Unusual Rate-limiting Proton Transfer in the Acid-catalysed Reactions of *N*-Nitroso Compounds

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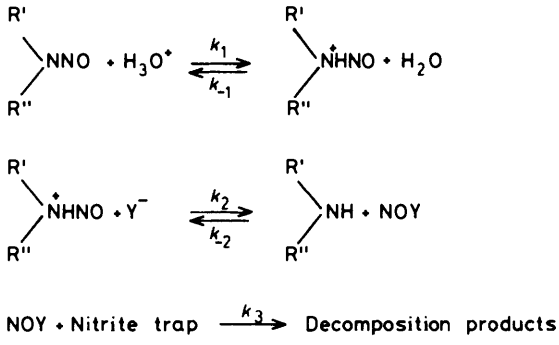
For both *N*-methyl-*N*-nitrosoaniline and *N*-nitrosodiphenylamine, the catalytic effect of halide ion, thiocyanate ion, and thiourea in the denitrosation reaction in acid solution disappears at high nucleophile concentrations. This suggests a change to an earlier rate-limiting step. The data, including the variation of rate constant with acidity, are quantitatively in accord with a reaction mechanism involving protonation of the nitrosamine followed by nucleophilic attack, either stage being rate limiting, depending on the reactivity and concentration of the nucleophile. The kinetic solvent isotope effect k_{H_2O}/k_{D_2O} decreases from 1.59 at 0.43M-thiourea to 0.71 at 0.015M-thiourea, which is consistent with a change from general acid catalysis at high [nucleophile] to specific hydrogen ion catalysis at low [nucleophile]. Substituent effects at the amino-nitrogen atom and also in the 4-position of a phenyl substituent are very small, the largest effect being a three-fold reduction in rate constant effected by a 4-NO_2 group. These results are in accord with the known dipolar nature of nitrosamines. There is a close analogy between this system and the acid-catalysed cleavage reaction of carbamate derivatives. A similar mechanism is proposed involving a pre-association of the reactants forming a hydrogen-bonded intermediate.

Rate measurements of the acid-catalysed denitrosation (or hydrolysis) reactions of nitrosamines have shown that in general[1-3] the reactions are strongly catalysed by non-basic nucleophilic species such as halide ion, thiocyanate ion, and thiourea, just as in the reverse reaction of nitrosation of amines.[4] Denitrosation also occurs in the absence of an added nucleophile, but at a much reduced rate, when the solvent is believed to act as the nucleophile. The experimental facts are all accommodated by the outline mechanism given in Scheme 1 where Y^- is the nucleophile. Here the initial protonation is regarded as rapid and occurring only to a small extent and the rate-limiting step is the attack by Y^-. Irreversibility is ensured by the presence of a sufficient concentration of a nitrite trap (such as sulphamic acid, hydrazine, or azide) such that k_3[nitrite trap] $\gg k_{-2}$[R'R''NH]. The following sequence of reactivity for various Y^- species was established[5] for one nitrosamine in aqueous solution, $H_2O < Cl^- \sim$ cysteine $< Br^- \sim$ methionine $< SCN^- < SC(NH_2)_2 \sim SC(NR_2)_2 \sim I^-$. Specific hydrogen ion catalysis is demonstrated, under these conditions, by the observation[1] of a solvent isotope effect k_{H_2O}/k_{D_2O} of 0.31.

However it had been noted[3,6] that at high [Cl^-] and [Br^-] the kinetic dependence upon [Cl^-] or [Br^-] was lost for *N*-nitrosodiphenylamine. Further the kinetic solvent isotope effect became inverted to a small primary effect of *ca.* 1.3. In addition there are a number of other cases in the literature where there is no kinetic dependence upon halide ion, and where the solvent isotope effects are in the range 1.3—1.9. These include the denitrosation of nitrosamides,[7,8] a nitrososulphonamide,[9] a nitrosourea,[10] and alkylnitrosoureas,[11] all in aqueous acid solution and also for the denitrosation of nitrosamines in ethanol solvent.[12] All these results are consistent with the mechanism outlined in Scheme 1 if the inequality $k_2[Y^-] \gg k_{-1}$ applies. This is certainly more likely (a) at high concentration of Y^-, (b) with more powerful nucleophiles, (c) with less basic amines (*e.g.* those containing >C=O and $-SO_2-$ groups), and (d) in a less polar solvent. In each case the rate-limiting step now becomes the initial protonation of the nitroso compound and not the attack of the nucleophile. Experimentally this can be detected by the concurrent loss of rate dependence upon Y^- and a change from a large inverse solvent isotope effect to a small primary effect. Since this is, on the face of it, a rather unusual example of a rate-limiting proton transfer



Scheme 1.

to a nitrogen site, we have set out to investigate it more fully, in the hope of establishing the detailed mechanism. Some of the results were presented at a conference and have been published.[13]

The loss of nucleophilic catalysis in denitrosation also has repercussions for the reverse reaction, *i.e.* of nitrosation generally; there are a number of references in the literature which note the loss of the usual nucleophilic catalysis *e.g.* in the diazotisation of anilines at high [Br^-],[14] the nitrosation of diphenylamine at high [Cl^-] and [Br^-],[6] and also for diazotisation in ethanol solvent.[15] Further it is known that there is complete absence of nucleophilic catalysis in the nitrosation of amides[7,10,11,16] and one analysis[10] accounts for this by the operation of the same inequality $k_2[Y^-] \gg k_{-1}$ as for the reverse case.

Results

The first-order rate constants k_0 for the denitrosation of *N*-methyl-*N*-nitrosoaniline (NMNA) in 0.48M-H_2SO_4 at 25 °C (in the presence of excess of azide) were obtained as a function of [Y^-] for Y^- = Br^-, SCN^-, and $SC(NH_2)_2$. The results are presented graphically in Figure 1 and show that for Br^- over the concentration range studied the relationship is linear, whereas for both SCN^- and $SC(NH_2)_2$, at low [Y^-] the

Table 1. Values of $k_1[H_3O^+]$ and k_{-1}/k_2 for the reaction of NMNA with Br^-, SCN^-, I^-, and $SC(NH_2)_2$ in sulphuric acid

Y^-	$[H_2SO_4]$/M	$k_1[H_3O^+]/s^{-1}$	k_{-1}/k_2/mol l^{-1}	$k_1k_2[H_3O^+]/k_{-1}$/l mol^{-1} s^{-1}
Br^-	0.64			2.2×10^{3}
	0.94			4.6×10^{3}
	1.72			14×10^{3}
SCN^-	0.36	1.3×10^{2}	8.3×10^{2}	0.16
	0.74	3.0×10^{2}	9.3×10^{2}	0.32
	1.55	8.8×10^{2}	9.3×10^{2}	0.94
I^-	0.36	1.1×10^{2}	2.5×10^{2}	0.44
	0.74	2.1×10^{2}	2.1×10^{2}	1.00
	1.55	7.7×10^{2}	2.9×10^{2}	2.65
$SC(NH_2)_2$	0.36	1.2×10^{2}	2.4×10^{2}	0.50
	0.74	2.8×10^{2}	2.6×10^{2}	1.08
	1.55	7.5×10^{2}	2.5×10^{2}	3.00

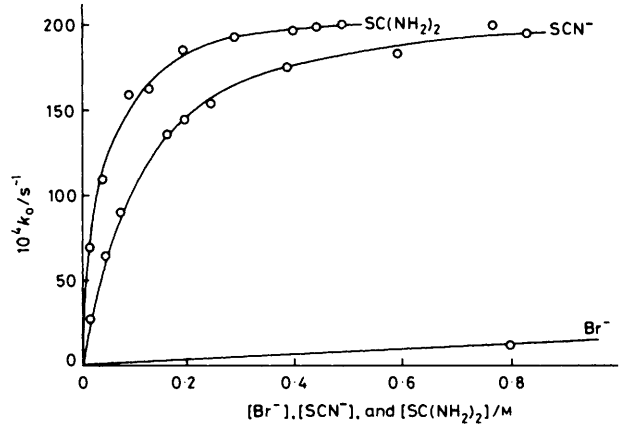


Figure 1. Catalysis of denitrosation by Br , SCN , and $SC(NH_2)_2$

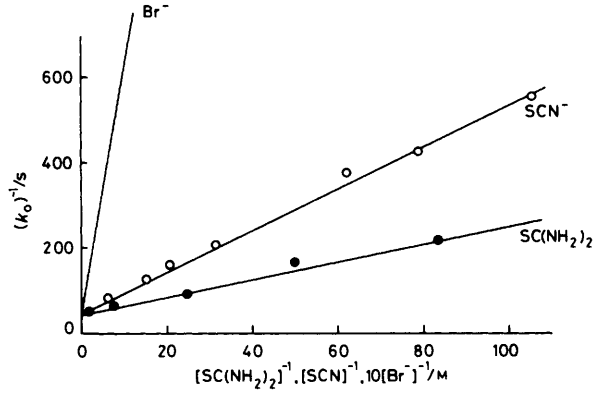


Figure 2. Double reciprocal plots for Br^-, SCN^-, and $SC(NH_2)_2$ catalysis

reaction is approximately first-order in $[Y^-]$ but as $[Y^-]$ is increased there is a change towards a zero-order dependence, with the same limiting value for k_0 for both SCN^- and $SC(NH_2)_2$ at *ca.* 200×10^{-4} s^{-1}. This can be examined more quantitatively in terms of Scheme 1. The general expression for k_0 deduced from this scheme (assuming k_3 [Nitrite trap] $\gg$ k_{-2}[R′R″NH]) is given in equation (1) and its double reciprocal form by equation (2). If $k_2[Y^-] \ll k_{-1}$ then limiting-form equation (3) obtains, whereas for the other limit when $k_2[Y^-] \gg k_{-1}$ equation (4) is to be expected. Throughout, all

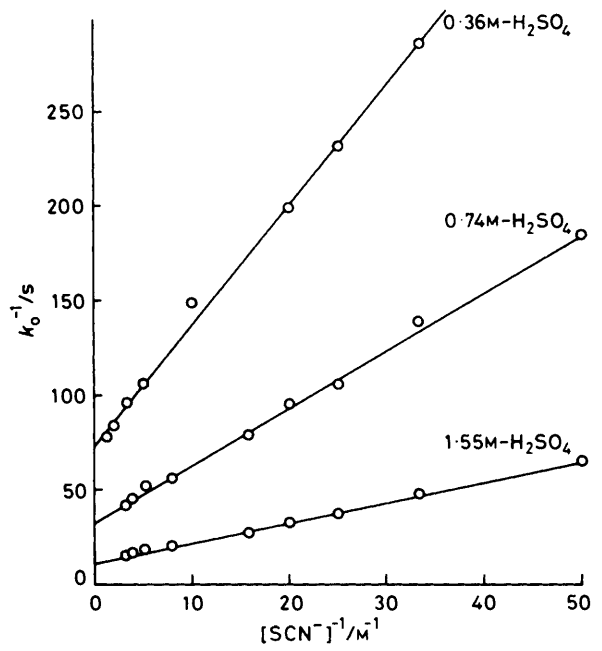


Figure 3. Double reciprocal plots for acid catalysis

experiments were carried out in the presence of a sufficient excess of a nitrite trap. Thus in the general case a plot of k_0^{-1} *versus* $[Y^-]^{-1}$ should be linear at any one acidity and values of $k_1[H_3O^+]$ and k_{-1}/k_2 readily obtained from the slopes and intercepts of such plots. The data from Figure 1 are presented in the double reciprocal form in Figure 2 and show the expected behaviour with $k_1[H_3O^+]$ 2.1×10^{-2} s^{-1} and k_{-1}/k_2 11, 0.10, and 0.04 mol l^{-1} respectively for Br^-, SCN^-, and $SC(NH_2)_2$ catalysis. This gives the relative values of k_2 for each nucleophile as 1:110:275 for Br^-:SCN^-:$SC(NH_2)_2$ which compares very well with the ratios 1:100:250 obtained earlier[2] from measurements at low $[Y^-]$ where a first-order dependence on $[Y^-]$ occurs.

$$k_0 = \frac{k_1[H_3O^+]k_2[Y^-]}{k_{-1} + k_2[Y^-]} \quad (1)$$

$$k_0^{-1} = \frac{k_{-1}}{k_1[H_3O^+]k_2[Y^-]} + \frac{1}{k_1[H_3O^+]} \quad (2)$$

$$k_0 = \frac{k_1}{k_{-1}}[H_3O^+]k_2[Y^-] \quad (3)$$

$$k_0 = k_1[H_3O^+] \quad (4)$$

Similar results were obtained for the reaction of *N*-nitrosodiphenylamine (NDA) with Br^- and SCN^- yielding $k_1[H_3O^+]$ 3.2 × 10^{-2} s^{-1} at 0.28M; H_2SO_4 and k_{-1}/k_2 values of 8.7 × 10^{-2} for Br^- and 1.7 × 10^{-2} for SCN^- which again gives a SCN^- : Br^- reactivity ratio which agrees with measurements[3] at low $[Y^-]$. The same analysis using NDA in 50% aqueous ethanol for a smaller range of experimental points showed Cl^- to be the least reactive nucleophile but, strangely, revealed Br^- and SCN^- to have comparable reactivity.

As a further test of the generality of equation (2) the experiments were repeated using NMNA at each of three different acidities using the same nucleophiles Br^-, SCN^-, and $SC(NH_2)_2$ and also I^- which behaves similarly unless the acidity is too high, when oxidation to I_2 can occur. The results are shown graphically in Figure 3 in the double reciprocal form. As predicted the plots are linear with positive slopes and intercepts, both of which *increase* with *decreasing* acid concentration. The collected results for all four nucleophiles are given in Table 1 as $k_1[H_3O^+]$ and k_{-1}/k_2 ratios for each of three acid concentrations. There are no values for Br^- since plots of k_0 *versus* $[Br^-]$ are linear and limiting equation (3) applies (as it surely would for the less reactive Cl^-).

For any one nucleophile the k_{-1}/k_2 ratios are constant with acidity, within the experimental error, and as expected the $k_1[H_3O^+]$ values increase, whereas at any one acidity $k_1[H_3O^+]$ is constant for all nucleophiles and k_{-1}/k_2 ratios decrease along the series $SCN^- > I^- \sim SC(NH_2)_2$ as expected from their known nucleophilicities. The final column in Table 1 gives $k_1k_2[H_3O^+]/k_{-1}$, evaluated for Br^- from the slope of k_0 *versus* $[Br^-]$ and for the other nucleophiles from the preceding two columns so that the reactivity of Br^- can be compared as well. The results show quite clearly that Br^- is significantly less reactive than SCN^-, again as predicted.

These results all confirm and extend the earlier observations[3,5] and point clearly to a change in rate-limiting step (*i.e.* to rate-limiting proton transfer) as k_2 or $[Y^-]$ is increased. This is further confirmed by noting the changing kinetic solvent isotope effect for denitrosation carried out at one acidity at different [thiourea] as shown in Table 2. At high [thiourea] where we find rate-limiting proton transfer k_{H_2O}/k_{D_2O} is 1.59, *i.e.* a small primary kinetic isotope effect, whereas as [thiourea] is reduced this changes to the normal inverse solvent isotope effect expected for specific hydrogen ion catalysis. The limiting value expected is *ca.* 0.3 which has not quite been achieved at 0.015M-thiourea. General acid catalysis has also been observed in the normal way of noting the variation of k_0 with [HA] at constant buffer ratio for both the denitrosation of nitrosamides[7,8] and a nitrososulphonamide.[9]

The effect of substituents on the rate constant for denitrosation was examined under conditions where no Y^- catalysis occurs. Substitution directly at the amino nitrogen atom (R′) and also in the 4-position of R″ = XC_6H_4 was examined. Two sets of experimental conditions were chosen: (a) in the presence of high thiourea concentration in aqueous acid solution and (b) in ethanol solvent in the absence of any added nucleophile. The results are summarised in Table 3 for the series PhN(R)NO with R = Me, Et, Pr^i, and Pr^n. For experimental conditions (a) k_1 values were obtained from the double reciprocal plots over a range of thiourea concentrations, whereas for (b) results are presented as k_0/[HCl] at [HCl] 0.40M. Similarly, in Table 4 we have the results for the denitrosation of 4-XC_6H_4N(Me)NO. In this case k_1 values for (a) were obtained from single rate measurements at 0.8M-$SC(NH_2)_2$ where the rate constant is independent of $[SC(NH_2)_2]$ and as before the results for (b) are presented as k_0/[HCl] from interpolated values at HCl 0.40M.

The striking feature for both sets of substituents and also for both sets of experimental conditions is that the rate constant is very insensitive to substituent changes either at the amino nitrogen atom or at the 4-position in a phenyl substituent. The largest effect is a *ca.* 3-fold reduction in k_0 brought about by a 4-NO_2 substituent. In addition, the relative effects, although small, are virtually identical for the two sets of experimental conditions (a) and (b).

Table 2. The kinetic solvent isotope effect for denitrosation as a function of [thiourea]

[Thiourea]/M	k_{H_2O}/k_{D_2O}
0.015	0.71
0.031	0.91
0.430	1.59

Table 3. Rate constants for the denitrosation of PhN(R)NO (a) in the presence of $SC(NH_2)_2$ in water and (b) in ethanol solvent

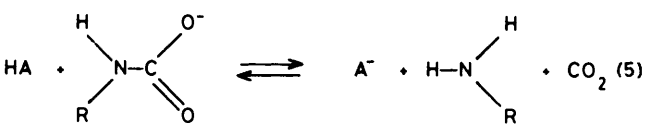
R	(a) 10^2k_1/l mol^{-1} s^{-1}	(b) $10^2k_0[HCl]^{-1}$/l mol^{-1} s^{-1}
Me	3.8	2.0
Et	4.2	2.8
Pr^i	4.8	4.1
Pr^n	2.6	2.0

Table 4. Rate constants for the denitrosation of 4-XC_6H_4N(Me)NO (a) at 0.8M-$SC(NH_2)_2$ in water and (b) in ethanol solvent

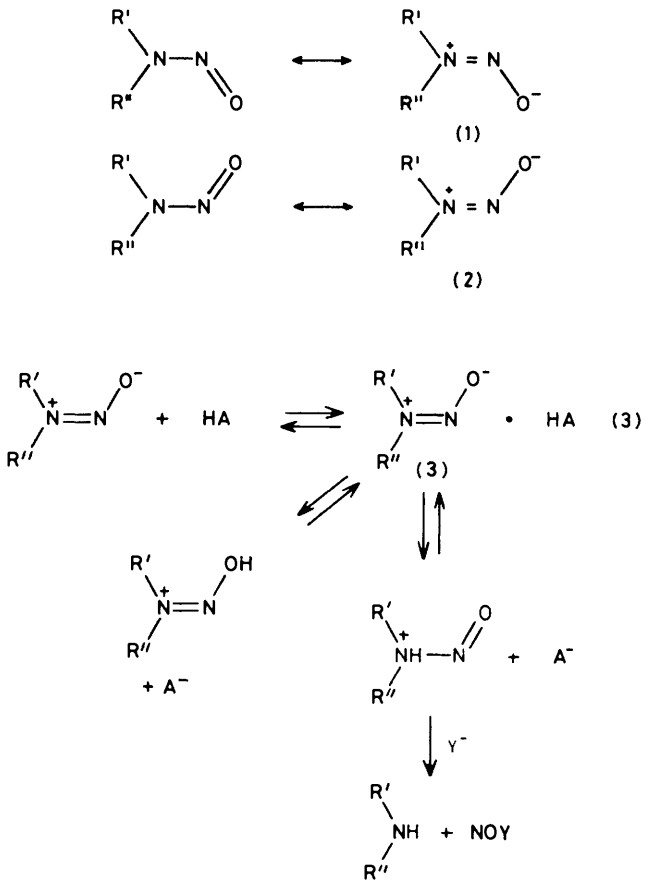
X	(a) 10^2k_1/l mol^{-1} s^{-1}	(b) $10^2k_0[HCl]^{-1}$/ l mol^{-1} s^{-1}
H	3.2	1.9
Me	3.7	1.7
OMe	3.8	1.7
Cl	2.7	1.5
NO_2	1.3	0.6

Discussion

It is clear from the results that the change in rate-limiting step is accompanied by a change from specific hydrogen ion catalysis to general acid catalysis. This situation resembles closely that of the acid-catalysed cleavage reaction of carbamates studied by Jencks *et al.*[17] and by earlier workers,[18] and which is represented by equation (5). The overall reaction is formally quite similar to the denitrosation of nitrosamines with C–N cleavage being equivalent to N–N cleavage. The major difference is that for the latter reaction nucleophilic assistance occurs whereas the loss of CO_2 is a unimolecular process. For the more basic amine groups, rate-limiting C–N bond cleavage occurs in the protonated carbamate, whereas when the amine is much less basic (and hence is a better leaving group) the rate-limiting step becomes the initial protonation, which is now associated with general acid catalysis. For the carbamate reaction, the change-over in rate-limiting step is observed experimentally by the change in the solvent isotope effect k_{H_2O}/k_{D_2O} from *ca.* 0.28 (specific hydrogen ion catalysis for cyclohexyl carbamate) to *ca.* 1.5 (general acid catalysis for 4-nitrophenyl carbamate). In our case we have additionally the



(5)



Scheme 2.

change involving the kinetic involvement or otherwise of the nucleophile. For nitroso compounds the change to rate-limiting proton transfer and general acid catalysis can be brought about by (1) increasing $[Y^-]$, (2) change to a more powerful nucleophile *i.e.* increasing k_2, (3) increasing the leaving group ability *i.e.* increasing k_2 for *e.g.* amides, and (4) change to a less polar solvent *e.g.* from water to ethanol (ref. 12 and this paper) where all the *N*-nitroso compounds studied to date appear to involve rate-limiting proton transfer. This is easily rationalised *via* Scheme 1 by the larger k_2 value expected in the less polar solvent for a reaction between a cation and an anion.

There are two possible protonation sites in a nitrosamine. We have written reaction *via* the *N*-protonated form in Scheme 1 but it is likely that the more basic site is the oxygen atom. Evidence for this comes from n.m.r. studies[19] and also from INDO calculations,[20] as well as from the well established dipolar structure of nitrosamines. It is difficult however to write a convincing mechanism involving reaction of the *O*-protonated species (even though this might account for the small kinetic substituent effects), particularly since many studies of the reverse reaction (nitrosation of amines) point very strongly to the involvement of the *N*-protonated intermediate.[21] It is not unusual for reaction to occur *via* the least favoured protonated intermediate, *e.g.* in the Bamberger rearrangement of phenylhydroxylamines reaction is believed[22] to occur *via* the less favoured *O*-protonated form.

The dipolar structures (**1**) and (**2**) are believed[23] to make major contributions to the structures of nitrosamines generally. There is strong evidence of substantial charge separation from electron diffraction studies, dipole moment studies, i.r. measurements, n.m.r. spectra, and by the physical separation by t.l.c. and h.p.l.c. of the *E*- and *Z*-isomers. If the reactant is more accurately represented by (**1**) and (**2**) then only small kinetic substituent effects are to be expected for *N*-protonation by substitution in R′ and R″ as we find experimentally. The small acceleration by releasing groups and conversely for electron-withdrawing groups suggests that the extent of positive charge on the amino nitrogen atom is slightly larger in the transition state leading to the *N*-protonated intermediate than it is in the reactant.

Table 5. Typical run for the denitrosation of *N*-nitroso-*N*-n-propylaniline in sulphuric acid containing thiourea and sodium azide

t/s	0	6	12	18	24	30	36
Absorbance	0.651	0.605	0.563	0.524	0.491	0.459	0.428
$10^2k_0/s^{-1}$		1.43	1.43	1.43	1.40	1.40	1.41
t/s	42	48	54	60	66	72	∞
Absorbance	0.400	0.371	0.349	0.328	0.308	0.288	0.092
$10^2k_0/s^{-1}$	1.42	1.45	1.44	1.44	1.44	1.46	

Average value of k_0 1.43 ± 0.02 × 10^{-2} s^{-1}

The close correspondence between our results and those of Jencks *et al.*,[17] particularly the value of the solvent isotope effect when proton transfer is rate-limiting, suggests that similar mechanisms operate. We set out in Scheme 2 (for one isomer only) such a mechanism for reaction with a general acid HA involving a pre-association. Intermediate (**3**) is believed to be a hydrogen-bonded species which then leads to the *N*-protonated form. The magnitude of the kinetic isotope effect when proton transfer is rate-limiting (which is also similar to that found in the cleavage of *N*-carboxy-2-imidazolidone[24]) is believed[25] to be in the region expected for a proton-transfer involving a pre-association mechanism with the formation of a hydrogen-bonded species when ΔpK_a *ca.* 0. The pK_a values of nitrosamines generally are not known because of their decomposition in solutions of high acid concentration but an estimate of *ca.* −2 has been suggested[26] for NMNA itself from the levelling off of the curve of k_0 *versus* acidity for the denitrosation reaction. It seems that the ΔpK_a *ca.* 0 condition is met in this case.

Experimental

Materials.—All the nitrosamines were prepared from the corresponding secondary amines by the usual procedure of treatment with nitrous acid. They were purified by distillation or recrystallisation and had b.p. or m.p. similar to the literature values. Thiourea was recrystallised from ethanol. All reagents were of the highest purity grade available and were used as such. Ethanol solutions of hydrogen chloride were prepared on the day of use in the kinetic experiments.

Kinetics.—All rate measurements were carried out at 25 °C using a conventional double-beam u.v.–visible spectrophotometer, noting the disappearance of the nitrosamine absorption (in the range 300—315 nm) as a function of time using a chart recorder. Good first-order behaviour was generally found and the first-order rate constants obtained in the usual way using the value of the absorbance at infinity. A typical run is given in Table 5 for the reaction of *N*-nitroso-*N*-n-propylaniline (3×10^{-4}M) in sulphuric acid (0.48M) containing thiourea (0.15M) and sodium azide (8.4×10^{-3}M).

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