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Effect of Picolinic Acid and Dipicolinic Acid on the Stability of Mixed Ligand Cu (II) Complexes Containing Amino Acids

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Formation constants of mixed ligand Cu(II) complexes [MLA] where L = picolinic acid (PA) or dipicolinic acid (DPA) and A = alanine, serine threonine, methionine, phenylalanine, tyrosine and tryptophan were determined by potentiometric pH titrations at 35°C and $\mu = 0.2$ (KNO_3) and the stability of the mixed ligand and the corresponding binary complexes were quantitatively compared in terms of the parameter $\Delta \log K$ ($\Delta \log K = \log K^{ML}_{MLA} - \log K^{M}_{MA}$). Mixed ligand complexes containing PA as primary ligand were found to be more stable than the corresponding complexes containing DPA. In mixed complexes involving PA, the amino acids with an aromatic side chain, *viz.*, phenylalanine, tyrosine and tryptophan exhibit enhanced stability due to intramolecular metal ion mediated stacking interactions between the aromatic moieties of the two ligands, and the intramolecular equilibrium between the stacked and open forms, have been evaluated. Due to steric considerations stacking interactions were not observed in DPA containing mixed complexes.

INTRODUCTION

Mixed ligand metal complexes play a vital role in numerous biochemical processes. In order to gain a better understanding of the formation and the factors contributing to the stability of such complexes we have been investigating *in vitro* model mixed ligand metal complexes.[1-6] In the present investigation a detailed physico-chemical investigation of mixed ligand complexes (MLA) formed in solutions containing a 1 : 1 : 1 molar ratio of picolinic acid (PA) or dipicolinic acid (DPA), Cu(II) and the amino acid (A), alanine (Ala), phenylalanine (Phe), tryptophan (Try), tyrosine (TyrH), serine (Ser), threonine (Thr) and methionine (Met) was carried out and the formation constants of these mixed ligand complexes have been determined potentiometrically at 35°C and $\mu = 0.2$ (KNO_3). The relative ability of the various amino acids to bind Cu(II) in the presence of PA or DPA have been quantitatively assessed and possible explanations are offered in terms of the nature of the amino acid side chains and the nature of the pyridyl derivatives.

EXPERIMENTAL

The racemic amino acids α-alanine, phenylalanine, tryptophan, tyrosine, serine, threonine, methionine and picolinic and dipicolinic acids were obtained from Sigma Chemical Company, USA. A stock solution of Cu(II) was prepared

and standardized by titrating with standard disodium salt of EDTA using murexide as the metallochrome indicator.[7] Carbonate-free sodium hydroxide was prepared and standardized by titrating with a pure sample of potassium hydrogen phthalate.

Potentiometric titrations were carried out with triprotonated DPA and diprotonated PA to determine the dissociation constants of these ligands and binary systems involving a 1 : 1 molar ratio of Cu(II) and PA or DPA in the diprotonated form were studied to determine their stability. The experimental procedure for studying mixed complexes involved the potentiometic titration of solutions containing a 1 : 1 : 1 molar ratio of diprotonated PA/DPA, Cu(II) and the diprotonated amino acids with standard carbonate free NaOH. The potentiometric titrations were carried out in a double-walled titration cell maintained at 35° ± 0.02°C and $\mu = 0.2$ (KNO_3). The concentration of Cu(II) in each experiment was *ca* 0.002 M. The pH measurements were carried out with a Digisun digital pH meter attached to a combination glass electrode. The electrode system was calibrated by direct titration of acetic acid with standard NaOH, the observed pH meter readings being compared with the actual hydrogen ion concentration calculated from the data tabulated by Harned and Owen.[8] The pH regions below 3.5 and above 10.00 were calibrated by measurements in HCl and NaOH solutions, respectively. In this manner the hydrogen ion concentrations could be directly obtained from the observed pH meter readings.

RESULTS AND DISCUSSION

The potentiometric titration curve for DPA in the triprotonated form shows a moderate inflexion at a = 2 followed by a steep inflexion at a = 3 (a = moles of base added per mole of ligand). The first acid dissociation constant (pK_a) could not be calculated as it is fully dissociated. The second (pK_{2a}) and third (pK_{3a}) dissociation constants were calculated in the buffer regions of a = 1 to 2 and a = 2 to 3 respectively and are listed in Table 1. The titration curve for diprotonated PA shows a moderate inflexion at a = 1 followed by a buffer region. The pK_a and pK_{2a} values were calculated in the lower and upper buffer regions respectively and are listed in Table-1. For binary systems containing a 1 : 1 molar ratio of Cu(II) and diprotonated DPA or PA, the initial pH of the experimental solutions shows that both the protons are completely liberated indicating that the 1 : 1 binary Cu(II)-PA/DPA complex is fully formed. The potentiometric titration curves for experimental solutions containing a 1 : 1 : 1 molar ratio of bidentate DPA/PA-Cu(II) various bidentate amino acids exhibits an inflexion at m = 4 m = moles of base added per mole of metal ion). The formation constants for the mixed ligand complexes (K^{ML}_{MLA}) formed according to equilibrium (1),

$$ML + A \rightleftharpoons MLA, \qquad (1)$$

were calculated from the potentiometric data using the computer programme SCOGS.[9] The formation constants of the various mixed complexes are listed in Table 1. The differences in the ability of the various amino acids to bind the 1:1 Cu(II)-PA/DPA binary complex relative to the aquo cupric ion have been

quantitatively expressed in terms of the parameter Δ log K given by expression (2).

$$\Delta \log K = \log K^{ML}_{MLA} - \log K^{M}_{MA} \quad (2)$$

In order to obtain precise Δ log K values the formation constants of the binary Cu(II) complexes with PA/DPA and the various amino acids (MA) were determined under identical experimental conditions of 35°C and μ = 0.2 (KNO_3). The Δ log K values for the various ternary systems are listed in Table-1.

TABLE-1
FORMATION CONSTANTS* AND RELATED PARAMETERS FOR MIXED Cu(II) COMPLEXES CONTAINING DIPICOLINIC ACID OR PICOLINIC ACID
T = 35°C μ = 0.2 (KNO_3)

Primary ligand (L)	DPA			PA				
Secondary ligand (A)	log K^{M}_{MA}	log K^{ML}_{MLA}	Δ log K	log K^{ML}_{MLA}	Δ log K	ΔΔ log K	K_I	$(\%MLA)_{st}$
α-Alanine	7.94	6.88	−1.06	7.38	−0.56			
Serine	7.80	6.42	−1.38	6.80	−1.00			
Theronine	7.90	6.51	−1.39	6.70	−1.20			
Methionine	7.70	6.54	−1.16	6.76	−0.94			
Phenylalanine	7.64	6.55	−1.09	7.15	−0.49	+ 0.07	0.174	14.81
Tyrosine[a]	7.72	6.72	−1.00	7.62	−0.10	+ 0.46	1.884	65.32
Tryptophan	7.96	6.96	−1.00	7.90	−0.04	+ 0.52	2.311	69.76

*Constants accurate to ± 0.03. [a]Constants for protonated complexes. Dissociation constants for DPA: pK_{2a} = 2.26, pK_{3a} = 4.70; for PA; pK_{2a} = 5.25 at 35°C and μ = 0.2 M (KNO_3).

A comparison of the stability constants and Δ log K values (Table 1) for systems containing alanine shows that the mixed ligand complex containing PA as primary ligand is more stable than the corresponding complexes containing DPA. The pyridine nitrogen in PA as well as in DPA is a π-acceptor and hence participates in metal dπ → ligand pπ backbonding causing the metal ion to be more positive or more electronegative. Hence binding of the amino acid anion is facilitated for both PA as well as DPA system. However, DPA is a planar terdentate ligand which binds to three equatorial sites of Cu(II). The incoming bidentate amino acid will therefore be able to bind only one strong equatorial site and is forced to bind a weak axial site of the tetragonally distorted octahedral Cu(II) ion. This leads to loss in stablility since in the binary complexes (MA), bidentate amino acids bind to two strong equatorial sites. In the case of bidentate PA only two equatorial sites on Cu(II) are blocked and the amino acid will still be able to bind two equatorial sites. Further the incoming amino acid anion will be electrostatically repelled more by the dinegative DPA rather than the mononegative PA. Due to these two reasons mixed complexes containing DPA as primary ligand are less stable than the corresponding complexes containing PA. A

schematic representation of the PA-Cu(II)-Ala and DPA-Cu(II) -Ala complexes are shown in Fig. 1.

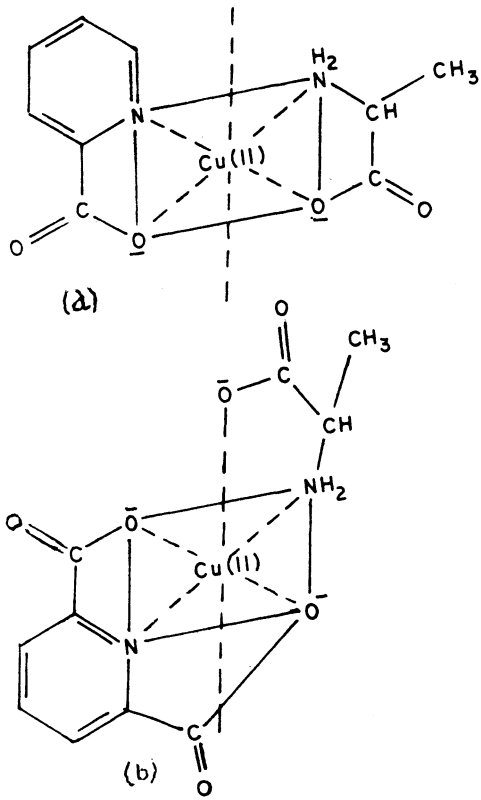

Fig. 1. (a) Proposed structure of a picolinic acid-Cu(II)-alanine complex;
(b) Proposed structure of dipicolinic acid-Cu(II)-alanine complex

For both PA and DPA, mixed complexes involving the amino acids Ser, Thr and Met are less stable (*i.e.* Δ log K is more negative) than the corresponding Ala containing complexes. This is probably due to the fact that the above amino acids are tridentate in binary Cu(II) complexes while in the mixed complexes they are weakly bidentate. The decrease in denticity could lead to the lower stability of mixed complexes containing amino acids with side chains containing donor atoms.

In mixed systems containing PA as the primary ligand, Δ log K values for complexes containing amino acids with an aromatic side chain, *viz.* Phe, TyrH and Try are more positive than the corresponding values for systems containing Ala. The enhanced stabilization has been quantitatively expressed in terms of the parameters $\Delta\Delta$ log K:

$$\Delta\Delta \log K = \Delta \log K_1 - \Delta \log K_2 \quad (3)$$

where $\Delta \log K_1$ relates to the mixed complexes containing Phe, TyrH or Try and

$\Delta \log K_2$ relates to mixed complexes containing Ala. The $\Delta\Delta \log K$ values are listed in Table 1. In the case of Ala, the methyl side chain does not take part in intramolecular metal ion mediated stacking interactions with the aromatic pyridyl moiety of PA. The positive $\Delta\Delta \log K$ values for systems involving Phe, TyrH or Try show that the enhanced stability arises from the stacking stacking interactions between the pyridine ring of PA and the phenyl or indole ring of the above amino acids. In these systems the isomeric intramolecular equilibrium between the stacked and the unstacked forms has been expressed in terms of a concentration independent and dimensionless constant K_I using the relationships

$$K_I = 10^{\Delta\Delta \log K} - 1 \quad (4)$$

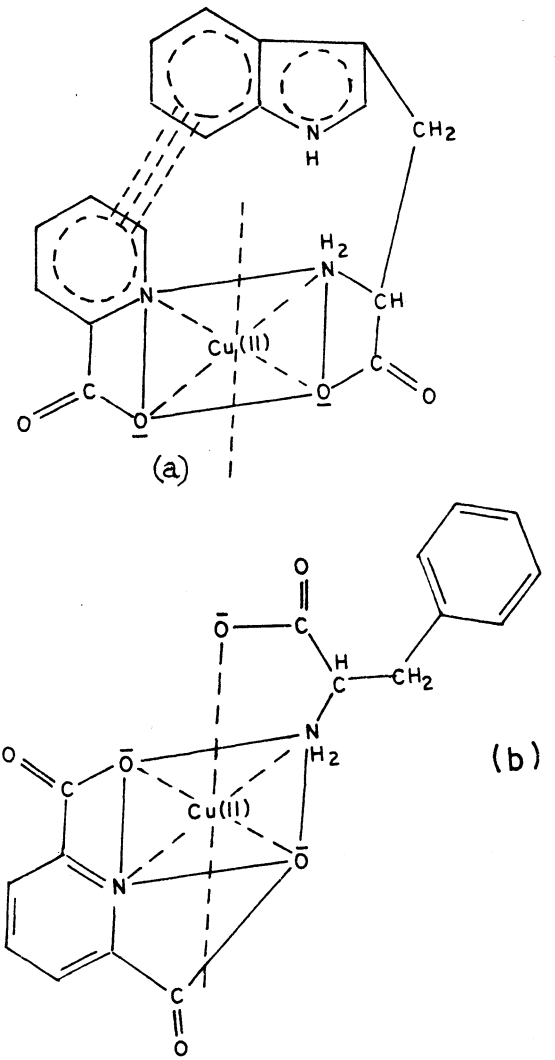

Plate 2. (a) Proposed structure of tryptophan-Cu(II)-picolinic acid complex;
(b) Proposed structure of phenylalanine-Cu(II)-dipicolinic acid complex

The percentage of the stacked isomer in these complexes was calculated with the relationship

$$[\%MLA]_{stacked} = [K_I/(1 + K_I)] \times 100 \quad (5)$$

The values of K_I and the percentage of the stacked isomer for the above systems are listed in Table-1. In systems involving Try or TryH stacking interactions are of considerable extent and the stacked form exists to the extent of *ca.* 70 per cent.

In mixed complexes containing DPA as primary ligand the stability of the systems containing Phe, TryH or Try are similar to those containing Ala indicating the absence of enhanced stabilisation arising from noncovalent stacking interactions. Models show that when DPA binds to three equatorial sites of Cu(II), it is sterically not feasible for the amino acid aromatic side chain to come above the pyridine ring of DPA. Hence stacking interactions are not favoured for these systems. A schematic representaion of the ternary complexes involving PA-Cu(II)-Trypt and DPA-Cu(II)-Phe are shown in Fig. 2.

The present investigation shows that the denticity, charge and geometry of the primary ligand greatly influence the nature of bonding and extent to which the secondary ligand binds the metal ion. These factors could play an important role in the specificity and selectivity observed in biological processes involving metal ions.[10]

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