

Studies of stability constant on ternary chelates of bivalent zinc (II) metal ion with aspartame and ethambutol hydrochloride as primary ligands and amino acids as secondary ligands

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ABSTRACT

The stability constant of (1:1:1) ternary chelates of bivalent zinc (II) metal ion with some biomolecules (drugs) such as aspartame (L_4) and ethambutol hydrochloride (L_7) as primary ligands and amino acids, such as Leucine (R_3) and phenylalanine (R_6) as secondary ligands have been carried out in 20% (v/v) ethanol - water medium pH-metrically at 30°C and 0.1 M (NaClO_4) ionic strength. The stability constants of binary complexes ML and ML_2 are also determined under similar experimental conditions. The stability constants of ternary complexes are evaluated and their relative stabilities compared to the corresponding binary complexes are expressed in terms of statistical parameters $\Delta \log K$, K_R , K_L and K_p . Formation of complex species with respect to pH have been discussed by Irving-Rossotti technique and evaluated by using the computer SCOGS program.

Keywords: Biomolecules, binary complex, ternary complex, stability constant, SCOGS.

INTRODUCTION

Metal complexes play a vital role in nature. Recently, there has been considerable interest in the study of binary and ternary complexes by pH-metric method [1-3] using biomolecules (drugs). Drugs have various functional groups present in its structure, which can bind to metal ions present in human body.[4] Metal complexes of drugs are found to be more potent than parent drugs.[5] Chemistry of drugs attracts many researchers because of its applications in medicinal chemistry. Interesting results have been reported earlier on complex formation reactions of drug-amino acid-metal ion, mixed ligand complexes.[6-10] The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity. Metal Complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc. The present investigation aims the pH-metric study of $\text{Zn}[\text{II}]$ complexes with ethambutol hydrochloride (L_7) chemically known as (+) 2, 2' -(ethane-1,2 diylidimino)dibutan-1-ol is an anti-tubercular drug.[11] Aspartame (N -(1- α -aspartyl)-l-phenylalanine-1-methyl ester) (L_4) is a dipeptide of aspartic acid and phenylalanine, used as an artificial, non-saccharide sweetener in the pharmaceutical and food industry as primary ligands and amino acids, leucine and phenylalanine as secondary ligands.

MATERIALS AND METHODS

Drug sample of ethambutol hydrochloride and aspartame in pure form were obtained from pharma industries. Ethanol was purified as described in literature.[12] Double distilled water was used for the preparation of ethanol-water mixture and stock solution of aspartame and ethambutol hydrochloride. All chemicals NaOH , NaClO_4 , HClO_4 and metal salts were of Analar grade. The solutions used in the potentiometric titrations were prepared in double distilled water. The NaOH solution was standardized against oxalic acid solution (0.1 M) and then standard alkali

solution was used for standardization of HClO₄. The metal salt solutions were also standardized using EDTA titrations.[13] Experimental procedure by potentiometric titration technique, involves the titration of carbonate free solution of

- (1) Free HClO₄ (A),
- (2) Free HClO₄ + Ligand-Drug,
- (3) Free HClO₄ + Ligand-Drug + Metal ion,
- (4) Free HClO₄ + Ligand-Amino acid,
- (5) Free HClO₄ + Ligand-Amino acid + Metal Ion,
- (6) Free HClO₄ + Ligand-Drug + Ligand-Amino acid + Metal Ion,

Against standard solution of sodium hydroxide, with drug ethambutol hydrochloride or aspartame and amino acids. The total volume of solution was kept 50 ml by the adding distilled water. Titrations were carried out using a digital pH meter (Elico model (LI-127) in conjunction with combined glass electrode. The ionic strength of solutions was maintained constant i.e. 0.1 M by adding appropriate amount of 1M sodium perchlorate solution. Titrations were carried out in 20% (v/v) ethanol-water medium at 30°C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrode to expel out CO₂. The proton-ligand and metal-ligand binary formation constants were determined by Irving-Rossotti method.[14] The formation constants and various statistical parameters of ternary complexes were evaluated by using computer program SCOGS.[15,16]

RESULTS AND DISCUSSION

(a) Binary metal complexes

Proton ligand stability constant of Primary ligand and secondary ligand have been determined by Irving-Rossotti [14] method .Their metal-ligand formation constants were also determined for the comparison with those of the ternary system. For this we have given emphasis on studies of binary systems under identical condition with those for ternary systems. The values are presented in Table 1. Primary ligand and secondary ligand both forms ML and ML₂ complexes with Zn (II) ions. The stabilities of binary complexes are found to be ML>ML₂ as expected on statistical grounds.[17]

Table 1: Proton-ligand and metal-ligand stability constants in binary system

Ligands	pK ₁	pK ₂	logK ₁	logK ₂
Aspartame (L ₄)	3.6134	8.3301	5.1328	3.5967
Ethambutol hydrochloride (L ₇)	-	6.3248	5.6016	5.3962
Leucine (R ₃)	2.1333	10.4844	4.2980	4.0720
Phenyl alanine (R ₆)	2.2157	9.2296	4.3554	3.6213

(b) Ternary metal complexes

Only ternary complex (1:1:1) have been used in this study to ensure the exclusive formation of the simplest ternary complex MLR. By considering the proton-ligand and metal-ligand constants of ligands, the species that exist in complexation equilibria have been plotted in figures 1,2,3,4 as a function of pH. The parameters K_L , K_R , K_f and $\Delta \log K$ are generally used to indicate the relative stability of ternary complexes as compared to the binary complexes. In all the ternary systems, distinct inflections were observed in the titration curves, indicating the formation of chelates. Formation of ternary complexes was further confirmed from the non-superimposable nature of theoretical composite curves on the experimental curve in the region of ternary complex formation. The species distribution curves, as a function of pH were generated using the computer program SCOGS, also supports the formation of ternary chelates. Similarly the percentage curves of the species FM, FL and FR are shows that the initial concentration of free metal is decrease with increasing pH. This indicates that all of the metal is in bound state in the form of binary and ternary complexes.

The free ligand concentration of FL and FR show slight increase during the process with increasing pH. This may be attributed to the dissociation of slight excess ligands present in the system.

In case of R₃L₄Zn(II) system. Fig.1.shows that, The initial percentage concentration of ternary complex MLR is 15.7 at pH 2.3 and then slowly increases until it reaches to maximum value i.e. about 40 percent at pH 5.1. The percentage of H₂L and MR represented by C₁ and C₇ are highest at the initial stage i.e. 48 and 46 respectively. The concentrations of these species decrease with pH and reaches to minimum value at pH 4.0. The decreasing trend of these species indicates that they are utilized in the formation of ternary complex. This is supported by the increasing concentration of the ternary complex in the same pH range. The concentration of ternary complex species also

reaches to its maximum value at pH 4.0. After this pH, the formation rate becomes slow and tends to about constant value.

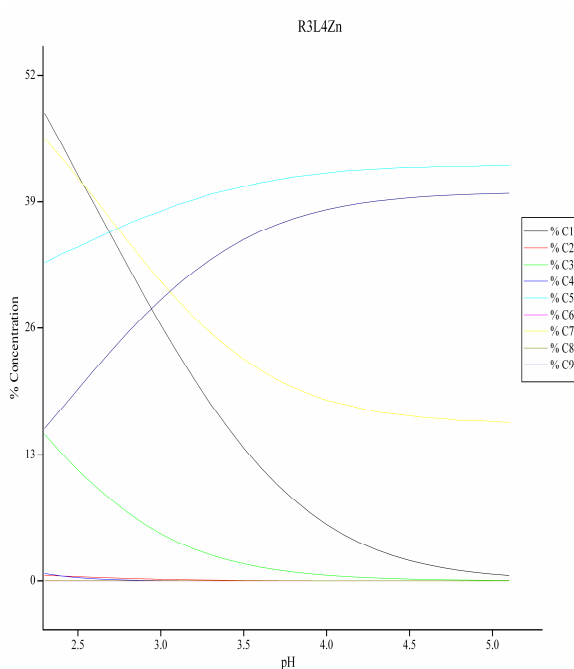


Figure 1

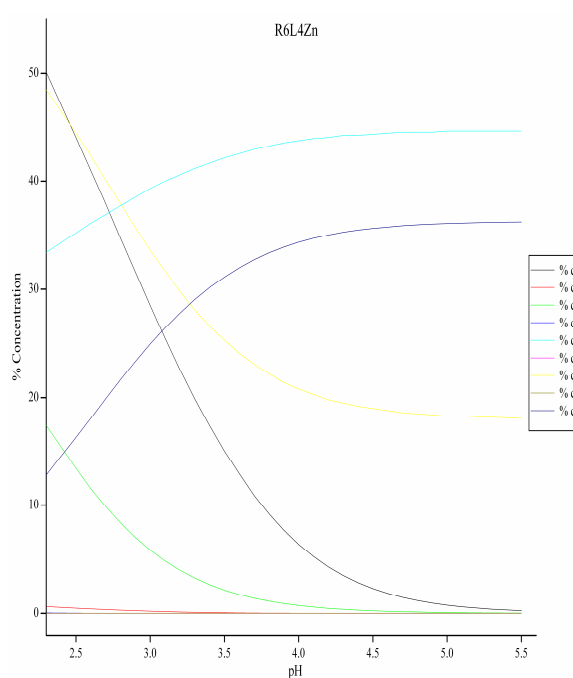


Figure 2

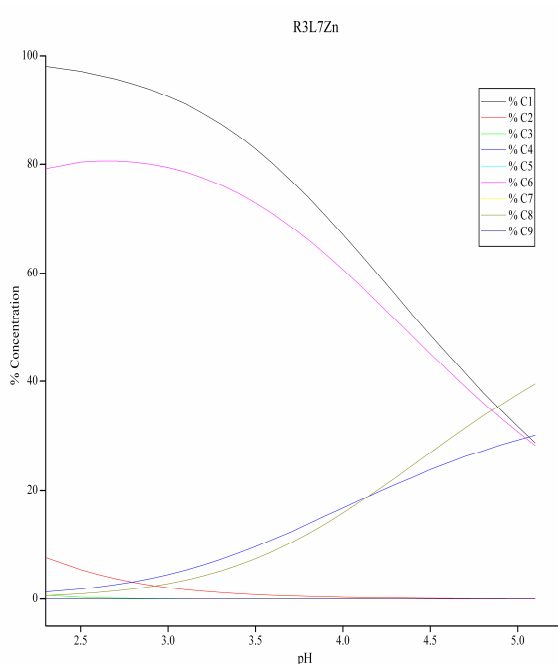


Figure 3

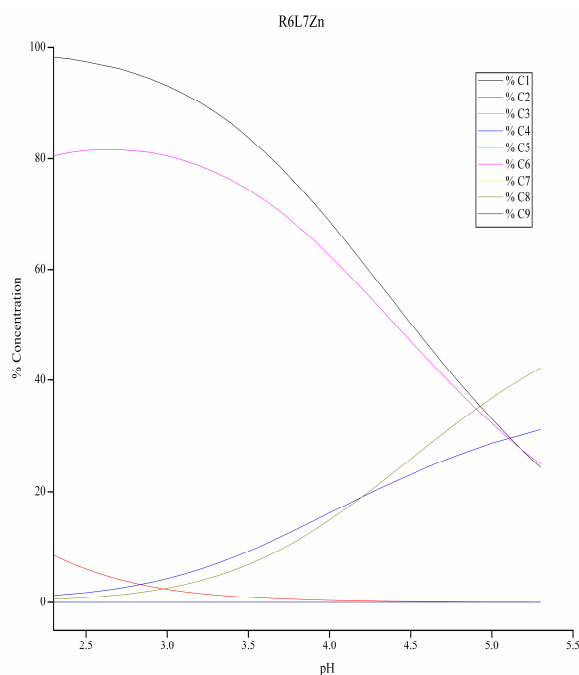


Figure 4

From this observation it may be concluded that the initial higher concentration of primary ligand sharply decreases because of its rapid dissociation resulting in to the formation of free ligand L. This species then interacts with MR to give final product MLR. The decrease in concentration of primary ligand is more as compared to that of MR. It practically reaches to zero at pH 5.1. Therefore it may be concluded that the excess formation of free primary ligand (L) species might be utilized in the formation of ML since its concentration also increases with increasing pH. The initial concentration of ternary complex i.e. 15.7 is due to the initial reaction between M, L and R. The mechanism

of formation of ternary complex by different equilibria discussed in previous Zn(II) system is totally applicable to $R_6L_4Zn(II)$ system and the stability constant of this complex is 8.74 which is smaller than $R_3L_4Zn(II)$ system.

In case of $R_3L_7Zn(II)$ system. Fig.3.shows that, The initial percentage of ternary complex MLR is 0.607 at pH 2.3 and then increases until it reaches to maximum value i.e. about 40 percent at pH 5.1. The percentage of HL and MR represented by C_1 and C_6 are highest at the initial stage i.e. 98 and 79 respectively. The concentrations of these species decrease with pH and attain minimum value at pH 5.1. The decreasing trend of these species indicates that they are utilized in the formation of ternary complex. This is supported by the increasing concentration of the ternary complex in the same pH range.

From this observation it may be concluded that the higher concentration of primary ligand sharply decreases because of its rapid dissociation resulting in to the formation of free ligand L. This species then interacts with MR to give final product MLR. The decrease in concentration of primary ligand is more as compared to that of MR. Therefore, it may be concluded that the excess formation of free primary ligand (L) species might be utilized in the formation of ML since its concentration also increases with increasing pH. The initial concentration of ternary complex i.e. 0.607 is due to the initial reaction between M, L and R.

The mechanism of formation of ternary complex by different equilibria discussed in previous Zn(II) system is totally applicable to the $R_6L_7Zn(II)$ system and the mixed ligand stability constant of this complex is 9.46 which is greater than Zn(II)- L_7 - R_3 system.

Table 2: Stability constants in ternary complexes of Zn(II).

L	R	β_{111}	β_{02}	β_{20}	K_L	K_R	K_r	$\Delta \log K$
L_4	Leucine (R_3)	9.1777	8.37	8.7295	4.0449	4.8797	1.2559	-0.2531
L_4	Phenylalanine (R_6)	8.7371	7.9767	8.7295	3.6043	4.3817	0.768	-0.7511
L_7	Leucine (R_3)	8.6731	8.37	10.9978	3.0715	4.3751	-2.022	-1.2265
L_7	Phenylalanine (R_6)	9.457	7.9767	10.9978	3.8554	5.1016	-0.061	-0.5

It has been observed from Table 2 that the stability constant of ternary complex of L_4 is found to be higher than L_7 in case of Leucine whereas stability constant of L_4 is less than L_7 in case of Phenylalanine. The result shows that ternary complex formation is less favoured over corresponding binary 1:1 complexes. It is possible due to availability of less number of coordination sites for secondary ligands on primary complex ML than on free metal ion.[18,19]

CONCLUSION

It is observed that the negative $\Delta \log K$ values indicate that the ternary complexes are relatively less stable than 1:1 binary complexes of primary as well as secondary ligands.

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