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Ternary copper(II) complexes containing imidazole as a primary ligand & amino acids as secondary ligands

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The formation constants of ternary complexes CuLA and CuL_2A (where L = imidazole and A = valine, phenylalanine, tryptophan, methionine, ethionine and histidine) are reported at 35.0°C and $\mu = 0.2$ *M* (KNO_3). Stacking and hydrophobic interactions in these and analogous ternary complexes, are found to increase in the order: Cu-[imidazole]$_2$A < Cu-[bis(imidazol-2-yl)methane] A < Cu-(Bipyridyl]A. The biological relevance of these model ternary complexes is discussed.

Non-covalent interactions in biological systems are the key to biological flexibility and specificity[1]. In our recent work dealing with ternary Cu(II) complexes, enhanced stabilities due to metal ion mediated stacking or hydrophobic interactions were observed when the primary ligand was bipyridyl[2,3] (bipy) or bis(imidazol-2-yl)methane[4] (BIM) and the secondary ligands were amino acids with suitable side chains. Title investigation is an extension of our earlier work.

DL-Amino acids, viz. valine (val), phenylalanine (Phala) tryptophan (trypt), methionine (met), ethionine (eth) and histidine (hist) were obtained from Sigma Chemicals Co., USA. Imidazole (Im), ethylenediaminetetraacetic acid (EDTA), potassium hydrogen phthalate, potassium nitrate, cupric nitrate and sodium hydroxide were of AR (BDH) grade.

Imidazole was used in the monoprotonated form, histidine was used in the triprotonated form while all other amino acids were used in the diprotonated form. The equilibrium constants of ternary complexes were determined by potentiometric titration of solutions containing a 1:1:2 molar ratio of Cu(II), amino acid and imidazole respectively, with standard carbonate-free sodium hydroxide. The concentration of Cu(II) was ~ 2.0×10^{-3} *M*. Details of the experimental procedure have been reported in our earlier publications[2,3,6].

Equilibrium constants for the ternary complexes K^{Cu}_{CuLA} and $K^{Cu}_{CuL_2A}$ were computed as described in our previous works[5-8]. The stepwise formation constants K^{CuL}_{CuLA} and $K^{CuL_2}_{CuL_2A}$ were calculated employing the K^{Cu}_{CuLA}, $K^{Cu}_{CuL_2A}$ and binary constants (K^{Cu}_{CuA}) of Cu(II)- amino acid complexes taken from our previous works[2,3]. The binary constants for the Cu(II)-imidazole complexes (log K^{Cu}_{CuLn}) were determined under identical experimental conditions, i.e. at 35°C and $\mu = 0.2$ *M* (KNO_3). The stepwise stability constants for the binary and ternary complexes are listed in Table 1.

The relative stabilities of the ternary complexes as compared to the corresponding binary complexes have been quantitatively expressed in terms of the parameter $\Delta\log K$ as follows: $\Delta\log K_1 = \log K^{CuL}_{CuLA} - \log K^{Cu}_{CuA}$ and $\Delta\log K_2 = \log K^{CuL_2}_{CuL_2A} - \log K^{Cu}_{CuA}$. The $\Delta\log K_1$ and $\Delta\log K_2$ values for var-

Table 1—Formation constants for binary* and ternary complexes and comparison of $\Delta\log K$ values
[Temp = 35.0°C; $\mu = 0.2$ *M*(KNO_3)]

Secondary ligands (A)	log K^{Cu}_{CuA}	log K^{CuL}_{CuLA}	log $K^{CuL_2}_{CuL_2A}$	Imidazole (L)		BIM[a](L′)	Bipy[a](L′)
				$\Delta\log K_1$	$\Delta\log K_2$	$\Delta\log K$	$\Delta\log K$
Valine	8.08	7.55	7.26	−0.53	−0.82	−0.69	−0.40
Phenylalanine	7.64	7.28	6.98	−0.36	−0.66	−0.19	+0.20
Tryptophan	7.96	7.52	7.43	−0.44	−0.53	+0.19	+0.96
Methionine	7.70	7.16	6.93	−0.54	−0.77	−0.60	−0.51
Ethionine	7.54	6.99	6.71	−0.55	−0.83	−0.49	−0.26
Histidine	9.76	8.99	8.38	−0.77	−1.38	−0.85	−0.79

*Binary constants for amino acids are from references 2 and 3.
For imidazole (L) the values of log K^{Cu}_{CuL}, log $K^{CuL}_{CuL_2}$, log $K^{CuL_2}_{CuL_3}$ at 35°C and $\mu = 0.2$ *M*(KNO_3) are 4.11, 3.33, 2.72 respectively.
[a]$\Delta\log K$ values from references 2-4 ($\Delta\log K = \log K^{CuL'}_{CuL'A} - \log K^{Cu}_{CuA}$).

ious ternary complexes are listed in Table 1. The negative values of $\Delta\log K$ for all ternary systems (Table 1) are statistically expected since there are fewer coordination positions available for the amino acids to bind to the CuL complex than to the aquo Cu(II) ion. For any given amino acid the $\Delta\log K_2$ values are more negative than the corresponding $\Delta\log K_1$ values. In the ternary complexes involving histidine the relatively more negative values of $\Delta\log K_1$ and $\Delta\log K_2$ as compared to the corresponding values of ternary systems containing other amino acids may result from steric hindrance between the imidazole moieties of the primary and secondary ligands.

The $\Delta\log K$ values of the ternary complexes involving Cu-Im_2, Cu-BIM and Cu-bipy complexes show that the ability of any given amino acid to bind various Cu(II) complexes increases in the order: $Cu(Im)_2 < Cu(BIM) < Cu(bipy)$ (Table 1). This order of complexing ability has been discussed in terms of the increasing π-acceptor capacity of the Cu(II)-amino complexes[9]. For amino acids without any aromatic side chain (e.g. valine, methionine etc.) statistically expected negative values of $\Delta\log K$ are observed for interaction with Cu-bipy and Cu-BIM complexes. However, for amino acids with an aromatic side chain (e.g. tryptophan or phenylalanine) positive or less negative values of $\Delta\log K$ are obtained[2-4]. The statistically unexpected enhanced stability observed in these systems has been attributed to the intramolecular stacking interactions between the aromatic moieties of the primary ligand and the indole or phenyl moieties of the amino acids[2-4]. The difference in the behaviour of Cu-Im_2,Cu-BIM and Cu-bipy complexes towards amino acids such as tryptophan and phenylalanine can be rationalized if we consider that in Cu-Im_2 complex stacking interactions with aromatic side chain of amino acid are hindered since the two *cis*-coordinated imidazole moieties are out-of-plane[10], while they are facilitated by the in-plane aromatic moieties in Cu-BIM and Cu-bipy (see Fig. 1).

Recent studies on stacking interactions in Cu(II) ternary complexes[11] have shown that while the aromatic side chain of tyrosine is able to stack with aromatic amine ligands coordinated to Cu(II), deprotonation or phosphorylation of the tyrosine phenyl side chain inhibits stacking from taking place. It was suggested that stacking interactions in metalloenzymes may be regulated *in vivo* by phosphorylation or sulfation of the $-OH$ group[11]. The results of the present work suggest that *in vivo* stacking interactions between the enzyme and the substrate may also be regulated by the imidazole

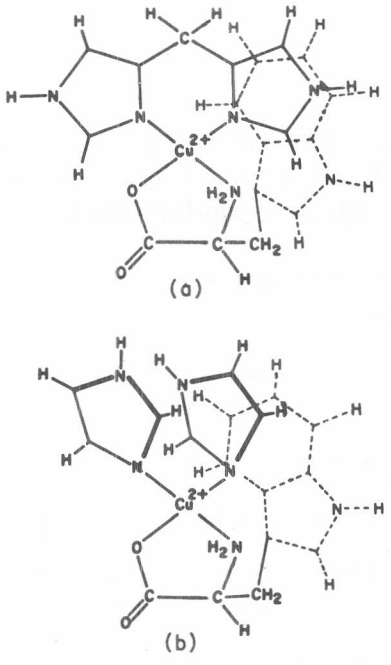

Fig. 1—(a) Tentative structure of Cu(II)-BIM-trypt ternary complex showing intramolecular stacking interaction. (b) Tentative structure of Cu(II)-Im_2-trypt ternary complex showing out-of-plane *cis*-coordinated imidazole (Im)

moieties of the enzyme being in-plane or out of plane with the aromatic moieties present on the substrate. The $\Delta\log K$ values for the ternary complex containing ethionine as the secondary ligand shows that the affinity of ethionine for the Cu(II)-aromatic amine complex increases in the order: Cu-Im_2 < Cu-BIM < Cu-bipy. The higher stability of the Cu-bipy-ethionine complex has been attributed to hydrophobic interaction between the side chain of ethionine and the pyridyl rings of bipyridyl[2]. The more negative $\Delta\log K_2$ value for Cu-$(Im)_2$-ethionine system again suggests that hydrophobic interactions are inhibited by out-of-plane imidazole moieties.

The present work on model ternary complexes suggests that in *in vivo* situations stacking and hydrophobic interactions could be regulated by the imidazole moieties of the polypeptide chain and this may be one of the factors by which enzymes achieve high substrate specificity.

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