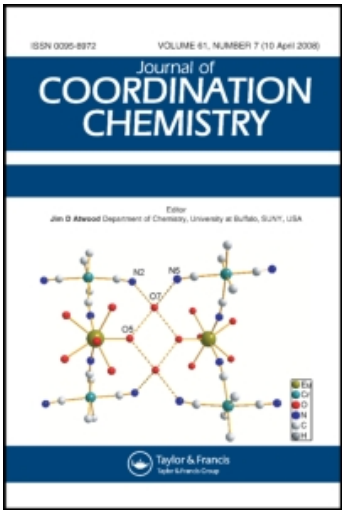

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K. Prasad[a]; A. Koteswara Rao[a]; M. Srinivas Mohan[a]
[a] Department of Chemistry, Osmania University, Hyderabad, India

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STUDIES ON BIOLOGICALLY RELEVANT BINARY AND TERNARY METAL COMLEXES II. Cu(II) TERNARY COMPLEXES INVOLVING BIPYRIDYL AND A SERIES OF TERDENTATE AMINO ACIDS

K. PRASAD, A. KOTESWARA RAO and M. SRINIVAS MOHAN†
Department of Chemistry, Osmania University, Hyderabad 500 007, India.

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Formation constants of Cu(II) ternary complexes involving bipyridyl as the primary ligand and the amino acids asparagine, citrulline, aspartic acid, glutamic acid, histidine, arginine, lysine and 3,4-dihydroxyphenylalanine as the secondary ligands are reported at 35.0°C and $\mu = 0.2$ M (KNO_3). The difference between the stability of the ternary complexes and the corresponding binary complexes has been quantitatively expressed in terms of the parameter $\Delta\log K_T$. With the exception of the protonated ternary complex of 3,4-dihydroxyphenylalanine the $\Delta\log K_T$ values for all other ternary complexes are negative. In the case of the normal ternary complexes involving aspartic acid, histidine and 3,4-dihydroxyphenylalanine the $\Delta\log K_T$ values are appreciably negative and provide substantial evidence for these amino acids to be bidentate in the ternary complexes. This is in contrast to the normal terdentate behaviour of these ligands in corresponding binary complexes. The ternary complexes involving protonated 3,4-dihydroxyphenylalanine show considerably positive $\Delta\log K_T$ values. The enhanced stability of this ternary complex as compared to the corresponding protonated binary complex of 3,4-dihydroxyphenylalanine is attributed to intramolecular stacking interactions between the phenyl ring of 3,4-dihydroxyphenylalanine and the Cu(II)-bound bipyridyl.

Key words: copper, aminoacid complexes, stability constants, hydrophobic bonding

INTRODUCTION

Ternary complexes involving biomolecules serve as useful models for *in vivo* enzyme-metal ion-substrate complexes involved in metalloenzyme-catalysed biological reactions.[1-2] Detailed studies of the *in vitro* biomimetic ternary complexes would lead to a better understanding of the factors contributing to the stability and the dynamics of the metalloenzyme-catalysed reactions. In our previous work on model ternary complexes a major interest has been to elucidate the influence which a primary ligand already attached to a metal ion exerts upon an incoming secondary ligand.[3-8] We have recently started a comprehensive and systematic research programme to investigate binary and ternary complexes involving biologically relevant metal ions and biomolecules. In an earlier paper[9] we reported the interaction of a series of bidentate amino acids with bipyridyl bound Cu(II). In the present paper we report the results of studies of ternary complexes of Cu(II) with bipyridyl and a series of potentially terdentate amino acids.

EXPERIMENTAL

Materials

The *DL*-amino acids (AA), asparagine (ASN), citrulline (CIT), aspartic acid (ASP),

†Author for correspondence.

glutamic acid (GLU), histidine (HIS), arginine (ARG), lysine (LYS) and 3,4-dihydroxyphenylalanine (DOPA) were obtained from Sigma Chemical Co., U.S.A. The α,α'-bipyridyl (BPY), ethylenediaminetetraacetic acid (EDTA), potassium hydrogen phthalate, potassium nitrate, copper(II) nitrate trihydrate and sodium hydroxide were of B.D.H. Analar grade.

Methods

A stock solution of Cu(II) was prepared and standardised by titrating with standard EDTA.[10] Carbonate-free sodium hydroxide was prepared and standardised with potassium hydrogen phthalate.[11] Acid dissociation constants of the free ligands and stability constants of the binary and ternary metal complexes were determined by potentiometric titration of the various ligands with standard carbonate-free NaOH in the absence and the presence of Cu(II), respectively; 1:1 and 1:2 molar ratios of metal-ligand were employed in the binary systems, while a 1:1:1 molar ratio of BPY-Cu(II)-amino acid was employed in the ternary systems. 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 passed through the experimental solutions throughout the titration to maintain an inert atmosphere. The ionic strength was maintained constant at 0.2 by suitable additions of potassium nitrate. 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 the data tabulated by Harned and Owen.[12] The pH regions below 3.5 and above 10.5 were calibrated by measurements in HCl and NaOH solutions, respectively. Titration data have been deposited with the Editor and are available on request.

Acid Dissociation Constants

The acid dissociation constants for the stepwise dissociation of protons for the various ligands were calculated by using algebraic equations.[13] The acid dissociation constants for the simultaneous dissociation of protons from the various ligands were calculated by means of a graphical method.[14]

Formation Constants for Binary Complexes

For the amino acids ASN and CIT the stability constants for the simultaneous formation of the ML and ML_2 complexes were calculated in the buffer region $m = 0$ to 4 by the graphical method of Rosotti and Rosotti,[15] as were those for ASP, GLU and HIS in the buffer region $m = 0$ to 6.

For the amino acids LYS and ARG, the stability constants of the protonated complexes represented by the equilibrium (*1*) were calculated in the buffer region $a = 0$ to 2 using the following equations.

$$M + HA \rightleftharpoons MHA \tag{1}$$

$$K^{M}_{MHA} = [MHA] + [M][HA] \tag{2}$$

where

$$[MHA] = T_L - [M] \tag{3}$$

$$[M] = [HA][H]^2/k_a k_{2a} + [HA][H] + k_{2a} + [HA] \tag{4}$$

$$[HA] = (2-a)T_L - [H] + [OH] \; /(2[H]^2/k_a k_{2a} + [H]/k_{2a}) \quad (5)$$

In the case of DOPA the stability constant of the diprotonated complex (MH_2A) represented by the equilibrium (*6*) was calculated by using the following equations in the buffer region a = 0 to 2.

$$M + H_2A \rightleftharpoons MH_2A \quad (6)$$

$$K^M_{MH_2A} = [MH_2A]/[M][H_2A] \quad (7)$$

where

$$[MH_2A] = T_L - [M] \quad (8)$$

$$[M] = [H_2A][H]^2/k_a k_{2a} + [H_2A][H] + k_{2a} + [H_2A] \quad (9)$$

$$[H_2A] = (2-a)T_L - [H] + [OH] \; /(2[H]^2/k_a k_{2a} + [H]/k_{2a}) \quad (10)$$

Similarly the stability constant for the normal complex MA represented by the equilibrium (*11*) was calculated by the following equations in the buffer region a = 2 to 4.

$$M + A \rightleftharpoons MA \quad (11)$$

$$K^M_{MA} = [MA]/[M][A] \quad (12)$$

where

$$[MA] = T_L - [M] \quad (13)$$

$$[M] = [H]^2/k_{3a}k_{4a} + [H]/k_{4a} + 1 \; [A] \quad (14)$$

$$[A] = (2-a)T_L - [H] + [OH] \; /(2[H]^2/k_{3a}k_{4a} + [H]/k_{4a}) \quad (15)$$

Formation Constants of Ternary Complexes

In the calculations for the ternary metal complexes formed in systems containing Cu(II), BPY and amino acid in a 1:1:1 molar ratio, the 1:1 Cu(II)-BPY complex was considered to be completely formed before the coordination of the amino acid takes place. This is justified since in earlier investigations[4–6] we have shown that the ternary constants obtained using this assumption and the constants obtained by sophisticated computer programmes which take into consideration all possible species at equilibrium are essentially the same.

In the case of ternary complexes involving the amino acids ASN or CIT the stability constants for the ternary complex [MLA] represented by the equilibrium (*16*) was calculated using the following equations in the buffer region m = 0 to 4.

$$ML + A \rightleftharpoons MLA \quad (16)$$

$$K^{ML}_{MLA} = [MLA]/[ML][A] \quad (17)$$

where

$$[MLA] = T_L - [ML] \quad (18)$$

$$[ML] = [A] \times Y \quad (19)$$

$$[A] = \alpha/X \quad (20)$$

and

$$\alpha = (2-a)T_L - [H] + [OH] \quad (21)$$

$$Y = [H]^2/k_a k_{2a} + [H]/k_{2a} + 1 \quad (22)$$

$$X = 2[H]^2/k_a k_{2a} + [H]/k_{2a} \quad (23)$$

In the case of ternary complexes involving the amino acids ASP, GLU and HIS the stability constants for the ternary complex [MLA] represented by equilibrium (*16*) was calculated in the buffer region m = 0 to 5 using equation (*17*) where

$$[MLA] = T_L - [ML] \quad (24)$$

$$[ML] = [A] \times Y \quad (25)$$

$$[A] = \alpha/X \quad (26)$$

$$\alpha = (3-a)T_L - [H] + [OH] \quad (27)$$

$$Y = [H]^3/k_a k_{2a} k_{3a} + [H]^2/k_{2a} k_{3a} + [H]/k_{3a} + 1 \quad (28)$$

$$X = 3[H]^3/k_a k_{2a} k_{3a} + 2[H]^2/k_{2a} k_{3a} + [H]/k_{3a} \quad (29)$$

In the case of amino acids LYS and ARG the stability constants of the protonated ternary complex MLHA which is represented by the equilibrium (*30*) was calculated by the following equations in the buffer region m = 0 to 4.

$$ML + HA \rightleftharpoons MLHA \quad (30)$$

$$K^{ML}_{MLHA} = [MLHA]/[ML][HA] \quad (31)$$

where

$$[MLHA] = T_L - [ML] \quad (32)$$

$$[ML] = [HA][H]^2/k_a k_{2a} + [HA][H]/k_{2a} + [HA] \quad (33)$$

$$[HA] = (2-a)T_L - [H] + [OH] \; /(2[H]^2/k_a k_{2a} + [H]/k_{2a}) \quad (34)$$

In the case of DOPA the stability constant for the protonated ternary complex MLH_2A represented by equilibrium (*35*) was calculated by the following equations in the buffer region m = 0 to 4.

$$ML + H_2A \rightleftharpoons MLH_2A \quad (35)$$

$$K^{ML}_{MLH_2A} = [MLH_2A]/[ML]\,[H_2A] \quad (36)$$

where

$$[MLH_2A] = T_L - [ML] \quad (37)$$

$$[ML] = [H_2A]\,[H]^2/k_a k_{2a} + [H_2A]\,[H]/k_{2a} + [H_2A] \quad (38)$$

$$[H_2A] = (2-a)T_L - [H] + [OH]\ /(2[H]^2/k_a k_{2a} + [H]/k_{2a}) \quad (39)$$

For ternary complexes involving DOPA, the stability constant for normal ternary complex MLA, represented by equilibrium (*16*) was calculated using equation (*17*), by the following equations in the buffer region m = 4 to 6.

where

$$[MLA] = T_L - [ML] \quad (40)$$

$$[ML] = \left\{[H]^2/k_{3a}k_{4a} + [H]/k_{4a} + 1\right\}[A] \quad (41)$$

$$[A] = (2-a)T_L - [H] + [OH]\ /(2[H]^2/k_{3a}k_{4a} + [H]/k_{4a}) \quad (42)$$

RESULTS AND DISCUSSION

Acid Dissociation Constants

The acid dissociation constants for the monoprotonated BPY and the various di-, tri- and tetraprotonated amino acids are tabulated in Table I.

TABLE I

Acid dissociation constants* of free ligands; temperature = 35°C, μ = 0.20 mol dm^{-3} (KNO_3).

Ligand	pK_a	pK_{2a}	pK_{3a}	pK_{4a}
Bipyridyl	a	4.34		
Asparagine	a	2.01	8.32	
Citrulline	a	2.14	8.90	
Aspartic acid	1.77	3.63	9.25	
Glutamic acid	2.29	3.97	9.12	
Histidine	1.68	5.86	8.73	
Arginine	1.85	8.95	11.97	
Lysine	2.00	8.92	10.12	
DOPA	2.17	8.61	9.55	11.71

*Constants accurate to ±0.02. [a]Competitively dissociated.

Binary Stability Constants

Potentiometric titration curves of systems containing a 1:2 molar ratio of Cu(II) and the amino acids ASN and CIT, show a single inflexion at m = 4 (m = moles of base added per mole of metal ion), whereas titration curves involving the amino acids ASP, GLU and HIS show inflexions at m = 6. The stability constants for MA and MA_2 formed in

TABLE II
Stability constants* of binary Cu(II)-amino acid complexes; temperature = 35°C, μ = 0.20 mol dm^{-3} (KNO_3).

Ligand	$\log K^{Cu}_{CuH_2A}$	$\log K^{Cu}_{CuHA}$	$\log K^{Cu}_{CuA}$	$\log K^{CuA}_{CuA_2}$	$\Delta\log K_B$
Asparagine			7.37	6.35	−1.02
Citrulline			7.46	6.43	−1.03
Aspartic acid			8.38	6.64	−1.74
Glutamic acid			7.66	6.22	−1.44
Histidine			9.76	8.01	−1.75
Arginine		7.69			
Lysine		7.76			
DOPA	7.88		13.41		

*Constants accurate to ±0.05. $\Delta\log K_B = \log K^{CuA}_{CuA_2} - \log K^{Cu}_{CuA}$.

the above systems are listed in Table II. Potentiometric titration curves of systems containing a 1:1 molar ratio of Cu(II) and the amino acids LYS and ARG show an inflexion at a = 2 (where a = moles of base added per mole of ligand), followed by precipitation around a = 2.2. The stability constants for the protonated complexes MHA are also listed in Table II. Because of precipitation after a = 2 the stability constants for the normal complexes (MA) of LYS and ARG could not be evaluated. Potentiometric titration curves of the system containing a 1:1 molar ratio of Cu(II) and DOPA shows an inflexion at a = 2 and another step inflexion at a = 4. The stability constants of the protonated complex (MH_2A) and the normal complex (MA) are listed in Table II.

The differences between the stabilities of the 1:1 Cu-amino acid complexes and the corresponding 1:2 complexes are expressed quantitatively in terms of the parameter $\Delta\log K_B$ which is defined by equation (*43*).

$$\Delta\log K_B = \log K^{MA}_{MA_2} - \log K^{M}_{MA} \qquad (43)$$

The values of $\Delta\log K_B$ are listed in Table II. Although the acid dissociation constants and the 1:1 and 1:2 constants for Cu(II)-amino acids were reported earlier by others, we have redetermined them, since it is essential that for a proper and precise comparison of the binary and ternary constants, identical experimental conditions should be used for their evaluation.[16] Wherever experimental conditions permit comparison, the acid dissociation constants and the binary constants determined in this work are in agreement with those reported earlier.[17]

Ternary Stability Constants

For ternary systems involving a 1:1:1 molar ratio of Cu(II), BPY and ASN or CIT the titration curves exhibit a single steep inflexion at m = 4. Ternary systems involving the amino acids ASP, GLU and HIS show an inflexion at m = 5. The stability constants for the normal complexes MLA for the above five amino acids are listed in Table III. In the case of LYS and ARG, potentiometric titration curves, show an inflexion at m = 4. The stability constants for the protonated complexes MLHA formed in lower buffer regions, and the stability constants for the normal complexes MLA formed in the upper buffer region are also listed in Table III. Representative potentiometric titration curves for the 1:1:1 ternary systems involving ASN, ASP and ARG are given in Figure 1. In ternary systems involving DOPA as the amino acid, an inflexion was obtained at m = 4. The stability constants of the protonated complexes MLH_2A formed in the buffer region

TABLE III

Stability Constants* of ternary complexes; Temperature = 35°C, μ = 0.20 mol dm^{-3} (KNO_3).

L = Bipyridyl

Ligand A	$\log K^{CuL}_{CuL(H_2A)}$	$\log K^{CuL}_{CuL(HA)}$	$\log K^{Cu}_{CuLA}$	$\Delta\log K_T$
Asparagine			7.04	−0.33[a]
Citrulline			7.15	−0.31[a]
Aspartic acid			7.92	−0.46[a]
Glutamic acid			7.27	−0.39[a]
Histidine			8.97	−0.79[a]
Arginine		7.19	5.68	−0.50[b]
Lysine		7.28	4.08	−0.48[b]
DOPA	8.53		7.34	+0.65[c] and −6.07[a]

*Constants accurate to ± 0.005. [a] $\Delta\log K_T = \log K^{CuL}_{CuLA} - \log K^{Cu}_{CuA}$.

[b] $\Delta\log K_T = \log K^{CuL}_{CuLHA} - \log K^{Cu}_{CuHA}$.

[c] $\Delta\log K_T = \log K^{CuL}_{CuL(H_2A)} - \log K^{Cu}_{Cu(H_2A)}$.

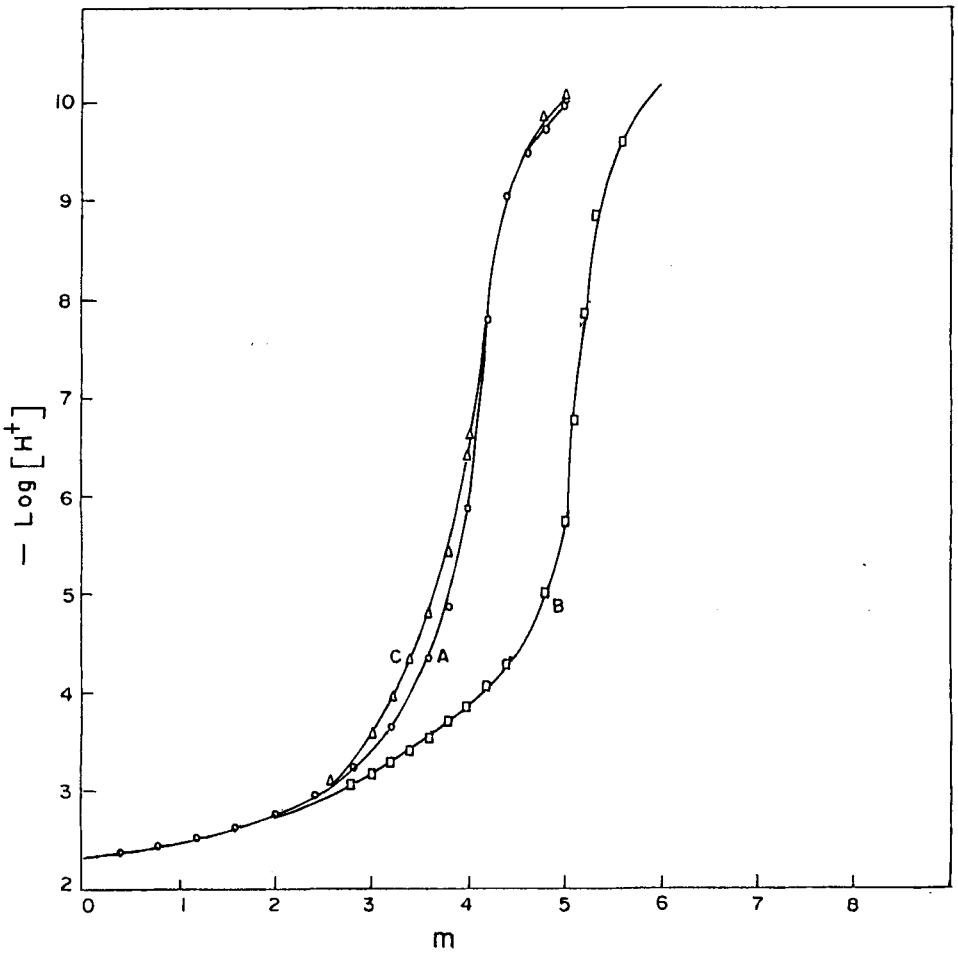

FIGURE 1 Potentiometric titration curves for Cu(II)-BPY-ASN [A], Cu(II)-BPY-ASP [B] and Cu(II)-BPY-ARG [C] systems in a 1:1:1 molar ratio at 35°C and μ = 0.2 M (KNO_3). [m = moles of base added per mole of metal ion].

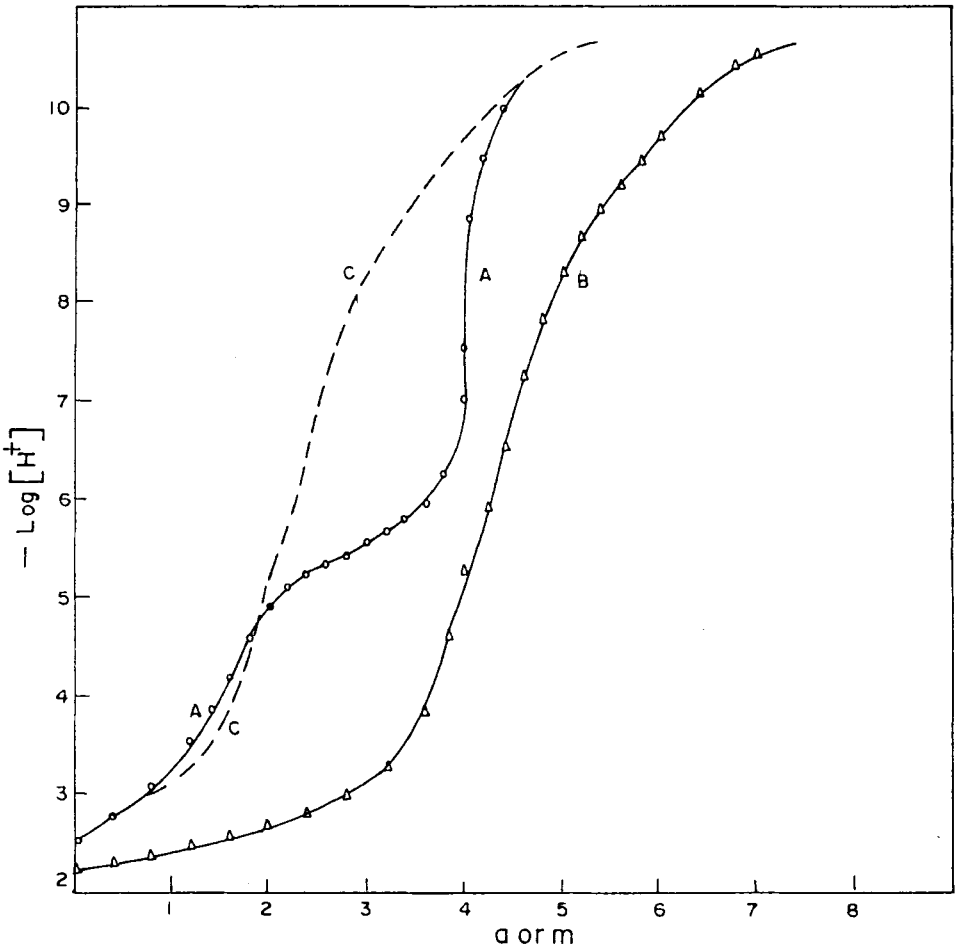

FIGURE 2 Potentiometric titration curves for 1:1 Cu(II)-DOPA [A], 1:1:1 Cu(II)-BPY-DOPA [B] and Cu(II)-BPY-DOPA curve [C] superimposed on the 1:1 Cu(II)-DOPA curve after deleting the curve (between m = 0 to 2) representing the interaction of Cu(II)-BPY. [a = moles of base added per mole of the ligand (for curve A), m = moles of base added per mole of the ligand (for curves B and C)].

m = 0 to 4, and the stability constants of the normal complexes MLA formed in the buffer region m = 4 to 6 are listed in Table III. The potentiometric titration curves for the binary and ternary systems involving DOPA are given in Figure 2.

The relative stabilities of ternary complexes as compared to the corresponding binary complexes can be quantitatively expressed in many different ways. We have expressed the relative stabilities in terms of the parameter $\Delta\log K_T$, (*44*).

$$\Delta\log K_T = \log K^{Cu(BPY)}_{Cu(BPY)AA} - \log K^{Cu}_{CuAA} \qquad (44)$$

The advantage of using $\Delta\log K_T$ for comparison of the stability of the binary and ternary complexes has been reviewed.[18] The $\Delta\log K_T$ values obtained in the present investigation on ternary complexes involving potentially terdentate amino acids are tabulated in Table III. In order to facilitate the discussion of the $\Delta\log K$ values for the ternary complexes investigated in this work, the $\Delta\log K_B$ values of the binary complexes

TABLE IV
$\Delta\log K_B$ and $\Delta\log K_T$ values for complexes containing bidentate amino acids*; Temperature = 35.0°C, μ = 0.2 mol dm^{-3} (KNO_3).

L = Bipyridyl		
Ligand A	$\Delta\log K_B$	$\Delta\log K_T$
Glycine	−1.14	−0.46
Alanine	−1.15	−0.41
Valine	−1.28	−0.40
Leucine	−1.31	−0.48
Phenylalanine	−0.95	+0.20
Tryptophane	−0.92	+0.96
Methionine	−1.09	−0.51
Ethionine		−0.26

*Data from reference 9. $\Delta\log K_B = \log K^{CuA}_{CuA_i} - \log K^{Cu}_{CuA}$; $\Delta\log K_T = \log K^{CuL}_{CuLA} - \log K^{Cu}_{CuA}$.

and the $\Delta\log K_T$ values of ternary complexes involving bidentate amino acids which we have reported earlier[9] are listed in Table IV. The $\Delta\log K_T$ values are of great utility in understanding the influence of the primary ligand already bound to a metal ion upon the incoming secondary ligand.

The $\Delta\log K_T$ values for ternary complexes involving bidentate amino acids such as glycine, alanine, valine, and leucine indicate that in the absence of other stabilizing factors the coordination of an amino acid through carboxylate oxygen and amino nitrogen leads to negative $\Delta\log K_T$ values of about −0.46. In the present investigation of ternary complexes involving potentially terdentate amino acids, the $\Delta\log K_T$ values for the normal complexes (MLA) of asparagine, citrulline, aspartic acid and glutamic acid are in the range of −0.31 to −0.46. It is therefore reasonable to suggest that the above amino acids bind to Cu(BPY) as bidentate ligands only, using the carboxylate oxygen and amino nitrogen. This result is particularly interesting in the case of ternary complexes involving aspartic acid, since in the binary complexes aspartic acid acts as a terdentate forming one 5 membered and one 6 membered ring.[19] The $\log K_T$ values for ternary complexes involving histidine further underline the transformation of a terdentate ligand in a binary complex to a bidentate ligand in a ternary complex. In binary complexes it is well established that histidine acts as a terdentate binding through the carboxylate oxygen, amino nitrogen and the imidazole nitrogen atoms.[19] However, when bipyridyl is already bound to copper(II), the strong ligand field exerted by the bipyridyl causes Cu(II) to be essentially square planar. In such a case histidine would be forced to be bidentate and this would lead to the decreased stability of the ternary complexes, which is reflected in the more negative $\Delta\log K$ value of −0.79.

In the case of the amino acids ARG and LYS the binary MHA complexes would be necessarily bidentate with a proton on the side chain. Comparison of these binary MHA complexes with the corresponding ternary MLHA complexes leads to the expected decrease in $\Delta\log K_T$ of about −0.48 to −0.50. For ARG and LYS the stability of the normal ternary complexes MLA cannot be compared with the corresponding binary complexes MA, since the latter are not formed in the binary systems.

The ternary complexes of 3,4-dihydroxyphenylalanine provide some novel results. A comparison of the stability of the diprotonated ternary complex MLH_2A with the corresponding binary complex MH_2A shows that the stability has increased with the $\Delta\log K_T$ becoming +0.65. This result is in accordance with the positive $\Delta\log K_T$ values observed in ternary complexes involving phenylalanine and tryptophane (Table IV). The positive $\Delta\log K_T$ values for these three ligands with aromatic side chains can be attributed to stacking interactions between the phenyl ring of the amino acid side chain

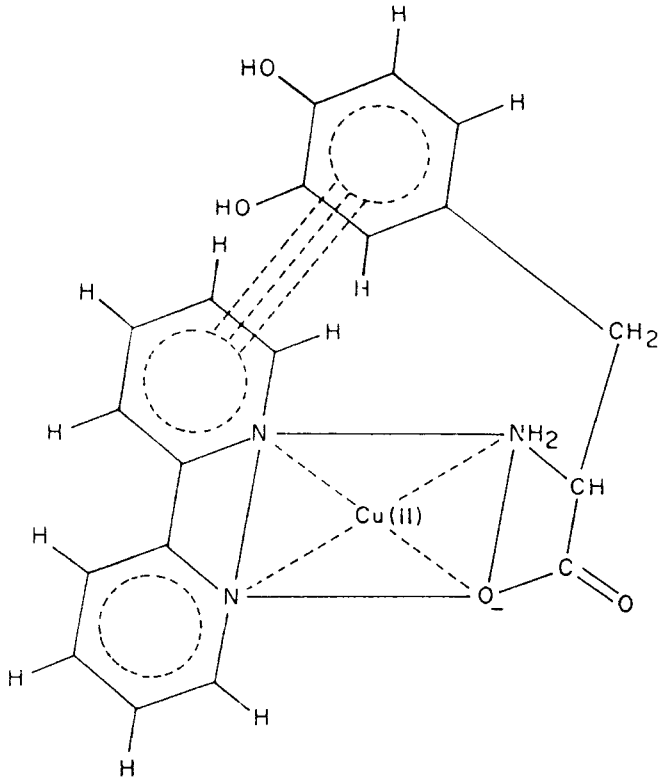

FIGURE 3 A tentative structure for the ternary complex Cu(II)-BPY-DOPA [MLH_2A], showing the intramolecular stacking interaction between the aromatic rings of the two ligands.

and a pyridine ring of the Cu(II)-coordinated BPY. The increased electron density on the phenyl ring of DOPA induced by the presence of two undissociated hydroxyl groups seems to enhance the stacking interaction in the MLH_2A complexes of DOPA ($\Delta\log K_T = +0.65$) as compared to MLA complexes of phenylalanine ($\Delta\log K_T = +0.20$). A tentative structure for the protonated ternary complex of DOPA, showing the intramolecular stacking interactions between the aromatic rings of the two ligands is shown in Figure 3.

DOPA is an ambidentate ligand which can bind to a metal ion in a bidentate fashion either like glycine or catechol. In binary complexes it is suggested that in the lower buffer region DOPA chelates to the metal in a glycine mode. In the upper buffer region DOPA binds to Cu(II) like catechol through the two oxygens of the phenyl ring[20] (Fig. 4). This ambidentate behaviour of DOPA in its interaction with Cu(II) is reflected by the large increase in the stability constants in going from the MH_2A complex ($\log K^{Cu}_{CuH_2A} = 7.88$) to the MA complex ($\log K^{Cu}_{CuA} = 13.41$). The reasons for the enhanced stability of the MLH_2A complex have been discussed above.

In the ternary systems involving DOPA, deprotonation of the two hydroxyl protons leads to destabilisation of the resulting normal ternary complexes (MLA). This is reflected in the stability constants of the normal ternary DOPA complex MLA ($\log K^{Cu}_{CuLA} = 7.34$) and the corresponding normal binary DOPA complex MA ($\log K^{Cu}_{CuA} = 13.41$) leading to a negative $\Delta\log K_T$ value of 6.05. This large decrease in the stability is quite surprising because if DOPA in the upper buffer region binds to Cu(II) in a

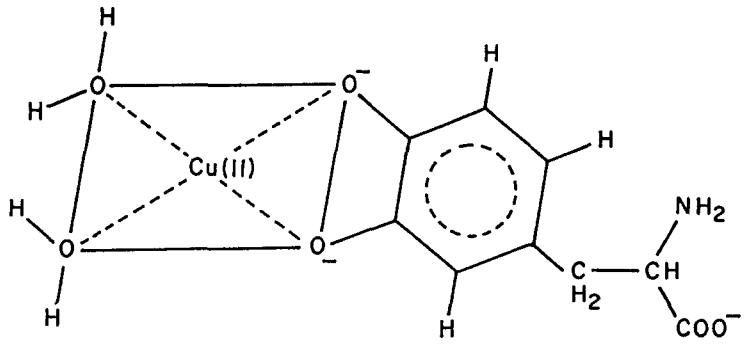

FIGURE 4 A tentative structure for the 1:1 Cu(II)-DOPA complex showing the coordination of DOPA in a catechol fashion.

catechol-like manner, it should have led to an increased stability for the ternary complex. This is based on earlier investigations of BPY-Cu(II)-catechol complexes which show that BPY enhances the affinity of Cu(II) for a secondary ligand having two oxygen donor atoms (leading to positive $\Delta\log K_T$ values).[1,4] The fact that the ternary MLA complexes of DOPA show a large decrease in stability, as compared to the corresponding binary DOPA complexes (MA), can be logically explained by postulating that in the ternary MLA complexes DOPA is bound to the Cu(II)-BPY core in a glycine mode, even though the phenyl hydroxyls are deprotonated. This explanation is justified in Fig. 2 where the superimposed ternary curve (curve 'C') in the region where MLH_2A forms lies below the binary MH_2A curve, while the ternary curve in the region where MLA forms lies above the binary MA curve.

The biomimetic model ternary systems reported in this investigation clearly show the dominant influence which the primary ligand already attached to a metal ion exerts upon the interaction of that metal ion with an incoming secondary ligand. The factors operating in the stabilization and destabilization of model ternary systems may also play an important role in determining the stability of enzyme-metal ion-substrate complexes formed in metalloenzyme-catalysed reactions in biological systems.

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