Kinetics and Equilibria of the *S*-Nitrosation of Alkylthioureas

By **Peter Collings, Khawla Al-Mallah, and Geoffrey Stedman,*** Chemistry Department, University College of Swansea, Singleton Park, Swansea SA2 8PP

The equilibrium constants for the addition of the nitrosonium ion to the sulphur atom of a range of alkylthioureas have been measured, and shown to correlate well with the ionisation constants of the corresponding conjugate acids. Stopped-flow studies of the rate of reaction show it to occur by an encounter-controlled process.

IN a previous paper we showed [1] that the transient yellow colour observed in the reaction between nitrous acid and thiourea was due to an intermediate *S*-nitroso-compound. The visible and u.v. spectrum of this species were

$$(NH_2)_2CS + H^+ + HNO_2 \rightleftharpoons (NH_2)_2\overset{+}{C}S\cdot NO + H_2O \qquad (1)$$

reported, together with the equilibrium constant for reaction (1). It was shown that the formation of sizeable amounts of the *S*-nitroso-compound accounted quantitatively for deviations in the kinetics of reaction (2). Some preliminary measurements on the kinetics of

$$(NH_2)_2CS + HNO_2 \longrightarrow HNCS + 2\,H_2O + N_2 \qquad (2)$$

the forward reaction for (1) were also reported. In the present paper we describe an extension of these measurements to a range of substituted thioureas, to thioacetamide, and to cysteine.

RESULTS AND DISCUSSION

For all of the substituted thioureas studied it was found that on addition of sodium nitrite solution to an acidified solution of the thiourea there was a rapid formation of a yellow colour, which was complete within a few seconds. Measurements were made at 420 nm, because at this wavelength there was no significant light absorption due to either nitrous acid or thiourea, and the absorbance gave a direct measure of the concentration of the yellow species.

TABLE 1

Equilibrium and spectroscopic data on the *S*-nitrosated alkylthioureas

	K	pK_a	$\lambda_{max.}$/nm	$10^{-4}\varepsilon$	$\lambda_{max.}$/nm	ε	ε_{420}
$NH_2\cdot CS\cdot NH_2$	5 000	−1.19	235	1.8	553	18.0	96
$MeNH\cdot CS\cdot NH_2$	9 340	−1.12	239	2.1	550	14.5	96
$Me_2N\cdot CS\cdot NH_2$	7 200	−1.08	241	2.1	550	19.2	114
$MeNH\cdot CS\cdot NHMe$	3 300	−1.32	245	2.5	550	16.8	114
$Me_2N\cdot CS\cdot NHMe$	1 230	−1.53	250	4.15	550	20.6	140
$Me_2N\cdot CS\cdot NMe_2$	8 200	−1.0	254	1.7	573	23.0	156
$EtNH\cdot CS\cdot NHEt$	10 300						96
$Bu^tNH\cdot CS\cdot NHBu^t$	(670)						(80)
$CH_2NH\cdot CS\cdot NHCH_2$	1 190	−1.9					109
$CH_3\cdot CS\cdot NH_2$	255	−1.76					100

The rapid initial formation of a yellow colour was followed in most cases by a much slower, secondary change. For thiourea and its tetramethyl derivative the yellow colour slowly faded to zero absorbance and for individual runs this fading obeyed simple second-order kinetics, $-dA/dt = kA^2$, where A is the absorbance at 420 nm. The products are known [2] to be αα-dithiobisformamidinium and nitric oxide [reaction (3)]. For other compounds, notably

$$2\,H^+ + 2\,HNO_2 + 2\,(HN_2)_2CS \longrightarrow 2\,NO + (NH_2)_2\overset{+}{C}\text{–}S\text{–}S\text{–}\overset{+}{C}(NH_2)_2 + 2\,H_2O \qquad (3)$$

N-methyl- and *NN'*-dimethyl-thiourea, the secondary change was a slow increase in absorbance, but we have not yet investigated the products of this reaction. For thioacetamide the rapid initial formation of a yellow species was followed by a decomposition process in which sulphur was precipitated. The present paper is concerned solely with the initial formation of the yellow species, and it is fortunate that the secondary processes are sufficiently slow that they do not overlap and interfere with the first reaction.

The variation of the absorbance at 420 nm with the concentration of nitrite, excess of perchloric acid, and alkylthiourea was very similar to that described previously for thiourea.[1] At low concentrations of reagents the absorbance is proportional to $[H^+][HNO_2]$[alkylthiourea], while at high concentrations of either alkylthiourea or perchloric acid the absorbance levels off to a value proportional to the initial nitrite concentration. For experiments with a large excess of acid and alkyl thiourea over nitrite plots of $1/A$ against 1/[alkylthiourea] gave good straight lines at constant acidity, with a slope proportional to $1/[H^+]$, very similar to our earlier data on thiourea. These results are entirely similar to those reported earlier for thiourea, and are consistent with an equilibrium similar to (1). We summarise values of the equilibrium constant K = [alkylthiourea,NO$^+$]/[H$^+$][HNO$_2$][alkylthiourea] in Table 1. together with some details of the visible and u.v. spectra. The data for trimethylthiourea are based upon three experiments only, because of shortage of material. *NN'*-di-t-butylthiourea was only very sparingly soluble in water, and

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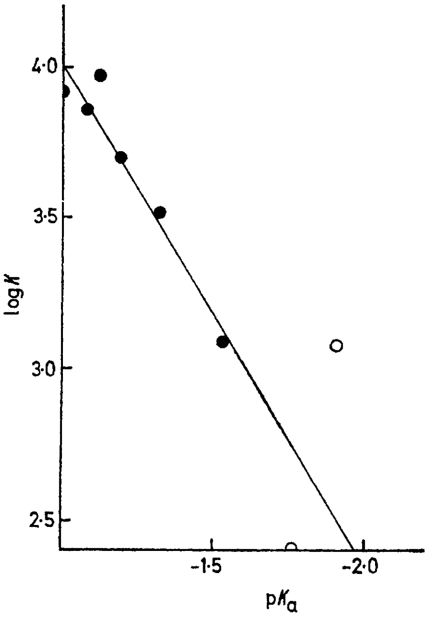
[1] K. Y. Al-Mallah, P. Collings, and G. Stedman, *J.C.S. Dalton*, 1974, 2469.

[2] A. E. Werner, *J. Chem. Soc.*, 1912, **101**, 2180.

the data for this compound are less reliable than for the others.

The evidence that the yellow species are *S*-nitroso-compounds is essentially the same as that discussed in detail[1] for the case of thiourea. The form of the expression for the equilibrium constant is consistent with a reaction of type (1). The kinetics of the formation of the yellow species (discussed below) are consistent with (1), and are of the form expected for an electrophilic nitrosation. The visible and u.v. spectra of the yellow species are similar to one another, and to the spectra of known isothionitrites.

There is a great deal of evidence[3] that thioacetamide and the thioureas are protonated on the sulphur atom, and so there is a formal analogy between this process and the present reaction where a nitrosonium ion is added at the sulphur. A plot of log K against pK_a (for the conjugate acid of the neutral compound) is shown in the Figure. The line, of slope 1.66, represents a least squares fit of the data for thiourea and its methyl derivatives. The data for ethylenethiourea was omitted from the calculation because uncertainties in the pK_a because of medium effects on the u.v. spectra.[4] The pK_a values of Janssen were based on the original H'_0 scale, and it is now clear that different classes of neutral base require different acidity functions to describe their acid–base equilibria. The nearest approach to an acidity function for the thioureas would appear to be the H_t function of Tissier[5] based upon thioamide indicators and he finds that $H_t = 1.3\ H'_0$. If we use this to correct Janssens pK_a values, then the slope of our plot of log K *versus* pK_a becomes 1.27. Although this looks to be a good correlation it must be noted that Rosenthal and Taylor's data[6] for thioacetamide do not fit onto the line for the thioureas.



Correlation of log K with pK_a of the conjugate acid of the alkylthioureas: ○, ethylenethiourea; ●, thioacetamide

The pK_a and K values do not vary regularly with changes in molecular structure, and in the former case Janssen has discussed this[4] in terms of opposing effects on basicity due to the release of electrons by the inductive effect and steric hindrance to solvation by the alkyl substituents. He also discussed the effect of steric repulsions in molecules such as tetramethylthiourea twisting the alkylamino-groups out of the plane of the N·CS·N system and reducing conjugation. We cannot usefully add to Janssen's analysis, but we note that the high basicity of tetramethylthiourea and the low basicity of trimethylthiourea which he commented upon are also reflected in our K values. Janssen also had difficulties in measuring the pK_a of ethylenethiourea, and he noted that the value of −1.9 was surprisingly low. Our own K value confirms that ethylenethiourea is indeed a fairly weak base, though on the basis of the Figure we would have expected a pK_a *ca.* 0.3—0.4 units less negative.

In addition to studying the equilibrium we have also briefly investigated the kinetics of formation of the yellow species. Runs were carried out at 25°, using a large excess of alkylthiourea and perchloric acid over nitrite in each run. Plots of log $(A_\infty - A)$ *versus* time were good straight lines over several half-lives in every case. Under the conditions of the kinetic runs the equilibrium did not lie completely to one side, and so the measured first-order rate constant is actually the sum $(k + k_{-1})$ of the pseudo-first-order rate constant for the forward and back reactions. The ratio k_1/k_{-1} can readily be calculated from the value K and the concentrations of perchloric acid and alkylthiourea, and hence the values of k_1 and k_{-1} can be found. The values are summarised in Table 2. Inspection of these values shows that k_1 is proportional to the concentrations of the excess of perchloric acid and of alkylthiourea, so the rate equation for the forward reaction is $v = k_2[H^+][HNO_2]$[alkylthiourea]. This is the same form of rate law that has been observed for the reaction of the nitrous acidium (or nitrosonium) ion with negatively charged, neutral, and positively charged nucleophiles. It is precisely what is expected for rate-determining electrophilic nitrosation. Ridd has presented arguments[7] that strongly suggest that for neutral and anionic nucleophiles the nitrosation is an encounter-controlled process, with a rate dependent mainly on the charge-type of the nucleophile. For aniline, *o*-toluidine, and *o*-chloroaniline the values of k_2 at 25° are 4 650, 4 940, and 4 900 mol^{-2} dm^6 s^{-1} respectively.[8] Our values of k_2 are very little affected by the degree of methyl substitution, and it thus appears that we too are measuring the rate of encounter between the electrophile and the nucleophile; there seems no point in attempting to explain

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[3] R. J. Gillespie and T. Birchall, *Canad. J. Chem.*, 1963, **41**, 2643; M. J. Janssen, *Spectrochim. Acta*, 1961, **17**, 475; W. Kutzelnigg and R. Mechke, *ibid.*, p. 530.

[4] M. J. Janssen, *Rec. Trav. chim.*, 1962, **81**, 650.

[5] C. Tissier and M. Tissier, *Bull. Soc. chim. France*, 1972, 2109.

[6] D. Rosenthal and T. I. Taylor, *J. Amer. Chem. Soc.*, 1957, **79**, 2684.

[7] J. H. Ridd, *Quart. Rev.*, 1961, **15**, 418.

[8] H. Schmid and C. Essler, *Monatsh.*, 1960, **91**, 484.

the small differences between the different alkylthioureas. We have measured the activation energy for the thiourea reaction, and find it to be 64.7 kJ mol^{-1}, close to the value reported for the encounter-controlled nitrosations of several singly charged anions.

Results for Cysteine.—The spectra observed for the yellow species formed when sodium nitrite is added to an acid solution of cysteine are very similar to those for the species formed from the alkylthioureas. The rate of formation of the yellow colour followed the same rate law, $v = k[H^+][HNO_2][HS\cdot CH_2\cdot CH(NH_3^+)\cdot CO_2H]$, and we can see no reason to doubt that the yellow species is $ON\cdot S\cdot CH_2\cdot CH(NH_3^+)\cdot CO_2H$ [at the acidity of these experiments cysteine exists very largely as $HS\cdot CH_2\cdot CH(NH_3^+)\cdot CO_2H$]. However in all the runs studied the infinity absorbance was the same value (for a given nitrite concentration), and did not vary with $[H^+]$ or $[HS\cdot CH_2\cdot CH(NH_3^+)\cdot CO_2H]$. This implies that in this case the equilibrium similar to (1) lies strongly in favour of the S-nitroso-compound, and we have not worked at low enough concentrations to see evidence for its dissociation. Thus the measured rate constant is the rate constant for the forward reaction, k_1, rather than $k_1 + k_{-1}$ as in the other cases. The value of k_2 is about an order of magnitude less than the values for thiourea, and is similar to the value of 650 mol^{-2} dm^6 s^{-1} for the substitution of NH_3^+ NH_2 at the nitrous acidium ion.[9] As the rate of substitution of singly charged anions is about an order of magnitude greater than for aromatic amines at the nitrous acidium ion, and both are thought to be encounter-controlled processes, it seems likely that the low rate of reaction for cysteine is merely the effect of coulombic repulsion on the encounter rate.

TABLE 2

Kinetic data on the nitrosation of the alkylthioureas at 25°, 10^3[alkylthiourea]/M, $10^3[H^+]$/M, $10^4[HNO_2]$/M, k_1/s^{-1}, k_2/dm^6 mol^{-2} s^{-1}, k_{-1}/s^{-1}

	10^3[alkylthiourea]/M	$10^3[H^+]$/M	$10^4[HNO_2]$/M	k_1/s^{-1}	k_2/dm^6 mol^{-2}	k_{-1}/s^{-1}
$NH_2\cdot CS\cdot NH_2$	25	5	5	0.865	6 960	1.39
	25	25	5	4.34		
	5	50	5	1.66		
	25	50	10	9.25		
	25	50	2	8.60		
$MeNH\cdot CS\cdot NH_2$	40	50	5	10.6	5 620	0.60
	8	50	5	2.53		
	40	10	5	2.09		
$MeNH\cdot CS\cdot NHMe$	20	50	5	7.67	6 610	2.0
	4	50	5	1.24		
	20	10	5	1.19		
$Me_2N\cdot CS\cdot NH_2$	20	50	5	5.43	5 790	0.80
	4	50	5	1.14		
	20	10	5	1.25		
$Me_2N\cdot CS\cdot NMe_2$	4	50	5	0.867	4 340	0.53
	20	50	5	4.25		
	20	10	5	0.887		
$HS\cdot CH_2\cdot CH(NH_3^+)\cdot CO_2H$	20	400	10	3.65	456	
	4	400	10	0.719		
	20	100	10	0.925		

EXPERIMENTAL

Materials.—*NNN′*-Trimethylthiourea was a gift from I.C.I. *NN*-Dimethylthiourea was prepared by a standard method,[10] treating dimethylcyanamide with hydrogen sulphide in triethylamine–pyridine solution. All other materials were commercially available substances, purified by recrystallisation where necessary.

Kinetic Methods.—The kinetic measurements were made on a Nortech Canterbury SF3-A stopped flow apparatus, together with a Tetronix storage oscilloscope. A few preliminary measurements were made in the case of cysteine with a Unicam SP 600, coupled to a Servoscribe recorder.

Equilibrium Constant Measurements.—In most cases these measurements were made on a Unicam SP 500, with a thermostatted cell holder. Reaction was started by injecting the appropriate volume of thermostatted sodium nitrite solution through a small hole in the cell compartment lid. In a few cases measurements were made with a Unicam SP 600 fitted with a thermostatted cell holder, and coupled to a Servoscribe recorder.

K. A. M. thanks the University of Mosul for study leave. We are indebted to Mr. M. Garley for skilful technical assistance.

[5/912 *Received*, 14*th May*, 1975]

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[9] J. R. Perrott, Ph.D. Thesis, University of Wales, 1972.

[10] F. Kurzer and P. M. Sanderson, *J. Chem. Soc.*, 1957, 4461.