Metal Ion Promoted Hydrophobic Interaction - Bivalent Metals with Benzimidazoles and Amino Acids - pH metry

G. Usha Rani and Dev Das Manwal*

Department of Chemistry, Nizam college, Osmania University, HYDERABAD - 500 001. India

Stability constants of the ternary complexes of the type MLA (where, M = Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}: L= Benzimidazole or 2(2'-pyridyl)benzmidazole: A = alanine, methionine or ethionine) are determined potentiometrically. Enhanced stability of ternary complexes containing ethionine is attributed to hydrophobic interactions.

The factors which enhance the stability constants of mixed ligand complexes in biological systems are:

(i) hydrogen bonding between the amino acids and the nucleic acid bases [1],

(ii) polar interactions between positively charged ammonium groups of amino acids and negatively charged phosphate groups of nucleotides [2,3]

(iii) aromatic ring stacking between the purine or pyrimidine bases and suitable aromatic side chain residues of the amino acids, like the indole [3-7] or imidazole group [8] and

(iv) the related hydrophobic interactions [9-10].

It has also been shown that two such interactions may occur simultaneously [3,6], thus leading to cooperativity.

In continuation of our earlier studies on the coordinating tendencies of benzimidazole and 2-substituted benzimidazoles [11,12], we report herein the stability constants of the ternary complexes of the type MLA, where M = Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}: L= Benzimidazole (Benz) or 2(2-pyridyl) benzmidazole (py-benz): A = alanine (ala), methionine (meth) or ethionine (eth).

EXPERIMENTAL

The ligands, benzimidazole and 2(2'-pyridyl)benzimidazole are obtained from Sigma Chemical Company and Aldrich Chemical Company (USA) respectively. The amino acids are obtained from Fluka Chemical Company. The metals used were of AnalaR grade and the metal ion content in solution was determined volumetrically by titration with sodium salt of EDTA [13]. Potentiometric measurements were carried out at 30°C

© E.C.S.I. Bangalore

with 0.1 mol.dm^{-3} KNO_3 as background electrolyte in 40% (v/v) dioxan - water mixture, using Control Dynamics pH meter. The pH of the solution in 40% dioxan - water mixture was corrected according to the method suggested by Van Uitert and Haas [14]. 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 with the help of personal computer CASIO PB 110.

RESULTS AND DISCUSSION

The potentimetric titration curves of 1:1:1 (M-L-A) (where L = benzimidazole or 2(2'-pyridyl)benzimidazole; A = alanine, methionine or ethionine) show a steep inflection at m=1 followed by another at m=2. The ternary curve coincides with binary curve upto m=1. This indicates that only 1:1 (M-L) complex is formed in the region m=0 to m=1 and amino acid does not coordinate with metal ions in this region. The divergence of mixed ligand curve from the binary (M-L) curve beyond m = 1 suggests the coordination of amino acid as a secondary ligand. Hence the formation of ternary complexes can be considered to occur in stepwise equilibria. The stability constants for the ternary complexes are calculated in the region m=1 to 2 using pK_a of the amino acids and the values K^{ML}_{MLA} thus obtained are presented in Table 1.

The stability of ternary complexes are characterised by a parameter $\Delta\log K$. This parameter has been calculated and included in Table 1. Negative $\Delta\log K$ values suggest that the binary complexes are more stable than the ternary complexes, whereas a positive $\Delta\log K$ suggest greater stability to the ternary complexes.

A perusal of the $\Delta\log K$ values reveal that the value for ternary complexes of ethionine is less negative as compared to ternary complexes of methionine or alanine. This points in the direction of intramolecular ligand - ligand interaction in ternary complexes of ethionine. A model of ternary complex $[(Bzm)\text{-}Cu\text{-}(Eth)]^+$ shows that side chain of

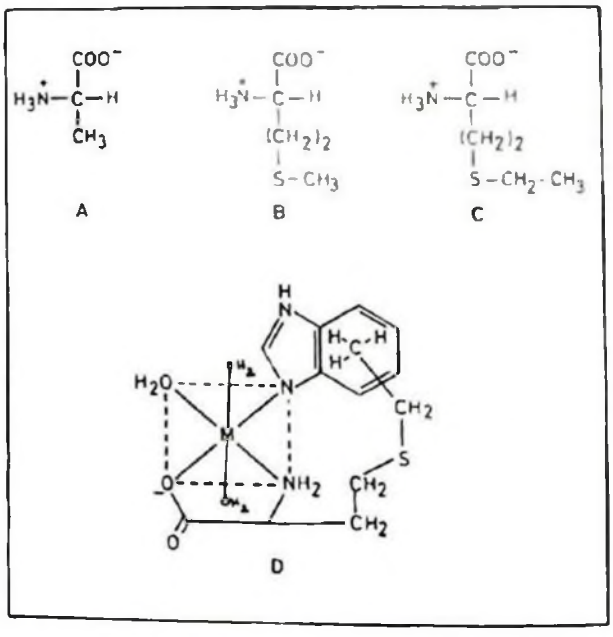


Fig. 1 Structures of the Ligands & Complex under study
A = L-alanine; B = L-methionine; C = L-Ethionine
D = A tentative structure showing intramolecular hydrophobic interaction in the ternary complex of $[(Bzm)\text{-}M\text{-}(Eth)]^+$

Table 1

Stability Constants & Other Derived Parameters

Medium 0.1 M KNO_3 in 40% dioxan-water Mixture; Temp 30°C

Metal Ion	Alanine Complexes log K	Δlog K	Methionine Complex log K	Δlog K	ΔΔlogK	Ethionine Complexes log K	Δlog K	ΔΔlog K	K_t	%(MLA)$_{III}$
Metal -amino acid Binary Complexes										
Co^{2+}	4.28±0.08	-	3.98±0.05	-	-	5.10±0.05				
Ni^{2+}	5.50±0.06	-	5.32±0.08	-	-	6.17±0.05				
Cu^{2+}	7.92±0.05	-	7.68±0.05	-	-	7.18±0.01				
Zn^{2+}	4.80±0.01	-	4.42±0.04	-	-	5.18±0.02				
Metal -(py)bzm- amino acid Ternary Complexes										
Co^{2+}	3.87±0.04	-0.41	3.55±0.04	-0.43	-0.02	4.81±0.05	-0.29	+0.12	0.318	24.12
Ni^{2+}	5.08±0.05	-0.42	4.93±0.03	-0.39	+0.03	5.98±0.02	-0.19	+0.23	0.698	41.10
Cu^{2+}	7.44±0.04	-0.48	7.21±0.04	-0.47	+0.01	6.98±0.05	-0.20	+0.28	0.905	47.50
Zn^{2+}	4.35±0.02	-0.45	3.94±0.02	-0.48	-0.03	4.94±0.05	-0.24	+0.21	0.621	38.30
Metal - bzm- amino acid Ternary Complexes										
Co^{2+}	4.01±0.06	-0.27	3.69±0.04	-0.29	-0.02	4.92±0.01	-0.18	+0.09	0.230	18.69
Ni^{2+}	5.25±0.03	-0.25	5.05±0.05	-0.27	-0.02	6.03±0.05	-0.14	+0.11	0.288	22.36
Cu^{2+}	7.71±0.06	-0.21	7.50±0.08	-0.18	+0.03	7.06±0.06	-0.12	+0.09	0.230	18.69
Zn^{2+}	4.57±0.05	-0.23	4.16±0.06	-0.26	-0.03	5.05±0.04	-0.13	+0.10	0.258	20.50

$\Delta\log K = \log K^{ML}_{MLA} - \log K^{M}_{MA}$ $\Delta\Delta\log K = \Delta\log K_1 - \Delta\log K_2$

where $\Delta\log K_2$ = M-L-Ala reaction; $\Delta\log K_1$ = Ternary const. with any other amino acid •

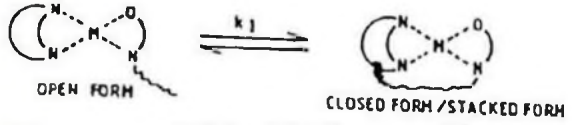
$K_t = 10^{\Delta\Delta\log K} - 1$; $\%(MLA)_{III} = 100 * K_t/(1+K_t)$; III indicates hydrophobic interaction

ethionine is large enough to interact hydrophobically with the benzene ring of benzimidazole or pyridine ring of 2(2'-pyridyl)benzimizadole. This intramolecular hydrophobic interaction in the ternary complexes of ethionine may lead to the modest increase in the stability of [(Bzm)-M-(Eth)]$^+$ or [(py-Bzm)-M-(Eth)]$^+$ complex. The extent of the intramolecular hydrophobic interaction in the ternary complexes should be dependent on the length and possibly also on the volume of the aliphatic side chain of amino acids.

A tentative structure of a ternary complex [(Bzm)-M-(Eth)]$^+$ is shown in Fig. 1. In this structure the CH_3 group of ethionine is located above the aromatic benzene ring of benzimidazole and these two ligands are linked together by the metal ion. In other words, the metal ion promotes the hydrophobic interaction.

Isomeric equilibria of M(bzm)(Aa) or M(py-bzm)(Aa) Complex

An intramolecular equilibrium exists between the "open form" (where no ligand-ligand interaction exists) and a "closed form" (where ligand-ligand interaction exists) in solution: the equilibrium between two isomers is indicated below:



OP M(Bzm)(AA) CL

The constant of this intramolecular (and therefore concentration independent) equilibrium is defined as:

$$K_I = \frac{[M(Bzm)(Aa)]_{Cl}}{[M(Bzm)(Aa)]_{Op}} \quad \ldots (1)$$

Unless K_I is very large, appreciable amounts of the open isomer is present in the mixture.

K_I can also be determined using the stability constants obtained from the potentiometric pH titrations using the equation 2.

$$K_I = \frac{10^{(\Delta \log K)expt}}{10^{(\Delta \log K)op}} - 1 \quad \ldots . (2)$$

In the above equation (Δlog K)expt is the experimentally determined value for the ternary complex in question, while (Δlog K)op is the corresponding value for a related ternary complex having no intramolecular hydrophobic interaction. As the intramolecular hydrophobic interaction in the complex [M(Bzm)(Alanine)]$^+$ is very small or even nonexistent. we may use the corresponding value of Δlog K as (Δlog K)op. K_I can be calculated using the equation 3.

$$K_I = 10^{\Delta\Delta \log K} - 1 \quad \ldots . (3)$$

where $\Delta\Delta \log K = \Delta \log K_1 - \Delta \log K_2$ ($\Delta \log K_1$ is for the reaction [M+L+Aa except alanine], $\Delta \log K_2$ is for the reaction [M+L+Alanine]. Alanine is taken as a reference with zero hydrophobic interactions because the Δlog K value with this ternary complex is as expected on just sfatistical considerations.

The percentage of hydrophobic interaction in these systems are calculated with the following relationship:

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

All the related parameters associated with the intramolecular hydrophobic interactions are included in the Table 1.

The Δlog K values of methionine are more or less same as that of alanine within the limits of experimental errors. Since

alanine complex is assumed to have no hydrophobic interaction, we can conclude that the behaviour of methionine is similar to alanine in its mixed ligand complexes. Methionine complex shows only a limited tendency for hydrophobic interactions [15].

The hydrophobic interaction in [(py-Bzm)-M-(Eth)]$^{+}$ or [(BZm)-M-(Eth)]$^{+}$ complex for the different metal ions follow the order: $Cu^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+}$, which is in conformity with the Irving Williams natural order of stabilities [16].

The extent of hydrophobic interaction is marginally more in (py)Bzm ternary complexes than the ternary complex of benzimidazole. This may be because the CH_3 group of ethionine in the (py-Bzm)-M-(eth) ternary complex overlaps on the pyridyl group which is bound to metal ion; but in benzimidazole complex, the overlapping is on benzene ring of benzimidazole.

ACKNOWLEDGEMENT

One of the authors (G. Usha Rani) is thankful to the Head, Department of Chemistry, Nizam College, for providing necessary research facilities. And UGC, New Delhi the award of JRF.

REFERENCES

1 (a) L. G. Marzilli and T. J. Kistenmacher, *Acc.Chem.Res.*, **10** (1977) 146; (b) C.C Chiang, T. Sorrell, T. J. Kistenmacher, and L. G. Marzilli, *J.Am.Chem.Soc.*, **100** (1978) 5102 and (c) G. Lancelot, R. Mayer and C. Helene, *J.Am.Chem.Soc.*, **101** (1979) 1569

2 (a) Y. Suzuki, K. Hara, T. Hirahara, *Bull.Chem.Soc.Jpn.*, **48** (1975) 2149; (b) G. Schwarz, T. J. Gilligan, *Biochemistry*, **16** (1977) 2835 and (c) T. M. Lohman, P.L. de Haseth and M.T.Jr. Record, *Biochemistry*, **19** (1980) 3522

3. J.B. Orenberg, B.E. Fischer and H. Sigel, *J.Inorg.Nucl.Chem.*, **42** (1980) 785

4 (a) Y. Suzuki, K. Hara, T. Hirahara, *Bull.Chem.Soc.Jpn.*, **48** (1975) 2342; (b) J. Reuben, *FEBS lett.*, **94** (1978) 20

5. H. Sigel, C.F. Naumann, *J.Am.Chem.Soc.*, **98** (1976) 730

6. J.C. Maurizot, G. Boubault and C. Helene, *Biochemistry* **17** (1978) 2096

7. P. R. Mitchell, B. Prijs and H. Sigel, *Helv.Chim.Acta.*, **62** (1979) 1723

8. H.H. Mantsch and K. Neurohr, *FEBS lett.*, **86** (1978) 57

9. E. Frieden, *J.Chem.Educ.*, **52** (1975) 754

10. H. Scheraga, *Acc.Chem.Res.*, **12** (1979) 7

11. Dev Das Manwal and Syed Aijaz Hussain, *Proc. Nat. Acad. Sci. India* **67(A) III** (1997) 301

12. S.Bhanumathi, A.V.Chandrapal and Dev Das Manwal, *Proc.Nat.Acad.Sci.India* **65(A) II** (1995) 157

13. G. Schwarzenbech, *Complexometric Titration*, **Interscience, New York** (1957) P. 77

14. L. G. van Uitert and C. G. Haas, *J.Am.Chem.Soc.*, **75** (1952) 451

15. B.E. Fischer and H. Sigel, *J.Am.Chem.Soc.*, **102** (1980) 2998

16. H. Irving and R. J. P. Williams, *J.Chem.Soc.* **(1953)** 3192