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Der Pharmacia Sinica, 2015, 6(5):71-74

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Equilibrium studies on mixed ligand complexes of drug amitriptyline hydrochloride with copper and zinc metal ions

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ABSTRACT

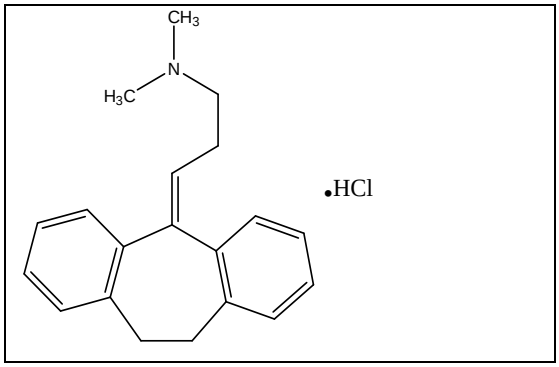
Equilibrium studies on metal-ligand complex equilibria involving Copper(II) and Zinc (II)metal ions with drug, Amitriptyline HCl with Amino acids Isoleucine and Glutamic acid in 20% (v/v) ethanol-water mixture at $30^0C \pm 0.1^0C$ and ionic strength of 0.1M ($NaClO_4$) has been studied. Formation of complex species with respect to pH have been discussed by Irving-Rossotti technique and evaluated by SCOGS computer programme.

Keywords: Equilibrium constant, Ionic strength, pH, ΔlogK, SCOGS.

INTRODUCTION

Complex formation of metal ions of biological importance with drug and amino acid and their derivatives are of great significance as many of these systems can offer simple model of complexes of metal drug and amino acid equilibria in different enzymatic processes. Drugs have various functional groups present in their structure, which can bind to metal ions present in human body.[1]Chemistry of drugs attract many researchers because of its applications in medicinal study. Interesting results have been reported earlier on complex formation reactions of drug-amino acid-metal ion mixed ligand complexes.[2-6]

Expecting some useful information on mixed ligand complexes a detailed pH metric study involving drug Amitriptyline HCl with Copper(II) and Zinc (II) metal ions has been carried out and discussed with results.



Amitriptyline Hydrochloride

MATERIALS AND METHODS

All the reagents used were of A.R. grade and all the solutions were prepared in 20%(v/v) ethanol-water mixture and standardized by known procedures.[7]Titrations were carried out using a digital pH meter (Elicomodel LI-127) in conjunction with combined electrode. All titrations were carried out at $30^0C \pm 0.1^0C$ temp. All sets of solutions were titrated against 0.2N sodium hydroxide solution. The titration curves were plotted by using the experimental data. On the basis of these plots, proton ligand and metal-ligand formation constants were calculated. Concentrations of total metal, total ligands, free metal, free ligands and various possible species that are formed during the complexation are calculated by using SCOGS computer program.[8-9]

RESULTS AND DISCUSSION

Binary complexes

Amitriptyline HCl is a tricyclic antidepressant drug and chemically known as 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-ylidene)-*N*,*N*-dimethylpropan-1-amine.[10] It is used for the treatment of several psychiatric disorder.[11-13]

These types of tricyclic also ease migraines, tension, headaches, anxiety attacks and some schizophrenic symptoms. The protonation constants (pKa) Amitriptyline HCl, amino acids isoleucine and Glutamic acid and their metal-ligand formation constants (LogK) have been determined (Table1).

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

Ligands	pK_1	pK_2	Cu(II) M_1		Zn(II) M_2	
			$LogK_1$	$LogK_2$	$LogK_1$	$LogK_2$
Amitriptyline HCl	7.39	--	--	2.7901	2.9296	3.0936
Isoleucine	2.5335	9.7256	9.5442	6.6896	4.2821	3.4403
Glutamic acid	2.5872	4.9984	10.293	8.3329	5.0977	4.2894

Proton ligand constant of primary ligand L_1 and secondary ligand R_4 and R_7 have been determined by Irving-Rossotti technique. Their metal ligand formation constants were also determined for comparison with those of the ternary system. For this we have given emphasis on studies of binary system under identical condition with those of the ternary system. The primary ligand amitriptyline hydrochloride and secondary ligand, Isoleucine, bothform1:1and1:2 complexes with Cu(II) and 1:1and1:2 complexes with Zn (II).

Mixed ligand complexes

The study of ternary complexes in solution provides simple models for more complicated biochemical reactions. [14-17]Complexes in which metal ion has two or more types of ligands in its coordinating sphere are called as mixed ligand complexes.

Figure: 1. Cu (II)-L_1-R_4

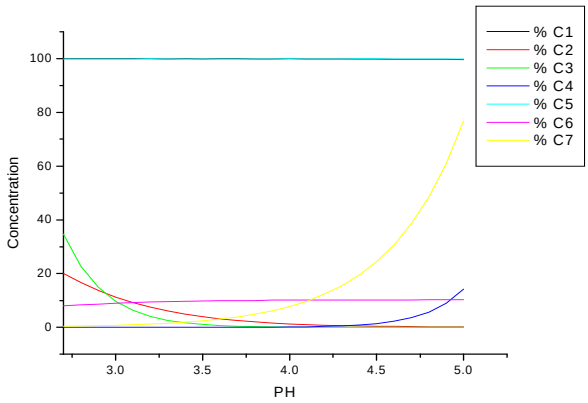
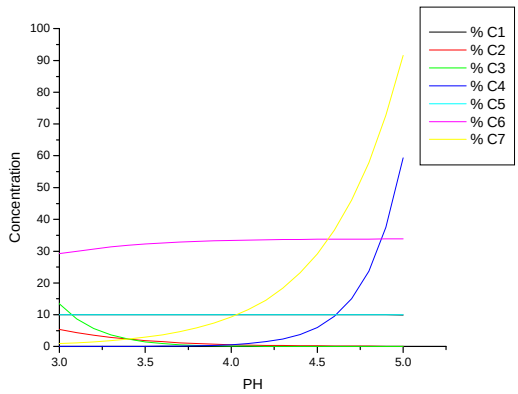


Figure: 2. Cu (II)-L_1-R_7



In case of Cu (II)-L_1-R_4, the nature of speciation curves shows that 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 minimum i.e. 0.396 % and then increases slowly to reach to 76.7%. 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 favorable for its formation.

Figure: 3. Zn (II)-L_1-R_4

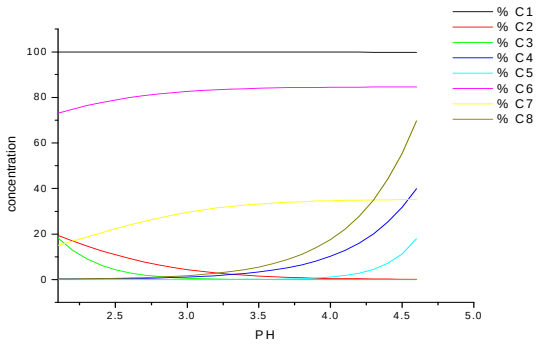
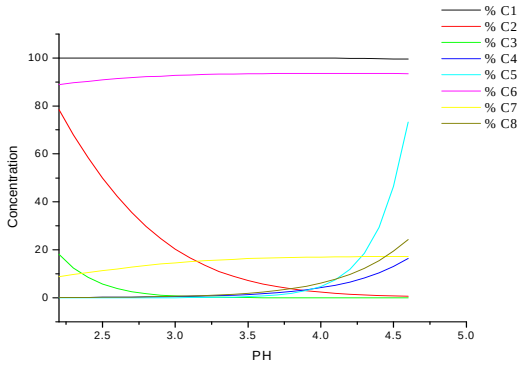


Figure: 4.Zn (II)-L_1-R_7



In case of Zn (II)-L_1-R_4 System, the percentage concentrations of various species have been calculated. These values are plotted as a function of pH. It can be seen from the table that the concentrations of all the species except H_2L, ML, MR and MLR are almost negligible at the initial pH 2.1. Therefore, these species do not involve in the formation of ternary complex. The initial percentage concentration of ternary complex MLR is 0.201 at pH 2.1 and then slowly increases until it reaches to maximum value i.e. about 69.7 percent at pH 4.6. The percentage of H_2L and MR represented by C1 and C6 are highest at the initial stage i.e. 100 and 73.1 respectively. The concentrations of these species decrease with pH and reaches to minimum value at pH 4.6. 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 4.6. After this pH, the formation rate becomes slow and tends to about constant value.

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 maximum formation of MLR is therefore.

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. 0.201 is due to the initial reaction between M, L and R.

Table: 2 Stability constants of ternary complexes of Drug Amitriptyline HCl

Metal ion	Amino acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	$\Delta \log K$
Cu(II)	Isoleucine	9.5442	16.2338	2.7901	9.5442	0	32.5321	0
	Glutamic acid	8.8718	18.6259	2.7901	8.8718	-1.4212	33.5794	-1.4212
Zn(II)	Isoleucine	6.7115	7.7224	6.023	3.7821	2.4294	15.1224	-0.5
	Glutamic acid	8.0273	9.3871	6.0232	5.0977	2.9296	19.4185	0

CONCLUSION

The relative stabilities of the binary and ternary complexes are quantitatively expressed in terms ofβ_{111}, β_{20}, β_{02}, K_L, K_R, K_r and ΔlogK values which are presented in Table No.2. The comparison of $\beta_{111}$with $\beta_{20}$and $\beta_{02}$of this system shows preferential formation of ternary complexes over binary complex of primary as well as secondary ligand. The considerably low positive value of K_L and K_R indicate less stability of ternary complex with respect to that of primary and secondary ligands. The Kr value of this complex is positive but less which indicate lower stability of ternary complex. The ΔlogK value of this system indicates less stability of ternary complex.

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