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The Rapid Formation of Ternary Complexes of Copper(II) with Serinate, Histamine, and Ethylenediamine

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Rates of formation and dissociation in Cu(II)–serinate (ser$^-$)–L systems (37°, 0.15 I) have been investigated where L = ethylenediamine (en) or histamine (hm). The binary complexes react *via* the paths $Cu^{2+} + ser^- \rightleftarrows Cu(ser)^+$, $Cu(ser)^+ + ser^- \rightleftarrows Cu(ser)_2$, $Cu^{2+} + L \rightleftarrows Cu(L)^{2+}$, $Cu(L)^{2+} + L \rightleftarrows Cu(L_2)^{2+}$, $Cu^{2+} + {}^+HL \rightleftarrows Cu(L)^{2+} + H^+$, and $Cu(L)^{2+} + {}^+HL \rightleftarrows Cu(L)_2{}^{2+} + H^+$. The first four paths show "normal" water replacement rate constants. Deprotonation is rate limiting in the last two. In addition, paths involving reaction of Cu(II) with both the zwitterion and neutral forms of Hser have been uncovered. The ternary complexes are formed principally through the reactions $Cu(L)^{2+} + ser^- \rightleftarrows Cu(L)(ser)^+$ and $Cu(ser)_2 + {}^+HL \rightleftarrows Cu(L)(ser)^+ + Hser$. The former is essentially a "normal" water-replacement reaction. Both the forward and reverse paths of the latter involve deprotonation of the incoming ligand mediated by the leaving ligand. The dependence of the rate constants on the nature of the ligands suggests that ligand substitution is associative (S$_N$2) in character with Cu(II).

The initial studies by Stuehr[2,3] on the reactions of amino acidate ions with Cu(II) have generated considerable interest in the rapid reactions of this metal ion with various ligands to form binary complexes.[4]

However, it is only recently that attention has been directed toward the kinetics of formation of ternary complexes in labile metal ions. Such studies are pertinent to our understanding of reactions between two ligands which are mediated by metal ions since an initial step in such reactions often involves the formation of a mixed-ligand complex. Margerum and Rosen[5] have investigated the rates of formation of mixed polyamine–ammonia complexes of Ni(II); Pasternack and Sigel[6] have determined the rate of the reaction $Cu(bipy)(H_2O)_2{}^{2+} + gly^- \rightarrow Cu(bipy)(gly)^+ + 2H_2O$, and Hague[7] has examined the kinetics of similar water-replacement reactions of polydentate complexes of Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} with pyridine-2-azo-*p*-dimethylaniline (pada). Similar to the binary reaction mechanisms, these water-replacement reactions appear to be "normal," in the Eigen-Tamm sense; that is, they are governed by the rate-determining loss of coordinated water[8] and exhibit rate constants that are typical of these mechanisms.

Very little information appears to be available regarding the kinetics of replacement of a ligand other than water coordinated to Cu(II), however. Pearson and Lanier[9] have investigated the nmr exchange rates in binary systems of various ligands coordinated to Cu(II) (as well as Ni(II) and Co(II)) with excess ligand in the bulk of the solution, $Cu(L)_2 + L^* \rightleftarrows Cu(L)(L^*) + L$. In accordance with an associative mechanism for Cu(II) exchange, they found a second-order rate law, $d[Cu(L)(L^*)]/dt = k_{ex}[Cu(L)_2][L^*]$, for which the rate constant, k_{ex}, is highly dependent on the nature of L. A mechanism involving facile solvent removal from the axial position followed by the rate-limiting structural rearrangement step was proposed.[9]

Accurate equilibrium data for several mixed complexes of Cu(II) with diamines and amino acidate ions have been determined at 37° and an ionic strength of 0.15.[10] Also, we have written a computer program, CORNEK,[11] which is capable of treating, without simplifying assumptions, the complicated sets of equations that occur in mixed-ligand relaxation systems and of finding the best least-squares fits of the rate constants for any trial rate law. From this starting point we set out on an investigation of the kinetics of formation of the mixed-ligand complexes $Cu(hm)(ser)^+$ and $Cu(en)(ser)^+$, with the particular goal of determining the rate at which an entering ligand replaces one other than water coordinated to Cu(II).

A preliminary report of some of the Cu(II)–hm results has appeared.[12] A slightly modified interpretation of these initial results is presented here as well as the results of further investigations of these interesting systems using the temperature-jump technique.

Experimental Section

Reagent grade *l*-serine, histamine (Sigma Chemical Co.), cupric nitrate, sodium hydroxide, nitric acid, and potassium nitrate (all Baker Analyzed reagents) were used without further purification. Ethylenediamine was twice redistilled. All stock solutions were prepared in doubly distilled, degassed water.

The probe solutions were made by pipetting the appropriate amounts of stock solutions and diluting to the proper volume. The ionic strength of the final solutions was maintained at 0.15 by adding calculated amounts of a KNO_3 stock solution and the solutions were adjusted to the desired pH at 37° by the dropwise addition of concentrated base and/or acid using a Radiometer pH meter (Model PHM25a) with a PHA925 scale expander. Efforts were made in each set of experiments to vary the total concentrations of each reactant by at least a factor of 10 and to vary the pH over as wide a range as feasible.

A Durrum–Gibson combined stopped-flow temperature-jump instrument was used. The temperature-jump cell of 200-μl capacity was thermostated at 27° and a 10° jump to 37° was employed. The temperature jump was calibrated by comparing the changes in transmittance of phenolphthalein in an alkaline

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buffer which occur on manually changing the temperature of the water bath with the changes which occur on "jumping" the temperature by electrical discharge. Good agreement, of the order of a few tenths of 1°, was obtained between the calibrated values and those which were calculated theoretically from the dissipation of the electrical energy.

The relaxations could be observed spectrophotometrically in some of the systems without the use of indicators. With others, however, it was found necessary to employ indicators.

The kinetic runs in this work were generally characterized by only one relaxation. This behavior appears to be common, and reasons why other possible relaxations are not observed have been cited.[13] Other reasons pertinent to this work are given below. The relaxation curves for the spectral changes which were observed in the region 540–590 nm were recorded both photographically and digitally, the latter using a Nova computer with an Analogic analog to digital converter (10-μsec conversion for 10 bits). Good agreement between the two techniques was obtained. The use of the digital computer afforded the advantage that several replicate runs (at least 10) could be easily summed to improve the signal to noise ratio and the relaxation time could be rapidly obtained by a least-squares fit of a theoretical decay curve to the summed values. By reducing the signal to noise ratio, the digital computer offered the advantage of enabling the use of points at longer times (closer to equilibrium) than is usually possible with photographic data. Thus, the slowest relaxation could be obtained more accurately without interference from faster relaxations, if any were present.

Mention should be made of an artifact in the temperature-jump instrument which was uncovered during the course of this study. An early cell design gave rise to a noticeable thermal relaxation after about 20 msec when large, ~10°, temperature jumps were employed. The three slowest relaxations reported in ref 12 are in serious error due to this effect. After the presence of the artifact was recognized, experiments were designed to give sufficiently fast relaxations so that infinity values of transmittance could be obtained in less than 20 msec.

The full details of CORNEK are given elsewhere.[11] What follows here are some notes on its effective use. For each system studied in the present work several mechanisms were tried. For selecting one mechanism over others the following factors were considered: (1) the value of the sum square at the "best fit," (2) the standard deviation in the estimated constants, (3) agreement between the observed and calculated relaxation times, and (4) the reasonability of the magnitude of the constant and the corresponding mechanism. Between two mechanisms equivalent in all respects the one with better statistical parameters is preferred.

The process of constant refinement can be started by varying estimates of all the unknown constants simultaneously for a specified number of cycles. In the early stages of a computation the program may not converge. In this case the cycle giving smallest variance in the sum square is picked out and those constants deleted which show a standard deviation greater than the values found. The process is repeated until no further improvement in statistical parameters is observed. Experience shows that sometimes it is worthwhile to repeat the process in reverse, *i.e.*, keep the minimum number of constants obtained earlier fixed and introduce other constants one by one until no significant improvement in the variance is observed. None of the methods is infallible, and which one will work best in any given situation can be determined only by experience. Difficulties may arise in refining the constants for relatively minor reaction paths. Estimates of these constants can be obtained by treating them as fixed parameters in each run and locating the best fit by using different values in successive runs.

It is important not to accept the results obtained in a single run as the final values of the constants for an assumed rate law. Rather, the results should be tested by trying alternate mechanisms and paths and by using different initial estimates for the constants being refined.

Results

The formation constants for the binary and ternary complexes of Cu(II) concerned in this work are presented in Table I. Total metal, total ligand, and pH, and observed and calculated relaxation times for various experiments are given in Table II. The reaction paths and the rate constants found here are given in Table III.

TABLE I

STABILITY CONSTANTS OF BINARY AND TERNARY COMPLEXES OF Cu(II) WITH HISTAMINE (hm), SERINATE (ser^-), AND ETHYLENEDIAMINE (en)[a] (37°, μ = 0.15 (KNO_3))

Species	Log β	Species	Log β	Species	Log β
Hen^+	9.696	H_2ser^+	11.021	$Cu(ser)^+$	7.565
H_2en^{2+}	16.628	$Cu(en)^{2+}$	10.175	$Cu(ser)_2$	14.012
Hhm^+	9.569	$Cu(en)_2{}^{2+}$	18.940	$Cu(serH)^{2+}$	0.7[b]
H_2hm^{2+}	15.581	$Cu(hm)^{2+}$	9.278	$Cu(en)(ser)^+$	16.87
Hser	8.841	$Cu(hm)_2{}^{2+}$	15.577	$Cu(hm)(ser)^+$	16.27

[a] Reference 10. [b] Reference 2.

Cu(II)–Serinate.—This system has been investigated[14] under different conditions of ionic strength and temperature than employed here (0.1, 25°). Very good agreement between the observed and theoretical relaxations had been obtained by assuming the reaction sequence

$$Cu^{2+} + ser^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Cu(ser)^+ \qquad (1)$$

$$Cu(ser)^+ + ser^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Cu(ser)_2 \qquad (2)$$

with $k_1 = 2.5 \times 10^9\ M^{-1}\ sec^{-1}$ and $k_2 = 5 \times 10^8\ M^{-1}\ sec^{-1}$.

Applying this model to our data we found that a satisfactory fit could be obtained for the observations recorded in Table II, except for the three slowest relaxations which differed by a factor of 2 from the theoretical values. Adjusting constants to bring these relaxations into line caused other values to fall out of range giving a poorer overall fit. Repetition of the experiments verified the original results, so it was concluded that the reaction model required amending.

The present experiments were run at substantially lower values of pH and at higher ligand levels than those described in ref 14, so reactions involving the protonated complex $Cu(serH)^{2+}$ seemed likely. These seemed most reasonably to be

$$Cu^{2+} + serH^{\pm} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} Cu(serH)^{2+} \qquad (3)$$

and

$$Cu(serH)^{2+} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} Cu(ser)^+ + H^+ \qquad (4)$$

Introduction of paths 3 and 4 into the reaction scheme increased the number of theoretical relaxation times from 2 to 3, and with the use of CORNEK it was found possible to fit all of the observed relaxation times within their experimental uncertainities. See Table II. The values of k_1 and k_2 found here, 1.8×10^9 and $2.8 \times 10^8\ M^{-1}\ sec^{-1}$, are comparable to those reported earlier,[14] giving credence to the results produced by CORNEK. Because of differences in ionic strength and in the treatment of the data, it is probably not safe to draw conclusions concerning activation energies from the two sets of constants, however.

Cu(II)–Ethylenediamine or –Histamine. The reaction paths found by Kirschenbaum and Kustin[15] in

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TABLE II

EXPERIMENTAL CONDITIONS AND RECIPROCALS OF OBSERVED AND THEORETICAL RELAXATION TIMES
($\lambda = 1/\tau$, 37°, $\mu = 0.15$ (KNO_3))

A. Cu(II)–Serinate

pH	$10^2[\text{Cu}]_{\text{tot}}$, M	$10^2[\text{ser}]_{\text{tot}}$, M	λ_{obsd}, $\sec^{-1}$	λ_{calcd},[a] $\sec^{-1}$
3.24	1.00	5.00	392	172, *362*, 471
3.05	1.00	5.00	548	140, 271, *467*
3.43	0.50	2.00	436	146, 342, *447*
3.19	0.50	10.0	606	172, 354, *608*
2.79	0.50	10.0	243	117, *237*, 507
2.49	0.50	10.0	252	103, *186*, 498
2.75	2.00	1.00	177	102, *189*, 463
2.96	2.00	16.00	309	183, *352*, 621
4.02	2.00	16.00	1549	425, *1559*, 3578
3.59	0.20	16.00	531	328, *436*, 1777

B. Cu(II)–Ethylenediamine
(Indicator: 10^{-5} M Bromocresol Green)

pH	$10^2[\text{Cu}]_{\text{tot}}$, M	$10^2[\text{en}]_{\text{tot}}$, M	λ_{obsd}, $\sec^{-1}$	λ_{calcd}, $\sec^{-1}$
4.12	0.5	0.5	241	43, *229*
4.71	0.5	0.5	763	11, *779*
4.51	0.5	0.5	517	18, *569*
4.32	0.2	1.0	309	24, *282*
4.02	0.2	1.0	193	49, *135*
3.71	0.2	1.0	103	49, *108*
3.83	0.2	3.0	214	70, *172*
4.06	0.2	3.0	486	41, *290*
4.70	0.2	0.3	315	12, *310*
4.54	0.2	0.3	243	17, *224*
5.00	0.05	0.7	142	15, *147*
5.32	0.05	0.705	156	26, *130*
5.50	0.05	0.705	207	38, *136*
5.32	0.10	0.705	270	22, *237*
5.04	0.10	0.50	279	10, *311*
5.56	0.10	0.50	250	22, *249*

C. Cu(II)–Histamine

pH	$10^2[\text{Cu}]_{\text{tot}}$, M	$10^2[\text{hm}]_{\text{tot}}$, M	λ_{obsd}, $\sec^{-1}$	λ_{calcd}, $\sec^{-1}$
3.50	2.0	1.00	576	280, *510*
3.77	0.261	1.60	274	237, *283*
3.23	1.00	0.89	162	*153*, 280
3.61	1.00	0.89	347	279, *364*
3.50	0.50	0.89	151	*157*, 280
3.98	0.50	0.89	459	277, *492*
3.33	1.00	5.00	607	280, *539*
4.26	1.00	0.89	1215	273, *1189*
3.94	1.00	0.89	810	278, *847*
4.03	0.56	0.79	263	*277*, 557
3.51	0.50	0.89	102	*160*, 280

D. Cu–Ethylenediamine–Serine (Indicator: 10^5 M Bromocresol Green (pH ≤5.0); Bromocresol Purple (pH >5.0))

pH	$10^2[\text{Cu}]_{\text{tot}}$, M	$10^2[\text{en}]_{\text{tot}}$, M	$10^2[\text{ser}]_{\text{tot}}$, M	λ_{obsd}, $\sec^{-1}$	λ_{calcd}, $\sec^{-1}$
4.16	0.10	0.20	0.40	670	35, 44, 158, 386, *611*
4.66	0.10	0.20	0.40	1824	19, 109, 319, 441, *2277*
4.11	0.20	0.20	0.20	614	16, 48, 118, 238, *633*
4.51	0.20	0.20	0.20	2208	23, 35, 141, 243, *1865*
4.59	0.05	0.20	0.10	474	20, 27, 144, 233, *613*
4.31	0.05	0.20	0.10	335	14, 33, 123, 211, *322*
4.20	0.50	0.30	0.20	1308	29, 44, 116, 200, *1375*
5.0	0.10	7.05	0.40	693	46, 156, *606*, 1155, 7182
4.51	0.05	0.06	0.06	375	9, 23, 118, 171, *405*
4.91	0.05	0.06	0.06	1079	13, 22, 142, 180, *1079*
5.04	0.10	0.50	0.30	2753	21, 167, 529, 688, *2599*
5.59	0.10	0.50	0.30	2351	30, 432, 1181, 2376, *2562*
5.25	0.10	0.50	0.30	2353	24, 236, 694, 1101, *2497*
5.06	0.05	0.50	0.40	2275	18, 262, 562, 1094, *2058*
5.30	0.05	0.50	0.40	2434	19, 374, 819, 1858, *2167*
5.53	0.05	0.50	0.40	1758	20, 547, 1297, *2382*, 3269
5.65	0.20	0.30	0.20	4714	27, 213, 623, 911, *5458*
5.87	0.20	0.30	0.20	5294	33, 321, 740, 1522, *5357*
5.56	0.05	0.20	0.20	2152	20, 308, 679, 1529, *1838*
5.92	0.05	0.20	0.20	2463	25, 584, 1256, *1974*, 3713

E. Cu–Histamine–Serine

pH	$10^2[\text{Cu}]_{\text{tot}}$, M	$10^2[\text{hm}]_{\text{tot}}$, M	$10^2[\text{ser}]_{\text{tot}}$, M	λ_{obsd}, $\sec^{-1}$	λ_{calcd}, $\sec^{-1}$
4.99	0.5	6.0	4.0	283	132, 203, *332*, 553, 2684
5.52	0.5	6.0	4.0	1621	206, *1619*, 2659, 4809, 33777
4.52	0.5	6.0	4.0	315	175, *298*, 506, 644, 3084
5.00	1.0	4.0	4.0	515	240, *505*, 761, 1329, 7680
5.50	1.0	4.0	4.0	1010	227, *1022*, 1964, 3870, 25895
4.40	1.0	4.0	4.0	304	116, *282*, 388, 963, 1944
5.00	2.0	8.0	8.0	907	252, *999*, 1432, 2454, 15234
4.80	2.0	8.0	8.0	693	254, *624*, 1300, 1682, 9353
5.00	0.2	1.2	1.2	241	*209*, 305, 732, 1393, 8775
5.50	0.2	1.2	1.2	190	*200*, 236, 486, 930, 5437
5.30	0.2	1.2	1.2	836	233, 636, *769*, 1523, 9346

[a] The values shown for λ_{calcd} are the eigenvalues of the characteristic equation which is obtained for each system when using the appropriate rate constants given in Table III.

TABLE III

FORWARD AND BACKWARD RATE CONSTANTS FOR Cu(II)–SERINATE–ETHYLENEDIAMINE–HISTAMINE COMPLEXES
(37°, $\mu = 0.15$ (KNO_3))

i[a]	Reaction	Forward rate constant, k_1, $M^{-1}\sec^{-1}$ [b]	Backward rate constant, k_{-1}, $\sec^{-1}$ or $M^{-1}\sec^{-1}$
	I. Solvent–Substitution Reactions		
1	$Cu^{2+} + ser^- \rightleftarrows Cu(ser)^+$	$(1.8 \pm 0.2) \times 10^9$	$(4.8 \pm 0.5) \times 10^1$
2	$Cu(ser)^+ + ser^- \rightleftarrows Cu(ser)_2$	$(2.8 \pm 0.1) \times 10^8$	$(1.00 \pm 0.05) \times 10^2$
3	$Cu^{2+} + serH^{\pm} \rightleftarrows Cu(serH)^{2+}$	$(1.2 \pm 0.2) \times 10^3$	$(2.4 \pm 0.4) \times 10^2$
7	$Cu(en)^{2+} + en \rightleftarrows Cu(en)_2{}^{2+}$	$(3.6 \pm 0.5) \times 10^9$	6.1 ± 0.09
9	$Cu^{2+} + hm \rightleftarrows Cu(hm)^{2+}$	$(2.6 \pm 1.1) \times 10^9$	1.4 ± 0.6
11	$Cu(hm)^{2+} + hm \rightleftarrows Cu(hm)_2{}^{2+}$	$(5.6 \pm 0.5) \times 10^8$	$(2.8 \pm 0.3) \times 10^2$
12	$Cu(en)^{2+} + ser^- \rightleftarrows Cu(en)(ser)^+$	$(6.2 \pm 0.8) \times 10^8$	$(1.2 \pm 0.1) \times 10^2$
20	$Cu(hm)^{2+} + ser^- \rightleftarrows Cu(hm)(ser)^+$	$(1.1 \pm 0.1) \times 10^8$	$(1.3 \pm 0.1) \times 10^1$
	II. Solvent-Substitution Reactions Accompanied by Release of a Proton to Solvent		
4	$Cu(serH)^{2+} \rightleftarrows Cu(ser)^+ + H^+$	$(1.9 \pm 0.4) \times 10^2$ [c]	$(1.8 \pm 0.4) \times 10^4$
6	$Cu^{2+} + enH^+ \rightleftarrows Cu(en)^{2+} + H^+$	$(1.7 \pm 0.1) \times 10^5$	$(5.6 \pm 0.3) \times 10^4$
8	$Cu(en)^{2+} + enH^+ \rightleftarrows Cu(en)_2{}^{2+} + H^+$	$(6.3 \pm 1.8) \times 10^4$	$(5.4 \pm 1.5) \times 10^5$
10	$Cu^{2+} + hmH^+ \rightleftarrows Cu(hm)^{2+} + H^+$	$(7.1 \pm 0.4) \times 10^4$	$(1.4 \pm 0.2) \times 10^5$
	III. Ligand Substitution Accompanied by Transfer of a Proton from Entering to Leaving Ligand		
14	$Cu(ser)_2 + enH^+ \rightleftarrows Cu(en)(ser)^+ + serH$	$(8.3 \pm 1.7) \times 10^6$	$(8.3 \pm 1.7) \times 10^4$
22	$Cu(ser)_2 + hmH^+ \rightleftarrows Cu(hm)(ser)^+ + serH$	$(1.1 \pm 0.1) \times 10^5$	$(3.2 \pm 0.3) \times 10^3$

[a] Numbered in order of appearance in text. [b] The uncertainties assigned to the rate constants are to be construed as being a measure of how well a particular value is defined by the present data, not how close to a "true" value the given value lies. [c] In $\sec^{-1}$.

an investigation of the Cu(II)–en system are

$$Cu^{2+} + en \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} Cu(en)^{2+} \tag{5}$$

$$Cu^{2+} + Hen \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} Cu(en)^{2+} + H^+ \tag{6}$$

$$Cu(en)^{2+} + en \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} Cu(en)_2^{2+} \tag{7}$$

$$Cu(en)^{2+} + {}^+Hen \underset{k_{-8}}{\overset{k_8}{\rightleftharpoons}} Cu(en)_2^{2+} + H^+ \tag{8}$$

with $k_5 = 3.8 \times 10^9\ M^{-1}\ sec^{-1}$, $k_6 = 1.4 \times 10^5\ M^{-1}\ sec^{-1}$, $k_7 = 1.9 \times 10^9\ M^{-1}\ sec^{-1}$, and $k_8 = 3.1 \times 10^4\ M^{-1}\ sec^{-1}$. Our results support this choice of reaction paths and the constants found in this work (Table III) for our experimental conditions (Table II) are once again seen to be highly consistent with the earlier results.

Comment has been made in ref 15 regarding the exceptionally high value of the rate constant for the reaction $Cu(en)^{2+} + en \rightarrow Cu(en)_2^{2+}$ (defined as k_7 in this paper) and this observation is also confirmed in the present work. In preliminary calculations, a high variance was obtained for k_5 ($Cu^{2+} + en \rightarrow Cu(en)^{2+}$), indicating that path 5 is not sufficiently important under the experimental conditions described in Table II to yield an accurate value of the rate constant. Better defined, but still somewhat uncertain, is the value given for the rate constant of reaction 8. These variances in the rate constants as given by CORNEK indicate that under the acidic conditions where the 1:1 complex predominates, the reaction path involving free amine (5) becomes slower than that involving Hen^+ (6) due to the repression of the free amine concentration by protons. On the other hand, in the less acidic solutions, the increase in the concentration of $Cu(en)_2^{2+}$ is paralleled by an increase in the concentration of free en. The path involving free amine (7) then assumes dominance over that involving the protonated ligand (8).

Similar results were found for the Cu(II)–histamine reactions, with the observed paths being

$$Cu^{2+} + hm \underset{k_{-9}}{\overset{k_9}{\rightleftharpoons}} Cu(hm)^{2+} \tag{9}$$

$$Cu^{2+} + {}^+Hhm \underset{k_{-10}}{\overset{k_{10}}{\rightleftharpoons}} Cu(hm)^{2+} + H^+ \tag{10}$$

$$Cu(hm)^{2+} + hm \underset{k_{-11}}{\overset{k_{11}}{\rightleftharpoons}} Cu(hm)_2^{2+} \tag{11}$$

Owing to the lower value of β_{H_2L} of histamine relative to ethylenediamine and the consequent higher levels of free hm in solution, the situation was reversed from that with en: it was possible to obtain a reasonably accurate value for the free amine path (9), but the path

$$Cu(hm)^{2+} + {}^+Hhm \rightleftharpoons Cu(hm)_2^{2+} + H^+ \tag{12}$$

was not well defined.

The rate constants for the formation of the histamine complexes are similar in magnitude to but are consistently lower than those for the analogous en reactions. This difference may arise from one or more of the following: hm is bulkier than en; forms a six-membered chelate ring with metal ions; and has a lower overall basicity than en.

Ternary Systems. Assuming fast proton–ligand reactions, five theoretical relaxation times are predicted for a system which contains the species Cu^{2+}, $Cu(L)^{2+}$, $Cu(L)_2^{2+}$, $Cu(ser)^+$ $Cu(ser)_2$, $Cu(L)(ser)^+$, L_Σ, and ser_Σ where L = en or hm and the subscript Σ denoted the sum over all uncomplexed forms of the species so designated.[16]

Confining the discussion at first to the Cu(II)–en–ser system, the following eight paths for the formation of the ternary complex, $Cu(en)(ser)^+$, from a binary complex are possible

$$Cu(en)^{2+} + ser^- \rightleftharpoons Cu(en)(ser)^+ \tag{13}$$

$$Cu(ser)_2 + {}^+Hen \rightleftharpoons Cu(en)(ser)^+ + Hser \tag{14}$$

$$Cu(en)_2^{2+} + Hser \rightleftharpoons Cu(en)(ser)^+ + {}^+Hen \tag{15}$$

$$Cu(en)^{2+} + Hser \rightleftharpoons Cu(en)(ser)^+ + H^+ \tag{16}$$

$$Cu(ser)^+ + {}^+Hen \rightleftharpoons Cu(en)(ser)^+ + H^+ \tag{17}$$

$$Cu(ser)_2 + en \rightleftharpoons Cu(en)(ser)^+ + ser^- \tag{18}$$

$$Cu(en)_2^{2+} + ser^- \rightleftharpoons Cu(en)(ser)^+ + en \tag{19}$$

$$Cu(ser)^+ + en \rightleftharpoons Cu(en)(ser)^+ \tag{20}$$

Estimates of the rate constants for the water replacement reactions 13, 16, 17, and 20 were made from the analogous binary reactions. Reactions 18 and 19 are Pearson and Lanier exchange reactions[9] and a preliminary value close to their upper limit, $1 \times 10^6\ M^{-1}\ sec^{-1}$, was chosen for these rate constants. Reactions 14 and 15 are of a type that has not previously been described and, thus, are the only ones which are essentially unknown.

Simple preliminary calculations using the calculated concentrations of the species and the estimated rate constants showed that rates along path 13 were larger by up to several orders of magnitude than those for paths 16–20. Thus, at best, the present set of experiments can provide information regarding only paths 13–15. The preliminary reaction model, therefore, was set up in terms of reactions 13–15, the relevent protolytic equilibria, and the reactions of binary systems. The remaining reactions (16–20) were ignored at this stage but were introduced for the final refinement.

Exhaustive numerical analyses of the data were then made using CORNEK. Initial estimates of k_{14} ranging from 1×10^5 to $1 \times 10^7\ M^{-1}\ sec^{-1}$ and k_{15} ranging from 1×10^2 to $8 \times 10^5\ M^{-1}\ sec^{-1}$ were employed. Even when k_{15} was initially greater than k_{14}, the program converged to the same values within the calculated uncertainties: k_{15} was reduced to negligible levels and k_{13} and k_{14} were brought to the values given in Table III within the listed standard deviations. In a similar manner remaining minor paths were tested and discarded. Lack of any significant contribution from these paths was further confirmed by the fact that calculations using the estimated values of rate constants for these paths (as fixed parameters) did not affect significantly the values of k_{13}, k_{14}, and sum square of the residuals. Thus, in spite of a large number of possible reaction paths, only two, (13) and (14), are observed to be important under the present conditions. This is probably another important factor in causing the observed relaxation spectra to be so simple.

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(16) Owing to the higher basicity of the solutions employed to investigate the ternary reactions, paths 3 and 4 involving Cu^{2+}–serH could be safely ignored.

Similar calculations were made for the Cu(II)–hm–ser system and once again only the paths

$$\mathrm{Cu(hm)^{2+} + ser^- \rightleftarrows Cu(hm)(ser)^+} \qquad (21)$$

and

$$\mathrm{Cu(ser)_2{}^+ + {}^+Hhm \rightleftarrows Cu(hm)(ser)^+ + Hser} \qquad (22)$$

were found.[17]

Discussion

The reaction paths listed in Table III have been classified into three categories depending on the general nature of the complex formation reaction: (I) solvent substitution, (II) solvent substitution with transfer of a proton to solvent, and (III) ligand substitution (other than solvent) with transfer of a proton from the entering to the leaving ligand.

I. Solvent Substitution.—It is generally accepted that "normal" reactions of category I involve a fast preequilibrium to yield a solvent-separated ion pair, followed by rate-limiting elimination of a water molecule from the primary coordination sphere of the metal ions[8]

$$\mathrm{M_{aq} + L \overset{fast}{\rightleftarrows} M(H_2O)L \xrightarrow{k_{-H_2O}} ML + H_2O}$$

This model yields the equation $k_f = K_o k_{-\mathrm{H_2O}}$, where k_f is the experimentally observed second-order formation rate constant, K_o is the outer-sphere ion-pair equilibrium constant, and $k_{-\mathrm{H_2O}}$ is the metal ion–water exchange rate constant.[13] A statistical correction should be applied when comparing rate constants for the successive addition of a ligand to a given metal ion or for the addition of a given ligand to various metal ions which differ in coordination number.[6]

The binary reactions in category I have been well discussed[2,3,6,14,15] so attention will be focused on the formation reactions of the ternary complexes. In this category fall the reactions

$$\mathrm{Cu(en)^{2+} + ser^- \rightleftarrows Cu(en)(ser)^+} \quad (k_{12} = 6.2 \times 10^8)$$

and

$$\mathrm{Cu(hm)^{2+} + ser^- \rightleftarrows Cu(hm)(ser)^+} \quad (k_{20} = 1.1 \times 10^8)$$

It is of interest to compare the rate constants for these reactions with the rate constant for the "normal" reaction which has the same statistical parameters in the forward direction

$$\mathrm{Cu(ser)^+ + ser^- \rightleftarrows Cu(ser)_2} \quad (k_2 = 2.8 \times 10^8)$$

Electrostatic differences between the first two reactions and the last can be corrected through their effects on K_o. Using the Fuoss equation[13] and assuming an approach of 5 Å, the ratios of the rate constants for the reactions $\mathrm{M^{2+} + L^- \rightarrow ML^+}$ and $\mathrm{M^+ + L^- \rightarrow ML}$ are calculated to be 2.4:1. The ratios $k_{12}:k_{20}:k_2$ are observed to be 2.2:0.39:1. Thus, the rate of the reaction of ser$^-$ with Cu(en)$^{2+}$ is consistent with "normal" substitution, while the presence of the bulky histamine molecule is once again seen to yield a relatively slow rate.

Furthermore, in Table III it is seen that k_{-20}, the rate constant for dissociation of ser$^-$ ion from Cu(hm)(ser)$^+$ is, also, substantially lower than the rate constant for the dissociation of this ion from the other serinato complexes (k_{-1}, k_{-2}, k_{-12}) which all have the same value within a factor of 2. This rate reduction may indicate steric hindrance between the coordinated histamine molecule and an entering water molecule. In a dissociative mechanism for ligand substitution (SN1) bulky nonleaving ligands enhance the rate.[18] The opposite effect shown here by histamine suggests that an associative (SN2) mechanism holds for Cu(II) substitution.

The Cu(II)–bipyridyl–glycinate system has also been found to exhibit nearly normal behavior for ternary complex formation, but the ratio of the rate constants for the reactions

$$\mathrm{Cu(bipy)^{2+} + gly^- \longrightarrow Cu(bipy)(gly)^+} \quad (k_f = 1.6 \times 10^9\ M^{-1}\ \mathrm{sec}^{-1})$$

and

$$\mathrm{Cu(gly)^+ + gly^- \longrightarrow Cu(gly)_2} \quad (k_f = 4 \times 10^8\ M^{-1}\ \mathrm{sec}^{-1})$$

is slightly larger than observed here, amounting to 4:1. The back-reactions have been found to be nearly the same, however, after taking into account a statistical factor of 2 favoring the latter reaction. Thus, the Cu(II)–bipy–gly$^-$ system seems to exhibit small, but appreciable, differences from those studied here.

The reaction

$$\mathrm{Cu^{2+} + serH \rightleftarrows Cu(serH)^{2+}} \quad (k_3 = 1.2 \times 10^3\ M^{-1}\ \mathrm{sec}^{-1})$$

is seen in Table III to have an unusually low rate constant for a simple water replacement reaction of category I. This value was calculated using the total concentration of monoprotonated serine in solution. Since the ratio of the zwitterion, $\mathrm{{}^+NH_3CRCO_2{}^-}$, to neutral form, $\mathrm{NH_2CRCO_2H}$, is about 10^5:1 for serine,[19] k_3 has essentially been evaluated using the zwitterion concentration. If instead, the rate constant is evaluated for the reaction which involves the neutral species

$$\mathrm{Cu^{2+} + H_2NCRCO_2H \underset{k_{-3'}}{\overset{k_{3'}}{\rightleftarrows}} Cu(NH_2CRCO_2H)^{2+}} \qquad (3')$$

a more nearly normal value for $k_{3'}$ of about 1.2×10^8 M^{-1} sec^{-1} is obtained. The carboxylic acid group of $\mathrm{Cu(NH_2CRCO_2H)^{2+}}$ is fairly acidic and under the influence of the metal ion probably undergoes rapid proton loss followed by ring closure. Thus, reaction 3′ is a rate-limiting step in a path alternate to (1) for the formation of Cu(ser)$^+$. A similar conclusion was reached in a study of Ni(II)–pyridinecarboxylate reactions.[4c]

II. Reactions Involving Solvent Substitution Accompanied by a Release of Proton to Solvent.—The rate constants for the reactions $\mathrm{Cu^{2+} + HL^+ \rightarrow CuL^{2+} + H^+}$ are seen in Table III to be of the order of 10^5 M^{-1} sec^{-1} for L = en and hm. These values are substantially lower than those in category I by a factor much greater than can be accounted for by the effects of electrostatic repulsion on K_o. It has been postulated[15] that rate-determining proton loss from intermediate

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[17] The reaction $\mathrm{Cu(ser)^+ + {}^+Hhm \rightleftarrows Cu(hm)(ser)^+ + H^+}$ had been proposed earlier.[11] However, the instrumental artifact influenced the conclusions regarding this minor path. It is worth noting that the rate constant for the major path (14) is relatively free of error from this effect.

[18] F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed, Wiley, New York, N. Y., 1968, Chapter 3.

[19] The pK_a of ethyl serinate has been determined to be 7.0 (25°) (ref 20). Assuming that this value is the same for the protonation of the amine group of $\mathrm{H_2NCRCO_2H}$ and using the value 1.5×10^2 M^{-1} for the second protonation constant of Hser + H$^+$ ⇄ H$_2$ser$^+$, the ratio $\mathrm{[H_3N^+CRCO_2{}^-]/[H_2NCRCO_2H]}$ is calculated to be about 1×10^5.

[20] B. E. Leach and R. A. Angelici, *J. Amer. Chem. Soc.*, **91**, 6296 (1969).

$Cu(enH)^{3+}$ is the cause for the relatively low value for the Cu^{2+}–enH^+ reaction.

This conclusion may be verified through a rough calculation. The free amine group of ethylenediamine which is monodentately bound to Pt(II) has recently been reported[21] to have a pK_a of 8.0, 25°. Assuming diffusion-controlled protonation, the rate of the proton dissociation reaction

$$Pt^{II}NH_2CH_2CH_2NH_3^+ \xrightarrow{k_{-H}} Pt^{II}NH_2CH_2CH_2NH_2 + H^+$$

is calculated to be about 1×10^2 sec^{-1}. The combined effects of the smaller Cu(II) ion and the higher temperature in this work may cause this value to be slightly higher, becoming about 5×10^2 sec^{-1}. Consistent with this estimate the deprotonation of an ammonium group in Cu(II)-coordinated carnosine proceeds with a rate constant which has been directly determined[22] to be 2.3×10^2 sec^{-1}, 25°. The first step in the reaction

$$Cu^{2+} + enH^+ \rightleftarrows Cu(enH)^{3+} \qquad (6')$$

may be reasonably assumed to be in preequilibrium owing to combination of a high forward rate constant, a relatively high level of enH^+, and a relatively low stability of the protonated complex. From the reported value of about 10 M^{-1} for the equilibrium constant for

$$Ni^{2+} + NH_2CH_2CH_2N(CH_3)_3^+ \rightleftarrows Ni(NH_2CH_2CH_2N(CH_3)_3)^{3+}$$

and applying the factor of 20–30 which is observed for the ratios of Cu:Ni stability constants with monodentate amines, the value of the equilibrium constant, $K_{6'}$, for reaction 6′ is estimated to be about 200–300 M^{-1}. The value of k_6, as calculated from the product $K_{6'}k_{-H}$, is therefore predicted to lie in the range $(0.7\text{–}2) \times 10^5$ M^{-1} sec^{-1}. The observed value of k_6, 1.7×10^5 M^{-1} sec^{-1}, is therefore of the correct magnitude expected for rate-determining proton loss.

Reaction 4 involves a proton loss to solvent by a first-order process. The value of the rate constant is also consistent with rate-limiting proton loss from an ammonium group of a Cu(II)-coordinated ligand. Therefore, the rate-limiting step of this reaction is assigned to the deprotonation of a coordinated serine in the zwitterion form. Because of the high zwitterion levels coordination to Cu(II) should be fast, leading to the formation of $Cu(ser)^+$ through the sequence

$$Cu^{2+} + {}^-O_2CCRNH_3^+ \underset{}{\overset{\text{fast}}{\rightleftarrows}} Cu(O_2CCRNH_3)^{2+}$$

$$Cu(O_2CCRNH_3)^{2+} \underset{\substack{k_{-4} \\ \text{slow}}}{\overset{k_4}{\rightleftarrows}} Cu(ser)^+ + H^+$$

III. Ligand Substitution with Transfer of a Proton from Entering to Leaving Ligand.—These reactions bear a resemblance to those in category II in the sense that one of the reactants is a protonated ligand. However, a major difference is that a bidentate ligand is replaced rather than a pair of coordinated water molecules. Since bond breaking is important in determining rates of both SN1 and SN2 reactions, it may be expected that the rates in this last category will be slower than those in the previous category. Inspection of Table III shows that the opposite situation occurs.

Proton transfer to solvent was shown to be rate limiting for category II reactions. The faster category III rates imply that this step is mediated by transfer of the proton either directly or indirectly, through an intervening water molecule,[23] from the entering ligand to a basic group of the leaving ligand. Indeed, because of the high proton-transfer rates of this type,[23] proton transfer in category III reactions may no longer be rate determining.[24]

There are no charge differences involved in comparing the forward and backward reactions of paths 14 and 22. The outer-sphere complexes if formed will have the same equilibrium constants and therefore the rate constants k_{14}, k_{-14}, k_{22}, and k_{-22} can be compared directly. Three trends that emerge are as follows. (1) If the ligand coordinated to the central metal ion remains the same and the incoming ligand varies, the rate constants for the bulkier histamine molecule are smaller than the corresponding rate constants for ethylenediamine (reactions 14 and 22). (2) If the incoming ligand is the same (Hser in k_{-14} and k_{-22}) and the nonleaving ligand varies, the rate constants are again smaller for the chelate in which a bulkier ligand is coordinated to the metal ion. (3) Rates are faster if the incoming ligand is a diamine rather than an amino acid, *i.e.*, the greater the affinity of the incoming ligand for the metal ion, the faster is the reaction. In short, these rate constants are distinctly dependent on the nature of the incoming and departing ligand. These observations support the conclusions of Pearson and Lanier[9] that the Cu(II)-exchange reactions are essentially associative (SN2) in nature.

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[21] M. J. Carter and J. K. Beattie, *Inorg. Chem.*, **9**, 1233 (1970).

[22] R. F. Pasternack and K. Kustin, *J. Amer. Chem. Soc.*, **90**, 2295 (1968).

[23] E. Grunwald, A. Lowenstein, and S. Meiboom, *J. Chem. Phys.*, **27**, 630 (1957).

[24] The lower electrostatic effects in the ternary systems described here cannot account for the results since even higher rate constants are found in the exchange reactions $Cu(hm)_2^{2+} + Hen^+ \rightleftarrows Cu(hm)(en)^{2+} + H^+hm$ and $Cu(en)_2^{2+} + H^+hm \rightleftarrows {}^+Hen$: V. S. Sharma and D. L. Leussing, to be reported.