

## **Formation of binary and ternary complex of Cu (II) with amitriptyline hydrochloride and furosemide as primary ligands and amino acids as secondary ligands**

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### **ABSTRACT**

Mixed ligand stability constant of copper complexes with Amitriptyline hydrochloride and Furosemide drug with amino acid, Isoleucine and Glutamic acid have been studied pH metrically in 20% v/v ethyl alcohol water medium at 30°C temperature and 0.1 M ionic strength. The equilibrium constant of copper ternary complexes have been correlated with  $\Delta \log K$ ,  $K_L$ ,  $K_R$  and  $K_r$  stability related parameters. The percentage concentrations of various possible species with pH were determined by using computer program and possible equilibria were predicted.

**Keyword:** Ternary complexes, Transition metal ions, stability constant, glutamic acid, SCOGS.

### **INTRODUCTION**

Coordination chemistry plays an important role in the medicinal, analytical, environmental and biological sciences. The stability constants of metal complexes with drugs have been determined so as to know the proper dose of drugs and their effect with all other components of blood streams. [1] Amino acid with one or more than one coordination site along with different functional group has a significant role in metal complexes of drugs play an important role in numerous chemical and biological system.

Copper is essential in all plants and animals. Copper is present in large number of enzymes. [2, 3] because its role in facilitating iron uptake, copper deficiency can often produce anaemia like symptoms.

Amitriptyline hydrochloride is tricyclic antidepressant drug and chemically known as 3-(10, 11, dihydro-5H-dibenzo [a,d]cycloheptene-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride. [4] It is used for the treatment of several psychiatric disorder. [5-7] These types of tricyclic also ease migraines, tension, headaches, anxiety attacks and some schizophrenic symptoms.

Furosemide is 4-chloro-N-furfuryl-5 sulphamoylanthranilic acid. Furosemide has a Saluretic effect. [8] Clinical toxicity of furosemide involves abnormalities. [9] It is effective for the treatment of edemas connected with cardiac, hepatic and renal sites. One of the use of this drug is for the treatment of hypertension.

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

### **MATERIALS AND METHODS**

All the chemicals used in the present study were A.R. grade. The metals were used as nitrates. Pure drugs were procured as a gift sample from pharmaceutical Industries. The pure samples of amino acids were obtained from S.D. Fine Ltd. Mumbai. The solutions of all reagents were prepared in double glass distilled water having pH 6.80-6.90.

The solution of drug was prepared in 20% ethanol-water mixture. The fresh solution of NaOH was used as a titrant for pH titrations. It was standardized with oxalic acid.[10] The 1.0 M NaClO<sub>4</sub> solution was used to maintain the 0.1 M ionic strength by taking requisite amount of sodium perchlorate solution. The metal solutions were standardized by usual procedure. [11]

The digital pH meter [Elico model LI-127, inbuilt temperature compensation and 0.0 to 14 pH range with an accuracy of  $\pm 0.01$  pH Unit] in conjunction with combined glass electrode were used for pH measurements and experiments were carried out at 30°C temperature and inert atmosphere by maintaining 0.1 M ionic strength (NaClO<sub>4</sub>) in aqueous solution. The pH meter was calibrated before every set of titrations by using 4.00 and 9.00 pH standard buffer solutions. All the necessary precautions were taken for smooth working of electrode. [12] The Calvin Bjerrum pH titration techniques as modified by Irving Rossotti were applied to determine the equilibrium constants of 1:1:1 ternary complex. [13] Titration procedure involves following steps:

- 1) Free acid (HClO<sub>4</sub>) (A)
- 2) Free acid (HClO<sub>4</sub>) + primary ligand (A+L)
- 3) Free acid (HClO<sub>4</sub>) + primary ligand + Metal ion (A+L+M)
- 4) Free acid (HClO<sub>4</sub>) + secondary ligand (A+R)
- 5) Free acid (HClO<sub>4</sub>) + secondary ligand+ Metal ion (A+R+M)
- 6) Free acid (HClO<sub>4</sub>) + primary ligand + secondary ligand+ metal (A+L+R+M)

The above thermostatic mixtures were titrated with standard NaOH solution. The total volume of solution was kept at 50 ml by the adding distilled water. The proton ligand stability constants (pK<sub>a</sub>) and metal ligand stability constants (LogK) of binary complexes of drugs and amino acids were determined with the help of computer (MSOffice, Excel) by using Irving and Rossotti methods.

It is used to calculate stability constants of ternary complexes. The equilibrium constants of ternary complexes along with concentrations various species formed during complexation were directly obtained as output of 'SCOGS' computer program which employs non-linear least square approach.

## RESULTS AND DISCUSSION

Proton ligand constant of Primary ligand L<sub>1</sub>,L<sub>2</sub> and Secondary ligand R<sub>4</sub>,R<sub>7</sub> 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<sub>2</sub> complexes with Cu (II) ions.

TABLE-1 Proton-ligand and metal-ligand stability constants in binary system

Ligands	pK <sub>1</sub>	pK <sub>2</sub>	logK <sub>1</sub>	logK <sub>2</sub>
Amitriptyline hydrochloride	7.39	--	--	2.7901
Furosemide	3.4406	-	5.0695	4.3253
Isoleucine	2.5335	9.7256	9.5442	6.6896
Glutamic acid	2.5872	4.9984	10.293	8.3329

### 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 ligand constants of ligands, the species that exist in complexation equilibria have been plotted in Figure 1,2,3,4 as a function of pH. The parameters  $\Delta \log K$ , K<sub>L</sub>, K<sub>R</sub> and K<sub>r</sub> are generally used to indicate the relative stability of ternary complexes.

In all the ternary system, 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 computer programme 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 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 system.

In case of Cu(II) L<sub>1</sub>-R<sub>4</sub> 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 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 by 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. The mechanism of formation of ternary complex by different equilibria discussed in previous Cu (II) system is totally applicable to Cu(II) L<sub>1</sub>-R<sub>7</sub> system and the stability constant of this complex is 8.87 which is greater than the first complex which may be due to the change of secondary ligand.

In case of Cu(II) L<sub>2</sub>-R<sub>4</sub>, 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 2.0 and further decreases. Therefore, these species do not involve in the formation of ternary complex after pH2.0. From the values of different species it can be concluded that the concentration of ternary complex at beginning is minimum i.e.0.505 percent and then increases slowly to reach to 36.8% at pH 4.0.

The percentage of HL and MR represented by C<sub>1</sub> and C<sub>6</sub> is 99.7 and 99.9 of both the species at the initial stage. The concentration of these species decreases with pH and reaches to minimum at pH 4.0. 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 0.505 to 36.8 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.

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. The mechanism of formation of ternary complex of Cu (II) L<sub>2</sub>-R<sub>4</sub> 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.

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

L	R	$\beta_{111}$	$\beta_{02}$	$\beta_{20}$	KL	KR	Kr	$\Delta\log K$
L <sub>1</sub>	Isoleucine	9.5442	16.2338	2.7901	9.5442	0	32.5321	0
L <sub>1</sub>	Glutamic acid	8.8718	18.6259	2.7901	8.8718	-1.4212	33.5794	-1.4212
L <sub>2</sub>	Isoleucine	10.5012	16.234	2.7068	7.7944	0.9568	34.5296	-1.75
L <sub>2</sub>	Glutamic acid	12.4986	18.6262	2.7068	9.7918	2.2053	40.9166	-0.5015

It has been observed from table-2 that stability constant of ternary complexes of L<sub>1</sub> is found to be less than L<sub>2</sub>.The result shows that ternary complex formation is less favored over corresponding binary ML complex.

**Fig-1Cu (II) L<sub>1</sub>-R<sub>4</sub>**

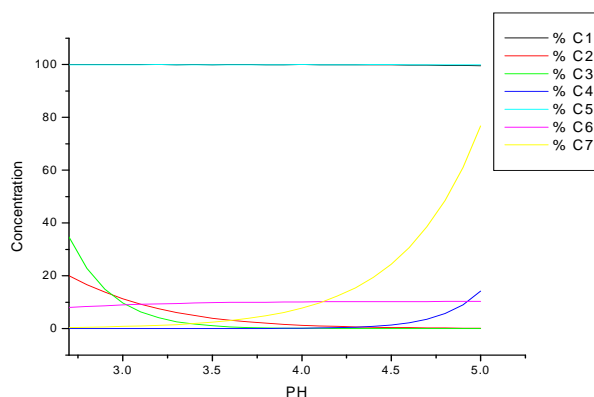
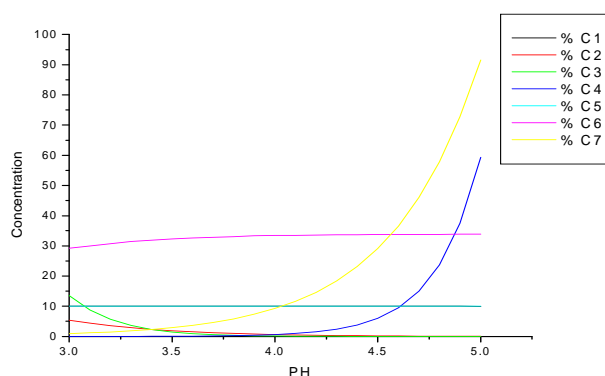
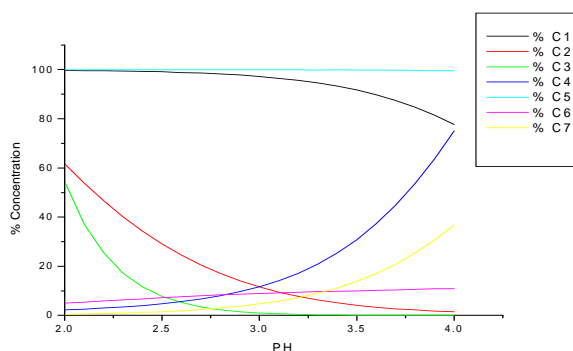
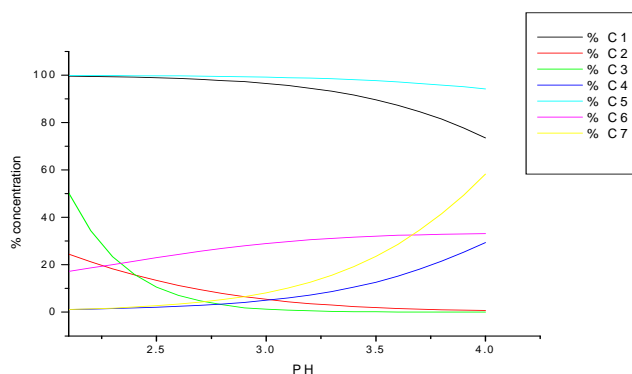


Fig-2 Cu (II) L<sub>1</sub>-R<sub>7</sub>Fig-3 Cu (II) L<sub>2</sub>-R<sub>4</sub>Fig-4 Cu (II) L<sub>2</sub>-R<sub>7</sub>

## 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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