Denitrosation and nitrosation: a kinetic and mechanistic investigation

Meyer, Thomas Allan

DENITROSATION AND NITROSATION : A KINETIC AND MECHANISTIC INVESTIGATION

By

THOMAS ALLAN MEYER, B.A.

(University College)

A Thesis submitted for the degree of Doctor of Philosophy in the University of Durham

Department of Chemistry

1981

- To Mom and Dad -

ACKNOWLEDGEMENTS

I should like to express my special thanks to Dr. D.L.H. Williams for his continual advice and encouragement, and under whose supervision this work was accomplished.

Many beneficial discussions are acknowledged with S.E. Aldred, L.R. Dix and S.S. Al-Khabi. I should also like to express my gratitude to Professor T.F. Grady for his steady support throughout the period of research.

The receipt of a research studentship funded by the North of England Cancer Research Campaign is gratefully acknowledged.

Finally, I should like to thank Mrs. Margaret Chipchase for the typing of this manuscript.

MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1978 and October 1981 and has not been submitted for any other degree. It is the original work of the author except where acknowledged by reference.

ABSTRACT

Section one of this thesis is concerned with the kinetics and mechanism of the process of denitrosation. At high concentrations of sufficiently reactive nucleophiles the rate of reaction of several N-alkyl-N-nitrosoanilines becomes independent of both the nature and the concentration of such species. This has been intrepreted in terms of a shift in the rate-determining to an earlier one in the reaction pathway, namely the protonation. Support for such a proposal comes from the solvent isotope effects $k_{H_2O} : k_{D_2O}$ of 1.4 and 0.7, respectively.

The denitrosation of D,L-N-acetyl-N-nitrosotryptophan (NANT) has been studied in water in the acid range 4×10^{-2} - 1M H_2SO_4 and also at the lower acidities in buffer solution pH 2-6. The reaction was irreversible, giving D,L-N-acetyltryptophan (NAT) and nitrous acid quantitatively. At higher acidities the rate of reaction was independent of added parent amine NAT and also of the addition of various nucleophiles. The kinetic solvent isotope effect $k_{H_2O} : k_{D_2O}$ was 1.3 and 1.1 at 0.7M H_2SO_4 and 0.1M H_2SO_4, respectively. At pH 6, however, the addition of various nucleophiles did catalyse the reaction, with increasing efficiency along the series $Cl^- < Br^- < SCN^- < I^- \sim N_3^-$. As the concentration of nucleophile increased the reaction rate constant tended to become independent of the [nucleophile]. The results are discussed in terms of two acid-catalysed reaction pathways, one predominate in the region pH 4-7 and the other at acidities greater than pH 1, as clearly shown by the pH - rate profile. At the higher acidities, NANT was used to nitrosate 4 - nitroaniline but only in the absence of a nitrous acid trap, thereby implicating the intermediacy of free nitrous acid.

Section two is concerned with the reverse process, nitrosation. Thiourea is shown to be a very efficient catalyst in the nitrosation of morpholine in acid solution. Compared with other known catalysts the order of efficiency

is $SC(NH_2)_2 > SCN^- > Br^-$ in the ratio 4200 : 240 : 1. The data are explained in terms of an equilibrium formation of the ion $ON\text{-}\overset{+}{S}=$, which acts directly as an nitrosating agent. Similarily, the diazotisation of aniline occurs via $ON\text{-}\overset{+}{S}=$ in the presence of thiourea. Individual values of k_2 for attack of the appropriate nitrosyl species NOX (X= Br^-, SCN^-, $SC(NH_2)_2$) on the unprotonated form of the amine are given in each case, and the overall efficiency of these species as nitrosating agents is discussed in terms of the values of the respective equilibrium constants for the formation of NOX and the magnitude of the values of k_2.

C O N T E N T S

SECTION ONE

SECTION ONE

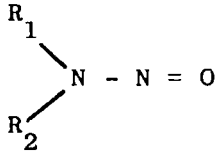
CHAPTER 1

An Introduction to the Acid-Catalysed Reactions of N-Aromatic-N-Nitrosamines : The Mechanism of Denitrosation

1.1 General Introduction

In recent years considerable research into the formation and toxicology of N-nitrosamines has greatly accelerated, ever since the report of Magee and Barnes[1] in 1956 on the carcinogenic effects of dimethylnitrosamine in rats. The investigation of the biological actions, including carcinogenicity, mutagenicity, and teratogenicity, has been extensively documented[2,3,4,5]. Although there is no evidence of a direct nature linking nitrosamine exposure to cancer in man, nitrosamines are potent animal carcinogens. Over 100 N-nitroso-compounds have been tested for cancer-causing potential in a wide variety of animals, with a high percentage of these producing tumours in one or more species and in one or more organs[5]. Yet, comparatively little is known of the chemistry of these compounds, and more specifically of their reaction mechanisms.

N-nitrosamines (I) are characterised by the direct attachment of the nitroso group - NO to the amine nitrogen center[6,7]. In practice, only those compounds where R_1 and R_2 are not a hydrogen atom have any real existence, although methylnitrosamine[8], where $R_1 = CH_3$ and $R_2 = H$, has been prepared and identified in ethereal solutions at $-70^{\circ}C$.



I ($R_1 = R_2$ = alkyl or aryl)

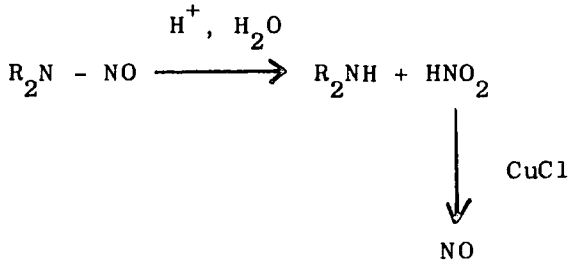
Upon warming to $-25^{\circ}C$ it decomposes to diazomethane. In most cases, when either substituent is a hydrogen atom the unstable tautomeric

diazoic acid (II) is obtained.

$$R - N = N - OH$$

II

Early qualitative studies on the decomposition of several nitrosamines in aqueous mineral acid have shown that the reaction proceeds virtually quantitatively and smoothly to form the secondary amine, provided the formed nitrous acid is removed from the reaction mixture. In 1932, Jones and Kenner[9] achieved this by carrying out the reaction in the presence of cuprous chloride, a mild reducing agent which converts the nitrous acid to nitric oxide, as illustrated in the scheme below.



Similarly, for reasons that will emerge later in the chapter, Macmillen and Reade[10] found that the elimination of the nitroso group occurred rapidly in the presence of urea and thiourea, but not in the presence of potassium thiocyanate.

The first attempts to fit a mechanistic scheme to a set of experimentally-determined kinetic data came from a group of Russian workers[11,12,13]. They examined the denitrosation of aromatic N-nitrosamines in hydrochloric and sulphuric acids, and found the reaction faster in the former.

They suggested that a hydrogen bonded complex between the nitrosoamine and an acid HA was formed, which yielded the product amine either by unimolecular scission of NO^+ or by nucleophilic attack on the complex by the anions HSO_4^- or Cl^-. Further, it was claimed that the reaction of para-substituted aromatic N-nitrosamines supported such a mechanism. Later, a paper by the same authors[14] proposed reaction in sulphuric acid by way of the mono- and di-protonated forms of the nitrosamine.

These mechanistic interpretations are open to severe criticism. First, their conclusion from a simple correlation of the Hammett type, in particular from a minimum in the log k against σ plot[15], that two parallel mechanisms operate concurrently. For reactions which proceed via protonated substrates such a correlation is meaningless, unless all of the substrates show exactly the same acidity dependence for the initial protonation. It is now known that the relative reactivities for several ring substituted N-methylanilines toward denitrosation do indeed depend upon the acidity, as exemplified by the different slopes for log k_o against $-H_o$ plots for p-NO_2 and p-CH_3 and by the activating and deactivating behavior relative to the unsubstituted nitrosamine of p-NO_2 at different acidities[16]. Any mechanistic inferences, therefore, are futile.

Secondly, it seems highly improbable under the acid conditions employed that denitrosation to give kinetically free NO^+ as the nitrosating agent would occur. Nitrosation by the free nitrosonium ion is only thought to occur at high acidity[17], for example at 60% $HClO_4$ or at acidities in excess of $9\underline{M}$ H_2SO_4 where $-H_o \sim 4.5 - 5.0$ and the water activity is sufficiently low to prevent effective solvation to H_2ONO^+. Spectroscopic evidence for the total conversion of stoichiometric concentrations of nitrous acid to NO^+ at these acidities has been reported[18,19].

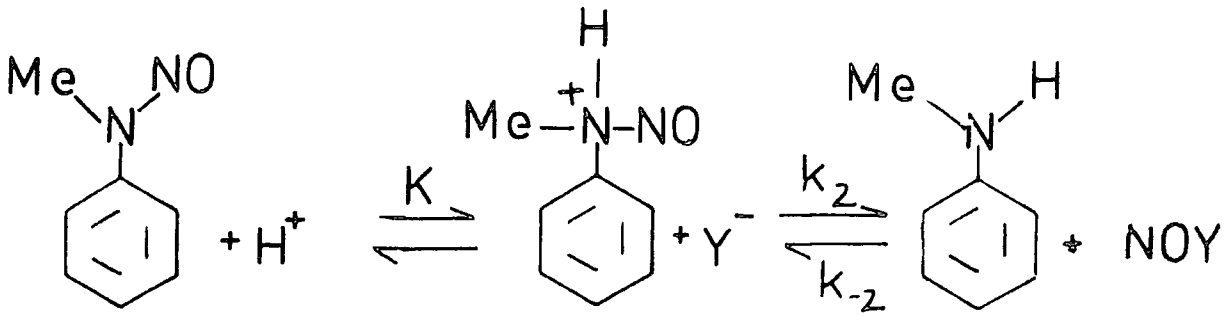
Under these circumstances, it seems more likely that the reverse reaction, N-nitrosation of amine, takes place via $H_2\overset{+}{O}NO$, which in turn implies the importance of nucleophilic assistance by H_2O in the denitrosation process.

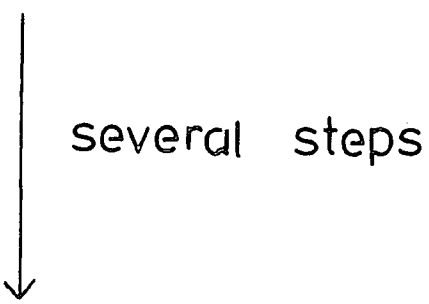
On the basis of the foregoing arguments, the best mechanism put forward, at least for aromatic N-nitrosamines, is one by Williams, the details of which are presented below.

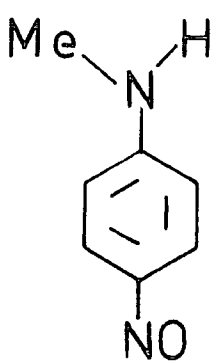
Much of what is known of the mechanism of denitrosation stems from the investigation of one particular species, namely N-methyl-N-nitrosoaniline (NMNA) in connection with the Fisher-Hepp rearrangement of aromatic N-nitrosamines, discovered in 1886[20]. Until recently, it was believed that the mechanism was intermolecular[21], but it has now been firmly established, via a detailed kinetic examination[22], as being intramolecular, with a concurrent, competing pathway of denitrosation. It will be noted in the scheme below that the protonated form the nitrosamine is common to both reaction pathways.

The products of either reaction pathway may be maximised by imposing certain physical limits upon the system. Thus denitrosation can be made quantitative by the addition of a critical concentration of nitrite trap, X, and by the presence of an efficient nucleophile, Y^-. The so-called critical concentration of nitrite trap, by experimental definition, is the minimum amount required to suppress completely the reverse of denitrosation, N-nitrosation, such that $k_3[X] >>> k_{-2}[NMA]$. What this means physically is that NOY is rapidly removed as soon as it is formed in an irreversible reaction with a nitrous acid trap usually to form molecular nitrogen.

For example, Williams[23] demonstrated for the denitrosation of







$$NOY + X \xrightarrow{k_3} \text{various decomposition products (X = urea, sulphamic acid, hydrazine, etc.).}$$

NMNA in 3.05 M HCl, where $Y^- = Cl^-$, that k_o, the observed first-order rate constant, increased with increasing concentrations of urea until it gradually levelled off to a limiting value of $14.0 \times 10^{-4} s^{-1}$, as shown in Table 1. It is here on the flat part of the curve where the rearrangement product is no longer detectable and where the reaction rate becomes zero-order with respect to the concentration of nitrite trap. The same limit was realized for other traps, to wit sodium azide

Table 1

[urea]/M	$10^4 k_o$ (s^{-1})
0.01	6.25
0.05	11.7
0.10	14.4
0.25	12.9

and sulphamic acid, albeit at different concentrations because of their varying reactivities. Hence, with the rearrangement and the general reversibility of the denitrosation completely suppressed, it is possible to examine the mechanistic features of the denitrosation process, and, perhaps, to compare the results with the reverse reaction N-nitrosation, a reaction now well understood.

In aqueous hydrochloric acid solutions, using sulphamic acid as the nitrous acid trap to ensure irreversibility, the denitrosation of NMNA resulted in curved plots for k_o against $[Cl^-]$ and h_o, respectively, while a plot of k_o against $h_o[Cl^-]$ was linear over the entire acid range[24]. The results clearly show that chloride ion and hydrogen ion catalysis are operative, both of which are accounted for in the following mechanistic scheme.

$$PhN(Me)NO + H^+ \underset{}{\overset{K}{\rightleftharpoons}} PhNH^+(Me)NO$$

$$PhN^+H(Me)NO + Cl^- \xrightarrow[\text{slow}]{k_2} PhNHMe + NOCl$$

$$NOCl + NH_2SO_3H \xrightarrow[\text{fast}]{k_3} N_2 + SO_3 + H_2O + HCl$$

The inverse solvent isotope effects $k_{D_2O} : k_{H_2O}$ of 2.9 and 3.2 at 3.05 M and 1.55 M HCl respectively, are typical of reactions that have as their first step a rapid pre-equilibrium of a small concentration of substrate followed by a slower, therefore rate-determining nucleophilic attack[25]. For convenience, the protonation is shown to occur in a single step at the amino nitrogen atom, when, in fact, it may not be this simple. Indeed, research by Jaffé and co-workers[26] indicate at least four spectroscopically distinguishable protonated species in aqueous sulphuric acid solution, with the proportion of each dependent upon the concentration of acid. The precise structures, however, were not described. Further discussion concerning the step of protonation will be found in Chapter 2 of this thesis.

An analogous scheme is held to be operative as the first stages of the Orton rearrangement of N-chloroanilides[27].

Assuming a Hammett acidity dependence for the initial protonation, the experimentally derived rate expression for the observed first-order rate constant, k_o, is given by

$$k_o = K\, k_2\, h_o \left[Y^- \right]$$

It must be noted here that the nitrite trap concentration is conspicuously absent from the rate expression. The following reasons are given: (1) at the limiting conditions of nitrite trap concentration k_o loses its

kinetic dependence on both the nature and the concentration of X and (2) a direct reaction between the trap and the nitrosamine is believed not to occur. Evidence for this latter point lies in the observation of halide ion catalysis in the nitrosation of such traps as hydrazoic acid in the presence of either a nitrosamine[28] or nitrous acid[29].

While the above statements hold true for most of the conventional nitrite traps, there is a discrepancy in the case of the anilines. Challis and Osborne studied nitrosations brought about by N-nitroso-diphenylamine and found that a direct transfer of NO^+ to N-methylaniline occurred, while for HN_3 an indirect transfer through the intermediacy of the nitrous acid derivative was favoured[28]. No such reaction between NMNA and aniline, however, was observed[24]. Later, Thompson et al. put forward strong evidence for reaction between the protonated form of N-nitrosodiphenylamine and the anilinium ion, with initial attack taking place at the ring to form a π-complex rather than at the amine-nitrogen atom[30]. Substituent effects along with the acidity dependence support their proposal for such a mechanism.

The denitrosation of N-nitrosodiphenylamine (NDA)[30] in aqueous acid media also obeys the above rate expression for k_o when a sufficient concentration of nitrite trap is present to maintain the irreversibility of the reaction such that $k_3[X] >>> k_{-2}[Ph_2NH]$. The much reduced bascisity of diphenylamine in comparison with N-methylaniline dictates that significantly greater concentrations of trap are required to reach the limiting condition, since N-nitrosation typically occurs via the free base form of the amine at moderate acidities.

Catalysis by different nucleophiles, Y^-, is easily demonstrated by effecting reactions in sulphuric acid at any one acidity by varying the concentrations of the appropriate nucleophile. Experiments by Williams[24]

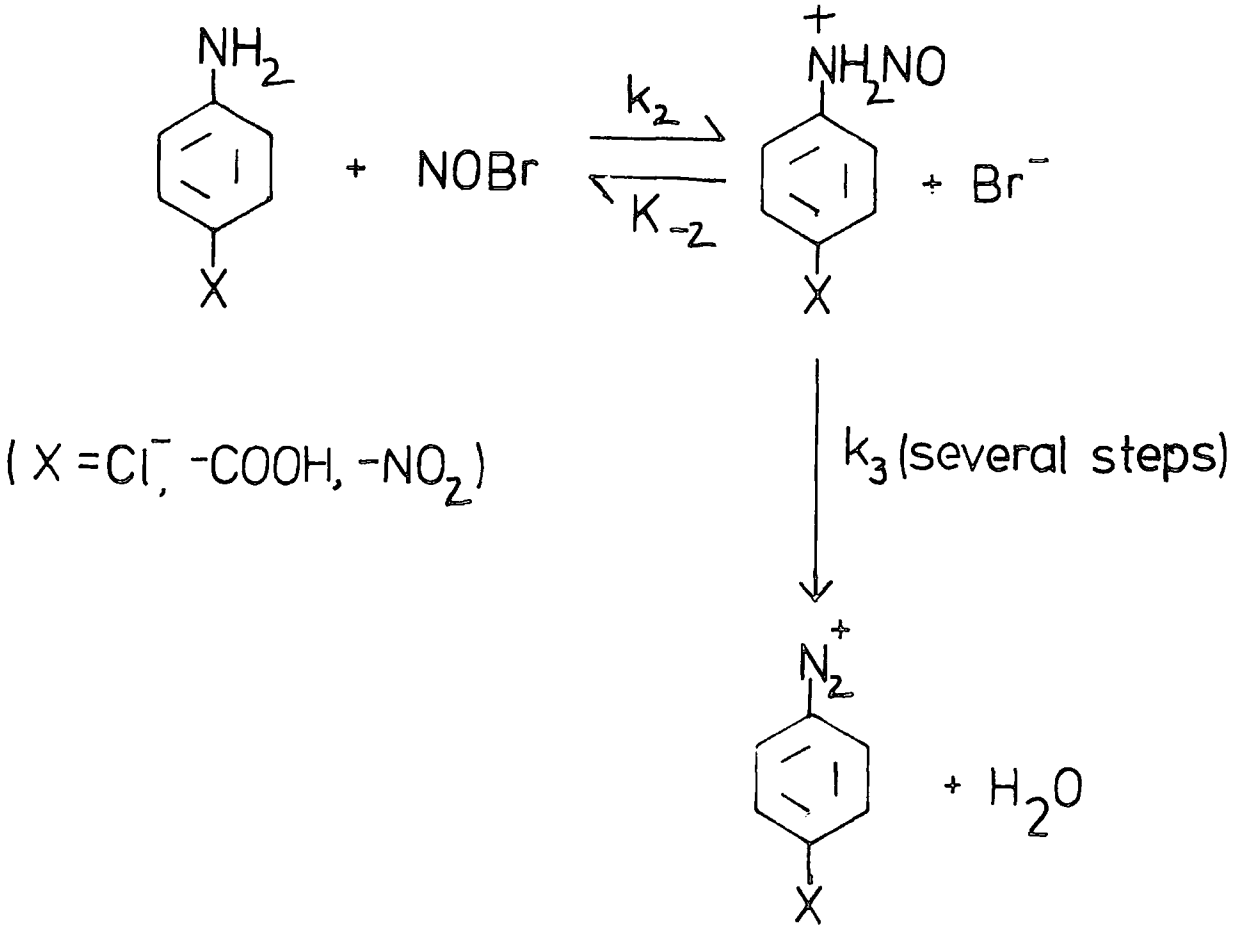
on the denitrosation of NMNA at constant acidity resulted in good linear lines for plots of k_o against added [nucleophile] for a number of nucleophiles, and from the individual slopes and a knowledge of h_o, values for k_2K can be calculated. As predicted, these values were independent of the solvent acidity and the nitrite trap concentration, provided the critical concentration was present to enforce the limiting condition $k_3[X] >>> k_{-2}[NMA]$. The sequence of nucleophilic reactivity is in the expected order:

$$Cl^- < Br^- < SCN^- < SC(NH_2)_2 < I^-$$

with the relative rate constants for denitrosation of 1 : 55 : 5500 : 13,500 : 15,000. The singular aspects of thiourea catalysis will be discussed later in the chapter.

In the same way, Thompson[39] established the identical sequence of reactivity for the same nucleophiles and obtained values of k_2K for the denitrosation of NDA. The K values for nitrosamines have never been determined directly, presumably due to their considerable instability in acid solution, and, therefore, the k_2K values are taken to represent the corresponding reactivity of each nucleophile toward the nitrosamine in question. Application of the Swain-Scott[31] equation to both sets of data give reasonable correlation of log k_2K against 'n', the determined nucleophilic constant of each nucleophile given by Pearson[32]. All the points for NMNA lie close to the line, while for NDA the points for iodide and thiourea lie significantly below the line and are ascribed to a steric effect. The slope of the lines give a quantity 's', the susceptibility constant, a measure of the denitrosation reactions toward changes in 'n'. A slope of 1.41 for NMNA compares with that of 0.97 for NDA, reflecting the former's greater selectivity and lower reactivity.

In fact, NDA is a factor of 100 more reactive than NMNA. The rationale for this is not easily ascertained, since k_2K are not separable quantities. Assuming that K is probably smaller for NDA, the determining factor must reside with k_2, the rate constant for nucleophilic attack. It seems not unreasonable that k_2 should be increased given the electron attraction of a phenyl group relative to a methyl group. This would make the amine lone-pair of electrons generally less available, thereby facilitating attack by nucleophilic species, Y^-. The effect of bascisity on nucleophilic attack is illustrated in the scheme below for the nitrosation via nitrosyl bromide of aniline derivatives containing electron withdrawing substituents.



It was found that the denitrosation step, k_{-2}, became kinetically dominant at higher concentrations of bromide ion for aniline derivatives whose $pK_a < 4$; while for X = H, OMe, Me the denitrosation step was not kinetically important[33].

Denitrosation has also been carried out in the absence of added salts over a range of sulphuric acid concentrations. In comparable hydrochloric acid concentrations the corresponding reactions in sulphuric acid were much lower, as anticipated if water is the effective nucleophile. Under these conditions, Biggs and Williams[24] found that the alternative, simultaneous pathway of rearrangement now constituted an important contribution to k_o, which was corrected based upon the observed yield of rearrangement product, to yield the rate constant for denitrosation, k_o'. A plot of log k_o' against H_o was linear, but a value of -1.58 for the slope is not in accordance with a simple first-order dependency upon h_o. The possibility of nucleophilic catalysis by hydrogen sulphate was ruled out when substantial amounts of added sodium sulphate produced no increase in k_o beyond what may be attributed to salt effects. The best correlation resulted in a graph with two discrete lines, with a sharp break occurring at 5 $\underline{M}$ H_2SO_4. This was interpreted in terms of the two equations below.

$$H_2O + PhNH(Me)NO^+ \longrightarrow PhNHMe + H_2ONO^+$$

$$H_3O^+ + PhNH(Me)NO^+ \longrightarrow PhNH_2Me^+ + H_2ONO^+$$

At low acidity water is believed to be the active nucleophile, in agreement with the graphs of k_o against added $[\text{nucleophile}]$ where the

common intercept represents reaction brought about by the solvent water molecule; whereas at higher acidity attack by the hydronium ion, H_3O^+ is thought to occur. That reaction between two positively charged species may occur was proposed by Ridd and Kalatzis[34] for reaction between a protonated aromatic amine and the nitrous acidium ion, and more recently by Kalatzis et al.[35] for the nitrosation of p-aminopyridines.

For similar reactions with NDA[30], up to 3.0 $\underline{M}$ H_2SO_4, no counterpart of the p-nitroso-species could be detected spectrophotometrically and a graph of log k_o versus $-H_o$ produced a good straight line with slope of 1.0. The results are in full agreement with nucleophilic attack on the protonated form of the nitrosamine by a water molecule.

It was stated previously that denitrosation is virtually quantitative in the presence of an excess of nitrite trap when the limiting condition $k_3[X] >>> k_{-2}[NMA]$ is satisfied. Moreover, it was shown that for Y^- = Cl^- at higher concentrations and Y^- = Br^-, SCN^-, I^- and $SC(NH_2)_2$ at all concentrations, the experimentally-determined rate expression is described by:

$$k_o = k_2 K h_o [Y^-]$$

If, however, the denitrosation is carried out in the presence of a varying concentration of excess N-methylaniline, the product of denitrosation of NMNA, the limiting condition is no longer applicable and k_o must now be defined by a more general rate expression to account for the overall reversibility of the reaction.

$$PhN(Me)NO + H^+ \underset{}{\overset{K}{\rightleftharpoons}} PhNH(Me)NO^+$$

$$PhNH(Me)NO^+ + Y^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} PhNHMe + NOY$$

$$NOY + X \xrightarrow{k_3} \text{various decomposition products}$$

The rate equation for the above scheme is:-

$$k_o = \frac{k_2 k_3 Kh_o [Y^-][X]}{k_{-2}[NMA] + k_3[X]}$$

which reduces to $k_o = k_2 Kh_o [Y^-]$ when the irreversibility of the reaction is maintained. Rewriting this equation in the reciprocal form

$$k_o^{-1} = \frac{k_2[NMA]}{k_2 Kh_o k_3 [Y^-][X]} + \frac{1}{k_2 Kh_o [Y^-]}$$

leads to the determination of k_3/k_{-2} ratios from a plot of k_o^{-1} against $[NMA]$ at constant acidity, nucleophile, and nitrite trap concentrations. In this manner, Williams[36,37] developed an indirect kinetic method to establish the relative reactivities of a number of nitrite traps toward the free nitrosating agent, NOY, and thereby obtained information concerning their efficiencies as nitrite traps. For each nucleophile, Y^-, the following order is deduced:

hydrazoic acid > hydrazine > sulphamic acid ∿ ascorbic acid

> aniline > hydroxylamine > urea

A factor of 10^4 approximately covers the range. Hence, urea is needed in the highest concentration and hydrazoic acid in the lowest concentration to ensure the limiting condition of zero-order behaviour in the concentration and nature of X.

Apart from establishing the efficiency of nitrite traps in acid solution, the above procedure also enables a comparison of the various nitrosating agents, themselves. For each X species the rate ratios, k_3/k_{-2}, are smallest for the nitrosyl thiourea adduct and nitrosyl thiocyanate and largest for the nitrous acidium ion. They are arranged in the following sequence of relative reactivity:

$$ONSC(NH_2)_2^+ \sim ONSCN < NOBr < NOCl < H_2ONO^+$$

In terms of the selectivity-reactivity principle, it would seem that whilst the two sulphur containing nitrosating agents show similar reactivities toward the various trap species, their reactivity is considerably less than NOBr. Thus, it would seem that NOSCN and $NOSC(NH_2)_2^+$ are not particularly reactive nitrosating agents. More discussion centering on this point can be found in the second half of this thesis.

Nitrosation reactions in acidic media are known to involve the free base form of the amine in the presence of halide ions[38], and as such the k_3/k_{-2} ratios do not represent the true rate coefficients for the various nitrosation reactions. However, the true rate constants, k'_3/k_2', can be obtained from the k_3/k_{-2} values by allowing for protonation equilibria of N-methylaniline and the X species in acidic solution. These new k_3'/k_{-2}' ratios observe the same trend of reactivity outlined above.

Subsequently, Stedman and co-workers, working under substantially different experimental conditions of acidity and halide ion concentrations, nitrosated hydrazine[39] and hydroxylamine[40] directly using a fast reaction technique. Their results show disturbing discrepancies for the halide ion catalysed reaction. For example, for the relative reactivities of hydrazine to hydroxylamine Stedman obtained ratios of .024 and .00062 for the chloride ion and bromide ion catalysed reactions, respectively, while the corresponding values for the indirect method above yielded values of .004 and .000038.

To explain the lack of satisfactory agreement between the two procedures, Williams[41] re-determined k_3/k_{-2} ratios for a number of traps over a wider range of acid and bromide ion concentration. The results of the study show quite clearly that the k_3/k_{-2} values are subject to change with changing experimental conditions, particularly at different acidity but also with the concentration of bromide ion. It must be emphasized, therefore, that the k_3/k_{-2} ratios do give a measure of the relative reactivities of the nitrosating agents, but only under the defined conditions of the experiment.

Hitherto the discussion has referred to reactions in moderate acidity, either in HCl or H_2SO_4 in the presence or absence of added nucleophiles where the observed first-order rate constant loses its kinetic dependence upon the concentration and nature of X. Biggs and Williams[42] also report results for the denitrosation of NMNA in the presence of an excess concentration of X for an extensive range of acidity. Experiments in aqueous HCl show that a graph of log k_o against $-H_o$ is linear up to 5.5 M HCl, whilst above this acid concentration the linear relationship breaks down. The deviation in linearity first occurs for urea, followed by hydroxylamine, and then sulphamic acid, with

hydrazine and hydrazoic acid showing relatively little change. Interestingly, this is the identical sequence of reactivity of the traps toward various nitrosating agents established earlier. It is suggested, therefore, that the change in behaviour at higher acidity is due principally to the departure from zero-order dependency in X, which is furthermore associated with the relative efficiences of these species as nitrite traps.

For the least reactive traps, urea, hydroxylamine, and sulphamic acid k_o increases in a linear fashion with increasing acidity until a maximum is reached, after which a further increase in $-H_o$ causes a decrease in k_o. The position of the maximum varies from trap to trap, and also with the concentration of the trap. At low acidity it is assumed that the reactive forms toward electrophilic nitrosation are $CO(NH_2)_2$, NH_2SO_3H (and $\overset{+}{N}H_3SO_3^-$) and $\overset{+}{N}H_3OH$. At higher acidities it seems reasonable that further protonation to other mono - or di-protonated forms are possible, to an extent that the concentrations of the reactive forms are significantly reduced such that $k_3[X]$ is no longer markedly greater than $k_{-2}[NMA]$. Thus, the simple linear relationship between log k_o and $-H_o$ can no longer exist, and k_o is more aptly described by the general form of the rate expression:

$$k_o = \frac{k_2\, h_o\, K\, k_3[X][Y^-]}{k_3[X] + k_{-2}[NMA]}$$

For the more reactive traps, hydrazine and hydrazoic acid, it is now known that the reactive species toward nitrosation are N_3H and $\overset{+}{N}H_3NH_2$. Further protonation to $H_2\overset{+}{N}_3$ and $\overset{+}{N}H_3\overset{+}{N}H_3$ does not occur to an appreciable extent at the acidities used in the study. Consequently, it is expected that the inequality $k_3[X] \ggg k_{-2}[NMA]$ remains valid at

all acidities, when k_o reduces to:-

$$k_o = k_2 h_o K[Y^-]$$

Experimentally, there is no indication of a rate maximum, as for the less reactive traps, up to 8.9 M HCl. The lack of linear correlation then must be sought elsewhere. It is, in fact, ascribed to a large proportion of protonation of the nitrosamine, whence the limiting form of the rate equation should be replaced by:-

$$k_o = \frac{k_2 K[Y^-] h_o}{1 + K h_o}$$

which simplifies further to:-

$$k_o = k_2[Y^-]$$

when the nitrosamine is completely protonated for all practical purposes. Thus, at high acidity k_o becomes independent of h_o. The slope of log k_o against $-H_o$ decreases but does not reach a maximum as the transition between the limiting forms of the rate equations from low acidity to high acidity occurs, since the dependence in HCl becomes proportional to only $[Cl^-]$ rather than to $h_o[Cl^-]$.

It may be concluded that the effectiveness of a particular nitrite trap in acid solution is mainly dependent upon the nature of the reactive species toward electrophilic nitrosation.

Kinetic effects of N-, meta-, and para-substituents in the denitrosation of N-nitrosoaromatic amines have been examined[16]. For bromide ion catalysed reactions in sulphuric acid media a factor of 10

covered the reactivity range for the rate sequence of N-alkyl-N-nitrosoanilines:-

$$NMe < NBu^{t} < NEt \sim Npr^{n} < Npr^{i}$$

A similar sequence was established for reactions in HCl, with the reactivity of butylnitroso-amine paralleling n-propylnitroso-amine.

In H_2SO_4 in the absence of added halide ions, where H_2O is thought to act as the nucleophile, the same pattern of reactivity is found. With the notable exception of the tertiary-butyl group it is argued that the rate sequence may reflect the increasing values of the bascisities of the nitroso-compounds, if their pK_a values follow thc same trend as the parent amines. The atypical reactivity of the tertiary-butyl group is then attributed to steric effects. Indeed, the relative rate constant ratios $k_o(Bu^t)$: $k_o(Me)$ of 2.45, 2.39, 1.45, 0.94 for Cl^-, H_2O, Br^- and I^-, respectively, formally demonstrates the degree of difficulty the larger nucleophiles have in approaching the nitroso-nitrogen atom when the bulky tert-butyl group is present at the nitrogen centre. Although the observed rate constants are a function of the product of the initial protonation, K, and the rate constant, k_2, for nucleophilic attack, it appears that the dominant factor for the N-substituted derivatives is that exerted on K by the electron-donating abilities of the different alkyl groups. It is probable, however, that both effects operate.

For meta- and para- ring substituents, the steric complications for nucleophilic attack are removed, and the overall small magnitude in the range of reactivity is interpreted as the result of the two opposing effects on k_2 and K. In general, electron-releasing substituents retard the reaction rate, while electron-attracting substituents increase

the reactivity. For example, the rate sequence for the halide catalysed reactions for para-substituents is:-

$$Cl > H > Me > OMe$$

indicating that the major effect is the influence on k_2. This sequence is just reversed for the uncatalysed reaction in H_2SO_4, and is taken as confirmatory evidence for the attack on the protonated nitrosamine by the positive species H_3O^+. It will be recalled that H_3O^+ is responsible for the displacement of NO^+ from the protonated nitrosamine at higher acidities[24].

One aspect of the denitrosation reaction of current interest is the ability of neutral sulphur containing species to catalyse the reaction. The direct reaction between nitrous acid and several sulphur derivatives is well known[43,44], but their reaction with a nitrosamine is comparatively new. In a preliminary communication, thiourea was reported to exhibit nucleophilic reactivity somewhat between that of bromide ion and iodide ion for its reaction toward NMNA[45]. Greater details of the reaction were presented by Williams[46] in a later publication, the essential points of which are discussed below.

Historically, Storch[47] was first to study the reaction of thiourea with nitrous acid in moderate concentrations of mineral acids. Upon mixing solutions of acidified thiourea and nitrous acid, he observed the formation of a short-lived red colouration. The new product CC'-dithiodiformamidinium ion, depicted below, was isolated in high yield from the reaction mixture.

$$(NH_2)_2\overset{+}{C}SS\overset{+}{C}(NH_2)_2$$

Later, Werner[48] showed that either a red or a yellow coloured solution could be obtained depending upon the concentration of acid and that two separate, but simultaneous reaction pathways were evident. One reaction was favoured at low acidity and one was favoured at high acidity[49]:-

$$HNO_2 + SC(NH_2)_2 \xrightarrow[\text{Acidity}]{\text{Low}} H^+ + SCN^- + N_2 + H_2O$$

$$2H^+ + 2HNO_2 + 2SC(NH_2)_2 \xrightarrow[\text{Acidity}]{\text{High}} (NH_2)_2 \overset{+}{C}S\overset{+}{S}C (NH_2)_2 + 2NO + 2H_2O$$

In a kinetic investigation using a fast reaction technique, Stedman and co-workers[50] concluded that the yellow colour was due to an initial S-nitrosation to form the unstable intermediate $ON\text{-}\overset{+}{S} = C(NH_2)_2$, which slowly fades to yield either of the above products.

For reaction between thiourea and NMNA in the absence of a nitrite trap Williams[46] also observed the formation of the transient yellow colour, and obtained the product CC'-dithiodiformamidinium ion in high yield. The results suggest that, as for reaction with nitrous acid, thiourea reacts with the nitrosamine to give the S-nitroso-adduct, which subsequently decomposes to the disulphide, as shown in the scheme below.

$$PhN(Me)NO + H^+ \underset{}{\overset{K}{\rightleftharpoons}} \overset{+}{PhNH}(Me)NO$$

$$\overset{+}{PhNH}(Me)NO + SC(NH_2)_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ON\text{-}\overset{+}{S} = C(NH_2)_2 + PhNHMe$$

$$ON\text{-}\overset{+}{S} = C(NH_2)_2 \xrightarrow{k_3} (NH_2)_2 \overset{+}{C}S\overset{+}{S}C (NH_2)_2 + 2NO$$

(yellow)

The dissolved nitric oxide undergoes aerial oxidation to form nitrous acid, and when all of the thiourea has been consumed, the nitrosamine is eventually regenerated by the action of nitrous acid on N-methylaniline. In deoxygenated solutions, re-nitrosation of the secondary amine could not be detected spectrophotometrically.

In the presence of a nitrite trap, however, no characteristic yellow colour is observed, and the major isolable product is N-methylaniline, the product of denitrosation, rather than the disulphide. Under these conditions, the trap reacts rapidly and irreversibly with the nitrosyl thiourea adduct to re-form thiourea, as outlined below.

$$H^+ + PhN(Me)NO \underset{}{\overset{K}{\rightleftharpoons}} PhNH(Me)NO^+$$

$$PhNH(Me)NO^+ + SC(NH_2)_2 \xrightarrow{k_2} PhNHMe + ONSC(NH_2)_2^+$$

$$ONSC(NH_2)_2^+ + X \xrightarrow{k_3} SC(NH_2)_2 + \text{various decomposition products}$$

The kinetics of the system were conducted under strictly first-order conditions, with $[\text{thiourea}] >>> [\text{nitrosamine}]$ and with sodium azide present in sufficient excess to prevent complications from reversibility. By alternately varying the concentrations of thiourea and acid, good first-order behaviour with respect to each was determined. Assuming a Hammett acidity dependence, as before, for the initial protonation, one may write:-

$$k_o = k_2 K h_o [Y^-]$$

The slope of the line from the graph of k_o against thiourea is $k_2 K h_o$, and since h_o is a known quantity the value for k_2K is calculated to be 0.55. This compares with .63 for I^-, .22 for SCN^-, .0022 for Br^- and .000042 for Cl^-. Thus, thiourea is very near iodide ion in its nucleophilic reactivity, and is also in line with Pearson's 'n' values. The results lie in direct contrast with the relatively small spread of rate constants for the reaction of these nucleophiles with the nitrous acidium ion, where it is believed the reaction rates approach those expected for a diffusion-controlled reaction[38].

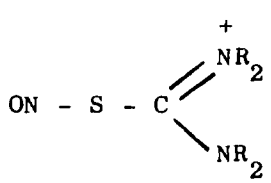
More recently, an extension of this work to other types of neutral sulphur sites, including a number of N-alkylthioureas, was conducted by Hallett et al.[51]. For convenience, the results are summarised in Table 2, along with previous results, in terms of their relative reactivities. It is postulated that each nucleophile behaves similarly to thiourea towards NMNA, in that the same reaction scheme is followed and that reaction occurs at the sulphur atom. By mere inspection of the data in Table 2, it is apparent that the introduction of an S-methyl group for S-methylcysteine and methionine increases the reactivity of nitrosation in comparison with the $-CH_2SH$ group for cysteine and glutathione.

The striking feature of Table 2 is the similar reactivity, within experimental error, of the N-alkylthioureas. It is thought that this does not reflect a tendency of the reaction rates toward the diffusion-controlled limit. If this were the case, then a reasonable value for k_2 would be 1.0×10^{10} ℓ $mol^{-1}s^{-1}$, leading to value of -10 for the pK_a of NMNA. While this has never been measured directly, it has been estimated to be near -2. In addition, the Pearson plot shows no indication of levelling off at the higher 'n' value for iodide ion, and a value of 1.41

Table 2

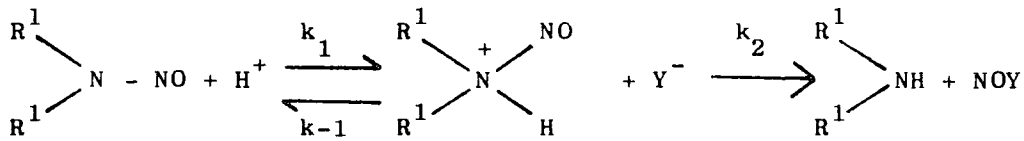
Nucleophile	Relative Reactivity
Chloride ion	1
Cysteine	2
Glutathione	3
S-methylcysteine	35
Bromide ion	55
Methionine	65
Thiocyanate ion	550
Trimethylthiourea	12250
Thiourea	13000
N-methylthiourea	14250
N-N'-dimethylthiourea	14500
Tetramethylthiourea	14250
Iodide ion	15750

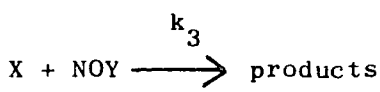
for the slope affirms the sensitivity of NMNA to the reactivity of the nucleophile. Rather, the preferred interpretation is one in which the contribution from structures shown below to stabilize the positive charge on S and C in the transition state is neglible.



In such circumstances, increased N-methyl substitution is not expected to stabilize the transition state to any great extent, and the thioureas, therefore, exhibit similar reactivities.

Denitrosation reactions so far have been confined to aqueous media. In changing solvents from water to ethanol, however, many differences occur. Consider the general scheme outlined below.





Applying the qualitative theory of solvent effects proposed by Hughes and Ingold[52] allows predictions to be made concerning the relative magnitudes of $k_2[Y^-]$ and k_{-1}. Simply, the theory states that the destruction and diffusion of charges will be inhibited by an increase in the ion-solvating power of the medium. In terms of the above reaction scheme, the effect of an increase in the ion solvating ability of the solvent would then be to lower the magnitude of k_{-1}. Conversely, a solvent of lower ionising power would increase the magnitude of k_{-1}. This seems reasonable given the greater degree of stabalisation of the protonated form of the nitrosamine in solvents of higher ionising power.

Similarly, the effect upon k_2 is also a retarding one in solvents of greater ionising ability, so that in moving to a solvent of greater ionising power whilst maintaining the concentration of Y^- constant results in a lowering of the magnitude of $k_2[Y^-]$. In contrast, turning to solvents of lower ionising ability whilst keeping the concentration of Y^- constant results in an increase in the magnitude of $k_2[Y^-]$.

Although these effects of the solvent alter $k_2[Y^-]$ and k_{-1} in the same direction , it might be expected that the main effect operates on k_2, since this step demands a greater delocalisation of charge.

With the foregoing remarks in mind, it is anticipated that $k_2[Y^-]$ would become significantly greater than k_{-1} for the denitrosation of NMNA as the solvent is changed from water to absolute ethanol. Indeed, a study conducted by Johal et al.[53] on the denitrosation of NMNA in ethanolic HCl reports that the addition of 4.59×10^{-3} M NaBr produced no observable change in the rate of reaction. In contrast, the same concentration of Br^- increased the rate about five-fold for reaction in aqueous solvent. The much more powerful nucleophile SCN^- also had no effect on the rate of reaction in ethanolic solvent.

These results demonstrate that the nucleophile plays no direct role in determining the rate of reaction. This further suggests either (a) that loss of NOY is an unassisted unimolecular process, or (b) that the rate-determining step is an earlier one in the reaction sequence, namely the protonation. It is difficult to rationalize a unimolecular scission of NO^+ in this case, and, therefore, explanation (b) is preferred. A kinetic solvent isotope effect k_{EtOH}/k_{EtOD} of 3.8 is in full support of a rate-controlling proton transfer. Under these conditions, $k_2[Y^-] >>> k_{-1}$ and the rate expression for k_o is described by:-

$$k_o = k_1 h_x$$

where h_x refers to some appropriate acidity function. Denitrosation of NDA[53] in HCl/ethanol solutions behaved in a similar fashion to NMNA.

CHAPTER 2

The Effect of Increasing Concentrations of Nucleophiles on the Mechanism of Denitrosation

2.1 Introduction

In the preceeding introduction discussion referred to reaction of N-nitrosamines in aqueous acid solvent in the presence of moderate concentrations of various nucleophiles. Under such conditions the reaction is subject to acid and nucleophile catalysis, with the solvent isotope effect $k_{D_2O}/k_{H_2O} > 1.0$ supporting a mechanism in which the rate is governed by nucleophile attack upon the protonated substrate. The work presented in this chapter investigates the effect of the concentration and the nature of the nucleophile in much greater detail.

Challis and Osborne[28] first reported that the effect of increasing concentrations of nucleophile in 50% $^{EtOH}/H_2O$ solvent was to make the observed first-order rate constant essentially independent of the concentration of such nucleophilic species. These observations of Challis and Osborne for the denitrosation of N-nitrosodiphenylamine (NDA) were confirmed in 100% aqueous solvent by Thompson[54] using sufficiently high concentrations of bromide ion and by Hallett[55] using both bromide ion and thiocyanate ion.

All agreed that the disappearance of nucleophilic catalysis at high concentrations of the appropriate nucleophile was the result of a shift in the rate-determining step to an earlier one in the reaction pathway. Given the scheme

$$Ph_2NNO + H+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ph_2\overset{+}{N}HNO + Y^- \xrightarrow{k_2} Ph_2NH + NOY \xrightarrow[\text{trap}]{\text{nitrite}} \text{products}$$

this must now mean that the proton transfer from the solvent to the nitrosamine effectively becomes the rate-controlling factor. A solvent isotope effect k_{D_2O}/k_{H_2O} of 0.8 for the denitrosation of NDA at high

concentrations of bromide ion corroborates their hypothesis[54].

An extension of this to include N-nitroso-N-methylaniline for other nucleophiles and to offer further evidence for the existing mechanism of denitrosation is presented in the pages that follow.

2.2 Denitrosation in the Presence of High Concentrations of Nucleophile

2.2.1 Derivation of the Rate Equation

Consider the reaction scheme set forth by Williams:

$$SH^+ + PhN(Me)NO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{+}{PhNH(Me)NO} + S$$

$$Y^- + \overset{+}{PhNH(Me)NO} \xrightarrow{k_2} PhNHMe + NOY$$

$$NOY + X \xrightarrow{k_3} \text{various decomposition products}$$

where s = solvent and X = nitrite trap.

In the presence of an excess concentration of nitrite trap, X,

$$\text{Rate} = k_2\left[Y^-\right]\left[\overset{+}{PhNH(Me)NO}\right]$$

Assuming that $\left[\overset{+}{PhNH(Me)NO}\right]$ is relatively small and does not accumulate during the course of the reaction allows the application of the stationary-state approximation. Thus,

$$\text{rate of formation} = \text{rate of destruction}$$

$$\left[SH^+\right]\left[PhN(Me)NO\right] k_1 = \left[\overset{+}{PhNH(Me)NO}\right]\left[S\right] k_{-1} + k_2\left[\overset{+}{PhNH(Me)NO}\right]\left[Y^-\right]$$

so that,

$$\left[\overset{+}{\text{PhNH(Me)NO}}\right] = \frac{k_1\left[SH^+\right]\left[\text{PhN(Me)NO}\right]}{\left[S\right]k_{-1} + \left[Y^-\right]k_2}$$

The concentration of solvent, $\left[S\right]$, is necessarily constant, and therefore is incorporated into k_{-1}. Hence,

$$\text{Rate} = \frac{k_1 k_2\left[Y^-\right]\left[SH^+\right]\left[\text{PhN(Me)NO}\right]}{k_{-1} + k_2\left[Y^-\right]}$$

However, since the observed first-order rate constant, k_o, is defined by:

$$\text{Rate} = \frac{-\,d\left[\text{PhN(Me)NO}\right]}{dt} = k_o\left[\text{PhN(Me)NO}\right]$$

one may write,

$$k_o = \frac{k_1 k_2\left[Y^-\right]\left[SH^+\right]}{k_{-1} + k_2\left[Y^-\right]}$$

Two limiting conditions of the above equation for k_o exist:

(1) If $k_2\left[Y^-\right] \lll k_{-1}$, a kinetic dependence upon both the acid and nucleophile concentrations are expected, as k_o reduces to:

$$k_o = \frac{k_1}{k\text{-}1} k_2\left[Y^-\right]\left[SH^+\right]$$

This is the experimental form for k_o observed by Williams for low nucleophile concentrations.

(2) If $k_2[Y^-] >>> k_{-1}$, the kinetic terms for nucleophilic catalysis are removed from the rate expression, as k_o now becomes:

$$k_o = k_1 [SH^+]$$

Thus, the rate of reaction for any one nitrosamine is dependent only upon the concentration of acid.

2.2.2 The Limiting Condition $k_2 [Y^-] >>> k_{-1}$

Reactions were carried out in aqueous sulphuric acid solvent with sodium azide present as the nitrite trap in sufficient excess to prevent complications from reversibility. Each individual kinetic run showed good first-order behaviour when log (a-x) against time was plotted. The data for bromide, thiocyanate and thiourea are set out in Tables 3-5 for k_o as a function of added nucleophile at constant acidity and sodium azide concentrations.

Constant conditions for each kinetic experiment:

$[H_2SO_4] = .476$ M, $[NaN_3] = 3.1 \times 10^{-3}$ M, $[NMNA] = 1.0 \times 10^{-4}$ M

Table 3

$[KBr]$/M	$10^{-4} k_o (s^{-1})$
.8	11.1
1.6	26,3
2.2	46.7
3.0	25.7

Table 4

$10^2[SC(NH_2)_2]/M$	$10^4 k_o\ s^{-1}$
1.2	46.2
1.5	57.1
1.8	68.9
3.0	87.2
4.0	109
9.0	159
12.8	163
29.3	185
28.8	192
39.7	196
42.1	199
48.8	201

Table 5

$10^2[KSCN]/M$	$10^4 k_o\ s^{-1}$
.32	6.69
.64	12.5
.96	18.0
1.27	23.4
1.61	26.6
3.21	49.1
4.82	63.4
6.83	79.8
7 60	89.5
16.1	136
19.1	144
24.2	154
38.2	175
59.0	184
76.4	200
83.2	195
103	202
108	202

These same data are illustrated graphically in Figure 1. Clearly, k_o becomes independent of the concentration of both thiocyanate and thiourea. Whilst bromide successfully reached the limit for NDA[54], it appears to be insufficiently reactive toward NMNA as the required high concentrations of its salt actually depressed k_o. On the flat part of the curve $k_2[Y^-] >>> k_{-1}$ and the rate expression is given by:-

$$k_o = k_1[SH^+]$$

Thus, since the same nitrosamine is used and since the acidity is maintained at a constant level throughout the study, the limit to which the different nucleophiles extend should be the same, regardless of the reactivity of each nucleophile. That this is patently the case is exhibited by the common limiting value of $2.0 \times 10^{-2} s^{-1}$ for thiourea and thiocyanate ion, although different concentrations of each were required.

Pertinent details of reactions in D_2SO_4 - D_2O solvent at high and low concentrations of thiourea are drawn up in Table 6. Generally, for acid catalysed reactions that proceed via:-

$$S + H^+ \rightleftharpoons SH^+ \qquad (1)$$

$$SH^+ \longrightarrow \text{products} \qquad (2)$$

where S represents the substrate, there are three plausible mechanistic choices. These are designated as the A-S_E2, A - 2 and the A - 1 mechanisms. The analogue of the A - 1 mechanism, which involves a slow unimolecular reaction of the protonated substrate in step 2, is eliminated under the present conditions by the observation of thiourea catalysis.

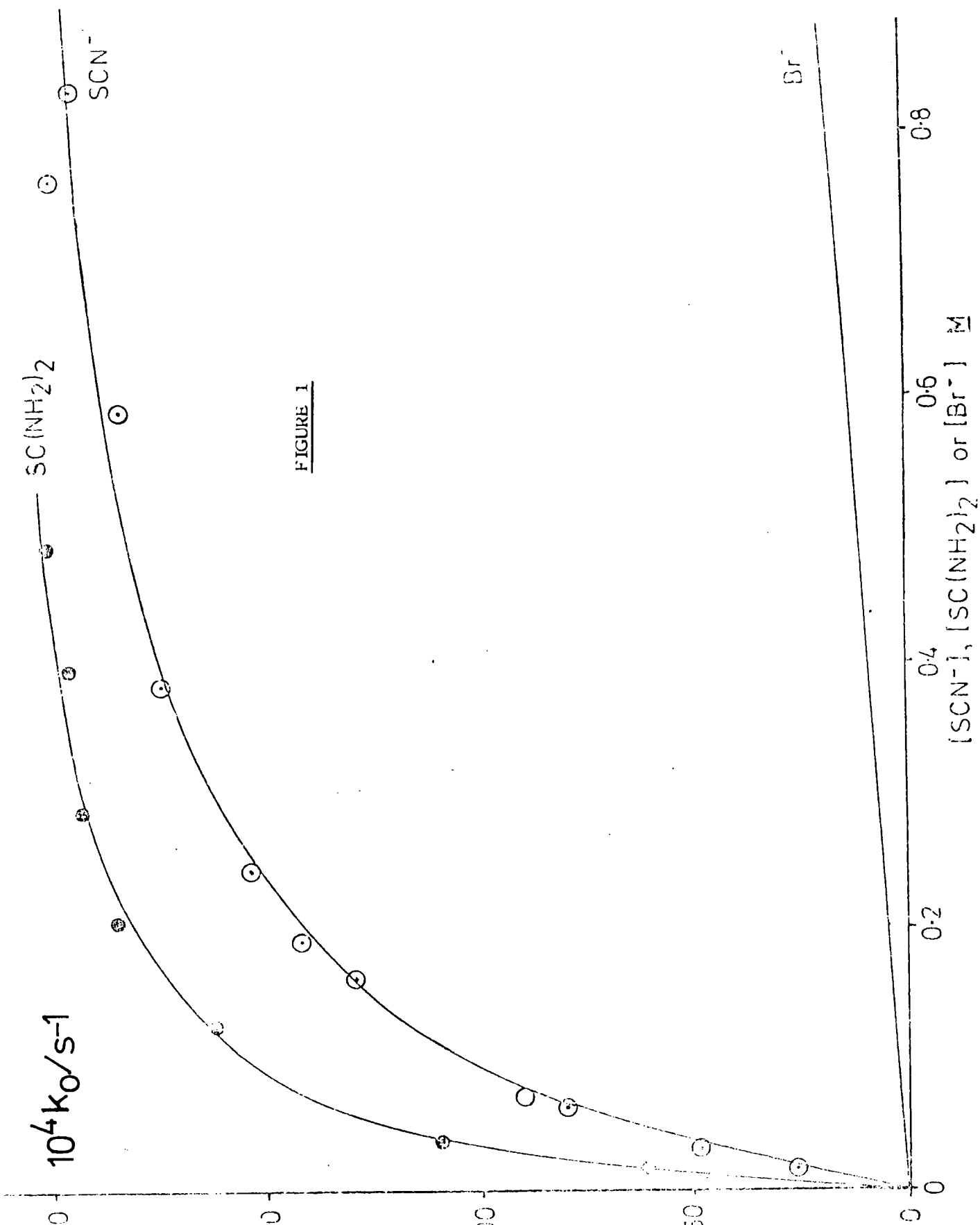

$10^4 k_o/s^{-1}$
200
150
100
50
0
0
0·2
0·4
0·6
0·8
$[SCN^-]$, $[SC(NH_2)_2]$ or $[Br^-]$ M
$SC(NH_2)_2$
SCN^-
Br^-

FIGURE 1

Table 6

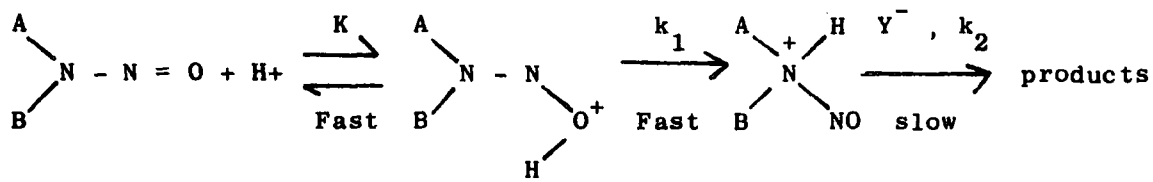
Acid	[Thiourea] /M	$10^4 k_o (s^{-1})$	k_{D_2O}/k_{H_2O}
.478M H_2SO_4	.421	199	.63
.474M D_2SO_4	.431	126	
.478M H_2SO_4	.030	87.2	1.1
.470M D_2SO_4	.031	94.3	
.480M H_2SO_4	.015	56.2	1.4
.474M D_2SO_4	.015	81.2	

For an A-S_E2 mechanism proton transfer from the solvent to the substrate is rate-controlling, and statistical mechanical calculations predict that the solvent isotope effect k_{D_2O}/k_{H_2O} will be less than unity[56]. The value of 0.63 for k_{D_2O}/k_{H_2O} at high concentrations of thiourea is in line with such a mechanism. It appears, therefore, that the initial proton transfer from the solvent to N-methyl-N-nitrosoaniline is indeed rate-determining under the stated conditions. There is an extraordinarily close analogy here between this work and some studies carried out on the acid-catalysed decomposition of carbamates, in that a rate-limiting proton transfer from the solvent to the substrate is also observed to occur[75]. This isotope effect compares favourably with that of 0.8 for denitrosation of NDA at high bromide ion concentrations and with that of 0.5 for N-nitrosoamides[57,58] and 0.7 for N-methyl-N-nitrosotoluene-p-sulphonamide[59], where the initial proton transfer is thought to be rate-determining at all nucleophile concentrations.

The A-2 mechanism is defined by a fast, reversible protonation followed by a rate-determining step with some nucleophilic reagent in step 2 of the above scheme. It is found that these reaction rates

typically proceed faster in heavy water than in light water by factors varying from $\sim$ 1.5 - 3.5[60]. The smallness of the k_{D_2O}/k_{H_2O} ratios in the present case for the lower thiourea concentrations may be taken to reflect the limiting curve for k_o verus [thiourea] in D_2O, but generally the results are consistent with the A-2 mechanism for specific acid catalysis.

It is interesting to point out, however, that larger isotope effects are not necessarily expected if the second step shows an isotope effect. This could be the case, for example, if the protonation included a series of steps rather than the simple, single-stage protonation at the amine nitrogen centre.



Under these conditions, an increase in the observed rate constant, due to an increase in the equilibrium concentration of the O-protonated species in D_2SO_4-D_2O solvent, is masked by the retarding effect of the re-arrangement process in step k_1. Hence, the k_{D_2O}/k_{H_2O} ratios may be smaller than usual. The subject of protonation is discussed more fully in section 2.3 of this chapter.

2.2.3 Non-limiting Conditions

In the intermediate ranges of nucleophile concentrations for thiocyanate and thiourea, neither of the limiting conditions apply and the general form of the rate expression for k_o must now be used.

$$k_o = \frac{k_1 k_2 [Y^-][SH^+]}{k_{-1} + [Y^-] k_2}$$

Rewriting this equation in the reciprocal form

$$k_o^{-1} = \frac{k_{-1}}{k_1 k_2 [Y^-][SH^+]} + \frac{1}{[SH^+]k_1}$$

should thus yield a linear line for a graph of k_o^{-1} against $[1/Y^-]$. The data listed in Tables 7 and 8 are taken from the previous section, and a graph of k_o^{-1} versus $[Y^-]^{-1}$ is depicted in Figure 2. Bromide ion is shown for comparison purposes.

Table 7

$[SC(NH_2)_2]^{-1}$	k_o^{-1}
83.8	216
66.7	175
55.5	145
33.3	115
25.0	91.7
11.1	62.9
7.81	61.3
3.47	52.1
4.93	54.1
2.52	51.0
2.38	50.3
2.05	49.8

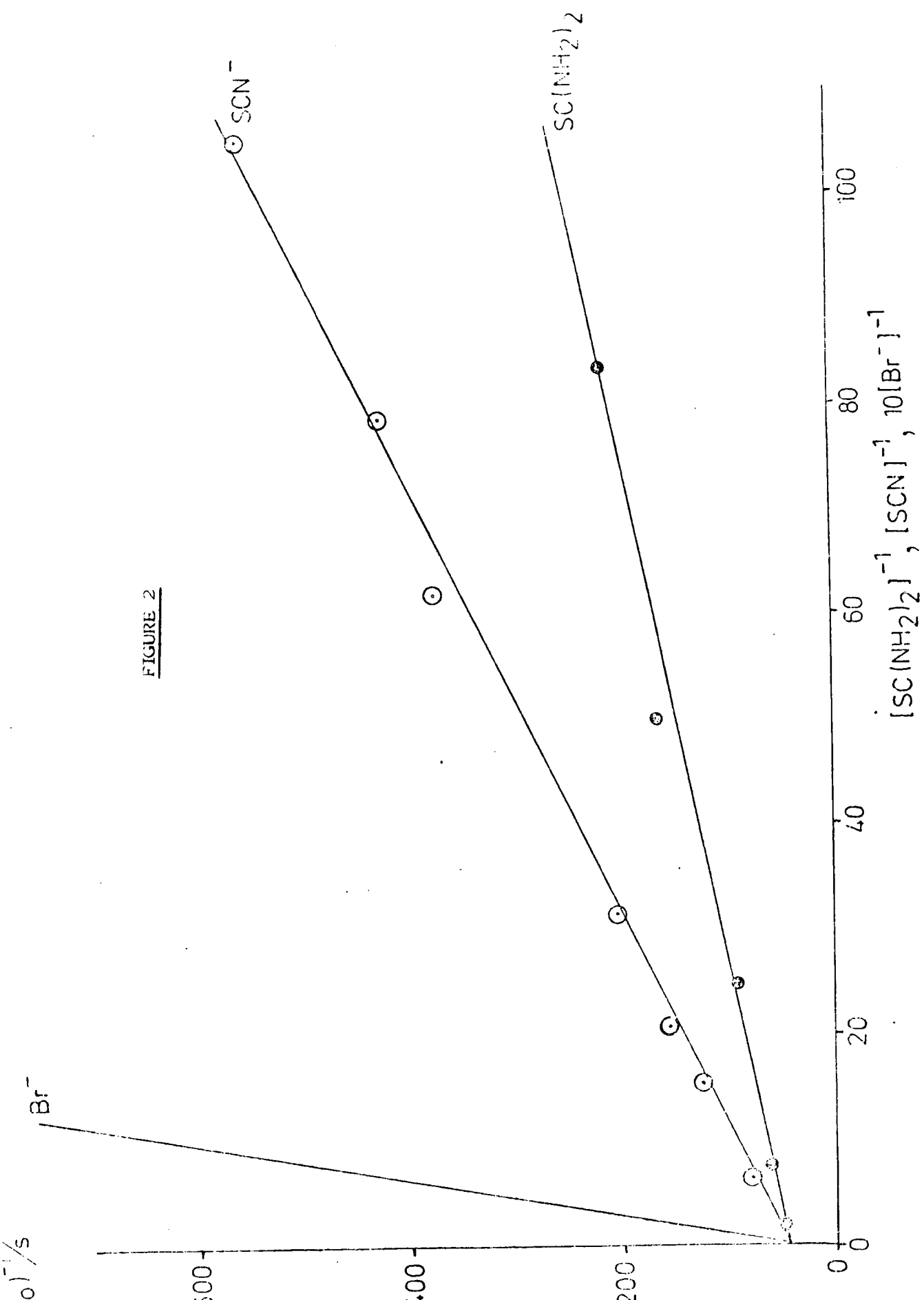

$(k_0)^{-1}/s$
600
400
200
0
Br^-
SCN^-
$SC(NH_2)_2$
0
20
40
60
80
100
$[SC(NH_2)_2]^{-1}$, $[SCN^-]^{-1}$, $10[Br^-]^{-1}$

FIGURE 2

Table 8

$[KSCN]^{-1}$	k_o^{-1}
313	1495
157	800
105	556
78.7	427
62.1	376
3.12	204
20.7	158
15.5	125
13.2	112
6.21	76.9
5.24	69.4
4.13	65.0
2.62	57.1
1.70	54.0
1.31	50.0
1.20	51.3
.971	49.5
.926	49.5

Such a plot is indeed linear for each of the nucleophiles, with the values for the slopes and y-intercepts summarized in Table 9.

Table 9

Nucleophile	slope	y-intercept
Br^-	526	-
SCN^-	4.67 ± .004	52.8 ± .07
$SC(NH_2)_2$	1.98 ± .003	44.5 ± .10

The slopes of the lines represent the value of $k_{-1}/k_1k_2[SH^+]$, and in the case for bromide ion this was obtained from the slope of k_o against $[Br^-]$. Since k_{-1} and k_1 are necessarily constant at any one acidity for a given nitrosamine, these values may be taken to yield the following ratios:-

$$\frac{k_2(SCN^-)}{k_2(Br^-)} = 113$$

$$\frac{k_2(SC(NH_2)_2)}{k_2(SCN^-)} = 2.4$$

In this form the ratios give an inverse measure of the relative reactivities of the nucleophiles, and these compare quite well with the values of $SCN^-/Br^- = 100$ and $SC(NH_2)_2/SCN^- = 2.5$ obtained by Williams[24,46] from measurements at low nucleophile concentrations. The present value of 113 for SCN^-/Br^- is also in direct comparison with the value of 5.4 for reaction of NDA obtained by Hallett[55], reflecting NMNA's greater discrimination between bromide and thiocyanate ions.

The y-intercept is given by $1/k_1[SH^+]$. Given that the acidity is a known quantity, the calculation of k_1, the bimolecular rate constant for reaction between the proton and the nitrosamine, is therefore possible. The difference in the values of the y-intercepts, and hence in the values for k_1, almost certainly lies in a significant degree of protonation of these nucleophiles at higher concentrations. The nominal acidity, therefore, was corrected in the following way to make allowances.

$$pK_a = -\log K_a$$

$$\text{TOTAL } [\text{Nucleophile}] = \text{Free } [\text{Nucleophile}] + \text{Protonated } [\text{Nucleophile}]$$

$$\text{Protonated } [\text{Nucleophile}] = \frac{\text{TOTAL } [\text{Nucleophile}]}{1 + \frac{Ka}{[H^+]}}$$

$$\text{Corrected } [H_2SO_4] = \text{TOTAL } [H_2SO_4] - \frac{[NaN_3] + \text{Protonated } [\text{Nucleophile}]}{2}$$

The pKa values of thiocyanate[61] and thiourea[62] are -0.701 and -1.19, respectively. Assuming sodium azide is fully protonated, and extrapolating from the point on the graph where k_o reaches a limiting value for the concentrations of thiocyanate and thiourea, the corrected H^+ is, approximately, .560 M for SCN^- and .600 for $SC(NH_2)_2$. The H^+ concentration was interpolated from a graph of H^+M against H_2SO_4 M taken from information reported by Robertson and Dunford,[63]. Thus,

$$k_1(SCN^-) = 3.5 \times 10^{-2} \text{ } \ell \text{ mol}^{-1} \text{ s}^{-1}$$

$$k_1(SC(NH_2)_2) = 3.8 \times 10^{-2} \text{ } \ell \text{ mol}^{-1}\text{s}^{-1}$$

Clearly, the determined value of k_1 is independent of the concentration, as well as the nature of the nucleophile.

From considerations of the basicities of diphenylamine (pK_a = 0.85) and N-methylaniline (pK_a = 4.85), it is anticipated that the magnitudes of k_1 for NMNA should be significantly greater than k_1 for NDA. Unfortunately, the pK_a values of nitrosamines are not known, but it is perhaps expected that they should show the same trend as the corresponding parent amines. In fact, the value for k_1 for NDA as computed by

Hallett is 0.14 ℓ mol^{-1} s^{-1}, a factor of 4 larger than that for NMNA. In ethanol solvent, k_1 was also larger for NDA by a factor of 5[53]. It will be recalled that the increased reactivity $\sim$ 100, measured in the form of the product K k_2, in water solvent was rationalised in terms of enhanced nucleophilic attack due to the greater electron withdrawing character of a phenyl group relative to a methyl group. It now seems that this cannot be the entire explanation.

With this apparent ambiguity in mind, the study was extended to include several N-alkylated N-nitroso-amines.

2.3 Denitrosation of a Series of N-alkyl-N -nitrosoanilines

2.3.1 Introduction

Reactions of several N-alkyl substituents have been examined with the express purpose of investigating the electron-donating effects of the alkyl groups on the rate of protonation. This is achieved by using high concentrations of thiourea and by conducting the reaction in ethanolic solvent. The substituents are listed in Table 10, along with the pK_a values of their respective parent amine taken from Smith[64].

Table 10

N-alkyl substituent (R)	pk_a
Me	4.85
Et	5.11
Pr^n	5.02
Pr^i	5.77

Williams previously studied these same substituted compounds in sulphuric acid containing sodium bromide[16]. The reactions were catalysed by both acid and bromide ion, and at constant concentrations of each the rates of reaction increased as the pK_a of the parent amine increased. A factor of 10 covered the reactivity range. Given the reaction sequence

$$NRNA + H^+ \underset{}{\overset{K}{\rightleftharpoons}} NRNAH^+ + Br^- \xrightarrow{k_2} NRA + NOBr \xrightarrow[\text{trap}]{\text{nitrite}} \text{decomposition products}$$

it is expected by increasing N-alkyl substitution that K should be increased, whilst k_2 may be understood to be affected in the opposite direction. Although k_2 may be affected adversely, it appears from the data that the overriding influence is exerted on K and that this component of k_2K is therefore responsible for the observed range of reactivity. It is predicted, therefore, that this, in turn, should be reflected in the values of k_1.

2.3.2 Reactions using high concentration of thiourea

Results for k_o as a variation of thiourea are recorded in Tables 11-13, and presented graphically in Figure 3. The data for the methyl substituent may be found in the previous section.

Table 11

$[H_2SO_4]$ = .479M, $[NaN_3]$ = 8.40 x 10^{-3}M, [NEtNA] = 3.76 x 10^{-4}M

$10^2[SC(NH_2)_2]$	$10^4 k_o (s^{-1})$
1.64	138
4.93	198
8.22	220
16.4	231
24.7	229
44.1	240
58.8	227
73.5	235

Table 12

$[H_2SO_4]$ = .479 M, [NaN3] = 6.94 x 10^{-2} M, [N-Pr^{i}NA] = 3.34 x 10^{-3} M

$10^2[SC(NH_2)_2]$	$10^4 k_o (s^{-1})$
1.64	209
8.22	254
16.4	247
25.8	274
38.7	260
51.6	278
58.1	282

Table 13

$[H_2SO_4] = .479\ \underline{M}$, $[NaN_3] = 8.40 \times 10^{-3}\ \underline{M}$, $[N\text{-}Pr^n\ NA] = 2.95 \times 10^{-4}\ \underline{M}$

$10^2[SC(NH_2)_2]$	$10^4 k_o (s^{-1})$
1.47	93.4
2.94	110
4.92	128
5.88	129
12.3	140
14.7	145
24.6	178
36.9	177
44.1	144
48.6	145
61.5	146

As for NMNA, the observed rate constant, k_o, for each nitrosamine becomes independent of added thiourea at sufficiently high concentrations, when k_o simplifies to:

$$k_o = k_1[SH^+]$$

For moderate concentrations of thiourea the double reciprocal plots of k_o^{-1} against $[\text{thiourea}]^{-1}$ produced reasonably linear lines, with slope of $k_{-1}/k_1k_2[SH^+]$ and y-intercept of $1/k_1[SH^+]$. The results are summarised in Table 14.

FIGURE 3

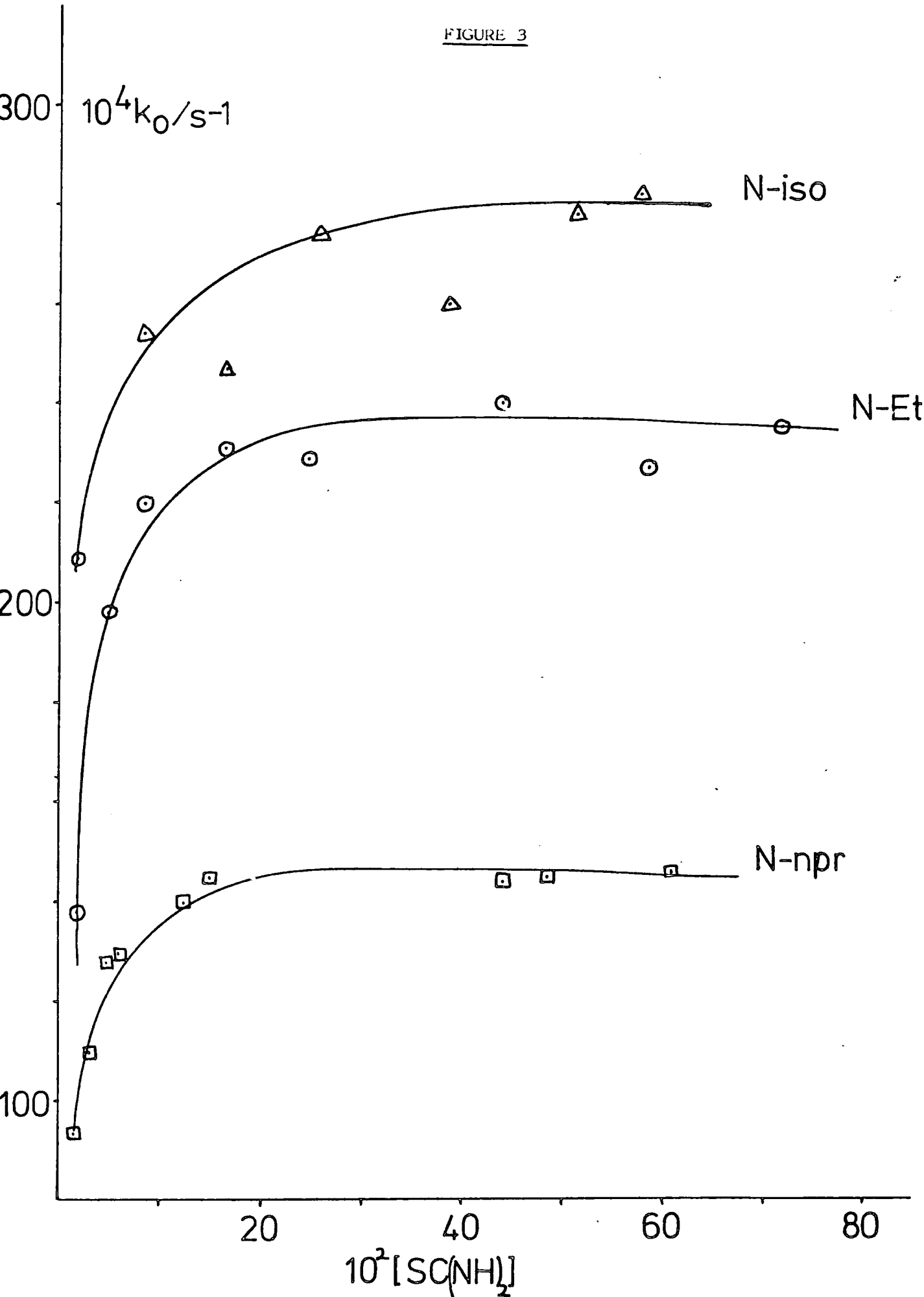


Table 14

N-substituent	slope	y-intercept
Me	1.98 ± .003	44.5 ± .1
Et	.523 ± .018	40.3 ± .5
Pr^n	.626 ± .080	66.1 ± 2.5
Pr^i	.200 ± .016	35.8 ± .4

By maintaining the acidity at a constant concentration, the slopes of the lines may be taken to calculate the relative reactivities of the substituted compounds relative to NMNA in the form of the ratio:

$$\frac{\text{slope (Me)}}{\text{slope (R)}} = \frac{k_2K(R)}{k_2K(Me)}$$

The results tabulated in Table 15 are shown with data obtained by Williams[42] for reaction in 2.15 M H_2SO_4 containing .24 M NaBr. While the trend in reactivity is not exact between the two, the agreement is generally quite good.

Table 15

N-substituent	Rel k $\left(SC(NH_2)_2\right)$	Rel k(Br^-)
Me	1	1
Et	3.8	2.2
Pr^n	3.2	2.4
Pr^i	10	11

Consider the values of the y-intercepts. Correcting the solvent acidity, as before, for the protonation of the high concentrations of thiourea (pK_a = -1.19), and assuming complete protonation of sodium azide, the values for k_1 were computed.

Table 16

N-substituent	10^2 k_1 ℓ $mol^{-1}s^{-1}$
Me	3.81
Et	4.21
Pr^n	2.56
Pr^i	4.75

On first inspection, it is noted that while the values for k_1 are in the expected order, with the exception of the anomalous values of the n-propyl group, the spread of the values is rather small, and certainly does not reflect the overall reactivity evident at moderate thiourea concentrations given in Table 15, contrary to predictions. This suggests that another factor apart from the electronic effects of the alkyl groups is indeed making an important contribution toward the rate of protonation. On further inspection, it is noted that the individual magnitudes of k_1 fall markedly below those expected for a simple single-stage protonation at the amino nitrogen atom. These results will be compared and discussed at greater length with the results in the next section for reactions carried out in ethanol.

2.3.3. Reactions in Ethanol Solvent

Reactions were conducted under strictly first-order conditions in ethanolic HCl, with [Ascorbic Acid] >>> [nitrosamine]. Linear plots for log (a-x) against time were obtained in the determination of each rate

constant. The individual rate constants are listed in Tables 17-20, as a function of added HCl, accompanied by values of H_x, an acidity function for HCl in ethanol given by Braude[65]. Clearly, the reactions are acid catalysed.

Table 17

$[\text{Ascorbic Acid}] = 4.22 \times 10^{-3}\text{M}$, $[\text{NMNA}] = 3.54 \times 10^{-4}\text{M}$

$[HCl]$	$-H_x+1$	$10^4 k_o (s^{-1})$
0	0	0
.214	.711	33.8
.414	1.01	85.9
.615	1.18	157
.813	1.31	222
1.01	1.42	289

Table 18

$[\text{Ascorbic Acid}] = 4.22 \times 10^{-3}\text{M}$, $[\text{NEtNA}] = 2.12 \times 10^{-4}\text{M}$

$[HCl]$	$-H_x+1$	$10^4 k_o (s^{-1})$
0	0	0
.128	.787	12.7
.302	.867	75.2
.597	1.18	191
.901	1.35	339
1.23	1.49	484

Table 19

$[\text{Ascorbic Acid}] = 4.27 \times 10^{-3}\underline{M}$, $[\text{N-Pr}^{n}\text{ NA}] = 2.12 \times 10^{-4}\underline{M}$

$[HCl]/\underline{M}$	$-H_x+1$	$10^4 k_o (s^{-1})$
0	0	0
.107	.403	17.2
.257	.795	45.2
.502	1.09	113
.758	1.28	188
1.01	1.41	286

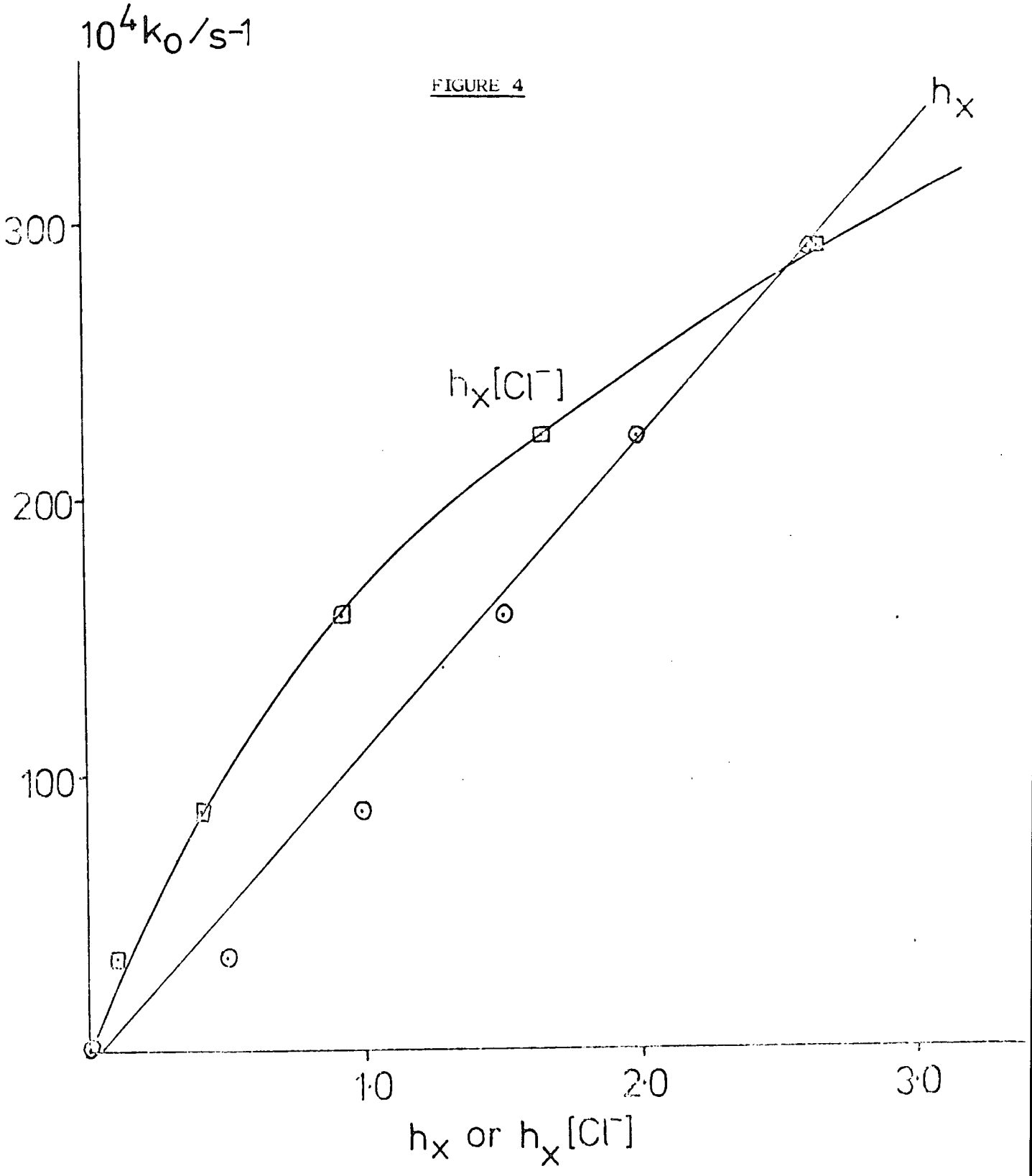
Table 20

$[\text{Ascorbic Acid}] = 4.36 \times 10^{-2}\underline{M}$, $[\text{N-Pr}^{i}\text{ NA}] = 2.28 \times 10^{-3}\underline{M}$

$[HCl]/\underline{M}$	$-H_x+1$	$10^4 k_o (s^{-1})$
0	0	0
.264	.804	105
.533	1.12	240
.754	1.28	376
1.05	1.43	540

A typical graph is given in Figure 4 for NMNA in the form k_o against h_x and $h_x[Cl^-]$, respectively. The first point of interest is observed from the graphical data in that the effect of changing solvents from water to ethanol is undoubtedly to make the protonation the rate-determining stage, as a plot of k_o against $h_x[Cl^-]$ is significantly curved, whereas the plot of k_o against h_x is linear over the entire acid range. Under these circumstances, for all concentrations of

FIGURE 4



chloride ion, $k_2[Y^-] >>> k_{-1}$, and the rate expression for k_o is aptly described by

$$k_o = k_1 h_x$$

Thus, for each N-substituted nitrosamine the slope of the line for each plot of k_o against h_x represents the actual value of k_1. Calculation of the slopes, via a least squares treatment, are summarised in Table 21.

Table 21

N-substituent	$10^2 k_1$ (ℓ $mol^{-1} s^{-1}$)
Me	1.14 ± .06
Et	1.62 ± .08
Pr^i	1.11 ± .06
Pr^n	2.03 ± .07

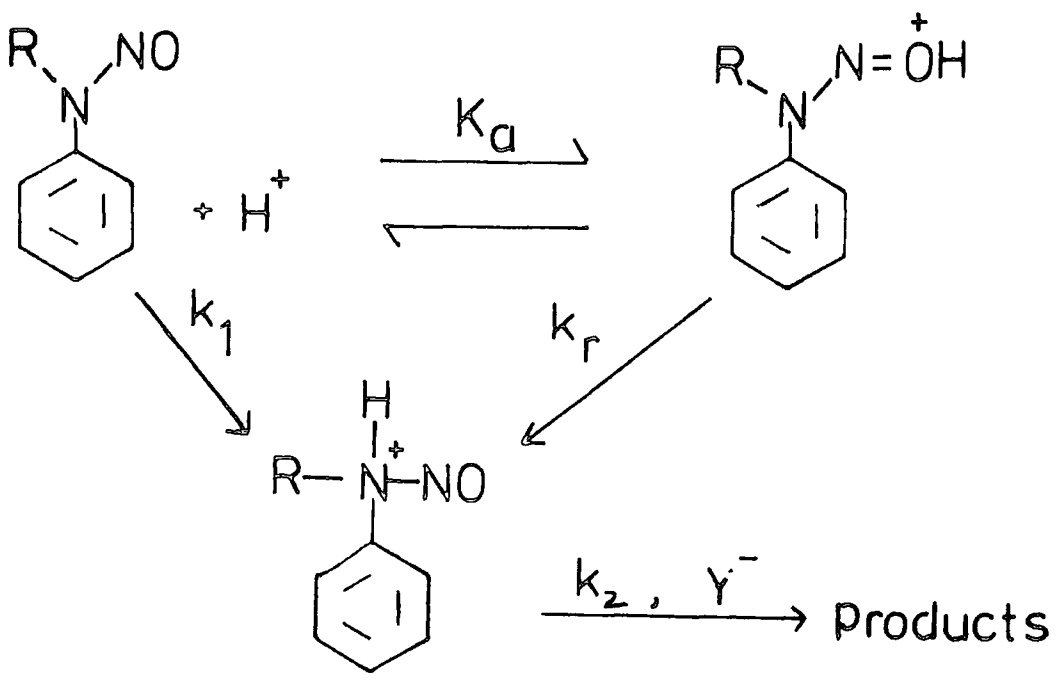
As for reactions subject to high concentrations of thiourea, the range in the k_1 values is extremely small, and the individual magnitudes of k_1, too, lie far below those expected for a single-stage protonation. Unquestionably, the above results are indicative of a more complex stage of protonation. Indeed the great similarity in the established trend of reactivity for k_1 between reactions in ethanol and in aqueous media containing high concentration of thiourea shown in Table 22 represents the most outstanding feature of the study, for it lends evidence to the conclusion that the rate-determining step of the protonation is at least common to both experimental systems.

Table 22

N-substituent	k_1(high thiourea)	k_1(EtOH)
Me	1.0	1.0
Et	1.1	1.4
Pr^n	.7	1.0
Pr^i	1.3	1.8

Moreover, the plots in Figure 5 for log k_o against $-H_x$ are all approximately parallel, indicating that each of the N-alkyl-N-nitrosoanilines responds in precisely the same way toward the step of protonation.

One plausible mechanistic alternative to the simple one-stage protonation at the amine nitrogen atom is a two-step protonation, of the type outlined below.



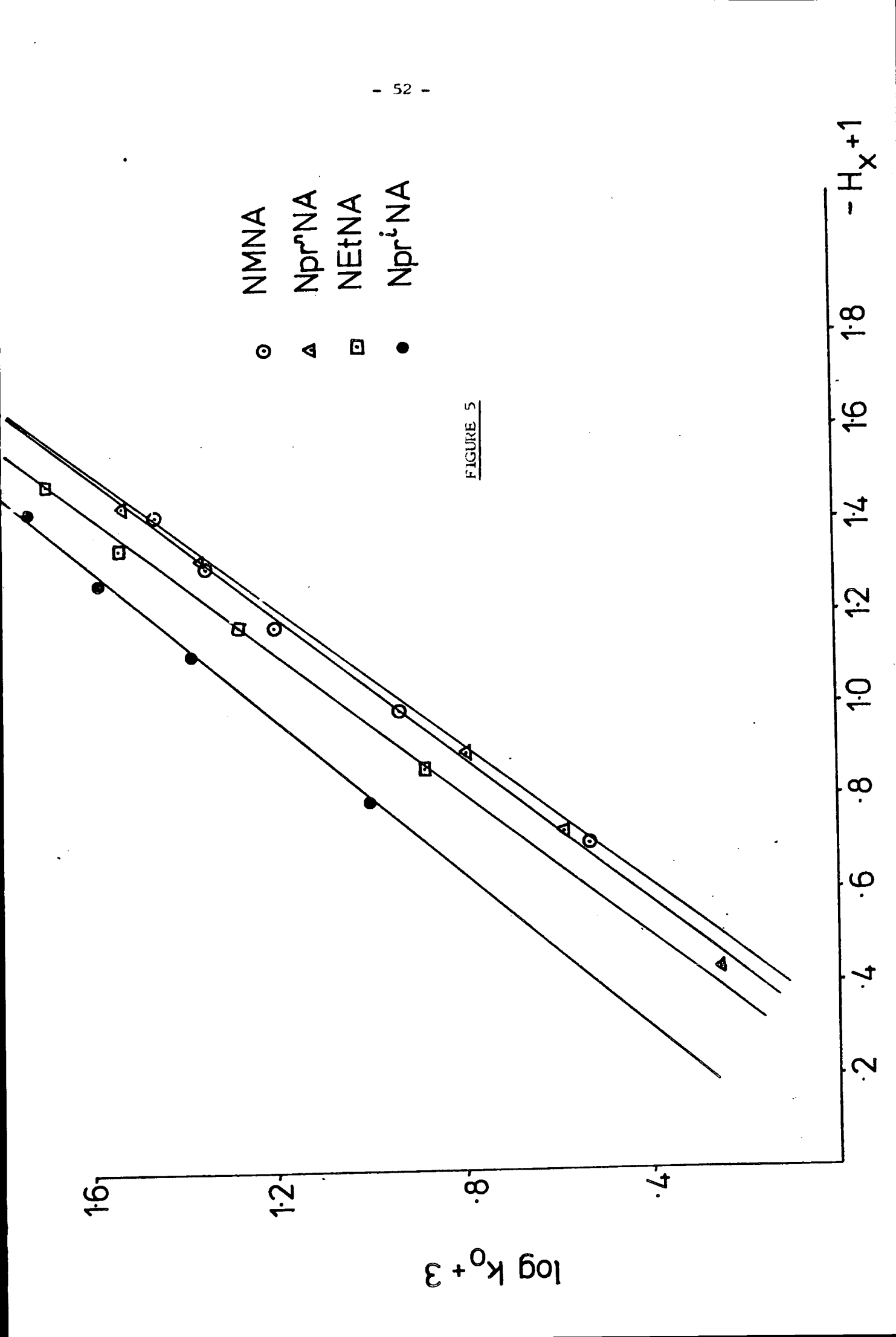
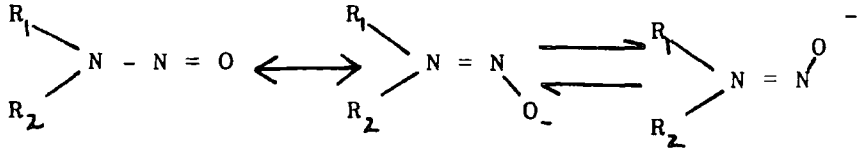

NMNA
NprⁿNA
NEtNA
NprⁱNA
log k_o + 3
1·6
1·2
·8
·4
·2
·4
·6
·8
1·0
1·2
1·4
1·6
1·8
- H_x +1

FIGURE 5

Here a fast, initial protonation occurs at the oxygen atom of the nitroso group, followed by a slower, hence rate-determining, rearrangement to the amine nitrogen centre. The rate-controlling step is now represented by k_r, and the values of k_1 more accurately describe a composite rate constant, incorporating the product $K_a k_r$. Certainly, this offers a reasonable rationale for the small magnitudes of the experimentally-derived values of k_1. Challis and Osborne[28] first proposed such a scheme in an attempt to explain neglible solvent isotope effects at high halide ion concentrations for the indirect transfer of the nitroso group from NDA to sodium azide.

Protonation of the nitroso-oxygen is fully consistent with the well known dipolar character of N-nitrosamines, firmly established by the work of Phillips[66] and Karabatsos[67].



I II

These two isomes, I and II, have been isolated by TLC at low temperatures [68,73] and by HPLC[69], and evidence that the dipolar form makes a significant contribution to the structure of N-nitrosamines is presented by X-ray crystallography[70] and electron diffraction studies[71].

Kuhn and McIntyre[72] offer evidence from nmr investigations of N,N-dialkylnitrosamines in solutions of fluorosulphuric acid that only one proton is captured by the nitrosamine and that the site of protonation is the oxygen atom of the nitroso group rather than the nitrogen centre.

However, other protonation studies by Jaffé and his co-workers[26] led them to conclude that there are at least four spectroscopically distinguishable protonated species present in aqueous sulphuric acid solutions, with the proportions of each dependent upon the concentration of acid, although their precise structures were not given. In non-polar solvents they also observed the existance of two protonated nitrosamines, both of which are a result of hydrogen bonding with the undissociated acid, first at the O-site of the nitroso group and then at the O-site and the nitrogen centre, simultaneously[74].

It must be stated, therefore, that while the above proposal for a two-stage protonation satisfactorily accounts for the present experimental observations, it may not necessarily be applicable to other experimental conditions. In particular, it may well be, for example, that the site of protonation is highly dependent upon the solvent acidity, with O-site protonation predominating at lower acidities and direct protonation at the amine nitrogen becoming important at higher acidities.

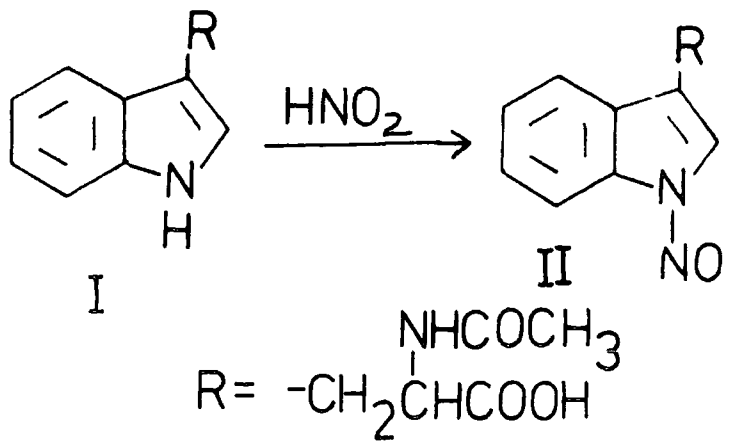
In the lack of further experinental evidence, no definite conclusions concerning the site of protonation may be reached. However, whatever the complexity of the protonation of N-nitrosamines, and irrespective of whether or not initial protonation occurs at the oxygen atom of the nitroso group, it is currently held that the active protonated species leading to denitrosation is the N-protonated form.

CHAPTER 3

Denitrosation of D,L-N-Acetyl-N-Nitrosotryptophan

3.1 Introduction

Tryptophan (I), R = $-CH_2CH(NH_2)CO_2H$ is one of the many essential naturally occurring amino acids found in a variety of foods, and is known to be a precursor of serotonin, a regulator of gastric juice secretion[76].



To avoid complication due to possible attack in the side chain R, leading to deamination, the N-acetyl derivative was used throughout the study. The nitrosation of D,L-N-acetyltryptophan (I) (NAT) yields the N-nitroso derivative II (NANT), where substitution takes place at the ring indole nitrogen atom[77]. The methyl ester of I behaves similarly. These nitrosamines which are model compounds for nitrosation studies of peptides and proteins have been shown[78] to be mutagenic, suggesting that nitrosation of side chains of α-amino acids may be important in the aetialogy of cancer of the gastrointestinal tract. In contrast to nitrosamines generally[79], the nitroso-tryptophan derivatives do not require external metabolic activation such as enzymatic hydroxylation before becoming biologically active. It seems important and relevant to the possibilities of nitrosamine - induced carcinogenesis in humans to examine nitroso-tryptophan derivatives as potential nitrosating agents. Such a kinetic analysis is presented and discussed in this chapter for the denitrosation of NANT.

There are two distinct classes of nitroso-compounds[80], the N-nitrosamines and the N-nitrosoamides. The latter are N-nitrosoamines where one of the substituents is an acyl group; because the same characteristics are found when one of the substituents is a sulfonyl group, these compounds may also be considered to fall within the category of nitrosoamides. The overall mechanism for N-nitrosamines was discussed in considerable detail in the introduction, and some finer mechanistic features were discussed in chapter 2. Generally, for reaction in aqueous media the denitrosation of nitrosamines are characterised by acid and nucleophile catalysis, with a solvent isotope effect $^{k}H_2O/k_{D_2O}$ of 0.3 arguing in favour of a rate-determining attack by a nucleophile on the protonated form or the nitrosamine.

N-nitrosoamides, however, all undergo denitrosation with acid catalysis but without any kinetic dependence upon the concentration or nature of the nucleophile. Further, all show kinetic solvent isotope effects within the range 1.5 - 1.9[81]. This pattern of behaviour has also been accomplished for nitrosamines, as shown for NMNA in the previous chapter, by reaction at high concentrations of a sufficiently reactive nucleophile and for reaction in ethanol solvent.

Interestingly, the denitrosation of NANT(II) follow the pattern set by nitrosamines at very low acidities, while behaving as a nitrosamide at the higher acidities. The present study of NANT was carried out over a range of acidity and in the presence of various nucleophiles. The first-order rate constant, k_o, is defined by:-

$$\frac{-d[\text{NANT}]}{dt} = k_o[\text{NANT}]$$

and in practice good first-order behaviour in NANT was always observed,

as verified by the linearity of the log (a-x) versus time plots for each kinetic experiment.

3.2 Reactions in Sulphuric Acid

3.2.1 The Effect of a Nitrite Trap

The variation of k_o with added sodium azide, at the constant acidity of 3.96×10^{-2} M H_2SO_4, is given in Table 23. In this concentration range and under these experimental conditions it is known that sodium azide is an excellent trap for free nitrous acid[36]

Table 23

$10^3[NaN_3]$	$10^4 k_o (s^{-1})$
0	32.4
3.38	29.2
6.75	30.9
13.5	30.1

It is clear that k_o is independent of the sodium azide concentration, demonstrating that under these conditions the rate of the reverse reaction, N-nitrosation of NAT, is insignificantly small compared with that of denitrosation. This conclusion is also borne out by the failure of added NAT to reduce the observed values of k_o, as discussed in section 3.2.4. Under these circumstances, the presence of a nitrous acid trap should have no effect on the rate of denitrosation. In contrast, the rates of reaction for NMNA[36] and NDA[30] showed a marked dependency upon the sodium azide concentration, until a sufficient concentration was reached at which the reaction became irreversible and independent of additional increases in concentration.

A similar trap dependency, however, was found in the case of the nitrosoamides. For example, Williams[59] found the rate of denitrosation for N-methyl-N-nitroso-p-sulphonamide to be independent of sulphamic acid, and Challis and his co-workers too found the rates of reaction for N-n-butyl-N-nitrosoacetamide[57] and N-nitroso-2-pyrrolidone[58] to be independent of the concentration of nitrous acid trap, in their case sulphanilamide.

Apart from a neglibly slow rate for the reverse reaction, a second reason for the independence from the nitrite trap concentration may be due to a competing pathway to denitrosation which does not involve the release of kinetically free nitrous acid. This situation is observed for the decomposition of the two nitrosoamides studied by Challis and co-workers, where denitrosation is accompanied and sometimes dominated by the concurrent pathway of deamination.

To investigate the possibility of an alternative, competing pathway for the denitrosation of NANT, a typical run was carried out in the presence of an excess of p-chloraniline to determine the total release of nitrous acid. After ten half lives, an aliquot containing the resultant diazo compound, produced by the reaction between p-chloroaniline and the free nitrosating agent, NOY, was removed and coupled with an excess concentration of 2-Napthol-3,6-di sulphonic acid in borax. The resulting absorbance from the red azo dye was measured at 500 nm ($\log \varepsilon = 4.34$). Based upon the initial concentration of NANT, the yield of nitrous acid was 101%. Moreover, the rate constant, k_o, for this particular reaction containing 3.96×10^{-2} M H_2SO_4 was $31.1 \times 10^{-4} s^{-1}$, in excellent agreement with the data in Table 23.

Thus, the denitrosation of NANT is entirely quantitative under these conditions, ruling out any kinetic complications due to an alternative reaction pathway and confirming the irreversibility of the reaction. In this respect, NANT resembles MNTS[59], which also gave quantitative release of nitrous acid in acid solution.

3.2.2 Variation of k_o with [Nucleophile]

A number of kinetic runs containing various nucleophiles in varying concentrations were carried out to determine the exact role of the nucleophile in the denitrosation of NANT. Since the reaction was formally shown to be independent of the nitrite trap concentration, the present reactions were conducted in the absence of such species, although it was added to some runs as a check. The results are tabulated in Table 24 for reaction at 3.96×10^{-2} M H_2SO_4.

Table 24

[Nucleophile]	$10^4 k_o (s^{-1})$
0	32.4
4.15×10^{-3} M KBr	32.1
20.7 " " "	31.8
41.5 " " "	30.9
8.0×10^{-3} M KSCN	34.6
16.0 " " "	32.9
24.0 " " "	33.7
9.38×10^{-3} M $SC(NH_2)_2$	33.3 *
18.8 " " "	33.2

* containing 1.69×10^{-2} M NaN_3

Clearly, the addition of the nucleophiles produced no catalytic effect on the rate of reaction, in comparison with NMNA and NDA where similar concentrations produced substantial increases in k_o. For example, the addition of 9.5×10^{-4} KSCN increased the rate of reaction for NMNA[24] by a factor of 96, and for the more reactive NDA[82] the addition of 3.8×10^{-3} M KSCN increased the rate 9 fold.

Another important mechanistic observation, therefore, is that the nucleophile plays no direct role in determining the rate of reaction. In conjunction with the previous section, this means that neither the attack by the nitrous acid on the nitrite trap nor the release of nitrous acid from the conjugate acid complex is kinetically significant. Instead, an earlier step in the reaction pathway must now be rate-determining, namely the protonation. In this way, the denitrosation of NANT behaves generally as a nitrosoamide, where the absence of nucleophilic catalysis has been well documented for several compounds[81].

With reference to the scheme below, this different behaviour for nitrosoamides is explained as follows. It was shown in the last chapter for nitrosamines that the presence or absence of nucleophilic catalysis is governed by the inequalities $k_{-1} >>> k_2[Y^-]$ and $k_{-1} <<< k_2[Y^-]$

$$R_1R_2NNO + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_1R_2\overset{+}{N}HNO + Y^- \xrightarrow{k_2} R_1R_2NH + NOY$$

It appears for nitrosamines generally in aqueous acidic solvent at low nucleophile concentrations that the former inequality applies,

leading to a first-order dependence upon $[Y^-]$; whereas for nitrosoamides the zero-order dependency upon $[Y^-]$ is rationalised in terms of the powerfully electron-withdrawing substituents $>C = O$ and $-SO_2-$, both of which serve to increase markedly the value for k_2, such that the latter inequality applies for all concentrations of $[Y^-]$. Independence from $[Y^-]$ for nitrosamines is also accomplished by working in the less polar solvent ethanol and by working at high concentrations of powerful nucleophiles, such as SCN^- or $SC(NH_2)_2$ thus increasing $k_2[Y^-]$ relative to k_{-1}. This explanation is consistent with the dependence of k_o upon $[Y^-]$ or otherwise, and also with the simultaneous change in the kinetic solvant isotope effects.

However, since the attack by the nucleophile is post-limiting, the kinetic analysis does not altogether rule out a unimolecular loss of NO^+ from the protonated form of the nitrosoamide. It could well be, for example, that the N-N bond is considerably weakened by the electron-withdrawing substituent to such an extent that there is extensive bond breaking in the transition state, so that it resembles more of the final state and no nucleophilic catalysis therefore is observed.

Direct evidence for the existence of a rate-limiting proton transfer from the solvent to NANT comes from the solvent deuterium isotope effects. The experimental details are drawn up in Table 25, and are also represented graphically in Figure 6 along with reactions in H_2SO_4 - H_2O.

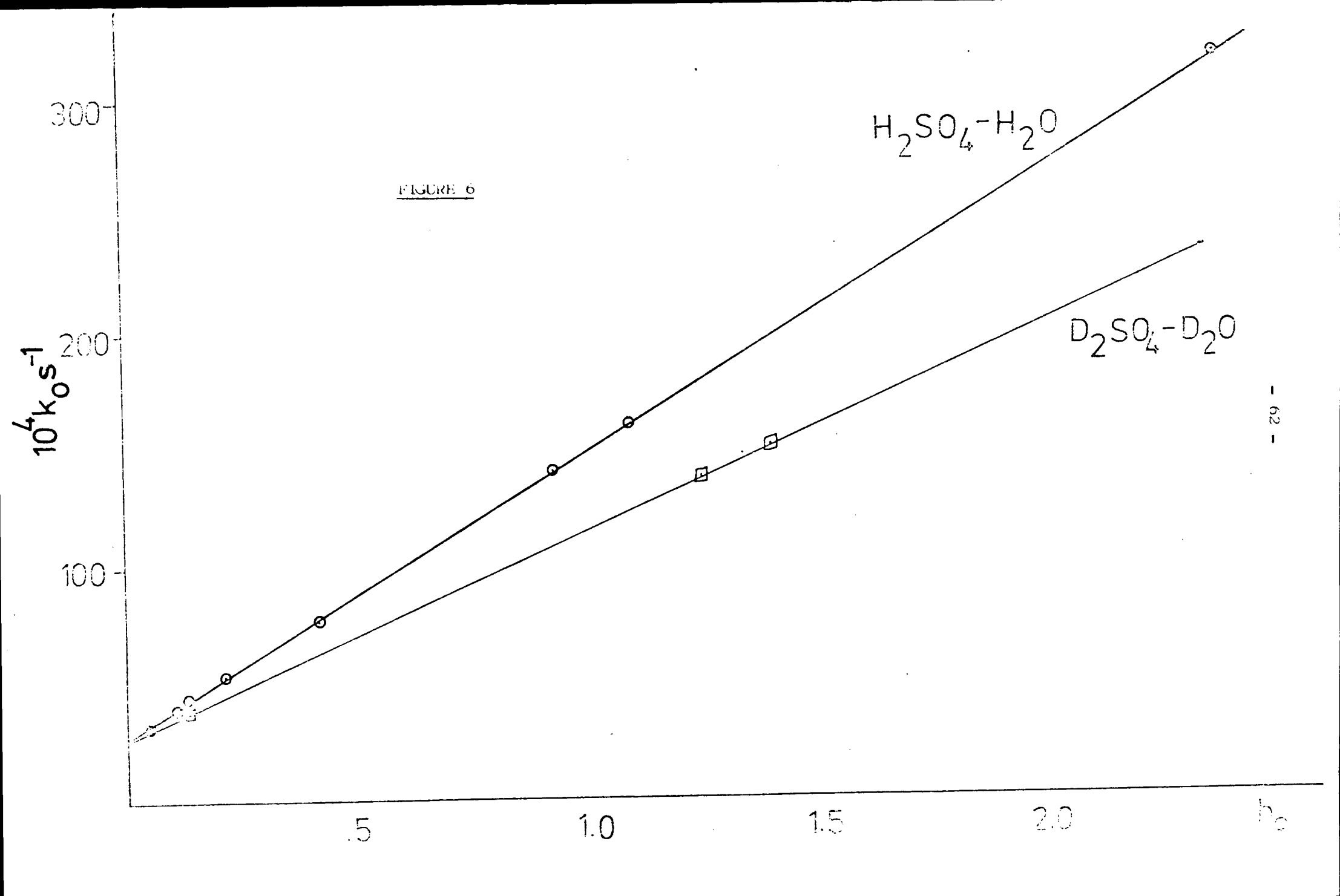


FIGURE 6

Table 25

$[D_2SO_4]$	$10^4 k_o(s^{-1})$
.105	39.8
.769	138
.827	151

From the slopes of the two individual plots in Figure 6, the isotope effect $^{k}H_2O/^{k}D_2O$ is 1.3, in full support of a rate-controlling proton transfer and arguing against a fast pre-equilibrium formation of the conjugate acid complex of NANT, as is the case for other nitrosamines at low nucleophile concentrations. This isotope effect is perhaps smaller than that expected, but it does agree reasonably well with other reactions believed to undergo a rate-limiting proton transfer, such as 1.5 for MNTS[59], 1.6 for NMNA at high thiourea concentrations, and 1.9 for N-nitroso-2-pyrrolidone[58].

It is known, with the exception of one or two cases[83,84] that proton transfer to both oxygen and nitrogen bases is typically fast, often occurring at the diffusion-controlled limit[85]. The slow proton transfer for nitrosoamides is thought to be reflected in the extremely low bascisity of these compounds. For example, consider the nitrosoamide MNTS. Benzene sulphonamide itself has a pK_a[86] value of approximately -7, and the nitroso group is expected to reduce this value by several units. Thus, the amino nitrogen atom is very weakly basic, and the rate of protonation is expected to lie considerably below the diffusion-controlled limit. It is worth bearing in mind, however, the proposal presented in the

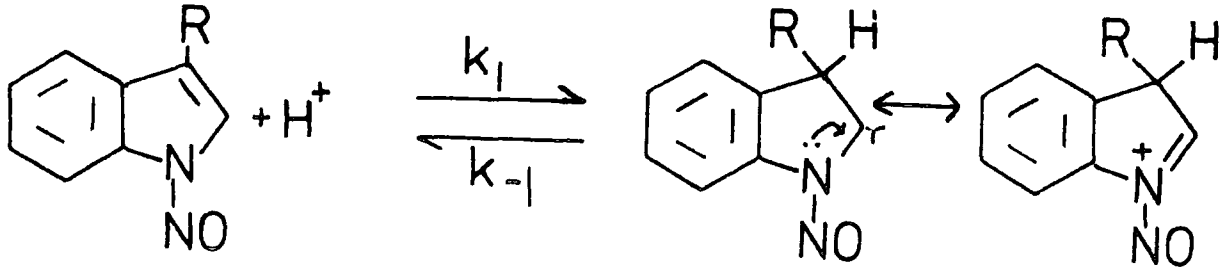
previous chapter for nitrosamines for a two-stage protonation, as the N-protonated form of the nitrosoamide may arise by a similar type of O $\longrightarrow$ N rearrangement.

Clearly, as for nitrosoamides, the structure of NANT is such as to predispose it toward a rate-limiting proton transfer from the solvent. Unlike nitrosamines and nitrosoamides, where the active protonated form leading to denitrosation is the N-protonated one, a more likely site for protonation at these acidites in case of the tryptophan derivative is in fact at the C-3 position of the indole ring. Furthermore, this single feature is held to be responsible for the nitrosoamide-like character of NANT under these experimental conditions.

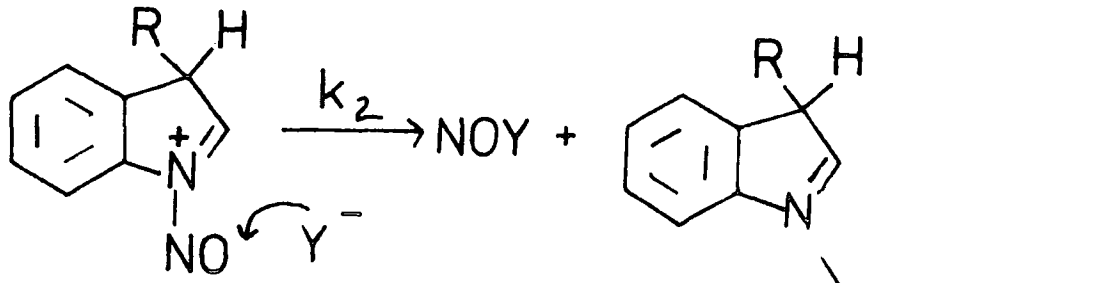
Evidence for protonation at the C-3 position comes from UV and NMR spectroscopic studies of indoles in strong acidic solutions, in which the principal conjugate acid is shown to be the C-3 protonated isomer, even with a substituent at C-3[87,88]. Moreover, bascisity studies of a number of indoles led Hinman and Lang to conclude that the UV spectra of a number of partially protonated indoles are compatible with just two species, the free base form and the C-3 conjugate acid, and that no significant protonation at the nitrogen atom occurs[89]. This is consistent with the basic structure of indoles[90], where the unshared pair of electrons on the nitrogen atom are extensively delocalised to the carbon atoms of the ring, particularly to C-3. Indeed this simple characteristic correctly predicts some of the most fundamental chemical properties of the indole ring.

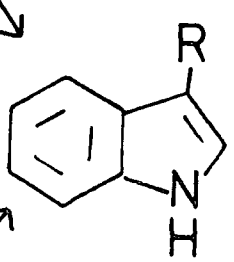
With the foregoing remarks in mind, the scheme below outlines two of the possible mechanistic alternatives in which the release

of NO^+ from the conjugate acid of NANT occurs either (a) by nucleophilic assistance or (b) by a unimolecular process. In alternative (a) it is understood that the water molecule acts as the effective nucleophile, Y^-, in the absence of any added nucleophile.

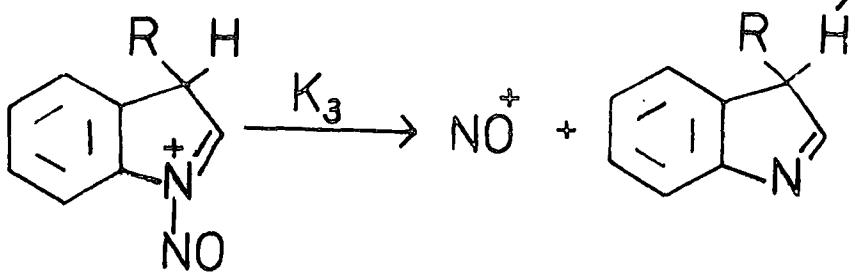


(a)





(b)



Assuming an h_o acidity dependence, alternative (a) leads to an expression for k_o given by:-

$$k_o = \frac{k_1 k_2 h_o [Y^-]}{k_{-1} + k_2 [Y^-]}$$

which accounts for the zero-order behaviour in $[Y^-]$ only if $k_2[Y^-] >>> k_{-1}$ when k_o reduces to

$$k_o = k_1 h_o$$

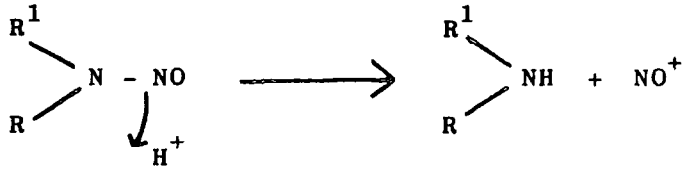
the form observed experimentally.

Alternative (b) accommodates the experimental observations without the necessary imposition of a limiting condition, as k_o is described by:-

$$k_o = \frac{k_1 k_3 h_o}{k_{-1} + k_3}$$

Thus, since the same kinetic relationship is established for both mechanisms, namely a first-order dependence upon h_o and indedendence upon $[Y^-]$, it is not possible to make a firm conclusion as to which is operational under these experimental conditions. On the other hand, since there is no compelling evidence to suggest why nucleophilic participation by Y^- might not be necessary in this, and other, situations alternative (a) is the preferred scheme.

The kientic evidence here is also in accord with a one step mechanism given by:



in which NO^+ is expelled simultaneously with H^+ attack. It would, however, be difficult to explain a change even to this mechanism for nitrosamines at high concentrations of thiocyanate and thiourea, where the same experimental characteristics are found as for nitrosoamides and here now for NANT. In that case, it seems clear that the rate-limiting step must change to an earlier one as a result of an increase in $[Y^-]$. This effect should be more pronounced for the most powerful nucleophiles, as shown in chapter 2 for NMNA.

3.2.3 The Variation of k_o with $[H_2SO_4]$

To confirm the presence of acid catalysis, reactions were carried out over a range of sulphuric acid concentrations, given in Table 26. The corresponding h_o values were interpreted from data given by Robertson and Dunford[63].

Table 26

$10^2[H_2SO_4]/M$	h_o	$10^4 k_o (s^{-1})$
3.96	.051	32.4
7.92	.109	40.4
9.90	.137	44.3
15.8	.218	54.1
29.7	.418	76.7
59.4	.927	141
69.3	1.10	160 *
119	2.37	315

*containing 7.43×10^{-2} M NaN_3

A graph of k_o against $[H^+]$ deviated significantly from linearity at the higher acidities, and therefore use of the h_o acidity function was made. The graph of k_o against h_o is given in Figure 6.

Clearly, the reactions are acid catalysed, and the graph further denotes a first-order dependency upon h_o. Under these circumstances, the experimentally-derived first-order rate constant k_o is defined by:-

$$k_o = k_1 h_o$$

From the slope of the graph for k_o versus h_o the value for k_1 is 0.012 $\ell\ mol^{-1}s^{-1}$, which compares with 0.035 $\ell\ mol^{-1}s^{-1}$ for NMNA and 0.059 $\ell\ mol^{-1}s^{-1}$ for MNTS[59].

There is a small but significant intercept to the k_o versus acidity plot indicating that the reaction has an uncatalysed, spontaneous pathway in addition to the acid-catalysed route.

3.2.4 The Variation of k_o with NAT

The overall reversibility of the denitrosation of NANT was investigated further by noting the variation in k_o as a function of added excess parent amine, NAT. The results of the experiments are recorded in Tables 27 and 28 for reaciton in 3.96×10^{-2} M and .297 M H_2SO_4, respectively.

Table 27

$10^3[NAT]$	$10^4 k_o (s^{-1})$
0	31.4
1.67	38.2
3.33	40.1
6.67	41.3

Table 28

$10^3[NAT]$	$10^4 k_o (s^{-1})$
0	78.5
1.73	89.4
3.45	91.4
6.90	99.7
11.7	99.7

It is apparent that k_o is not decreased by the addition of NAT. In fact, at each acidity there is a small but undoubtedly real increase in the values of k_o. This may be attributed to the effect of NAT on the acidity of the medium, or possibly NAT itself is acting as a general acid here, though the effect does seem perhaps a little large for this.

The one certain conclusion, however, concerning the data is that the reaction is eesentially irreversible under the stated experimental conditions. An analogous situation exists for the denitrosation of MNTS[59], where the addition of similar concentrations of parent amine also produced no observed change in the value of the rate constants.

Thus, the denitrosation of NANT closely parallels the denitrosation of MNTS, in that both were found to be independent of the concentrations of added nitrite trap, nucleophile, and, as demonstrated here, parent amine.

3.2.5 The Effect of Methanol on the Rate Constant

The effect of change of solvent on NANT denitrosation was examined briefly using a series of methanol-water solvent mixtures, for two specific reasons. First, a small quantity of methanol (<5%), necessary for the solution of NANT, was present in all the experiments; and secondly, because of the insolubility of NAT in water the stock solution contained 15%

methanol, with the result that the percent composition over the range of NAT concentrations in the kinetic runs varied from 5 - 10% methanol.

The results in Table 29 indicate that there is a small decrease in k_o as the methanol component of the solvent is increased. Whilst contrasting with the typical behaviour of nitrosamines at low nucleophile concentrations where a large increase in the rate of reaction occurs as the polarity of the solvent is lowered[53], the results here are similar to those for MNTS in ethanol solvent[53].

Table 29

% MeOH	$10^4 k_o (s^{-1})$
5	31.4
14	30.5
24	23.6
43	19.8
62	12.8

Thus, there are now three experimental criteria which distinguish between the two limiting forms of the mechanism of denitrosation. These are summarised in Table 30. Features in the left-hand column are generally shown by nitrosamines, while those in the right-hand column are typical of nitrosoamides, nitrosamines at very high $[Y^-]$, nitrosamines in ethanol solvent, and in the present case NANT. Again, the explanation as to why NANT should follow the pattern set by nitrosamides rather than the nitrosamines is thought to be a direct result of C-3 protonation, such that the inequality $k_{-1} <<< k_2[Y^-]$ is favoured.

Table 30

	Rate-limiting Y^- attack, $k_{-1} >>> k_2[Y^-]$	Earlier Rate-limiting step, $k_2[Y^-] >>> k_{-1}$
1.	Nucleophilic catalysis	NO nucleophilic catalysis
2.	$k_{H_2O}/k_{D_2O} \sim 0.3$	k_{H_2O}/k_{D_2O} 1.3 - 1.9
3.	Large rate increase with decreasing solvent polarity	Small rate decrease with decreasing solvent polarity

3.3 Denitrosation of NANT in McIlvaine's Citric Acid-Phosphate Buffer

3.3.1 Introduction

The examination of the kinetics of the denitrosation of NANT was undertaken at much lower acidities, over the pH range 2-6 in a citric acid-phosphate buffer solution[93], since these conditions are somewhat closer to the *in vivo* situation than are the higher sulphuric acid concentrations. Denitrosation again occurred readily and irreversibly as shown by the complete disappearance of the absorbance at 335 nm due to NANT, and the excellent first-order kinetic behaviour over greater than two half-lives. The pH of each kinetic run was measured on a pH meter, after first standardising with known buffer strengths of pH 4.0 and pH 9.0. The results for k_o as a variation of added nucleophiles and of pH are presented and discussed below.

3.3.2 Reactions at pH6

As at higher acidity, the reactions are acid catalysed, as demonstrated by the data in Table 31 for k_o as a variation of pH.

Table 31

pH	$10^4 k_o (s^{-1})$
2.41	28.0
3.12	27.7
3.96	23.3
4.93	17.1
5.45	12.1
5.88	7.38
6.15	5.88
6.82	2.16

The situation regarding nucleophilic catalysis, however, is surprisingly quite different at pH6, compared with the previous results for reaction at 3.96×10^{-2} M H_2SO_4 (pH $\sim$ 1) in that very definite catalysis is observed. The results are listed in Tables 32-36 for k_o as a function of added Cl^-, Br^-, SCN^-, I^- and N_3^-.

Table 32

$10^2 [KCl]/M$	$10^4 k_o (s^{-1})$
0	5.88
3.79	6.36
7.59	6.76
15.2	7.63
22.7	8.24

Table 33

10^2 [KBr]/M	$10^4 k_o (s^{-1})$
0	5.88
1.58	9.66
3.17	11.5
6.33	14.0
11.0	15.2
21.9	17.3
32.9	18.0

Table 34

10^3 [KSCN]	$10^4 k_o (s^{-1})$
0	5.88
2.15	8.80
5.82	11.8
8.60	12.5
11.6	14.0
23.3	16.4
34.9	17.5
52.4	18.4

Table 35

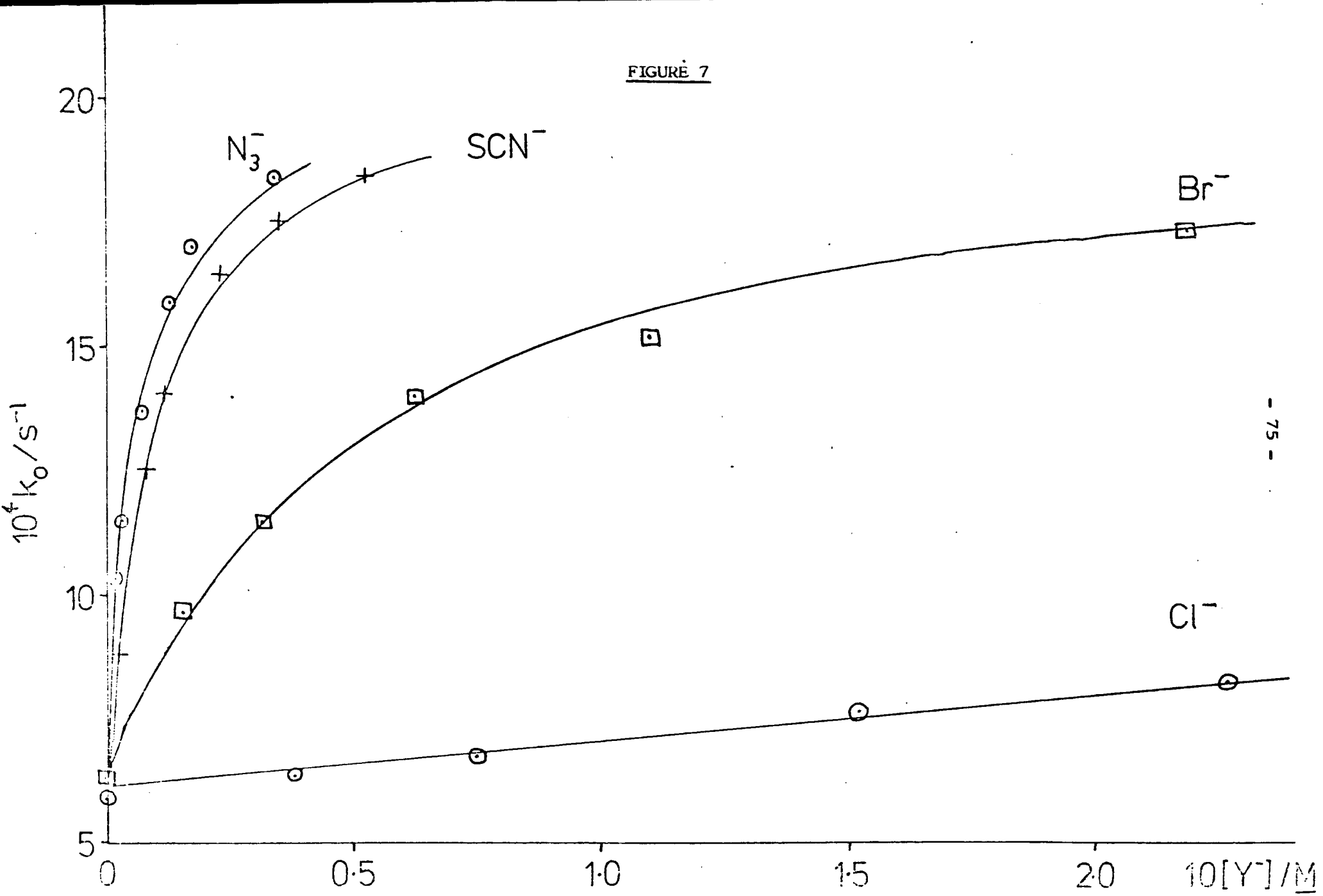
10^4 [KI]	$10^4 k_o (s^{-1})$
0	5.88
9.73	8.60
19.6	9.92
38.9	12.1
58.4	12.7
63.2	13.6
126	15.7
190	17.0
253	17.6

Table 36

10^3 [NaN_3]	$10^4 k_o (s^{-1})$
0	5.88
3.50	11.5
7.59	13.7
13.0	15.9
17.4	17.0
34.4	18.4
43.8	18.0

These results are shown graphically in Figure 7 for all nucleophiles except I^-, where the graph is very close to that of N_3^-. For chloride ion, over the concentration range studied, k_o is linearly

FIGURE 7



dependent upon $[Cl^-]$, but for the more powerful nucleophiles the first-order dependence is soon lost with increasing concentrations, as k_o tends toward the limiting value for each nucleophile of $19.0 \times 10^{-4} s^{-1}$. This lies in direct contrast with the results obtained at 3.96×10^{-2} M H_2SO_4, where there is no indication of any nucleophilic catalysis.

From Figure 7 it is apparent that order of reactivity is as expected, with $Cl^- < Br^- < SCN^- < I^- \sim N_3^-$. This is the first time that nucleophilic attack by the azide ion has been detected in denitrosation reactions. In other situations[30,36], the work was conducted at much higher acidities where the azide ion exists almost completley in its protonated form HN_3, and in this capacity acts as an efficient nitrous acid trap, not reacting directly with the conjugate acid of the nitrosamine. At pH6, however, this is not the case, with the predominate species now being the free form of azide, N_3^-. For example, using the K_a value of 2.0×10^{-5} given by Smith[94] and the equation

$$[N_3^-] = \frac{\text{Total } [\text{azide}]}{1 + \frac{[H^+]}{K_a}}$$

to determine the concentration of free azide, it is calculated for the total concentration of 4.38×10^{-2} M that $[N_3^-]$ is 4.17×10^{-2} M. Thus, the azide ion appears to have reactivity comparable with that of iodide ion toward NANT.

Because the individual plots of k_o against $[Y^-]$ are curved, the rate equation for all nucleophiles but chloride ion for k_o is that of the general form:-

$$k_o = \frac{k_1 k_2 [Y^-][H^+]}{k_{-1} + k_2 [Y^-]}$$

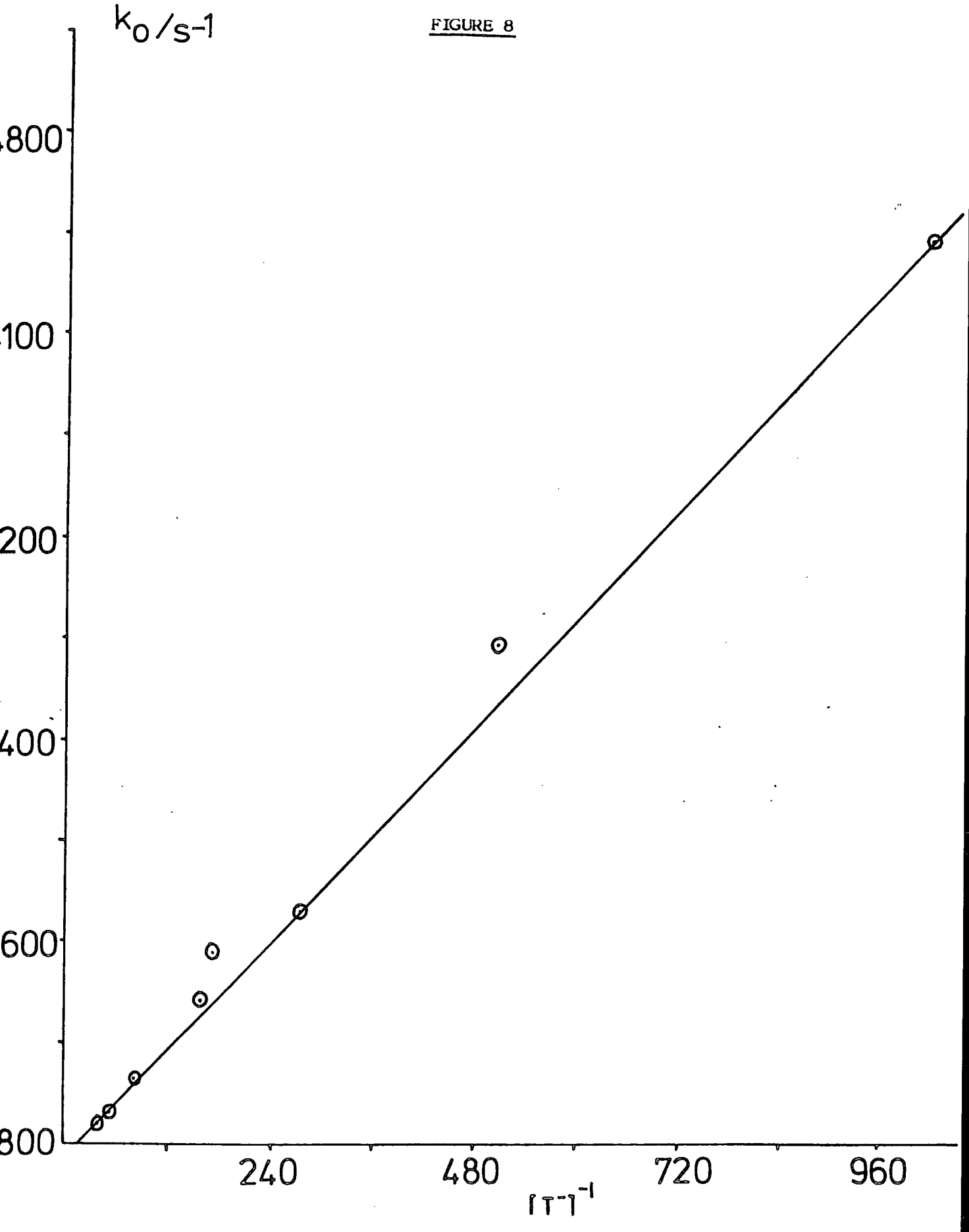
since neither of the limiting conditions are now applicable. For chloride ion, $k_{-1} >>> k_2[Y^-]$ leading to a first order dependence upon $[Cl^-]$. As described in section 2.3.3. the simple algebraic manipulation of this equation leads to an expression which predicts a linear correlation for the graph of $1/k_o$ against $[1/Y^-]$. In the present case, the values of k_o from Tables 32-36 were corrected to allow for the uncatalysed component of the reaction, since it represents a significant contribution toward k_o, so that the reciprocal values of k_o are those of the catalysed component only. The pH of the solutions over the range of concentration of each nucleophile drifted slightly from 6.11 to 6.01, and the average value of 6.06 was taken to interpolate the value of the uncatalysed reaction from a graph of k_o against pH. This was determined to be $6.30 \times 10^{-4} s^{-1}$.

A representative graph is shown in Figure 8 for k_o^{-1} against $[I^-]^{-1}$ disclosing that such a plot is indeed linear. The slopes of the individual graphs for each nucleophile are assembled in Table 37. The value for chloride ion is the reciprocal of the slope taken from a plot of k_o against $[Cl^-]$.

Table 37

Nucleophile	Slope
Cl^-	990
Br^-	35.2 ± .7
SCN^-	7.09 ± .16
I^-	3.51 ± .12
N_3^-	4.31 ± .22

FIGURE 8



The slope of the line is given by $k_{-1}/k_1k_2[H^+]$, and assuming the acidity is constant for all the nucleophile allows the calculation of the ratios

$$\frac{k_2(X)}{k_2(Cl^-)}$$

given in Table 38, shown in comparison with those obtained for the denitrosation of NMNA[24] and H_2ONO^+[38].

Table 38

X	NANT	NMNA	H_2ONO^+
Cl^-	1	1	1
Br^-	28	54	1.2
SCN^-	140	5,300	1.5
I^-	282	15,000	1.4
N_3^-	230	-	-

Thus, while the denitrosation of NANT is distinctly less sensitive to the nature of the nucleophile than is NMNA, it lies in marked contrast to the corresponding reaction of those nucleophiles with the nitrous acidium ion, H_2ONO^+, where the rate constants change only by a factor of 1.5 over the range. This lack of discrimination has been explained in terms of the rates being close to the diffusion-controlled limit. It is quite clear that this cannot be the case here for NANT. Given that the reaction is acid catalysed, the levelling off of k_o at high concentration of added nucleophile is therefore only consistent with

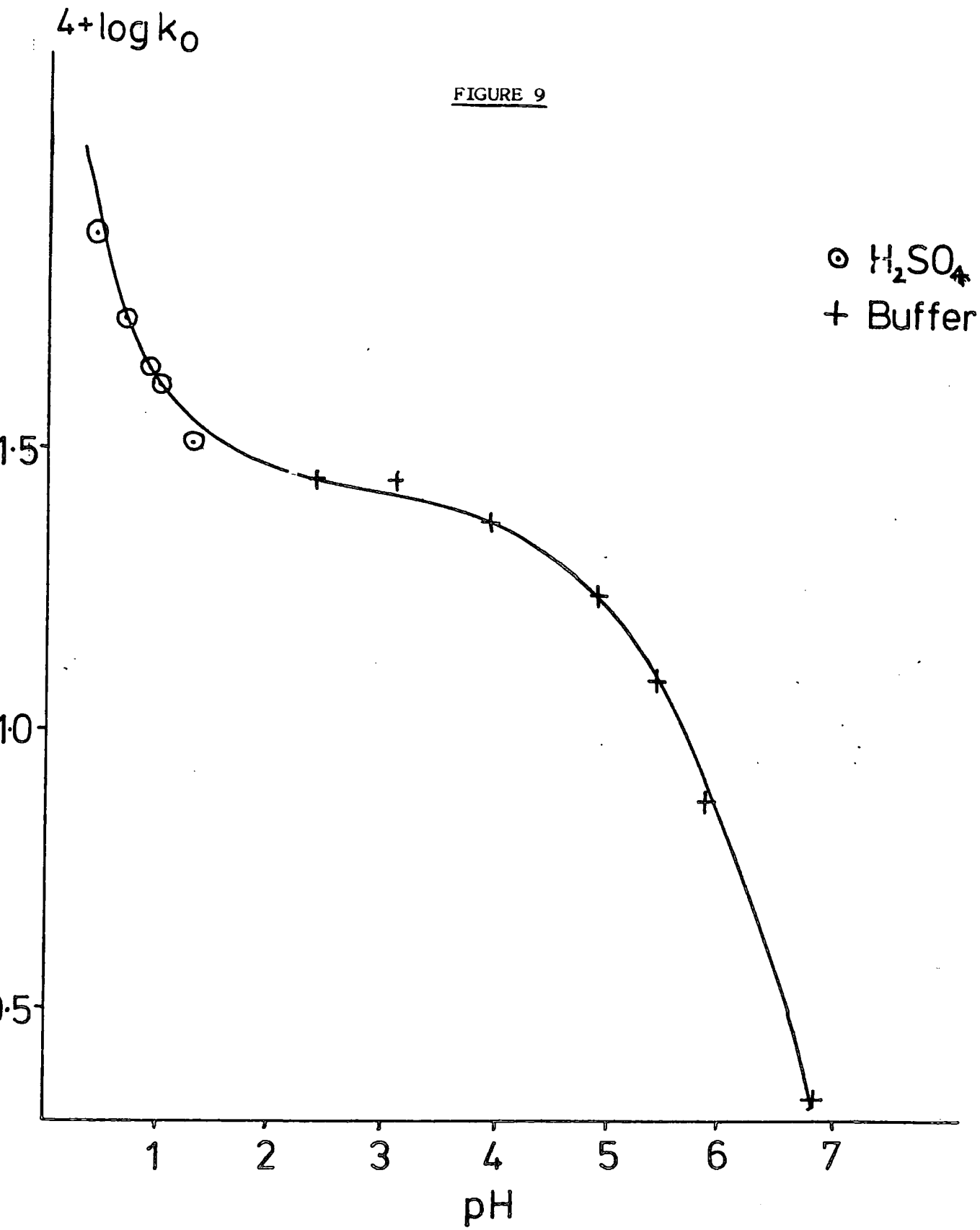
the transferral of the rate-limiting step to an earlier one in the reaction pathway, and is not a result of the rate constants encroaching upon the diffusion-controlled limit.

It is difficult to see why a zero-order dependency upon $[Y^-]$ is observed at higher acidities, whereas a first-order dependence upon $[Y^-]$ is observed at pH6 at least for chloride ion and low concentrations of the other nucleophiles. As explained earlier, this difference depends upon the relative magnitudes of the terms k_{-1} and $k_2[Y^-]$, and there is no reason to suppose why this should be pH dependent. A more likely explanation of the different behaviour is that different sites of protonations are involved at the two different acidities. This explanation is borne out by the examination of the log k_o versus pH profile given in Figure 9.

The profile includes all the results for the experiments in the buffer solutions and some of the results obtained in sulphuric acid. Even though both sets of results do not correspond to exactly the same experimental conditions, the graphical representation is quite clear, that there are indeed two different acid-catalysed pathways, one operative in the pH range 5-7 and the other below pH2.

Between pH2 and pH4 there is little change in the rate constants, corresponding to the formation of one fully pronotated form. Taking the extrapolated limiting value for that mechanism as $4 + \log k_o = 1.45$, it is possible to calculate the pK_a value of ~ 5.5 for this protonation. Hinman and Lang have measured the pK_a value of 3-methyl-indole, a good model for NAT, as -4.55, probably for protonation at C-3. It seems very unlikely that either amino-N-protonation or nitroso O-protonation in NANT could have a pK_a value approaching 5.5. Little of the free base form is apparently protonated in NAT at around pH6[95], as measured by spectral

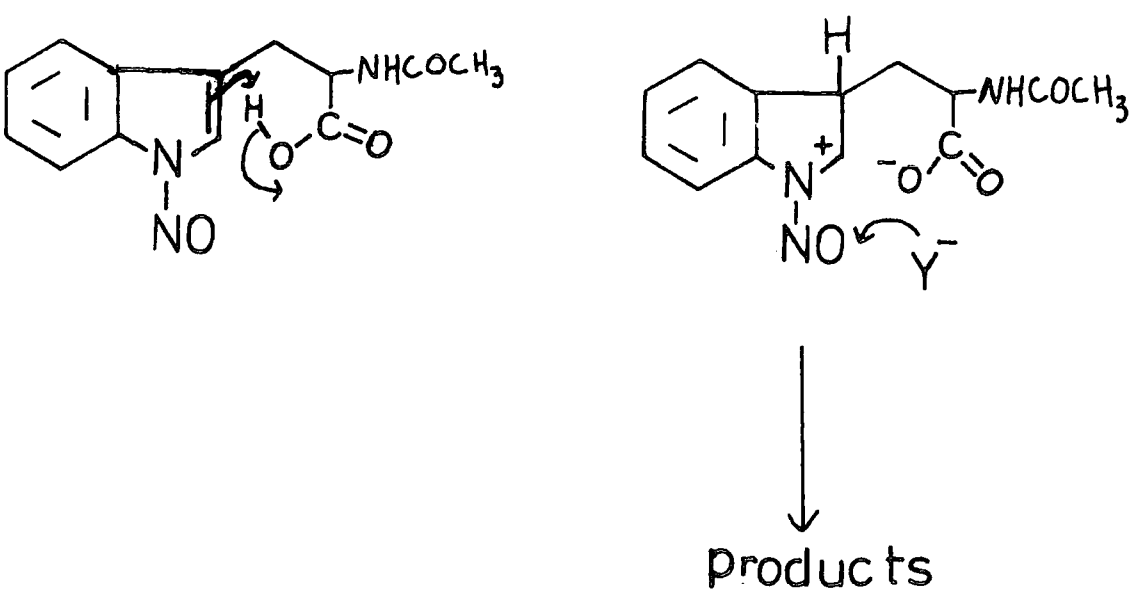
FIGURE 9



changes, and certainly no significant changes in this region were detected in this work.

Generally, a sigmoidal log k_o versus pH curve that has its maximum at low pH is indicative of general acid catalysis by the un-ionised form of a neighbouring group, in this particular case the carboxyl group. Thus, at these much reduced acidities a much more feasible site for protonation, and one which accounts for the determined pK_a value of 5.5, is the carboxylate anion of the side chain.

The proposed intramolecular acid-catalysed mechanism is set out below, in which a hydrogen atom is donated internally from the carboxyl group to the C-3 position of the indole ring. From the viewpoint of ring size, the hydrogen atom is conveniently located as to form a six-membered ring. Other examples of this type of mechanism are well known, specifically in the hydrolysis reactions of 2-carboxylphenyl-β-D-glucaside[97], 2-methoxy-methoxybenzoic acid[98], and several polyuronides[99].



This is the first time an intramolecular mechanism has been proposed for the denitrosation reaction.

Thus, it is clear that two mechanistic pathways exist for the denitrosation, as shown by the pH profile and by the different dependencies upon the nucleophile concentration at the two different acid concentrations. It is probable that direct C-3 protonation occurs at the higher acidities, whilst it is probable that protonation occurs via an intramolecular mechanism at the lower acidities.

3.4 Nitrosation of 4-nitroaniline using NANT

Transnitrosation reactions by the methyl ester of NANT, in which the nitroso group is transferred to another amine, have been reported in the literature, specifically for the nitrosation of diphenylamine[96]. Conceivably, this may occur either by a direct reaction with the NANT derivative, itself, or by an indirect reaction whereby a prior hydrolysis occurs to give kinetically free nitrous acid, which then acts as the effective nitrosating agent. Taking into consideration the results of the present study, it seems more likely that this takes place by the indirect route via the intermediacy of nitrous acid.

This was tested further with NANT, using 4-nitroaniline as the receptor amine. This was chosen because of its reactivity in diazotisation[33] and also for spectral reasons, so that the product diazonium ion and the amine itself could be observed spectrophotometrically without much interference from NANT or NAT. When the reaction was carried out in the absence of sulphamic acid, the product diazonium ion was detected by an increase in its absorbance at 310 nm and also by a concurrent decrease in the absorbance at 360 nm due to 4-nitroaniline. However, when NANT was added to an 4.0 $\underline{M}$ H_2SO_4 solution containing 4-nitroaniline with a slight excess of sulphamic acid no product diazonium ion could be

detected and the peak at 360 nm remain unchanged. While this confirms that NANT does not directly act as a nitrosating species, preferring to undergo initial denitrosation to yield nitrous acid, it must be emphasised that this applies only at the higher acidities where direct C-3 protonation is favoured. It is possible at much reduced acidities that some type of adduct between NANT and the receptor amine could be formed, and certainly the results obtained at pH6 do not altogether discount this possibility.

SECTION TWO

SECTION TWO

4.1 Introduction

N-nitrosation is classified as an electrophilic substitution reaction, in which the electrophile, NO^+, bonds with the unshared pair of electrons at the nitrogen atom[100]. As discussed subsequently, the electrophile, depending upon the conditions of the reaction medium, may be a free positive ion or may be a positive species attached to a carrier which breaks off in the course of attack or shortly after:

Further reaction of the ammonium ion intermediate depends largely on the other groups attached to the nitrogen atom. Hence, nitrosation of secondary amines[101], both aliphatic and aromatic, stop at the nitrosamine stage; whereas primary nitrosoarylamines are typically transformed into relatively stable diazonium salts[102]. Nitrosamine formation occurs also with ammonia and primary aliphatic amines, but the resultant diazonium ions are extremely unstable and normally at ordinary temperatures undergo deamination to form molecular nitrogen and short-lived carbonium ions[102]. At low temperatures, however, both aromatic primary nitrosamines[8] and primary aliphatic diazonium ions[103] have been identified in ethereal solutions of the amine and nitrosyl chloride.

Tertiary amines have also been nitrosated[104,105] in which initial nitrosation at the nitrogen atom leads to an expulsion of one of the groups around nitrogen and to the formation of nitrous oxide. The product nitroso-derivative is then formed by the action of nitrous acid on the resultant secondary amine. The expelled group appears in the products as an aldehyde or a ketone. Linzinsky and Singer[106],

however, concluded that such nitrosations do not proceed via secondary amines. Their conclusion was based upon the observation that the nitrosation of the tertiary amine, aminopyrine, to give nitroso-dimethylamine proceeds more readily than the nitrosation of dimethylamine itself under similar conditions, but any further mechanistic details were not reported.

Thus, the various products obtained from reaction with nitrous acid and a particular amino-compound all proceed by way of an initial N-nitrosation, and can be conveniently represented by the following general scheme where it is understood that $R' = H$ for primary substrates.

$$RRNH \longrightarrow RRNNO \longrightarrow RN_2^+ \longrightarrow R^+ \longrightarrow \begin{matrix}\text{deamination} \\ \text{products}\end{matrix}$$

Except for diazotisation in very concentrated acid, it is now known that the first step of nitrosation is rate-controlling for all these reactions, regardless of whatever subsequent steps may occur. Therefore, the observed kinetics for diazotisation, nitrosation of secondary amines,and deamination are largely dominated by the various mechanisms of nitrosation. Confirmation of this as a general phenomenon is provided by the work of Kalatzis and Ridd[34], where similar rate equations were obtained for the diazotisation of aniline and the nitrosation of N-methylaniline.

Investigation into the mechanisms of nitrosation, however, are complicated by the fact that there are several inorganic nitrosating agents which may exist in equilibrium with molecular nitrous acid depending upon the conditions. For nitrosation in an aqueous system

containing either sulphuric or perchloric acid, sodium nitrite, and an aromatic amine, for example, the only active species possible are NO^+, $H_2\overset{+}{O}NO$, and N_2O_3. It is thought that nitrous acid, HNO_2, itself, is too unreactive to nitrosate amines directly, and the nitrite ion NO_2^- is also readily disregarded as it can hardly be thought of as an electrophilic reagent. In the presence of halide ion, the formation of the corresponding nitrosyl halide becomes important. In increasing order of reactivity these are:

N_2O_3	nitrous anhydride
NOX	nitrosyl halide
$H_2\overset{+}{O}NO$	nitrous acidium ion
NO^+	nitrosonium ion

Additional kinetic complexities stem from the fact that there are several mechanisms for nitrosation, some of which include two potentially rate-determining steps. Under these circumstances, the active nitrosating species is removed as quickly as it is formed by reaction with the amine, and the overall rate equation is then best described by the formation of the nitrosating agent.

Since the field of nitrosation has been reviewed in considerable detail elsewhere [38,101,107], the following introduciton into the various mechanisms of nitrosation is given with the intention of serving as a basic background for the work in this section on halide ion catalysis.

4.2 Nitrous Anhydride Mechanism

At high concentrations of sodium nitrite and comapartively low concentrations of acid, typically < 0.5 M H_2SO_4 or $HClO_4$ and < 0.1 M

HCl, this is the predominant mechanism for the nitrsoation of amines comparable in bascisity to aniline.

In 1928 Taylor[108] observed third-order kinetics for the deamination of methylamine in dilute aqueous solutions of nitrous acid, described by the rate equation:

$$\text{Rate} = k\,[\text{amine}]\,[HNO_2]^2$$

The same kinetic form was observed by Taylor for the deamination of ammonia[108] and dimethylamine[109], and subsequently by Schmid[110] for the diazotisation of aniline in 0.2 $\underline{M}$ H_2SO_4.

To explain the second-order dependence upon nitrous acid and the overall observed third-order rate expression, Hammett[111] suggested a mechanism in which nitrous anhydride, N_2O_3, was formed in a fast pre-equilibrium step which then entered into a slower, hence rate-determining reaction with the unprotonated amine in the next step.

$$H^+ + HNO_2 \underset{}{\overset{\text{FAST}}{\rightleftharpoons}} H_2ONO^+$$

$$H_2ONO^+ + NO_2^- \overset{\text{FAST}}{\rightleftharpoons} N_2O_3 + H_2O$$

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

$$ArNH_2NO^+ \xrightarrow{\text{FAST}} ArN_2^+ + H_2O$$

Confirmation of the proposed scheme was later shown by Hughes, Ingold and Ridd[112,113], who in addition to duplicating the third-order

kinetics of Schmid at about .01 M $HClO_4$, succeeded in obtaining second-order kinetics of the form

$$\text{Rate} = k\left[HNO_2\right]^2$$

at the much reduced acidities of .002 M. Under these conditions, the proportions of nucleophilic free amine base is significantly higher and being more reactive than the protonated form towards electrophilic attack it effectively removes N_2O_3 as rapidly as it is formed, before a significant proportion can undergo hydrolysis. Thus, the second-order kinetics then correspond with rate-determining formation of nitrous anhydride, and as predicted the rate equation is independent of the concentration of amine.

Interestingly, Hantzsh and Schuman[114], who published the first kinetic results on diazotisation in 1899, also observed second-order kinetics but incorrectly attributed the observance to a first-order dependence upon the concentrations of protonated amine and nitrous acid. Other early workers supported this claim, as well, for diazotisation[115] and deamination[116].

Further evidence for the intermediate formation of nitrous anhydride comes from studies of the exchange of oxygen-18 between nitrous acid and water, which occurs mainly via the hydrolysis and the formation of nitrous anhydride,[117] viz:-

$$N_2O_3 + H_2O^* \rightleftharpoons HNO_2 + HNO_2^*$$

At very low acidities and at high concentrations of nitrite ion, the

rate of this oxygen exchange is not only second-order with respect to nitrous acid, but it also proceeds at a similar rate to the diazotisation reaction under similar conditions. Hence, both processes must have the same rate-determining step, namely the rate of formation of N_2O_3.

Nitrous anhydride is regarded as a weak electrophile in comparison with $H_2\overset{+}{O}NO$ and the nitrosyl halides since it does not react with highly deactivated amines, such as 4-nitroaniline and 2,4-dinitroaniline[118]. Rate data for reaction between N_2O_3 and a number of other amines, however, are known, and shows that there is a reasonable correlation between reactivity and bascisity within each class of amine, although this trend does not continue for the aliphatic amines which are far less reactive than their high bascisities would suggest[38].

As the equilibrium constant for the formation of nitrous anhydride is known,[119,129] the true rate coefficients for the reaction between the free amine and nitrous anhydride may be estimated. For aniline, this value has been calculated to be $\sim 10^7$ ℓ $mol^{-1}s^{-1}$ at 25°C, which is indeed considerably less than the diffusion-controlled limit[121].

4.3 Acid-catalysed Mechanisms

Given that nitrous anhydride is such a weak electrophile incapable of reacting with the protonated form of the amine, one would expect the observed rate constant to decrease with increasing acidity because of the decrease in the concentration of free amine. In fact, this is observed with those amines such as aniline for which the nitrous anhydride mechanism is applicable; but as the acidity is increased further, typically greater than 0.5 M $HClO_4$, the rate profile passes through a minimum and then increases with increasing concentrations of acid. This subsequent increase is attributed to a change in mechanism.

The first of the acid catalysed mechanisms to be identified assumed the kinetic form:-

$$\text{Rate} = k\left[ArNH_2\right]\left[HNO_2\right]\left[H^+\right]$$

which Hughes, Ingold and Ridd[122] interpreted as evidence for rapid pre-equilibrium formation of the nitrous acidium ion, which then reacts with the free amine in the rate controlling step, in accordance with the following scheme.

$$HNO_2 + H^+ \underset{\longleftarrow}{\overset{\text{FAST}}{\longrightarrow}} H_2\overset{+}{O}NO$$

$$ArNH2 + H_2\overset{+}{O}NO \xrightarrow{\text{slow}} ArNH_2\overset{+}{N}O + H_2O$$

$$ArNH_2\overset{+}{N}O \xrightarrow{\text{FAST}} Ar\overset{+}{N}_2 + H_2O$$

The reaction is most easily studied with the weakly basic amines for which complications from competition with the N_2O_3 mechanism do not apply. Moreover, unlike the nitrous anhydride mechanism, the rate of formation of the nitrous acidium ion cannot be made rate-determining, probably due to the fast proton transfer to and from oxygen.

The above kientic form is also in accord with reaction of the nitrosonium ion, NO^+, with the free amine, but has been ruled out on the basis of the result obtained from oxygen-18 experiments, as well as by a consideration of the catalytic effect of halide ions on the rate of diazotisation.

The fact that the nitrous accidium ion is capable of diazotising the nitroanilines suggests that it is a more reactive electrophile than N_2O_3. Indeed, Larkworthy [118] has shown for the diazotisation of amines over a similar decrease in pK_a values that the nitrous acidium ion shows little discrimination in its reactions, whereas for the less reactive nitrous anhydride a factor of 50 covered the reactivity range in its reactions. For the nitrous acidium ion, this further suggests diffusion-control, although the true bimolecular rate constant for the encounter between $H_2\overset{+}{O}NO$ and an aniline derivative cannot be calculated since the equilibrium constant for the initial protonation is unknown. However, since it is now known[33] that the diazotisation of aniline derivatives of pK_a >4.0 via NOBr and NOCl closely approach a diffusion-controlled process and since $H_2\overset{+}{O}NO$ is expected to be even more reactive than either of the nitroyl halides, it is argued that the encounter between $H_2\overset{+}{O}NO$ and the anilines should also be diffusion-controlled.

A further increase in the concentration of acid necessitates the consideration of two main factors, which modify the observed kinetic form at the higher acidities. The first factor is essentially a salt effect, and is observed as the only modifying factor for the less basic amines in solutions of perchloric acid up to 3.0 M [17]. The alternative suggestion[124] of catalysis via nitrosyl perchlorate seems highly unlikely, as this compound is ionic and not covalant under the present experimental conditions[19,123]. For 4-nitroaniline increasing the concentration of perchloric acid while maintaining constant ionic strength by the addition of sodium perchlorate results in the rate expression:-

$$\text{Rate} = k[ArNH_2][HNO_2]h_o$$

with the insertion of h_o for H^+ being necessary in the more concentrated acid solutions[17]. The observed rate constant for the reaction is virtually independent of the acidity, since any increase in h_o is offset by the corresponding decrease in the concentration of free amine. Generally, the mechanism is the same as the one diagrammed above, namely rate-determining attack upon the free amine by $H_2\overset{+}{O}NO$, with the only difference in the kinetic form being the substitution of the more appropriate acidity function h_o for H^+ at the higher acidities.

For the more basic amines, a second modifying factor manifests itself in the form of a new mechanistic pathway. Thus, the much stronger catalytic effect of perchloric acid, apart from the rate enhancement associated with the ionic strength effect noted for the feebly basic amines, assumes the kinetic form:-

$$\text{Rate} = k[\overset{+}{ArNH_3}][HNO_2]h_o$$

corresponding to rate-determining attack by the nitrous acidium ion on the protonated form of the amine[125,126]. Reaction still occurs much more readily through the free amine, and it is believed that this mechanism only becomes kinetically significant when the proportion of free amine becomes neglibly small at the higher acidities. Hence, its applicability to the more basic amines.

Although all the mechanistic details are not entirely clear, a mechanism involving the formation of an intermediate π-complex has been proposed on the basis of a study of ring substituent effects in which the proton being displaced is still present in the transition state[126].

An analogous situation exists for diazotisation of aniline by N-nitrosodiphenylamine, in which a direct reaction between the protonated form of the amine and the nitrosamine appears to be the property of the aromatic system, since the replacement of aniline with aliphatic amines proved to be virtually inert under the same experimental conditions[30]. However, Stedman and co-workers[127] have obtained convincing evidence for nitrosation of the N-conjugate acid of hydroxylamine, $\overset{+}{N}H_3OH$, and in this case initial nitrosation is beleived to occur at the more basic oxygen atom. In general, though, N-nitrosation via the protonated amine appears to be confined to the most basic aromatic amines.

At these higher acidities, the exact nature of the nitrosating agent is in some doubt as the nitrosation by the nitrosonium ion, NO^+, becomes increasingly more important. It could be, for exmaple, that both $\overset{+}{H_2}ONO$ and NO^+ are operative. Because NO^+ is expected to be the most reactive of the electrophiles, the incursion of this mechanism should first become apparent for the less basic amines. The kinetic form observed for the reaction between nitrous acid and benzamide in strong sulphuric acid has been explained in this way[128].

4.4 Nitrosation at High Acidities

As the acidity is increased still further, the rate profile is observed to reach a maximum at $HClO_4$ = 6 M and thereafter to decrease with increasing concentrations of acid. The reaction then follows the equation:

$$\text{Rate} = k\left[\overset{+}{ArNH_3}\right]\left[HNO_2\right]h_o^{-2}$$

The rates of reaction for such amines as aniline, p-nitroaniline, and p-toluidine are reported to follow the above expression[17].

At such acidities nitrous acid is virtually quantitatively present as free nitrosonium ion, as shown by Raman[129] and UV studies,[18,19] and in view of the large solvent isotope[17] effect k_{H_2O}/k_{D_2O} = 10 the following mechanism has been proposed[17] to account for the experimental observations:

$$ArNH_2 + NO \underset{}{\overset{\text{FAST}}{\rightleftharpoons}} ArNH_2NO + H^+$$

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

$$ArNHNO \xrightarrow{\text{FAST}} ArN_2^+ + OH^-$$

It is difficult to reconcile the kinetic form and the solvent isotope effect with rate-determining N-nitrosation, as is the case at the lower acidities. Two factors operate that probably make the second step rate-determining. First, proton transfer from $ArNH_2NO$ to a highly acidic media would not be expected to occur easily; and secondly, reversion of $ArNH_2NO$ to reactants via displacement of NO^+ by a proton would be expected to become rapid at high acidity.

4.5 Nitrosyl Halide Mechanism

Although the catalysis of diazotisation by hydrochloric acid had been previously reported by a number of authors[140], the catalytic effect of chloride and bromide ions was first elucidated by Schmid[131,132], who established first-order kinetics in each hydrogen ion, amine, nitrous acid and halide ion. The rate equation had the form:-

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

where X^- = Cl^-, Br^- or I^-. The same equation applies for diazotisation in perchloric or sulphuric acid containing the appropriate added halide ion. Typically, this mechanism first becomes important in the presence of rather low concentrations of halide ion, as demonstrated by the fact that the nitrosation of aniline via nitrosyl chloride is the predominate mechanism in hydrochloric acid concentrations exceeding about 0.1 M.

Hammett[111] made the suggestion that the observation of catalysis was consistent with the rapid pre-equilibrium formation of the corresponding nitrosyl halide, which then undergoes a rate-controlling step in the nitrosation of the amine, viz:-

$$HNO_2 + H^+ \underset{}{\overset{\text{FAST}}{\rightleftharpoons}} H_2\overset{+}{O}NO$$

$$H_2O^+NO + X^- \overset{\text{FAST}}{\rightleftharpoons} NOX + H_2O$$

$$ArNH_2 + NOX \xrightarrow{\text{slow}} ArNH_2\overset{+}{N}O + X^-$$

$$ArNH_2\overset{+}{N}O \xrightarrow{\text{FAST}} ArN_2^+ + H_2O$$

As for the nitrous anhydride mechanism, the nitrosyl halide mechanism possesses as its first stage a potentially rate-determining inorganic step, and therefore the validity of Hammett's proposal may be tested by adjusting the experimental conditions such that the rate of formation of the nitrosyl halide, NOX, becomes rate-controlling. Indeed, this was achieved when Hughes and Ridd[133] showed

that for bromide ion and iodide ion the formation of the nitrosyl halide could be made rate-determining by conducting reactions in the presence of a sufficient excess of amine, which serves to remove the nitrosating agent, NOX, as rapidly as it is formed. The rate equation is now described by:-

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

which corresponds to formation of NOX from the action of X^- on $H_2\overset{+}{O}NO$ rather than on N_2O_3, since otherwise a second-order dependence upon nitrous acid would be observed.

On the basis of simple electronegativity principles, NOCl is expected to be more reactive than either of its counterparts NOBr or NOI, even though the rate of formation of NOCl has not been made rate-determining, at least in the diazotisation of aromatic amines. The reason for this lies in the actual magnitudes of the equilibrium constants, K_x, for the formation of NOX, which are in the expected order I > Br > Cl. Thus, the concentration of NOCl is never large enough to make the step of nitrosation faster than the rate of its own formation. This is also apparent in that the above limiting law for bromide ion catalysis was not realized for aniline but was realized for the weaker base O-chloroaniline; whereas for iodide ion catalysis the limiting law was succeeded easily with aniline. Thus, NOX formation is made most easily rate-determining for iodide ion. Moreover, the size of the K_x value also explains the pronounced catalytic efficiencies of iodide over bromide and bromide over chloride ion.

Studies in methanolic hydrogen chloride have shown that the mechanism remains unchanged from the one above, although the reaction

is considerably slower[134]. This has been ascribed to the reduction of the NOCl concentration by methanolysis[135].

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

Given the availability of the equilibrium constants for the formation of the nitrosyl halides at several temperatures enabled Schmid and co-workers to calculate the true bimolecular rate coefficients, defined by:

$$\text{Rate} = k_1 [\text{Amine}][\text{NOX}]$$

for the reaction of the unprotonated amine with both nitrosyl chloride [136,137,138] and nitrosyl bromide[131,138].

For NOCl nitrosation at 25°C, the values of k_1 all fell within the range 1-3 x 10^9 ℓ $mol^{-1}s^{-1}$ for a number of ring-substituted anilines, the bascisities of which varied by a factor of 250. Originally, Schmid attempted to correlate these results with the bascisities of the amines, but the variation is very small and it was later suggested[38] that the rate constants do in fact closely approach those expected for a diffusion-controlled process. Support for this proposal came from the calculation of the activation energies observed from the dependence of k_1 upon temperature. The values of 19.1 k J mol^{-1} for aniline and 20.7 k J mol^{-1} for O-chloraniline are reasonably near the value of 20 k J mol^{-1} expected for a diffusion-controlled reaction in aqueous media. Similarly, the reaction between NOBr and aniline at 25°C was 3.0 x 10^9 ℓ $mol^{-1}s^{-1}$, and the activation energy was determined as 6.1 k J mol^{-1}.

It must be pointed out, however, that the kinetic method of Schmid and co-workers usually involved the analysis of one or two quickly taken points, and a number of assumptions were made in evaluating the second-order rate coefficients. In addition, an indirect kinetic method developed by Williams[146] showed that for NOCl a large range of reactivity covered the 4-nitro to 4-methoxy anilines, an unexpected result if the rate coefficients k_1 are near the diffusion-controlled limit.

These controversial findings led Crampt on et al[33] to extend the early work of Schmid and co-workers for diazotisation of a number of substituted anilines via NOCl and NOBr at 25°C using the fast reaction technique of stopped-flow spectrophotometry. This approach also differs from the earlier work by taking into consideration the reversibility of the N-nitrosation reaction, particularly at high concentrations of halide ion and also for aniline derivatives containing electron withdrawing derivatives.

In general, the results of the study revealed that at low pK_a values, especially for 4-nitroaniline, NOCl is significantly more reactive than NOBr, as expected, and that the bimolecular rate constants for the diazotisation reactions do indeed approach the diffusion-controlled limit[121] of 7.4×10^9 $\ell\ mol^{-1}s^{-1}$ for reactions in water at 25°C, particularly for aniline derivatives of $pK_a > 4.0$.

These results compare with the values of $\sim 10^7$ $\ell\ mol^{-1}s^{-1}$ for the corresponding N_2O_3 reactions[38], and suggests that the nitrosyl halides are more efficient electrophiles.

In addition to the halide ions, thiocyanate ion has also been shown to effect catalysis of nitrosation reactions[139,140,141]. As discussed previously, the greater catalytic effect of these ions appears to be dependent, for the most part, on the magnitudes of the individual values

of K_x, the equilibrium constants for the formation of the respective nitrosyl halide or nitrosyl thiocyanate, NOX.

The particularly high efficiency of added thiocyanate ion in nitrosation, then, is readily attributable to the large value of K_x for NOSCN formation. Indeed the K_x values of 32 ℓ^2 mol^{-2} at 20°C for NOSCN[142] compares with 1.1 x 10^{-3} ℓ^2 mol^{-2} and 5.1 x 10^{-2} l^2 mol^{-2} at 25°C for NOCl[138] and NOBr[143], respectively. Thus, even though the true rate constants for NOX attack are larger for chloride ion than for bromide ion, it is generally found that bromide ion catalysis is significantly greater than chloride ion catalysis.

Recently, Stedman and co-workers[50,144] have measured the rate constants for the forward and backward steps for the direct nitrosation of thiourea, alkylthioureas, and cysteine. The reactions were very rapid, forming the initially unstable nitrosulphonium ion ON - $S^+\langle$. The derived equilibrium constant for thiourea is 5000 ℓ^2 mol^{-2} at 25°C and the reaction is virtually quantitative for cysteine. In this single fact alone, and in comparison with the halide ions and thiocyanate ion, it is predicted that thiourea may be an excellent catalyst generally for nitrosation and diazotisation.

Indirect evidence from earlier work suggests that these nitrososulphonium ions can themselves act as nitrosating agents. This stems from the kinetic method developed by Williams[46] to establish the efficiencies of various nitrite traps toward the different nitrosating agents, NOX, as outlined in chapter 1 of this thesis. It will be recalled that the range of selectivity shown by $ON^+C(NH_2)_2$ for a number of nitrite traps, including hydrazine, hydrazoic acid, and sulphamic acid, was very similar to that shown by NOSCN; whereas both showed a significantly larger selectivity range than either NOBr or NOCl.

This implies not only that the latter are more reactive nitrosating agents, but that $ONSC(NH_2)_2^+$ and ONSCN are of comparable reactivity.

Any reaction via $ONSC(NH_2)_2^+$ can, of course, be studied directly by the observation of catalysis of nitrosation by thiourea. This has been reported in the literature[145] for the nitrosation of dimethylamine in aqueous acetate buffer at pH4, and from a concentration-time curve the authors showed that for similar concentrations of added catalyst, thiocyanate ion exhibited essentially no catalytic effect, whereas thiourea accelerated the formation of the nitrosamine considerably. However, no rate constants for the reactions were calculated, and in general no kinetic analysis of the experimental results was given.

It is the intention of this work to examine the catalysis of nitrosation and diazotisation effected by thiourea, together with the corresponding reactions in the presence of thiocyanate and bromide ions for comparison purposes, and to discuss the results in terms of the reactivity of the various nitrosating agents involved.

CHAPTER 5

Catalysis of Nitrosation and Diazotisation by Thiourea

5.1 Introduction

In this chapter is presented a detailed kinetic analysis of the catalysis of nitrosation and diazotisation effected by thiourea. Morpholine and aniline were chosen as typical examples of secondary and primary amines, respectively, for the study. Catalysis by bromide ion and thiocyanate ion were also carried out for comparison purposes, the results of which are given and discussed in the next chapter.

For each amine all the kinetic measurements were performed with the concentration of the respective amine in constant excess over the nitrous acid concentration. Since good first-order behaviour upon $[HNO_2]$ was found for each kinetic experiment, a mechanistic pathway incorporating nitrosation via nitrous anhydride may be excluded. Under these circumstances, the observed first-order rate constant, k_o, is defined by:

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

In the case of morpholine, the kinetics were monitored at 31°C in the cell of Beckman model 25 recording spectrophotometer by observing the increase in absorbance at 342nm due to the product N-nitrosomorpholine. For aniline, however, the reactions were sufficiently fast as to require the usage of a Canterbury stopped-flow spectrophotometer at 30°C. The kinetics were followed by noting the increase in absorbance at 325nm due to the formation of the product diazonium ion, which was found to be relatively stable over the length of time needed for complete reaction. For the aniline experiments the determined values of k_o were taken from the mean value of at least five separate kinetic runs, and the reproducibility of the measurements in all cases was better than ±5%.

5.2 N-nitrosation of Morpholine

The catalytic effect of added thiourea was investigated at constant acid and morpholine concentrations, and the results are given in Table 39 and shown graphically in Figure 10, together with the results for bromide ion and thiocyanate ion, for convenience.

Table 39

$[NaNO_2] = 9.46 \times 10^{-3}M$, $[H_2SO_4] = .113M$, $[\text{Morpholine}] = .154M$

$10^3[SC(NH_2)_2]$	$10^4k_o(s^{-1})$
1.27	69.3
2.54	170
3.81	261
5.08	334
6.35	421

Clearly, there is significant catalysis by thiourea, and from the slopes of k_o against [nucleophile] in Figure 10 the overall catalytic efficiency for the series $Br^- < SCN^- < SC(NH_2)_2$ is, more quantitatively, 1 : 240 : 4200. Indeed, this represents the first positive direct identification of nitrosyl thiourea as a nitrosating agent in its own right, although the indirect kinetic analysis referred to earlier suggested this possibility.

A series of experiments containing varying concentrations of morpholine were carried out with the aim of determining the order with respect to [morpholine]. The results are tabulated in Table 40 and portrayed graphically in Figure 11.

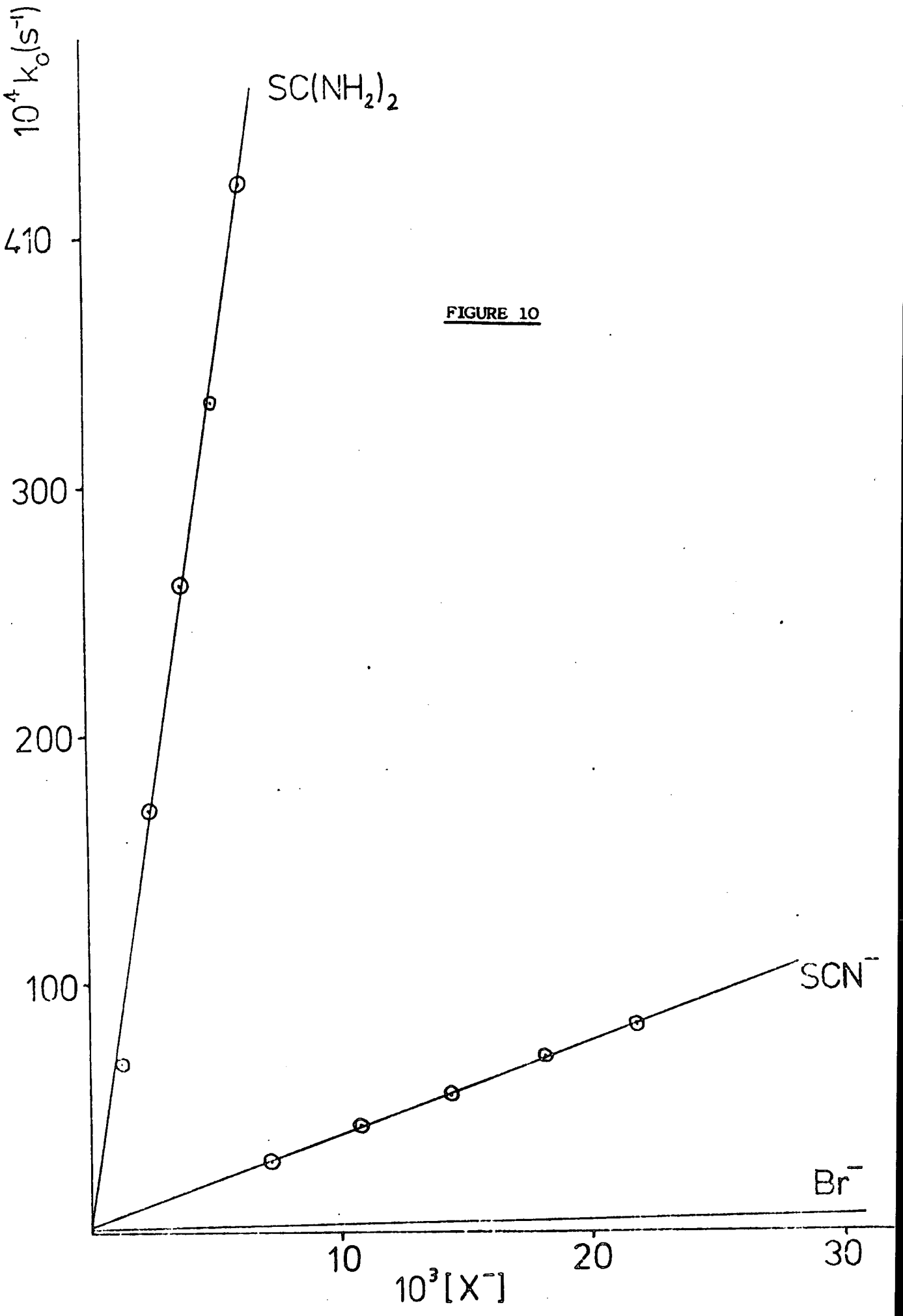


FIGURE 10

Table 40

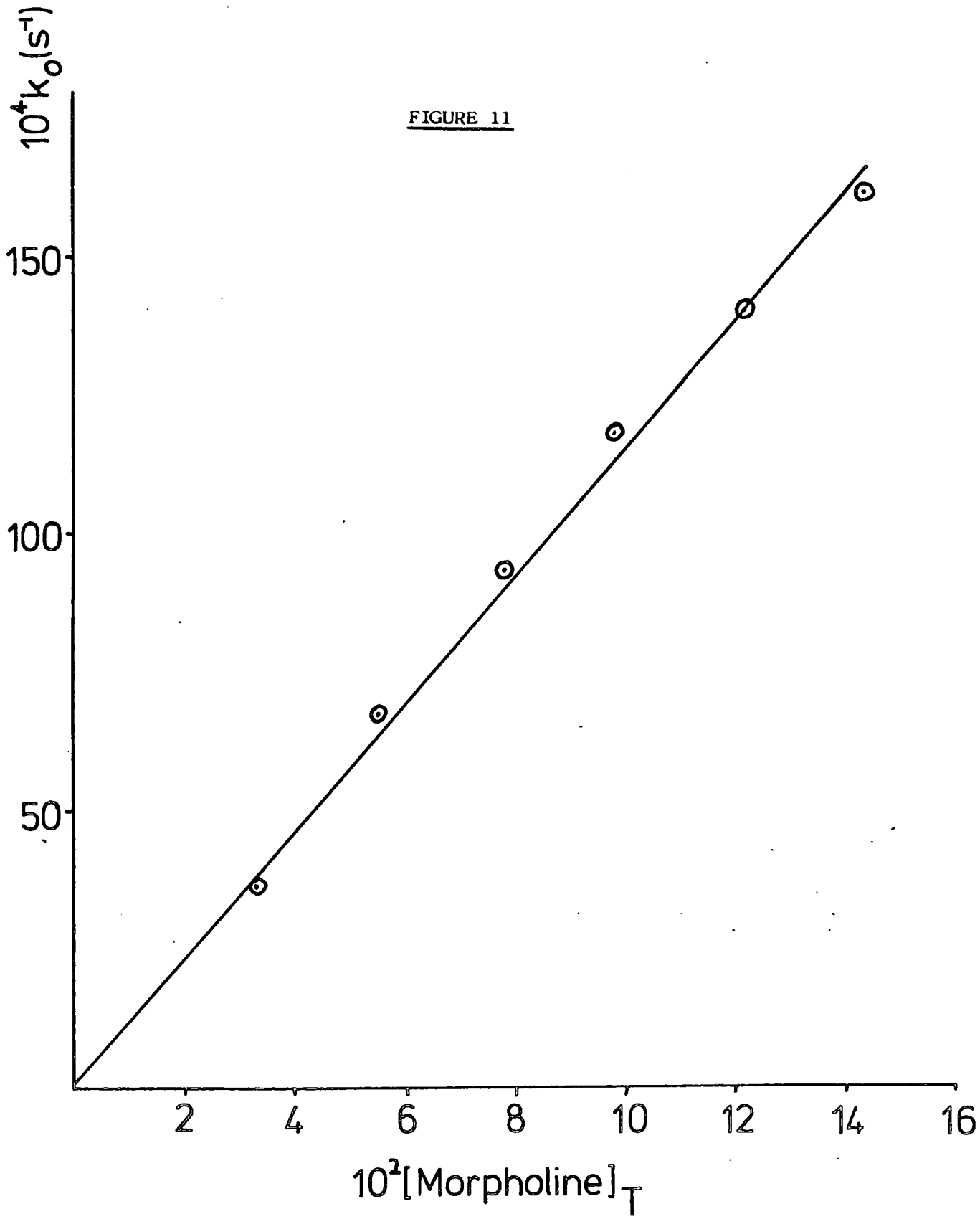
$[NaNO_2] = 8.46 \times 10^{-3}\underline{M}$, $[H_2SO_4] = .124\underline{M}$, $[KSCN] = 3.33 \times 10^{-2}\underline{M}$

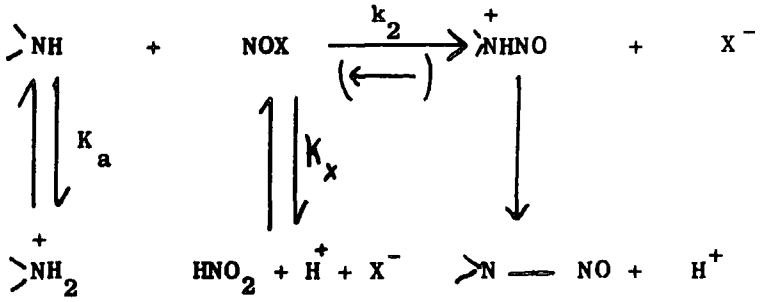
$10^2[\text{Morpholine}]$	$10^4 k_o (s^{-1})$
0	0
3.32	36.2
5.54	67.7
7.76	93.1
9.97	118
12.2	140
14.4	161

The origin is shown as a viable point, through which the line must now pass; and, as expected, the observed first-order rate constant, k_o, is directly proportional to the concentration of morpholine, thus establishing good first-order behaviour over the range of morpholine concentrations.

It is generally believed that nitrosation of a secondary amine proceeds by direct attack by NOX (X = Cl^-, Br^-, SCN^-, etc.) at the free base form of the amine[38,101], and the above results for thiourea are entirely consistent with such a scheme, as outlined below. In the present case, it is understood that X = $SC(NH_2)_2$ and the secondary amine is in fact, morpholine.

FIGURE 11





K_a is the acid dissociation constant of the protonated secondary amine $>NH_2^+$, and K_x is the equilibrium constant for the formation of NOX from HNO_2, H^+, and X^-. The value for K_a at 31°C was interpolated from a graph of ln K_a against $^1/_T$ from data listed by Perrin[149]. Similarly, Stedman and co-workers[50] have measured the equilibrium constant, K_x, for the formation of the nitrososulphonium ion over a range of temperatures, and the value of K_x at 31°C for the present work was interpolated from a graph of ln K_x against $^1/_T$.

Thus, the rate equation for the above mechanism is given by the expression:

$$\text{Rate} = k_2 [\text{NOX}] [\text{Free Morpholine}]$$

However, the concentration of NOX may be easily calculated as follows:

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

and if, by definition,

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

$$[NOX] = \frac{[\text{Total Nitrite}]}{1 + \frac{1}{K_x[H^+][X^-]}}$$

Similarly, for Free Morpholine ,

$$K_a = \frac{[\text{Free Morpholine}][H^+]}{[\text{Protonated Morpholine}]}$$

where [Protonated Morpholine] represents, for all practical purposes, the total concentration of morpholine present, designated below as $[\text{Morpholine}]_T$. Thus,

$$[\text{Free Morpholine}] = \frac{K_a [\text{Morpholine}]_T}{[H^+]}$$

Substituting these expressions back into the above rate equation yields:

$$\text{Rate} = \frac{k_2 K_a [\text{Total Nitrite}][\text{Morpholine}]_T}{\left(1 + \frac{1}{K_x[H^+][X^-]}\right)[H^+]}$$

and since the observed first-order rate constant is defined by:-

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

where $[HNO_2]$ refers to the [Total Nitrite] , one may write:

$$k_o = \frac{k_2 K_a [\text{Morpholine}]_T}{\left(1 + \frac{1}{K_x[H^+][X^-]}\right)[H^+]}$$

If K_x is very small, as it is for bromide ion, for example, with $K_x = 6.00 \times 10^{-2}\ \ell^2\ mol^{-2}$ at 31°C, then at reasonably low concentrations of bromide ion the limiting condition $^1/K_x[H^+][X^-] >>> 1$ applies, whence k_o reduces to:

$$k_o = k_2 K_a [\text{Morpholine}]_T K_x [X^-]$$

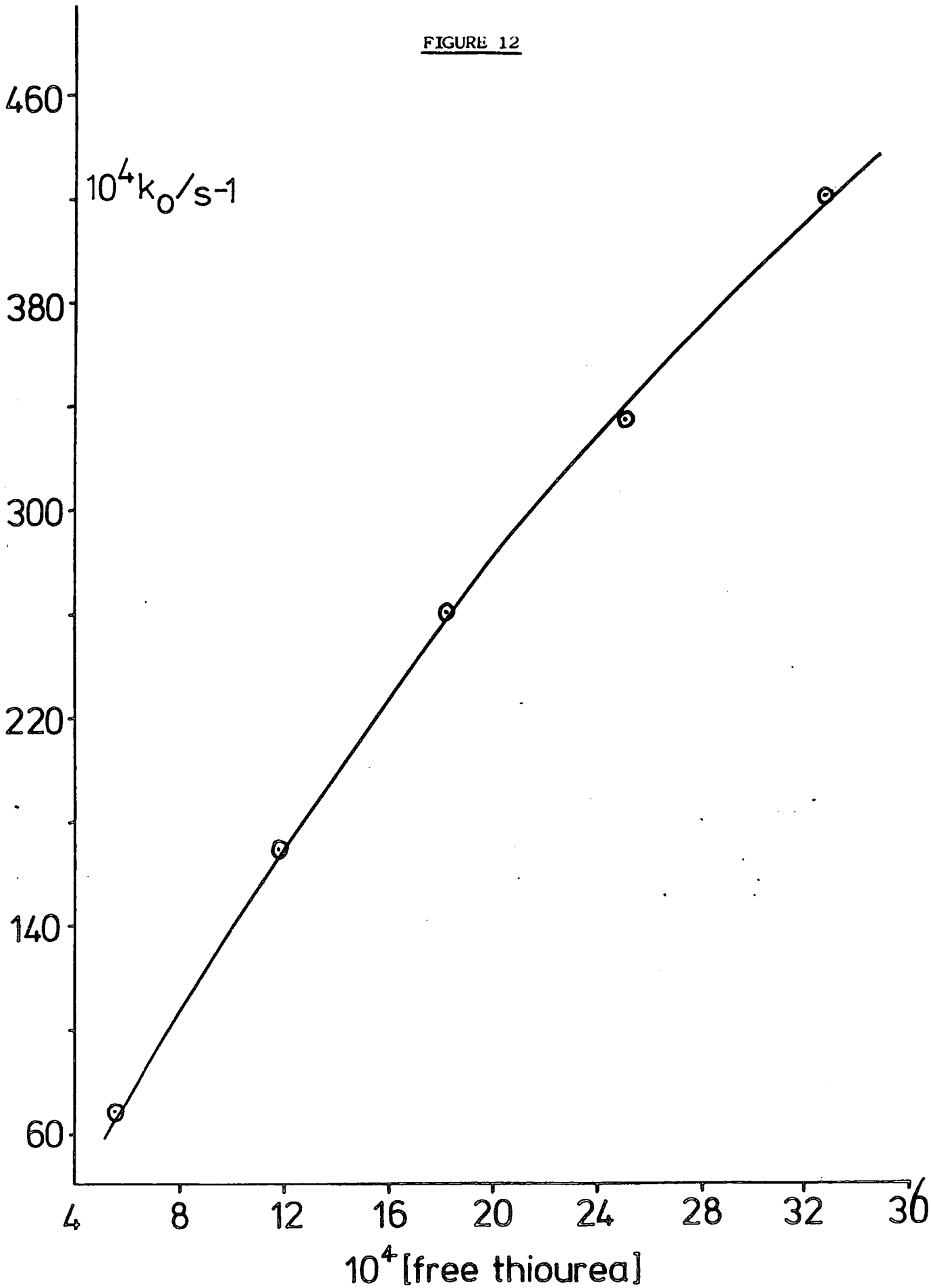
which predicts a first-order dependency upon $[X^-]$ and independence from the acidity.

However, for thiourea K_x has the much larger value of 3656 $\ell^2\ mol^{-2}$ at 31°C, and the limiting condition does not now apply, as $^1/K_x[H^+][X^-]$ is typically less than six. Thus, even though the graph of k_o versus [total thiourea] in Figure 10 is shown as being linear, once the concentration of total thiourea is corrected for the considerable conversion into $^+ONSC(NH_2)_2$ a plot of k_o against [Free thiourea] shown in Figure 12 is in fact significantly curved, as indeed it should be if the limiting form does not apply.

It is possible to evaluate the values of k_2, however, for each individual thiourea concentration by using the general form of the rate equation for k_o. The application of this equation necessitates the calculation of two correction factors. First the nominal solvent acidity must be corrected to allow for complete protonation of morpholine and the total conversion of nitrite to nitrous acid. Protonation of thiourea at these concentrations is neglible, and therefore is omitted from any further calculations. The correction was carried out as follows:

$$\text{Residual } [H_2SO_4] = \frac{[\text{Morpholine}]_T/\underline{M} + [NaNO_2]/\underline{M}}{2}$$

FIGURE 12


460
380
300
220
140
60
$10^4 k_o/s^{-1}$
4
8
12
16
20
24
28
32
36
10^4[free thiourea]

This residual $[H_2SO_4]/\underline{M}$ was then taken to estimate the true $[H^+]/\underline{M}$, from interpolation of data given by Robertson and Dunford[63], and in the present case was calculated to be $4.0 \times 10^{-2}\underline{M}$.

Secondly, because a significant proportion of the total thiourea concentration, X^-, will necessarily be tied up in the form of $ONSC(NH_2)_2^+$, the concentration of free thiourea needs to be calculated in each individual case. This involves the calculation of $[NOX]$, and by defining

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

and,

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

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

Since the values for $[\text{Total Nitrite}]$, $[\text{Total } X^-]$, $[H^+]$, and K_x are all known quantities, the value for $[NOX]$, and hence $[\text{Free } X^-]$ may be easily obtained.

Using these corrected values, the individual values of k_2 for each thiourea concentration in Table 39 is given in Table 41.

Table 41

10^4 [Free Thiourea]	$10^4 k_o s^{-1}$	$10^{-6} k_2$ ℓ $mol^{-1} s^{-1}$
5.52	69.3	5.5
11.8	17.0	6.9
18.2	261	7.4
25.1	334	7.4
32.9	421	7.7

Bearing in mind that there are a number of assumptions made in the evaluation of k_2, and excluding the first value of k_2 at the lowest thiourea concentration, the average of k_2 is:

$$k_2 = (7.4 \pm 0.3) \times 10^6 \text{ ℓ } mol^{-1} s^{-1}$$

which is a generally satisfactory rate constant.

Contrasting with Cl^-, Br^-, and SCN^- catalysis, a further consequence of thiourea catalysis is that k_o is not now independent of the solvent acidity, if the general form of the rate equation for k_o is applicable. The data drawn up in Table 42 shows quite clearly that this is the case, as k_o decreases rather sharply.

Table 42

$[NaNO_2] = 9.58 \times 10^{-3}$M, [Thiourea] $= 2.59 \times 10^{-3}$M, $[\text{Morpholine}]_T = .170$M

$[H_2SO_4]_T$/M	$10^4 k_o (s^{-1})$
.113	184
.147	96.5
.170	74.6
.227	23.7

In addition to the elucidation of the mechanism and kinetics of the formation of the $ONSC(NH_2)_2^+$ adduct, Stedman and co-workers[50] also made a kinetic study of the reaction between nitrous acid and thiourea at low acidity to form molecular nitrogen and thiocyanic acid.

$$HNO_2 + SC(NH_2)_2 \longrightarrow HNCS + N_2 + 2H_2O$$

The fact that nitrogen is one of the main products of the reaction strongly suggests N-nitrosation, and Stedman and his co-workers interpreted their results in terms of a rate-determining migration of the nitrosyl group from the sulphur atom to nitrogen in the conjugate base of the S-nitroso-compound.

$$H^+ + HNO_2 + SC(NH_2)_2 \underset{\text{Fast}}{\rightleftharpoons} ONSC(NH_2)_2^+ + H_2O$$

$$ONSC(NH_2)_2^+ \underset{\text{Fast}}{\rightleftharpoons} ONSC(NH)NH_2^{+-} + H^+$$

$$ONSC(NH)NH_2^{+-} \xrightarrow{\text{Slow}} NH_2C(S)NHNO$$

$$NH_2C(S)NHNO \xrightarrow{\text{Fast}} H^+ + HNCS + N_2 + OH^-$$

Thus, the decrease in k_o at the higher acid concentrations may be explained by an acid catalysed increase in the concentration of $ONSC(NH_2)_2^+$ and a concurrent decrease in the availability of unprotonated morpholine. The $ONSC(NH_2)_2^+$ adduct then predominantly follows the alternative pathway of nitrosyl migration from S⟶N to eventually form the observed decomposition products, as outlined above. Indeed, in the present work,

at the higher acidities, there was observed an increasingly greater evolution of gaseous bubbles, presumed to be nitrogen. The data are not significantly detailed, however, to examine this point more thoroughly.

The effect of temperature on reaction rate was investigated with the purpose of measuring the activation energy for the N-nitrosation step for reaction of $\overset{+}{O}NSC(NH_2)_2$. The results for reaction at 21°C and 40°C are listed in Table 43, along with the individual values of k_2 calculated as described previously. The K_x values at 21°C and 40°C are 5486 l^2 mol^{-2} and 2581 l^2 mol^{-2}, respectively.

Table 43

10^4 [Total Thiourea]	T(°C)	$10^4 k_o (s^{-1})$	$10^{-6} k_2$ l $mol^{-1} s^{-1}$
25.3	21	41.5	3.58
38.0	21	62.1	3.74
7.24	40	135	12.1
10.9	40	180	10.6
18.1	40	260	9.78
25.3	40	371	10.1
32.6	40	491	10.6

Taking the mean value of k_2 at each of the three temperatures:

$$\bar{k}_2 \text{ at } 21^\circ C = (3.7 \pm 0.1) \times 10^6 \text{ l mol}^{-1} \text{ s}^{-1}$$

$$\bar{k}_2 \text{ at } 31^\circ C = (7.4 \pm 0.3) \times 10^6 \text{ l mol}^{-1} \text{ s}^{-1}$$

$$\bar{k}_2 \text{ at } 40^\circ C = (10.6 \pm 0.9) \times 10^6 \text{ l mol}^{-1} \text{ s}^{-1}$$

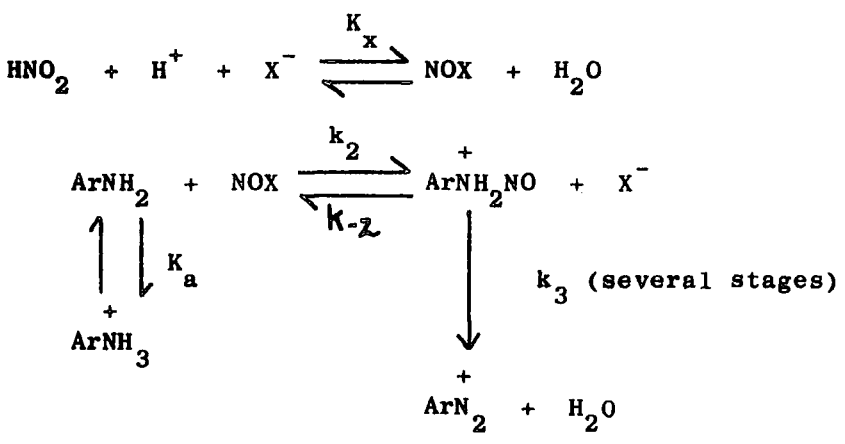
By invoking the Arrenhius equation

$$\log k = \frac{-E_a}{2.303\ RT} + \text{Constant}$$

and by plotting log $\bar{k}_2$ against $^1/T$, a value of 42 ± 6 k J mol^{-1} is obtained for the energy of activation. Although the error is quite large, the value is significantly higher than the range 6-21 k J mol^{-1} found for other diffusion-controlled reactions[147]. Similarly Fen and Tannenbaum[148] have found the activation energy for the nitrosation of morpholine in the presence of thiocyanate ion to be 40 k J mol^{-1}.

5.3 Diazotisation of Aniline

A kinetic analysis of diazotisation of a number of ring-substituted anilines[33] at 25°C effected by nitrosyl bromide and nitrosyl chloride revealed that for bromide ion catalysed reactions the reversibility of the reaction for all those anilines whose $pK_a < 4.0$ was kinetically significant. For the more weakly nucleophilic chloride ion the reversibility was much less marked, with the notable exception of the weakly basic 4-nitroaniline derivative. Hence, the reversibility of $ArNH_2NO^+$ formation competes with the process leading to the diazonium ion, as depicted in the following scheme.



The reversibility is reflected in the ratio k_{-2}/k_3, and it is pertinent to point out that for the same amine the ratio is markedly greater for the bromide ion catalysed reaction than for the corresponding chloride ion catalysed reduction, typically by factors within the range 20 - 80 fold[33]. That this is as expected is not surprising given the greater efficiency of bromide ion over chloride ion catalysed reactions in the denitrosation of secondary nitrosamines. For example, for NMNA[24] $k(Br^-) > k(Cl^-)$ by a factor of 50, and for NDA[30] it is greater by a factor of 25.

Since thiourea is again many times more efficient than bromide ion in the denitrosation of nitrosamines, typically by a factor of 250 for NMNA[46], it may be concluded that the reversibility of thiourea catalysed diazotisation of aniline must also be taken into consideration. Indeed, the data for k_o as a function of added thiourea at constant acid and aniline concentrations set out in Table 44 and portrayed graphically in Figure 13 in the form of k_o versus [Free Thiourea] demonstrates quite clearly that the reverse step is kinetically important.

Table 44

$[Aniline]_T = 6.32 \times 10^{-3}$M, $[NaNO_2] = 2.50 \times 10^{-4}$M, $[H_2SO_4] = .113$M

10^4 [Total Thiourea]	$k_o(s^{-1})$
4.82	.264 ± .005
9.64	.455 ± .009
19.3	.759 ± .007
38.5	1.15 ± .02
57.8	1.33 ± .02
106	1.51 ± .06

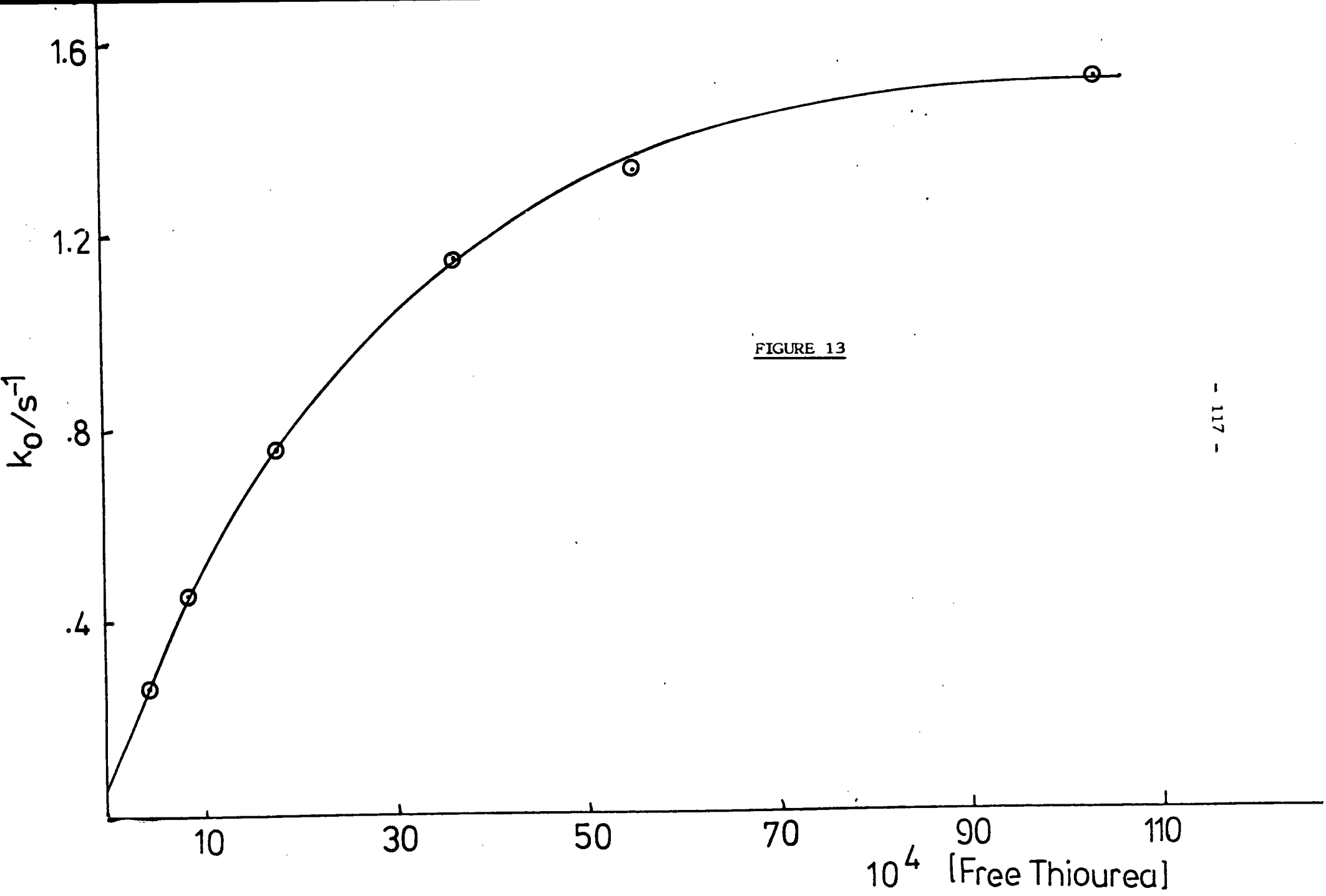


FIGURE 13

Thus, the above scheme is retained for the work in this section, where X^- now represents thiourea.

Assuming $ArNH_2NO^+$ to behave as a reactive intermediate, so that its concentration remains relatively small and constant during the course of the reaction, allows the application of the steady state hypothesis.

$$\text{Rate of formation of } ArNH_2NO^+ = \text{Rate of destruction of } ArNH_2NO^+$$

$$[ArNH_2][NOX]k_2 = [ArNH_2NO^+][X^-]\,k_{-2} + [ArNH_2NO^+]k_3$$

$$[ArNH_2NO^+] = \frac{[ArNH_2][NOX]\,k_2}{k_{-2}[X^-] + k_3}$$

However,

$$\text{Rate} = \frac{d[ArN_2^+]}{dt} = k_3[ArNH_2NO^+]$$

So that,

$$\text{Rate} = \frac{k_2k_3[ArNH_2][NOX]}{k_{-2}[X^-] + k_3}$$

Further,

$$\text{Since } [ArNH_2] = \frac{K_a[ArNH_2]_T}{[H^+]}$$

where $[ArNH_2]_T$ refers to the total concentration of aniline, which may be assumed to be completely protonated,

and,

$$\text{Since } [NOX] = \frac{[\text{Total Nitrite}]}{1 + \frac{1}{K_x [H^+][X^-]}}$$

$$\text{Rate} = \frac{k_2 k_3 [ArNH_2]_T \, K_a [\text{Total Nitrite}]}{(k_{-2}[X^-] + k_3)[H^+]} \left(\frac{1}{1 + \frac{1}{K_x [H^+][X^-]}} \right)$$

But the observed first-order rate constant, k_o, is defined as:-

$$\frac{d[ArN_2^+]}{dt} = k_o [\text{Total Nitrite}]$$

so that,

$$k_o = \frac{k_2 k_3 K_a [ArNH_2]_T}{(k_{-2}[X^-] + k_3)[H^+]} \left(\frac{1}{1 + \frac{1}{K_x [H^+][X^-]}} \right)$$

Thus, the kinetic model predicts that at reasonably low concentrations of thiourea, $k_3 >>> k_{-2}[X^-]$, when k_o reduces to:-

$$k_o = \frac{k_2 K_a [ArNH_2]_T}{\left(1 + \frac{1}{K_x [H^+][X^-]}\right)[H^+]}$$

At constant acidity and thiourea concentration a graph of k_o against $[ArNH_2]_T$ should therefore yield a linear line, and since the slope represents the value of

$$\frac{k_2 K_a}{[H^+]\left(1 + \frac{1}{K_x [H^+][X^-]}\right)}$$

the bimolecular rate constant k_2 may be calculated. The data for such a plot is given in Table 45, and from Figure 14 it is noted that a reasonably linear line is obtained at the lower concentrations of aniline.

Table 45

$[NaNO_2] = 2.57 \times 10^{-4}$M, [Total Thiourea] $= 1.14 \times 10^{-3}$M, $[H_2SO_4] = .113$M

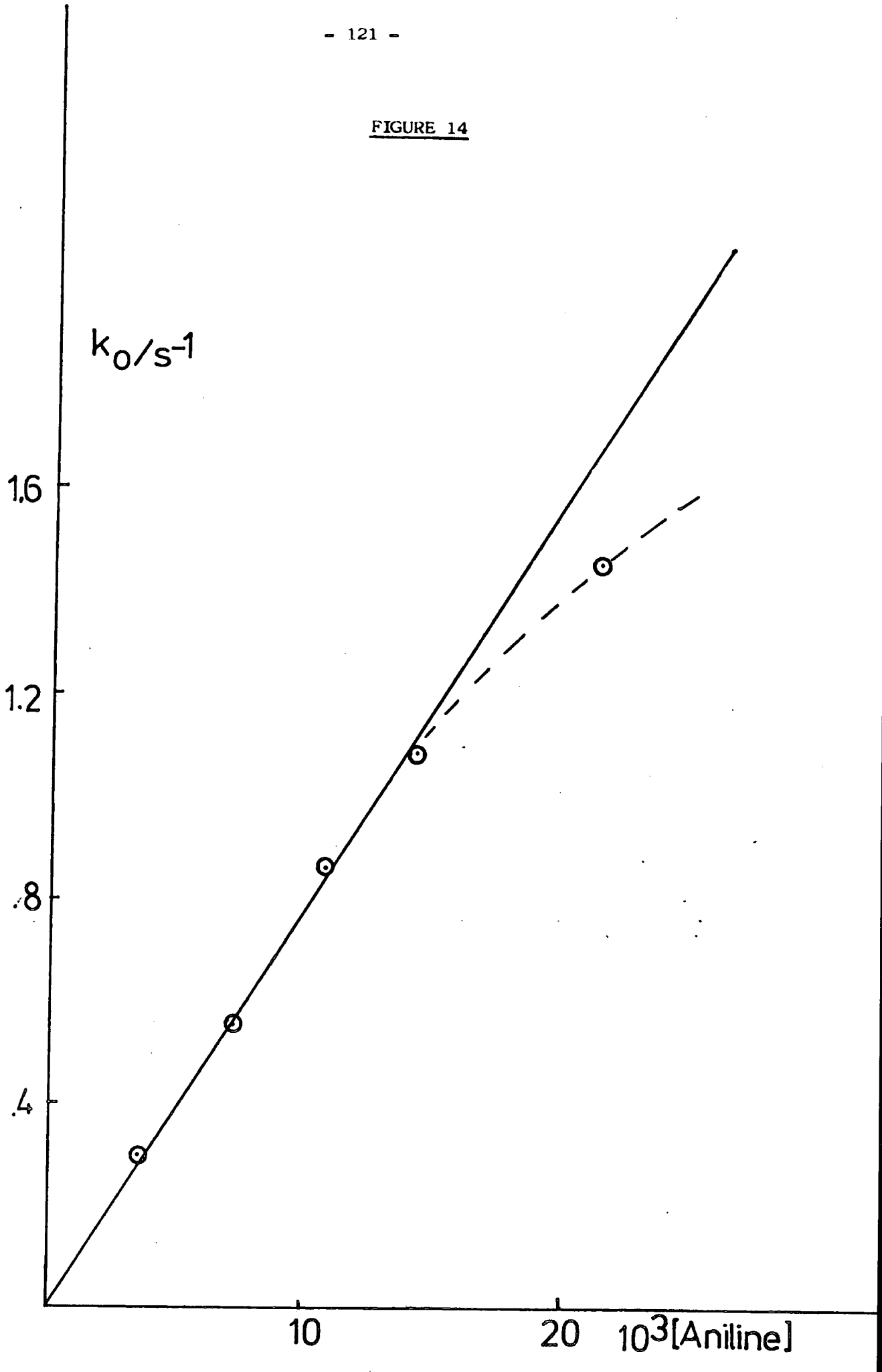
$10^3[ArNH_2]_T$	$k_o(s^{-1})$
0	0
3.54	.304 ± .007
7.07	.558 ± .006
10.6	.861 ± .011
14.1	1.08 ± .03
21.2	1.45 ± .05

The value of the slope of the linear line is 80.3 ± 2.0, leading to the value of k_2 as:-

$$k_2 = 1.04 \times 10^6 \text{ ℓ mol}^{-1}\text{s}^{-1}$$

It is not possible to compare these findings regarding $ONSC(NH_2)_2^+$ reactivity with any other work, since this is, as far as it is known, the first report of such results for direct thiourea catalysis in nitrosation. Hence, the subject of reactivity of $ONSC(NH_2)_2^+$ toward aniline and

FIGURE 14



morpholine will be pursued further in Chapter 6, in conjunction with the reactivities of NOBr and NOSCN.

Reactions were also carried out at $0^{o}C$, and under these conditions there is virtually quantitative conversion of the minor component nitrous acid into $ONSC(NH_2)_2^+$, as the value of K_x is 13,280. The kinetics were followed at 420nm by noting the decrease in the absorbance due to the yellow nitrososulphonium ion. Good first-order plots of log(a-x) versus time were obtained in every case. The results in Table 46 describe k_o as a function of added aniline, at constant acid and thiourea concentrations.

Table 46

$\left[H_2SO_4\right] = .170\underline{M}$, $\left[NaNO_2\right] = 5.45 \times 10^{-4}$, $\left[\text{Thiourea}\right] = 1.08 \times 10^{-2}\underline{M}$

$10^2\left[ArNH_2\right]_T$	$k_o(s^{-1})$
0	0
1.09	.136 ± .010
1.56	.216 ± .012
1.95	.270 ± .018
2.34	.330 ± .015
3.12	.484 ± .023

In terms of the more general rate equation for k_o, the limiting conditions $1 >>> {}^1/K_x\left[H^+\right]\left[X^-\right]$ applies, whence k_o reduces to:-

$$k_o = \frac{k_2\, k_3\, K_a \left[ArNH_2\right]_T}{\left(k_2\left[X^-\right] + k_3\right)\left[H^+\right]}$$

At low concentrations of thiourea, $k_3 >>> k_{-2}[X^-]$, and k_2 may be easily evaluated from the slope of the k_o versus $[ArNH_2]_T$ graph. In this case, however, the concentrations of thiourea is rather high, and from consideration of the results in Figure 13 at 30°C the reversibility of the reaction undoubtedly is kinetically important. Thus, although the graph of k_o against $[ArNH_2]_T$ is reasonably linear, the value of the slope more accurately represents the composite value $k_2\ k_3\ K_a/(k_{-2}[X^-] + k_3)[H^+]$, from which k_2 may not be evaluated. Further work at 0°C was not carried out.

CHAPTER 6

Catalysis by Thiocyanate and Bromide Ions

6.1 Introduction

This chapter is a continuance of the previous chapter in that results are presented here for the bromide ion and thiocyanate ion catalysed reactions of N-nitrosation of morpholine and diazotisation of aniline. The same experimental procedures are used here as were described previously.

6.2 N-nitrosation of Morpholine

It will be recalled from section 5.2 that a first-order dependency upon the concentration of morpholine was established and that the general rate expression for k_o is aptly described by:-

$$k_o = \frac{k_2 K_a \left[\text{Morpholine}\right]_T}{\left(1 + \frac{1}{K_X\left[H^+\right]\left[X^-\right]}\right)\left[H^+\right]}$$

The equilibrium constants, K_X, for the formation of NOBr and NOSCN were interpolated from the appropriate graph of $\ln K_X$ versus $^1/T$ from data given by Schmid and Fouad[143] for NOBr and by Stedman and co-workers[142] for NOSCN formation.

The data for bromide ion and thiocyanate ion catalysed reactions at 31°C are listed in Tables 47 - 50, where a repeated set of experiments are also given for each nucleophile at different morpholine concentrations.

Table 47

$\left[H_2SO_4\right]$ = .113M, $\left[\text{Morpholine}\right]_T$ = .111M, $\left[NaNO_2\right]$ = 9.10 x 10^{-3}M

$\left[KBr\right]$/M	$10^4 k_o (s^{-1})$
.171	3.64
.285	4.71
.570	9.35
.855	13.0
1.14	17.6

Table 48

$[H_2SO_4]$ = .113M [Morpholine] = .181M, $[NaNO_2]$ = 8.64×10^{-3}M

[KBr]/M	$10^4 k_o (s^{-1})$
.21	6.44
.49	11.7
.98	22.1

Table 49

$[H_2SO_4]$ = .113M, [Morpholine] = .118M, $[NaNO_2]$ = 8.74×10^{-3}M

10^3[KSCN]	$10^4 k_o (s^{-1})$
7.69	46.6
15.9	93.5
23.9	138
31.8	179

Table 50

$[H_2SO_4] = .113\underline{M}$, [Morpholine] = $.111\underline{M}$, $[NaNO_2] = 9.10 \times 10^{-3}\underline{M}$

$10^3[KSCN]$	$10^4 k_o (s^{-1})$
7.22	29.0
10.8	43.4
14.4	55.8
18.1	70.3
21.8	83.0
32.2	123
36.4	138
50.9	186
64.4	224
70.8	252
77.3	274
96.6	342
129	440
161	552

For bromide ion catalysis, the value of K_x is 6.00 ℓ^2 mol^{-2} at 31°C, and for all concentrations of bromide ion the limiting condition $^1/K_x[H^+][X^-] >>> 1$ is applicable. Similarly, for thiocyanate ion, the value of K_x is 27.4 ℓ mol^{-2}, and at the lower concentrations of its salt, typically < $0.04\underline{M}$, the preceeding limiting condition is also applicable. Under these conditions, the general form of the above rate equation for k_o now reduces to:-

$$k_o = k_2 K_a [\text{Morpholine}]_T K_x [X^-]$$

Thus, the equation predicts that at constant morpholine and acid concentrations k_o should be linearly dependent upon $[X^-]$ and that at constant concentrations of catalyst and morpholine k_o should be independent from the concentration of solvent acidity.

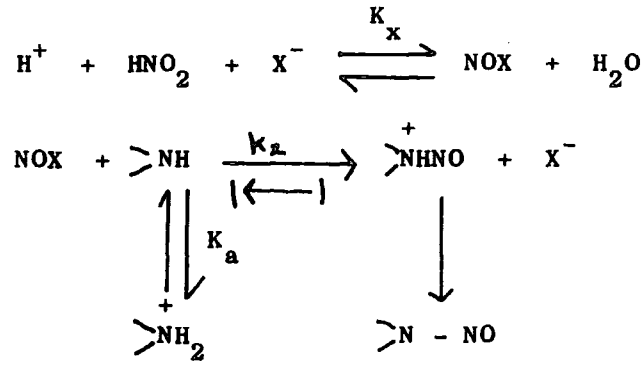
The latter point is borne out by the examination of the data in Table 51, in which it is clearly shown that k_o is indeed unaffected by an increase in the acidity.

Table 51

$[KBr] = .490M$, $[Morpholine] = .170M$, $[NaNO_2] = 8.60 \times 10^{-3}M$

$[H_2SO_4]$	$10^4 k_o (s^{-1})$
.113	11.2
.170	11.2
.227	11.2
.340	11.1
.420	11.7

With reference to the scheme below, the probable explanation for the constancy of k_o over the acid range is that the resultant increase in the equilibrium concentration of NOX is offset by a corresponding decrease in the concentration of unprotonated morpholine. Thompson and Williams likewise found for the analogous situation of the diazotisation of aniline via NOBr that k_o remained unchanged upon doubling the acid concentration[33].



The linear dependence of k_o upon the concentrations of bromide ion and thiocyanate ion at the lower concentrations is shown Figure 10. At the higher concentrations of thiocyanate ion, the plot of k_o against $[SCN^-]$ does curve off as the limiting form becomes less applicable, which is as expected if the value of K_x is markedly larger than for bromide ion.

Since the slopes of such plots represent the value of $k_2K_aK_x\text{Morpholine}_T$, the bimolecular rate constant, k_2, for attack of NOX on the free form of morpholine may be calculated. The slopes of the individual graphs and their corresponding values of k_2 are set out below in Table 52.

Table 52

X^-	slope	$10^{-7}k_2(\ell\ mol^{-1}s^{-1})$
Br^-	$(1.45 \pm .04) \times 10^{-3}$	5.22
Br^-	$(2.04 \pm .06) \times 10^{-3}$	4.50
SCN^-	$.370 \pm .006$	2.92
SCN^-	$.550 \pm .008$	2.66

The mean values of k_2 for the NOBr and NOSCN reactions are $(4.9 \pm 0.5) \times 10^7$ ℓ $mol^{-1}s^{-1}$ and $(2.8 \pm 0.2) \times 10^7$ ℓ $mol^{-1}s^{-1}$, respectively. In addition, for the NOSCN reaction, a value of k_2 may also be determined from the variation of k_o with $[Mopholine]_T$ at constant $[SCN^-]$, as shown in Figure 11. This yielded a value of 2.9×10^7 ℓ $mol^{-1}s^{-1}$ in excellent agreement with the value quoted above.

Thus, the bimolecular rate constants for the N-nitrosation of morpholine have been determined for each of the nitrosating agents, NOBr, NOSCN, and $ONSC(NH_2)_2^+$, and, for convenience, these are drawn up in Table 53.

Table 53

NOX	$10^7 k_2$ (ℓ mol^{-1} s^{-1})
NOBr	4.9
NOSCN	2.8
$NOSC(NH_2)_2^+$	.74

Recently, there has been considerable interest in the area of diffusion-controlled reactions[147], and the interesting feature in the data in Table 53 is the overall small range of reactivity, which in itself suggests that the reaction rates are approaching the diffusion-controlled limit. However, not only are the individual magnitudes of the k_2 values approximately 100 times smaller than those expected for such reactions in water at 31°C, but the measured energy of activation of 42 ± 6 k J mol^{-1} for the $NOSC(NH_2)_2^+$ reaction lends strong evidence to the conclusion that the reaction rates are not nearing those expected for a diffusion-controlled process.

Unexpected as this small range of reactivity may be, Stedman and co-workers[40] showed that a similar situation exists for the nitrosation of hydroxylamine and its O-methyl derivative, where NOBr and NOCl have much the same reactivity. Yet, the k_2 values for these reactions are again approximately 100 times lower than those expected for diffusion-controlled processes. However, the result presented here are in accord with the earlier observation that NOBr is more reactive than NOSCN in the nitrosation of hydroxylamine and O-methylhydroxylamine[40], as well as in the nitrosation of the hydrazinium ion[150].

It seems clear, then, that an explanation of the overall catalytic efficiency of these nitrosating agents toward morpholine does not lie in the individual magnitudes of k_2. Rather, because the range of reactivity for k_2 is so close together, the main factor deciding the extent of catalysis seems to be the actual size of the equilibrium constant, K_x, for the formation of NOX. Therefore, since K_x for $NOSC(NH_2)_2^+$ is markedly larger than either K_x for NOSCN or NOBr, thiourea is observed to have a significantly greater acceleratory effect on the rate of reaction. Similarly, for the same reasons, thiocyanate catalyses the reaction to a much greater extent than bromide ion.

6.3 Diazotisation of Aniline

Reactions were carried out at 30°C and 0°C, and the results measured at 30°C are given below in Tables 54 and 55 for the variation of k_o with $[Br^-]$ and $[SCN^-]$. Each value of k_o is in fact the mean value of at least five separate determinations.

Table 54

$[H_2SO_4] = .113\underline{M}$, $[ArNH_2]_T = 1.83 \times 10^{-2}\underline{M}$, $[NaNO_2] = 9.61 \times 10^{-4}M$

$10^2 [KBr]$	$k_o(s^{-1})$
1.73	1.48 ± .03
2.59	2.11 ± .04
3.45	2.70 ± .06
4.32	3.28 ± .05
5.18	3.77 ± .04
6.90	4.79 ± .06
8.63	5.63 ± .09

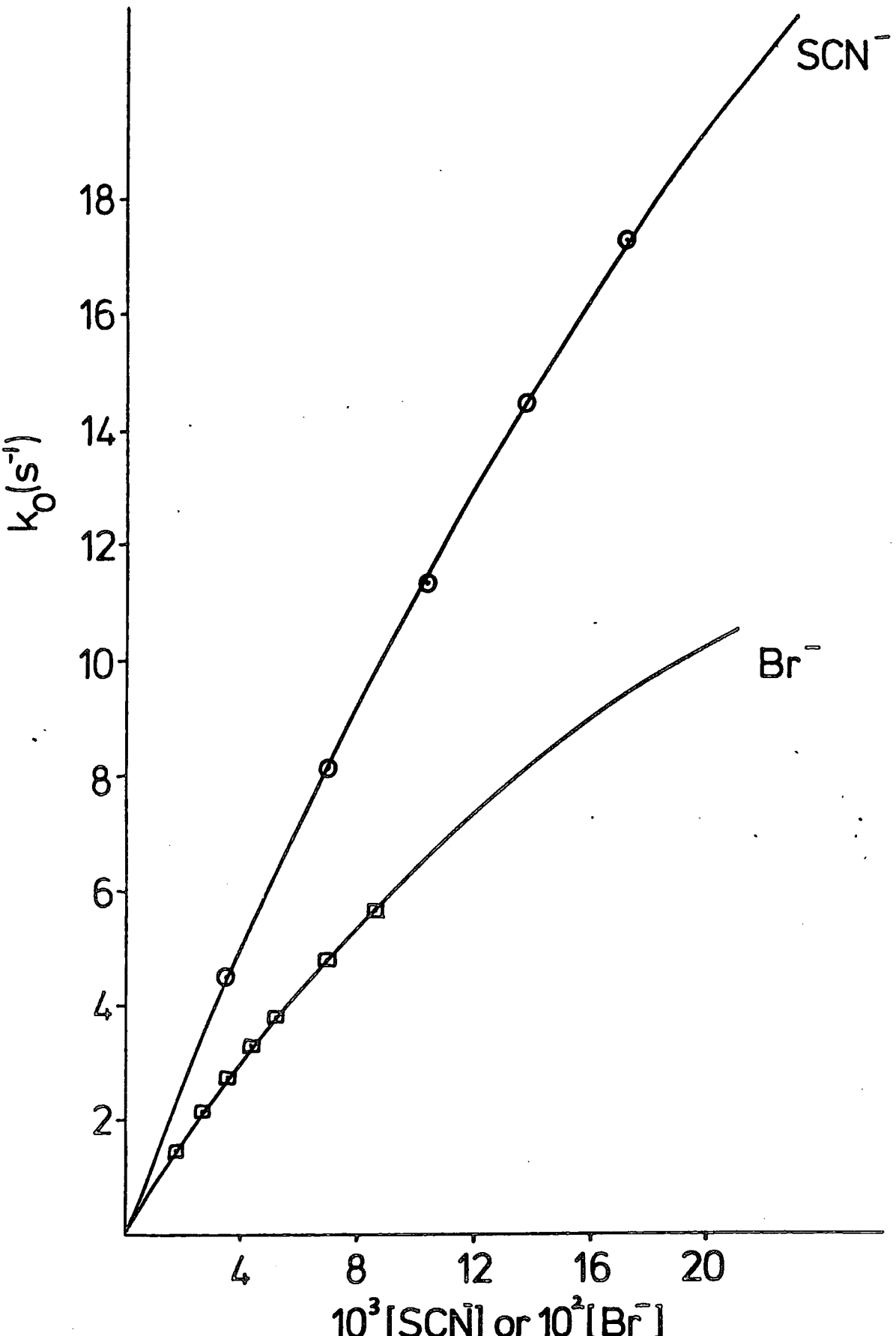
Table 55

$[H_2SO_4] = .113\underline{M}$, $[ArNH_2]_T = 1.87 \times 10^{-2}\underline{M}$, $[NaNO_2] = 1.03 \times 10^{-3}\underline{M}$

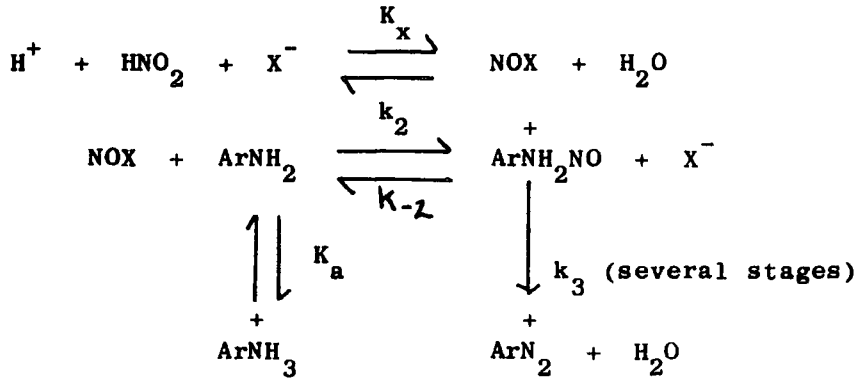
$10^3 [KSCN]$	$k_o(s^{-1})$
3.47	4.51 ± .13
6.94	8.14 ± .07
10.4	11.3 ± .2
13.9	14.4 ± .3
17.4	17.3 ± .5

Clearly, there is catalysis in each case, and this is further represented graphically in Figure 15. Under the prevailing experimental conditions, it is noted that the plot for each nucleophile is decidely curved, indicating that at the higher concentrations of bromide ion and thiocyanate ion the reverse reaction, denitrosation of the primary

FIGURE 15



nitrosamine becomes kinetically significant. The results are consistent with the mechanism outlined below.



As before in section 5.3, a steady-state treatment on the reactive intermediate $ArNH_2^+NO$ leads to the following rate expression for k_o:-

$$k_o = \frac{k_2\, k_3\, K_a\, K_x \left[X^-\right]\left[ArNH_2\right]_T}{k_{-2}\left[X^-\right] + k_3}$$

This equation differs from the one derived for the thiourea catalysed reactions in section 5.3 in that for all concentrations of bromide ion and thiocyanate ion used $^1/K_x\left[H^+\right]\left[X^-\right] >>> 1$.

Rewriting this equation in the reciprocal form

$$k_o^{-1} = \frac{1}{k_2\, K_a\, K_x \left[ArNH_2\right]_T \left[X^-\right]} + \frac{k_{-2}}{k_2\, k_3\, K_a\, K_x \left[ArNH_2\right]_T}$$

it is apparent that a straight line should result from the graph of k_o^{-1} against $\left[X^-\right]^{-1}$. Indeed, the linearity of the plots of k_o^{-1} versus $\left[X^-\right]^{-1}$ is shown in Figure 16, and the values of the slopes and y-intercepts

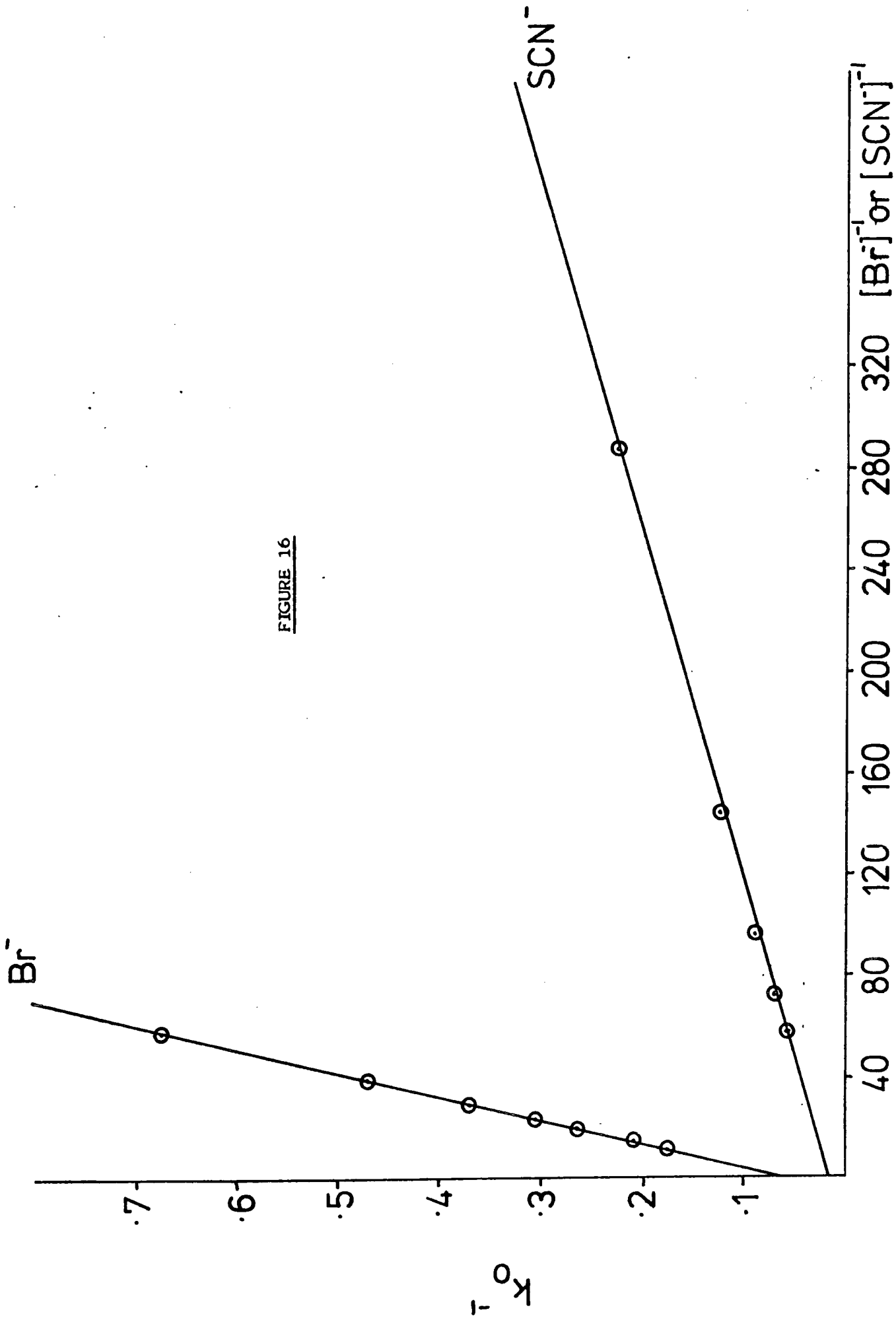


FIGURE 16

are given in Table 56.

Table 56

X^-	slope	y-intercept
Br^-	$(1.08 \pm .01) \times 10^{-2}$	$(5.50 \pm .20) \times 10^{-2}$
SCN^-	$(7.10 \pm .09) \times 10^{-4}$	$(1.88 \pm .15) \times 10^{-2}$

Given that the slope of the line represents the value of $^1/_{k_2 K_x K_a ArNH_2 T}$ the following values of k_2 were determined for the reactions of NOBr and NOSCN with the unprotonated form of aniline.

$$k_2 \text{ (NOBr)} = 2.70 \times 10^9 \text{ ℓ mol}^{-1}\text{s}^{-1}$$

$$k_2 \text{ (NOSCN)} = 8.81 \times 10^7 \text{ ℓ mol}^{-1}\text{s}^{-1}$$

For the NOBr reaction, the present value quoted here is in satisfactory agreement with the k_2 value of 3.2×10^9 ℓ $mol^{-1}s^{-1}$ determined by Schmid[143] and with that of 1.8×10^9 ℓ $mol^{-1}s^{-1}$ obtained by Thompson[33]. It is not possible to compare the finding for the NOSCN reaction, since, as far as it is known, this is the first recorded value for its reaction with aniline.

A repeated set of experiments for the thiocyanate ion catalysed reaction was carried out, the results of which are presented in Table 57.

Table 57

$[H_2SO_4] = .113\underline{M}$, $[ArNH_2]_T = 1.59 \times 10^{-2}\underline{M}$, $[NaNO_2] = 8.04 \times 10^{-4}\underline{M}$

$10^3[KSCN]/\underline{M}$	$k_o(s^{-1})$
4.37	5.26 ± .07
5.45	6.45 ± .14
8.20	9.07 ± .17
10.9	11.6 ± .23

Again, plotting the reciprocal values of k_o against $[SCN^-]$ and calculating the value for k_2 from the slope of the line leads to the determination of k_2 as:-

$$k_2(NOSCN) = 9.76 \times 10^7 \text{ ℓ mol}^{-1} \text{ s}^{-1}$$

Taking the mean value of the two separate evaluations yields:-

$$\bar{k}_2 (NOSCN) = (9.29 \pm .67) \times 10^7 \text{ ℓ mol}^{-1}\text{s}^{-1}$$

The agreement between the two values is, therefore, quite good.

The numerical values of the y-intercepts represent the value of $k_{-2}/k_2\ k_3\ K_a\ K_x [ArNH_2]_T$ and by substitution of the above values for k_2 enables the calculation of the ratio k_{-2}/k_3, which gives a measure of the extent of reversibility for each of the reactions.

$$k_{-2}/k_3 (NOBr) = 5.09$$

$$k_{-2}/k_3 (NOSCN) = 26.5$$

The present value for the NOBr reaction agrees quite nicely with that of 3.63 determined by Thompson[151].

Recalling that SCN^- is a much more powerful nucleophile than Br^- by a factor of 100 in denitrosation of NMNA[24] and by 7 in the denitrosation of NDA[30], it is expected that the above ratio for the thiocyanate ion catalysed reaction should be significantly larger than the corresponding ratio for the bromide ion catalysed reaction.

Thus, given that ratios presented here are greater than unity, it must be emphasized that the principle of reversibility for the diazotisation of aniline is always kinetically important for the more powerful nucleophiles. This in contrast to the much weaker nucleophilic chloride ion catalysed reaction, where the ratio was found to be 0.10[151].

Rate measurements carried out at 0^oC for both of these anion-catalysed reactions are given in Tables 58 and 59 in the form of k_o^{-1} and $\left[X^-\right]^{-1}$.

Table 58

$\left[H_2SO_4\right] = .113\underline{M}$, $\left[ArNH_2\right]_T = 1.89 \times 10^{-2}\underline{M}$, $\left[NaNO_2\right] = 1.=1 \times 10^{-3}\underline{M}$

$\left[Br^-\right]^{-1}$	k_o^{-1}
8.93	1.49
10.5	1.69
12.9	2.22
16.6	2.72
19.3	3.13
23.1	3.65
29.0	4.42

Table 59

$[H_2SO_4] = .113\underline{M}$, $[ArNH_2] = 2.57 \times 10^{-2}\underline{M}$, $[NaNO_2] = 1.16 \times 10^{-3}\underline{M}$

$[SCN^-]^{-1}$	k_o^{-1}
49.0	.541
16.3	.641
81.6	.826
123	1.18
245	2.15

From the graphs of k_o^{-1} versus $[X^-]^{-1}$ the slopes of the individual plots are .147 ± .004 and (8.20 ± .11) x 10^{-3} for the Br^- and SCN^- catalysed reactions, respectively. Determining k_2 in the same way as for the reactions at 30°C, leads to the following values:

$$k_2 \text{ (NOBr)} = 2.01 \times 10^9 \ell \text{ mol}^{-1} \text{ s}^{-1}$$

$$k_2 \text{ (NOSCN)} = 1.26 \times 10^7 \ell \text{ mol}^{-1} \text{ s}^{-1}$$

Invoking the Arrenhius equation gives the activation energies for both reactions as 6.9 k J mol^{-1} for NOBr and 46.3 k J mol^{-1} for NOSCN. The value for the NOBr reaction falls within the range expected for a diffusion-controlled reaction, and compares well with that of 6.1 k J mol^{-1} obtained by Schmid and Fouad [143] for the same reaction. The value for the NOSCN reaction, however, is significantly higher than the range 6-21 k J mol^{-1} found for other diffusion-controlled reactions[147].

Thus, the bimolecular rate constants for the diazotisation of aniline at 30°C effected by NOBr, NOSCN and $ONSC(NH_2)_2^+$ have been calculated, and these are summarised in Table 60.

Table 60

NOX	$10^{-9}k_2$ (ℓ $mol^{-1}s^{-1}$)
NOBr	2.70
NOSCN	.093
$ONSC(NH_2)_2^+$	.001

Clearly, $ONSC(NH_2)_2^+$ is not as reactive towards aniline as is NOSCN or NOBr; however, because of the large equilibrium constant for its formation from nitrous acid and thiourea, the overall effect is that thiourea is a better catalyst than bromide ion, but not in this case as good as thiocyanate ion. Moreover, because the values for k_2 are not as close together, the effect here is not so marked as in the case of morpholine where the overall catalytic efficiency is governed almost totally by the magnitudes of the K_x values. In general, however, thiourea makes a good catalyst for the diazotisation of aniline.

On first inspection, it is surprising to note that the free base form of morpholine (pK_a = 8.38 at 30°C) is less reactive than aniline (pK_a = 4.51 at 30°C) towards nitrosation. However, there are a number of examples in which the k_2 values for the nitrosation of aliphatic amines brought about by the nitrosyl halides are significantly less than their high bascisities would suggest. For example, for the NOBr reaction, the k_2 value for ammonia (pK_a = 9.24 at 25°C) is smaller than the k_2 value for aniline by a factor of 100[107]. In addition, when the

Pearson 'n' value is used as a measure of nucleophilicity, there are a number of examples where the bascisity and nucleophilicity trends are not parallel, such as for imidazole and aniline[32].

6.4 N-nitrosation of Diethanolamine

Nitrosation of diethanolamine, DEA, has been reported in the literature, chiefly in connection with the possible contamination of various cosmetics and industrially-used cutting fluids by nitroso-diethanolamine, NDELA[152]. Given the indisputable carcinogenicity of nitrosamines in animals, there is considerable concern that NDELA may also present a human health hazard, especially to those people who are exposed to it regularly. Because DEA is another example of a typical aliphatic secondary amine and because no detailed kinetic examinations have been reported, it was thought of interest to undertake such a study. The results for the bromide ion and thiocyanate ion catalysed nitrosation of DEA are presented and discussed in this section.

For each individual kinetic experiment the $[\text{Amine}] >>> [HNO_2]$, and linear plots of log (a-x) against time were always obtained, thus establishing good first-order behaviour with respect to the nitrous acid concentration. Under these conditions, the first-order rate constant, k_o, is defined by

$$\text{Rate} = -d[HNO_2]/dt = k_o[HNO_2]$$

where HNO_2 refers to the total nitrite concentration.

The kinetic order with respect to the diethanolamine concentration was investigated, and the data for k_o as a function of added DEA are tabulated in Table 61.

Table 63

$[H_2SO_4] = .106\underline{M}$, $[DEA] = .102\underline{M}$, $[NaNO_2] = 2.04 \times 10^{-4}\underline{M}$

$10^3[KSCN]/\underline{M}$	$10^4 k_o (s^{-1})$
3.21	4.50
6.42	8.45
12.8	17.0
19.3	25.2
25.7	33.6
32.1	40.6

The above results may all be interpreted in terms of the reaction scheme outlined below.

$$H^+ + HNO_2 + X^- \underset{}{\overset{K_x}{\rightleftharpoons}} NOX + H_2O$$

$$NOX + (HO\,CH_2\,CH_2)_2\,NH \xrightarrow{k_2} (HO\,CH_2\,CH_2)_2\,\overset{+}{N}HNO + X^-$$

$$\uparrow\downarrow K_a \qquad\qquad \downarrow$$

$$H_2\overset{+}{N}\,(CH_2\,CH_2\,OH)_2 \qquad\qquad H^+ + (HOCH_2\,CH_2)_2\,NNO$$

As for the Br^- and SCN^- catalysis of the N-nitrosation of morpholine $^1/_{K_x[X^-][H^+]} >>> 1$ and the rate expression for k_o is accurately described by:

$$k_o = k_2\,K_a\,K_x\,[DEA]_T\,[X^-]$$

FIGURE 17

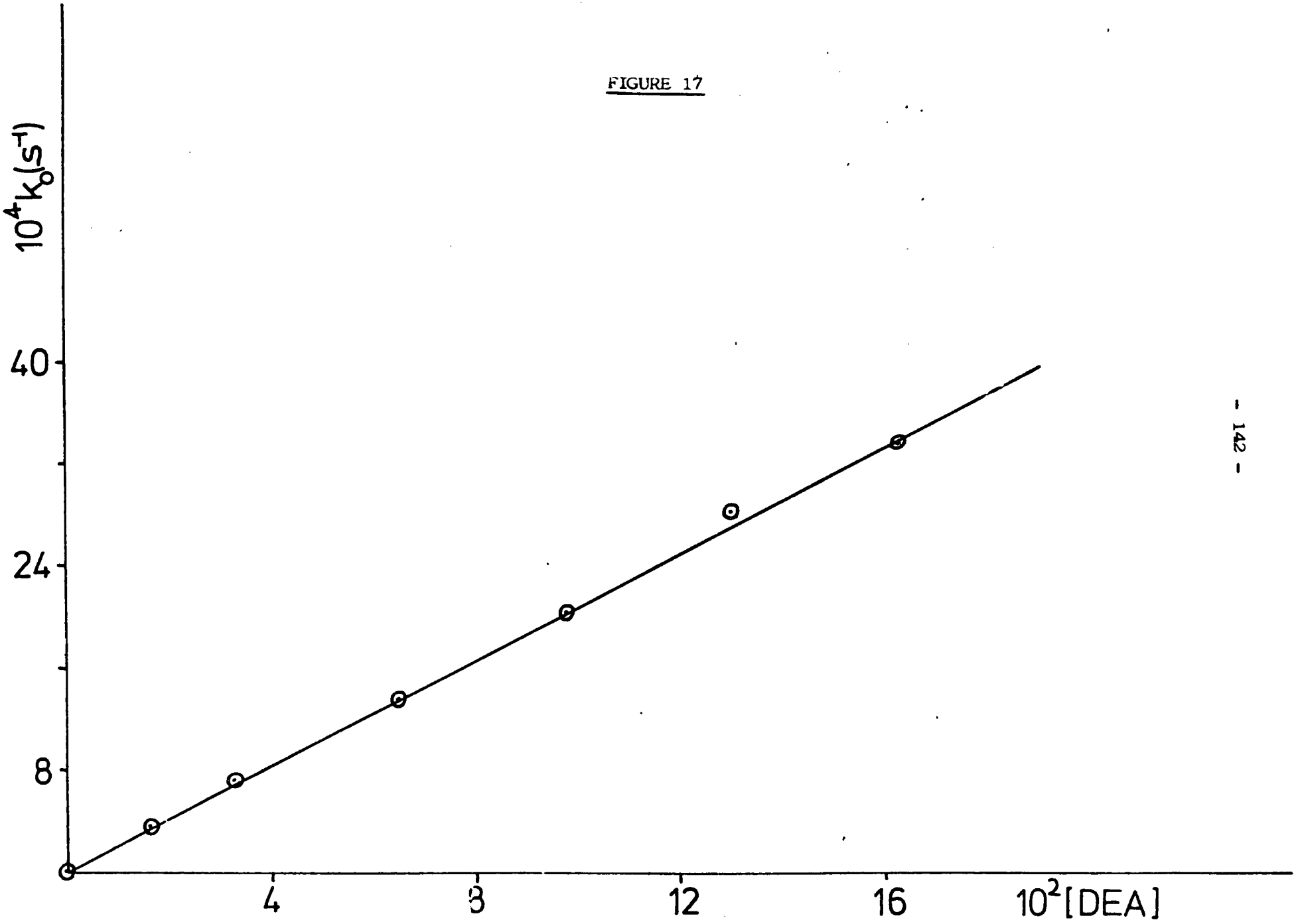


Table 61

$[H_2SO_4] = .416\underline{M}$, $[KSCN] = 2.19 \times 10^{-2}\underline{M}$, $[NaNO_2] = 2.86 \times 10^{-4}\underline{M}$

$[DEA]/\underline{M}$	$10^4 k_o (s^{-1})$
0	0
1.63	3.67
3.26	7.17
6.52	13.6
9.78	20.4
13.0	28.3
16.3	33.7

As expected the graphical representation of these date in Figure 17 clearly establishes a first-order dependency with respect to $[DEA]$.

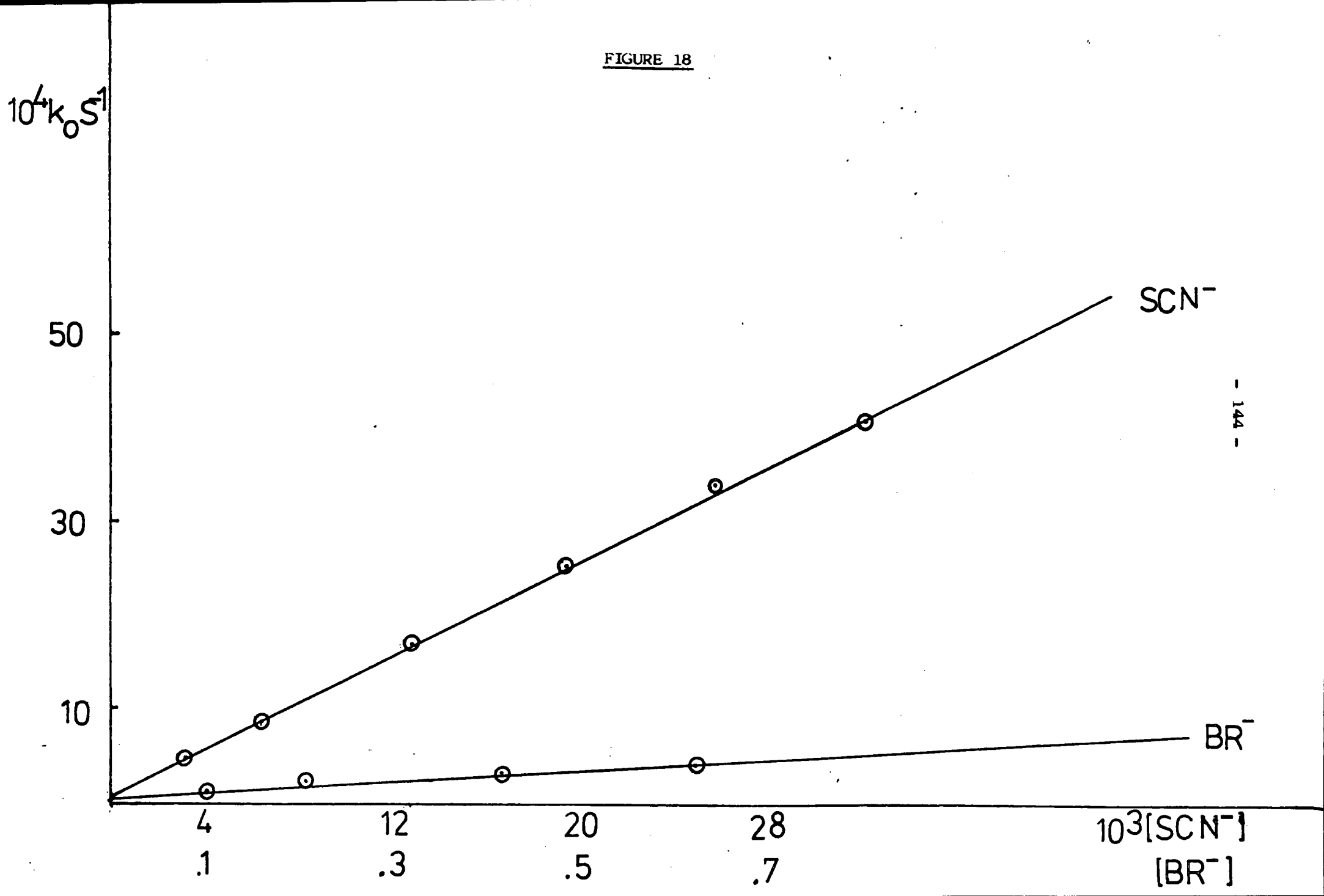
The results for k_o with [catalyst] at constant DEA and acid concentrations are given in Tables 62 and 63, and portrayed graphically in Figure 18. Clearly, there is catalysis in each case, with the extent of catalysis for SCN^- markedly greater than that for Br^-.

Table 62

$[H_2SO_4] = .106\underline{M}$, $[DEA] \simeq .102\underline{M}$, $[NaNO_2] = 1.02 \times 10^{-3}\underline{M}$

$[KBr]/\underline{M}$	$10^4 k_o (s^{-1})$
.107	1.16
.208	1.84
.416	3.06
.624	4.05

FIGURE 18



which predicts a first-order dependence upon $[X^-]$ and independence from the solvent acidity. The data in Figure 18 do indeed give linear plots of k_o against $[X^-]$ and Table 64 formally demonstrates the constancy of k_o, within experimental error, over the acidity range .1 - .41M H_2SO_4. In fact, there is a slight decrease in the values of k_o, which may be attributed to an increasing degree of protonation of thiocyanate ion. Thus, the decrease in the concentration of unprotonated amine is offset by the acid concentration term in the equilibrium constant for NOX formation from nitrous acid, and, in this case, thiocyanate ion.

Table 64

$[DEA]_T$ = .102M, $[KSCN]$ = 1.42×10^{-3}M, $[NaNO_2]$ = 2.04×10^{-4}M

$[H_2SO_4]$/M	$10^4 k_o (s^{-1})$
.106	9.10
.211	8.57
.317	8.31
.422	8.01

Values of k_2 for both of these anion-catalysed reactions are obtained from the slopes of the linear plots of k_o against $[X^-]$.

$$k_2 \text{ (NOBr)} = 6.31 \times 10^7 \text{ ℓ mol}^{-1} \text{ s}^{-1}$$

$$k_2 \text{ (NOSCN)} = 3.13 \times 10^7 \text{ ℓ mol}^{-1} \text{ s}^{-1}$$

For the NOSCN reaction, a value of k_2 of 3.16×10^7 ℓ mol^{-1} s^{-1} was also obtained from data in Table 61 for the variation of k_o with $[DEA]$ at constant $[SCN^-]$.

As in the nitrosation of morpholine, the bimolecular rate constants for the nitrosation of diethanolamine via NOBr and NOSCN are rather close together, so that the main influence governing the enhanced catalytic effect of thiocyanate ion over bromide ion is the larger magnitude of the K_x value for NOX formation.

The pK_a of diethanolamine[149] is 8.84 at 31°C, and for the same reasons outlined earlier for morpholine, and in accordance with other aliphatic secondary amines, to wit ammonia, hydroxylamine and its O-methyl derivative, the actual magnitudes of k_2 are markedly less than expected from the high pK_a value.

CHAPTER 7

Experimental Details

7.1 Experimental Details for Chapter 2

7.1.1 Preparation and Purification of Chemical Reagents

N-methyl-N-nitrosoaniline was prepared from sodium nitrite and N-methylaniline in the usual manner[153], and was purified by fractional distillation under reduced pressure using an automated Fisher Spalthor HMS 500 column and stored under nitrogen. The other N-substituted-N-nitrosoanilines, N-Et, N-pr^n, N-pr^i, were prepared in a similar fashion.

Analar grades of inorganic reagents potassium bromide, potassium thiocyanate, thiourea, sodium azide, and sulphuric acid were used as supplied.

Analar grades of ascorbic acid were used. Ethanolic HCl solutions were made by passing dry gaseous HCl into absolute ethanol. The gaseous HCl was dried by first bubbling it through a tower of concentrated sulphuric acid.

7.1.2 Rate Measurements

The kinetics of the system was monitored spectrophotometrically using a conventional double beam Beckman model 25 recording spectrophotometer. Reactions were carried out in 1cm silica cells. Typically, one silica cell containing the solvent and one containing the reaction mixture were placed in electrically-thermostatted compartments for the reference and the sample beams, respectively, and maintained at the constant temperature of 31^{o}C. The rate constants were determined by noting the disappearance of the nitrosamine absorption at fixed wavelength, in the range 300 - 315 nm, as a function of time.

Generally, for a simple first-order reaction A $\rightarrow$ B + C the rate is proportional to the instantaneous concentration of the reactant A, so that:-

$$\frac{dx}{dt} = k_o (a - x)$$

where X represents the concentration of A that has decomposed, a is the initial concentraton of A, and (a - x) is the remaining concentration of A after time, t. Integration of this equation yields:-

$$- \ln (a - x) = k_o t + \text{constant}$$

The limits of integration are taken as X = o at t = o, whence the constant of integration is equivalent to -lna, and the integrated equation becomes:-

$$\ln (a - x) = -k_o t + \ln a$$

Thus a plot of ln (a - x) versus time should be linear with slope = $-k_o$.

One of the advantages of first-order kinetics is that the value of the molar absorptivity constant relating the concentration of A to its absorbance is not required. Thus, a consideration of the values of absorbance as a function of time for the disappearance of the nitrosamine leads to the direct determination of k_o, the observed first-order rate constant.

In terms of absorbance, the concentration of A at time t then corresponds to $A_t - A_\infty$, where A_t is the absorbance at time, t, and A_∞ is the absorbance when > 99% of reaction is complete. The infinity value, A_∞ was determined in each case after a period of ten half-lives, and the disappearance of A_t was followed for at least two half-lives.

For the kinetic experiments in aqueous media, two flasks, one containing the stock nitrosamine solution and one containing 49 ml

volumes of sulphuric acid, sodium azide, and the appropriate nucleophile were thermostatted in a water bath at 31°C for a minimum of 15 minutes. Reaction was initiated by injecting 1 ml volume of the stock nitrosamine solution into the 49 ml volumes of the sulphuric acid solution containing all other reagents to make up a total of 50 ml volumes. An aliquot of this reaction mixture was then transferred to a silica cell and placed immediately in the spectrophotometer. This experimental procedure provides an easy method of varying [nucleophile] whilst maintaining all else constant by varying the number of ml volumes of stock nucleophile solution added to make up the 49 ml volumes of the sulphuric acid solution, and adjusting the corresponding water content so that the total volume equals 49 ml.

For example, the kinetic run quoted in Table 65 contains 1 ml volume of stock N-npropyl-N-nitrosoaniline (1.48×10^{-2}M), 20 ml volumes of stock sulphuric acid (1.20M), 2 ml volumes of stock sodium azide (0.21M), 5 ml volumes of stock thiourea (1.47M) and 22 ml volumes of demineralised water. Values of k_o have been calcualted at each time from the equation:-

$$k_o = \frac{1}{t} \ln \frac{A_o - A_\infty}{A_t - A_\infty}$$

In general, good first-order behaviour was found for every kinetic experiment.

Table 65

t (sec)	A_t	$10^2 k_o (sec^{-1})$
0	.651	-
6	.605	1.43
12	.563	1.43
17	.524	1.43
24	,491	1.40
30	.459	1.40
36	.428	1.41
42	.400	1.42
48	.371	1.45
54	.349	1.43
60	.328	1.44
66	.308	1.44
72	.288	1.41
∞	.092	

$$k_o = (1.43 \pm .02) \times 10^{-2} \text{ sec}^{-1}$$

A similar experimental procedure was adopted for the kinetic runs in ethanolic HCl solvent. The stock solutions of ethanolic HCl and of ascorbic acid were not infinitely stable, and fresh solutions of each were prepared daily. The following example is for reaction of N-isopropyl-N-nitrosoaniline (2.28×10^{-3} M) containing ascorbic acid (4.36×10^{-2} M) and hydrochloric acid (.264M). Again, values of k_o were calculated at each time using the equation quoted above.

Table 66

t (sec)	A_t	$10^2 k_o (sec^{-1})$
0	.787	-
15	.703	1.01
30	.629	1.02
45	.562	1.04
60	.508	1.04
75	.460	1.04
90	.421	1.05
105	.387	1.05
120	.358	1.05
∞	.187	

$k_o = (1.04 \pm 01) \times 10^{-2}\ sec^{-1}$

A measurement of the acidity was obtained by titration of a suitably sized aliquot of an reaction mixture with a standardised solution of sodium hydroxide using phenol red as an indicator. In case of the ethanolic HCl solutions, the indicator was first dissolved in demineralized water to prevent its precipitation in absolute ethanol.

7.2 Experimental Details for Chapter 3.

7.2.1 Preparation and Purification of chemical Reagents

NANT was prepared and purified by Professor Ray Bonnett from Queen Mary College, London, who first reported its synthesis[77].

NAT was of the highest purity grade available commercially and was used without further purification. Salts such as potassium bromide, potassium chloride, potassium thiocyanate, potassium iodide, thiourea, sodium azide, citric acid and disodium phosphate were all of analar grade. 4-nitroaniline and 4-chloroaniline were recrystallised from

aqueous ethanol.

For reactions carried out in McIlvaine's citric acid-disodium phosphate buffer over the pH range 2-7, the constituents of each pH composition are given in Table 67. The pH of each individual reaction mixture was measured on a pH meter after first standardising with known buffer strengths of pH4 and pH9.

Table 67

pH	.10M citric acid (ml)	.20M disodium phosphate
2.41	98	2
3.12	79	21
3.96	62	38
4.93	49	51
5.45	42	58
5.91	37	63
6.15	34	66
6.82	18	82

For reactions at constant pH, a buffer solution consisting of 660 ml volumes of 0.2M disodium phosphate and 340 ml volumes of 0.1M citric acid was prepared to give a measured pH value of 6.10. All stock solutions of various salts were made up with this buffer solution.

7.2.2 Rate Measurements

Rate measurements were made using a Pye-Unicam SP8-100 or a Beckman model 25 recording spectrophotometer at 31°C. A reaction monitored by each instrument gave values of k_o that differed from each other by less than 3%. The kinetics were followed by continuously monitoring the disappearance of the peak at 335 nm due to NANT as a function of time. NANT was found to be extremely unstable in solution, and therefore all reactions were started by first dissolving NANT in 1 ml volume of analar methanol.

For these experiments conducted at higher acidity a flask containing an aqueous solution of 24 ml volumes of sulphuric acid and the appropriate additive and a flask of analar methanol were pre-warmed in a water bath at 31°C. Reaction was initiated by dissolving a suitable quantity of NANT in 1 ml volume of analar methanol, and then to this was added the aqueous sulphuric acid solution containing any other reagent. Good first-order plots were obtained from the normal integrated rate equation and the rate constants were reproducible to within ± 5%. A typical run is given in Table 68 for reaction of NANT (6.0×10^{-5}M) in sulphuric acid (4×10^{-2}M) containing sodium azide (1.35×10^{-2}M). Instantaneous values of k_o were calculated from $k_o = {}^{1}/_{t} \ln \frac{A_t - A_\infty}{A_o - A_\infty}$.

For reactions in the buffer solution at constant pH6, the same experimental procedure was adopted. The following example in Table 69 is for reaction of NANT (5.5×10^{-6}M) in buffer solution (pH 6.07) containing potassium iodide (4.73×10^{-4}M). Instantaneous values of k_o were determined from the equation quoted above.

Table 68

t (sec)	A_t	$10^3 k_o (sec^{-1})$
0	.743	-
20	.701	3.08
40	.664	2.98
60	.628	2.97
80	.592	3.01
100	.560	3.01
120	.529	3.02
140	.600	3.02
160	.473	3.02
180	.449	3.00
200	.427	2.98
220	.401	3.02
240	.381	3.01
∞	.039	-

$k_o = (3.01 \pm .3) \times 10^{-4} sec^{-1}$

Table 69

t (sec)	A_t	$10^4 k_o (sec^{-1})$
0	.521	-
100	.483	7.89
200	.450	7.64
300	.412	8.12
400	.380	8.26
500	.352	8.23
600	.324	8.33
700	.299	8.36
800	.277	8.34
900	.258	8.27
1000	.238	8.32
1100	.224	8.19
1200	.206	8.24
∞	.020	

$k_o = (8.18 \pm .21) \times 10^{-4} sec^{-1}$

The ultraviolet spectra of the reaction solution after >10 half-lives was identical in every case with those of NAT in the appropriate solvent.

The total release of nitrous acid was determined quantitatively by running a typical reaction of NANT (3.902×10^{-4}M) in the presence of p-chloroaniline (5.72×10^{-3}M), and no other nitrite trap, in aqueous sulphuric acid (3.96×10^{-2}M) containing potassium bromide (4.36×10^{-3}M). After ten half-lives a 4 ml aliquot from this reaction mixture was removed and added to 16 ml volumes of a solution containing an excess of 2-naphthol-3,6-disulphonic acid (4.93×10^{-3}M) in borax. The absorbance of the resultant red azo-dye was measured at 500 nm using a Pye-Unicam SP8-100 spectrophotometer. A similar 4 ml aliquot containing NAT in place of NANT and all other reagents produced no red azo-dye when added to 16 ml volumes of an excess of naphthol solution. Substitution of sodium nitrite for NANT yielded a value of 21,847 for $\varepsilon_{500\ nm}$ for the diazo-dye. Thus, the percentage of nitrous acid released from NANT was determined as 101%.

7.3 Experimental Details for Chapters 5 and 6

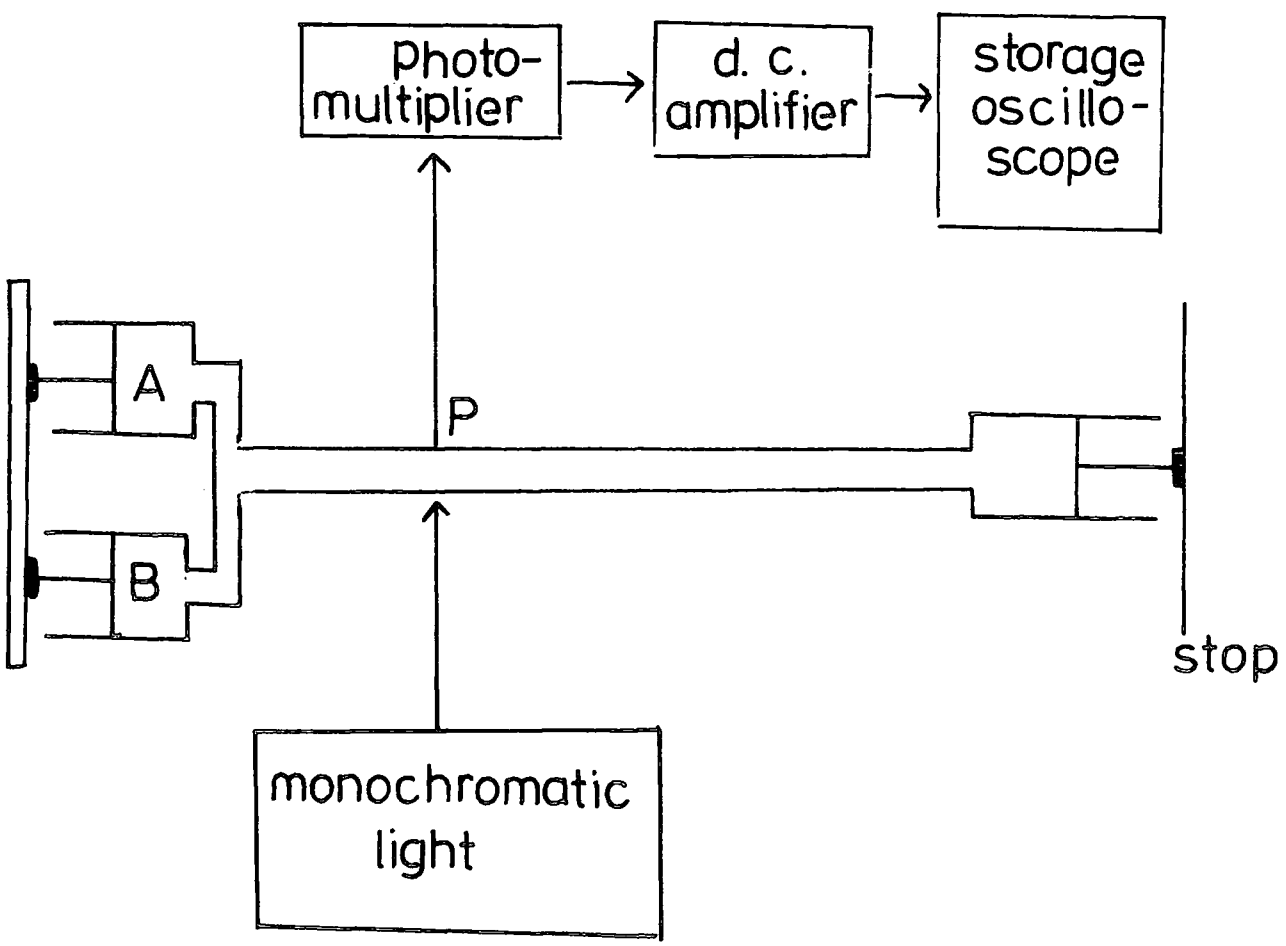
7.3.1 Preparation and Purification of Chemical Reagents

Diethanolamine, morpholine, and aniline were obtained commercially, and were redistilled under reduced pressure with centre fractions collected at constant b.p.s. Salts such as thiourea, potassium bromide, potassium thiocyanate and sodium nitrite were all of analar grade.

7.3.2 Kinetic Measurements

The kinetics of diazotisation was studied using a Canterbury stopped-flow spectrophotometer. The technique involves rapid mixing of two solutions A and B which are initially contained in two hypodermic

syringes of equal volume. The syringes are mounted on a block and a pushing carriage ensures that the solutions leave the syringes with identical velocity (see diagram below). On leaving the syringes the solutions enter the mixing cell where the reaction A + B $\longrightarrow$ C takes place. The reaction mixture then enters a third syringe arranged so that the plunger is forced against a stop, which triggers the recording device at observation point, P. A beam of monochromatic light passes through the solution at this point and its intensity is converted into a proportional electrical signal which is then displayed on the storage oscilloscope. The rate constant for the first-order kinetics is then determined directly from a consideration of the values of the voltage at various times, t.



The mixing cell is immersed in a thermostat bath, and in practice measurements were carried out either at $30^{o}C$ or $0^{o}C$. The reactions were followed by monitoring the increase in absorbance due to the formation of the diazonium ion at 325 nm, apart from the measurements taken at $0^{o}C$ for thiourea catalysed reactions, where the decrease in absorbance at 420 nm due to $=\overset{+}{S}\text{-NO}$ was followed. Under the prevailing experimental conditions, and over the period of time required for complete reaction, the product diazonium ion was relatively stable.

In general, the runs were carried out by mixing equal volumes of solutions A and B. For example, the following data in Table 70 refers to the diazotisation of aniline via nitrosyl thiourea for a single run. The values quoted for k_o in chapters 5 and 6, however, actually represents the mean value of five individually repeated runs.

Solution A consists of 6 ml volumes of stock sulphuric acid (2.08$\underline{M}$), 5 ml volumes of stock thiourea ($2.12 \times 10^{-2}\underline{M}$), 10 ml volumes of stock aniline ($6.95 \times 10^{-2}\underline{M}$) and 34 ml volumes of demineralised water, so that the total volume equals 55 ml volumes.

Solution B consists of aqueous sodium nitrite ($5.0 \times 10^{-4}\underline{M}$). On mixing, the concentration of all species are halved. A measure of the acidity was obtained by titration of suitably sized aliquots of solution A with standardised sodium hydroxide using phenol red as indicator.

Instantaneous values for k_o can be calculated from the equation:-

$$k_o = \frac{1}{t} \ln \frac{v_t - v_\infty}{v_o - v_\infty}$$

Table 70

t (sec)	v_t	$k_o(sec^{-1})$
0	.355	-
.5	.290	.484
1.0	.240	.478
1.5	.203	.468
2.0	.170	.473
2.5	.148	.463
3.0	.130	.463
3.5	.113	.462
∞	.053	

$k_o = (4.70 \pm .009)\ sec^{-1}$

For the much slower process of nitrosation of morpholine, reactions were carried out at 31°C in the cell of a Beckman model 25 recording spectrophotometer. The kinetics were followed by continuously noting the absorbance at 342 nm, measuring the formation of product N-nitroso-morpholine. Although λ_{max} for N-nitrosomorpholine is at 235 nm, the substantial absorbtion of the parent amine and thiourea at this wave-length make it simpler to use 342 nm.

A flask containing 49 ml volumes of sulphuric acid, morpholine, and the appropriate nucleophile and a flask containing stock aqueous sodium nitrite were pre-warmed in a water bath at 31°C for a minimum of 15 minutes. Reaction was started by the injection of 1 ml volume of sodium nitrite into the 49 ml volumes of aqueous sulphuric acid containing all other reagents, so that the total volume was 50 ml. An aliquot of this

reaction mixture was immediately transferred to a silica cell and placed in the spectrophotometer.

Good first-order behaviour was generally found for at least 80% of the reaction. A typical run is quoted in Table 71 for reaction of nitrous acid (9×10^{-3}M) with morpholine (.154M) in sulphuric acid (.113M) containing thiourea (2.54×10^{-3}M).

Table 71

t (sec)	A_t	$10^2 k_o$ (sec^{-1})
0	.173	-
12	.226	1.72
24	.269	1.70
36	.303	1.69
48	.332	1.70
60	.356	1.71
72	.374	1.69
∞	.458	-

$k_o = (1.70 \pm .01) \times 10^{-2}\ sec^{-1}$

In the case of the nitrosation of diethanolamine, the same experimental procedure was used as for the nitrosation of a morpholine. Fellion et al.[154] have shown that NDELA absorbs strongly at 254 nm, and this wavelength was deemed suitable for the present study. A typical run showing good first-order behaviour is given in Table 72 for reaction of nitrous acid (2.86×10^{-4}M) with diethanolamine (9.78×10^{-2}M) in sulphuric acid (.416M) containing potassium thiocyanate (2.19×10^{-2}M). Instantaneous values of k_o may be calculated from $k_o = {}^1/t \ln \frac{A_t - A_\infty}{A_o - A_\infty}$

Table 72

t (sec)	A_t	$10^3 k_o (sec^{-1})$
0	.026	-
60	.092	1.84
120	.153	1.88
180	.210	1.92
240	.260	1.93
300	.310	2.00
360	.350	2.00
420	.388	2.03
480	.414	1.99
540	.442	1.99
600	.469	2.02
660	.490	2.02
∞	.656	

$k_o = (1.97 \pm .06) \times 10^{-3} sec^{-1}$

References

1. P.N. Magee and J.M. Barnes, Br. J. Cancer, 10, 114, (1956).

2. H. Druckrey, Xenobiotica, 3, 271, (1973).

3. W. Linjinsky, "Chemical Mutagens", Plenum Press, New York-London, Vol. 4, 193, (1976).

4. H. Druckrey, S. Preussmann, S. Ivankovis, and D. Schmahl, Z. Krebsforsch, 69, 103, (1967).

5. P.N. Magee, R. Montesaus, and S. Preussmann, "Chemical Carcinogens", E. Searle ed., ACS Monograph No. 173, Washington D.C., 491, (1976).

6. N.V. Sidgwick, "Organic Chemistry of Nitrogen", Clarendon Press, Oxford, 592, (1966).

7. J.H. Boyer, "The Chemistry of the Nitro and Nitroso Groups", H. Feuer ed., Part 1, Interscience, New York (1969).

8. E. Miller and H. Hais, Chem. Ber., 96, 576 (1963).

9. E.C.S. Jones and J. Kenner, J. Chem. Soc., 711, (1932).

10. W. MacMillen and T.H. Reade, J. Chem. Soc., 585, (1929).

11. B.A. Porai-Koshits, E.Y. Belyaev, E. Szadowski, and V.I. Zaionts, Doklady Akad. Nauk. S.S.S.R., 157, 629 (1964).

12. A.B. Porai-Koshits, E.Y. Beluaev, and J. Szadowski, Reakts. Spos. Org. Soed., 1, 10 (1964).

13. A.B. Porai-Koshits and E.Y. Belyaev, Reakts. Spos. Org. Soed., 1, 204 (1964).

14. E.Y. Belyaev, T.I. Nikulicheva, and B.A. Porai-Koshits, Zhur. Org. Khim., 5, 2141 (1965)

15. J. Shorter, "Correlation Analysis in Organic Chemistry. An Introduction to Linear Free Energy Relationships", Clarendon Press, Oxford, 20 (1973).

16. I.D. Biggs and D.L.H. Williams, J.C.S. Perkin II, 691 (1976).

17. B.C. Challis and J.H. Ridd, Proc. Chem. Soc., 245, (1960).

18. N.S. Bayliss and D.W. Watts, Austral. J. Chem., 319 (1956).

19. K. Singer and P.A. Vamplew, J. Chem. Soc., 3971 (1956).

20. O. Fisher and E. Hepp, Ber. Dtsch. Chem. Ges., 19, 2991 (1886).

21. J. Houben, Ber. Btsch. Ges., 46, 3984 (1913).

22. D.L.H. Williams, Inter. J. Chem. Kinetics, Vol. VIII, 215, (1975).

23. D.L.H. Williams and J.A. Wilson, J.C.S. Perkin II, 13 (1974).

24. I.D. Biggs and D.L.H. Williams, J.C.S. Perkin II, 107, (1975).

25. J. Hine, "Physical Organic Chemistry", 2nd ed., McGraw-Hill, 120 (1962).

26. W.S. Layne, H.H. Jaffé, and H. Zimmer, J.Amer. Chem. Soc., 85, 1816 (1963).

27. K.J. Orton, F.G. Soper, and G. Williams, J. Chem. Soc., 998 (1928).

28. B.C. Challis and M.R. Osborne, J.C.S. Parkin II, 1526 (1973).

29. G. Stedman, J. Chem. Soc., 2949 (1959).

30. J.T. Thompson and D.L.H. Williams, J.C.S. Perkin II, 1932 (1977).

31. C.G. Swain and C.B. Scott, J. Amer. Chem. Soc., 75, 141 (1953),

32. R.G. Pearson, H. Sobel, and J. Songstad, J. Amer. Chem. Soc., 90, 319 (1968).

33. M.R. Crampton, J.T. Thompson, and D.L.H. Williams, J.C.S. Perkin II, 18 (1979).

34. E. Kalatzis and J.H. Ridd, J. Chem. Soc. (B), 529 (1966).

35. E. Kalatzis and P. Papadopondous, J.C.S. Perkin II, 248 (1981).

36. D.L.H. Williams, J.C.S. Perkin II, 655 (1975).

37. D.L.H. Williams, Fd. Cosmet. Toxicol., 16, 365 (1978).

38. J.H. Ridd, Quarterly Rev., 15, 418 (1961).

39. J.R. Perrot, G. Stedman, and N. Uysal, J.C.S. Dalton, 2, 2058 (1972).

40. M.N. Hughes, T.C.B. Morgan and G. Stedman, J. Chem. Soc. (B), 344 (1968).

41. G. Ellison and D.L.H. Williams, J.C.S. Perkin II, 669 (1981).

42. I.D. Biggs and D.L.H. Williams, J.C.S. Perkin II, 601 (1976).

43. M. Shultz and D.R. McCalla, Canad. J. Chem., 47, 2021 (1969).

44. W. Walker and J. Voss "The Chemistry of Amides", J. Zabisky ed., Interscience, New York, 449 (1970).

45. D.L.H. Williams, J.C.S. Chem. Comm., 375, (1975).

46. D.L.H. Williams, J.C.S. Perkin II, 128 (1977).

47. L. Storch, Monatsch., 11, 452 (1890).

48. E.A. Werner, J. Chem. Soc., 101, 2180 (1912).

49. M.E. Coade and E.A. Werner, 102, 1221 (1913).

50. K. Al-Mallah, P. Collings, and G. Stedman, J.C.S. Daton, 2469 (1974).

51. G. Hallett and D.L.H. Williams, J.C.S. Perkin II, 624 (1980).

52. E.S. Amis, "Solvent Effects on Reaction Rates and Mechanisms", Academic Press, New York and London, 209 (1966).

53. S.S. Johal, D.L.H. Williams and E. Buncel, J.C.S. Perkin II, 165 (1980).

54. J.T. Thompson, Ph.D. Thesis, University of Durham (1978).

55. G. Hallett, Ph.D. Thesis, University of Durham (1981).

56. F.A. Long and J. Bigeleisen, Trans. Faraday Soc., 55, 2077 (1959).

57. C.N. Berry and B.C. Challis, J.C.S. Perkin II, 1638 (1974).

58. B.C. Challis and S.P. Jones, J.C.S. Perkin II, 153 (1975).

59. D.L.H. Williams, J.C.S. Perkin II, 1838 (1976).

60. K. Wisberg, Chem. Rev., 55, 713 (1955).

61. J.O. Edwards, J. Amer. Chem. Soc., 76, 1540 (1954).

62. M.J. Janssen, Rec. Trav. Chim., 81, 650 (1962).

63. E.B. Robertson and H.B. Dunford, J. Amer. Chem. Soc., 86, 5080 (1964).

64. J.W. Smith, "The Chemistry of the Amino Group", Wiley, London, 188 (1968).

65. E.A. Braude, J. Amer. Chem. Soc., 1971 (1948).

66. C.E. Looney, W.D. Phillips, and E.L. Reilly, J. Amer. Chem. Soc., 79, 6136 (1957).

67. G.J. Karabatsos and R.A. Taller, J. Amer. Chem. Soc., 86, 4373 (1964).

68. A. Mannschreck, H. Munsch, and A. Matthews, Agnew. Chem. Inter. 5, 728 (1966).

69. E. Suzuki, M. Iogosbi, and M. Oheils, Chem. Pharm. Bull., 28, 979 (1980).

70. B. Krebys and J. Mandt, Chem. Ber., 108, 1130 (1975).

71. P. Rademacher, R. Stølevik, and W. Lüttke, Agnew. Chem. Anter., 7, 806 (1968).

72. J.J. Kuhn and T.S. McIntyre, Canad. J. Chem., 44, 105 (1966).

73. A. Mannschreck and H. Münsch, Agnew. Chem. Inter., 6, 984 (1967).

74. W. Layne, H.H. Jaffe, and H. Zimmer, J. Amer. Chem. Soc., 85, 1816 (1963).

75. S.P. Ewing, D. Lockskon, and W.P. Jencks, J. Amer. Chem. Soc., 102, 3072 (1980).

76. A.L. Lehninger, "Biochemistry", 2nd ed., Worth Publishers, 217 (1975).

77. R. Bonnett and R. Holleyhead, J.C.S. Perkin I, 962 (1974).

78. S. Venitt, C. Crofton-Sleigh, S.L. OOi, and R. Bonnett, Carcinogens, 1, 523 (1980).

79. D.F. Heath, Biochem. J., 85, 72 (1962).

80. J. Anselme "N-nitrosamines", ACS Symposium Series 101, 14, (1979).

81. See References 57, 58, 59, 91, and .

82. J.T. Thompson, Ph.D. Thesis, University of Durham, 50 (1978).

83. M.L. Bade, J. Amer. Chem. Soc., 93, 949 (1971).

84. F. Hibbert, J.C.S. Chem. Comm., 463 (1973).

85. M. Eigen, Agnew. Chem., 3, 1 (1964),

86. D.O.I. Virtanen and M. Maikkula, Tetrahedron Lett., 4855 (1968).

87. R.L. Hinman and E.B. Whipple, J. Amer. Chem. Soc., 84, 2534, (1962).

88. G. Berti, A. deSeltima and D. Segnini, Gazzeta, 91, 571 (1961).

89. R.L. Hinman and J.G. Lang, J. Amer. Chem. Soc., 86, 3796 (1964).

90. W.A. Remers and R.K. Brown "Heterocydic Cmpds. Indoles", Part 1, John Wiley and Sons, 4 (1972).

91. G. Hallett and D.L.H. Williams, J.C.S. Perkin II, 1372 (1980).

92. J.K. Snyder, and L.M. Stock, J. Org. Chem., 45, 1990 (1950).

93. "C.R.C. Handbook of Biochemistry", 3rd ed., 362 (19).

94. J.W. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", W.A. Benjamin, Inc., Volume 1, 11, (1965).

95. A.H. Jackson and A.E. Smith, J. Chem. Soc., 5510 (1964).

96 R. Bonnett and P. Nicolaidau, Heterocycles, 7, 637 (1977).

97. B. Capon, Tetrahedron Lett., 911 (1963).

98. B. Capon and M.C. Smith, Chem. Comm., 21, 523 (1965).

99. O. Smidsrod, A. Hang, and B. Larsen, Acta. Chemica Scand., 20, 1026 (1966).

100. C.K. Ingold "Structure and Mechanism in Organic Chemistry", 2nd ed., G. Bell and Sons Ltd., London, 242 (1969).

101. T.A. Turney and G.A. Wright, Chem. Rev., 59, 497 (1959).

102. H. Zollinger, "Azo and Diazo Chemistry", chap. 1, Interscience (1961).

103. E. Muller, H. Hais and W. Rundel, Chem. Ber., 93, 1541 (1960).

104. J. Hein, J. Chem. Educ., 40, 181 (1963).

105. . Smith and . Loeppky, J. Amer. Chem. Soc., 89, 1147 (1967).

106. W. Lijinsky and S. Singer, "N-Nitroso Compounds: Analysis, Formation and Occurrence", E.A. Walker et al ed., IARC Scietific Publications, 31, (1980).

107. A.R. Butler and B.C. Challis, "Chemistry of the Amino Group", S. Patai ed., Chap. 6, Wiley, Interscience, (1968).

108. T.W.J. Taylor, J. Chem. Soc., 1099 (1928).

109. T.W.J. Taylor and L.S. Price, J. Chem. Soc., 2052 (1929).

110. H. Schmid, Z. Electrochem., 42, 579 (1936).

111. L.P. Hammett "Physical Organic Chemistry", McGraw-Hill, 294 (1940).

112. E.D. Hughes, C.K. Ingold, and J.H. Ridd, J. Chem. Soc., 65, (1958).

113. E.D. Hughes and J.H. Ridd, J. Chem. Soc., 70, (1958).

114. A. Hantzsch and M. Schümann, Ber., 32, 1691 (1899).

115. J.C. Earle and N.G. Hills, J. Chem. Soc., 1089 (1939).

116. J.H. Dusenbury and R.E. Powell, J. Amer. Chem. Soc., 73, 3266, 3269 (1951).

117. C.A. Bunton, D.R. Llewellyn, and G. Stedman, J. Chem. Soc., 568 (1959).

118. L.F. Larkworthy, J. Chem. Soc., 3304 (1959).

119. T.A. Turney, J. Chem. Soc., 4263 (1960).

120. C.A. Bunton and G. Stedman, J. Chem. Soc., 2440 (1958).

121. S.W. Benson, "The Foundations of Chemical Kinetics", McGraw-Hill, New York, 497 (1960).

122. E.D. Hughes, C.K. Ingold, and J.H. Ridd, J. Chem. Soc., 83 (1958).

123. N.S. Bayliss, R. Dingle, D.W. Watts, and J.J. Wilkie, Austral. J. Chem., 16, 933 (1963).

124. H. Schmid and C. Essler, Monatsch. Chem., 91, 484 (1960).

125. B.C. Challis and J.H. Ridd, J. Chem. Soc., 5208 (1962).

126. E.C.R. de Fabrizio, E. Kalatzis, and J.H. Ridd, J. Chem. Soc. (B), 533 (1966).

127. M.N. Hughes, T.D.B. Morgan, and G. Stemdan, Chem. Comm., 241 (1966).

128. H. Ladenheim and M.L. Bendor, J. Amer. Chem. Soc., 82, 1895 (1960).

129. W.R. Angus and A.H. Leckie, Proc. Roy. Soc., A150, 615 (1935).

130. H.A.J. Shoutissen, J. Amer. Chem. Soc., 58, 259 (1936).

131. H. Schmid, Z. Electrochem., 43, 626 (1937).

132. H. Schmid and G. Muhr, Ber., 70, 421 (1937).

133. E.D. Hughes and J.H. Ridd, J. Chem. Soc., 82 (1958).

134. H. Schmid and G. Muhr, Monatsh., 91, 1198 (1960).

135. H. Schmid and G. Muhr, Monatsh., 93, 102 (1962).

136. H. Schmid, Monatsh., 85, 424 (1954).

137. H. Schmid and C. Essler, Monatsh., 88, 1110 (1957).

138. H. Schmid and E. Hallaba, Monatsh., 87, 560 (1956).

139. E. Boyland and S.A. Walker, Nature, 248, 601 (1974).

140. E. Boyland, E. Nice, and K. Williams, Fd. Cosmet. Toxic., 9, 639 (1971).

141. S. Singer, J. Org. Chem., 43, 4612 (1978).

142. G. Stedman and P.A.E. Whincup, J. Chem. Soc., 5796 (1963).

143. H. Schmid and M.G. Fouad, Monatsh. Chem., 88, 631 (1957).

144. P. Collings, K. Al-Mallah, and G. Stedman, J.C.S. Perkin II, 1734, (1975).

145. M. Masui, C. Ueda, T. Yasuoka, and H. Ohmori, Chem. Pharm. Bull., 27, 1274 (1979).

146. D.L.H. Williams, J.C.S. Perkin II, 502 (1977).

147. J.H. Ridd, Adv. Phys. Org. Chem., 16, 128 (1978).

148. T.Y. Fan and S.R. Tannenbaum, J. Agric. Food Chem., 21, 237 (1973).

149. D.D. Perrin "Dissociation Constants of Organic Bases in Aqueous Solution", Butterworths, London (1965).

150. J.R. Perrot, G. Stedman, and N. Uysal, J. Chem. Soc. Dalton Trans., 2058 (1976).

151. J. Thompson, Ph.D. Thesis, University of Durham, (1978).

152. L. Fishbein, The Science of the TOTAL Environment, 13, 157 (1979).

153. A.I. Vogel "Textbook of Practical Organic Chemistry", Longmans, 572 (1966).

154. Y. Fellion, J. de Smedt, and N. Brudney, "N-Nitroso Compounds: Analysis, Formation and Occurrence", E.A. Walker et al. ed., IARC Scientific Publications, 31, (1980).

APPENDIX

Appendix

(a) Lectures and Seminars organised by the Department of Chemistry during the period 1978-1981

(* denotes those attended).

15th September 1978

Professor W. Siebert (University of Marburg, West Germany),
"Boron Heterocycles as Ligands in Transition Metal Chemistry".

22nd September 1978

Professor T. Fehlner (University of Notre Dame, USA),
"Ferraboranes : Syntheses and Photochemistry".

* 12th December 1978

Professor C.J.M. Stirling (University of Bangor).
"'Parting is such sweet sorrow' - the Leaving Group in Organic Reactions".

14th February 1979

Professor B. Dunnell (University of British Columbia),
"The Application of NMR to the study of Motions in Molecules".

16th February 1979

Dr. J. Tomkinson (Institute of Laue-Langevin, Grenoble).
"Properties of Adsorbed Species".

14th March 1979

Dr. J.C. Walton (University of St. Andrews),
"Pentadienyl Radicals".

20th March 1979

Dr. A. Reiser (Kodak Ltd.,),
"Polymer Photography and Mechanism of Cross-link Formation in Solid Polymer Matrices".

25th March 1979

Dr. S. Larsson (University of Uppsala),

"Some Aspects of Photoionisation Phenomena in Inorganic Systems".

25th April 1979

Dr. C.R. Patrick (University of Birmingham),

"Chlorofluorocarbons and Stratospheric Ozone : An Appraisal of the Environmental Problem".

* 1st May 1979

Dr. G. Wyman (European Research Office, U.S. Army),

"Excited State Chemistry in Indigoid Dyes".

* 2nd May 1979

Dr. J.D. Hobson (University of Birmingham)

"Nitrogen-centred Reactive Intermediates".

8th May 1979

Professor A. Schmidpeter (Institute of Inorganic Chemistry, University of Munich).

"Five-membered phosphorus Heterocycles Containing Dicoordinate Phosphorus".

* 9th May 1979

Dr. A.J. Kirby (University of Cambridge),

"Structure and Reactivity in Intromolecular and Enzymic Catalysis".

9th May 1979

Professor G. Maier (Lahn-Giessen),

"Tetra-tert-butyltetrahedrane".

10th May 1979

Professor G. Allen, F.R.S. (Science Research Council).

"Neutron Scattering Studies of Polymers".

16th May 1979

Dr. J.F. Nixon (University of Sussex),

"Spectroscopic Studies on Phosphines and their Coordination Complexes".

23rd May 1979

Dr. B. Wakefield (University of Salford)

"Electron Transfer in Reactions of Metals and Organometallic Compounds with Polychloropyridine Derivatives".

13th June 1979

Dr. G. Heath (University of Edinburgh).

"Putting Electrochemistry into Mothballs - (Redox Processes of Metal Porphyrins and Phthalocyanines)".

* 14th June 1979

Professor I. Ugi (University of Munich),

"Synthetic Uses of Super Nucleophiles".

20th June 1979

Professor J.D. Corbett (Iowa State University, Ames, Kowa, USA).

"Zintle Ions : Sunthesis and Structure of Homo-polyatomic Anions of the Post-Transition Elements".

27th June 1979

Dr. H. Fuess (University of Frankfurt),

"Study of Electron Distribution in Crystalline Solids by X-ray and Neutron Diffraction".

21st November 1979

Dr. J. Muller (University of Bergen),

"Photochemical Reactions of Ammonia".

28th November 1979

Dr. B. Cox (University of Stirling)

"Macrobicyclic Cryptate Complexes, Dynamics and Selectivity".

5th December 1979

Dr. G.C. Eastmond (University of Liverpool).

"Synthesis and Properties of Some Multicomponent Polymers".

12th December 1979

Dr. C.I. Ratcliffe (University of London),

"Rotor motions in Solids".

* 19th December 1979

Dr. K.E. Newman (University of Lausanne),

"High Pressure Multinuclear NMR in the Elucidation of the Mechanisms of Fast, Simple Reactions".

30th January 1980

Dr. M.J. Barrow (University of Edinburgh),

"The Structures of Some Simple Inorganic Compounds of Silicon and Germanium -Pointers to Structural Trends in Group IV".

6th February 1980

Dr. J.M.E. Quirke (University of Durham),

"Degradation of Chlorophyll-a in Sediments".

23rd April 1980

B. Grievson B.Sc., (University of Durham)

"Halogen Radiopharmaceuticals".

14th May 1980

Dr. R. Hutton (Waters Associates, USA),

"Recent Developments in Multi-milligram and Multi-gram Scale Preparative High Performance Liquid Chromatography".

* 21st May 1980

Dr. T.W. Bentley (University of Swansea),

"Medium and Structural Effects in Solvolytic Reactions".

10th July 1980

Professor P. des Marteau (University of Heidelburg),

"New Developments in Organonitrogen Fluorine Chemistry".

7th October 1980

Professor T. Felhner (Notre-Dame University, USA),

"Metalloboranes - Cages or Coordination Compounds?"

* 15th October 1980

Dr. R. Adler (University of Bristol),

"Doing Chemistry Inside Cages - Medium Ring Bicyclic Molecules"

12th November 1980

Dr. M. Gerloch (University of Cambridge),

"Magnetochemistry is about Chemistry".

* 19th November 1980

Dr. T. Gilchrist (University of Liverpool),

"Nitroso Olefins as Synthetic Intermediates".

3rd December 1980

Dr. J.A. Connor (University of Manchester),

"Thermochemistry of Transition Metal Complexes".

18th December 1980

Dr. R. Evans (University of Brisbane, Australia),

"Some Recent Communications to the Editor of the Australian Journal of Failed Chemistry".

18th February 1981

Professor S.F.A. Kettle (University of East Anglia),

"Variations in the Molecular Dance at the Crystal Ball".

* 25th February 1981

Dr. K. Bowden (University of Sussex),

"The Transmission of Polar Effects ofSubstituents".

4th March 1981

Dr. S. Craddock (University of Edinburgh),

"Pseudo-Linear Pseudohalides".

11th March 1981

Dr. J.F. stoddard (I.C.I. Ltd./Unive r sity of Sheffield),
"Stereochemical Principles in the Design and Function of Synthetic Molecular Receptors".

* 17th March 1981

Professor W. Jencks (Brandsis University, Massechusetts),
"When is an Intermediate not an Intermediate?".

18th March 1981

Dr. P.J. Smith (International Tin Research Institute),
"Organotin Compounds - A Versatile Class of Organoemtallic Compounds".

9th April 1981

Dr. W.H. Meyer (RCA Zurich),
"Properties of Aligned Polyacetylene".

* 6th May 1981

Professor M. Szware, F.R.S.,
"Ions and Ion Pairs"

10th June 1981

Dr. J. Rose (I.C.I. Plastics Division),
"New Engineering Plastics".

17th June 1981

Dr. P. Moreau (University of Montpellier)
"Recent Results in Perfluoroorganometallic Chemistry".

(b) First year induction course (October-November 1978)

A series of one hour presentations on the services available in the Department.

i. Departmental organisation.

ii. Safety matters.

iii. Electrical appliances.

iv. Chromatography and microanalysis.

v. Library facilities.

vi. Atomic absorption and inorganic analysis.

vii. Mass spectrometry.

viii. Nuclear magnetic resonance spectroscopy.

ix. Glassblowing technique.