The Relative Efficiencies of a Number of Nitrite Traps at Different Acidities and Bromide Ion Concentrations

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A previously developed kinetic method (based on the reversible denitrosation of nitrosamines) for establishing quantitatively the relative efficiencies of nitrite traps has been extended (a) to cover a range of acidities 0.95—3.94M-H_2SO_4 and (b) to include a range of bromide ion concentrations 0.1—0.4M. For many of the traps the reactivity rate constant ratios do depend upon $[H^+]$ and also $[Br^-]$, and the results can be explained in terms of the protonation equilibria of the various traps and also in terms of the reversibility of the initial nitrosation step (at high $[Br^-]$) for some of the traps. These results go some way towards explaining why there is not always good agreement between the relative reactivities established by this indirect method and a few cases where the rate constants have been measured directly by special fast-reaction techniques.

In recent years we have developed [1,2] a kinetic method which gives quantitatively the relative reactivities of a whole range of conventional nitrite traps X, in aqueous acid solution, towards a number of nitrosating agents, nitrous acid itself, nitrosyl chloride, nitrosyl bromide, nitrosyl thiocyanate, and the *S*-nitroso derivative of thiourea. In all cases the following sequence of reactivity was deduced, $HN_3 > NH_2\overset{+}{N}H_3 > NH_2SO_3H \sim$ ascorbic acid $> C_6H_5NH_2 > \overset{+}{N}H_3OH > CO(NH_2)_2$. The method, which does not require special fast-reaction techniques, is based on carrying out a denitrosation reaction of a nitrosamine in the presence of a constant excess of the nitrite trap X and then varying the concentration of an excess of added product of the denitrosation (the corresponding secondary amine, in our case *N*-methylaniline). Scheme 1 shows the sequence of reactions involved for the nitrosamine *N*-methyl-*N*-nitrosoaniline (NMNA) with bromide ion as the nucleophile. Under these conditions the nitrosation of X generally and of PhNHMe (NMA) is expected to involve equilibrium concentrations of free nitrosyl bromide. If the initial protonation is rapid (and we have assumed that this occurs at the nitrogen atom, but this is not an important point here) and follows the Hammett acidity function h_0, with an equilibrium constant K, then the expression for the first order observed rate constant k_0 is given by equation (1). The exact acidity function required is not important in this paper so we retain h_0 for convenience. When equation (1) is rewritten in the reciprocal form (2) then it is easy to see that the rate coefficients ratio k_2/k_{-1} can readily be obtained from a plot of $(k_0)^{-1}$ *versus* [NMA] at constant acidity, $[Br^-]$ and [X]. The procedure can be repeated for a range of X species and hence a quantitative reactivity order established since k_{-1} is not dependent upon the nature of X. Further, by using different nucleophiles it is possible to obtain the same figures for, *e.g.*, nitrosation by NOCl, NOSCN, and $NO\overset{+}{S}C(NH_2)_2$. The observed trends give the relative reactivities of these nitrosation agents. Most of our results were obtained with NMNA but similar results were found using the denitrosation of *N*-nitrosodiphenylamine,[3] so that it is likely that the procedure is quite general. The work is limited to reactions at quite high acid concentrations, for convenience of the rate measurements, since the reactions are inconveniently slow at low acidities.

$$\mathrm{PhN(Me)NO} \overset{H^+}{\rightleftharpoons} \mathrm{Ph\overset{+}{N}H(Me)NO} \underset{k_{-1}}{\overset{k_1,\ Br^-}{\rightleftharpoons}} \mathrm{PhNHMe} + \mathrm{NOBr}$$

$$\mathrm{NOBr} + \mathrm{X} \xrightarrow{k_2} \text{Various products}$$

SCHEME 1

$$k_0 = \frac{k_1 K h_0 [\mathrm{Br^-}] k_2 [\mathrm{X}]}{k_{-1}[\mathrm{NMA}] + k_2[\mathrm{X}]} \qquad (1)$$

$$(k_0)^{-1} = \frac{k_{-1}[\mathrm{NMA}]}{k_1 K h_0 [\mathrm{Br^-}] k_2 [\mathrm{X}]} + \frac{1}{k_1 K h_0 [\mathrm{Br^-}]} \qquad (2)$$

Stedman and his co-workers [4,5] have measured the rate constants directly for the nitrosation of some of these traps (notably hydrazine and hydrazoic acid) using stopped-flow spectrophotometry and have found the same trend in reactivities of the nitrosating agents as we found. There was reasonably good agreement between the two methods for the relative reactivity of some of the traps for reaction proceeding *via* the nitrous acidium ion $H_2\overset{+}{N}O_2$, but the agreement was less than satisfactory for reactions proceeding by the way of nitrosyl bromide. The experimental conditions used for the two approaches were considerably different in terms of both acidity and bromide ion concentration, but nevertheless the lack of quantitative agreement is clearly undesirable and we have sought an explanation. Accordingly we have measured the k_2/k_{-1} values for a number of nitrite traps at each of four acidities and three or four bromide ion concentrations to see if there is a variation which would account for the discrepancy, which could then be rationalised in terms of an extension to the outline mechanism in Scheme 1.

It is to be expected that k_{-1} as designated is a composite rate constant, including a term in $[H^+]$, or an appropriate acidity function, and the dissociation constant of $Ph\overset{+}{N}H_2Me$ if, as is believed, reaction occurs through the free amine. Similarly k_2 may also include other terms in $[H^+]$ and also possibly in $[Br^-]$ if, for example, the initial nitrosation of X is reversible. The results are presented in this paper.

EXPERIMENTAL

All materials were of the highest purity grade available and were recrystallised from an appropriate solvent where necessary. The kinetic method has been described previously.[1,2] Generally the reaction was followed by the disappearance of the absorption at 275 nm due to the nitrosamine, but for the substituted anilines it was more convenient and accurate to monitor the appearance of the absorption at *ca.* 340 nm due to the diazonium ion. In all cases good first-order plots were obtained using either the observed infinity value or the Guggenheim method.[6] Individual runs were reproducible to ±4%. For all the X species studied, plots of $(k_0)^{-1}$ *versus* $[\text{Added NMA}]_{\text{Total}}$ were linear, and k_2/k_{-1} ratios were calculated from the slopes and intercepts.

RESULTS AND DISCUSSION

Values of k_2/k_{-1} have been determined as a function of (a) the acidity and (b) the bromide ion concentration for the following nitrite traps, hydrazoic acid, hydrazine, sulphamic acid, aniline, hydroxylamine, *o*- and *p*-nitroanilines and 2,5-dichloroaniline. The results are presented in Table 1 for the acidity and in Table 2 for the bromide ion concentration. It is quite clear that within this range of nitrite traps hydrazoic acid is the most efficient, followed by the protonated form of hydrazine. The aniline derivatives studied all contained electron-withdrawing groups and were all efficient traps due to their reduced basicity and hence higher concentration of the reactive free base form in these acid solutions, compared with for example aniline itself. A few of these represent repeat determinations of previous measurements[1,2] at one acidity or one bromide ion concentration, and the agreement is acceptable. The reproducibility of these ratios is shown in Table 2 for two sets of measurements using sulphamic acid as the nitrite trap, and is considered to be generally good bearing in mind that each value is obtained from the slope and intercept of a plot of four or five separate rate constant determinations.

TABLE 1

Variation of k_2/k_{-1} ratios with $[H_2SO_4]$ for a number of nitrite traps (X) at constant $[Br^-] = 0.2$M

Trap (X)	0.95M-H_2SO_4	1.95M-H_2SO_4	2.97M-H_2SO_4	3.94M-H_2SO_4
HN_3	7.9	16	28	37
$NH_2\overset{+}{N}H_3$	2.9	6.4	12	15
NH_2SO_3H	0.53	0.73	0.69	0.83
$\overset{+}{N}H_3OH$	3.3×10^{-2}	4.9×10^{-2}	6.4×10^{-2}	10.9×10^{-2}

	2.7M-H_2SO_4	4.0M-H_2SO_4
p-Nitroaniline	11	10

	2.0M-H_2SO_4	3.4M-H_2SO_4
Aniline	1.0	0.9

Let us first consider the variation of the acidity of the medium (Table 1). The results fall reasonably clearly into two categories, (1) where the ratios are virtually unaffected by the acidity, for aniline and *p*-nitroaniline, (2) where the ratios increase steadily with M-H_2SO_4, *i.e.* for HN_3, $NH_2\overset{+}{N}H_3$, and $\overset{+}{N}H_3OH$. There is one intermediate case of sulphamic acid, where the increase across the Table is quite small, but is probably real.

TABLE 2

Variation of k_2/k_{-1} ratios with [Br] for a number of nitrite traps (X) at constant acidity 2.7M-H_2SO_4

Trap (X)	0.1M-Br^-	0.2M-Br^-	0.3M-Br^-	0.4M-Br^-
HN_3	32	31	40	
$NH_2\overset{+}{N}H_3$	24	19	11	
NH_2SO_3H	1.30	0.59	0.36	
NH_2SO_3H *	1.15	0.65	0.42	
$\overset{+}{N}H_3OH$	7.8×10^{-2}	7.0×10^{-2}	6.5×10^{-2}	
o-Nitroaniline	25	14	10	
p-Nitroaniline	21	11	9.1	7.9
2,5-Dichloroaniline	25	20	18	13
Aniline	1.0		1.0	

* Duplicate experiments.

The rate constant that we have designated k_{-1} for the *N*-nitrosation of NMA is not a simple second-order rate constant, but necessarily includes the dissociation constant K_A for the protonated form of the amine and also a term in $[H^+]$ or the appropriate acidity function which describes the protonation equilibrium of NMA This assumes that the nitrosation of NMA at these acidities occurs *via* the free base form. There is evidence available[7] which suggests that the nitrosation of NMA in the absence of halide ions (when the nitrosating agent is $H_2\overset{+}{N}O_2$ or free $\overset{\cdot +}{N}O$) occurs *via* the protonated form $Ph\overset{+}{N}H_2Me$. This has never been suggested for nitrosation *via* the nitrosyl halides, where measurements of the rate constants at different acidities for both NOCl and NOBr suggest[8] that reaction of a number of substituted anilines occurs *via* the free base. Thus k_{-1} as written previously should in fact take the form given by equation (3) where k_{-1}' is the true rate constant and H is some

$$k_{-1} = k_{-1}'K_A/H \qquad (3)$$

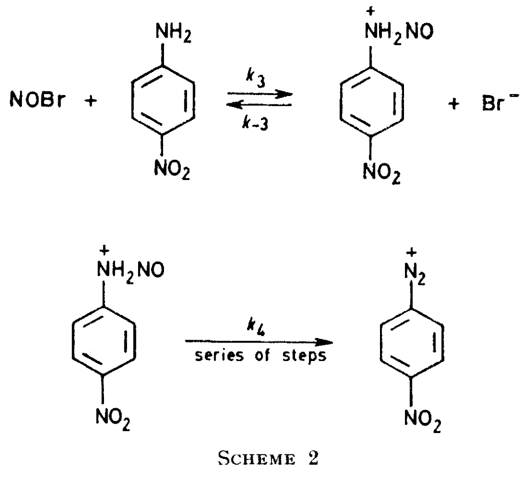
acidity function. The same principle applies also to the nitrosation of X. We would expect at these acidities that aniline and *p*-nitroaniline would behave in a similar way to NMA, *i.e.* that they should exist primarily in the protonated form, that the free base form is the reactive one to nitrosation. So k_2 should also include a similar term K_X/H where K_X is the acid dissociation constant of XH^+. Thus, if the acidity forms are at all comparable the effect of changing the acidity should cancel out when the k_2/k_{-1} values are obtained, as is observed for both aniline and *p*-nitroaniline. If, on the other hand, X is virtually completely protonated and that the protonated form is the reactive form, then k_2 is the true rate constant and no acid term is contained therein. That being the case the measured ratios k_2/k_{-1} should increase with increasing acidity because of the acidity function term in k_{-1} [equation (3)]. It is known[5] that the reactive forms of azide and hydrazine in nitrosation are HN_3 and

$NH_2\overset{+}{N}H_3$ respectively and from the second pK_a values published,[9] it is unlikely that any significant degree of further protonation occurs. Similarly the protonated form of hydroxylamine is believed [10] to be the reactive form towards nitrosation at these acidities. In these three cases we find, as expected, that the observed k_2/k_{-1} ratios do increase with acidity. The case of sulphamic acid is not so clear cut. There is a small increase in the ratio from 0.95—3.94M-H_2SO_4, but this is not much greater than the experimental error. The situation is probably complicated since it is known [11] that both sulphamic acid and the sulphamate ion are reactive in nitrosation and various acid–base equilibria involving the zwitterion may be involved.

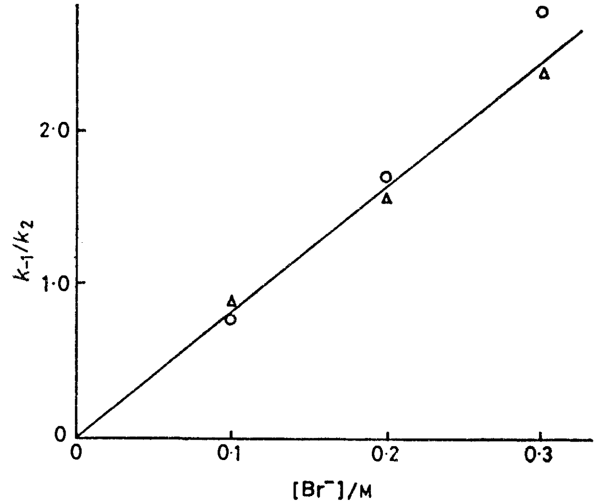
If we turn to the variation with [Br$^-$] at constant acidity a similar pattern exists in that for some X species the ratio decreases steadily as [Br$^-$] is increased whilst for others the ratio is essentially constant. For the reaction scheme as written (Scheme 1) there is no obvious reason (other than of salt effects) why the measured ratio k_2/k_{-1} should vary with [Br$^-$]. We can regard those substrates where the ratio is constant therefore as showing normal behaviour; HN_3 and $\overset{+}{N}H_3OH$ fall into this category. An explanation must be sought for the variation shown by the other group, *i.e.* $NH_2\overset{+}{N}H_3$, NH_2SO_3H, *o*- and *p*-nitroaniline, and 2,5-dichloroaniline. It has been shown recently [8] that in the diazotisation of aniline derivatives containing electron-withdrawing groups by nitrosyl bromide in water, the initial *N*-nitrosation step is significantly reversible, *i.e.* the denitrosation of the primary *N*-nitrosamine competes with the various proton transfer reactions leading to the formation of the diazonium ion. This was shown experimentally by noting the variation of the observed rate constant with increasing [Br$^-$] and noting a levelling off effect. A double reciprocal plot showed that the data were consistent with a mechanism outlined in Scheme 2. If this reversibility is important for a particular nitrite trap X then clearly k_2 is not a single rate constant but is given by equation (4). This in turn means that the measured ratio k_2/k_{-1} should *decrease* with increasing

$$k_2 = \frac{k_3k_4}{k_{-3}[\mathrm{Br}^-] + k_4} \qquad (4)$$

[Br$^-$] as is in fact observed for the aniline derivatives and for $NH_2\overset{+}{N}H_3$ and NH_2SO_3H. More quantitatively k_{-1}/k_2 as measured should give a linear plot against [Br$^-$] with a positive slope and intercept. This is observed reasonably well for each of these X species, bearing in mind the limited number of points available and the experimental error. It has been noted [11] that the nitrosation of sulphamic acid is not subject to bromide ion catalysis. The reason for this maybe that the reverse reaction (step k_{-3}) is now so fast, with the strongly electron-withdrawing SO_3H group present, that nitrosation occurs *via* free nitrous acid. This is claimed to be the case [12] for the nitrosation of *N*-methylurea and amides generally. Whatever the reason, the measured k_2/k_{-1} ratios should also decrease with increasing [Br$^-$] if X is not subject to Br$^-$ catalysis in nitrosation. If there is no kinetic dependence on [Br$^-$] for the nitrosation of X then the k_{-1}/k_2 ratios as measured should give a straight line with a zero intercept. The Figure shows that the data for sulphamic acid fit this prediction.



Scheme 2



Variation of k_{-1}/k_2 with bromide concentration: ○, △ duplicate experiments

Woppmann and Sofer [13] have reported that in the diazotisation of aniline in methanol solvent with both hydrogen chloride and hydrogen bromide, the initial *N*-nitrosation step is reversible and linear double reciprocal plots (k_0^{-1} *versus* [Br$^-$]$^{-1}$) were obtained. This, taken with our results for the aniline derivatives in water [8] (for both Br$^-$ and Cl$^-$ catalysed reactions) suggest that this is likely to be an important aspect to the mechanism of nitrosations generally; the available evidence shows that, as expected the denitrosation step is favoured (a) for the more powerful nucleophiles, and at high nucleophile concentrations, (b) in the less polar alcoholic solvents, compared with water, and (c) when there are electron-withdrawing substituents in the substrate.

The general conclusion is that whilst the k_2/k_{-1} ratios as measured by this indirect technique will yield the relative reactivity of the nitrite traps *under the stated experimental conditions*, the values could and do change, particularly at different acidity and, if nucleophilic anions are present, with the concentration of such ions. This makes extrapolation of data from one set of experimental conditions to another rather difficult. This analysis does however account for discrepancies in the literature which do refer to differing conditions, particularly for nitrosations involving the nitrosyl halides, when the concentration of the halide ion can be crucial.

TABLE 3

Reactivity of some possible nitrite traps

	k_2/k_{-1}
Methanol	*ca.* 0
Ethane-1,2-diol	*ca.* 0
2-Aminoethanol	*ca.* 0
1,2-Diaminoethane	*ca.* 2×10^{-3}

Reaction conditions: 2.7M-H_2SO_4, 0.1M-Br^-.

We have attempted to discover other suitable nitrite traps other than those listed in Tables 1 and 2. In particular we have looked at alcohols since it has recently been demonstrated [14] that methanol and other alcohols react rapidly but not quantitatively with nitrous acid to form the inactive alkyl nitrites. Table 3 shows that methanol, ethane-1,2-diol, and 2-aminoethanol all have negligible reactivity as nitrite traps in 2.7M-H_2SO_4 and 0.1-M-Br^-. Presumably this is because even though the corresponding alkyl nitrite is formed rapidly, it is an equilibrium process with much free HNO_2 or NOX remaining as the active nitrosating agents. The alkyldiamine shows some reactivity, but this is very low since here the basicity of the second amino-group is greater than that of, *e.g.*, aniline.

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