JOURNAL
OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 92, NUMBER 3 FEBRUARY 11, 1970

Physical and Inorganic Chemistry

A Thermodynamic Study of the Complexation Reactions for a Series of Amino Acids Related to Serine with Copper(II) and Nickel(II)[1]

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Received August 8, 1969

Abstract: The thermodynamic parameters for the complexation reactions of serine, threonine, homoserine, isoserine, 4-amino-3-hydroxybutyric acid, and β-aminobutyric acid with copper(II) and nickel(II) in aqueous solution at 25° and $\mu = 0.16$ are reported. Values for the formation constants were obtained from potentiometric titrations and enthalpy values determined calorimetrically. The α-amino acids studied, as well as β-aminobutyric acid, were postulated to form the typical amino-carboxyl chelates with copper(II) and nickel(II). The formation of a six-membered chelate ring was found to be less favorable thermodynamically than the formation of a five-membered chelate ring for both copper(II) and nickel(II) complexes. The thermodynamic data seem to indicate the formation of a chelate ring involving the amino and hydroxy groups of the isoserine with the copper(II). The isoserine ligand was postulated to be functioning as either a bidentate or tridentate ligand with copper(II).

It has been shown that for a number of aliphatic amino acids the formation of copper(II) complexes proceeds in a stepwise manner to form the mono and bis copper(II) species.[2] These complexes are formed by the elimination of a proton from the zwitterion form of 1 and 2 moles of amino acid, respectively. Chelation occurs between the carboxyl and amino groups of the amino acid and the copper(II) ion. The formation of nickel(II) complexes with aliphatic amino acids proceeds in the same manner, except that a third mole of amino acid can be chelated to the nickel(II) ion to form the tris nickel(II) species. In the case of amino acids interacting with copper(II) there seems to be some disagreement[3-5] as to whether or not the amino acid zwitterion can function as a monodentate ligand. Recent studies of the interaction of copper(II) with glycine[6] and with α-alanine[7] and β-alanine[8] indicate no interaction of the amino acid zwitterions with copper(II). The data presented here also indicate that no metal ion–zwitterion interactions occur under the conditions used in this study.

The amino acids studied in the present work are serine, threonine, homoserine, isoserine, 4-amino-3-hydroxybutyric acid, and β-aminobutyric acid. Except for β-aminobutyric acid, the possibility of chelation involving the hydroxy groups of the amino acids does exist. Stack and Skinner[8] have used heat data to invoke bonding contributions of the hydroxy group of serine with copper(II) and nickel(II). Recent crystal structure studies of bis(L-serinato)copper(II)[9] and diaquobis(L-serinato)nickel(II)[10] indicate no bonding between the hydroxy group of serine and the copper(II) or nick-

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(1) Based on the dissertation of J. E. Letter submitted to the Graduate School of the University of Missouri, Columbia, in partial fulfillment for the degree of Doctor of Philosophy, Aug 1969.

(2) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1961.

(3) R. M. Keefer, *J. Amer. Chem. Soc.*, 70, 476 (1948).

(4) R. M. Izatt, J. J. Christensen, and V. Kothari, *Inorg. Chem.*, 3, 1565 (1964).

(5) C. W. Childs and D. D. Perrin, *J. Chem. Soc., A*, 1039 (1969).

(6) A. F. Pearlmutter and J. Stuehr, *J. Amer. Chem. Soc.*, 90, 858 (1968).

(7) W. H. Makinen, A. F. Pearlmutter, and J. Stuehr, *ibid.*, 91, 4083 (1969).

(8) W. F. Stack and H. A. Skinner, *Trans. Faraday Soc.*, 63, 1136 (1967).

(9) D. van der Helm and W. A. Franks, *Acta Cryst.*, 25, 451 (1969).

(10) D. van der Helm and M. B. Hossain, *ibid.*, 25, 457 (1969).

el(II). Thus it was hoped that a thermodynamic study of a series of amino acids related to serine might shed some light on the bonding sites in some copper(II) and nickel(II) complexes.

The effect of the size of the chelate ring formed upon the thermodynamic quantities involved has been demonstrated for many different types of ligands with copper(II) and nickel(II).[11,-13] Thus in going from a five-membered chelate ring to a six-membered chelate ring, there is a decrease in positive entropy and a decrease in negative enthalpy, giving a smaller value for the formation constant for the complexation reaction in the latter case. This is true for a homologous series of ligands, provided other factors such as base strength remain about the same. In the case of α-aminobutyric acid compared to β-aminobutyric acid chelating with copper(II) there is an increase in chelate ring size from five to six, respectively. This is reflected in a decrease in positive entropy and a decrease in negative enthalpy for the latter amino acid.[14] Although ring size is not the only important thermodynamic consideration, the thermodynamic parameters may give some insight into the form of the copper(II) and nickel(II) complexes and the bonding interactions present.

Experimental Section

Materials. Carbonate free sodium hydroxide solutions were prepared by diluting a saturated, filtered solution of reagent grade (J. T. Baker Chemical Company, "Baker Analyzed") sodium hydroxide pellets with boiled distilled water. Carbonate free sodium hydroxide was also obtained from Bio-Rad Laboratories, and any necessary dilutions were made with boiled distilled water. All sodium hydroxide solutions were standardized with Baker and Adamson potassium acid phthalate before use. Nitric acid solutions were prepared from Baker Analyzed Reagent Grade acid. All inorganic salts were of reagent grade. Solutions of copper nitrate were filtered and analyzed by electrodeposition before use. Nickel nitrate solutions were filtered and analyzed gravimetrically with dimethylglyoxime. All solutions were prepared with an ionic strength of 0.16 *M*. Potassium nitrate was used as the added electrolyte when necessary.

The amino acids DL-serine, DL-threonine, L-homoserine, isoserine, and DL-β-aminobutyric acid were obtained from Nutritional Biochemicals Corporation. The amino acid DL-4-amino-3-hydroxybutyric acid was obtained from Aldrich Chemical Company. All amino acids were obtained as the free base and used without further purification after drying for 24 hr at 100°.

Potentiometric Titrations. A Corning Model 12 Research pH meter and either a Sargent S-30070-10 combination electrode or a Fisher 13-639-62 reference electrode with a Corning 476022 glass electrode were used. The expanded scale allowed pH readings to 0.001 pH unit with a reproduciblity of 0.003 pH unit. The pH meter was standardized before and after each titration with NBS certified buffer solutions (Fisher Scientific Company). All titrations were performed in a constant temperature cell at 25 ± 0.05°. Presaturated nitrogen was kept over the surface of the cell to prevent carbon dioxide absorption.

Acid dissociation constants for the amino acids were determined by the addition of sodium hydroxide solution to a solution of the amino acid. Formation constants for the metal ion complexes were determined by adding standard sodium hydroxide solution to a solution containing a 2–5:1 mole ratio of amino acid to copper nitrate or a solution containing a 3–5:1 mole ratio of amino acid to nickel nitrate. All solutions of amino acids were prepared immediately before use. From two to four independent titrations were performed for each system. Usually 15 to 30 points on the titration curve were used to calculate the acid dissociation constants or the formation constants. Each set of constants were also checked by back-titrating the solutions with standard nitric acid. Concentrations of amino acid were on the order of 2×10^{-3} *M* and concentrations of metal ion on the order of about 5×10^{-4} *M*.

Calorimetric Titrations. The thermometric titration calorimeter used has been previously described by Meyer.[15] Thermal equilibrium of the calorimeter and its contents was reached by immersing the calorimeter assembly in the constant temperature bath at least 16 hr before the enthalpy titrations were performed. The temperature measuring circuit and the heater circuit were turned on at least 1 hr before each enthalpy titration to stabilize the electronics. A pH probe (Sargent S-30070-10 combination electrode) connected to a Corning Model 12 Research pH meter was used in all of the heat runs. A volume of about 100 ml of solution was used in the calorimeter and each addition of titrant consisted of 0.5–2.0 ml. From five to ten heat measurements were made during each titration. Nitrogen gas was bubbled through the solution and then into the calorimeter before the equilibration process.

The calorimeter was calibrated using the heat of neutralization of sodium hydroxide with nitric acid using the value of −13.43 kcal/mole at an ionic strength of 0.32 reported by Hale, Izatt, and Christensen.[16] The heats of protonation for the amino acids were determined by the addition of nitric acid to the nearly completely deprotonated form of the amino acid. At least two independent heat titrations were performed for each amino acid. Corrections to the observed heat for the heat of neutralization of hydrogen ion with hydroxide ion were made for each point in a given titration, using the concentrations of amino acid and nitric acid, the measured pH, and the heat of neutralization of hydrogen ion with hydroxide ion. Since a constant ionic strength was maintained in all the titrations, no corrections were necessary for heats of dilution of the amino acids.

Heats of complexation of the copper(II) and nickel(II) amino acid complexes were determined in the following ways: (1) addition of the completely deprotonated form of the amino acid to a solution of the metal ion in the calorimeter, (2) titration of a solution of metal ion and amino acid in the calorimeter with standard sodium hydroxide, (3) addition of the metal ion to a solution of the deprotonated form of the amino acid in the calorimeter. The first method was used in most cases because it resulted in small corrections to the observed heat for protonation reactions of the amino acids and neutralization reactions. Corrections to the observed heat were made using the heats of protonation for the amino acids, the concentrations of the substances in the calorimeter, the pH of the amino acid titrant, the pH of the solution in the calorimeter, and the various equilibrium constants.

Results and Discussion

Ligand Thermodynamics. The thermodynamic parameters for the proton dissociation reaction were first determined, where HL represents the zwitterion form of

$$\mathrm{HL} \longrightarrow \mathrm{H}^+ + \mathrm{L}^- \qquad K_{a2} = \frac{[\mathrm{H}^+][\mathrm{L}^-]}{[\mathrm{HL}]} \tag{1}$$

the amino acid and L^- represents the anionic form of the ligand. Under the conditions of this study it was found that the amino acids were present as either the zwitterion or the anion only. Therefore thermodynamic functions for the deprotonation of the carboxyl group were not de-

$$\mathrm{H_2L}^+ \longrightarrow \mathrm{HL} + \mathrm{H}^+ \qquad K_{a1} \tag{2}$$

termined. The values for the acid dissociation constants were calculated in the usual manner using the measured pH and initial concentrations. The protonation heats were also determined calorimetrically. The thermodynamic functions along with various values from the literature are given in Table I. The precision of the pK_a values is estimated to be ±0.01 log unit, and for the ΔH values ±0.15 kcal/mole. These error esti-

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[16] J. D. Hale, R. M. Izatt, and J. J. Christensen, *J. Phys. Chem.*, 67, 2605 (1963).

Table I. Thermodynamic Functions for the Amino Proton Dissociation Reactions[a]

Ligand	pK_a	ΔG, kcal/mole	ΔH, kcal/mole	ΔS, cal/(mole deg)	Ref
Serine	9.18	12.52	10.05	8.3	*b*
	9.880		10.405		*c*
	9.12				*d*
	9.24				*e*
Threonine	9.07	12.37	9.78	8.7	*b*
	9.10		10.04		*f*
	8.86				*d*
	9.00				*e*
			9.96		*c*
Homoserine	9.43	12.86	10.23	8.8	*b*
Isoserine	9.25	12.61	10.09	8.5	*b*
4-Amino-3-hydroxybutyric acid	9.73	13.27	10.88	8.0	*b*
β-Aminobutyric acid	10.14	13.83	11.02	9.4	*b*
	10.19				*g*

[a] At 25° and $\mu = 0.16$. [b] Present study. [c] P. K. Smith, A. T. Gorham, and E. R. Smith, *J. Biol. Chem.*, **144**, 737 (1942); 20°, $\mu = 0.0$. [d] D. D. Perrin, *J. Chem. Soc.*, 3125 (1958); 20°, $\mu = 1.0$. [e] N. C. Li and E. Doody, *J. Amer. Chem. Soc.*, **74**, 4184 (1952); 25°, $\mu = 0.10$. [f] Reference 4; 25°, $\mu = 0.0$. [g] Reference 14; 25°, $\mu = 0.2$.

mates include random and systematic uncertainties caused by the equipment and the calculations.

The enthalpy and entropy values for the deprotonation reactions given in Table I do not vary much. This observation has been made for other amino acids.[4] The relatively constant entropy values seem to reflect the solvation of the proton and ordering of the water molecules in the ionization of the amino acid zwitterions to form the anions. The enthalpy values for the β-aminobutyric acid and 4-amino-3-hydroxybutyric acid deprotonations are more endothermic than the other amino acids, perhaps due to the distance of the amino group from the carboxyl group thus rendering the amino nitrogens as better proton acceptors.

Thermodynamic Parameters for the Complexation Reactions. The following equilibria can be used to express the formation of the metal ion–amino acid complexes except for the serine–, threonine–, and homoserine–Ni(II) systems where equilibrium 5 must also be

$$M^{2+} + L^- \rightleftharpoons ML^+ \qquad K_1, \Delta H_1 \tag{3}$$

$$ML^+ + L^- \rightleftharpoons ML_2 \qquad K_2, \Delta H_2 \tag{4}$$

$$ML_2 + L^- \rightleftharpoons ML_3^- \qquad K_3, \Delta H_3 \tag{5}$$

considered. Initial values for the formation constants were obtained using the method described by Rossotti and Rossotti[17] from the linear equation

$$\frac{(\bar{n} - 1)[L^-]}{\bar{n}} = K_2\frac{[L^-]^2(2 - \bar{n})}{\bar{n}} - \frac{1}{K_1} \tag{6}$$

The symbol $\bar{n}$ is defined as the average number of ligands bound per metal ion and $[L^-]$ as the free ligand concentration. Values for $\bar{n}$ and $[L^-]$ can be calculated from the experimental data using

$$\bar{n} = \frac{C_L - [L^-](1 + [H^+]^2/K_{a1}K_{a2} + [H^+]/K_{a2})}{C_M} \tag{7}$$

$$[L^-] = \frac{C_L - C_B + [OH^-] - [H^+]}{2[H^+]^2/K_{a1}K_{a2} + [H^+]/K_{a2}} \tag{8}$$

where C_L is the initial concentration of amino acid (zwitterion), C_B is the concentration of base, $[H^+]$ and $[OH^-]$ can be obtained from pH readings, and C_M is the total concentration of metal ion. The formation constants were then refined using a least-squares iterative procedure[15,18] to find the set of constants which best fit the data to a specified theoretical curve. The iterative procedure was to first calculate $[L^-]$ from eq 8 and estimate $\bar{n}$ from eq 7. The free metal ion concentration could then be calculated from

$$[M^{2+}] = \frac{C_M}{1 + K_1[L^-] + K_1K_2[L^-]^2} \tag{9}$$

Iterations were performed until self-consistent values were obtained using the formation constants obtained from eq 6. The problem was then to minimize

$$S(K_1,K_2) = \sum_{i=1}^{n} [\bar{n}_i - f([L]_i,[H^+]_i,K_1,K_2)]^2$$

This was done by varing K_1 and K_2 over a specified interval and calculating the squares of the deviations of the theoretical $\bar{n}$ values

$$\bar{n} = \frac{2K_1K_2[L^-]^2 + K_1[L^-]}{1 + K_1K_2[L^-] + K_1[L^-]} \tag{10}$$

from the calculated experimental $\bar{n}$, eq 7, values. The formation constant value which gave the smallest deviation was stored and used to calculate the next constant. After the best values of the formation constants were obtained, the process was repeated and the interval over which the constants were varied was decreased until convergence was attained. Initial selection of good values for the formation constants was essential for this procedure. For the serine–, threonine–, and homoserine–Ni(II) systems initial values for K_3 were obtained from graphical plots of pL *vs.* $\bar{n}$. The least-squares refinements were done with the aid of an IBM 7040 electronic computer. The precision is estimated to be ±0.02 log unit for the formation constants.

Values for ΔH_1 and ΔH_2 were obtained from the calorimetric titrations by first defining a function, $\overline{\Delta H}$, as the average heat per mole of ligand complexed to the metal ion.

$$\overline{\Delta H} = \frac{\Delta H_1[ML^+] + (\Delta H_1 + \Delta H_2)[ML_2]}{[ML^+] + 2[ML_2]} \tag{11}$$

Using the equilibria of (3) and (4) in (11) the following equation can be obtained

$$\overline{\Delta H} = \frac{\Delta H_1 + (\Delta H_1 + \Delta H_2)K_2[L^-]}{1 + 2K_2[L^-]} \tag{12}$$

which can be arranged to the linear form

$$\overline{\Delta H}(1 + \theta) = \Delta H_2\theta + \Delta H_1 \tag{13}$$

where $\theta = K_2[L^-]/(1 + K_2[L^-])$. Thus ΔH_1 and ΔH_2 can be determined from the intercept and slope of the line of a plot of $\overline{\Delta H}(1 + \theta)$ *vs.* θ. The free ligand concentration could be calculated from (8), and $\overline{\Delta H}$ was calculated by dividing the total corrected heat by the total moles of ligand bound to the metal ion. Values for ΔH_3 for the serine–, threonine–, and homoserine–Ni(II)

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(17) F. J. C. Rossotti and H. Rossotti, "The Determination of Stability Constants," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(18) E. A. Unwin, R. G. Beimer, and Q. Fernando, *Anal. Chim. Acta*, 39, 95 (1967).

Table II. Thermodynamic Parameters for the Complexation of Copper(II)[a]

Reaction	Ligand	Log K	$-\Delta G$, kcal/mole	$-\Delta H$, kcal/mole	ΔS, cal/(mole deg)	Ref
$Cu^{2+} + L^- \rightarrow CuL^+$	Serine	7.85	10.71	5.51	17.5	*b*
		7.56				*c*
		7.57				*d*
	Threonine	7.95	10.83	5.56	17.7	*b*
		8.44		5.3		*e*
		7.55				*c*
	Homoserine	8.00	10.91	5.45	18.3	*b*
	Isoserine	7.31	9.97	5.78	14.1	*b*
	4-Amino-3-hydroxybutyric acid	6.48	8.84	4.87	13.3	*b*
	β-Aminobutyric acid	7.12	9.71	4.94	16.0	*b*
		7.18		5.0		*f*
	α-Aminobutyric acid	7.84	10.69	5.52	17.3	*g*
$CuL^+ + L^- \rightarrow CuL_2$	Serine	6.65	9.07	6.13	9.9	*b*
		6.45				*c*
		6.45				*d*
	Threonine	6.74	9.19	6.09	10.4	*b*
		6.96		6.1		*e*
		6.46				*c*
	Homoserine	6.69	9.12	5.94	10.7	*b*
	Isoserine	7.06	9.63	6.16	11.6	*b*
	4-Amino-3-hydroxybutyric acid	6.06	8.26	5.55	9.1	*b*
	β-Aminobutyric acid	5.73	7.81	5.58	7.5	*b*
		5.59		4.6		*f*
	α-Aminobutyric acid	6.64	9.06	5.98	10.3	*g*

[a] At 25° and $\mu = 0.16$. [b] Present study. [c] V. S. Sharma, *Biochem. Biophys. Acta*, **148**, 37 (1967); 37°, $\mu = 0.16$. [d] D. D. Perrin, I. G. Sayce, and V. S. Sharma, *J. Chem. Soc., A*, 1755 (1967); 37°, $\mu = 0.16$. [e] Reference 4; 25°, $\mu = 0.0$. [f] Reference 14; 25°, $\mu = 0.2$. [g] Reference 15; 25°, $\mu = 0.16$.

Table III. Thermodynamic Parameters for the Complexation of Nickel(II)[a]

Reaction	Ligand	Log K	$-\Delta G$, kcal/mole	$-H$, kcal/mole	ΔS, cal/(mole deg)	Ref
$Ni^{2+} + L^- \rightarrow NiL^+$	Serine	5.45	7.43	3.76	12.3	*b*
		5.44		5.22		*c*
		5.21				*d*
	Threonine	5.46	7.45	3.81	12.2	*b*
		5.15				*d*
	Homoserine	5.51	7.51	3.92	12.1	*b*
	Isoserine	4.19	5.71	3.09	8.8	*b*
	4-Amino-3-hydroxybutyric acid	3.99	5.44	2.60	9.4	*b*
	β-Aminobutyric acid	4.56	6.22	2.70	11.8	*b*
		4.60		3.8	8.4	*e*
	α-Aminobutyric acid	5.46		4.8	8.9	*e*
$NiL^+ + L^- \rightarrow NiL_2$	Serine	4.53	6.18	4.27	6.4	*b*
		4.38		5.67		*c*
		4.38				*d*
	Threonine	4.51	6.15	4.36	6.0	*b*
		4.22				*d*
	Homoserine	4.60	6.27	4.48	6.0	*b*
	Isoserine	3.66	4.99	3.73	4.2	*b*
	4-Amino-3-hydroxybutyric acid	3.18	4.34	2.71	5.5	*b*
	β-Aminobutyric acid	3.30	4.50	2.89	5.4	*b*
		3.32		4.8	−1.0	*e*
	α-Aminobutyric acid	4.36	5.95	4.8	3.9	*e*
$NiL_2 + L^- \rightarrow NiL_3^-$	Serine	3.54	4.83	5.28	−1.5	*b*
		2.97		6.27		*c*
		2.90				*d*
				5.7		*f*
	Threonine	3.45	4.71	5.20	−1.6	*b*
		2.47				*d*
	Homoserine	3.26	4.45	5.49	−3.5	*b*

[a] At 25° and $\mu = 0.16$. [b] Present study. [c] S. Pelletier, *C. R. Acad. Sci., Paris*, **245**, 160 (1967); 20°. [d] V. S. Sharma, *Biochem. Biophys. Acta*, **148**, 37 (1967); 37°, $\mu = 0.16$. [e] Reference 14; 25°, $\mu = 0.2$. [f] Reference 8; 22° $\mu = 0.1$.

systems were determined by adding Ni(II) to a large excess of the anionic form of the ligand to obtain the heat for the reaction, and then using the value of ΔH_{0-3} in

$$Ni^{2+} + 3L^- \longrightarrow NiL_3^- \qquad \Delta H_{0-3} \tag{14}$$

conjunction with the values of ΔH_1 and ΔH_2 to obtain ΔH_3. A plot of $\overline{\Delta H}(1 + \theta)$ *vs.* θ for the copper(II)–serine system is shown in Figure 1. The precision of the ΔH values is estimated to be ±0.10 kcal/mole.

The thermodynamic parameters for the copper(II) systems are summarized in Table II and for the Ni(II) systems in Table III. The value for ΔH_2 is more exothermic than the value of ΔH_1 for each of these ligands. The coordination of the first amino acid by the metal ion may result in a weakening of the remaining metal–water bonds in the complex and additional release of water molecules from the metal ion in the formation of the ML^+ species compared to the formation of the ML_2 complex.[19] The values for ΔS_1 are more positive than the values of ΔS_2 for these systems. This is a further indication of additional release of water molecules in the first step of complexation as compared to the second step. The contact of the positive metal ion with the anionic ligand donor atoms results in an effective charge neutralization and a positive entropy of association. The release of water resulting in a positive entropy is the most important factor in determining the entropy of association.[20]

The most important contribution to the exothermic heat of chelation of an amino acid to copper(II) or nickel(II) seems to be the bonding of the neutral amino nitrogen to the metal ion.[8,14,20] The negatively charged carboxyl group forms a bond to copper(II) or nickel(II), the formation of which is endothermic.[13] The carboxyl group interaction with the positive metal ion does contribute substantially to the positive entropy changes. Thus one-half of the heat of complexation for the formation of CuL^{2+} (6.5 kcal/mole) and CuL_2 (6.2 kcal/mole) for the copper(II)–ethylenediamine complexes[12] is very nearly equal to the values of ΔH_1 and ΔH_2, respectively, found for the α-amino acids used in the present study. Comparison of $^1/_2\Delta S$ for the copper(II)–oxalate complex (14.2 cal/(mole deg))[13] with ΔS_1 for the copper(II)–α-amino acid systems shows that the values of ΔS and ΔS_1 are quite similar. The very similar values for the thermodynamic functions for serine, threonine, homoserine, and α-aminobutyric acid in Table II and Table III do not indicate any bonding interactions of the hydroxy group of the first three ligands with copper(II) or nickel(II). Stack and Skinner[8] have invoked possible coordination of the hydroxy group in serine with copper(II) to explain low values of ΔS for complex formation compared to ΔS values for glycine. The value of ΔH used by Stack and Skinner seems to be too exothermic, and this is more likely the cause of the low entropy value obtained by them for the copper(II)–serine system. Stack and Skinner have also suggested that the carboxyl, amino, and hydroxy groups of serine could be octahedrally coordinated to the nickel(II) in the mono complex to form two five-membered chelate rings. If so, this can not be postulated from our data. Recent X-ray studies of bis(L-serinato)copper(II)[9] and diaquobis(L-serinato)nickel(II)[10] indicate no bond formation between the hydroxy group of serine and the metal ion.

Thermodynamic data for a number of polydentate ligands support the generalization that the formation of chelate complexes becomes less favorable in going from a five- to a six-membered ring for a homologous series of ligands.[11–13] The ΔH values for the formation of the larger rings are less exothermic and the ΔS values less positive than for the formation of the five-membered rings. This is perhaps due to an increased metal–ligand bond distance in the *xy* plane of the metal ion for six- as compared to five-membered rings.[14] The heat and entropy data listed in Tables II and III for α-aminobutyric acid and β-aminobutyric acid reflect the formation of five- and six-membered chelate rings, respectively. The isoserine ligand might be expected to form a six-membered chelate ring with the amino nitrogen and carboxyl oxygen of the ligand and the metal ion. However, the heat data for the isoserine–copper(II) system in Table II very strongly indicate the formation of a five-membered chelate ring with chelation occurring through the amino nitrogen and the hydroxy oxygen. The enthalpy values for the isoserine–copper(II) system are very similar to the enthalpy values for the α-amino acids, and significantly more exothermic than the enthalpy values for the β-aminobutyric acid–copper(II) system.

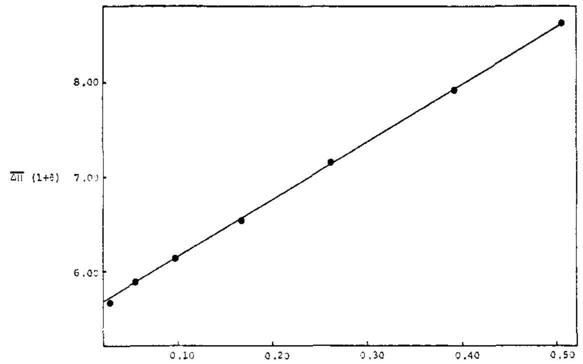

Figure 1. Heats of complexation for serine with copper(II).

Several explanations are possible for the isoserine–copper(II) thermodynamic data in Table II. (1) The chelation of the protonated hydroxy oxygen and the amino nitrogen of isoserine could lead to a less effective charge neutralization. This would give less positive ΔS_1 values for isoserine than for the α-amino acid chelates in Table II. This does not explain the apparent reversal of ΔS_2 values found in Table II for isoserine and the α-amino acids. The bonding of the protonated hydroxy group of an alcohol to copper(II), as well as other transition metal ions, has been inferred for methanol and ethylene glycol.[21] (2) The charged carboxyl oxygen could be bonded to the copper(II), giving a tridentate isoserine molecule. This type of interaction has been recently proposed for the bis(histidine)copper(II) complex[22] and for the L-histidinato-L-threonatoaquocopper(II) complex.[23] The thermodynamic data for the isoserine–nickel(II) system in Table III are also consistent with the formation of a tridentate isoserine chelate. In addition, enthalpy data for isoserine with nickel(II) are consistent with the formation of a very stable bis nickel(II)–isoserine complex at isoserine to nickel(II) mole ratios up to 23:1. No evidence for a tris complex was found with nickel(II). (3) Isoserine could chelate through the amino nitrogen and the deprotonated negatively charged hydroxy oxygen. The hydroxy proton would be associated with the carboxyl group in this complex. The present data do not rule out any of the proposed forms of the copper(II)–isoserine complex because the principal bonding sites are the

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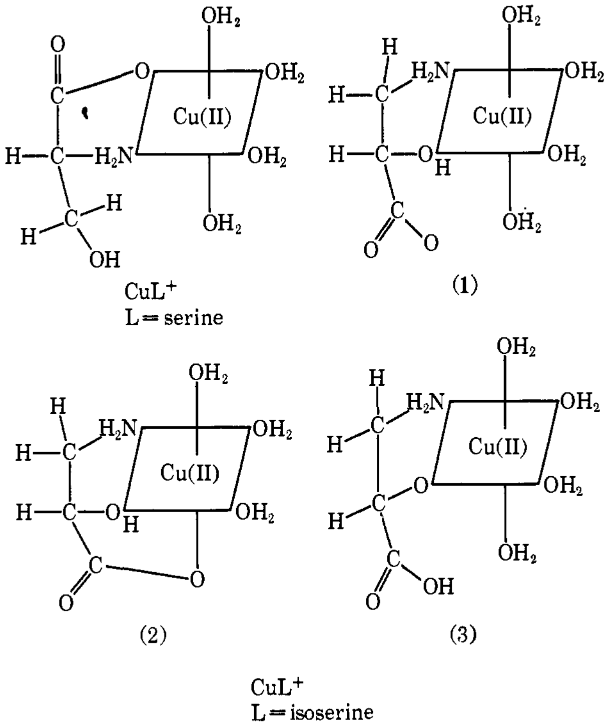
Table IV. Thermodynamic Functions for the $M^{2+} + 2L^- \rightarrow ML_2$ Reactions[a]

	Cu(II)				Ni(II)			
Ligand	Log β_2	$-\Delta G$, kcal/mole	$-\Delta H$, kcal/mole	ΔS, cal/(mole deg)	Log β_2	$-\Delta G$, kcal/mole	$-\Delta H$, kcal/mole	ΔS, cal/(mole deg)
Serine	14.50	19.77	11.64	27.3	9.98	13.61	8.03	18.7
Threonine	14.68	20.02	11.65	29.0	9.97	13.60	8.17	18.2
Homoserine	14.69	20.03	11.39	28.1	10.11	13.79	8.40	18.1
Isoserine	14.37	19.60	11.94	25.7	7.85	10.71	6.82	13.5
4-Amino-3-hydroxybutyric acid	12.54	17.10	10.42	22.4	7.17	9.78	5.31	15.0
β-Aminobutyric acid	12.85	17.52	10.52	23.6	7.86	10.72	5.59	17.0

[a] At 25° and μ = 0.16.

amino and hydroxy groups in all cases. Proposed structures for the mono copper(II) complexes of serine and isoserine, which are consistent with the thermodynamic parameters, are shown in Figure 2.



CuL+
L = serine

(1)

(2)

(3)

CuL+
L = isoserine

Figure 2. Possible structures for the mono copper(II) complexes of serine and isoserine.

The heat data for 4-amino-3-hydroxybutyric acid in Table II and Table III are too exothermic to be reasonably explained by the formation of only an amino-carboxyl-metal chelate, giving a seven-membered ring. There seems to be some contribution for this ligand by the chelation of the amino and hydroxy groups to form a five-membered ring. Perhaps both types of rings are formed. Precipitation problems prevented the measurement of K_3 and ΔH_3 values for 4-amino-3-hydroxybutyric acid, as well as β-aminobutyric acid, with nickel(II).

Comparison of the ML_2 Formation Thermodynamics. Table IV summarizes the thermodynamic parameters for the reaction

$$M^{2+} + 2L^- \longrightarrow ML_2 \quad \log \beta_2 \tag{15}$$

The value of log β_2 for a particular amino acid with copper(II) is much larger than the corresponding value of log β_2 with nickel(II). This is in agreement with the general order of stability of complexes of bivalent transition metal ions proposed by Irving and Williams.[24] Values for ΔH for a particular amino acid with copper(II) are more exothermic than the corresponding values for ΔH with nickel(II). The Jahn-Teller tetragonal distortion for copper(II) could result in four shortened metal-ligand bonds in the *xy* plane of the metal.[19] The shortened metal-ligand distance would result in more exothermic heats for the formation of the tetragonal copper(II) complexes than for the formation of nickel(II) complexes. The chelation of copper(II) with an amino acid seems to result in a more effective charge neutralization and a greater water release than for nickel(II). Thus the entropy values in Table IV are more positive for copper(II) than for nickel(II) complex formation. There is a dramatic change in the thermodynamic parameters for complex formation in going from the octahedral d^8 nickel(II) to the tetragonally distorted d^9 copper(II). The formation of a six-membered chelate ring is less favorable than the formation of a five-membered chelate ring for both copper(II) and nickel(II).

Acknowledgments. J. E. L. wishes to thank the Monsanto Chemical Company and the University of Missouri Space Sciences Research Center for summer scholarships. J. E. L. particularly expresses his gratitude to the American Chemical Society (Petroleum Research Fund) for a fellowship for 1968–1969.

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