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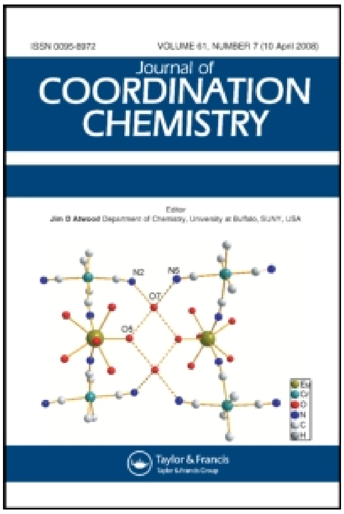

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KINETICS OF FORMATION AND STABILITY CONSTANTS OF MONO AND BIS *l*-TYROSINE COMPLEXES OF Cu(II), Co(II), AND Ni(II)

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KINETICS OF FORMATION AND STABILITY CONSTANTS OF MONO AND BIS *l*-TYROSINE COMPLEXES OF Cu(II), Co(II), AND Ni(II)[1]

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The kinetics and stability constants of *l*-tyrosine complexation with copper(II), cobalt(II) and nickel(II) have been studied in aqueous solution at 25° and ionic strength 0.1 *M*. The reactions are of the type $M(HL)_{n-1}^{(3-n)+} + HL^- \rightleftarrows M(HL)_n^{(2-n)+}$ (k_n, forward rate constant; k_{-n}, reverse rate constant); where M =Cu, Co or Ni, HL^- refers to the anionic form of the ligand in which the hydroxyl group is protonated, and $n = 1$ or 2. The stability constants ($K_n = k_n/k_{-n}$) of the mono and bis complexes of Cu^{2+}, Co^{2+} and Ni^{2+} with *l*-tyrosine, determined by potentiometric pH titration are: Cu^{2+}, $\log K_1 = 7.90 \pm 0.02$, $\log K_2 = 7.27 \pm 0.03$; Co^{2+}, $\log K_1 = 4.05 \pm 0.02$, $\log K_2 = 3.78 \pm 0.04$; Ni^{2+}, $\log K_1 = 5.14 \pm 0.02$, $\log K_2 = 4.41 \pm 0.01$. Kinetic measurements were made using the temperature-jump relaxation technique. The rate constants are: Cu^{2+}, $k_1 = (1.1 \pm 0.1) \times 10^9\ M^{-1}\ sec^{-1}$, $k_{-1} = (14 \pm 3)\ sec^{-1}$, $k_2 = (3.1 \pm 0.6) \times 10^8\ M^{-1}\ sec^{-1}$, $k_{-2} = (16 \pm 4)\ sec^{-1}$; Co^{2+}, $k_1 = (1.3 \pm 0.2) \times 10^6\ M^{-1}\ sec^{-1}$, $k_{-1} = (1.1 \pm 0.2) \times 10^2\ sec^{-1}$, $k_2 = (1.5 \pm 0.2) \times 10^6\ M^{-1}\ sec^{-1}$, $k_{-2} = (2.5 \pm 0.6) \times 10^2\ sec^{-1}$; Ni^{2+}, $k_1 = (1.4 \pm 0.2) \times 10^4\ M^{-1}\ sec^{-1}$, $k_{-1} = (0.10 \pm 0.02)\ sec^{-1}$, $k_2 = (2.4 \pm 0.3) \times 10^4\ M^{-1}\ sec^{-1}$, $k_{-2} = (0.94 \pm 0.17)\ sec^{-1}$. It is concluded that *l*-tyrosine substitution reactions are normal. The presence of the phenyl hydroxyl group in *l*-tyrosine has no primary detectable influence on the forward rate constant, while its influence on the reverse rate constant is partially attributed to substituent effects on the basicity of the amine terminus.

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INTRODUCTION

The mechanism of formation for the first-row divalent transition metal ion α-amino acid complexes has been well characterized in recent years.[2, 3] Substitution has been shown to proceed via rapid ion pair formation followed by rate determining water release, allowing penetration of the ligand into the inner coordination sphere of the metal ion. For normal substitution this latter step, essentially insensitive to ligand characteristics such as basicity and polarizability,[2] is controlled by the loss of the first water molecule from the metal ion's inner coordination sphere. Exceptions to this mechanism have been explained in terms of a shift to a sterically controlled rate determining step, such as in the formation of six membered chelate rings;[4, 5, 6] and, in the case of polyamines,[7] by the enhancement of water loss from the metal ion's inner coordination sphere due to a proposed internal conjugate base mechanism.

For normal substitution reactions, the relative stability of the ligand-metal complex is governed by the magnitude of the dissociation rate constant.[8] An important factor in this regard is the relative basicity of the amino acid. Generally, the efficiency of the ligand as a leaving group will be a strong function of this property. While recent kinetic studies of metal complexation with serine[9] and phenylalanine[10] have shown this trend to be the case, the kinetics of *l*-dopa (3,4-dihydroxyphenylalanine)[10] and hydroxyproline[11] appear to be anomalous. The irregularities were discussed in terms of hydrogen bonding between the hydroxyl group of the ligand and waters in the coordination sphere of the metal ion. The present investigation into the complexation of *l*-tyrosine (hydroxyphenylalanine) with Cu(II), Co(II) and Ni(II) was undertaken to aid in understanding the reported anomalous behavior of these α-amino acids.

EXPERIMENTAL

Reagent grade Fisher $Ni(NO_3)_2 \cdot 6H_2O$, $Co(NO_3)_2 \cdot 6H_2O$, Baker $Cu(NO_3)_2 \cdot 3H_2O$ and KNO_3 were used without further purification as were all other chemicals. *l*-Tyrosine was obtained from Mann/Schwartz. Indicators used were Aldrich phenol red, Eastman chlorophenol red and bromocresol green.

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Stock solutions of KNO_3, metal nitrates, ligand and indicators were prepared by weight. The metal content of the stock solutions was determined by passing aliquots of the solutions through a cation exchanger (Dowex 50), and titrating the liberated acid with standardized sodium hydroxide solution. Solutions to be studied kinetically were prepared either by dissolving weighed amounts of solid materials in Belmont Springs distilled water, or by mixing the desired volumes of stock solution into 100 ml volumetric flasks. Appropriate volumes of the indicator stock solutions were added and the ionic strength brought up to 0.1 *M* by the addition of KNO_3. The final pH was adjusted by dropwise addition of NaOH and/or HNO_3 to ± 0.02 pH unit measured with a Radiometer TTTlc titrator assembly (Copenhagen) used as a pH meter. Hydrogen ion concentrations were obtained by dividing the measured hydrogen ion activities by $\gamma = 0.739$ from the Davies equation. The temperature in all experiments was $25 \pm 1°$ C.

$$HL^- \rightleftharpoons H^+ + L^{2-} \qquad K_a' = [H^+][L^{2-}]/[HL^-]$$

$$H_2L \rightleftharpoons H^+ + HL^- \qquad K_b = [H^+][HL^-]/[H_2L]$$

$$H_3L^+ \rightleftharpoons H^+ + H_2L \qquad K_a = [H^+][H_2L]/[H_3L^+]$$

$$M^{2+} + HL^- \rightleftharpoons M(HL)^+ \qquad K_1 = [M(HL)^+]/[M^{2+}][HL^-]$$

$$M(HL)^+ + HL^- \rightleftharpoons M(HL)_2 \qquad K_2 = [M(HL)_2]/[M(HL)^+][HL^-]$$

The details of the temperature-jump apparatus have been described elsewhere.[12-14] Blank experiments with metal ions (2.00 to 10.0×10^{-3} *M*) and indicator, and with ligand and indicator gave no discernible relaxation effects for copper and cobalt. Solutions of nickel and indicator showed relatively small effects over a wide range of pH and are attributed either to complexation with indicator or metal hydrolysis. This problem was circumvented by carefully controlling the conditions of the experiments such that the blank effects were either negligible, or the time constants would not interfere with the desired effect (typical relaxation times for the blanks were longer than 100 msec).

In determining the stability constants of the complexes, and the acid dissociation constants for tyrosine, a double walled cell of approximately 200 ml capacity was used. It's teflon cover was fitted with inlets for nitrogen gas, electrodes, and a 2 ml Gilmont microburet. The temperature of the solutions was kept at $25 \pm 0.1°$ C by circulating water from a thermostat through the wall of the cell. The glass electrode was calibrated with standard buffer solutions and checked before and after each titration. The solutions introduced into the cell were in stoichiometric ratios of 1 : 1, 2 : 1, and 3 : 1 ligand to metal.

RESULTS AND TREATMENT OF DATA

Stability Constants.—Values of the stepwise stability constants for Cu(II), Co(II) and Ni(II) with *l*-tyrosine have not been previously reported at an ionic strength of 0.1 *M*, although values have been reported at ionic strengths of 0.37 *M* (Ni and Cu), and 0.01 *M*.[15,16]

To interpret the temperature-jump data, only two metal-ligand equilibria are necessary. As explained below, the stability constant data is most reliable in the titration region where no more than two complexes, particularly the first two, predominate. Under these circumstances, the equilibria between the species present in the solutions are as follows

where H_3L^+ is the fully protonated species, H_2L is the neutral zwitterion, and HL^- and L^{2-} are the anionic forms of the ligand; M^{2+} is the free metal ion; and $M(HL)^+$ and $M(HL)_2$ are the complexed species.

Values of $\bar{n}$,[17] the average number of ligand molecules bound per metal ion, and $[HL^-]$ were obtained for each point along the titration curve. One, two or three parameters were adjusted in a nonlinear least squares program (ORGLS)[18] run on a DEC PDP-10 computer in order to obtain the best fit of calculated *vs.* experimental values of $\bar{n}$. The results are listed in Table I. The maximum relative errors in these determinations are $\pm 11\%$.

Relaxation Spectra.—The concentrations of the various species were calculated by means of a Newton-Raphson iteration method. Use was made of the constants listed in Table I. The experimental relaxation times listed in Table II were obtained by averaging at least three oscillographic traces. The deviations were usually less than $\pm 20\%$ in these averaged relaxation times. The exponentiality of

TABLE I

Stoichiometric Equilibrium Constants at 25° C

Metal Complexation of Tyrosine

metal ion	log K_1	log K_2	log K_1K_2	ionic strength (M)
Ni(II)	5.14 ± .02	4.41 ± .01	9.55 ± .02	0.1[a]
	4.76	3.82	8.58	0.37[b]
	—	—	10.1	0.01[c]
Co(II)	4.05 ± .02	3.78 ± .04	7.83 ± .02	0.1[a]
	—	—	8.1	0.01[c]
Cu(II)	7.90 ± .02	7.27 ± .03	15.18 ± .04	0.1[a]
	7.80	6.92	14.72	0.37[b]
	—	—	15.0	0.01[c]

Acid Dissociation of Tyrosine[d]

pK_a	pK_b	pK_a'
2.34	9.11	10.13

Acid Dissociation of Indicators[e]

indicator	$K_{In}(M)$
chlorophenol red	1.00×10^{-6}
phenol red	1.26×10^{-8}
bromocresol green	2.19×10^{-5}

[a] present study; [b] ref. 15; [c] ref. 16; [d] R. B. Martin, *et al.*, *J. Biol. Chem.*, **233**, 1429 (1958); [e] I. M. Kolthoff, *J. Phys. Chem.*, **34**, 1466 (1930).

the effects were checked by semilogarithmic plots of absorbance against time.

The observed relaxation processes have been interpreted by the following reaction scheme, assuming only HL^- to be the attacking form of the ligand

$$M(HL)_{n-1}^{(3-n)+} + HL^- \rightleftarrows M(HL)_n^{(2-n)+} \quad K_n = k_n/k_{-n} \tag{1}$$

where *n* is one or two. In the anionic form of the ligand, HL^-, the phenolic hydroxyl group is assumed to be protonated. The experimental conditions were controlled so that this assumption would be true for all experiments. Except in the case of cobalt, the observed relaxation times always represented two coupled reactions. Cobalt was also studied under pseudo first order conditions, where *n* equals one in (1). The general treatment proposed by Hammes and Steinfeld[19] has been applied in calculating the relaxation times, τ, which can be found from the set of linearized rate expressions by the solution of a quadratic secular determinant in those cases where coupling for n=1 and n=2 is important. For cases where $n=1$ only and total metal concentration $\gg$ total ligand concentration, a linear plot of $1/\tau$ *vs.* corrected equilibrium

$$1/\tau \cong k_1\,[M^{2+}]/(1+\alpha) + k_{-1} \tag{2}$$

concentrations according to eq. (2) yields both k_1 and k_{-1}; a least squares plot is shown in Figure 1. The alpha term in Eq. (2) arises from coupling to the faster protolytic equilibria of both the ligand and indicator.[19] From the slope, $k_1 = 1.30\,(\pm 0.04) \times 10^6\ M^{-1}\ \text{sec}^{-1}$ and from the intercept, $k_{-1} = 1.10\ (\pm 0{\cdot}05) \times 10^2\ \text{sec}^{-1}$. The ratio of these quantities, $K_1 = 1.2 \times 10^4\ M^{-1}$, is in excellent agreement with the value of $1.1 \times 10^4\ M^{-1}$ obtained by potentiometric titration for Co(II).

In evaluating the rate constants for the Cu(II) studies, we used a nonlinear least squares program

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TABLE II

Relaxation Spectra of Tyrosine Complexes[a]

$[\mathrm{Cu(II)}]_0 \times 10^3$	$[\mathrm{Tyrosine}]_0 \times 10^3$	pH	$[\mathrm{Ind}]_0$[b] $\times 10^5$	τ_{exp} (msec)	τ_{calc} (msec)
0.500	1.20	4.03	1.2	31	28
0.500	2.04	4.01	1.2	21	24
1.00	2.06	4.02	1.2	15	17
2.00	2.09	4.01	1.2	13	11
1.50	3.06	4.09	1.2	8.0	9.3
0.500	2.15	4.44	1.2	7.3	9.2
4.00	2.14	4.01	1.2	7.4	7.0
5.00	2.04	4.10	1.2	4.3	5.0
6.00	2.21	4.13	1.2	4.3	4.1
6.50	4.01	4.13	1.2	2.9	2.8
3.00	1.94	4.42	1.2	2.8	2.9
3.00	3.20	4.43	1.2	2.2	2.2
$[\mathrm{Co(II)}]_0 \times 10^3$			$[\mathrm{Ind}]_0$[c] $\times 10^5$		
0.500	2.10	7.26	2.0	3.7	3.4
1.00	2.99	7.35	2.0	2.8	3.1
1.50	1.11	5.82	1.25	3.8	3.8
1.00	1.99	6.01	1.25	3.0	2.8
3.00	1.27	5.91	1.25	1.7	1.9
2.00	2.11	6.40	1.25	1.1	0.80
4.00	2.10	6.02	1.25	0.88	0.87
6.00	2.43	6.32	1.25	0.39	0.31
7.99	0.223	5.95	1.25	2.8	2.9
4.00	0.223	5.95	1.25	4.5	4.3
2.00	0.223	5.98	1.25	5.7	5.7
9.99	0.223	5.83	1.25	3.1	3.1
0.999	0.119	5.74	1.25	9.8	8.6
7.99	0.447	5.96	1.25	2.0	1.7
$[\mathrm{Ni(II)}]_0 \times 10^3$			$[\mathrm{Ind}]_0$[d] $\times 10^5$		
7.55	7.60	7.00	3.0	13	10
5.04	7.00	7.40	1.2	13	16
4.00	5.98	7.15	2.0	17	18
3.68	7.30	6.95	4.0	19	20
3.68	5.96	6.93	4.0	21	20
3.00	5.36	7.15	2.0	21	24
8.94	3.76	5.91	1.25	42	42
7.45	2.91	5.92	1.25	50	57
7.00	2.99	5.94	1.25	68	56
5.96	2.40	5.92	1.25	89	79
4.51	4.62	5.74	2.4	111	121
6.71	1.31	5.90	1.25	109	127
2.48	5.07	5.75	2.4	222	184

[a] All concentrations are molar; subscript zero refers to stoichiometric concentration at 25° C and ionic strength 0.1 *M*.

[b] Ind = bromocresol green.

[c] Ind = phenol red for first two experiments reported; i.e. pH = 7.26 and 7.35; Ind = chlorophenol red for remainder of experiments.

[d] Ind = phenol red for first 6 experiments reported; Ind = chlorophenol red for the remainder.

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(ORGLS) based on the quadratic secular determinant. In the cases of Co(II) and Ni(II), it was found that this function was inadequate due to the relatively large errors generated by the quadratic expression. Therefore, an iterative trial and error program was employed, instead, to obtain rate constants corresponding to the best fit of calculated *vs.* observed relaxation times. In both programs, two parameters were adjusted corresponding to k_I and k_2. The reverse rate constants were then calculated from the expression $K_n = k_n/k_{-n}$ as defined in Eq. (1). The results are summarized in Table III. The maximum relative errors in the forward rate constants are ± 20% while the maximum errors in the reverse rate constants are ±25%.

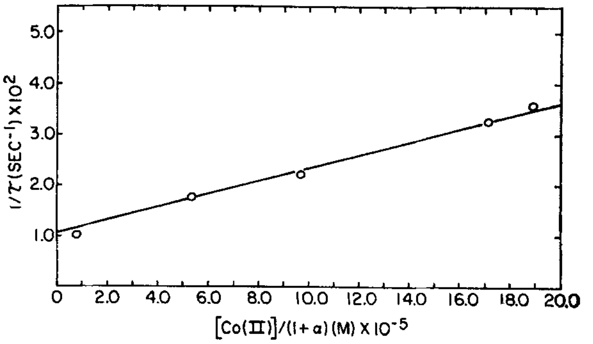

FIGURE 1 Plot of $1/\tau$ vs. $[Co(II)]/(1+\alpha)$.

The observed lack of a pronounced pH-dependence of the rate constants of the type produced by two or more attacking species excludes any reaction pathways via hydrolytic species such as MOH^+ or other protonated forms of the ligand, within experimental error. In fact, if this conclusion were not true, then the rate expressions would not be consistent with the assumed reaction mechanism and additional pH dependent terms would appear in the rate law. The anions of a large number of amino acids and pyridine carboxylates have been shown to be the sole attacking species.[6,19,20]

For Co(II) and Cu(II), only one relaxation time is observed. Observation of one, rather than two effects is due to the fact that the other relaxation time either lies outside the limits of the temperature-jump instrument, or its magnitude is too small to be detected. Nickel spectra, on the other hand, frequently yield an extremely slow relaxation time in addition to the one reported in Table II. Its time constant is effectively infinitely long with respect to the time scale of the instrument. This slow effect is due to a special set of conditions leading to an additional relationship amongst the concentration variables, so that the maximum number of relaxation times reduces to one, within the approximations made in the linearized rate expressions.[11]

DISCUSSION

Stability Constants.—In the *p*H range studied (5 to 8), the potentiometric titrations indicate essentially only the mono and bis complexes to be present. Although it was found that for all three metal ions studied, best fit to the experimental data was obtained for either two or three parameters, in the cases of nickel and cobalt the maximum value of $\bar{n}$ was less than 1.6. It was thus assumed that the tris complex, if present at all, is insignificant under experimental conditions. Indeed, when only two complexes are assumed, the treatment used by Kustin and Liu[11,17] yielded no deviations from linearity when $\bar{n}/(1-\bar{n})[HL]$ was plotted *vs.* $[HL](\bar{n}-2)/(\bar{n}-1)$. The slope yields K_1K_2 and the intercept yields K_1. Values of the stability constants for Co(II) and Ni(II) reported in Table I varied by ±20%when a third parameter was fit.

In the case of copper, values of $\bar{n}$ exceeded 2.0 and such a linear treatment yielded minor deviations from linearity at the upper pH limit. However, the value of K_3 for copper-tyrosine was three orders of magnitude lower than the mono or bis complex stability constants. The deviation from linearity and the low value of K_3 may be due to hydrolytic species of Cu(II).

TABLE III

Rate Constants of Metal Complexation at 25° C and Ionic Strength 0.1 *M*

metal	$k_1(M^{-1}\,sec^{-1})$	$k_2(M^{-1}\,sec^{-1})$	$k_{-1}(sec^{-1})$	$k_{-2}(sec^{-1})$
Ni(II)	$(1.4 \pm 0.2) \times 10^4$	$(2.4 \pm 0.3) \times 10^4$	0.10 ± 0.02	0.94 ± 0.17
Co(II)	$(1.3 \pm 0.2) \times 10^6$	$(1.5 \pm 0.2) \times 10^6$	$(1.1 \pm 0.2) \times 10^2$	$(2.5 \pm 0.6) \times 10^2$
Cu(II)	$(1.1 \pm 0.1) \times 10^9$	$(3.1 \pm 0.6) \times 10^8$	14 ± 3	16 ± 4

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The stability constants reported here are in reasonable agreement with those determined at different ionic strengths.[15, 16] In those studies no evidence was found for the tris complex of Ni(II) or Cu(II). Values of the acid dissociation constants of tyrosine, also quoted in Table I, were determined at ionic strength 0.16 *M*.[16] Our results are within experimental error of these values.

Relaxation Spectra.—*l*-Tyrosine is a bidentate chelating agent which forms five membered ring complexes with the first row divalent transition metal ions. The detailed multistep mechanism of complex formation for such systems has been described elsewhere.[2] The postulated results for normal substitution are that $k_1 = K_{ip}k_o$, where k_o is the water exchange rate constant,[21] K_{ip} is the ion pair formation constant and k_1 is the forward rate constant for complexation. The kinetic results indicate that the k_1 rate constants of 1.1×10^9, 1.3×10^6 and $1.4 \times 10^4\ M^{-1}\ \text{sec}^{-1}$ for Cu(II), Co(II) and Ni(II), respectively, compare favorably with other amino acids with a single negative charge.[4, 5, 6, 9, 10, 22, 23] Thus, allowing for variation in the ion pair formation constant, the kinetics of the metal ions studied with tyrosine follow the normal substitution pattern.

A characteristic of Cu(II) complex formation is that $k_1 > k_2$. This inequality may result from the inhibition of an inversion process of equatorial and axial waters when a bidentate ligand is present in the inner coordination sphere of copper.[4] This relation between the rate constants is also true for Cu(II)-tyrosine.

Unlike the forward rate constant, the reverse rate constant should reflect the ability of the ligand to function as a leaving group, and is therefore dependent upon ligand characteristics. Substitution of electron withdrawing groups should lower the basicity of the ligand and facilitate dissociation of the complex. For a given metal ion, the overall stability of the complex may be reflected in the basicity of the leaving group, if normal substitution holds and other effects do not interfere. A comparison of k_{-1} for proline,[11] alanine,[5] tyrosine, phenylalanine[10] and serine[9] listed in Table IV

TABLE IV

Dissociation Rate Constants of Some Cu(II), Co(II) and Ni(II) α-Amino Acid Complexes and Amine $\mathrm{pK}(-\mathrm{HN}_3+)$[a] Values at 25° C and Ionic Strength 0.1 *M*

metal ion	ligand[b]	$k_{-1}(\text{sec}^{-1})$	$\mathrm{pK}(\mathrm{NH}_3+)$
Ni(II)	serine	0.11	9.12[c]
	tyrosine	0.10	9.11
	glycine	0.057	9.70
	alanine	0.033[d]	10.01[d]
	aminobutyric acid	0.032[d]	10.18[d]
	proline	0.024	10.60[e]
	hydroxyproline	0.014	9.47
Co(II)	tyrosine	1.1×10^2	9.11
	serine	93	9.12[c]
	carnosine	87	9.36
	glycine	34	9.70
	alanine	1.1×10^2[d]	10.01[d]
	aminobutyric acid	11[d]	10.18[d]
	proline	3.1	10.60[e]
	hydroxyproline	1.2	9.47
Cu(II)	serine	32	9.12[c]
	phenylalanine	22	9.13[e]
	tyrosine	14	9.11
	alanine	10[d]	9.86[d]
	dopa	8.3	8.71
	hydroxyproline	3.1	9.47
	proline	3.0	10.60[e]

[a] Compiled in reference 16; [b] serine—reference 9, glycine—reference 23, aminobutyric acid—reference 6, proline—reference 11, alanine—reference 4, hydroxyproline—reference 11, dopa—reference 10, phenylalanine—reference 10, carnosine—*J. Am. Chem. Soc.*, **90**, 2805 (1968); [c] at ionic strength 0.2 *M*; [d] at 20° C; [e] at unknown ionic strength.

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shows this trend with decreasing bascity of the α-amino group; viz., 3.0, 10, 14, 22, 32 sec^{-1} respectively for Cu(II). Figures 2 and 3 illustrate this trend for Co(II) and Ni(II). (A plot of pH of the α- amino group *vs.* log K_1 lends additional support to this hypothesis.[24])

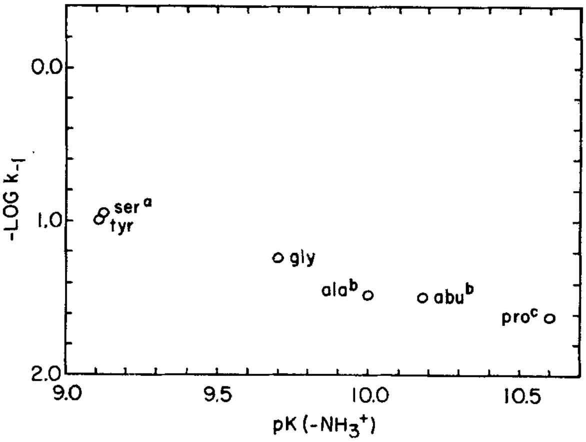

FIGURE 2 Plot of pK ($-NH_3+$) vs. log reverse rate constant (k_{-1}) for Co(II) α-amino acid complexes at 25° C and ionic strength 0.1 *M*. The data is compiled in Table IV:

(a) pK value determined at ionic strength 0.2 *M*;
(b) values determined at 20° C;
(c) at unknown ionic strength.

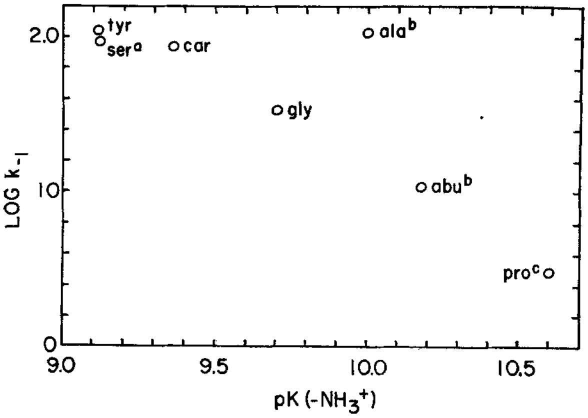

FIGURE 3 Plot of pK ($-NH_3+$) vs. log reverse rate constant (k_{-1}) for Ni(II) α-amino acid complexes at 25° C and ionic strength 0.1 *M*. (*Vide* Figure 2 for (a), (b) and (c).)

Recent kinetic studies of hydroxyproline[11] and *l*-dopa[10] with metal ions have demonstrated exceptions to this trend. It is apparent that the substituent effects discussed above do not operate for these ligands. For Cu(II)-dopa and Cu(II)-hydroxyproline, the k_{-1} rate constants are 8.3 and 3.1 sec^{-1} respectively; these values are less than most of the other amino acids studied. These observations have been explained in terms of hydrogen bonding between the hydroxyl group of the ligand and water molecules in the coordination sphere of the metal ion.[10, 11] This anomalous behavior appears to hold for the forward rate constant as well, where hydrogen bonding may misorient the incoming ligand. The fact that all the amino acids containing hydroxyl groups do not follow this behavior suggests that the steric requirements of the ligand molecule can play an important role in the kinetics of complexation.

The above discussion is interesting in light of the study of polyamine complexation with metal ions.[7] Here, hydrogen bonding between an amine group and water molecules about the metal ion results in enhancement of the overall substitution rate constant, while in the cases of *l*-dopa and hydroxyproline, hydrogen bonding results in a depression of the overall rate constant. The interest in these two diverse systems lies in the possible variation of substitution rate constants of the first row divalent transition metal ions. Therefore, under certain circumstances, characteristics of the ligand may contribute to the magnitude of the forward substitution rate constant, even though water loss is the rate determining step.

REFERENCES

1. The authors gratefully acknowledge partial support from the Public Health Service for Research Grant GM-08893-11 from the National Institute of General Medical Sciences.
2. (a) M. Eigen and R. G. Wilkins; "The Kinetics and Mechanisms of Formation of Metal Complexes" in "Mechanisms of Inorganic Reactions", *ACS Advances in Chemistry Series* **49**, 55 (1965). (b) F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed., John Wiley and Sons, New York, N.Y., 1967.
3. K. Kustin and J. Swinehart, *Prog. Inorg. Chem.* **13**, 107 (1970).
4. (a) W. B. Makinen, A. F. Pearlmutter and J. E. Stuehr, *J. Am. Chem. Soc.* **91**, 4083 (1969). (b) R. F. Pasternack *et al.*, *J. Inorg. Nucl. Chem.*, in press.
5. K. Kustin, R. F. Pasternack and E. M. Weinstock, *J. Am. Chem. Soc.* **88**, 4610 (1966).
6. (a) A. Kowalak, K. Kustin, R. F. Pasternack and S. Petrucci, *J. Am. Chem. Soc.* **89**, 3126 (1967). (b) R. F. Pasternack, K. Kustin, G. Hughes and E. Gibbs, *J. Am. Chem. Soc.* **91**, 4401 (1969).
7. D. B. Rorabacher, *Inorg. Chem.* **5**, 1891 (1966).

8. G. A. Melson and R. G. Wilkins, *J. Chem. Soc.* **1962**, 4208.
9. R. L. Karpel, K. Kustin and R. F. Pasternack, *Bioch. Biophys. Acta* **177**, 434 (1969).
10. R. L. Karpel, K. Kustin, A. Kowalak and R. F. Pasternack, *J. Am. Chem. Soc.* **93**, 1085 (1971).
11. K. Kustin and S. T. Liu, In press, *J. Chem. Soc.* 1973.
12. P. Hurwitz and K. Kustin, *Inorg. Chem.* **3**, 823 (1964).
13. M. Eigen and L. DeMaeyer in A. Weissberger "Techniques of Organic Chemistry", Vol. VIII part II, Interscience, New York, N.Y. 1963, ch. XVIII.
14. K. Kustin, ed. "Fast Reactions", Methods in Enzymology Vol XVI, p. 3. Academic Press, New York, N.Y. 1969.
15. O. A. Weber and V. L. Simeon, *Biochem. Biophys. Acta* **244**, 94 (1971).
16. L. G. Sillén and A. E. Martell, ed., "Stability Constants of Metal Ion Complexes," Special Publication 17. The Chemical Society 1964 and 1969 (addendum).
17. Rossotti and Rossotti, "The Determination of Stability Constants", McGraw Hill 1961, ch. 5.
18. W. R. Busing and H. A. Levy, Oak Ridge National Laboratories Least Squares Program, ORNL-TM-271.
19. G. G. Hammes and J. I. Steinfeld, *J. Am. Chem. Soc.* **84**, 4639 (1962).
20. J. C. Cassat and R. G. Wilkins, *J. Am. Chem. Soc.* **90**, 6045 (1968).
21. (a) T. J. Swift and R. E. Connick, *J. Chem. Phys.* **37**, 307 (1962). (b) *ibid.* **41**, 2553 (1964). A recent redetermination of the nickelous water exchange rate constant (*J. Am. Chem. Soc.* **94**, 8646 (1972)) leads to a somewhat higher value for this quantity. This paper may be consulted for other references to determinations of this value.
22. G. Davies, K. Kustin and R. F. Pasternack, *Int. J. Chem. Kin.* **1**, 45 (1969).
23. G. Davies, K. Kustin and R. F. Pasternack, *Inorg. Chem.* **8**, 1535 (1969).
24. J. E. Gorton and R. F. Jameson, *J. Chem. Soc.* Dalton, **3**, 310, (1972),

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