The Nitrosation of *NN'*-Dialkylthioureas

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The reaction between nitrous acid and *NN'*-dimethylthiourea and imidazolidine-2-thione (ethylenethiourea) involves a rapid, reversible initial nitrosation at sulphur, followed by a slower transfer of the nitroso group to the secondary amino group to form an *N*-nitrosothiourea. The kinetics exclude the possibility of the *N*-nitroso compound being formed by direct *N*-nitrosation and require the *S*-nitroso compound to be a precursor. The conversion of the *S*-nitrosoalkylthiourea into the *N*-nitroso product involves rate-determining proton loss to form an intermediate which is partitioned between steps involving reprotonation and transfer of the nitroso group from sulphur to nitrogen.

It is well known[1] that thiourea and its alkyl derivatives react rapidly with nitrous acid to form thionitrosyl compounds containing the $>C{=}S{-}NO^+$ group which have characteristic red or yellow colours in solution. With *NN'*-dialkylthioureas the reaction products also contain secondary *N*-nitrosothioureas[2] under some conditions, $NHR{\cdot}CS{\cdot}N(NO)R$. Thionitrosyl compounds are rather unstable, and can react in a variety of ways. Reviews of their chemistry have been published by Oae *et al.*,[3] and by Williams.[4] One common reaction is the formation of disulphides and nitric oxide, as examplifed in (1) and (2) for thiourea. In this particular case the products can

$$H^+ + HNO_2 + (NH_2)_2CS \rightleftharpoons [(NH_2)_2CSNO]^+ + H_2O \quad (1)$$

$$2[(NH_2)_2CSNO]^+ \longrightarrow [(NH_2)_2CSSC(NH_2)_2]^{2+} + 2NO \quad (2)$$

be a function of acidity, as was established by the original work of Werner.[5] The disulphide and nitric oxide are formed at pH *ca.* 1, but at lower acidities the products are isothiocyanic acid and dinitrogen, presumably arising from an *N*-nitroso compound (Scheme 1). An unresolved question is the extent to which the processes of *S*- and *N*-nitrosation are related. In a study of the kinetics of formation of thiocyanate it was suggested[1] that the *S*-nitroso compound was a precursor to the *N*-nitroso compound, and that there was an S to N migration of the nitroso group. Reaction was postulated to proceed *via* the conjugate base of the thionitrosyl compound. An alternative view has been proposed by Lown, based mainly upon ^{15}N n.m.r. studies of the nitrosation of *NN'*-dialkylthioureas. Lown suggests[6] that the *N*-nitroso derivatives are produced by direct *N*-nitrosation at low acidities such as 0.05—0.1 mol dm^{-3} HCl, though he notes that the n.m.r. method imposes sensitivity limits. Lown suggests that the position of nitrosation may vary with the reaction conditions. In the nitrosation of thioproline[7] nitrosation by $[NO]^+$ occurs at sulphur, followed by an S to N migration, while with ClNO, BrNO, or NCSNO nitrosation occurs directly at nitrogen.

$$NH_2CSNHNO \longrightarrow NH_2CSN{=}NOH \longrightarrow H^+ + HNCS + N_2 + OH^-$$

Scheme 1.

$$[(NH_2)_2CSNO]^+ \underset{\text{fast}}{\rightleftharpoons} H^+ + NH_2{\cdot}C(SNO)({=}NH) \xrightarrow[\text{slow}]{} NH_2CSNHNO \quad (3)$$

In an attempt to resolve the question of whether nitrosation by $[NO]^+$ in thioureas occurs initially at nitrogen or sulphur we have carried out a detailed kinetic study of the reaction of imidazolidine-2-thione, commonly known as ethylenethiourea (ENTU), and *NN'*-dimethylthiourea (DMTU) with nitrous acid.

Experimental

Materials.—Ethylenethiourea and *NN'*-dimethylthiourea were reagent grade chemicals (Aldrich), while sodium nitrite, perchloric acid, and sodium perchlorate were AnalaR materials. All were used without further purification.

Kinetic Methods.—Rapid reactions were followed by stopped-flow spectrophotometry using a Canterbury SF-3A instrument with a 2 mm path length. The data were collected by a transient recorder and processed by computer. Slower reactions were followed on a Unicam SP8-200 or a Kontron Uvikon 820 instrument, using a thermostatted cell holder. Temperature and ionic strength were kept constant at 25 °C and 0.30 mol dm^{-3} $NaClO_4$, respectively. Rate constants were calculated by least-squares methods from the integrated form of the rate equation. Stopped-flow rate constants were typically reproducible to $\pm 4\%$, and rate constants by conventional spectrophotometry to $\pm 3\%$.

Results and Discussion

With moderately concentrated solutions of nitrous acid and *NN'*-dialkylthiourea (DATU), *ca.* 0.05—0.15 mol dm^{-3}, mixing produced a rapid initial formation of a red colour, followed by a much slower change to a yellow solution. Measurements at 420 nm showed biphasic behaviour with a rapid initial increase in absorbance to a value dependent upon both $[H^+]$ and [DATU], followed by a much slower increase to a final value independent of $[H^+]$ and [DATU], and dependent only upon the initial nitrite concentration. The initial reaction was followed by stopped-flow spectrophotometry at 420 nm with the dialkylthiourea and acid in large and constant excess over nitrous acid. The formation of the red colour followed first-order kinetics [equation (4)], where Abs represents absorbance.

$$dAbs/dt = k_{obs}(Abs_\infty - Abs) \quad (4)$$

The observed first-order rate constants k_{obs} varied with acidity

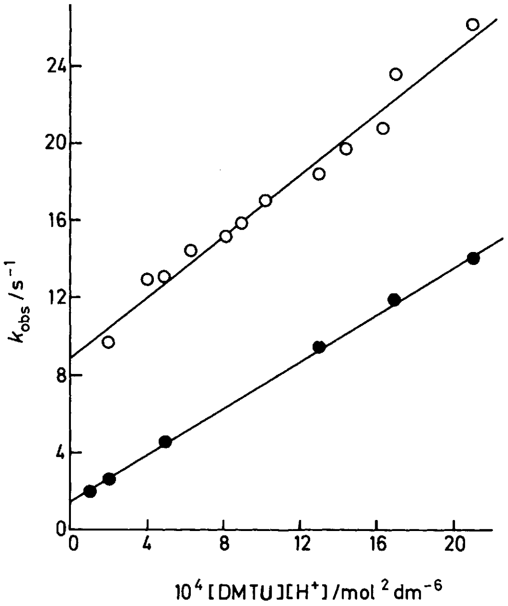


Figure 1. The influence of acidity and dialkylthiourea concentration upon k_{obs} for the initial reaction with nitrous acid at 25 °C. DMTU = *NN'*-dimethylthiourea ●; ethylenethiourea ○

and dialkylthiourea concentration, [DATU], according to equation (5). Values of k_1 were obtained from the slopes of plots

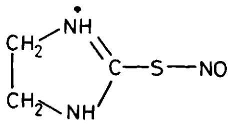
$$k_{obs} = (k_1[H^+][DATU] + k_{-1}) \qquad (5)$$

of k_{obs} *versus* [DATU] or [H$^+$]. Typical data are shown in Figure 1. For ethylenethiourea the value of k_{-1} was obtainable from the intercept of such plots; for *NN'*-dimethylthiourea the intercept was rather small, and k_{-1} was calculated from the relation $K = k_1/k_{-1}$ where K is the equilibrium constant for the formation of the thionitrosyl species. Values of K were calculable from the Abs$_\infty$ data as discussed[1] previously, on the assumption that the total stoicheiometric nitrite concentration, [nit], is the sum of the concentrations of molecular nitrous acid

$$\frac{1}{Abs_\infty} = \frac{1}{\varepsilon l[nit]} + \frac{1}{\varepsilon l K[H^+][DATU]} \qquad (6)$$

and the thionitrosyl species, with ε as the extinction coefficient and l as the path length. There is an error in the printed form of (6) in the original paper. Values of K from k_1/k_{-1} were in agreement with the directly determined values from Abs$_\infty$ measurements for ethylenethiourea. The values are set out in Table 1.

The k_1 values are similar to those observed for other reactive nucleophiles reacting with H$^+$ + HNO$_2$, and are consistent with the idea of an encounter-controlled reaction between NO$^+$ and the dialkylthiourea. The interesting feature of the k_{-1} values is the figure of 8.9 s^{-1} for ethylenethiourea. This is about an order of magnitude higher than the corresponding values found for open-chain *NN'*-dialkylthioureas. If the electronic structure of the thionitrosyl species contains a significant contribution from form (**I**), then ring strain might account for this accelerated rate of the denitrosation reaction. It might also account for the low basicity of ethylenethiourea.



(**I**)

Table 1. Kinetic and equilibrium data on *S*-nitrosated thioureas

	K^a/mol^{-2} dm^6	ε/mol^{-1} dm^3 cm^{-1}	k_1/mol^{-2} dm^6 s^{-1}	k_{-1}/s^{-1}	K^c/mol^2 dm^{-6}
ENTU	1 070 ± 11	118 ± 4	7 760 ± 400	8.9 ± 0.5	872 ± 66
	1 190^b	109^b			
DMTU	4 275 ± 66	96 ± 1	6 125 ± 85	1.45 ± 0.1	4 224 ± 300
	3 300^b	114^b	6 610^b	2.0^b	3 305^b

^{a} From equilibrium spectrophotometry. ^{b} Ref. 1. ^{c} Calculated from $K = k_1/k_{-1}$.

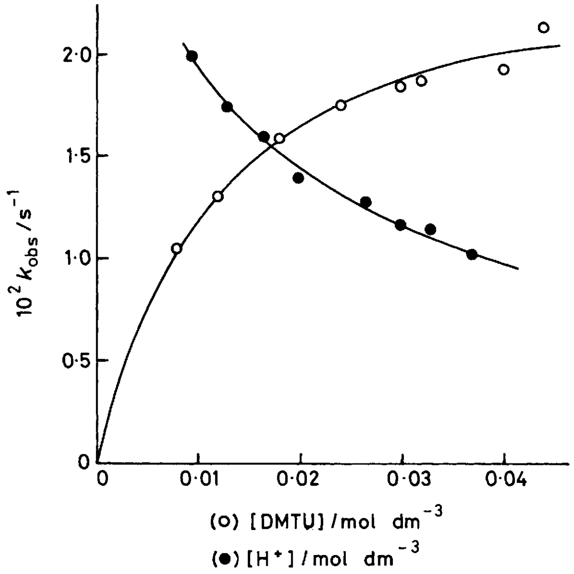


Figure 2. The influence of acidity and concentration of *NN'*-dimethylthiourea, [DMTU], upon k_{obs} for the second reaction with nitrous acid at 25 °C. [X] = [DMTU] ○; [H$^+$] ●

Turning to the second reaction, it should be noted that once again the reaction follows good first-order kinetics. The value of Abs$_\infty$ for the second reaction is independent of [H$^+$] and of the excess of *NN'*-dialkylthiourea, and the spectrum has a maximum $\lambda_{max.}$ 261 nm (ε 10 560) for ethylenethiourea and $\lambda_{max.}$ 268 nm (ε 10 360) for *NN'*-dimethylthiourea. These values agree well with those reported by Lown and Chauhan for *N*-nitrosothioureas (typically $\lambda_{max.}$ 266—270 nm, ε 11 000—12 000) and confirm that the products of the second reaction are *N*-nitrosothioureas. The disulphide [(RNH)$_2$CSSC(NHR)$_2$]$^{2+}$ which is a common product of decomposition of thionitrosyl compounds does not appear to be a significant product under our conditions. These results make it clear that the sulphurnitroso compound is formed in equilibrium amounts before the *N*-nitroso product is formed in significant amounts. This does not, in itself, show that the *S*-nitroso compound is a precursor of the *N*-nitroso species, as it might be formed in a side equilibrium (Scheme 2).

$$(NHR)_2CS + H^+ + HNO_2 \underset{fast}{\rightleftharpoons} [(NHR)_2CSNO]^+ + H_2O$$

$$H^+ + HNO_2 + (NHR)_2CS \xrightarrow[slow]{} (NHR)CS[N(NO)R] + H^+ + H_2O$$

Scheme 2.

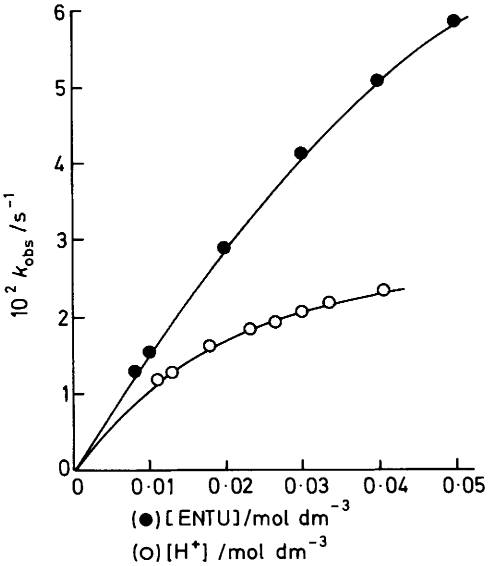


Figure 3. Influence of acidity and concentration of ethylenethiourea, [ENTU], upon k_{obs} for the second reaction with nitrous acid at 25 °C. [X] = [ENTU] ●; [H$^+$] ○

The dependence of k_{obs} upon [H$^+$] and [DATU] for the second reaction is shown in Figures 2 and 3. The dependence upon [DATU] shows an increase that is linear at low concentrations and tends to level off towards higher concentrations. The results fit equations of the form (7). The dependence upon

$$k_{obs} = \frac{a[\mathrm{DATU}]}{1 + b[\mathrm{DATU}]} \qquad (7)$$

[H$^+$] is apparently quite different for the two substrates. The data for ethylenethiourea can be fitted to an equation similar in form to (7), but with [H$^+$] replacing [DATU], but data for *NN'*-dimethylthiourea do not fit this type of expression, k_{obs} decreasing with increase of [H$^+$] over the range 0.01—0.037 mol dm^{-3}.

The simplest mechanism, a rate-determining transfer of the nitroso group from S to N, shown in (8), leads to rate equation (9). This is not satisfactory. Attempts to fit the data for

$$\mathrm{H^+ + HNO_2 + (NHR)_2CS} \underset{\text{fast}}{\overset{K}{\rightleftharpoons}} \mathrm{[(NHR)_2CSNO]^+} \xrightarrow[\text{slow}]{k_a} \mathrm{(NHR)CS[N(NO)R]} \qquad (8)$$

$$k_{obs} = k_aK[\mathrm{DATU}][\mathrm{H^+}]/(1 + K[\mathrm{DATU}][\mathrm{H^+}]) \qquad (9)$$

ethylenethiourea to (9) gives an apparently reasonable fit, but the value of K does not agree with the values obtained from the measurements of the first reaction. It does not account for the decrease in k_{obs} with increase of [H$^+$] for the dimethyl compound, and it requires k_{obs} to show the same dependence upon [DATU] as an [H$^+$], which is clearly not the case for either compound. We can at the same time dipose of the alternative view which follows from Lown's suggestion that reaction occurs through a direct *N*-nitrosation. If this were so and the rate law were to have the form normal for *N*-nitrosation reactions [equation (10)], then as [HNO$_2$]/[nit] = 1/(1 + K[DATU][H$^+$]), this would give rise to a rate equation of the same form as (9) but with k_b in place of k_aK.

$$\text{rate} = k_b[\mathrm{H^+}]\,[\mathrm{HNO_2}]\,[\mathrm{DATU}] \qquad (10)$$

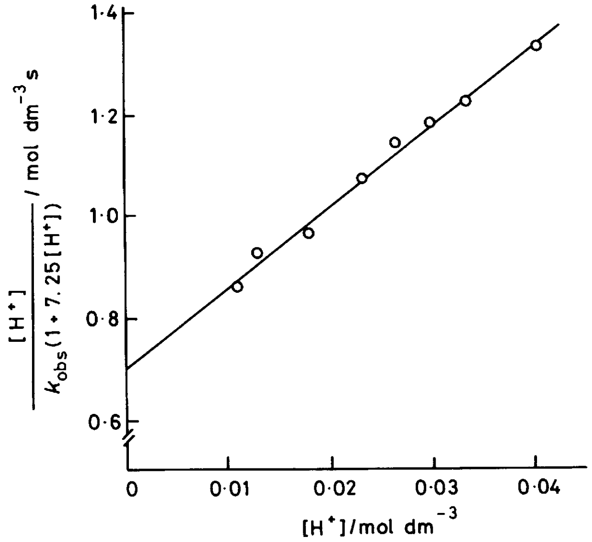


Figure 4. The influence of acidity upon k_{obs} for the second reaction of ethylenethiourea with nitrous acid, plotted as equation (13)

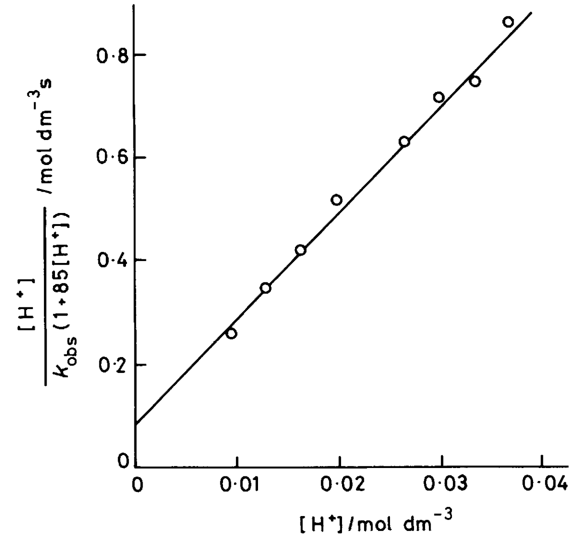


Figure 5. The influence of acidity upon k_{obs} for the second reaction of *NN'*-dimethylthiourea with nitrous acid, plotted as equation (13)

The fact that k_{obs} can decrease with increased [H$^+$] requires that there is some step that is reversed by increased acidity. It cannot be the final stage, as the results indicate that all reactions go to the same final product, the *N*-nitrosothiourea. There is no sign of decreased *N*-nitrosothiourea formation at higher acidities. The only alternative appears to be that some intermediate stage is reversed, involving the loss of a proton. As we are concerned with the conversion of [(NHR)$_2$CSNO]$^+$ to (NHR)CS[N(NO)R] + H$^+$ we can see only one plausible explanation, set out in (11). This is analogous to the mechanism

$$\mathrm{[(NHR)_2CSNO]^+} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{[(NHR)C(SNO)({=}NR)] + H^+}$$
$$\mathrm{[(NHR)C(SNO)({=}\,NR)]} \xrightarrow{k_3} \mathrm{(NHR)CS[N(NO)R]} \qquad (11)$$

proposed by Castro *et al.*[8,9] for the nitrosation of ureas and amides, and has the advantage of bringing ureas and thioureas into a common scheme. If our rate equation is modified to take

Table 2. Comparison of ureas and thioureas

	$(NHMe)_2$-CO	$(NHMe)_2$-CS	$(-CH_2NH)_2$-CO[a]	$(-CH_2NH)_2$-CS[b]
$K/mol^{-2}\ dm^6$	2.8×10^{-7}	4.3×10^3	6.6×10^{-7}	1.1×10^3
k_2/s^{-1}	10^9	1.5×10^{-1}	10^9	1.9×10^{-1}
Kk_2	280	645	660	209

[a] Imidazolin-2-one. [b] Imidazoline-2-thione.

account of (11) it becomes (12). This can be rearranged to (13) which can be plotted in a linear form. Figures 4 and 5 showed

$$k_{obs} = \frac{K[DATU][H^+]k_2k_3}{(1 + K[DATU][H^+])(k_3 + k_{-2}[H^+])} \quad (12)$$

$$\frac{[H^+]}{k_{obs}(1 + K[DATU][H^+])} = \frac{1}{K K_2[DATU]} + \frac{k_{-2}[H^+]}{K k_2 k_3[DATU]} \quad (13)$$

how well this expression fits the experimental data, using K 950 and 4 250 mol^{-2} dm^6 for ethylenethiourea and NN'-dimethylthiourea, respectively. From the intercepts and slopes of these plots the following results were obtained: ethylenethiourea k_2 0.186 ± 0.004 s^{-1}, k_3/k_{-2} 0.046 ± 0.0022; NN'-dimethylthiourea k_2 0.149 ± 0.034 s^{-1}, k_3/k_{-2} 0.003 78 ± 0.0086. The basic difference between this scheme and the one put forward earlier for thiourea is that we are proposing a partitioning of the intermediate (NHR)C(SNO)(=NR) between forward and reverse steps, whereas previously the reverse step was held to dominate so that proton loss was an equilibrium phenomenon, *i.e.* $k_{-2}[H^+] \gg k_3$. Upon re-examining the earlier data it is not possible to detect any significant drift in rate constants with acidity of the type that we have observed with NN'-dialkylthioureas. If we assume that we might have detected a 10% deviation in rate constant in the earlier work with thiourea, then this implies that for thiourea $k_3/k_{-2} < 5 \times 10^{-4}$. So far as the ratio k_3/k_{-2} for ethylenethiourea and NN'-dimethylthiourea is concerned, the back-reaction (k_{-2}) is the protonation of a base and such reactions often occur at rates close to the encounter limit, and are not very sensitive to the nature of the base. Thus we suspect the difference in the k_3/k_{-2} also depends upon the value of k_3. Possibly the strained nature of the five-membered ring containing the double bond in ethylenethiourea may make it more reactive.

Equation (11) can be differentiated with respect to $[H^+]$ to find the value of $[H^+]$ corresponding to the maximum of k_{obs}. This gives the relationship $[H^+]_{max.} = (k_3/Kk_{-2}[DATU])^{\frac{1}{2}}$ which enables one to calculate the parameters of the maximum for ethylenethiourea as $(k_{obs})_{max.}$ 2.58 × 10^{-2} s^{-1}, $[H^+]_{max.}$ 0.0776 mol dm^{-3}, and for NN'-dimethylthiourea $(k_{obs})_{max.}$ 1.95 × 10^{-2}, $[H^+]_{max.}$ 0.006 67. Thus the different slopes of the plots of k_{obs} *versus* $[H^+]$ observed for ethylenethiourea and NN'-dimethylthiourea correspond to opposite flanks of the curve.

Although the mechanisms proposed for the nitrosation of amides and thioamides are similar, it must be noted that the magnitude of the rate and equilibrium constants are very different, as shown in Table 2. For conditions under which proton loss is rate determining and the initial nitrosation is a fast equilibrium, then $k_{obs} = Kk_2$[substrate], and as can be seen from the third line of Table 2 this does not vary much between the urea and the corresponding thiourea, the larger value of K for thioureas being cancelled by the smaller value of k_2. Urea and thiourea have similar Brönsted basicities, the pK_a of the conjugate acids being *ca.* −1, and protonation occurs on oxygen and sulphur, respectively. Some additional factor must come into play when NO^+ is added on to give such different K values. We suggest that back-donation of sulphur 3*p* electrons to a π^* orbital of the nitroso group probably accounts for the increased stability of the thionitrosyl compound. The much higher rates of proton loss, the k_2 values, in the case of urea we ascribe to the much greater electronegativity of oxygen than of sulphur, reducing the electron density at the nitrogen acid and thus facilitating proton loss. The reverse reaction to proton loss, measured by k_{-2}, will have a maximum value of *ca.* 10^{10} mol^{-1} dm^3 s^{-1}, and so the pK_a for $[(NHMe)_2CSNO]^+$ is at least 10.8.

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