The Rapid Kinetics of Formation of a Mixed Ligand Complex of Copper(II)

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Summary Histamine replaces serinate which is co-ordinated to Cu^{II} *via* dissociative (replacement of serine by H_2O) and associative (second order) paths; under the reaction conditions employed the protonated form of histamine is the attacking species.

INTEREST in the catalytic activity of metal ions in mixed ligand complexes operating *via* template,[1] promnastic,[2] or electron-transfer[3] mechanisms has prompted interest in the rates and mechanisms of formation of the mixed ligand complexes themselves. Of particular importance is information concerning the rate of replacement of one ligand by another. Extensive studies have been made on reactions of labile metal ions in which a co-ordinated water molecule is replaced by an entering ligand, but relatively little is known regarding the rate laws which hold when substitution of a ligand other than water occurs.

Accurate equilibrium constants of mixed Cu^{II}–amino-acid complexes at 37° and at an ionic strength of 0·15 (KNO_3) have been reported.[4] The system we chose is that containing Cu^{II}, histamine (hm), and serinate (ser^-). Owing to the relatively high stability (greater than statistical) of the mixed ligand complex, $Cu(hm)(ser)^+$, and the relatively low stability of $Cu(hm)_2^{2+}$ (from ligand–ligand steric interactions) it is relatively easy to arrange conditions so that the predominant species in a reaction system are $Cu(ser)_2^0$ and $Cu(hm)(ser)^+$. Under a perturbation, such as a temperature jump, the interconversion of these species can readily be examined.

A Durrum–Gibson stopped-flow apparatus equipped with a temperature-jump modification was used to examine the reaction kinetics. Temperature rises of 10° from 27·0° to a final temperature of 37·0° ± 0·1 were employed. The reaction conditions and the relaxation times which were observed spectrophotometrically at 540 and 570 nm are

TABLE 1

Relaxation times in Cu^{II}*–histamine–serine solutions:*

	37°, 0·15M-KNO_3			
Cu tot M	Histamine tot M	Serine tot M	pH	$1/\tau$ (sec^{-1})
0·0050	0·060	0·040	4·99	836
0·0050	0·060	0·040	5·52	1621
0·0050	0·060	0·040	4·52	315
0·0100	0·040	0·040	5·00	515
0·0100	0·040	0·040	5·50	1010
0·0100	0·040	0·040	4·40	304
0·0200	0·080	0·080	5·00	907
0·0200	0·080	0·080	4·80	693
0·0020	0·012	0·012	5·00	283
0·0020	0·012	0·012	5·50	241
0·0020	0·012	0·012	5·30	190
0·0020	0·0080	0·0080	5·70	137
0·0020	0·0080	0·0080	5·90	117
0·0020	0·0080	0·0080	6·10	112

listed in Table 1. Over the range of all the experiments, a variation by a factor of ten in the concentration of each of the two ligands, metal ion, and hydrogen ion was obtained.

Determinations on the simple binary systems gave values of the rate constants for the reactions, $Cu^{2+} + Hhm^+ \xrightarrow{k_1} Cu(hm)^{2+} + H^+$; and $Cu^{2+} + ser^- \xrightarrow{k_3} Cu(ser)^+$; $Cu(ser)^+ + ser^- \xrightarrow{k_4} Cu(ser)_2$. Under the acidic conditions employed in these studies it is the monoprotonated form of histamine which reacts, whereas serine, which is less basic, reacts in a manner typical of the reaction of amino-acids with Cu^{II},[5,6] *i.e.* primarily as the anion. With our apparatus we were not able to find conditions in the binary system suitable for observing the rate of complexing of the second molecule of histamine to Cu^{II}. Sufficiently high pH to form appreciably high concentration levels of the relatively unstable $Cu(hm)_2^{2+}$ caused the relaxation times to be too fast for accurate observation. On the other hand, coupling of this path with the observable paths in the ternary systems permitted its rate constant to be evaluated.

Using the binary rate constants which were obtained separately it was found possible to fit the ternary relaxation times with excellent agreement (in most cases less than 20% and no more than 30% in any case) by including the additional paths, $Cu(ser)_2 + Hhm^+ \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} Cu(hm)(ser)^+ + ser^- + H^+$, $Cu(hm)^+ + Hhm^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Cu(hm)_2^{2+} + H^+$, and $Cu(ser)^+ + Hhm^+ \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} Cu(hm)(ser)^+ + H^+$. The values of the rate constants, which were obtained by a least-squares fit, are given in Table 2. Details of the computer program by which the fit was obtained will appear elsewhere.[7]

Reaction paths analogous to those found here for the reaction of monoprotonated histamine with Cu^{II} have been reported for ethylenediamine.[8] Values of $1·4 \pm 0·3 \times 10^5$ and $3·1 \pm 2·1 \times 10^4$ l $mole^{-1}$ sec^{-1} (25°) are given for the reactions $Cu^{2+} + Hen^+ \rightarrow Cu(en)^{2+} + H^+$ and $Cu(en)^{2+} + Hen^+ \rightarrow Cu(en)_2^{2+} + H^+$. The respective reaction rates with the bulkier histaminium ion are about 30% less than these. Pearlmutter and Stuehr[9] reported an identical rate law for the histaminium–Cu^{II} reactions at 25° with rate constants having values about $5 \pm 2 \times 10^4$ l $mole^{-1}$ sec^{-1} for both steps. The relatively low values found for these reactions no doubt arise from proton loss. The rate constants, k_3 and k_4, for the serinate reactions have values typical of those found for aminoacidate–Cu^{II} reactions. The lower value for k_4 probably arises from a combination of statistical effects and steric hindrance by the CH_2OH side-chain of the co-ordinated serinate with the entering ion.

Histamine is observed to replace co-ordinated serinate *via* two reaction paths: one involving an associative second-order reaction of Hhm^+ with $Cu(ser)_2$ and a second involving dissociation of a serinate followed by reaction of the aquated complex with histaminium ion, $Cu(ser)_2^0 \xrightarrow{k_{-4}} Cu(ser)^+ + ser^-$, $Cu(ser)^+ + Hhm^+ \xrightarrow{k_6} Cu(hm)(ser)^+ + H^+$. The first of these paths is the predominant path under our reaction

TABLE 2

Rate constants for the formation of binary and ternary Cu^{II}*–histamine–serine complexes*, 37°, 0·15M-KNO_3

Reaction	k_1 (M^{-1} sec^{-1})	log (k_1/k_{-1})
(1) $Cu^{2+} + Hhm^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Cu(hm)^{2+} + H^+$	$7·9 \pm 0·7 \times 10^4$	−0·29
(2) $Cu(hm)^{2+} + Hhm^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Cu(hm)^{2+}_2 + H^+$	$2·1 \pm 0·1 \times 10^4$	−0·86
(3) $Cu^{2+} + ser^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} Cu(ser)^+$	$1·8 \pm 0·2 \times 10^9$	7·56
(4) $Cu(ser)^+ + ser^- \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} Cu(ser)^0_2$	$2·8 \pm 0·1 \times 10^8$	6·45
(5) $Cu(ser)^0_2 + Hhm^+ \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} Cu(hm)(ser)^+ + ser^- + H^+$ ..	$1·0 \pm 0·03 \times 10^5$	−7·31
(6) $Cu(ser)^+ + Hhm^+ \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} Cu(hm)\,(ser)^+ + H^+$	$(3·1 \pm 0·9 \times 10^6)$	−0·86

conditions, but "leakage" through the second path is not negligible.

Pearson and Lanier[10] have found similar second-order reaction paths for the exchange of the excess of uncoordinate ligands in bulk solution with $Cu(en)_2^{2+}$ and $Cu(gly)_2$. These associative paths have been attributed to the attack of the entering ligand along the axial positions of Cu^{II}, and a similar mechanism has been suggested for Cu^{II}-substitution reactions in general.[11] The en and gly^- exchange rate constants are over an order of magnitude greater than those found here for the replacement of serinate by histamine. Deprotonation of histamine, no doubt, contributes to the slower rate.

The rate of histaminium attack on Cu^{II} is faster when serinate is co-ordinated to Cu^{II} than when either co-ordinated water or histamine is present, $k_6 > k_5 > k_1 > k_2$. Since deprotonation of the histaminium ion is probably rate-limiting in these reactions, the catalytic effect of the serinate ion is postulated to arise from transfer of the proton from histamine to the carboxylate of co-ordinated serine, followed by rapid transfer to solvent, $Cu(hmH)(ser)^{2+} \rightarrow Cu(hm)(serH)^{2+} \rightarrow Cu(hm)(ser)^+ + H^+$. This mechanism is analogous to the internal conjugate acid–base-assisted reactions suggested to account for enhanced rates of amine substitution reactions in polyamine systems.[12]

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