Metal ion Mediated Intramolecular Stacking Interactions - Bivalent Metal ion with Benzimidazole & Amino Acids

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Interaction of bivalent metal ions with benzimidazole and selected amino acids (alanine, phenylalanine, tyrosine, tryptophan, 3,4-dihydroxy phenylalanine) has been investigated by potentiometric pH measurements. The extra stabilization observed in ternary complexes are attributed to stacking interactions.

Metal ion interactions with ligands having different donor atoms provide an opportunity to study their contributions to the stabilities of metal complexes. This type of investigation becomes much more relevant when ligands of biological importance are considered. In continuation of our earlier work [1-6] on the ligands of biological importance, the present paper reports the interaction of bivalent metal ions with benzimidazole in presence of selected amino acids.

EXPERIMENTAL

The ligands benzimidazole (Benz) and amino acids [alanine (Ala), phenylalanine (Ph.ala), tyrosine (Tyr), tryptophan (Try) and 3,4 - dihydroxy phenylalanine (DOPA))] are obtained from Sigma Chemical Company and Aldrich Chemical Company Ltd. (USA) respectively. The metal salts used were of Analar grade and the metal ion solutions were standardized volumetrically by titration with sodium salt of EDTA [7]. Potentiometric measurements were carried out at 30°C with 0.1 mol.dm^{-3} KNO_3 as background electrolyte in 40 % dioxan-water mixture using Control Dynamics pH meter. The pH of solution in 40% (v/v) dioxan-water mixture was corrected according to the method suggested by van Uitert and Haas [8]. The pH meter readings were plotted against 'a' (mole of base added per mole of ligand) or 'm' (mole of base added per mole of metal ion). Calculations were carried out on Personal Computer Casio PB 110.

RESULTS AND DISCUSSION

The acid dissociation and stability constants pertaining to the interaction of amino acids and bivalent metal ions are determined by pH-metry. Stability constant for binary complexes of amino acids were reported earlier, but these have been remeasured here because it is preferable to have log K values

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of binary and ternary complexes under the same conditions to get reliable Δlog K values. The acid dissociation constants of the ligands and stability constants for the binary and ternary complexes are included in Table 1.

The Δlog K values for ternary complexes (MLA) are computed and included in Table 1. These values are positive for all amino acids under study except alanine (Table 1). All amino acids chosen except alanine have a ring structure in the molecule. Positive Δlog K value indicats that these amino acids bind to 1:1 [M(II) - Benz] binary complex with greater affinity than with aquo metal ions. This extra stability of the ternary complexes can be attributed to metal ion mediated intramolecular stacking interactions between the aromatic moieties of benzimidazole and aromatic amino acids. Amino acids having ring structure in the

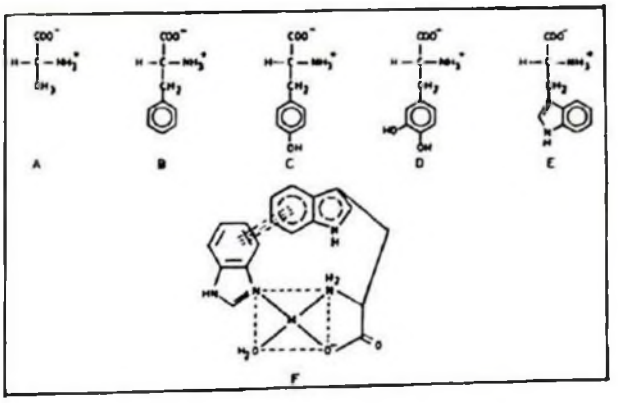


Fig1. Structures of the Ligands
a Tentative Structure showing the Intramolecular Stacking Interaction in Ternary Complex
A L-alanine; B L-phenyl alanine; C tyrosine; D 3,4 dihydroxy phenyl alanine (DOPA) E L-tryptophan F Complex M-benz-tryp

Table 1

Acid Dissociation Constants and Stability Constants of Different Complexes

Medium - 0.1 mol.dm^{-3} KNO_3 in 40% Dioxan; T = 30°

In ternary complexes Primary Ligand - Benzimidazole; Secondary Ligand - Amino acids

Ligands	Acid dissoc		Binary Log K^{M}_{ML}				Ter. Log K^{ML}_{MLA}				Δlog K of			
	pK_{a1}	pK_{a2}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
Benzimidazole	5.40	-	2.30	2.71	3.30	2.38	This is the primary ligand in ternary complexes							
Alanine	9.29	-	4.28	5.50	7.92	4.80	4.01	5.25	7.71	4.57	-0.27	-0.25	-0.21	-0.23
Ph.alanine	8.98	-	4.10	5.10	7.68	4.70	4.16	5.28	7.84	4.78	+0.06	+0.18	+0.16	+0.08
Tryptophan	8.96	-	4.15	5.20	7.82	4.62	4.27	5.46	8.12	4.81	+0.12	+0.26	+0.30	+0.19
Tyrosine	8.81	-	3.51	4.71	6.83	4.10	3.61	4.91	7.08	4.22	+0.10	+0.20	+0.25	+0.12
DOPA	8.51	9.80	4.12	5.10	7.80	4.42	4.19	5.28	7.98	4.51	+0.07	+0.18	+0.18	+0.09
Accuracy			±0.05		±0.05				±0.03 log units					

Δlog K = log K^{ML}_{MLA} - log K^{M}_{MA}

molecule are capable of forming stacking interactions. Alanine, with no phenyl ring in its structure is incapable of stacking interactions. Hence ternary complex of alanine is chosen as reference with zero stacking interactions.

The stacking interactions, can be quantised with suitable parameters as follows:

The parameter $\Delta\Delta\log K$ is given by the relationship

$$\Delta\Delta\log K = (\Delta\log K_1 - \Delta\log K_2) \quad \ldots (1)$$

where $\Delta\log K_2$ is for the reaction [M^{2+} + Benz + Ala] and $\Delta\log K_1$ relates to the reaction [M^{2+} + Benz + other Amino acids]. The values thus obtained are given in Table 2.

The concentration independent and dimensionless constant K_i for intramolecular equilibrium is calculated by the relationship:

$$K_i = 10^{\Delta\Delta\log K} - 1 \quad \ldots (2)$$

The percentage of stacked isomers in the systems are also calculated with the relationship:

$$\%(MLA)_{st} = [100 * K_i / (1 + K_i)] \quad \ldots (3)$$

The values of K_i and $\%(MLA)_{st}$ for these systems are included in Table 2. The perusal of parameters associated with stacking interactions reveal the following observations:

a) The stacking interactions decrease in the order tryptophan > tyrosine > DOPA > ph.alanine.

Table 2

ΔΔlog K Values & Parameters Showing Extent of Stacking Interaction in Ternary Complexes

Primary Ligand - Benzimidazole; Secondary Ligand - Amino acids
Medium - 0.1 mol.dm^{-3} KNO_3 in 40% Dioxan; T = 30°

Ligand	ΔΔlog K of				K_i				%)MLA)$_{st}$			
	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
Ph.alanine	+0.33	+0.43	+0.37	+0.31	1.137	1.691	1.344	1.041	53.20	62.83	57.33	51.00
Tryptophan	+0.39	+0.51	+0.51	+0.42	1.454	2.235	2.235	1.630	59.25	69.08	69.08	61.97
Tyrosine	+0.37	+0.45	+0.46	+0.35	1.344	1.818	1.884	1.238	57.33	64.51	65.33	55.31
DOPA	+0.34	+0.43	+0.39	+0.32	1.187	1.691	1.454	1.089	54.27	62.83	59.25	52.13

$\Delta\Delta\log K = \Delta\log K_1 - \Delta\log K_2$ (Alanine is taken as reference)
$K_i = 10^{\Delta\Delta\log K} - 1$; $\%(MLA)_{st} = 100 * K_i/(1+K_i)$

This order can be correlated with the size of the aromatic side chain. Stacking in ternary complexes containing tryptophan results in maximum stabilization since the surface area of the indole ring is large and permits for efficient stacking with benzimidazole. The phenyl rings of ph.alanine and tyrosine are small and hence lower efficiency of stacking.

Tyrosine forms better stacked isomers than ph.alanine due to the presence of OH group on phenyl ring of tyrosine which increase the ring electron density on phenyl ring, thus making it a better π electron donor. During stacking, this ligand donates π electron cloud to the aromatic ring of benzimidazole bound to metal ion.

The ligand DOPA is an ambidentate ligand. DOPA can bind to metal ion either like glycine using amino carboxylic group or it can bind like pyrocatechol using both oxygens present on phenyl ring. It is well known that in lower pH, DOPA binds to metal ion through amino carboxylate end; at higher pH, it binds like catechol. However, as observed by Bhattacharya [9], the present study also shows that DOPA binds in ternary complexes from the amino carboxylate end over the pH range of 4 -7.

b) The % of stacking interaction decrease in the order $Cu^{2+} < Ni^{2+} > Zn^{2+} > Co^{2+}$ with respect to the metal ions. This order is in confirmity with Irving Williams natural order of stabalities [10].

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