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Formation of binary and ternary complex of Cu(II) with ethambutol hydrochloride and aspartame as primary ligands and amino acid as secondary ligands

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ABSTRACT

The stability constant of (1:1:1) ternary chelates of bivalent Cu(II) metal ion with some 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 30^0C and 0.1 M (NaClO4) 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_r. Formation of complex species with respect to pH have been discussed by Irving-Rossotti technique and evaluated by using the computer SCOGS program.

KEYWORDS

Drugs;
Binary complex;
Ternary complex;
Stability constant;
SCOGS.

INTRODUCTION

Recently, there has been considerable interest in the study of binary, ternary and quaternary complexes of drug molecules by pH metric method[1-4]. The main motive of this work is to lower the side effects while maintaining similar or higher efficacy then the parent drug. The literature survey reveals that very little work of ternary complexes of transition metals with drugs and amino acids have been reported in the past[5-7].

Copper is essential in all plants and animals. The human body contains at a level of about 1.4 to 2.1 mg/kg weight of human body[8]. Copper is distributed in the body and occurs in liver, muscle and bone. Copper is transported in the blood stream on a plasma protein called ceruloplasmin. Copper metabolism and excretion is controlled delivery of copper to the liver by ceruloplasmin, where it is excreted in bile.

Copper is found in a variety of enzymes, like cytochrome oxidase and superoxide dismutase. The recommended dietary allowances for copper in normal healthy adults is 0.9 mg/day[9]. Because of its role in fecilatating iron uptake, copper deficiency can often produce anemia like symptoms. In humans, the symptoms of Wilson's disease are caused by an accumulation of copper in body tissues. In addition to its enzy-

matic roles, copper is used for biological electron transport. The blue copper proteins that participate in electron transport include azurin and plastocynin.

Ethambutol hydrochloride chemically known as (+) 2, 2'-(ethane-1,2-diyldiimino) dibutan-1-ol is an antitubarcular drug[10]. It is white, crystalline powder with molecular formula $C_{10}H_{24}N_2O_2$. HCl. Studies on metal complexes of ethambutol are largely limited to copper[11,12] with isolated reports on other metals like Zinc and Platinum[13,14].

Aspartame (N-(L-α-aspartyl)-L-phenylalanine-1-methyl ester) is a dipeptides of aspartic acid and phenylalanine, used as an artificial, non-saccharide low-calorie sweetener in the pharmaceutical and has been approved as a food additive[15] and appears to relieve pain, induce mild antithrombotic effects in humans and decrease fever in animals[16].

Hence the present paper deals with the systematic study of Cu(II) complex with ethamutol hydrochloride and aspartame as primary ligands (L), Amino acids as secondary ligands (R), in 20% ethanol-water mixture.

EXPERIMENTAL

Drug sample of ethambutol hydrochloride and aspartame in pure form were obtained from pharma industries. Ethanol was purified as described in literature[17]. 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 A.R. 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 $HClO_4$. The metal salt solutions were also standardized using EDTA titrations.[18] 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 Co_2. The proton-ligand and metal-ligand binary formation constants were determined by Irving-Rossotti method[19]. The formation constants and various statistical parameters of ternary complexes were evaluated by using computer program SCOGS[20,21].

RESULTS AND DISCUSSION

Binary metal complexes

Proton ligand constant of Primary ligand L_4,L_7 and secondary ligand R_3,R_6 have been determined by Irving-Rossotti technique. 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 ML_2 complexes with Cu(II) ions.

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	9.1612	6.7708
Ethambutol hydrochloride (L_7)	-	6.3248	9.7215	8.3901
Leucine (R_3)	2.1333	10.4844	9.0482	6.1789
Phenyl alanine (R_6)	2.2157	9.2296	9.8462	7.1209

Ternary metal complexes

Only 1:1:1 ternary complex 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

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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_r and $\Delta \log K$ are generally used to indicate the relative stability of ternary complexes as compared to the binary complexes.

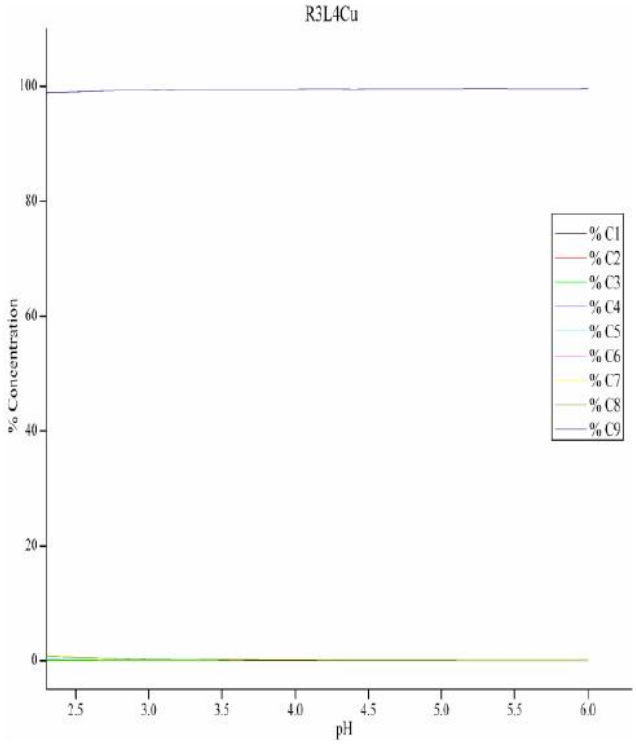

Figure 1

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-superimposible 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 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 $R_3L_4Cu(II)$ system Figure 1 shows that, the nature of speciation curves except the species MLR i.e. mixed ligand complex, all other are at negligible concentrations even at the initial pH and further decreases to attain zero value. The concentration of ternary complex at beginning is maximum i.e. 98.9 and then increases slowly to reach to 99.6%. From this observation it may be concluded that the formation of ternary complex has been fully completed at the initial pH and there is no any other equilibria further involved in its formation. It may be attributed to the fact that the stability constant of this complex is very high and the lower pH is favourable for its formation. The mechanism of formation of ternary complex by different equilibria discussed in previous Cu(II) system is totally applicable to $R_6L_4Cu(II)$ system and the stability constant of this complex is 17.76 which is smaller than $R_3L_4Cu(II)$ system.

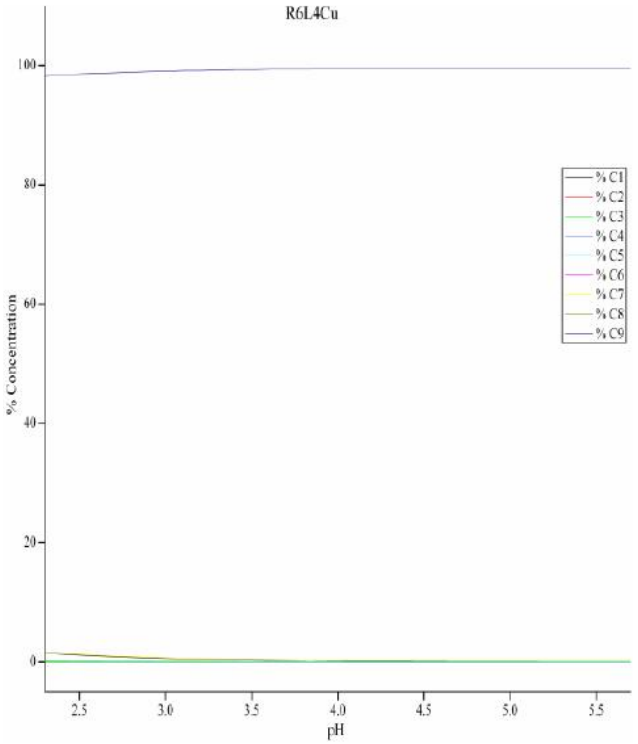

Figure 2

In case of $R_3L_7Cu(II)$ system (Figure 3). The nature of speciation curves shows that except the species HL, MR and MLR, all others are at almost negligible concentration even at the initial pH 2.3 and further decreases to attain zero value. Therefore, these species do not involve in the formation of ternary complex after pH 2.3. From the values of different species it can be concluded that the concentration of ternary complex at beginning is maximum i.e. 96.7 percent and then in-

creases slowly to reach to 99.8% at pH 5.7.

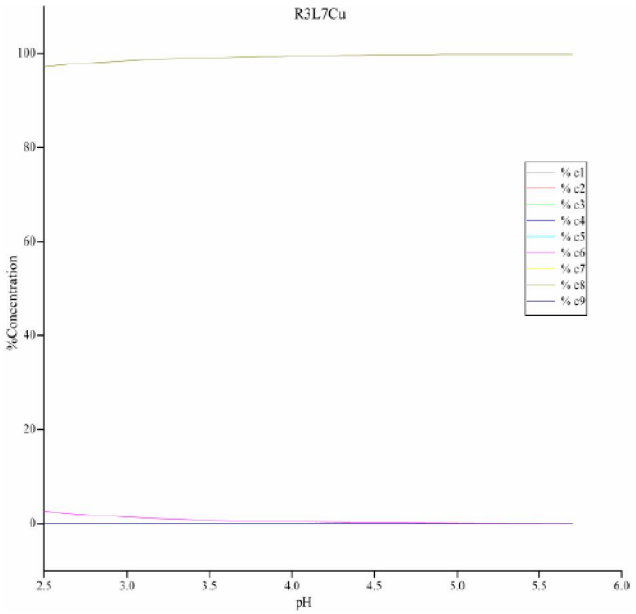

Figure 3

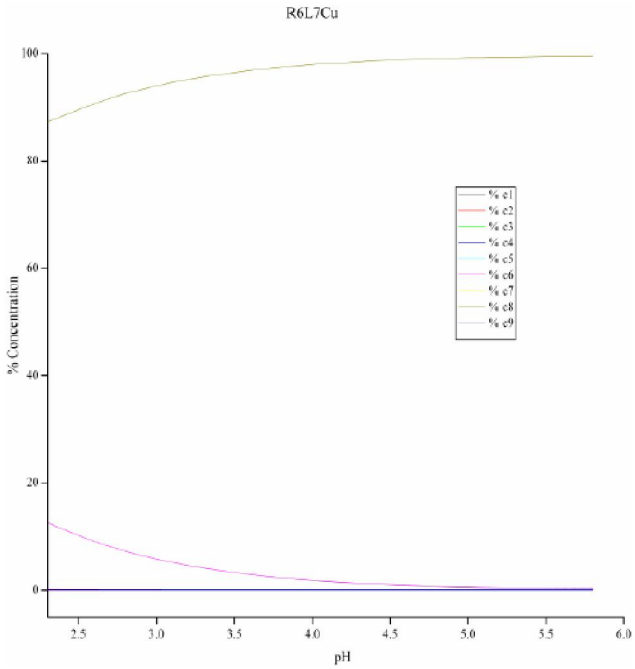

Figure 4

The percentage of HL and MR represented by C_1 and C_6 is 3.15 of both the species at the initial stage. The concentration of these species decreases with pH and reaches to minimum at pH 3.4. The decreasing trend of these species indicates that they are utilize in the formation of ternary complex. This is supported by the increasing concentration of the ternary complex from 96.7 to 99.8 percent in the same pH range. From this observation it may be concluded that the concentration of primary ligand decreases because of its dissociation, resulting in the formation of free ligand L. This species then interacts with MR to give final product MLR. This can be further supported by the observation that the rate of disappearance of these species is approximately same as that of the formation of mixed ligand complex. The stability constant of this complex is very high and the lower pH is favourable for its formation. The mechanism of formation of ternary complex of $R_6L_7Cu(II)$ system can be explained as similar to that of the previous system. The change in secondary ligand does not affect the mechanism of complex formation as well as the extent of its formation. The only difference between these two complexes is that the stability constant of first complex is less than that of second one.

It has been observed from TABLE 2 that the stability constant of ternary complexes of L_4 is found to be less than L_7. The result shows that ternary complex formation is less favoured over corresponding binary ML 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[22,23].

TABLE 2: Stability constants in ternary complexes of Cu(II)

L	R	β_{111}	β_{02}	β_{20}	K_L	K_R	Kr	ΔlogK
L_4	Leucine (R_3)	17.9589	15.2271	15.932	8.7977	8.9107	4.7587	-0.2505
L_4	Phenylalanine (R_6)	17.757	16.9671	15.932	8.5958	7.9108	2.6149	-1.2504
L_7	Leucine (R_3)	18.7696	15.2271	18.1116	9.0481	9.7214	4.2005	-1E-04
L_7	Phenylalanine (R_6)	19.3177	16.9671	18.1116	9.5962	9.4715	3.5567	-0.25

CONCLUSION

It is observed that the negative 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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