Kinetics and Mechanism of the Denitrosation of Nitrosamines in Ethanol

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Rate constants have been determined for the denitrosation of *N*-methyl-*N*-nitrosoaniline (NMNA), *N*-nitrosodiphenylamine (NDA), and *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (MTS) in ethanolic solutions of hydrogen chloride. For both NMNA and NDA the change is reversible in the absence of a trap for the nitrosyl chloride formed; the equilibrium position is dependent upon [HCl]. A kinetic analysis in the case of NMNA gives the rate constants for both the forward and reverse reactions. A more accurate determination of the forward rate constant was obtained for both NMNA and NDA by using an excess of added ascorbic acid to remove the free nitrosating species. Under these conditions the rate law, rate = k_2 [Nitrosamine][HCl], prevails. The reaction of MTS was irreversible even in the absence of a nitrite trap and the same rate law was established. All three reactants show the absence of catalysis by added sodium bromide and potassium thiocyanate and gave kinetic deuterium solvent isotope effects k_{EtOH}/k_{EtOD} in the range 2.6—3.8. The results are in accord with a rate-determining proton transfer to the nitrosamine, contrasting with the behaviour (of NMNA and NDA) in water solvent. The rate of denitrosation of NMNA decreases as water is added to the solvent, and nucleophilic catalysis begins to be effective. The Fischer–Hepp rearrangement of NDA is observed when ascorbic acid is absent; the rate constant for rearrangement is much less than that for denitrosation at the same acidity.

We have examined in some detail the kinetics of the denitrosation of nitrosamines [1,2] and a nitrososulphonamide [3] in aqueous acid solution, in the presence of the following nucleophiles, H_2O, Cl^-, Br^-, I^-, SCN^-, and $SC(NH_2)_2$. For the two nitrosamines *N*-methyl-*N*-nitrosoaniline (NMNA) and *N*-nitrosodiphenylamine (NDA) the reaction was acid-catalysed, first order in the concentration of nucleophile Y^- (except for NDA at high bromide ion concentration, see later), and very sensitive, from a reactivity point of view, to the nature of the nucleophile. Both nitrosamines gave (perhaps surprisingly) reasonably good correlations of log (rate constant) with the nucleophilicity parameter *n* of Pearson,[4] with slopes of 1.41 and 0.95, respectively. The reactions were also subject to a kinetic solvent isotope effect k_{D_2O}/k_{H_2O} of 2.0—2.9. These results are consistent with the mechanism set out in Scheme 1. The reactions are best studied in the presence of a trap (X) for the free nitrosating species NOY (*e.g.* NOCl or $H_2NO_2^+$), at a concentration such that $k_3[X] \gg k_{-2}[R'R''NH]$. Under

$$R'R''NNO + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R'R''\overset{+}{N}HNO$$

$$R'R''\overset{+}{N}HNO + Y \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R'R''NH + NOY$$

$$NOY + X \xrightarrow{k_3} \text{Decomposition products}$$

SCHEME 1

these conditions, the overall reaction is effectively irreversible, zero-order in X, with the k_2 step rate-limiting, *i.e.* the proton transfer to the nitrosamine from the solvent is rapid. However, the kinetic characteristics of the corresponding reaction of *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide in water are quite different, in that whilst the reaction is acid catalysed, it is not catalysed by any of the nucleophiles Y^- and the kinetic solvent isotope effect k_{D_2O}/k_{H_2O} was 0.7. These results are very similar to those obtained previously for the denitrosation pathways of *N*-n-butyl-*N*-nitrosoacetamide [5] and *N*-nitroso-2-pyrrolidone.[6] Where strongly electron-withdrawing groups (such as C=O or SO_2) are present in the nitrosamine, it appears that the step k_1 becomes rate limiting. This is in accord with the expected low basicity of these compounds and the accelerating effect such groups are expected to have on step k_2, the nucleophilic attack at the nitroso-nitrogen atom.

It was thought to be of interest to extend the range of solvents, beyond aqueous solvents, in the denitrosation of nitrosamines. Non-aqueous solvents have been used qualitatively for this reaction, as well as the use of HBr in acetic acid in the quantitative analysis of nitrosamines by chemiluminescence [7] and other spectrophotometric [8] methods. We here report the results of a study in ethanol solvent.

EXPERIMENTAL

The nitrosamines NMNA and NDA and the nitrososulphonamide were prepared and purified as has been described previously.[1-3] AnalaR ethanol was dried using the normal magnesium method, as was the deuterio-analogue, C_2H_5OD. Hydrogen chloride, either directly from a cylinder or prepared from concentrated sulphuric acid and sodium chloride, was dried (H_2SO_4) before dissolution in ethanol. Its concentration was determined by titration with standard sodium hydroxide.

Kinetic measurements were carried out in a Pye–Unicam SP 8000 recording spectrophotometer or a Beckmann model 25 in cells maintained at 31°. Reaction was followed by noting the fall in the absorption due to the reactant (272 nm for NMNA, 310 nm for NDA, 260 nm for MNTS). Good first-order plots were obtained when reaction went to completion; first-order rate coefficients were reproducible to within ±4%.

RESULTS AND DISCUSSION

In the absence of a nitrite trap (such as sulphamic acid, ascorbic acid, *etc.*) the denitrosation of NMNA proceeds smoothly in ethanol containing hydrogen chloride to give an equilibrium mixture of *N*-methyl-

aniline and unchanged NMNA. The composition of the equilibrium mixture varies with the acid concentration, but it is clear that the equilibrium lies considerably more towards denitrosation in this solvent than for corresponding reactions in water. Table 1 shows the variation of the equilibrium *N*-methylaniline (NMA) yield with [HCl]. The results suggest that the forward and reverse steps have different dependencies on [HCl]. Scheme 2 gives a representation of the probable equilibria involved. It is to be expected that the forward reaction (denitrosation) will depend upon [HCl] whereas the reverse reaction (NMA + NOCl ⟶), should not have a rate dependence upon [HCl] as a first approximation since the protonation of NMA and the equilibrium formation of ethyl nitrite have opposite dependencies

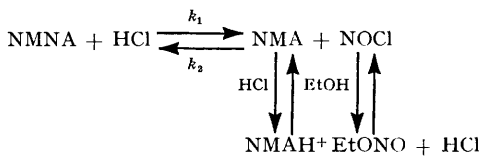
TABLE 1

Yield of *N*-methylaniline at equilibrium as a function of [HCl]

[HCl]/M	% *N*-methylaniline
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
0.663	68.2
0.791	71.9
0.949	74.3

upon [HCl]. This lack of rate dependence upon [HCl] has been noted in the diazotisation of aniline derivatives in hydrochloric acid.[9]

In principle this reaction can be analysed in terms of a reversible reaction, first order in the forward direction (since [HCl] is greatly in excess) and second order in the reverse direction.[10,11] The first-order rate constant ($k_1' = k_1$[HCl]) can be obtained from a plot of $\ln[ax_e + x(a - x_e)]/a(x_e - x)$ *versus* time, and the second-order rate constant k_2 for the reverse step is given by $k_1'(a - x_e)/x_e^2$. The symbols have their usual meaning,



SCHEME 2

i.e. a is the initial concentration of the reactant, x the concentration of the product at any time t, and x_e the concentration of the product at equilibrium. Such a plot is given in Figure 1 from which k_1' is 5.91×10^{-3} s^{-1} and k_2 37.2 l mol^{-1} s^{-1}. The variation of both k_1' and k_2 with [HCl] was determined; the results are presented in Figure 2. It is clear that k_1' is directly proportional to [HCl] giving a value for the second-order rate constant k_1 (defined by $-$d[NMNA]/dt = k_1[HCl][NMNA]) of 189×10^{-4} l mol^{-1} s^{-1}. For the reverse reaction of *N*-nitrosation of NMA there is little change in the rate constant k_2 with [HCl], as expected. There is a little scatter of points for both plots inherent in the method for separation of the two rate constants.

An alternative method for obtaining k_1' and hence k_1, which was used for the corresponding reactions in water solvent, would be to arrange for denitrosation to be irreversible by the removal of the free nitrosating agent, NOCl in this case. In water, the following traps for

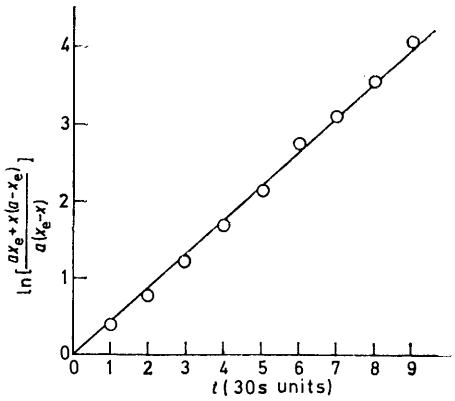


FIGURE 1 Analysis of a kinetic run, first order in the forward direction and second order in the reverse direction

' free nitrite ' have been used to achieve this end: HN_3, $NH_2\overset{+}{N}H_3$, NH_2SO_3H, $\overset{+}{N}H_3OH$, $C_6H_5NH_2$, ascorbic acid, urea. From this range it was found that only ascorbic acid proved to be a suitable trap in ethanol. Undoubtedly the very low solubility of some of the species in ethanol accounts for this lack of reactivity at least in part. Addition of ascorbic acid had the effect of increasing the yield of denitrosation product until the limit of 100% reaction was achieved. Figure 3 shows the

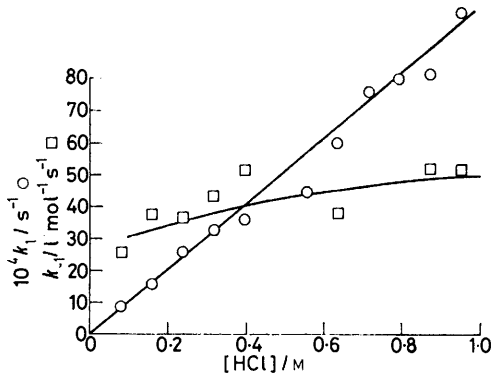


FIGURE 2 Variation of k_1 and k_{-1} with [HCl]

observed first-order rate constant k_1' as a function of added ascorbic acid. At [ascorbic acid] $> 4 \times 10^{-3}$M the denitrosation reaction is virtually irreversible. A little ascorbic acid added to an equilibrium mixture also had the effect of converting the remaining NMNA to the product NMA. The dependence of k_1' determined in this way (in the presence of excess ascorbic acid) upon [HCl] is shown in Figure 4. The first-order rate constant k_1' here is plotted against both [HCl] and [HCl]^2. Without doubt there is a direct proportionality between

k_1 and [HCl] but not between k_1 and [HCl]^2. In water a second-order dependence was found (as $k_0[Cl^-]$) and interpreted as a rate-determining attack by Cl^- upon the protonated nitrosamine. For reaction in ethanol, the

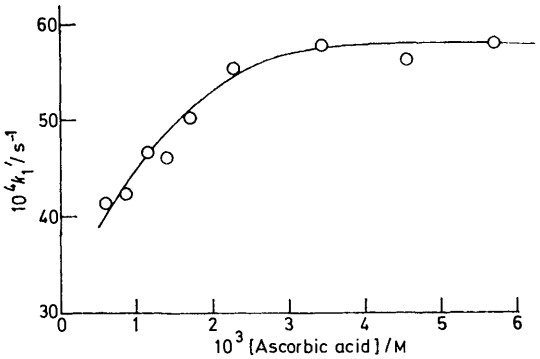


FIGURE 3 Variation of the observed first order rate constant k_1' with [ascorbic acid]

mechanism is clearly different. The plot gives k_1 as 106×10^{-4} l mol^{-1} s^{-1}, as compared with 189×10^{-4} l mol^{-1} s^{-1} from the analysis of the equilibrium mixture (Figure 2). The discrepancy between these two values

TABLE 2

Absence of bromide ion catalysis for k_1'

10^3[Br$^-$]/M	$10^4k_1'/s^{-1}$
0	70.7
0.51	69.7
1.02	68.7
1.53	69.2
4.59	68.3

is somewhat greater than one would like, but is probably due to the large error in the value of 189×10^{-4} l mol^{-1} s^{-1}.

The effect of added sodium bromide was examined, again at [ascorbic acid] *ca.* 4×10^{-3}M. The results are presented in Table 2. No bromide-ion catalysis is

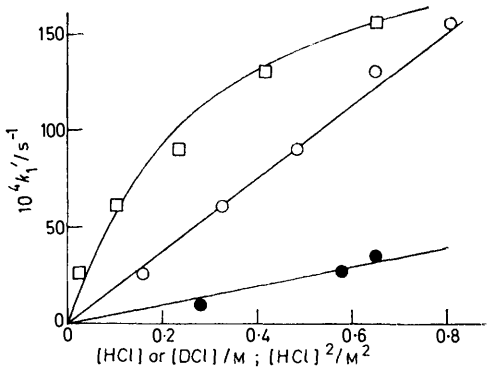
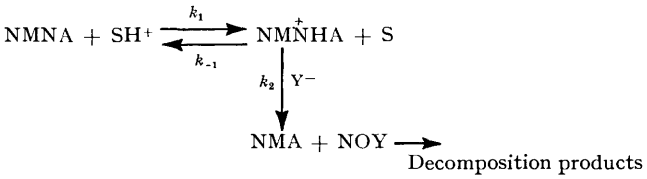


FIGURE 4 k_1' as a function of [HCl] (○), [DCl] (●), and [HCl]^2 (□)

apparent over the range considered. In water the addition of sodium bromide (4.59×10^{-3}M) gave a rate increase of *ca.* 5-fold. Similarly for the reaction in ethanol, no thiocyanate catalysis was found for a range of added thiocyanate, $0—7 \times 10^{-3}$M.

All these results for the denitrosation of NMNA in ethanol solution show that the nucleophilic species plays no part in determining the rate of the reaction, in contrast to the same reaction in water. This suggests that either (a) loss of NO^+ is a unimolecular unassisted process, or (b) that the rate-determining stage now precedes the nucleophilic attack. We prefer explanation (b) since we can see no reason why in this case the NO^+ loss should be unimolecular. The lack of kinetic dependence upon the nature and concentration of the nucleophile has now been observed for three situations: (i) the denitrosation of two nitroso-amides [5,6] and a nitroso-sulphonamide [3] in water, (ii) the denitrosation of *N*-nitrosodiphenylamine [2] in water at high [Br$^-$], and now (iii) for the denitrosation of *N*-methyl-*N*-nitrosoaniline in ethanol solvent. Both cases (i) and (ii) show primary kinetic solvent isotope effects, $k_{H_2O} > k_{D_2O}$. We have measured the rate constants for denitrosation of NMNA in ethanol at three different acidities. The results are included in Figure 4 and show a kinetic solvent isotope effect k_{EtOH}/k_{EtOD} of 3.8, which fully supports explanation (b) above for a rate-determining proton transfer.

In general we would expect (for solvent S) Scheme 3 to



SCHEME 3

represent the steps involved in the denitrosation process when the reverse step (*N*-nitrosation of *N*-methylaniline NMA) is eliminated by the use of ascorbic acid. A steady-state treatment yields expression (1) for the first-order rate constant k_1' (defined by $-d[NMNA]/dt = k_1'[NMNA]$). For a first-order dependence upon [Y$^-$] it

$$k_1' = k_1[SH^+]k_2[Y^-]/(k_{-1}[S] + k_2[Y^-]) \quad (1)$$

is necessary that $k_{-1}[S] \gg k_2[Y^-]$. This appears to be the situation for the reaction of NMNA and NDA in water, except for the latter nitrosamine at high Y$^-$ (=Br$^-$) when this inequality no longer holds. It is easy to envisage, on the basis of elementary qualitative theory of solvation, that a change to a less polar solvent could result in a large increase in k_2 (where charged species are involved) and a small increase in k_{-1}. Under these circumstances it is quite conceivable that the other limit $k_2[Y^-] \gg k_{-1}[S]$ could be achieved in ethanol solvent, so resulting in a zero-order dependence upon [Y$^-$] and with $k_1' = k_1[SH^+]$, as is observed experimentally.

Both *N*-nitrosodiphenylamine (NDA) and *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (MTS) also underwent denitrosation in ethanolic hydrogen chloride solution. For NDA the reaction was reversible (as for NMNA) and it was necessary to add ascorbic acid to ensure complete denitrosation. The observed first-order rate constant k' increased with [ascorbic acid] until it levelled off when [ascorbic acid] $> 9 \times 10^{-3}$M. Thus a greater concentration of ascorbic acid is necessary to ensure ir-

reversibility in the case of NDA as compared with NMNA, as expected if the rate of *N*-nitrosation of diphenylamine exceeds that of *N*-methylaniline as it does for reaction in water.[2] Again for NDA a plot of k_1' *versus* [HCl] gave a good straight line through the origin yielding a value of 500×10^{-4} l mol^{-1} s^{-1} for k_1, compared with 106×10^{-4} l mol^{-1} s^{-1} for the corresponding reaction of NMNA. Again there was no catalysis by added potassium thiocyanate. In water solvent (except at very high nucleophile concentration) NDA is also more reactive than NMNA, by a factor of *ca.* 100 although this varied with the choice of nucleophile. Under those conditions it was thought that the phenyl group assisted the process of nucleophilic attack significantly more than did a methyl group,[2] although it is possible that relief of steric strain was an important factor. However in the present case, this cannot be the case since the reaction in ethanol is zero order in added nucleophile. At first sight, using the basicities of the parent amines as a guide, one would expect NMNA to react more rapidly than NDA whereas in fact there is a small (*ca.* 5-fold) change in the other direction. Two explanations seem possible: (a) the basicities of the nitrosamines may not parallel those of the corresponding amines (it is known that steric effects are very important in this area—the additional NO group may have a significant steric effect which could be greater in the case of NDA) and (b) *N*-protonation may in fact involve a rather more complicated series of reactions, possibly *O*-protonation followed by rearrangement. Substituent effects could then be much more complicated to analyse.

Similarly, nitrososulphonamide (MTS) showed the same pattern of behaviour, although it was less reactive than either NMNA or NDA, k_1 from the plot of k_1' against [HCl] having the value 51×10^{-4} l mol^{-1} s^{-1}. In this case the reaction rate was independent of the presence of a nitrite trap and the reaction proceeded completely to denitrosation, implying that the reverse reaction (*N*-nitrosation of *N*-methyltoluene-*p*-sulphonamide) has a negligibly small rate constant under these conditions. This was confirmed by the observation that the observed rate constant was independent of excess added *N*-methyltoluene-*p*-sulphonamide. There was no bromide-ion catalysis, the reaction was first order in [HCl], and there was an observed solvent isotope effect, $k_{EtOH} : k_{EtOD}$ of 2.6. So, for MTS the pattern of behaviour for denitrosation in acid solution is the same in ethanol solvent as it is in water,[3] although the reactivity in water is greater by a factor of *ca.* 10. Presumably, for this substrate, even without the assistance of the change to ethanol solvent, the rate constant for the reaction of the nucleophile with the protonated reactant is increased so much by the strongly electron-withdrawing SO_2 group, that the limiting condition (leading to a zero-order dependence upon the nucleophile) prevails.

We have written the proton transfer to the amino-nitrogen atom of the nitrosamine, in one stage. It is quite likely that the oxygen atom is the more basic site, but a mechanism for denitrosation involving the *O*-protonated species does not fit so well, particularly with the accepted mechanisms for the reverse reaction, the formation of the nitrosamines from *e.g.* nitrosyl halides and secondary amines. Protonated nitrosamine species have never been positively identified, although there are indications [12] that several structures survive at different acidities. It is quite possible that our ' one-stage protonation ' may in fact include other intermediates, *e.g.* hydrogen-bonded species. Our kinetic results throw no light on this issue.

Change of Solvent.—The effect of a gradual change in the solvent, from ethanol to water, upon the reactivity and rate law governing the denitrosation of NMNA has been examined. Figure 5 shows the variation in the observed first-order rate constant k_1' with % water in the solvent, over the range 0—10% water, for denitrosation in 0.40M-HCl in the presence of excess of ascorbic acid. Clearly there is a considerable reduction in the rate constant over the first 2.5% added water; thereafter the value of k_1' changes only little as the % water is further increased. Since the reaction in water is subject to nucleophilic catalysis, it is to be expected that this effect should become evident as the water content of the solvent is increased. Added potassium thiocyanate has very little effect on the rate of reaction between 0 and 5% added water, whereas some noticeable catalysis occurs at 10% added water as shown in Figure 6. A first-order dependence is apparent at low [SCN$^-$] but a limit is reached at *ca.* 5×10^{-3}M-SCN$^-$, where the

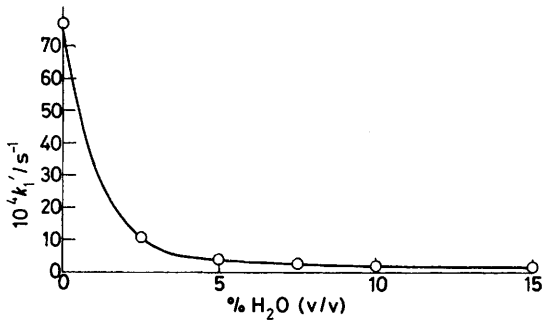


FIGURE 5 Variation of k_1' with % added water

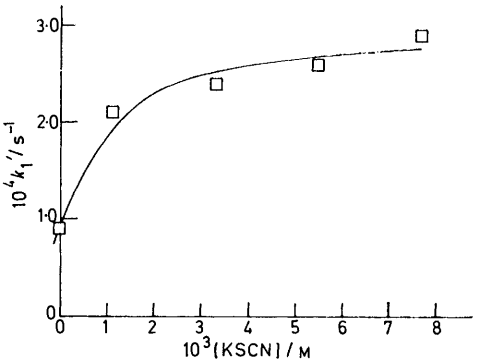


FIGURE 6 k_1' *versus* [KSCN] for reaction in 10% aqueous ethanol

rate of the second step now significantly exceeds that of the initial protonation. Similar behaviour was found for added bromide ion at a number of different solvent compositions.

Reversibility.—The results obtained for denitrosation of both NMNA and NDA in the absence of ascorbic acid show clearly that the reaction is reversible, with the equilibrium lying increasingly over to the denitrosation product as the acidity is increased. For the reaction of NMNA in ethanolic HCl the presence of added *N*-methylaniline reduces the value of the observed rate

TABLE 3

k_1' as a function of *N*-methylaniline added

10^3[NMA]/M	$10^4k_1'/s^{-1}$
0	70.7
1.02	45.5
3.07	27.4
5.12	21.0
7.16	19.1
9.21	16.4

constant k_1', whilst retaining good first-order behaviour, so long as the added *N*-methylaniline is in sufficient excess for its concentration to be effectively constant within any one given kinetic run. Table 3 shows the results of such a series of experiments where [HCl] is 0.403M, [ascorbic acid] is 4×10^{-3}M, and [NMNA] 2×10^{-4}M. The plot of $k_1'^{-1}$ against [NMA] is linear (see Figure 7), as expected, and as has been observed previously [1,13] for reactions in water with a variety of nucleophiles and nitrite traps. In this case it is not possible to get much information regarding relative rate

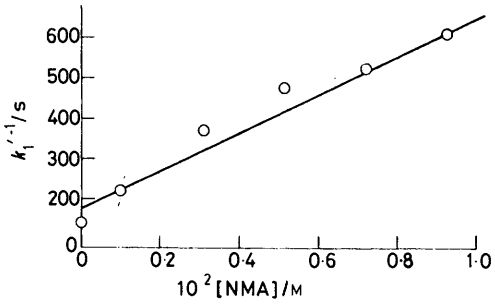


FIGURE 7 $k_1'^{-1}$ *versus* [*N*-methylaniline] added

constants since the rate-limiting step is now different from that in the case where water is the solvent.

Rearrangement.—For NMNA no trace of the Fischer–Hepp rearrangement product, *p*-nitroso-*N*-methylaniline, was observed in any of the reactions over the time scale studied. It is clear that the rate of rearrangement is very much less than that for denitrosation in ethanol, whereas in water the rates are more comparable. This is undoubtedly due to the enhanced rate constant for denitrosation in ethanol solvent. The absence of rearrangement product is perhaps a little surprising since, on the preparative scale, NMNA in ethanolic hydrogen chloride readily forms the rearrangement product.[14] It appears that the reactant concentration plays an important part. The kinetic experiments were all performed at high dilution, with [NMNA] *ca.* $1—2 \times 10^{-4}$M. For NDA, however, in the absence of ascorbic acid, rearrangement did occur (alongside reversible denitrosation) to form *p*-nitrosodiphenylamine, in high yield. This reaction is very much slower than the reaction leading to denitrosation, by a factor of *ca.* 700. The *p*-nitroso-product could also be obtained directly from diphenylamine, sodium nitrite, and ethanolic hydrogen chloride, with rate constants very similar to those found for the reaction of the *N*-nitroso-reactant. This suggests that the latter undergoes a relatively rapid (but reversible) denitrosation, rearrangement then occurring more slowly. The mechanism of the rearrangement in water solvent has clearly been established as being intramolecular [15] which takes place concurrently with reversible denitrosation. With the limited results available for the reaction in ethanol solvent, it is not possible to distinguish such a mechanism here from an intermolecular one where direct *C*-nitrosation of the secondary amine by a free nitrosating agent operates. The situation is made more difficult in this case, so far as using kinetic analysis methods to establish the mechanism, by the fact that in this solvent the rate-limiting step is now the initial protonation, and also by the fact that there are large differences between the denitrosation and rearrangement rates of reaction. With a judicious choice of substrate, however, it should still be possible to make the mechanistic distinction, for the Fischer–Hepp rearrangement in this and other solvent systems.

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