

Alkyl Nitrites as Nitrosating Agents. Kinetics and Mechanism of the Reactions of Propyl Nitrite in Propan-1-ol

By S. Elaine Aldred and D. Lyn H. Williams,* Department of Chemistry, Durham University, Durham DH1 3LE

Propyl nitrite in acid solution in propan-1-ol acts as an effective nitrosating (or diazotising) agent towards aniline derivatives only in the presence of halide ion or thiourea as catalysts. In the absence of such catalysts the reaction is extremely slow, which indicates that the alkyl nitrite or its protonated form is a very poor nitrosating agent towards aniline derivatives under these conditions. At low concentrations of added nucleophiles the rate constant is approximately proportional to the concentration, but at higher concentrations the rate constant levels off and tends towards being independent of the nucleophile concentration. For aniline and *N*-methylaniline there is no acid catalysis whilst the diazotisation of *p*-nitroaniline is subject to acid catalysis. All the experimental findings are consistent with a mechanism involving rapid equilibrium formation of the corresponding nitrosyl halide or nitrosothiourea adduct, which attacks the free base form of the aniline derivative in the rate-limiting stage. The *N*-nitrosation stage is itself reversible where the denitrosation of the primary (except for *N*-methylaniline) *N*-nitroso-intermediate competes favourably with proton loss *etc.* which leads to the diazonium ion formation. This accounts for the rate constant dependence upon [halide ion].

ALKYL nitrites have been used widely as nitrosating agents,¹ particularly where the use of inorganic nitrites in aqueous acid solution has proved to be unsuitable. Little mechanistic work has been carried out, however, for alkyl nitrite nitrosation reactions under heterolytic conditions, although reactions involving homolysis to give nitric oxide, both thermally and photochemically, are well known. Acid- and base-catalysed hydrolysis experiments have been carried out,^{2,3} the acid-catalysed reactions being particularly rapid; nitrosation could then occur by reaction of the free nitrous acid. Recently it has been established⁴ that the nitrosation of methanol is a rapid reversible process under acid conditions and rate constants for the forward and reverse steps have been obtained by stopped-flow spectrophotometry. It has been concluded⁵ that the nitrosation of sulphanyl-amide by cyclohexyl nitrite in aqueous acid occurred by prior hydrolysis to give nitrous acid which then effects nitrosation. In alkaline solution it has been claimed⁶ that alkyl nitrites bearing β -electron-withdrawing groups rapidly bring about the nitrosation of secondary amines.

Since alkyl nitrites can readily be formed in aqueous solutions containing alcohols it is of some interest to establish whether the alkyl nitrites themselves under acid conditions can bring about nitrosation of suitable substrates. Schmid and Woppmann and their co-workers^{7,8} have measured rates of diazotisation of aniline in methanol where they believe that methyl nitrite is formed. There is no report where it has been shown unambiguously that an alkyl nitrite does act directly in acid solution as a nitrosating agent. It is the purpose of this work to establish whether this is so. We have chosen to work under non-aqueous conditions to avoid the complication of hydrolysis and probable reaction *via* nitrous acid, and decided to examine the reaction of propyl nitrite in propan-1-ol. Aniline and *N*-methylaniline were chosen as suitable substrates as an example of a diazotisation reaction and one of nitrosamine formation. Kalatzis and Ridd^{9,10} have shown

that in aqueous acid solutions similar rate equations can be measured for the diazotisation of aniline and *N*-nitrosation of *N*-methylaniline. Further we chose to examine the reaction with *p*-nitroaniline as an example of a much less basic amine where, under the acid conditions chosen by us, *p*-nitroaniline exists mostly in the free base form.

The mechanisms of nitrosation in aqueous acid solutions containing various nucleophilic species, halide ion, *etc.* have been well established,¹¹ and the equilibrium constants for *e.g.* nitrosyl halide formation in these solutions measured. It is of interest to establish the mechanisms involved in alcohol solvents using alkyl nitrites and to note any comparisons with the aqueous systems.

EXPERIMENTAL

Propyl nitrite was prepared according to the method of Noyes¹² from propan-1-ol and sodium nitrite. It was purified by careful distillation at atmospheric pressure and stored in the refrigerator. Aniline and *N*-methylaniline were purified by a reduced-pressure distillation. Lithium bromide and lithium chloride were used as supplied. *p*-Nitroaniline was recrystallised from aqueous ethanol. Hydrogen chloride and tetraethylammonium chloride were dried before use. Propan-1-ol, sulphuric acid, and thiourea were obtained as analytical grade reagents and were used without further purification.

For the kinetic studies all the solutions were made up in propan-1-ol and the reactions carried out in the cell compartment (at 31 °C) of a Beckman model 25 spectrophotometer. Reactions were started by the addition of 1 ml of a standard solution of propyl nitrite to a solution containing all the other reagents. Reaction was followed at 290 nm (or 310 nm for the thiourea experiments) for aniline and *N*-methylaniline, noting the appearance of the absorption due to the benzenediazonium ion and *N*-methyl-*N*-nitrosoaniline respectively. In the case of *p*-nitroaniline measurements were carried out at 285 nm on the shoulder of the *p*-nitroaniline absorption, again noting the diazonium ion formation. The amine was always in large excess (>10 fold)

over the alkyl nitrite, and good first-order kinetics were always obtained by plots of $\ln(A_\infty - A_t)$ versus time. Observed rate constants k_o generally had a standard deviation of $\pm 2\%$ and duplicate runs gave acceptable agreement.

RESULTS AND DISCUSSION

In the absence of added nucleophiles $[\text{Cl}^-]$, $[\text{Br}^-]$, $[\text{SC}(\text{NH}_2)_2]$ the reaction of propyl nitrite in propan-1-ol containing sulphuric acid, with both aniline and *N*-methylaniline was very slow indeed. For example at $0.14\text{M-H}_2\text{SO}_4$ and $4.5 \times 10^{-3}\text{M-N}$ -methylaniline the first-order rate constant was $4 \times 10^{-5}\text{ s}^{-1}$ for a reaction followed for ca. 30% reaction. This value is typically at least 10^2 smaller than the corresponding value for reaction in the presence of added nucleophiles. This result means that the alkyl nitrite, or more probably its protonated form, has a very low reactivity as a direct nitrosating agent towards aniline derivatives under these conditions. However in the presence of chloride ion, bromide ion, or thiourea, reaction did occur readily and the expected products of nitrosation or diazotisation were obtained.

The Cl^- , Br^- , and $\text{SC}(\text{NH}_2)_2$ Catalysed Reactions.—Series of reactions were carried out in propan-1-ol containing sulphuric acid and either lithium chloride, lithium bromide, tetraethylammonium chloride, or thiourea, and also in propan-1-ol containing dissolved hydrogen chloride. Good first-order behaviour was observed in the kinetic experiments with the amine always in >10 -fold excess. The observed first-order rate constant k_o (defined by $d[\text{Product}]/dt = k_o[\text{Pr}^n\text{ONO}]$) was also independent of the initial concentration of propyl nitrite (see Table 1). Their reactions also showed a first-order dependence upon each of the amines

TABLE 1

Dependence of the rate constant upon $[\text{propyl nitrite}]_{\text{initial}}$	
$10^4[\text{Pr}^n\text{ONO}]/\text{M}$	$10^3 k_o/\text{s}^{-1}$
0.75	10.9
1.49	10.8
2.99	10.6

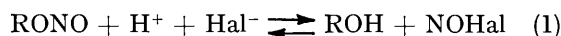
$[\text{Aniline}] 2.08 \times 10^{-3}\text{M}$, $[\text{HCl}] 0.075\text{M}$.

studied. The data for the aniline reactions are shown graphically in Figure 1.

The kinetic dependence upon $[\text{Cl}^-]$, $[\text{Br}^-]$, and $[\text{SC}(\text{NH}_2)_2]$ was also examined. Practical difficulties, solubility, and side-reactions were encountered when it was attempted to do experiments with the other two possible nucleophiles, SCN^- and I^- . At low concentrations of each of the added nucleophiles k_o versus $[\text{nucleophile}]$ was found to be approximately linear, whereas at higher concentrations k_o levelled off and eventually became independent of the concentration of added nucleophile. The results for chloride ion and *N*-methylaniline, which were typical, are shown in Figure 2.

Halide ion catalysis is to be expected, by analogy with the reactions of nitrous acid, if the corresponding

nitrosyl halide is formed, which then acts as a nitrosating agent [equation (1)].



An explanation of the levelling-off of k_o at high $[\text{Hal}^-]$ would be if the size of the equilibrium constant K_x for equation (1) were such that at high $[\text{Hal}^-]$, NOHal has been formed virtually quantitatively. This

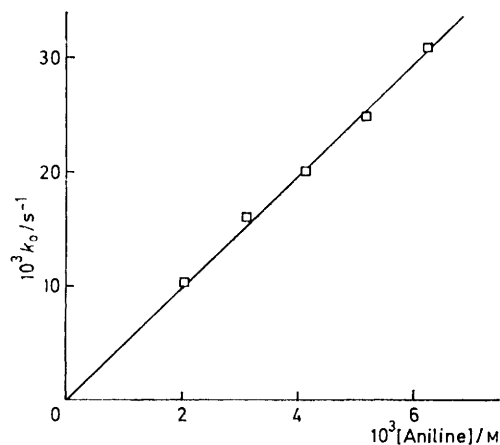


FIGURE 1 Results showing the first-order dependence upon aniline concentration

requires that $(K_x[\text{H}^+][\text{Cl}^-])^{-1}$ is $\ll 1$. In water the corresponding K_x values for the nitrous acid equilibria are 1.1×10^{-3} for Cl^- and $5.1 \times 10^{-2}\text{ l}^2\text{ mol}^{-2}$ for Br^- at 25°C . K_x is known to be larger than these values for certain alcohols in acetic acid solvent¹⁵ and carbon tetrachloride-acetic acid solvent mixtures,¹⁶ and has been reported for methanol by Woppmann and Sofer⁸ as 5×10^{-2} for NOCl and $2.0\text{ l}^2\text{ mol}^{-2}$ for NOBr at 0°C . Even so, and allowing for the temperature difference and the extrapolation from methanol to propan-1-ol, at the concentrations of H^+ , Cl^- , and Br^- used in this work we come nowhere near the inequality

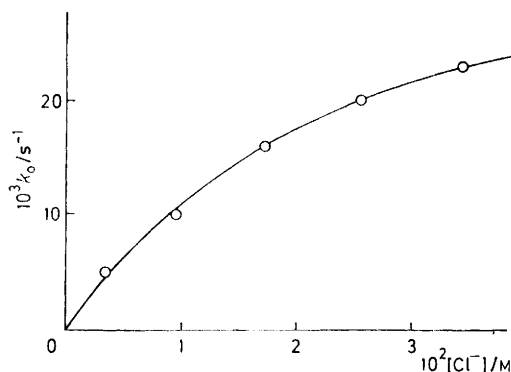
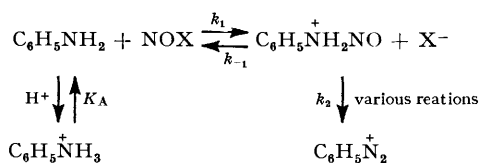


FIGURE 2 Chloride ion catalysis for the reaction of propyl nitrite with *N*-methylaniline

$(K_x[\text{H}^+][\text{Hal}^-])^{-1} \ll 1$. Further, we find no evidence spectroscopically of any nitrosyl chloride in solutions of propyl nitrite and hydrogen chloride in propan-1-ol, nor of nitrosyl bromide in solutions containing bromide ion. Thus we must look elsewhere for an explanation

of the fall-off in halide ion catalysis at higher concentrations.

It has been established^{8,17} that the diazotisation of aniline in methanol solutions of HCl and HBr is a reversible process involving the corresponding nitrosyl halides as shown in the Scheme. This situation has



SCHEME

also been found¹⁸ for diazotisation involving nitrosyl halides in water solvent and is more easily observed experimentally when there are electron-withdrawing groups in the aromatic ring. This reversibility is quite likely to occur in the present system and would account for a fall-off of the halide ion (and thiourea) catalysis. Step k_{-1} is analogous to that, much recently studied,¹⁹ of the denitrosation of nitrosamines which has been shown to be much increased in rate in ethanol solvent²⁰ compared with water, and also when electron-withdrawing groups are present,²¹ and competes effectively with step k_2 involving proton transfer and loss of a water molecule. If it is assumed that reaction occurs through the free base form of the aniline and that the total amine concentration is approximately equal to that of the protonated form (this will be true for both aniline and *N*-methylaniline) then it is easy to deduce for the Scheme the expression given in equation (2) for the observed first-order rate constant k_0 . The two limiting forms $k_{-1}[\text{X}^-] \ll k_2$ and $k_{-1}[\text{X}^-] \gg k_2$ lead to, re-

$$k_0 = \frac{k_1 k_2 K_x [\text{X}^-] K_A [\text{Amine}]_{\text{Total}}}{k_{-1} [\text{X}^-] + k_2} \quad (2)$$

spectively, first-order and zero-order dependence on $[\text{X}^-]$. In general, however, a plot of $(k_0)^{-1}$ versus $[\text{X}^-]^{-1}$ should be linear with a positive slope and intercept,

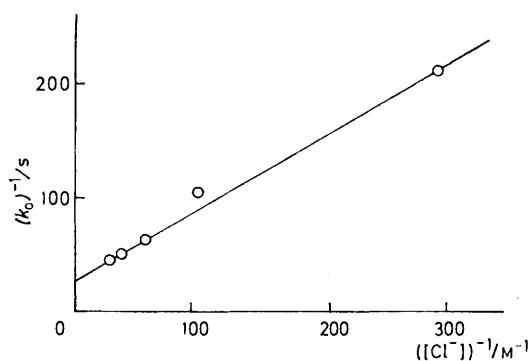


FIGURE 3 Double reciprocal plot k_0^{-1} versus $[\text{Cl}^-]^{-1}$ for chloride ion catalysis

and the ratio slope : intercept gives k_2/k_{-1} . Such a plot is given in Figure 3 for the reaction of propyl nitrite with *N*-methylaniline with varying concentrations of added chloride ion. It can be seen that the results fit

the required equation well. Similar plots were obtained for aniline and *p*-nitroaniline at constant acidity and for the bromide ion and thiourea catalysed reactions.

Thiourea has recently been established²² as an excellent catalyst for nitrosation and diazotisation reactions in water, as exemplified by the reactions of morpholine and aniline. This arises by the equilibrium formation of the *S*-nitroso-adduct $\text{NO}-\dot{\text{S}}\text{C}(\text{NH}_2)_2$ which itself acts as a nitrosating agent. The catalytic action of thiourea therefore occurs in a similar fashion to that of halide ion. However, in water, the equilibrium constant for the formation of the *S*-nitroso-derivative is large,²³ much larger than for each of the nitrosyl halides and nitrosyl thiocyanate, which accounts for the high catalytic activity of thiourea in nitrosation.

Collected values of $k_2 : k_{-1}$ ratios, each determined from the double reciprocal plots, are given in Table 2 for the

TABLE 2

$k_2 : k_{-1}$ Values for nitrosation and diazotisation

Catalyst	<i>N</i> -Methyl-aniline	Aniline	<i>p</i> -Nitro-aniline
Cl^-	2.5×10^{-2}	3.6×10^{-2}	3.7×10^{-2}
Br^-	2.1×10^{-2}	3.2×10^{-2}	3.2×10^{-2}
$\text{SC}(\text{NH}_2)_2$	1.0×10^{-2}	1.3×10^{-2}	

three substrates studied and for the three catalysts Cl^- , Br^- , and $\text{SC}(\text{NH}_2)_2$. The striking feature is that there is very little spread among the values. For each amine there is a decrease in the ratio as we go from Cl^- to Br^- and to $\text{SC}(\text{NH}_2)_2$, *i.e.* as the nucleophilicity of the species is increased. This is the trend to be expected *i.e.* k_{-1} should increase along this series whereas k_2 should not be affected. The range, however, is very small, at best a factor of three covering the whole range. This itself suggests that the denitrosation reactions (rate constant k_{-1}) are very rapid and thus show little selectivity among the nucleophiles. This is consistent with expectation, since if this step is to compete effectively with step k_2 which involves proton transfers *etc.*, then it must be rapid. Any change in these ratios with changing substrate at any one nucleophile, is less easy to predict, since substitution in the aniline, at nitrogen or *para*-carbon is likely to affect both k_2 and k_{-1} , probably in the same sense. In any case the spread of values found experimentally is very small indeed and it does not seem sensible to comment further on any possible trend.

Incidentally since *N*-methylaniline and aniline show the same sort of dependence here on Cl^- , Br^- , and $\text{SC}(\text{NH}_2)_2$, it would appear that the kinetically important step in stage k_2 is the proton transfer to the solvent, since this is the only reaction for the *N*-methylaniline case, whereas for aniline further reactions involving further proton transfers and loss of a water molecule are involved before the diazonium ion is formed.

Acid Catalysis.—Equation (2) contains no term in $[\text{H}^+]$ so that the nitrosation of *N*-methylaniline and diazotisation of aniline by propyl nitrite should not be

acid catalysed. Results for the variation of k_0 with acidity are shown for these two amines in Table 3. Clearly for *N*-methylaniline, k_0 values are constant within the experimental error for the acid range considered as predicted. For aniline, however, there

TABLE 3

Variation of k_0 with acidity		Aniline	
<i>N</i> -Methylaniline		Aniline	
$10^2 \text{H}_2\text{SO}_4/\text{M}$	$10^2 k_0/\text{s}^{-1}$	$10^2 \text{H}_2\text{SO}_4/\text{M}$	$10^2 k_0/\text{s}^{-1}$
1.75	3.28	1.90	14.1
3.50	3.20	3.81	12.1
7.00	3.34	5.71	11.7
10.5	3.45	7.61	11.2
		9.52	11.0

[Br⁻] $3.5 \times 10^{-2}\text{M}$, [N-Methylaniline] $1.7 \times 10^{-3}\text{M}$.
 [Br⁻] $4.1 \times 10^{-2}\text{M}$, [Aniline] $2.9 \times 10^{-3}\text{M}$.

appears to be a small downward drift of k_0 values as the acidity increases. The effect is small, but outside the experimental error of measurement, and its origin difficult to establish, particularly in view of the results found for *N*-methylaniline. However, this apart it can be said to a reasonably good approximation that k_0 is independent of acidity as required by equation (2). A different picture is to be expected for the reaction of the much less basic *p*-nitroaniline, where now a significant fraction of the total amine exists as the free base form. In general this requires the inclusion of an additional term of $[\text{H}^+](1 + [\text{H}^+]/K_A)^{-1}$ in the expression for k_0 [equation (2)]. For aniline and *N*-methylaniline the $\text{p}K_A$ values are such that at all acidities studied in this work $1 \ll [\text{H}^+]/K_A$ (typically 3 000) so that acid catalysis disappears, as is observed. For *p*-nitroaniline, however, ($\text{p}K_A$ in water 1 : 1) the situation is quite different. We have measured the $\text{p}K_A$ in propan-1-ol and found it to be *ca.* 0.9 so that typically $[\text{H}^+]/K_A$ is *ca.* 0.2 and a considerable degree of acid catalysis is to be expected. This is borne out in practice as shown by the results in Table 4. In fact a plot of k_0 versus $[\text{H}_2\text{SO}_4]$ is linear, but

TABLE 4

Acid catalysis in the diazotisation of *p*-nitroaniline

$10^2 \text{H}_2\text{SO}_4/\text{M}$	$10^3 k_0/\text{s}^{-1}$
2.39	2.70
4.77	4.03
7.15	5.84
9.54	7.50

[Br⁻] 0.083M, [*p*-nitroaniline] $8.38 \times 10^{-4}\text{M}$, [PrⁿONO] $7.6 \times 10^{-5}\text{M}$.

we do not have available the data for the H⁺ concentration in these propan-1-ol solutions.

It is conceivable that at high amine concentrations or with more reactive substrates, that the denitrosation of the alkyl nitrite might become rate-limiting. This has been achieved in the corresponding reactions in water for NOBr²⁴ and NOI²⁵ formation. In the present work k_0 versus [Amine] is strictly linear over the range studied; we have attempted to measure the nitrosation of hydra-

zoic acid, hydrazine, and sulphamic acid by propyl nitrite in propan-1-ol, but solubility problems have prevented such experiments from being performed. There was some reaction with ascorbic acid, but the reactions were not first-order and were not examined further. However, in a parallel study²⁶ of nitrosation using a thionitrite, similar results have been obtained, except that it has been found possible to achieve the situation of rate-limiting attack by Cl⁻ or Br⁻ in the nitrosation of hydrazoic acid in water.

It has not been possible to calculate k_1 values (Scheme) from this work because of the uncertainties of the $\text{p}K_A$ values in propan-1-ol and also of the K_x values in this solvent. These values would be of interest with reference to the possibility of diffusion-controlled reactions.²⁷ For aniline and aniline derivatives containing electron-releasing groups diazotisation *via* both NOCl and NOBr in water occurs at rates close to the diffusion-controlled limit, whereas for anilines containing electron attracting groups this is not so.¹⁸ In methanol, however, Woppmann and Sofer⁸ have reported rate constant values around 10^2 less than the diffusion-controlled limiting value.

We thank the S.R.C. for a research assistantship to S. E. A., and the Royal Society for an equipment grant.

[0/1878 Received, 5th December, 1980]

REFERENCES

- For example see O. Touster, *Org. React.*, 1953, Coll. Vol. VII, 327.
- A. D. Allen, *J. Chem. Soc.*, 1954, 1968.
- S. Oae, N. Asai, and K. Fujimori, *J. Chem. Soc., Perkin Trans. 2*, 1978, 571.
- S. E. Aldred and D. L. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1980, 73.
- A. J. Shenton and R. M. Johnson, *Int. J. Chem. Kinet.*, 1972, 4, 235.
- B. C. Challis and D. E. G. Shuker, *J. Chem. Soc., Chem. Commun.*, 1979, 315.
- H. Schmid and P. Muhr, *Monatsh. Chem.*, 1967, 98, 1783.
- A. Woppmann and H. Sofer, *Monatsh. Chem.*, 1972, 103, 163.
- E. Kalatzis and J. H. Ridd, *J. Chem. Soc.*, 1962, 5208.
- E. Kalatzis and J. H. Ridd, *J. Chem. Soc. B*, 1966, 529.
- J. H. Ridd, *Quart. Rev.*, 1961, 15, 418.
- W. A. Noyes, *Org. Synth.*, 1943, Coll. Vol. II, 108.
- H. Schmid and E. Hallaba, *Monatsh. Chem.*, 1956, 87, 560.
- H. Schmid and M. G. Fouad, *Monatsh. Chem.*, 1957, 88, 631.
- A. Dalq and A. Bruylants, *Tetrahedron Lett.*, 1975, 377.
- V. Napoleone and Z. A. Schelly, *J. Phys. Chem.*, 1980, 84, 17.
- A. Woppmann, *Monatsh. Chem.*, 1974, 105, 419.
- M. R. Crampton, J. T. Thompson, and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1979, 18.
- I. D. Biggs and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1975, 107; D. L. H. Williams, *ibid.*, 1977, 128.
- S. S. Johal, D. L. H. Williams, and E. Buncl, *J. Chem. Soc., Perkin Trans. 2*, 1980, 165.
- G. Hallett and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1372 and references therein.
- T. A. Meyer and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1981, 361; M. Masui, C. Ueda, T. Yasuoka, and H. Ohmori, *Chem. Pharm. Bull. Jpn.*, 1979, 27, 1274.
- K. Al-Mallah, P. Collings, and G. Stedman, *J. Chem. Soc., Dalton Trans.*, 1974, 2469.
- G. Stedman, *J. Chem. Soc.*, 1959, 2949.
- E. D. Hughes and J. H. Ridd, *J. Chem. Soc.*, 1958, 82.
- D. L. H. Williams, unpublished results.
- J. H. Ridd, *Adv. Phys. Org. Chem.*, 1978, 16, 13.