Kinetics and Mechanism of the Nitrosation of Alcohols, Carbohydrates, and a Thiol

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Rate constants have been determined by stopped-flow spectrophotometry for the nitrosation in water of the following alcohols and carbohydrates: methanol, ethanol, propan-1-ol, propan-2-ol, ethane-1,2-diol, propane-1,2,3-triol, mannitol, sucrose, and glucose, in some cases at 25° and others at 0°. In all cases the reactions were reversible, forming equilibrium concentrations of the corresponding alkyl nitrites. With a large excess of the alcohol present over the total nitrous acid concentration, the observed first-order rate constants increased linearly with the alcohol concentration, and from the slope and the intercept the rate constants for the forward and reverse reactions were obtained. Both reactions were acid-catalysed and also catalysed by chloride and bromide ion. The forward reaction is interpreted as one involving *O*-nitrosation by $H_2NO_2^+$ (or NO^+), NOCl, or NOBr. For methanol, rate constants for attack by nitrosyl chloride and by nitrosyl bromide were 2.1×10^5 and 2.0×10^4 l mol^{-1} s^{-1}, respectively. There was little difference between the rate constants for chloride ion and bromide ion attack for the reverse reaction, suggesting that the reactions for attack on the protonated alkyl nitrite are very rapid, possibly approaching the diffusion-controlled limit. There was a decrease in the overall equilibrium constant for the non-halide ion-catalysed pathway, along the series MeOH, EtOH, Pr^{i}OH, and Bu^{t}OH; the value for the latter was so small as to make the quantitative determination of the rate constants impossible by this method. This decrease was due almost entirely to a decreasing value for the forward rate constant along the series, which implies that a steric effect is operational. All the carbohydrates studied had very similar equilibrium constants of *ca.* 1.5. In contrast the nitrosation of *N*-acetylpenicillamine gave the thionitrite quantitatively at low acidities. Again the reaction was acid- and halide (and thiocyanate) ion-catalysed and the reactivity sequence NOCl > NOBr > NOSCN was established. For both the alcohols and the thiol, the forward rate constants are well below the diffusion controlled values and are several powers of ten less than the corresponding values for the reactions of aniline. The results are discussed in terms of the nucleophilicities of the oxygen and sulphur sites for the forward reaction and in terms of the protonation equilibria of the nitrites and thionitrite for the reverse reaction.

EVEN though alkyl nitrites are well known compounds, readily prepared, and have been widely used in synthesis, particularly involving nitrosation reactions in non-aqueous solvents, there has been no mechanistic investigation into their formation from alcohols and nitrous acid. Preparatively this reaction is quite common,[1] but the apparent rapidity of the reaction has precluded a kinetic study. Now that stopped-flow spectrophotometry and other techniques are available for the measurement of fast reactions, it is possible to examine these reactions quantitatively. A preliminary account of some of this work has already been published.[2] There have been two recent investigations involving alkyl nitrite formation in non-aqueous solvents, one [3] where rate and equilibrium constants have been determined for the reaction of nitrosyl chloride with some aliphatic alcohols in acetic acid. Here too the reactions were rapid and a stopped-flow method used. The authors claimed that the rate and equilibrium constants were sensitive to electronic effects for a number of butyl alcohol systems. Another report [4] discusses the reaction of nitrosyl chloride with butan-1-ol in CCl_4–HOAc solvent mixtures. Measurements were made using a solvent-jump relaxation method and the variation of the thermodynamic and activation parameters were discussed in terms of the solvent properties. No work has been reported for any nitrosation of alcohols in water, although the reverse reaction, the hydrolysis of alkyl nitrites, has been studied mechanistically for both acid- and base-catalysed reactions in aqueous dioxan.[5,6] For the acid-catalysed reactions rate constants were determined at 0°, together with the equilibrium constants for the overall reaction. The acid-catalysed hydrolysis of an alkyl nitrite in the presence of ^{18}O-labelled solvent gave the alcohol without ^{18}O incorporation, thus indicating that oxygen–nitrogen bond fission occurred. This was confirmed using an optically active nitrite. The implication must be that the reverse reaction involves *O*-nitrosation by a carrier of NO^+. It was the purpose of this work to examine nitrosation of alcohols in water from a mechanistic viewpoint. In alkaline solution alkyl nitrites can also effect nitrosation of *e.g.* amines. The base-catalysed hydrolysis reaction has recently been studied in detail [6] and the results compared with those of base-catalysed reactions of carboxylic esters. A concerted mechanism, rather than one involving addition–elimination, has been proposed [7] for the reaction of alkyl nitrites with amines in aqueous dioxan, under basic conditions.

Much less is known about the chemistry of the nitrosation of thiols, because thionitrites generally are much less stable than are the corresponding nitrites. The kinetics of the reaction between RSH (R = Bu^t) and nitrous acid in acid solution have been examined.[8] A first-order dependence upon [RSH], [HNO_2], and [H^+] was found and all the results were consistent with an electrophilic *S*-nitrosation by $H_2NO_2^+$ or NO^+. More recently the kinetics of the nitrosation of cysteine have been determined.[9] The product was not isolated but was believed to be *S*-nitrosocysteine. The rate of the reaction was very rapid in dilute acid solution and was essentially irreversible. Direct *S*-nitrosation of cysteine and methionine by nitrosamines has also been reported [10]

and the kinetic measurements revealed that cysteine has a nucleophilic reactivity comparable with chloride ion, and methionine (and *S*-methylcysteine) is similar in reactivity to bromide ion. We have recently [11] examined the nitrosating ability of the stable thionitrite (I) pre-

$$ONSC(Me)_2CH(NHAc)CO_2H$$
(I)

pared from *N*-acetylpenicillamine.[12] Reaction does occur, promoted by the solvent (water), Cl^-, Br^-, SCN^-, and $SC(NH_2)_2$, but the reaction is strongly reversible, and can only be examined in the presence of ' nitrite traps ', such as hydrazine and hydrazoic acid. In this paper we report the rate constants for the nitrosation of *N*-acetylpenicillamine under various conditions (but always where the reverse reaction rate is negligible) and compare the results with those obtained for the nitrosation of alcohols.

EXPERIMENTAL

All the alcohols and sugars together with *N*-acetylpenicillamine were commercial samples of the highest purity grade available and were used without further purification, as were the various salts used.

The kinetic measurements were carried out using a Canterbury model stopped-flow spectrophotometer. Some measurements were made on the equipment at University College Swansea and the remainder in the University of Durham. Duplicate measurements with the two sets of apparatus gave good agreement. Reactions were carried out under first-order conditions with [ROH] or [RSH] $\gg$ [HNO_2] and good first-order behaviour was obtained throughout. Rate constants are reported at either 25 or 0° for the alcohols (and 31° for the thiol) and represent the mean of at least five determinations. The standard errors for the alcohols work are rather larger than is desirable, but represent the difficulty of getting accurate rate constant data with the relatively small optical density changes which occurred in many cases. The measurements with the alcohols and sugars were carried out at *ca.* 360 nm where there was a small difference between the spectrum of RONO and HNO_2.[13] For the experiments involving the thiol, measurements were carried out at 338 nm, noting the appearance of an absorption at 338 nm due to the thionitrite. The thiol did not absorb at this wavelength.

RESULTS AND DISCUSSION

Acid-catalysed Nitrosation of Alcohols and Carbohydrates.—The initial experiments were carried out with methanol, where the spectral changes during reaction were greatest. The product, methyl nitrite, was identified by its characteristic absorption spectrum in the region 300—400 nm.[13] With a large excess of methanol present over nitrous acid, the yield of methyl nitrite varied with the methanol concentration, suggesting an equilibrium reaction. A plot of the observed first-order rate constant k_0 [defined by $-d(Abs)/dt = k_0(Abs_\infty - Abs)$] against [MeOH] was linear with a positive slope and intercept, as shown typically in Figure 1, for the uncatalysed and catalysed reactions. This is characteristic of a reversible reaction [equation (1)], first-order in both directions, and where the observed first-order rate constant k_0 is the sum of those for the forward and reverse reaction [equation (2)]. The overall reaction

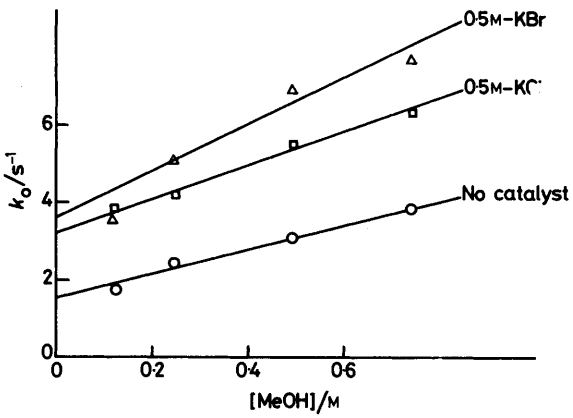


FIGURE 1 Variation of k_0 with [MeOH] for the uncatalysed and Cl^-- and Br^--catalysed reactions in 0.03M-H_2SO_4 at 0°

$$ROH + HNO_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RONO + H_2O \quad (1)$$

$$k_0 = k_1[ROH] + k_{-1} \quad (2)$$

is subject to acid catalysis (see Figure 2) indicating that both nitrosation and denitrosation are acid-catalysed

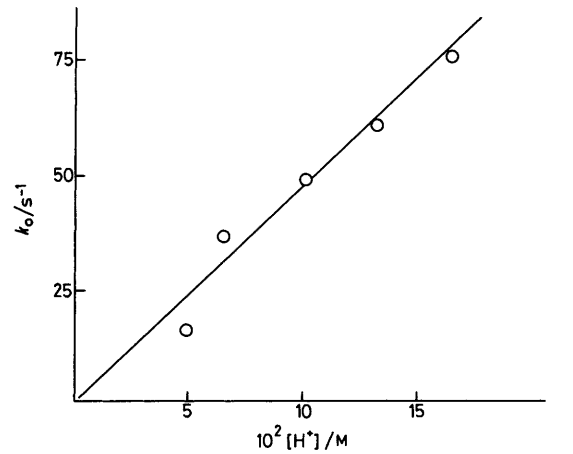


FIGURE 2 Acid catalysis for the non-halide ion-catalysed reaction of EtOH (0.257M) at 25 °C

processes. Values of the third-order rate constant k_2 [defined by equation (3)] for the forward reaction, and the second-order rate constant k_{-2} [defined by equation

$$Rate = k_2[ROH][HNO_2][H^+] \quad (3)$$

$$Rate = k_{-2}[RONO][H^+] \quad (4)$$

(4)] were determined as 700 ± 100 l^2 mol^{-2} s^{-1}, and 576 ± 57 l mol^{-1} s^{-1} respectively (at 25°) from a series of experiments where both the [ROH] and [H^+] were separately varied over the range 0—1M and 0—0.17M respectively. In some cases there was a tendency for the k_0 *versus* [ROH] plot to curve off at very high [ROH]; this was attributed to a solvent effect, and

the slopes are taken from the linear part of the graph. Rate measurements were also carried out for methanol at 0°, and for ethanol (at 25° and 0°), propan-1-ol (at 0°), propan-2-ol (at 0°), ethane-1,2-diol (at 25°), and propane-1,2,3-triol (at 0°). In all cases the rate profile was similar to that of methanol, and the rate constants for the forward and reverse reactions were obtained. The nitrosation of 2-methylpropan-2-ol was attempted but the plot of k_0 *versus* [ROH] had slope *ca.* 0 within the experimental error, indicating that the rate constant for the forward reaction was so small as not to be measurable by this technique. This agrees with the observation by Allen [5] that (in a dioxan–water solvent at 0°) the hydrolysis of t-butyl nitrite goes to completion at low acid concentration. The combined results for the alcohol series are given in Table 1 together with some results for

TABLE 1

Values of k_2 and k_{-2} for the nitrosation of a number of alcohols and carbohydrates

Alcohol	k_2/l^2 mol^{-2} s^{-1}	k_{-2}/l mol^{-1} s^{-1}	K	Temp. (°)
MeOH	700 ± 100	576 ± 57	1.2	25
MeOH	73 ± 10	31 ± 6	2.4	0
MeOH *	67 ± 7	27 ± 5	2.5	0
EtOH	248 ± 23	282 ± 10	0.88	25
EtOH	38 ± 0.3	47 ± 0.2	0.81	0
Pr^{n}OH	29 ± 1	44 ± 1	0.66	0
Pr^{i}OH	11 ± 1	44 ± 2	0.25	0
Bu^{t}OH	Too small to measure	*ca.* 103	<0.05	0
$(CH_2OH)_2$	460 ± 20	332 ± 5	1.4	25
Glycerol	52 ± 10	46 ± 7	1.1	0
Sucrose	100 ± 10	65 ± 2	1.5	0
Glucose	124 ± 18	81 ± 3	1.5	0
Mannitol	677 ± 14	355 ± 5	1.9	25

* Duplicate set of experiments.

three sugars, sucrose, glucose, and mannitol. It is clear that the equilibrium constant K does not vary very much with structure over the whole series. When this is analysed further, it can be seen that any changes in K arise from changes in k_2 rather than in k_{-2}. In other words, the reverse reaction seems unaffected by structural changes whereas there are trends for the forward reaction. One such trend easily recognisable is the decrease in k_2 along the series MeOH > EtOH > Pr^{i}OH > Bu^{t}OH. The value for Bu^{t}OH was not obtained but it is certainly much less than the value for Pr^{i}OH. The trend is the opposite to that expected on electronic grounds, where the increasing methyl substitution should increase the nucleophilicity of the oxygen atom and so increase the rate constant. It appears that this effect is completely dominated by another in the opposite direction, and can only be ascribed to a steric effect.

It is interesting to note that the three sugars studied all react rapidly and reversibly with nitrous acid. The products, although not isolated in the present study, had absorption spectra in the 300—400 nm region characteristic of alkyl nitrites. Within the experimental error their reactivity seems to be the same, both for the forward and reverse reactions. As all the equilibrium constants for the alcohols and sugars studied (except for Bu^{t}OH) lie in the range 0.25—2.5 this confirms that these compounds do not make efficient ' nitrite traps ', for although the *O*-nitrosation is very rapid, it proceeds only to an equilibrium position and unless very large excesses of the alcohols or sugars are used, substantial quantities of free nitrous acid remain. This was demonstrated recently [14] when rate constants for the *N*-nitrosation of amines were measured in the presence of varying concentrations of different alcohols and sugars. Although rate reductions were observed in all cases (and the equilibrium constants for RONO formation determined), it was not possible to achieve complete suppression of nitrosation of *e.g.* *N*-methylaniline. This contrasts with the behaviour of thiols (to be discussed in detail later) where complete suppression of *N*-nitrosation was achieved by the addition of cysteine and *N*-acetylpenicillamine, by competition with *irreversible* *S*-nitrosation. All the evidence [15] shows that under these conditions both alkyl nitrites and thionitrites are themselves inactive as direct nitrosating agents towards amines.

Halide Ion Catalysis in the Nitrosation of Alcohols.—Catalysis by added chloride and bromide ion has been investigated in detail for the nitrosation of methanol and of propan-2-ol. In both cases catalysis was observed with bromide ion being slightly the more efficient. Over the range of concentration studied k_0 was linearly dependent on [Cl$^-$] and [Br$^-$] although there is in both cases a large contribution to the non-halide ion-catalysed reaction. Some typical results are shown in Table 2.

TABLE 2

Typical example of chloride ion and bromide ion catalysis in the nitrosation of methanol at 25°

[Cl$^-$]/M	k_0/s^{-1}	[Br$^-$]/M	k_0/s^{-1}
0	51 ± 5	0	47 ± 3
0.2	65 ± 6	0.2	60 ± 4
0.4	70 ± 5	0.4	77 ± 4
0.6	84 ± 5	0.6	78 ± 9
0.8	96 ± 7	0.8	108 ± 10
1.0	109 ± 5		
[MeOH] 0.593M		[MeOH] 0.494M	
[H$^+$] 0.052M		[H$^+$] 0.054M	

Analysis of the kinetic results obtained by separately varying [ROH] and [halide ion] enabled the rate constants for the forward and reverse reactions to be obtained. Acid catalysis was also observed. We assume that reaction occurs *via* low equilibrium concentrations of NOCl and NOBr, and have taken the equilibrium constants (K_{NOY}) to be [16] 1.14×10^{-3} and 5.1×10^{-2} l^2 mol^{-2}, respectively, at 25°. The fourth-order rate constants k_3 [defined by equation (5)] for methanol at 25° are

$$\text{Rate} = k_3[\text{ROH}][\text{HNO}_2][\text{H}^+][\text{Halide ion}] \quad (5)$$

240 ± 50 and 1 000 ± 100 l^3 mol^{-3} s^{-1} for the chloride and bromide ion-catalysed reactions respectively, yielding values of 2.1×10^5 and 2.0×10^4 l mol^{-1} s^{-1} for the second-order rate constants for reaction between NOCl and NOBr and methanol. It is to be expected that NOCl is the more reactive, on a simple electronegativity

argument, and this has previously been demonstrated for the nitrosation of alkenes,[17] aniline derivatives both in water [18] and in methanol [19] solvent, and also for the nitrosation of the hydrazinium ion.[20] The actual values of these rate constants for the methanol reaction are well below the diffusion-controlled values found for some aniline derivatives in water.[18,21] The corresponding rate constants at 0° were found to be 5.5×10^4 l mol^{-1} s^{-1} for NOCl and 3.6×10^3 l mol^{-1} s^{-1} for NOBr giving activation energy values of 54 and 46 kJ mol^{-1}, respectively; these values are higher than those expected for diffusion-controlled reaction between two formally neutral reactants. Similar results for propan-2-ol at 0° also showed that NOCl was more reactive than NOBr by a factor of *ca.* 15.

For the reverse reaction, the halide ion-catalysed denitrosation of alkyl nitrites, the third-order rate constants k_{-3} [defined by equation (6)] were found to have values of 930 ± 100 and $1\,050 \pm 100$ l^2 mol^{-2} s^{-1} for methanol at 25° respectively for the chloride and bromide

$$\text{Rate} = k_{-3}[\text{RONO}][\text{H}^+][\text{Halide ion}] \qquad (6)$$

ion reactions, and 70 ± 5 and 91 ± 8 l^2 mol^{-2} s^{-1} for the same reactions at 0°. Thus bromide ion appears to be marginally more reactive than chloride ion, although the difference is very small and barely outside the experimental error. It is to be expected, from their relative nucleophilicities, that bromide ion is more reactive than chloride ion, but the very closeness of the values, at both temperatures, suggests that the actual rate constants for halide ion attack at the protonated alkyl nitrite [equation (7)] are so large (possibly close to diffusion-control) as to

$$\text{RONO} + \text{H}^+ \rightleftharpoons \underset{\text{H}}{\overset{+}{\text{R}}\text{ONO}} \xrightarrow{\text{Y}^-} \text{ROH} + \text{NOY} \qquad (7)$$

make the ion $\overset{+}{\text{R}}$O(H)NO very undiscriminating between the nucleophiles. The activation energies are not so diagnostic here for reaction between two charged species.

Since the pK_a values of RONO species generally are not known, it is not possible to calculate the actual rate constants for Y$^-$ attack. If we assume that they are at the diffusion-limit (of 7×10^9 l mol^{-1} s^{-1}) then this means that the minimum value of the pK_a for protonated methyl nitrite is *ca.* −7, which is a reasonable value. Similar results were found for the denitrosation of 1-methylethyl nitrite at 0°. The same calculation carried out for the denitrosation [11] of the thionitrite (RSNO) give a minimum pK_a value for $\overset{+}{\text{R}}$S(H)NO of *ca.* −13, which is again in the region expected.

Nitrosation of N-*Acetylpenicillamine* (RSH).—These reactions were carried out in water at 31° (the temperature at which the reverse reaction was studied),[11] noting the appearance of the absorption at 338 nm due to the thionitrite RSNO (I), again using a stopped-flow technique. There was no evidence of reversibility of the reaction of the acidities used in this study (1×10^{-2}—1×10^{-3}M–H$^+$) as expected since the reverse reaction has been studied separately [11] and requires very much higher acid concentrations before it can be measured, typically 1—4M-H_2SO_4. The reaction was first-order in [HNO_2] as shown by the excellent first-order behaviour for reactions carried out with a large excess of RSH over HNO_2, and was also first-order in both [RSH] and [H$^+$] as shown by the results in Table 3, when both [RSH] and [H$^+$] were separately varied. The kinetics are all consistent with a mechanism involving attack by $H_2\overset{+}{N}O_2$ (or NO$^+$) at the sulphur atom of RSH. Stedman and his co-workers [9] found similar results for the nitrosation of cysteine, where again the equilibrium lies well over towards the thionitrite form. This contrasts markedly with the situation found for alcohols and carbohydrates, discussed earlier in this paper. The difference probably arises from the markedly different equilibrium constants

TABLE 3

Rate data for the nitrosation of penicillamine (RSH)

10^3[RSH]/M	10^3[H$^+$]/M	$10^2 k_0$/s^{-1}
2.40	9.5	2.94
4.81	9.5	6.14
3.69	3.28	2.11
3.69	6.93	3.14
3.69	10.57	4.27
3.69	14.22	5.42

$$\text{RSNO} + \text{H}^+ \rightleftharpoons \overset{+}{\text{R}}\text{SHNO} \xrightarrow{\text{H}_2\text{O}} \text{RSH} + \text{H}_2\overset{+}{\text{N}}\text{O}_2 \qquad (8)$$

for protonation expected for the RSNO [equation (8)] and RONO species. Since the reaction is acid-catalysed (and halide ion-catalysed, see later) it is likely that the first step in the reaction is a rapid, reversible protonation probably at the sulphur atom in the thionitrite and the oxygen atom of the nitrite. The basicity of both compounds is expected to be very low, as discussed earlier, with the thionitrite being several orders of magnitude less basic than the nitrite, resulting from the expectation that sulphur sites are less basic (but more nucleophilic) than their oxygen counterparts, approximately by 5 pK_a units in the case of thiols and alcohols.[22] Similarly, the pK_a values of diethyl sulphide and diethyl ether are [23] respectively −6.8 and −2.4. We would expect a similar sort of difference *i.e. ca.* 5 pK_a units in the case of thionitrites and nitrites, and this would give rise to a large difference in the rate constants for denitrosation of nitrites and thionitrites. The experimentally measured difference is [11] *ca.* 2×10^6.

The value of the third-order rate constant for nitrosation k_2 [defined by equation (9)] is 840 l^2 mol^{-2} s^{-1} at

$$\text{Rate} = k_2[\text{HNO}_2][\text{H}^+][\text{RSH}] \qquad (9)$$

31°. We cannot make an exact direct comparison with the corresponding alcohol, but Bu^{t}OH would make a reasonable model. Here the k_2 value was too small to be measured by the reversibility method used for the other alcohols, but it is likely to be at least a power of ten less than the value for Pr^{i}OH *i.e.* it is probably <10 l^2 mol^{-2} s^{-1} at 31°, thus showing the markedly greater nucleophilicity of the more polarisable sulphur atom compared

with the oxygen atom, probably by at least a factor of 100. It does appear that *N*-acetylpenicillamine is about ten times less reactive than is thiourea and the alkylthioureas to nitrosation. The latter [9] are believed to occur at around the diffusion-controlled rate limit.

We have also examined the effects of added Cl^-, Br^-, SCN^-, and I^- on the rate constants of *S*-nitrosation. All show significant catalysis as is demonstrated by the collected results in Table 4, increasing as expected in the

TABLE 4

Catalysis of *S*-nitrosation by Cl^-, Br^-, SCN^-, and I^-

[Nucleophile]	$10^2k_0/s^{-1}$	[Nucleophile]	$10^2k_0/s^{-1}$
0	2.73	3.83×10^{-2}M-Br^-	3.62
1.92×10^{-2}M-Cl^-	3.23	7.66×10^{-2}M-Br^-	4.37
4.81×10^{-2}M-Cl^-	3.19	9.62×10^{-2}M-Br^-	4.57
9.61×10^{-2}M-Cl^-	3.89	11.5×10^{-2}M-Br^-	4.79
19.2×10^{-2}M-Cl^-	4.47	19.2×10^{-2}M-Br^-	6.69
		28.9×10^{-2}M-Br^-	8.38

All at $[HClO_4]$ 7.4×10^{-3}M and [RSH] 3.68×10^{-3}M

[Nucleophile]	$10^2k_0/s^{-1}$	[Nucleophile]	$10^2k_0/s^{-1}$
0.74×10^{-2}M-SCN^-	3.58	0.59×10^{-2}M-I^-	4.08
1.47×10^{-2}M-SCN^-	4.87	1.00×10^{-2}M-I^-	6.45
2.94×10^{-2}M-SCN^-	5.95	2.01×10^{-2}M-I^-	10.4
4.42×10^{-2}M-SCN^-	6.62	3.02×10^{-2}M-I^-	10.8
8.83×10^{-2}M-SCN^-	7.36	4.02×10^{-2}M-I^-	10.9
		5.03×10^{-2}M-I^-	10.5

All at $[HClO_4]$ 9.5×10^{-3}M and [RSH] 2.40×10^{-3}M

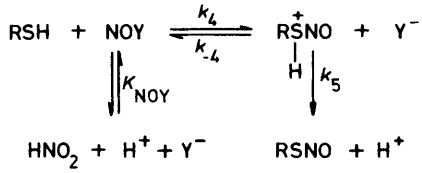
order $Cl^- < Br^- < SCN^- < I^-$. Both chloride and bromide ion show linear plots (for the concentration range studied) for k_0 *versus* [nucleophile], whereas both SCN^- and I^- give curved plots, with k_0 levelling off at high concentration at *ca.* 11×10^{-2} s^{-1} for I^-. It is likely that reaction occurs *via* the corresponding nitrosyl halide (or thiocyanate); the observed results can be explained if it is assumed that the initial *S*-nitrosation is reversible. This reversibility of nitrosation by nitrosyl halides has been introduced previously to account for similar behaviour in the diazotisation of aniline derivatives both in methanol [19] and also in aqueous solution.[18] It may seem surprising that attack by Y^- on the intermediate $[R\overset{+}{S}HNO]$ can compete effectively with proton loss from that intermediate to the solvent, but this does seem to be the most reasonable explanation of the facts. From the Scheme the expression for the first-order rate constant k_0 (defined by $-d[HNO_2]/dt = k_0[HNO_2]$) is given by equation (10) and includes a term for the uncatalysed reaction (not shown in the Scheme) which can readily be obtained from the intercept for each reaction at $[Y^-] = 0$. K_{NOY} is the equilibrium constant for the formation of NOY and is known for NOCl,[16] NOBr,[16] and

$$k_0 = k_{HNO_2}[RSH][H^+] + \frac{k_4k_5K_{NOY}[RSH][H^+][Y^-]}{k_{-4}[Y^-] + k_5} \quad (10)$$

NOSCN.[24] For the less reactive chloride and bromide ion nucleophiles $k_5 \gg k_{-4}[Y^-]$ applies over the whole concentration range so that equation (10) reduces to (11)

$$k_0 = k_{HNO_2}[RSH][H^+] + k_4K_{NOY}[RSH][H^+][Y^-] \quad (11)$$

which is observed experimentally. Values of k_4 calculated are 2.6×10^6 l mol^{-1} s^{-1} for NOCl and 1.4×10^5 l mol^{-1} s^{-1} for NOBr, again showing the same relative reactivity as for the alcohols. For SCN^- and I^- k_4 can be obtained *via* equation (10) by plots of $(k_0 - k_{HNO_2}[RSH][H^+])^{-1}$ *versus* $[Y^-]^{-1}$. Such a plot for SCN^- was linear and gave k_4 as 3.0×10^3 l mol^{-1} s^{-1}. The value of K_{NOY} for NOI is not known so k_4 cannot be calculated for that reaction. Although much is known about the relative reactivities of NOBr and NOCl in solution, less work



SCHEME

has been concerned with the corresponding NOSCN reactions, although catalysis by SCN^- is well known.[25] Stedman and his co-workers [26] have shown that NOSCN is significantly less reactive than NOBr and NOCl in the nitrosation of hydroxylamine and *O*-methylhydroxylamine, and recently [27] the same finding has been established for the nitrosation of both morpholine and aniline; the greater catalytic effect of thiocyanate ion over bromide ion arising from the larger equilibrium constant for NOSCN formation compared with NOBr. This is in line with what we found here for the *S*-nitrosation of RSH where NOBr is *ca.* 50 times more reactive than NOSCN.

Collected rate constants are shown in Table 5 for nitrosation by NOY of MeOH, RSH, and (for comparison

TABLE 5

Rate constants for nitrosation by NOY

Reagent	Substrate	k_4/l mol^{-1} s^{-1}	Temp. (°)
NOCl	MeOH	2.1×10^5	25
NOBr	MeOH	2.0×10^4	25
NOCl	MeOH	5.5×10^4	0
NOBr	MeOH	3.6×10^3	0
NOCl	RSH	2.6×10^6	31
NOBr	RSH	1.4×10^5	31
NOSCN	RSH	3.0×10^3	31
NOCl	$C_6H_5NH_2$	2.2×10^9	25
NOBr	$C_6H_5NH_2$	1.7×10^9	25
NOSCN	$C_6H_5NH_2$	1.1×10^7	31

purposes) $C_6H_5NH_2$.[18,27] The values for methanol and the thiol are well below the values for aniline for all three reactions. The NOCl and NOBr values for aniline are believed to be near or at the diffusion limit. However, because aniline is very largely protonated in the dilute acid solution usually employed for these nitrosations, whereas MeOH and RSH are not, the *overall* reactivity difference is by no means as large as is given by the values in Table 5. For example, k_0 for the NOBr reaction can readily be calculated from equation (11) for both MeOH and RSH, and k_0 for the NOBr reaction of aniline from equation (12), which includes K_A the dis-

sociation constant for the anilinium ion, but not a term

$$k_0 = k_4 K_{NOY} K_A [\text{Amine}]_{total} [Y^-] \qquad (12)$$

in $[H^+]$. The relative *overall* reactivity, as given by the ratio of the k_0 values for aniline and RSH, for equal concentrations of total amine and thiol, at some bromide ion concentrations and typically at 0.1M-H^+, is then 1.7×10^9 $K_A/1.4 \times 10^5 \times 0.1$ which is only *ca.* 4 (ignoring the uncatalysed reaction). At higher acidities the ratio would be even smaller and the thiol could be the more reactive overall.

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