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Influence of electronic, steric and stacking interactions in ternary Ni(II) and Cu(II) complexes containing 2,2′,2″-terpyridine and a series of amino acids

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Formation constants for ternary complexes MLA, where M = Cu(II) or Ni(II), L = 2,2′,2″-terpyridine (terpy) and A = alanine (ala), phenylalanine (phe), tyrosine (tyr), tryptophan (trypt), threonine (thr), methionine (met) or histidine (hist) have been determined *p*H-metrically in aqueous solutions at 35.0°C and $\mu = 0.2\ M$ (KNO_3). The ability of the various amino acids to bind the binary (M(II)-terpy)) complex relative to the aquo metal ion has been quantitatively assessed in terms of the parameter $\Delta \log K$. With respect to the metal ion, Cu(II) ternary complexes have been found to be substantially unstable relative to the corresponding Ni(II) complexes. In ternary Ni(II) complexes amino acids without an aromatic side chain form stable complexes due to Ni(II)→terpy π-interaction, whereas amino acids with an aromatic side chain form still more stable complexes due to similar π-interactions and also metal ion mediated stacking interactions. The intramolecular equilibrium between the stacked and unstacked isomers and the percentage of the stacked isomer have been quantified in terms of the parameters K_I and $(\%\,MLA)_{st}$, respectively.

Solution studies on the formation and stability of ternary complexes involving Ni(II) or Cu(II), 2,2′,2″-terpyridine (terpy) and various amino acids have been investigated. Terpyridine which is a tridentate ligand coordinating via three pyridyl groups with a metal ion serves as a useful model for *in vivo* ternary complexes in which the metal ion is simultaneously bound to three imidazole moieties of the polypeptide chain. Formation constants for ternary complexes formed in solutions containing 1:1:1 molar ratio of Ni(II) or Cu(II), terpy and the amino acids alanine (ala), leucine (leu), threonine (thr), methionine (met), histidine (hist), phenylalanine (phe), tyrosine (tyr) or tryptophan (trypt) have been determined *p*H-metrically at 35.0°C and $\mu = 0.2\ M$ (KNO_3) in aqueous solutions. The stability of the ternary complexes have been quantitatively compared with the corresponding binary amino acid complexes and various factors influencing the stabilities have been identified and discussed. The present study is a continuation of our earlier investigation on ternary complexes containing various pyridyl derivatives and amino acids[1-5].

Materials and Methods

2,2′,2″-Terpyridine and the racemic amino acids were obtained from Sigma Chemical Co., USA. Histidine and tyrosine were employed in the triprotonated form while all other ligands were used in the diprotonated form. Stock solutions of Ni(II) and Cu(II) were prepared from reagent grade nitrate salts and standardized by titrating with disodium salt of EDTA using murexide as an indicator[6]. Carbonate free NaOH was prepared and standardized by titrating with a pure sample of potassium hydrogen phthalate.

The experimental procedure involved the *p*H-metric titration of the following solutions with standard NaOH at 35°C and $\mu = 0.2\ M$ (KNO_3): Terpyridine (0.001 *M*); solution 1 + M(II) (0.001 *M* each); solution 2 + amino acid (0.001 *M* each).

The details of the experimental procedure are given elsewhere[1-5]. The relevant equilibrium constants were computed from the *p*H-metric data with a computer programme SCOGS[7].

Results and Discussion

The second and third dissociation constants for terpy are listed in Table 1. The first dissociation constant could not be precisely evaluated due to its high acidity. In binary systems (solution 2), the metal complex (ML) was completely formed on mixing the two reactants. For ternary systems (solution 3), involving diprotonated amino acids, the stability of the ternary complex MLA which was formed according to the equilibrium ML + A ⇌ MLA was calculated by taking into consideration the

species ML, H_2A, HA and A. Since ML is completely formed initially, the species M(II) and MA were not considered. For triprotonated hist, the H_3A species was also considered. The formation constants for the various ternary complexes are listed in Tables 1 and 2. The relative ability of the various amino acids to bind the [M-terpy] complex and the aquo M(II) ion has been quantified in terms of the parameter $\Delta \log K$ (Eq. 1).

$$\Delta \log K = \log K^{\mathrm{Ml}}_{\mathrm{MLA}} - \log K^{\mathrm{M}}_{\mathrm{MA}} \quad \ldots (1)$$

In order to obtain $\Delta \log K$ values, the formation constants for the binary amino acid complexes (MA) were also determined under identical experimental conditions and are listed in Tables 1 and 2.

Ternary Ni(II) complexes

Terpyridine is a rigid tridentate ligand which can bind a metal ion in a meridional fashion using the three pyridine nitrogens as donor atoms. The statistical effect expected for the binding of a bidentate secondary ligand to the Ni-terpy complex (ML) relative to the octahedral aquo metal ion is 2/12, i.e., $\Delta \log K = -0.78$. The $\Delta \log K$ values (Table 1) for ternary systems containing amino acids without an aromatic side chain, viz., ala, leu, thr or met are substantially more positive than expected on statistical ground. This enhanced stability may be attributed to back donation of electron density from metal $d\pi$ to $p\pi$ orbitals of the three pyridine nitrogens of terpy causing the metal ion to become more positive or more electronegative and thereby facilitate the stronger binding of the

Table 1—Formation constants* and related parameters for ternary metal complexes (MLA) containing terpyridine-Ni(II)-amino acids

[Temp = 35.0°C; $\mu = 0.2$ $M(KNO_3)$]

Secondary ligand (A)	$\log K^{\mathrm{Ml}}_{\mathrm{MLA}}$	$\log K^{\mathrm{M}}_{\mathrm{MA}}$	$\Delta \log K$	$\Delta\Delta \log K$	K_1	$(\%\ \mathrm{MLA})_{st}$
Alanine	4.99	5.60	−0.61			
Leucine	4.82	5.47	−0.65			
Threonine	5.02	5.52	−0.50			
Methionine	4.79	5.32	−0.53			
Histidine	7.51	8.35	−0.84			
Phenylalanine	4.84	5.13	−0.29	+0.32	1.089	52.12
Tyrosine[a]	4.88	5.14	−0.26	+0.35	1.238	55.23
Tryptophan	5.42	5.25	+0.17	+0.78	5.025	83.39

*Constants accurate to ±0.04.

[a]Constants refer to protonated complexes. For terpy $pK_{2a} = 3.00 \pm 0.02$; $pK_{3a} = 4.58 \pm 0.02$.

Table 2—Formation constants* and $\Delta \log K$ values for ternary metal complexes (MLA) containing terpyridine/bipyridyl-Cu(II)-amino acids

[Temp = 35.0°C; $\mu = 0.2$ $M(KNO_3)$]

Amino acid (A)	$\log K^{\mathrm{M}}_{\mathrm{MA}}$	2,2′,2″-terpyridine (L)		2,2′-bipyridyl[a] (L)	
		$\log K^{\mathrm{Ml}}_{\mathrm{MLA}}$	$\Delta \log K$	$\log K^{\mathrm{Ml}}_{\mathrm{MLA}}$	$\Delta \log K$
Alanine	7.94	5.04	−2.90	7.53	−0.41
Leucine	8.04	4.84	−3.20	7.56	−0.48
Threonine	7.90	4.49	−3.40	7.38	−0.52
Methionine	7.70	4.30	−3.40	7.19	−0.51
Histidine	9.76	6.74	−3.02	8.97	−0.79
Phenylalanine	7.64	5.01	−2.64	7.84	+0.20
Tyrosine[b]	7.72	5.18	−2.54	8.22	+0.50
Tryptophan	7.96	5.27	−2.69	8.92	+0.96

*Constants accurate upto ±0.04.

[a]Constants for binary complexes ($K^{\mathrm{M}}_{\mathrm{MA}}$) and ternary complexes containing bipyridyl taken from references 4 and 5.

[b]Constants refer to protonated complex (MLHA).

amino acid anion. The still more positive $\Delta\log K$ values for ternary systems with an aromatic side chain may be attributed to stabilization resulting from intramolecular metal ion mediated stacked interactions between the aromatic moieties of the two ligands. The stabilization due to back donation from metal dπ to ligand pπ orbitals and stacking interactions have been reported earlier[8-12] in ternary complexes containing bidentate aromatic amines and amino acids. A schematic representation of the stacking interaction in the terpy-Ni(II)-phe complex is shown (Structure I).

The extent of stabilization resulting from stacking has been quantified in terms of the parameter $\Delta\Delta\log K$ given by the expression (2)

$$\Delta\Delta\log K = \Delta\log K_1 - \Delta\log K_2 \quad \ldots (2)$$

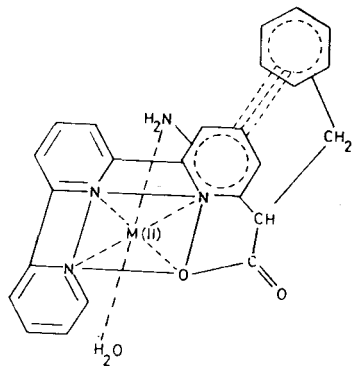
where $\Delta\log K_1$ relates to the stacked ternary complex of trypt, phe or tyr and $\Delta\log K_2$ relates to the ternary ala complex wherein no stacking is possible. The $\Delta\Delta\log K$ values listed in Table 1 are all positive indicating enhanced stabilization due to stacking. In solution, these ternary complexes exist in a "stacked" and "open" form which are in equilibrium. The constant for this equilibrium (K_I) and the percentage of the stacked isomer in these systems were calculated by Eqs 3 and 4 respectively.

$$K_I = {}_{10}\Delta\Delta\log K_{-1} \quad \ldots (3)$$

$$(\%)\mathrm{MLA}_{st} = [K_I/(1+K_I)] \times 100 \quad \ldots (4)$$

The comparison of $\Delta\Delta\log K$, K_I and (%) MLA_{st} for ternary systems containing phe, tyr or trypt (Table 1) shows that while substantial stacking occurs in the three systems, it is most favoured when trypt is involved. The larger surface area of the indole ring relative to the phenyl ring of phe or tyr promotes better overlap and stacking with the pyridine rings of terpy leading to greater stabilization. In regulating biological specificity and selectivity, stacking interactions play a vital role[13].

The tridentate amino acid hist forms ternary complexes of low stability as revealed by the more negative $\Delta\log K$ values (Table 1). In binary Ni-terpy complex, three equatorial sites may be occupied by three pyridine nitrogens leaving one equatorial and two axial sites free. Due to steric constraints, tridentate hist can bind only in a facial manner to an octahedral metal ion using two equatorial and one axial site[14]. In ternary complexes, hist can bind to the [Ni-terpy] complex to only one equatorial and an axial site in a bidentate manner via the amino and carboxylate moieties (with an unbound imidazole group) or the amino and imidazole moieties (with an unbound carboxylate group) leading to decreased stability.



(I)

Ternary Cu(II) complexes

The highly negative $\Delta\log K$ values obtained for ternary Cu(II) complexes containing terpy shows that the various amino acids bind the Cu(II)-terpy complex with a much lower affinity relative to the Ni(II)-terpy complex (Tables 1 and 2). Since terpy binds to three equatorial sites, the incoming amino acid can bind to only one strong equatorial site and a long weak axial site of the Jahn-Teller tetragonally distorted Cu(II)-terpy complex, causing low stability. The effect of the additional pyridyl ring in terpy on ternary complex formation is manifested by a comparison of the $\Delta\log K$ values (Table 2) of ternary Cu(II) complexes containing tridentate terpy and bidentate bipyridyl (bipy). The values for the ternary complexes containing bipy are considerably more positive than for the corresponding ternary complexes involving terpy. The amino acids can bind strongly to the two vacant equatorial sites on the Cu(II)-bipy complex but bind strongly to only one vacant equatorial site on the Cu(II)-terpy complex leading to destabilization of amino acid binding. The magnitude of destabilization is such that stabilization due to stacking interactions found in ternary Cu(II) complexes containing bipy and amino acids with an aromatic side chain are not manifested in the corresponding ternary complexes involving terpy. The calculations of the species concentrations with the Computer Programme BEST[15] shows that at *p*H 7.5, the concentration of the MLA complex in solutions containing a 1:1:1 molar ratio of ligand L, Cu(II) and tryptophan is 71 per cent when L = bipy but only 1 per cent when L = terpy.

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