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Kinetics and mechanisms of acid catalysed denitrosation reactions of n-nitrosoamines in ethanol solvent

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A   T H E S I S

entitled

Kinetics and Mechanisms of Acid Catalysed Denitrosation

Reactions of N-nitrosoamines in Ethanol Solvent

Submitted

by

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A C K N O W L E D G E M E N T S

MEMORANDUM

All experimental work presented in this thesis was carried out at the University of Durham, under the supervision of Dr. D.L.H Williams between October 1976 to September 1978. This work wholly or partly has not been submitted for any other degree and is the original work of the author except where acknowledged by a reference.

S.S.J.

S U M M A R Y

SUMMARY

Rate constants for the acid catalysed denitrosation reactions
of N-methyl N-nitrosoaniline (NMNA), Nitrosodiphenylamine
(NNDP), and N-methyl N-nitrosotoluene p-sulphonamide (MNTS)
were determined in ethanol solvent at $31^{o}C$. The first order
rate constants were found to be proportional to [HCl]. The
reaction of NMNA was first carried out in the absence of a
"nitrite trap" which gave an equilibrium mixture consisting of
the nitrosoamine and the denitrosated product, N-methylaniline.
The equilibrium position was found to be dependent on the [HCl] .
From this the rates of forward and reverse reactions were calculated.

In the presence of an excess of ascorbic acid, NMNA and
NNDP gave quantitative denitrosation. MNTS gave denitrosation
product even in the absence of a nitrite-trap. The reactions of
these nitrosoamines were found to be independent of concentrations
of a nucleophile (sodium bromide and potassium thiocyanate).
This therefore suggested that the rate-limiting factors in the
reactions were their initial protonation. This was confirmed
by the isotopic solvent effect results which gave k_{o}(EtOH) :
k_{o}(EtOD) of 2.6 for MNTS and 3.8 for NMNA.. In contrast,
the reactions of NMNA and NNDP show nucleophilic catalysis in
aqueous solutions. However the reaction of MNTS was found to
be irreversible, whereas the reaction of NMNA was retarded by
the added N-methylaniline.

The reaction of NMNA was examined in aqueous-ethanol and reaction rate constants were found to decrease sharply with increase in water content of the solvent. The thiocyanate ion catalysis was found to be effective at 10% H_2O in the solvent. The effect was explained in terms of qualitative theory of solvent effects.

NNDP gave rearrangement in the absence of a nitrite-trap. Also diphenylamine, (the denitrosated product) was found to be more reactive towards nitrosation than NMA. Reactions of some substituted nitrosoamines in pure methanol solvent were also observed. However, these included the reverse component leading to nitrosation of the secondary amine. Therefore the rate constants gave only a rough indication of the structural kinetic effects.

Contents

CHAPTER ONE

INTRODUCTION

The family of N-nitroso- compounds contains some of the most potent carcinogenic substances discovered[1]. Therefore, interest in the N-nitrosoamines, the related amides and urethanes has recently increased to a considerable extent. Barnes and Magee[2][3] observed hepatoxicity and carcinogenicity of N-nitrosodiethylamine, Schoental[4] and Druckery[5] et alia found similar results with N-methyl-N-nitrosourethane and N-methyl N-nitrosourea. More recently the carcinogenic activity of the N-nitroso compounds, in general, has been reviewed[6].

In acidic solutions the chemistry of aromatic N-nitrosoamines is dominated by two processes, i.e. the denitrosation to the corresponding secondary amines and if aromatic, the Fischer-Hepp rearrangement[7] to the corresponding para-C-nitroso isomers.

DENITROSATION

Although the denitrosation reaction has been well known preparatively for a long time, its mechanistic pathway was not examined until recently[8]. Denitrosation is brought about preparatively[9] by heating the N-nitrosoamine with hydrogen chloride and excess of urea. In this reaction urea presumeably removes nitrosyl chloride, NOCl, thus preventing it from nitrosating the secondary amine formed. But it has been shown recently[10] that urea is the least reactive "nitrite trap" and is only completely effective when present in high concentrations, i.e. at concentrations greater than 0.1M in reaction solution. In aqueous solutions sulphamic acid, hydrazine, and aniline are much more reactive towards free nitrous acid and are required only in low concentrations to give the same effect as urea. Ferrous ion has also been used[11] to accomplish denitrosation and now further research into the possibility of ferrous-organic compounds as "nitrite traps" is in progress[12].

The relative efficiencies of the above traps has been determined qualitatively in aqueous solutions[13], by a kinetic analysis method.
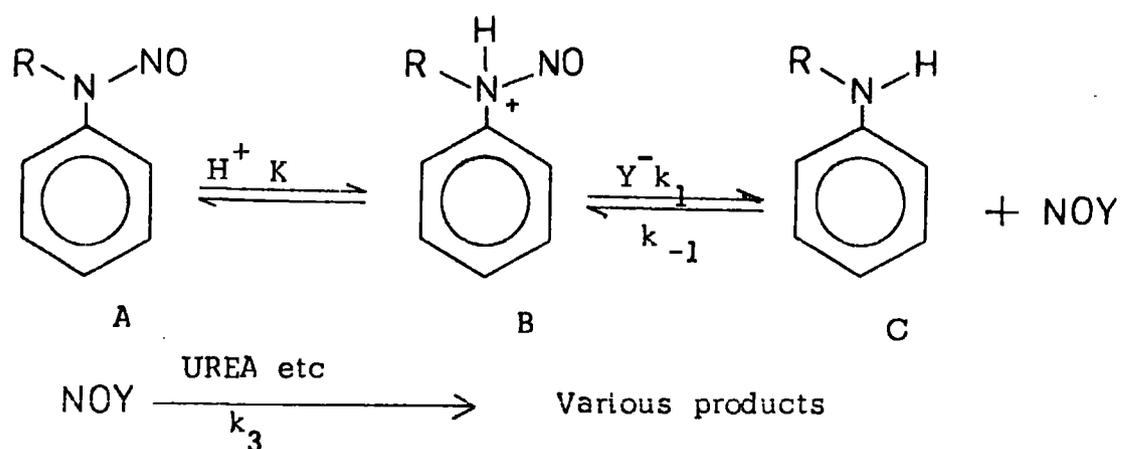
SCHEME 1

If the reaction leading to the denitrosation product occurs as shown in Scheme 1, then in the presence of a large excess of X, (Urea, sulphamic acid etc.) such that we have the condition $k_3[X] \gg k_{-1}[C]$, the overall first-order rate constant, k_o, is given by:

$$k_o = k_1 K h_o [Y]$$

This assumes a Hammett acidity dependence for the protonation of the nitrosoamine and also that this protonation is fast, reversible, and occurs only to a very small extent.

Under these conditions for reaction in hydrochloric acid and excess of sulphamic acid, it has been shown[8] that the rate of reaction is proportional to the product $h_o[Cl^-]$. Also the reaction was found to be of first-order in added Cl^-, Br^-, I^-, SCN^- and $SC(NH_2)_2$. These observations are consistent with Scheme 1 above, where we have rate determining attack by the nucleophile at the protonated nitroso-nitrogen atom. The process is also very sensitive to the nature of the nucleophile. The relative reactivities of the nucleophile are given in the order:

$$H_2O < Cl^- < Br^- < SCN^- < I^- \lessgtr SC(NH_2)_2.$$
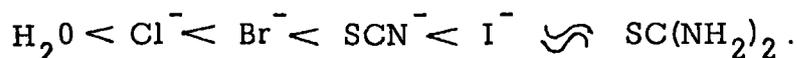
However, this is the qualitatively expected order of reactivity with increasing nucleophilicity. Several workers , namely Swain and Scott[14] and Pearson[15] and co -workers, have attempted to assign values to these nucleophilic constants on the basis of S_N2 reaction at carbon. A linear relationship between $\log k_1 K$ and the Pearson[15] nucleophilicity parameter, n, has been shown[16,17] (see Figure 1) for two nitrosoamines (N-methyl N-nitrosoaniline NMNA, and N-nitrosodiphenylamine, NNDP) where k_1 is the rate constant for rate -determining attack by a nucleophile (eg. Cl^-, Br^-, and $SC(NH_2)_2$) on the protonated form of the nitrosoamine, K is the equilibrium constant for initial protonation of the nitrosoamine (see Scheme 1).

Figure 1 also shows that the reaction leading to denitrosation of N-nitrosodiphenylamine is faster than the corresponding reaction of

Removed by a nitrite-trap.
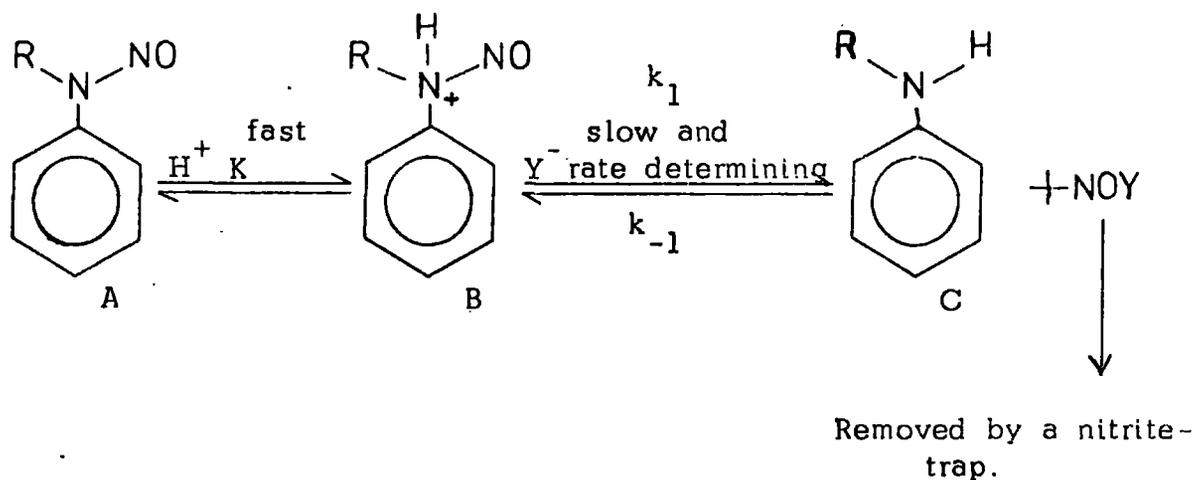
SCHEME 1.

N-methyl N-nitrosoaniline by a factor of 100.   Further the slope of the line for NMNA is 1.41 compared to the value of 0.95 for theNNDP line. This quite clearly indicates that NMNA shows. greater selectivity reflecting its lower reactivity than NNDP .

Also the values of I^- and $SC(NH_2)_2$ for the reaction of NNDP deviate somewhat from the straight line drawn through the other points. This may be brought about by the possible steric effect which may become operative for these bigger nucleophiles. But this effect is not observed in the NMNA reaction.

4

3

2

1

0

$4 + \log(k_1 K)$ ⊙ PhNMeNO

$2 + \log(k_1 K)$ ● Ph_2NNO

SLOPE 0·95

SLOPE 1·41

4   5   6   7

n
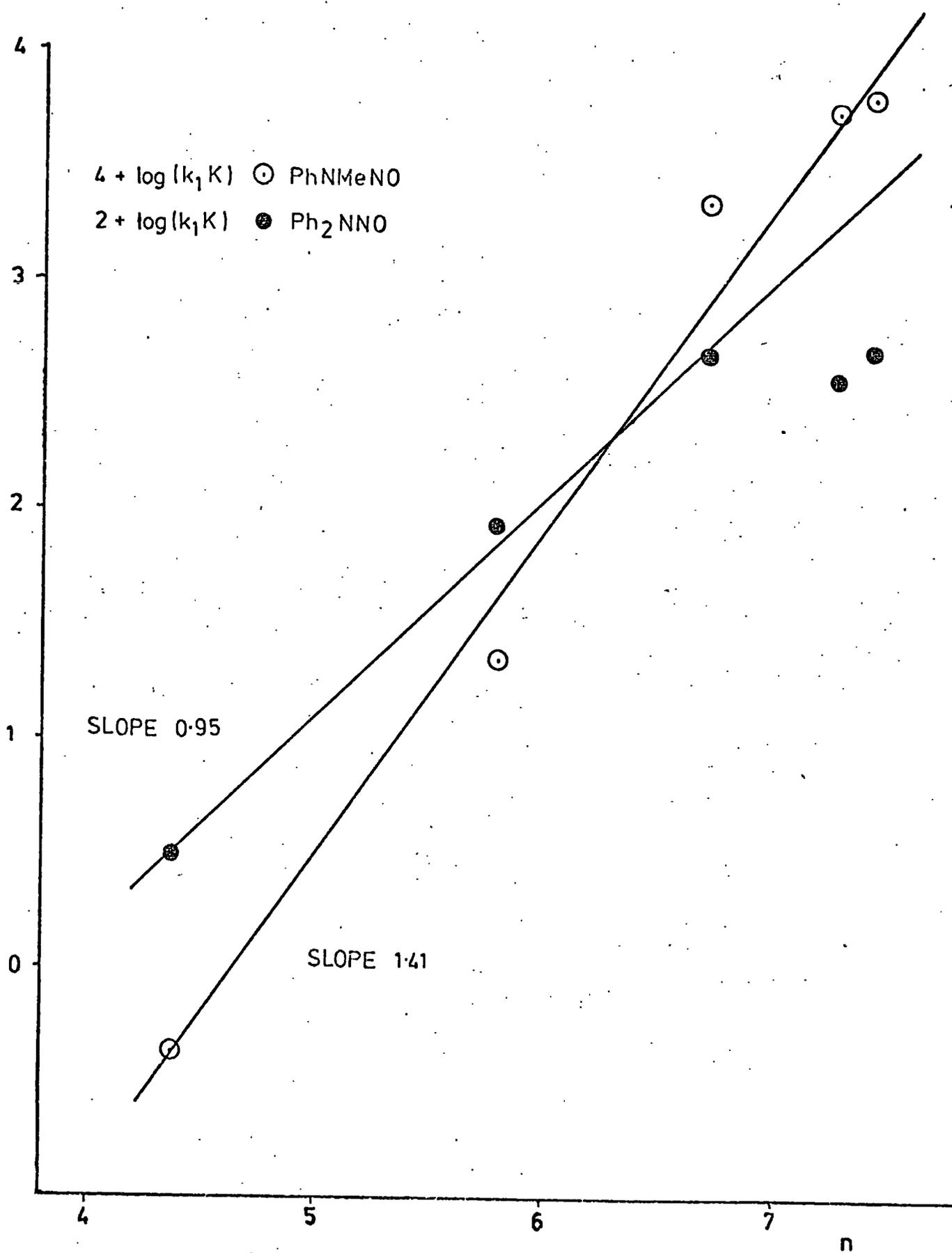
Figure 1   A plot of $\log k_1 K$ against Pearson nucleophilicity constant   n

The obtained order of reactivity of the nucleophiles above, is much more marked in the reaction of NMNA than their attack on the even more reactive $H_2N^+O_2$. In the reaction of NMNA, the attack by I^- increases[18] the rate of reaction by a factor of 15,000 than when the reaction is carried out in chloride ions. However in their attack on nitrous acidium ion the rate coefficients only change[19] by a factor of 1.5 over the range chloride to iodide ions. But this low value for the reaction of $H_2N^+O_2$ may be because the rate of the reaction taking place is diffusion controlled. Also, the rate-determining step is confirmed to be the attack by the nucleophile on the protonated nitrosoamine by the solvent isotope effect. The reaction[8] of NMNA in D_2O has been found to be about 2.5 times faster than in H_2O.

For the reaction of NMNA in the presence of a "nitrite-trap" (hydroxylamine), the addition of the product C, (N-methylaniline when $R = CH_3$ in Scheme 1) to the reaction mixture results[13] in decreasing values of k_o with increasing concentrations of N-methylaniline. This therefore suggests that the second part of the reaction leading to denitrosation is reversible as shown above in Scheme 1.

In contrast to the reactions of NMNA and NNDP in aqueous solutions, the denitrosation reaction of N-methyl N-nitrosotoluene p-sulphonamide, (MNTS) has been shown[20] to be of zero-order in added C, the denitrosation product (N-methyltoluene p-sulphonamide, MTS) chloride ions, bromide ions, and thiourea. It therefore suggests that for MNTS, the denitrosation process is effectively irreversible under these experimental conditions, as shown below in Scheme 2, since the addition of MTS has no effect on the observed rate-coefficients, k_o.

$H_3C-N-NO$ | SO_2 — benzene ring — CH_3 (A)

$\xrightarrow{H^+ \quad K}$

$H_3C-N^+(H)-NO$ | SO_2 — benzene ring — CH_3 (B)

$\xrightarrow[\text{fast and irreversible}]{Cl^- \quad k_1}$

H_3C-N-H | SO_2 — benzene ring — CH_3 (C) $+ NOY$

nitrite-trap $\downarrow$

various products
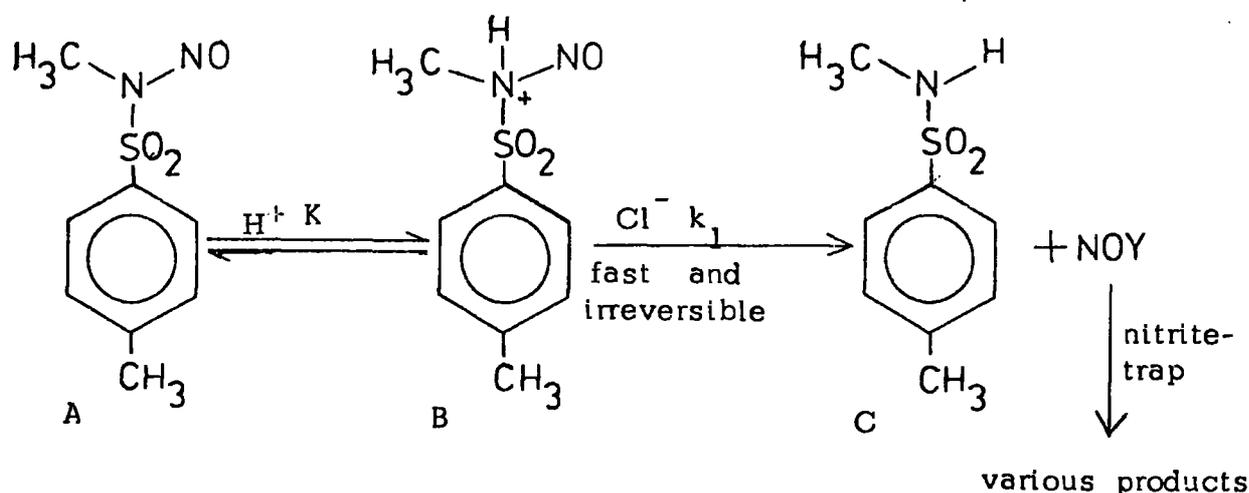
SCHEME 2

This denitrosation reaction of MNTS is shown[20] to be first-order in acid concentrations but there is slightly different reactivities shown by different acids, eg. the reaction with $HClO_4$ + $NaClO_4$ is faster than for HCl and H_2SO_4. This effect, however, probably arises from a salt-effect. The absence of a nucleophile attack catalysis (i.e. effect of added chloride ions, bromide ions, and thiourea), could be due to their reaction with the conjugate acid (the protonated form of the nitrosoamine, B) at a rate which is much faster than the initial protonation. It therefore suggests that the rate-determining step in the reaction is the proton transfer from the solvent to the nitroso-sulphonamide. Challis[21,22] and co-workers, also found that for the reactions of N-nitrosoamides and for N-nitroso-2-pyrrolidone, the rate-determining step was the initial protonation.

Now the initial protonation of the nitroso-compounds has been observed to be the rate-determining step in two cases[20,21]. These results have been confirmed by solvent isotope effect studies. For the denitrosation reaction of nitroso-sulphonamide[20] the ratio of $k_o(H)$: $k_o(D)$ has been shown to be 1.5. Similarly for the reaction of N-n-butyl N-nitrosoacetamide[21], this ratio of $k_o(H)$ to $k_o(D)$ was found to be 1.9. These results therefore show quite clearly that the initial transfer of the proton to the nitroso nitrogen-atom is the rate-limiting step in the reaction.

It has also been shown in aqueous solutions that MNTS undergoes denitrosation even in the absence of a "nitrite-trap" since it is unable to rearrange -NO group to p-position. Also it reacts at a rate much faster than that of NMNA, and N-n-butyl N-nitrosoacetamide[21] and N-nitroso-2-pyrrolidone. Challis and workers also found that the denitrosation reaction of nitrosoamides was independent of added "nitrite-trap" concentrations and predicted a scheme for this reaction in which the loss of NO^{+} from the protonated nitrosoamide occurs unimolecularly. However, if the denitrosation is irreversible, as it has been shown to be in the case of the nitroso-sulphonamide,[20] or even if the rate of reverse reaction (k_{-1} in Scheme 1, the nitrosation of the secondary amine) is slow compared to the denitrosation, then the "nitrous-acid-trap" is not expected to have any effect or at least not an appreciable effect on the rate of reaction. The denitrosation of aromatic nitrosoamines has also been observed by some Russian[23][24] workers who suggested that the reaction occurs via two pathways, (1) that the hydrogen bonded complex of the nitrosoamine-acid is attacked by a nucleophile (Cl^{-} or HSO_{4}^{-})

$$>N\text{---}NO + Nuc^{-} \rightleftharpoons >N + Nuc.NO$$
$$\underset{H^{+}}{|} \qquad\qquad\qquad \underset{H}{|}$$
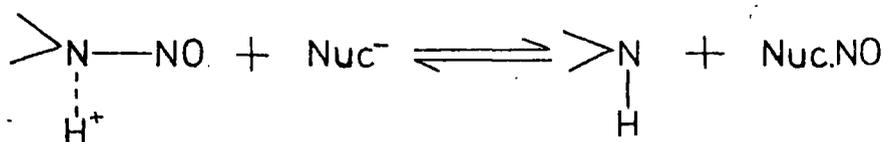
to give the denitrosation product; (2) the loss of $N^{+}O$ from the complex

$$>N\text{---}NO \rightleftharpoons >N + N^{+}O$$
$$\underset{H^{+}}{|} \qquad\qquad \underset{H}{|}$$
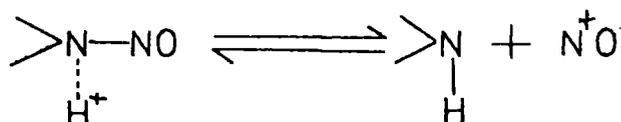
in (1) occurs unimolecularly. It was also observed that the denitrosation reaction occurs faster in hydrochloric acid than in sulphuric acid solution suggesting that a nucleophile plays an important role in this reaction.

It therefore appears that reaction is more likely to proceed by the way of attack of a nucleophile since Cl^- is a better nucleophile than HSO_4^-. Some other Russian Workers[25] have also found that the introduction of electronegative substituents into the aromatic ring increases the denitrosation and was thought to occur as a result of the decrease in the N-N bond strength and also the decrease in the rate of reaction of the reverse step leading to the nitrosation of secondary amine formed.

The denitrosation reaction of NMNA is independent of the concentration of added sulphamic acid (a well known 'nitrite-trap') as long as it exceeds some minimum value. The same values for the rate-coefficient, k_o, are obtained with other nitrite-scavengers under the limiting condition that $k_3[X] \gg k_{-1}[NMA]$.
Also there is no evidence that a direct reaction between the protonated form of the nitrosoamine and 'nitrite traps' takes place, as the reaction is zero-order in X.

The mechanism leading to denitrosation as put forward in scheme 1 is supported by the observed solvent isotope effects

$$k_o(D_2O) : k_o(H_2O) = 2.9 \text{ at } 3.05M \text{ HCl}$$
$$\text{and } k_o(D_2O) : k_o(H_2O) = 3.2 \text{ at } 1.55M \text{ HCl}$$

thus ruling out any rate-determining proton transfer for reaction of NMNA in aqueous solvent.

Now if a Hammett acidity dependence is assumed for the initial protonation of the nitrosoamine, then the denitrosation rate-coefficient is given by:

$$k_o = k_1 K h_o[Y].$$

However the value for K is not known for aromatic nitrosoamines since protonated nitrosoamines rapidly decompose. It has been suggested[27] that there is more than one form of the protonated form of the nitrosoamine existing at different acid concentrations. Therefore it may be that the actual reaction mechanism-pathway is much more complicated than is represented in Scheme 1.

Fischer-Hepp rearrangement[7]

In 1886 Fischer and Hepp discovered that aromatic nitrosoamines underwent rearrangement in acid solution to give the corresponding para-6-nitroso isomers,
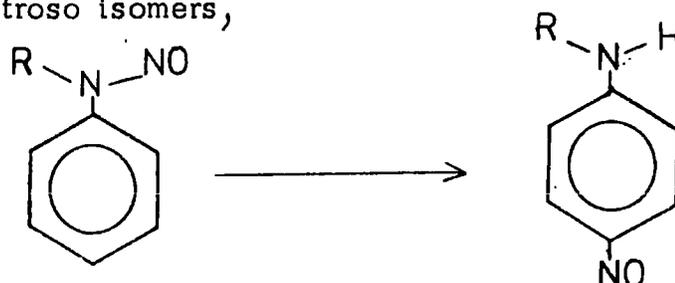
and under certain conditions denitrosation also occured,
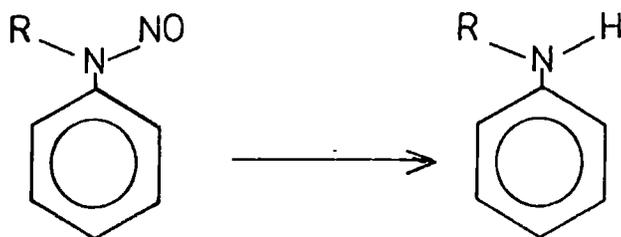
They also found[28] [29] that rearrangement was observed for the naphthylamines.
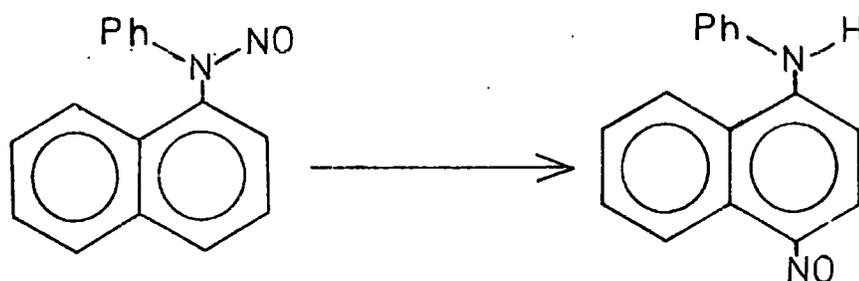
However, in the rearrangement of the compounds of the type PhNR.NO, in no case has the nitroso group been reported to attack at the ortho-position of the ring.

Conditions of reaction.

A solution of the N-nitrosoamine in dry Et_2O or EtOH is treated with a solution of hydrogen chloride in dry EtOH. Anhydrous solvents are not absolutely necessary but generally give better yields of the rearrangement product. Hydrochloric acid is the best acid to use although HBr will also work. However HBr tends to brominate the free amine. Sulphuric acid gives poor yields and nitric acid gives no rearrangement at all[29]. When the following substituted compounds were used, the yields of the rearranged
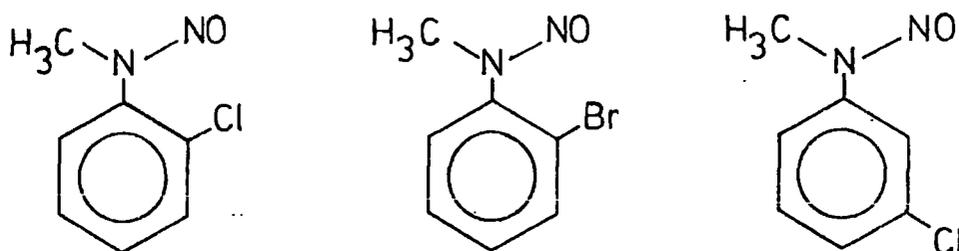
product never exceeded[30] 30%.

This reaction has traditionally been regarded as an intermolecular process, since its proposal by J. Houben[26]. The first step is reversible denitrosation caused by the acid HY.
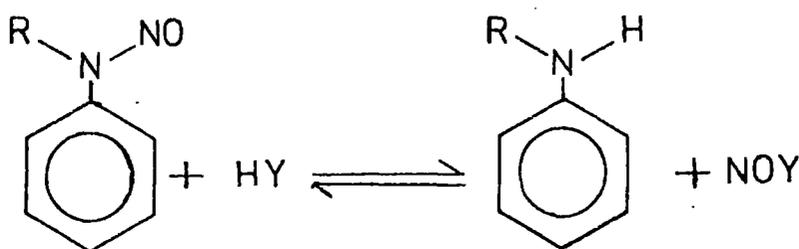
(probably by attack of Y^- on the protonated form of the nitrosoamine) The second step is the conventional electrophilic attack by the free nitrosating agent NOY (nitrosyl halide). Since its proposal, the
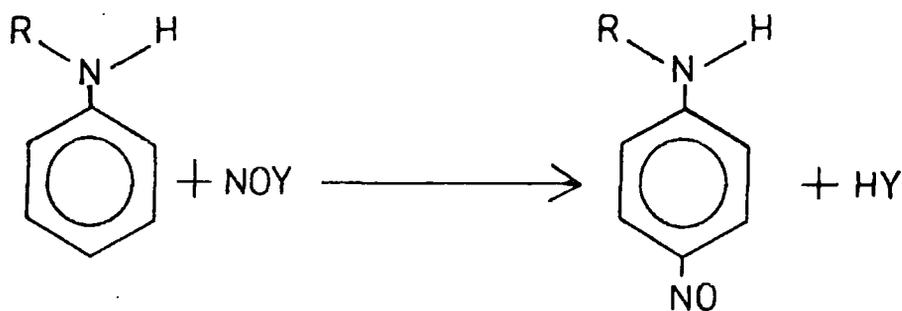
later results seem to verify this mechanism scheme. However the mechanism was only put forward and based on the observations that:

(i)   Hydrogen chloride as catalyst gives greater rearranged product yield than does sulphuric acid. This therefore implies that chloride ions play some role in the reaction mechanism.

(ii) The addition of $NaNO_2$ increased[26] the rearranged product

(iii) It has been reported [26] that a number of transnitrosations occur e.g. when the reaction of diphenyl-N-nitrosoamine is carried out in the presence of N, N-dimethylaniline the para positions of the aromatic rings for both of these compounds is nitrosated.
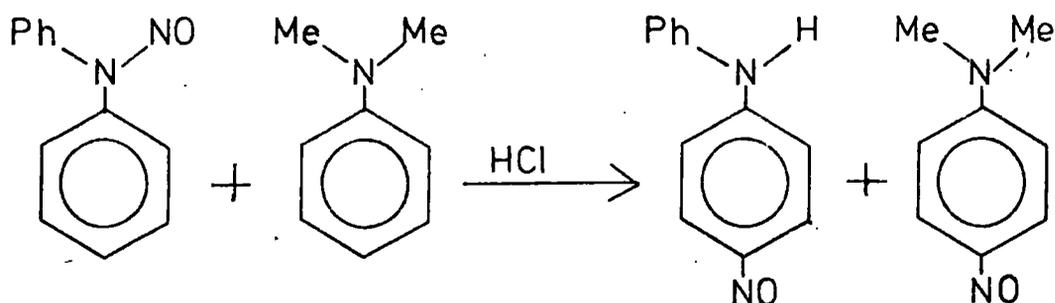
Also the reaction of NMNA, when observed[29] in the presence of an alkene (1) gives (2) instead of p-nitroso-N-methylaniline.

(1)   (2)
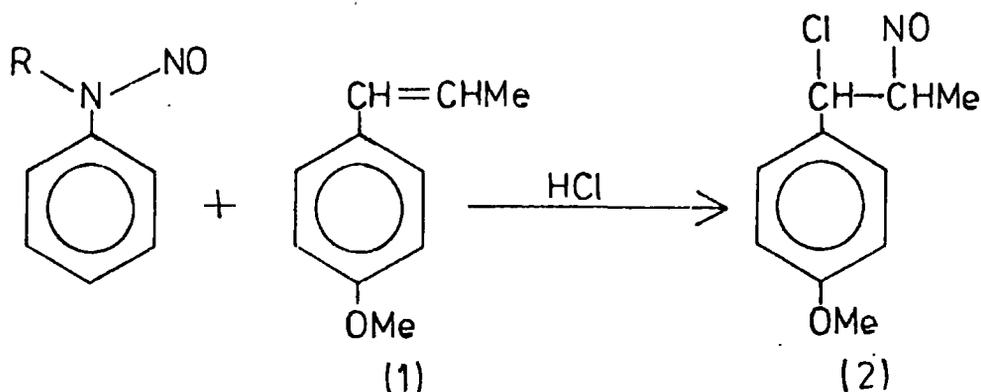
However as a rule denitrosation will occur whenever the para-position of the nitrosoamine is blocked. But the nitroso group can be transferred to another molecule, such as an amine when present.

(iv) In the presence of excess of urea (which removes NOY) denitrosation rather rearrangement occurs[31].

..............ONLY PRODUCT
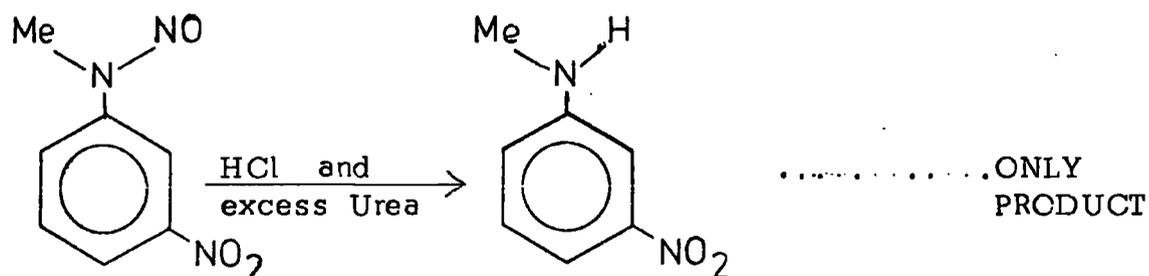
Although the mechanism seems quite reasonable in terms of these observations, the lack of kinetic evidence has been pointed out by several workers[32,33]. However the proposed scheme had several similarities to the Orton[34] rearrangement which has been shown[35] by a detailed kinetic analysis to be an intermolecular process as shown below in Scheme 3.

SCHEME 3
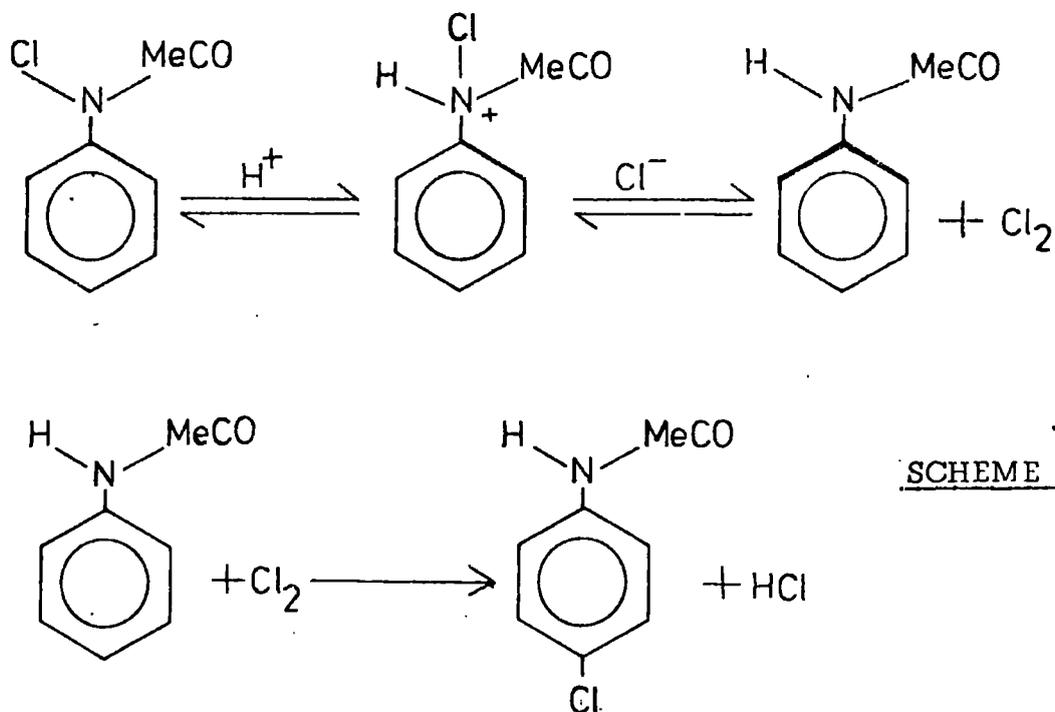
The reaction occurs by the nucleophilic attack by the chloride ion on the protonated N-chloroanilide, giving free chlorine and the anilide. These two react again in an electrophilic substitution manner to form the C-chloro-anilide as the final product. This mechanism (Scheme 3) is similar to the intermolecular mechanism of Fischer-Hepp rearrangement in the following ways:-

(i) Dechlorination occurs by the nucleophilic attack by chloride ion.

(ii) Crossed chlorination to a more reactive substrate (e.g. phenol) can occur.

(iii) Free chlorine can be removed from the reaction mixture.

The reaction of N-chloro-anilide has been found to be of second-order in hydrogen chloride, and has been interpreted as rate proportional to $[H^+]$ and $[Cl^-]$.

$$Rate = k [H^+] [Cl^-] [N\text{-chloro-anilide}].$$

Although the Fischer-Hepp rearrangement has been used quite extensively as a preparative method[36] for synthesising p-nitrosoamines for a long time, its mechanism was never fully examined, but accepted to be intermolecular as proposed by Houben[26]. Recently the Fischer-Hepp rearrangement has been the topic of a much more detailed mechanistic study. From this study a number of features have emerged which argued against the intermolecular mechanism. Baliga[37] while working with N-nitrosodiphenylamine in MeOH solvent containing hydrogen chloride, found that the rate of reaction was of first-order in both nitrosoamine and hydrogen chloride. He also found that the reaction was independent of the added chloride ions. Baliga also put forward a tentative mechanism featuring a 'cage-like' complex. However this mechanism has been found to be inconsistent with the observations[38], in particular a

primary ring deuterium isotope effect, indicating that the final proton transfer from the para-position is the rate-determining step. Also the rearrangement reaction was found[39] to be independent of the added concentration of chloride ions or any other added nucleophile, which is inconsistant with Orton-type rearrangement mechanism for the N-chloroaniline. The intermolecular mechanism is also questioned when it is observed[38,40] that rearrangement still occurs in the presence of urea.

An alternative mechanism was put forward[41] in which rearrangement occured by some intramolecular reaction of the protonated form of the nitrosoamine. It was suggested that the reaction occurs concurrently with denitrosation to form the secondary amine.

INTRAMOLECULAR OR INTERMOLECULAR MECHANISM

For many aromatic rearrangements the decision between these two mechanismscan be made simply by observing the "pick-up" of isotopic label in the products from the unlabelled reactants, i.e. in the rearrangement reaction of N-hydroxy-aniline to para-hydroxyaniline, full up take of ^{18}O from the solvent, therefore suggests[42] that the mechanism is intermolecular.
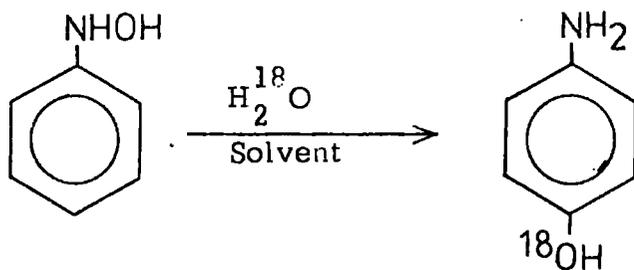
Similarly the failure[43] to pick up ^{15}N from the added $^{15}NO_3^-$ or $^{15}NO_2^-$ in the rearrangement of N-nitroaniline suggests that its reaction is intramolecular.

However, the case of Fischer-Hepp rearrangement[7] has been made complicated by the fact that NMNA exchanges ^{15}N label with added $NaNO_2$ at a rate $\ggg$ rate of rearrangement. It therefore appears that the only way a choice between these two mechanisms can be made is by a detailed kinetic study. Both mechanisms are outlined below

Mechanism (a)

$$NOY + X \xrightarrow{k_3} \text{various products}$$
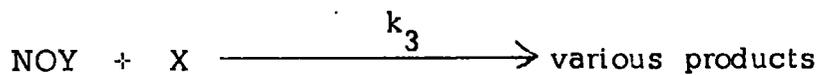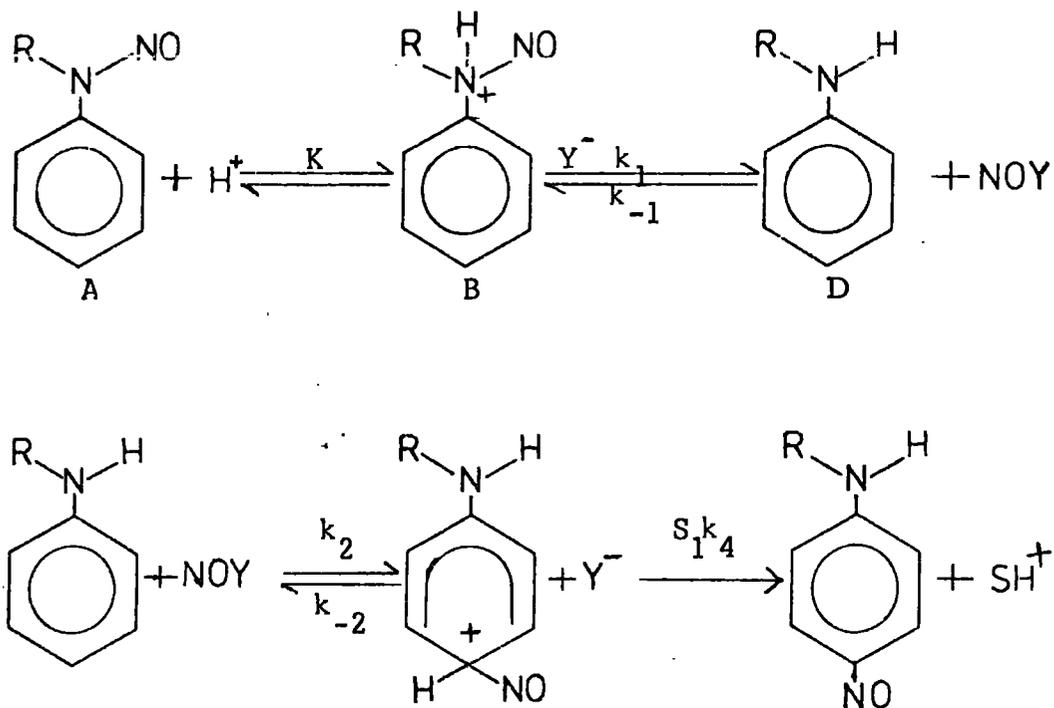
$Y^- =$ some nucleophile (e.g. Cl^- Br^- and SCN^- etc.)

$S =$ solvent and

$X =$ some suitable "nitrite-trap" such as Urea.

From the intermolecular mechanism (mechanism (a)), using a steady-state treatment, the first-order rate-coefficient, k_o, is given by :

$$k_o = \frac{k_1 [Y^-] \, Kho \, (k_3 [X] + k_2^1 [C])}{k_3 [X] + (k_{-1} + k_2^1) [C]}$$

where $k_2^1 = k_2 - \dfrac{k_{-2} \, k_2 [Y^-]}{k_{-2} [Y^-] + k_4}$

and if $B = Kho [A]$

In the alternative intramolecular mechanism (see Mechanism (b) below) the rearrangement occurs concurrently with the denitrosation reaction.

<u>Mechanism (b)</u>

$$NOY + X \xrightarrow{k_3} \text{Various products}$$
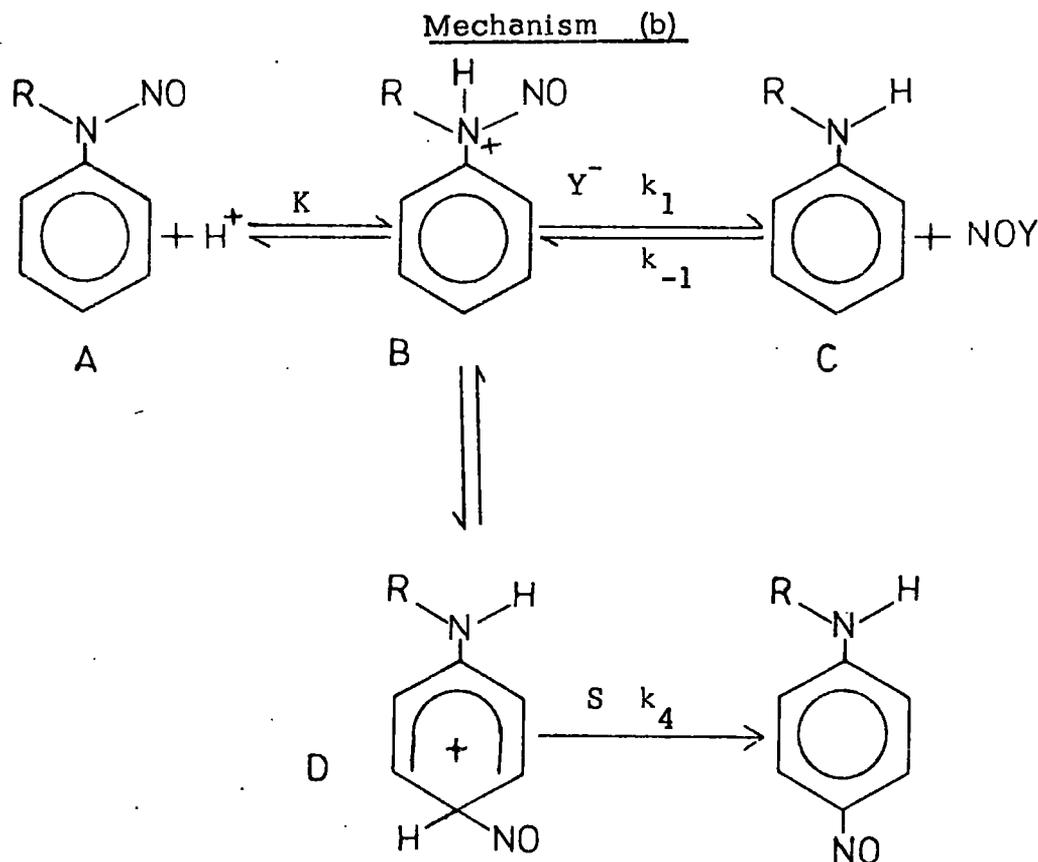
$Y^- =$ some nucleophile such as Cl^- Br^- or SCN^-,
$S =$ solvent
$X =$ some suitable 'nitrite-trap' (sulphamic acid etc).

In the reaction leading to rearrangement in Mechanism (b) the formation of the complex D from the protonated form of the nitrosoamine has been represented in one step for simplicity This, however, seems unlikely to occur in one step due to the large distance involved. It is probably brought about by several steps occuring via a π − complex, but the overall rate coefficient will not be affected.

The intramolecular mechanism similarly gives an expression for the rate-coefficient, k_o, as :

$$k_o = \frac{k_4 k_5 Kh_o}{k_4 + k_{-5}} + \frac{k_1 [Y^-] Kh_o k_3 [X]}{k_3 [X] + k_{-1} [C]}$$

Now it can be seen that the first-order rate equations for both mechanisms eq (1) and eq. (2) are different. Thus by observing the reaction rate constants at the limiting concentration values of C (the denitrosation product) and the "nitrite-trap" X, etc., it should be possible to establish which mechanism prevails in the Fischer-Hepp rearrangement.

In aqueous solvent the reaction of NMNA has been found to be of zero-order in X at high concentrations of X. However, both the mechanisms predict this at high concentrations of the nitrite-trap. Under these conditions, (i.e. when $k_3 [X] \gg k_{-1} [C]$), the limiting forms of the equations (1) and (2) become equations (3) and (4) respectively.

$$k_o = k_1 [Y^-] Kh_o \qquad \dots\dots\dots\dots\dots (3)$$

$$k_o = \frac{k_4 k_5 Kh_o}{k_4 + k_{-5}} + k_1 [Y^-] Kh_o \quad \dots\dots (4)$$

Now the expression, k_1 $[Y^-]$ Kho, (common to equations (3) and (4)), represents the formation of the denitrosation product. But it has been found by several workers in this field, notably some Russians[40] and Williams[38] and co-workers, that rearrangement of the nitrosoamine still occurs to a small extent even in the presence of excess of urea and sulphamic acid. This observation is only consistent with the intramolecular mechanism scheme.

However MacMillen and Reade[31] had observed earlier that no rearrangement occurs with the meta-nitro N-methyl N-nitroso compound in the presence of large excess of urea. But recently it has been shown that this compound (meta-nitro-N-methyl-N-nitrosoaniline) failed to rearrange even in the absence of urea. Therefore the support by MacMillen and Reade[31] in the favour of intermolecular mechanism is negated. However, it has been suggested[44] that the Fischer-Hepp rearrangement may have intramolecular and intermolecular pathways which are dependent on the type of solvent used.

CHANGE OF SOLVENT

. There are many empirical expressions which relate the rate of chemical reactions with the solvent in which they are taking place. However, as to the influence of solvent on the reaction rates involving charged molecule intermediates, one is more concerned with the evaluation of the energy of activation of the reactants and the stablisation of the charged intermediate product formed, e.g the protonated form of the nitrosoamine in the denitrosation reaction, (Scheme 1).

A qualitative theory of the effect of the solvent on the rates of reaction has been proposed by Hughes and Ingold[48]. This can be summerised as follows: The "creation" and concentration of charges will be accelerated and destruction or diffusion of charges will be decreased by an increase in the ion solvating power of the solvent. It has also been suggested[49] that the rates of substitution reactions can vary by as much as 10^6 in reactions involving charge creation or destruction when change from ethanol to water. In contrast some S_N2 reactions which only require charge dispersal, are only 3 to 10 times as fast in ethanol than in water. Hughes and Ingold[50] also put forward some expected effects of ionising solvent on the reaction rates.

For example the S_N2 reaction of the type will be accelerated in

$$Y + RX \longrightarrow Y^+R + X^-$$
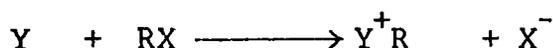
the solvent with higher ionising power.

This above theory is consistent with the Menschutkin[50] reaction which occurs faster in polar solvents.

$$R_3N + R^1I \longrightarrow R^1N^+R_3 + I^-$$
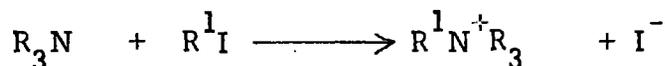
e.g. faster in alcohols than in hydrocarbons in the order

$$MeOH > EtOH > Me_2CO > C_6H_6 > C_6H_{14}$$
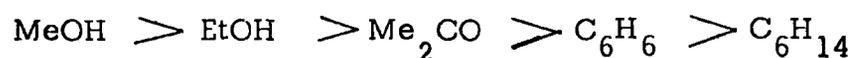
There are also many other examples[51,52] where the rate of reaction is dependent on the solvating power of the solvent. Further, it has also been pointed[48,53] out that not only the rate of reaction, but the order of the reactions have also been known to change in different solvents.

For example[54], the hydrolysis of secondary and tertiary halides.

$$RX + OH^- \longrightarrow ROH + X^- \qquad (S_N2)$$

$$RX \longrightarrow R^+ + X^-$$

$$R^+ + H_2O \longrightarrow ROH + H^+ \qquad \Big\} \quad (S_N1)$$
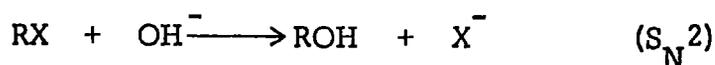
Also in the hydrolysis of t-butyl chloride, the rates of reaction increased as the percentage of water in the composition solvent of aqueous-ethanol was increased. The effect, in general, of solvent on reaction rates and mechanism appears in several text books[55].

Now the first part of the reaction leading to denitrosation of nitrosoamines (see Scheme 1) involves "creation" of charged transition states (protonation of the nitrosoamine): and the second part leads to destruction of charged species by attack of chloride ion on the protonated form of the nitrosoamine. It therefore appears that the reaction rates should be solvent dependent.

So far all the evidence in favour of the denitrosation mechanism of the aromatic nitrosoamines (Scheme 1) has come from the data obtained in aqueous solutions, e.g. the reaction coefficients have been shown to be proportional to the product h_o [Cl^-] in aqueous solution. Also the reactions involving the nucleophiles and the nitrite-traps have all been observed in water solvent. However, little is known about the mechanism of the above reaction in organic solvents and yet the reaction is mostly used in non-aqueous media[9]. Clearly the solubilities of some reactants i.e. the nitrite-traps, could play a part in accomplishing the reaction in organic solvent. It would therefore be of interest to establish the mechanism for the denitrosation reaction in ethanol and aqueous-ethanol solutions.

CHAPTER TWO

EXPERIMENTAL TECHNIQUES

MATERIALS

The following chemical compounds were available in the laboratory from previous studies. The N-nitroso compounds had all been prepared by direct nitrosation (using sodium nitrite and hydrochloric acid) of the corresponding secondary amines.

-N-methyl N-nitrosoaniline   (NMNA)

-N-nitrosopiperidine

-p-methoxy N-methyl N-nitrosoaniline

-N-t(But) N-nitrosoaniline

-2, 6, N-trimethyl N-nitrosoaniline

-N-methylaniline (NMA)

-N-nitrosodiphenylamine   (NNDP)

-N-methyl toluene p-sulphonamide (MTS)

N-methyl N-nitrosotoluene p-sulphonamide was obtained commercially (from Koch-Light Laboratories Ltd. Colnbrook), under the alternative name of p-tolysulphonyl-methyl nitrosoamide. Before use, this compound was recrystallised from 40/60° light petroleum.

Preparation of p-nitroso N-methylaniline

This compound was prepared from N-methyl N-nitrosoaniline by the transfer of the -NO group from the side chain to the para-position in the usual method[56]. The product was recrystallised from benzene. The m.p. of product was found to be 117.5 to 119°C (Literature Value 118°C).

Preparation of Hydrogen Chloride Solution

In most cases the HCl used was from HCl gas cylinders (supplied by B.D.H. Chemicals Ltd. Poole). At other times it was prepared in the laboratory by action of concentrated sulphuric acid on sodium chloride in the usual manner[57]. In both cases the gas was first dried by passing it through conc. sulphuric acid bottle. This gas was then bubbled through the desired solvent such as ethanol or methanol. A large empty round-bottomed flask was introduced into the system as a precaution against "sucking-back" of the acid solution into the "drying trap" containing conc. H_2SO_4.

On each occasion about 300ml of the acid solution was prepared. The final acid strength of the solution was determined by titrating it against standard aqueous sodium hydroxide solution using phenol red indicator.

"Super-Drying" of Ethanol

Before use ethanol was "Super-dried" by the normal Lund-Bjerrum method[58]. The procedure depends on the following reactions

$$Mg + 2C_2H_5OH \longrightarrow H_2 + Mg(OC_2H_5)_2 \quad \text{and}$$

$$Mg(OC_2H_5)_2 + 2H_2O \longrightarrow Mg(OH)_2 + 2C_2H_5OH$$
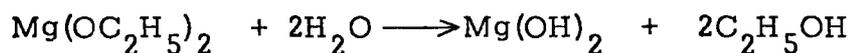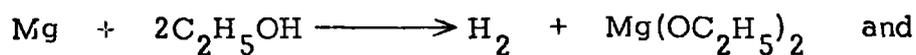
Ethanol was distilled-off at $78^{\circ}C$ directly into the flasks in which it was stored. Care was taken not to introduce water vapour from the atmosphere into the flasks.

Preparation of Reaction Mixtures

The reaction mixtures for the kinetic experiments were prepared in 100ml "Quick-fit" conical flasks. All the reactants except the nitroso-amine solution, were mixed together in desired quantities at laboratory temperature. Below is the preparation of the reaction-run mixtures for the observation of the "effect of added thiocyanate ions on the reaction N-methyl N-nitrosoaniline in ethanol solvent". These flasks were then

Run	HCl (1.681M)		Ascorbic Acid (1.471×10^{-2}M)		KSCN (2.21×10^{-2}M)		EtOH	NMNA (4.09×10^{-2}M)
445	5ml	+	5ml	+	--		9ml	1ml
446	5ml	+	5ml	+	2ml	+	7ml	1ml
447	5ml	+	5ml	+	4ml	+	5ml	1ml
448	5ml	+	5ml	+	6ml	+	3ml	1ml
449	5ml	+	5ml	+	8ml	+	1ml	1ml
450	5ml	+	5ml	+	9ml	+	--	1ml

placed in the constant temperature "water-bath" kept at 31°C. The nitrosoamine solution was then added to each mixture in turn and the kinetic measurements taken immediately.

Kinetic Measurements

The reactions observed were the decompositions of the corresponding nitrosoamines in acid solutions. These kinetic measurements were carried out on either "PYE SP8000" or "Beckman Model 25", recording spectrophotometers. These reactions were carried out at 31°C for each solvent. The "cell-jackets" on both machines were also thermostatically kept at the same temperature (31°C) and were within 0.1°C.

The flasks containing reaction mixture were kept in the bath for about ten minutes before adding the nitrosoamine solution. The sample of this reacting solution was then quickly placed in the sample block of the spectrophotometers in 1cm. cuvettes. The reaction was followed by the disappearance of the nitroso-amine absorbance peak with time. On the PYE spectrophotometer the changes in absorbance were recorded by the repeated scan of a convenient range of spectrum (e.g. 220nm to 450nm), whereas on the "Beckman" model absorbance was recorded directly as a function of time at a constant wavelength.

N-methyl N-nitrosoaniline has a large absorbance peak at 272nm in ethanol and at 275nm in methanol. However, due to the overlap of the absorption peak of the "nitrite-trap" used (ascorbic acid) near this region, the reactions in ethanol solvent were observed at 300nm.

Some typical "reaction-runs" in different solvents are given below:

1. The effect of increasing acidity on the reaction of NMNA in ethanol.

<u>RUN 418</u>

Time (X 30 sec)	Absorbance	$2 + \log (a - \infty)$
0	0.913	1.884
1	0.810	1.821
2	0.712	1.751
3	0.627	1.681
4	0.554	1.609
5	0.490	1.534
6	0.435	1.458
7	0.390	1.384
8	0.350	1.365
9	0.316	1.225
10	0.286	1.140
11	0.263	1.061
12	0.245	0.986
13	0.229	0.908
14	0.214	0.820
15	0.203	0.740
∞	0.149	

$[NMNA] = 2.045 \times 10^{-4} M$ $\quad\quad [HCl] = 0.323 M$

and $[\text{ascorbic acid}] = 3.99 \times 10^{-4} M$

A graph of $2 + \log (a - \infty)$ against Time was then plotted. The graph yielded a straight line with negative slope and the rate-coefficient, k_o, was given by the slope where

$k_o = -2.303 \times$ slope.

2. Effect of added thiocyanate ions on the reaction of NMNA in aqueous ethanol solvent.

RUN 452

Time (X 300 sec)	Absorbance	$10^4 k_o/sec^{-1}$
0	0.950	
1	0.818	5.56
2	0.704	5.62
3	0.608	5.64
4	0.528	5.63
5	0.460	5.63
6	0.403	5.63
7	0.354	5.64
8	0.314	5.62
9	0.276	5.69
10	0.248	5.67
11	0.224	5.65
12	0.203	5.66
13	0.184	5.70
14	0.169	5.71
15	0.155	5.77
16	0.145	5.76
∞	0.091	

Average $10^4 k_o = 5.7 sec^{-1}$

[NMNA] = 2.045 X 10^{-4} M   [HCl] = 0.420M

[ascorbic acid] = 3.68 X 10^{-3} M and [KSCN] = 1.11 X 10^{-3} M

In calculating the k_o values sometimes the method of Guggenheim was used when infinity value was not available. The method of Guggenheim gave value for k_o of $5.8 \times 10^{-4} \sec^{-1}$ compared to a value of $5.7 \times 10^{-4} \sec^{-1}$ obtained by plotting graph of $2 + \log(a - \infty)$ against Time, for Run 452 above.

3. The effect of increasing acidity on unreacted NMNA and evaluation of k_1 and k_{-1} in the absence of a "nitrite-trap"

RUN 372

For Frost and Pearson[59] equation for a reversible reaction of the type $A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B + C$ we have

$a=1.511 \qquad X_e = 1.470 - 0.808 = 0.662 \therefore aX_e = 1.00282$

TIME (X 30 sec)	$(O.D)_o - (O.D)_t = X$		$\therefore \ln \left\{ \dfrac{aX_e + X(a - X_e)}{(X_e - X) \quad a} \right\}$
0	1.470-1.470	0	0.413
1	-1.388	0.082	0.612
2	-1.300	0.170	0.844
3	-1.212	0.258	1.105
4	-1.136	0.334	1.365
5	-1.068	0.402	1.641
6	-1.012	0.458	1.918
7	-0.968	0.502	2.188
8	-0.932	0.538	2.464
9	-0.903	0.567	2.747
10	-0.883	0.587	2.995
11	-0.865	0.605	3.279
12	-0.851	0.619	3.569
13	-0.841	0.629	3.839
14	-0.832	0.628	4.163
15	-0.828	0.642	4.347

A graph of $\ln \left\{ \dfrac{aX_e + (a - X_e)}{a (X_e - X)} \right\}$ against time was

plotted and was found to be a straight line with positive slope

of $9.13 \times 10^{-3} \sec^{-1}$ (for Run 372). From the Frost and Pearson

equation the slope of the line is given by

$$k_1 \times \frac{2a - X_e}{X_e}$$

Therefore $\quad k_1 = 9.13 \times 10^{-3} \dfrac{X_e}{(2a - X_e)} = 25.6 \times 10^{-4} \sec^{-1}$

and $\quad k_{-1} = k_1 \dfrac{(a - X_e)}{X_e^2} \cdot \epsilon$.

The molar extinction coefficient, ϵ, was found to be $7352/M$
for NMNA in ethanol solvent at 272nm.

Therefore at HCl concentration of 0.237M the value of k_{-1}
was found to be $36.5 \ 1. \ \text{mole}^{-1} \sec^{-1}$.

RESULTS AND DISCUSSION

CHAPTER THREE

Reactions of N-methyl N-nitrosoaniline, N-nitrosodiphenylamine and N-methyl N-nitrosotoluene-p-sulphonamide in acidic ethanol .

By following procedure used earlier for the denitrosation reactions in water solvents, it was found that in the absence of a "nitrite trap" an equilibrium mixture of the product (the secondary amine), and the reactant nitrosoamine (NMNA) remained. This reaction then was carried out in the presence of several well established "nitrite traps" in water solvent, such as urea, sulphamic acid, sodium azide, aniline and hydrazine etc. In ethanol however these "traps" failed to show any catalysis upto their maximum concentration permitted in this solvent. However these maximum concentrations achieved in ethanol exceeded the concentrations in which they were required in aqueous solvents[10]. But this failure to observe any catalysis may be due to the low solubilities of these traps which were now required in high concentrations in this solvent.

Now even in the absence of a "nitrite-trap" denitrosation was still observed and there were no traces of the rearranged product. This therefore suggested that the solvent (EtOH), may itself be acting as a "nitrite trap" by forming EtONO, which was shown to exist in the reacted solutions, but in very low concentrations.

It was later realised after a closer examination of the equilibrium mixture and concentration of HCl, that all the traps studied were ineffective, except for ascorbic acid. When ascorbic acid was added to the equilibrium mixture, it converted the remaining NMNA to the denitrosation product NMA. In the presence of an effective "nitrite trap" (ascorbic acid) all the nitrosoamine should be converted into the denitrosation product, C, since it eliminates the reverse reaction (the nitrosation of the secondary amine formed) by removing NOY (see Scheme 1).

The observed first-order rate constant k_o was measured as a function of added ascorbic acid. Where k_o is defined by

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

where A = N-methyl N-nitrosoaniline.

The results are shown below in Table 1. These show that rate-coefficients k_o increase with increase in the concentration of ascorbic acid.

Table 1

Variation of k_o with [ascorbic acid].

10^3[ascorbic acid] /M	$10^4 k_o$/sec^{-1}
0.57	41.3
0.86	42.3
1.14	46.6
1.43	46.1
1.71	50.2
2.28	55.3
3.42	57.7
4.56	56.3
5.70	58.0

[HCl] = 0.403M and [NMNA] = 2.045 X 10^{-4}M

The reaction eventually becomes zero-order in ascorbic acid (see Figure 2). Similar results have been obtained[13] in aqueous solutions but with all the well known "nitrite-traps", such as urea, sulphamic acid, hydrazoic acid and hydroxylamine etc.
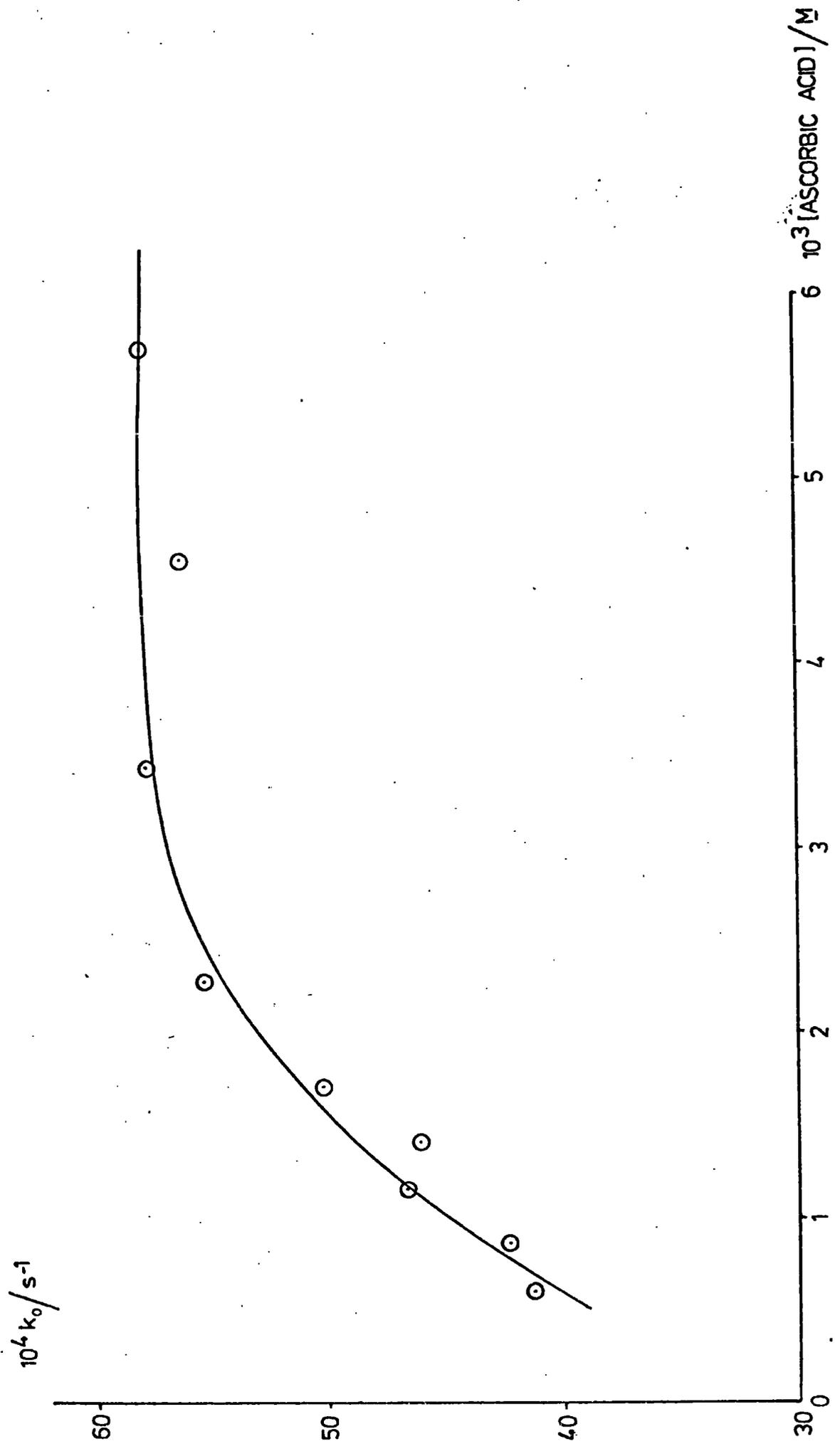
Figure 2   Variation of k_o with concentration of ascorbic acid for reaction of NMNA

This has been however, predicted by the rate equation derived from Scheme 1. Under these conditions the limiting form of the rate equation is given when $k_3 [X] \ggg k_{-1} [C]$. Now having established the kinetic conditions, i.e. when the [ascorbic acid] is greater than 3×10^{-3} M in solution (Figure 2) the denitrosation reaction essentially becomes irreversible and therefore can be examined mechanically, free from a reversibility complication.

The variation of the observed rate-coefficient k_o, with the concentration of hydrogen chloride was determined (Table 2).

Table 2

Variation of k_o with concentration of HCl

[HCl] /M	$10^4 k_o/\text{sec}^{-1}$
0.161	25.9
0.323	60.4
0.484	90.0
0.645	130.4
0.807	155.0

[NMNA] = 2.045×10^{-4} M and [ascorbic acid] = 3.99×10^{-3} M.

The relationship was found to be linear over the acid range studied (see Figure 3). These results show that the rate-coefficient is proportional only to [HCl] and not $[HCl]^2$ for denitrosation in ethanol. This is in contrast with the results obtained[8] in aqueous solutions where k_o was found to be proportional to the product $h_o [Cl^-]$. Also at low concentrations of HCl the rate of reaction is faster in ethanol than in aqueous solution by a factor of about 900.
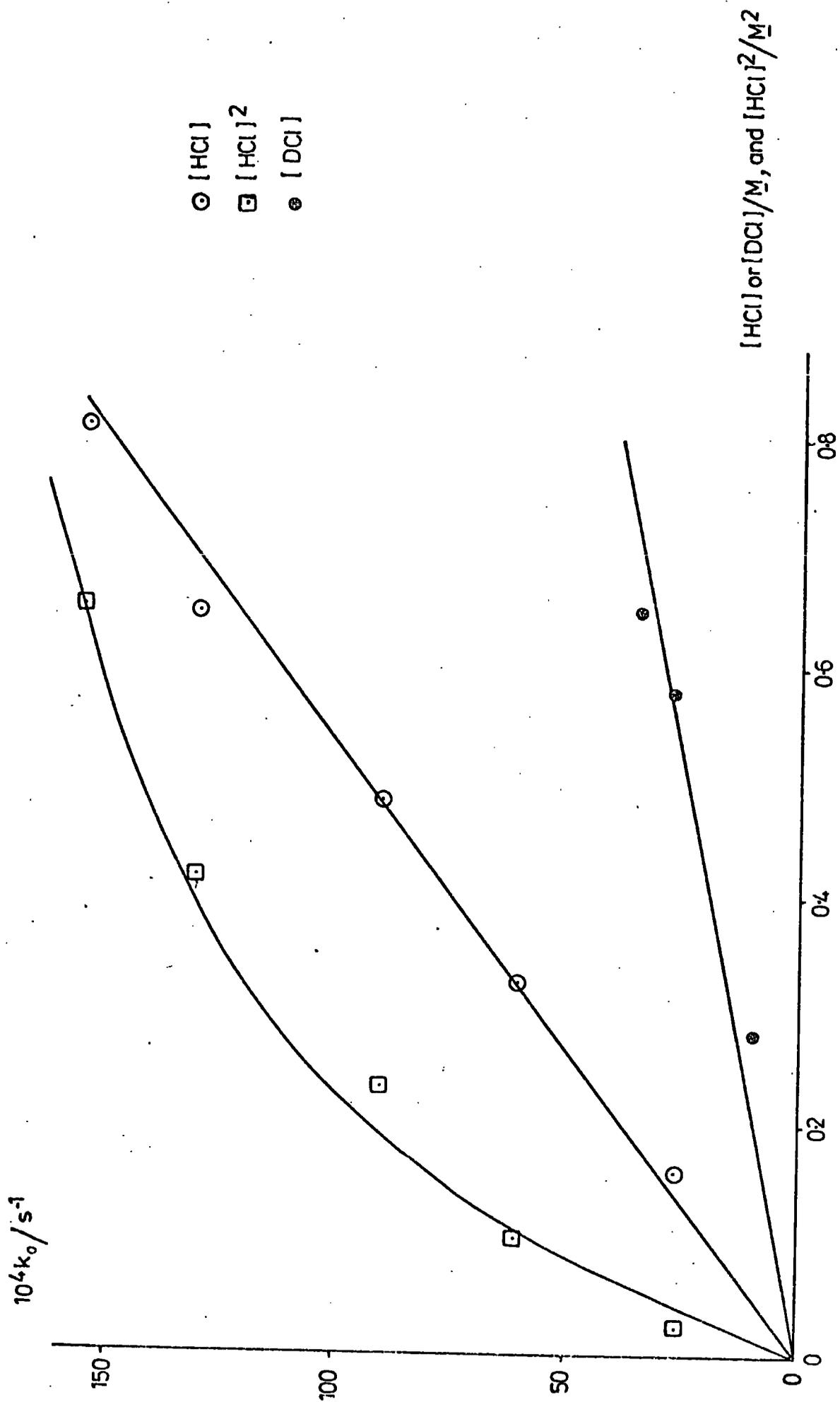
Figure 3 Variation of k_o with concentration of HCl $[HCl]^2$ and $[DCl]$.

When the reaction of NMNA is carried out in the absence of a "nitrite-trap" the equilibrium position changes with acidity as shown in Table 3. The amount of the denitrosation product formed at equilibrium increases sharply with the increase in concentration of hydrogen chloride (see Figure 4).

Table 3

Variation of unreacted NMNA with [HCl]

[HCl] /M	% N-methylaniline formed (at equilibrium)
0.079	30.0
0.158	36.7
0.237	48.4
0.316	54.9
0.396	60.2
0.475	62.9
0.554	63.7
0.633	68.2
0.712	70.6
0.791	71.9
0.870	70.9
0.949	74.3

$[NMNA] = 2.045 \times 10^{-4} M$

This suggests that the rates of forward reaction and reverse reaction have different dependences upon the concentration of HCl. Under these conditions a simple first-order rate coefficient is not expected. It was however, possible to obtain the overall rate constants for the forward (k_1) and the reverse (k_{-1}) reaction from the equation given by Frost and Pearson[59] which applies to the general situation.

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B + C$$
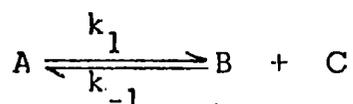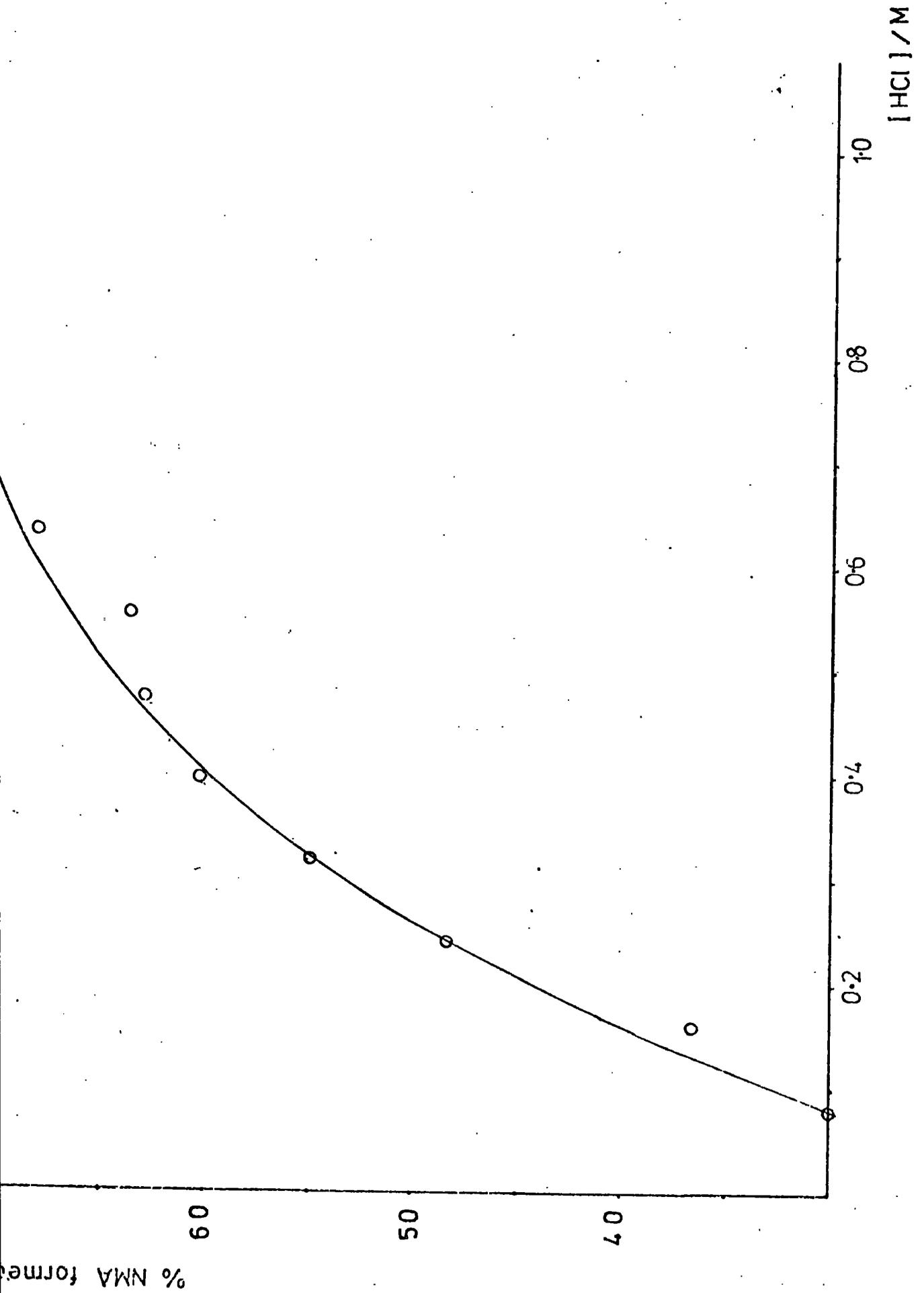
Figure 4 Variation of % NMA formed at equilibrium with concentration of HCl

Now we can apply this equation to the denitrosation reaction of NMNA (see Scheme 1 where R= CH_3). Here A = NMNA, B = N-methylaniline and C= EtONO. If we start from pure A, then it turns out that the integrated rate equation is given by

$$\ln \frac{X_e + X(a - X_e)}{a(X_e - X)} = k \frac{(2a - X_e)}{X_e} t$$

where a = initial concentration of nitrosoamine
(optical density units).

X_e = concentration of product at equilibrium

$$((O.D)_{start} - (O.D)_{equilibrium})$$

and   X = concentration of product at any time, t

$$((O.D_{start} - (O.D)_t)$$

Now if we plot a graph of

$$\ln \frac{X_e + X(a - X_e)}{a(X_e - X)} \quad \text{Vs time t}$$

then the slope of this graph is equal to

$$k_1 \cdot \frac{2a - X_e}{X_e} \cdot \sec^{-1} \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Also at equilibrium we have

$$k_1 [A]_e = k_{-1}[B]_e [C]_e$$

or $\quad k_1 (a - X_e) = k_{-1} (X_e)^2$

Therefore having calculated k_1 from the slope of the graph and then k_{-1} is given by

$$k_{-1} = k_1 \frac{a - X}{X_e^2} \sec^{-1} O.D \quad \ldots\ldots\ldots\ldots\ldots (6)$$

(see chapter 2 example 3 page 27)

This value of k_{-1} is given in optical density units and therefore has to be multiplied by the molar extinction coefficient ϵ, for the nitrosoamine solution. This value in ethanol solvent was found to be 7352 l. mole^{-1} and then the units of k_{-1} become l. mole^{-1} sec^{-1}. The results are shown in Table 4. The values obtained for k_1 by this process should be the same as the values of rate coefficient k_o obtained in the presence of an excess of ascorbic acid i.e when the reverse reaction k_{-1} (the nitrosation of the secondary amine) is supressed under the conditions that

$$k_3 \ [X] \ggg k_{-1} \ [C].$$

Table 4

Calculated values of k_1 and k_{-1} at various [HCl]

[HCl] /M	$10^4 k_1$/sec^{-1}	k_{-1} l.mole^{-1}sec^{-1}
0.079	8.7	25.7
0.158	15.6	37.4
0.237	25.6	36.5
0.316	32.5	43.1
0.396	35.8	51.4
0.554	43.6	43.1
0.633	60.0	37.8
0.712	75.8	27.1
0.791	59.8	67.7
0.870	81.2	51.7
0.949	100.5	51.6

[NMNA] = 2.045 X 10^{-4} M

The slope of the line k_1 against the concentration of HCl is 106 X 10^{-4} l.mole^{-1}sec^{-1} (see Figure 5). The corresponding second-order rate constant k_1 where $k = \dfrac{k_1}{[HCl]}$ for the reaction

Figure 5   Calculated values of k_1 and k_{-1} at various concentrations of HCl

$10^4 k_1 \, (s^{-1})$ ⊙

$k_{-1} \, (l \, mol^{-1} \, s^{-1})$ ▣

using a "nitrite-trap" (ascorbic acid) is 189×10^{-4} l.mole^{-1}sec^{-1} (see Figure 3). The fact that these values differ slightly could be due to the error in obtaining these values for k_1 and k_{-1} from observed rate constant using equations (5) and (6).

The results in Table 4 also show that whilst k_1 is proportional to the concentration of the acid, k_{-1} appears to be almost indendent of the concentration of HCl (see Figure 5). In these reactions carried out in the absence of "nitrite-trap" no rearranged product was obtained. This observation is different from the results obtained in water solvent[38] where under the same conditions 28% rearrangement was obtained at 5.9M HCl.

The effect of added bromide ions was observed on the rate-coefficients in the presence of excess of ascorbic acid. The results are shown below in Table 5.

Table 5

Effect of added bromide ions on k_o

10^3 [Br$^-$] /M	$10^4 k_o$/sec^{-1}
0	70.7
0.51	69.7
1.02	68.7
1.53	69.2
4.59	68.3

[NMNA] $= 2.045 \times 10^{-4}$M   [HCl] $= 0.403$M
and [ascorbic acid] $= 3.76 \times 10^{-3}$M

The results show that no catalysis is observed at 0.403M HCl. This observed effect is however, different from the results obtained in aqueous solvent[13], where the dependence of the reaction rate upon the nucleophile is very marked.

It therefore suggests that, unlike in water solvent the nucleophilic attack by the chloride or bromide ions, occurs after the rate determining step in the reaction in ethanol solvent. The rate-determining step, therefore, appears to be the protonation of the N-nitrosoamine as shown in Scheme 5 below.

SCHEME 4
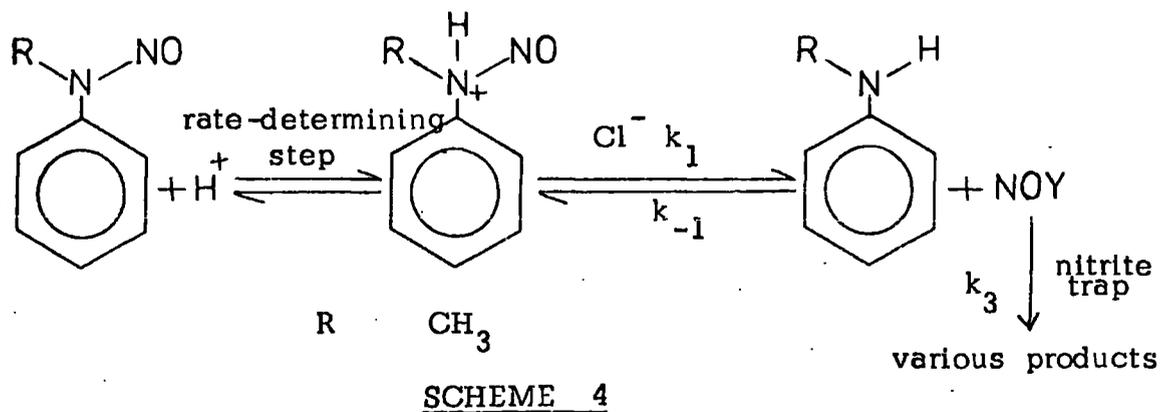
This was also confirmed by the primary isotope solvent effect carried out at three different acidities. These gave a ratio of k_o(EtOH) to k_o(EtOD) of about 3.8, which suggests that protonation of the nitrosoamine is the rate-determining step. Similar results to these above, for the nucleophilic attack on the nitrosoamine have also been found for two nitrosoamides[21,22] in aqueous solvents at 25^oC.

The effect of added N-methylaniline, NMA, (the denitrosation product) on the rate-coefficient was also determined. These results are expressed in Table 6. They show that as the concentration of NMA is increased in the solution, the rate coefficients, k_o, decrease showing the reversibility of the reaction (see Figure 6).
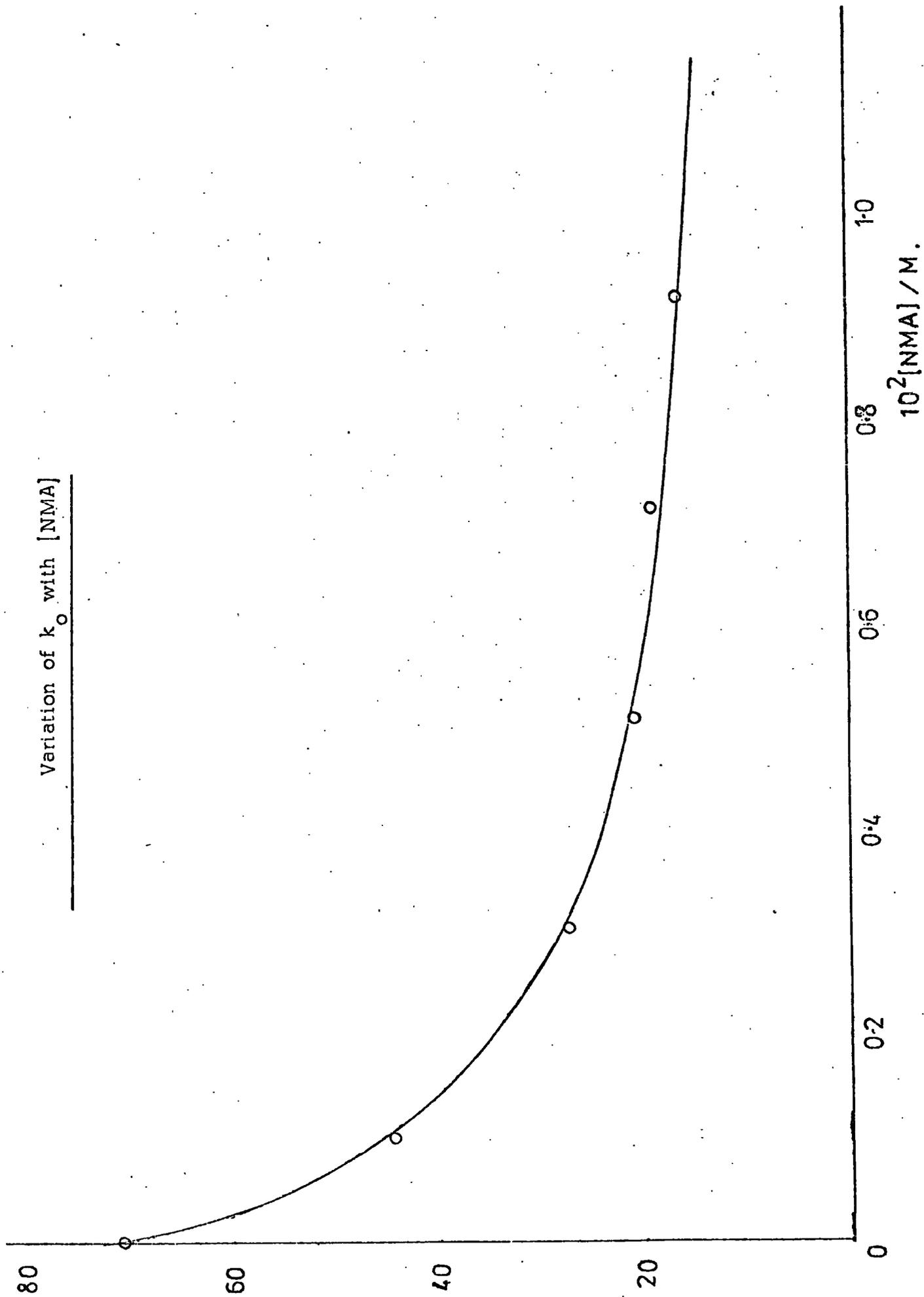
Variation of k_o with [NMA]

Table 6

The effect of added NMA on rate-coefficients k_o

$10^3 [NMA] / M$	$10^4 k_o / sec^{-1}$
0	70.7
1.02	45.5
3.07	27.4
5.12	21.0
7.16	19.10
9.21	16.4

$[NMNA] = 2.045 \times 10^{-4} M$ and $[HCl] = 0.403 M$

A plot of $1/k_o$ against the concentration of the added N-methyl-aniline (NMA) at constant acidity, nucleophile concentration and the "nitrite-trap" concentration was found to be linear with a slope of 5.0 (see Figure 7). From this it is possible to evaluate the rate constants ratio for k_{-2}/k_3 of 1.1.

The reactions of N-nitrosodiphenlamine (NNDP) in ethanol solvent was also looked at. The variation of k_o with the concentrations of an effective nitrite-trap (ascorbic acid) was determined.

Table 7

Variation of k_o with concentration of ascorbic acid

$10^3 [ascorbic\ acid] / M$	$10^4 k_o / sec^{-1}$
0.76	20.6
1.53	37.9
2.29	46.3
3.82	55.7
5.34	58.5
6.87	64.6
8.39	66.7
11.45	65.3

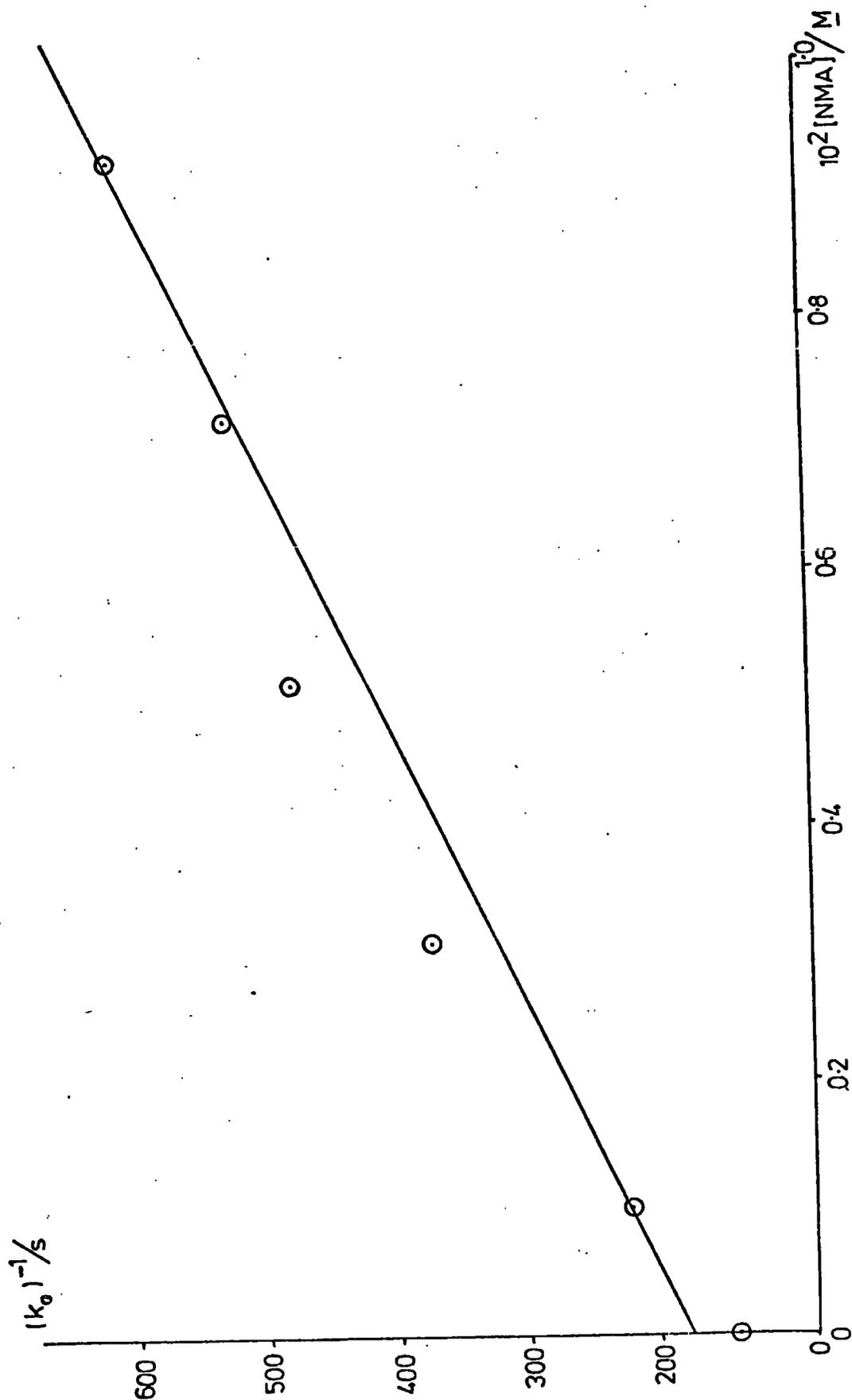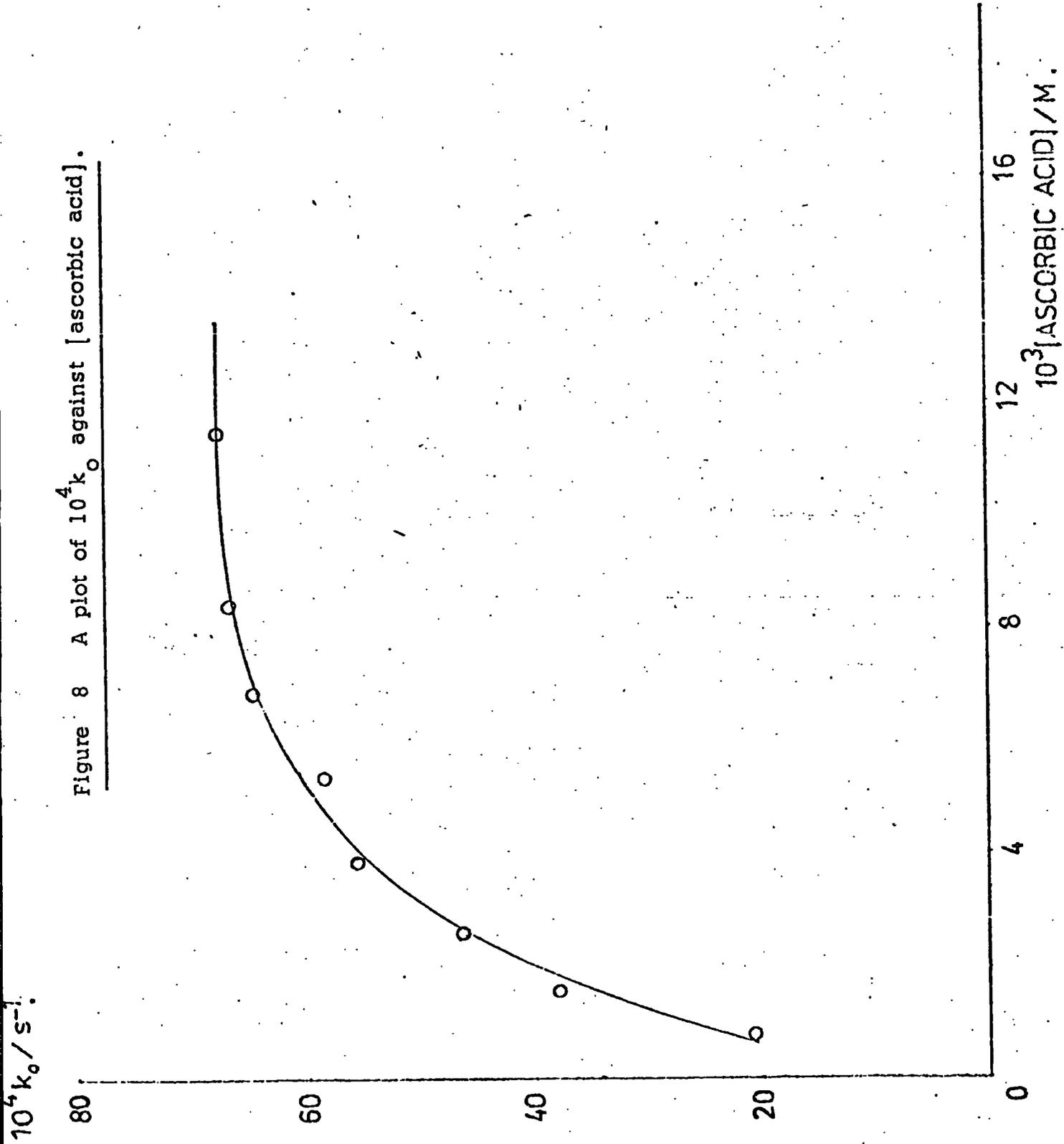$[NNDP] = 2.93 \times 10^{-4} M$ and $[HCl] = 0.121 M$

43

Figure 7   Plot of k_0^{-1} against concentration of NMA added

Figure 8   A plot of $10^4 k_o$ against [ascorbic acid].

The results are shown in Table 7. The rate coefficients, k_o values increase linearly with increasing concentrations of the ascorbic acid, and eventually reach a steady value of about $67.8 \times 10^{-4} \text{sec}^{-1}$ at $[\text{HCl}]$ of 0.121M (see Figure 8). Under these conditions the reaction becomes independent of the concentrations of X and therefore the condition that $k_3[X] \ggg k_{-1}[C]$ is reached. Also it must be pointed out that the minimum concentration of the ascorbic acid at which the reaction of NNDP becomes zero order in X is at the $[\text{ascorbic-acid}]$ of 9×10^{-3}M i.e. the limiting condition where $k_3[X] \ggg k_{-1}[C]$ (see Figure 8). This is, however, 3 times the concentration of ascorbic acid required in the reactions of NMNA. This therefore suggests that the denitrosated product diphenylamine is more reactive towards nitrosation (step k_{-1} Scheme 1) than the corresponding N-methylaniline. Similar results have been found[16] in aqueous solutions for sodium azide as nitrite-trap. In the reactions of NNDP, sodium azide concentration required in solution to bring about the condition where $k_3[X] \ggg k_{-1}[C]$ was 0.13M[16] compared to $6.5 \times 10^{-4}\text{M}$[13] for the denitrosation reaction of NMNA.

The reaction of NNDP in the presence of ascorbic acid goes to complete denitrosation and no traces of the rearranged product were obtained. But when this reaction of NNDP was observed in the absence of ascorbic acid, the main product observed was the rearrangement of NNDP under these conditions (see Table 8 below).

The results show that the relationship between the first-order rate-coefficients with the concentration of HCl is linear over the acid range studies. These also show that the denitrosation reactions are about 400 times faster than the rearnagement reactions at the same acidity.

Table 8

Variation of k_o with acidity

[HCl] /M	$10^5 k_o$/sec^{-1}
0.233	2.7
0.350	3.5
0.475	4.6
0.712	4.8
0.791	4.6
1.107	5.7
1.186	7.1
1.582	8.6
1.977	14.0
2.372	22.6

$[NNDP] = 2.48 \times 10^{-4} M$

The direct nitrosation of the diphenylamine (DPA) was also examined. The nitrosation was brought about by sodium nitrite and hydrochloric acid in EtOH solvent. The results are shown in Table 9. The relationship between k_o and acidity for this reaction is not simple one (see Figure 10). Therefore some further work in this field is required to establish a clear relationship.

The rate-coefficients, k_o, for the reaction of N-methyl N-nitrosotoluene p-sulphonomide (MNTS) were also observed. The reaction in HCl showed complete denitrosation even in the absence of a nitrite-trap. This behaviour of MNTS here in ethanol solution is similar to its reaction in water-solvent[20]. Table 10 shows the variation of k_o with acidity for the decomposition of MNTS in acidic ethanol (see Figure 11). In this reaction the denitrosation product is favoured and in fact no other product was detected.

Figure 9: Variation of k_o with acidity in the reaction of NNDP
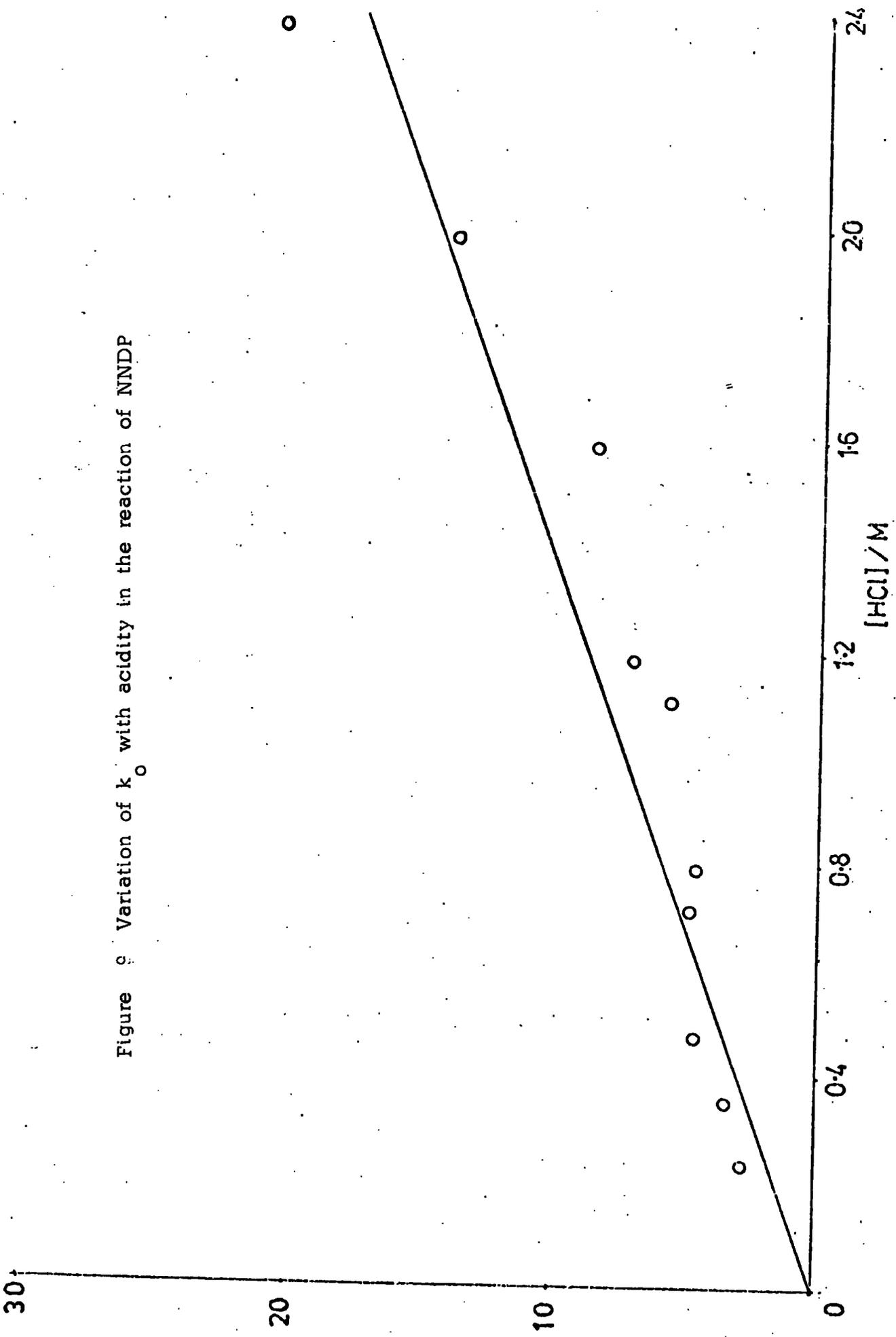
Table 9

Variation of k_o with acidity for nitrosation of DPA

[HCl] /M	$10^5 k_o/sec^{-1}$
0.14	1.8
0.40	3.6
0.47	5.7
0.71	5.4
0.93	10.7
1.11	17.5
1.27	21.9
1.55	28.5
1.80	28.5
2.06	28.3

[DPA] = 1.44×10^{-4}M and [NaNO$_2$] = 1.92×10^{-4}M

Table 10

Variation of k_o with concentration of HCl

[HCl] /M	$10^4 k_o/sec^{-1}$
0.14	7.2
0.28	11.0
0.42	20.5
0.57	29.4
0.76	38.2

[MNTS] = 2.54×10^{-4}M

Figure 10   Variation of k_o with acidity for nitrosation of DPA

$10^5 k_o / s^{-1}$.

[HCl]/M
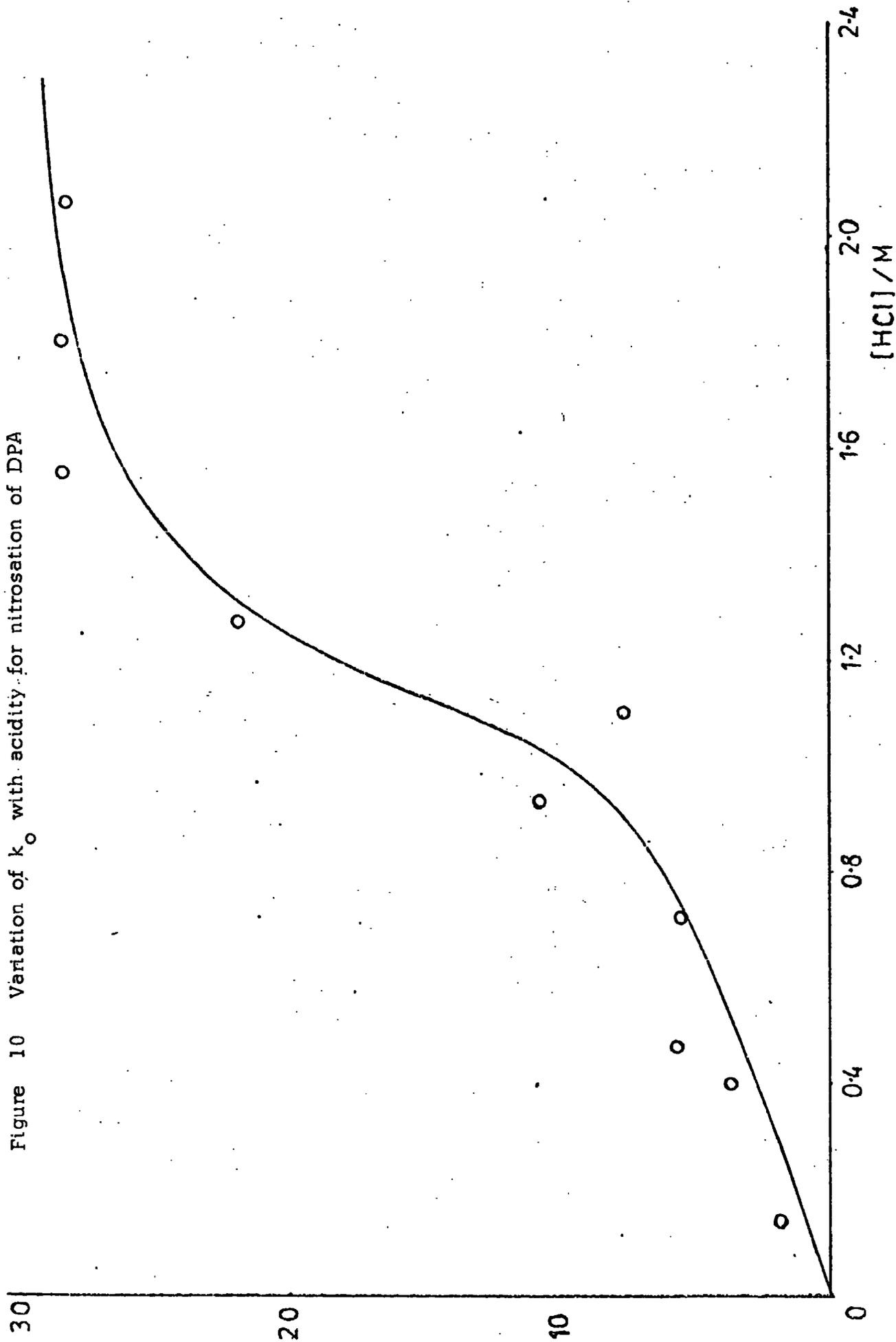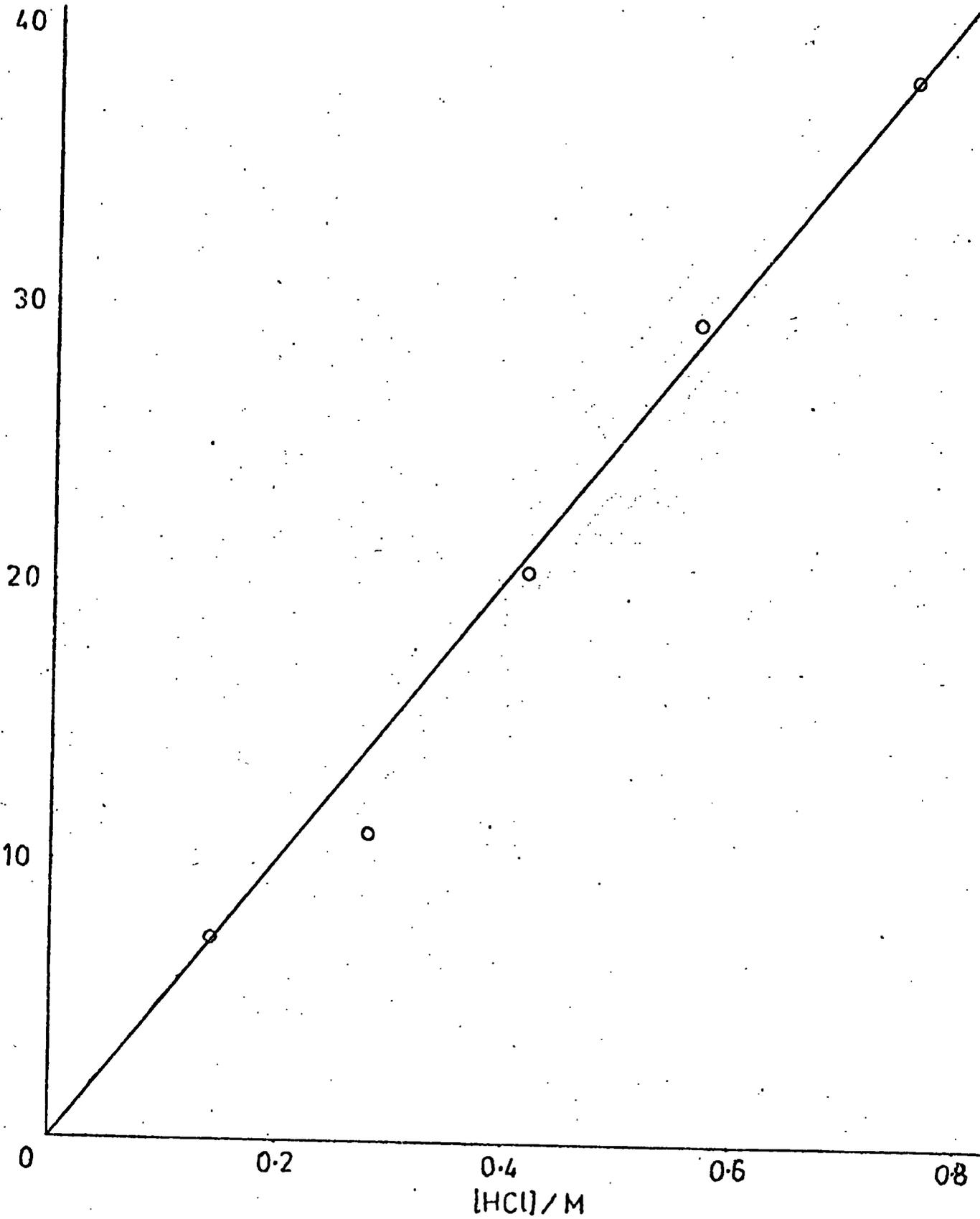
Figure 11 Variation of k_o with acidity for reaction of MNTS

Similarly complete denitrosation was shown to occur in aqueous solutions[20] as well. The effects of added nucleophile, a nitrite-trap and N-methyltoluene - p-sulphonamide, MTS, (the denitrosation product) on the reaction rates were observed. The results are tabulated below in Table 11.

Table 11

Variation of k_o with added Br$^-$ sulphamic acid and MTS

| $10^3[$Br$^-]$/M	$10^3[$Sulphamic Acid$]$/M	$10^3[$MTS$]$/M	10^4k_o/sec^{-1}
--	2.3	--	28.4
--	4.6	--	29.5
1.7	2.3	--	26.5
3.4	2.3	--	29.8
--	2.3	1.06	28.9

$[$MNTS$]$ = 1.10 X 10^{-4}M   and $[$HCl$]$= 0.76M

These show that the reaction is independent of the concentration of the nucleophile, Br$^-$, suggesting that in this reaction the rate-determining step is the proton transfer to the nitrosoamine from the solvent. This has been confirmed in the present work by the solvent isotope effect for the ratio of k_o (EtOH) to k_o (EtOD) of 2.6. The results above in Table 11 also show that the addition of MTS to the reaction mixture also has no effect on k_o. This suggests that the second part of the reaction leading to denitrosation is essentially irreversible, which was also the case for its reaction in water solvent[20] (see Scheme 2 p.6). All the results obtained above for the reactions of NMNA, NNDP, and MNTS are consistent with denitrosation mechanism outlined earlier (Scheme 1). However it was not possible to comment on the matter between intermolecular or intramolecular for the Fischer-Hepp rearrangement, as no rearrangement was observed.

CHAPTER FOUR

Reactions of various other substituted N-nitrosoamines in
aqueous-ethanol and methanol solvents.

The solvent system was changed to aqueous-ethanolic and the reaction observed was the decompositon of N-methyl N-nitrosoaniline (NMNA) as before (Chapter 3). All the other conditions of the reaction were kept the same. The effect on the rate coefficient k_o, with the increase in water content in the solvent was determined. The results are shown below in Table 12.

Table 12

Variation of k_o with the composition of the solvent

% H_2O in solvent (by volume)	$10^4 k_o/sec^{-1}$
0	77.0
2.5	10.4
5.0	4.1
7.5	2.6
10.0	1.8
15.0	1.0

$[NMNA] = 2.045 \times 10^{-4} M$ and $[HCl] = 0.403 M$

The results show that the rate coefficient k_o, decreases very sharply with increase in the water content of the solvent, (see Figure 12), at constant acidity and constant concentrations of the nitrite-trap. This is however to be expected. To explain this effect consider the reaction mechanism scheme (scheme 5) for solvent S under irreversible conditions.

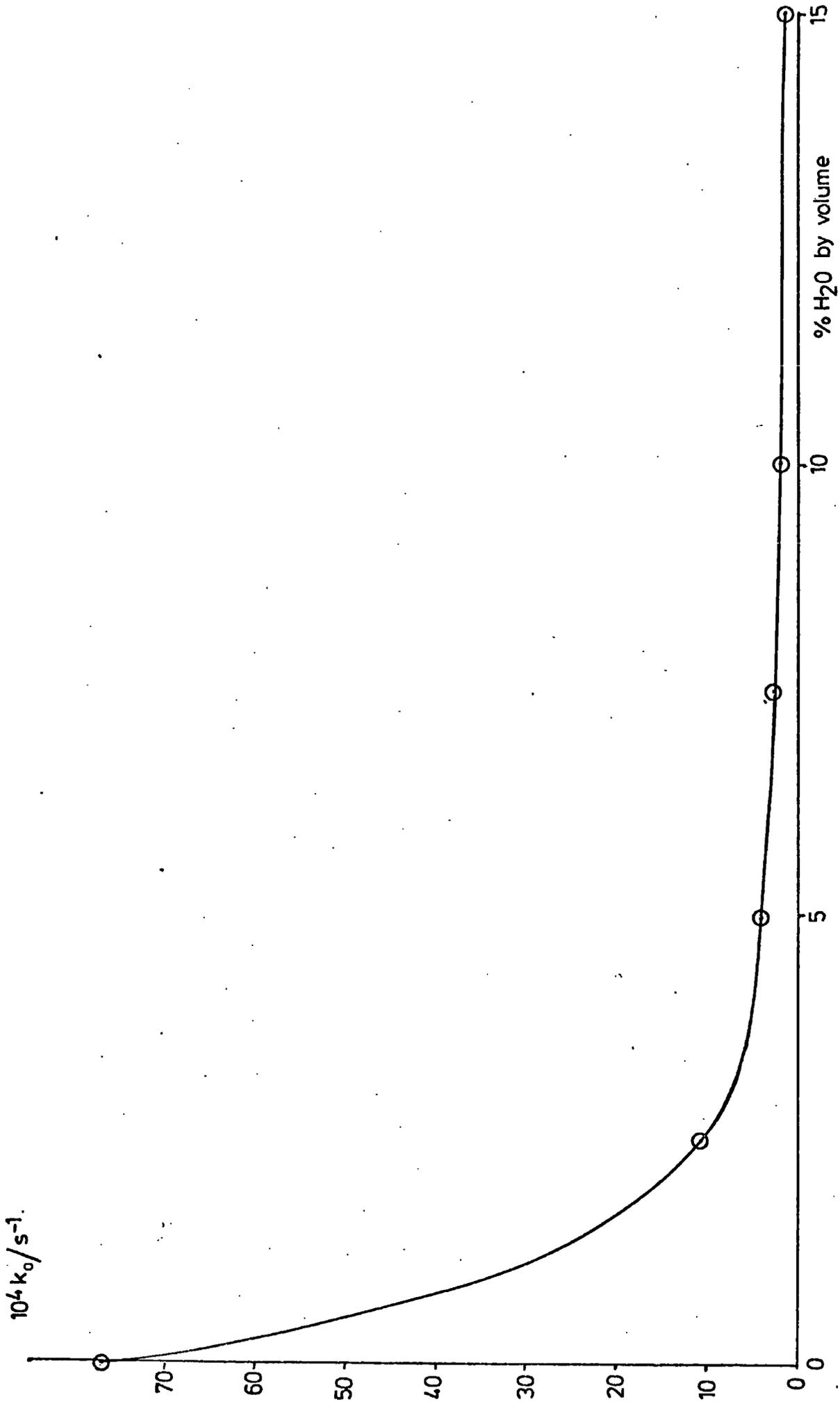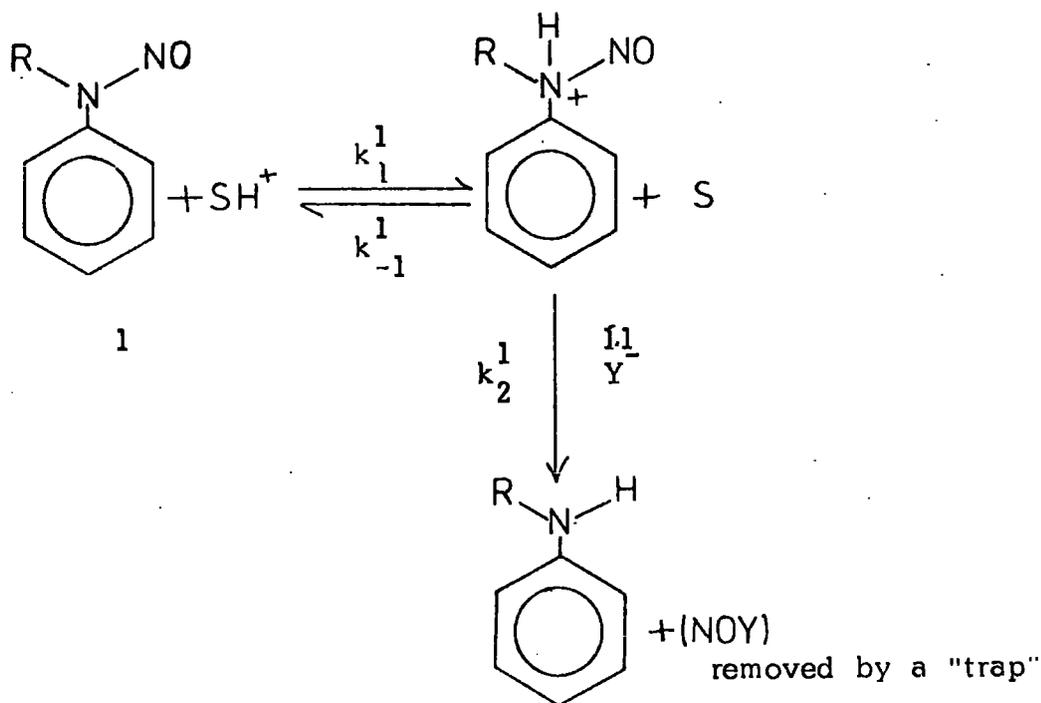Figure 12   Variation of k_o with water content in the solvent

SCHEME 5

Now if we apply steady-state treatment on (11) we have:

$$k_1^1 [I][SH^+] - k_{-1}^1 [11][S] - k_2^1 [11][Y^-] = 0$$

therefore

$$[11] = \frac{k_1^1 [I][SH^+]}{k_{-1}^1 [S] + k_2^1 [Y^-]}$$

therefore Rate $= k_2^1 [Y^-][11] = k_o [I]$

$$k_o = \frac{k_1^1 [SH^+][Y^-] k_2^1}{k_{-1}^1 [S] - k_2^1 [Y^-]} \qquad \ldots \ldots \ldots \ldots (7)$$

Now in order to observe dependence on $[Y^-]$ we must have the condition that $k^1_{-1} [S] \gg k^1_2 [Y^-]$. Under these conditions the equation (7) becomes equation (8).

$$k_o = \frac{k^1_1 [SH^+] [Y^-] k^1_2}{k^1_{-1} [S]} \qquad \dots\dots\dots\dots\dots (8)$$

This appears to the situation in water solvent. Further this Y^- catalysis should disappear under the condition that $k^1_2 [Y^-] \gg k^1_{-1} [S]$ ... Here the equation (7) becomes equation (9) and therefore

$$k_o = k^1_1 [SH^+] \qquad \dots\dots\dots\dots\dots (9)$$

and shows zero order reaction in Y^- as it is the case in ethanol. This is to be expected since k^1_2 will increase considerably more in ethanol than in water on the basis of qualitative theory put forward by Hughes and Ingold[48]. It is therefore reasonable to expect, on going from one solvent system (water) to the other, (ethanol) that we go from one limiting form of the system to the other.

The effect of added nucleophile (potassium thiocyanate) on the rate coefficient was then observed at several water-ethanol compositions. The earliest, i.e. the minimum amount of water in the solvent before the thiocyanate ions catalysis was detected was 10% water to 90% ethanol solvent system (see Table 13). As shown by the results, there is a definite increase in the rate coefficients by a factor greater than 3 when the reaction is carried out in the presence of a nucleophile. Under these conditions therefore, we are changing over towards the other limiting form of $k^1_{-1} [S] \gg k^1_2 [Y^-]$ and the rate-determining step becomes the nucleophilic attack on the protonated form of the nitrosoamine.

Table 13

The effect of added thiocyanate ions on k_o

10^3 [KSCN] /M	$10^4 k_o$/sec^{-1}
0	0.9
1.10	2.1
3.29	2.4
5.48	2.6
7.67	2.9

[HCl] = 0.420M   and   [NMNA] = 2.045 X 10^{-4}M

[ascorbic acid] = 3.69 X 10^{-3}M

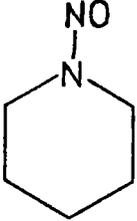However under these conditions the rate of the first part of the reaction will not differ considerably from the rate of the second part.

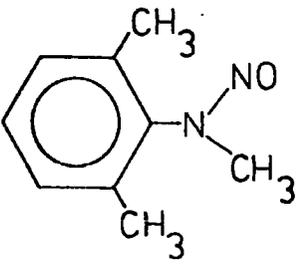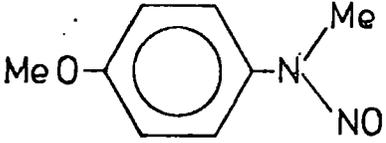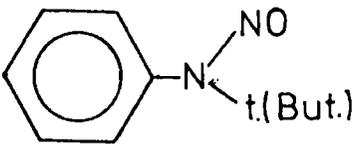For the reaction of NNDP, in water however the condition that k_{-1}^1 [S] $\gg k_2^1$ [Y$^-$] , no longer holds at high bromide concentrations. The reaction has, therefore, been shown[16] to become zero-order at high [Br$^-$] .

The reactions of various substitued nitrosoamines in methanol solvent were observed (see Table 14). The reactions were looked-at under non-limiting conditions, i.e. in the absence of a nitrite-trap or C. The reactions of N-nitroso-piperidine and 2, 6 ,-N-trimethyl N-nitrosoaniline were found to be too slow to measure. In aqueous solution N-nitrosopiperidine was shown to react very slowly as well[60]. It had also been shown[61] that the electron releasing substituent at meta- or para-position retard the reaction whereas the electron-attracting substituents increase the overall reactivity. In aqueous solutions the relative value of k for k_o(NMNA) to k_o (p-methoxy substitued NMNA) is 0.3, under irreversible conditions. It appears that a similar ratio exists in methanol solvent.

The reaction rate-coefficient of N-t(But) N-nitrosoaniline is 3.5 times faster than the reaction rate of NMNA in methanol solvent. But in aqueous solutions it is only 1.5 times faster and was suggested[61] that nucleophilic attack on amino-nitrogen atom is hindered by the bulky t(But), group. However the effect on the reaction by the substitutions is not only a simple relationship with their resulting basicity. The analysis is complicated since the rate constants are a function of Kk_1. It could be that these substituents influence k_1 and this effect is greater than the effect on the basicity of the nitrosoamine as is the case in aqueous solvent[61].

However the measured rate-constants k_o include a component for the reverse reaction as well (i.e. for the nitrosation of the secondary amine) so that these relative rate constants give a rough indication of the structural kinetic effects. Further work using nitrite-traps in methanol solvent is therefore needed for these substrates..

Table 14

Nitrosoamine	10^4[Nitrosoamine] /M	$[H^+]$ /M	$10^4 k_o$ /sec^{-1}
	1.456	0.105	to slow to measure
	1.115	0.105	to slow to measure
	1.10	0.210	6.36
NMNA	1.495	0.105	10.25
NNDP	0.526	0.021	15.48
	1.189	0.105	35.32

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APPENDIX

Research Colloquia Seminars and Lectures attended.

.1976 -- 1977

(a)   University of Durham Colloquia.

(i)   Wednesday 20th October

"New research on old element - Sulphur"

by Professor J.B. Hyne (University of Calgary)

(ii)   Wednesday 10th November

"The characterisation of high temperature species by

matrix-isolation"

by Dr. J.S. Ogden (Southampton University).

(iii) Wednesday 17th November

"Familiar but remarkable inorganic solids"

by Dr. B.E.F. Fender (University of Oxford)

(iv)   Wednesday 24th. November

"Large and small rate enhancements of intramolecular

catalysed reactions"

by Dr. M.I. Page (Huddersfield Polytechnic)

(v)   Wednesday 8th   December

"Liquid Crystals"

by Professor A.J. Leadbetter (University of Exeter)

(vi)   Wednesday 26th. January

-"The weathering of polymer materials"

by Dr. A. David (E.R.D.R.)

(vii) Wednesday 2nd. February

"Structural deductions from the vibrational spectrum of

water in condensed phases"

by Dr M. Falk (N.R.C. Canada)

(viii) <u>Wednesday 9th February</u>

"Radical cations intermidiates in organic reaction"

by Professor R.O.C. Norman (University of York)

(ix) <u>Wednesday 23rd February</u>

"Halogen adducts of phosphines and arsines"

by Dr. G. Harris (University of St. Andrews)

(x) <u>Wednesday 2nd March</u>

"Fast reaction studies of slow proton transfers involving

nitrogen and oxygen acide"

/ by Dr. F. Hibbert (Birkbeck College London)

(xi) <u>Wednesday 25th May</u>

"The dynamics of proton transfer in solution"

by Professor M.M. Kreevoy.

(b) The Durham University Chemical Society

(xii) <u>Tuesday 19th October</u>

"A light hearted look at chemistry and energy"

by Dr. J.A. Salthouse (University of Manchester)

(xiii) <u>Tuesday 26th October</u>

"NMR measurements on intact biological tissue"

by Dr. R.E. Richards (University of Oxford)

(xiv) <u>Tuesday 16th November</u>

"The graduate in industry"

by Mr. R. Ficken (Rohn & Haas)

(xv) <u>Tuesday 30th November</u>

"The chemistry of the atmosphere"

by Dr. R.J. Donovan (University of Edinburgh)

(xvi) <u>Tuesday 8th February</u>

"Platinum Group Metal Compounds as anti-cancer agents"

by Dr. M.J. Cleare (Johnson Matthey Research Centre)

(xvii) <u>Tuesday 1st. March</u>

"Double Resonance"

by Professor J.A.S Smith (Q.E. College London)

1.2 <u>1977 - 1978</u>

(a) University of Durham Chemical Colloquia

(xviii) <u>Friday 3rd February</u>

"Surprising recent studies in Organo-magnesium chemistry"

by Dr. A. Hartog (Free University Amsterdam Holland)

(xix) <u>Wednesday & Thursday 24th & 25th May</u>

1. "Planer Tetra-co-ordinate methanes perpendicular Ethylenes and planarallenes"

2. "Aromaticity in Three Dimensions"

3. "Non classical Carbocations"

by Professor P. Von R. Schleyer (University of Erlangen Nurnberg)

(b) Durham University Chemical Society

(xx) <u>Thursday 13th October</u>

"Experiments and considerations Touching Colour"

by Dr. J.C. Young Mr. A.J.S. Williams (University of Aberystwyth)

(xxi) <u>Thursday 16th February</u>

"Home Wine-making"

by Professor G.W.A. Fowler (University of Reading)