of more base ($a = 5$), the 1670-cm^{-1} band disappears and two types of amidic carbonyls can be distinguished from the spectrum. The two N-coordinated negative amides absorb at 1570 cm^{-1} and the O-coordinated neutral amide absorbs at 1645 cm^{-1}. The IDA-coordinated carboxylates are at *ca.* 1613 cm^{-1} and the ionized terminal carboxylate absorbs at 1596 cm^{-1}. This structure is best represented by XV.

Conclusions

Once again it was found that the derivatization of the amino group is a tool of immense importance for the study of metal ion interactions with specific donor groups.

Specifically, the addition of two acetic acid groups onto the amino groups at diglycine, triglycine, and tetraglycine achieved the following results.

1. The metal:ligand interaction stoichiometry was fixed at exactly 1:1, thus greatly simplifying the interpretation of the data. In contrast, the parent oligopeptides bind with Ni(II) and Cu(II) also in ratios of 1:2 and 1:3.

2. The mechanism of metal ion incorporation into the ligand was fixed from the amino nitrogen end of the molecule. The polyglycines react with either end depending on the metal ion.

3. The study of peptide interaction with Co(II) (and Fe(III) with some success[2a]) was made possible. Previously, metal ions such as Co(II) precipitated before the pH could be raised high enough to observe the desired interaction with the groups under study.

4. Perhaps most important of all was the new, unequivocal assignment of the band at *ca.* 1560 cm^{-1} as arising from the group frequency belonging to two adjacent N-coordinated (negatively charged) peptide groups.

Throughout the infrared study, a further conclusion became more strongly evident. Coordinated carboxylates mitigate the ability of the metal ion to polarize peptide linkages. Thus for example, Ni(II) which is hexacoordinate (possessing one more bound acetate than tetracoordinate Cu(II)) will always assist in the ionization of amide groups at a higher pH than Cu(II) will. Or, comparing *N*G with *N*GDA, all chelate amide proton association constants are higher for a given metal ion in the case of *N*GDA as compared to *N*G.

Registry No. $BrCH_2CO_2H$, 79-08-3; $H_2NCH_2CONHCH_2CO_2H$, 556-50-3; $H_2NCH_2CONHCH_2CONHCH_2CO_2H$, 556-33-2; $H_2NCH_2CONHCH_2CONHCH_2CONHCH_2CO_2H$, 637-84-3; $H_3$2GDA, 43101-36-6; $H_3$3GDA, 43068-75-3; $H_3$4GDA, 43101-37-7; CuH2GDA, 43116-09-2; Cu2GDA$^-$, 43116-10-5; CuH$_{-1}$2GDA^{2-}, 43116-11-6; NiH2GDA, 43116-12-7; Ni2GDA$^-$, 43116-13-8; CoH2GDA, 43116-14-9; Co2GDA$^-$, 43064-73-9; CoH$_{-1}$2GDA^{2-}, 43116-15-0; ZnH2GDA, 49567-93-3; Zn2GDA$^-$, 43116-16-1; FeH2GDA$^+$, 43116-17-2; Fe2GDA, 43116-18-3; CuH3GDA, 43116-19-4; Cu3GDA$^-$, 43116-20-7; CuH$_{-1}$3GDA^{2-}, 43116-21-8; CuH$_{-2}$3GDA^{3-}, 43116-22-9; NiH3GDA, 43116-23-0; Ni3GDA$^-$, 43116-24-1; NiH$_{-1}$3GDA^{2-}, 43116-25-2; CoH3GDA, 43116-26-3; Co3GDA$^-$, 43116-27-4; CoH$_{-1}$3GDA^{2-}, 43116-28-5; CoH$_{-2}$3GDA^{3-}, 43116-29-6; ZnH3GDA, 43116-30-9; Zn3GDA$^-$, 43116-31-0; FeH3GDA$^+$, 43117-67-5; Fe3GDA, 43117-68-6; CuH4GDA, 43117-69-7; Cu4GDA$^-$, 43117-70-0; CuH$_{-1}$4GDA^{2-}, 43117-71-1; CuH$_{-2}$4GDA^{3-}, 43117-72-2; NiH4GDA, 43117-73-3; Ni4GDA$^-$, 43117-74-4; NiH$_{-1}$4GDA^{2-}, 43117-75-5; NiH$_{-2}$4GDA^{3-}, 43117-76-6; CoH4GDA, 43117-77-7; Co4GDA$^-$, 43117-78-8; CoH$_{-1}$4GDA^{2-}, 43117-79-9; CoH$_{-2}$4GDA^{3-}, 43117-80-2; ZnH4GDA, 43117-81-3; Zn4GDA$^-$, 43117-82-4; FeH4GDA$^+$, 43117-83-5; Fe4GDA, 43117-84-6.

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Copper(II) Chelation Kinetics. III. Steric Effects

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Rate constants for the formation of Cu(II) complexes with valine and bicine (*N,N*-dihydroxyethylglycine) have been measured by stopped-flow and temperature-jump spectrometry. The forward rate constants for valine were 1.1×10^9 and $2.3 \times 10^8\ M^{-1}\ sec^{-1}$ for mono and bis complex formation, respectively; for bicine, the corresponding rate constants were 9.5×10^8 and $3.2 \times 10^7\ M^{-1}\ sec^{-1}$. When compared with rate constants for less hindered amino acids, these results show that steric effects are more pronounced for bis complex formation, particularly when bulky groups are coordinated to the amino nitrogen.

Of the transition metal ions Cu(II) is one of the most kinetically labile.[2] As a result, kinetic investigations involving this metal ion have been particularly difficult. However, if the protonated form of a ligand is relatively unreactive, Cu(II) complexation reactions involving the free ligand may be studied at low pH values where the concentration of reactive ligand is greatly reduced.[3] By means of this technique, a series of copper(II)–amino acid reactions have been characterized.[3-8] From these investigations the following generalizations can be made. (1) The rate constant for the formation of the mono complex from the anionic form of the amino acid is on the order of $(1\text{-}3) \times 10^9\ M^{-1}\ sec^{-1}$. (2) In all instances the major kinetic pathway involves reaction with the unprotonated ligand, with only small or negligible contributions from the zwitterionic form. (3) The rate constant for the formation of the bis complex is never larger than that for the mono and, in many instances, has been found to be much smaller.[3-8] (4) The formation rate constants for β-amino acids (six-membered chelate rings) are smaller than

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those for the corresponding α-amino acids (five-membered chelate rings).[3b] Observations 1, 2, and 4 generally apply to other transition metal ions; however, observation 3 appears to be unique for Cu(II).

Previous kinetic studies directed toward steric effects in metal complexation have focused attention primarily on the effect of changing chelate ring size.[3b] From crystallographic studies it is known that for virtually all amino acids, Cu(II) binds to the carboxyl oxygen and the unprotonated amino nitrogen.[9] In order to define more clearly the dynamics of these interactions, the kinetics of Cu(II) binding to α-amino acids having bulky groups attached either to the carbon atom adjacent to the amino nitrogen or to the amino nitrogen itself were examined. Kinetic data are presented here for the formation of the mono and bis complexes of Cu(II) with valine, $(CH_3)_2CHCH(NH_2)COOH$, which has a bulky group attached to the α carbon, and bicine (*N,N*-dihydroxyethylglycine), $(C_2H_4OH)_2NCH_2COOH$, which has bulky groups attached to the amino nitrogen.

Two systems—glycine, $H_2C(NH_2)COOH$, and α-alanine, $CH_3HC(NH_2)COOH$, for which data had been previously reported[3]—were reinvestigated. This reexamination was done using an improved stopped-flow apparatus of higher sensitivity. In both systems the improved stopped-flow apparatus allowed the detection and unambiguous assignment of two separate, but kinetically coupled, relaxation times.

Experimental Section

Matheson Coleman and Bell reagent grade $Cu(NO_3)_2 \cdot 3H_2O$, Fisher reagent grade KNO_3, Calbiochem L-valine and bicine, and Baker glycine and α-alanine were used without further purification. Experimental solutions were prepared by volumetric dilution of fresh stock solutions made up with degassed triply distilled water and maintained at 0.1 ionic strength using KNO_3. The overall range of metal ion concentration was typically 10^{-3}–10^{-1} *M*; that of the ligands, 10^{-3}–0.5 *M*. The pH range utilized was fairly acidic, between 2 and 4.

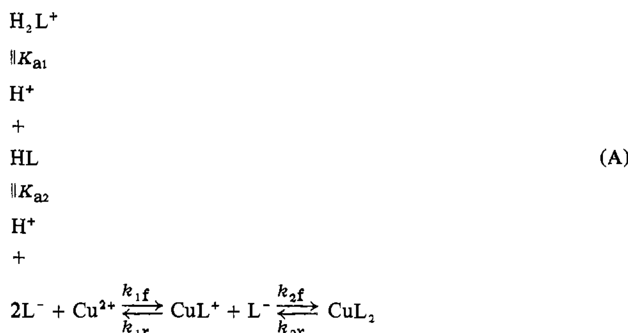
Kinetic runs at 25° were made on a Gibson-Durrum stopped-flow apparatus (Model D-110) and a temperature-jump spectrometer[10] purchased from Messanlagen Studiengesellschaft, Gottingen, West Germany. The temperature-jump spectrometer was thermostated at 20°, with a temperature jump of 5°. Both temperature-jump and stopped-flow experiments were performed with the glycine, valine, and bicine systems; α-alanine was studied by the stopped-flow apparatus alone. Blank experiments with either ligand or Cu(II) alone showed no kinetic effects.

For all *T*-jump measurements, the absorbance changes brought about by shifts in the metal complex equilibria were sufficiently large to eliminate the need for a pH indicator. With Cu(II) and bicine the reaction was monitored at 625 nm on the stopped-flow apparatus while the temperature-jump measurements were made at 600 nm. With valine, two independent relaxation times could be detected on the stopped-flow apparatus at two different wavelengths, 550 and 600 nm. Temperature-jump measurements with Cu(II) and valine were made at 550 nm. Glycine was monitored at 600–700 nm on the stopped-flow apparatus and at 600–650 nm on the temperature-jump apparatus, the best wavelengths being somewhat dependent on the glycine and Cu(II) concentrations. α-Alanine, like valine, had two coupled relaxation times which could be observed at two different wavelengths (550 and 650 nm).

The data from stopped-flow measurements were treated as concentration perturbations, as described previously.[3a] Relaxation times were determined from at least three oscilloscope traces by enlarging the traces and plotting on semilog paper. The appropriate equilibrium constants are given in Table I. Equilibrium concentrations were calculated using an iterative technique on a Univac 1108 computer.

Results

A tabulation of initial concentrations and measured relaxation times for the four copper(II)-amino acid systems is given in Table II. The relaxation times correspond to the formation of the mono and bis complexes with Cu(II) for all systems. The mechanism which fits the data is the two-step complexation pathway involving reaction only with the amino acid anion as in previous investigations[3-7]



where H_2L^+ is the amino acid with both the amino and carboxyl groups protonated, HL is the zwitterion, L^- is the anion, and CuL^+ and CuL_2 are the mono and bis complexes, respectively. The fast proton transfers are signified by equals signs and the complexation steps by arrows. The two relaxation times (τ_1, τ_2) for mechanism A are obtained by solving the two differential equations for restoration of equilibrium and are given by[3,11]

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

where τ_1 corresponds to the positive sign and τ_2 to the negative. The a_{ij} coefficients are calculated from mole balance and preequilibrium relationships.[12] The data of Table II were fitted to the best 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 predicted values for τ_1^{-1} and τ_2^{-1} with those observed experimentally. The best fit was determined by minimizing the quantity σ, the

Table I. Equilibrium Constants for Cu(II) Systems at 25° and $I = 0.1$

Symbol	Reaction	log *K* Glycine[a]	α-Alanine[b]	Valine[c]	Bicine[d]
K_{a1}	$H^+LH = H^+L^- + H^+$	−2.33	−2.34	−2.29	−1.68[e]
K_{a2}	$H^+L^- = L^- + H^+$	−9.68	−9.75	−9.72	−8.11
K_1	$Cu^{2+} + L^- = CuL^+$	8.27	8.09	8.13	8.26
K_2	$CuL^+ + L^- = CuL_2$	6.92	6.65	7.01	5.34
K_{MOH}	$Cu^{2+} = CuOH^+ + H^+$		−6.8		

[a] H. Sigel and R. Griesser, *Helv. Chim. Acta*, 50, 1842 (1967). [b] C. B. Monk, *Trans. Faraday Soc.*, 47, 285 (1951); data at $I = 0$ adjusted to $I = 0.1$ by means of the Davies equation. [c] R. L. Rebertus, Dissertation, University of Illinois, 1954, as quoted in *Chem. Soc., Spec. Publ.*, No. 17, 463 (1957); data at $I = 0.02$ adjusted to $I = 0.1$ by means of the Davies equation. [d] Adjusted to 25° from data at 20° [V. Spranger, R. Kailicek, and J. Majer, *Collect. Czech. Chem. Commun.*, 32, 785 (1967)] and at 30° [S. Chaberek, R. C. Courtney, and A. E. Martell, *J. Amer. Chem. Soc.*, 75, 2185 (1953)]. [e] At 20°.

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(12) The a_{ij} coefficients are identical with those in ref 3a, except that $\alpha = [[H](K_{a1} + [H] + [HL])]/[K_{a2}(K_{a1} + 2[HL]) + [L](K_{a1} + 2[H])]$.

Table II. Initial Concentrations and Measured Relaxation Times[a]

$[Cu]^0$, M	$[L]^0$, M	pH[b]	τ_1^{-1},[d] sec^{-1}	τ_2^{-1},[d] sec^{-1}
		Valine		
0.005	0.025	3.30	34 (25)	24 (24)
0.005	0.025	3.65	63 (51)	32 (30)
0.005	0.025	3.89	69 (91)	34 (37)
0.005	0.025	4.00	107 (121)	46 (42)
0.005	0.05	3.35	36 (32)	29 (28)
0.005	0.05	3.50	67 (41)	29 (33)
0.005	0.05	3.85	99 (83)	55 (52)
0.01	0.05	3.25	53 (33)	33 (28)
0.01	0.05	3.46	75 (50)	34 (32)
0.01	0.05	3.70	99 (86)	36 (41)
0.01	0.05	3.90	117 (139)	42 (55)
0.015	0.002	3.21	26 (23)	19 (19)
0.015	0.002	3.50	51 (36)	22 (23)
0.015	0.002	3.80	77 (77)	23 (23)
0.01	0.20	3.50	126 (108)	(52)
0.01	0.20	3.62	162 (140)	(62)
0.01	0.20	3.82	198 (217)	(89)
0.01	0.20	4.00	232 (323)	(127)
0.025	0.20	3.50	138 (105)	(65)
0.025	0.20	3.70	154 (159)	(96)
0.025	0.20	4.05	232 (330)	(211)
		α-Alanine		
0.002	0.0002	4.22	(94)	36 (36)
0.002	0.002	3.68	(95)	30 (29)
0.002	0.005	3.58	(96)	33 (31)
0.005	0.005	3.40	(95)	41 (33)
0.005	0.02	3.50	(103)	43 (52)
0.005	0.05	3.48	126 (110)	66 (61)
0.005	0.250	3.70	301 (313)	210 (180)
0.01	0.02	3.13	82 (97)	43 (36)
0.01	0.05	3.30	122 (106)	59 (54)
0.01	0.125	3.47	129 (132)	78 (106)
0.01	0.250	3.63	263 (263)	(180)
0.01	0.50	3.90	(957)	374 (365)
0.015	0.002	3.03	79 (94)	(23)
0.015	0.005	3.16	96 (95)	54 (36)
0.015	0.10	3.45	163 (137)	74 (93)
0.015	0.20	3.47	(154)	143 (151)
0.015	0.40	3.68	(454)	231 (241)
0.015	0.40	3.83	(639)	315 (311)

$[Cu]^0$, M	$[L]^0$, M	pH[b]	τ_1^{-1},[d] sec^{-1}	τ_2^{-1},[d] sec^{-1}
		Bicine		
0.00078	0.00078	3.03	(146)	12.8 (12.7)
0.00078	0.00078	3.17	(147)	11.3 (15.1)
0.00078	0.00078	3.28	(147)	15.1 (17.6)
0.0000975	0.0000975	4.31	(147)	21.8 (21.1)
0.000195	0.000195	4.01	(147)	21.0 (21.1)
0.00039	0.00039	3.71	(147)	23.0 (21.1)
0.00078	0.00078	3.41	(147)	19.9 (21.1)
0.000781	0.000781	3.40	(147)	20.2 (20.8)
0.00156	0.00156	3.13	(147)	22.4 (21.7)
0.00312	0.00312	2.90	(147)	22.3 (24.1)
0.00625	0.00625	2.60	(147)	29.5 (23.9)
0.0125	0.0125	2.46	(147)	31.5 (30.6)
0.025	0.025	2.26	(148)	39.9 (35.7)
0.05	0.05	2.06	(148)	56.0 (41.8)
0.05	0.50	2.60	(937)	240[c] (211)
0.05	0.50	2.71	(1230)	254[c] (237)
0.05	0.50	2.80	(1540)	264[c] (264)
0.05	0.50	3.00	(2480)	352[c] (360)
0.05	0.50	3.20	(3960)	441[c] (529)
		Glycine		
0.005	0.005	2.79	(121)	30.0 (30.0)
0.001	0.001	3.91	(123)	41.6 (56.7)
0.01	0.005	2.91	(121)	44.8 (41.2)
0.005	0.005	3.25	(122)	51.2 (54.2)
0.01	0.002	3.30	(121)	63.6 (63.3)
0.01	0.005	3.33	(127)	84.0 (90.2)
0.01	0.02	3.21	(136)	88.5 (88.4)
0.01	0.03	3.21	(141)	89.8 (91.6)
0.01	0.04	3.21	(144)	96.9 (95.6)
0.04	0.075	2.80	146[c] (140)	(93.4)
0.20	0.01	2.80	294[c] (203)	(119)
0.04	0.075	3.12	247[c] (228)	158 (118)
0.04	0.075	3.67	960[c] (929)	177 (165)
0.005	0.25	3.70	517[c] (882)	297 (348)
0.01	0.20	3.39	(343)	218 (220)
0.01	0.30	3.47	(604)	265 (283)
0.10	0.01	2.67	(123)	133 (97.3)
0.10	0.01	2.80	(140)	130 (116)
0.01	0.40	3.52	(901)	340 (351)

[a] All results from stopped-flow experiments 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 (≅0.80). [c] Measurements with the temperature-jump apparatus. [d] Experimental values given first. Values in parentheses were calculated *via* eq 1 using k_{1f} and k_{2f} as in the text.

error function defined by

$$\sigma = \Sigma \left(\frac{\tau^{-1}_{calcd} - \tau^{-1}_{exptl}}{\tau^{-1}_{exptl}} \right)^2 \qquad (2)$$

for each system. The best fit forward rate constants are given in Table III, along with data for other systems. The reverse rate constants, k_{1r} and k_{2r}, are as follows: 23 and 120 sec^{-1} for glycine, 14 and 93 sec^{-1} for α-alanine, 8 and 23 sec^{-1} for valine, and 5.2 and 145 sec^{-1} for bicine. A check of the internal consistency of the mechanism is provided by a check of τ_2 in dilute solutions. By algebraic manipulation it can be shown that τ_2^{-1} approaches the smaller of the reverse rate constants in dilute solutions, and this is indeed the case (Table II). The numerical values for some of the rate constants differ from those we originally reported.[3] In particular, the numerical value of k_{2f} is somewhat increased by the inclusion of $H_2L^+ = HL + H^+$ as a preequilibrium.

The complete mechanism tested by the computer included parallel pathways involving the direct reaction between Cu(II) and the zwitterion ($Cu + HL \rightleftharpoons CuL + H + HL \rightleftharpoons CuL_2 + 2H$). For both systems this pathway was found to be negligible within experimental error. This is in agreement with other studies of metal ions and amino acids.[4-7,11,13]

We were also concerned about how dependent our rate constants were on the particular equilibrium constants utilized. As a consequence, we analyzed the data with other sets of equilibrium constants reported in the literature. In an extreme case (α-alanine) some of the log K values differed from those in Table I by 0.22 unit. In most instances the best fit rate constants obtained with these other sets of equilibrium constants did not differ significantly from those reported in Table III. In the extreme case cited above for α-alanine, k_{1f} increased to 1.8×10^9 and k_{2f} to 0.57×10^9 M^{-1} sec^{-1}. All other dependences of rate constants upon sets of chosen equilibrium constants were considerably smaller. What appears to happen is that there is considerable compensation occurring, such that the concentration functions (but not the equilibrium concentrations themselves) utilized in eq 1 are not appreciably changed.

Discussion

In virtually all studies of Cu(II) complexation kinetics with α-amino acids, the zwitterion has been found to be amazingly unreactive. In those systems where it has been

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Table III. Chelate Formation Rate Constants for Cu(II) with α-Amino Acids ($I = 0.1$, $T = 25°$ unless indicated otherwise)

Ligand		$10^{-9}k_{1f}$, M^{-1} sec^{-1}	k_{1r}, sec^{-1}	$10^{-9}k_{2f}$, M^{-1} sec^{-1}	k_{2r}, sec^{-1}	Ref
Glycine	H H–C–COOH NH$_2$	4.3[a] 4.0	23	1.0[a] 0.4	120	This paper 3a
Alanine	H CH_3–C–COOH NH$_2$	1.7[a] 1.3	14	0.42[a] 0.15	93	This paper 3b
Serine	H $HOCH_2$–C–COOH NH$_2$	2.5[b] 1.8[a]	32 48	0.5[b] 0.28	150 100	4 8 (37°, $I = 0.15$)
Leucine	H_3C, H $CHCH_2$–C–COOH H_3C, NH$_2$	1.6[b]	12	0.8[b]	15	5
Phenylalanine	H C_6H_5–CH_2C–COOH NH$_2$	1.2[c]	22	0.3[d]	30	6
Valine	CH_3, H CH–C–COOH CH_3, NH$_2$	1.1[a]	8	0.23[a]	23	This paper
Sarcosine	H H–C–COOH N H, CH_3	2.8[c]	32	0.10[c]	22	7
Bicine	H H–C–COOH N HOC_2H_4, C_2H_4OH	0.95[a]	5	0.032[a]	145	This paper

[a] Estimated error ±10%. [b] No error estimates given in reference cited. [c] Estimated error ±20–25%. [d] Estimated error ±50%.

possible to estimate the rate of complexation for Cu(II) with an α-amino acid zwitterion,[8] the forward rate constant is 1,000,000 times slower than that with the anion.

The rate constants for the formation of the mono and bis complexes, k_{1f} and k_{2f}, respectively, for glycine and its derivatives are shown in Table III. Rate constants in Table III determined by other workers were examined for best fit to their data and in all instances the rate constants were found to be consistent with those reported in the original sources. The table displays rate constants for eight systems, six of which differ in degree of substitution of the α carbon. These systems are arranged in approximate order of the complexity of the α carbon substituent, as indicated by space-filling molecular models. These systems were investigated in different laboratories over varying ranges of metal ion and ligand concentrations, utilizing pK_a values and stability constants from different sources. Also the quality of fit of the rate constants to experimental data varies from system to system. In spite of these factors, it is still possible to observe trends and to make several generalizations.

Values of k_{1f} are all on the order of (1–4) × 10^9 M^{-1} sec^{-1}. The largest value of k_{1f}, as expected, is found for the parent compound glycine. Although there is some variation from system to system, k_{1f} appears to decrease as the bulkiness of the α-carbon substituent increases. This decrease in the value of k_{1f} may be interpreted as (1) a systematic decrease due to the increasing bulkiness of the α-carbon substituent or (2) a constant value of approximately 1.2 × 10^9 M^{-1} sec^{-1} for the k_{1f} value when any group other than hydrogen is present on the α carbon. By either rationale, the numerical value for serine at 25° appears to be high.

Bis complex formation usually occurs with a rate constant 0.1–0.5 that for the mono. Although this reduction is somewhat less than originally thought,[3] nonetheless it is distinctly different from that of both Ni(II) and Co(II) for which k_{2f} is generally equal to or greater than k_{1f}.[11] These smaller k_{2f} values found for Cu(II) are probably a direct result of Jahn–Teller distortion of the d^9 Cu(II) ion (ref 3 includes a discussion of this). More pronounced steric effects are seen in bis complex formation. The values of k_{2f} decrease from 1.0 to 0.2 × 10^9 M^{-1} sec^{-1} as the bulk of the substituent on the α carbon increases.

Thus, groups attached to the α carbon have no dramatic effect on the value of k_{1f}. In fact, it took a series of such reactions to see any discernible trend. On the other hand, a trend is immediately apparent when one looks at the series of k_{2f} values. They vary by an order of magnitude, decreasing with an increase in bulkiness of the group on the α carbon. This is to be expected if this rate constant were influenced by the rate of inversion of axial-equatorial water molecules, as originally proposed.[3a]

In contrast to α-carbon substituents, much more pronounced effects upon complexation rates can be seen when substitutions are made on the amino nitrogen. Although the rates of mono complex formation show no large effects, bis complex formation decreases drastically in rate. Sarcosine, in which an amino hydrogen has been replaced by a methyl group, forms a mono chelate at approximately the same rate as glycine; however, bis complex formation occurs at a rate only 0.1 that of glycine. Thus, bulky groups on the amino nitrogen appear to be much more effective in slowing axial-equatorial inversion of water molecules than in hindering the formation of the mono complex.

Bicine, in which both hydrogens of the amino nitrogen are replaced by hydroxyethyl groups, is the best example of this slow down seen thus far. Formation of the mono

complex occurs at a rate 0.22 that found with glycine. The reason for this decrease is ambiguous. The presence of the bulky ethanol groups may act as a steric hindrance; or, as suggested by Chaberek, *et al.*,[14] the mono complex might be tridentate and the slower rate of reaction would then be due to the longer time required to form a tridentate chelate compared with a bidentate chelate. Formation of the bis complex with bicine occurs at a rate ~0.03 that seen with glycine. This may be due to the necessity for displacement of one of the coordinating groups of a tridentate mono complex to form the bis-bidentate chelate, which could result in a very substantial decrease in the rate of bis complex formation. An alternative explanation may be found in a close examination of the crystal structure of Cu(II) α-amino acid complexes.[9] In these complexes, Cu(II) is coordinated to a carboxyl oxygen and the amino nitrogen. Groups on the α carbon, such as is found in α-alanine, glutamic acid, and histidine, all point in a direction away from the nitrogen and oxygen bonds. Thus, substitutions on this carbon would not be expected to have large effects on chelation rates. Indeed, this has been confirmed experimentally. On the other hand, the amino nitrogen is directly involved in the chelate bond. Bulky groups attached to this atom might lie in a direction that would interfere with the addition of a second chelate. The magnitude of steric effects on the formation rate constants would depend not only upon the nature of the bulky group introduced into the molecule but also upon the position of such a group in relation to the location of the bonds formed.

The *reverse* rate constants, k_{nr}, are generally obtained from the forward rate constants and the corresponding stability constant. As a consequence, they could be inaccurate due to the resulting accumulation of errors. Nevertheless, some interesting differences and comparisons are to be seen in Table III. The bis complexes generally dissociate more rapidly than the corresponding mono complexes (sarcosine appears to be an exception). If one examines the effect of aliphatic substituents on the α carbon, it is seen that the values of k_{1r} for glycine, alanine, leucine, and valine decrease progressively, paralleling the behavior of k_{1f}. The monosarcosine complex is less stable than that of glycine, presumably due to distortions produced by the presence of the CH_3 group on the nitrogen. This effect should be still more evident in bicine if the alcohol groups did not participate in binding. The fact that k_{1r} is *less* is consistent with the possibility mentioned earlier, *viz.*, that the ethanolic OH groups are participating in the chelate, thus increasing the stability of the complex. Further support for this hypothesis is provided by comparing the values of k_{2r} for sarcosine and bicine: that for bicine is in this case much larger, indicating the presence of repulsive effects which are not compensated for by binding of the OH groups. For the series of aliphatic α substituents, the order for k_{2r} is gly > ala > leu, val. If, as suggested earlier, the rate constants for the second step reflect the rate of inversion of axial-equatorial water molecules, then the value of k_{2r} would be expected to decrease as the α substituents become larger.

In conclusion, we have studied the formation of Cu(II) with two sterically hindered amino acids. These data, when compared with values from other laboratories as well as previous work in this laboratory, allow several conclusions to be reached. First, there is a small but definite reduction of k_{1f} as steric hindrance increases. Such effects on k_{1f} values are relatively small, amounting to a factor of 4 or less. Second, for bis complexation, these effects are considerably larger than for the formation of the mono complex and approach reductions of two orders of magnitude. Finally, substitution on the amino nitrogen is much more effective in reducing k_{2f} than substitution on the α carbon.

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Registry No. Cu(glycine)$_2$, 13479-54-4; Cu(α-alanine)$_2$, 14263-10-6; Cu(L-valine)$_2$, 14267-13-1; Cu(bicine)$_2$, 39465-57-1.

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Covalency Effects on the Ligand Field Splittings of Octahedral 5f[1] Compounds[1]

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Optical spectra have been recorded for $(NEt_4)_2PaCl_6$ and $(NEt_4)_2PaBr_6$ (0.4–2.2 μ) and the experimental results interpreted in terms of two ligand field parameters and the spin–orbit coupling constant. Similar interpretations are provided for data available on uranium(V)-hexahalogeno complexes and NpF_6. Trends in the ligand field parameters can be explained qualitatively in terms of molecular orbital theory with large variations in σ bonding dominating the total ligand field splittings as the halide ion is varied.

Introduction

Over the past 30 years the problem of covalency in d transition metal complexes has been thoroughly studied both theoretically and experimentally.[2] For octahedral complexes the simple model of d-electron orbitals interacting with ligand orbitals within a molecular orbital framework has proved useful since it enables parameters which describe the bonding in the complex to be determined from experimental data.

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