Mixed Ligand Complexes. Log β, Δ*H*°, and Δ*S*° Values for the Cu^{2+}–Glycine, –Alanine, –α-Aminoisobutyric Acid, and Sarcosine Systems

By **Austin Yingst, Reed M. Izatt,** and **James J. Christensen,*** **Departments of Chemistry and Chemical Engineering and No. 14 from the Center for Thermochemical Studies, Brigham Young University, Provo, Utah 84601**

Values of log β, Δ*H*°, and Δ*S*° are reported for mixed-ligand complex formation of Cu^{2+} with amino-acids in dilute aqueous solution. The reaction $Cu^{2+} + A^- + B^- = CuAB$ is characterized for the systems involving glycine, alanine, sarcosine, and aminoisobutyric acid as ligands. The thermochemical results are discussed in terms of a statistical model and it is shown that the enhancement factor term applied to mixed-ligand formation constants does not necessarily arise from the entropy term.

THE interaction of Cu^{2+} with various amino-acids has received considerable attention in these laboratories.[1-5] Previous reports have included thermochemical quantities for Cu^{2+} and/or H^+ interaction with the anions of glycine, alanine, phenylalanine, α-aminoisobutyric acid, threonine, and sarcosine in reactions of the form:

$$Cu^{2+} + A^- = CuA^+ \qquad (1)$$

$$Cu^{2+} + 2A^- = CuA_2 \qquad (2)$$

$$A^- + H^+ = HA \qquad (3)$$

We report here the interactions of some of these ligands with Cu^{2+} to form mixed ligand complexes according to reaction (4) where $A \neq B$.

$$Cu^{2+} + A^- + B^- = CuAB \qquad (4)$$

Cu^{2+}–Amino acid systems were selected for this study

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[1] R. M. Izatt, J. W. Wrathall, and K. P. Anderson, *J. Phys. Chem.*, 1961, **65**, 1914.

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[4] K. P. Anderson, W. O. Greenhalgh, and R. M. Izatt, *Inorg. Chem.*, 1966, **5**, 2106.

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for a variety of reasons; the reactions involved are simple and unambiguous in behaviour, and the thermodynamic quantities (log K and ΔH°) for the interactions of a number of these ligands with Cu^{2+} in unmixed complexes have been previously reported. The data for mixed complexes should permit some insight into the effects of ligand structure upon this class or reactions, as well as provide some clues concerning the source of enhanced stability in mixed ligand systems.

A number of equilibrium constants have been reported for mixed ligand complex formation involving amino-acids and other chelates in solution, but there appear to be virtually no calorimetric data for this class of complexes. Leussing and Shultz[6] report ΔH values estimated from the variation of log K values at two temperatures for the formation of mixed ligand and Schiff base complexes. Degischer and Nancollas[7] have recently reported calorimetric results of mixed ligand–Cu^{2+} systems with ethylenediamine and either ethylenediaminediacetic acid or ethylenediaminedipropionic acid. The results were discussed in terms of electrostatic interaction between solute and solvent and between donor groups of the ligand.

Most authors observe an enhanced stability of mixed ligand complexes relative to the parent complexes containing the same number of ligands. For instance, several investigations[8] have reported numerous mixed ligand formation constants of amino-acids and similar ligands with Cu^{2+} and Ni^{2+}. In general their results, obtained at high ionic strengths (0·1—1·0M), indicate that the mixed complex is generally 0·2—0·5 log units more stable than can be accounted for on statistical grounds alone. L'Heureux and Martell[9] report a large enhancement in the stabilities of Cu^{II} mixed complexes in which 2,2′-bipyridyl is one of the ligands; they attribute the observed stability to coulombic and solvation factors. Similar observations have been reported by Sigel[10] who also noted ligand-field stabilization effects in mixed complexes. Perrin and co-workers[11] report formation constants of mixed complexes involving Cu^{2+} and ethylenediamine, histamine, serinate ion, and salicylate ion.

EXPERIMENTAL

Apparatus.—The titration calorimeter used in these experiments has been previously described,[12] and is capable of detecting 0·005 cal (0·02 J) of heat during an experiment.

Reagents.—The amino-acids used were obtained from Calbiochem (glycine and sarcosine), Eastman Chemical (alanine), and Sigma (aminoisobutyric acid), and were recrystallized before use. Copper carbonate (J. T. Baker) was used as received. Copper carbonate was treated separately with aqueous solutions of the various amino-acids. The resulting slurries were heated gently to remove CO_2 and to obtain the desired complex, CuA_2. Stoicheiometric purity of solid CuA_2 after recrystallization and drying was checked by treating the appropriate copper salt in a heavily buffered solution (pH $\simeq$ 5) with potassium iodide followed by titration under a nitrogen atmosphere with sodium thiosulphate. The sodium thiosulphate was previously standardized against potassium iodate. Solutions of the CuA_2 complexes were prepared for calorimetric study by dissolving carefully weighed samples in double distilled and boiled water and diluting the solutions to a known volume.

Calorimetric Runs.—Reactions were carried out by titrating a solution of the appropriate amino-acid, HB, into a calorimeter containing a 100-ml solution of a copper salt of a second amino-acid, CuA_2. Typical concentrations for titrant HB were 0·35—0·55M; for the titrant, CuA_2, the concentration range was 12—20 mM. All runs were made in a pH range where the concentration of the H_2A^+ and H_2B^+ species were negligible (pH > 5).

Calculations.—Species distributions from all reactions in the calorimeter conform to the stoicheiometric relationships:

$$\text{Total Metal} = [M^{2+}] + [MA^+] + [MA_2] + [MB^+] + [MB_2] + [MAB]$$

$$\text{Total Ligand A} = [A^-] + [HA] + [MA^+] + 2[MA_2] + [MAB]$$

$$\text{Total Ligand B} = [B^-] + [HB] + [MB^+] + 2[MB_2] + [MAB]$$

$$\text{Total Neutralizable Acid} = [H^+] - [OH^-] + [HA] + [HB]$$

The formation constants pertinent to the systems studied are defined as follows (neglecting charges):

$$\begin{aligned} \beta^{\mathrm{H}}_{\mathrm{A}} &= [HA]/[H][A] & \beta^{\mathrm{H}}_{\mathrm{B}} &= [HB]/[H][B] \\ \beta_{10} &= [MA]/[M][A] & \beta_{01} &= [MB]/[M][B] \\ \beta_{20} &= [MA_2]/[M][A]^2 & \beta_{02} &= [MB]_2/[M][B]^2 \\ \beta_{11} &= [MAB]/[M][A][B] & K_{\mathrm{w}} &= [H][OH] \end{aligned}$$

The metal–ligand formation constant β_{ij}, is that constant appropriate to a complex containing one copper atom, i ligands of type A, and j ligands of type B. This type of notation is used throughout the paper for other thermodynamic quantities also. Direct algebraic solution of the mass balance equations to calculate concentrations of species present proved intractable, and the above equations were solved by an iterative process for the quantities $[A^-]$ and $[B^-]$. Numerous numerical tests revealed that this method yielded a single set of concentration values in the concentration range of interest (*viz.* 0·1 to 10^{-10}M) for a given set of stoicheiometric and formation constant conditions. Typical values for the quantities $[A^-]$ and $[B^-]$ were in the range $\sim 10^{-4}$ to $\sim 10^{-5}$M.

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[11] D. D. Perrin, I. G. Sayce, and V. S. Sharma, *J. Chem. Soc.* (*A*), 1967, 1755.

[12] J. J. Christensen, R. M. Izatt, and L. D. Hansen, *Rev. Sci. Instr.*, 1965, **36**, 779.

Thermodynamic data for reactions (1), (2), and (3) have been reported so that the only unknown thermodynamic quantities were those pertaining to reaction (4) for the mixed ligand complex.[1-5] The log β_{11} and ΔH_{11} values for reaction (4) were calculated, using the concentrations of species calculated above, from the calorimetric data using numerical methods similar to those described previously.[13,14] These values were obtained by systematically varying log β_{11} in a one-dimensional grid search, calculating for each trial β_{11} value a corresponding ΔH value and an error-square-sum according to the relationship

$$U = \sum_i (Q_i - \Delta H^\circ \Delta n_i)^2$$

where Q_i is the heat rise at point i following correction of the total heat for heat of dilution of the titrant, heat of stirring, temperature difference between titrant and calorimeter contents, and heat-capacity change due to addition of titrant, and Δn_i is the change in the number of moles of CuAB from the beginning of the titration to point i. The search was controlled to seek a minimum in U, and the corresponding log β_{11} (not corrected for activity coefficients) and the calculated ΔH_{11} were assumed to be the appropriate thermodynamic quantities valid at zero ionic strength, since the ionic strengths of the solutions rarely exceeded 0·001. Values for ΔG°_{11} and ΔS°_{11} were obtained from the appropriate relationships.

TABLE 1

Thermodynamic functions for the formation of copper–amino-acid mixed ligand systems, CuAB [a]

Ligands	log β_{11}	ΔH_{11} [b]	ΔS_{11} [b]	Δ log β [c]
Glycinate–sarcosinate	15·59 ± 0·03	−10·91 ± 0·03	34·8 ± 0·4	0·33
Glycinate–alanate	15·81 ± 0·03	−12·35 ± 0·09	30·9 ± 0·1	0·33
Alanate–aminoisobutyrate	15·77 ± 0·01	−12·02 ± 0·03	31·8 ± 0·1	0·29
Glycinate–aminoisobutyrate	15·89 ± 0·01	−11·49 ± 0·03	34·2 ± 0·1	0·31

[a] Valid at $\mu = 0$ and 25°. Uncertainties are expressed as standard deviations among 5 runs. [b] ΔH° Values in kcal mol^{-1} and ΔS° values in cal deg^{-1} mol^{-1}. [c] See equation (5).

RESULTS

The thermodynamic quantities [pertaining to reaction (4)] for the systems studied are summarized in Table 1 together with the quantity Δ log β, which is defined by the relation (5). The Δ log β values are a measure of enhancement of the formation of the mixed complex beyond that

$$\Delta \log \beta = \log \beta_{11} - 0{\cdot}5\,(\log \beta_{20} + \log \beta_{02}) \qquad (5)$$

predicted by the mean of the 1 : 2 unmixed complexes. The log β, ΔH°, and ΔS° values for the reaction of single ligands with Cu^{2+} were taken from the literature and are summarized in Table 2.

TABLE 2

Thermodynamic quantitites for the indicated reactions [a—c]

	$Cu^{2+} + A^- = CuA^+$			$Cu^{2+} + 2A^- = CuA_2$		
Ligand	log β_1	ΔH°_1	ΔS°_1	log β_2	ΔH°_2	ΔS°_2
Glycinate	8·62	−6·00	19·3	15·59	−12·40	29·7
Alanate	8·51	−5·60	20·1	15·37	−11·80	30·7
Aminoisobutyrate	8·54	−5·40	21·0	15·80	−11·10	34·0
Sarcosinate	8·14	−4·60	21·8	14·92	−10·00	34·7

[a] Data assembled from references 1—5. [b] Data valid at $\mu = 0$ and 25 °C. [c] ΔH° (kcal mol^{-1}), ΔS° (cal deg^{-1} mol^{-1}).

DISCUSSION

In addition to the results reported in Table 1, the measurement of the formation constants of copper glycinate aminoisobutyrate and copper alanate sarcosinate were also attempted but proved unsuccessful. For these two systems, the thermograms consisted of an initial short period of exothermicity followed by endothermic behaviour whereas all runs for the other four systems were completely endothermic over the entire run. The source of this exothermic period is not known. Attempts to analyse the thermogram well after the initial period gave values dependent upon the number of points analysed and their relative position in the thermogram. Attempts to analyse the data from the reverse titration, $CuB_2 + HA = CuAB + HB$, were also unsuccessful. Execution of the reaction $CuA + B = CuAB$ was not attempted by titration of CuA^+ with B^- since formation constants for this reaction are too large to be calculated from the calorimetric data.

The enhancement of the formation constant values (Δ log β in Table 1) is, within experimental error, what one would predict from the addition of the statistical factor, 0·301 (ref. 15) to the arithmetic mean of the parent 1 : 2 complexes.

Because the equilibrium constants here are so close to those predicted from statistical considerations, it is desirable to compare the corresponding experimental ΔH° and ΔS° values with those calculated from a consideration of the ΔH° and ΔS° values of the parent complexes.

Thermodynamic quantities calculated for reaction (4) contain information about the interaction of MB with A as well as MA with B, but these interactions are not easily separated within the framework of reaction (4). Consideration of the related expression, reaction

$$MA^+ + B^- = MAB \qquad (6)$$

(6), makes possible direct comparisons and contrasts between simple and mixed complexes.

In Table 3 are tabulated the experimental enthalpy

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[13] R. M. Izatt, D. Eatough, J. J. Christensen, and R. L. Snow, *J. Phys. Chem.*, 1968, **72**, 1208.

[14] J. J. Christensen, D. P. Wrathall, and R. M. Izatt, *Analyt. Chem.*, 1968, **40**, 175.

[15] For a discussion of statistical corrections and how they are calculated in mixed ligand systems, see V. S. Sharma and J. Schubert, *J. Chem. Educ.*, 1969, **46**, 506.

and entropy change values for reaction (6) for various combinations of A and B found in Table 1 together with the mean value for the thermodynamic quantities as defined in equation (7).

$$\text{Mean} = \Delta\bar{X}_{11} = 1/2(\Delta X_{02} + \Delta X_{20}) \qquad (7)$$

where ΔX_{02} and ΔX_{20} ($X = H$ or S) are the thermodynamic quantities for reaction (6) where A = B and B = A, respectively. Also found in Table 3 are the ΔH° and ΔS° values for the reaction $MB + B = MB_2$.

Examination of Table 3 reveals that the enhancement factor in mixed complexes does not necessarily arise from the ΔS° value. For instance, the ΔH° value upon addition of alanate ion to monoglycinatocopper(II) ion agrees to within 0·15 kcal mol^{-1} with either the ΔH° value predicted by the mean, equation (7), or that for the addition of a second glycinate. The ΔS° value for the reaction of alanate ion with monoglycinatecopper(II) ion is 1·1 cal deg^{-1} mol^{-1} higher than the mean value and thus accounts for the statistical correction in the enhanced stability of the mixed complex, CuAB. By contrast, the ΔH° value for the reaction of glycinate ion with monoalanatocopper(II) ion is 0·45 kcal mol^{-1} more exothermic than the mean value although the ΔS° value for the same reaction is very close to that predicted from equation (7). More extensive examination of Table 3 reveals that frequently there is a significant difference between $\Delta H^\circ_{\text{exptl}}$ and $\Delta H^\circ_{\text{mean}}$ and that the enhanced stability of the CuAB species arises from unpredicted variations in the ΔH° and ΔS° values.

Table 3

Thermodynamic functions for the reaction $MA^+ + B^- = MAB$

Ligands		ΔH°			ΔS°		
A	B	Exptl.	Mean [a]	MB + B [b]	Exptl.	Mean [a]	MB + B [b]
Glycinate	Alanate	−6·35	−6·30	−6·20	11·6	10·5	10·6
Glycinate	Sarcosinate	−4·91	−5·90	−5·40	15·5	11·1	12·9
Glycinate	Aminoisobutyrate	−5·49	−6·05	−5·70	14·9	11·7	13·1
Alanate	Glycinate	−6·75	−6·30	−6·40	10·8	10·5	10·4
Alanate	Aminoisobutyrate	−6·42	−5·95	−5·70	11·7	11·8	13·1
Sarcosinate	Glycinate	−6·31	−5·90	−6·40	13·0	11·1	10·4
Aminoisobutyrate	Glycinate	−6·09	−6·05	−6·40	13·2	11·7	10·4
Aminoisobutyrate	Alanate	−6·62	−5·95	−6·20	10·8	11·8	10·6

[a] Calculated using equation (7) and data from Tables 1 and 2. [b] ΔH° (kcal mol^{-1}) or ΔS° (cal deg^{-1} mol^{-1}) for the reaction indicated.

The enhancement factor also cannot be explained on the basis of steric repulsion in the mixed complex. For example, the addition of sarcosinate ion to monoglycinatocopper(II) ion might be expected to be sterically unfavourable, and this idea is substantiated by the fact that $\Delta H^\circ_{\text{mean}}$ is considerably more negative than $\Delta H^\circ_{\text{exptl}}$. In the converse reaction, the addition of glycinate ion to monosarcosinatocopper(II) ion, there is a more modest difference between $\Delta H^\circ_{\text{mean}}$ and $\Delta H^\circ_{\text{exptl}}$ and the ΔS° value is too large to be accounted for statistically.[15] In contrast, both the addition of aminoisobutyrate ion to alanatocopper(II) ion and alanate ion to aminoisobutyratocopper(II) ion result in ΔH_{exptl} values which are much more negative than the corresponding $\Delta H^\circ_{\text{mean}}$ values. If steric factors were dominant one would not expect more exothermic $\Delta H^\circ_{\text{exptl}}$ values in both cases. The difference between the $\Delta S^\circ_{\text{exptl}}$ and $\Delta S^\circ_{\text{mean}}$ values is that predicted for the addition of alanate ion to aminoisobutyratocopper(II) ion, but 1·0 cal deg^{-1} mol^{-1} less than that predicted for the converse reaction.

No distinct explanation based on a single factor such as statistical distribution of ligands, steric repulsion between ligands, ligand basicity, or electrostatic repulsion between ligands could be found to interpret all the data, and it must be concluded that the models generally used to interpret metal–chelate interaction are too naive to explain all the subtleties of mixed ligand complexation. Thus the so-called enhancement factor appears to arise from several sources, only one of which is the statistical distribution of ligands on a given metal ion. Other sources undoubtedly include various steric repulsion terms, specific hydration terms, and altered charge distribution in the mixed complexes.

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