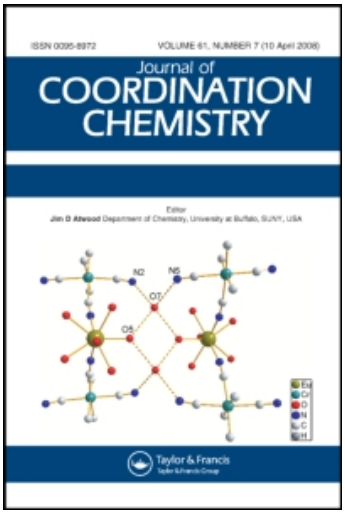

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STUDIES ON BIOLOGICALLY RELEVANT BINARY AND TERNARY METAL COMPLEXES. III. TERNARY Cu(II) COMPLEXES CONTAINING IMIDAZOLE DERIVATIVES AND AMINO ACIDS

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Biologically relevant Cu(II) ternary complexes containing bis(imidazol-2-yl)methane (BIM) and bis(imidazol-2-yl)nitromethane (NBIM) as the primary ligands and various bidentate and terdentate amino acids as secondary ligands have been investigated. The dissociation constants for BIM and NBIM, the association constants of their binary Cu(II) complexes and the ternary Cu(II) complexes are reported at 35°C and $\mu = 0.2$. When the amino acid has no aromatic side chain for intramolecular stacking interactions the relative ability of the above complexes to bind the secondary amino acids is found to be Cu(NBIM) > Cu(BIPY) > Cu(BIM). In ternary systems involving intramolecular stacking interactions the relative ability of the binary Cu(II) complexes to bind the amino acids is Cu(BIPY) > Cu(NBIM) > Cu(BIM).

Keywords: Copper, aminoacid, stability constants, imidazoles, ternary complexes

INTRODUCTION

In metalloenzymes the enzyme is usually bound to the metal ion through two or more imidazole groups and other coordinating sites on the metal are occupied by the substrate.[1] Although each imidazole is monodentate, the conformation of the protein chain is such that two or more distant imidazoles can come close enough to simultaneously bind a given metal ion.[2] We therefore felt that information regarding enzyme-metal ion-substrate ternary complexes could be obtained by studying model ternary complexes containing the imidazole derivatives bis(imidazol-2-yl)methane (BIM) or bis(imidazol-2-yl)nitromethane (NBIM) and various bidentate and terdentate amino acids. In earlier work[3,4] on ternary complexes of Cu(II) we had used bipyridyl as the primary ligand. Comparisons between these systems are made.

EXPERIMENTAL

Reagents

Bis(imidazol-2-yl)methane (BIM) and bis(imidazol-2-yl)nitromethane (NBIM) were synthesised by a reported procedure.[5] The amino acids glycine (GLY), alanine (ALA) valine (VAL), leucine (LEU), phenylalanine (PHE), tryptophan (TRYPT), methionine (MET), aspartic acid (ASP), histidine (HIST), lysine (LYS) and 3,4-dihydroxyphenylalanine (DOPA) were obtained from Sigma Chemical Company,

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U.S.A. Except for glycine all amino acids were in the racemic form. Other reagents were of B.D.H. AnalaR grade.

Methods

Carbonate-free sodium hydroxide was prepared and standardised with potassium hydrogen phthalate by the procedure reported by Schwarzenbach and Biederman.[6] A stock solution of Cu(II) was prepared and standardised with EDTA.[7] Acid dissociation constants of the free ligands and formation constants of the mono and bis binary metal complexes were determined by potentiometric titration of various ligands with standard carbonate-free NaOH in the absence and the presence of Cu(II) respectively. A 1 : 1 or 1 : 2 metal–ligand ratio was employed in the study of the binary systems. In determining the formation constants of the ternary complexes a 1 : 1 : 1 molar ratio of BIM or NBIM–Cu(II)–amino acids was employed. The concentration of Cu(II) in the binary and ternary systems was $\sim 2.0 \times 10^{-3}$ M. The formation constants were determined at 35°C ± 0.1 and $\mu = 0.2$ (KNO_3). Details of the experimental procedures used have been reported previously.[3,4] Titration data have been deposited with the Editor.

RESULTS AND DISCUSSION

Acid dissociation constants

Potentiometric titration of diprotonated BIM $[H_2L]^{2+}$ shows a moderate inflexion at a = 1 (Fig. 1L) indicating the dissociation of the two protons corresponding to (1) and (2).

$$H_2L^{2+} \rightleftharpoons HL^{+} + H^{+} \quad (1)$$

$$HL^{+} \rightleftharpoons L + H^{+} \quad (2)$$

TABLE I
Dissociation constants and association constants for primary ligands at T = 35.0°C and μ = 0.2 M (KNO_3).

Ligand	pK_a	pK_{2a}	log K^{M}_{ML}
Bis(imidazol-2-yl)methane	4.38	6.69	9.41
Bis(imidazol-2-yl)nitromethane	C[a]	4.10	F[a]

[a]C = Completely dissociated; F = Fully formed. Constants are accurate to ±0.05.

For neutral NBIM in the presence of 2 moles of acid, the potentiometric titration curve shows an inflexion at a = 2. However, the initial pH of the curve shows that one proton is completely dissociated. The acid dissociation constants for BIM and NBIM are listed in Table I. The dissociation constants for the various amino acids used as secondary ligands were determined earlier under identical experimental conditions.[3,4] These constants were used for calculating the formation constants of the ternary complexes investigated in the present work.

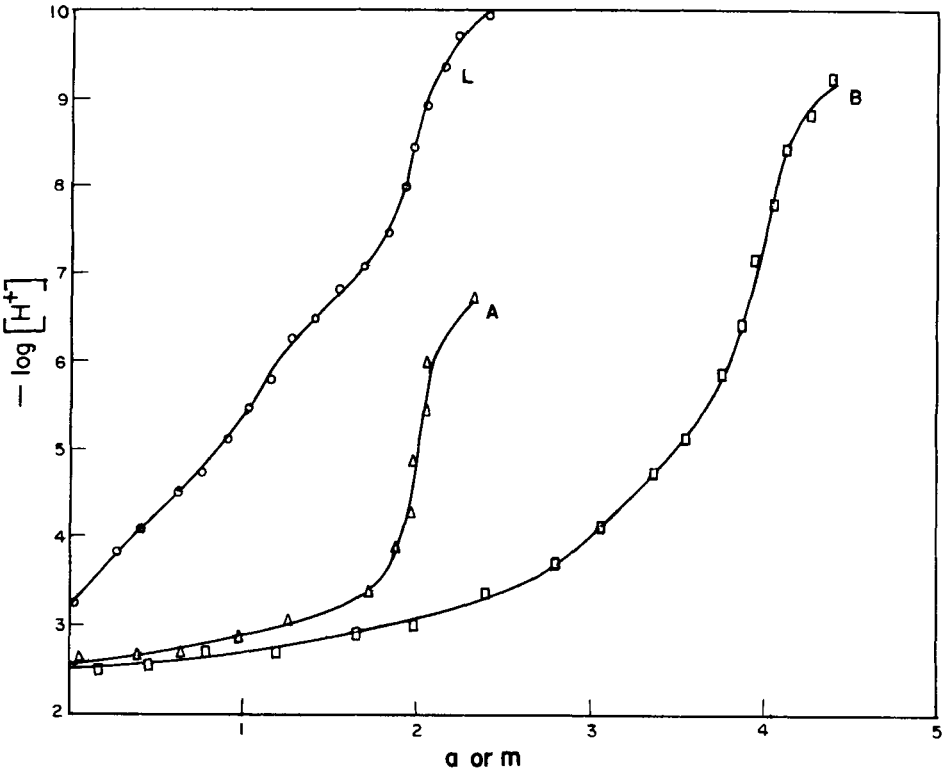

FIGURE 1 Potentiometric titration curves for the free ligand bis(imidazol-2-yl)methane (BIM) [L], 1 : 1 BIM–CU [A] and 1 : 1 : 1 BIM–Cu–GLY [B] systems. For curves [L] and [A] the abscissa represents a and for curve [B] m, where a = moles of base added per mole of ligand and m = moles of base added per mole of metal ion.

Binary Systems

Potentiometric titration of diprotonated BIM $[H_2L]^{2+}$ and Cu(II) in a 1 : 1 molar ratio shows an inflexion at a = 2 (Fig. 1A) indicating the formation of a normal complex represented by (3).

$$M^{2+} + L \rightleftharpoons ML^{2+} \tag{3}$$

In the case of monoprotonated NBIM–Cu(II) 1 : 1 binary systems the initial pH indicates that the metal complex $[NBIM–Cu]^{2+}$ is fully formed initially. The stability constant for the normal 1 : 1 complex of Cu(II) with BIM is listed in Table I. The formation constants for the mono and bis binary complexes of Cu(II) with various amino acids have also been determined under identical experimental conditions.[3,4]

Ternary Complexes

Potentiometric titration curves for BIM, Cu(II) and the bidentate amino acids GLY, ALA, VAL, LEU, PHE, TRYPT and MET show a steep inflexion at m = 4 (Fig. 1B) and with the terdentate amino acids ASP and HIST a steep inflexion was obtained at m = 5. An inflexion at m = 4 indicates that four protons *i.e.*, two from

the primary ligand and two from the amino acid are neutralized in a single step represented by the buffer region of m = 0 to 4 and the formation of a normal complex $[MLA]^+$. An inflexion at m = 5 indicates that five protons *i.e.*, two from the primary ligand and three from the amino acid are neutralized in a single step represented by the buffer region of m = 0 to 5 and the formation of a normal complex [MLA]. The stability constants for the normal complexes formed in these ternary systems were calculated in these buffer regions. In the cases of triprotonated lysine and tetraprotonated DOPA, a steep inflexion was obtained at m = 4, followed by precipitation. In the case of lysine the stability constant for the complex $[MHLA]^{2+}$ and in the case of DOPA the stability constant for the complex $[MH_2LA]^+$ was calculated in the buffer region m = 0 to 4. The various constants found in this study are listed in Tables I and II.

A comparison of the dissociation constants for the ligands BIM and NBIM (Table I) shows that the presence of the nitro group in NBIM increases acidity to such an extent that one of the protons is completely dissociated. Hence only one pK value is reported for NBIM.

In the normal $[ML]^{2+}$ complexes of BIM with Cu(II), the metal ion is bound to the two imidazole nitrogens of BIM forming a chelate ring. The stability constant (log K^M_{ML} = 9.41) compares with that for Cu-1,3-diamino propane[8] (log K^M_{ML} = 9.36). Since BIM is much less basic (pK_a = 4.38, pK_{2a} = 6.69) than 1,3-diamino propane (pK_a = 8.84, pK_{2a} = 10.53), the stability of the BIM–Cu(II) complex can be attributed to both BIM → Cu(II) σ-donation and Cu(II) → BIM π-donation. Imidazole is known to be a reasonably good π-acceptor.[9] In the case of the 1 : 1 NBIM-Cu(II) complex, although the σ-basicity of NBIM is lower, the presence of the nitro group makes NBIM a better π-acceptor compared with BIM. Both $[ML]^{2+}$ complexes are thus completely formed initially.

For the ternary complexes, the effect of the bonded primary ligand ion towards an incoming secondary ligand can be expressed in terms of the parameter Δlog K, (4).

$$\Delta\log K = \log K^{ML}_{MLA} - \log K^{M}_{MA} \quad (4)$$

The Δlog K values for the ternary systems investigated are given in Table II. For comparison, corresponding values for systems involving BIPY[2,3] are also included in Table II.

In ternary Cu(II) systems containing BIM and amino acids which do not have an aromatic side chain, the Δlog K values are found to be negative. These values (and magnitudes) are expected on the basis of statistical factors and the metal to ligand back bonding expected for N–O donors.[10] In ternary Cu(II) systems containing amino acids with aromatic side chains (TRYPT, PHE and DOPA), the Δlog K values are more positive, implying more stable ternary complexes. This may arise from intramolecular stacking interactions between the aromatic rings of the primary and secondary ligands. In ternary systems involving NBIM and the amino acids GLY and ALA Δlog K values are more positive than in corresponding systems containing BIPY or BIM. In ternary systems containing an aromatic side chain such as tryptophan, the Δlog K values show that the order in which the primary ligands promote the interaction of Cu(II) with such amino acids is: BIPY > NBIM > BIM.

Thus it appears that in such ternary systems BIPY is the most effective primary ligand, while in ternary systems which do not involve aromatic stacking, NBIM is the most effective primary ligand. The present study shows clearly the manner in which the ability of a metal ion to coordinate a secondary ligand is significantly modified by small changes in the nature of the primary ligand.

TABLE II
Ternary constants and $\Delta \log K$ values at T = 35.0°C and μ = 0.2 M (KNO_3).

	α-α'-bipyridyl		Bis[imidazol-2-yl]methane		Bis[imidazol-2-yl]nitromethane	
	$\log K^{ML}_{MLA}$	$\Delta \log K$[a]	$\log K^{ML}_{MLA}$	$\Delta \log K$	$\log K^{ML}_{MLA}$	$\Delta \log K$
Glycine	7.54	−0.46	7.28	−0.72	8.39	+0.39
Alanine	7.53	−0.41	7.29	−0.65	8.38	+0.44
Valine	7.68	−0.40	7.39	−0.69		
Leucine	7.56	−0.48	7.29	−0.75		
Phenylalanine	7.84	+0.20	7.45	−0.19		
Tryptophan	8.92	+0.96	8.15	+0.19	8.60	+0.64
Methionine	7.19	−0.51	7.10	−0.60		
Aspartic acid	7.92	−0.46	7.76	−0.62		
Histidine	8.97	−0.79	8.91	−0.85		
Lysine	7.28[d]	−0.48[b]	7.10[d]	−0.66[b]		
DOPA	8.53[e]	+0.65[c]	8.02[e]	+0.14[c]		

[a] $\Delta \log K = \log K^{ML}_{MLA} - \log K^{M}_{MA}$; [b] $\Delta \log K = \log K^{ML}_{MLHA} - \log K^{M}_{MHA}$; [c] $\Delta \log K = \log K^{ML}_{MLH_2A} - \log K^{M}_{MH_2A}$; [d] $\log K^{ML}_{MLHA}$; [e] $\log K^{ML}_{MLH_2A}$.

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