Kinetics and Mechanism of the Fischer–Hepp Rearrangement and Denitrosation. Part VII.[1] Reactions at High Acidity

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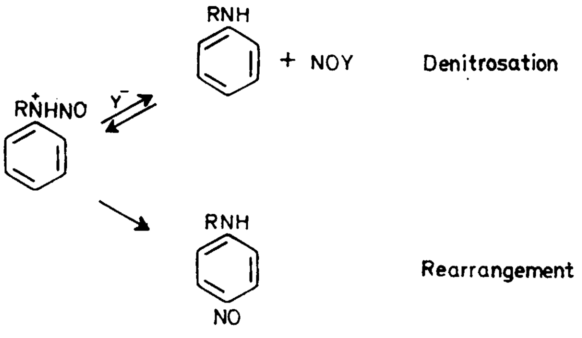
Rate constants for the denitrosation and also for the rearrangement of *N*-methyl-*N*-nitrosoaniline have been obtained in acid solution up to 10M-HCl and 12M-H_2SO_4. For denitrosation the shape of the rate–acidity profile changes as the acidity of the medium is increased; the zero-order behaviour in X (the added nitrite trap which ensures the irreversibility of denitrosation) is lost and the shape of the plot becomes dependant upon the nature and concentration of X. For X = HN_3 and NH_2NH_2 a change to a smaller slope occurs at *ca.* 4.5M-HCl, whereas for X = NH_2OH, $CO(NH_2)_2$ and NH_2SO_3H there is a maximum value of the observed rate constant k_0, and a decreasing value at higher acidities. The results are interpreted in terms of the possible protonation equilibria involving some of the X species at high acidities, with a consequent loss of reactivity towards electrophilic nitrosation. The rate constant for rearrangement levels off at *ca.* 9.7M-H_2SO_4, and thereafter decreases with increasing acidity. This is discussed in terms of the (partly rate-determining) final proton transfer from the *para*-position in the nitrosoamine to the solvent.

N-ALKYL-*N*-NITROSOANILINES undergo both rearrangement and denitrosation in aqueous acid solution.[2] There is much evidence [1,3] in favour of a mechanistic scheme in which both products are formed by concurrent reactions of the protonated nitroso-amine (see Scheme 1). In particular it has been established that the rearrangement product does not result from a direct *C*-nitrosation of the formed secondary amine by the free nitrosating agent NOY, as was formerly believed.[2] All the evidence points towards an intramolecular mechanism for that part of the reaction leading to rearrangement. Denitrosation occurs [4] (normally reversibly) by nucleophilic attack of Y^- (*e.g.*, Cl^-) at the nitroso-nitrogen atom of the protonated nitroso-amine and is markedly dependent upon the reactivity of Y^-. It is possible to suppress denitrosation completely by the addition of a large excess of the secondary amine. This so increases the rate of the reverse step, *i.e.* *N*-nitrosation, that now only rearrangement takes place. Presumably the same effect could be obtained by the addition of sodium nitrite; Houben [5] had noted higher yields of rearrangement product when sodium nitrite was added, but this subsequently, was interpreted differently. Similarly, if NOY is removed very rapidly (with *e.g.*, sulphamic acid), denitrosation occurs irreversibly and in parallel with rearrangement. With Y = Cl, Br, SCN, or I, the rate of denitrosation so exceeds that of rearrangement that quantitative denitrosation occurs, except when [Cl^-] is low. All our previous work on this system refers to reaction in moderately acidic media, *e.g.* in 2—5M hydrochloric acid. The detailed mechanism of *N*-nitrosation of amines (diazotisation if the amine is primary) is very much dependent upon the acidity of the medium. Ridd *et al.*[6] have shown



SCHEME 1

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[1] Part VI, D. L. H. Williams, *J.C.S. Perkin II*, 1975, 655.

[2] H. J. Shine, 'Aromatic Rearrangements,' Elsevier, Amsterdam, 1967, pp. 221—230.

[3] D. L. H. Williams, *Internat. J. Chem. Kinetics*, 1975, 215.

[4] I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1975, 107.

[5] J. Houben, *Ber.*, 1913, **46**, 3984.

[6] J. H. Ridd, *Quart. Rev.*, 1961, **15**, 427 and references quoted therein.

that the observed rate equation changes as the acidity increases from that given by equation (1) at 0.5—3.0M-perchloric acid to equation (2) at acidities greater than this. Equation (3) is observed for reactions in 60%

$$\text{Rate} = k[\text{ArNH}_2][\text{HNO}_2][\text{H}^+] \qquad (1)$$

$$\text{Rate} = k[\text{Ar}\overset{+}{\text{N}}\text{H}_3][\text{HNO}_2]h_0 \qquad (2)$$

$$\text{Rate} = k[\text{Ar}\overset{+}{\text{N}}\text{H}_3][\text{NO}^+]h_0^{-2} \qquad (3)$$

perchloric or 60% sulphuric acid. These results have been interpreted in terms of a changing mechanism as the acidity is increased. At low acid concentration, reaction is believed to occur by reaction of the nitrous acidium ion, $H_2\overset{+}{N}O_2$, with the free amine, whereas at higher acidity the nitrous acidium ion reacts with the protonated form of the amine. At very high acidities, a rapid reversible denitrosation preceeds a slow proton transfer to the medium. In view of the variety of mechanisms shown by *N*-nitrosation, it was thought to be of interest to examine mechanistically the reverse reaction, *i.e.* denitrosation of nitroso-amines, over a wide range of acidities. By using either of the limiting experimental conditions of (a) an added excess of sulphamic acid or hydrazoic acid *etc.*, or (b) an added excess of *N*-methylaniline, it is possible to measure the rate constants for the denitrosation and rearrangement reactions separately.

RESULTS AND DISCUSSION

Rate constants for the overall disappearance of the nitroso-amine in hydrochloric acid containing no added nitrite trap X or secondary amine NMA, are shown in Figure 1 as a function of the acidity of the medium (H_0). Both rearrangement and denitrosation occur under these conditions, the yield of rearrangement product decreasing with increasing concentration of hydrochloric acid; this is to be expected if (as has been shown [3,4]) the rate of denitrosation is proportional to the product $h_0[\text{Cl}^-]$, whereas the rate of rearrangement is independent of the chloride ion concentration, and depends only upon the acidity. The free nitrosating agent (NOCl or HNO_2) reacts not only with the formed secondary amine to regenerate the nitroso-amine (*N*-nitrosation), but also undergoes decomposition by reaction with the solvent,[7] so that the concentration of secondary amine builds up in solution, and rearrangement will not be quantitative. Up to *ca.* 6.2M-HCl (H_0 −2.2) log k_0 increases linearly with $-H_0$ as expected for a reaction proceeding *via* the protonated form of the nitroso-amine. There is a rate maximum at H_0 −2.5 and a decrease in k_0 at acidities higher than this. It is to be expected that k_0 should become independent of the acidity (but not of the chloride ion concentration) when the nitroso-amine is fully protonated. The sharply decreasing value of k_0 observed at the higher acidities clearly indicates some change in the mechanism in this region. Although the pK_a value of *N*-methyl-*N*-nitrosoaniline is not known, there is evidence from the change in its absorption spectrum that a substantial amount of the base exists in its protonated form at *ca.* 6.5M-HCl. Earlier work by Jaffé and his co-workers [8] with aliphatic nitroso-amines suggests that several variously protonated species exist, but their structures were not established. It is important to separate the denitrosation and rearrangement reactions, in order to examine the mechanism of each reaction in this higher acid region.

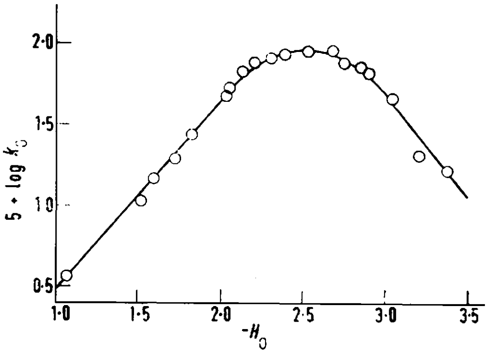

FIGURE 1 Variation of the total rate constant with acidity

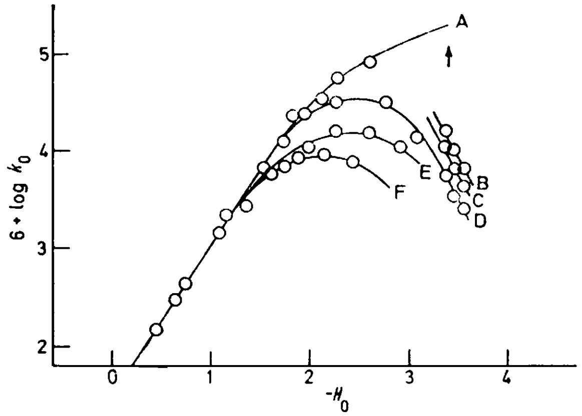

FIGURE 2 Rate of denitrosation as a function of acidity and of the nitrite trap X: A, HN_3, $NH_2\overset{+}{N}H_3$; B, 4.1 × 10^{-3}M-NH_2SO_3H; C, 2.8 × 10^{-3}M-NH_2SO_3H; D, 1.4 × 10^{-3}M-NH_2SO_3H; E, $\overset{+}{N}H_3OH$; F, $CO(NH_2)_2$

(1) *Denitrosation.*—An earlier Part [4] reports that the rate of denitrosation when carried out in the presence of a nitrous acid trap X (sulphamic acid, hydrazoic acid, *etc.*) is independent of the nature and concentration of X, so long as its concentration exceeded some critical value necessary to ensure the irreversibility of the denitrosation process. This critical value was found to be dependent upon the reactivity of the particular X towards nitrosation. Below 5.5M-HCl the zero-order behaviour in X holds well for all nitrous acid traps

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[7] N. S. Bayliss and D. W. Watts, *Austral. J. Chem.*, 1956, **9**, 319.

[8] W. S. Layne, H. H. Jaffé, and H. Zimmer, *J. Amer. Chem. Soc.*, 1963, **85**, 1816.

studied, and the experimental results are all interpreted in terms of a rate-determining attack by the nucleophile (Y^-) upon the protonated form of the nitrosamine. Above this acidity however, the reaction begins to lose the zero-order dependence on X. This is shown clearly by Figure 2, where the shape of the curve depends upon the nature and concentration of X. At the lower acidities the mechanism of denitrosation is that given in Scheme 2.

$$\mathrm{PhNMeNO} + \mathrm{H}^+ \underset{}{\overset{K}{\rightleftharpoons}} \mathrm{Ph\overset{+}{N}H(Me)NO}$$

$$\mathrm{Ph\overset{+}{N}H(Me)NO} + \mathrm{Y}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{PhNHMe} + \mathrm{NOY}$$

$$\mathrm{NOY} + \mathrm{X} \xrightarrow{k_3} \text{Various products}$$

SCHEME 2

The general expression for the observed first-order rate constant k_0 {defined by $-\mathrm{d}[(\mathrm{I})]/\mathrm{d}t = k_0[(\mathrm{I})]$} is given by equation (4) which reduces to equation (5) when $k_3[\mathrm{X}] \gg k_{-1}[\mathrm{PhNHMe}]$ readily accounting for the zero-order behaviour in X.

$$k_0 = \frac{k_1[\mathrm{Y}^-]Kh_0k_3[\mathrm{X}]}{k_3[\mathrm{X}] + k_{-1}[\mathrm{PhNHMe}]} \qquad (4)$$

$$k_0 = k_1[\mathrm{Y}^-]Kh_0 \qquad (5)$$

We have examined denitrosation under these circumstances (when the rate of rearrangement is negligible) for X = urea, sulphamic acid, hydrazine, aniline, hydrazoic acid, and hydroxylamine, all of which react rapidly and irreversibly with free nitrosating agents such as NOCl or HNO_2. None of these X species are sufficiently powerful nucleophiles in aqueous acid solution to react directly with the protonated nitroso-amine. Denitrosation has been brought about by the following nucleophiles, in increasing order of reactivity: H_2O, Cl^-, Br^-, SCN^-, $SC(NH_2)_2$, and I^-. It is interesting to note that as the acidity is increased the departure from zero-order behaviour in X occurs first for urea then hydroxylamine, followed by sulphamic acid, with relatively little change for hydrazine and hydrazoic acid, both of which appear to follow the same curve. This order represents the increasing order of reactivity of X towards electrophilic nitrosation by $H_2\overset{+}{N}O_2$ or NOCl[1] and suggests that the change of behaviour is associated with the relative reactivities of X. It seems appropriate to discuss hydrazine and hydrazoic acid together and separately from the other X species.

(a) *Denitrosation with added hydrazoic acid and hydrazine.* It is likely, from an inspection of the relative pK_a values that the reactive species towards nitrosation by nitrosyl halides *etc.*, when sodium azide and hydrazine are added to the acid solutions, are in fact HN_3 and $NH_2\overset{+}{N}H_3$ respectively. Further protonation of the hydrazinium ion to $\overset{+}{N}H_3\overset{+}{N}H_3$ and of hydrazoic acid to $H_2N_3^+$ can occur, but from the estimated pK_a values[9] of these species, not to any appreciable extent at the acidities studied in this work. We would therefore expect the inequality $k_3[\mathrm{X}] \gg k_{-1}[\mathrm{PhNHMe}]$ to be maintained in the high acid region, thus continuing the pattern of zero-order behaviour in X. As before, k_0 is independent of the nature and concentration of X = HN_3 or $NH_2\overset{+}{N}H_3$. The change in the shape of the rate profile can readily be understood in terms of the protonation of the nitroso-amine. If significant quantities of the nitroso-amine exist as the protonated form, then equation (5) should be replaced by equation (6) which, if the protonation is virtually complete, simplifies to (7). Equations (7) and (5) are of course the high and low acid limiting forms respectively of the general equation (6), and intermediate behaviour is to be expected.

$$k_0 = k_1[\mathrm{Y}^-]Kh_0/(1 + Kh_0) \qquad (6)$$

$$k_0 = k_1[\mathrm{Y}^-] \qquad (7)$$

As the change from (5) to (7) occurs the slope of the log k_0 against $-H_0$ plot should change (decrease) since in hydrochloric acid the rate dependence becomes proportional to $[Cl^-]$ and not to $h_0[Cl^-]$ as expected (and observed[4]) at lower acidities. Our data are somewhat limited in this region since the reactions become too fast to measure accurately by our method. There is no sign however, of a rate maximum (as for urea, sulphamic acid, and hydroxylamine) and at 8.9M-HCl (H_0 -3.4) k_0 is $>10^{-1}$ s^{-1}. From the point at which the plot changes slope it is possible to estimate the pK_a of the nitroso-amine at *ca.* -2.

(b) *Denitrosation with added urea, sulphamic acid, and hydroxylamine.* For each of these added nitrite traps, the reaction rate constant passes through a maximum value and thereafter decreases as the acidity of the solution is increased. The position of the maximum varies from one X to another and also with the concentration of each as shown in Figure 2. Clearly we have now lost the zero-order dependence upon X which was observed at lower acidities. This state of affairs would obtain if the inequality $k_3[\mathrm{X}] \gg k_{-1}[\mathrm{PhNHMe}]$ no longer applies. The most obvious explanation of this is that in this higher acid region, sulphamic acid, urea, and hydroxylamine are converted to some further protonated forms, which would be much less reactive towards electrophilic nitrosation by the free nitrosating agent NOY. This would explain, at least qualitatively, the individual variations between the three compounds, and also for the concentration dependence. At lower acidities, it appears from the published pK_a values that urea, sulphamic acid, and hydroxylamine exist largely as $CO(NH_2)_2$, NH_2SO_3H (and $\overset{+}{N}H_3SO_3^-$), and $\overset{+}{N}H_3OH$, each of which is expected to react rapidly and irreversibly with nitrosyl chloride. Although the pK_a values for further protonation are not generally known (except for urea[10]), it seems reasonable that further protonation to mono- or di-protonated forms of urea, $\overset{+}{N}H_3SO_3H$, and $\overset{+}{N}H_3\overset{+}{O}H_2$ is possible at these

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[9] P. A. S. Smith, 'The Chemistry of Open-chain Nitrogen Compounds,' Benjamin, New York, vol. I, pp. 9, 11.

[10] E. P. Parry, D. H. Hern, and J. G. Burr, *Biochim. Biophys. Acta*, 1969, **182**, 570.

higher acidities. If this occurs to a significant extent then the $k_3[X]$ term in equation (4) should be divided by $(1 + h_0K_x)$ where K_x represents the equilibrium constant for the protonation $X + H^+ = XH^+$; this assumes that this equilibrium is adequately expressed in terms of the h_0 function. It is probable that the protonation of some of the X bases are better represented by other acidity functions (*e.g.* H_A), but it is thought that this will not change our mechanistic conclusion, as differences are not large between the various scales in the region studied, particularly in hydrochloric acid, and also since our analysis does not require a precise knowledge of the acidity dependence. The limiting condition $1 \gg h_0K_x$ would apply at low acidities and lead to equation (4) whereas at high acidities $1 \ll h_0K_x$ and equation (8) results. If the nitroso-amine is also virtually completely protonated then (8) becomes (9). As $h_0K_x \gg 1$

$$k_0 = \frac{k_1[Y^-]k_3[X]Kh_0}{h_0K_x\left\{k_{-1}[PhNHMe] + \dfrac{k_3[X]}{h_0K_x}\right\}} \qquad (8)$$

$$k_0 = \frac{k_1[Y^-]k_3[X]}{h_0K_x\left\{k_{-1}[PhNHMe] + \dfrac{k_3[X]}{h_0K_x}\right\}} \qquad (9)$$

it is now reasonable to assume that $k_{-1}[PhNHMe]$ is not now negligibly small compared with $k_3[X]/h_0K_x$, and it is to be expected that the value of k_0 given by equation (9) will decrease as the acidity is increased as observed for X = urea, sulphamic acid, and hydroxylamine. The zero-order behaviour in X is now destroyed, and the various X species would be expected to behave differently, as they have different values of K_x and k_3. Further, there is now a concentration dependence upon X. These expectations are borne out experimentally for these X as shown in Figure 2 B—D for sulphamic acid at different concentrations and by E and F respectively for hydroxylamine and for urea.

Similar behaviour has been noted for other nitroso-amines. The results for *p*-methoxy-*N*-methyl-*N*-nitrosoaniline are shown in the Table. The rate of denitrosation in the presence of sulphamic acid goes through a maximum at *ca.* 7.5M and thereafter decreases rapidly, whereas with hydrogen azide the rate constant continues to increase beyond 8.82M.

Rate data for denitrosation of *para*-$OMeC_6H_4N(Me)NO$ in hydrochloric acid

$[H^+]$/M	$10^3[NH_2SO_3H]$/M	10^4k/s^{-1}
6.62	2.96	236
7.45	2.96	346
8.32	2.96	209
10.0	4.15	9.68
	$10^3[HN_3]$/M	
6.60	1.04	271
6.99	1.04	486
7.43	1.04	662
8.82	1.12	>1 000

Kinetic solvent isotope effects are often useful guides to mechanism, particularly of acid catalysed reactions. Figure 3 shows the rate profile for denitrosation in the presence of sulphamic acid (1.39×10^{-3}M) in D_2O–DCl as well as for H_2O–HCl. At low acidities the solvent isotope effect $(k_0)_H : (k_0)_D$ is <1 whilst at higher acidities it is reversed. Up to $H_0 - 2$ we observe the normal solvent isotope effect associated with a reaction which involves as a first step a fast reversible proton transfer. The equilibrium constant K [in equation (4)] for protonation of the nitroso-amine is expected to be greater in D_2O than in H_2O as is generally found.[11] At high acidities where it is probable that the nitroso-amine is virtually completely protonated the isotope effect should decrease to 1. However it is necessary here to consider also the solvent isotope effect upon the protonation of X, the nitrite trap. Again it is expected that $(K_x)_D$ is greater than $(K_x)_H$, so that at any one acidity more X is converted to its less reactive protonated form in D_2O than in H_2O. This is of no consequence at lower acidities where $k_3[X] \gg k_{-1}[PhNHMe]$, but at higher acidities where equation (9) obtains, and where $k_{-1}[PhNHMe]$ is not negligibly small compared with $k_3[X]/h_0K_x$, it is easy to see that $(k_0)_H$ should be greater than $(k_0)_D$, as observed. It is thus possible to explain the various trends in k_0 for the denitrosation reaction at different acidities as a function of the nature and concentration of a number of nitrite traps X, if allowance is made for the protonation of X and the nitroso-amine at higher acidities. Similar results have been obtained for reactions in sulphuric acid where denitrosation is thought to be brought about by a water molecule, although of course more slowly than by the more nucleophilic chloride ion. These results are not as complete as for those in hydrochloric acid since there is a complicating feature due to the incursion of a second mechanism of denitrosation,[4] particularly at high acidities, involving attack by H_3O^+ at the amino nitrogen atom of the protonated nitroso-amine, with the

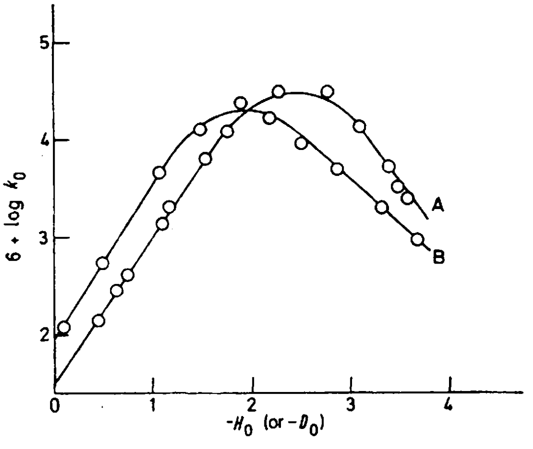

FIGURE 3 Solvent isotope effect on denitrosation: A, HCl–H_2O; B, DCl–D_2O

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[11] R. P. Bell, 'Acids and Bases,' Methuen, London, 1969, 2nd edn., p. 92.

consequent displacement of NO^+, possibly *via* a ring-bonded species. The rate of this reaction increases markedly with acidity as expected and eventually exceeds that of the 'normal' denitrosation by chloride ion in hydrochloric acid. This makes it difficult to compare the chloride ion and H_2O reactions directly. At these higher acidities the reaction rate in sulphuric acid becomes too large to be measured accurately, so that the rate profile is necessarily less complete than that in hydrochloric acid.

(2) *Rearrangement.*—The rearrangement of aromatic *N*-nitroso-amines to the *para*-nitroso-isomer can be studied without complication due to denitrosation, if reaction is carried out without a nitrite trap X, but in the presence of added secondary amine derived from the nitroso-amine, in sufficient excess to ensure that the rate of *N*-nitrosation of the secondary amine is rapid enough to ensure that no loss of free nitrosating agent occurs by reaction with the solvent. We have discussed features of the rearrangement reaction at acidities up to 8M-HCl and 6M-H_2SO_4 in an earlier paper,[12] and have extended the study here to higher acidities. Figure 4 shows the rate profile for rearrangement in sulphuric acid up to 12M. Up to *ca.* 6.5M log k_0 is proportional to $-H_0$ with a slope of 0.9, thereafter the rate levels off going through a flat maximum at *ca.* 10M and decreasing linearly above this acidity. It is to be expected that the rate constant should become independent of the acidity once the nitroso-amine is fully protonated. The u.v. spectrum of the reactant is consistent with this change at *ca.* 10M-H_2SO_4. The decreasing value of k_0 at higher acidities could well be due to the rapidly decreasing activity of water in this region. The rate constant for rearrangement is given by $k_0 = k_4k_5Kh_0/(k_4 + k_{-5})$ when the nitroso-amine is only protonated to a small extent. It is difficult to see how the intermediate (A) can be formed directly from the protonated nitroso-amine; it is probable that another intermediate exists (possibly a π-complex) before the formation of the σ-complex (A). k_5 Is thus a composite rate constant, but is treated as a single term for simplicity. As there is a primary ring deuterium isotope effect $(k_0)_H : (k_0)_D$ of 2.4,[12] it appears that k_4 is not $\gg k_{-5}$, *i.e.* that the final proton loss to the solvent is at least in part rate determining. At very high acidities it is not unreasonable to expect that this final step (k_4) becomes reduced, leading to a lower value of k_0. This would account for the early observation by Fischer and Hepp [13] that the substrate remains substantially unchanged in concentrated sulphuric acid over a period of several weeks.

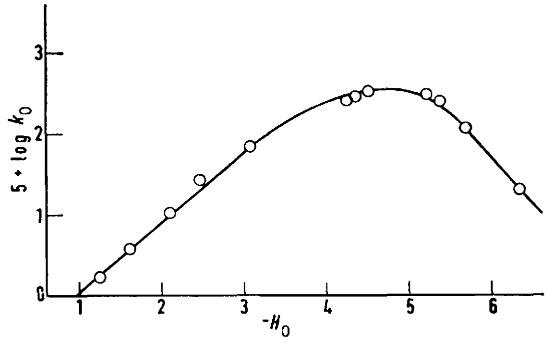
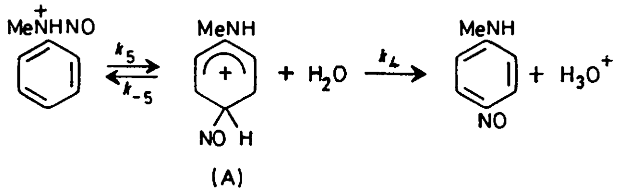


FIGURE 4 Rate of rearrangement as a function of acidity



At these higher acidities the yield of rearrangement product drops significantly, even in the presence of added secondary amine. Increasing the concentration of the secondary amine does result in increasing the rearrangement yield, suggesting that under these conditions it is more difficult to cut out denitrosation altogether. This is consistent with the very rapidly increasing rate of denitrosation at high acidities. A further complication occurs in this region in the form of another product which is yellow in acid solution with an absorption maximum at 450 nm. To date we have not been able to isolate a stable compound corresponding to this absorption, it may well be that this is a side-reaction giving rise to an oxidation product possibly derived from cation-radical intermediates, although at this stage this is merely speculation. There is however no doubt that the rate of formation of the rearrangement product decreases at high acidity. We have found the same behaviour for *m*-methoxy-*N*-methyl-*N*-nitrosoaniline, which at lower acidities gives virtually quantitative rearrangement, even without the addition of the corresponding secondary amine.

EXPERIMENTAL

Both nitroso-amines were prepared from the corresponding secondary amines and sodium nitrite in acid solution. Kinetic measurements were carried out in a Pye-Unicam SP 8000 spectrophotometer at 31 °C as has been previously described.[4]

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[5/1702 *Received, 4th September,* 1975]

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[12] T. D. B. Morgan, D. L. H. Williams, and J. A. Wilson, *J.C.S. Perkin II*, 1973, 473.

[13] O. Fischer and E. Hepp, *Ber.*, 1887, **20**, 1247.