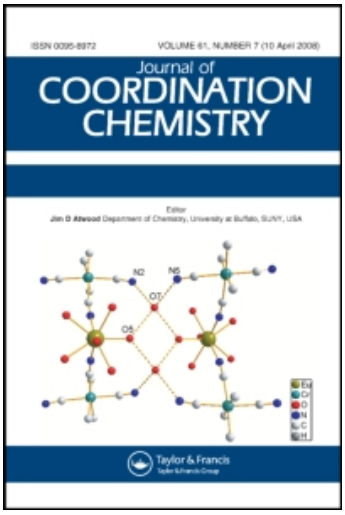

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STUDIES ON BIOLOGICALLY RELEVANT BINARY AND TERNARY METAL COMPLEXES. I. TERNARY Cu(II) COMPLEXES WITH BIPYRIDYL AND BIDENTATE AMINO ACIDS

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Formation constants of Cu(II) ternary complexes involving bipyridyl as the primary ligand and the bidentate amino acids glycine, alanine, valine, leucine, phenylalanine, tryptophan, methionine and ethionine as the secondary ligands were determined at 35.0°C and $\mu = 0.2$ (KNO_3). Comparison of the stabilities of the ternary and the corresponding binary complexes in terms of ΔlogK shows that the ternary complexes of tryptophan and phenylalanine are more stable. This enhanced stability has been attributed to intramolecular metal-bridged stacked adducts. Such stacking interactions on a more modest scale are observed even in the *bis* Cu(II) binary complexes of tryptophan and phenylalanine. In the case of ternary complexes involving ethionine, intramolecular metal-bridged hydrophobic interaction was observed. Enhanced stability of the ternary complexes is not observed when the secondary amino acids are glycine, alanine, leucine, valine or methionine. These amino acids show the usual stabilities expected for ternary systems based on a combination of π-electron withdrawal from the metal by bipyridyl and statistical effects.

Keywords: Copper(II), complexes, stabilities, bipyridyl, amino acids.

INTRODUCTION

We are undertaking a comprehensive and systematic research programme to investigate binary and ternary metal complexes involving biologically relevant metal ions and ligands. The study of ternary complexes involving an aromatic amine as the primary ligand, a metal ion and various biomolecules as secondary ligands can serve as useful models for gaining a better understanding of enzyme-metal ion - substrate complexes, which play an important role in metalloenzyme catalysed biochemical reactions.[1] In the present investigation we have studied the coordination of a series of bidentate amino acids with bipyridyl bound-Cu(II). Formation constants for the following equilibria have been evaluated.

$$M + A \xrightleftharpoons{K^{M}_{MA}} MA \qquad (1)$$

$$MA + A \xrightleftharpoons{K^{MA}_{MA_2}} MA_2 \qquad (2)$$

$$ML + A \xrightleftharpoons{K^{ML}_{MLA}} MLA \qquad (3)$$

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EXPERIMENTAL

Reagents

The amino acids glycine (GLY), alanine (ALA), valine (VAL), leucine (LEU), phenylalanine (PHEN), tryptophan (TRYPT), methionine (MET) and ethionine (ETH), all racemic except for glycine, were obtained from Sigma Chemical Company U.S.A. The 2,2'-bipyridyl (BPY), ethylenediaminetetraacetic acid (EDTA), potassium hydrogen phthalate, potassium nitrate, Cu(II) nitrate trihydrate and sodium hydroxide were of BDH Analar grade. A stock solution of Cu(II) was prepared and standardised by titrating against EDTA.[2] Carbonate-free sodium hydroxide was prepared and standardised by titrating with potassium hydrogen phthalate.

Methods

Acid dissociation constants of the free ligands and formation constants of metal complexes were determined by potentiometric titration of the various ligands with standard carbonate-free NaOH, in the absence and presence of Cu(II), respectively. In binary systems, a 1:2 metal-ligand ratio was used, while in ternary systems a 1:1:1 molar ratio of BPY-Cu(II)-amino acid was employed. The concentration of Cu(II) was 2.0×10^{-3} M. Titrations were carried out in a double jacketted cell at 35.0 ± 0.1°C, serviced by a constant temperature bath. Presaturated nitrogen was bubbled through the experimental solutions, whose ionic strength was initially adjusted to 0.2 by suitable additions of KNO_3.

The pH measurements were carried out with a Digisun digital pH meter fitted with a combination glass electrode assembly. The electrode system was calibrated by direct titration of acetic acid, the observed pH meter readings being compared with the actual hydrogen ion concentration calculated from data tabulated by Harned and Owen.[3] The pH regions below 3.5 and above 10.5 were calibrated by measurements in the HCl and NaOH solutions respectively. Full lists of titration data are available from the authors upon request.

Calculations

The successive acid dissociation constants (k_a and k_{2a}) were calculated using equations (*4*) and (*5*)

$$k_a = \frac{[H^+]\ \{aT_L + [H^+] - [OH^-]\}}{T_L - \{aT_L + [H^+] - [OH^-]\}} \tag{4}$$

$$k_{2a} = \frac{[H^+]\ \{(a-1)T_L + [H^+] - [OH^-]\}}{T_L - \{(a-1)T_L + [H^+] - [OH^-]\}} \tag{5}$$

where a = moles of base added per mole of ligand and T_L = total concentration of the ligand species. The dissociation constant values are listed in Table I.

The stability constants for binary 1:1 and 1:2 Cu(II)-amino acid complexes were calculated from the potentiometric titration data using a Rosotti-Rosotti modification of Bjerrum's method.[4]

The stability constants of the 1:1:1 ternary complexes, Cu(BPY)A were calculated by considering that the 1:1 Cu(BPY) complex is completely formed before the coordina-

TABLE I
Dissociation constants of free ligands and stability constants of the binary Cu(II)-amino acid complexes. [temp. = 35°C, μ = 0.2 (KNO_3)].

Ligand	pK_a†	pK_{2a}	$\log K^{Cu}_{CuA}$	$\log K^{CuA}_{CuA_2}$	$\Delta\log K_B$
Glycine	2.28	9.32	8.00	6.86	−1.14
Alanine	2.27	9.33	7.94	6.79	−1.15
Valine	2.25	9.27	8.08	6.80	−1.28
Leucine	2.27	9.23	8.04	6.73	−1.31
Phenylalanine	2.12	8.73	7.64	6.69	−0.95
Tryptophan	2.22	8.94	7.96	7.04	−0.92
Methionine	2.08	8.75	7.70	6.61	−1.09
Ethionine	2.08	8.69	7.54	—	—

†Constants accurate to ± 0.02 units. $\Delta\log K_B = \log K^{CuA}_{CuA_2} - \log K^{Cu}_{CuA}$. pK_{2a} for BPY = 4.34.

tion of the amino acid takes place. This situation is represented by equilibrium (*3*). The ternary constants for equilibrium (*3*) were calculated using equation (*6*),

$$K^{ML}_{MLA} = \frac{[MLA]}{[ML]\ [A]} \qquad (6)$$

where

$$[MLA] = T_L - [ML] \qquad [ML] = [A] \times Y, \qquad [A] = \alpha/X,$$

$$\alpha = (2-a)T_L - [H^+] + [OH^-], \quad Y = \frac{[H]^2}{k_a k_{2a}} + \frac{H}{k_{2a}} + 1, \quad X = \frac{2[H]^2}{k_a k_{2a}} + \frac{H}{k_{2a}}$$

The assumption that Cu(BPY) is completely formed before the addition of the amino acid takes place is justified since in an earlier investigation[5] we have shown that the ternary constants obtained by using this assumption and the constants obtained by computation which takes into consideration all possible species at equilibrium are essentially the same.

RESULTS

Binary Systems

Potentiometric titration curves (Figure 1) of systems containing a 1:2 molar ratio of Cu(II) and the amino acids GLY, ALA, VAL, LEU, PHEN and TRYPT show inflections at m = 4 (m = moles of base added per mole of the metal ion). In the case of MET precipitation was observed at m = 3.7. However the stability constants were calculated well ahead of the precipitation point. The constant $\log K^{CuA}_{CuA_2}$ for Cu(II)-ETH could not be calculated because of precipitation at m = 3.25. The 1:1 and 1:2 binary constants are listed in Table I. The difference between the stabilities of the 1:1 Cu-amino acid complexes and the corresponding 1:2 complexes are expressed quantitatively in terms of $\Delta\log K_B$, which is defined by equation (*7*).

$$\Delta\log K_B = \log K^{MA}_{MA_2} - \log K^{M}_{MA} \qquad (7)$$

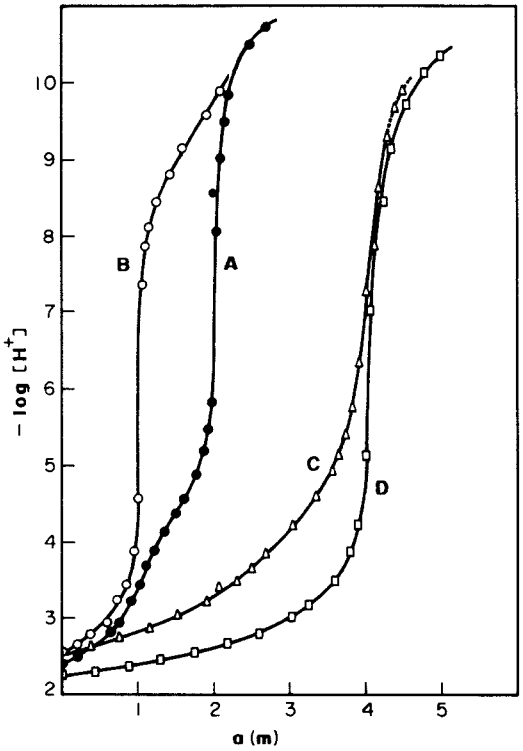

FIGURE 1 Potentiometric titration curves for the ligands BPY [A] and TRYPT [B], and the 1:2 Cu(II)-TRYPT [C] and the 1:1:1 Cu-BPY-TRYPT [D] systems. For curves A and B the abscissa represents a and for curves C and D m. [a = moles of base added per mole of ligand, m = moles of base added per mole of metal ion].

The values of $\Delta\log K_B$ are also listed in Table I. Although the 1:1 and 1:2 constants for Cu(II)-amino acid complexes were reported earlier by others, we have again redetermined them, since it is essential that for a proper comparison the binary and ternary constants should be evaluated under identical experimental conditions.[6] Where experimental conditions permit comparisons, the results obtained in the present investigation are in good agreement with previously reported values.[7]

TABLE II
Stability constants for the ternary complexes.
[Temp. = 35°C, μ = 0.2 (KNO_3)].

Ligand A	log K^{CuL*}_{CuLA}	$\Delta\log K_T$
Glycine	7.54	−0.46
Alanine	7.53	−0.41
Valine	7.68	−0.40
Leucine	7.56	−0.48
Phenylalanine	7.84	+0.20
Tryptophan	8.92	+0.96
Methionine	7.19	−0.51
Ethionine	7.28	−0.26

[+]Constants accurate to ± 0.03 units. $\Delta\log K_T = \log K^{CuL}_{CuLA} - \log K^{Cu}_{CuA}$. L = 2,2'-bipyridyl.

Ternary Systems

Potentiometric titration curves for ternary systems containing BPY, Cu(II) and the various bidentate amino acids in a 1:1:1 molar ratio also exhibit sharp inflections at m = 4. Calculations show that in all these systems ternary complexes are formed. The stability constants for the ternary metal complexes are listed in Table II.

The relative stabilities of the ternary complexes compared to the corresponding binary complexes can be quantitatively expressed in many different ways. We have expressed the relative stabilities in terms of $\Delta\log K_T$ (*8*).

$$\Delta\log K_T = \log K^{Cu(BPY)}_{Cu(BPY)A} - \log K^{Cu}_{CuA} \qquad (8)$$

The advantage of using $\Delta\log K_T$ for comparison of the stability of binary and ternary complexes has been reviewed.[8] The $\Delta\log K_T$ values obtained in the present investigation are also tabulated in Table II.

DISCUSSION

Studies on ternary systems containing BPY as the primary ligand have shown that in the presence of an aromatic nitrogen donor metal ions become more selective and discriminate between the donor groups on the incoming secondary ligand.[5,9–12] Cu(BPY) binds secondary ligands with anionic oxygen donors ($^-O - O^-$) much more firmly than ligands with neutral nitrogen donors (N - N). The affinity for ligands with N and O donors (N - O^-) lies between that observed for pure $^-O - O^-$ and N - N ligands.

A critical analysis of the $\Delta\log K_T$ values obtained in the present study (Table II) show that these values can be categorised in three classes. In the first case, for ternary complexes where the amino acids are glycine, alanine, valine, leucine or methionine the $\Delta\log K_T$ values are negative and around −0.45. In the second case the $\Delta\log K_T$ value (−0.26) for the Cu(BPY)-ethionine complex is more positive as compared to the abovementioned systems. This shows that some stabilizing factor is involved. A model of the BPY-Cu-ETH complex shows that the side chain of ethionine is long enough to hydrophobically interact with one of the pyridine rings of bipyridyl (Figure 2). This intramolecular hydrophobic interaction in BPY-Cu-ETH complex may lead to the

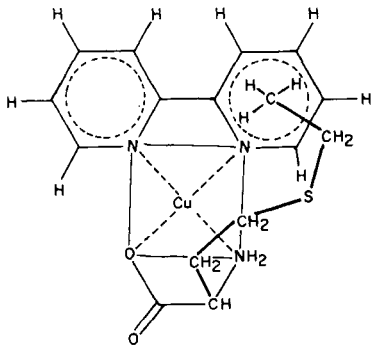

FIGURE 2 A tentative structure of the mixed ligand chelate Cu(II)-BPY-ETH, showing the hydrophobic interaction between BPY and the side chain of ETH.

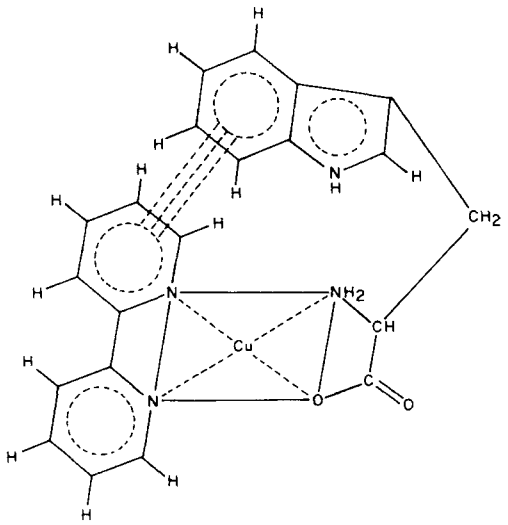

FIGURE 3 A tentative structure for the ternary complex Cu(II)-BPY-TRYPT, showing the intramolecular stacking interaction between the aromatic fragments of the two ligands.

modest increase in the stability of the BPY-Cu-ETH complex. In the third case, the positive $\Delta\log K_T$ values for the ternary complexes of Cu(II)-bipyridyl and tryptophan or phenylalanine indicate that these amino acids bind to the Cu(BPY) complex more strongly than to the aquo-Cu(II) complex. Models of the BPY-Cu-tryptophan complex show that the phenyl group of the indole ring of tryptophan can stack reasonably well with one of the pyridine rings of bipyridyl (Figure 3). Such stacking interactions probably cause the increased stability observed in this system. In the case of phenylalanine the more modest positive $\Delta\log K_T$ value can again be attributed to stacking of the phenyl ring of the amino acid with one of the pyridine rings of bipyridyl. The more positive $\Delta\log K_T$ value for tryptophan as compared to that of phenylalanine may be due to the fact that the indole fragment with a wider hydrophobic surface area stacks better with bipyridyl, than phenylananine. It is interesting to note that even when we consider the $\Delta\log K_B$ values for the binary Cu-amino acid complexes, the value of $\Delta\log K_B$ is around -1.1 for amino acids such as glycine, alanine, valine, leucine and methionine. On the other hand the $\Delta\log K_B$ values for the amino acids phenylananine and tryptophan are more positive with $\Delta\log K_B$ values around -0.93. This enhanced stability of the *bis* complexes of phenylalanine and tryptophan can be due to stacking interaction of the indole groups in the case of tryptophan and the phenyl groups in the case of phenylalanine. Models of these two *bis* complexes provide positive support for the formation of such stacking interactions. Thus in the case of phenylalanine and tryptophan these factors seem to play an important role in enhancing the stabilities of the *bis* binary metal complexes and the corresponding ternary metal complexes. Apart from this, in all the systems investigated, the $\Delta\log K_T$ values are higher than the corresponding $\Delta\log K_B$ values, a fact which can be attributed to two factors. First, the electrostatic repulsion between the two bound carboxylate oxygens will serve to destabilise the *bis* binary complexes. Secondly, in the ternary complexes the bipyridyl ligand withdraws electron density from the $d\pi$-orbitals of Cu(II) making it effectively more positive than in the 1:1 amino acid-Cu(II) complex of the aquo Cu(II) complex. Hence the interaction of the incoming amino acid will decrease in the order Cu(BPY) > Cu(aq) > Cu-amino acid complexes. When the amino acid is phenyl-

alanine or tryptophan, the stabilisation due to stacking the interactions is superimposed on the above two effects. The formation of relate stacked adducts between the indole group of tryptophan and the adenine ring of ATP has been observed by Sigel and coworkers, who also obtained spectroscopic evidence for such metal-ion bridged stacked adducts.[13]

The results obtained in the present investigation have interesting biological implications with regard to metalloenzyme-catalysed reactions. In these systems, one of the factors contributing to the stability of the enzyme-metal ion-substrate complexes may be the same kind of stacking interaction observed in the present model system studies involving (BPY)-M-tryptophan and phenylalanine or hydrophobic interactions as observed in the BPY-M-ETH system.

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