A Kinetic and Equilibrium Study of the Reactions of Potassium and Sodium Biscysteinato(*N,O,S*)-chromate(III) in Moderately Acidic Solutions

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Chromium(III) complexes with the peptide glutathione (GSH-γ-glutamylcysteinylglycine) may be important in the expression of the toxicity of chromium(VI) [1], chromium(III) nutrition [2], or both. A number of glutathione complexes of chromium have recently been shown to contain Cr–S bonds [3] and other complexes containing Cr–S bonds are known [4, 5]. One problem with the study of chromium complexes in biological systems is that sulphur to chromium linkage readily hydrolyses in both acidic and basic media [4, 5]. There are a number of reasons why this may be important: a labile Cr–S linkage may provide a reactive site on an otherwise inert chromium(III) complex, the free thiols generated may be insulin mimetic in GTF assays, and the topology and/or charge of the chromium complex may also be altered on hydrolysis.

Although there are a number of excellent studies, mainly by Deutsch and coworkers [4, 5], of the acid hydrolysis of chromium sulfur linkages, little is known of the behaviour of the Cr–S bond at near neutral pH. One of the best characterized chromium(III) complexes containing a Cr–S bond is the R-cysteine complex $K[Cr(cys)_2]$ [6]. As a starting point, we have studied the reaction of this complex at near neutral pH.

Experimental

The complex anion $[Cr(cys)_2]^-$ was prepared as both the sodium and potassium salt by literature methods [3, 6]. The samples used in quantitative studies were recrystallized from water/ethanol mixtures. Electronic spectra were measured with a Perkin-Elmer, model 330, spectrophotometer and pH was measured with a Corning model 7 meter.

Equilibrium Studies

Preliminary spectrophotometric titrations on the complex were attempted, in the hope that the results could be refined in terms of the equilibria (1) and (2):

$$\underset{(C^-)}{[Cr(cys)_2]^-} + H^+ \rightleftharpoons \underset{(HC)}{[Cr(cys)(cysSH)]} \quad (K_1) \quad (1)$$

$$\underset{(HC)}{[Cr(cys)(cysSH)]} + H^+ \rightleftharpoons \underset{(H_2C^+)}{[Cr(cysSH)_2]^+} \quad (K_2) \quad (2)$$

and quantified in terms of the corresponding equilibrium constants, K_1 and K_2. The results did not refine satisfactorily in terms of a model in which K_1 and K_2 were sufficiently well separated to be treated as independent equilibria. A rough estimate of $\log_{10} K_1 \sim 4.9$ was obtained and it was decided to investigate the equilibrium potentiometrically.

Potentiometric results were processed into values of $\bar{j}$, the average number of protons bound per mole of complex, and plots of $\bar{j}$ *versus* pH constructed. At values of pH above 4.5 the values from various experiments formed a single curve (Fig. 1). A linear least-squares procedure, as described by Rossotti [7], gave values of 5.31 and 4.46 for $\log_{10} K_1$ and $\log_{10} K_2$ respectively (no ionic strength control, 0 °C); using these values for the equilibrium constants the distribution curve, shown in Fig. 2, was constructed.

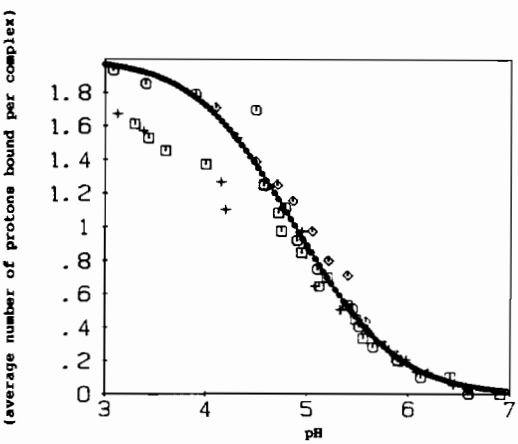

Fig. 1. Plot of $\bar{j}$ *vs.* pH (for experimental conditions see text); the different points represent three independent titrations. The solid line was calculated using the equilibrium constants reported in the text. Note the deviation of some points at pH < 4.5; these solutions were allowed to equilibrate for several minutes at each point.

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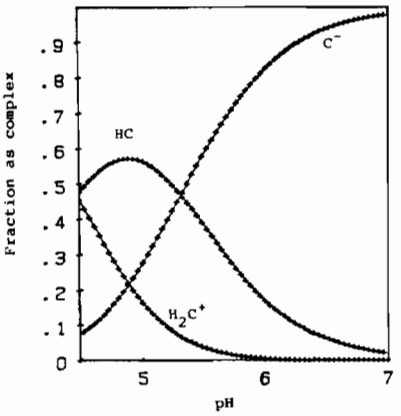


Fig. 2. Speciation of the various chromium(III) cysteine complexes in the region of reversible equilibria.

The titration of the complex with acid was followed spectrophotometrically at 260 nm. The band centred at 260 nm (S → Cr charge transfer was still appreciable at values of pH in the range 1–2.) The electronic spectra of solutions which had been titrated to such high acidities were not restored to their original intensity on neutralization with base. Similar results were obtained when the system was studied by circular dichroism.

These observations may mean that competitive N and S-bond fission is occurring in these solutions. Deutsch has recently suggested [5] that a pendant protonated thiol may assist the hydrolysis of adjacent groups in some related chromium complexes. Our results show that the protic equilibria in solutions containing this complex are not as simple as has been recently suggested by Blackwell *et al.* [8]. However, by confining our attention to a limited pH range we were able to obtain some interesting kinetic results for this system.

Kinetic Studies

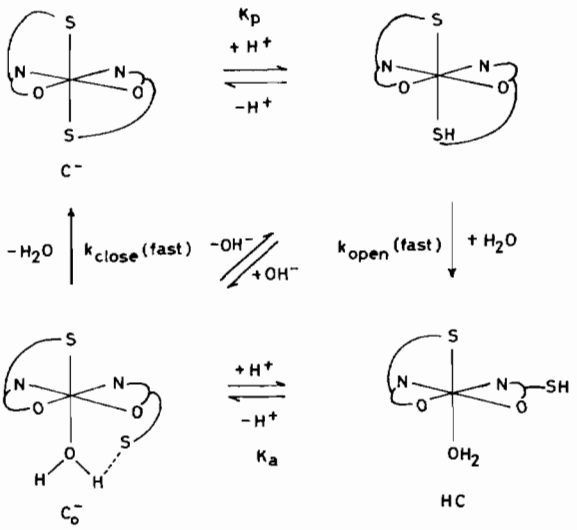
Our knowledge of the protic equilibria for $[Cr(cys)_2]^-$ enabled an informed study of ring opening and closure reactions to be made. The ring opening reaction is complicated by the fact that at moderately acidic values of pH (pH < 5.5) the reaction proceeds to an equilibrium mixture of three complexes (H_2C^+, HC and C^-), Fig. 2. The pseudo-first order rate constant for ring opening (pH = 5.5, 25.5 °C, $I = 0.1$) is 5.05×10^{-4} s^{-1}. Thus, in moderately acidic buffers, the Cr–S bond readily hydrolyses.

Solutions with a pH in the region 5.6–5.7 contain only the complexes HC and C^-. We can hence, by neutralizing these solutions, study the reaction of HC to C^- in a simple system, in which the reaction proceeds to completion. The results of such studies are summarized in Table I. In the accessible range of pH values the rate is acid independent. The reaction

TABLE I. Observed Rate Constants for the Ring Closure of [Cr(cys)(cys-SH)] [a]

Temperature (°C)	$10^3 k_{obs}$ (s^{-1})	pH
0.0	0.58	7.00
0.5	0.59	7.00
25.5	1.94	7.00
25.5	1.95	7.00[b]
25.5	1.93	7.50[c]
25.5	2.10	6.70
34.0	2.54	7.00
35.5	2.53	7.00
40.2	3.36	7.00

[a]In $NaClO_4$ and phosphate buffer ($I = 0.1$ mol dm^{-3}), followed at 605 nm. [b]Imidazole buffer. [c]Followed at 260 nm, phosphate buffer.



Scheme 1. Ring opening and closure reactions.

is also unaffected by the buffer used. This suggests that ring closure may proceed by a mechanism of the kind illustrated in Scheme 1.

The fact that the reaction is independent of pH in the region studied indicates that for this scheme the term K_a in eqn. (3) (referring to the deprotonation of the ring open complex) is much greater than the hydrogen-ion activity.

$$k_{obs} = kK_a/(H^+ + K_a) \quad (3)$$

$$\text{rate} = k|C_o|$$

This pK_a would refer either to the RSH group or to the coordinated water molecule in the complex HC. A comparison with literature values favours the latter alternative. The rate constant measured would, in this case, be the unimolecular rate constant for the ring closure of the deprotonated complex. Activation

parameters for this process are $\Delta H^{\neq} = 32.7\ (\pm 1.3)$ kJ mol^{-1} and $\Delta S^{\neq} = 1.49$ J K^{-1} mol^{-1}. The low value of the activation energy may suggest a concerted proton transfer and ring closure.

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