Kinetics of the Thiocyanate Catalysed Decomposition of the *C,C′*-dithiodiformamidinium Ion†

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The thiocyanate ion catalysis of the decomposition of $(NH_2)_2CSSC(NH_2)_2^{2+}$ occurs by nucleophilic attack to form a mixed disulfide rather than by general base catalysis.

The oxidation of thiourea by a wide range of oxidising agents produces the disulfide $(NH_2)_2CSSC(NH_2)_2^{2+}$, the *C,C′*-dithiodiformamidinium ion. This is frequently described in the earlier literature as the doubly protonated form of formamidine disulfide, $FDSH_2^{2+}$. A summary of some of its chemistry has been given by Foss, Johnsen and Tvedten.[1] It decomposes in aqueous solution, yielding the products shown in eqn. (1). The reaction follows first-order kinetics, k_1/s^{-1}, and the rate constant increases rapidly with increase of pH. The reaction has been studied[2] in buffered solutions, using a range of different buffers, and the kinetics show clear evidence for buffer catalysis, $k_1 = k_a + k_b[\text{buffer}]$. A detailed kinetic analysis showed that this is due to general base catalysis, and the variation of k_a with pH was quantitatively interpreted to yield values of 5.49 and 7.66 for pK_1 and pK_2 respectively of the dictation. During this investigation the possibility of the buffer anion acting as a nucleophilic catalyst was considered, but rejected. However, although added NaBr had no effect on the reaction when NaNCS was added there was a large increase in rate, eqn. (2). Typical results are shown in Fig. 1. The difference between bromide and thiocyanate prompted this study.

$$(NH_2)_2CSSC(NH_2)_2^{2+} \rightarrow (NH_2)_2CS + NH_2CN + S + 2\,H^+ \quad (1)$$

$$k_1 = k_c + k_d[NCS^-] \quad (2)$$

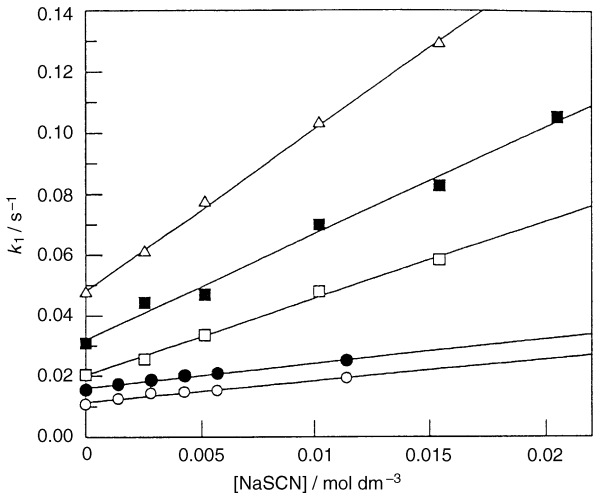

Fig. 1 Variation of rate constant k_1 with $[SCN^-]$ pH = 4.69 ○, 4.86 ●, 5.00 □, 5.25 ■, 5.52 △

The catalytic constant k_d increased with decreasing acidity as can be seen from the slopes of the lines in Fig. 1. A plot of k_d as a function of pH is shown in Fig. 2. Although the stoichiometry of eqn. (1) is well established we decided to check whether the thiocyanate ions was a true catalyst or was involved stoichiometrically in the reaction. We examined the reaction of $FDSH_2^{2+}$ with ^{13}C enriched KNCS (90 atom%), but could not detect any NMR peaks other than that due to the thiocyanate ion itself. Because of the low sensitivity of the NMR method it was necessary to use much higher concentrations of $FDSH_2^{2+}$, 0.028 mol dm^{-3}, than were used in the spectrophotometric kinetic studies (*ca.* 2×10^{-5} mol dm^{-3}). One possible reaction that was considered in detail was the oxidation of thiocyanate to thiocyanogen, eqn. (3), followed by the hydrolysis/disproportionation reaction, eqn. (4)

$$(NH_2)_2CSSC(NH_2)_2^{2+} + 2\,SCN^- \rightleftharpoons 2\,(NH_2)_2CS + (SCN)_2 \quad K_3 \quad (3)$$

$$3\,(SCN)_2 + 4\,H_2O \rightarrow H_2SO_4 + HCN + 5\,HNCS \quad (4)$$

The unfavourable reduction potentials[3,4] make this unlikely to be a major pathway: E° $(NH_2)_2CSSC(NH_2)_2^{2+}/2(NH_2)_2CS$ 0.418 V, E° $(SCN)_2/2SCN^-$ 0.77 V, corresponding to $K_3 = 1.2 \times 10^{-12}$. However as the hydrolysis of thiocyanogen is an essentially irreversible reaction under our conditions there may be trace amounts of this pathway, and as summarised below we did find small amounts of sulfate for reaction at very much higher concentrations of $FDSH_2^{2+}$ than were used in our rate studies. The kinetics of reaction (4) are shown in eqn. (5). This unusual kinetic form was reported by Bjerrum and Kirschner,[5] and is interpreted in terms of a rapidly established hydrolytic

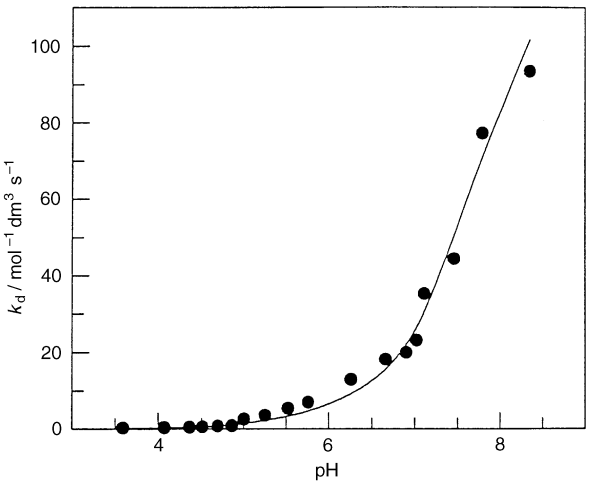

Fig. 2 Variation of rate constant k_d with pH

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equilibrium (6) followed by a rate determining bimolecular reaction (7).

$$-\mathrm{d}[(SCN)_2]/\mathrm{d}t = k[(SCN)_2]^2/([H^+]^2[SCN^-]^2) \quad (5)$$

$$(SCN)_2 + H_2O \rightleftharpoons HOSCN + H^+ + SCN^- \quad K_4 \quad (6)$$

$$2\ HOSCN \rightarrow HOS(O)CN + H^+ + SCN^- \quad k_2 \quad (7)$$

This is followed by two further rapid steps, the first a further oxidation to $HOS(O)_2CN$ and the second a rapid hydrolysis to $H_2SO_4 + HCN$. Thus if reactions (3) + (4) occurred, the predicted rate law would be eqn. (8), and substitution of the expression for $[(SCN)_2]$ into the equilibrium expression for (3) would yield eqn. (9).

$$\text{rate} = k_2K_4^2[(SCN)_2]^2/([H^+]^2[SCN^-]^2) \quad (8)$$

$$\text{rate} = k_2K_4^2K_3^2[FDSH_2^{2+}][SCN^-]^2/([(NH_2)_2CS]^4[H^+]^2) \quad (9)$$

Thus if eqn. (3)+(4) contributed significantly to the overall rate it would lead to deviations from simple first-order dependence on $[FDSH_2^{2+}]$, and a non-linear dependence of k_1 on $[SCN^-]$. However individual runs gave excellent first-order kinetics, showing no sign of deviation, and the linear dependence of k_1 on $[SCN^-]$ is clear in Fig. 1. Because the kinetics of eqn. (4) are second order with respect to $[(SCN)_2]$ such effects are likely to show up at higher concentrations of reactants. With equal concentrations of NaSCN and $FDSH_2^{2+}$ of 0.5 mol dm^{-3}, pH 4.05, cloudiness was observed when $BaCl_2$ was added to the reaction solution, presumably indicating some sulfate formation. With 0.025 mol dm^{-3} $FDSH_2^{2+}$ turbidity measurements gave 7% sulfate formation, while gravimetric determination of precipitated sulfur gave a yield of 83%. We conclude that at the very much lower concentrations used in our kinetic study, reactions (3) + (4), are likely to be of very minor importance.

The thiocyanate ion is a very weak base[6] (pK_a HNCS = −17) so the variation of k_d with pH is ascribed to the acid–base equilibria of $FDSH_2^{2+}$. If we define the bimolecular rate constants for the reaction of SCN^- with $(NH_2)_2CSSC(NH_2)_2^{2+}$, $NH_2(NH{:})CSSC(NH_2)_2^{+}$ and $NH_2(NH{:})CSSC(:NH)NH_2$ as k_3, k_4 and k_5 respectively the variation of k_d with $[H^+]$ is given by eqn. (10).

$$k_d = \frac{(k_3[H^+]^2 + k_4K_1[H^+] + k_5K_1K_2)}{([H^+]^2 + K_1[H^+] + K_1K_2)} \quad (10)$$

Fitting our data to this expression by means of a non-linear least squares program leads to the values $k_3 = 0.1 \pm 0.05$, $k_4 = 5.4 \pm 0.7$ and $k_5 = 121 \pm 14$ mol^{-1} dm^3 s^{-1} at 25 °C. The continuous line in Fig. 2 shows the degree of fit of the equation to the data. The reactivity sequence $k_5 \geqslant k_4 \geqslant k_3$ shows that the data cannot be interpreted on the basis of simple Coulombic attraction factors, as the dication is much less reactive than the monocation, and other explanations must be sought. The values confirm that the mechanism is not the same as that observed previously in our buffer catalysed study. The thiocyanate ion is not acting as a general base. Thus although it is a much weaker base than the acetate ion (pK_a $CH_3COOH = 4.75$), k_4 for attack of SCN^- on $NH_2(NH{:})CSSC(NH_2)_2^{+}$ is orders of magnitude greater than the rate constant for attack by acetate ion of 1.54×10^{-3} mol^{-1} dm^3 s^{-1}. The factor that does increase with increase in pH is the fraction of the disulfide containing the conjugate base fragment $-SC(:NH)NH_2$. The very low value for k_3, only two standard deviations from zero, could be due to the presence of a small amount of a tautomer containing the $-SC(:NH)NH_2$ fragment. The involvement of a very small proportion of a tautomer was postulated in the previous study[2] of the general base catalysed decomposition reaction. This fragment was postulated to have an essential role in the general base catalysed decomposition of $FDSH_2^{2+}$ by removal of the imino proton leading to the formation of NH_2CN and S [eqn. (11)].

$$(NH_2)_2CSSC(NH_2)(:NH)^+ + B \rightarrow (NH_2)_2CS + S + NH_2CN + BH^+ \quad (11)$$

In the reaction of the *C*,*C*′-dithiodiformamidinium ion with cysteine to form thiourea and cystine Toennies[7] obtained evidence for the formation of a mixed disulfide, and we have found[8] ^1H NMR evidence for the formation of a mixed disulfide in its reaction with tetramethylthiourea. Thus we think that the mechanism may be written as eqn. (12) + (13), choosing the monocation as an illustration, a nucleophilic attack by the sulfur of thiocyanate at the disulfide linkage, with thiourea as a leaving group, followed by a rapid breakdown of the mixed disulfide.

$$NH_2(NH{:})CSSC(NH_2)_2^+ + SCN^- \rightarrow NH_2(NH{:})CSSCN + SC(NH_2)_2 \quad (12)$$

$$NH_2(NH{:})CSSCN \rightarrow NH_2CN + S + H^+ + SCN^- \quad (13)$$

An alternative would be to run these two reactions into one, nucleophilic attack by thiocyanate leading to fragmentation. It seems likely that other sulfur nucleophiles may react similarly with the formation of a mixed disulfide. These observations are consistent with the well known role[9] of $(NH_2)_2CSSC(NH_2)_2^{2+}$ as an inhibitor for the enzyme amidinase transferase, where the enzyme sulfhydryl group is thought to react with the displacement of thiourea and the formation of a species enzyme–$SSC(:NH)(NH_2)$, blocking the use of the enzyme SH function.

Experimental

The kinetics were measured spectrophotometrically at 235 nm, by the increase in absorbance due to the formation of thiourea. For some of the higher thiocyanate concentrations the background absorbance due to SCN^- made it necessary to work at higher wavelengths up to 250 nm. The chemicals were AnalaR reagents used without further purification. The *C*,*C*′-dithiodiformamidinium chloride was prepared as described previously. The ^{13}C-labelled KNCS was supplied by Amersham International.

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