Nechanistic aspects of some nitrosation reactions

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MECHANISTIC ASPECTS OF SOME NITROSATION REACTIONS

Submitted by

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To my Parents and Jeff

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MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1982 and June 1985 and has not been submitted for any other degree. It is the original work of the author except where acknowledged by reference.

Abstract

Mechanistic studies on a range of reactions involving both N- and S-nitrosation have been performed.

N-nitrosation reactions of diphenylamine, ammonia, dimethylamine, and hydrazine sulphate have been studied. As expected, the reactions were catalysed by added nucleophiles. Possibly the most significant overall result from this study is that further evidence is provided which supports the theory that the encounter-controlled limit for the nitrosation of non-aromatic amines by NOX species, where X^- is a nucleophile, is approximately one hundred times lower than for aromatic amines.

A kinetic study of the nitrosation of benzenesulphinic acid (BSA) has been carried out. The acidity dependence revealed that reaction with $H_2NO_2^+/NO^+$, the nitrosyl halides or nitrosyl thiocyanate occurs via both the neutral acid molecule of BSA and its anion. The overall reactivity of benzenesulphinic acid towards nitrosation is very high, and it appears that the reaction of the sulphinate anion with $H_2NO_2^+/NO^+$ is encounter-controlled. This high reactivity suggests that water soluble sulphinic acids may have potential use as nitrite traps, where it is important to remove nitrous acid quantitatively, rapidly and irreversibly.

The ability of the nitrosothiosulphate anion to act directly as a nitrosating agent was also investigated, and compared directly with nitrosyl bromide and nitrosyl thiosulphate. It appears that this anion may act directly as a nitrosating agent, at least towards reactive substrates, and thus it represents an unusual example of a negatively charged electrophilic nitrosating agent.

The mechanism of nitrosation of dimethyl sulphide has not been completely elucidated. However, it seems likely that a S-nitroso species is formed which apparently may act directly as a nitrosating agent.

It is proposed that the mechanism of denitrosation of N-acetyl-S-nitroso-D, L-penicillamine in the presence of mercuric chloride occurs via the intermediacy of a mercury-sulphur complex.

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CHAPTER ONE

INTRODUCTION

1.1. Introduction to Diazotisation and Nitrosation Reactions

Griess,[1] in 1858, discovered aromatic diazo compounds when he isolated the diazotised form of picramic acid as the product of the reaction in which his intention was to replace the amino group of the acid by a hydroxyl group. Soon after this Mène[2] formed diazoaminobenzene from the reaction of nitrous fumes with aniline. Griess' method of forming diazo compounds, which used nitrous gases as the nitrosating agent, was soon replaced by less complicated methods, e.g. the use of sodium nitrite as the nitrosating agent.[3] The complete history of the discovery of diazo compounds is well documented in several reviews.[4]

Bamberger[5] proposed that the mechanism of diazotisation of an amine proceeded via the intermediacy of a nitroso alkylaryl amine (1), according to equation 1.1.

$$ArNH_2 \xrightarrow{\text{slow}} \underset{(1)}{Ar\text{-}NH\text{-}NO} \xrightarrow{\text{fast}} ArN_2OH \xrightarrow{\text{fast}} ArN_2^+ \qquad 1.1$$

This proposal was validated by the work of Ridd and Kalatzis,[6] and it is now generally accepted that the initial N-nitrosation step of the reaction of nitrous acid with an amine is the rate-determining step.

The N-nitrosamine formed from the nitrosation of a secondary amine is sufficiently stable for the reaction to proceed no further. Similarly reaction of tertiary amines with nitrous acid stops after the nitrosamine has been formed, although this reaction involves the cleavage of an N-C bond. With primary aliphatic amines the reaction proceeds to the formation of a range of deamination products. e.g. alcohols and alkenes, via the intermediacy of a carbocation ion. With primary aromatic amines however, the reaction effectively stops after

the diazonium ion has been formed since the aromatic π system reduces the leaving group ability of nitrogen.[7,8]

The upsurge of interest in nitrosation reactions may, at least in part, be attributable to the discovery that N-nitrosodimethylamine was carcinogenic in rats.[9] Since then numerous biochemical studies have been carried out in an attempt to investigate the possibility that carcinogenic N-nitroso compounds may be formed in food, in storage or preparation, and in vivo, e.g. in the stomach.[10-14] The components required for the formation of N-nitroso compounds are ubiquitous in the environment.[11,12] Amines are present in foodstuffs, wine, tobacco products and pharmaceuticals, and nitrite is present in cured meat and fish and may be formed by the reduction of nitrate present in the saliva and in some vegetables. Other nitrosatable substances, e.g. quarternary ammonium salts, guanidines, carbamates and ureas are also present in the environment. The carcinogenity of dialkylnitrosamines has been attributed to their ability to act as alkylating agents, formed from a sequence initiated by enzymatic oxidation followed by a series of non-enzymatic steps, in particular towards the oxygen atom at position 6 in guanine.[14-16]

Until recently the majority of work in the area of nitrosation was concerned with N-nitrosation, however, it has now been established that nitrosation reactions, brought about by a wide range of nitrosating agents, may also occur at carbon, halide, oxygen, sulphur and transition metal sites.[8]

The remainder of this introduction will discuss the mechanisms of nitrosation reactions and particular reference will be made to reactions involving S- and N-nitrosation. Nitrosation at oxygen and carbon, denitrosation mechanisms, and mechanisms involving nitrogen oxides and transition metal complexes will be discussed briefly.

1.2. Mechanisms of nitrosation and diazotisation in acid solution

1.2.1. Nitrous anhydride mechanism

Early work by Hantzsch and Schümann[17] on the diazotisation of several aromatic amines showed that the overall reaction was second order. They expressed their results by equation 1.2, despite having no direct evidence that the protonated amine was the reacting species

$$\text{Rate} = k[\text{ArNH}_3^+][\text{HNO}_2] \qquad 1.2$$

or, since they worked with equal concentrations of both reactants, that the reaction was first order in both substrates.

Later, work by both Taylor,[18] on the nitrosation and deamination of aliphatic amines, and by Schmid,[19] on the diazotisation of aromatic amines, was found to be consistent with a third order reaction, the rate of which may be expressed by equation 1.3.

$$\text{Rate} = k[\text{Amine}][\text{HNO}_2]^2 \qquad 1.3$$

Hammett[20] interpreted the third order kinetics of the reaction in terms of a rate limiting reaction between the free base form of the amine and nitrous anhydride (N_2O_3), formed from two molecules of nitrous acid. (Scheme 1). Later work by Hughes, Ingold and Ridd[21,22]

$$2HNO_2 \underset{}{\overset{K \quad \text{fast}}{\rightleftharpoons}} N_2O_3 + H_2O$$

$$ArNH_2 + N_2O_3 \xrightarrow{\text{slow}} ArNH_2NO^+ + NO_2^-$$

$$ArNH_2NO^+ \xrightarrow{\text{fast}} ArN_2^+$$

Scheme 1

confirmed that this proposed reaction mechanism was correct. They also studied the diazotisation of aniline at the low acidities,

ca. 0.002M, used by Hantzsch and Schümann,[17] and found that the reaction was zero order in the amine, but overall of the second order. The correct rate expression for nitrosation or diazotisation under these experimental conditions is given by equation 1.4, and the rate-

$$\text{Rate} = k[HNO_2]^2 \qquad 1.4$$

limiting step is then the formation of the nitrosating agent, N_2O_3.

Further proof for the formation of nitrous anhydride has been provided by the work of Bunton, Llewellyn and Stedman.[23] They found that the rate of ^{18}O exchange between water and nitrous acid was second order with respect to nitrous acid, and that rate of formation of nitrous anhydride was comparable with that estimated from the rate of diazotisation of aniline using equation 1.4.

Recently the value of the equilibrium constant, K, for the formation of nitrous anhydride, Scheme 1, has been redetermined[24] as 3.03×10^{-3} l mol^{-1}. Using this value of K it was found[25] that the value of the rate constant k, equation 1.3, for a number of amines with a wide range of bascities (pKa 5.55 to 11.25) was of the order of 10^8. This result, together with the experimentally determined energy of activation for the reaction led to the conclusion that the reaction of the amines with nitrous anhydride was diffusion controlled.[26] Moreover it now seems likely that N_2O_3 is as reactive as the nitrosyl halides in nitrosation reactions.

1.2.2. Nitrosation by $H_2NO_2^+$ or NO^+

At pH<2 Larkworthy found[27] that the diazotisation of a range of amines was subject to acid catalysis. The results were consistent with the rate expression (equation 1.5), where [S] is the concentration of

$$\text{Rate} = k[S][HNO_2][H^+] \qquad 1.5$$

substrate. Further, the value of k did not appear to depend on the basicity of the amine, which suggests that the nitrosating agent is very reactive.

The rate expression defined in equation 1.5 is not specific to amines, and has been observed for a wide range of substrates, e.g. thiols, alcohols, azide ion.[7,8,26] The active nitrosating agent is believed to be either the nitrous acidium ion, $H_2NO_2^+$, or the free nitrosonium ion, NO^+ (scheme 2), which are indistinguishable kinetically.

$$HNO_2 + H^+ \overset{K}{\rightleftharpoons} H_2NO_2^+$$

$$H_2NO_2^+ \rightleftharpoons NO^+ + H_2O$$

Scheme 2

Early work by Hughes and co-workers[28] on the diazotisation of o-chloroaniline, and by Larkworthy,[27] on the diazotisation of nitroanilines, was interpreted[22, 27] in terms of the formation of $H_2NO_2^+$ as the active nitrosating agent. However, Bayliss and co-workers[29] have now established that there is no spectroscopic evidence for this ion, contrary to their earlier reports.[30]

In contrast, there are numerous reports in the literature where the nitrosonium ion has been detected spectroscopically in concentrated acid solution,[29, 30, 31] and it is now assumed that NO^+ is the effective nitrosating agent at these acidities.

In an attempt to elucidate which is the active nitrosating agent in weaker acid solutions several kinetic experiments have been performed. Bunton and Stedman[32] studied the mechanism of the reaction between azide and nitrite in ^{18}O water. Under the experimental conditions that they used they found that the rate of reaction of nitrous

acid with azide ion was faster than the rate of oxygen exchange between nitrous acid and the solvent, which corresponds to the rate of formation of NO^+.

This work therefore, argues against the formation of NO^+ as the active nitrosating agent. However, it does assume that the lifetime of NO^+ is long enough to enable ^{18}O exchange to occur. More recently a study of the nitrosation of hydrogen peroxide[33] has provided evidence which favours rate limiting NO^+ formation. A plot of the first order rate constant k_o (with $[H_2O_2] >> [HNO_2]$) versus $[H_2O_2]$ was found to increase linearly at first and then levelled off towards a limiting value of ca. 1M H_2O_2. The experimental results were consistent with the mechanism given in scheme 3. At high $[H_2O_2]$, $k_2[H_2O_2] >> k_{-1}[H_2O]$,

$$H^+ + HNO_2 \underset{\text{fast}}{\overset{K}{\rightleftharpoons}} H_2NO_2^+$$

$$H_2NO_2^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} NO^+ + H_2O$$

$$NO^+ + H_2O_2 \xrightarrow{k_2} HOONO + H^+$$

Scheme 3

and the rate-determining step is then considered to be formation of NO^+. Doubt is cast on this interpretation however, in view of the large concentrations of hydrogen peroxide required to bring about the transition from first to zero order kinetics, and since this behaviour may just as well be explained in terms of a medium effect.

A similar transition from first to zero order kinetics has been reported in a study of the nitrosation of a range of alcohols,[34] for which the limiting value of k_o for the three alcohols studied in detail[35] was different. This is inconsistent with rate limiting

formation of NO^+, where k_o would be expected to be independent of the particular alcohol studied. The results may be interpreted in terms of a medium effect as in the case of the nitration of aromatic substrates.[36] Thus it seems likely that the zero order dependence observed for the hydrogen peroxide reaction was not due to rate limiting NO^+ formation.

Theoretical calculations on the protonated form of nitrous acid[37] have found that the most stable structural form of $H_2NO_2^+$ is as the hydrated NO^+ species. Moreover, their studies revealed that the dissociation energy of $H_2NO_2^+$ is considerable, from which it was concluded that the concentration of NO^+ would be very small in all except the strongest acid solutions. This is in agreement with very recent theoretical calculations[38] which support $O\overset{+}{N}-OH_2$ as the effective nitrosating agent in weakly acid solutions.

The nitrosation of many substrates, whose rate may be expressed by equation 1.5, react at the encounter rate. These reactions have been discussed in a recent review.[26] For the reaction of $H_2NO_2^+$ or NO^+ with neutral substrates in water at 25°C it is believed[26] that a value of k of ca. 7000 $l^2\ mol^{-2}\ s^{-1}$ is the upper limit for diffusion controlled species. It would be expected that this value of k would be larger for negatively charged substrates purely from a consideration of electrostatic effects. Recent studies[39] have enabled a value of k of 11700 $l^2\ mol^{-2}\ s^{-1}$ to be determined for the nitrosation of thiocyanate ion. This compares well with the value of k of 11800 $l^2\ mol^{-2}\ s^{-1}$ determined for nitrosation of the benzenesulphinate anion (Chapter 3), and it seems likely that this value of k represents the limiting value for the diffusion-controlled reaction of $H_2NO_2^+$ or NO^+ with singly negatively charged substrate. A value of k of

18000 l^2 mol^{-2} s^{-1} has recently been determined[40] for the nitrosation of the thiosulphate ion, and this again is believed to represent the diffusion-controlled limit for double negatively charged substrates.

1.2.3. Nitrosation at high acidities

It has been found that the rate of diazotisation of aniline passes through a maximum at ca. 6M $HClO_4$, after which the observed rate constant is found to decrease rapidly with a further increase in acidity.[41] The rate of reaction may then be expressed by equation 1.6

$$\text{Rate} = k[ArNH_3^+][HNO_2]h_o^{-2} \qquad 1.6$$

The Raman spectrum of 60% $HClO_4$ solution containing nitrite indicates that at these acidities nitrous acid is almost completely present as the free nitrosonium ion.[29,30,31(a),(d)] The mechanism proposed is outlined in scheme 4 and involves a rapid reversible nitrosation followed by a slow proton transfer to the solvent.

$$ArNH_3^+ + NO^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} ArNH_2NO^+ + H^+$$

$$ArNH_2NO^+ \xrightarrow{\text{slow}} ArNHNO + H^+$$

$$ArNHNO \xrightarrow{\text{fast}} ArN_2^+ + HO^-$$

Scheme 4

1.3 Nitrosation by nitrosyl halides

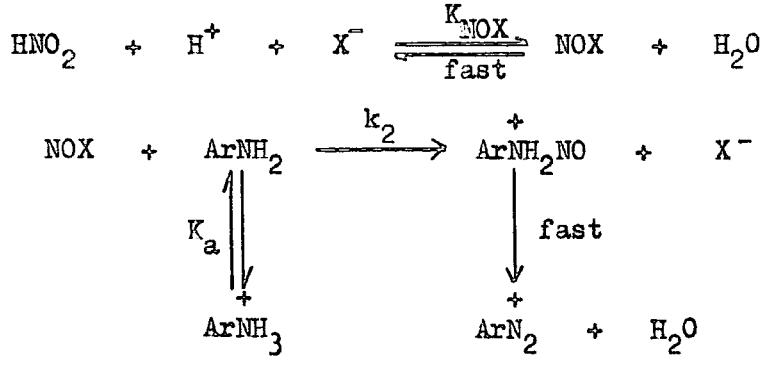
One of the first reports of halide catalysis was made by Schoutissen,[42] who reported that hydrochloric acid had a catalytic effect on the rate of diazotisation of several aromatic amines.

Later Schmid studied the diazotisation of aniline in hydrochloric[43] and hydrobromic[44] acid. He found that the reaction was catalysed by chloride and bromide ions, and that it was consistent with rate expression given in equation 1.7, where $[X^-]$ is the concentration of

$$\text{Rate} = k[ArNH_2][H^+][HNO_2][X^-] \qquad 1.7$$

the halide ion.

It was Hammett[20] however, who first proposed the involvement of the nitrosyl halides, and it is now believed that the mechanism of nitrosation reactions in the presence of halide ions occurs as outlined in scheme 5. The first step of this scheme is a potentially rate-determining inorganic reaction, which involves the formation of low equilibrium concentrations of the nitrosyl halides. In the vast majority of nitrosation reactions studied formation of the nitrosyl



Scheme 5

halide is not rate determining. However, under certain experimental conditions this may be achieved. In a study of the diazotisation of o-chloroaniline Hughes and Ridd[45] succeeded in making attack of $H_2NO_2^+$ (or NO^+) on the halide ion, when $X^- = Br^-$ or I^-, the rate-determining step when they used a sufficient excess of the amine. Similarly the rate of formation of nitrosyl chloride was made rate-determining in the nitrosation of hydrazoic acid.[46]

The nitrosation of aniline in methanolic hydrogen chloride has been studied.[47] The results obtained were consistent with reaction via NOCl, however, the rate of reaction was considerably slower and this was attributed to a reduction in the concentration of nitrosyl chloride by methanolysis (equation 1.8).

$$NOCl + MeOH \rightleftharpoons MeONO + HCl \qquad 1.8$$

Schmid and co-workers used the experimentally determined values of the equilibrium constants for the formation of the nitrosyl halides, K_{NOX} (1.18×10^{-3} and 5.1×10^{-2} l^2 mol^{-2} for $X=Cl^-$[48] and Br^-[49] respectively), to obtain values of the bimolecular rate constants k_2 (equation 1.9) for the nitrosation of a range of amines by NOCl[48,50,51] and NOBr.[49,50]

$$\text{Rate} = k_2 [\text{amine}]_{\text{Free}} [NOX] \qquad 1.9$$

This rate equation may be expressed in terms of the total concentration of the amine, $[A]_{Total}$, and the concentration of added halide ion, $[X^-]$.

From scheme 5 $\quad K_a = \dfrac{[A]_{Free}[H^+]}{[\overset{+}{A}H]}$

and $\quad K_{NOX} = \dfrac{[NOX]}{[H^+][X^-][HNO_2]}$

Except for non-basic amines $\quad [A]_{Total} = [\overset{+}{A}H]$

substitution gives $\quad \text{Rate} = k_2 K_a K_{NOX} [A]_{Total} [X^-] [HNO_2]$

This predicts the first order dependence upon $[X^-]$ which has been observed for the nitrosation of a range of substrates in the presence of added nucleophiles.

In order to determine values of the bimolecular rate constants k_2 (equation 1.9) it is essential that reliable values of K_{NOX} are available. The reaction of sodium nitrite with acidic iodide solution has been studied[52] however, as yet a satisfactory value for K_{NOI} has not been determined. The method used by Schmid and Hallaba[48] to determine a value of K_{NOCl} has been criticised by Bayliss and Watts.[30] However, this value is still used and values of k_2 (equation 1.9) obtained when it is used show the expected trend of reactivity.

In a study of the nitrosation of a range of aniline derivatives by nitrosyl chloride and nitrosyl bromide,[53] it was found that the difference in reactivity of the two nitrosating agents decreased as the bascity of the amine increased and the rate of reaction approached the calculated value for a diffusion-controlled process.[26] More recently iodide ion catalysis of diazotisation of a similar range of amines has been examined and found to be significant.[54] However, values of the bimolecular rate constant, k_2, could not be determined since the value of K_{NOI} is not known.

The nitrosation of aliphatic amines is, not surprisingly, also catalysed by halide ions,[55] although for these substrates a limiting value of k of the order of 10^7 l mol^{-1} s^{-1} was observed, which is 100 times smaller than the calculated diffusion limit.[26] This anomaly is discussed further in Chapter 2.

Nitrosation of a range of amines, in aqueous acid solution, by dissolved gaseous nitrosyl chloride has also been studied.[56] The expected products, i.e. the diazonium ion or N-nitrosamine, were obtained together with nitrite ion, formed by hydrolysis of nitrosyl chloride.

Catalysis of nitrosation reactions by added halide ions is not restricted only to N-nitrosation. There are many examples in the

literature where such catalysis has been observed for the nitrosation of both sulphur[8,34,57,58] and oxygen[8,34] analogues.

The catalytic effect of added chloride, bromide, and iodide ions, and other nucleophiles, e.g. thiocyanate ions and thiourea (Section 1.5) is attributed to the fact that these nucleophiles increase the concentration of nitrosating agent present. It has been found that the catalytic effect of the halide ions increases in the order: $Cl^- < Br^- < I^-$, whereas the order of reactivity of the nitrosyl halides is: $NOI < NOBr < NOCl$.[7,8,53,54] This order of reactivity may easily be explained in terms of the electronegativity of the halogens. The nitrosyl halide bond in nitrosyl chloride will be more polarised, and thus more electrophilic, than the corresponding bond in nitrosyl bromide and nitrosyl iodide. It has been found that the value of K_{NOX} governs the overall catalytic efficiency for the added nucleophile X^-,[59] thus the greater catalytic effect of bromide ion compared to chloride ion is attributed to the larger value of K_{NOX} when $X^- = Br^-$.

1.4. The Mechanism of Denitrosation

1.4.1. Denitrosation of nitrosamines

In strongly acid solutions and in the absence of nitrite traps aromatic nitrosamines undergo two concurrent reactions; denitrosation and Fischer-Hepp rearrangement, which gives the para C-nitrosamine. Despite the early controversy about the Fischer Hepp rearrangement it has now been established[60] that it involves an intramolecular rearrangement which occurs concurrently with denitrosation of the protonated N-nitrosamine.

The mechanism of denitrosation of N-nitrosamines has been studied extensively and is the subject of many papers in the literature.[60-62]

1.4.2. Denitrosation of thionitrites

This subject is discussed in the following section: reactions involving S-nitrosation.

1.5. Reactions involving S-nitrosation

1.5.1. Introduction

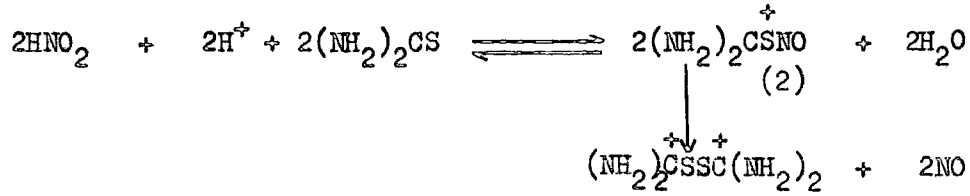
There are many examples in the literature of O-nitrosation reactions. However, despite the formal similarity to O-nitrosation and the fact that sulphur sites would be expected to be more nucleophilic,[63] and consequently more susceptible to electrophilic nitrosation than the corresponding oxygen sites, until recently very little was known about S-nitrosation. It has now been established that the S-nitroso species formed during this reaction are often very unstable and this presumably is one of the reasons for the lack of information in this area.

In addition to the interest in this reaction from a synthetic and mechanistic aspect, S-nitrosation appears to have at least one important biological implication. It is thought that the action of vasodilatory drugs, e.g. alkyl nitrites, alkyl nitrates and the nitroprusside ion, may occur via the intermediacy of S-nitrosothiols, formed by in vivo nitrosation of -SH sites.[64] S-nitrosothiols also bring about inhibition of human platelet aggregation.[65]

1.5.2. S-nitrosation reactions

Probably the first investigation in this area was performed as early as 1912 by Werner[66] when he studied the reaction of nitrous

acid with thiourea. (It is not surprising that electrophilic nitrosation of thiourea occurs since, according to Pearsons' nucleophilicity parameter[67], it is as reactive as iodide ion). Werner found that the product of the reaction depended on the acidity of the medium. It has been established[68] that at high acidity S-nitrosation occurs followed by decomposition to give the disulphide (scheme 6). The S-nitroso species (2) formed is red/yellow in colour



Scheme 6

and this fades as the disulphide is formed. The mechanism of the reaction at lower acidity has been the subject of a controversy.[68] It has been suggested[68] that S-nitrosation occurs initially, followed by a migration of the -NO group from S to N, however, as a result of recent studies by ^{15}N nmr spectroscopy,[69] it now seems likely that direct N-nitrosation occurs. The N-nitrosothiourea formed undergoes acid catalysed hydrolysis to give the corresponding S-nitroso species.

The reaction of nitrous acid or other nitrosating agents with thiols (equation 1.10) to produce thionitrites, has been known for a long time and appears to be a general reaction for a range of thiols and nitrosating agents.[58,70,71] The reaction occurs readily since the

1.10

sulphur site is nucleophilic and there is a good leaving group in the form of H^+.

Thionitrites are characterised by their instability. They readily decompose to give the disulphide and nitric oxide

(equation 1.11). Recently the most stable thionitrite yet prepared

$$2RSNO \longrightarrow RSSR + 2NO \qquad 1.11$$

N-acetyl-S-nitroso-D, L-penicillamine(3), has been synthesised by Field and co-workers.[72] It is stable in the solid form but decomposes slowly in solution. This led to a study of the nitrosation of

$$ONSC(Me)_2CH(NHAc)(CO_2H)$$

(3)

the corresponding thiol, N-Acetyl-D, L-penicillamine,[34] and it was found that catalysis by added nucleophiles was in the expected order: $Cl^- < Br^- < SCN^- < I^-$.

The rate of S-nitrosation of a range of thiols, in the absence of added nucleophiles, has been independently examined by three groups who found that the rate of reaction may be expressed by equation 1.12.[57,73,74] This rate law applies to a wide range of sub-

$$\text{Rate} = k[HNO_2][H^+][RSH] \qquad 1.12$$

strates[8] e.g. hydrazine, alcohols, hydrazoic acid, amines, and is generally interpreted in terms of attack on the substrate by the positively charged nitrosating agent $H_2NO_2^+$ or NO^+. For many substrates[57,68,74] it has been found that S-nitrosation occurs close to the encounter-controlled limit.[26]

Sulphinic acids, sulphides and the thiosulphate ion are believed to react with nitrous acid via the intermediacy of an S-nitroso species. Further details about these reactions may be found in Chapters 3, 4 and 5 of this thesis.

Nitrosyl thiocyanate is believed to represent another example of a S-nitroso species. However, due to its instability, it decomposes[75]

according to equation 1.13, its structure has not been established. The formation of an S-nitroso rather than an N-nitroso species may

$$2\ ONSCN \longrightarrow 2NO + (SCN)_2 \qquad 1.13$$

be rationalised in terms of the 'Hard-Soft-Acid-Base' theory.[76] Moreover, recent theoretical calculations have revealed that nitrosyl thiocyanate is considerably more stable than nitrosyl isothiocyanate.[77]

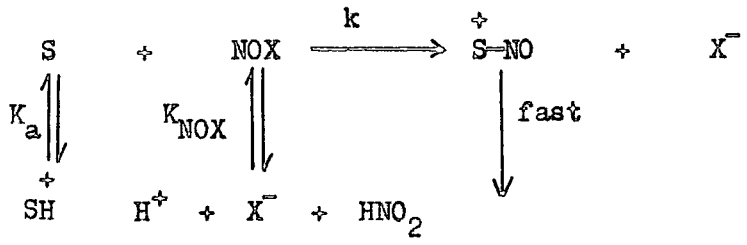
1.5.3. Nitrosation reactions involving S-nitroso species

It is now generally accepted that nitrosation reactions of a wide range of substrates are catalysed by added nucleophiles.[7,8]

Catalysis by thiocyanate ion of the nitrosation of hydroxylamine and its methyl derivatives,[78] morpholine,[59,79] hydrazoic acid,[46] alcohols,[34] and thiols,[57] and the diazotisation of aniline[23,54] has been observed. Thiourea catalysis for the diazotisation of aniline[59] and nitrosation of morpholine[59] and dimethylamine has also been found. Possible catalysis of nitrosation reactions, in particular nitrosation of N-methylaniline by thiosulphate ion and dimethylsulphide is discussed in Chapters 4 and 5 of this thesis. Catalysis by these nucleophiles is interpreted in terms of the formation of the corresponding S-nitroso species, which are present in larger concentrations than the nitrosating agents derived from nitrous acid alone.

It has now been established[53,54,59] that the efficiency of the common catalysts used in nitrosation reactions increases in the order: $Cl^- < Br^- < SCN^- < SC(NH_2)_2$. Thus thiourea is one of the best nitrosation catalysts known, although catalysis by this nucleophile has not been as extensively studied as catalysis by thiocyanate ion, presumably

due to the relative instability of the S-nitroso thiourea. As has been discussed previously, the catalytic efficiency of the different nucleophiles is governed by the magnitude of equilibrium constant for the formation of the nitroso species, NOX, rather than by the value of the bimolecular rate constant, k (scheme 7) for attack of NOX on the substrate, S.



Scheme 7

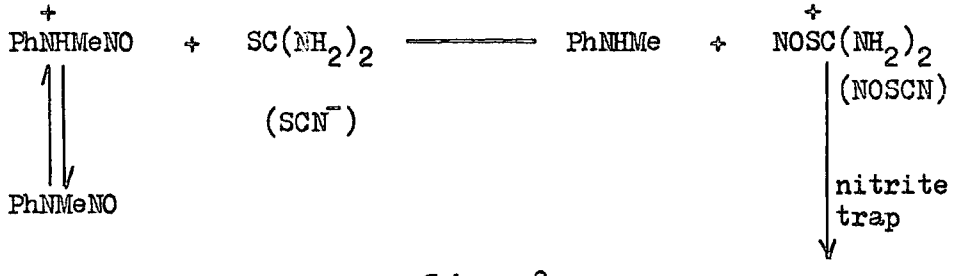
The equilibrium constant for the formation of nitrosyl thiocyanate[81] and S-nitroso thiourea[68] have been determined, and are 32 l^2 mol^{-2} at 20°C and 5000 l^2 mol^{-2} at 25°C respectively. Thus it is easy to rationalise the sequence of catalytic efficiencies. The reactivity of the nitrosating agents increases in the order: $NOS\overset{+}{C}(NH_2)_2$ < NOSCN < NOBr < NOCl. The difference in reactivity between NOCl and NOBr has previously been discussed (Section 1.3), and the difference between NOCl and NOSCN has been the subject of some recent theoretical calculations.[77]

The catalysis of N-nitrosamine formation by thiocyanate ion has important implications with regard to possible in vivo nitrosation. As discussed in Section 1.1 amines and nitrite are readily introduced into the body. Thiocyanate ion is present in gastric juices[82] and is secreted in saliva.[83] (In smokers the level of thiocyanate ion present in saliva is 3-4 times the concentration of that in non-smokers).[83] The nitrosation of secondary amines is very dependent on pH.[11,79]

Samples of saliva containing thiocyanate ion were used to catalyse the nitrosation of N-methylaniline and it was found that the optimum pH of the reaction shifted from pH 3.4, for the uncatalysed reaction, to pH 1. Thus the optimum pH of the catalysed reaction is nearer to that of the gastric juices.[83]

1.5.4. Denitrosation reactions involving S-nitroso species

Denitrosation of N-methyl-N-nitrosoaniline in the presence of a sufficient excess of a nitrite trap, to ensure complete irreversibility, has been found to be catalysed by thiocyanate ion[61(a),62] and thiourea[62,84] and its alkyl derivatives.[85] These results were found to be consistent with the mechanism outlined in scheme 8, and involve the formation of S-nitroso thiourea or nitrosyl thiocyanate, as appropriate.



Scheme 8

The reactivity of the different nucleophiles towards denitrosation of nitrosamines increases in the order: $Cl^- < Br^- < SCN^- < SC(NH_2)_2 < I$, with the reactivity of thiourea being very close to that of iodide ion.[61(b)]

Nitrosation of aniline derivatives by propyl nitrite in propanol was found to be subject to catalysis by thiourea and other nucleophiles.[86] This reaction was interpreted in terms of catalysis, by the nucleophile, of the denitrosation reaction of the alkyl nitrite followed by a reaction in which $NOSC(NH_2)_2^+$ was the active nitrosating

agent. Similarly thiourea and thiocyanate were found to catalyse the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine.[87]

Cysteine, glutathione, S-methyl cysteine and methionine have also been found to catalyse the denitrosation of N-methyl-N- nitroso-aniline. It is believed that the reaction involves the formation of a $\rangle\overset{+}{S}-NO$ type intermediate.[85] The denitrosation of N-methyl-N-nitrosoaniline in the presence of three mercaptocarboxylic acids; cysteine, 3-mercaptopropanoic and mercaptosuccinic, was studied.[57] It was found that these species, which are believed to react via the intermediacy of a $\rangle\overset{+}{S}-NO$ species, were more reactive to the nitrous acid produced in the reaction than conventional nitrous acid traps, e.g. hydrazine.

In conclusion it appears that many sulphur compounds which react with nitrous acid or its derivatives rapidly and irreversibly have potential use as nitrite traps.

1.5.5. Denitrosation of S-nitroso species

The nitrosation of thiols is essentially an irreversible reaction. However, under certain experimental conditions, i.e. in the presence of a sufficient excess of a nitrite trap and in strongly acidic solution, the reverse reaction, denitrosation of the thionitrite, may be studied.

The denitrosation of N-acetyl-S-nitroso-D, L-penicillamine has recently been extensively studied.[87] The mechanism of denitrosation of thionitrites is discussed in Chapter 6.

1.6 Reactions involving O-nitrosation

For a long time it has been known[88] that alkyl nitrites may be synthesised from the reaction of nitrous acid with alcohols, although it is only recently that the mechanism of the O-nitrosation has been elucidated.

A study of the nitrosation of a range of alcohols and carbohydrates has revealed that the reaction is reversible (equation 1.14) and that both reactions are catalysed by both acid and nucleophiles,

$$ROH + H_2NO_2^+ \rightleftharpoons RONO + H_3O^+ \qquad 1.14$$

e.g. Cl^-, Br^-, SCN^-. This highlights an important difference between O- and S-nitrosation reactions since the latter are essentially irreversible. The reversibility of the O-nitrosation reaction has been explained[34] in terms of the higher basicity of oxygen in the alkyl nitrite compared with sulphur in the thionitrite.

Alkyl nitrites have been used synthetically as nitrosating agents[89] and are particularly useful when the conditions are such that it is impossible to use nitrous acid itself, e.g. in non-aqueous solvents.

Recently it has been proposed[90] that tertiary butyl nitrite is an effective reagent for acid catalysed trans-nitrosation. It is known that hydrolysis of alkyl nitrites occurs rapidly in acid solution[91] and recent results have revealed that the nitrosation of aniline derivatives by n-propyl-nitrite, in propanol, is slow except in the presence of added nucleophiles.[86] Thus, it seems unlikely that alkyl nitrites act directly as nitrosating agents, at least in acid solution, and it is thought that hydrolysis to nitrous acid or its derivatives occurs initially.

Under basic conditions however, it appears that alkyl nitrites may act as efficient nitrosating agents for amines.[92] It is believed that reaction proceeds via direct nucleophilic attack of the amine on the neutral alkyl nitrite (equation 1.15). Also

$$XCH_2CH_2ONO + R_2NH \longrightarrow XCH_2CH_2OH + R_2NNO \qquad 1.15$$

reported in the literature is a study of the effectiveness of tertiary butyl nitrite as a nitrosating agent in non-aqueous solvents.[93] It was successfully used to synthesise a range of thionitrites, and alkyl nitrites derived from steroidal alcohols.

1.7 Reactions involving C-nitrosation

Nitrosation may also occur at carbon sites[94] although few mechanistic studies have been performed.

It is an important reaction synthetically as it provides a means of introducing a nitrogen function into an organic molecule, through the addition of a nitrosating agent, e.g. NOCl across a carbon-carbon double bond.[95] This reaction has also found use for carbon-carbon bond cleavage of certain ketones and ketone acetals.[95]

There are many reports in the literature of nitrosoalkene formation[96]. However, the predominant interest in these compounds appears to be their potential use as synthetic reaction intermediates.

The reaction of nitrous acid with phenol has been known for a long time and is the basis of the Libermann colour test for phenols.[97] It has been proposed[98] that the mechanism of C-nitrosation of aromatic substrates involves the well-known two-stage $A\text{-}S_E2$ process for aromatic electrophilic substitution.

1.8. Reactions of metal nitrosyl complexes and other nitrosating agents

Apart from the conventional nitrosating agents discussed earlier in this introduction there are reports in the literature of a wide range of species which have been shown to facilitate nitrosation, but whose reactions have not been as extensively studied.

1.8.1 Metal nitrosyl complexes

It is now generally accepted that metal nitrosyl complexes may act as nitrosating agents and this is the subject of a recent report.[99] Some of the first work in this area was a study of the copper-catalysed reaction of nitric oxide with diethylamine.[100] It was proposed that the active nitrosating agent was a nitrosyl-copper complex e.g. $Cu^{II}NO$.

The nitroprusside ion, $[Fe(CN)_5NO]^{2-}$, is probably one of the best known metal nitrosyl complexes and it is known that in aqueous alkaline solution it may act as an electrophilic nitrosating agent for a wide range of substrates, including amines[101] and acetone.[102]

There are also a number of reports in the literature where ruthenium nitrosyl complexes apparently act as NO^+ carriers.[8]

1.8.2. Reactions of nitrogen oxides

Nitrogen dioxide, dinitrogen tetroxide, dinitrogen trioxide, and nitric oxide have all been implicated in the formation of N-nitroso compounds.[103] Acidic conditions are not required and all except nitric oxide can react unaided.

Nitrosation of secondary amines by nitric oxide in ethanol and under anaerobic conditions is promoted by a range of metal salts, including $CuCl_2$ and $AgClO_4$,[103,104] and iodine[105] and hydrogen iodide.[106]

Oxygen and air promote the reaction by oxidising nitric oxide to nitric dioxide.[107]

N-nitrosamines may also be formed from the reaction of nitric oxide with secondary amines via the 'Drago complex', $Et_2NH_2^+Et_2NN_2(O_2^-)$.[108]

It has been found that both gaseous dinitrogen trioxide,[109] and dinitrogen tetroxide[107,110] in organic solvents may act as nitrosating agents towards amines.

1.8.3. Other nitrosating agents

Nitrosylhaems, formed from the reaction with nitric oxide with haems, have been shown to act as nitrosating agents towards secondary amines.[111]

Similarly potassium nitrosodisulphonate, Fremy's salt,[112] and nitrosyl acetate[113] may act as nitrosating agents towards amines under certain experimental conditions.

Results obtained from a study of the mechanism of the nitrosation of secondary amines in the presence of formaldehyde were found to be consistent with the formation of a new nitrosatable species, an iminium ion, rather than a new nitrosating agent.[114]

In conclusion, it appears that nitrosation of a number of different substrates by a wide range of nitrosating agents may occur in acidic, neutral or basic conditions.

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CHAPTER TWO

N-NITROSATION

2.1. Introduction

N-Nitrosation reactions of a wide variety of substrates have been studied, both mechanistically and synthetically, and is the subject of many reviews.[1-4]

A kinetic study of the nitrosation of diphenylamine, dimethylamine, ammonia and hydrazine has been performed and the results are presented in this chapter.

2.2. N-Nitrosation of diphenylamine

N-Nitrosodiphenylamine formation can be effected under a range of experimental conditions, including the reaction of the amine with nitrogen dioxide in diethylether[5] or with hexyl nitrite in hexanolic hydrogen chloride.[6]

Challis and co-workers have studied[7] the reaction of diphenylamine with gaseous oxides of nitrogen under alkaline and neutral conditions. Nitrosation of the amine by dinitrogen tetraoxide in 0.1M sodium hydroxide solution is believed[8] to occur via the unsymmetrical $ON\text{-}ONO_2$ isomer. In the presence of silver(I) salts the nitrosamine is formed[9] from the reaction of the amine with nitric oxide. This reaction is thought to proceed through a Ag^{II}- amine complex.

Under certain experimental conditions N-nitrosodiphenylamine formation is reversible, and it has been found that it is even possible to make reverse reaction, denitrosation of the nitrosamine, irreversible if the reaction is carried out in acid solution in the presence of a relatively high concentration of sodium azide, a nitrous acid trap. Under these experimental conditions the effects of halide ions, thiocyanate ion and thiourea on the denitrosation of N-nitrosodiphenylamine were examined.[10] The reactivity of the

nucleophiles was established: $I^- > SC(NH_2)_2 > SCN^- > Br^- > Cl^-$, and found to correlate reasonably well with the Pearson nucleophilicity parameter, n.[11] However, there appear to be no reports in the literature of a kinetic study of the nitrosation of diphenylamine in acidic solution. The nitrosation of diphenylamine in acidic solution in the presence of added nucleophiles was examined, and the results are presented below.

In all of the experimental runs, carried out on a Stopped-Flow spectrophotometer, there was a large excess of sodium nitrite over the concentration of amine. The reaction was followed by monitoring the change in absorbance at 320nm, due to the product nitrosamine, as a function of time. In addition, all kinetic runs were measured in 50% methanol water because of the very low solubility of diphenylamine in water

2.2.1. The acid catalysed reaction

All kinetic runs showed good first order behaviour with respect to the initial amine concentration. The observed first order rate constant is defined in equation 2.1.

$$\frac{d\,[Ph_2NNO]}{dt} = k_o\,[Ph_2NH]_T \qquad 2.1$$

where $[Ph_2NH]_T$ is the total stoichmetric concentration of substrate.

The effect of added nitrite on k_o, at constant acid and diphenylamine concentrations, was determined and the results are shown in table 2.1.

Table 2.1 dependence of k_o on $[NaNO_2]$

$[H^+] = 0.26M$

$[Ph_2NH] = 4.2 \times 10^{-5}M$

$10^4[NaNO_2]/M$	$10^2 k_o/s^{-1}$
8.17	1.88 ± 0.06*
16.3	3.32 ± 0.06
81.7	17.7 ± 0.26
163	35.0 ± 0.88

$[H^+]$ is the free hydrogen ion concentration assuming complete protonation of the nitrite.

A plot of k_o versus $[NaNO_2]$ is linear and through the origin indicating that under the experimental conditions used the nitrosation of diphenylamine is an irreversible reaction, and is first order in nitrous acid, so reaction with nitrous anhydride (N_2O_3) can be ignored.

The active nitrosating agent is believed to be either the nitrous acidium ion ($H_2NO_2^+$) or possibly the free nitrosonium ion (NO^+). For the remainder of this chapter the active nitrosating species is assumed to be $H_2NO_2^+$.

The variation of k_o with added acid was determined at two different concentrations of sodium nitrite. The results, presented in tables 2.2 and 2.3, and figure 1, clearly show that the reaction is acid catalysed. However, at higher concentrations of hydrogen ion the plot of k_o versus $[H^+]$, which goes through the origin, levels off.

* The quoted error represents the standard deviation.

Figure 1 Acid catalysis of N-nitrosodiphenylamine formation

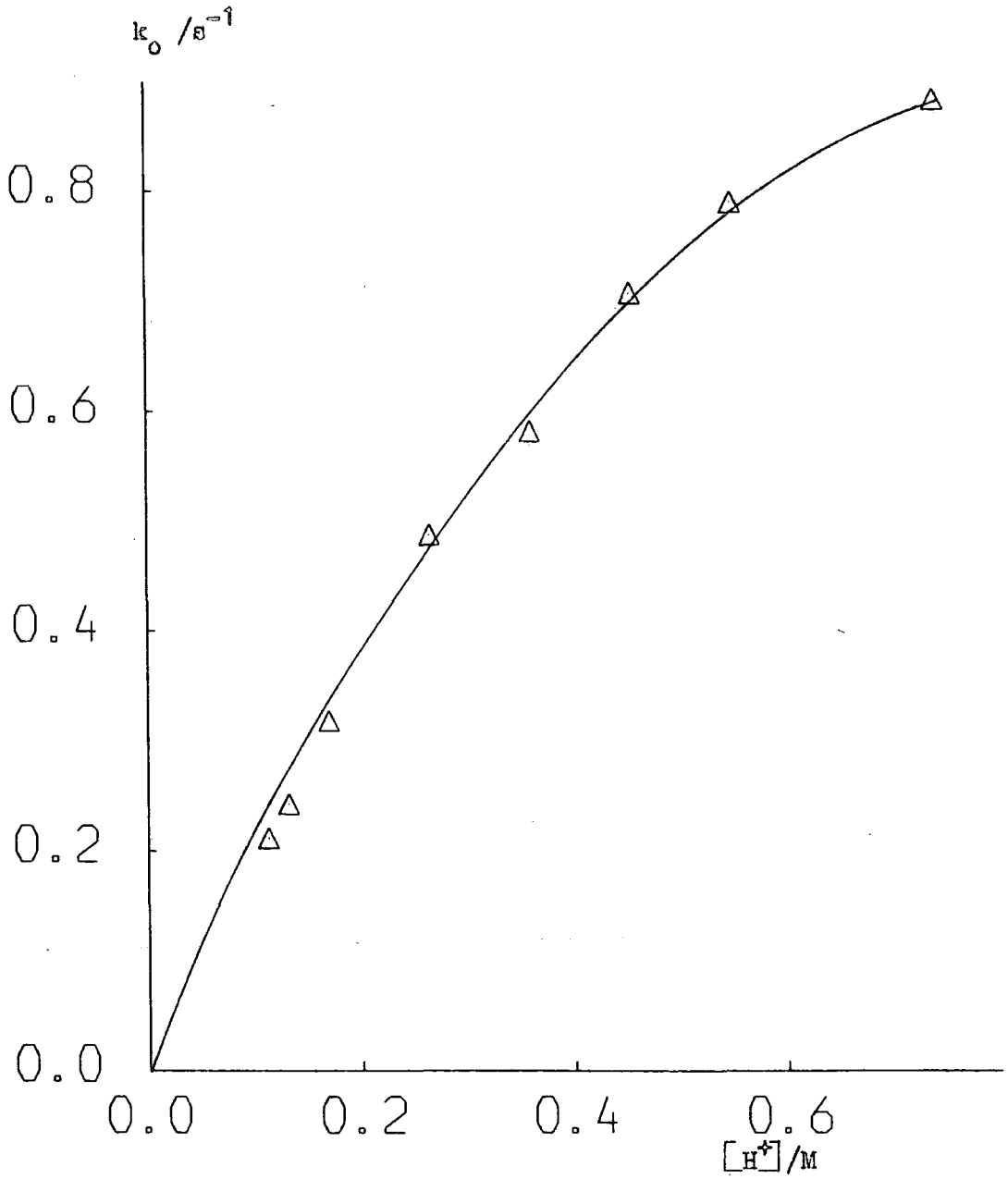


Table 2.2 dependence of k_o on $[H^+]$

$[NaNO_2] = 1.63 \times 10^{-3}M$

$[Ph_2NH] = 4.2 \times 10^{-5}M$

$10^2[H^+]/M$	$10^2k_o/s^{-1}$
18.6	2.43 ± 0.02
26.1	3.34 ± 0.07
37.4	4.63 ± 0.02
56.2	6.24 ± 0.01
75.0	7.59 ± 0.03

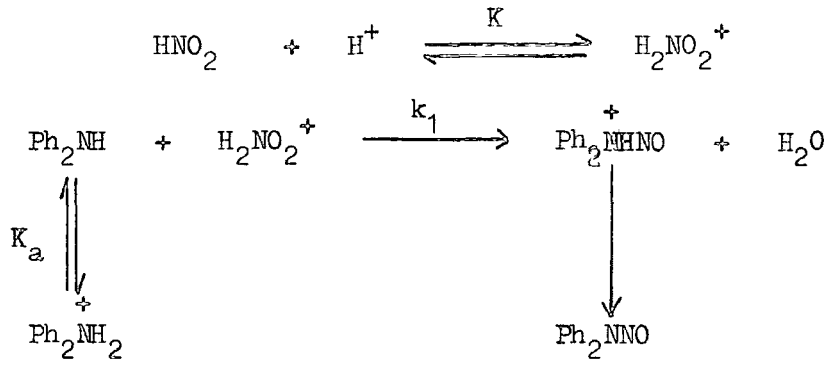
Table 2.3 dependence of k_o on $[H^+]$

$[NaNO_2] = 2.04 \times 10^{-2}M$

$[Ph_2NH] = 4.2 \times 10^{-5}M$

$10^2[H^+]/M$	k_o/s^{-1}
11.3	.212 ± 0.004
13.2	.243 ± 0.004
17.0	.319 ± 0.002
26.5	.488 ± 0.015
36.0	.582 ± 0.028
45.5	.708 ± 0.004
55.0	.791 ± 0.013
74.0	.885 ± 0.018

The observed results are consistent with the generally accepted mechanism for the nitrosation of amines[1] which is outlined in scheme 2.1. The rate determining step is attack of the nitrous acidium ion on the free base form of the amine.



Scheme 2.1

The rate equation for scheme 2.1 is given by the expression:

$$\text{Rate} = k_1[H_2NO_2^+][Ph_2NH]_F$$

where $[Ph_2NH]_F$ is the concentration of the free base form of the amine.

The concentration of $H_2NO_2^+$ may be expressed in terms of $[HNO_2]$:

$$K = \frac{[H_2NO_2^+]}{[HNO_2][H^+]}$$

If by definition:

$$[Ph_2NH]_T = [Ph_2NH]_F + [Ph_2\overset{+}{N}H_2]$$

where $[Ph_2NH]_T$ is the total concentration of amine used

and

$$Ka = \frac{[Ph_2NH]_F[H^+]}{[Ph_2\overset{+}{N}H_2]}$$

$$[Ph_2NH]_F \left(1 + \frac{[H^+]}{Ka}\right) = [Ph_2NH]_T$$

Substitution gives

$$\text{Rate} = \frac{k[H^+][HNO_2][Ph_2NH]_T}{\left(1 + \frac{[H^+]}{K_a}\right)}$$

where $k = Kk_1$

From equation 2.1

$$\text{Rate} = k_o[Ph_2NH]_T$$

thus $$k_o = \frac{k\ Ka\ [HNO_2][H^+]}{(Ka + [H^+])} \qquad 2.2$$

Ka is the acid dissociation constant of the protonated amine,

K is the equilibrium constant for the formation of the nitrous acidium ion, and

k_1 is the rate constant as defined in scheme 2.1.

Two limiting cases exist for the expression for k_o (equation 2.2)

1) At low acid concentrations

$$Ka >> [H^+]$$

and k_o reduces to equation 2.3

$$k_o = k[H^+][HNO_2] \qquad 2.3$$

2) At higher acid concentrations

$$[H^+] >> Ka$$

and k_o reduces to equation 2.4

$$k_o = kKa[HNO_2] \qquad 2.4$$

These two limiting forms of equation 2.2 account for the behaviour illustrated in figure 1. At low acid concentrations there is a first order dependence on $[H^+]$ (equation 2.3) which reduces to a zero order dependence on $[H^+]$ (equation 2.4) at higher acid concentrations, and this accounts for the observed levelling off at higher acid concentrations.

Rewriting equation 2.2 in the reciprocal form gives

$$\frac{1}{k_o} = \frac{1}{k[H^+][HNO_2]} + \frac{1}{kK_a[HNO_2]}$$

The linearity of the plots of $(k_o)^{-1}$ versus $1/[H^+]$ are shown in figures 2 and 3. The values of the gradients and y-intercepts obtained from the two plots are given in table 2.4.

Table 2.4

$10^3[NaNO_2]/M$	slope /s mol l^{-1}	y-intercept /s
1.63	6.66 ± 0.13	4.4 ± 0.4
20.4	0.49 ± 0.01	0.37 ± 0.06

Given that the slope of the line represents $\frac{1}{k[HNO_2]}$ and the y-intercept $\frac{1}{kK_a[HNO_2]}$ values of K_a and $k(= Kk_1)$, shown in table 2.5 were determined.

Table 2.5

$10^3[NaNO_2]/M$	$k/l^2mol^{-2}s^{-1}$	K_a	K_a(mean)
1.63	92.1	1.51	1.44 ± 0.1
20.4	100	1.36	

No direct comparison can be made between the value of k determined in this study and those reported[2,12] for the nitrosation of a series of aromatic amines because of differences in experimental conditions. When it is compared with the value of k of $2.7 \times 10^3 l^2 mol^{-2} s^{-1}$ for the acid-catalysed nitrosation of 4-nitroaniline, an amine with a similar pKa value (literature value[13] 1.0) it is obviously at least an order of magnitude smaller. However, both values of the third order rate constant are well below the

Figure 2 Acid catalysis of N-nitrosodiphenylamine formation - double reciprocal plot ($[NaNO_2] = 1.63 \times 10^{-3}$M)

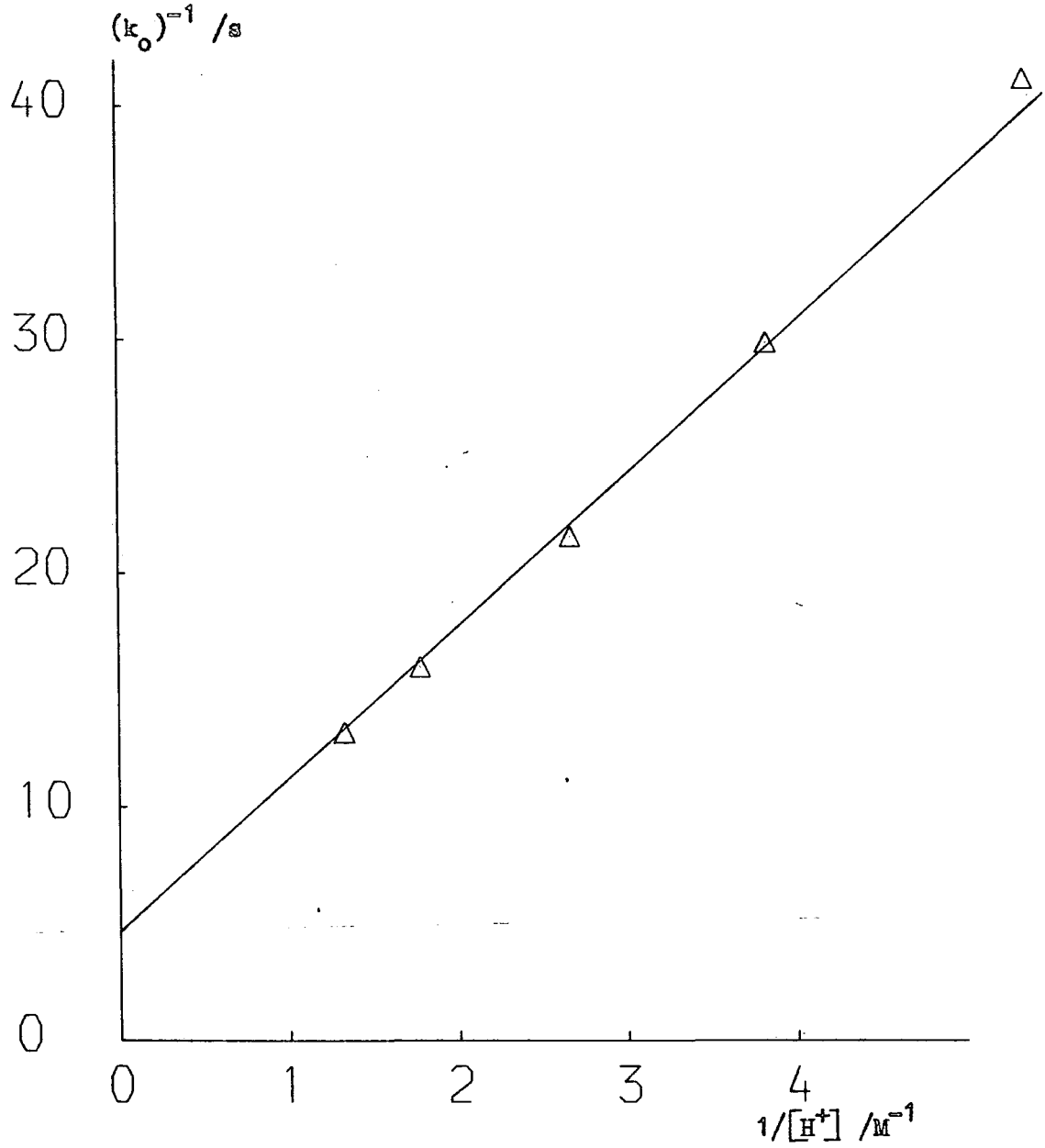
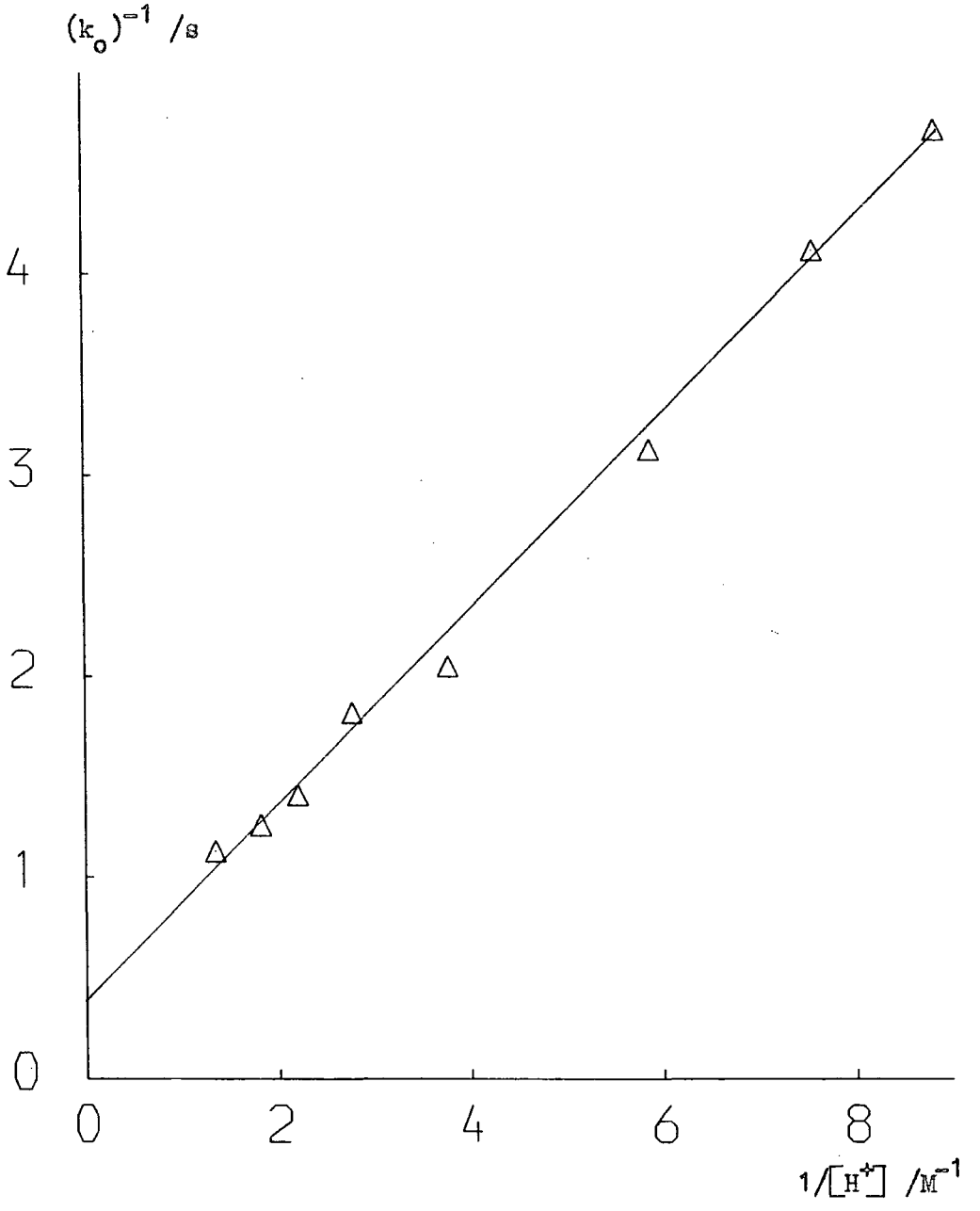


Figure 3 Acid catalysis of N-nitrosodiphenylamine formation - double reciprocal plot ($[NaNO_2] = 2.04 \times 10^{-2}$M)



limiting value[2] of ca.7 x 10^3 l^2 mol^{-2} s^{-1} for a diffusion-controlled process in water at 25°C.

2.2.2. The nucleophile catalysed reaction

Initial experiments indicated that the nitrosation of diphenylamine in acidic solution was subject to catalysis by added nucleophiles, as has previously been found for other similar systems.[1, 11, 14] Catalysis of the reaction by added chloride ions, bromide ions, thiocyanate ions and thiourea was examined and found to be significant. The results of the kinetic runs, all of which showed good first order behaviour with respect to the initial amine concentration, are given in tables 2.6, 2.7, 2.8 and 2.9 and in figure 4.

Table 2.6 catalysis by chloride ions

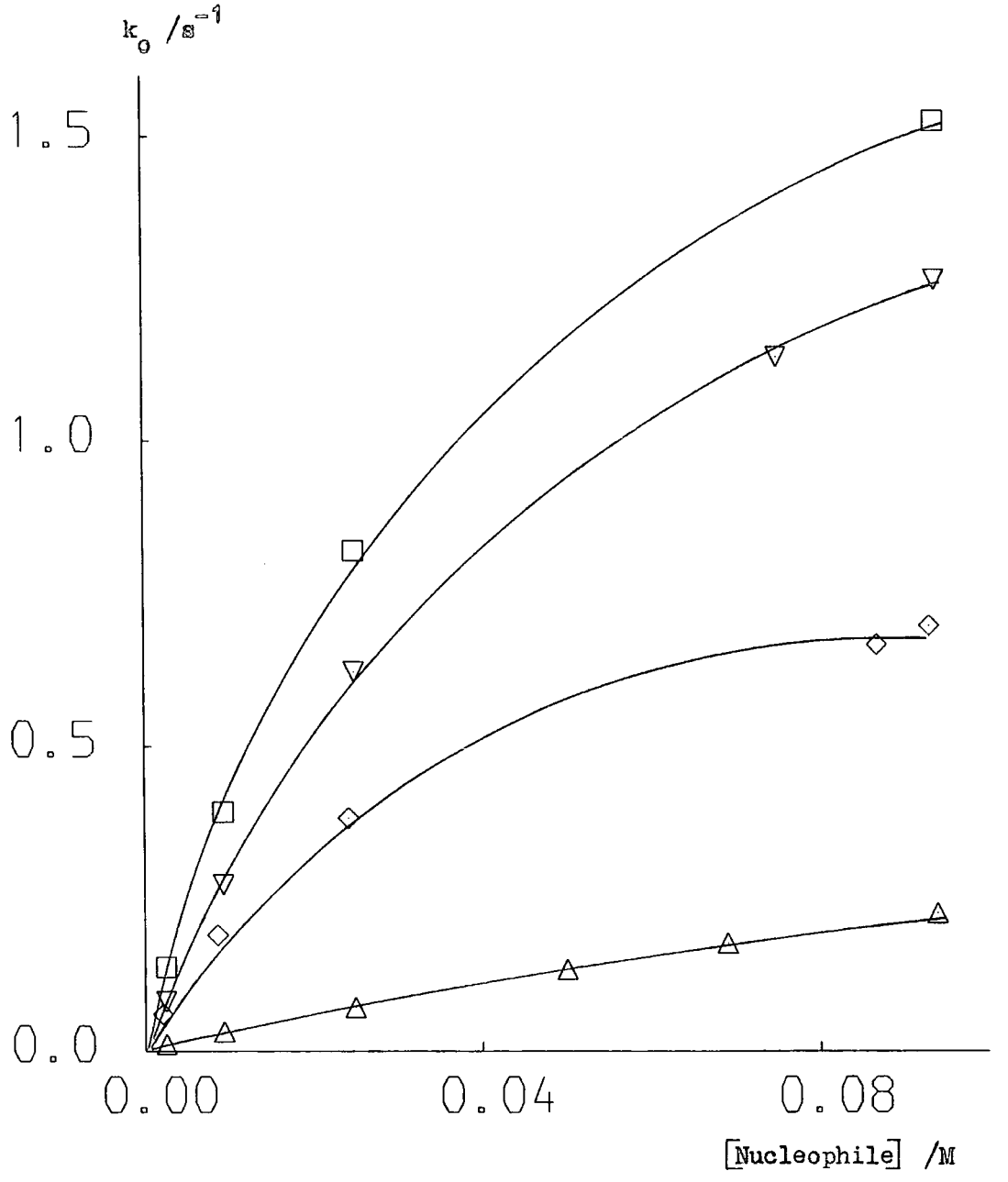
$[Ph_2NH] = 4.14 \times 10^{-5}M$

$[HClO_4] = 9.38 \times 10^{-2}M$

$[NaNO_2] = 8.15 \times 10^{-4}M$

$10^3[NaCl]/M$	$10^2k_o/s^{-1}$
2.50	1.18 ± 0.05
9.39	3.21 ± 0.07
25.0	7.26 ± 0.07
50.1	13.4 ± 0.08
69.0	17.7 ± 0.17
93.9	22.7 ± 0.25

Figure 4 Nucleophile catalysis of N-nitrosodiphenylamine formation



◇ thiourea
□ thiocyanate ion
▽ bromide ion
△ chloride ion

Table 2.7 catalysis by bromide ions

$[Ph_2NH] = 4.12 \times 10^{-5}M$

$[HClO_4] = 9.57 \times 10^{-2}M$

$[NaNO_2] = 8.16 \times 10^{-4}M$

$10^3[NaBr]/M$	$10^2 k_o s^{-1}$
2.50	8.19 ± 0.15
9.39	27.3 ± 0.51
25.0	62.2 ± 1.10
75.1	114 ± 2.94
93.9	127 ± 1.83

Table 2.8 catalysis by thiocyanate ions

$[Ph_2NH] = 4.14 \times 10^{-5}M$

$[HClO4] = 9.51 \times 10^{-2}M$

$[NaNO_2] = 8.16 \times 10^{-4}M$

$10^3[NaSCN]/M$	k_o/s^{-1}
2.50	0.14 ± 0.001
9.39	0.39 ± 0.004
25.0	0.82 ± 0.002
93.9	1.53 ± 0.002

Table 2.9 catalysis by thiourea

$[Ph_2NH] = 4.14 \times 10^{-5}M$

$[HClO4] = 9.13 \times 10^{-2}M$

$[NaNO_2] = 8.16 \times 10^{-4}M$

$10^3[SC(NH_2)_2]/M$	$10^3[SC(NH_2)_2]Free/M$	$10^2k_o/s^{-1}$
2.5	2.11	6.06 ± 0.16
9.39	8.74	19.0 ± 0.05
25.0	24.3	38.2 ± 0.26
87.6	86.8	66.7 ± 0.17
93.9	93.1	69.8 ± 0.56

For the thiourea catalysed reaction k_o is plotted against the concentration of free thiourea, $[SC(NH_2)]_F$. This is because a significant amount of the total thiourea is tied up as the S-nitroso adduct, $ONS^+(NH_2)_2$, due to the large equilibrium constant[15] ($K = 5000\ l^2\ mol^{-2}$ at 25°C) for its formation

$$(NH_2)_2CS + HNO_2 + H^+ \underset{}{\overset{K}{\rightleftharpoons}} (NH_2)_2CSNO^+ + H_2O$$

The concentration of free thiourea can easily be determined once the value of [NOX], where $X = SC(NH_2)_2$, has been calculated.

The value of the equilibrium constant, K_{NOX} for the formation of S-nitroso thiourea, NOX, can be expressed as:

$$K_{NOX} = \frac{[NOX]}{[H^+][HNO_2][X]_{Free}}$$

where $[H^+]$ is the concentration of the hydrogen ion after allowing for full protonation of the nitrite ion.

If, by definition

$$[\text{Total X}] = [\text{Free X}] + [\text{NOX}]$$

and

$$[\text{Total nitrite}] = [HNO_2] + [\text{NOX}]$$

substituting gives

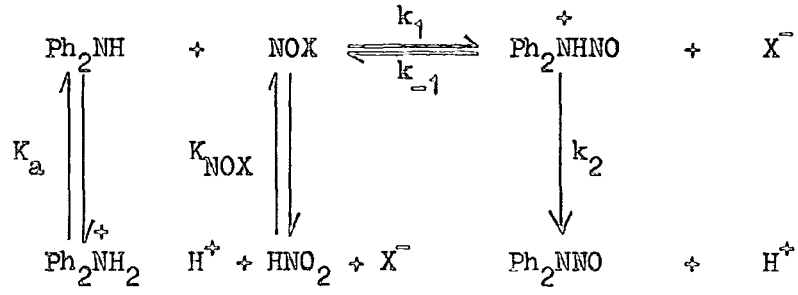
$$K_{NOX} = \frac{[\text{NOX}]}{[H^+]([\text{Total nitrite}] - [\text{NOX}])([\text{Total X}] - [\text{NOX}])}$$

The values of K_{NOX}, $[H^+]$, [Total nitrite] and [Total X] are all known so a value of [NOX] can be obtained, and thus the concentration of free thiourea determined.

It is widely believed[1,15] that nitrosation of secondary amines, in acid solution in the presence of added nucleophiles occurs via direct attack of the nitrosyl species, NOX, on the free base form of the amine.

The small positive intercept in figure 4, the plot of k_o versus [nucleophile], indicates that the acid catalysed reaction is insignificant relative to the nucleophile catalysed reaction, and so it is ignored in the determination of a rate expression for the reaction. Moreover, the plots of k_o versus [nucleophile] are distinctly curved at higher concentrations of added nucleophile, which suggests that the reverse reaction, denitrosation of nitrosamine, is important under the experimental conditions used.

A mechanism for the nucleophile catalysed nitrosation of diphenylamine is outlined in scheme 2.2.



Scheme 2.2

The overall equation for the above mechanism is given by:

$$\text{Rate} = k_1 [Ph_2NH]_F[NOX] - k_{-1} [Ph_2\overset{+}{N}HNO][X^-]$$

Assuming that $Ph_2\overset{+}{N}HNO$ is a reactive intermediate and therefore that its concentration remains small and constant during the course of the reaction, enables the steady state principle[16] to be used.

$$\frac{d[Ph_2\overset{+}{N}HNO]}{dt} = 0$$

$$0 = k_1 [Ph_2NH]_F[NOX] - k_{-1}[Ph_2\overset{+}{N}HNO][X^-] - k_2[Ph_2\overset{+}{N}HNO]$$

$$[Ph_2\overset{+}{N}HNO] = \frac{k_1 [Ph_2NH]_F[NOX]}{k_{-1}[X^-] + k_2}$$

but $[Ph_2NH]_F \left(1 + \frac{[H^+]}{K_a}\right) = [Ph_2NH]_T$ from equation 2.1

substituting

$$\text{Rate} = \frac{k_1 k_2 [NOX][Ph_2NH]_T}{(k_{-1}[X^-] + k_2)(1 + \frac{[H^+]}{K_a})}$$

since

$$K_{NOX} = \frac{[NOX]}{[HNO_2][H^+][X^-]}$$

$$\text{Rate} = \frac{k_1 k_2 K_a K_{NOX}[H^+][X^-][HNO_2][Ph_2NH]_T}{(k_{-1}[X^-] + k_2)(K_a + [H^+])}$$

The observed first order rate constant is defined by:

$$\frac{d[Ph_2NNO]}{dt} = k_o[Ph_2NH]_T$$

thus

$$k_o = \frac{k_1 k_2 K_a K_{NOX}[H^+][X^-][HNO_2]}{(k_{-1}[X^-] + k_2)(K_a + [H^+])} \qquad 2.6$$

$[H^+]$ is the free hydrogen ion concentration assuming complete protonation of the nitrite, K_{NOX} is the equilibrium constant for the formation of NOX, K_a is the acid dissociation constant of the protonated amine, and $k_1 k_2$ are the rate constants as defined in scheme 2.2.

Rewriting equation 2.6 in the reciprocal form

$$\frac{1}{k_o} = \frac{(k_{-1}[X] + k_2)(K_a + [H^+])}{k_2 k_1 K_a K_{NOX}[H^+][HNO_2][X^-]}$$

$$\frac{1}{k_o} = \frac{k_{-1}(K_a + [H^+])}{k_2 k_1 K_a K_{NOX}[H^+][HNO_2]} + \frac{(K_a + [H^+])}{k_1 K_a K_{NOX}[H^+][HNO_2][X^-]}$$

The observed experimental results are consistent with this expression since, for each nucleophile, plots of $(k_o)^{-1}$ versus $[X^-]^{-1}$ are linear with a positive intercept.

Values of the y-intercept which represents $\frac{k_{-1}(K_a + [H^+])}{k_2 k_1 K_{NOX} K_a [H^+][HNO_2]}$

and gradient, which represents $\frac{K_a + [H^+]}{k_1 K_{NOX} \quad K_a[H^+][HNO_2]}$

for each nucleophile are given in table 2.10.

Table 2.10 values of gradient and y-intercept

Nucleophile	Gradient /s mol l^{-1}	y-intercept /s
Chloride ion	$(2.77 \pm 0.07) \times 10^{-1}$	1.86 ± 0.4
Bromide ion	$(2.93 \pm 0.01) \times 10^{-2}$	$(4.82 \pm 0.24) \times 10^{-1}$
Thiocyanate ion	$(1.68 \pm 0.05) \times 10^{-2}$	$(5.8 \pm 1) \times 10^{-1}$
Thiourea	$(3.23 \pm 0.06) \times 10^{-2}$	1.25 ± 0.1

Using the known values of K_{NOX} for nitrosyl chloride (1.1×10^{-3} l^2 mol^{-2}),[17] nitrosyl bromide (5.1×10^{-2}),[18] and S-nitroso thiourea (5000 l^2 mol^{-2})[15] at 25°C in water and for nitrosyl thiocyanate (32 l^2 mol^{-2})[19] at 20°C in water, and the experimentally determined value of K_a of 1.44 (table 2.5) values of k_1 and of the ratio k_{-1}/k_2 have been calculated and are shown in table 2.11.

For the thiourea catalysed reaction a fraction of the hydrogen ion concentration will be tied up in the formation of the S-nitroso adduct. The variation in [Free H^+] for each thiourea concentration is negligible, 0.0901 to 0.0897. For the purposes of determining k_1 and the ratio k_{-1}/k_2 for the thiourea catalysed reaction $[H^+]$ was taken to be 0.09M.

Table 2.11 rate constants for the nucleophile catalysed nitrosation of diphenylamine

nucleophile	k_1/l mol^{-1} s^{-1}	k_{-1}/k_2
Chloride ion	4.45×10^7	7.0
Bromide ion	9.21×10^6	16.5
Thiocyanate ion	2.58×10^4	34.6
Thiourea	90	38.9

The rate constants, k_1 for the nucleophile catalysed nitrosation of diphenylamine are compared with values obtained for the nitrosation of aniline in table 2.12.

Table 2.12 rate constants for nitrosation by NOX

NOX	substrate	k_1 /l mol^{-1} s^{-1}	T/°C	Ref.
NOCl	aniline	2.5×10^9	25	20
	Ph_2NH	4.62×10^7	25	
NOBr	aniline	1.7×10^9	25	20
	Ph_2NH	9.22×10^6	25	
NOSCN	aniline	1.87×10^8	25	21
	Ph_2NH	2.68×10^4	25	
$NOSC(NH_2)_2^+$	aniline	3.7×10^5	0	14
	Ph_2NH	90	25	

The values of k_1 in table 2.12 may not be compared directly since the values of k_1 for diphenylamine were determined using values of K_{NOX} reported in the literature for the formation of the NOX species in water, and which will undoubtedly be different to those in 50% CH_3OH/H_2O solution. Woppman and Sofer[22] have reported values of

K_{NOX} of 5 x 10^{-2} and 2.0 l^2 mol^{-2} for NOCl and NOBr respectively in 100% methanol at 0°C. These are significantly different from the values of K_{NOX} 1.14 x 10^{-3} and 5.1 x 10^{-2} l^2 mol^{-2}, for NOCl and NOBr respectively, which were used in this work.

Although the nitrosation of diphenylamine by nitrosyl halides, nitrosyl thiocyanate and S-nitroso thiourea is rapid under the experimental conditions used it is probably not subject to diffusion control, whereas the reaction of aniline with NOCl and NOBr does approach the diffusion limit[2] of 7.4 x 10^9 l^2 mol^{-1} s^{-1}. However, the values of k_1 are consistent with the now established trend[4] of reactivity NOCl > NOBr > NOSCN > $NOS\overset{+}{C}(NH_2)_2$. The greater reactivity of nitrosyl chloride compared to nitrosyl bromide can be explained purely on electronegativity grounds since nitrosation of diphenylamine occurs by electrophilic attack by the NOX species. On account of the greater electronegativity of chlorine the nitrosyl-halide bond in NOCl will be more polarised than the corresponding bond in NOBr and consequently the -NO group more electrophilic. More recently Jørgensen[23] has used theoretical calculations to demonstrate that nitrosyl thiocyanate is a poorer nitrosating agent than nitrosyl chloride.

The results obtained for the ratio k_{-1}/k_2 for the nucleophile catalysed reactions are compared in table 2.13 with those obtained by Williams and co-workers.[21,22]

Table 2.13 ratios of k_{-1}/k_2 for the nucleophile catalysed nitrosation of amines.

Substrate	NOCl	NOBr	NOSCN	$\overset{+}{N}OSC(NH_2)_2$
Ph_2NH	6.7	16.5	34.6	38.9
$X - C_6H_4NH_2$				
X				
$4 - NO_2$	1.6^{20}	25^{20}		
4 - Cl	0.096^{20}	5.6^{20}	52^{21}	
$4 - CO_2H$	0.42^{20}	13^{20}	63^{21}	

For the same amine the ratio k_{-1}/k_2 increases as the nucleophile is changed from chloride to thiourea. Since k_2 is independent of the nuclephile the ratio k_{-1}/k_2 gives a direct comparison of the efficiencies of the catalysts in step k_{-1} i.e. the denitrosation of N-nitrosodiphenylamine. The results indicate that the reactivity increases in the order $Cl < Br < SCN < SC(NH_2)_2$ which is consistent with increasing nucleophilicity as predicted by the Pearson nucleophilicity parameter, n,[11] and with what has previously been found.[10, 14,24]

For the nitrosation of a substrate, S, in the presence of a nucleophile, X, the degree of catalysis is dependent upon two factors:

(a) the equilibrium constant for NOX formation, and

(b) the rate constant, k_1 in scheme 2.2, for attack by NOX on S. According to the results in table 2.12 S-nitroso thiourea is the least reactive nitrosating agent of those studied and so the greater catalytic effect of thiourea relative to the other nucleophiles may be explained in terms of the large equilibrium constant for the formation of $\overset{+}{N}OSC(NH_2)_2$ ($5000\ l^2\ mol^{-2}$)[15]

In conclusion it appears that the magnitude of K_{NOX} is the more important factor in explaining the overall catalytic efficiency in these reactions.

2.3. Nitrosation of ammonia

Nitrosation of ammonia has been studied by many groups of workers,[25] with the aim of determining the mechanism of decomposition of ammonium nitrite. Catalysis of the nitrosation by chloride and bromide ion has been studied[26], however the authors neglected to consider decomposition of the nitrous acid which is significant under the experimental conditions that they used.

A kinetic study of the nucleophile catalysis of the nitrosation of ammonium sulphate was made and the results are presented below. It proved impossible to compare the catalytic efficiency of thiourea since the decomposition of the S-nitroso adduct was faster than the nitrosation reaction.

All kinetic measurements were made at 25°C following the decrease in absorbance at 384nm, due to nitrous acid using a conventional UV/visible spectrophotometer. In all experiments there was a large excess of ammonium sulphate over the concentration of sodium nitrite. The observed rate of reaction was quite slow and because of this, and the problems associated with the evolution of gas in the reaction cell the initial rate method was used to determine the observed first order rate constant, k_o (defined in equation 2.7).

$$\frac{-d[HNO_2]_T}{dt} = k_o[HNO_2] \qquad 2.7$$

where $k_o = k_{o1} - k_{o2}$ 2.8

k_{o1} is the observed first order rate constant for the reaction of nitrous acid with NH_4^+ in the presence or absence of added nucleophile, as required.

k_{o2} is the observed first order rate constant for the decomposition of nitrous acid under identical conditions to those at which the corresponding k_{o1} value was measured.

Each value of k_{o1} and k_{o2} quoted is the mean of at least three separate runs.

2.3.1 The acid catalysed reaction.

The effect of added nitrite on the observed first order rate constant at constant acid and ammonium sulphate was examined, and the results shown in table 2.14.

Table 2.14 variation of k_o with nitrite

$[(NH_4)_2SO_4] = 0.75M$

$[HClO_4] = 3.48M$

$10^3[NaNO_2]/M$	10^4(mean k_{o1})/s^{-1}	10^4(mean ko_2)/s^{-1}	10^4(mean k_o)/s^{-1}
3.82	7.3 ± 0.2	2.7 ± 0.2	4.6
7.64	10 ± 0.9	5.3 ± 0.1	4.7

The first order dependence upon $[HNO_2]$indicates that any reaction involving dinitrogen trioxide as the active nitrosating agent can be ignored, and is consistent with reaction with either $H_2NO_2^+$ or NO^+, which cannot be distinguished kinetically.

In the absence of a nucleophile the observed acid catalysed reaction was so slow that it could not be measured with any accuracy.

2.3.2. The nucleophile catalysed reaction

Catalysis of the nitrosation of ammonium sulphate by bromide and thiocyanate ion was investigated. The results presented in tables 2.15 and 2.16, and in figure 5 clearly show that the addition of these anions does have the expected[4] catalytic effect $Br^- < SCN^-$

Table 2.15 catalysis by bromide ions

$[(NH_4)_2SO_4] = 0.75M$

$[HClO_4] = 0.1M$

$[NaNO_2] = 3.75 \times 10^{-3}M$

$[NaBr]/M$	$10^4(\text{mean } k_o)/s^{-1}$
0.2	1 ± 0.04
0.4	2.9 ± 0.2
0.6	2.9 ± 0.2
0.8	5.3 ± 0.1
1.0	6 ± 0.5

Table 2.16 catalysis by thiocyanate ions

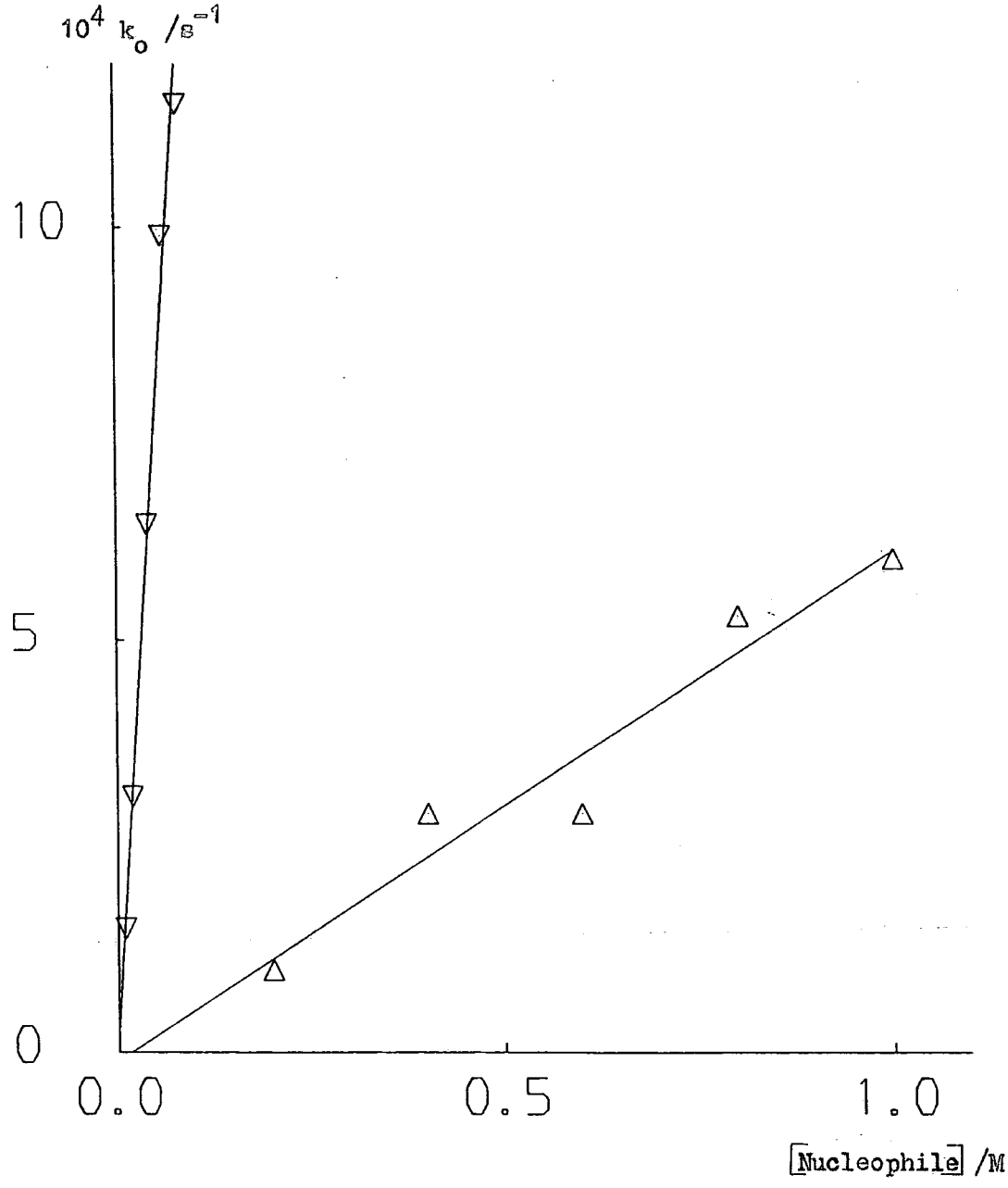
$[(NH_4)_2SO_4] = 0.75M$

$[HClO_4] = 0.1M$

$[NaNO_2] = 3.76 \times 10^{-3}M$

$10^2[NaSCN]/M$	$10^4(\text{mean } k_o)/s^{-1}$
1	1.5 ± 0.2
2	3.1 ± 0.3
4	6.4 ± 0.1
6	9.9 ± 0.3
8	11.5 ± 0.1

Figure 5 Nucleophilie catalysis for the nitrosation of ammonia



▽ thiocyanate ion

△ bromide ion

For both nucleophiles the plot of k_o versus [nucleophile] was linear with a small positive intercept from which the third order rate constant for the acid catalysed reaction can be determined.

The dependence of k_o on $[(NH_4)_2SO_4]$ in the presence of a fixed concentration of either bromide or thiocyanate ion was also examined. The results are presented in tables 2.17 and 2.18, and in figure 6. For a plot of k_o versus $[NH_4^+]$ the point 0,0 is valid.

Table 2.17 dependence of k_o on $[(NH_4)_2SO_4]$

$[HClO_4] = 0.1M$

$[NaBr] = 0.4M$

$[NaNO_2] = 3.76 \times 10^{-3}M$

$[(NH_4)_2SO_4]/M$	10^4(mean k_o)/s^{-1}
0	0
0.38	0.6 ± 0.1
0.75	1.5 ± 0.1
1.5	2.8 ± 0.2

Table 2.18 dependence of k_o on $[(NH_4)_2SO_4]$

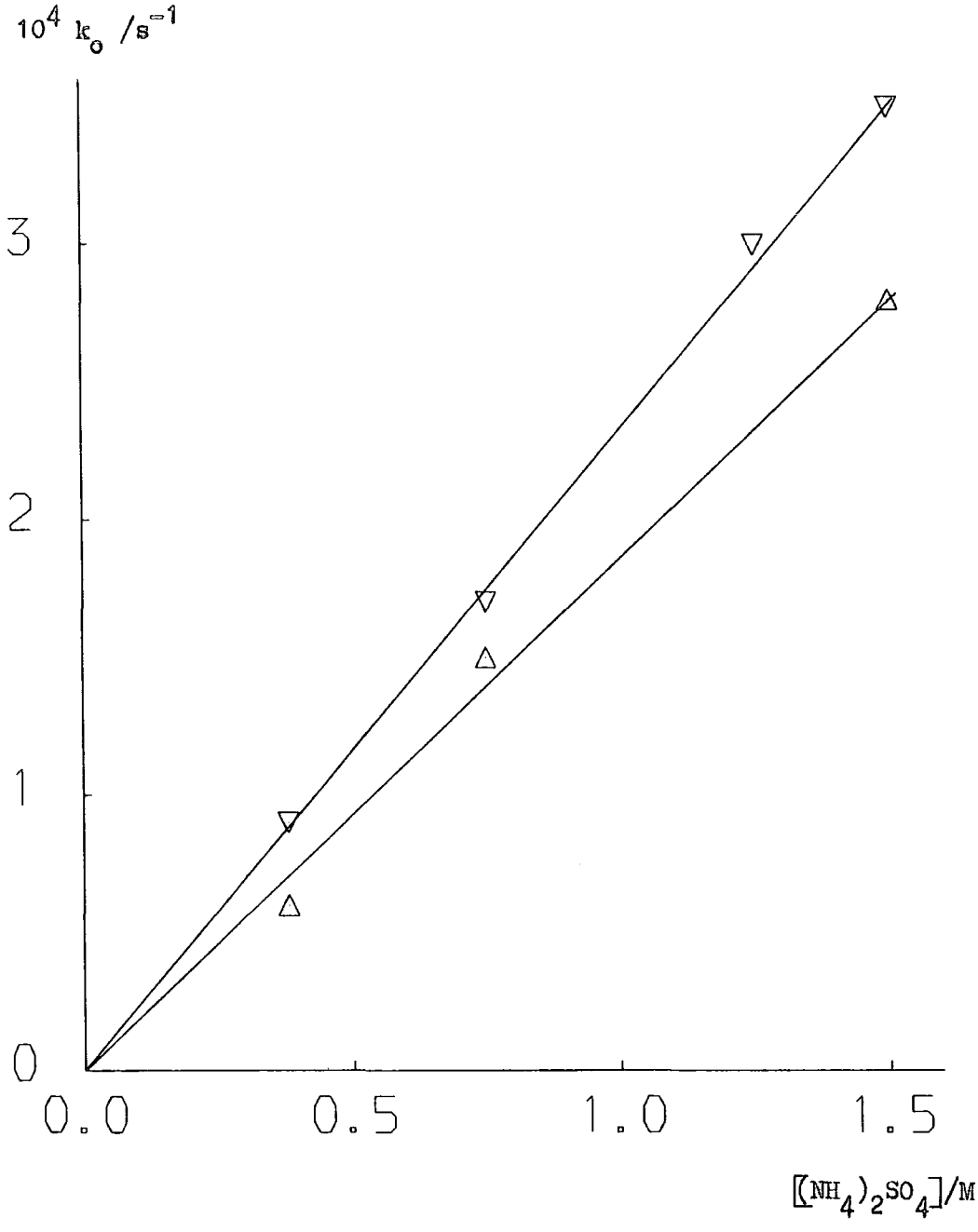
$[HClO_4] = 0.1M$

$[NaSCN] = 2 \times 10^{-2}M$

$[NaNO_2] = 3.76 \times 10^{-3}M$

$[(NH_4)_2SO_4]/M$	10^4(mean k_o)/s^{-1}
0	0
0.38	0.9 ± 0.2
0.75	1.7 ± 0.3
1.25	3.0 ± 0.4
1.5	3.5 ± 0.4

Figure 6 Variation of k_o with $[(NH_4)_2SO_4]$

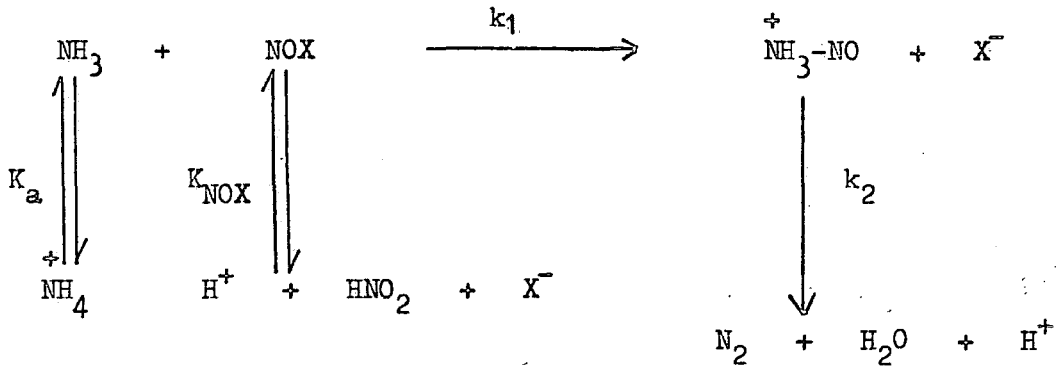


▽ thiocyanate ion

△ bromide ion

The linearity of the plots in figure 6 establish that the reaction is, as expected, first order in ammonium sulphate.

It is likely that the reaction occurs via attack of the nitrosating agent, NOX, on the free base form of the amine as outlined in scheme 2.3



Scheme 2.3

The rate of reaction can be expressed as defined in equation 2.9

$$\text{Rate} = k_1[NH_3]_F[NOX] \qquad 2.9$$

where $[NH_3]_F$ is the concentration of the free base form of the amine, assuming the contribution from the acid catalysed reactions is negligible.

since $$K_{NOX} = \frac{[NOX]}{[H^+][X^-][HNO_2]}$$

and if, by definition

$$[HNO_2]_T = [HNO_2] + [NOX]$$

where $[HNO_2]_T$ is the total nitrous acid concentration

$$NOX = \frac{[HNO_2]_T}{\left(1 + \frac{1}{K_{NOX}[H^+][X^-]}\right)}$$

$$K_a = \frac{[NH_3]_F[H^+]}{[NH_4^+]}$$

Under the experimental conditions used $[NH_4^+]$ represents the total concentration of ammonium sulphate, $[NH_3]_T$, present.

substituting

$$\text{Rate} = \frac{k_1 K_a [NH_3]_T [HNO_2]_T K_{NOX}[X^-]}{(1 + K_{NOX}[H^+][X^-])} \qquad 2.10$$

from equation 2.7 $\quad \text{Rate} = k_o[HNO_2]_T$

$$k_o = \frac{k_1 K_a K_{NOX}[NH_3]_T[X^-]}{(1 + K_{NOX}[H^+][X^-])} \qquad 2.11$$

K_a is the acid dissociation constant of the protonated amine

K_{NOX} is the equilibrium constant for the formation of NOX

and k_1 is the rate constant as defined in scheme 2.3.

For nitrosyl bromide K_{NOBr}[18] is small, 5.1×10^{-2} l^2 mol^{-2}, so at reasonably low concentrations of bromide and acid the limiting condition (equation 2.12) applies,

$$1 >> K_{NOX}[H^+][X^-] \qquad 2.12$$

and equation 2.11 reduces to

$$k_o = k_1 K_a [NH_3]_T K_{NOX}[X^-] \qquad 2.13$$

This reduced form of the expression for k_o is consistent with observed experimental results. It predicts the first order dependence on $[Br^-]$ and $[(NH_4)_2SO_4]$ that was found.

The value of K_{NOX} for X = thiocyanate ion is much larger, 32 l^2 mol^{-2} at 20°C.,[19] however at low concentrations of thiocyanate ion and acid the limiting form of the rate expression still applies. As the concentration of thiocyanate and or acid is increased significantly a plot of k_o versus $[SCN^-]$ would be expected

to curve off as the limiting form for k_o (equation 2.12) becomes less applicable.

Values of the gradients, which represent $k_2K_a[NH_3]_TK_{NOX}$ for a plot of k_o versus $[X^-]$, and $k_2K_a[X^-]K_{NOX}$ for a plot of k_o versus $[(NH_4)_2SO_4]_T$, are given in table 2.19. Using the figures in table 2.19,

Table 2.19

Nucleophile	Gradient / 1 mol^{-1} s^{-1}	
	from $[X^-]$ dependence	from $[NH_3]_T$ dependence
Bromide ion	$(5.74 \pm 0.9) \times 10^{-4}$	$(1.87 \pm 0.1) \times 10^{-4}$
Thiocyanate ion	$(1.47 \pm 0.1) \times 10^{-2}$	$(2.33 \pm 0.1) \times 10^{-4}$

the known values of K_{NOX} for $X = Br^-$ (5.1×10^{-2} l^2 mol^{-2}),[18] $X = SCN^-$ ($32 \cdot 1^2$ mol^{-2}),[19] and pKa[13] (NH_4^+) = 9.5, values of the bimolecular rate constants for the nitrosation of ammonium sulphate by nitrosyl bromide and nitrosyl thiocyanate have been determined and are shown in table 2.20.

Table 2.20 bimolecular rate constant s for nucleophile catalysed nitrosation of NH_4^+

Nucleophile	k_1 / 1 mol^{-1} s^{-1}		
	from $[X^-]$ dep.	from $[NH_3]_T$ dep.	average
Bromide ion	2.36×10^7	2.90×10^7	$(2.63 \pm 0.4) \times 10^7$
Thiocyanate ion	9.69×10^5	1.15×10^6	$(1.06 \pm 0.1) \times 10^6$

The results in table 2.20, which are discussed in detail in section 2.5, clearly show the now established trend[4] of reactivity NOBr $>$ NOSCN.

2.4. N-nitrosation of dimethylamine

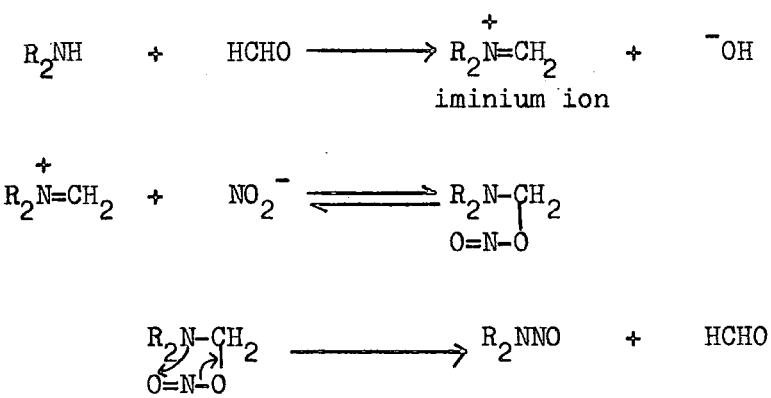
One of the first studies of the reaction of nitrous acid with dimethylamine was made by Taylor and Price.[27] They found that the nitrosation followed the expression below (equation 2.14) under the conditions that they used.

$$\text{Rate} = k[Me_2NH][HNO_2]^2 \qquad 2.14$$

However, it was the discovery, by Magee and Barnes,[28] that N-nitrosodimethylamine was carcinogenic in rats that prompted much research into the area of N-nitrosamine formation and toxicology.

It has been found[29] that N-nitrosodimethylamine can be produced in vivo from the reaction of nitrite and aminopyrine, a common tertiary amine drug.

Catalysis of N-nitrosamine formation has attracted a lot of attention. Casado and co-workers[30] have found that formaldehyde acts as a catalyst for N-nitrosodimethylamine formation in neutral and alkaline conditions. Rather than forming a new nitrosating agent, as is the case for the halides, it catalyses the reaction by forming an iminium ion, a new nitrosable species, as outlined in scheme 2.4.



Scheme 2.4

The effect of added nucleophiles on the reaction of dimethylamine with nitrous acid has been studied by many groups of workers.[27,31,32] Casado and co-workers found[31] that the reaction was subject to

catalysis by added chloride and bromide ion. As expected[1] the active nitrosating agent under these conditions was the nitrosyl halide. In another study of catalysis of N-nitrosodimethylamine formation Masui and co-workers found[32] that the overall catalytic efficiency of the alkyl thioureas depended not only on the equilibrium constant for the formation of S-nitroso alkyl thiourea, but also on the decomposition of the thiourea by nitrous acid. Out of a series of alkyl thioureas studied tetramethylthiourea was found to exhibit the largest catalytic efficiency.

The aim of this work, presented below, was to make a study of the nitrosation of dimethylamine in the presence of bromide and thiocyanate ion and to compare the results with those obtained for the nitrosation of ammonium sulphate.

In all experiments the reaction was followed by monitoring the increase in absorbance at 332nm, due to the product nitrosamine using a conventional UV/visible spectrophotometer. Reactions were carried out at 25°C under first order conditions with a large excess of amine over the concentration of sodium nitrite. Individual values of k_o, the observed first order rate constant, defined in equation 2.15, were determined using the initial rate method

$$\frac{d[(CH_3)_2NNO]}{dt} = k_o[HNO_2] \qquad 2.15$$

where $[HNO_2]$ is the total nitrite concentration.
The k_o values quoted are the mean of at least three separate determinations.

In the absence of added nucleophile the observed rate of nitrosation was too slow to be followed.

2.4.1. The nucleophile catalysed reaction

Since dimethylamine is present as the hydrochloride salt there will be a contribution from the chloride ion catalysed reaction in all experimental runs.

The catalytic effect of added bromide and thiocyanate ion at constant pH and concentration of sodium nitrite and amine was investigated. The results are presented in tables 2.21 and 2.22 and in figure 7.

Table 2.21 catalysis by bromide ion

$[(CH_3)_2NHHCl] = 1$ M

$[NaNO_2] = 7.9 \times 10^{-3}$ M

pH = 1.5

$[NaBr]$/M	10^5 (mean k_o) /s^{-1}
1	2.1 ± 0.05
1.4	3 ± 0.07
1.6	3.4 ± 0.09
2.08	4.2 ± 0.09

Table 2.22 catalysis by thiocyanate ion

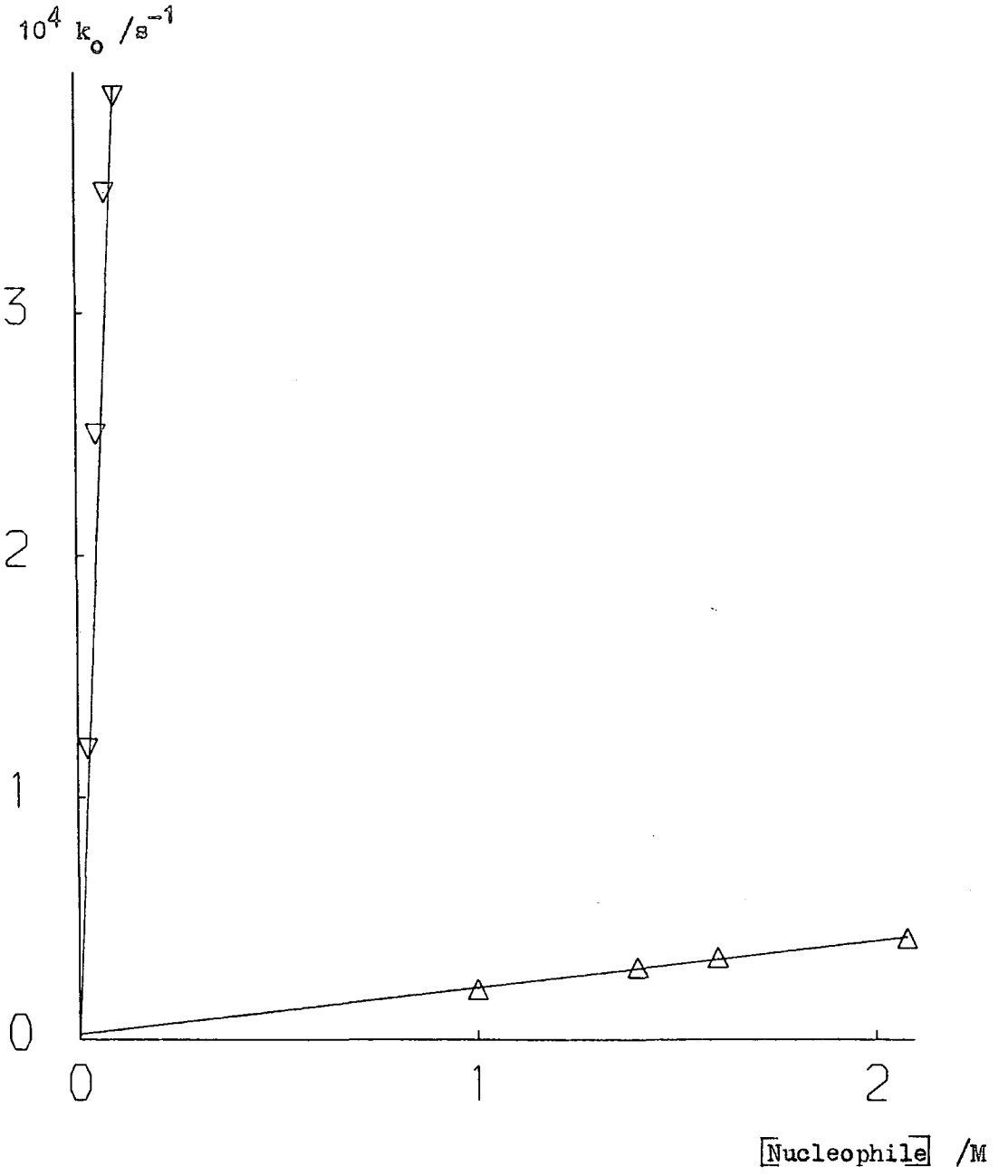
$[(CH_3)_2NHHCl] = 0.5$ M

$[NaNO_2] = 7.9 \times 10^{-3}$ M

pH = 1.5

$10^2[NaSCN]$ /M	10^4 (mean k_o) /s^{-1}
2.5	1.2 ± 0.05
5	2.5 ± 0.04
7.5	3.5 ± 0.07
10	3.9 ± 0.03

Figure 7 Nucleophile catalysis of N-nitrosodimethylamine formation



▽ thiocyanate ion

△ bromide ion

The results in table 2.21 show that the variation of k_o with added [NaBr] is very small, and it may well be attributable to a salt effect. However, for the remainder of this study it is assumed that bromide ion does act as a catalyst for this reaction.

The variation of the observed first order rate constant with added dimethylammonium chloride was examined and the results are shown in table 2.23. These reactions were carried out in the presence of a constant concentration of sodium thiocyanate and at constant pH. Sodium chloride was also added to the reaction solutions in order to maintain a constant chloride ion concentration.

Table 2.23 dependence of k_o on $[(CH_3)_2NHHCl]$

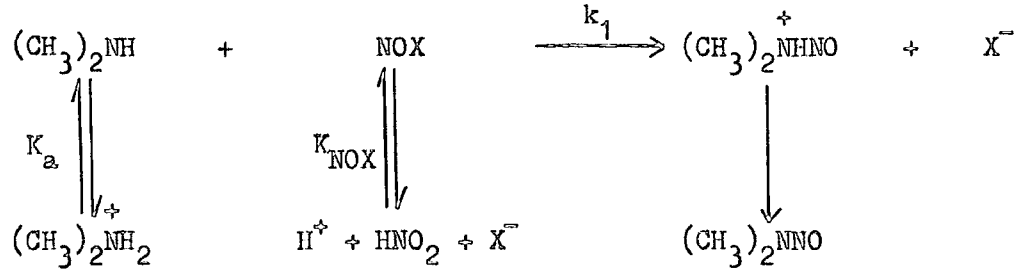
$[NaSCN] = 5 \times 10^{-2}$ M

$[NaNO_2] = 7.9 \times 10^{-3}$ M

pH=1.5

$[(CH_3)_2NHHCl]$/M	10^4(mean k_o) /s^{-1}
0	0
0.4	2 ± 0.09
0.71	3.7 ± 0.09
1.01	5.2 ± 0.08

The linearity of the plots of k_o versus [nucleophile], and k_o versus [amine] indicates that the reaction exhibits a first order dependence on [nucleophile] and [amine]. In addition, within experimental error, there was quantitative formation of the product nitrosamine. The results may all be interpreted in terms of attack by the nitrosyl bromide or nitrosyl thiocyanate on the free base form of the amine, as would be expected,[15] and as is outlined in scheme 2.5.



Scheme 2.5

Ignoring the contribution from the acid catalysed and chloride catalysed reaction the rate of reaction is defined in equation 2.16

$$\text{Rate} = k_1 [(CH_3)_2NH][NOX] \qquad 2.16$$

and using an identical derivation to that used in 2.3.2 the rate of reaction can be expressed as:

$$\text{Rate} = \frac{k_1 K_a [(CH_3)_2NH]_T [HNO_2]_T K_{NOX} [X^-]}{(1 + K_{NOX}[H^+][X^-])} \qquad 2.17$$

Since $\text{Rate} = k_o [HNO_2]_T$ from equation 2.15

$$k_o = \frac{k_1 K_{NOX} K_a [(CH_3)_2NH]_T [X^-]}{(1 + K_{NOX}[H^+][X^-])} \qquad 2.18$$

K_a is the acid dissociation constant of the protonated amine, K_{NOX} is the equilibrium constant for the formation of NOX and k_1 is the rate constant as defined in scheme 2.5.

As was previously discussed in Section 2.3.2, if $1 >> K_{NOX}[H^+][X^-]$ then equation 2.18 reduces to

$$k_o = k_1 K_a [(CH_3)_2NH]_T K_{NOX} [X^-] \qquad 2.19$$

A linear correlation was obtained for the plot of k_o versus $[Br^-]$, however the plot of k_o versus $[SCN^-]$ is linear except at the highest concentration of sodium thiocyanate used since here the limiting equation 2.19 no longer applies. Using values of K_{NOBr}[18] $= 5.1 \times 10^{-2}$ l^2 mol^{-2}, K_{NOSCN}[19] $= 32$ l^2 mol^{-2} and pKa[15] $(CH_3)_2NH = 10.77$ the bimolecular rate constants for the bromide and

thiocyanate ion catalysed nitrosation of $(CH_3)_2NH$ were obtained from the slope of the plot of k_o versus $[X^-]$ and are given in table 2.24. The value of k_1 for the bromide ion catalysed reaction

Table 2.24 values of k_1 for the nitrosation of dimethylamine by nitrosyl bromide and nitrosyl thiocyanate

nucleophile	$10^7 k_1$/l mol^{-1} s^{-1}
bromide ion	2.26
thiocyanate ion	1.74

compares favourably with the value of 3.36×10^{-7} l mol^{-1} s^{-1} obtained by Casado and co-workers[31] for the same reaction, indicating that the small change in k_o observed as [NaBr] was increased may not be attributable to a salt effect.

As expected,[4] nitrosyl bromide is more reactive than nitrosyl thiocyanate, however, it is interesting to note the similarity between the two k_1 values.

2.5 Comparison of the rates of nitrosation of $(CH_3)_2NHHCl$ and $(NH_4)_2SO_4$.

The experimentally determined bimolecular rate constants, k_1, for the nitrosation of ammonia and dimethylamine by nitrosyl bromide and nitrosyl thiocyanate are given in table 2.25. For comparison purposes listed with them are the values of k_1 for the nitrosation by NOX of a range of substrates.

Table 2.25 Values of the bimolecular rate constants for the reaction of NOX with a range of substrates.

Substrate	pKa	$10^7 k_1$/l mol^{-1} s^{-1}			Temp/°C	Ref.
		NOSCN	NOBr	NOCl		
Ammonia	9.5	0.106	2.63		25	*
Ammonia			190	300	25	26
Dimethylamine	10.77	1.74	2.26		25	*
Dimethylamine			3.36	3.1	25	31
Morpholine	8.38	2.8	4.9		31	14
Hydroxylamine		0.36	3.7	3.5	0	33
Hydroxylamine		1.2	17	59	25	12
O-methyl hydroxylamine		0.13	1.8	1.6	0	33
Aniline	4.51	270	910		30	14

* This work

The anomalously high values of k_1 obtained by Schmid and co-workers[26] for the nitrosation of ammonia by nitrosyl halides may be due to the fact that the authors neglected the decomposition of nitrous acid when determining their rate constants.

For aromatic amines it has been found[20] that k_1 rose with the pKa value of the amine and that it levelled off only as the calculated diffusion controlled limit, of 7.4×10^9 l mol^{-1} s^{-1} for reactions at 25°C in water[34], was approached.

The overall range of experimentally determined bimolecular rate constants for the nitrosation of ammonium sulphate and dimethylamine is noticeably small and the actual values are approximately one hundred times smaller than the calculated encounter rate. In fact, as can be seen from the collected results in table 2.25, this seems

to be the case for all of the substrates mentioned, with the exception of aniline and for the reaction of hydroxylamine with nitrosyl chloride. In addition there appears to be no correlation between bascity of the amine and the bimolecular rate constant. Combined together these results suggest that the nitrosation of non-aromatic substrates by NOX approach diffusion control despite the fact that the bimolecular rate constants for the reactions are only of the order of 10^7 l mol^{-1} s^{-1}. The reason for this discrepancy in k_1 values is not understood.

As was discussed previously in section 2.2, the degree of catalysis by added nucleophiles for the nitrosation of an amine in acidic solution is dependent on two factors: (a) the value of K_{NOX} and (b) the value of the bimolecular rate constant, k_1. Clearly, because of the close proximity of k_1 values for the nitrosation of the amine by NOBr or NOSCN, the explanation for the overall catalytic efficiency of thiocyanate compared to bromide ion does not lie in the magnitude of k_1 but depends on the value of K_{NOX}, which is significantly larger for X = SCN^- (K_{NOSCN}[19] = 32 l^2 mol^{-2}, K_{NOBr}[18] = 5.1 x 10^{-2} l^2 mol^{-2}).

2.6. pH dependence for the nitrosation of $(CH_3)_2NHHCl$ by NOSCN

It is generally accepted that the nitrosation of secondary amines is pH dependent.[1] Since the report by Sander and co-workers[35] that nitrosation of both aromatic and aliphatic amines by nitrous acid gave optimum yields of nitrosamine in the pH range 1 to 3, which corresponds to conditions found in human and animal stomachs, a number of pH studies have been performed.

In the absence of added nucleophiles the chief nitrosating agent under acidic conditions with pH > 1 is nitrous anhydride, which is formed reversibly from two molecules of nitrous acid (scheme 2.6). Under these conditions the reaction rate will depend on the

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O$$

$$R_2NH + N_2O_3 \longrightarrow R_2NNO + HNO_2$$

Scheme 2.6

concentrations of nitrous acid and amine, in its free base form.

Mirvish[36] made a study of the nitrosation of dimethylamine under conditions where N_2O_3 is the nitrosating agent and found the rate of reaction was maximal at pH 3.4. This is consistent with the theory proposed by Fan and Tannenbaum,[37] that the nitrosation of any amine whose pKa is greater than 5 will react fastest at pH 3.36, or the corresponding value of pka for nitrous acid at the reaction temperature.

It has been found that the extent of catalysis for the nitrosation of N-methylaniline,[38] morpholine,[37] hydroxylamine[33] amd amino acids[39] by thiocyanate ion is dependent on the pH of the solution and the relative reactant concentrations. However in general the overall effect is to shift the maximal reaction rate from pH 3.37 to lower pH.

The aim of this work was to investigate the effect of pH on thiocyanate ion catalysis on N-nitrosodimethylamine formation, and to compare the results with those obtained in the presence of bromide ion[31] and in the absence of added nucleophile.[36]

The reaction was followed by monitoring the increase in absorbance at 332nm, due to the product nitrosamine, on a conventional UV/visible spectrophotometer. The reactions were carried out at 25°C

under first order conditions with excess amine over the sodium nitrite concentration. The observed first order rate constant, k_o, is defined in equation 2.20.

$$\frac{d[(CH_3)_2NNO]}{dt} = -\frac{d[HNO_2]}{dt} = k_o[HNO_2] \qquad 2.20$$

Since dimethylamine is added as the hydrochloride salt there will be a contribution from the chloride catalysed reaction in all experimental runs.

2.6.1. Variation of k_o with pH

The dependence of k_o on pH was examined at two different thiocyanate ion concentrations. The results are presented in tables 2.26 and 2.27 and in figure 8.

Table 2.26

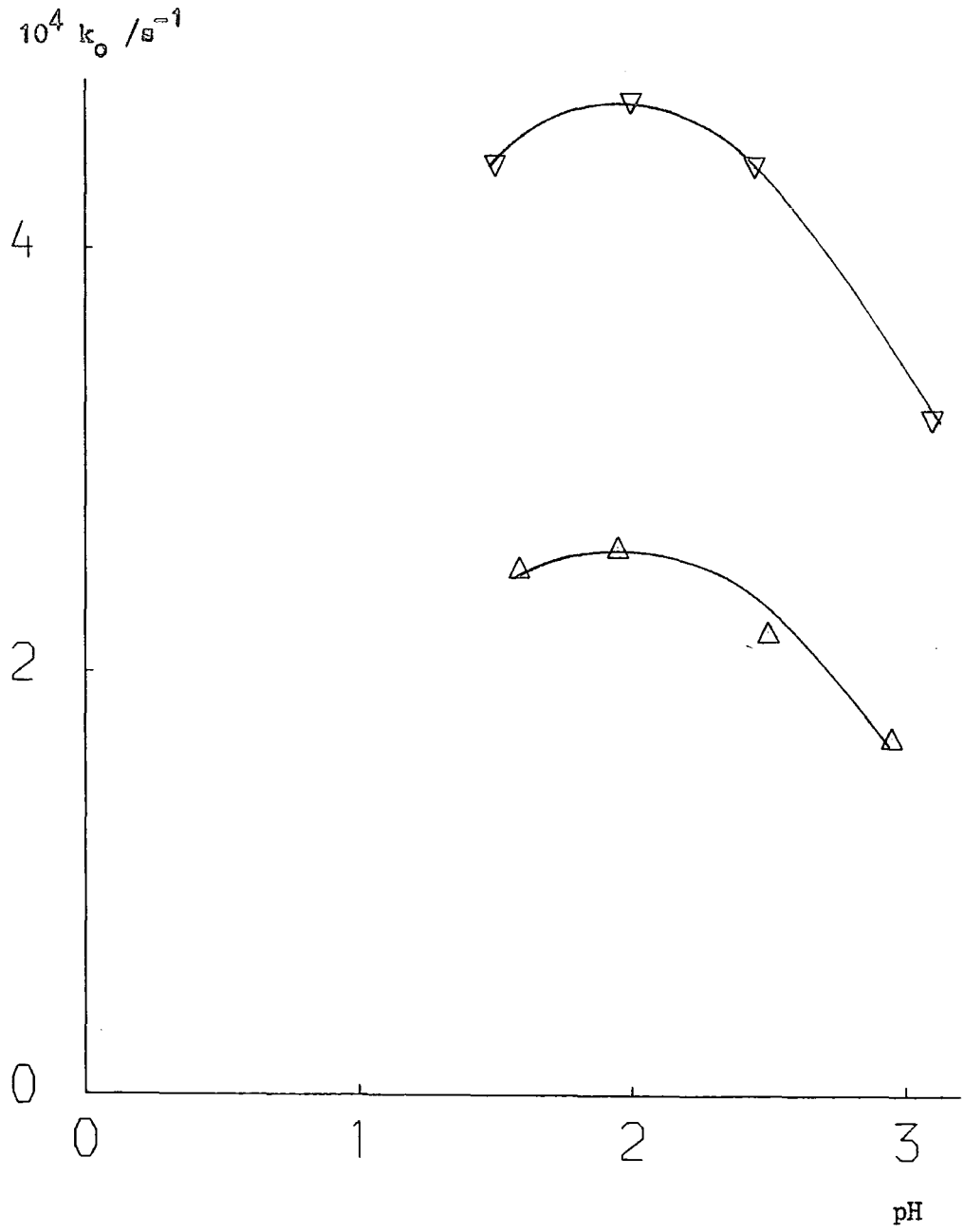
$[(CH_3)_2NHHCl] = 0.508M$

$[NaSCN] = 5 \times 10^{-2}M$

$[NaNO_2] = 8 \times 10^{-3}M$

pH	$10^4 k_o/s^{-1}$
1.59	2.5
1.95	2.6
2.5	2.2
2.95	1.7

Figure 8 pH dependence for N-nitrosodimethylamine formation



▽ [NaSCN] = 0.1M

△ [NaSCN] = 5 x 10^{-2}M

Table 2.27

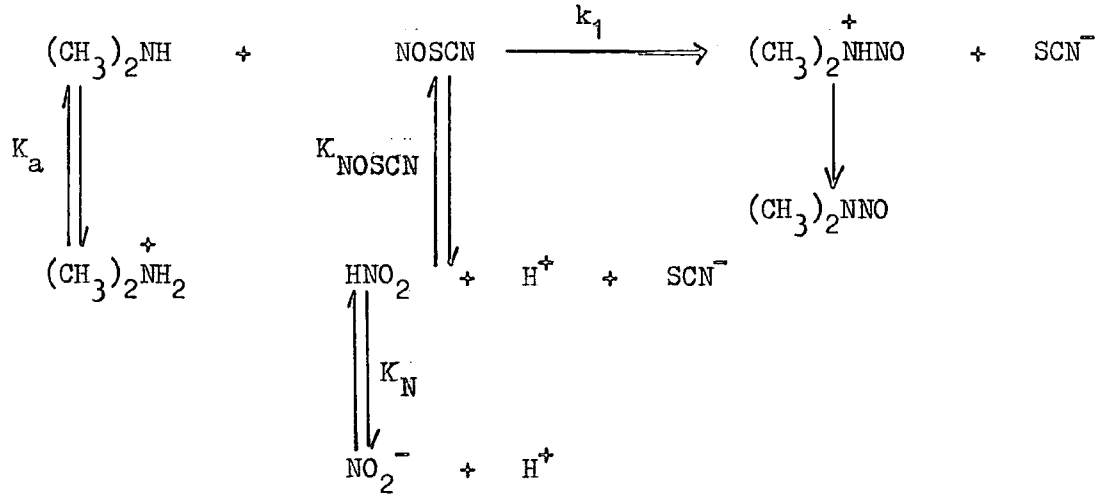
$[(CH_3)_2NHHCl] = 0.508M$

$[NaSCN] = 0.1M$

$[NaNO_2] = 8 \times 10^{-3}M$

pH	$10^4 k_o/s^{-1}$
1.5	4.4
2	4.7
2.45	4.4
3.1	3.2

The results show that the reaction rate is maximal at pH 2 which is consistent with results obtained by Fan and Tannenbaum[37] for the nitrosation of morpholine in the presence of thiocyanate ion. The mechanism for the reaction, scheme 2.7, is identical to that outlined in section 2.4.1. However, under the experimental conditions used for this study it is also necessary to include the acid dissociation constant of nitrous acid, K_N.



Scheme 2.7

Since the rate of reaction for nitrosation by nitrous anhydride is maximal at pH3.37 its contribution to the overall rate of reaction has been ignored for simplicity, as has the contribution from chloride ion catalysed nitrosation.

$$\text{Rate of reaction} = k_1 [(CH_3)_2NH]_F[NOSCN] \qquad 2.21$$

This can be expressed as

$$\text{Rate} = \frac{k_1 K_a [(CH_3)_2NH]_T[HNO_2]}{[H^+]\left(1 + \frac{1}{K_{NOSCN}[H^+][X^-]}\right)} \qquad 2.22$$

from equation 2.17 where T = total and F = Free

If, by definition $[NO_2^-]_T = [HNO_2] + [NO_2^-]_F$

and $$K_N = \frac{[NO_2^-][H^+]}{[HNO_2]}$$

$$[NO_2^-]_T = [HNO_2] + \frac{K_N[HNO_2]}{[H^+]}$$

$$[HNO_2] = \frac{[NO_2^-]_T}{1 + \frac{K_N}{[H^+]}}$$

substituting,

$$\text{Rate} = \frac{k_1 K_a [(CH_3)_2NH]_T[NO_2^-]_T K_{NOSCN}[H^+][X^-]}{(1 + K_{NOSCN}[H^+][SCN^-])([H^+] + K_N)} \qquad 2.23$$

From the definition of k_o, equation 2.20

$$\text{Rate} = k_o [HNO_2]$$

$[HNO_2]$ refers to the total nitrite concentration

$$k_o = \frac{k_1 K_a [(CH_3)_2NH] K_{NOSCN}[H^+][SCN^-]}{(1 + K_{NOSCN}[H^+][SCN^-])([H^+] + K_N)} \qquad 2.24$$

K_a is the acid dissociation constant of the protonated amine,

K_{NOSCN} is the equilibrium constant for the formation of NOSCN,

K_N is the acid dissociation constant of HNO_2, and

k_1 is the rate constant as defined in Scheme 2.7.

When the pH of the solution is greater than 2

$1 >> K_{NOSCN}[H^+][SCN^-]$ so the expression for k_o reduces to equation 2.25

$$k_o = \frac{k_1 K_a [(CH_3)_2NH]_T K_{NOSCN}[SCN^-][H^+]}{([H^+] + K_N)} \qquad 2.25$$

At pH2 the nitrite ion becomes fully protonated so $[H^+] >> K_N$ and equation 2.25 reduces to that given in equation 2.26

$$k_o = k_1 K_a [(CH_3)_2NH]_T K_{NOSCN}[SCN^-] \qquad 2.26$$

which predicts that the optimum pH for nitrosation, at reasonably high thiocyanate concentrations, is pH 2, which was observed (figure 8)

As the pH is reduced below 2 the limiting form (equation 2.23) becomes less applicable and k_o must be expressed by equation 2.24.

Mirvish[36] studied the pH dependence for the nitrosation of dimethylamine and found a maximal rate of reaction and yield of nitrosamine at pH 3.4. The drop in rate and yield as pH was reduced below pH 3.4 was attributed to a decrease in the concentration of the reactive free base form of the amine.

In a study of the pH dependence for the nitrosation of dimethylamine in the presence of bromide ion Casado and co-workers[31] found that the maximum rate of reaction occured at increasingly higher pH values as the concentration of nitrite was increased. In

addition they observed a decrease in k_o when the pH of the solution was reduced below pH 2. This contrasts with results obtained by Fan and Tannenbaum[37] for the nitrosation of morpholine by nitrosyl bromide who found the reaction rate was constant in the pH range 1 - 2, but decreased over the same range when nitrosyl thiocyanate was the active nitrosating agent. This decrease seen for SCN^- is attributed to the formation of the weak acid, HSCN below pH 2.[36,40]

To summarise, thiocyanate and halide catalysed nitrosation of amines will compete favourably with the nitrous anhydride mechanism under three conditions:-

(1) at high concentrations of added nucleophile

(2) when pH < 2.5

and (3) at low concentrations of nitrite

2.7. Nitrosation of Hydrazine

Both the acid and nucleophile catalysed nitrosation of hydrazine have been extensively studied.[12,41] Over the pH range 0 - 8 hydrazine exists as the cation, $NH_2NH_3^+$, however nitrosation is facile since the $-NH_2$ group is nucleophilic.

Hydrazine and other related species, e.g. hydroxylamine and urea, react quantitatively, rapidly and irreversibly with nitrous acid and, for this reason, are often used as nitrous acid scavengers. This reaction may be applied, for example, to (1) the removal of nitrous acid in vivo, and thus prevent possible nitrosamine formation and (2) the Purex process where it is necessary to remove nitrous acid to prevent re-oxidation of plutonium (III).[42]

It has been found[12] that the efficiency of these traps for nitrous acid is very dependent on the acidity of the medium and that the hydrazinium ion appears to be most efficient at approximately 1.3M H^+.

Koltunov and Marachenko[41] studied the nitrosation of hydrazine in hydrochloric acid but reported no catalytic effect due to chloride ion. This contrasts with what has been observed[1] for the nitrosation of amines in the presence of added nucleophiles, and more recently with results obtained by Stedman and co-workers.[41] They found that the nitrosation of hydrazine was catalysed by chloride, bromide and thiocyanate ion but was only significant for the latter. More recently Williams and co-workers studied the reaction in the presence of the same nucleophiles. They attributed the small increase in k_o, the observed first order rate constant, as the concentration of added nucleophile was increased, to a salt effect. This result fitted their observed pattern that nitrosation of substrates containing powerful electron withdrawing groups e.g. NH_3^+, $\geq C = O$ etcetera are not subjectto nucleophile catalysis.

The aim of this work was to establish whether nitrosation of hydrazine is subject to catalysis by thiocyanate ion in view of the apparent contradictory results obtained by Stedman[41] and Williams.[12]

The kinetic measurements were all made at 25°C using a stopped-flow spectophotometer.

The reaction was followed by monitoring the change in absorbance at 360nm, due to nitrous acid, as a function of time. All experiments were carried out under first order conditions with a large excess of hydrazine over the concentration of sodium nitrite. The observed first order rate constant, k_o, is defined by equation 2.27

$$\frac{-d[HNO_2]}{dt} = k_o[HNO_2] \qquad 2.27$$

2.7.1. The thiocyanate ion catalysed reaction

When the results of Stedman[41] and Williams[12] were compared it was observed that their reactions were performed in the presence of

widely differing concentrations of acid. The effect of added thiocyanate ion on the nitrosation of hydrazine at different acidities was examined and the results presented in tables 2.28, 2.29, 2.30, 2.31, 2.32 and 2.33.

Table 2.28

$[N_2H_5^+] = 1 \times 10^{-2}M$

$[HClO_4] = 0.203M$

$[NaNO_2] = 5 \times 10^{-4}M$

$10^3[NaSCN]/M$	k_o/s^{-1}
5	2.16
10	2.13
50	2.19

Table 2.29

$[N_2H_5^+] = 8 \times 10^{-3}M$

$[HClO_4] = 1.58 \times 10^{-2}M$

$[NaNO_2] = 8 \times 10^{-4}M$

$10^3[NaSCN]/M$	$10^2k_o/s^{-1}$
0	6.57
1.25	7.28
4.83	8.56
7.23	8.84
10	9.21
12.5	9.30

Table 2.30

$[N_2H_5^+] = 4 \times 10^{-2}M$

$[HClO_4] = 4 \times 10^{-2}M$

$[NaNO_2] = 4 \times 10^{-3}M$

10^3 [NaSCN]/M	k_o/s^{-1}
0	1.32
0.6	1.63
1.2	1.73
6	1.96
10	2.03
20	2.18
40	2.4

Table 2.31

$[N_2H_5^+] = 4 \times 10^{-2}M$

$[HClO_4] = 0.1M$

$[NaNO_2] = 4 \times 10^{-3}M$

10^3 [NaSCN]/M	k_o/s^{-1}
0	2.89
0.6	3.15
3	3.85
6	4.21
10	4.4
20	4.46
30	4.51

Table 2.32

$[N_2H_5^+] = 4 \times 10^{-2}M$

$[HClO_4] = 0.47M$

$[NaNO_2] = 4 \times 10^{-3}M$

$10^3[NaSCN]/M$	k_o/s^{-1}
6	21.7
10	22.2
20	22

Table 2.33

$[N_2H_5^+] = 4 \times 10^{-2}M$

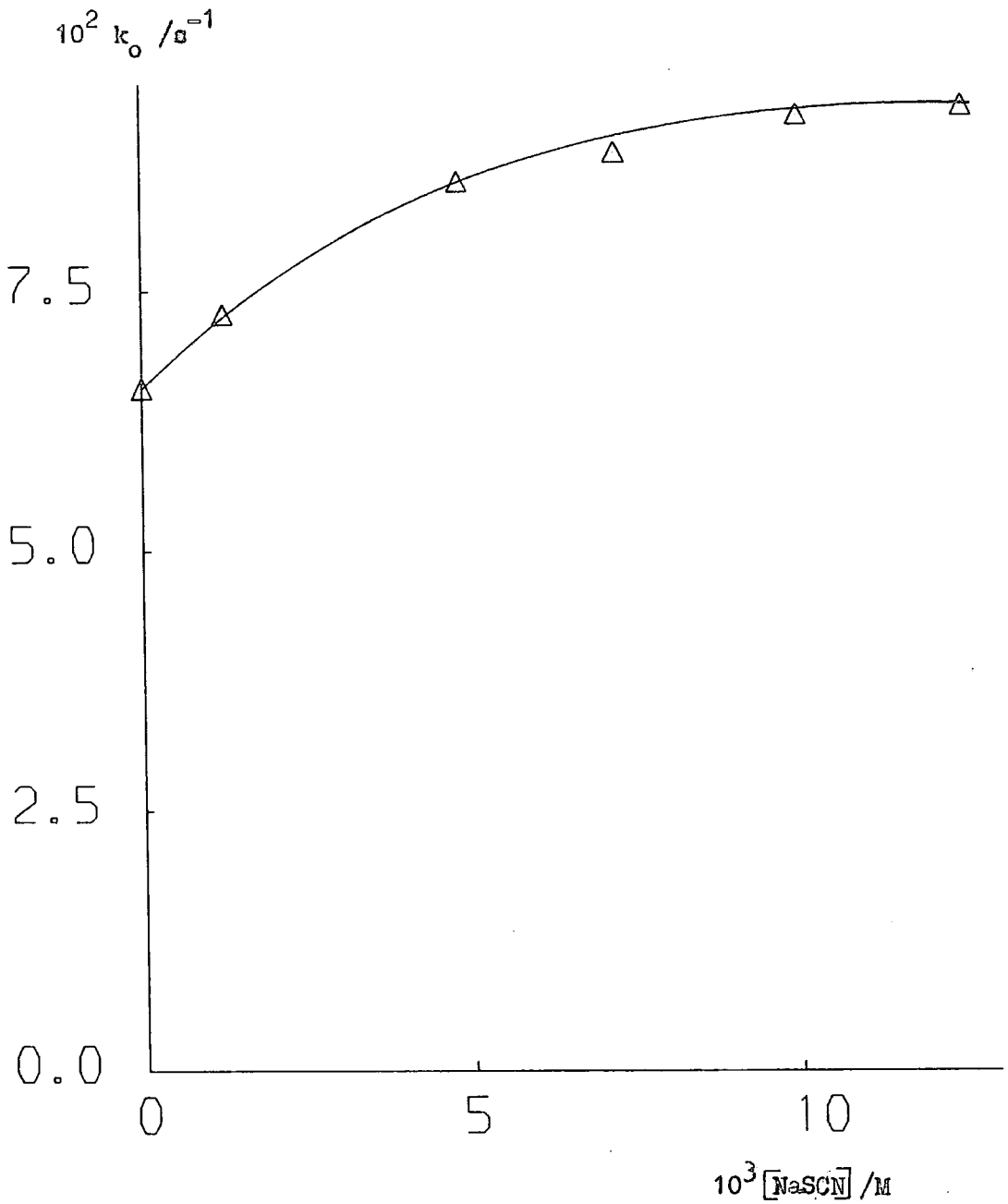
$[HClO_4] = 1.03M$

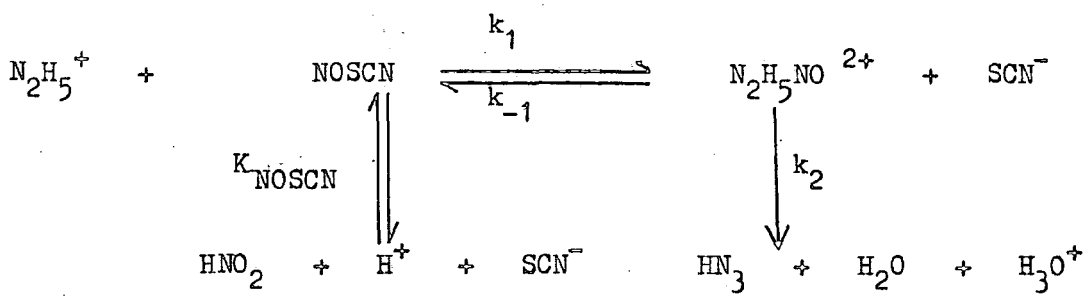
$[NaNO_2] = 4 \times 10^{-3}M$

$10^3[NaSCN]/M$	k_o/s^{-1}
3	44.2
6	44.1
10	44
20	44.7

As the acid concentration is increased, at constant substrate concentration, the dependence of k_o on the thiocyanate ion concentration seems to disappear. However, in the presence of lower concentrations of acid thiocyanate ion does catalyse the nitrosation of hydrazine although a plot of k_o versus $[SCN^-]$ figure 9 is curved at higher concentrations of thiocyanate as has been found for other systems.[15,43] The results are consistent with the mechanism outlined in scheme 2.8.

Figure 9 Thiocyanate ion catalysis for the nitrosation of hydrazine sulphate





Scheme 2.8

The overall rate of reaction, ignoring the acid catalysed process, is given by:

$$\text{Rate} = k_1[N_2H_5^+][NOSCN] - k_{-1}[N_2H_5NO]^{2+}[SCN^-] \qquad 2.28$$

The steady state principle can be applied to $[N_2H_5NO]^{2+}$, if it is assumed to be a reactive intermediate

$$\frac{d[N_2H_5NO]^{2+}}{dt} = 0$$

$$0 = k_1[N_2H_5^+][NOSCN] - k_{-1}[N_2H_5NO]^{2+}[SCN^-] - k_2[N_2H_5NO]^{2+}$$

$$[N_2H_5NO]^{2+} = \frac{k_1[N_2H_5^+][NOSCN]}{k_1[SCN] + k_2}$$

substituting

$$\text{Rate} = k_1[N_2H_5^+][NOSCN] - \frac{k_1k_{-1}[N_2H_5^+][NOSCN][SCN^-]}{k_{-1}[SCN^-] + k_2}$$

$$\text{Rate} = \frac{k_1k_2[N_2H_5^+][NOSCN]}{k_{-1}[SCN^-] + k_2} \qquad 2.29$$

From equation 2.27

$$\text{Rate} = k_o[HNO_2]$$

and since

$$K_{NOSCN} = \frac{[NOSCN]}{[HNO_2][H^+][SCN^-]}$$

$$k_o = \frac{k_1 k_2 K_{NOSCN} [N_2H_5^+][H^+][SCN^-]}{k_{-1}[SCN^-] + k_2} \qquad 2.30$$

When $k_2 >> k_{-1}[SCN^-]$ equation 2.30 reduces to

$$k_o = k_1 K_{NOSCN} [N_2H_5^+][H^+][SCN^-] \qquad 2.31$$

The explanation for the curving off seen in figure 9, for a plot of k_o versus $[SCN^-]$, is that the inequality $k_2 >> k_{-1}[SCN^-]$ is reversed and equation 2.30 now reduces to

$$k_o = \frac{k_2 k_1}{k_{-1}} K_{NOSCN} [N_2H_5^+][H^+] \qquad 2.32$$

which is independent of [thiocyanate ion].

Surprisingly Stedman[41] found that a plot of the observed first order rate constant versus $[SCN^-]$ was linear even at relatively high concentrations of added nucleophile, where it would usually be expected to level off.

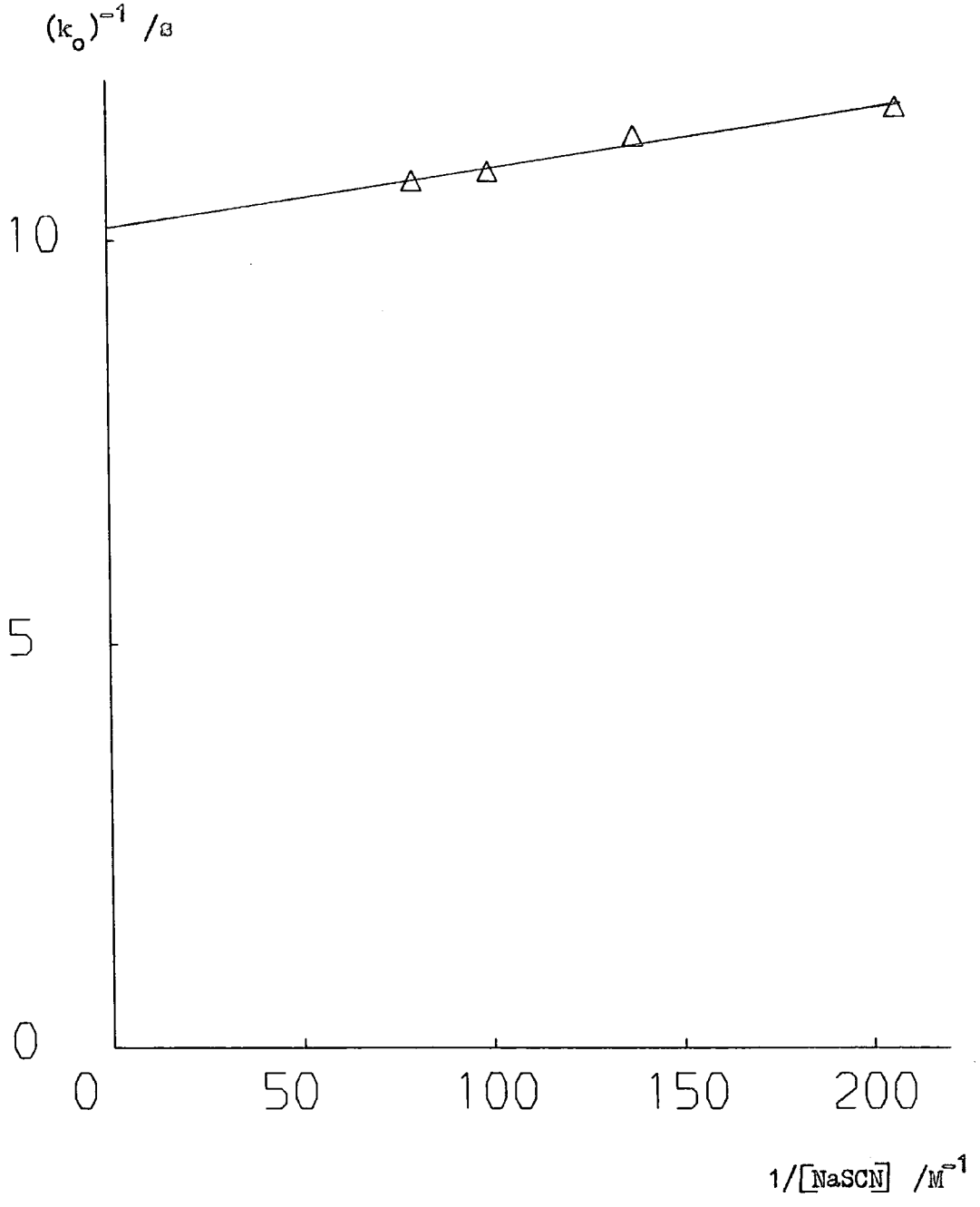
Rewriting equation 2.30 in the reciprocal form gives:

$$\frac{1}{k_o} = \frac{k_{-1}}{k_1 k_2 K_{NOSCN} [H^+][N_2H_5^+]} + \frac{1}{k_1 K_{NOSCN} [H^+][N_2H_5^+][SCN^-]} \qquad 2.33$$

The value of k_1, the bimolecular rate constant for nitrosation of hydrazine by nitrosyl thiocyanate, may be obtained from the slope of a plot of $1/k_o$ versus $1/[SCN^-]$. Figure 10 shows the double reciprocal plot for the results in table 2.29. From this a value of $k_1 = (3.4 \pm 0.5) \times 10^4$ l mol^{-1} s^{-1} was determined.

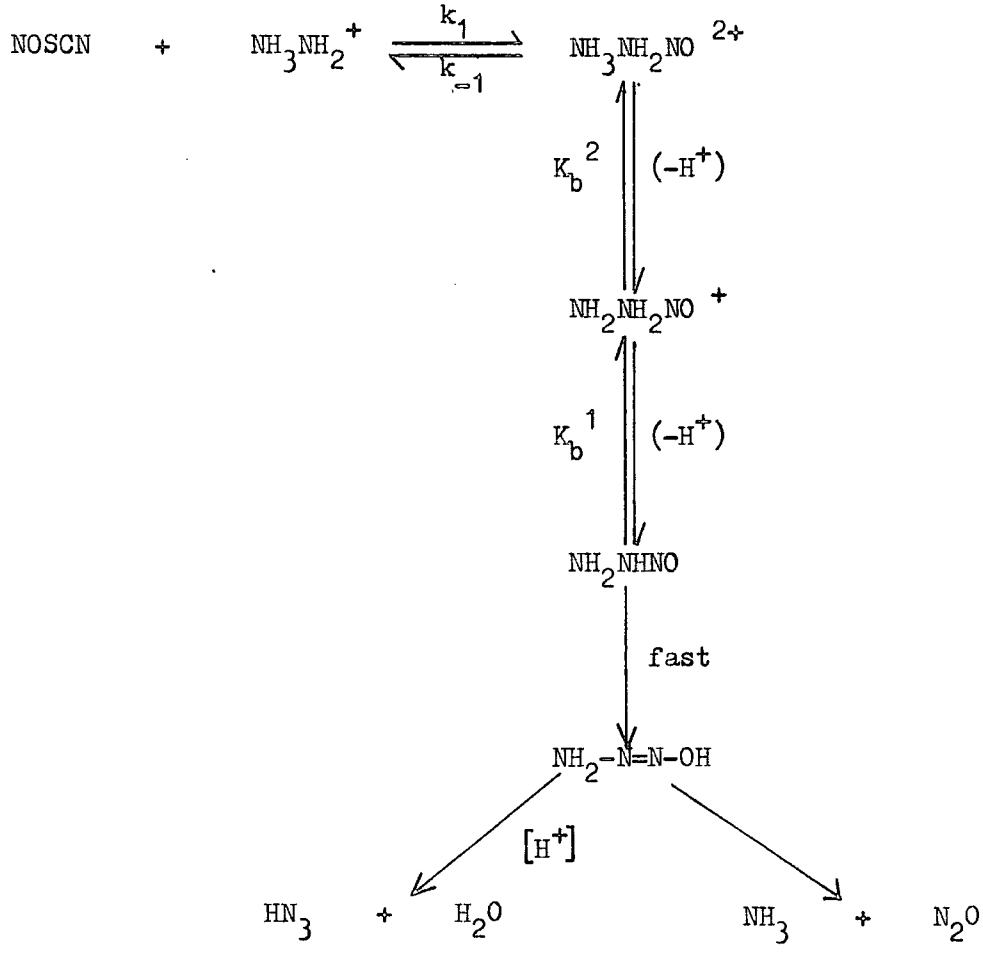
The large error associated with this value is probably a result of the large errors in the x-coefficients of the plot, which represent the reciprocals of small numbers.

Figure 10 Thiocyanate ion catalysis for the nitrosation of hydrazine sulphate - double reciprocal plot



The value of k_1 is several orders of magnitude lower than those obtained for other substrates, and listed previously in table 2.25. The low reactivity of hydrazine as a nucleophile can be explained in terms of its bascity. It exists as the cation $NH_3NH_2^+$ over the pH range 0.8. However, unlike amines and other amino compounds, this is the reactive form and explains why it is particularly successful as a nitrous acid trap.

In an attempt to explain the apparent lack of dependence of k_o on [thiocyanate ion] at low $[SCN^-]$, as the acid concentration is increased it is necessary to consider the second stage of the reaction as depicted below (scheme 2.9). For simplicity the stereochemistry of the reaction will be ignored.



Scheme 2.9

The reaction (equation 2.34) can be ignored [41] if $[H^+] = 0.1M$

$$NH_2N_2OH \longrightarrow NH_3 + N_2O \qquad 2.34$$

and there is a large excess of hydrazine over the concentration of sodium nitrite. The overall rate constant, k_2, for the process (equation 2.35) encompasses two acid dissociation equilibrium

$$NH_3NH_2NO^{2+} \xrightarrow{k_2} HN_3 + H_2O \qquad 2.35$$

constants and their corresponding H^+ terms. As the acidity is increased the equilibrium concentration of NH_2NHNO is reduced due to the effect of the acid concentration on the position of the two protonation equilibria. This results in a reduction in the value of the overall rate constant k_2 so that the inequality (equation 2.36)

$$k_{-1}[SCN] >> k_2$$

is more readily achieved. The expression for k_o then reduces to equation 2.37 which predicts the zero order dependence

$$k_o = k_1 k_2 K_{NOSCN}[N_2H_5^+][H^+] \qquad 2.37$$

on thiocyanate ion concentration which was observed.

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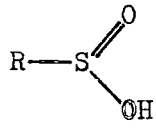
CHAPTER THREE

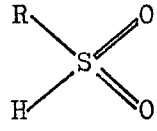
NITROSATION OF BENZENESULPHINIC ACID

3.1 Introduction

Sulphinic acids, particularly in their anion form, behave as sulphur rather than oxygen nucleophiles, however the choice between the two conceivable structures for the acids, (1) and (2), has been the subject of controversy.[1]



(1)

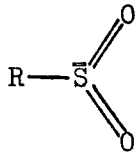


(2)

The anion form reacts readily with alkyl halides, according to equation 3.1, yielding the corresponding sulphone which is consistent

$$RSO_2Na + IC_2H_5 \longrightarrow RSO_2C_2H_5 + NaI \qquad 3.1$$

with the suggestion[2] that the sulphinate ion exists, at least partially, in the form (3).



(3)

The reaction of benzenesulphinic acid with nitrous acid and the oxides of nitrogen was first reported a long time ago.[3] It is now known that this reaction with sulphinic acids generally gives N, N - bis(alkane or aryl) sulphonyl hydroxylamines (equation 3.2). This reaction has been specifically used[4] for the characterisation

$$2RSO_2H + HNO_2 \rightleftharpoons (RSO_2)_2NOH + H_2O \qquad 3.2$$

of 1-dodecane sulphinic acid ($C_{12}H_{25}SO_2H$) and more generally,[5] in an analytical method for the determination of a range of sulphinic acids by titration with sodium nitrite in dilute sulphuric acid.

More recently Glidewell and Birchall[3] have used this reaction to produce a range of N, N - bis (arylsulphonyl) hydroxylamines which they then oxidised with the aim of generating neutral analogues of Fremy's radical ion, of the form $(RSO_3)_2NO$ and $(RSO_2)_2NO$.

The aim of the work described in this chapter was to establish the mechanism of nitrosation of sulphinic acids, particularly with regard to the nature and reactivity of any intermediate.

All the kinetic experiments were carried out at 25°C in water under first order conditions with a large excess of benzenesulphinic acid over the concentration of sodium nitrite. The stopped-flow technique was used for all the measurements and each value of k_o, the observed first order rate constant (defined in equation 3.3), quoted is the mean of at least five individual runs.

$$\frac{d[\text{Product}]}{dt} = -\frac{d[HNO_2]}{dt} = k_o[HNO_2] \qquad 3.3$$

For the remainder of this chapter $[BSA]_T$ represents the total stoichmetric concentration of substrate.

3.2 The acid-catalysed reaction

All kinetic runs showed good first order behaviour with respect to the initial nitrous acid concentration. The variation of the observed first order rate constant with the concentration of sodium nitrite, benzenesulphinic acid (BSA), and acid were all measured. Reactions were carried out by monitoring the decrease in absorbance at 360nm, due to nitrous acid, although some measurements were also made by noting the increase in absorbance at 260nm, due to product formation.

3.2.1. Variation of k_o with the sodium nitrite concentration.

The first order rate constant was determined at two concentrations of sodium nitrite and the results are shown in table 3.1.

Table 3.1 dependence of k_o upon $[NaNO_2]$

$[BSA]_T = 4 \times 10^{-2}M$
$[HClO_4] = 9.4 \times 10^{-2}M$

$10^3[NaNO_2]/M$	k_o/s^{-1}
1	7.08 ± 0.06 *
2	7.04 ± 0.06

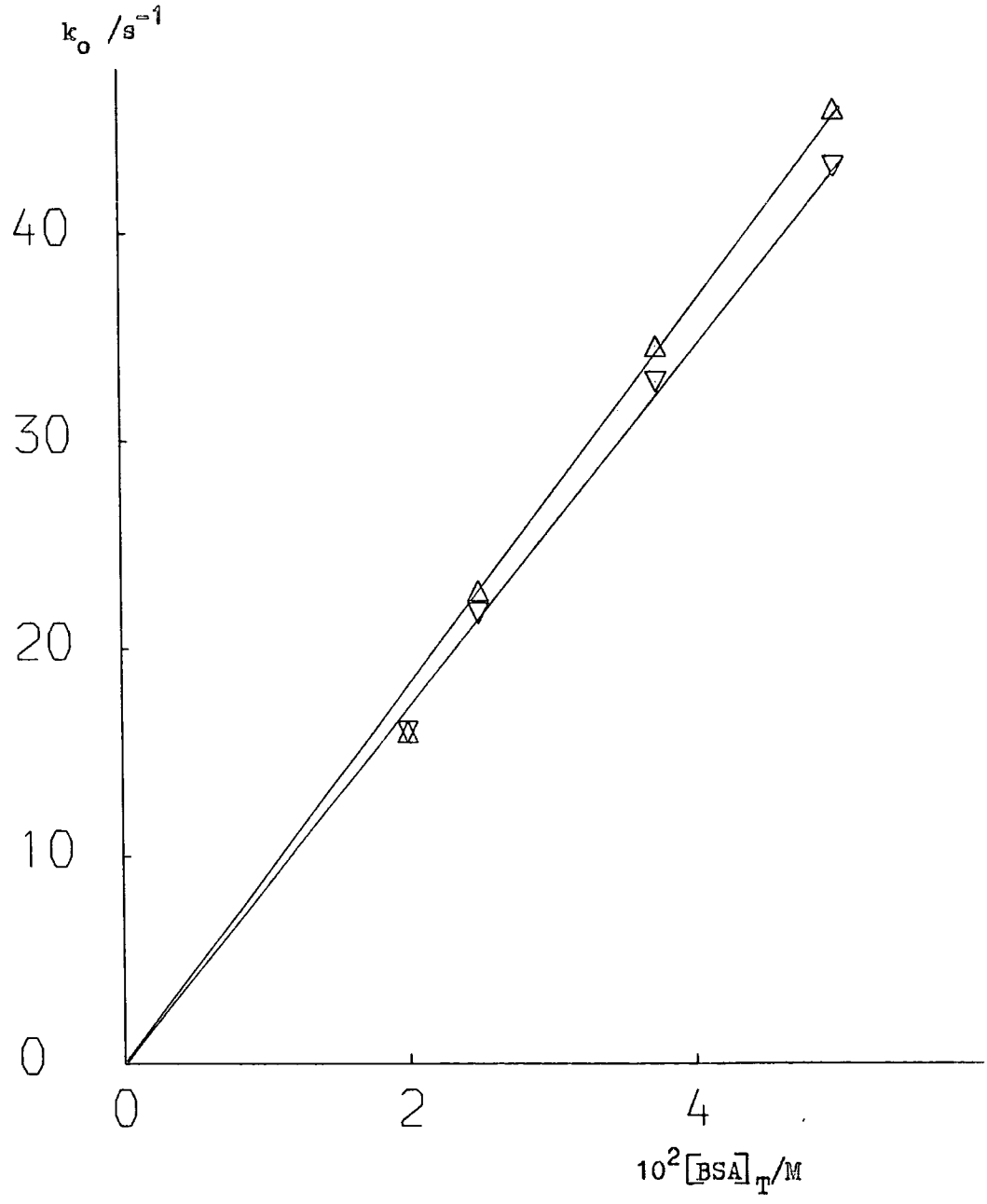
The first order dependence upon $[HNO_2]$ which was found means reaction involving nitrous anhydride, N_2O_3, as the active nitrosating agent can be ignored. It is consistent with reaction via either $H_2NO_2^+$ or NO^+, which are not kinetically distinguishable. For the remainder of this study $H_2NO_2^+$ is assumed to be the active nitrosating agent

3.2.2. Variation of k_o with $[BSA]_T$

The effect of added BSA on k_o at constant acidity was measured at two wavelengths, 360 and 260nm, and the results are shown in table 3.2 and figure 1.

* The quoted error is the standard deviation

Figure 1 Variation of k_o with $[\text{Benzenesulphinic acid}]_T$



▽ k_o^{360}

△ k_o^{260}

Table 3.2 dependence of k_o on $[BSA]_T$

†$[HClO_4] = 0.932M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^2[BSA]_T/M$	k_o^{260}/s^{-1}	k_o^{360}/s^{-1}
2.0	16.0 ± 0.3	16.0 ± 0.3
2.5	22.8 ± 0.8	21.7 ± 0.8
3.75	34.6 ± 0.7	32.9 ± 1.1
5.0	46.1 ± 0.9	43.3 ± 0.4

†This acid concentration will obviously vary a little as $[BSA]_T$ is increased.

k_o^{260} is the value of k_o measured at 260nm

k_o^{360} is the value of k_o measured at 360nm

Clearly there is a first order dependence of k_o upon $[BSA]_T$, and since the plot of k_o versus $[BSA]_T$ passes through the origin the reaction must be essentially irreversible.

3.2.3. Variation of k_o with acidity

The effect of acid on the reaction, where $[H^+]$ represents the free $[H^+]$ after allowance is made for the complete protonation of nitrite and partial protonation of benzene sulphinate ion (both were added as the sodium salts), was examined at two concentrations of substrate. The results are presented in tables 3.3 and 3.4, and figure 2 shows a plot of k_o versus $[H^+]$ for the results in table 3.3.

Table 3.3 acid catalysis

$[BSA]_T = 4.0 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

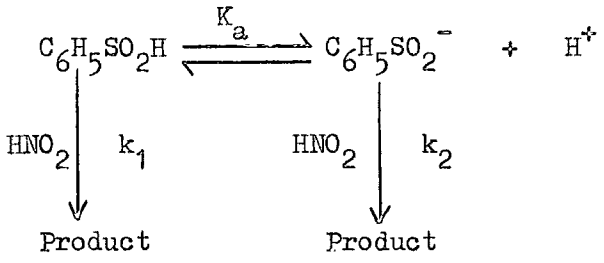
$10^2[H^+]/M$	k_o/s^{-1}
2.20	4.50 ± 0.05
4.40	6.40 ± 0.2
6.00	7.10 ± 0.1
15.0	10.5 ± 0.1
42.8	20.4 ± 0.6

Table 3.4 acid catalysis

$[BSA]_T = 2.5 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

$[H^+]/M$	k_o^{260}/s^{-1}	k_o^{360}/s^{-1}
0.219	-	6.50 ± 0.1
0.480	-	11.5 ± 0.3
0.674	14.1 ± 1.2	14.4 ± 0.4
0.999	21.0 ± 2.3	20.3 ± 0.6
1.279	28.5 ± 0.8	28.8 ± 0.4
1.465	31.9 ± 1.5	30.8 ± 0.7
2.024	44.7 ± 0.8	44.3 ± 1.0

Plots of k_o versus $[H^+]$ are linear above acidities of ca. 0.06M (but with a positive intercept). However, below this acidity a plot of k_o versus $[H^+]$ (figure 2) is distinctly curved towards the origin. If it is assumed that reaction occurs via both the neutral substrate, $C_6H_5SO_2H$, and the sulphinate ion, $C_6H_5SO_2^-$, (see scheme 3.1) this behaviour may be readily explained.



Scheme 3.1

The overall rate of reaction is given by equation 3.4

$$\text{Rate} = k_1[H^+][HA][HNO_2] + k_2[H^+][A^-][HNO_2] \qquad 3.4$$

$[HA]$ represents the concentration of sulphinic acid,

$[A^-]$ represents the concentration of sulphinate ion

and k_1 and k_2 are the rate constants as defined in scheme 3.1 and which incorporate the value of K, the equilibrium constant for the formation of $H_2NO_2^+$.

since
$$K_a = \frac{[C_6H_5SO_2^-][H^+]}{[C_6H_5SO_2H]}$$

$$\text{Rate} = [H^+][HNO_2][HA]\left(k_1 + \frac{k_2K_a}{[H^+]}\right) \qquad 3.5$$

if, by definition $[BSA]_T = [HA] + [A^-]$

$$[BSA]_T = [HA]\left(1 + \frac{K_a}{[H^+]}\right) \qquad 3.6$$

$$\text{Rate} = \frac{[H^+]^2[HNO_2][BSA]_T}{\left([H^+] + K_a\right)}\left(\frac{k_1[H^+] + k_2K_a}{[H^+]}\right)$$

Since, from equation 3.3

$$\text{Rate} = k_o[HNO_2]$$

Thus,
$$k_o = \frac{[H^+][BSA]_T\left(k_1[H^+] + k_2K_a\right)}{\left(K_a + [H^+]\right)} \qquad 3.7$$

where K_a is the acid dissocation constant of benzenesulphinic acid.

A range of values for the pKa of benzenesulphinic acid exist in the literature[6,7] but the choice of pKa[6] of 1.84 seems the most reliable.

When $[H^+] >> K_a$ the expression for k_o (equation 3.7) reduces to that given in equation 3.8. This equation predicts that a plot of

$$k_o = [BSA]_T (k_1[H^+] + k_2K_a) \qquad 3.8$$

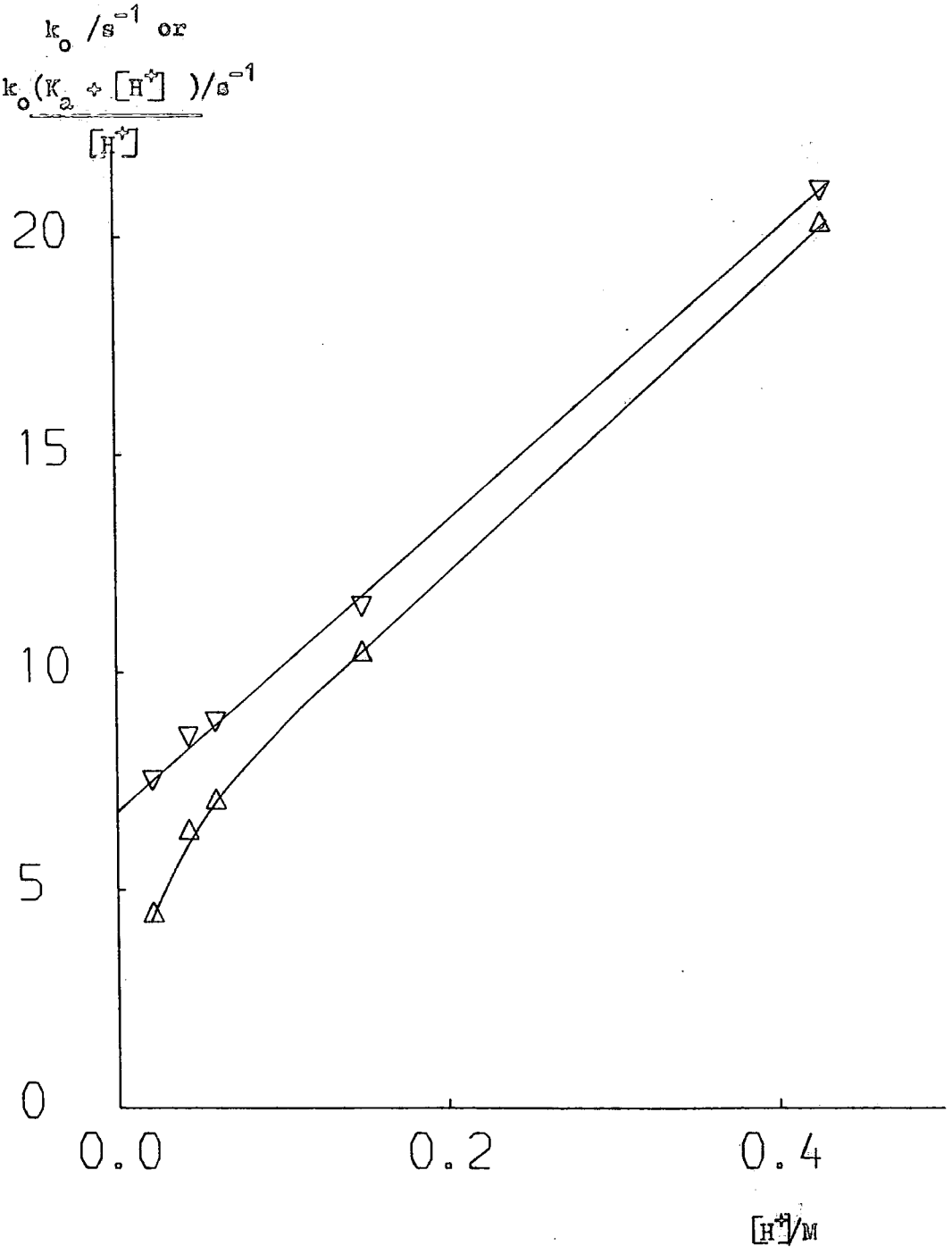
k_o versus $[H^+]$ should be linear with a positive intercept, as was observed in figure 2, when $[H^+] >> 6 \times 10^{-2}$M. If the expression for k_o, as defined in equation 3.7, is consistent with the experimental results a plot of $\frac{k_o}{[H^+]} (K_a + [H^+])$ versus $[H^+]$ should be linear throughout the whole acid range and have a positive intercept. Such a plot is shown in figure 2, from which the following values of k_1 and k_2 were easily determined. Thus it appears that both benzenesulphinic acid and the benzenesulphinate ion are very reactive towards nitrosation.

$$k_1 = 820 \pm 10 \text{ l}^2 \text{ mol}^{-2} \text{ s}^{-1}$$

$$k_2 = 11800 \pm 500 \text{ l}^2 \text{ mol}^{-2} \text{ s}^{-1}$$

A calculated value of 930 l mol^{-1} s^{-1} was obtained for the slope of a plot of k_o versus $[BSA]_T$ using equation 3.7, the values of k_1 and k_2 listed above and an acidity of 0.93M, which is equivalent to $[H^+]$ present for the results in table 3.2. This value compares favourably with values of 920 l mol^{-1} s^{-1}, for rate measurements at 260nm, and 870 l mol^{-1} s^{-1}, for rate measurements at 360nm, obtained from the plots of k_o versus $[BSA]_T$ in figure 1, and indicates that the values of k_1 and k_2 determined experimentally are internally consistent.

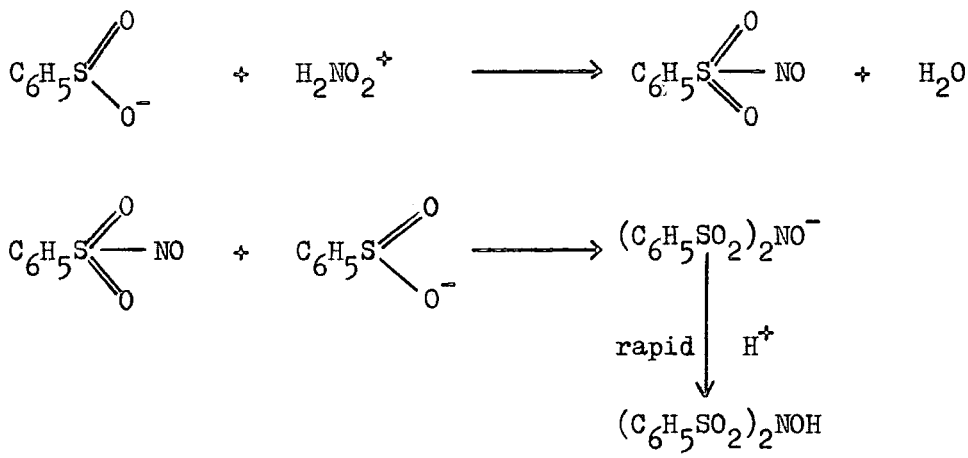
Figure 2 Plot of k_o vs. $[H^+]$, and $k_o(K_a + [H^+])/[H^+]$ vs. $[H^+]$ for the nitrosation of benzenesulphinic acid



▽ $\dfrac{k_o(K_a + [H^+])}{[H^+]}$

△ k_o.

The product of the reaction of nitrous acid with benzenesulphinic acid is a hydroxylamine derivative containing two benzenesulphinate groups, which suggests that the reaction is at least a two stage process. (The product hydroxylamine was isolated from reaction solutions and its uv and ir spectra measured see Chapter 7 section 7.3). A possible mechanism for the reaction is outlined in scheme 3.2. For the sake of simplicity only the reaction of the anion is included.



Scheme 3.2

The results in tables 3.2 and 3.4 show that k_o is independent of the wavelength at which the reaction is measured, within experimental error. Since the reaction is clearly first order in substrate, as shown by figure 2, it is likely that the reaction of $H_2NO_2^+$ with benzenesulphinic acid and benzenesulphinate ion, yielding the nitrososulphinate intermediate, is rate-limiting otherwise a second-order dependence upon $[BSA]_T$ would be expected.

The second stage of the reaction is the reaction of the intermediate with another molecule of substrate followed by a rapid protonation to give the product hydroxylamine. Nitrososulphinates (or sulphonyl nitrites) have previously been suggested as intermediates for this reaction,[3] for the reaction of sulphinic acids with nitrosyl

chloride in ether,[8] and for the reaction of sulphinic acids with alkyl nitrites.[9] Recently some sulphonyl nitrites have been isolated[10] as brown crystals when the corresponding acids were treated with dinitrogen tetroxide at -20°C. According to Oae and Shinhama[11] sulphonyl nitrites are the most powerful nitrosating agents known, reacting readily with amines, alcohols and thiols to yield the corresponding nitroso compound and often the N,N -bis (aryl sulphonyl) hydroxylamine as well, by nitrosation of the sulphinic acid.

There are other examples in the literature of S-nitroso-compounds which can act as transfer-nitrosating agents. It has been shown that the S-nitroso-adduct of thiourea, $ONSC(NH_2)_2^+$ can directly nitrosate amines.[12] Thionitrites are also known to effect nitrosation of amines, alcohols and thiols although it has not been established whether this is a direct reaction or that it occurs via hydrolysis, to form $H_2NO_2^+$ as the active nitrosating agent.

For comparison purposes values of the third order rate constant for the acid catalysed nitrosation of a range of substrates are presented in table 3.5 together with the results obtained in this study.

Table 3.5 Values of k in Rate = $k[H^+][HNO_2][Substrate]$ for the acid catalysed nitrosation in water at 25°C.

Substrate	$k/l^2\ mol^{-2}\ s^{-1}$	Reference
Urea	0.89	14
2,4-Dinitroaniline	2.5	14
Hydrazoic Acid	160	14
Hydrazinium ion	620	14
	611	15
Methanol	700	16
Benzenesulphinic Acid	820	*
3-Mercapto-propanoic Acid	4800	17
Thiourea	6960	18
Sulphanilic Acid	7300	14
Thiocyanate ion	11700	14
Benzenesulphinate ion	11800	*

* This work

Clearly both benzenesulphinic acid and benzenesulphinate ion are amongst the most reactive substrates towards nitrosation, and are far more reactive than other conventional nitrous acid traps e.g. hydrazine, urea and azide ion. For reactions of $H_2NO_2^+$ or NO^+ with neutral substrates in water at 25°C it is believed[19] that a value of k in the region of ca. $7 \times 10^3\ l^2\ mol^{-2}\ s^{-1}$ is indicative of a reaction which is subject to diffusion-control. Thus the nitrosation of the acid, which is very close in terms of reactivity to methanol, occurs at a rate constant ten times below this limit. As expected, the nitrosation of the anion occurs much faster since it is a reaction between two oppositely charged ions. The value of k obtained for the sulphinate ion is very close to that determined for the nitrosation of the thiocyanate ion. This together with the value of the activation energy for the reaction of $H_2NO_2^+$ with thiocyanate ion of ca. 56 $kJmol^{-1}$, which is

close to that expected for an encounter-controlled reaction between a cation and anion, suggests that a value of k of ca. 11800 $l^2\ mol^{-2}\ s^{-1}$ represents the limiting value for a reaction between a positively charged nitrosating agent and an anion in water at 25°C.

As can be seen from equation 3.7 the values of the third order rate constants, k_1 and k_2, are very dependent on the value of K_a, the dissocation constant of benzenesulphinic acid. The similarity in the value of k obtained for the reaction of the sulphinate ion with $H_2NO_2^+$ compared with that for the reaction of the thiocyanate ion with $H_2NO_2^+$ suggests that the choice of pKa, chosen from a plethora of values available in the literature, is reasonable. The excellent linear plot in figure 1, of $k_o\frac{(K_a + [H^+])}{[H^+]}$ versus $[H^+]$, together with the good agreememt between the calculated value of the slope for a plot of k_o versus $[BSA]_T$ and that determined experimentally suggests that changes in ionic strength over the acid range used must be small, and because of the uncertainty over the value for the pKa they were neglected in the calculation of k_1 and k_2.

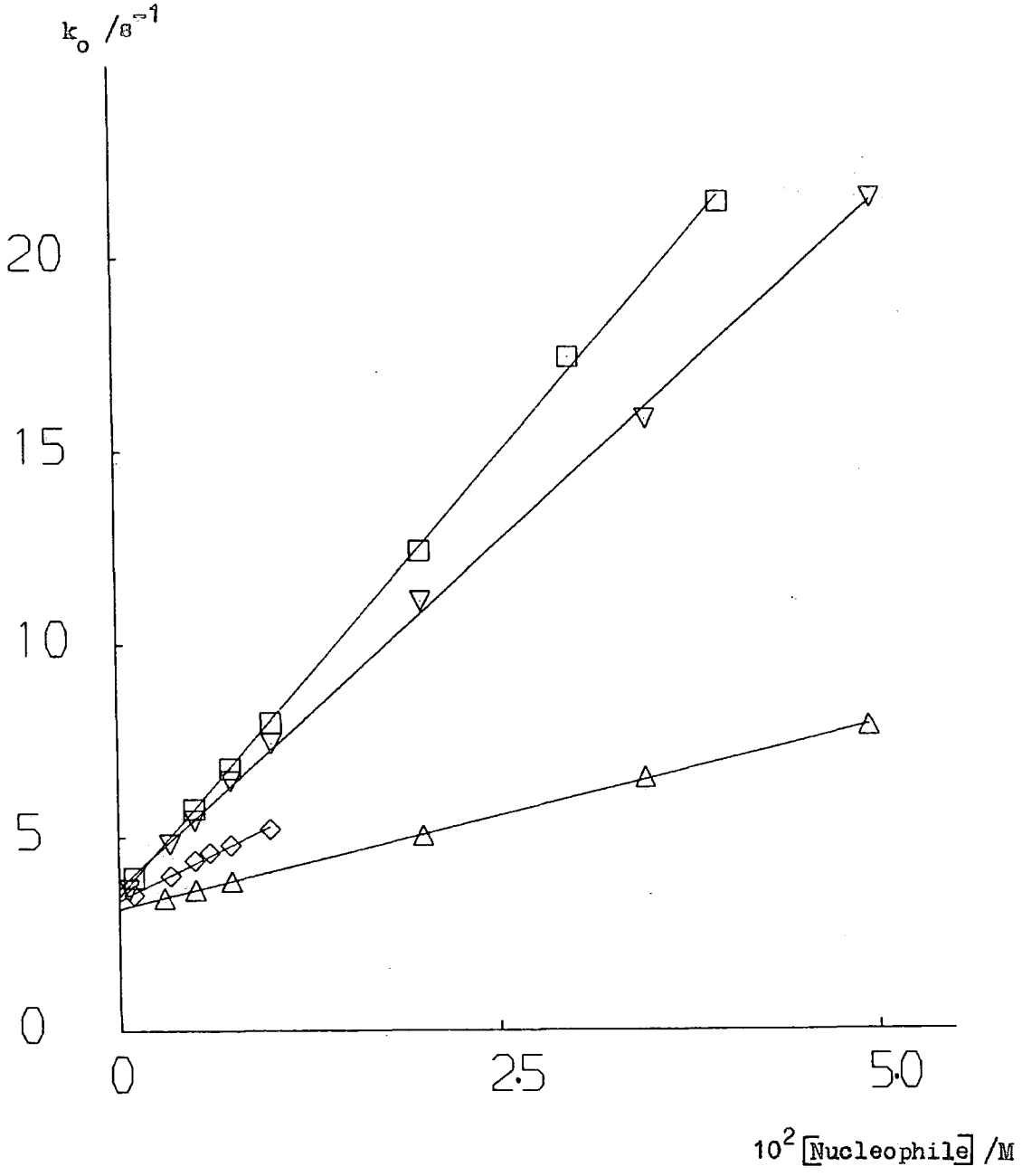
3.3 The nucleophile catalysed reaction

The effect of added nucleophile on the nitrosation of benzenesulphinic acid was examined and, as expected, found to have a catalytic effect. All reactions were followed by monitoring the decrease in absorbance at 360nm, due to nitrous acid.

3.3.1. Variation of k_o with [nucleophile]

The results of the kinetic runs are presented in tables 3.6, 3.7, 3.8 and 3.9 and in figure 3.

Figure 3 Nucleophile catalysis for the nitrosation of benzenesulphinic acid



◇ thiourea

□ thiocyanate ion

▽ bromide ion

△ chloride ion

Table 3.6 catalysis by chloride ion

$[BSA]_T = 2.5 \times 10^{-2}$M
$[H^+] = 2.9 \times 10^{-2}$M
$[NaNO_2] = 1 \times 10^{-3}$M

$10^3[KCl]$/M	k_o/s^{-1}
3.0	3.44 ± 0.03
5.0	3.65 ± 0.02
7.4	3.87 ± 0.01
20	5.04 ± 0.07
35	6.53 ± 0.1
50	7.85 ± 0.05

Table 3.7 catalysis by bromide ion

$[BSA]_T = 2.5 \times 10^{-2}$M
$[H^+] = 2.9 \times 10^{-2}$M
$[NaNO_2] = 1 \times 10^{-3}$M

$10^3[KBr]$ /M	k_o/s^{-1}
0.7	3.65 ± 0.1
3.4	4.82 ± 0.05
5.0	5.44 ± 0.3
7.4	6.46 ± 0.1
10	7.43 ± 0.03
20	11.1 ± 0.1
35	15.8 ± 0.1
50	21.5 ± 0.1

Table 3.8 catalysis by thiocyanate ion

$[BSA]_T = 2.5 \times 10^{-2}M$
$[H^+] = 2.9 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^3[KSCN]/M$	k_o/s^{-1}
1.0	3.96 ± 0.1
5.0	5.73 ± 0.1
7.4	6.79 ± 0.1
10	7.96 ± 0.1
20	12.4 ± 0.2
30	17.4 ± 0.5
40	21.4 ± 1.1

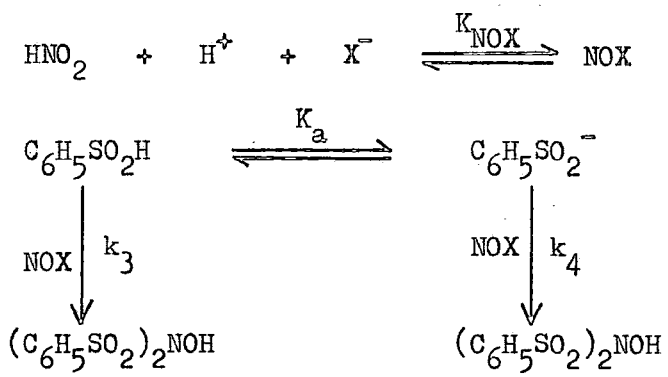
Table 3.9 catalysis by thiourea

$[BSA]_T = 2.5 \times 10^{-2}M$
$[H^+] = 2.9 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

10^3[Total $SC(NH_2)_2$]/M	10^3[Free $SC(NH_2)_2$]/M	k_o/s^{-1}
1.0	0.90	3.5 ± 0.03
3.4	3.06	4.0 ± 0.1
5.0	4.62	4.4 ± 0.1
6.0	5.57	4.6 ± 0.1
7.4	6.89	4.8 ± 0.1
10	9.44	5.2 ± 0.1

For the thiourea catalysed reaction it is necessary to plot k_o versus [Free Thiourea] since a significant proportion of [Total Thiourea] will be tied up in the form of $ONSC(NH_2)_2^+$, because of the large equilibrium constant for the formation of this species.

It is thought that nitrosation of a substrate in the presence of added halide ion,[20] thiocyanate ion[21] and thiourea[22] occurs via the intermediacy of the corresponding NOX species (where X = Cl^-, Br^-, SCN^- or $SC(NH_2)_2$) which are more efficient nitrosating agents than those derived from acidic nitrous acid. The mechanism for the nucleophile catalysed reaction is outlined in scheme 3.3.



Scheme 3.3

The rate of the nucleophile catalysed reaction is given by:-

$$\text{Rate} = k_3[HA][NOX] + k_4[A^-][NOX] \qquad 3.9$$

but $$K_a = \frac{[H^+][A^-]}{[HA]}$$

thus $$\text{Rate} = [NOX][HA](k_3 + k_4K_a) \qquad 3.10$$

since $$K_{NOX} = \frac{[NOX]}{[HNO_2][H^+][X^-]}$$

$$\text{Rate} = K_{NOX}[HNO_2][X^-][HA](k_3[H^+] + k_4K_a) \qquad 3.11$$

From equation 3.6

$$[BSA]_T = [HA]\left(1 + \frac{K_a}{[H^+]}\right)$$

and from equation 3.3

$$\text{Rate} = k_o[HNO_2]$$

thus

$$k_o = \frac{K_{NOX}[X^-][BSA]_T[H^+](k_3[H^+] + k_4K_a)}{(K_a + [H^+])} \qquad 3.12$$

Combining equations 3.7 and 3.12 the overall expression for k_o for the uncatalysed and nucleophile catalysed reaction is given by:-

$$k_o = \frac{[BSA]_T[H^+](k_1[H^+] + k_2K_a)}{(K_a + [H^+])} + \frac{[BSA]_T[H^+]K_{NOX}[X^-](k_3[H^+] + k_4K_a)}{(K_a + [H^+])} \qquad 3.13$$

where

K_a is the acid dissociation constant of benzenesulphinic acid,

K_{NOX} is the equilibrium constant for the formation of NOX,

$[BSA]_T$ is the total substrate concentration,

k_1 and k_2 are the rate constants as defined in scheme 3.1

and k_3 and k_4 are the rate constants as defined in scheme 3.3.

As for the uncatalysed reaction a plot of $\frac{k_o(K_a + [H^+])}{[H^+]}$ versus $[H^+]$ should be linear, with the slope of the line representing $([BSA]_T (k_1 + k_3K_{NOX}[X^-]))$ and the intercept $([BSA]_TK_a (k_2 + k_4K_{NOX}[X^-]))$. In order to extract the values of k_3 and k_4 using this method it was necessary to measure the rate constant for the nitrosation of benzenesulphinic acid over a range of acid concentrations in the presence of fixed concentrations of the different nucleophiles.

3.3.2. Variation of k_o with $[H^+]$

The variation of k_o with $[H^+]$ over the range $2 \times 10^{-2} - 1.2 \times 10^{-1}$M $[H^+]$ in the presence of either KCl, KBr, KSCN or $SC(NH_2)_2$ was investigated and the results are shown in tables 3.10, 3.11, 3.12 and 3.13.

Table 3.10 acid catalysis in the presence of KCl

$[BSA]_T = 2.5 \times 10^{-2}M$
$[KCl] = 5 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^2[H^+]/M$	k_o/s^{-1}
2.16	6.62 ± 0.26
2.93	7.85 ± 0.05
5.01	10.5 ± 0.13
7.32	12.6 ± 0.30
11.8	17.4 ± 0.70

Table 3.11 acid catalysis in the presence of KBr

$[BSA]_T = 2.5 \times 10^{-2}M$
$[KBr] = 2.5 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^2[H^+]/M$	k_o/s^{-1}
2.16	10.3 ± 0.13
2.93	12.6 ± 0.15
5.01	19.6 ± 0.60
7.32	27.6 ± 0.49
11.8	42.6 ± 0.60

Table 3.12 acid catalysis in the presence of KSCN

$[BSA]_T = 2.5 \times 10^{-2}M$
$[KSCN] = 4 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^2[H^+]/M$	k_o/s^{-1}
2.24	16.5 ± 0.2
3.01	20.8 ± 0.5
5.11	30.4 ± 0.5
7.32	40.6 ± 0.3
9.08	49.9 ± 1.2

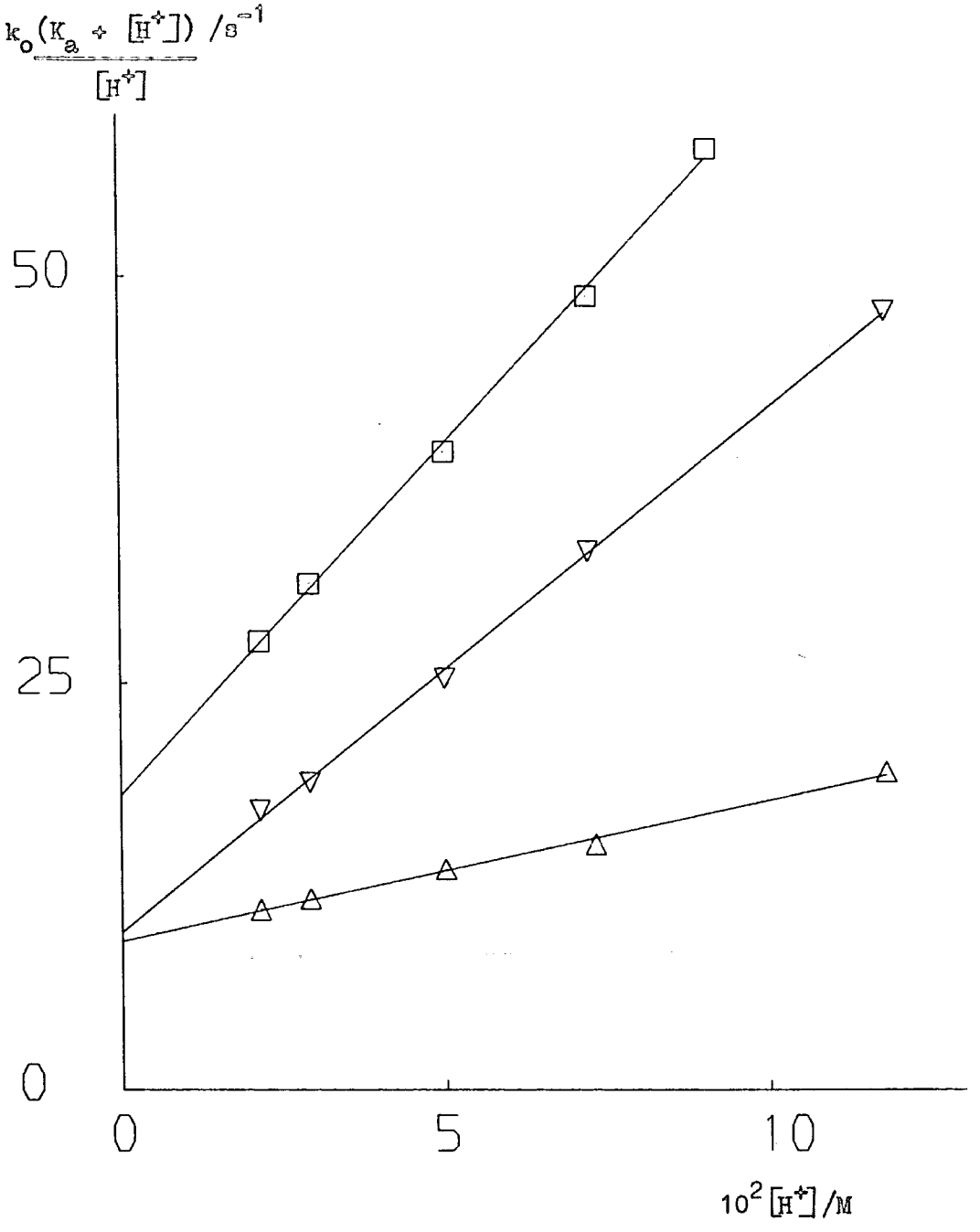
Table 3.13 acid catalysis in the presence of thiourea

$[BSA]_T = 2.5 \times 10^{-2}M$
$[SC(NH_2)_2] = 6 \times 10^{-3}M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^2[H^+]/M$	k_o/s^{-1}
2.14	3.54 ± 0.2
2.93	4.62 ± 0.1
4.96	6.54 ± 0.3
7.14	8.21 ± 0.1

For each nucleophile, with the exception of thiourea, the plot of $k_o\frac{(K_a + [H^+])}{[H^+]}$ versus $[H^+]$ was a good straight line with a positive intercept as can be seen in figure 4. The problem with the reaction in the presence of thiourea was that as the acidity was increased the concentration of free thiourea present decreased. The values and slopes of the plots are given in table 3.14, however, it must be noted

Figure 4 Plots of $k_o(K_a + [H^+])/[H^+]$ vs. $[H^+]$ for the nitrosation of benzenesulphinic acid in the presence of added nucleophiles



□ [NaSCN] = 4 x 10^{-2}M

▽ [NaBr] = 2.5 x 10^{-2}M

△ [NaCl] = 5 x 10^{-2}M

that the values for the thiourea reaction can only be considered to be of the correct order of magnitude.

Table 3.14 Slopes and intercepts of plots of $\frac{k_o(K_a + [H^+])}{[H^+]}$ versus $[H^+]$

Nucleophile	Slope /l mol^{-1} s^{-1}	Intercept /s^{-1}
Cl^-	86 ± 2.7	9.2 ± 0.2
Br^-	323 ± 6	9.8 ± 0.4
SCN^-	432 ± 10	18 ± 0.6
$SC(NH_2)_2$	78 ± 6	4.4 ± 0.3

Values of the bimolecular rate constants, k_3 and k_4, were easily calculated from these slopes and intercepts using the literature values for K_{NOX} (K_{NOCl}[22] = 1.14 x 10^{-3} l^2 mol^{-2}, K_{NOBr}[23] = 5.1 x 10^{-2}, K_{NOSCN}[24] = 32 l^2 mol^{-2} and $K_{NOSC(NH_2)_2^+}$[25] = 5000 l^2 mol^{-2}) and the values of k_1 and k_2 determined in this study, and are shown in table 3.15. It must be remembered that the values of k_3 and k_4 for the reaction in the presence of thiourea have large associated errors because the plot of $\frac{k_o (K_a + [H^+])}{[H^+]}$ versus $[H^+]$ was not a good straight line.

Table 3.15 Values of k_3 and k_4 for the reactions of NOCl, NOBr, NOSCN and $NOSC(NH_2)_2^+$ with HA and A^-

Nucleophile	k_3/l mol^{-1} s^{-1}	k_4/ l mol^{-1} s^{-1}
Cl^-	4.6 x 10^7	2.4 x 10^8
Br^-	9.5 x 10^6	1.2 x 10^7
SCN^-	1.3 x 10^4	3.0 x 10^4
$SC(NH_2)_2$	7.6 x 10	11

As was found for the uncatalysed reaction, the benzenesulphinate ion is more reactive than the acid. However, for the nucleophile catalysed reaction the differences in reactivity are not so pronounced and this may be due to electrostatic effects, since the active nitrosating agent, NOX, is neutral rather than positively charged, as was the case for the acid catalysed reaction.

The measured slopes intercepts of plots of k_o versus $[X^-]$ (figure 3) are compared in table 3.16 with those calculated using the values of k_1, k_2, k_3 and k_4 determined in this study.

Table 3.16 Observed and calculated values of the slopes and intercepts of k_o versus $[Cl^-]$, $[Br^-]$ and $[SCN^-]$

Nucleophile	Slope/ 1 mol^{-1} s^{-1}	Intercept /s^{-1}	
Cl^-	95	3.2	Observed
	93	3.3	Calculated
Br^-	354	3.7	Observed
	380	3.3	Calculated
SCN	446	3.4	Observed
	428	3.3	Calculated

The agreement between the two sets of results is excellent which proves that the kinetic analysis used is valid, and that the values of k_1, k_2 k_3 and k_4 determined are reliable. This, together with the excellent linear plots obtained for the function $\frac{k_o(K_a + [H^+])}{[H^+]}$ vs. $[H^+]$ validates the assumption that the change in ionic strength is an insignificant factor in the calculation of the rate constants, k_3 and k_4 and can be neglected.

Clearly the now well established trend of reactivity[26] for a range of substrates, NOCl > NOBr > NOSCN > $NOSC(NH_2)_2^+$ also applies to this system.

The values of k_3 and k_4 for this reaction are listed in table 3.17 together with the values of bimolecular rate constants for the reaction of NOX with a range of substrates for comparison purposes.

Table 3.17 Values of the bimolecular rate constants for the reaction of NOX with a range of substrates at 25°C in water.

Substrate	k/ l mol^{-1} s^{-1}			Reference
	NOCl	NOBr	NOSCN	
Methanol	2.1×10^5	2.0×10^4	-	16
Cysteine	1.2×10^6	5.8×10^4	7×10^2	27
Mercaptopropanoic acid		4.5×10^5	9×10^3	17
Benzenesulphinic acid	4.6×10^7	9.5×10^6	1.3×10^4	*
Benzenesulphinate ion	2.4×10^8	1.2×10^7	3×10^4	*
Hydroxylamine	5.9×10^8	1.7×10^8	1.2×10^7	14
Aniline	2.5×10^9	1.7×10^9		28
Aniline			1.9×10^8	29

* This work

Both benzenesulphinic acid and its anion are more reactive towards NOX than methanol and some thiols, although they are less reactive than aniline. However, the values of k_3 and k_4 are large, and for the reaction of the sulphinate ion with nitrosyl chloride approach diffusion-control. Since many amines, aniline included, are largely protonated in acid solution, except at low acid concentrations, and reaction by the NOX species occurs with the free base form of the substrate it is likely that the overall reactivity of benzenesulphinic acid towards nitrous acid, in the presence of an added nucleophile, would be greater than that of aniline.

In conclusion benzenesulphinic acid and its anion, and probably other water soluble sulphinic acids generally, are very reactive towards nitrous acid and its derivatives in acid solution, and this coupled with the irreversibility of the reaction, suggests sulphinic acids have potential use as nitrite traps, when it is necessary to remove excess nitrous acid quantitatively, rapidly and irreversibly. Preliminary experiments were performed to investigate the possibility that benzenesulphinic acid may act as a catalyst for nitrosation reactions since sulphonyl nitrites (RSO_2NO) are known[11] to be excellent nitrosating agents. No catalytic effect was observed however, for the nitrosation of morpholine, presumably because the sulphonyl nitrite once formed reacts immediately with another molecule of benzenesulphinic acid or benzenesulphinate ion to form the corresponding hydroxylamine.

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CHAPTER FOUR

THE NITROSOTHIOSULPHATE ION, $S_2O_3NO^-$, AS A NITROSATING AGENT

4.1. Introduction

Since the observation by Akiya and co-workers[1] that the reaction of sodium nitrite with sodium thiosulphate in acidic solution gave rise to a yellow coloured solution, which faded gradually, this system has been the subject of several investigations.[2,3]

Preliminary studies by Edwards and Sorum[2] were consistent with the rate law as defined in equation 4.1, and have been interpreted[4] as involving rate limiting formation of the nitrosonium ion, NO^+.

$$\text{Rate} = k\,[NO_2^-][S_2O_3^{2-}]^{0.2}[H^+]^2 \qquad 4.1$$

Abel[5] studied the iodine - thiosulphate reaction in the presence of nitrous acid, and proposed a mechanism involving reaction of NO^+ with the thiosulphate ion to explain the formation of the sulphate ion which they observed.

More recently Garley and Stedman[4] have investigated the reaction of nitrous acid with thiosulphate ion using the stopped-flow technique. They found the yellow coloured species had a visible spectrum and a value of the extinction coefficient at 420nm similar to that of other sulphur-nitroso compounds previously studied.[6,7] This, together with the constancy of the calculated equilibrium constant, of $1.66 \times 10^7\ l^2\ mol^{-2}$, led them to identify the yellow coloured species as the nitrosothiosulphate ion, $S_2O_3NO^-$. For reactions at 25°C in perchloric acid they found that the rate expression (equation 4.2) fitted the observed experimental results.

$$\text{Rate} = k_1[H^+][HNO_2][S_2O_3^{2-}] \quad + \quad k_2[HNO_2]^2 \qquad 4.2$$

This was interpreted in terms of two concurrent pathways:

(a) rate limiting reaction between NO^+ (or $H_2NO_2^+$) and $S_2O_3^{2-}$ and (b) rate limiting formation of nitrous anhydride (N_2O_3), which then effects nitrosation of thiosulphate more rapidly than its

hydrolysis to nitrous acid. Both reaction pathways have previously been observed for a number of substrates.[8]

Together the values of k_1, of 18000 l^2 mol^{-2} s^{-1}, and the experimentally determined[4] energy of activation for the reaction, of 50k J mol^{-1}, support the theory that nitrosation of thiosulphate occurs close to encounter-controlled limit.

The decomposition of the nitrosothiosulphate ion has been studied,[9] and found to occur rapidly according to equation 4.3.

$$2S_2O_3NO^- \longrightarrow S_4O_6^{2-} + 2NO \qquad 4.3$$

The results were interpreted in terms of the rate expression as defined in equation 4.4.

$$\text{Rate} = k_1[S_2O_3NO^-] + k_2[S_2O_3NO^-]^2 \qquad 4.4$$

The second order term was explained in terms of the reaction of two nitrosothiosulphate ions with concurrent S-N bond breaking and S-S bond formation. (equation 4.5)

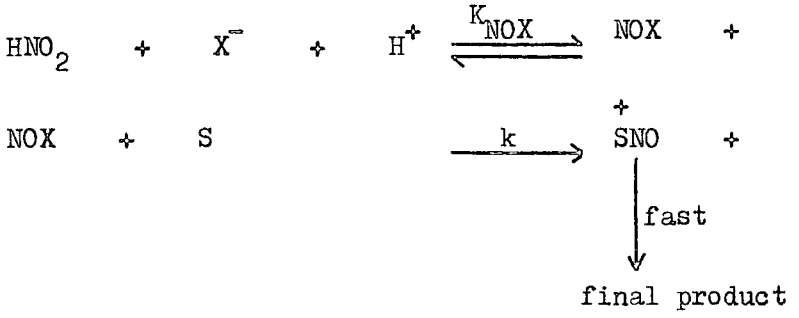
$$2S_2O_3NO^- \longrightarrow \left[\begin{array}{l} {}^-O_3S\text{-}S\text{---}NO \\ \quad\vdots \\ {}^-O_3S\text{-}S\text{---}NO \end{array}\right]^{\ddagger} \longrightarrow \begin{array}{l} {}^-O_3S\text{-}S \\ \quad\vdots \\ {}^-O_3S\text{-}S \end{array} + 2NO \qquad 4.5$$

The mechanism used to interpret the first order term is outlined in equation 4.6 and involves rate limiting formation of the radical anion, $S_2O_3^{\cdot-}$, followed by rapid dimerisation to give the observed product.

$$S_2O_3NO^- \xrightarrow{\text{slow}} S_2O_3^{\cdot-} + NO^{\cdot} \qquad 4.6$$

$$2S_2O_3^{\cdot-} \xrightarrow{\text{fast}} S_4O_6^{2-}$$

Catalysis of nitrosation reactions by added halide ions, thiocyanate ion, and thiourea is well established,[10,11] and has been interpreted in terms of the formation of equilibrium concentrations of the species NOX (where X = Cl^-, Br^-, SCN^- or $SC(NH_2)_2$). A mechanism for the reaction of the nitrosating agent (NOX) with a substrate, S, is given in scheme 4.1.



Scheme 4.1

Clearly, if the reaction between NOX and S is the rate determining step the degree of catalysis of the different nucleophiles X, depends on: (a) the magnitude of K_{NOX}, and (b) the rate constant k . As has been found experimentally (Chapters 2 and 3) and discussed previously, the overall catalytic efficiency is governed principally by the magnitude of K_{NOX}, with the net result that catalytic efficiency increases in the order: $Cl^- < Br^- < SCN^- < SC(NH_2)_2$ On the basis of this argument, if the nitrosothiosulphate ion can act as a nitrosating agent, thiosulphate ion catalysis of nitrosation should be pronounced because of the large value of K_{NOX}, where NOX = $S_2O_3NO^-$ of 1.66×10^7 l^2 mol^{-2}.

The aim of this work was to investigate the possibility that the nitrosothiosulphate ion may act as a nitrosating agent. Nitrosation of N-methylaniline in the presence of thiosulphate ion was examined, and the results compared with those obtained for the bromide and thiocyanate ion catalysed nitrosation of the same amine, in order to

obtain a measure of the relative catalytic efficiency of $S_2O_3^{2-}$. To test whether the nitrosothiosulphate ion may generally act as a nitrosating agent nitrosation of both methanol and a thiol, N-acetylpenicillamine, in the presence of thiosulphate ion was also investigated.

In all the experiments there was a large excess of substrate over the concentration of sodium nitrite so k_o, the observed first order rate constant, is defined by equation 4.7.

$$\frac{d[NNMA]}{dt} = k_o[HNO_2] \qquad 4.7$$

where NNMA is the concentration of N-nitroso-N-methylaniline.

4.2. Nitrosation of N-methylaniline

The effect of added thiosulphate ion and, for comparison purposes, of added bromide and thiocyanate ion on the N-nitrosation of N-methylaniline (NMA) was examined. The results are presented in tables 4.1, 4.2 and 4.3 and in figure 1.

Table 4.1 catalysis by thiosulphate ion

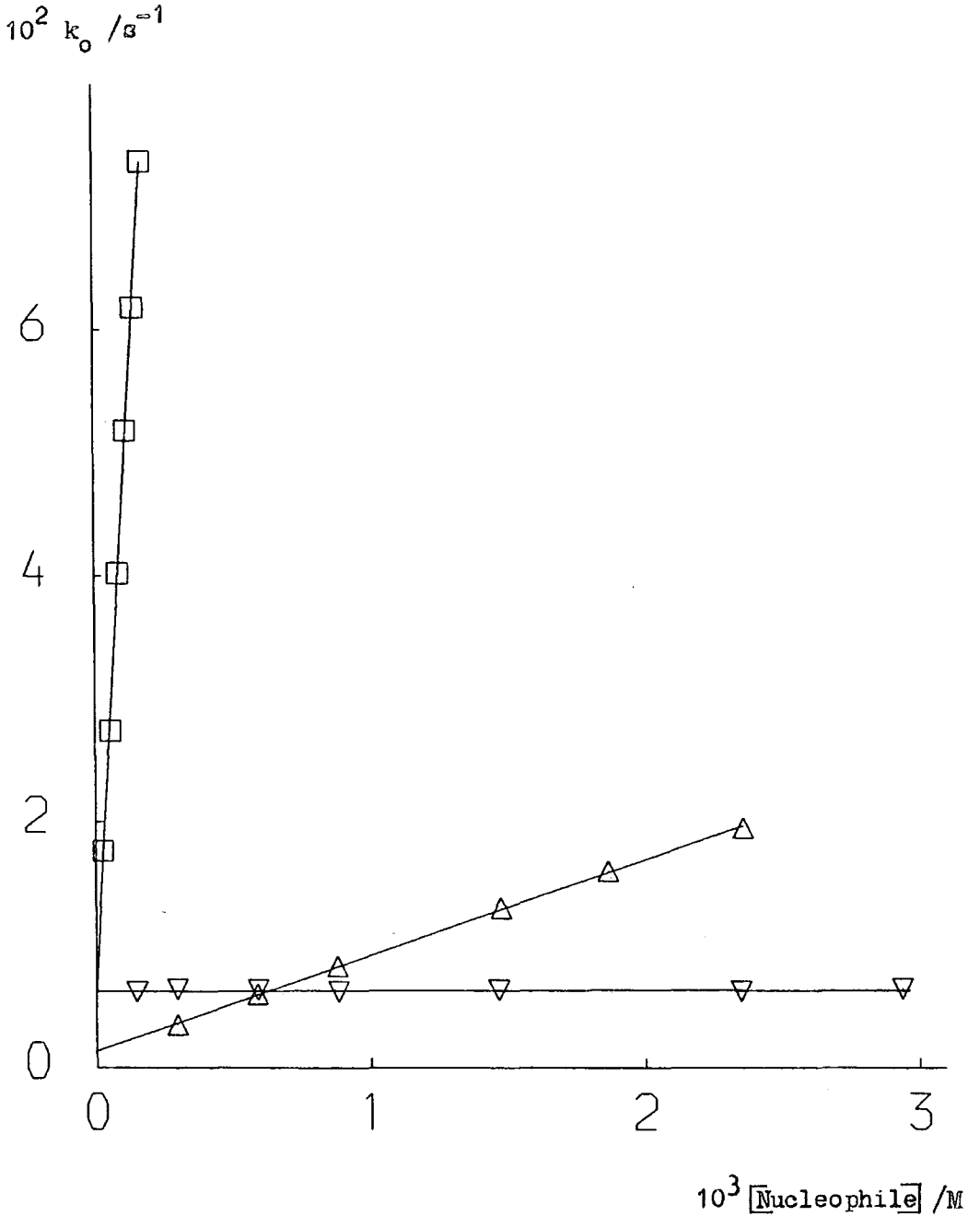
$[NMA] = 3.63 \times 10^{-3}M$

$[HClO4] = 0.1M$

$[NaNO_2] = 1 \times 10^{-4}M$

$10^4[Na_2S_2O_3]/M$	$10^3k_o/s^{-1}$
1.48	6.18
2.94	6.36
5.89	6.33
8.83	6.17
14.7	6.32
23.5	6.23
29.4	6.41

Figure 1 Nucleophile catalysis of N-nitroso-N-methylaniline formation



□ thiocyanate ion

▽ thiosulphate ion

△ bromide ion

Table 4.2 catalysis by bromide ion

$[NMA] = 3.63 \times 10^{-3}M$

$[HClO_4] = 0.1M$

$[NaNO_2] = 1 \times 10^{-4}M$

$10^5 [NaBr]$	$10^3 k_o/s^{-1}$
2.93	1.26
5.86	1.50
8.80	1.90
29.3	3.41
58.6	6.05
88.0	8.37
147	13.3
187	16.0
235	19.4

Table 4.3 catalysis by thiocyanate ion

$[NMA] = 3.63 \times 10^{-3}M$

$[HClO_4] = 0.1M$

$[NaNO_2] = 1 \times 10^{-4}M$

$10^5 [NaSCN]/M$	$10^2 k_o/s^{-1}$
2.93	1.77
5.85	2.74
8.78	4.02
11.7	5.18
14.6	6.18
17.6	7.37

The results show the expected linear dependence of k_o upon both $[Br^-]$ and $[SCN^-]$, and a complete independence of k_o upon $[S_2O_3^{2-}]$.

The dependence of k_o upon [NMA] for three reactions with $[Br^-] = [SCN^-] = [S_2O_3^{2-}] = 2 \times 10^{-4}$M and a constant concentration of acid and sodium nitrite was also investigated. The results are given in tables 4.4, 4.5 and 4.6 and in figure 2.

Table 4.4 variation of k_o with [NMA]

$[Na_2S_2O_3] = 2 \times 10^{-4}$M

$[HClO4] = 0.1$M

$[NaNO_2] = 1 \times 10^{-4}$M

10^3 [NMA]/M	$10^3 k_o/s^{-1}$
0	0
1.8	2.95
3.6	6.19
4.8	8.00

Table 4.5 variation of k_o with [NMA]

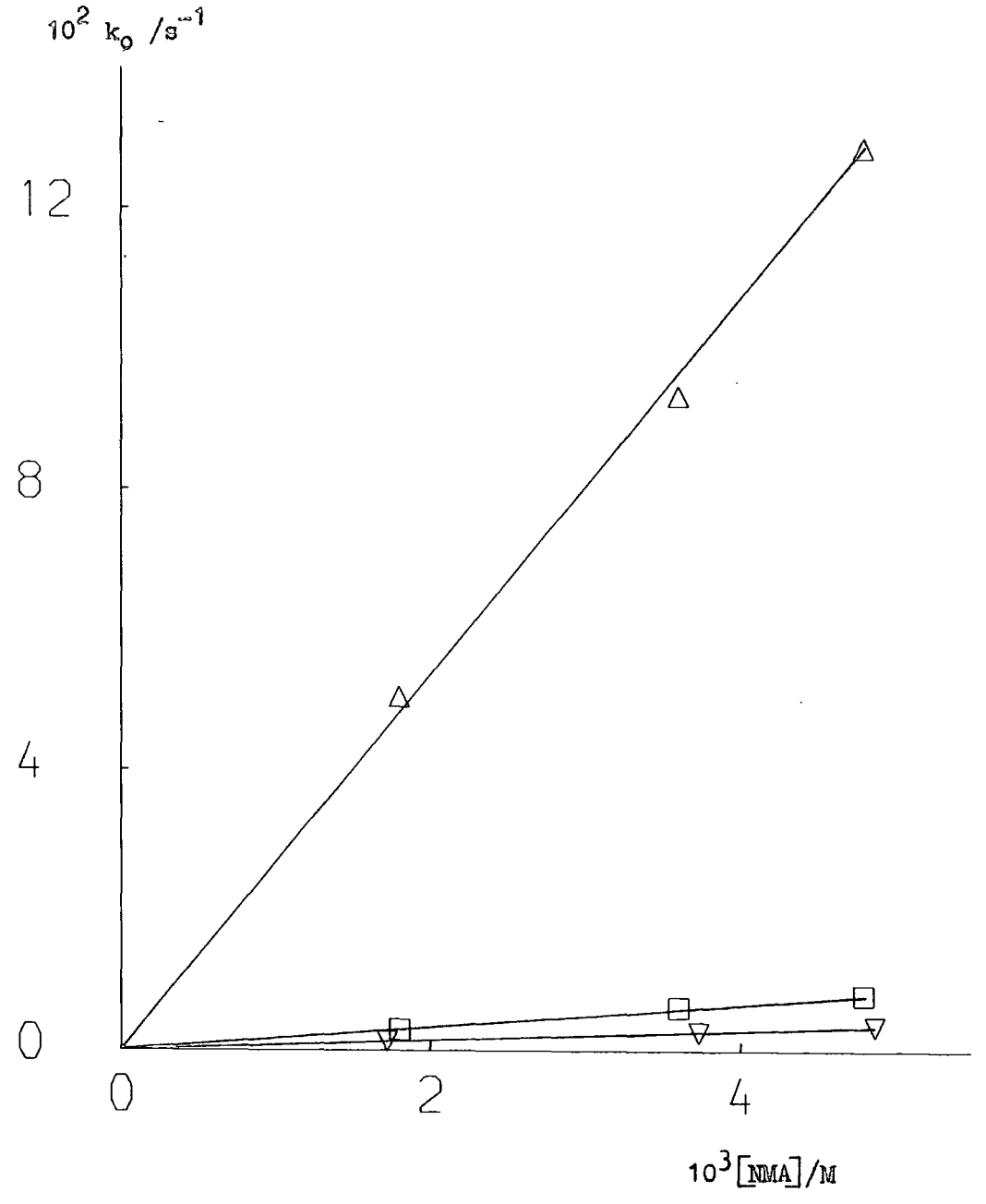
$[NaBr] = 2 \times 10^{-4}$M

$[HClO4] = 0.1$M

$[NaNO_2] = 1 \times 10^{-4}$M

10^3 [NMA]/M	$10^3 k_o/s^{-1}$
0	0
1.72	1.31
3.73	2.64
4.87	3.53

Figure 2 Variation of k_o with [N-methylaniline]



□ thiosulphate ion

▽ bromide ion

△ thiocyanate ion

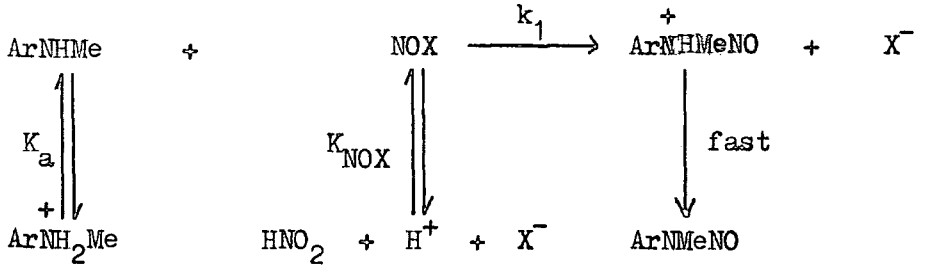
Table 4.6 variation of k_o with [NMA]

$[NaSCN] = 2 \times 10^{-4}$M
$[HClO_4] = 0.1$M
$[NaNO_2] = 1 \times 10^{-4}$M

10^3 [NMA] /M	$10^2 k_o / s^{-1}$
0	0
1.8	5.04
3.7	9.34
4.8	12.9

Within experimental error there was quantitative formation of the product N-methyl-N-nitrosaniline. Under the experimental conditions used rearrangement of the nitrosamine to give the C-nitroso product can be ignored.[12]

The experimental results are consistent with the mechanism outlined in scheme 4.2.



Scheme 4.2

Ignoring the contribution from the acid catalysed pathway the rate of reaction may be defined as:-

$$\text{Rate} = k_1 [\text{ArNHMe}]_F [\text{NOX}]$$

where $[\text{ArNHMe}]_F$ refers to the concentration of the free base form of the amine and since

$$K_{NOX} = \frac{[\text{NOX}]}{[\text{HNO}_2][\text{H}^+][\text{X}^-]}$$

and if, by definition

$$[\text{Total nitrite}] = [HNO_2] + [NOX]$$

$$[\text{Total nitrite}] = [NOX]\left(\frac{1}{K_{NOX}[H^+][X^-]} + 1\right)$$

thus $$[NOX] = \frac{[\text{Total nitrite}]}{\left(\frac{1}{K_{NOX}[H^+][X^-]} + 1\right)}$$

for $[ArNHMe]_{Free}$ $\quad K_a = \frac{[H^+][ArNHMe]_F}{[ArNH_2Me]^+}$

and if, by definition

$$[NMA_T] = [ArNHMe]_F + [ArNH_2Me]^+$$

where $[NMA]_T$ = total concentration of added N-methylaniline

$$[ArNHMe]_F = \frac{[NMA]_T}{\left(1 + \frac{[H^+]}{K_a}\right)}$$

substitution gives

$$\text{Rate} = \frac{K_{NOX}K_a k_1 [NMA]_T[H^+][X^-][HNO_2]}{(K_a + [H^+])(K_{NOX}[H^+][X^-] + 1)} \qquad 4.8$$

since from equation 4.7

$$\text{Rate} = k_o[HNO_2]$$

$$k_o = \frac{K_{NOX}K_a k_1 [NMA]_T[H^+][X^-]}{(K_a + [H^+])(K_{NOX}[H^+][X^-] + 1)} \qquad 4.9$$

In all kinetic runs $[H^+]$ was 0.1M and since the pKa of N-methylaniline is 4.85[13] $[H^+] >> K_a$ and so the expression for k_o (equation 4.9) reduces to that given in equation 4.10.

$$k_o = \frac{K_{NOX}K_a k_1 [NMA]_T[X^-]}{(K_{NOX}[H^+][X^-] + 1)} \qquad 4.10$$

For nitrosyl bromide K_{NOX} is small, 5.1×10^{-2} l^2 mol^{-2} at 25°C[14], so at reasonably low concentrations of $[Br^-]$ and $[H^+]$ the limiting condition $1 >> K_{NOX}[H^+][Br^-]$ applies and k_o reduces to the expression given in equation 4.11

$$k_o = k_1 K_{NOX} K_a [NMA]_T [X^-] \qquad 4.11$$

K_a is the acid dissociation constant of the protonated amine, K_{NOX} is the equilibrium constant for the formation of NOX and k_1 is the rate constant as defined in scheme 4.2.

For nitrosyl thiocyanate although K_{NOX} is now larger, 32 $l^2 mol^{-2}$ at 20°C,[15] at the low concentrations of thiocyanate ion used in this study ($0 - 2 \times 10^{-4}$ M) the limiting form of the expression for k_o still applies.

This expression for k_o predicts the linear dependence of k_o upon [nucleophile] for both bromide and thiocyanate ion, and the first order dependence upon $[NMA]_T$, in the presence of either bromide or thiocyanate ion, which was observed. However, it does not predict the results observed when the reation was performed in the presence of thiosulphate ion. This is because the value of K_{NOX} for $X = S_2O_3^{2-}$ is very large (1.66×10^7 l^2 mol^{-2} at 25°C)[4] so the inequality $K_{NOS_2O_3^-}[H^+][S_2O_3^{2-}] >> 1$ applies, and the expression for k_o is now given by equation 4.12.

$$k_o = \frac{k_1 K_a [NMA]_T}{[H^+]} \qquad 4.12$$

This expression predicts the first order dependence of k_o upon $[NMA]_T$ and independence of k_o upon $[S_2O_3^{2-}]$ found experimentally.

A plot of k_o versus $[NMA]_T$ is linear with a slope equal to $k_1 K_{NOX} K_a [NOX]$ for $X = Br^-$ and SCN^-, and to $\frac{k_1 K_a}{[H^+]}$ for $X = S_2O_3^{2-}$ so values of k_1 may be easily evaluated. Similarly values of k_1 may also be determined from the variation of k_o with $[X^-]$.

A plot of k_o versus $[X^-]$ is linear with a slope of $k_1 K_{NOX} K_a [NMA]_T$ for $X = Br^-$ and SCN^-, and the mean value of k_o is equal to $\frac{k_1 K_a [NMA]_T}{[H^+]}$ for $X = S_2O_3^{2-}$. The values of k_1 determined as described above are given in table 4.7.

Table 4.7 values of k_1 for the reaction of NMA with NOBr, NOSCN and $S_2O_3NO^-$

Electrophile	k_1/l mol^{-1} s^{-1}	
	from k_o versus $[X]$ plot	from k_o versus $[NMA]_T$ plot
NOBr	3.1×10^9	5.0×10^9
NOSCN	2.5×10^8	3.1×10^8
$S_2O_3NO^-$	1.2×10^4	1.2×10^4

For both thiosulphate and thiocyanate ion the agreement between the values of k_1 determined from the two methods is excellent, and for bromide ion is acceptable.

There does not appear to be any report in the literature of values of k_1 for the reaction of nitrosyl bromide and nitrosyl thiocyanate with N-methylaniline. For comparison purposes the values of k_1 obtained in this study are listed in table 4.8. together with k_1 values that have been reported in the literature for other aromatic amines.

Table 4.8 values of k_1 for the reaction of NOBr and NOSCN with some aromatic amines.

Substrate	pK_a	k_1/l mol^{-1} s^{-1}		Temp/°C	Ref.
		NOBr	NOSCN		
N-methylaniline	4.85	3.1×10^9	2.5×10^8	25	*
		5.0×10^9	3.1×10^8	25	*
Aniline	4.59	1.7×10^9		25	16
			1.9×10^8	25	17
p-methoxy-aniline	5.4	2.8×10^9		25	16
		3.2×10^9		25	16
			7.5×10^8	25	17
p-nitro-aniline	1.0	4.3×10^7		25	16

* this work

From the information available in table 4.8 it can be seen that N-methylaniline is slightly more reactive than aniline towards nitrosyl bromide and nitrosyl thiocyanate. This is consistent with results obtained previously,[16,17] some of which are given in table 4.8, where it was found that values of k_1 increase with increased pKa of the amine levelling off only when k_1 is close to the value predicted for a diffusion controlled reaction.[18] In conclusion it appears that the reaction of N-methylaniline with nitrosyl bromide occurs close to the encounter-controlled limit.

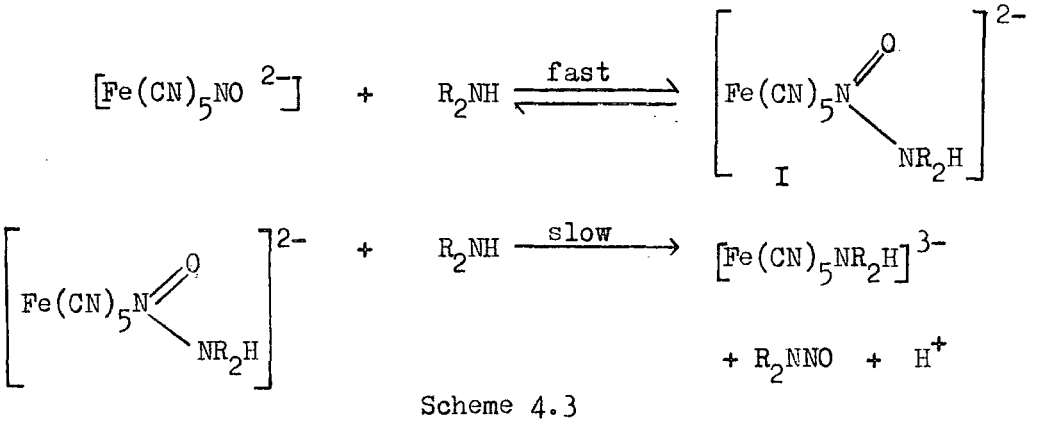
Meyer and Williams[11] obtained a quantitative measure of the catalytic efficiencies of different nucleophiles for the nitrosation of morpholine from the slope of a plot of k_o versus [nucleophile], and found they increased in the order $Br^- < SCN^- < SC(NH_2)_2$ in the ratio 1 : 240 : 4200. This ratio emphasises the importance of the magnitude of K_{NOX}, which for X = thiourea is very large 5000 $l^2\ mol^{-2}$,[19] in determining the catalytic efficiency of the added nucleophile.

Clearly, from the results obtained, thiosulphate ion does act as a catalyst for the nitrosation of N-methylaniline, although it is not possible to compare catalytic efficiences by the method described above for this study. This is because the rate law for the nitrosation of N-methylaniline in the presence of thiosulphate ion (equation 4.12) is different to that for the reaction in the presence of either bromide or thiocyanate ion (equation 4.11). This point is illustrated in figure 1 where, although thiocyanate ion is always a better catalyst than either bromide or thiosulphate ion, the relative efficiencies of these latter two nucleophiles is dependent on their concentrations. Since K_{NOX} for $X = S_2O_3^{2-}$ is very large, under the conditions used in this study there will be complete

conversion of nitrous acid into the nitrosothiosulphate ion, whereas for bromide as the concentration of added nucleophile is increased so the concentration of nitrosyl bromide formed also increases. When $[Br^-] = [S_2O_3^{2-}] < 6 \times 10^{-4}$M thiosulphate ion is the better catalyst, whereas above this concentration bromide ion is the better catalyst since the concentration of nitrosyl bromide formed is increased.

Since the nitrosothiosulphate ion is a species with a negative charge it is not surprising that it is less reactive than nitrosyl bromide and nitrosyl thiocyanate, by factors of 4×10^5 and 1.5×10^4 respectively, for its reaction with N-methylaniline. However, despite its lower reactivity, that nitrosation by nitrosothiosulphate does occur is interesting, since it represents a rather unusual example of electrophilic nitrosation brought about by a negatively charged species.

It has been found[20] that the reaction of nitroprusside, $[Fe(CN)_5NO^{2-}]$, one of the most common nitrosyl complexes, with secondary amines in alkaline conditions yields N-nitrosamines. Casado and co-workers[21] have studied the reaction of morpholine with nitroprusside and have proposed a mechamism for the reaction as outlined in scheme 4.3.



Scheme 4.3

Unlike the reaction of N-methylaniline with the nitrosothiosulphate ion this mechanism involves the formation of an intermediate complex (I), where the nitrogen atom of the nitroso group is bound to the iron and amino nitrogen atom. Nevertheless, this reaction with nitroprusside represents another example of electrophilic nitrosation by a negatively charged nitrosating agent.

4.3 Nitrosation of methanol and a thiol

In order to assess the ability of the nitrosothiosulphate ion to act as a more general nitrosating agent like, for example, nitrosyl bromide, its reaction with methanol and N-acetylpenicillamine, two substrates which readily undergo nitrosation with nitrosyl chloride and nitrosyl bromide,[22] was investigated.

For the reaction with methanol it was necessary to generate the nitrosothiosulphate ion, from nitrous acid and thiosulphate ion, before methanol was added, otherwise competition for the nitrous acid from both the thiosulphate ion and methanol would have resulted, since nitrosation of the latter occurs rapidly. The reaction was followed by monitoring the decrease in absorbance at 386nm using the stopped-flow technique. The rate of reaction measured when equal volumes of methanol and the nitrosothiosulphate ion were mixed, was compared with that determined for the reaction in the absence of the thiosulphate ion. It was found that the nitrosation of methanol occured slightly faster in the presence of the thiosulphate ion. The nitrosation of N-acetylpenicillamine was also investigated using the stopped-flow technique and the reaction followed by noting the increase in absorbance at 330nm, due to product formation. Again the results showed that thiosulphate ion catalysed the reaction. These preliminary investigations suggest that the nitrosothiosulphate ion may act as a nitrosating agent for both methanol and N-acetylpenicillamine.

It has been found[9] that both hydrazine and sulphamic acid catalyse the decomposition of the nitrosothiosulphate ion. Examination of the product solutions revealed that they contained the products expected[23, 24] from nitrosation of hydrazine and sulphamic acid. The assumption drawn from this study was that the

nitrosothiosulphate ion may act as a nitrosating agent for hydrazine but not for sulphamic acid, since the latter is not subject to nitrosation by other NOX species.[25]

The results presented in this chapter clearly show that the nitrosothiosulphate ion, despite having a negative charge, may act as a nitrosating agent in electrophilic nitrosation. However, as indicated by the values of the bimolecular rate constants in table 4.7, it is not very reactive, although the efficiency of thiosulphate ion as a catalyst is comparable with that of bromide ion, as can be seen in figures 1 and 2. This again emphasises the importance of the magnitude of the equilibrium constant for the formation of the NOX species in determining catalytic efficiency.

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CHAPTER FIVE

NITROSATION OF DIMETHYL SULPHIDE

5.1. Introduction

In recent years the area of S-nitrosation has become more extensively studied and it now forms the subject of a recent review.[1] One of the major problems associated with this area of work, and presumably one of the reasons why less is known about S-nitrosation than N-nitrosation, is the instability of the S-nitroso compounds formed.

Probably the first class of compounds to be studied were the thiols, RSH, which react with nitrosating agents, for example $H_2NO_2^+$, to form the corresponding thionitrite (equation 5.1)

$$RSH + H_2NO_2^+ \longrightarrow RSNO + H_3O^+ \qquad 5.1$$

Thionitrites are unstable compounds and readily decompose to give the disulphide and nitric oxide (equation 5.2).

$$2RSNO \longrightarrow RSSR + 2NO \qquad 5.2$$

The reaction of disulphides with dinitrogen tetroxide, N_2O_4, has been studied.[2] It was found that reaction occured with the formation of RSNO and RSO^+ as intermediates (equation 5.3) Photolysis of methyl disulphide in the presence of nitric oxide has also been examined by two groups[3,4] and both found the sole product of the

$$RSSR + N_2O_4 \longrightarrow \underset{\downarrow}{RSNO}\ (\text{Product}) + \underset{\downarrow}{RSO^+}\ (\text{Product}) \qquad 5.3$$

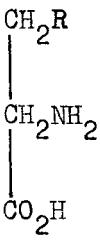
reaction was the corresponding thionitrite (equation 5.4). Thus it appears that S-nitroso species may be formed from disulphides.

$$CH_3SSCH_3 \xrightarrow{h\nu} 2CH_3S\cdot \xrightarrow{NO} 2CH_3SNO \qquad 5.4$$

It has been known for a long time that simple alkyl sulphides react with alkyl nitrites and some organic nitro compounds, for

example tetranitromethane and halonitromethanes to give coloured solutions which fade on standing.[5] The authors concluded that coloured solutions were only formed when the nitro compounds were reacted with substrates containing unsaturated groups or atoms capable of exhibiting a higher valency. It is quite plausible that the coloured intermediates formed with sulphides are S-nitroso ions since alkyl nitrites may act as nitrosating agents,[6,7] although it has not yet been established whether prior hydrolysis to give HNO_2 occurs.

The effect of cysteine (1), S-methylcysteine (2), and methionine (3) on the denitrosation of N-methyl-N-nitrosoaniline (4) in the presence of a sufficiently large excess of hydrazine to ensure

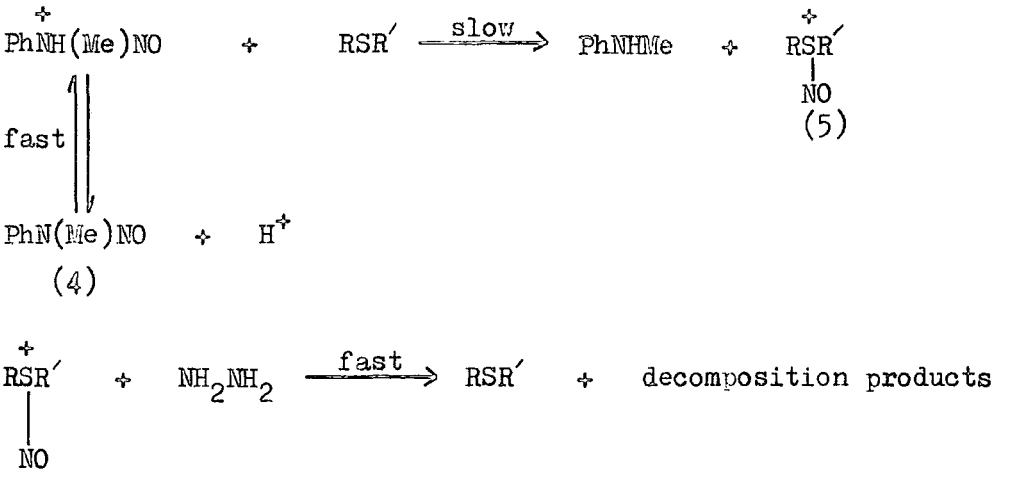


(1) R = -SH

(2) R = $-SCH_3$

(3) R = $-CH_2SCH_3$

irreversibility, was examined.[8] It was found that S-methylcysteine and methionine, both of which contain the $-SCH_3$ group, were far more reactive than the thiol cysteine which suggests that sulphides generally should undergo S-nitrosation more readily than thiols. The mechanism proposed[8] for the overall reaction, which is outlined in scheme 5.1, also implies that S-nitroso species (5) formed from the sulphide may itself nitrosate hydrazine.



Scheme 5.1

The aim of the work described in this chapter was to investigate the nitrosation of dimethylsulphide since there appears to be no reports in the literature of such a study. If it is assumed that the sulphur atom in a sulphide is as nucleophilic as that in a thiol it would seem likely that sulphides would undergo electrophilic nitrosation, except that, unlike the thiols, there is no suitable leaving group in the case of the sulphides.

In all of the experiments carried out there was a large excess of substrate over the concentration of sodium nitrite and good first order plots were obtained for each individual run.

The observed first order rate constant, k_o, is defined by equation 5.5. The stopped-flow technique was used to follow the

$$\frac{d[\text{Product}]}{dt} = -\frac{d[HNO_2]}{dt} = k_o[HNO_2] \qquad 5.5$$

reaction and all measurements were made at 330nm, monitoring the increase in absorbance due to product formation.

5.2 The acid catalysed reaction

5.2.1. Variation of k_o with $[NaNO_2]$.

The effect of added nitrite on the observed rate constant at constant concentrations of acid and dimethyl sulphide, $(CH_3)_2S$, was examined and the results are shown in table 5.1.

Table 5.1 dependence of k_o upon $[NaNO_2]$

$[(CH_3)_2S] = 1.18 \times 10^{-3}M$
$[HClO_4] = 0.15M$

$10^3[NaNO_2]/M$	k_o/s^{-1}
1	1.74 ± 0.02 *
2	1.70 ± 0.05

Since all the kinetic runs showed a first order dependence upon $[HNO_2]$ any reaction pathway involving dinitrogen trioxide, N_2O_3, as the active nitrosating agent may be eliminated. The results are consistent with reaction via either the nitrous acidium ion, $H_2NO_2^+$, or the nitrosonium ion, NO^+, which are indistinguishable kinetically. For the remainder of this chapter $H_2NO_2^+$ is assumed to be the active nitrosating agent.

5.2.2. Variation of k_o with $[(CH_3)_2S]$.

The dependence of k_o upon the concentration of substrate was examined at four different perchloric acid concentrations. The results are presented in tables 5.2 to 5.5 and in figure 1.

* The quoted error represents the standard deviation.

Table 5.2 dependence of k_o upon $[(CH_3)_2S]$

$[HClO_4] = 3 \times 10^{-2}M$

$[NaNO_2] = 1 \times 10^{-3}M$

$10^2\,[(CH_3)_2S]/M$	k_o/s^{-1}
1.32	0.33 ± 0.01
2.88	0.54 ± 0.01
4.73	0.77 ± 0.01
5.84	0.92 ± 0.01
7.76	1.17 ± 0.01

Table 5.3 dependence of k_o upon $[(CH_3)_2S]$

$[HClO_4] = 5.93 \times 10^{-2}M$

$[NaNO_2] = 1 \times 10^{-3}M$

$10^2\,[(CH_3)_2S]/M$	k_o/s^{-1}
1.18	0.65 ± 0.01
1.79	0.76 ± 0.01
2.77	1.04 ± 0.03
4.55	1.47 ± 0.01
6.51	1.90 ± 0.03
7.95	2.21 ± 0.01

Table 5.4 dependence of k_o upon $[(CH_3)_2S]$

$[HClO_4] = 0.1M$
$[NaNO_2] = 1 \times 10^{-3}M$

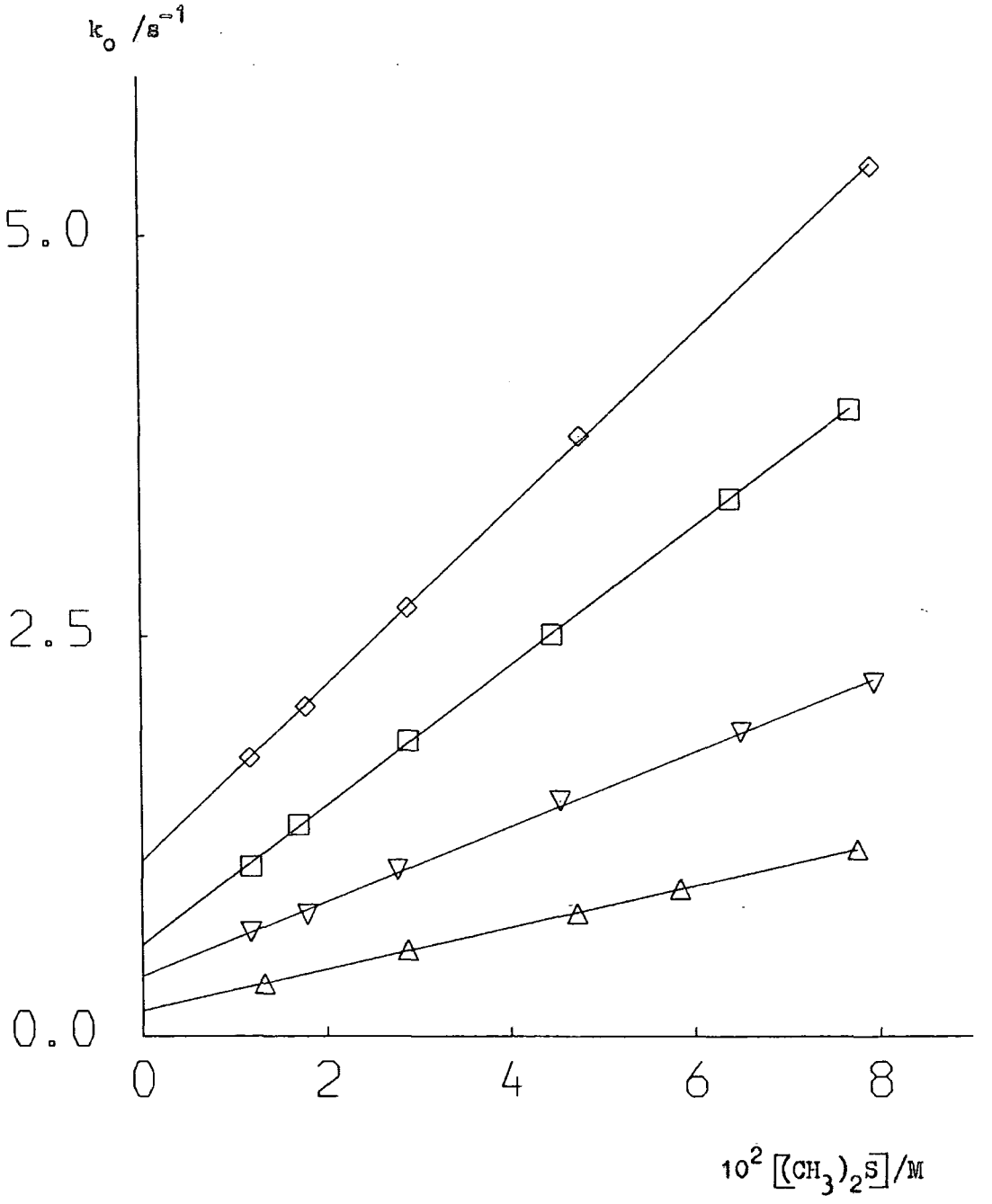
$10^2 [(CH_3)_2S]/M$	k_o/s^{-1}
1.18	1.06 ± 0.03
1.70	1.32 ± 0.01
2.90	1.85 ± 0.02
4.47	2.51 ± 0.02
6.40	3.36 ± 0.03
7.70	3.92 ± 0.03

Table 5.5 dependence of k_o upon $(CH_3)_2S$

$[HClO_4] = 0.15M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^2 [(CH_3)_2S]/M$	k_o/s^{-1}
1.18	1.74 ± 0.02
1.78	2.06 ± 0.04
2.90	2.68 ± 0.04
4.77	3.75 ± 0.02
7.94	5.44 ± 0.07

Figure 1 Variation of k_o with [dimethyl sulphide]



◇ $[HClO_4]$ = 0.15M
□ $[HClO_4]$ = 0.1M
▽ $[HClO_4]$ = 5.93×10^{-2}M
△ $[HClO_4]$ = 3.0×10^{-2}M

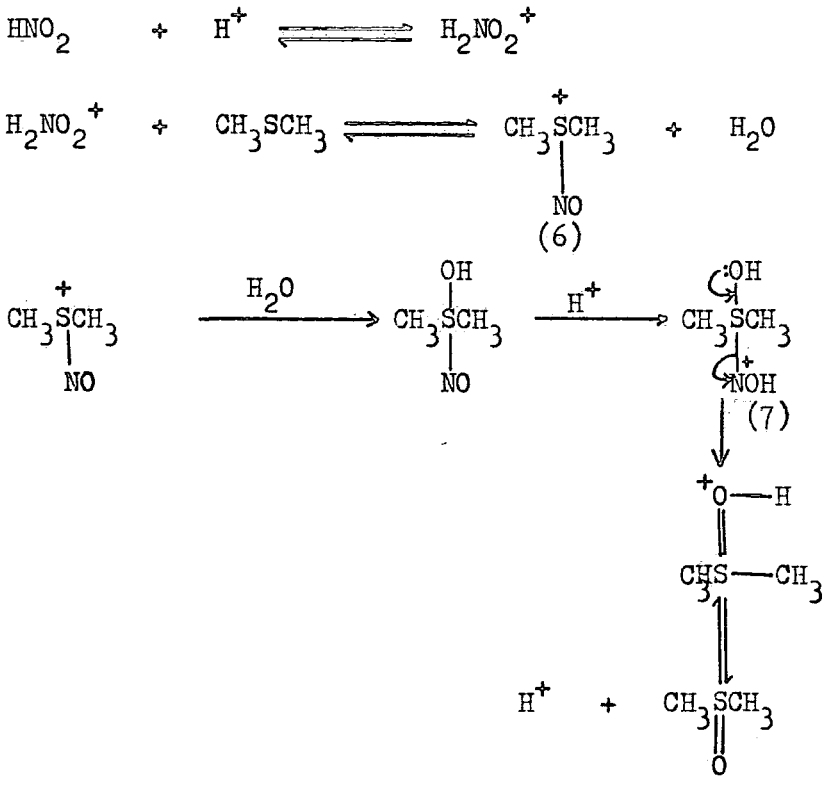
The four plots of k_o versus $[(CH_3)_2S]$ are all linear and each has a positive intercept, which suggests that the reaction of $H_2NO_2^+$ with dimethyl sulphide is reversible. Moreover, the slopes and intercepts of these linear plots, which are quoted in table 5.6, indicate that both the forward and reverse reactions are subject to acid catalysis.

Table 5.6 Slopes and intercepts for plots of k_o versus $[(CH_3)_2S]$

$10^2[H^+]$/M	Slope / l mol^{-1} s^{-1}	Intercept /s^{-1}
2.90	12.2 ± 0.02	0.19 ± 0.003
5.83	23.1 ± 0.16	0.38 ± 0.008
9.90	41.9 ± 0.09	0.64 ± 0.004
14.9	58.1 ± 0.15	1.07 ± 0.007

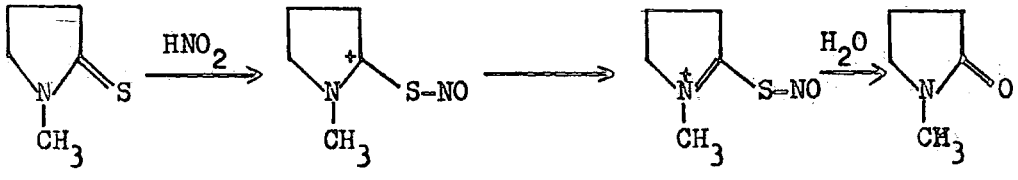
The overall reaction of dimethyl sulphide with nitrous acid was followed qualitatively by n.m.r., over a period of at least one hour. By comparison the reaction monitored by noting the increase in absorbance at 330nm due to product formation, which gave the results in tables 5.2 to 5.5, was only followed for a period of several seconds. The signal of the peak due to the $(CH_3)_2S$ was found to decrease as the signal of another peak, later identified as being due to dimethyl sulphoxide, increased as a function of time. This confirmed that the overall product of the reaction was dimethyl sulphoxide and is consistent with results obtained by Balla and Heicklen,[9] who found that the reaction of dimethyl sulphide with nitrogen dioxide gave the same product.

A possible mechanism for the reaction of dimethyl sulphide and nitrous acid is outlined in scheme 5.2 and involves the formation of a cationic S-nitroso intermediate (6). This type of intermediate



Scheme 5.2

has previously been proposed[8] to explain the catalytic effect S-methylcysteine and methionine had on the denitrosation of N-methyl-N-nitrosoaniline. An S-nitroso intermediate has also been used[10] to explain the formation of N-methyl-2-pyrrolidone(9) from the reaction of N-methyl-2-thiopyrrolidine(8) with sodium nitrite in aqueous acid solution (equation 5.6). In addition a solution of

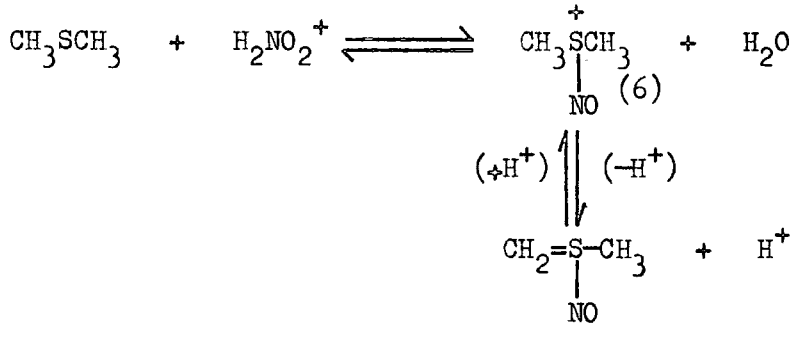


5.6

(8) (9)

dimethyl sulphide and nitrous acid gave rise to a yellow coloured solution which faded on standing. This compares well with the behaviour of thionitrites, RSNO, which are known to be similarly coloured in solution and, generally, to decompose quite rapidly with time. Moreover, the U.V. and visible spectrum of a reaction solution showed an absorption maximum in the region of 340nm, which is characteristic of thionitrites,[11] and peaks which characterise HNO_2 in the region 390nm - 330nm, indicating that the idea that the nitrosation of dimethyl sulphide is a reversible reaction is valid.

The kinetic results showed that both the forward and reverse reaction were acid catalysed. In the proposed mechanism the acid catalysed reverse reaction is the formation of the hydroxylamine derivative (7). An alternative explanation would be the formation of $CH_2{=}\underset{\underset{NO}{|}}{S}{-}CH_3$ according to scheme 5.3. However, this seems unlikely since there appears to be no driving force for the loss of H^+, and reprotonation would be necessary before dimethyl sulphoxide would form.



Scheme 5.3

In order to try to elucidate the mechanism of the reaction, spectra of reaction solutions were measured as a function of concentration. The amount of the S-nitroso species formed was found to be independent of the concentration of acid but dependent on the

concentration of added sulphide. This suggests that the equilibrium constant for the formation of the intermediate (6) may be defined by equation 5.7, where [DMS] is the concentration of dimethyl sulphide, [ ]e represents the equilibrium concentration of the species, and [I] represents the concentration of the

$$K = \frac{[I]_e}{[HNO_2]_e [DMS]_e} \qquad 5.7$$

intermediate (6) (scheme 5.2).

Since $[DMS]_T >> [I]$ where $[DMS]_T$ is the total concentration of dimethyl sulphide, $[DMS]_e = [DMS]_T$, and if, by definition $[HNO_2]_T = [HNO_2]_e + [I]_e$ substitution gives:

$$I = \frac{K[DMS_T][HNO_2]_T}{1 + K[DMS]_T}$$

Assuming the absorbance at 330nm due to $[HNO_2]_T$ and $[DMS]_T$ is negligible the Beer-Lambert law[12] gives:

$$\text{Absorbance}_{330nm} = \varepsilon_I [I] l$$

substitution for [I] gives:

$$Abs_{330nm} = \varepsilon_I l \left(\frac{K[DMS]_T[HNO_2]_T}{1 + K[DMS]_T} \right) \qquad 5.8$$

Rewriting equation 5.8 in the reciprocal form gives equation 5.9. This equation predicts that a plot of $\frac{1}{Abs_{330}}$ versus $\frac{1}{[DMS]_T}$ should be

$$\frac{1}{Abs_{330}} = \frac{1}{\varepsilon_I l [HNO_2]_T} \left(1 + \frac{1}{K[DMS]_T} \right) \qquad 5.9$$

linear with a slope which represents $\frac{1}{K \varepsilon_I l [HNO_2]_T}$ and an intercept of $\frac{1}{\varepsilon_I l [HNO_2]_T}$. The variation of the absorbance at 330nm with $[DMS]_T$

was measured and the results, from which a value of K of 4.5 l mol^{-1} was determined, are shown in table 5.7

Table 5.7 dependence of the absorbance at 330nm upon $[(CH_3)_2S]$

$10^2[(CH_3)_2S]/M$	10^3 Absorbance
1.25	6.48
1.72	8.53
2.02	9.95
2.76	12.7
3.92	18.2
4.82	21.2
5.79	25.3
7.54	32.3

5.3. The nucleophile catalysed reaction

Preliminary experiments showed that the addition of bromide ions, chloride ions, thiocyanate ions, and thiourea had a catalytic effect on the reaction of nitrous acid with dimethyl sulphide. The reactions were studied in detail by monitoring the increase in absorbance at 330nm, due to product formation, and good reproducible results, which showed a first order dependence upon $[HNO_2]$, were obtained for all the nucleophiles with the exception of thiourea.

5.3.1. Variation of k_o with [nucleophile].

The variation of the observed first order rate constant with the concentration of added nucleophile was investigated and the results are presented in tables 5.8 to 5.10. and in figure 2. All the experiments were carried out at a constant ionic strength of 0.2M($NaClO_4$).

Table 5.8 catalysis by chloride ion

$[(CH_3)_2S] = 1.1 \times 10^{-2}M$
$[HClO_4] = 6.0 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^2[NaCl]/M$	k_o/s^{-1}
5.0	1.39 ± 0.09
8.0	1.77 ± 0.01
10.0	2.11 ± 0.04

Table 5.9 catalysis by bromide ions

$[(CH_3)_2S] = 1.1 \times 10^{-2}M$
$[HClO_4] = 6.0 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

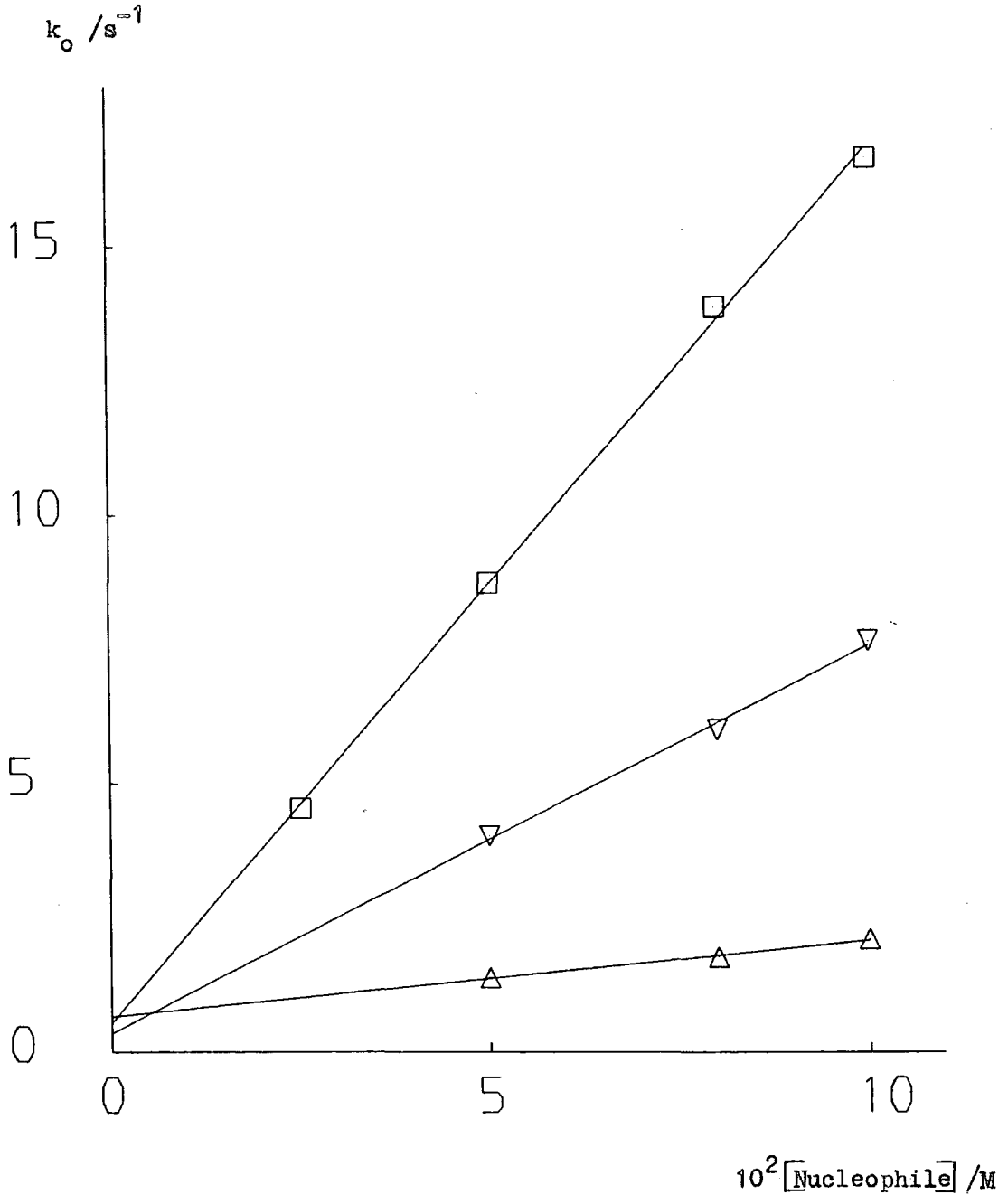
$10^2[NaBr]/M$	k_o/s^{-1}
5.0	4.03 ± 0.02
8.0	6.01 ± 0.06
10	7.68 ± 0.03

Table 5.10 catalysis by thiocyanate ion

$[(CH_3)_2S] = 1.1 \times 10^{-2}M$
$[HClO_4] = 6.0 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$

$10^2[NaSCN]/M$	k_o/s^{-1}
2.5	4.54 ± 0.04
5.0	8.75 ± 0.10
8.0	13.9 ± 0.07
10	16.7 ± 0.11

Figure 2 Nucleophile catalysis for the nitrosation of dimethyl sulphide



□ thiocyanate ion

▽ bromide ion

△ chloride ion

For the thiourea catalysed reaction the reproducibility of the values of k_o obtained were poor, presumably due to the decomposition of the S-nitroso adduct, $(NH_2)_2\overset{+}{C}SNO$, which is believed[13] to be active nitrosating agent under the experimental conditions used.

As can be seen from figure 2 plots of k_o versus [nucleophile] for Cl^-, Br^- and SCN^- were all good straight lines with a common positive intercept. The order of efficiency of the nucleophiles as catalysts increased in the expected order[13] $Cl^- < Br^- < SCN^-$ in the ratio 1 : 5 : 12 (obtained from the slope of the plots of k_o versus [nucleophile]). Since the results obtained for the reaction in the absence of added nucleophile suggest that the nitrosation of dimethyl sulphide is reversible, it was necessary to examine the dependence of k_o upon $[(CH_3)_2S]$, in the presence of fixed concentrations of each nucleophile, in order to extract kinetic data about the effect of added nucleophiles on both the forward and reverse reactions. Previously the nitrosation of alcohols has been studied.[14,15] The reaction was found to be reversible and both the forward and reverse reactions were catalysed by chloride and bromide ion. The mechanism for the reaction was interpreted in terms of nitrosation by NOX, where X = Cl^- or Br^-, as outlined in equation 5.10.

$$ROH + NOX \rightleftharpoons \underset{\underset{H}{|}}{\overset{+}{R}ONO} + X^- \rightleftharpoons RONO + H^+ \qquad 5.10$$

5.3.2. Variation of k_o with $[(CH_3)_2S]$

The dependence of k_o upon $[(CH_3)_2S]$ in the presence of a fixed concentration of either NaCl, NaBr or NaSCN was investigated and the results are presented in tables 5.11 to 5.19. All the reactions were carried out at a constant ionic strength of 0.2M [$NaClO_4$] and concentrations of reactants of $[HClO_4] = 6.0 \times 10^{-2}M$ and $[NaNO_2] = 1 \times 10^{-3}M$.

Table 5.11 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 5×10^{-2}M NaCl

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
1.10	1.39 ± 0.09
2.35	1.85 ± 0.03
4.41	2.53 ± 0.02
6.53	3.27 ± 0.02
8.02	3.94 ± 0.03

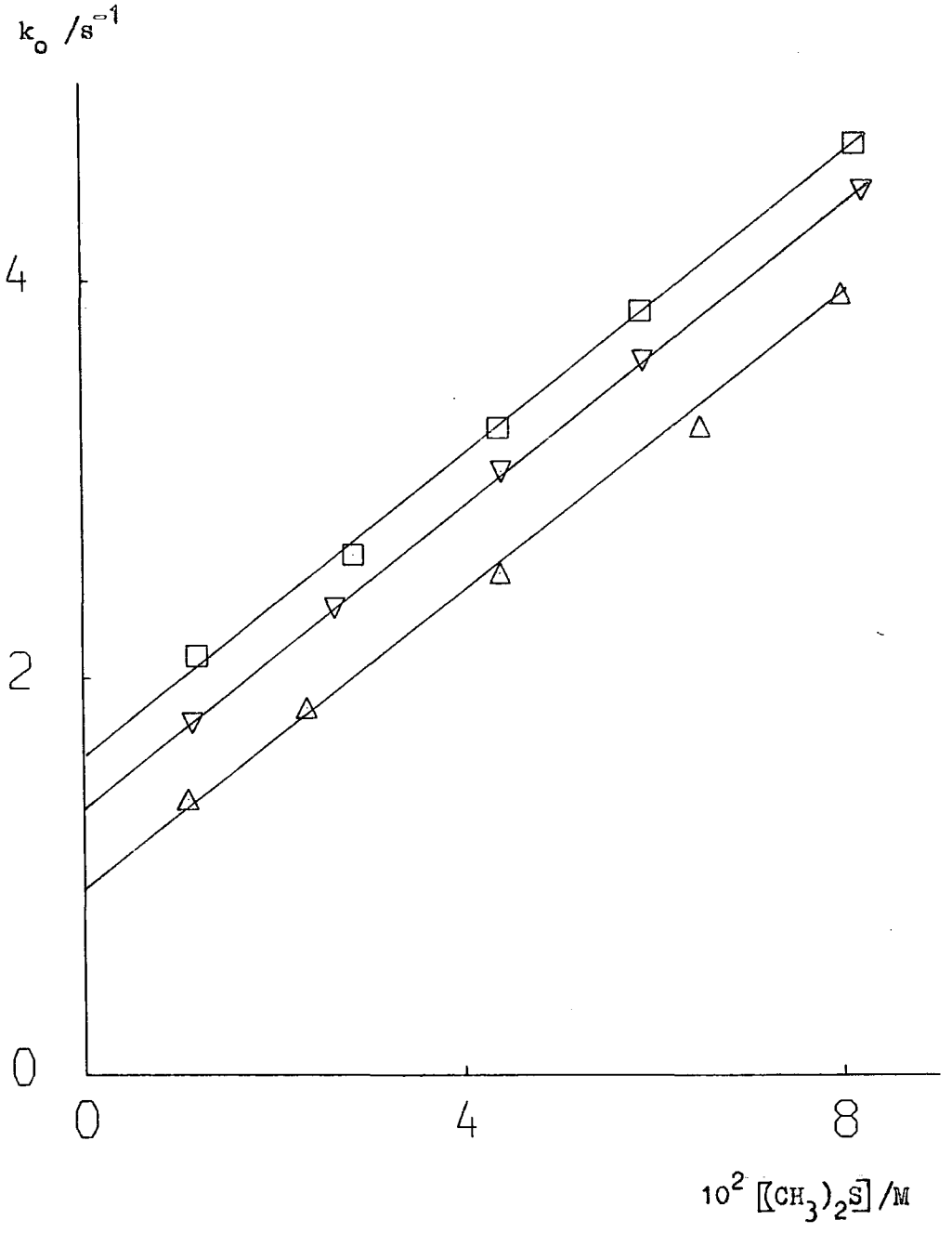
Table 5.12 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 8×10^{-2}M NaCl

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
1.15	1.77 ± 0.01
2.65	2.35 ± 0.02
4.43	3.04 ± 0.04
5.92	3.60 ± 0.02
8.25	4.46 ± 0.01

Table 5.13 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 0.1M NaCl

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
1.20	2.11 ± 0.04
2.85	2.62 ± 0.03
4.40	3.26 ± 0.03
5.90	3.85 ± 0.03
8.17	4.70 ± 0.05

Figure 3 Variation of k_o with [dimethyl sulphide] in the presence of chloride ions



□ [NaCl] = 0.1M
▽ [NaCl] = 8 x 10^{-2}M
△ [NaCl] = 5 x 10^{-2}M

Table 5.14 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 5×10^{-2}M NaBr

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
1.15	4.03 ± 0.02
2.24	4.55 ± 0.05
3.15	5.00 ± 0.09
5.09	5.68 ± 0.05
7.45	6.71 ± 0.06

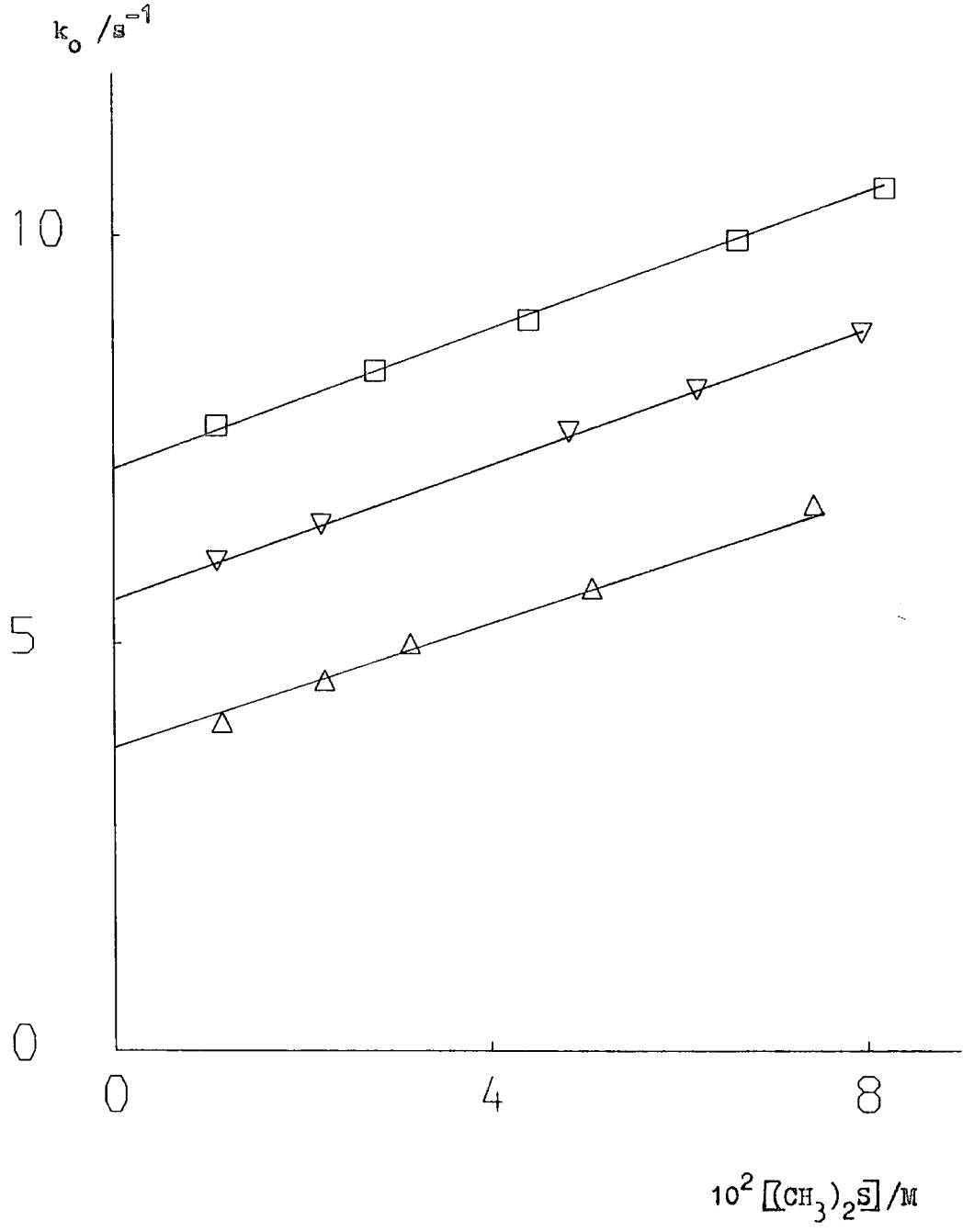
Table 5.15 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 8×10^{-2}M NaBr.

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
1.10	6.01 ± 0.06
2.21	6.46 ± 0.05
4.85	7.60 ± 0.01
6.21	8.12 ± 0.04
7.97	8.82 ± 0.12

Table 5.16 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 0.1M NaBr

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
1.10	7.68 ± 0.03
2.79	8.35 ± 0.10
4.43	8.96 ± 0.06
6.65	9.95 ± 0.06
8.22	10.6 ± 0.11

Figure 4 Variation of k_o with [dimethyl sulphide] in the presence of bromide ions



□ [NaBr] = 0.1M

▽ [NaBr] = 8 x 10^{-2}M

△ [NaBr] = 5 x 10^{-2}M

Table 5.17 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 5×10^{-2}M NaSCN

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
1.09	8.75 ± 0.10
2.68	9.52 ± 0.05
4.24	10.3 ± 0.09
6.09	11.3 ± 0.10
8.08	12.3 ± 0.08

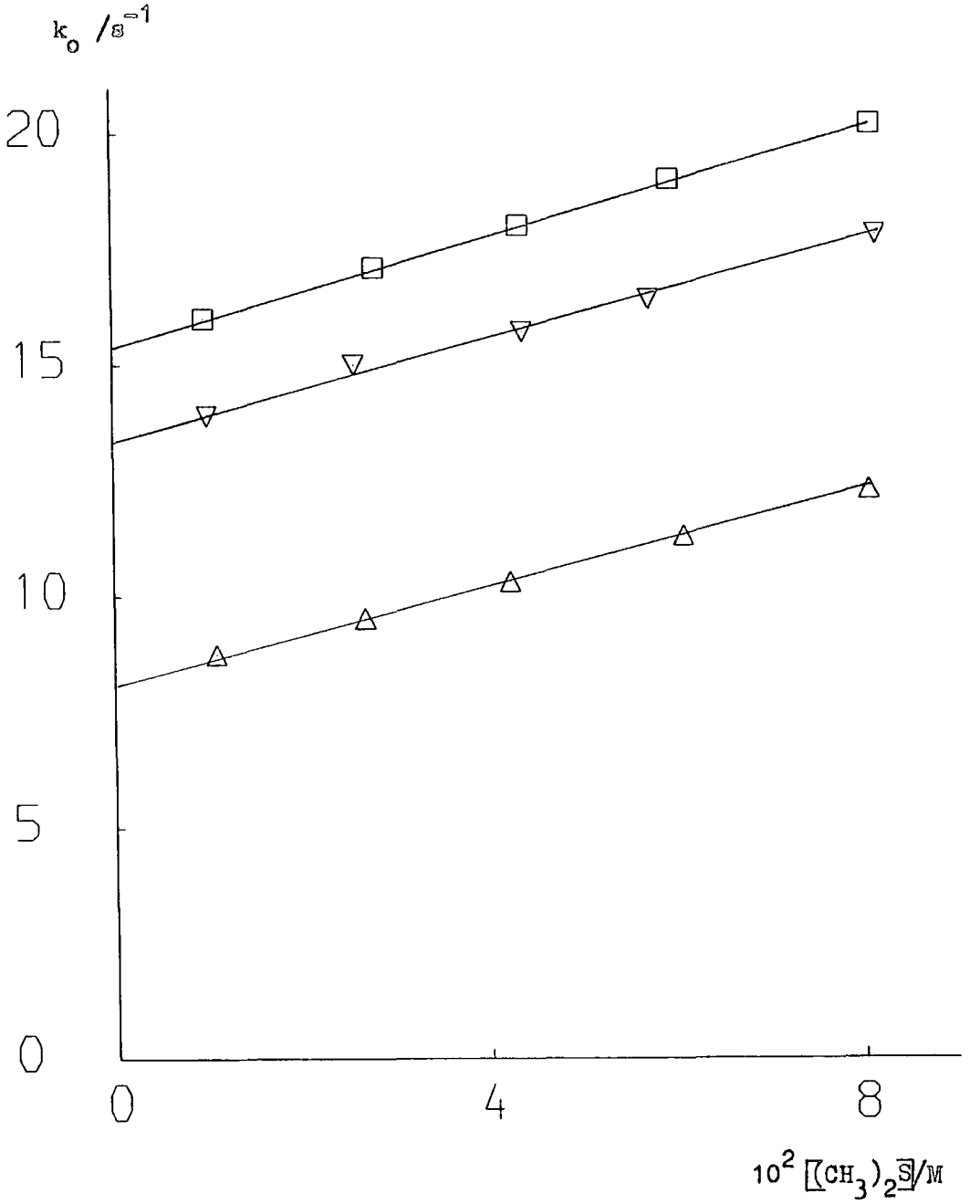
Table 5.18 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 8×10^{-2}M NaSCN

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
1.01	13.9 ± 0.07
2.58	15.0 ± 0.08
4.38	15.7 ± 0.07
5.74	16.4 ± 0.11
8.17	17.8 ± 0.14

Table 5.19 dependence of k_o upon $[(CH_3)_2S]$ in the presence of 0.1M NaSCN

$10^2[(CH_3)_2S]$/M	k_o/s^{-1}
0.98	16.0 ± 0.20
2.80	17.1 ± 0.06
4.35	18.0 ± 0.13
5.96	19.0 ± 0.13
8.12	20.2 ± 0.23

Figure 5 Variation of k_o with [dimethyl sulphide] in the presence of thiocyanate ions



□ [NaSCN] = 0.1M
▽ [NaSCN] = 8 x 10^{-2}M
△ [NaSCN] = 5 x 10^{-2}M

As can be seen from figures 3 to 5 the plots of k_o versus $[(CH_3)_2S]$ are all good straight lines each with a positive intercept, which again indicates the reversible nature of the overall reaction. Moreover each set of three plots for the three nucleophiles at different nucleophile concentrations are parallel. This suggests that the reverse reaction is catalysed by added nucleophiles, whereas the forward reaction is not, so no direct comparison can be drawn with the alcohols, which is perhaps not surprising since there is no convenient leaving group (H^+) in the case of the sulphides. However, the observed results appears to contravene the principle of microscopic reversibility, which states that "the mechanism of a reversible reaction is the same in microscopic detail (except for the direction of reaction) for the reaction in one direction as in the other under a given set of conditions".[16] As yet no satisfactory explanation for these results is available.

As a further extension of this work it was decided to examine the effect added dimethyl sulphide had on the nitrosation of a range of substrates; N-methylaniline, morpholine, and the hydrazinium ion.

5.4. Nitrosation of N-methylaniline, morpholine and the hydrazinium ion.

The preceding work in this chapter indicates that the reaction of nitrous acid with dimethyl sulphide does involve the intermediacy of a protonated S-nitroso species, $CH_3\overset{+}{S}(NO)CH_3$, although the mechanism of the reaction has yet to be elucidated. It was decided to investigate the possibility that this intermediate might itself act directly as a nitrosating agent since it has now been established[17] that

S-nitroso thiourea, $(NH_2)_2\overset{+}{C}SNO$, and its alkyl derivatives, all of which are positively charged S-nitroso species, act as nitrosating agents in their own right. The nitrosation of N-methylaniline, morpholine, and the hydrazinium ion were all examined in the presence of dimethyl sulphide and the results are presented below. All reactions were carried out under first order conditions, with excess substrate over the sodium nitrite concentration, and the observed first order rate constant is defined in equation 5.11, where $[HNO_2]$ is the total nitrite

$$\frac{d[\text{Product}]}{dt} = \left[\frac{-d[HNO_2]}{dt}\right] = k_o[HNO_2] \qquad 5.11$$

concentration.

5.4.1. Nitrosation of N-methylaniline (NMA)

The reaction was followed by monitoring the increase in absorbance at 280nm, due to the formation of the product nitrosamine, and individual runs all showed a good first order behaviour with respect to the initial nitrite concentration. In addition there was quantitative conversion of the amine to the nitrosamine, within experimental error.

Catalysis of the nitrosation of N-methylaniline by dimethyl sulphide was examined and the results are presented in table 5.20 and figure 6.

Figure 6 Dimethyl sulphide catalysis of N-nitroso-N-methylaniline formation

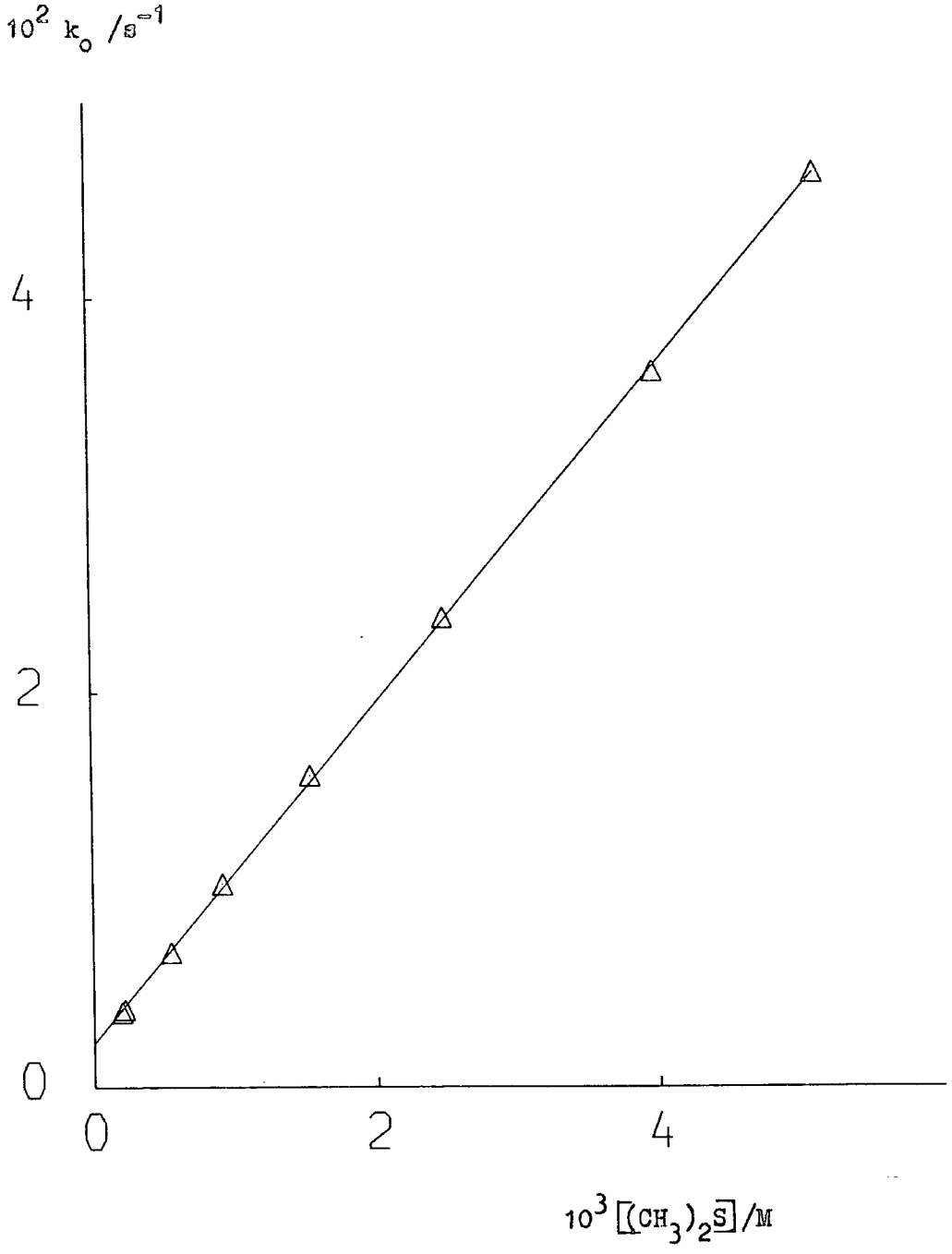


Table 5.20 catalysis by dimethyl sulphide

$[NMA] = 3.5 \times 10^{-3}M$
$[HClO_4] = 0.1M$
$[NaNO_2] = 1 \times 10^{-4}M$

$10^4 [(CH_3)_2S]/M$	10^3 ko/s^{-1}
2.02	3.79 ± 0.05
2.20	3.95 ± 0.06
5.50	6.83 ± 0.56
9.17	10.3 ± 0.11
15.4	15.8 ± 0.47
24.9	23.8 ± 0.11
39.9	36.3 ± 0.23
51.3	46.4 ± 0.05

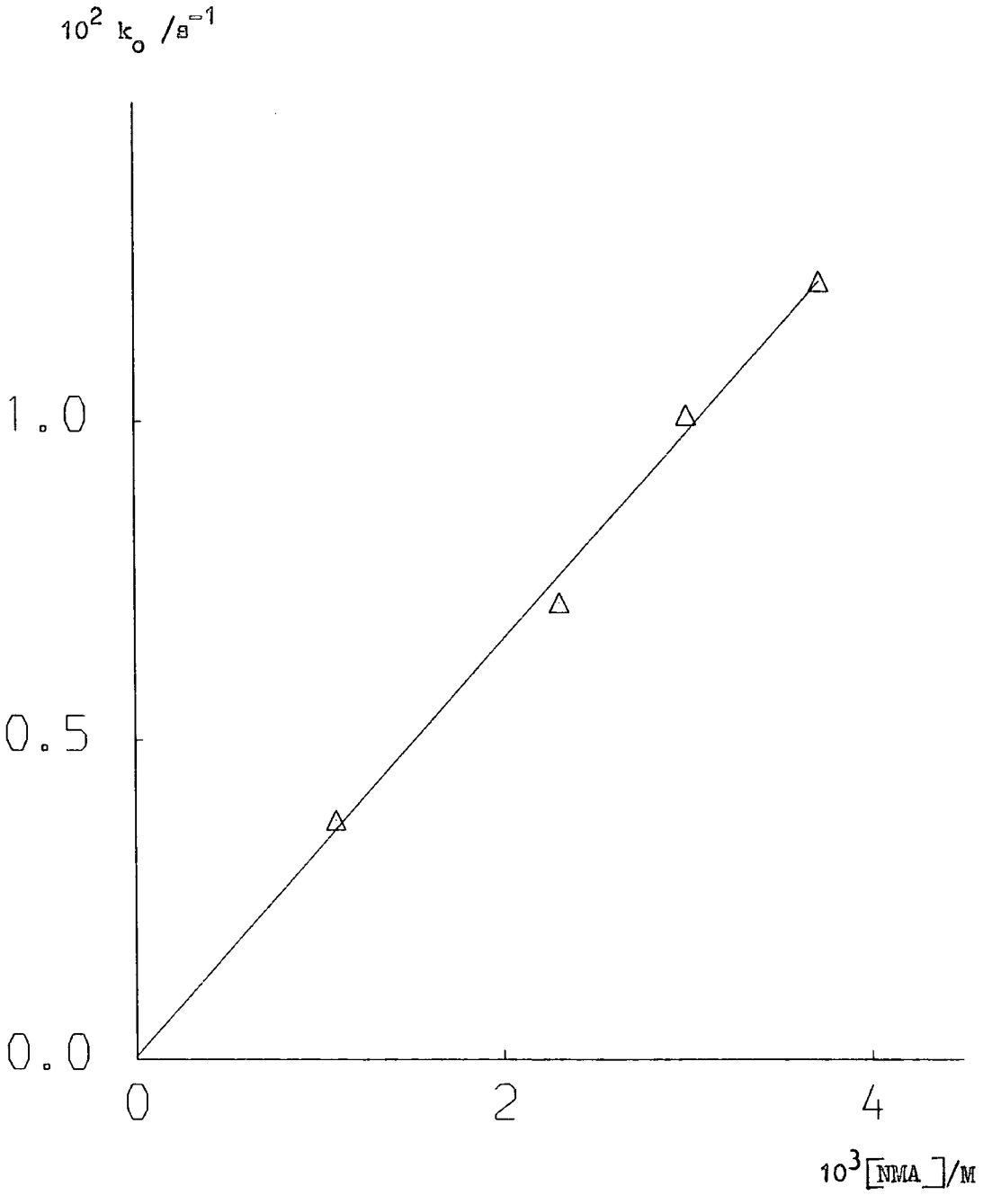
The dependence of k_o on [NMA] was also examined and the results are shown in table 5.21 and figure 7. The plot of k_o versus [NMA] was linear and passed through the origin indicating that the reaction is first order in [NMA] and is irreversible.

Table 5.21 dependence of k_o upon [NMA]

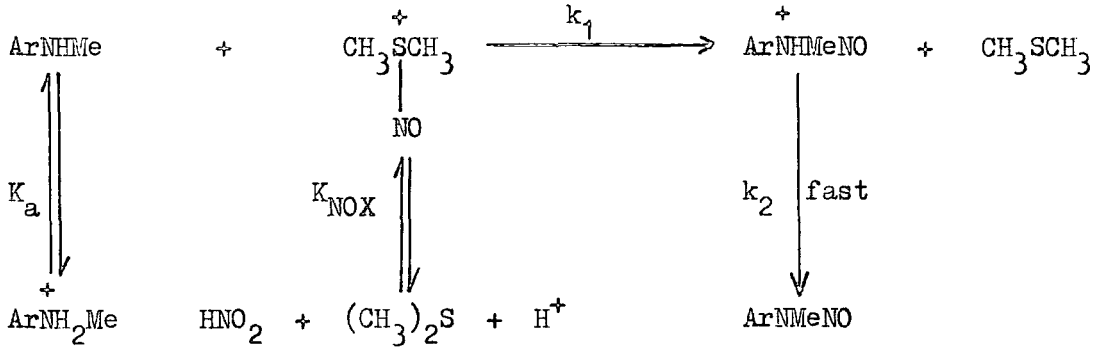
$[(CH_3)_2S] = 1 \times 10^{-3}M$
$[HClO_4] = 0.1M$
$[NaNO_2] = 1 \times 10^{-4}M$

$10^3[NMA]/M$	$10^3 k_o/s^{-1}$
1.09	3.75 ± 0.01
2.31	7.16 ± 0.17
3.00	10.1 ± 0.24
3.73	12.2 ± 0.04

Figure 7 Variation of k_o with [N-methyl-aniline] in the presence of dimethyl sulphide



It seems likely that the mechanism of the reaction involves rate-limiting attack of the S-nitroso species on the free base form of the amine as outlined in scheme 5.4.



Scheme 5.4

The rate of reaction may be expressed as:

$$\text{Rate} = k_1 [\text{ArNHMe}]_F [(CH_3)_2\overset{+}{S}NO] \qquad 5.12$$

where $[\text{ArNHMe}]_F$ represents the concentration of NMA in its free base form.

Using the derivation in Chapter 4 Section 4.2 the expression for k_o is given by equation 5.13

$$k_o = \frac{k_1 K_a K_{NOX} [\text{NMA}]_T [(CH_3)_2S][H^+]}{(1 + K_{NOX}[H^+][(CH_3)_2S])(K_a + [H^+])} \qquad 5.13$$

K_a is the acid dissociation constant of the protonated amine,

K_{NOX} is the equilibrium constant for the formation of $(CH_3)_2\overset{+}{S}NO$,

$[\text{NMA}]_T$ is the total concentration of substrate,

$[H^+]$ is the hydrogen ion concentration

and k_1 is the rate constant as defined in scheme 5.4.

However, since $[H^+]$ = 0.1M and pKa (NMA) = 4.85[18] $[H^+] >> K_a$ and so the expression for k_o reduces to that given by equation 5.14.

$$k_o = \frac{k_1 K_a K_{NOX} [NMA]_T [(CH_3)_2\bar{S}]}{(1 + K_{NOX}[H^+][(CH_3)_2\bar{S}])} \qquad 5.14$$

A value of K_{NOX}, when X = CH_3SCH_3, of 4.5 was obtained in the earlier part of this study. However, assumptions made and results obtained using this value must be regarded with a certain amount of scepticism, since its determination depended on the mechanism of the formation of $CH_3\overset{+}{S}(NO)CH_3$, which has not been established with any certainty. If we assume K_{NOX} = 4.5 then the inequality $1 >> K_{NOX}[H^+][(CH_3)_2S]$ applies and so the expression for k_o can be simplified even further to that given in equation 5.15. This equation predicts the first order

$$k_o = k_1 K_a K_{NOX} [NMA]_T [(CH_3)_2S] \qquad 5.15$$

dependence on $[NMA]_T$ and $[(CH_3)_2S]$ that was observed experimentally.

A plot of k_o versus $[NMA]_T$ was linear with a slope equal to $k_1 K_a K_{NOX} [(CH_3)_2S]$ and so a value of k_1 was easily determined. Similarly a value of k_1 was determined from the plot of k_o versus $[(CH_3)_2S]$, since the slope now represents $k_1 K_a K_{NOX} [NMA]_T$. For comparison purposes the values of k_1, determined as described above, are listed in table 5.22, together with those determined for the nitrosation of N-methylaniline in the presence of bromide, thiocyanate and thiosulphate ion (Chapter 4). As can be seen, the agreement between the values obtained by the two methods is generally acceptable for each nucleophile.

Table 5.22 values of k_1

Nucleophile, (X)	k_1 / l mol^{-1} s^{-1}	
	from [X] dependence	from $[NMA]_T$ dependence
$(CH_3)_2S$	3.9×10^7	5.2×10^7
Br^-	3.1×10^9	5.0×10^9
SCN^-	2.5×10^8	3.1×10^8
$S_2O_3NO^-$	1.2×10^4	1.2×10^4

Clearly the results suggest that $CH_3\overset{+}{S}(NO)CH_3$, assuming that it is formed, can act as a nitrosating agent in its reaction with N-methylaniline, and that it is quite reactive.

5.4.2. Nitrosation of morpholine

The reaction was followed by monitoring the increase in absorbance at 342nm, due to the formation of the product nitrosomorpholine. The change in k_o, the observed first order rate constant, as the concentration of dimethyl sulphide was increased significantly was small. Thus it was concluded that dimethyl sulphide does not catalyse the nitrosation of morpholine

5.4.3. Nitrosation of hydrazine

Possible catalysis of the nitrosation of hydrazine by dimethyl sulphide was investigated by monitoring the decrease in absorbance at 330nm, thought to be due to the S-nitroso species $CH_3\overset{+}{S}(NO)CH_3$. Preliminary results suggested that addition of hydrazine sulphate does not affect the overall rate of decomposition of $CH_3\overset{+}{S}(NO)CH_3$.

Possibly the reason why dimethyl sulphide does not catalyse the nitrosation of either morpholine or hydrazine is that under the experimental conditions used they are not as reactive as N-methyl-aniline, towards nitrosation, and thus further reaction of the S-nitroso adduct of dimethyl sulphide, ultimately to give dimethyl sulphoxide, competes with its nitrosating reactions for less reactive substrates.

In conclusion, the results obtained during this study suggest that nitrosation of dimethyl sulphide does occur, and that an equilibrium (equation 5.15) is established.

$$CH_3SCH_3 + H_2NO_2^+ \underset{}{\overset{K}{\rightleftharpoons}} CH_3\overset{+}{S}(NO)CH_3 + H_2O \qquad 5.15$$

Since the S-nitroso species formed is positively charged and, unlike the thiols there is no good leaving group to enable formation of a more stable neutral analogue, it is expected that the value of K would be smaller than for thionitrite formation. However, it does appear that this S-nitroso species may act as a nitrosating agent for at least relatively reactive substrates.

A similar equilibrium to that given in equation 5.15 has previously been used[14] to explain the supression of the nitrosation of p-nitro N-methylaniline by two sulphides, methionine and S-methycysteine, where the latter are essentially behaving as nitrous acid scavengers.

Since both alcohols and thiols are known[15] to undergo nitrosation fairly easily it is interesting to speculate as to whether the oxygen analogues of sulphides, ethers, undergo nitrosation. Such a study has been performed[14] and no evidence was found for the formation of

O-nitroso cations, $R\overset{+}{R}ONO$, although perhaps this is not too surprising since the oxygen atom in a compound is known to be less nucleophilic[19] than a corresponding sulphur atom.

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CHAPTER SIX

DENITROSATION OF N-ACETYL-S-NITROSO-D, L-PENICILLAMINE

6.1. Introduction

N-Acetyl-S-nitroso-D, L-penicillamine (II), a green crystalline material, with a known crystal structure, is a particularly stable thionitrite. It was first prepared by Field and his co-workers,[1] from the reaction of N-acetyl-D, L-penicillamine (I) with sodium nitrite and methanolic hydrogen chloride and is stable in the solid form and only decomposes slowly in solution.

$$\underset{\text{(I)}}{HSCMe_2CH(NHAc)CO_2H} \xrightarrow{HNO_2} \underset{\text{(II)}}{ONSCMe_2CH(NHAc)CO_2H}$$

Earlier work[2] has studied the denitrosation of this thionitrite (RSNO) with the aim of determining whether it can act as a nitrosating agent. It was found that denitrosation of the thionitrite would occur only in strongly acidic solution (ca. 3M H_2SO_4) in the presence of sufficient excess of a nitrite trap (eg. sodium azide, sulphamic acid).

$$RSNO \xrightarrow[H_2O]{H^+} RSH + HNO_2 \xrightarrow{NaN_3} N_2O + N_2$$

These traps have previously been used in the study of the denitrosation of nitrosamines[3,4] to remove the nitrous acid produced, and thus prevent re-nitrosation. The denitrosation of the thionitrite was found[2] to be catalysed by added nucleophiles, Cl^-, Br^-, SCN^- and $SC(NH_2)_2$, and the reactivity correlated reasonably well with the Pearson nucleophilicity parameter,[5] with the exception of thiourea, as was found for the denitrosation of N-nitrosodiphenylamine.[6] In the

absence of an added nitrite trap N-acetyl-S-nitroso-D, L-penicillamine converted N-methyl-4- nitroaniline to the corresponding nitrosamine quantitatively. However, in the presence of sodium azide no nitrosamine was detected indicating that the thionitrite was not transferring the NO group directly but by means of prior hydrolysis or nitrosyl halide formation.

It has been found[7] that mercuric, silver and cupric salts catalyse the hydrolysis of some thionitrites, e.g. S-nitrosocysteine in the presence of ammonium sulphamate, which is a nitrite trap.

This reaction forms the basis of an analytical method for the determination of thiols. If the thionitrite, formed from reacting

$$RSNO \xrightarrow[H_2O]{Hg^{2+}} HONO + RSH$$

$$HONO \xrightarrow{NH_2SO_3^-NH_4^+} NH_4HSO_4 + N_2 + H_2O$$

the thiol, or any molecules possessing -SH groups with excess nitrous acid, is added to a solution containing the mercuric salt, a nitrite trap and a reactive aromatic amine, e.g. sulphanilamide, the amine competes favourably with the nitrous acid to form a diazonium salt. This salt, which is formed in amounts equivalent to the thiol used, can be coupled with an amine to form an azo dye, whose concentration can easily be determined.

There are also reports in the Russian patent literature[8] where mercury salts are considered to act as catalysts for the nitrosation of amines, and where the selectivity and yield of nitrosylaryl amines has been improved by nitrosating mercurated amines.

The aim of this work was to establish whether metal ions, in particular mercuric ions, would catalyse the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine in acid solution.

6.2. The effect of added mercuric ion on the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine

To ensure complete irreversibility the denitrosation of the thionitrite was carried out in strongly acidic solution (approximately 2M) in the presence of a nitrite trap. When experimental conditions were such that the nitrite trap was present in large excess over the thionitrite the denitrosation, at 25°C, was followed by monitoring the decrease in absorbance at 338nm (the maximum of the broad RSNO peak). Preliminary investigations indicated that sodium azide would be the best trap to use despite the problems associated with nitrogen evolution. The results, shown in table 6.1, indicate that a concentration of sodium azide of 3×10^{-2}M at an acid concentration of 2.05M is sufficient to guarantee irreversibility of the denitrosation reaction.

Table 6.1 dependence of k_o on $[NaN_3]$

$[RSNO] = 2 \times 10^{-4}$M
$[H_2SO_4] = 2.04$M
$[HgCl_2] = 7.4 \times 10^{-7}$M

$10^3 [NaN_3]$/M	$10^4 k_o/s^{-1}$
9.25	3.90
18.5	5.20
37.0	5.45
55.5	5.50

6.2.1. Variation of k_o with the thionitrite concentration.

From the results shown in table 6.2 the value of the observed first order rate constant seems to be independent of the thionitrite concentration. The decrease in the value of k_o at higher concentrations could be due to complexing between RSNO and mercuric ion. Thiols are known[9] to react with mercuric compounds to form insoluble mercaptides.

Table 6.2 dependence of k_o on [RSNO]

$[H_2SO_4] = 2.04M$

$[HgCl_2] = 5.1 \times 10^{-4}M$

$[NaN_3] = 3 \times 10^{-2}M$

$10^4[RSNO]/M$	$10^4\ k_o/s^{-1}$
1.45	9.6
1.92	9.6
2.37	10.1
5.10	7.1
6.00	5.6

6.2.2. Variation of k_o with the mercuric chloride concentration.

Working with a constant ionic strength of $2 \times 10^{-4}M$ (NaCl) the results obtained are shown in table 6.3 and Figure 1. The results clearly indicate that the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine is catalysed by added mercuric ions.

Figure 1 Variation of k_o with $[HgCl_2]$ in the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine

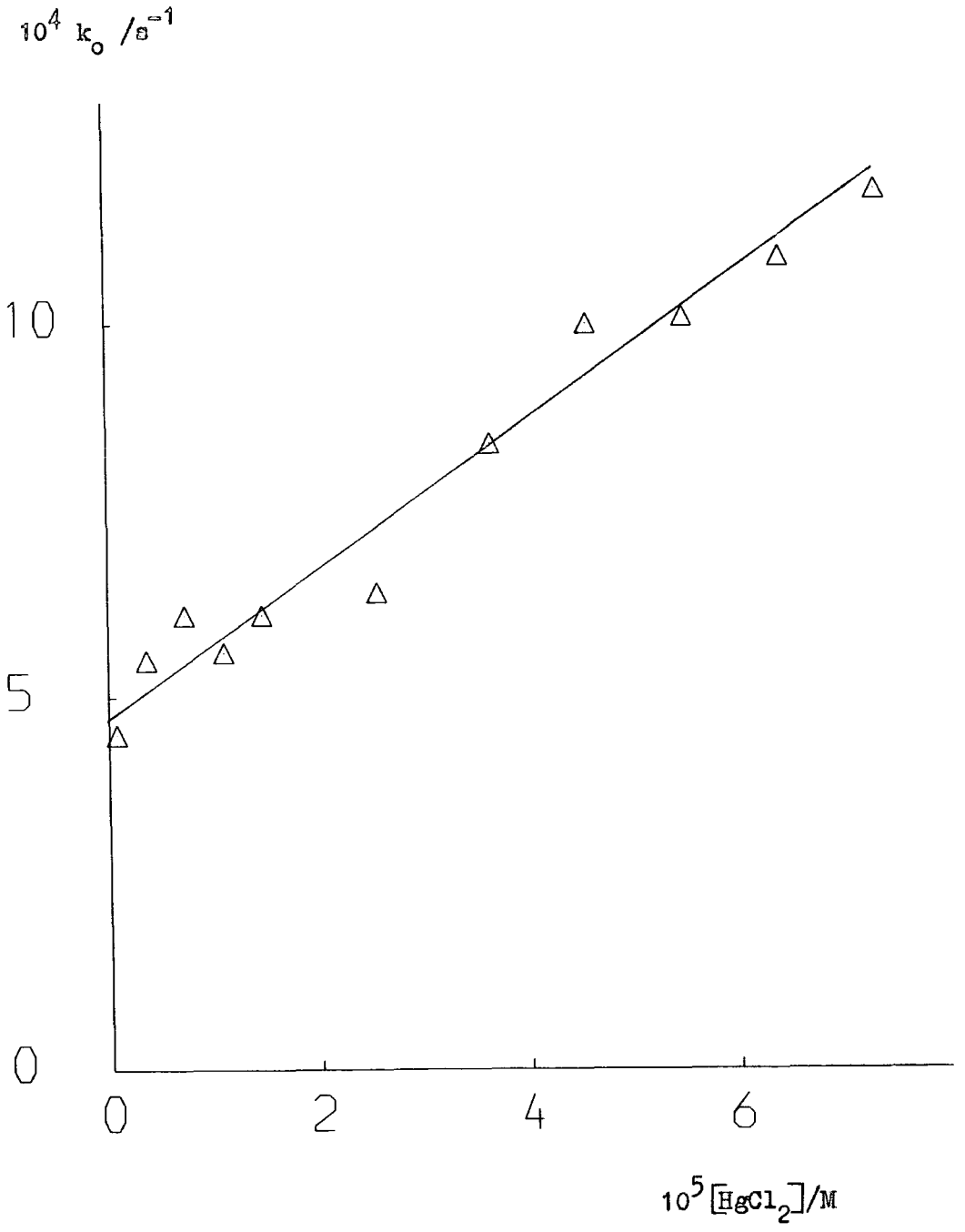


Table 6.3 dependence of k_o on $[HgCl_2]$

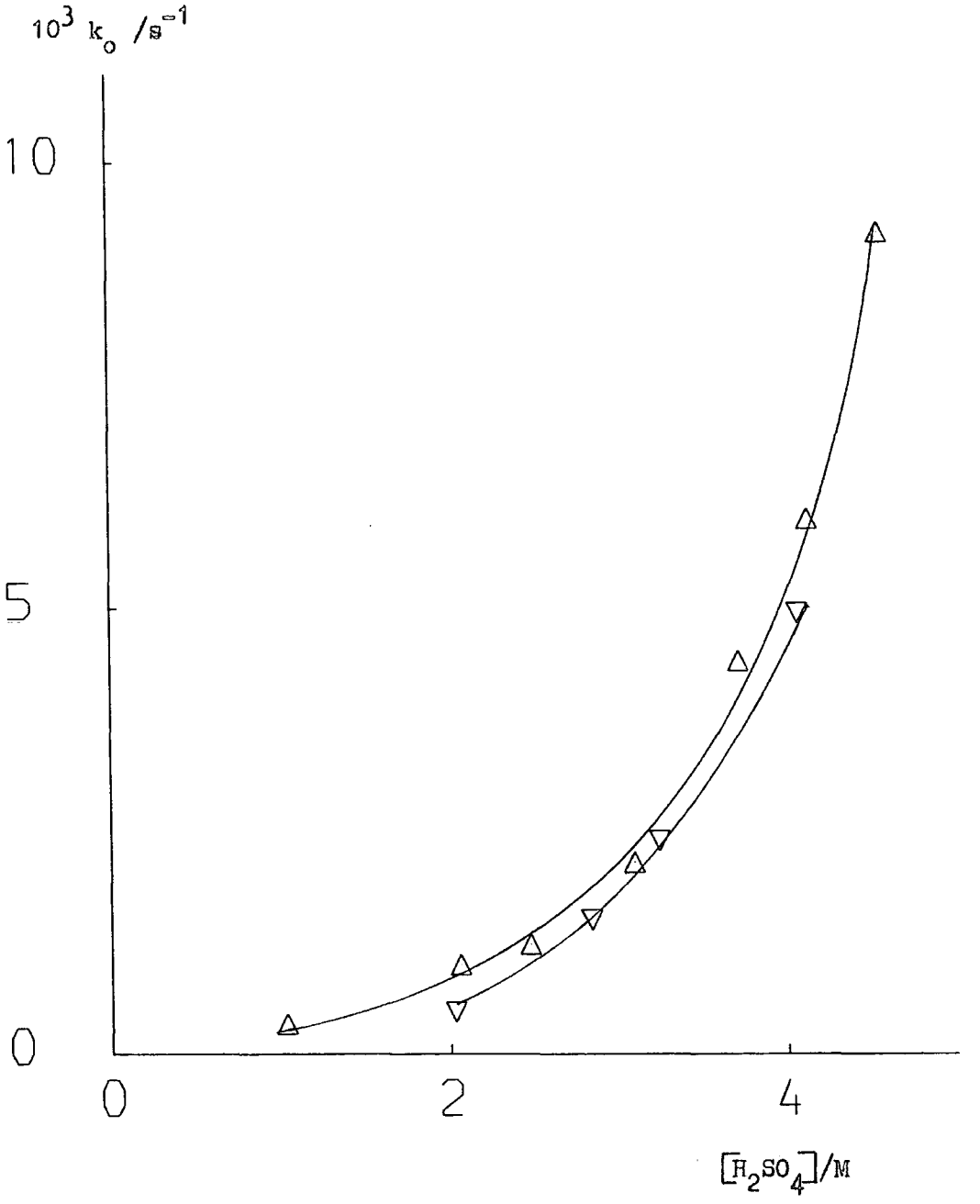
$[RSNO] = 2 \times 10^{-4}M$
$[H_2SO_4] = 2.06M$
$[NaN_3] = 3 \times 10^{-2}M$

$10^7 [HgCl_2]/M$	$10^4 k_o/s^{-1}$
7.35	4.5
36.5	5.5
73.5	6.1
110	5.6
147	6.1
257	6.4
365	8.4
459	10
551	10.1
643	10.9
735	11.8

6.2.3. Variation of k_o with acidity

The dependence of the observed first order rate constant on the acidity, in the presence and absence of mercuric chloride, is shown in tables 6.4 and 6.5 respectively and in figure 2.

Figure 2 Variation of k_o with acidity in the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine



▽ $[HgCl_2] = 0$

△ $[HgCl_2] = 5.5 \times 10^{-4}$M

Table 6.4 dependence of k_o on $[H_2SO_4]$ in the presence of added mercuric chloride

$[RSNO] = 2 \times 10^{-4}M$
$[NaN_3] = 3 \times 10^{-2}M$
$[HgCl_2] = 5.5 \times 10^{-4}M$

$[H_2SO_4]/M$	$10^4\ k_o/s^{-1}$
1.03	3.4
2.06	10.0
2.475	12.3
3.09	21.5
3.71	44.2
4.12	60.1
4.54	92.3

Table 6.5 dependence of k_o on $[H_2SO4]$

$[RSNO] = 2 \times 10^{-4}M$
$[NaN_3] = 3 \times 10^{-2}M$

$[H_2SO_4]/M$	$10^4\ k_o/s^{-1}$
2.03	4.7
2.84	15.0
3.24	23.9
4.06	49.5
5.27	216.2

The parallel nature of the curves in figure 2 suggests that the denitrosation of the thionitrite in the presence of the mercuric acid is not acid catalysed.

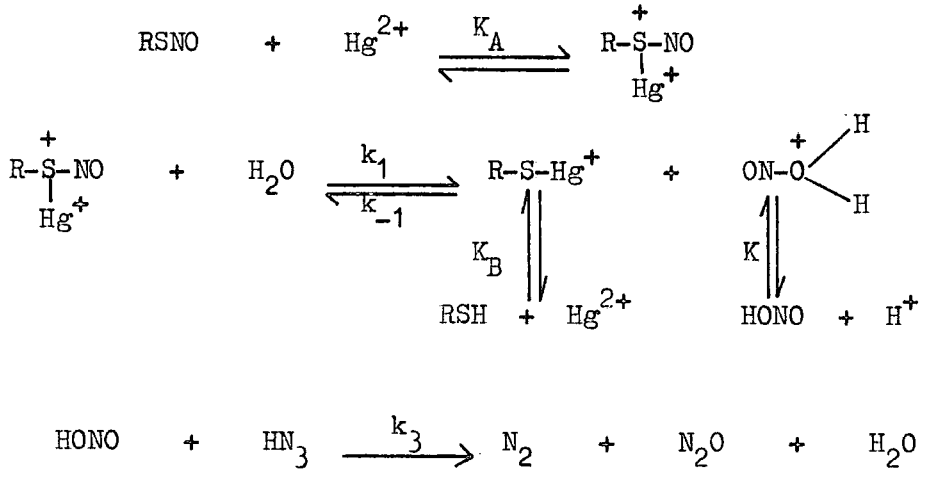
6.2.4 Discussion

The reaction of metal ions, in particular Hg^{2+} and Ag^{+}, with organo-sulphur compounds has been reviewed.[9] Mercury compounds have been used as specific reagents for thiol groups (SH) in biological systems for a long time because of the stable bond formed between mercury and the sulphur of the thiol group.[10]

Mercury mercaptides, $(RS)_2Hg$, were among the first mercaptides to be made.[11] In 1913 Rheinboldt and his co-workers prepared[12] tertiary butyl mercury mercaptide from the reaction of 2-methyl-2-propanethiol with mercuric cyanide in absolute ethanol. Mercaptides are useful in the isolation, identification and quantitative analysis of thiols, have characteristic melting points and can be recrystallised from organic solvents.

The ability of mercury compounds to form organo-mercury derivatives with thiols is the basis of an analytical method for the analysis of organic halomercury compounds.[13]

A possible mechanism for the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine in the presence of mercuric chloride, involving the intermediacy of an organo-sulphur, mercury system, is outlined in scheme 6.1.



Scheme 6.1

Under acidic conditions mercuric chloride is known[14] to react with cysteine and thioglycollic acid to form $Hg(S\text{-}R\text{-}CO_2H)_2$. The formation of a mercury sulphur bond can also be reconciled with the Hard and Soft Acid and Base Theory,[15] which states 'hard acids prefer to bind to hard bases and soft acids prefer to bind to soft bases.' The mercuric ion is a soft acid, characterised by its large size and acceptor properties, whereas sulphur in a thionitrite can be considered as a soft base.

The overall rate of the reaction is given by:

$$\text{Rate} = k_1[RS(NO)Hg]^{2+} - k_{-1}[HNO_2][H^+][RSHg^+]$$

Applying the steady state principle to $[HNO_2]$

$$\frac{d[HNO_2]}{dt} = 0$$

$$[HNO_2] = \frac{k_1[RS(NO)Hg]^{2+}}{(k_{-1}[RSHg^+] + k_3[HN_3])}$$

$$\text{Rate} = k_1[RS(NO)Hg]^{2+} - \frac{k_{-1}k_1[RS(NO)Hg]^{2+}}{(k_{-1}[RSHg^+] + k_3[HN_3])}$$

$$\text{Rate} = \frac{k_1k_3[RS(NO)Hg]^{2+}[HN_3]}{(k_{-1}[RSHg^+] + k_3[HN_3])}$$

If $k_3[HN_3] >> k_{-1}[RSHg^+]$

then $$\text{Rate} = k_1[RS(NO)Hg]^{2+} \qquad 6.1$$

Defining $[RSNO]_T = [RSNO] + [RS(NO)Hg]^{2+}$

and $$K_A = \frac{[RS(NO)Hg]^{2+}}{[RSNO][Hg]^{2+}}$$

$$[RSNO]_T = [RS(NO)Hg]^{2+}\left(1 + \frac{1}{K_A[Hg^{2+}]}\right)$$

substituting into equation 6.1 gives:

$$\text{Rate} = \frac{k_1[RSNO]K_A[Hg^{2+}]}{(K_A[Hg^{2+}] + 1)}$$

The observed first order rate constant, k_o, for Scheme 6.1 is defined:

$$-d\frac{[RSNO]}{dt} = k_o[RSNO]$$

$$k_o = \frac{k_1K_A[Hg^{2+}]}{(K_A[Hg^{2+}] + 1)} \qquad 6.2$$

In all of the experiments carried out the concentration of mercuric ion used was small, less than 6×10^{-4}M. This, combined with the expected small value of K_A, means that the limiting condition $1 >> K_A[Hg^{2+}]$ would apply, and therefore that equation 6.2 would reduce to

$$k_o = K_Ak_1[Hg^{2+}] \qquad 6.3$$

This reduced equation, equation 6.3, predicts a first order dependence of k_o upon $[Hg^{2+}]$ but an independence upon $[H^+]$, as was observed.

The experimental results obtained during the study of the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine in the presence of mercuric chloride, with a sufficient excess of nitrite trap to ensure the limiting condition $k_3[HN_3] >> KK_Bk_{-1}[Hg^{2+}]$ applies, are consistent with the rate expression as defined in equation 6.2. The

observed first order rate constant was independent of acidity and of the thionitrite concentration, but was linearly dependent on the concentration of added mercuric chloride. In addition product formation studies indicated that denitrosation of the thionitrite to give the thiol was quantitative, within experimental error.

6.3 The effect of added cupric ion on the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine

The same experimental conditions as used for the mercuric chloride catalysed denitrosation, including the use of sodium azide as a nitrite trap, were employed to investigate catalysis of the denitrosation of the thionitrite by copper sulphate, $CuSO_4 5H_2O$. Catalysis by added cupric ion was found to be negligible.

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CHAPTER SEVEN

EXPERIMENTAL DETAILS

7.1. Experimental Techniques used

Both conventional uv/visible spectrophotometry and stopped-flow spectrophotometry were used to determine the reaction rate constants quoted in this thesis. An essential requirement of both techniques is that either one of the reactants or one of the product absorbs in the uv/visible region of the electromagnetic spectrum. All the experiments were performed under first order conditions usually with a large excess of the substrate over the sodium nitrite concentration.

7.1.1. Conventional uv/visible spectrophotometry

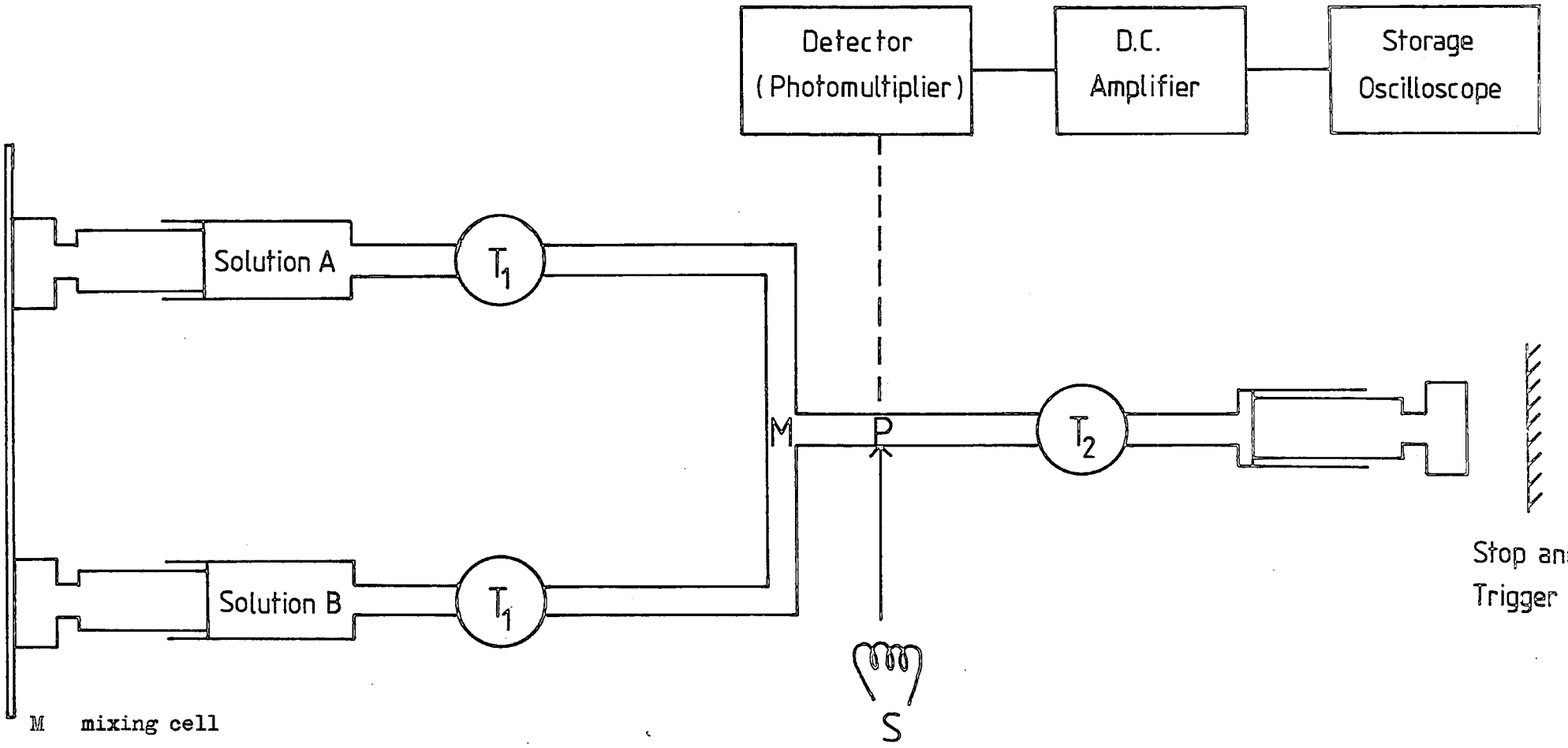
Rate measurements for the nitrosation of ammonia, dimethylamine and N-methylaniline, and for the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine were all carried out using a Beckman model 25 recording spectrophotometer at 25°C. The procedure adopted for all of these measurements, with the exception of the study of the denitrosation of the thionitrite (see 7.4.8.) was as follows: two solutions, one containing stock sodium nitrite and the other containing the substrate, acid and appropriate nucleophile, when necessary, were thermostatted. The reaction was started by adding $1cm^3$ of the nitrite solution to the solution containing all the other reagents (total volume 25mls). After mixing, a portion of this reaction solution was transferred to a 1cm silica cell, which was then placed in the thermostatted cell holder of the spectrophotometer. An identical cell containing the solvent, i.e. water, was used as the reference. The reaction was monitored by following the change in absorbance, at an appropriate wavelength (see later), as a function of time. Using this method the first few seconds of the reaction are missed however, this did not matter since the reactions studied were slow.

7.1.2. Stopped Flow Spectrophotometry

Conventional uv/visible spectrophotometry is not suitable for measuring reaction rates when the half-life of the reaction is less than 5-10 seconds, or when experimental conditions dictate that the concentration of reactant or product, and thus the absorbance change, is very small, e.g. nitrosation of diphenylamine. Instead stopped flow spectrophotometry may be used. The nitrosation of diphenylamine hydrazine, benzenesulphinic acid, dimethyl sulphide, methanol, N-methylaniline, and N-acetyl-penicillamine were all studied by this method.

Stopped-flow spectrophotometry is a technique which permits determination of the kinetics of reaction resulting from the mixing of two solutions. (On mixing the concentration of each reactant present is halved.) Reactions with half-lives between one millisecond and several seconds may be measured.

Initially the two solutions are stored in two identical syringes, i.e. equal volumes, which are filled from two resevoirs to facilitate repeat runs. The syringes are driven by a single piston mechanism thus ensuring that the solutions leave the syringes with equal velocity. The solutions pass through thermostatting coils into the mixing cell where the reaction A + B $\longrightarrow$ C occurs. The reaction solution then flows into a third syringe. On filling, the plunger of this syringe is forced against a stop, which triggers the recording device at the observation point, P, and halts the flow. A beam of monochromatic light passes through the solution at point P and its intensity is converted into an electrical signal, which is proportional to the light intensity under certain conditions. The change in signal voltage as a function of time is displayed on the storage oscilloscope.



M mixing cell

P observation point

S monochromated light source

T_1 3 way tap connects syringe to resevoir or mixing cell

T_2 3 way tap connects mixing cell to stopping syringe or waste

Figure 1 Stopped-Flow Spectrophotometry

If a non-absorbing solution is present in the stopped flow spectrophotometer the signal voltage from the photomultiplier is at its maximum value, e.g. minus six volts. If this solution is replaced by an absorbing solution the light reaching the photomultiplier decreases, and therefore the signal voltage decreases. However, since the signal voltage is negative this decrease appears as a positive change, therefore if a reaction is followed at a wavelength where the products absorbs, this will be seen on the oscilloscope as an increase in voltage as a function of time (figure 2). In practice such a change is small and in order to amplify it on the oscilloscope screen the signal voltage of -6 volts must be effectively cancelled by an opposite voltage of equal magnitude i.e. $^{+}6$ volts. This is referred to as a "biasing voltage" and since it is fixed, and initially equal, though opposite, to the signal voltage any increase in absorbtion is seen as a small positive change from zero volts, rather than from minus 6 volts.

If the two reactant solutions, A and B, are flushed through the system several times prior to any measurements being made, the apparatus will be filled with A and B as far as the mixing point, M, and the maximum concentration of product possible, $[C]_{max}$, after the mixing point. During a run A and B mix and a small amount of product $[C]_{min}$, is formed. A steady state is reached at each point after the mixing point, M, and is maintained until the flow is suddenly stopped. Assuming that the species C absorbs at the wavelength chosen for the study, the reaction $[C]_{min}$ to $[C]_{max}$ may then be monitored at point P. Figure 2 illustrates diagrammatically the variation of voltage with time that would be observed for this process.

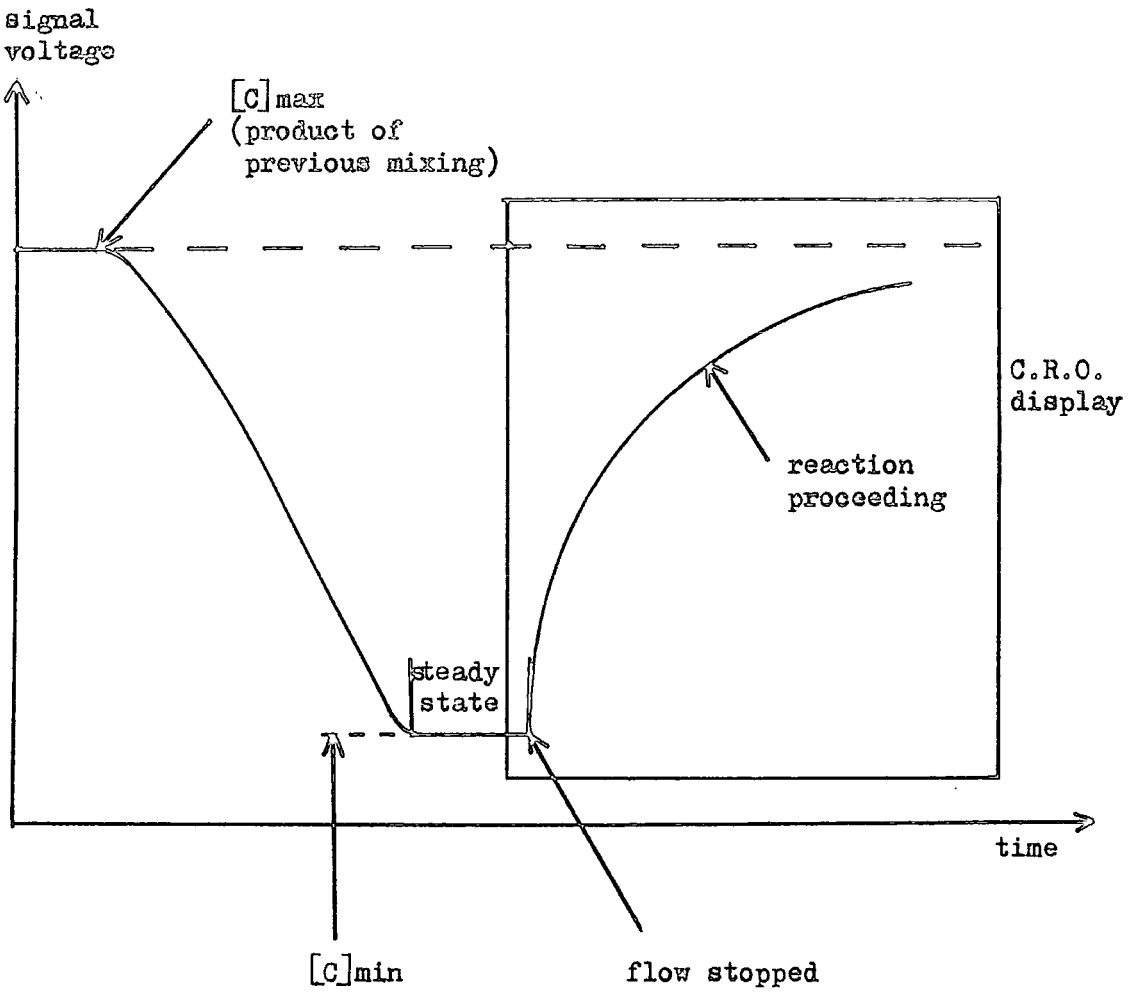


Figure 2.

The cell of the stopped-flow spectrophotometer is immersed in a thermostat bath and all experiments were carried out at 25°C.

7.2. Determination of the observed rate constants

As stated previously, all the experiments were performed under first order conditions, and the reaction was followed by monitoring the rate of disappearance of the reactant, present in the lowest concentration, or appearance of the product, with time. The relationship between concentration and absorbance is given by the Beer-Lambert law[1] and is simply: $A = \epsilon Cl$, where A is the absorbance, ϵ the extinction coefficient, C the concentration and l the path length. For a first order reaction R $\longrightarrow$ P, where R = reactant and P = product, $[P]_t = [R]_o - [R]_t$, where $[P]_t$ is the concentration of P at time t = t and $[R]_o$ is the concentration of R at time t = 0 etc., and the expression for the observed first order rate constant k_o is given by equation 7.1.

$$k_o = \frac{1}{t} \ln \frac{[R]_o}{[R]_t} \qquad 7.1$$

Using the Beer Lambert law the absorbance at time t = 0 may be defined as $A_o = \epsilon_R[R]_o$, if the pathlength of the cell is assumed to be 1 cm.

Similarly $$A_t = \epsilon_R[R]_t + \epsilon_p[P]_t$$

substituting for $[P]_t$

$$A_t = \epsilon_R[R]_t + \epsilon_p([R]_o - [R]_t)$$

$$A_\infty = \epsilon_p[P]_\infty = \epsilon_p[R]_o \qquad \text{since } [P]_\infty = [R]_o$$

subtracting

$$(A_t - A_\infty) = \epsilon_R[R]_t - \epsilon_p[R]_t$$

$$[R]_t = \frac{(A_t - A_\infty)}{(\epsilon_R - \epsilon_p)}$$

Similarly $$(A_o - A_\infty) = \varepsilon_R[R]_o - \varepsilon_p[R]_o$$

$$[R]_o = \frac{(A_o - A_\infty)}{(\varepsilon_R - \varepsilon_p)}$$

substituting into equation 7.1

$$k_o = \frac{1}{t} \ln \frac{(A_o - A_\infty)}{(A_t - A_\infty)} \qquad 7.2$$

Thus an instantaneous value of k_o at time $t = t$ may be obtained from this expression.

Since $\ln (A_t - A_\infty) = -k_o t + \ln(A_o - A_\infty)$, from equation 7.2, a plot of $\ln(A_t - A_\infty)$ should be linear with a slope of $-k_o$.

The infinity value, A_∞, was determined after a period of ten half-lives, and the disappearance or appearance of absorbance, depending on the reaction, was generally followed for at least two half-lives.

For experiments carried out using the stopped-flow technique the value of k_o was determined from the slope of a plot of $\ln(V_t - V_\infty)$, or $\ln(V_\infty - V_t)$ versus time, where V is the output signal voltage, and under the experimental condition used was proportional to the absorbance. Owing to the errors in measuring fast reactions the value of k_o quoted for these runs is the mean of at least five separate determinations and the error is the standard deviation.

In order to determine individual values of the observed rate constant for the nitrosation of ammonia and dimethylamine the method of initial rates was used. For the former the reaction was followed by monitoring the decrease in absorbance at 384nm, due to nitrous acid, and for the latter the increase in absorbance at 332nm, due to N-nitroso dimethylamine formation was followed. A tangent was drawn to the curve obtained for the change in the absorbance with time at the

point where time t = 0. The slope of this tangent gave the initial rate in units of absorbance, and this was converted into the appropriate units of reciprocal seconds using the experimentally determined extinction coefficients for nitrous acid (27), for the ammonia reaction, and for nitroso dimethylamine (84), for the dimethylamine reaction.

7.3 Chemical Reagents

N-Acetyl-S-nitroso-D, L-penicillamine was prepared from the reaction of N-acetyl-D, L-penicillamine with sodium nitrite and methanolic hydrogen chloride as described by Field et al[2]. It was stored in a refrigerator.

All amines used in this study were obtained commercially. Both N-methylaniline and morpholine were redistilled under reduced pressure and stored under nitrogen. Diphenylamine and dimethylammonium chloride were purified by recrystallisation from aqueous ethanol.

Dimethyl sulphide was obtained commercially and was redistilled before use. Benzenesulphinic acid was used as supplied and was stored at $0^{\circ}C$. Both methanol and N-acety-D, L-penicillamine were obtained commercially and were used as supplied.

The inorganic reagents used ($N_2H_5HSO_4$, $Na_2S_2O_3$, $(NH_4)_2SO_4$, $CuSO_4.5H_2O$, $HgCl_2$, NaN_3, NaCl, KCl, NaBr, KBr, NaSCN, KSCN, NaClO4, $SC(NH_2)_2$ and NaOH) were all available commercially and were used as supplied.

Sulphuric acid solutions were prepared by dilution of 96-98% sulphuric acid and standardised against sodium hydroxide using phenolphthalein as an endpoint indicator. Perchloric acid solutions were prepared by dilution of 60-62% perchloric acid and standardised as described above.

Solutions of sodium nitrite were prepared daily. Stock solutions of all the reagents were made up in distilled water with the exception of solutions used for the study of the nitrosation of diphenylamine, where all reagents were made up in 50% methanol, water because of the low solubility of diphenylamine in water.

7.4. Kinetic Measurements

7.4.1. Nitrosation of diphenylamine

The rate measurements were all made on a stopped-flow spectrophotometer. The reaction was started by mixing equal volumes of two solutions, one containing sodium nitrite and the other containing diphenylamine, acid and the appropriate nucleophile, when necessary. It was monitored by following the increase in absorbance at 320nm, due to the formation of N-nitroso diphenylamine. All the kinetic measurements were made in the presence of a large excess of sodium nitrite over the concentration of diphenylamine, and good first order plots of $\ln(V_\infty - V_t)$ versus time, where V = voltage (and is proportional to the absorbance providing that the voltage change during the reaction is less than 10% of background signal voltage (-6v)), were obtained over at least two half-lives.

A typical kinetic run is shown in table 7.1. The 'instantaneous' values of k_o were calculated from equation 7.2. ('Instantaneous' values of k_o are not normally calculated and are only given here to give an impression of the error involved in a run).

Table 7.1 a typical kinetic run for the chloride ion catalysed nitrosation of diphenylamine.

$[Ph_2NH] = 4.1 \times 10^{-5}M$
$[HClO_4] = 9.38 \times 10^{-2}M$
$[NaNO_2] = 8.15 \times 10^{-4}M$
$[NaCl] = 9.39 \times 10^{-2}M$

V_t/mV	t/s	k_o/s^{-1}
171	0	-
205	1	0.201
235	2	0.209
260	3	0.215
280	4	0.219
295	5	0.218
309	6	0.223
319	7	0.224
325	8	0.217
358	∞	-

$k_o = 0.216 \pm 0.008\ s^{-1}$

Table 7.2 shows a typical set of values of the observed first order rate constant, k_o, obtained for a series of duplicate runs.

Table 7.2 a typical set of duplicate runs (concentrations of the reagents are the same as in table 7.1)

run	k_o/s^{-1}
1	0.223
2	0.226
3	0.228
4	0.231
5	0.226

$k_o = 0.226 \pm 0.008\ s^{-1}$

7.4.2. Nitrosation of ammonia

The rate measurements for this study were all made using a conventional uv/visible spectrophotometer by following the disappearance of absorbance at 384nm, due to nitrous acid. The procedure adopted for staring the reaction has previously been described (Section 7.1.1). To overcome the problem of rapid evolution of nitrogen the method of initial rates (Section 7.2) was employed to determine individual values of the observed first order rate constant. The rate of decomposition of nitrous acid, also determined by initial rate method, was found to make a significant contribution to the overall observed rate of disappearance of nitrous acid so k_o is defined by equation 7.3.

$$k_o = k_{o1} - k_{o2} \qquad 7.3$$

k_o is the observed first order rate constant for the nitrosation of ammonia, k_{o1} is the observed first order rate constant for the overall reaction, and k_{o2} is the observed first order rate constant for the decomposition of nitrous acid, measured under identical conditions to those used for measuring the corresponding k_{o1} value.

Due to the inherent error involved in the use of initial rates three values of k_{o1} and k_{o2} were used to obtain a mean value of k_o. The reproducibility of individual values of the rate constants were not as good as previous kinetic values, but are judged to be accepted given the experimental details. Table 7.3 shows a typical set of observed first rate constants for a series of duplicate runs.

Table 7.3 a typical set of duplicate runs

$[(NH_4)_2SO_4]$ = 0.75M
$[HClO_4]$ = 0.1M
$[NaNO_2]$ = 3.76×10^{-3}M
[NaSCN] = 4×10^{-2}M

Run	$10^4 k_{o1}$ /s^{-1}	$10^4 k_{o2}$ /s^{-1}	k_o (= $k_{o1} - k_{o2}$) /s^{-1}
1	7.52	1.07	6.45
2	7.47	1.15	6.32
3	7.32	1.04	6.28

$$k_o = (6.4 \pm 0.1) \times 10^{-4}\ s^{-1}$$

7.4.3. Nitrosation of dimethylammonium chloride

All kinetic measurements for this study were carried out using a Beckman conventional spectrophotometer. In all of the experimental runs there was a large excess of the amine over the nitrous acid. Prior to starting the reaction, according to the method described in Section 7.1.1, the pH of both solutions, i.e. the sodium nitrite solution and the solution containing the amine, acid and appropriate nucleophile, were measured using a PTI-6 Universal Digital pH meter, which had been previously calibrated with buffers of pH 4 and pH 7. The pH of the solutions was adjusted to the required value using perchloric acid and sodium hydroxide. The reaction was followed by monitoring the increase in absorbance at 332nm, due to the product N-nitroso dimethylamine. The method of initial rates (Section 7.2) was again employed to deduce individual values of k_o. Thus the results obtained in this study could be compared directly with

those obtained for the nitrosation of ammonia. A spectrum of each reaction solution was measured after at least ten half-lives had passed, and from this the percentage product formation was calculated. Within experimental error, there was quantitative conversion of the amine to the nitrosamine. Values of k_o quoted in Section 2.4 are the mean of at least three separate determinations.

The pH dependence for the nitrosation of dimethylammonium chloride by nitrosyl thiocyanate was studied under identical conditions to those described above, except that the individual values of the observed first order rate constant, k_o, were determined from the slope of a plot of ln $(A_\infty - A_t)$ versus time, and not by the initial rate method. In all cases good linear correlations for the individual plots were obtained confirming that the reaction is first order in nitrous acid.

A typical kinetic run is given in table 7.4. 'Instantaneous' values of k_o were calculated using equation 7.2.

Table 7.4 a typical kinetic run for the thiocyanate ion catalysed nitrosation of dimethylammonium chloride.

$[(CH_3)_2NHHCl] = 0.508M$
$[NaSCN] = 5 \times 10^{-2}M$
$[NaNO_2] = 8 \times 10^{-3}M$
pH = 1.59

A_t	t/s	$10^4 k_o$ /s^{-1}
.125	0	-
.180	600	2.50
.225	1200	2.43
.265	1800	2.43
.300	2400	2.44
.332	3000	2.47
.360	3600	2.51
.382	4200	2.50
.402	4800	2.52
.417	5400	2.49
.520	∞	-

$$k_o = (2.48 \pm 0.04) \times 10^{-4}\ s^{-1}$$

7.4.4. Nitrosation of hydrazine

All the measurements for this study were made using the stopped-flow technique. Each run was carried out under first order conditions with a large excess of hydrazine sulphate over the concentration of sodium nitrite. The reaction was started by mixing equal volumes of a solution of sodium nitrite with a solution containing hydrazine sulphate, perchloric acid and sodium

thiocyanate. It was monitored by recording the decrease in absorbance at 360nm, due to nitrous acid, as a function of time. Plots of $\ln(V_t - V_\infty)$ versus time were good straight lines, the slope of which was equal to $-k_o$. A mean value of k_o was determined from at least five separate runs.

A typical kinetic run is shown in table 7.5 and the values of k_o were calculated using equation 7.2.

Table 7.5 a typical kinetic run for the thiocyanate ion catalysed nitrosation of hydrazine sulphate.

$[N_2H_5HSO_4] = 1 \times 10^{-2}M$
$[HClO_4] = 0.203M$
$[NaSCN] = 1 \times 10^{-2}M$
$[NaNO_2] = 5 \times 10^{-4}M$

V_t/mV	t/s	k_o /s^{-1}
254	0	-
228	.1	1.90
202	.2	2.13
182	.3	2.18
169	.4	2.09
156	.5	2.12
104	∞	-

$k_o = 2.08 \pm 0.1\ s^{-1}$

7.4.5. Nitrosation of Benzenesulphinic acid

A stopped-flow spectrophotometer was used for the rate measurements in this study. All the reactions were carried out under first order conditions with a large excess of benzenesulphinic acid over the sodium nitrite concentration. Most of the reactions were followed by monitoring the decrease in absorbance at 360nm, due to nitrous acid, although for comparison purposes some measurements were also made at 260nm, following the increase in absorbance due to product formation. The reactions were started by mixing equal volumes of two solutions, one containing sodium nitrite and the other containing the substrate, perchloric acid and the appropriate nucleophile, when necessary (Section 7.1.2). Good first order plots of $\ln(V_t - V_\infty)$ or $\ln(V_\infty - V_t)$ versus time were obtained for all the runs. The quoted rate constants represent the mean of at least five separate determinations and the error the standard deviation.

A typical kinetic run is given in table 7.6 together with 'instantaneous' values of k_o (equation 7.2). Table 7.7 shows a typical set of values of k_o obtained for a series of duplicate runs.

Table 7.6 a typical kinetic run for the bromide ion catalysed nitrosation of benzenesulphinic acid.

$[BSA]_T = 2.5 \times 10^{-2}M$
$[H^+] = 2.9 \times 10^{-2}M$
$[NaNO_2] = 1 \times 10^{-3}M$
$[KBr] = 2 \times 10^{-2}M$

V_t/mv	t/ms	k_o/s^{-1}
216	0	-
189	20	10.1
164	40	10.9
144	60	11.2
129	80	11.2
117	100	11.2
108	120	11.1
69	∞	-

$k_o = 11.0 \pm 0.43\ s^{-1}$

Table 7.7 a typical set of duplicate runs. (concentrations of reagents are the same as in table 7.6)

run	k_o/s^{-1}
1	11.2
2	11.3
3	11.1
4	11.0
5	11.1

$k_o = 11.1 \pm 0.1\ s^{-1}$

The product from the reaction of benzenesulphinic acid with nitrous acid is considered to be N, N-bis(phenylsulphonyl) hydroxylamine. This was prepared and isolated as described by Birchall and Glidewell.[2] It was also prepared in the presence of 0.1M KCl, and 0.1M KBr. (It must be noted that the concentrations of reagents used in these preparations were somewhat higher than those used in the kinetic experiments). The uv and ir spectra of the three samples were measured and found to be identical. The ir spectra were all characterised by strong absorptions at 3300 cm^{-1} (O-H stretch), and at ca. 1080 cm^{-1} (N-OH stretch), as had been previously found.[2] (Elemental analysis found: C, 47.1; H, 3.6; N, 4.6% Cal. for $C_{12}H_{11}NO_5S$: C, 46.0; H, 3.5; N, 4.5%

7.4.6. Nitrosothiosulphate ion as a Nitrosating Agent

The kinetic measurements for the nitrosation of N-methylaniline were all made at 275nm noting the appearance of absorbance due to the product N-nitroso-N-methylaniline. Some of the experiments were carried out in a conventional spectrophotometer, and then the reactions were started according to the procedure outlined in Section 7.1.1, whereas the more rapid reactions were studied using the stopped-flow technique. For the stopped-flow experiments reactions were started by mixing equal volumes of two solutions, one containing sodium nitrite and the other containing N-methylaniline, perchloric acid and the appropriate nucleophile. All experiments were carried out under first order conditions with a large excess of the amine over the sodium nitrite concentration, and plots of ln $(A_\infty - A_t)$ or ln $(V_\infty - V_t)$ versus time were all good straight lines.

A typical kinetic run is shown in table 7.8. 'Instantaneous' values of k_o were determined using equation 7.2.

Table 7.8. a typical kinetic run for the thiosulphate ion catalysed nitrosation of N-methylaniline.

$[NMA] = 3.63 \times 10^{-3}M$
$[HClO_4] = 0.1M$
$[NaNO_2] = 1 \times 10^{-4}M$
$[Na_2S_2O_3] = 2.35 \times 10^{-3}M$

A_t	t/s	$10^3 k_o$ /s^{-1}
0.243	0	-
0.285	15	5.89
0.323	30	5.85
0.360	45	5.96
0.395	60	6.08
0.427	75	6.17
0.457	90	6.26
0.480	105	6.17
0.503	120	6.17
0.740	∞	-

$$k_o = (6.07 \pm 0.15) \times 10^{-3}\ s^{-1}$$

The nitrosation of N-acetyl-D, L-penicillamine and methanol in the presence of thiosulphate ion was also examined. For the nitrosation of the thiol equal volumes of two solutions, one containing sodium nitrite, the other containing the thiol, acid, and thiosulphate ion were mixed. The reaction was followed by noting the increase in absorbance at 338nm, due to the product thionitrite. For the nitrosation of methanol the nitrosothiosulphate ion was first generated and then equal volumes of the nitrosothiosulphate ion and a solution of methanol were mixed. The reaction was followed by monitor-

ing the disappearance of absorbance at 386nm. The reactions were all carried out under first order conditions and all kinetic runs showed good first order behaviour.

7.4.7. Nitrosation of dimethylsulphide

All rate measurements were made at 330nm, by monitoring the increase in absorbance due to product formation, using the stopped-flow technique. In each run there was a large excess of dimethylsulphide present over the concentration of sodium nitrite. The reaction was started by mixing equal volumes of two solutions; one containing stock sodium nitrite and the other containing dimethylsulphide, perchloric acid, the appropriate nucleophile, when necessary, and sodium perchlorate, if required. Good linear correlations were obtained for the graphs of ln $(V_\infty - V_t)$ versus time indicating that the reaction is first order in nitrous acid.

A typical kinetic run is given in table 7.9. 'Instantaneous' values of k_o quoted in this table were determined using equation 7.2.

Table 7.9 a typical kinetic run for the chloride ion catalysed nitrosation of dimethylsulphide, DMS

$[DMS] = 2.65 \times 10^{-2}M$
$[H^+] = 6.0 \times 10^{-2}M$
$[NaCl] = 8.0 \times 10^{-2}M$
$[NaClO_4] = 0.12M$
$[NaNO_2] = 1 \times 10^{-3}M$

V_t, mV	t/ms	k_o /s^{-1}
215	0	-
230	5	2.14
247	10	2.43
258	15	2.29
270	20	2.32
280	25	2.31
290	30	2.36
298	35	2.35
305	40	2.34
363	∞	-

$k_o = 2.32 \pm 0.08\ s^{-1}$

The rates of nitrosation of N-methylaniline (NMA), morpholine and hydrazine, in the presence of dimethylsulphide, were all examined using a conventional spectrophotometer, at 280nm, 342nm and 330nm respectively. All the reactions were carried out in the presence of a large excess of the substrate over the concentration of sodium nitrite and they were started according to the procedure outlined in Section 7.1.1. Good first order plots were obtained for all the experimental runs.

A typical kinetic run is shown in table 7.10 together with the 'instantaneous' values of k_o (equation 7.2).

Table 7.10 a typical kinetic run for the nitrosation of N-methylaniline in the presence of dimethylsulphide.

$[NMA] = 3.50 \times 10^{-3}M$
$[DMS] = 9.17 \times 10^{-4}M$
$[NaNO_2] = 1 \times 10^{-4}M$
$[H^+] = 0.1M$

A_t	t/s	$10^2 k_o$ /s^{-1}
0.082	0	-
0.120	6	1.01
0.157	12	1.03
0.190	18	1.01
0.222	24	1.01
0.252	30	1.01
0.282	36	1.03
0.310	42	1.03
0.337	48	1.04
0.362	54	1.05
0.730	∞	-

$k_o = (1.02 \pm 0.015) \times 10^{-2}\ s^{-1}$

7.4.8. Denitrosation of N-acetyl-S-nitroso-D, L-penicillamine

This reaction was studied at 338nm, by monitoring the disappearance of absorbance due to the thionitrite, using a conventional spectrophotometer. Due to the instability of N-acetyl-S-nitroso-D, L-penicillamine in solution stock solutions of it were not prepared.

Instead, each kinetic run was started by adding dioxan (2mls), used for rapid dissolution, to a weighed sample of the thionitrite. To this a previously thermostatted solution containing acid, sodium azide, and mercuric chloride or copper sulphate, when necessary, was added. The solution was mixed and then a portion transferred to a 1 cm silica cell, which was placed in the sample compartment of the spectrophotometer. A cell containing the solvent was used as the reference.

For each reaction linear plots of $\ln(A_t - A_\infty)$ versus time were obtained over several half-lives. A typical kinetic run is shown in table 7.11.

Table 7.11 a typical kinetic run for the denitrosation of N-acetyl-S-nitroso-D, L-penicillamine (RSNO)

$[RSNO] = 2 \times 10^{-4}M$
$[H_2SO_4] = 2.06M$
$[NaN_3] = 3 \times 10^{-2}M$
$[HgCl_2] = 1.47 \times 10^{-5}M$

A_t	t/s	$10^4 k_o$ /s^{-1}
0.175	0	-
0.152	300	5.87
0.131	600	6.15
0.114	900	6.21
0.100	1200	6.23
0.089	1500	6.17
0.080	1800	6.10
0.072	2100	6.11
0.065	2400	6.16
0.060	2700	6.09
0.0325	∞	-

$k_o = (6.12 \pm 0.1) \times 10^{-4}\ s^{-1}$

References

1 P.W. Atkins, 'Physical Chemistry', Oxford University Press, Oxford, 1978, p.585.

2 J.D. Birchall and C. Glidewell, J. Chem. Soc., Dalton Trans., 1977, 10.

3 L. Field, R.V. Dilts, R. Ravichandran, P.G. Lenhert and G.E. Carnahan, J. Chem. Soc., Chem. Commun., 1978, 249.

APPENDIX

Lectures and Seminars Organised by the Department of Chemistry during the period 1982-1985

(* denotes lectures attended)

13.10.82* Dr. W.J. Feast (Durham)
"Approaches to the Synthesis of Conjugated Polymers"

14.10.82 Prof. H. Suhr (Tübingen, FRG)
"Preparative Chemistry in Nonequilibrium Plasmas"

27.10.82* Dr. C.E. Housecroft (Oxford High School/Notre Dame)
"Bonding capabilities of butterfly-shaped Fe_4 units. Implications for C-H bond activation in hydrocarbon complexes"

28.10.82 Prof. M.F. Lappert, FRS (Sussex)
"Approaches to Asymmetric Synthesis and Catalysis using electron-rich olefins and some of their metal complexes"

15.11.82* Dr. G. Bertrand (Toulouse, France)
"Curtius Rearrangement in Organometallic Series: A route for new hybridised species"

24.11.82 Prof. F.R. Hartley (R.M.C.S., Shrivenham)
"Supported Metal-Complex Hydroformylation Catalysts"

24.11.82 Prof. G.G. Roberts (Applied Physics, Durham)
"Langmuir-Blodgett films: Solid state polymerisation of diacetylenes"

8.12.82 Dr. G. Wooley (Trent)
"Bonds in transition metal-cluster compounds"

12.1. 83* Dr. D.C. Sherrington (Strathclyde)
"Polymer-supported phase transfer catalysts"

9. 2.83* Dr. P. Moore (Warwick)
"Mechanistic studies in solution by stopped flow F.T.-NMR and high pressure NMR line broadening"

21. 2.83 Dr. R. Lynden-Bell (Cambridge)
"Molecular motion in the cubic phase of NaCN"

2. 3.83* Dr. D. Bloor (Queen Mary College, London)
"The solid-state chemistry of diacetylene monomers and polymers"

8. 3.83* Prof. D.C. Bradley, FRS (Queen Mary College, London)
"Recent Developments in Organo-Imido-Transition Metal Chemistry"

9. 3.83* Dr. D.M.J. Lilley (Dundee)
"DNA, Sequence, Symmetry, Structure and Supercoiling"

11. 3.83* Prof. H.G. Viehe (Louvain, Belgium)
"Oxidations on Sulphur" and
"Fluorine substitutions in radicals"
(The W.K.R. Musgrave Lecture)

16. 3.83* Dr. I. Gosney (Edinburgh)
"New extrusion reactions: Organic synthesis in a hot-tube"

25. 3.83 Prof. F.G. Baglin (Nevada, USA)
"Interaction induced Raman Spectroscopy in supracritical ethane"

21. 4.83 Prof. J. Passmore (New Brunswick, Canada)
"Novel selenium-iodine cations"

4. 5.83* Prof. P.H. Plesch (Keele)
"Binary ionisation equilibria between two ions and two molecules. What Ostwald never thought of"

10. 5.83 Prof. K. Burger (Munich, FRG)
"New reaction pathways from trifluoromethyl-substituted heterodienes to partially fluorinated heterocyclic compounds"

11. 5.83* Dr. N. Isaacs (Reading)
"The application of high pressures to the theory and practice of organic chemistry"

13. 5.83* Dr. R. de Koch (Michigan/Amsterdam)
"Electronic structural calculations in organometallic cobalt cluster molecules. Implications for metal surfaces"

13. 5.83 Dr. T.B. Marder (UCLA/Bristol)
"The Chemistry of Metal-carbon and metal-metal multiple bonds"

16. 5.83 Prof. R.J. Lagow (Texas, USA)
"The chemistry of polylithium organic compounds. An unusual class of matter"

18. 5.83* Dr. D.M. Adams (Leicester)
"Spectroscopy at very high pressures"

25. 5.83 Dr. J.M. Vernon (York)
"New heterocyclic chemistry involving lead tetraacetate"

15. 6.83 Dr. A. Pietrzykowski (Warsaw/Strathclyde)
"Synthesis, structure and properties of Aluminoxanes"

22. 6.83 Dr. D.W.H. Rankin (Edinburgh)
"Floppy molecules - the influence of phase on structure"

5. 7.83* Prof. J. Miller (Camfinas, Brazil)
"Reactivity in nucleophilic substitution reactions"

5.10.83 Prof. J.P. Maier (Basel, Switzerland)
"Recent approaches to spectroscopic characterization of cations"

12.10.83 Dr. C.W. McLeland (Port Elizabeth, Australia)
"Cyclization of aryl alcohols through the intermediacy of alkoxy radicals and aryl radical cations"

19.10.83 Dr. N.W. Alcock (Warwick)
"Aryl tellurium (IV) compounds, patterns of primary and secondary bonding"

26.10.83 Dr. R.H. Friend (Cavendish, Cambridge)
"Electronic properties of conjugated polymers"

30.11.83 Prof. I.M.G. Cowie (Stirling)
"Molecular interpretation of non-relaxation processes in polymer glasses"

2.12.83* Dr. G.M. Brooke (Durham)
"The fate of the ortho-fluorine in 3,3-sigmatropic reactions involving polyfluoro-aryl and -heteroaryl systems"

14.12.83 Prof. R.J. Donovan (Edinburgh)
"Chemical and physical processes involving the ion-pair states of the halogen molecules"

10. 1.84* Prof. R. Hester (York)
"Nanosecond Laser Spectroscopy of Reaction Intermediates"

18. 1.84* Prof. R.K. Harris (UEA)
"Multi-nuclear solid state magnetic resonance"

8. 2.84 Dr. B.T. Heaton (Kent)
"Multi-nuclear NMR studies"

15. 2.84 Dr. R.M. Paton (Edinburgh)
"Heterocyclic Syntheses using Nitrile Sulphides"

7. 3.84* Dr. R.T. Walker (Birmingham)
"Synthesis and Biological Properties of some 5-substituted Uracic Derivatives; yet another example of serendipity in Anti-viral Chemotherapy"

21. 3.84* Dr. P. Sherwood (Newcastle)
"X-ray photoelectron spectroscopic studies of electrode and other surfaces"

21. 3.84* Dr. G. Beamson (Durham/Kratos)
"EXAFS: General Principles and Applications"

23. 3.84* Dr. A. Ceulemans (Leuven)
"The Development of Field-Type models of the Bonding in Molecular Clusters"

2. 4.84* Prof. K. O'Driscoll (Waterloo)
"Chain Ending reactions in Free Radical Polymerisation"

3. 4.84* Prof. C.H. Rochester (Dundee)
"Infrared Studies of Adsorption at the Solid-Liquid Interface"

25. 4.84* Dr. R.M. Acheson (Biochemistry, Oxford)
"Some Heterocyclic Detective Stories"

27. 4.84 Dr. T. Albright (Houston, U.S.A.)
"Sigmatropic Rearrangements in Organometallic Chemistry"

14. 5.84 Prof. W.R. Dolbier (Florida, USA)
"Cycloaddition Reactions of Fluorinated Allenes"

16. 5.84 Dr. P.J. Garratt (UCL)
"Syntheses with Dilithiated Vicinal Diesters and Carboximides"

22. 5.84 Prof. F.C. de Schryver (Leuven)
"The use of Luminescence in the study of micellar aggregates" and
"Configurational and Conformational control in excited state complex formation"

23. 5.84 Prof. M. Tada (Waseda, Japan)
"Photochemistry of Dicyanopyrazine Derivatives"

31. 5.84 Dr. A. Haaland (Oslo)
'Electron Diffraction Studies of some organo-metallic compounds"

11. 6.84* Dr. J.B. Street (IBM, California)
"Conducting Polymers derived from Pyrroles"

19. 9.84* Dr. C. Brown (IBM, California)
"New Superbase reactions with organic compounds"

21. 9.84 Dr. H.W. Gibson (Signal UOP, Illinois)
"Isomerization of Polyacetylene"

19.10.84 Dr. A. Germain (Languedoc, Montpellier)
"Anodic Oxidation of Perfluoro Organic Compounds in Perfluoroalkane Sulphonic Acids"

24.10.84* Prof. R.K. Harris (Durham)
"N.M.R. of Solid Polymers"

28.10.84* Dr. R. Snaith (Strathclyde)
"Exploring Lithium Chemistry: Novel Structures, Bonding and Reagents"

7.11.84* Prof. W.W. Porterfield (Hampden-Sydney College, U.S.A.)
"There is no Borane Chemistry (Only Geometry)"

7.11.84 Dr. H.S. Munro (Durham)
"New Information from ESCA Data"

21.11.84 Mr. N. Everall (Durham)
"Picosecond Pulsed Laser Raman Spectroscopy"

27.11.84 Dr. W.J. Feast (Durham)
"A Plain Man's Guide to Polymeric Organic Metals"

28.11.84 Dr. T.A. Stephenson (Edinburgh)
"Some recent studies in Platinum Metal Chemistry"

12.12.84 Dr. K.B. Dillon (Durham)
"^{31}P N.M.R. Studies of Some Anionic Phosphorus Complexes"

11. 1.85 Emeritus Prof. H. Suschitzky (Salford)
"Fruitful Fissons of Benzofuroxanes and Isobenzimidazoles (umpolung of o-phenylenediamine)"

13. 2.85 Dr. G.W.J. Fleet (Oxford)
"Synthesis of some Alkaloids from Carbohydrates"

19. 2.85 Dr. D.J. Mincher (Durham)
"Stereoselective Synthesis of some novel Anthracyclinones related to the anti-cancer drug Adriamycin and to the Steffimycin Antibiotics"

27. 2.85 Dr. R.E. Mulvey (Durham)
"Some unusual Lithium Complexes"

6. 3.85 Dr. P.J. Kocienski (Leeds)
"Some Synthetic Applications of Silicon-Mediated Annulation Reactions"

7. 3.85 Dr. P.J. Rodgers (I.C.I. plc. Agricultural Division Billingham)
"Industrial Polymers from Bacteria"

12. 3.85* Prof. K.J. Packer (B.P. Ltd/East Anglia)
"N.M.R. Investigations of the Structure of Solid Polymers"

14. 3.85 Prof. A.R. Katritzky F.R.S. (Florida)
"Some Adventures in Heterocyclic Chemistry"

20. 3.85 Dr. M. Poliakoff (Nottingham)
"New Methods for detecting Organometallic intermediates in Solution"

28. 3.85 Prof. H. Ringsdorf (Mainz)
"Polymeric Liposomes as Models for Biomembranes and Cells?"

24. 4.85* Dr. M.C.Grossel (Bedford College, London)
"Hydroxypyridone dyes - Bleachable one-dimensional Metals?"

25. 4.85* Major S.A. Shackelford (U.S. Air Force)
"In Situ Mechanistic Studies on Condensed Phase Thermochemical Reaction Processes: Deuterium Isotope Effects in HMX Decomposition, Explosives and Combustion"

1. 5.85 Dr. D. Parker (I.C.I. plc, Petrochemical and Plastics Division, Wilton)
"Applications of Radioisotopes in Industrial Research"

7. 5.85* Prof. G.E. Coates (formerly of University of Wyoming, U.S.A.)
"Chemical Education in England and America: Successes and Deficiencies"

8. 5.85 Prof. D. Tuck (Windsor, Ontario)
"Lower Oxidation State Chemistry of Indium"

8. 5.85* Prof. G. Williams (U.C.W. Aberystwyth)
"Liquid Crystalline Polymers"

9. 5.85* Prof. R.K. Harris (Durham)
"Chemistry in a Spin: Nuclear Magnetic Resonance"

14. 5.85 Prof. J. Passmore (New Brunswick, U.S.A.)
"The Synthesis and Characterisation of some Novel Selenium-Iodine Cations, aided by ^{77}Se N.M.R. Spectroscopy"

15. 5.85* Dr. J.E. Packer (Auckland, New Zealand)
"Studies of Free Radical Reactions in aqueous solution using Ionising Radiation"

17. 5.85 Prof. I.D. Brown (McMaster University, Canada)
"Bond Valence as a Model for Inorganic Chemistry"

21. 5.85* Dr. D.L.H. Williams (Durham)
"Chemistry in Colour"

22. 5.85 Dr. M. Hudlicky (Blacksburg, U.S.A.)
"Preferential Elimination of Hydrogen Fluoride from Vicinal Bromofluorocompounds"

22. 5.85* Dr. R. Grimmett (Otago, New Zealand)
"Some Aspects of Nucleophilic Substitution in Imidazoles"

4. 6.85 Dr. P.S. Belton (Food Research Institute, Norwich)
"Analytical Photoacoustic Spectroscopy"

13. 6.85 Dr.D. Woolins (Imperial College, London)
"Metal - Sulphur - Nitrogen Complexes"

14. 6.85* Prof. Z. Rappoport (Hebrew University, Jerusalem)
"The Rich Mechanistic World of Nucleophilic Vinylic Substitution"

19. 6.85 Dr. T.N. Mitchell (Dortmund)
"Some Synthetic and NMR - Spectroscopic Studies of Organotin Compounds"

26. 6.85 Prof. G. Shaw (Bradford)
"Synthetic Studies on Imidazole Nucleosides and the Antibiotic Coformycin"

12. 7.85* Dr. K. Laali (Hydrocarbon Research Institute, University of Southern California)
"Recent Developments in Superacid Chemistry and Mechanistic Considerations in Electrophilic Aromatic Substitutions; a Progress Report"

Lectures Organised by Durham University Chemical Society during the period 1982-1985

(* denotes lectures attended)

14.10.82* Mr. F. Shenton (County Analyst, Durham)
"There is death in the pot"

28.10.82 Prof. M.F. Lappert, F.R.S. (Sussex)
"The Chemistry of Some Unusual Subvalent Compounds of the Main Group IV and V Elements"

4.11.82* Dr. D.H. Williams (Cambridge)
"Studies on the Structures and Modes of Action of Antibiotics"

11.11.82 Dr. J. Cramp (I.C.I. plc)
"Lasers in Industry"
(Joint Lecture with the Society of Chemical Industry)

25.11.82* Dr. D.H. Richards P.E.R.M.E. (Ministry of Defence)
"Terminally Functional Polymers - their Synthesis and Uses"

27. 1.83 Prof. D.W.A. Sharp (Glasgow)
"Some Redox Reactions in Fluorine Chemistry"

3. 2.83* Dr. R. Manning (Dept. Zoology, Durham)
"Molecular Mechanisms of Hormone Action"

10. 2.83 Sir G. Allen, F.R.S. (Unilever Ltd)
"U.K." Research

17. 2.83* Prof. A.G. MacDiarmid (Pennsylvania)
"Metallic Covalent Polymers (SN)x and (CH)x and their Derivatives" (R.S.C. Centenary Lecture)

3. 4.83* Prof. A.C.T. North (Leeds)
"The Use of a Computer Display System in Studying Molecular Structures and Interactions"

20.10.83* Prof. R.B. Cundall (Salford)
"Explosives"

3.11.83* Dr, G. Richards (Oxford)
"Quantum Pharmacology"

10.11.83* Prof. J.H. Ridd (U.C.L.)
"Ipso-Attack in Electrophilic Aromatic Substitution"

17.11.83* Dr. J. Harrison (Sterling Organic)
"Applied Chemistry and the Pharmaceutical Industry (Joint Lecture with the Society of Chemical Industry"

24.11.83* Prof. D.A. King (Liverpool)
"Chemistry in 2-Dimensions"

1.12.83* Dr. J.D. Coyle (The Open University)
"The Problem with Sunshine"

26. 1.84* Prof. T.L. Blundell (Birkbeck College, London)
"Biological Recognition: Interactions of Macromolecular Surfaces"

2. 2.84* Prof. N.B.H. Jonathan (Southampton)
"Photoelectron Spectroscopy - a Radical Approach"

16. 2.84* Prof. D. Phillips (The Royal Institution)
"Luminescence and Photochemistry - A Light Entertainment"

23. 2.84* Prof. F.G.A. Stone F.R.S. (Bristol)
"The Use of Carbene and Carbyne Groups to Synthesise Metal Clusters"
(The Waddington Memorial Lecture)

1. 3.84* Prof. A.J. Leadbetter (Rutherford Appleton Labs.)
"Liquid Crystals"

8. 3.84* Prof. D. Chapman (Royal Free Hospital School of Medicine, London)
"Phospholipids and Biomembranes, Basic Science and Future Techniques"

28. 3.84 Prof. H. Schmidbaur (Munich, F.R.G.)
"Ylides in Coordination Sphere of Metal: Synthetic, Structural and Theoretical Aspects"
(R.S.C. Centenary Lecture)

18.10.84* Dr. N. Logan (Nottingham)
"N_2O_4 and Rocket Fuels"

25.10.84* Dr. W.J. Feast (Durham)
"Syntheses of Conjugated Polymers. How and Why?"

8.11.84 Prof. B.J. Aylett (Queen Mary College, London)
"Silicon - Dead Common or Refined?"

15.11.84* Prof. B.T. Golding (Newcastle-upon-Tyne)
"The Vitamin B_{12} Mystery"

22.11.84* Prof. D.T. Clark (I.C.I. New Science Group)
"Structure, Bonding, Reactivity and Synthesis as Revealed by ESCA"
(R.S.C. Tilden Lecture)

29.11.84* Prof. C.J.M. Stirling (University College of North Wales)
"Molecules Taking the Strain"

6.12.84* Prof. R.D. Chambers (Durham)
"The Unusual World of Fluorine"

24. 1.85* Dr. A.K. Covington (Newcastle-upon-Tyne)
"Chemistry with Chips"

31. 1.85* Dr. M.L.H. Green (Oxford)
"Naked Atoms and Negligee Ligands"

7. 2.85 Prof. A. Ledwith (Pilkington Bros.)
"Glass as a High Technology Material"
(Joint Lecture with the Society of Chemical Industry)

14. 2.85* Dr. J.A. Salthouse (Manchester)
"Son et Lumière"

21. 2.85 Prof. P.M. Maitlis, F.R.S. (Sheffield)
"What Use is Rhodium?"

7. 3.85* Dr. P.W. Atkins (Oxford)
"Magnetic Reactions"

FIRST YEAR INDUCTION COURSE, OCTOBER 1982

This course consists of a series of one hour lectures on the services available in the department.

1 Departmental organisation

2 Safety matters

3 Electrical appliances and infrared spectroscopy

4 Chromatography and Microanalysis

5 Atomic absorptiometry and inorganic analysis

6 Library facilities

7 Mass spectrometry

8 Nuclear magnetic resonance spectroscopy

9 Glassblowing technique