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Equilibrium Studies on Binary and Ternary Complexes of Transition Metal Ions Containing Substituted Pyrimidines

V. RAVINDER REDDY, SHIVARAJ and K. VENUGOPAL REDDY*
Department of Chemistry, Osmania University, Hyderabad-500 007, India

Equilibrium studies on the formation of binary MA and ternary MAL complexes [where M = Co(II), Ni(II), Cu(II) and Zn(II); A = orotic acid (OA) and isoorotic acid (IOA); L = alanine (ala) phenylalanine (phala) tryptophan (trypt) 2,2′-bipyridyl (bipy) and *o*-phenanthroline (*o*-phen)] have been carried out in aqueous medium using pH-metric technique at 25, 35, 45 ± 1°C and 0.1 M (KNO_3) ionic strength. All metal ions were formed 1 : 1 and 1 : 1 : 1 ternary complexes. The thermodynamic parameters ΔH_f^o, ΔG_f^o and ΔS_f^o associated with binary and ternary complex systems were calculated and discussed. The relative stabilities of ternary complexes are quantitatively expressed in terms of the statistical parameter Δ log K. The results were discussed in the light of the basicity of ligands, statistical aspects, electrostatic interactions, denticity, stacking interactions, nature of donor sites and stereochemical aspects. The concentration profiles have indicated the favourability of the formation of binary and ternary complexes in general as reflected in the Δ log K values.

Key Words: **Equilibrium studies, Binary, Ternary, Transition metal, Complexes, Pyrimidines.**

INTRODUCTION

The interaction of metal ions with purines and pyrimidines gained much interest as these bases constitute the backbone of DNA and RNA molecules. The study of interaction between metal ions and several pyrimidine and purine analogs has attracted much attention[1–5] for the last few years because the determination of metal-ligand binding sites is an early step in clarifying the biological role played by metal ions in many living systems[6–8]. Taqui Khan and Krishnamoorthy reported the stability of 1 : 1 chelates of monosubstituted and disubstituted purines[9, 10] and pyrimidines[11–14] with transition metal ions in aqueous medium at 45°C and $\mu = 0.10$ M (KNO_3). Considerable work has been carried out on the complexes of substituted purines and pyrimidines with a number of metal ions in the solid state[15–18]. The present paper reports the formation constants of binary and ternary complexes of orotic acid (2,4-dioxy-6-carboxylic pyrimidine) and isoorotic acid (2,4-dioxy-5-carboxylic pyrimidine) with bivalent transition metal ions in the presence of some other ligands (L) containing N,N and N,O donor sites in aqueous medium. The required dissociation constants and formation constants of other ligands with Co(II), Ni(II), Cu(II) and Zn(II) were determined under the present experimental conditions and the values thus obtained were found to be in good agreement with literature values.

EXPERIMENTAL

The ligands orotic acid and isoorotic acid were obtained from Sigma Chemical Co., U.S.A. 2,2′-Bipyridyl (bipy), *o*-phenanthroline (*o*-phen), alanine (ala), phenylalanine (phala) and tryptophan (trypt) were obtained from E. Merck. For binary complexes, the metal ligand ratios were kept 1 : 1 and 1 : 2. For studying the mixed ligand complexes the primary ligand, secondary ligand and metal ion ratios were kept 1 : 1 : 1. The acid dissociation constants of ligands, stability constants of binary and ternary complexes were calculated by direct algebraic method[19] by known equations. The results obtained (with an accuracy of ±0.06 log units) are listed in Tables 1 and 2. The distribution of various species as a function of pH were calculated by using BEST[20] computer program for binary and ternary complexes.

TABLE-1

STABILITY CONSTANTS AND THERMODYNAMIC PARAMETERS OF BINARY 1 : 1 METAL(II) OROTIC ACID AND ISOOROTIC ACID AT 0.1 M KNO_3 (25°C)

Ligand	pKa_1	pKa_2	log K	ΔH_f° (kcal/mol)	ΔG_f° (kcal/mol)	ΔS_f° (eV)
Cu(II)-OA	2.77	9.57	9.52	–2.59	–12.98	+34.86
Ni(II)-OA	2.77	9.57	7.10	–9.18	–9.68	+1.69
Zn(II)-OA	2.77	9.57	6.21	–6.08	–8.47	+8.03
Co(II)-OA	2.77	9.57	6.10	–4.39	–8.32	+13.19
Cu(II)-IOA	4.43	9.06	6.45	–5.83	–8.79	+9.94
Ni(II)-IOA	4.43	9.06	5.17	–5.82	–7.05	+4.15
Zn(II)-IOA	4.43	9.06	4.71	–5.24	–6.42	+3.96
Co(II)-IOA	4.43	9.06	4.28	–4.15	–5.48	+5.67

Values are accurate to ±0.06 log K.

TABLE-2

STABILITY CONSTANTS AND Δ log K VALUES AT 0.1 M KNO_3 (25°C)

	log K				Δ log K			
	Co(II)	Ni(II)	Cu(II)	Zn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)
M(II) OA ala	10.10	11.95	14.95	10.92	–0.57	–0.48	–2.77	–0.41
M(II) OA phala	10.57	12.31	16.38	11.60	0.26	0.05	–1.07	0.66
M(II) OA trypt	10.22	12.10	17.14	11.63	–0.40	–0.53	–0.74	0.25
M(II) OA bipy	5.50	6.55	6.90	6.09	–0.60	–0.55	–2.62	–0.12
M(II) OA phen	5.52	6.17	6.90	5.60	–0.58	–0.93	–2.62	–0.61
M(II) IOA ala	8.76	10.52	12.02	10.40	–0.09	–0.02	–2.65	10.57
M(II) phala	9.10	11.07	13.96	10.54	0.61	0.74	0.42	–1.10
M(II) IOA trypt	9.02	10.62	13.86	10.56	0.22	–0.08	–0.95	0.68
M(II) IOA bipy	4.26	4.56	5.90	4.38	–0.02	–0.61	–0.55	–0.33
M(II) IOA phen	4.50	4.63	6.46	4.47	–0.22	–0.54	0.01	–0.24

RESULTS AND DISCUSSION

Binary systems: The first dissociation of orotic acid and isoorotic acid (H_2L) involves the removal of a proton from the carboxyl group. H_2L^- is a weak acid and exists in a 1 : 1 mixture of enol and the diketo form in alkaline solution[21] in the neutral medium. They predominantly exist in the diketo form[22] in neutral medium. Since the second proton dissociation is not known with certainity, charge distributions of orotic and isoorotic acid are tentatively shown as delocalized on N_1 and N_3 atoms and C_2 and C_4 oxygen atoms.

Due to the presence of many potential binding sites the earlier studies report that coordination to the metal occurs *via* one oxygen atom of the carboxylate group and the N(I) nitrogen forming five-membered ring in the case of orotic acid and six-membered chelate ring in the case of isoorotic acid[23–29]. ^{13}C and ^1H NMR studies of metal isoorotic acid[30] show the downfield shift of C_6 carbon atom of the ring and also downfield shift of the proton attached to the C_6 carbon atom. This fact may be an indicative of the involvement of the N_1 atom in the metal-ligand bond. The dissociation constants and stability constants of binary complexes are presented in Table-1. The stabilities of the 1 : 1 metal-orotic acid and metal-isoorotic acid were increased in the order Co(II) < Ni(II) < Cu(II) < Zn(II) in accordance with the Irving-William's natural order. 1 : 1 Metal-orotic acid complexes are more stable than 1 : 1 metal-isoorotic acid complexes suggesting that the five-membered chelate ring is more stable than the six-membered chelate ring[31]. In order to understand the chelating behaviour of ligand with metal ion, the species distribution curves for major species as a function of pH for M(II)-OA and M(II)-IOA binary systems was obtained by using computer program BEST[20].

In order to see the effect of temperature on stabilities of binary complexes, the metal-ligand equilibria were studied at different temperatures, *viz.*, 25, 35, 45 ± 0.1°C. The stability constants of these chelates decreased with increase in temperature indicating that the formation equilibria are exothermic and spontaneous in nature. For both metal-orotic acid and metal-isoorotic acid enthalpy change (ΔH_f°) values are negative and entropy change (ΔS_f°) values are positive. The overall change in ΔH_f° and ΔS_f° values indicates that the complexes are stabilized by both enthalpy and entropy. The magnitude of ΔH_f° and ΔS_f° values indicates that the entropy is playing a dominant role in the formation of complexes.

Ternary Systems: In the mixed ligand 1 : 1 : 1 M(II)-OA or IOA and ala, phala or trypt systems the complex formation is simultaneous, whereas the complex formation for 1 : 1 : 1 M(II)-OA or IOA and bipy or *o*-phen is stepwise. The stability constants of ternary complexes are presented in Table-2. The $\Delta \log K$ values for metal OA or IOA acid and ala are negative or less positive, while in the case of phala, trypt, the $\Delta \log K$ values are positive whereas for Cu(II) systems the $\Delta \log K$ values are more negative. The $\Delta \log K$ values for the systems involving *o*-phen or bipy are negative. The stability of the metal-orotic acid or isoorotic acid ala, phala, trypt, systems decrease in the order Cu(II) > Ni(II) > Zn(II) > Co(II). In general, 1 : 1 : 1 metal-IOA-L systems are more stable than

1 : 1 : 1 metal-OA-L as seen from $\Delta \log K$ values. The more negative values for the ternary complexes of OA compared to IOA may be due to the higher stability of its binary complexes and reduced number of coordination sites. Ternary system containing one 5-membered ring and one 6-membered ring is more stable than a system containing two 6-membered rings. For the two ternary 1 : 1 : 1 systems the $\Delta \log K$ values are negative (Table-2) indicating that these systems are less stable than the binary 1 : 1 metal orotic or isoorotic acid. This is in accord with statistical considerations. The negative $\Delta \log K$ values do not mean that the complexes are not formed. The aromatic substitution on the side chains of the amino acids can promote stacking interactions between π-electrons of isoorotate anion and the anion of amino acid which would enhance the complex stability.

The charge transfer and hydrophobic or stacking interactions between aromatic moieties play an important role in biological systems. The ternary systems reported in this investigation clearly show the dominant influence which a primary ligand already attached to a metal ion exerts upon the interaction of that metal ion with an incoming secondary ligand. Tentative structures of M(II)-OA-ala and M(II)-IOA-phala complexes are shown in Figs. 1 and 2.

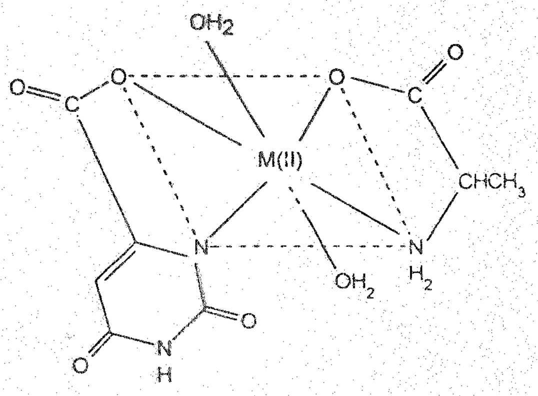

Fig. 1

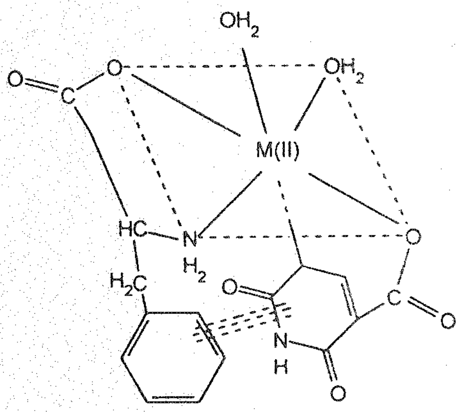

Fig. 2

Comparing the enthalpies of the 1 : 1 : 1 systems containing metal orotic acid or isoorotic acid and L it is clear that the enthalpies of the ternary system do not follow the regular trend. This irregular trend may be due to difference in the solution energies of the ligands involved in the mixed ligand complex formation. The less positive entropy values are responsible for the lower stability of ternary systems as compared to binary systems.

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