Copper(II) Chelation Kinetics. α-Alanine, β-Alanine, and Histidine

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Abstract: Rate constants for the formation of Cu^{2+} complexes with α- and β-alanate and the histidine zwitterion have been measured by temperature-jump and stopped-flow methods. The forward rate constants for α-alanine (1.3×10^9 and 1.5×10^8 M^{-1} sec^{-1}) illustrate "normal" kinetics for Cu^{2+}. Those for the mono and bis complexes of β-alanine are substantially smaller (2.0×10^8 and 8×10^6 M^{-1} sec^{-1}), and for histidine smaller yet (1.3×10^7 and 3.0×10^6 M^{-1} sec^{-1}). In addition, for β-alanine, a slow kinetic step following the complexation reactions was observed, probably associated with the formation of a partly half-bonded tris complex. For the formation of the five-membered chelate with α-alanine, the rate-determining step was ligand penetration, consistent with the Eigen–Tamm mechanism for the formation of a strong chelate. The substantially reduced rates for β-alanine and histidine are interpreted on the basis of ring closure as the rate-determining step, the effect being most pronounced for the formation of the histidine chelate.

Eigen and Tamm[2] proposed a multiple step mechanism for fast metal complex formation in which the rate-determining step was the loss of water from the inner coordination sphere of the metal ion. This mechanism, based largely on ultrasonic absorption spectra of 2:2 electrolytes, has been verified for a number of other complexes involving transition metal and alkaline earth ions. In the majority of such studies,[3] the rate constant for ligand penetration is characteristic of the metal ion alone. Among the exceptions are some chelation reactions in which steric effects, such as chelate ring formation, bring about a slow-down in the over-all complexation rate. Kustin, *et al.*,[4] in recent studies of amino acid complexing with Ni^{2+}, Co^{2+}, and Mn^{2+} showed that the β-amino acid reacted more slowly than the corresponding α-amino acid. This effect was attributed to a change in the rate-determining step from water displacement to ring closure upon the formation of the bidentate chelate. Further, a prediction was made that the most labile metal ions would have the largest steric effect.

This study was undertaken to determine if a more labile metal ion, such as Cu^{2+}, enhances this steric effect. Kinetic results are presented here for the reaction of Cu^{2+} with α-alanine, β-alanine, and histidine.

Experimental Section

Materials. Matheson Coleman and Bell reagent grade $Cu(NO_3)_2 \cdot 3H_2O$, Fisher reagent grade KNO_3 and α-alanine, Eastman Kodak β-alanine, and Calbiochem L-histidine were used without further purification. The solutions used were prepared by volumetric dilution of stock solutions made up with degassed Stokes water and maintained at 0.1 ionic strength using KNO_3.

Instrumentation. The pH of the solutions was adjusted with KOH and/or HNO_3 in conjunction with a pH meter (Beckman Expandomatic) calibrated with Fisher certified buffers. Spectra of reactant and product solutions were determined with a Beckman DU spectrophotometer to determine optimum wavelengths for the kinetic study. Kinetic runs at 25° were made on a Gibson–Durrum stopped-flow spectrophotometer, and a temperature-jump apparatus[5] obtained from Messanlagen Studiengesellschaft, Göttingen, W. Germany. For the latter, the enthalpy changes associated with the complexing reactions were sufficiently large in all instances that the use of pH indicators was not necessary.

Kinetic Runs. For the majority of the measurements with the stopped-flow technique, two distinct steps could be observed for a given system at a particular wavelength. In all instances where this was true, it was also possible to observe each step alone by proper choice of detection wavelength. In the temperature-jump measurements, a single relaxation process was evident at any one time for the alanine systems. Two relaxation times were observed for some of the histidine solutions; these, also, could be observed separately by varying the wavelength.

Relaxation times were determined from at least three oscilloscope traces, photographed with a Polaroid camera. The exponential traces were enlarged and plotted on semilog paper. In order to ensure close-to-equilibrium conditions, only the last portions of the stopped-flow traces were graphed. Computations of equilibrium concentrations from initial concentrations and the final pH were carried out on a Univac 1107 computer. The equilibrium constants relevant to this study are shown in Table I.

Table I. Log of Equilibrium Constants for Copper Complexes[a]

	Reaction	α-Alanine	β-Alanine	Histidine
K_{a1}	$H_2LH^{2+} = H^+ + H^+LH$	...	...	−1.83
K_{a2}	$H^+LH = H^+L^- + H^+$	−2.34	−3.55	−6.08
K_{a3}	$H^+L^- = H^+ + L^-$	−9.67[b]	−10.03[b]	−9.11[c]
K_1	$Cu^{2+} + L^- = CuL^+$	8.09[b]	7.26[b]	10.22[c]
K_2	$CuL^+ + L^- = CuL_2$	6.66[b]	5.63[b]	8.29[c]
K_3	$Cu^{2+} + H^+L^- = Cu(HL)^{2+}$	0.72	1.71	5.07[c]
K_4	$Cu(HL)^{2+} + H^+L^- = Cu(HL)_2^{2+}$	...	...	4.43[c]
K_m	$CuL^+ + H^+L^- = CuL(HL)^+$	...	...	9.93[c]

[a] At 25° and $I = 0.1$ unless otherwise noted: L. Sillen and A. Martell, Ed., "Stability Constants," Special Publication No. 17, The Chemical Society, London, 1964. [b] Values adjusted to $I = 0.1$ from data at $I = 0$. [c] 20° values adjusted to $I = 0.1$ from data at $I = 0.035$.

Results

A tabulation of initial concentrations and measured relaxation times is given in Table II. The symbols

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(2) (a) M. Eigen, *Z. Elektrochem.*, **64**, 115 (1960); (b) M. Eigen and K. Tamm, *ibid.*, **66**, 93, 107 (1962).

(3) M. Eigen and R. G. Wilkins, "Mechanisms of Inorganic Reactions," Advances in Chemistry Series, No. 49, American Chemical Society, Washington, D. C., 1965.

(4) (a) K. Kustin, R. F. Pasternak, and E. M. Weinstock, *J. Amer. Chem. Soc.*, **88**, 4610 (1966); (b) A. Kowalak, K. Kustin, R. F. Pasternak, and S. Petrucci, *ibid.*, **89**, 3126 (1967).

(5) M. Eigen and L. DeMaeyer, "Technique of Organic Chemistry," Vol. VIII, Part II, A. Weissberger, Ed., Interscience Publishers Inc., New York, N. Y., 1963, Chapter XVIII.

Table II. Tabulation of Initial Concentrations and Results[a]

[Cu]°, M	[Ligand]°, M	pH[b]	τ_1^{-1}, sec^{-1} [c]	τ_2^{-1}, sec^{-1} [c]	[Cu]°, M	[Ligand]°, M	pH[b]	τ_1^{-1}, sec^{-1} [c]	τ_2^{-1}, sec^{-1} [c]	τ_3^{-1}, sec^{-1}
α-Alanine					β-Alanine					
0.002	0.0002	4.20	(33)	25 (28)	0.002	0.0002	4.30	(19)	20 (13)	
0.002	0.0004	4.00	(33)	30 (25)	0.002	0.0004	4.00	(19)	15 (12)	
0.004	0.0008	3.75	(33)	33 (27)	0.004	0.0008	3.80	(19)	16 (12)	
0.008	0.0008	3.63	(33)	23 (29)	0.008	0.0008	3.69	(19)	17 (12)	
0.01	0.002	3.37	(33)	28 (28)	0.01	0.005	3.37	(19)	12 (12)	
0.01	0.004	3.25	(34)	27 (29)	0.01	0.02	3.55	(24)	17 (19)	
0.01	0.005	3.07	(33)	31 (22)	0.01	0.04	3.55	(36)	14 (19)	
0.01	0.020	3.25	(73)	29 (34)	0.015	0.001	4.50	(115)	31 (19)	
0.01	0.030	3.25	(93)	33 (35)	0.01	0.125	3.71	201 (157)[d]	(19)	
0.01	0.040	3.25	(110)	28 (36)	0.01	0.20	3.77	221 (267)[d]	(20)	
0.015	0.002	3.25	(33)	26 (26)	0.01	0.20	4.10	591 (850)[d]	(23)	
0.01	0.050	2.61	(34)	34 (21)	0.005	0.250	3.77	237 (162)[d]	(20)	
0.01	0.050	3.31	168 (149)[d]	(37)	0.01	0.40	4.00	527 (777)[d]	30 (27)	1.7
0.01	0.100	2.61	(34)	35 (28)	0.01	0.50	4.18	872 (1380)	44 (44)	2.0
0.005	0.100	3.05	72 (63)[d]	(38)	0.01	0.40	4.37	(2210)	(59)	1.1
0.01	0.125	3.30	235 (223)[d]	(50)	0.01	0.40	4.43	(2600)	(69)	1.6
0.01	0.200	3.29	285 (266)[d]	(66)	0.01	0.40	5.05	(10800)	(460)	4.8
0.01	0.200	3.63	(701)	133 (141)	0.01	0.40	5.20	(13000)	(704)	6.3
0.005	0.250	3.33	264 (206)[d]	(82)	0.01	0.40	5.26	(13600)	(831)	7.1
0.005	0.250	3.63	466 (446)[d]	(172)						
0.01	0.400	3.37	429 (444)	128 (146)						
0.01	0.400	3.63	1310 (894)	227 (292)						
0.01	0.500	3.31	422 (414)[d]	141 (154)						
Histidine										
0.002	0.0015	3.35	(217)	98 (118)	0.01	0.10	3.02	925 (1140)[d]	(511)	
0.01	0.04	2.69	506 (441)[d]	230 (174)[d]	0.01	0.10	2.61	760 (555)[d]	(248)	
			(441)	177 (174)	0.01	0.125	2.86	(976)	530 (452)[d]	
0.01	0.06	3.94	(3270)	1080 (710)[d]	0.01	0.125	2.82	(909)	430 (420)	
0.01	0.06	3.26	1100 (1210)[d]	(470)	0.01	0.30	3.63	(10100)	1760 (2060)[d]	
0.01	0.08	3.51	2150 (2070)[d]	(797)	0.01	0.30	3.35	(5350)	1050 (1580)[d]	
0.01	0.08	3.00	1150 (996)[d]	(413)	0.01	0.30	3.03	(2610)	900 (1060)[d]	
0.01	0.08	2.75	834 (655)[d]	(273)	0.015	0.03	4.00	1386 (1120)[d]	(267)	
0.01	0.08	2.46	550 (376)[d]	(176)	0.03	0.06	3.93	1500 (1380)[d]	(358)	
0.01	0.10	3.54	(2670)	1330 (953)[d]	0.03	0.06	2.87	1140 (1180)[d]	276 (229)[d]	

[a] All measurements are from stopped-flow data unless otherwise indicated. The superscript zero refers to total stoichiometric concentration. [b] [H] was calculated by dividing the measured hydrogen ion activity by γ_H ($\cong$0.80). [c] Experimental values given first. Values calculated from eq 1 are in parentheses using k_{1f} and k_{2f} in text. [d] Measurements with the temperature-jump apparatus.

τ_1 and τ_2 refer to relaxation times associated with the formation of the mono and bis complexes, respectively. τ_3 refers to a third slow relaxation time ($\sim$0.1 sec) observed only with β-alanine. The measured relaxation times are estimated to be reliable to ±15%.

The pH and concentration dependencies of τ_1 and τ_2 for the α- and β-alanine systems are consistent with the mechanism

$$\begin{array}{ccccc} & \text{I} & & \text{I} & \\ & \text{H}^+\text{L}^- & & \text{H}^+\text{L}^- & \\ & \| & & \| & \\ & \text{H}^+ & & \text{H}^+ & \\ & + & & + & \\ \text{Cu}^{2+} + \text{L}^- & \underset{k_{1r}}{\overset{k_{1f}}{\rightleftharpoons}} & \text{CuL}^+ + \text{L}^- & \underset{k_{2r}}{\overset{k_{2f}}{\rightleftharpoons}} & \text{CuL}_2 \\ \text{II} & & \text{III} & & \text{IV} \end{array} \qquad \text{(a)}$$

where H^+L^- is the zwitterion of the amino acid, L^- is the anion, and CuL^+ and CuL_2 are the mono and bis complexes, respectively. The fast proton-transfer reactions are indicated by = signs and the slower complexing steps by arrows. The two relaxation times for mechanism a, corresponding to metal-complex formation, are obtained by solving the determinant of the differential equations for restoration of equilibrium, and are given by[6]

$$\tau_{1,2}^{-1} = -\frac{1}{2}\left[(a_{11} + a_{22}) \pm \sqrt{(a_{11} + a_{22})^2 - 4(a_{11}a_{22} - a_{12}a_{21})}\right] \qquad (1)$$

where the shorter of the two relaxation times is given by the plus sign, the larger by the minus sign. The a_{ij} coefficients[7] are calculated from the appropriate mass-balance and preequilibrium relationships. Since the two relaxation times were often within a factor of 10 of each other, the rate constants could not be solved for directly. The data in Table II were fitted to the correct values of k_{1f} and k_{2f} by inserting a large number of combinations for the two unknown constants into a computer program and comparing the predicted values for τ_1 and τ_2 with those obtained experimentally. Those rate constants which predict the correct values for τ_1 and τ_2 are given in Table III. Algebraic manipulation of eq 1 shows that in dilute solutions τ_2^{-1} tends toward k_{1r}. This provides a test of the internal consistency of the mechanism. From Table II it can be seen that the correct limit for τ_2^{-1} is reached or approached for all the systems investigated.

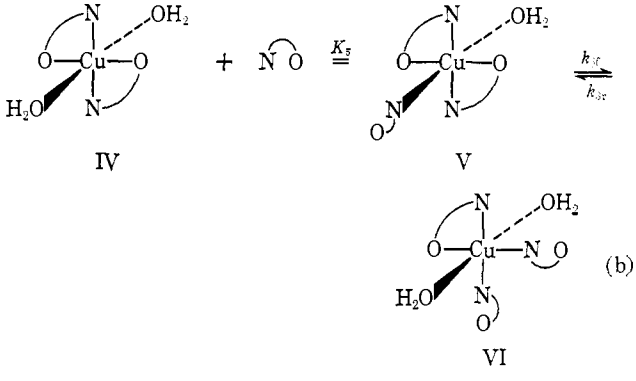
(6) (a) G. G. Hammes and J. I. Steinfeld, *J. Amer. Chem. Soc.*, **84**, 4639 (1962); (b) A. F. Pearlmutter and J. Stuehr, *ibid.*, **90**, 858 (1968).

(7) The a_{ij} coefficients for mechanism a are $a_{11} = -k_{1f}([\overline{Cu}]/(1 + \alpha) + [\overline{L}]) - k_{1r}$, $a_{12} = k_{1f}[\overline{Cu}]/(1 + \alpha) - k_{1r}$, $a_{21} = k_{2f}([\overline{CuL}]/(1 + \alpha) - [\overline{L}])$, $a_{22} = -k_{2f}([\overline{CuL}]/(1 + \alpha) + [\overline{L}]) - k_{2r}$, where $\alpha = [\overline{H}]/(Ka_3 + [\overline{L}])$ and the bars indicate equilibrium concentrations.

Table III. Rate Constants for $Cu(L)_{n-1} + L \underset{k_{nr}}{\overset{k_{nf}}{\rightleftharpoons}} Cu(L)_n$

Ligand	k_{1f}, M^{-1} sec^{-1}	k_{1r}, sec^{-1}	k_{2f}, M^{-1} sec^{-1}	k_{2r}, sec^{-1}
α-Alanine$^-$	$(1.3 \pm 0.3) \times 10^9$	12	$(1.5 \pm 0.5) \times 10^8$	33
β-Alanine$^-$	$(2.0 \pm 0.5) \times 10^8$	11	$(8 \pm 1) \times 10^6$	19
H^+ histidine$^-$	$(1.3 \pm 0.2) \times 10^7$	115	$(3.0 \pm 0.3) \times 10^6$	111

In contrast to the α-amino acid systems where only two relaxation times were observed, a third slower relaxation time[8] was seen for the reaction of Cu^{2+} with β-alanine (Table II). An interpretation of τ_3 which is both mathematically and chemically compatible with the data is the formation of a copper complex in which three β-alanine anions are coordinated: two of them as monodentate ligands, the third as a bidentate chelate. This is, in fact, the mechanism proposed by Pearson and Lanier[9] in a nmr study of the second-order exchange of glycine with bisglycinatocopper(II). This mechanism may be written as



IV V VI (b)

in which steps IV–V and V–VI directly follow the complexation reactions in mechanism a, and K_5 is the indicated stability constant. The step IV–V represents the fast replacement of a loosely bound axial water by β-alanate, and V–VI involves the formation of the tris chelate where two of the β-alanine ions are monodentate. Pearson and Lanier suggest that V rearranges through a trigonal-bipyrimidal intermediate, where one of the chelate rings opens and forms the square-planar species VI. If one assumes that V is present as a steady-state intermediate and that all the steps in mechanism a are preequilibria, the solution for the third relaxation time is

$$\tau_3^{-1} = K_5 k_{3f}[F(c)] + k_{3r}$$

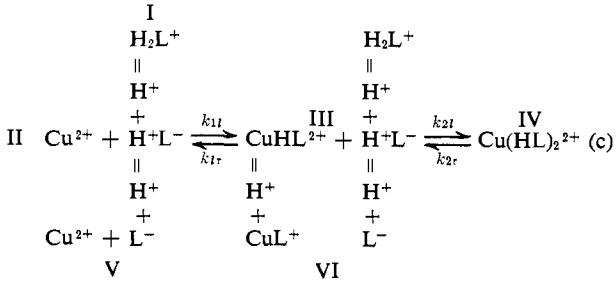
where

$$F(c) = \left\{\frac{[CuL_2]}{1+\alpha}[K_2(2[L] + 3K_1) + [L]^2] + \left[[L]^2 + \frac{3[Cu][L]}{1+\alpha} + \frac{[CuL]}{1+\alpha}(3K_1 + 2[L])\right][L]\right\} \Big/ \left\{K_2(K_1 + [L]) + [L]^2 + \frac{[Cu]}{1+\alpha}(K_2 + 2[L]) + \frac{[CuL]}{1+\alpha}(2K_1 + [L])\right\} \quad (2)$$

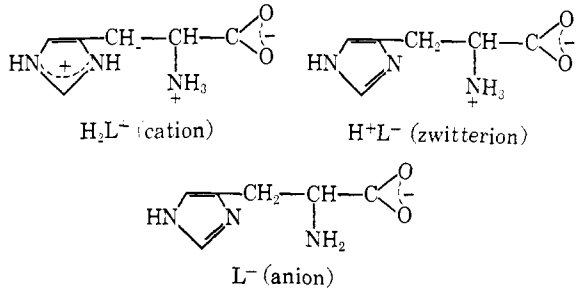
$\alpha = [H]/(K_{a3} + [L])$, and all concentrations are equilibrium values. A graph of τ_3^{-1} *vs.* $F(c)$ yields a line of slope K_5k_{3f} and intercept k_{3r}. The results[10] are $K_5k_{3f} = (3.0 \pm 0.5) \times 10^5\ M^{-1}$ sec^{-1} and $k_{3r} = 1.2 \pm 0.2$ sec^{-1}. Although K_5 is not known, the value for the analogous "tris" complex formed between Cu(II) and ethylenediamine[11] ($K_5 = 10$) may be taken as an approximate maximum value. Thus, for Cu(II) with β-alanine, $K_5 \leq 10$ and $k_{3f} \geq 3 \times 10^4$ sec^{-1}.

An interpretation of τ_3 in terms of the formation of a tris bidentate complex was also attempted. There is, however, no thermodynamic evidence for the existence of such a species and very little for tris bidentate complexes of Cu(II) in general. The data did fit this mechanism and yielded the same forward and reverse rate constants as above. Their ratio would be the equilibrium constant for the formation of the tris complex, *viz.* $\sim 3 \times 10^5$. This value is clearly not reasonable in view of all available thermodynamic evidence.

For the copper–histidine reaction, the mechanism which quantitatively accounts for the data is



where the various forms of the ligand are designated by



The species $CuHL^{2+}$ and $Cu(HL)_2^{2+}$ are the mono and bis complexes, respectively, of copper combined with the histidine zwitterion; CuL^+ is the complex of copper combined with the histidine anion. The = signs and arrows have the same meaning as before. The a_{ij} terms are obtained from mass balance and preequilibrium relationships, in the same manner as for mechanism a.[12] The rate constants were obtained from eq 1 as described above. The results are shown in Table III. Here also, τ_2^{-1} tends toward k_{1r} in dilute solutions.

Pathway V–VI as well as a pathway involving the formation of CuL_2 was found to be negligible over the pH range investigated. It was possible to vary the rate constant for V–VI from zero to $10^{11}\ M^{-1}$ sec^{-1} without affecting the predicted values of τ_1 and τ_2. This is not unexpected since at the pH values used the concentration of the histidine anion (L^-) is six orders of magnitude less than that of the zwitterion (H^+L^-),

(8) Since τ_3 is substantially slower than τ_1 and τ_2, its interpretation does not in any way influence the treatment of the faster steps.

(9) R. Pearson and R. Lanier, *J. Amer. Chem. Soc.*, 86, 765 (1964).

(10) Exact solution without the steady-state assumption yields virtually identical results.

(11) L. Sillen and A. Martell, Ed., "Stability Constants," Special Publication No. 17, The Chemical Society, London, 1964.

(12) The complete solution of eq 1 for mechanism c is given in an Appendix to this article.

The zwitterion (H^+L^-) exists in two forms. That illustrated as H^+L^- is the predominant species. Presumably, a complex of Cu^{2+} with H^+L^- would be a seven-membered ring chelate. However, approximately 0.1% of the zwitterion present has the imidazole ring protonated and the amino group unprotonated ($-NH_2$).[13] A complex of this latter zwitterion (HL′) with Cu^{2+} would be a five-membered ring leaving the imidazole ring protonated. When the zwitterion HL′ is substituted for the predominant H^+L^-, mechanism d results, which has somewhat different preequilibrium relationships as compared with c. If, as before, a large number of trial rate constants are inserted into eq 1, it is found that the τ_1 and τ_2 values which result

$$\begin{array}{l} H^+ + H^+L^- = H_2L^+ \\ \qquad\qquad \| \\ \qquad\qquad +H^+ \\ H^+ + L^- = HL' + Cu^{2+} \rightleftharpoons \\ \qquad\qquad Cu(HL')^{2+} + HL' \rightleftharpoons Cu(HL')_2^{2+} \end{array} \quad \text{(d)}$$

cannot be correlated with the data. Rate constants which yield correct results for part of the data for one of the relaxation times give widely scattered predictions, incorrect by orders of magnitude, for the other relaxation time. We conclude therefore that complexation does not occur *via* mechanism d.

Discussion

A general chelation mechanism for bidentate ligands[4] may be formulated as

$$\begin{array}{l} M(OH_2)_x + \overset{\frown}{A\ B} \overset{K_{os}}{=\!=} (H_2O)_{x-2}H_2OMOH_2\,\overset{\frown}{A\ B} \\ \qquad\qquad \text{I} \qquad\qquad\qquad\qquad \text{II} \\ (H_2O)_{x-2}H_2OMOH_2\,\overset{\frown}{A\ B} \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} (H_2O)_{x-2}H_2OM\text{—}\overset{\frown}{A\ B} + H_2O \\ \qquad\qquad \text{II} \qquad\qquad\qquad\qquad \text{III} \\ (H_2O)_{x-2}M\begin{array}{l}\diagup H_2O \\ \diagdown \overset{\frown}{A\ B}\end{array} \underset{k_{43}}{\overset{k_{34}}{\rightleftharpoons}} (H_2O)_{x-2}M\begin{array}{l}\diagup A \\ \diagdown B\end{array}\!\!\big) + H_2O \\ \qquad\qquad \text{III} \qquad\qquad\qquad\qquad \text{IV} \end{array} \quad \text{(e)}$$

$\overset{\frown}{A\ B}$ represents a bidentate ligand

The charges on the metal ion and ligand have been omitted. Step I–II represents the diffusion of the ions together to form the outer-sphere complex;[14] step II–III represents the formation of a monodentate inner-sphere complex; and step III–IV represents ring closure to form the bidentate complex. The outer-sphere equilibrium constant, K_{os}, may be estimated[6b] using electrostatic theory.

A recent paper[15] has afforded experimental verification of the two-step chelation mechanism. In a study of the formation of nickel malonate two relaxation times were found, corresponding to steps I–II–III and III–IV in mechanism e. Ring closure to form the chelate was found to be much slower than the ligand penetration rate into the inner hydration sphere of the cation.

When for a given complex only one relaxation time corresponding to the transformation from I through IV in mechanism e is seen, it is still possible to relate k_f to k_{23} and k_{34} with the assumptions that step I–II is very fast and that state III may be treated as a steady-state intermediate. The result[4,6a] is

$$k_f = K_{os}k_{23}\frac{1}{1 + (k_{32}/k_{34})} \qquad (5)$$

Note that k_f is always *diminished* by the factor $1/[1 + (k_{32}/k_{34})]$. There are two limiting cases. First, if $k_{34} \gg k_{32}$, then $k_f = K_{os}k_{23}$. This is identical with the relation between the observed forward rate constant and the ligand penetration rate derived from the Eigen–Tamm mechanism[2] for a strong monodentate complex. Second, if $k_{32} > k_{34}$ ring closure (step III–IV) becomes rate determining.[4,16] In this case the fractional term in the denominator must be considered. If $k_{32} \gg k_{34}$, then the limiting case $k_f = K_{os}K_{23}k_{34}$ is achieved.

α-Alanine. As indicated previously[6b] for the ligand glycine, step II–III in mechanism e is the rate-determining step. Comparison of k_{1f} and k_{2f} for copper–α-alanine with those for copper–glycine shows that these two sets of rate constants are virtually identical. Thus, we term these two ligands, as well as the acetate,[17] as having "normal" metal–ligand combination rates.

From experimental forward rate constants, the ligand penetration rate may be calculated using the equation $k_f = K_{os}k_{23}$. If one uses the same equations as in ref 6b, there result $K_{os} = 2$ and 0.7 at $I = 0.1$ for the formation of the mono and bis complexes, respectively; the latter includes a factor of $^4/_6$ to compensate for the two occupied positions.

The high numerical values of the calculated ligand penetration rate constants (Table IV) are a direct result

Table IV. Ligand Penetration Rate Constants for Cu(II)

Ligand	k_{23}, sec^{-1}		Ref
	Mono	Bis	
H_2O[18]	$\geq 3 \times 10^9$	...	*a*
Acetate	$\sim 1 \times 10^9$	...	*b*
Glycinate	2×10^9	5×10^8	*c*
Pyridine azo dye	1×10^9	...	*d*
α-Alanate	1×10^9	2×10^8	This work

[a] R. E. Connick and R. S. Marianelli, "Symposium on Relaxation Techniques," Buffalo, N. Y., June 1965; cited in F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1967, p 227. [b] Estimated from data in ref 17. [c] Reference 6b. [d] Reference 3.

(13) The approximate concentration of this species may be calculated using the concentration of H_2L^+ and the pK of a typical amino group. This calculation ignores the imidazole entity. For all reasonable amino group pK values, it turns out that HL′ is present at concentrations much higher than L^-.

(14) If the ligand is strongly solvated, state II may have the ligand and metal ion separated by two hydration layers. In such cases, an additional (fast) step would be observed in the relaxation spectrum; see ref 2.

(15) U. Nickel, H. Hoffmann, and W. Jaenicke, *Ber. Bunsenges. Physik. Chem.*, 72, 526 (1968).

(16) M. Eigen, *Pure Appl. Chem.*, 6, 105 (1963).

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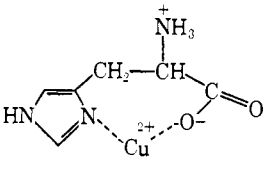
of Jahn–Teller distortion of the d^9 ion.[18] Two of the water molecules (axial) are more distant from the metal ion than the four planar (equatorial) waters resulting in greater lability of water in the axial positions. In addition there is a rapid inversion of this structure such that axial and equatorial molecules interchange. The rate of this inversion process relative to the water exchange rate has not yet been established. There are two limiting possibilities. First, if water at the axial positions exchanges at rates less than the inversion process, then the ligand penetration rate may be equated with the water exchange rate. On the other hand, if inversion is slower than axial water exchange, the inversion process itself becomes rate determining. That is, since coordination occurs *via* the loss of solvent from axial positions, inversion would have to occur before the second position (for a bidentate ligand) could be occupied. The first case would predict that the formation of the bis complex would be faster than the mono, due to the decreased charge on the cation (*cf.* Ni(II) and Co(II)[6a]). The slower formation rate of the bis complex actually observed argues for the second possibility, *i.e.*, inversion being rate determining,[19] as indicated in the earlier study.[6b]

β-Alanine. In the reaction of Cu^{2+} with β-alanine, the first two steps are considered analogous to those seen in the copper–α-alanine system. The rate constants for the complexation steps with β-alanine are slower than those determined for α-alanine (Table III). The steric factor, $[1 + (k_{32}/k_{34})]^{-1}$, can be evaluated by a comparison of the forward rate constants of the β-alanine system with those of the α-alanine system. Thus $k_f(\alpha\text{-ala}) = k_f(\beta\text{-ala})\cdot[1 + (k_{32}/k_{34})]$, resulting in a steric factor for the monocomplex of 0.15; for the bis complex 0.053. As a result, the k_{32}/k_{34} values are 5.5 and 18, respectively. In each case $k_{32} \gg k_{34}$; this is the condition which results in the rate-determining step being ring closure.

It remains to explain why we observe τ_3 with β-alanine, but not with glycine or α-alanine. The answer probably lies in the steric differences. From crystal structure measurements, it is known that, compared to five-membered amino acid chelates, the six-membered chelate rings have additional degrees of freedom.[20] The β-chelate ring has a boat configuration which is far more distorted than that of the α-chelate; this distortion is most noticeable in the large deviation from planarity of the –CC(=O)O—M. Thus the explanation may be that the β-chelate undergoes the V–VI transformation to a large enough extent so that it is visible under the conditions of our kinetic measurements. This unusual behavior of the β-alanine system is consistent with other known anomalous properties of this amino acid. It is the only β-amino acid of biological significance; yet its function, especially in mammals, is not known.

Histidine. In the reaction with histidine, the neutral histidine molecule reacts with Cu^{2+}. The rate constants for the formation of the mono and bis complexes are much slower than those found for α- and β-alanine and glycine (Table III). From currently available evidence,[21] two possible structures may be assigned to the species formed from the reaction of copper and histidine at low pH values.



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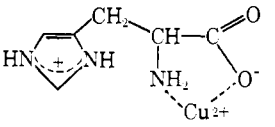

II

Even when the experiments were nearly identical, various workers have reached conflicting conclusions.[21a,d] In some investigations the pH values used were higher than those in this study[21d] while others failed to clarify the pH at which results were obtained.[21b] The preponderance of experimental evidence, including X-ray work, indicates that II is the structure of the complex. Our kinetic results rule out the *direct* interaction of Cu^{2+} and HL′ to yield this species. However, it is probable that as Cu^{2+} reacts with the neutral histidine zwitterion a rapid proton transfer, from the amino group to the imidazole ring, accompanies the chelation reaction. As suggested by Freeman,[20] the product is then the chelate shown as structure II. A rapid proton transfer following complexation would not be observed kinetically. The possibility also exists that initially structure I is formed which rearranges slowly to II; this appears unlikely.

By comparing the rate constants for copper–histidine with those of "normal" chelation ((Table IV), one finds the steric factor for the mono and bis complexes to be 0.01 and 0.02, respectively.

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Appendix

The rate equations for mechanism c are

$$\frac{d(\delta Cu)}{dt} = -\frac{1}{\tau}\delta Cu = -k_{1f}(Cu\delta HL + HL\delta Cu) + k_{1r}\delta CuHL$$

$$\frac{d(\delta Cu(HL)_2)}{dt} = -\frac{1}{\tau}\delta Cu(HL)_2 = k_{2f}(CuHL\delta HL + HL\delta CuHL) - k_{2r}\delta Cu(HL)_2$$

If one solves the mass-balance and preequilibrium equations,[22] the a_{ij} factors used in eq 1 are found to be

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(22)

$$\delta Cu + \delta CuL + \delta CuHL + \delta Cu(HL)_2 = 0$$

$$\delta H_2L + \delta HL + \delta L + \delta CuL + \delta CuHL + 2\delta Cu(HL)_2 = 0$$

$$2\delta H_2L + \delta HL + \delta H + \delta CuHL + 2\delta Cu(HL)_2 = 0$$

$$K_{a2}\delta H_2L - H\delta HL - HL\delta H = 0$$

$$K_{a3}\delta HL - H\delta L - L\delta H = 0$$

$$K_p\delta CuHL - CuL\delta H - H\delta CuL = 0$$

$$a_{11} = -k_{1f}\left(\frac{Cu}{A} + HL\right) - k_{1r}\left(\frac{1}{B}\right)$$

$$a_{12} = k_{1f}\left(\frac{Cu}{C}\right) - k_{1r}\left(\frac{1}{D}\right)$$

$$a_{21} = k_{2f}\left(\frac{CuHL}{A} - \frac{HL}{B}\right)$$

$$a_{22} = -k_{2f}\left(\frac{CuHL}{C} + \frac{HL}{D}\right) - k_{2r}$$

where $K_p = (K_1 \cdot K_{a3})/K_3$ and

$$A = NUM/[H(K_{a2} + HL)H + H(K_{a2} + 2HL)K_p + HK_{a2}(CuL + L)]$$

$$B = NUM/[H(K_{a2} + H + HL)H + L(K_{a2} + 2H)H + K_{a3}(K_{a2} + 2HL)H + H(K_{a2} + 2H)CuL]$$

$$C = NUM/[H(CuL + L + H + K_p)K_{a2} + H \cdot HL \cdot H + 2K_{a2} \cdot L \cdot K_p]$$

$$D = NUM/[H(K_{a2} + H + HL)H + L(K_{a2} + 2H)H + K_{a3}(K_{a2} + 2HL)H + CuL(2K_{a3} + H)K_{a2}]$$

$$NUM = [H + K_p] \cdot [H(K_{a2} + H + HL) + L(K_{a2} + 2H) + K_{a3}(K_{a2} + 2HL)] + [CuL(K_{a3} + H)K_{a2} + H \cdot CuL \cdot H]$$

A Cryoscopic Study of Copper(I) Hydride–Phosphine Complexes

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Abstract: Pyridine solutions of copper(I) hydride plus aryl or alkyl phosphines and phosphites have been studied by freezing point depression. Cryoscopic titration curves for the most basic phosphines show a molality minimum which corresponds to the formation of $R_3P(CuH)_2$. It is proposed that association occurs *via* hydride bridges. 1,2-Bis(diphenylphosphino)ethane (diphos) yields a molality minimum corresponding to diphos$(CuH)_2$. Solutions and solid samples of copper hydride–phosphine complexes do not have a high order of thermal stability, and this leads us to question the validity of a previous report on highly stable copper hydride–phosphine complexes.

The preparation of copper hydride was first reported by Würtz in 1844 making it the oldest properly characterized metal hydride.[2] By treating an aqueous solution of copper(II) sulfate with hypophosphorous acid, Würtz obtained a thermally unstable red-brown material of the approximate composition CuH. More recently, Wiberg[3] reported that copper hydride could be prepared by the metathesis of copper(I) iodide and lithium tetrahydroaluminate in a pyridine–ether solvent system. When prepared by this method, copper hydride was reported to be soluble in pyridine, and a pure compound could be obtained on repeated precipitation from this solvent by addition of ether. In contrast, a nondestructive solvent has never been found for the copper hydride prepared by the Würtz method.

The insoluble form of copper hydride has been the topic of much study and controversy.[4] Both X-ray[5] and neutron[6] powder diffraction studies indicated the compound has a wurtzite structure. There are no features in the infrared[7] or Raman[8] spectra of the solid compound which can be attributed to a copper–hydrogen vibration. Numerous variations[4,9] of the Würtz preparation have involved the reaction of aqueous Cu^{2+} with a variety of reducing agents, but all result in an insoluble copper hydride which contains variable amounts of water that cannot be removed without decomposition of CuH into the elements.

In a recent detailed investigation, soluble copper hydride was found to be monomeric in pyridine solution.[10] In spite of the original claim that soluble and insoluble copper hydride have identical properties, a number of differences were found. X-Ray powder patterns of soluble copper hydride indicated the solid exists in a high degree of subdivision unlike the insoluble form. Also, the pyridine-soluble copper hydride retains variable amounts of pyridine in addition to lesser amounts of copper(I) iodide and traces of LiI. The solubility of copper hydride prepared in this method may be attributed to the presence of pyridine and/or the high degree of subdivision.

With the thought that CuH occurs in pyridine solution as a complex, we have studied the interaction of copper hydride with other potential ligands such as phosphines, phosphites, and 2,2′-bipyridine. With available instrumentation we were unable to locate infrared, Raman, or nmr spectral features characteristic of the hydride in these solutions. Furthermore, we were unable to isolate stable solid copper hydride complexes. Therefore, a cryoscopic investigation was initiated, since this

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