A Kinetic Investigation of the Thionitrite from (±)-2-Acetylamino-2-carboxy-1,1-dimethylethanethiol as a Possible Nitrosating Agent

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In strongly aqueous acid solution (±)-2-acetylamino-2-carboxy-1,1-dimethylethyl thionitrite (RSNO) undergoes denitrosation to give the corresponding thiol. The reaction is reversible and normally lies well over on the side of the thionitrite, but can proceed in the denitrosation direction in the presence of traps for free nitrous acid such as added sodium azide or sulphamic acid. At sufficiently high trap concentration to ensure complete irreversibility, the reaction was found to be first-order in RSNO and acid-catalysed; the observed reaction rate constant is approximately proportional to h_0. Catalysis was observed by Cl^-, Br^-, SCN^-, and $SC(NH_2)_2$ and the second-order rate constants were 4.6×10^{-3}, 13.0×10^{-3}, 34×10^{-3}, and 27×10^{-3} l mol^{-1} s^{-1}, respectively. The order of reactivity is as expected with the exception of that of thiourea. *N*-Methyl-4-nitroaniline was converted quantitatively to the corresponding nitrosamine by RSNO, but in the presence of added sodium azide, no nitrosamine was detected; this shows that RSNO like nitrosamines generally and alkyl nitrites, acts as a nitrosating agent towards amines *etc.*, under these experimental conditions, by prior hydrolysis or *via* nitrosyl halide *etc.* formation. A kinetic analysis has enabled the reactivity of the nitrous acid traps hydrazoic acid and sulphamic acid to be established quantitatively.

THIONITRITES, RSNO, are much less commonly encountered than are their oxygen analogues, the nitrites, and their chemistry has not been extensively examined. Although they are generally less robust than are the corresponding nitrites, several examples of the class are known. The thionitrites derived from primary thiols are difficult to handle, but reddish brown *S*-nitroso-derivatives of cysteine [1] and of *N*-acetylcysteine methyl ester [2] have been described. Thionitrites derived from tertiary thiols are more stable. Thus trityl thionitrite has been prepared as a green crystalline solid by nitrosation of the corresponding thiol with acidified sodium nitrite [3] and with ethyl nitrite.[4] It can be stored at 0 °C for several days without decomposition.[5] t-Butyl thionitrite has also been described.[6] Thermal decomposition of thionitrites is believed to involve homolytic cleavage to give nitric oxide and the free radical RS which can abstract a hydrogen atom from the solvent yielding the thiol, or dimerise to give the disulphide.[5] Trifluoromethyl thionitrite decomposes very rapidly at room temperature but slowly at —78 °C, to give the disulphide and nitric oxide.[7] Photolysis of thionitrites in the presence of alkenes give *C*-nitroso-compounds and nitroxides.[8] Recently a number of aryl and alkyl thionitrites have been made from thiols and dinitrogen tetroxide and their reactions have been studied.[8] Treatment with secondary amines gave nitrosamines, with sulphinic acids gave unsymmetrical thiosulphonates, and with alcohols gave alkyl nitrites. There appears to be no previous studies of kinetics and mechnism in this series.

A particularly stable thionitrite (II) has recently been prepared and characterised (including an *X*-ray crystal analysis) by Field and his co-workers [9] from (±)-2-acetylamino-2-carboxy-1,1-dimethylethanethiol (I) by reaction with sodium nitrite and methanolic hydrogen chloride. The thionitrite (II) (henceforth called RSNO)

$$\underset{\text{(I)}}{\mathrm{HSCMe_2CH(NHAc)CO_2H}} \xrightarrow{\mathrm{HNO_2}} \underset{\text{(II)}}{\mathrm{ONSCMe_2CH(NHAc)CO_2H}}$$

is a deep green solid and is apparently indefinitely stable in the solid form, but decomposes slowly in solution. Some reactions of (II) were reported by Field and his co-workers; [9] some were clearly derived from an initial homolysis, but others were presumed to be heterolytic, including the formation of the nitrosamine from *N*-methylaniline and the diazonium ion from aniline.

It was thought to be of interest to examine in more mechanistic detail the chemistry of thionitrites, particularly with respect to transnitrosation reactions involving amines. The stable thionitrite (II) lends itself particularly well to this study, which has some bearing on the fate of ingested nitrite derived, for example, from foods and naturally occurring waters.[10] It is important to consider the possible *S*-nitrosation of thiols of this type and the subsequent reactions, if any, of the derived thionitrites. Nitrosations brought about by nitrosamines [11] and also by alkyl nitrites [12] have been examined kinetically and it has been shown that in acid solution denitrosation occurs for both substrates by nucleophilic attack of the protonated reactant by the non-basic nucleophiles Cl^-, Br^-, SCN^-, and $SC(NH_2)_2$ as well as the solvent; the situation regarding thionitrites has never been examined. We report in this paper the results of the study with (II) and make direct comparisons with the reactions of alkyl nitrites and nitrosamines.

EXPERIMENTAL

The thionitrite (II) derived from (I) was prepared as described by Field *et al.*[9] All reagents used were of the highest purity grade available. Kinetic measurements were carried out at 31 °C using a recording spectrophotometer, following the disappearance at the fixed wavelength of 338 nm, of the absorption due to (II). Because of the relative instability of (II) in stock solutions, *e.g.* in methanol, each kinetic run was started by weighing out a suitable quantity of the green solid, adding dioxan (1 ml) (for rapid dissolution), then adding the acid solution containing sodium azide *etc.* and sodium chloride *etc.* when necessary. Typical reaction conditions were: sulphuric acid (3M), sodium azide (1.7×10^{-2}M), sodium chloride (0.346M), and the thionitrite (1.4×10^{-3}M), total volume 21 ml. A portion of this reaction mixture was rapidly transferred to a u.v. cell and placed in the spectrophotometer. Good first-order kinetics were obtained throughout, over at least two half-lives of each reaction.

RESULTS AND DISCUSSION

Denitrosation of (II) occurred in acid solution. The reaction is, however, reversible with the equilibrium [equation (1)] lying well over to the side of the thionitrite.

$$RSNO + H_2O \overset{H^+}{\rightleftharpoons} RSH + HNO_2 \qquad (1)$$

This contrasts markedly with the corresponding situation of the nitrosation of alcohols [13,14] where, for example for methanol, the equilibrium constant for the formation of the alkyl nitrite is *ca.* 1—2. Since for RSNO the equilibrium is so far over to one side, it is not possible to treat the system kinetically as an equilibrium situation and obtain rate constants for the forward and reverse reactions simultaneously, as was achieved for the alcohols; [13] the two reactions have thus to be examined separately. The nitrosation of (I) has been studied at low acidity, where the rate of the reverse reaction (denitrosation) is negligible. The results will be discussed elsewhere.[15] Denitrosation can be studied if a nitrous acid trap is included to prevent the reverse reaction. Such traps, used before in nitrosamine denitrosations,[11,16] include sodium azide, hydrazine, sulphamic acid, hydroxylamine, ascorbic acid, aniline derivatives, and urea. In the present work we have used sodium azide and sulphamic acid only. For convenient reaction rates, the denitrosations of RSNO have been carried out at relatively high acid concentrations of 1—4M-H_2SO_4. Under these conditions and in the presence of excess added sodium azide, denitrosation occurs as measured by the disappearance of the absorption at 338 nm. The product has the same u.v. spectrum as the thiol (I) but cannot be determined quantitatively because of its relative instability, presumably to oxidation in these solutions.

Figure 1 shows the dependence of the observed first-order rate constant k_0 {defined by $-d[(II)]/dt = k_0[(II)]$} upon the concentration of added sodium azide, for reaction in 3.1M-H_2SO_4 containing 0.2M-Br^-. It is apparent that k_0 increases at first with increasing [NaN_3], soon levelling off and becoming independent of [NaN_3]. This behaviour is consistent with the mechanism given in the Scheme. At high [HN_3], the limiting case $k_2[HN_3] \gg k_{-1}[RSH]$ applies, so that effectively denitrosation is irreversible. Similar behaviour was found when using sulphamic acid as a trap for nitrous acid, when the same limiting value of k_0 was obtained at the same acidity and bromide ion concentration. The curve however was, as expected, different from the azide curve because it is known [16] that sulphamic acid is generally a less efficient trap than is hydrazoic acid, the concentration of sulphamic acid necessary to achieve the zero-order dependence being greater than the necessary concentration of added sodium azide.

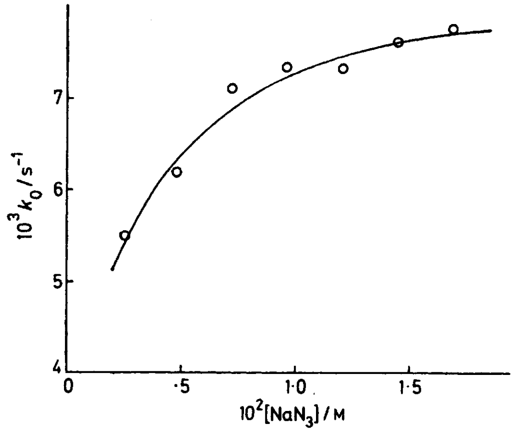

FIGURE 1 k_0 as a function of [added NaN_3] for the denitrosation of RSNO

$$RSNO + H^+ \rightleftharpoons R\overset{+}{S}HNO \underset{k_{-1}}{\overset{k_1,\ Br^-}{\rightleftharpoons}} RSH + NOBr$$

$$NOBr + HN_3 \xrightarrow{k_2} N_2 + N_2O + Br^- + H^+$$

SCHEME

The general equation for the first-order rate constant k_0 from the Scheme is given by equation (2). This assumes an initial rapid protonation of the thionitrite, probably at the sulphur atom; we have assumed for simplicity that this equilibrium (equilibrium constant K) follows the Hammett acidity function h_0. The equation includes the general nucleophile Y^- [= Cl^-, Br^-, SCN^-, $SC(NH_2)_2$, or H_2O]. At the limiting condition at high [HN_3], the equation reduces to equation (3). We have

$$k_0 = \frac{k_1Kh_0k_2[Y^-][HN_3]}{k_{-1}[RSH] + k_2[HN_3]} \qquad (2)$$

$$k_0 = k_1Kh_0[Y^-] \qquad (3)$$

examined the nucleophilic reactivity of Y^- by noting the variation of k_0 with [Y^-] for the range of nucleophiles indicated. Each shows good first-order dependence over the concentration range, as is shown in Figure 2. There is a substantial common positive intercept to each line, showing that there is a significant contribution by the solvent-promoted reaction. The slopes of the lines (for reactions at constant acidity) give a measure of the second-order rate constants (k_1) for the nucleophilic attack by Y^- and are shown in Table 1. The values increase in the expected order [17] of nucleophilicity, except that thiourea appears to be less reactive than expected; this may be due to a steric effect. There is a reasonable correlation between the reactivity [as measured by log-

(slope)] and the Pearson nucleophilicity parameter *n*. Reaction also occurred with *N*-methyl-4-nitroaniline (as a typical amine) to give quantitatively (in the absence of a nitrous acid trap) the corresponding nitrosamine which was measured spectrophotometrically. However, in the presence of the nitrous acid trap of added sodium azide, no nitrosamine is produced at all, showing that nitrosation of amines in this reaction occurs by prior denitrosation of the thionitrite, and conventional *N*-nitrosation *via* free nitrous acid. Thus, in common with nitrosamines generally and also alkyl nitrites, direct nitrosation of amines does not seem to occur, but rather can only be achieved by attack by a relatively strong non-basic nucleophile such as halide ion *etc.*, in these strongly acid solutions.

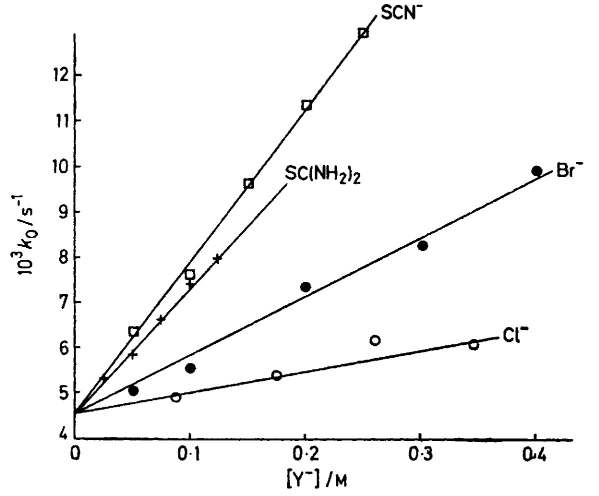

FIGURE 2 k_0 as a function of [Nucleophile] for the denitrosation of RSNO

TABLE 1

The slopes of plots of k_0 *versus* [Nucleophile] for reaction of RSNO in H_2SO_4 (3M) at 31 °C

Nucleophile	Slope of k_0 *versus* [Nucleophile] ($l\ mol^{-1}\ s^{-1}$)
Cl^-	4.6×10^{-3}
Br^-	13.0×10^{-3}
$SC(NH_2)_2$	27×10^{-3}
SCN^-	34×10^{-3}

Acid catalysis is to be expected from the Scheme and equation (3). Table 2 shows k_0 as a function of the acidity in sulphuric acid solution containing added sodium azide (1.7×10^{-2}M) but no added nucleophile. Clearly the reaction is strongly acid-catalysed, and a plot of log k_0 *versus* the Hammett acidity function H_0 gives a good line of slope −0.9, which shows that the protonation of the thionitrite is adequately expressed by this acidity function. Comparison of these results with those for denitrosation of methyl nitrite,[13] shows that the alkyl nitrite undergoes denitrosation *ca.* 10^6 times more rapidly than does RSNO. This effect may be due in part to a steric effect, since we are here comparing a primary and a tertiary system, but it is likely that the major effect lies in the size of the equilibrium constant for protonation of RONO and RSNO. It is known [18] that the pK_a values for diethyl ether and diethyl sulphide are respectively −2.39 and −6.8; a large difference in the direction expected for the much reduced reactivity of the thionitrite over the alkyl nitrite.

TABLE 2

Acid catalysis in the denitrosation of RSNO with no added nucleophile at 31 °C

$[H_2SO_4]$/M	10^4k_0/s^{-1}
0.94	3.21
1.58	7.98
2.20	14.4
3.08	42.1
3.77	81.7
4.35	143

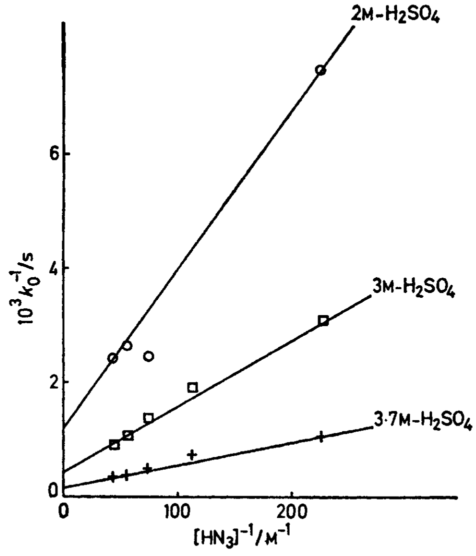

FIGURE 3 Double reciprocal plots k_0^{-1} *versus* $[HN_3]^{-1}$

The more general form of the rate equation [equation (2)] can be tested quantitatively by measuring k_0 values as a function of $[HN_3]$ at constant acidity and $[Y^-]$, and also in the presence of an excess of added RSH, so that [RSH] is effectively constant during any one kinetic run. The double reciprocal plot of k_0^{-1} *versus* $[HN_3]^{-1}$ should

$$k_0^{-1} = \frac{k_{-1}[RSH]}{k_1Kh_0k_2[Y^-][HN_3]} + \frac{1}{k_1Kh_0[Y^-]} \qquad (4)$$

be linear with a positive slope and intercept [see equation (4)]. Such plots are shown in Figure 3 for reaction at three different acid concentrations for the solvent-promoted denitrosation with a known excess of [RSH] present. As expected the slopes and intercepts decrease as the acidity is increased. This procedure enables the rate constant ratio k_{-1}/k_2 to be evaluated in each case since k_{-1}/k_2 = slope/intercept [RSH], the values obtained are laid out in Table 3 together with the appropriate $k_1Kh_0[Y^-]$ values ($Y^- = H_2O$ in this case). As expected the $k_1Kh_0[Y^-]$ results increase with increasing acidity and the k_{-1}/k_2 ratios are reasonably constant at *ca.* 1.9 for HN_3. This figure demonstrates that RSH is slightly

TABLE 3

Results from the double reciprocal plots

Trap	$[H_2SO_4]/M$	$k_1Kh_0[Y^-]$	k_{-1}/k_2
HN_3	2.0	9.1×10^{-4}	1.8
HN_3	3.0	2.5×10^{-3}	2.1
HN_3	3.7	6.2×10^{-3}	1.7
NH_2SO_3H	3.3	3.9×10^{-3}	55

more reactive than HN_3 towards free nitrous acid. Hitherto hydrazoic acid has been regarded [19] as the most effective trap known for nitrous acid. Clearly sulphur-containing species such as thiols present another range of species which can act *via* *S*-nitrosation as very efficient nitrous acid scavengers. Table 3 also includes the result of a double reciprocal plot analysis using sulphamic acid as the nitrous acid trap; at one acidity ($3.3M-H_2SO_4$) the $k_1Kh_0[Y^-]$ value of $3.9 \times 10^{-3}\ s^{-1}$ agrees very well with the interpolated value ($3.8 \times 10^{-3}\ s^{-1}$) from the HN_3 results for this acidity. The k_{-1}/k_2 ratio of 55 indicates that HN_3 is more reactive towards free nitrous acid than is sulphamic acid by a factor of 55/1.9, *i.e. ca.* 29. This result agrees quite well with an earlier report [19] of *ca.* 40 obtained from kinetic measurements of denitrosation of nitrosamines at somewhat higher acidity ($4.8M-H_2SO_4$). All our results are therefore consistent with the outline mechanism given in the Scheme.

We thank the Cancer Research Campaign for a research studentship to S. L. O.

[1/1098 *Received*, 13*th July*, 1981]

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