# Electrophilic Nitrosation at Sulphur and Nitrogen in Thiourea

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Thiourea reacts rapidly with nitrous acid in aqueous solution to form an equilibrium concentration of a coloured *S*-nitroso-compound. The equilibrium constant has been measured, together with a preliminary value of the rate constant for the nitrosation. The kinetics of the much slower reaction to form nitrogen and thiocyanic acid have been investigated. The mechanism proposed is a rate-determining sulphur-to-nitrogen migration of the nitroso-group in the conjugate base of the *S*-nitroso-compound.

EARLY work by Werner [1] showed that there were two reactions [(1) and (2)] occurring in parallel between nitrous acid and thiourea. The structure of the main product of reaction (2), *CC'*-dithiodiformamidinium, has been the subject of some dispute, but an *X*-ray study by Foss [2] has shown that the structure given above is correct. Werner showed [3] that reaction (2) was favoured by high acidities, whereas reaction (1) was predominant at low acidities. He also reported that when reaction (2) was used as a method of preparing dithiodiformamidinium a transient red colour was observed in the solution. We now report some work which throws light on these reactions.

$$HNO_2 + CS(NH_2)_2 \longrightarrow H^+ + SCN^- + N_2 + 2H_2O \qquad (1)$$

$$2H^+ + 2HNO_2 + 2CS(NH_2)_2 \longrightarrow (NH_2)_2\overset{+}{C}SS\overset{+}{C}(NH_2)_2 + 2NO + 2H_2O \qquad (2)$$

## EXPERIMENTAL

*Measurements of the Initial Absorbance.*—These experiments were carried out by injecting sodium nitrite solution into a mixture of the other reactants in a 4 cm cell. Measurements were made at 420 nm with a Unicam SP 500 or 600 instrument, and the dark current and 100% settings were made with cell and reactants (excluding the nitrite) in position; the nitrite was injected from a syringe through a small hole in the cell compartment lid. Absorbance readings could be obtained within a few seconds of mixing. Tests in which a stable coloured solution was injected into water confirmed the efficiency of our mixing technique. Reactant solutions were kept in a thermostat before mixing, and a thermostatted cell holder was used.

*Measurements of the Spectrum of the Intermediate.*—In the visible region of the spectrum neither nitrous acid nor thiourea absorbs to any significant extent, so it was straightforward to measure the spectrum of the intermediate. For the peak at 380 nm, measurements were made with solutions containing sufficiently large concentrations of thiourea and perchloric acid to convert all the nitrite into the intermediate, whose spectrum could thus be measured directly. The characteristic fine structure peaks of molecular nitrous acid had completely disappeared, confirming the completeness of the conversion. For measurements at 235 nm, solutions containing an excess of nitrous acid and perchloric acid were used. The equilibrium constant obtained from measurements at 420 nm was used to calculate the concentrations of thiourea, nitrous acid, and intermediate, and from the measured absorbance and the known extinction coefficients of the first two species the extinction coefficient of the intermediate was calculated.

*Kinetic Measurements.*—To measure the rate of formation of thiocyanate samples of reaction mixture were removed and quenched in sulphamic acid solution. Acidified iron(III) nitrate solution was added, and the absorbance due to $FeCNS^{2+}$ was measured at 460 nm. The method was calibrated with standard solutions of thiocyanate. To measure the initial rate of formation of the yellow species, a home-made stopped-flow apparatus constructed on the Canterbury design was used.

## RESULTS AND DISCUSSION

Experiments over a range of conditions showed us that the transient colour observed by Werner was much more intense at high than at low acidities. The colour was formed very rapidly, apparently in less than a second at room temperature and pH 1, with reagent concentrations in the range $10^{-3}$ to $10^{-2}$ mol dm$^{-3}$. The concentrations we used were much lower than those employed by Werner in his preparative work, and the colour appeared yellow rather than red. By using 4 cm cells and low concentrations it was possible to reduce the rate of fading sufficiently for the spectrum to be measured. The yellow colour is due to the long-wavelength side of a broad peak at 380 nm ($\varepsilon$ 130) with a point of inflection at 540 nm ($\varepsilon$ 17). There is a more intense peak at 235 nm ($\varepsilon$ 18 000). In order to study the reaction quantitatively we decided to work at 420 nm, where overlapping absorptions due to nitrous acid and thiourea can be neglected, and the absorbance is due to the yellow species alone. Reaction solutions were mixed as rapidly as possible and the absorbance at 420 nm measured immediately in order to avoid complications due to fading of the yellow colour. Experiments in which the solutions were deoxygenated by passage of nitrogen gave initial absorbances identical with those obtained with air- or oxygen-saturated solutions. Experiments carried out in vacuum, with degassed solutions, showed a transient yellow colour on mixing similar to that observed with air-saturated solutions. It is clear that dissolved oxygen does not affect the initial absorbance. When a solution of sulphamic acid, which rapidly destroys nitrous acid, was added to the reaction solution the transient yellow colour disappeared at once.

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[2] O. Foss, J. Johnsen, and O. Tvedten, *Acta Chem. Scand.*, 1958, **12**, 1782.

[3] M. E. Coade and A. E. Werner, *J. Chem. Soc.*, 1913, **102**, 1221.

The results of a typical group of experiments with deoxygenated solutions are shown in Table 1. When the concentrations of nitrous acid and perchloric acid are held constant, increasing thiourea concentration causes an increase in absorbance. At low concentrations the absorbance is directly proportional to [thiourea], but at higher concentrations it levels off to a constant value. Increasing the acidity increases the absorbance at low [thiourea], but the final levelled off value is unchanged. Similar results are obtained if the thiourea concentration is held constant and that of nitrous acid is increased; the final levelled off value of the absorbance is the same whether nitrous acid or thiourea is in excess (for a given molar concentration of the minor component). At low concentrations the absorbance is proportional to $[H^+]$[nitrite][thiourea]. This shows that we are dealing with a rapidly established equilibrium in which the yellow species is formed from a proton, a molecule of nitrous acid, and a molecule of thiourea [equation (3)].

TABLE 1

Measurements of the initial absorbance at 420 nm for mixtures of thiourea, perchloric acid, and nitrous acid ($I$ = 0·3, 25°, 4 cm cells)

| $10^2[H^+]$ | $10^3$[nitrite] | $10^3[CS(NH_2)_2]$ = | 3·08 | 6·22 | 9·41 | 28·8 | 48·9 |
|---|---|---|---|---|---|---|---|
| 2·08 | 0·84 | $A_{420}$ = | 0·074 | 0·122 | 0·155 | 0·238 | 0·262 |
| 2·08 | 1·68 | $10^3[CS(NH_2)_2]$ = | 2·92 | 5·97 | 9·06 | 28·3 | 47·7 |
| | | $A_{420}$ = | 0·135 | 0·218 | 0·289 | 0·441 | 0·515 |
| 16·6 | 1·68 | $10^3[CS(NH_2)_2]$ = | 2·20 | 5·18 | 8·33 | 27·8 | 47·4 |
| | | $A_{420}$ = | 0·412 | 0·521 | 0·566 | 0·618 | 0·630 |

Concentrations in mol $dm^{-3}$.

$$H^+ + HNO_2 + CS(NH_2)_2 \rightleftharpoons Y \qquad (3)$$

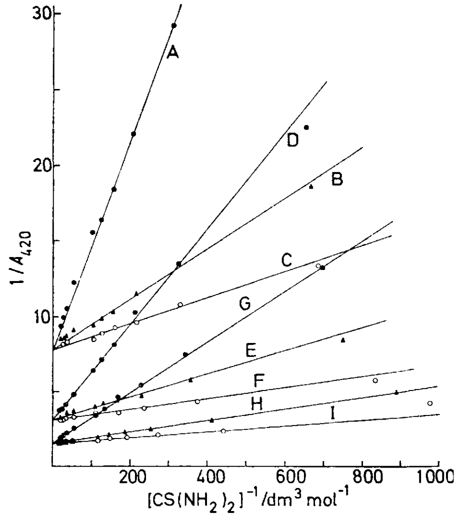
If we assume that the yellow compound Y is the only species absorbing significantly at 420 nm, equation (4)

$$\frac{1}{A_{420}} = \frac{\varepsilon d}{[\text{nitrite}]}\left(1 + \frac{1}{K[H^+][\text{thiourea}]}\right) \qquad (4)$$

can readily be derived ($d$ = path length). The total stoicheiometric concentrations of nitrite and thiourea are given by [nitrite] = $[HNO_2] + [Y]$ and [thiourea] = $[CS(NH_2)_2] + [Y]$. It has been assumed that the thiourea is in such large excess that its concentration is not affected by the conversion of some of it into the yellow species. Plots of $1/A_{420}$ against 1/[thiourea] give good straight lines, and from the intercept at 1/[thiourea] = 0 the value of the absorbance corresponding to complete conversion of nitrous acid into the yellow species can be obtained. This gives an extinction coefficient of 96 $mol^{-1}$ $dm^3$ $cm^{-1}$ at 420 nm. From this values of [Y] can be calculated, and hence the true value of the thiourea concentration, $[CS(NH_2)_2]$, corrected for the loss due to formation of Y, can be calculated. Corrected plots of $1/A_{420}$ *versus* $1/[CS(NH_2)_2]$ are shown in the Figure. From the slope of these lines the equilibrium constants $K = [Y]/[H^+][HNO_2][CS(NH_2)_2]$ = 5000 $mol^{-2}$ $dm^6$ at 25° can be calculated. Values of $K$ measured over a range of temperatures are 5000 (25·0°), 7800 (11·8°), and 3300 $mol^{-2}$ $dm^6$ (33·3°). A plot of ln $K$ against $1/T$ gives $\Delta H = -30$ kJ $mol^{-1}$. Measurements at 520 nm gave $K$ = 4800 $mol^{-2}$ $dm^6$ and $\varepsilon$ = 16·5 $mol^{-1}$ $dm^3$ $cm^{-1}$.

In an attempt to measure the rate at which the yellow species was formed in solutions four runs were carried out on a stopped-flow apparatus, and the initial rate of increase in absorbance at 420 nm was measured. The results are in Table 2. Although these constitute only a preliminary study, they suggest the rate law $(d[Y]/dt)_0 = k_3[H^+][HNO_2]_0[CS(NH_2)_2]_0$, which is fully consistent with the equilibrium measurements, with $k_3$ = 11 200 $mol^{-2}$ $dm^6$ $s^{-1}$ at 25°.

The kinetics of the formation of thiocyanate were investigated by measuring the initial rate of reaction ($v_0$). This avoids complications due to secondary formation of thiocyanate by reaction between dithiodiformamidinium and nitrous acid, a reaction also studied by Werner. The results are shown in Table 3. For the runs at the lowest values of $[H^+]$, $[\text{nitrite}]_0$, and $[\text{thiourea}]_0$, the results approximately fit the equation $v_0 = k_2[\text{nitrite}]_0[\text{thiourea}]_0$. If one compares runs at higher concentrations then the orders of reaction are clearly non-integral. The numbers in the fifth column ($k_2 = v_0/[\text{nitrite}]_0[\text{thiourea}]_0$) are far from constant, varying by a factor of 25, and this reflects the same phenomenon in a slightly different way. This rate constant has been calculated by using the total



Variation of absorbance at 420 nm with concentration of thiourea: $10^4$[nitrite] = 3·49 (A—B), 8·40 (D—F), or 16·80 (G—I); $10^2[H^+]$ = 2·08 (A, D, G), 8·32 (B, E, H), or 16·64 mol $dm^{-3}$ (C, F, I) stoicheiometric concentrations of nitrite and thiourea. However, at higher reagent concentrations there will be a higher concentration of the yellow species and a sizeable proportion of the nitrous acid and thiourea will be converted into the yellow species. Knowing the equilibrium constant $K$ it is possible to calculate the value of [Y], and hence the true corrected concentrations of nitrous acid and thiourea, and when these corrected concentrations are used to calculate $k_2^*$ $(= v_0/[HNO_2][CS(NH_2)_2])$ a much more satisfactorily constant rate constant is obtained, shown in column 6. These figures have also been corrected to allow for the ionisation of nitrous acid, which is significant at the lower acidities studied. This provides convincing evidence that a sizeable proportion of the reactants can be converted into the yellow species.

TABLE 2

Initial rate of formation of the yellow species

| $[H^+]$ | $[HNO_2]_0$ | $[CS(NH_2)_2]_0$ | $(d[Y]/dt)_0$ | $k_3$/ mol$^{-2}$ dm$^6$ s$^{-1}$ |
|---|---|---|---|---|
| 0·1 | 0·005 | 0·01 | 0·057 | 11 400 |
| 0·1 | 0·01 | 0·01 | 0·117 | 11 700 |
| 0·1 | 0·01 | 0·02 | 0·215 | 10 700 |
| 0·05 | 0·01 | 0·02 | 0·111 | 11 100 |

In interpreting our results, we note that the rate law for the formation of the yellow species has the characteristic form for an electrophilic nitrosation of free thiourea by either nitrous acidium or nitrosonium ion. The corresponding nitrosations of *o*-chloroaniline and *o*- and *p*-nitroanilines are thought [4] to be close to encounter-controlled processes, and have rate constants about 175 mol$^{-2}$ dm$^6$ s$^{-1}$ at 0°. Schmid and Essler report [5] that for *o*-chloroaniline the rate increases by a factor of 20 between 0 and 25°, which would give a rate constant of *ca.* 3500 mol$^{-2}$ dm$^6$ s$^{-1}$ at 25°. Our rate constant is higher than this, but as it is based upon only a few preliminary runs it is not appropriate to attempt an interpretation of the difference. The rate law is clearly consistent with the form of equilibrium constant that we have found, and suggests we have an electrophilic nitrosation to form an adduct $[CS(NH_2)_2 \cdot NO]^+$. From our equilibrium and rate constant we calculate the rate constant for the reverse reaction, denitrosation, to be 11 200/5000 = 2·2 s$^{-1}$. The fact that the yellow colour is rapidly destroyed on addition of sulphamic acid might be thought to be additional evidence that the yellow species is a nitroso-compound. However the same effect would be observed if the sulphamic acid reacted with nitrous acid, which was then regenerated by denitrosation of the yellow species. As the rate constant for the sulphamic acid–nitrous acid reaction is known, a kinetic study of the fading of the yellow colour in the presence of sulphamic acid might distinguish between these possibilities.

TABLE 3

Kinetics of formation of thiocyanate at 26°

| $10^2[H^+]$ | $10^4$[thiourea] | $10^4$[nitrite] | $10^8 v_0$ | $10k_2$ | $10k_2^*$ |
|---|---|---|---|---|---|
| 0·5 | 500 | 3 | 111 | 0·74 | 2·03 |
| 1 | 5 | 3 | 2·55 | 1·70 | 1·93 |
| 1 | 10 | 3 | 5·29 | 1·75 | 2·05 |
| 1 | 50 | 3 | 20·8 | 1·40 | 1·91 |
| 1 | 500 | 3 | 7·65 | 0·51 | 1·94 |
| 1 | 5 | 16 | 11·6 | 1·45 | 1·83 |
| 1 | 10 | 16 | 25·5 | 1·58 | 2·20 |
| 1 | 20 | 16 | 52·7 | 1·65 | 2·56 |
| 5 | 5 | 3 | 2·57 | 1·78 | 2·16 |
| 5 | 10 | 3 | 5·07 | 1·68 | 2·26 |
| 5 | 50 | 3 | 13·7 | 0·92 | 2·14 |
| 5 | 500 | 3 | 21·0 | 0·14 | 1·86 |
| 10 | 5 | 3 | 2·64 | 1·75 | 2·33 |
| 10 | 10 | 3 | 3·84 | 1·28 | 2·10 |
| 10 | 50 | 3 | 8·35 | 0·55 | 2·05 |
| 10 | 500 | 3 | 11·2 | 0·072 | 1·67 |
| 10 | 5 | 16 | 9·30 | 1·16 | 2·22 |
| 10 | 10 | 16 | 16·7 | 1·05 | 2·20 |
| 10 | 50 | 16 | 53·3 | 0·67 | 2·43 |

All concentrations in mol dm$^{-3}$; $k_2$ and $k_2^*$ in mol$^{-1}$ dm$^3$ s$^{-1}$.

There are two likely sites for the nitroso-group to be attached, sulphur and nitrogen. The fact that thionitrites (containing the $-S-N=O$ group) are often deep red coloured species suggests that sulphur is the likely site. Wavelength and extinction coefficients for absorption maxima are [6] $CF_3SNO$, **373** (ε 112) and 570sh (6); $C_2H_5SNO$, 342·5 (650) and 550sh nm (21 mol$^{-1}$ dm$^3$ cm$^{-1}$). $CF_3SNO$ is unstable at room temperature, rapidly decomposing to $CF_3-S-S-CF_3 + 2NO$. This suggests that our yellow species is a precursor of dithiodiformamidinium, and indeed the conditions which favour the formation of this product are also the conditions where the greatest concentrations of the yellow species are observed.

Gillespie and Birchall [7] have shown by n.m.r. that protonation of thioacetamide occurs on the sulphur, and they have presented strong evidence that the same is true for thiourea, *N*-methylthiourea, and thioacetanilide. Spectroscopic evidence (u.v. and i.r.) has been presented [8] in favour of protonation on sulphur in thioamides. The nitrosonium ion has been classified [9] as borderline between 'soft' and 'hard'. The equilibrium constants for the formation of nitrosyl chloride and nitrosyl bromide suggest that it tends towards 'softness'; this is consistent with the fact that nitrosyl thiocyanate is deep red in colour [10] [$\lambda_{max.}$ 460 nm (ε 100 mol$^{-1}$ dm$^3$ cm$^{-1}$)], suggesting a structure ON–SCN where the nitrosyl group bonds to 'soft' sulphur rather than to 'hard' nitrogen. Thus one might expect the nitrosonium ion to add preferentially to sulphur in thiourea. (This argument is weakened by the fact that protonation occurs at the sulphur.) Electrophilic attack in alkylation of thioamides normally occurs at the sulphur, and electrophilic acylation is thought [11] to occur initially at sulphur, and to be followed by rearrangement to the nitrogen. We propose that our yellow species is $(NH_2)_2C=\overset{+}{S}-N=O$.

The fact that nitrogen and thiocyanic acid are also

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[9] R. G. Pearson, *Chem. in Britain*, 1967, **3**, 103.

[10] G. Stedman and P. A. E. Whincup, *J. Chem. Soc.*, 1963, 5796.

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products of the nitrous acid–thiourea reaction strongly suggests that *N*-nitrosation occurs also. These are the products that would be expected from the sequence $CS(NH_2)_2 \xrightarrow{X\cdot NO} NH_2\cdot CS\cdot NHNO \longrightarrow NH_2\text{–}CS\text{–}N{=}N\text{–}OH \longrightarrow H^+ + HNCS + N_2 + OH^-$. Similar sequences of reactions are well established [4] for the nitrosation reactions of many aliphatic and aromatic amino-compounds. The formation of nitrogen points clearly towards *N*-nitrosation; however the rate law does not have the usual first-order dependence upon acidity. This could be explained if thiourea reacted as the anion [equations (5) and (6)]. This would require that $K_1k_1 = 0{\cdot}2$ mol$^{-1}$

$$CS(NH_2)_2 \underset{\text{fast}}{\rightleftharpoons} CS(NH_2)NH^- + H^+ \quad K_1 \quad (5)$$

$$H^+ + HNO_2 + CS(NH_2)NH^- \xrightarrow[\text{slow}]{} CS(NH_2)NHNO + H_2O \quad k_1 \quad (6)$$

dm$^3$ s$^{-1}$ at 25°. A reasonable value of $k_1$ at 25° would be 15 000 mol$^{-2}$ dm$^6$ s$^{-1}$ if it behaved like other nucleophilic anions and reacted at the encounter rate. This would lead to an absurdly high value for $K_1$, and this mechanism can be discounted.

A second possibility is that there is an equilibrium concentration of an *N*-nitroso-species that undergoes a slow rearrangement [equation (7)]. This would be consistent

$$HNO_2 + CS(NH_2) \underset{\text{fast}}{\rightleftharpoons} NH_2\text{–}CS\text{–}NH\text{–}NO + H_2O \xrightarrow[\text{slow}]{} NH_2\text{–}CS\text{–}N{=}N\text{–}OH \xrightarrow[\text{fast}]{} H^+ + HNCS + N_2 + OH^- \quad (7)$$

with the rate law; however tautomerisations of this type are usually very fast. Certainly in diazotisation and deamination the slow stage is the initial *N*-nitrosation, and the subsequent rearrangements to a diazohydroxide and a diazonium ion are fast.[4]

A third possibility is that the addition of NO$^+$ to the sulphur atom enhances the acidity of the protons, and that there is a sufficient concentration of the conjugate base for reaction to occur by a rate-determining migration of the nitroso-group from sulphur to nitrogen [equation (8)]. This would be followed by the last two stages of

$$H^+ + HNO_2 + CS(NH_2)_2 \underset{\text{fast}}{\overset{K}{\rightleftharpoons}} (NH_2)_2C\overset{+}{S}NO \underset{\text{fast}}{\overset{K_2}{\rightleftharpoons}} H + (NH_2)(\overset{-}{N}H)C\overset{+}{S}NO \xrightarrow[\text{slow}]{k_2} NH_2CSNHNO \quad (8)$$

(7), occurring as fast reactions. The rate law would be $v = KK_2k_2[HNO_2][CS(NH_2)_2]$. $K_2$ would have to be less than about $10^{-3}$ or deviations would have shown up in our measurements of $K$. This mechanism ties in well with an earlier suggestion [12] that in the deamination of primary amides nitrosation may initially occur on the carbonyl oxygen, with a subsequent O-to-N rearrangement. The great advantage of the present sytem is that because of the spectroscopic properties of the –S–N=O group there is direct evidence for initial nitrosation at S, while the products require that the nitroso-group must end up as the nitrogen. Some recent work on the kinetics of the deamination of aliphatic amides can readily be interpreted in this fashion too.[13] The suggestion of Challis and Challis [12] seems well founded.

Another possibility to be considered (for which we are indebted to a referee) is that of a rate-determining proton loss from $(NH_2)_2C\overset{+}{S}NO$, followed by a rapid S-to-N migration of the nitroso-group. For this to be consistent with our rate law it would have to involve deprotonation by the hydroxide ion. Calculating the rate constant for such a step from our data for $k_2$* and $K$ one obtains a figure of $5 \times 10^9$ mol$^{-1}$ dm$^3$ s$^{-1}$ at 25°, in fair agreement with the encounter limit. However, this requires that at pH 1 proton loss occurs to the hydroxide ion and not to water. This would require the rate constant for proton loss of $(NH_2)_2C\overset{+}{S}NO$ to water to be less $10^{-4}$ s$^{-1}$, otherwise we would expect to see $k_2$* vary with acidity. This seems too low to be at all likely.

We have also examined the reaction in deuterium oxide, and find $K(D)/K(H) = 2$ and $k_2^*(D)/k_2^*(H) = 0{\cdot}8$. The former value is based upon a single experiment, but is reasonable. The rate constant for substitution of the iodide ion at the nitrous acidium ion shows an isotope effect of 2·2, and the equilibrium constant for the formation of nitrosyl thiocyanate (a reaction of a different charge type to the thiourea case) has an isotope effect [14] of 3·3. Swain and Schowen have suggested [15] that for the transfer of a proton from oxygen to nitrogen the primary isotope effect may be close to unity. If this is correct then we cannot use our isotopic result to exclude a slow proton-transfer reaction. The isotope effect on $K_2$ is difficult to assess, as for weak acids $K(D)/K(H)$ is not a simple function of p$K_a$ (and in any case we do not know $K_2$). If we assume mechanism (3) to be correct and we reverse the calculation and use our result to predict $K_2(H)/K_2(D)$, a value of 2·5 is obtained which seems low. It appears that the solvent isotope effect is not very helpful in sorting out which mechanism is involved, but we feel the chemical arguments point very strongly towards (8).

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