Denitrosation of *N*-Methyl-*N*-nitrosotoluene-*p*-sulphonamide in Acid Solution

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N-Methyl-*N*-nitrosotoluene-*p*-sulphonamide (MNTS) undergoes quantitative denitrosation in dilute aqueous acid solution, to give *N*-methyltoluene-*p*-sulphonamide (MTS) and nitrous acid. The reaction is first order both in MNTS and acid, and zero order in added chloride, bromide, and thiourea. The rate of reaction is unaffected by the addition of nitrous acid traps such as sulphamic acid, and is also unchanged by the addition of MTS. From rate measurements in D_2SO_4–D_2O, the kinetic isotope effect $k_H : k_D$ was found to be 1.5. General acid catalysis was observed for dichloroacetic acid reactions. The observations are best fitted to a mechanism in which the proton transfer from the solvent to the reactant MNTS is rate limiting. Loss of NO^+ from the conjugate acid occurs either unimolecularly or by reaction with a nucleophile (such as bromide ion): it is not possible to distinguish between these alternatives. The results are very similar to those obtained for the denitrosation pathway of *N*-nitroso-amides, and contrast with those found for the denitrosation of *N*-nitroso-amines, where the protonation is fast, and nucleophilic catalysis is observed. The dominating effect in the present work appears to be the strong electron-withdrawing effect of the SO_2 group.

DENITROSATION of aromatic *N*-nitroso-amines has been shown [1,2] to occur in acid solution by rate-determining attack of a nucleophile Y[Cl^-, Br^-, I^-, SCN^-, $CS(NH_2)_2$, H_2O] at the nitroso-nitrogen atom of the amino-protonated form of the nitroso-amine (Scheme 1). The reaction is very sensitive to the nature of Y; a factor of 15 000 covers the reactivity range of chloride to iodide, and the rate constants correlate well with the nucleophilicity parameters of Pearson.[3] Normally the denitrosation is reversible, but this can be prevented if the reaction mixture contains enough of a nitrite trap (such as sulphamic acid, sodium azide, urea, *etc.*) to ensure that k_2[Nitrite trap] $\gg k_{-1}$[PhNHMe]. The solvent isotope effect $k_H : k_D$ was *ca.* 0.3, as expected for a scheme involving a rapid pre-equilibrium formation of a small concentration of the conjugate acid. The effects of various substituents have been discussed [4] in terms of their effects upon K and k_1.

$$\mathrm{PhN(Me)NO} + \mathrm{H_3O^+} \overset{K}{\rightleftharpoons} \mathrm{PhNH(Me)NO^+} + \mathrm{H_2O} \quad \text{fast}$$

$$\mathrm{PhNH(Me)NO^+} + \mathrm{Y^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{PhNHMe} + \mathrm{NOY}$$

$$\mathrm{NOY} + \text{nitrite trap} \xrightarrow{k_2} \text{various products} \quad \text{fast}$$

SCHEME 1

On the other hand, the denitrosation pathway (which

[1] I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1975, 107.

[2] D. L. H. Williams, *J.C.S. Chem. Comm.*, 1975, 375.

[3] R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, 1968, **90**, 319.

[4] I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1976, 691.

accompanies deamination) of *N*-nitroso-amides [5,6] shows somewhat different characteristics. There is no catalysis by added halide ions, and the solvent isotope effect $k_H : k_D$ is 1.9. These results were interpreted in terms of a rate-limiting proton transfer from the solvent to the nitroso-amide, with unimolecular loss of NO^+ from the conjugate acid. The difference in behaviour between the nitroso-amines and -amides can readily be explained in terms of the much reduced basicities of the latter.

This paper reports the results of a kinetic study of the decomposition of an *N*-nitrososulphonamide. These compounds are widely used as a convenient source of diazoalkanes, by their reaction with strong base,[7] and are also, in common with many *N*-nitroso-compounds, important biologically.[8] Relatively little is known of their behaviour in acid solution; it appears of interest to establish the mechanism of the reaction and to make a comparison with the corresponding reactions of *N*-nitroso-amides.

EXPERIMENTAL

Commercial samples of *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (MNTS) and *N*-methyltoluene-*p*-sulphonamide (MTS) were recrystallised (from light petroleum, b.p. 40—60°, and aqueous ethanol respectively) before use in the kinetic experiments. Dichloroacetic acid was purified by distillation. Rate measurements were carried out spectrophotometrically at 31°, usually by noting the decreasing absorption due to the reactant at 260 nm with time. A typical run is given in Table 1, for the reaction of MNTS (2×10^{-4}M) in D_2SO_4 (0.12M) in D_2O, containing sulphamic acid (3×10^{-3}M). Good first-order behaviour was found for all the runs; the k_0 values were reproducible within ±4%.

TABLE 1

t(30 s units)	0	1	2	3	4	5	6
Optical density	0.947	0.823	0.721	0.637	0.574	0.520	0.474
$10^4 k_0/s^{-1}$		69.4	69.9	70.5	69.4	69.4	70.1
t(30 s units)	7	8	9	10	11	12	∞
Optical density	0.439	0.410	0.386	0.368	0.532	0.340	0.287
$10^4 k_0/s^{-1}$	69.9	70.0	70.3	69.9	70.2	70.0	

The total nitrous acid liberated was determined for some runs by the addition of an excess of *p*-toluidine to the reaction mixture at the start of the reaction. After ten half-lives, a sample was added to a solution of the sodium salt of 2-naphthol-3,6-disulphonic acid in borax. The optical density of the resulting azo-dye was measured at 500 nm (log ε 4.32). Values of 96—98% yield of nitrous acid were obtained, based on the initial MNTS concentration. The yield of MTS was determined spectrophotometrically from the reaction solution after 10 half-lives and using a standard solution of MTS. The yields were virtually quantitative and there was no indication of the presence of any of the corresponding sulphonic acid.

RESULTS AND DISCUSSION

The yields of both nitrous acid and MTS from the reaction of MNTS in acid solution are virtually 100%, so there is no counterpart here to the deamination reaction which accompanies (and sometimes dominates) the denitrosation of *N*-nitroso-amides. Denitrosation of the nitroso-sulphonamide is thus quantitative over the acid range studies. The variation of the first-order rate constant k_0 (defined by $-d[MNTS]/dt = k_0[MNTS]$) with the acidity of the medium is shown in Figure 1 for a number of different acids. Clearly the reaction is first order in acid, but there are significant differences in the slopes of the lines (*i.e.* in the second-order rate constant $k_{NO} = k_0/[Acid]$) between HCl, H_2SO_4, and $HClO_4$ + $NaClO_4$ (at constant ionic strength of 1.0M). The line for $HClO_4$ without added salt follows quite closely that for HCl. Values of k_{NO} are 0.079 1 mol^{-1} s^{-1} for $HClO_4$ + $NaClO_4$, and 0.053 for $HClO_4$ alone. MNTS is much more reactive towards denitrosation than are *N*-methyl-*N*-nitrosoaniline, *N*-n-butyl-*N*-nitrosoacetamide, [5] and *N*-nitroso-2-pyrrolidine.[6] Table 2 shows the effect of added nucleophiles, sulphamic acid, and MTS upon the observed first-order rate constant, for reaction in 0.166M-HCl. It is clear that k_0 is independent both of added sulphamic acid (a well-known and efficient nitrous acid trap) [9] and of added MTS, which indicates that the denitrosation is essentially irreversible under these conditions, even in the absence of a nitrous acid trap. There is

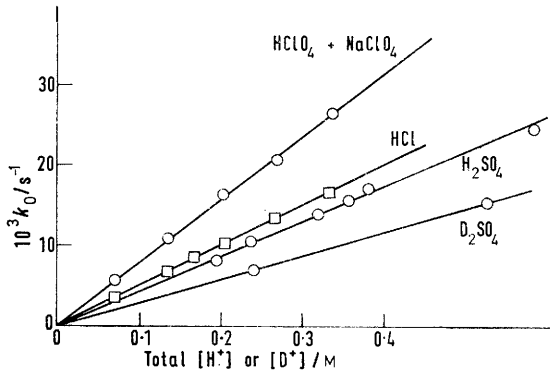

FIGURE 1 Variation of k_0 with $[H^+]$ for the decomposition of MNTS in a number of acids

TABLE 2

Effects of added nucleophiles, sulphamic acid, and MTS on the reaction rate constant

[Nucleophile]/M	[Sulphamic acid]/M	[MTS]/M	$10^4 k_0/s^{-1}$
			81
	3×10^{-3}		86
		1×10^{-3}	81
		2×10^{-3}	81
0.10 Cl^-	3×10^{-3}		88
0.20 Cl^-	3×10^{-3}		91
0.15 Br^-	3×10^{-3}		89
0.29 Br^-	3×10^{-3}		85
4×10^{-3} thiourea	3×10^{-3}		85

[5] C. N. Berry and B. C. Challis, *J.C.S. Perkin II*, 1974, 1638.
[6] B. C. Challis and S. P. Jones, *J.C.S. Perkin II*, 1975, 153.
[7] J. de Boer and H. J. Backer, *Org. Synth.*, 1954, **34**, 96.
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[9] D. L. H. Williams, *J.C.S. Perkin II*, 1975, 655.

also no catalysis by added chloride ion, bromide ion, or thiourea. By way of comparison with *N*-methyl-*N*-nitrosoaniline, the same concentration of added thiourea gave in that case a rate increase of *ca.* 13 fold. Here the absence of catalysis implies *either* that the bimolecular reaction between the nucleophile and the conjugate acid occurs after the rate-limiting step, *or* that the loss of NO^+ occurs unimolecularly. Reaction is slower in D_2SO_4–D_2O than in H_2SO_4–H_2O by a factor of 1.5 as shown in Figure 1. A similar value was obtained for $k_H : k_D$ in DCl–D_2O. This result in itself argues against a fast pre-equilibrium formation of the protonated form of the nitroso-sulphonamide, but rather suggests that the proton transfer is in fact rate-limiting here. These results are very similar to those obtained for the denitrosation of the *N*-nitroso-amides,[5,6] except that the nitroso-sulphonamides appear to react much faster. Scheme 2 represents the two possible mechanisms; alternative (a) represents unimolecular loss of NO^+ and (b) the bimolecular reaction. In the absence of added nucleophiles it is to be expected that the solvent acts as the nucleophile in alternative (b), as has been suggested for the nitroso-amine reactions.[1] For the H_3O^+ reaction, alternative (a) leads to an expression for k_o given by equation (1), which accommodates the experimental

$$RSO_2N(Me)NO + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RSO_2\overset{+}{N}H(Me)NO + H_2O$$

$$RSO_2N(Me)NO + HA \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} RSO_2\overset{+}{N}H(Me)NO + A^-$$

$$\text{(a)}\ RSO_2\overset{+}{N}H(Me)NO \xrightarrow{k_2} RSO_2NHMe + NO^+$$

$$\text{(b)}\ RSO_2\overset{+}{N}H(Me)NO + Y^- \xrightarrow{k_2'} RSO_2NHMe + NOY$$

SCHEME 2

$$k_0 = k_1k_2[H_3O^+]/[k_{-1} + k_2] \quad (1)$$

$$k_0 = k_1k_2'[H_3O^+][Y^-]/(k_{-1} + k_2'[Y^-]) \quad (2)$$

$$k_0 = k_1[H_3O^+] \quad (3)$$

results, whereas (b) leads to equation (2), which accounts for the zero-order behaviour in Y^- only if $k_2'[Y^-] \gg k_{-1}$, *i.e.* (2) becoming equation (3). Challis and Jones [6] preferred a reaction scheme involving unimolecular loss of NO^+ in the nitroso-amide case, on the basis of the independence of the rate constant upon the concentration of the nitrous acid trap. If the rate of the reverse reaction, *i.e. N*-nitrosation of the amide or sulphonamide, is negligibly slow compared with the denitrosation, then the presence of a nitrous acid trap should have no effect upon the rate of denitrosation, as we have found.

General acid catalysis is operative here, as for the nitroso-amides. The variation of k_o with [HA] at constant pH is shown in Figure 2 for the decomposition of MNTS in dichloroacetic acid (with a buffer ratio [HA]/[A^-] of 1.0). Clearly k_o is proportional to [HA] over the range studied. Here alternatives (a) and (b) in Scheme 2 lead to equations (4) and (5) respectively, which must take the limiting forms (6) and (7) to account for the linear dependence of k_o upon [HA], *i.e.* $k_2 + k_{-1} \gg k_{-1}'[A^-]$, and $k_2'[Y^-] \gg k_{-1} + k_{-1}'[A^-]$. If $k_2 \gg k_{-1}$ then equations (6)

$$k_o = \frac{k_1k_2[H_3O^+] + k_1'k_2[HA]}{k_{-1} + k_2 + k_{-1}'[A^-]} \quad (4)$$

$$k_o = \frac{k_1k_2'[H_3O^+][Y^-] + k_1'k_2'[HA][Y^-]}{k_{-1} + k_{-1}'[A^-] + k_2'[Y^-]} \quad (5)$$

$$k_o = \frac{k_1k_2[H_3O^+]}{k_{-1} + k_2} + \frac{k'k_{12}[HA]}{k_{-1} + k_2} \quad (6)$$

$$k_o = k_1[H_3O^+] + k_1'[HA] \quad (7)$$

and (7) are identical, but even if this is not the case, no experimental distinction can be made between these two equations, and hence between the two alternative mechanisms (a) and (b). The intercept in Figure 2 at [HA] = 0 is 31×10^{-4} s^{-1}, which agrees reasonably well with that calculated (39×10^{-4} s^{-1}) on the basis of the pH of the solution. The slope of line gives k_{NO} for dichloro-

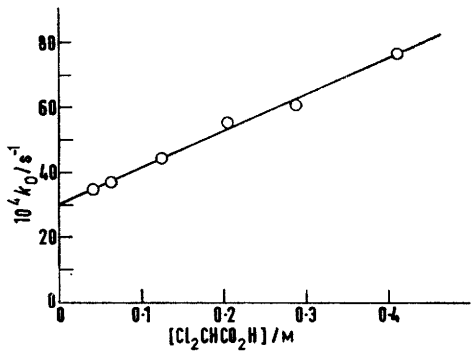


FIGURE 2 Variation of k_o with $[Cl_2CHCO_2H]$ for the decomposition of MNTS in dichloroacetic–dichloroacetate buffer (buffer ratio 1.0)

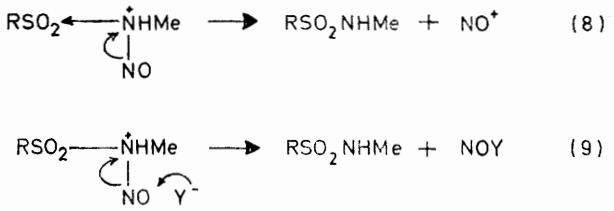
acetic acid (with added $NaClO_4$ to constant ionic strength of 1.0M) as 0.011 l mol^{-1} s^{-1}, compared with 0.079 l mol^{-1} s^{-1} for H_3O^+; this ratio of reactivities of 7.2 compares favourably with the value of 6.4. found for the nitroso-amides. We do not observe the levelling-off of k_0 at high [HA] noted for the nitroso-amides, and interpreted as a change towards another limiting form as $k_{-1}'[A^-]$ becomes larger. It is likely that activity effects might intervene if we extended our results to much larger [HA].

General acid catalysis is also demonstrated by the linearly decreasing value of k_o as [A^-] (dichloroacetate) is increased for $HClO_4$ = 0.336M. Under these circumstances the salt is virtually completely converted into the acid form. The decrease in k_0 is much less than that expected merely by the corresponding reduction in the acidity.

In an acetic acid–acetate buffer, reaction was very slow, *e.g.* $k_o = 0.48 \times 10^{-4}$ s^{-1} for 0.62M-HA and buffer ratio 1.0. Under these conditions reaction *via* H_3O^+ is negligible [k_o(calc) 9×10^{-7} s^{-1}].

The strong electron-withdrawing effect of the SO_2 group must be responsible for the high reactivity of MNTS towards denitrosation. Loss of NO^+ from the conjugate

acid, whether it occurs unimolecularly (8) or by reaction with Y^- (9), now occurs so rapidly that this step is no longer rate limiting as it was for the nitroso-amines. Our



results cannot distinguish between the two possible mechanisms, although it is perhaps to be expected that a bimolecular reaction occurs, as the denitrosation of the nitroso-amines is so susceptible to the reactivity of the nucleophile. On the other hand, it could well be that the N–N bond is weakened to such an extent by the SO_2 electron withdrawal that there is extensive bond breaking in the transition state, *i.e.* it resembles the final state, and no nucleophilic catalysis results.

The kinetic isotope effect ($k_H : k_D = 1.5$) is perhaps smaller than that expected for a rate-limiting proton transfer, although it is comparable with that found for the nitroso-amide reactions.[5,6] It may well be that the transition state for protonation is very unsymmetrical with extensive N–H bond formation.

The amino nitrogen atom in MNTS is expected to have an extremely low basicity. Benzenesulphonamide itself has a pK_a value [10] of *ca.* −7; the nitroso-group is expected to reduce this figure by several units. There is, however, general agreement in the literature [11] concerning the site of protonation (contrasting with the situation for the protonation of amides); all authors agree that protonation occurs at the nitrogen atom.

There are a few references in the literature in which MNTS is used as a nitrosating agent. Schulz and McCalla [12] carried out the reaction of MNTS with cysteine and obtained cystine and nitrous oxide. The first step is assumed to be the *S*-nitrosation of cysteine to form an intermediate of the type NO–$\overset{+}{S}<$, which then undergoes a series of rapid reactions. No claim was made as to whether the initial step occurred directly in a bimolecular process or *via* the prior formation of nitrous acid. The results described in this paper would support the latter mechanism, although unpublished work [13] has shown that cysteine has a nucleophilic reactivity towards the protonated form of *N*-nitroso-amines, which lies between that of the chloride ion and bromide ion. McCalla *et al.*[8] have measured the rates of decomposition of MNTS and other nitro-amines in acid solution, with a view to relating the hydrolysis rates with the biological activity of these compounds. They obtained a value of 6.3×10^{-2} l mol^{-1} s^{-1} for the second-order rate constant for reaction at 37° which agrees well with our value of 5.0×10^{-2} l mol^{-1} s^{-1} for reactions in hydrochloric acid at 31°.

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[13] D. L. H. Williams, unpublished work.