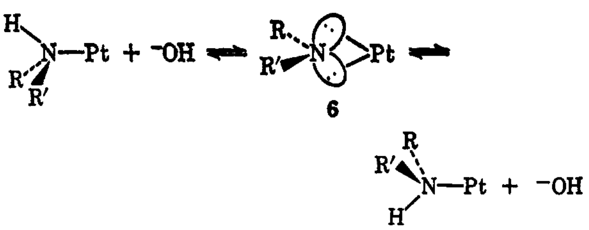
rate of displacement of chloride in Pt(II) complexes,[11] and it therefore can be said to have a considerably greater *trans* effect than ammonia and other simple amine ligands. Other exchange rates[12] on Pt(II) complexes also show a strong *trans* effect, so the same ligands which stabilize the transition state for displacement at Pt(II) also stabilize the transition state for proton exchange. We have previously found a *trans* effect in inversion at sulfur bonded to Pt(II) where the suggested mechanism involves an internal displacement of one sulfur pair of electrons by the other.[2] The most likely mechanism for displacement at platinum(II)[13,14] involves stabilization of a transition state with geometry near that of a trigonal bipyramid. These considerations suggest that the mechanism of proton exchange and inversion at nitrogen in Pt(II)–N<H complexes involves a process (eq 13) similar to the one we have suggested for inversion at sulfur in Pt(II)–sulfide complexes.[1b] The intermediate **6** is drawn to indicate possible stabilization through double coordination of nitrogen to platinum; **6**, then, is a distorted pentacoordinate intermediate. This mechanism would predict that inversion should proceed half as fast as exchange. This would be the maximum rate for inversion since an exchange mechanism (other than eq 13) involving a nitrogen pair not bonded to platinum could only give slower inversion due to protonation of $\geqslant$N: before inversion. Our results (eq 1 and 2) are within experimental error of agreement with eq 13. Therefore this may be an inversion at nitrogen which does not proceed through a planar state with trigonal hybridization at nitrogen, as has been found in other studies of inversion at nitrogen [3,15–17] and as may apply in Co(II) complexes.[4] Alternatively, the *trans* effect in inversion might be explained by π bonding to platinum when the nitrogen is in the trigonal planar configuration.



(13)

---

(11) P. Haake and P. A. Cronin, *Inorg. Chem.*, 2, 879 (1963).

(12) J. W. Palmer and F. Basolo, *J. Phys. Chem.*, 64, 778 (1960).

(13) C. H. Langford and H. B. Gray, "Ligand Substitution Processes," W. A. Benjamin, Inc., New York, N. Y., 1966.

(14) P. Haake, *Proc. Chem. Soc.*, 278 (1962).

(15) R. S. Berry, *J. Chem. Phys.*, 32, 933 (1960).

(16) (a) H. S. Gutowsky, *Ann. N. Y. Acad. Sci.*, 70, 786 (1953); (b) W. N. Speckamp, U. K. Pandit, and H. O. Huisman, *Tetrahedron Letters*, 3279 (1964); (c) T. J. Bardos, C. Szantay, and C. K. Navada, *J. Am. Chem. Soc.*, 87, 5796 (1965).

(17) (a) A. T. Bottini and J. D. Roberts, *ibid.*, 80, 5203 (1958); (b) A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, 82, 3599 (1960); (c) D. L. Griffith and J. D. Roberts, *ibid.*, 87, 4089 (1965); (d) F. A. L. Anet, R. D. Trepka, and D. J. Cram, *ibid.*, 89, 357 (1967); (e) F. A. L. Anet and J. M. Osyany, *ibid.*, 89, 352 (1967).

The Reactions of L-Carnosine with Metal Ions. Copper(II)[1,2]

Robert F. Pasternack[3] and Kenneth Kustin

Contribution from the Department of Chemistry, Brandeis University, Waltham, Massachusetts 02154. *Received September 12, 1967*

Abstract: The temperature-jump method has been used to determine the complexation rate constants for the reactions of L-carnosine (HL) with copper(II) at 25° and ionic strength 0.1 *M*. It had been previously postulated that L-carnosine is a bidentate ligand in the lower pH range forming a complex containing a seven-membered chelate ring. The complexation reactions observed are $Cu^{2+} + H_2L^+ \rightleftharpoons CuHL^{2+} + H^+$ and $Cu^{2+} + HL \leftrightarrows CuHL^{2+}$. The rate constants for the former reaction are $k_1 = 8.9 \times 10^2\ M^{-1}\ sec^{-1}$ and $k_{-1} = 5.0 \times 10^4\ M^{-1}\ sec^{-1}$; for the latter they are $k_2 = 3.5 \times 10^6\ M^{-1}\ sec^{-1}$ and $k_{-2} = 35\ sec^{-1}$. These rate constants are consistent with a sterically controlled substitution (SCS) mechanism. The complex $CuHL^{2+}$ can release a proton, producing CuL^+; this latter complex can also release a proton to form CuA. The rate constants for $CuHL^{2+} \rightleftharpoons CuL^+ + H^+$ are 230 sec^{-1} for the forward reaction and $1.0 \times 10^7\ M^{-1}\ sec^{-1}$ for the reverse process. For the reaction $CuL^+ \rightleftharpoons CuA + H^+$, the values are 360 sec^{-1} for the forward reaction and $5.0 \times 10^7\ M^{-1}\ sec^{-1}$ for the reverse process. Both reverse reactions are several orders of magnitude slower than the diffusion-controlled limit. This is attributed to intramolecular changes which are concurrent with proton attack.

Relaxation techniques have been used extensively in the study of complexation reactions of labile transition metal ions. A general two-step mechanism has proven consistent with the available experimental data.[4] This mechanism begins with the formation of a diffusion-limited ion pair between the aquated metal ion and the reactant ligand. Second, and rate-determining, is the substitution of the reactant ligand into the inner coordination sphere of the metal ion. For reactions obeying

---

(1) The authors gratefully acknowledge partial support from Public Health Service Research Grant GM-08893-04 from the National Institute of General Medical Sciences, Public Health Service, and wish to thank the National Science Foundation for College Faculty Summer Participation Grant GE-7569 and the Petroleum Research Fund for Grant 2982B to R. F. P.

(2) K. Kustin and R. F. Pasternack, *J. Am. Chem. Soc.*, in press.

(3) Department of Chemistry, Ithaca College, Ithaca, N. Y. 14850.

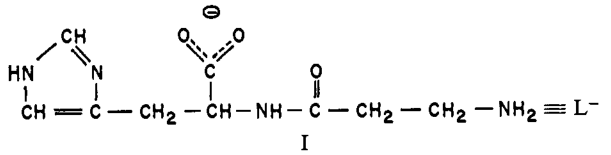
(4) M. Eigen and R. G. Wilkins in "Mechanisms of Inorganic Reactions," Advances in Chemistry Series, No. 49, American Chemical Society, Washington, D. C., 1965, pp 55–65.

what has been termed "normal substitution" kinetics, the rate of complexation is controlled by the release of the first water molecule from the inner hydration sphere of the transition metal ion and is thus independent of ligand.[4] However, for other reactions whose kinetics have been termed "sterically controlled substitution" (SCS), the rate has been shown to be ligand dependent.[5,6]

For these latter systems it was postulated that the rate-controlling process passes from the release of a water molecule from the inner hydration sphere of the metal ion to a sterically hindered formation of a metal chelate system. The systems for which evidence indicates sterically controlled substitution are β-alanine with cobalt(II) and manganese(II) and β-aminobutyric acid with cobalt(II). Thus, complexation rates which are lower than normal were observed with ligands forming six-membered chelate rings (β-amino acids) rather than the more stable five-membered chelate rings (*e.g.*, α-amino acids). The SCS effect was not observed when nickel(II) complexes were formed with β-amino acid ligands. The effect is evident when the inherent lability of the metal ion is so great that ring closure (itself usually very rapid) can become rate determining.

An investigation of the kinetics of complex formation of L-carnosine with nickel(II) and cobalt(II) has been carried out.[2] Although it seems very unlikely that L-carnosine forms a complex containing only five-membered rings,[7] normal substitution was observed in both cases. In particular, a rate constant of 4.2 × 10^5 M^{-1} $\sec^{-1}$ was obtained for the reaction with cobalt(II) with which the ligand has been postulated to form a seven-membered ring. Sterically controlled substitution effects should be more pronounced with copper(II), a more labile ion than cobalt(II), and the investigation of the interaction of L-carnosine with this ion is herein reported.

L-Carnosine (β-alanyl-L-histidine) is a dipeptide which exists in solution in the forms H_2L^+, HL, and L^-. The structural formula of the anion is given by I.



I

It has been postulated from potentiometric titration data that copper forms three complexes with L-carnosine differing in degree of protonation.[7] These are termed $CuHL^{2+}$, CuL^+, and CuA. However, a recent crystallographic study of the copper–L-carnosine system indicates that the complex is dimeric in a crystal obtained from a solution maintained at high pH.[8] Thus the nature of the species present in solution at high pH is somewhat uncertain.

Experimental Section

Fisher reagent grade nitrate salts of potassium and copper(II) were used. Nutritional Biochemicals Corp. L-carnosine was likewise used without further purification. The indicators were Eastman methyl orange and Aldrich phenol red, both of which were reagent grade, and Eastman *p*-nitrophenol, which was recrystallized from distilled water.

The temperature-jump apparatus has been described elsewhere.[9] Solutions were made up with requisite amounts of metal ion added to dissolved ligand and indicator. The ionic strength was brought to 0.1 *M* with KNO_3, and the pH was adjusted by dropwise addition of dilute NaOH and/or HNO_3. The temperature was 25 ± 1°.

Test solutions of either metal ion or ligand in the absence of the other showed no discernible effects, the concentration levels being characteristic of those of solutions containing all the reactants. The relaxation times for solutions containing all the reactants represent an average of at least three photographic determinations. The relative error for these measurements is ±10% for the low pH studies. At higher pH's, where two relaxation effects were observed, the relative error in relaxation times is somewhat greater, that is, about 25%.

Results and Treatment of Data

The various equilibrium constants pertinent to the study of the kinetics of the copper–L-carnosine system are listed in Table I. Charges have been neglected in this table and throughout the remainder of this paper unless otherwise specified.

Table I. Stoichiometric Equilibrium Constants[a] at Ionic Strength 0.1 *M* and 25°

$K_1 = [\mathrm{H}][\mathrm{HL}]/[\mathrm{H_2L}] = 1.74 \times 10^{-7}$

$K_2 = [\mathrm{H}][\mathrm{L}]/[\mathrm{HL}] = 4.37 \times 10^{-10}$

$K^{\mathrm{Cu}}{}_{\mathrm{CuHL}} = [\mathrm{CuHL}]/[\mathrm{Cu}][\mathrm{HL}] = 1.02 \times 10^{5}$

$K_1{}^{\mathrm{Cu}} = [\mathrm{CuL}]/[\mathrm{Cu}][\mathrm{L}] = 5.25 \times 10^{9}$

$K^{\mathrm{H}}{}_{\mathrm{CuHL}} = [\mathrm{CuHL}]/[\mathrm{CuL}][\mathrm{H}] = 4.47 \times 10^{4}$

$K^{\mathrm{H}}{}_{\mathrm{CuL}} = [\mathrm{CuL}]/[\mathrm{CuA}][\mathrm{H}] = 1.38 \times 10^{5}$

$K_{\mathrm{HIn_1}} = [\mathrm{H}][\mathrm{In_1}]/[\mathrm{HIn_1}] = 2.95 \times 10^{-4}$ [b]

$K_{\mathrm{HIn_2}} = [\mathrm{H}][\mathrm{In_2}]/[\mathrm{HIn_2}] = 1.26 \times 10^{-8}$ [b]

$K_{\mathrm{HIn_3}} = [\mathrm{H}][\mathrm{In_3}]/[\mathrm{HIn_3}] = 2.50 \times 10^{-8}$ [b]

[a] All carnosine and carnosine–copper constants are from ref 7. [b] I. M. Kolthoff, *J. Phys. Chem.*, **34**, 1466 (1930); HIn_1 ≡ methyl orange, HIn_2 ≡ *p*-nitrophenol, HIn_3 ≡ phenol red.

Even neglecting any ambiguity arising from the nature of the species in solution at high pH, the reactions of copper with L-carnosine are more complicated than those with nickel or cobalt, as indicated by the potentiometric titration data. In each case, the extent of the reaction is followed by a pH indicator, HIn, coupled to the ligand, and so the reactions

$$\mathrm{HIn} \rightleftharpoons \mathrm{H} + \mathrm{In}$$

$$\mathrm{H_2L} \rightleftharpoons \mathrm{H} + \mathrm{HL}$$

$$\mathrm{HL} \rightleftharpoons \mathrm{H} + \mathrm{L}$$

must also be considered. To simplify the analysis, we begin with the data at low pH.

Single-Step Kinetics. At the lowest pH values at which effects could be detected, the complete reaction scheme is given by eq 1.[10]

$$\begin{tikzcd}
\mathrm{Cu} + \mathrm{H_2L} \arrow[r, shift left, "k_1"] \arrow[d, shift left] & \mathrm{CuHL} + \mathrm{H} \arrow[l, shift left, "k_{-1}"] \\
\mathrm{Cu} + \mathrm{HL} \arrow[u, shift left, "\text{very fast}"] \arrow[r, shift left, "k_2"] & \mathrm{CuHL} \arrow[l, shift left, "k_{-2}"]
\end{tikzcd} \qquad (1)$$

The complexation reactions in this scheme are characterized by a single relaxation time according to the

---

(5) K. Kustin, R. F. Pasternack, and E. M. Weinstock, *J. Am. Chem. Soc.*, 88, 4610 (1966).

(6) A. Kowalak, K. Kustin, R. F. Pasternack, and S. Petrucci, *ibid.*, 89, 3126 (1967).

(7) G. R. Lenz and A. E. Martell, *Biochemistry*, 3, 750 (1964).

(8) H. C. Freeman and J. T. Szymanski, *Acta Cryst.*, 22, 406 (1967).

(9) P. Hurwitz and K. Kustin, *Inorg. Chem.*, 3, 823 (1964).

(10) M. Eigen, *Ber. Bunsenges. Physik. Chem.*, 67, 753 (1963).

relation

$$\tau^{-1} = k_2\{[\mathrm{Cu}]' + [\mathrm{HL}] + 1/K^{\mathrm{Cu}}{}_{\mathrm{CuHL}}\} + k_1\{[\mathrm{Cu}]'' + [\mathrm{H_2L}] + (1/K^{\mathrm{Cu}}{}_{\mathrm{CuHL}}K_1)([\mathrm{CuHL}]''' + [\mathrm{H}])\} \quad (2)$$

where

$$[\mathrm{Cu}]' = \left(\frac{K_1}{K_1 + [\mathrm{H}]} + \frac{\alpha_1}{\alpha_2}\frac{[\mathrm{HL}]}{K_1 + [\mathrm{H}]}\right)[\mathrm{Cu}]$$

$$[\mathrm{Cu}]'' = \alpha_1\left(1 - \frac{1}{\alpha_2}\frac{[\mathrm{HL}]}{K_1 + [\mathrm{H}]}\right)[\mathrm{Cu}] \quad (3)$$

$$[\mathrm{CuHL}]''' = \frac{\alpha_1}{\alpha_2}[\mathrm{CuHL}]$$

with

$$\alpha_1 = \frac{[\mathrm{H}]}{K_1 + [\mathrm{H}]}$$

$$\alpha_2 = \beta + \frac{[\mathrm{HL}]}{K_1 + [\mathrm{H}]} \quad (4)$$

$$\beta = \frac{K_{\mathrm{HIn}} + [\mathrm{H}] + [\mathrm{In}]}{K_{\mathrm{HIn}} + [\mathrm{H}]}$$

Values of k_1 and k_2 could thus be obtained by solving simultaneous equations using relaxation times obtained at low pH.

A summary of the experimental conditions in the pH 3.5–4.0 region, together with the observed and calculated relaxation times, is given in Table II. The rate constants which were determined in this pH range are: $k_1 = 8.9 \times 10^2\ M^{-1}\ \mathrm{sec}^{-1}$; $k_{-1} = 5.0 \times 10^4\ M^{-1}\ \mathrm{sec}^{-1}$; $k_2 = 3.5 \times 10^6\ M^{-1}\ \mathrm{sec}^{-1}$; and $k_{-2} = 35\ \mathrm{sec}^{-1}$. The relative error in these rate constants is estimated at not more than ±20%.

Table II. Relaxation Spectra of Copper(II)–L-Carnosine Solutions at Low pH

[L-Carnosine]$_0$ $\times 10^3$	[Cu]$_0$ $\times 10^3$	[H]	τ_{exptl} $\times 10^3$, sec	τ_{calcd} $\times 10^3$, sec
0.990	1.00	1.00×10^{-4}	9.7	11
0.483	0.564	1.00×10^{-4}	20	19
0.805	0.786	1.00×10^{-4}	16	14
1.11	2.05	3.09×10^{-4}	13	13
2.08	2.96	1.74×10^{-4}	7.2	6.2
3.67	4.18	1.45×10^{-4}	4.0	2.9

Multistep Kinetics. At higher pH values the concentrations of additional copper–carnosine species become appreciable. Thus, the complete reaction scheme is that given by eq 5. (The concentrations of L$^-$ and A^{2-} in solution never become appreciable.)

$$\begin{tikzcd}
\mathrm{Cu + H_2L} \arrow[r, shift left, "k_1"] \arrow[d, shift left] & \mathrm{CuHL + H} \arrow[l, shift left, "k_{-1}"] \\
\mathrm{Cu + HL} \arrow[u, shift left, "\text{very fast}"] \arrow[r, shift left, "k_2"] & \mathrm{CuHL} \arrow[l, shift left, "k_{-2}"] \arrow[d, shift left, "k_D"'] \\
 & \mathrm{CuL} \arrow[u, shift left, "k_P"'] \arrow[d, shift left, "k_A"'] \\
 & \mathrm{CuA} \arrow[u, shift left, "k_H"']
\end{tikzcd} \quad (5)$$

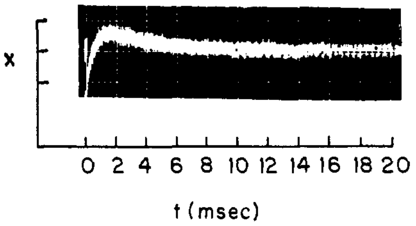


Figure 1. Relaxation spectrum for a copper(II)–L-carnosine solution. The initial concentrations for this solution are [Cu]$_0$ = $5.52 \times 10^{-4}\ M$, [L-carnosine]$_0$ = $4.73 \times 10^{-4}\ M$, and pH 6.01. In solutions in which the pH is $\geqslant 6$, two relaxation effects were observed. The relaxation time for the slower effect was always at least ten times longer than for the faster effect so that it was possible to resolve these spectra into two exponential curves and thereby determine the respective relaxation times. For this solution, the relaxation times were 4.1 and 0.29 msec.

Even though the processes $\mathrm{H_2L} \rightleftharpoons \mathrm{HL} + \mathrm{H}$ and $\mathrm{HIn} \rightleftharpoons \mathrm{In} + \mathrm{H}$ can be assumed to be very much more rapid than the reactions directly involving copper-containing species, the complete solution for the relaxation times of such a system of reactions involves a 3 × 3 matrix. The exact analysis thus leads to a cubic secular equation, the solution of which is difficult. However, a simplifying feature in this system is that at pH ≥6 two relaxation effects are observed (Figure 1).

The slower effect has been assigned to complexation, the process which could be treated independently at lower pH's. (The presence of additional protolytic steps serves only to modify the correction factors in [Cu]$'$, [Cu]$''$, and [CuHL]$'''$ in eq 3 and 4.) The values of k_1 and k_2 which were determined at pH ~4 were used to calculate relaxation times at these higher pH's. The experimental and calculated relaxation times are shown in columns 4 and 5, respectively, of Table III.

The faster of the two effects at higher pH is due to coupled reaction scheme 6. The complete solution for

$$\mathrm{CuHL} \underset{k_P}{\overset{k_D}{\rightleftharpoons}} \mathrm{CuL + H}$$
$$\mathrm{CuL} \underset{k_H}{\overset{k_A}{\rightleftharpoons}} \mathrm{CuA + H} \quad (6)$$

the relaxation times of this system leads to a quadratic secular equation which is readily solved as follows. The equation is obtained by first applying the conservation equations

$$0 = \delta[\mathrm{CuL}] + \delta[\mathrm{CuHL}] + \delta[\mathrm{CuA}]$$
$$0 = 2\delta[\mathrm{CuHL}] + \delta[\mathrm{CuL}] + \delta[\mathrm{H}] + \delta[\mathrm{HIn}] \quad (7)$$
$$0 = \delta[\mathrm{HIn}] + \delta[\mathrm{In}]$$

This leads to the result that

$$\frac{-\mathrm{d}\delta[\mathrm{CuHL}]}{\mathrm{d}t} = b_{11}\delta[\mathrm{CuHL}] + b_{12}\delta[\mathrm{CuA}]$$
$$\frac{-\mathrm{d}\delta[\mathrm{CuA}]}{\mathrm{d}t} = b_{21}\delta[\mathrm{CuHL}] + b_{22}\delta[\mathrm{CuA}] \quad (8)$$

Table III. Relaxation Spectra of Copper(II)–L-Carnosine Solutions at High pH

$[\text{L-Carnosine}]_0 \times 10^4$	$[\mathrm{Cu}]_0 \times 10^4$	[H]	$\tau_{\mathrm{slow}} \times 10^3$, sec Exptl	$\tau_{\mathrm{slow}} \times 10^3$, sec Calcd	$\tau_{\mathrm{fast}} \times 10^3$, sec Exptl	$\tau_{\mathrm{fast}} \times 10^3$, sec Calcd
9.70	9.76	7.76×10^{-7}	2.0	2.6		
4.73	5.52	9.77×10^{-7}	4.1	4.2	0.29	0.24
7.88	7.70	9.77×10^{-7}	2.6	3.8	0.25	0.22
9.90	10.0	1.12×10^{-7}	22	15	0.38	0.31
4.83	5.64	1.15×10^{-7}	6.7	4.7	0.44	0.65
8.05	7.86	1.00×10^{-7}	15	12	0.42	0.45
10.0	10.1	1.07×10^{-8}			1.3	1.7
4.87	5.70	1.58×10^{-8}			1.0	1.9

where

$$\begin{aligned} b_{11} &= k_{\mathrm{D}} + k_{\mathrm{p}}\left(\frac{[\mathrm{CuL}]}{1+\alpha_3} + [\mathrm{H}]\right) \\ b_{12} &= k_{\mathrm{p}}\left([\mathrm{H}] - \frac{[\mathrm{CuL}]}{1+\alpha_3}\right) \\ b_{21} &= k_{\mathrm{A}} - k_{\mathrm{H}}\frac{[\mathrm{CuA}]}{1+\alpha_3} \\ b_{22} &= k_{\mathrm{A}} + k_{\mathrm{H}}\left(\frac{[\mathrm{CuA}]}{1+\alpha_3} + [\mathrm{H}]\right) \end{aligned} \tag{9}$$

in which

$$\alpha_3 = \frac{[\mathrm{In}]}{K_{\mathrm{HIn}} + [\mathrm{H}]} \tag{10}$$

Relaxation times may be calculated from both (8) and (9) by using the relationship[11] (given in terms of the b_{ij})

$$\frac{1}{\tau_{+,-}} = {}^1/_2[(b_{11} + b_{22}) \pm \sqrt{(b_{11} + b_{22})^2 - 4(b_{11}b_{22} - b_{12}b_{21})}] \tag{11}$$

A summary of the experimental conditions for the higher pH studies, together with the observed and calculated relaxation times, is given in Table III.

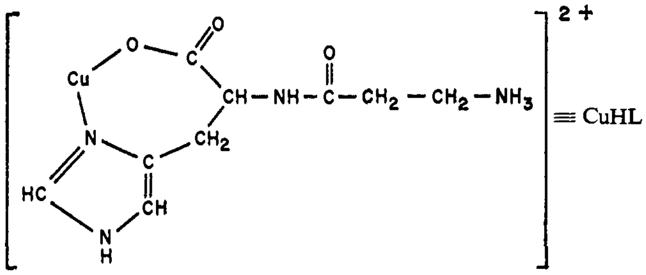
The rate constants which best fit the data are $k_{\mathrm{D}} = 2.30 \times 10^2\ \mathrm{sec}^{-1}$; $k_{\mathrm{p}} = 1.0 \times 10^7\ M^{-1}\ \mathrm{sec}^{-1}$; $k_{\mathrm{A}} = 3.60 \times 10^2\ \mathrm{sec}^{-1}$; and $k_{\mathrm{H}} = 5.0 \times 10^7\ M^{-1}\ \mathrm{sec}^{-1}$.

Discussion

Let us first consider the reaction

$$\mathrm{Cu} + \mathrm{HL} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{CuHL} \tag{12}$$

In this reaction the available evidence from other studies[7] indicates that the ligand, which is neutral, forms a seven-membered chelate ring with copper(II), *viz.*, II.

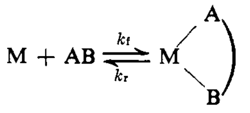


II

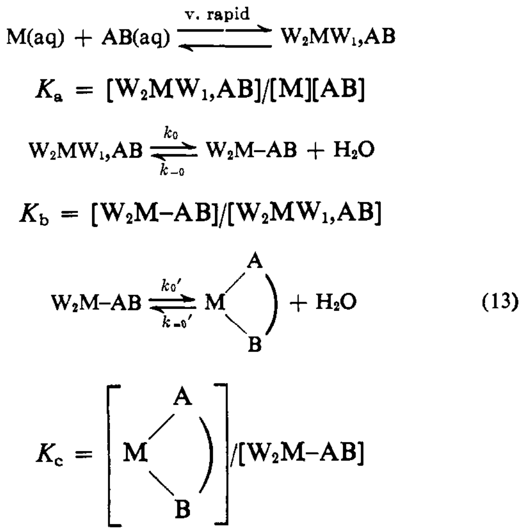
As in the case of the reaction of L-carnosine with cobalt(II), the second-order rate constant, k_2, may be compared directly with second-order rate constants which would obtain for a reaction in which copper(II) reacts with an anion with a single negative charge.[2] This latter value is referred to as k_{normal}: $k_{\mathrm{normal}} \sim 2 \times 10^8\ M^{-1}\ \mathrm{sec}^{-1}$;[10,11] whereas $k_2 = 3.5 \times 10^6\ M^{-1}\ \mathrm{sec}^{-1}$.

Since the rate constant for the L-carnosine reaction is nearly two orders of magnitude smaller than the normal value, it may be concluded that the release of coordinated water is not rate determining for this reaction. The free energy of activation for the formation of a seven-membered chelate ring is greater than that for the release of a coordinated water by this highly labile ion.

A mechanism[4,12] consistent with the results of the many studies performed on reactions of the type



in which M is a highly labile transition metal ion and AB is a bidentate ligand is



$$\mathrm{M(aq)} + \mathrm{AB(aq)} \xrightleftharpoons{\text{v. rapid}} \mathrm{W_2MW_1,AB}$$

$$K_{\mathrm{a}} = [\mathrm{W_2MW_1,AB}]/[\mathrm{M}][\mathrm{AB}]$$

$$\mathrm{W_2MW_1,AB} \underset{k_{-0}}{\overset{k_0}{\rightleftharpoons}} \mathrm{W_2M{-}AB} + \mathrm{H_2O}$$

$$K_{\mathrm{b}} = [\mathrm{W_2M{-}AB}]/[\mathrm{W_2MW_1,AB}]$$

(13)

W_1 and W_2 are the two water molecules in the inner coordination sphere of the metal ion which are replaced by AB.

---

(11) M. Eigen, *Pure Appl. Chem.*, **6**, 97 (1963).

(12) G. G. Hammes and J. I. Steinfeld, *J. Am. Chem. Soc.*, **84**, 4639 (1962).

When, as for copper(II) with L-carnosine, the third step is rate determining, then

$$k_f^{Cu} = k_0'K_aK_b \qquad (14)$$

For the reaction of cobalt(II) with L-carnosine, in which the second step is rate determining, we have

$$k_f^{Co} = k_0K_a \qquad (15)$$

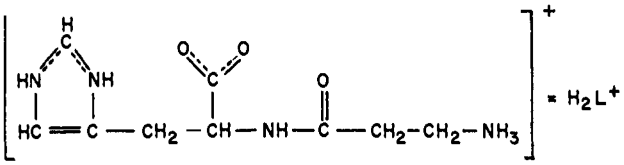
The K_a's are the same for both metal ions and, since no appreciable concentration of the monodentate species forms in solution, it is probably safe to estimate that $K_b \leq 10$. Hence, $k_0' \geq 3.5 \times 10^5$ sec^{-1}. Now, since k_0 for cobalt(II) is 2.5×10^5, this result is consistent with the lack of a SCS effect for cobalt(II).

We next focus attention on reaction 16.

$$Cu^{2+} + H_2L^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CuHL^{2+} + H^+ \qquad (16)$$

As in reaction 12, a seven-membered chelate ring is formed with copper(II). As we have seen, the rate constant for the forward reaction is $k_1 = 8.9 \times 10^2$ M^{-1} sec^{-1} as compared to $k_2 = 3.5 \times 10^6$ M^{-1} sec^{-1} for reaction 12.

The H_2L^+ form of L-carnosine is shown in III. The presence of two positive charges in this ligand ion, with one in close proximity to the binding sites, tends to reduce the magnitude of the equilibrium constant, K_a. This is consistent with the observation that $k_1 \ll k_2$ (*cf.* eq 14).



III

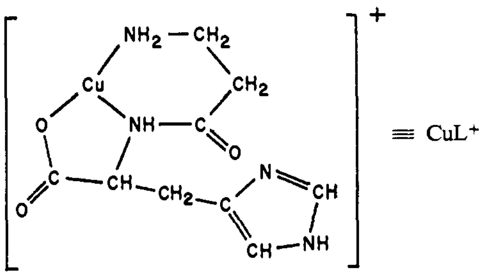
We turn next to the two protolytic reactions

$$\begin{aligned} CuL^+ + H^+ &\underset{k_D}{\overset{k_p}{\rightleftharpoons}} CuHL^{2+} \\ CuA + H^+ &\underset{k_A}{\overset{k_H}{\rightleftharpoons}} CuL^+ \end{aligned} \qquad (17)$$

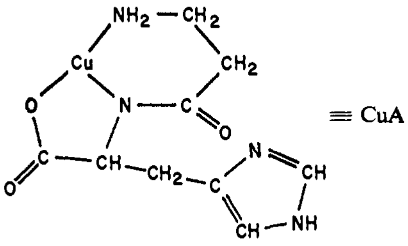
The structures of CuL^+ and CuA are most probably those of IV and V.[2,7,8] The rate constants for proton attack of these species (*cf.* eq 17) are $k_p = 1.0 \times 10^7$ M^{-1} sec^{-1} and $k_H = 5.0 \times 10^7$ M^{-1} sec^{-1}, whereas the reaction[13]

$$HOCu(H_2O)_5^+ + H^+ \underset{k_r}{\overset{k_f}{\rightleftharpoons}} Cu(H_2O)_6^{2+}$$

has a rate constant, k_f, of $\sim 10^{10}$.



IV



V

In a mechanism analogous to (5), the vertical steps are usually too rapid to be studied using the temperature-jump method.[10] It is only because these reactions are slower than diffusion controlled that they may be investigated using this technique. The rates of these reactions are, therefore, not controlled by the actual proton attack but rather by some intramolecular rearrangement subsequent to proton attack. Two possibilities are: (1) rearrangement of the ligand in the inner coordination sphere of the copper ion as, for example, a change in the actual binding sites (compare II with IV), and (2) a change in the geometry of the coordination sphere of the metal ion itself.

The crystallographic data obtained for the copper–L-carnosine dimer $(CuA)_2$ indicate that, in the monomeric unit, the amino and peptide nitrogen atom and carboxylic oxygen atom are bonded to the copper ion; the imidazole ring is not bound. However, the structure of the CuHL complex postulated by Lenz and Martell involves bonding to the imidazole ring. Hence, at least one of the protolytic steps might also involve the breaking of a metal–nitrogen bond with the nitrogen atom in the imidazole ring and the formation of bonds with other parts of the ligand.

Copper(II) complexes are most often found to be either square coplanar or octahedral. It is in fact quite possible that an equilibrium might exist between these two structures for a given protonated form of the copper–L-carnosine complex. Structural changes of this type have been investigated for other metal ions using the temperature-jump method.[14] In these cases the relaxation effects were in the region of 50–200 msec, the structural change being large, *i.e.*, tetrahedral $\rightleftharpoons$ octahedral. A possible contributing reason for the slowness of the protolytic steps for the copper–L-carnosine system could be an associated change in the stereochemistry about and coordination number of the copper ion.

---

[13] M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, 3, 1 (1964).

[14] (a) T. J. Swift, *Inorg. Chem.*, 3, 526 (1964); (b) J. H. Swinehart, private communication.