \text{NO}), \ 92 (27, \]
The compound was pure by n.m.r. implying approx. 95% purity and was used without further purification.

ii) Nitrosation

1-Ethyl-3-(4-nitrophenyl)urea (0.089 g, 0.425 mmols) and sodium acetate (0.17 g, 2.1 mmols) were dissolved in THF (30 ml) and stirred at 0°C. Dinitrogen tetroxide (27 μl, 0.426 mmols) was added and the solution stirred at 0°C for 30 minutes.

The solvent was removed at reduced pressure. The residue was taken up in dichloromethane (50 ml), washed with 5% aqueous sodium carbonate (2 x 30 ml), dried (MgSO₄) and the solvent removed at reduced pressure to give the nitrosourea (0.085 g, 84%) m.p. 104°C (decomp); (Found: M⁺ 238.0704. C₉H₁₀N₄O₄ requires 238.07025); νmax (nujol) 3294 m (NH), 1730 s (C = O), 1608 m (Amide II), 1332 s cm⁻¹ (ArNO₂); δH (90 MHz, CDCl₃) 9.15 (1H, s, br, ArNHCO), 8.3 (2H, d, ArH), 7.79 (2H, d, ArH), 3.97 (2H, q, J 7.1 Hz, -N(NO)CH₂CH₃), 1.10 (3H, t, J 7.1 Hz, -N(NO)CH₂CH₃); m/z 238 (M⁺, 10%), 164 (100%, M⁺-CH₃CH₂NNOH), 138 (14, NO₂C₆H₄NH⁺), 134 (29, NO₂C₆H₄N⁺), 118 (12, C₆H₄NHCO⁺), 99 (66, C₆H₄N⁺), 74 (30, CH₃CH₂NNO⁺).

9.5 AROMATIC ISOTHIOCYANATES

9.5.1 Preparation of 4-Nitrophenyl Isothiocyanate

4-Nitroaniline (2 g, 14.5 mmols) was dissolved in chloroform (40 ml) and added to a vigorously stirred emulsion of thiophosgene (2.5 ml, 33 mmols) in water (60 ml) at room temperature. After two hours the chloroform layer was separated, washed with water (30 ml) and dried (CaCl₂). Removal of the solvent at reduced pressure gave the crude product which was recrystallized from light petroleum (b.p. 60-80°C), giving 4-nitrophenyl isothiocyanate (2.34 g, 90%) m.p. 120-121°C (Lit. 121-122°C); νmax (nujol) 2105 s (N = C = S), 1337 s (ArNO₂), 851 s cm⁻¹ (ArH); λmax (MeCN) 312 nm (ɛ 42462 mol⁻¹ cm⁻¹ dm³⁻²); δH (90 MHz, CD₃CN) 8.19 (2H, d, ArH), 7.42 (2H, d, ArH); m/z 180 (M⁺, 100%), 150 (24%, M⁺ - NO), 134 (39, M⁺ - NO₂), 122 (18, M⁺ - NCS).
9.5.2 Preparation of 4-Chlorophenyl Isothiocyanate

This was prepared from resublimed 4-chloroaniline in 82% yield using the thiophosgene method described for the 4-nitro derivative.

Distillation at reduced pressure yielded the pure material m.p. 44-45 °C (Lit. 45 °C); \( \nu \text{ max (nujol)} 2045 \text{ s cm}^{-1} (N = C = S); \) \( \lambda \text{ max (MeCN)} 272 \text{ nm}. \)

9.5.3 Preparation of 4-Methoxyphenyl Isothiocyanate

This was prepared from resublimed 4-methoxyaniline in 70% yield, using the thiophosgene method. Distillation at reduced pressure gave the pure material b.p. 82 °C/0.15 mmHg (Lit. 126-129 /3.0 mmHg) \( \nu \text{ max (neat)} 2100 \text{ s cm}^{-1} (N = C = S), 1220 \text{ s cm}^{-1} (C - O); \lambda \text{ max (MeCN)} 272 \text{ nm}. \)

9.5.4 Measurement of Diazotate and Triazene Yields

Yields of triazenes and diazotates from the aromatic isothiocyanates were measured using the methods described for the corresponding isocyanates.

9.5.5 Kinetic Studies of Phenyl Isothiocyanate

The general kinetic method was as follows;

A solution of TEAN in acetonitrile (3 ml) was placed in a 10 mm cuvette. The cuvette was placed in the thermostatted cell holder of the UV spectrophotometer and allowed to equilibrate at 25 ± 0.1 °C. After 15 minutes the reaction was started by adding a small volume (10 - 20 \( \mu l \)) of a solution of phenyl isothiocyanate in acetonitrile, using an automatic adjustable pipette accurate to ± 5%.

The spectra of the solution was then scanned from 240 to 500 nm automatically at repeated intervals. In some cases the absorbance was monitored at a constant wavelength, either 276 nm for the loss of starting material or 420 nm for the formation of product.

The reaction was monitored for at least 3 half lives and an infinity spectra measured after 10 half lives.

A pseudo first order plot of \( \ln (OD_t - OD_\infty) \) versus time was drawn, where \( OD_t \) is the optical density at time t, and \( OD_\infty \) the optical density at infinity. From the gradient the pseudo first order rate constant was determined.
Results of a typical kinetic run are given in Table 50 and Fig. 25, for the rate of loss of the absorbance due to the isothiocyanate. The results for the formation of the product absorbance from the same kinetic run are given in Table 51 and Fig. 26. It can be seen that the rates of both processes are the same.

**TABLE 50: RESULTS FROM A TYPICAL KINETIC REACTION OF PHENYL ISOTHIOCYANATE AND TEAN IN ACETONITRILE AT 25°C.**

**LOSS OF ISOThIOCYANATE ABSORBANCE.**

**CONDITIONS:**

\[
\begin{align*}
\text{[RNCS]} & = 0.576 \times 10^{-4} \text{ mol dm}^{-3} \\
\text{[TEAN]} & = 23.30 \times 10^{-4} \text{ mol dm}^{-3}
\end{align*}
\]

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<th>k_\text{ols} / 10^{-4} s^{-1}</th>
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<tr>
<td>49</td>
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Average \(k_\circ = (8.98 \pm 1.45) \times 10^{-4} \text{ s}^{-1}\)

From Plot (Fig. 25)

\(k_\circ = (9.2 \pm 0.2) \times 10^{-4} \text{ s}^{-1}\)
FIG. 25: PSEUDO FIRST ORDER PLOT FOR LOSS OF ISOThIOCYANATE FROM TYPICAL KINETIC RUN (TABLE 50).
**TABLE 51:** RESULTS FROM TYPICAL KINETIC REACTION OF PHENYL ISOTHIOCYANATE AND TEAN IN ACETONITRILE AT 25°C. FORMATION OF PRODUCT

**CONDITIONS:**

\[
\begin{align*}
[r_{\text{NC}}] &= 0.576 \times 10^{-4} \text{ mol dm}^{-3} \\
[\text{TEAN}] &= 23.30 \times 10^{-4} \text{ mol dm}^{-3}
\end{align*}
\]

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Average \(k_o\) = (9.15 \pm 1.17) \times 10^{-4} \text{ s}^{-1}

From Plot (Fig. 26)

\(k_o = (9.25 \pm 0.2) \times 10^{-4} \text{ s}^{-1}\)
FIG. 26: PSEUDO FIRST ORDER PLOT FOR FORMATION OF PRODUCT FROM TYPICAL KINETIC REACTION (TABLE 51).
For reactions where the variations in the infinity absorbance due to the product were studied, reaction solutions were made up to constant volume in volumetric flasks, using pre-warmed solutions. Aliquots (3 ml) were then transferred into cuvettes and the kinetics run as before. Rates for the two methods were the same.

9.5.6 Trapping Experiments

9.5.6.1 Chlorotrimethylsilane

TEAN (0.0444 g, 0.252 mmols) was dissolved in acetonitrile (90 ml) and the solution cooled to 0°C. To the stirred solution was added phenyl isothiocyanate (25 µl, 0.21 mmols). Reaction was followed by removing samples, diluting into acetonitrile and measuring the absorbance at 420 nm. When the absorbance had reached a maximum, dry redistilled chlorotrimethylsilane (300 µl, 2.36 mmols) was added. The absorbance at 420 nm was reduced to zero.

Removal of the solvent at reduced pressure gave a yellow oil (0.107 g) and tlc examination (silica, dichloromethane) showed at least nine compounds.

9.5.6.2 Dimethyl Sulphate

TEAN (0.317 g, 1.80 mmols) was dissolved in acetonitrile (500 ml) and phenyl isothiocyanate (180 µl, 1.5 mmols) added to the stirred solution, cooled to 0°C. Reaction was followed as above. After 50 minutes redistilled dimethyl sulphate (500 µl, 5.3 mmols) was added.

After a further 30 mins. the solvent was removed at reduced pressure. The crude product mixture was washed with water (40 ml), extracted with dichloromethane (100 ml) and dried (MgSO₄). Removal of the solvent gave a yellow oil (0.44 g).

Examination by tlc (silica, dichloromethane) showed 10 products. Column chromatography on silica with dichloromethane as eluant, gave three bands pure by tlc. These were examined by mass spectrometry. Band 1: (10.6 mg, 22%); m/z 256 (M⁺, S₈), 192 (20%, S₆), 160 (32, S₅), 128 (45, S₄), 92 (18, S₃), 64 (100, S₂).

This band appeared to be elemental sulphur, and this was confirmed by a tlc comparison with the authentic compound.
Band 2 : 2-Nitrophenol (ca. 4%); m/z 139 (M⁺, 100%); 122 (8%, M⁺ - OH), 109 (18, M⁺ - NO), 93 (12, M⁺ - NO₂); 81 (11, M⁺ - CNO₂), 65 (20, C₅H₅⁺), 53 (10, C₅H₄⁺), 39 (22, C₃H₃⁺).

Band 3 : 4-Phenylnazophenol (11%); m/z 198 (M⁺, 59%), 121 (35%, M⁺ - C₆H₅), 105 (8, C₆H₅N⁺), 93 (10, C₆H₅O⁺), 77 (7, C₆H₅⁺), 65 (36, C₅H₅⁺), 51 (22, C₄H₃⁺), 39 (25, C₃H₃⁺).

9.5.7 Analysis for Isocyanates

9.5.7.1 Phenyl Isocyanate

The authentic phenyl urethane was prepared by dissolving phenyl isocyanate (1 g, 8.35 mmols) in methanol. After 10 minutes the solvent was removed to give the phenyl urethane (1.39 g, 100%); m.p. 45-47°C (Lit. 156-157°C); δH (90 MHz, CDCl₃) 7.36 (5H, m, ArH), 7.18 (1H, s, br, ArNHCO-), 3.77 (3H, s, -OCH₃).

The phenyl urethane was analysed using a Carlo Erba 4160 HRGC fitted with a 12 m BPO5 silica capillary column, with on column injection and an FID detector. An oven temperature of 120°C and a helium carrier gas pressure of 0.45 kg cm⁻². The retention time was 9.5 mins, and the corresponding thiourethane had a retention time of 7.2 mins. Injection volumes of 0.3 µl were used. Concentrations were determined by comparison of peak heights with those due to standard solutions of the authentic urethane. Peak heights were reproducible to ±10%.

A typical reaction was carried out as follows:

TEAN (0.021 g, 0.12 mmols) was dissolved in acetonitrile (10 ml) and the solution stirred and cooled to 0°C. Phenyl isothiocyanate (70 µl, 0.58 mmols) was added, followed by methanol (10 ml) five mins. later.

The reaction solution was left for one hour. Then samples were injected directly onto the gas chromatograph.

A control experiment showed that phenyl isocyanate in acetonitrile was quantitatively trapped by methanol under the same conditions.

9.5.7.2 4-Nitrophenyln Isocyanate

The authentic urethane was prepared as for the phenyl derivative in quantitative yield m.p. 178-179°C (Lit. 159°C 178-180°C).
Analysis was carried out using the same glc system as above with an oven temperature of 150°C and a helium gas pressure of 0.4 kg cm⁻². However detection was carried out using a Thermo electron model 610 nitrogen analyser on the nitrogen mode, using an interface temperature of 250°C and a pyrolyser temperature of 700°C. The retention time of 4-Nitrophenyl urethane was 5.75 mins.

A typical reaction was as follows:

4-Nitrophenyl isothiocyanate (0.126 g, 0.7 mmols) and TEAN (0.0258 g, 0.15 mmols) were dissolved in acetonitrile (25 ml) at 0°C. After one minute methanol (25 ml) was added and the solution left for one hour. The solvent was removed at reduced pressure and the residue taken up in toluene - THF (9:1, 10 ml) and a sample injected onto the gas chromatograph. The urethane concentration was determined by comparison with standard solutions.

9.5.8 Nitrite Consumption Experiments

The determination of nitrite was carried out by hplc analysis. A modular system was used comprising a Cecil C5 515 double beam UV detector, a Beckman 110B solvent delivery module and a 20 µl injection loop. A PRP 1 column was used with an eluant of 0.05 M aqueous borax containing 7.5% acetonitrile and 0.5% tetrabutyl-ammonium hydroxide. The flow was monitored at 214 nm. A flow rate of 1.2 ml per minute gave a retention time of 3.3 mins for nitrite ion (Fig. 27). The peaks were integrated using a LDC/Milton Roy Cl-10B computing integrator.

The system was calibrated using standard solutions of TEAN in acetonitrile, diluted into water to give only 10% organic solvent.

Reaction solutions were analysed by taking an aliquot (1 ml) diluting into acetonitrile (10 ml) and then further diluting by a factor of 10 with distilled de-ionized water. From the final concentration of nitrite the percentage consumption was determined.

Reactions carried out in DMSO were treated in a similar fashion. Aliquots (100 µl) were taken and diluted directly into water (10 ml). The DMSO gave a peak on the hplc but this did not interfere with the nitrite ion peak (Fig. 28.).
FIG. 27: HPLC TRACE FOR NITRITE ANALYSIS FROM ACETONITRILE SOLUTION

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START  AUT2

RUN TIME  4.94

NORMALIZATION METHOD USING AREA

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TOTAL  413964  100.000000

FIG. 28: HPLC TRACE FOR NITRITE ANALYSIS FROM DMSO SOLUTION

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RUN TIME  5.20

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TOTAL  336786  100.000000
9.5.9 kinetics of 4-substituted phenyl isothiocyanates

The kinetics of the reactions of 4-methyl, 4-methoxy and 4-chlorophenyl isothiocyanate with nitrite ion were measured by UV spectrophotometry using the method described for phenyl isothiocyanate (see Section 9.5.5).

Kinetics were carried out on the loss of the absorbance due to the isothiocyanate. Working with excess nitrite over isothiocyanate all three compounds gave good pseudo-first order kinetics for the decomposition of the starting material.

4-Methyphenyl isothiocyanate was monitored at 280 nm. A typical kinetic run is given in Table 52 and a pseudo first order plot in Fig. 29.

4-Methoxyphenyl isothiocyanate was monitored at 272 nm. A typical kinetic run is given in Table 53 and a pseudo-first order plot in Fig. 30.

4-Chlorophenyl isothiocyanate was monitored at 272 nm. A typical kinetic run is given in Table 54 and a pseudo first order plot in Fig. 31.
TABLE 52: TYPICAL KINETIC RUN FOR REACTION OF 4-METHYLPHENYL ISO THIOCYANATE AND TEAN IN ACETONITRILE AT 25°C.

CONDITIONS: 
\[ [RNCS] = 1.21 \times 10^{-4} \text{ mol dm}^{-3} \]
\[ [TEAN] = 10 \times 10^{-4} \text{ mol dm}^{-3} \]

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<th>(k_o/10^{-4} \text{ s}^{-1})</th>
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\(^a\) OD is quoted as number of squares on chart paper

Average \(k_o = (2.185 \pm 0.24) \times 10^{-4} \text{ s}^{-1}\)

From Plot (Fig. 29)

\(k_o = (2.08 \pm 0.03) \times 10^{-4} \text{ s}^{-1}\)
FIG. 29: PSEUDO-FIRST ORDER PLOT FOR TYPICAL KINETIC REACTION OF 4-METHYLPHENYL ISOTHIOCYANATE AND NITRITE ION (TABLE 52).
### TABLE 53: TYPICAL KINETIC REACTION OF 4-METHOXYPHENYL ISOThIOCYANATE AND TEAN IN ACETONITRILE AT 25°C.

**CONDITIONS:**
- \([\text{RNCS}] = 7.5 \times 10^{-5} \text{ mol dm}^{-3}\)
- \([\text{TEAN}] = 2.67 \times 10^{-3} \text{ mol dm}^{-3}\)

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Average \(k_{o} = (2.39 \pm 0.69) \times 10^{-4} \text{ s}^{-1}\)

From Plot (Fig. 30)

\(k_{o} = (2.417 \pm 0.032) \times 10^{-4} \text{ s}^{-1}\)

\(a - \text{OD quoted as number of squares on chart paper}\)
FIG. 30: PSEUDO-FIRST ORDER PLOT FOR TYPICAL KINETIC REACTION OF 4-METHOXYPHENYL ISOTHIOCYANATE AND NITRITE ION (TABLE 53).
### TABLE 54: TYPICAL KINETIC REACTION OF 4-CHLOROPHENYL ISOThIOCYANATE AND TEAN IN ACETONITRILE AT 25°C.

**CONDITIONS:**

- $[\text{RNCS}] = \text{ca. } 3 \times 10^{-5} \text{ mol dm}^{-3}$
- $[\text{TEAN}] = 1.9 \times 10^{-4} \text{ mol dm}^{-3}$

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<th>$\text{OD}_{272}^t$</th>
<th>$\text{In} (\text{OD}<em>t - \text{OD}</em>\infty)$</th>
<th>$k_o / 10^{-4} \text{ s}^{-1}$</th>
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<td>23.1</td>
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<td>18.8</td>
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<tr>
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<td>12</td>
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Average $k_o = (3.52 \pm 0.4) \times 10^{-4} \text{ s}^{-1}$

From Plot (Fig. 31)

$k_o = (3.61 \pm 0.05) \times 10^{-4} \text{ s}^{-1}$

$a$ - $\text{OD}_t$ quoted as number of squares on chart paper
FIG. 31: PSEUDO FIRST ORDER PLOT FOR TYPICAL KINETIC REACTION OF 4-CHLOROPHENYL ISOTHIOCYANATE AND NITRITE (TABLE 54).
9.5.10 15N n.m.r. Studies

i) Synthesis of 15N-labelled TEAN

Sodium nitrite - 15N (99 atom % 15N, 96.5% chemical purity) was obtained from MSD isotopes. The labelled sodium nitrite (0.5 g, 7.14 mmols) was dissolved in distilled water (2 ml) and added to a solution of silver nitrate (2.5 g, 0.015 mmols) in distilled water (5 ml). The precipitate of silver nitrite - 15N was filtered off and dried under vacuum. The yield was 87%.

The silver nitrite - 15N was then used to prepare TEAN - 15N using the method described in section 9.2.5. The yield after recrystallization from acetonitrile-diethyl ether was 66.5% (based on initial sodium nitrite - 15N).

ii) Spectra of Reaction Solution

The 15N n.m.r. spectra were run on a Bruker WM-250 instrument, and chemical shifts measured relative to the resonance due to 15NH4+, in an external standard solution of aqueous ammonium nitrate solution.

The reaction solution was made up as follows:

TEAN - 15N (0.05 g, 0.283 mmols) was dissolved in d3-acetonitrile (2 ml) and the solution cooled to 0°C. To the stirred solution was added phenyl isothiocyanate (23 μl, 0.192 mmols). The reaction solution was allowed to warm to room temperature and then transferred to a 10 mm n.m.r. tube, and the spectra measured.

The n.m.r. spectra of a solution of TEAN - 15N in acetonitrile was measured as a blank. Reaction with phenyl isocyanate was carried out under the same conditions.

9.6 ALKYL ISOThIOCYANATES

9.6.1 Kinetics

Kinetics of the reaction of cyclohexyl isothiocyanate and ethyl isothiocyanate with nitrite ion were determined by measuring the loss of nitrite by Shinn's method. 100

Typically, cyclohexyl isothiocyanate (0.423 g, 3 mmols) was dissolved in acetonitrile (10 ml) and allowed to equilibrate at 25 ± 0.1°C
by immersion in a thermostatted water bath. A solution of TEAN (0.639 g, 3.63 mmols) in acetonitrile (5 ml) was prepared, and after it had equilibrated, an aliquot (100 μl) was added to the isothiocyanate solution to start reaction. Aliquots (25 μl) were withdrawn at intervals and tested by Shinn's method, making the solution up to 10 ml. The absorbance at 541 nm was determined.

The results of a typical kinetic run are given in Table 55. Fig. 32 shows a plot of absorbance at 541 nm versus time, detailing the fast reaction observed initially and the infinity value taken. Fig. 33 then shows the pseudo first order plot.

Similar results were obtained for the ethyl derivative.

9.6.2 Analysis for Cyclohexyl Isocyanate

Analysis for cyclohexyl isocyanate was carried out using a Carlo Erba 4160 HRGC, fitted with a 12 m BPO5 silica capillary column with on-column injection and an FID detector. A helium carrier gas pressure of 0.45 kg cm$^{-2}$ was employed.

Temperature programming was used to separate the cyclohexyl isocyanate from cyclohexyl isothiocyanate. The temperature was maintained at 60°C for 6 minutes after sample injection, then warmed to 120°C at 20°C min$^{-1}$, and kept at this temperature for three minutes. Under these conditions cyclohexyl isocyanate had a retention time of 3.85 minutes and the cyclohexyl isothiocyanate a time of 9.3 minutes.

Reaction mixtures were injected directly onto the gas chromatograph. Samples of 0.3 μl were used.

Concentrations were determined by comparison of peak heights with those due to standard solutions of cyclohexyl isocyanate in acetonitrile.
**TABLE 55:** TYPICAL KINETIC RUN FOR REACTION OF CYCLOHEXYL ISOThIOCYANATE AND TEAN IN ACETONITRILE AT 25 ± 0.1°C.

**CONDITIONS:**

\[
\begin{align*}
[\text{TEAN}] & = 7.25 \times 10^{-3} \text{ mol dm}^{-3} \\
[\text{RNCS}] & = 0.3 \text{ mol dm}^{-3}
\end{align*}
\]

<table>
<thead>
<tr>
<th>TIME/MIN</th>
<th>( \text{OD}_{541}^t \text{ nm} )</th>
<th>( \ln (\text{OD}<em>t - \text{OD}</em>\infty) )</th>
<th>( k_o / 10^{-4} \text{ s}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>-0.744</td>
<td>-</td>
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<td>5</td>
<td>0.84</td>
<td>-0.88</td>
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<td>-1.09</td>
<td>7.00</td>
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<td>20</td>
<td>0.635</td>
<td>-1.56</td>
<td>7.83</td>
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<td>0.584</td>
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<td>40</td>
<td>0.525</td>
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<td>0.505</td>
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</table>

Average \( k_o = (5.9 \pm 1.8) \times 10^{-4} \text{ s}^{-1} \)

**From Plot (Fig. 33)**

\( k_o = (6.2 \pm 0.3) \times 10^{-4} \text{ s}^{-1} \)
FIG. 32: PLOT OF $OD_{541}$ VERSUS TIME FOR TYPICAL KINETIC REACTION OF CYCLOHEXYL ISOTHIOCYANATE AND TEAN IN ACETONITRILE (TABLE 55).
FIG. 33: PSEUDO-FIRST ORDER PLOT FOR KINETIC REACTION OF CYCLOHEXYL ISOTHIOCYANATE AND NITRITE IN ACETONITRILE (TABLE 55).
9.7 N-SULPHINYL AMINES

9.7.1 Preparation of N-Sulphonyl-4-Nitroaniline

4-Nitroaniline (10 g, 72.4 mmols) was dissolved in benzene (Na-dried, 70 ml) and thionyl chloride (6 ml, 82 mmols) added. The solution was refluxed for 12 hours and then the solvent removed at reduced pressure to give the crude product (13.3 g, 100%). Recrystallization from light petroleum (b.p. 60-80°C) gave the product as orange/yellow needles m.p. 68-70°C (Lit. 61 71°C); \( \nu \) max (nujol) 3103 m (Aromatic CH), 1341 s (ArNO₂), 1288 s and 1171 s cm⁻¹ (N = S = O); \( \lambda \) max (MeCN) 362 (\( \varepsilon \) 17540 mol⁻¹ cm³ dm⁻³) nm; \( \delta \)H (90 MHz, CDCl₃) 8.3 (2H, d, ArH), 7.9 (2H, d, ArH); m/z 184 (M⁺, 3%), 138 (100%, NH₂C₆H₄NO₂⁺).

9.7.2 Preparation of N-Sulphonylaniline

Aniline (10 g, 0.1 mols) was dissolved in benzene (Na-dried, 100 ml) and thionyl chloride (9 ml, 0.12 mols) added. The solution was refluxed for 12 hours, the solvent removed at reduced pressure and the crude product distilled at reduced pressure to give the product as a yellow liquid (11.2 g, 75%); b.p. 82-84°C/15 mm Hg (Lit. 84 80°C/12 mm Hg); \( \nu \) max (neat) 3060 m (ArCH), 1280 s and 1150 s (N = S = O), 770 s cm⁻¹ (ArH); \( \lambda \) max (MeCN) 312 nm; \( \delta \)H (90 MHz, CDCl₃) 7.85 (2H, m, ArH), 7.42 (3H, m, ArH).

9.7.3 Kinetics

The rate of reaction of N-sulphonylaniline with nitrite was determined spectrophotometrically. Working under pseudo-first order conditions with excess nitrite ion, the absorbance due to the N-sulphonylaniline at 312 nm was monitored. The decrease in this absorbance obeyed good first order kinetics, and the pseudo-first order rate constant was readily determined. The general method is described in section 9.5.5.

The results of a typical kinetic run are given in Table 56 and the corresponding pseudo-first order plot in Fig. 34.

Reactions were carried out with a range of nitrite concentrations so that a second order plot could be drawn. This showed the reaction to be also first order with respect to the nitrite.
TABLE 56: RESULTS FOR A TYPICAL KINETIC REACTION OF N-SULPHINYLAMLINE AND TEAN IN ACETONITRILE AT 25°C.

CONDITIONS: 
\[
\begin{align*}
[\text{PhNSO}] &= 1.15 \times 10^{-5} \text{ mol dm}^{-3} \\
[\text{TEAN}] &= 18.38 \times 10^{-4} \text{ mol dm}^{-3}
\end{align*}
\]

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<th>TIME/MINS</th>
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<th>k_o / 10^{-4} s^{-1}</th>
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<td>2.20</td>
</tr>
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<td>\infty</td>
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</tbody>
</table>

Average \( k_o \) = (2.17 + 0.14) x 10^{-4} s^{-1}

From Plot (Fig. 34)
\( k_o = (2.22 + 0.012) x 10^{-4} s^{-1} \)
FIG. 34: PSEUDO-FIRST ORDER PLOT FOR TYPICAL KINETIC REACTION OF N-SULPHINYLAMILINE AND TEAN IN ACETONITRILE (TABLE 56).
9.7.4 Hydrolysis Reaction

N-Sulphynylaniline (0.0182 g, 0.131 mmols) was dissolved in 10% aqueous acetonitrile (10 ml) and left overnight at 25°C.

The concentration of aniline was then determined using a Perkin Elmer F33 gas chromatograph with a Rb bead detector, and using a 2 m stainless steel column packed with 8% carbowax 20 M and 2% KOH on chromosorb W80-100 mesh. A temperature of 160°C and a nitrogen carrier gas pressure of 40 p.s.i. were employed. Aniline had a retention time of 5.8 minutes under these conditions.

Aliquots (1 µl) of reaction mixture were injected directly onto the gas chromatograph.

The aniline concentration was determined by comparison of the peak heights with those due to standard aniline solutions.

This gave a 100% yield of aniline from the reaction solution. A similar reaction carried out in 20% aqueous acetonitrile also gave a 100% yield.
CHAPTER 10

REFERENCES
10. **REFERENCES**

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