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## Potentiometric studies on mixed ligand complex formation copper (II) complexes with enalpril maleate and some amino acids

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### ABSTRACT

Potentiometric investigation on mixed ligand complex formation of copper (II) ion with (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline (enalpril maleate) as primary ligand and a series of eight amino acids as secondary ligand was made at  $27 \pm 0.1^\circ\text{C}$  and ionic strength of 0.1 M  $\text{NaClO}_4$  in aqueous medium by Irving-Rossoti technique. Formation constant have been calculated by using computer program SCOGS.

**Keywords:** Mixed ligand complexes, enalpril maleate, equilibrium constant,  $\Delta \log K$ .

### INTRODUCTION

Enalpril maleate drug is widely used in pediatric cardiology in the treatment of essential and renovascular hypertension [1] and in congestive heart failure. It is an antihypertensive [2-3] drug and angiotensin converting enzyme (ACE) inhibitor [4].

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. At low pH the drug enalpril maleate undergoes dissociation and metallation at carbonyl group of oxygen atom and deprotonation of secondary amine at slight higher pH.

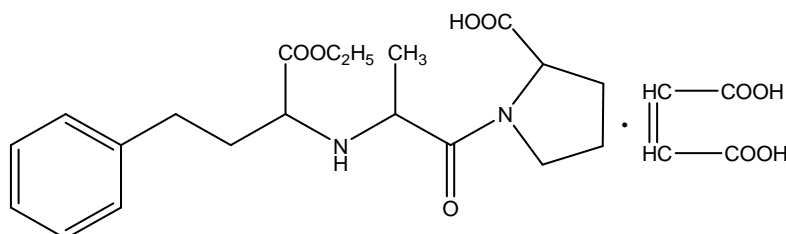


Fig. 1 Structure of (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline (enalpril maleate)

With a view of studying the chelating effect of drug with copper<sup>II</sup> and coordination of carboxyl and amine group in amino acid, the paper describes the results of a systematic equilibrium study of  $\text{Cu}^{\text{II}}$  with drug enalpril maleate (Fig. 1) with a series of amino acids viz. alanine, glycine, isoleucine, phenylalanine, serine, valine, tryptophan and glutamic acid in aqueous medium at  $I = 0.1 \text{ M NaClO}_4$  and at  $27 \pm 0.1^\circ\text{C}$  by potentiometric method. Formation

constants are correlated with the modes of the metal ion coordination by carboxyl and amine moieties, size of chelate ring and metal-ligand and ligand-ligand interactions.

### MATERIALS AND METHODS

All the reagents used were of A.R grade and all solutions were invariably prepared in double distil water and standardized by usual procedures [5]. The titrations were carried out using a digital pH meter [Elico model LI-120] in junction with combine electrode. All titrations were carried out at  $27 \pm 0.1^\circ\text{C}$ . For the determination of formation constant of ternary complexes, following solutions were prepared, 0.008M perchloric acid, 0.002M primary ligand (drug), 0.002M secondary ligands (amino acids), 0.002M metal solutions and the ionic strength was maintained using 0.1M sodium perchlorate. The titrations curves were obtained by plotting experimental data, which were utilized to determine the proton ligand formation constants of primary and secondary ligands and their metals complexes. Concentration of total metal, total ligands, free metal, free ligands and various possible species that are formed during the complexation and formation constant are calculated using SCOGS program [6]. Complex formation equilibria were elucidated with the aid of the species distribution curves obtained as an output of computer programme [7].

### RESULTS AND DISCUSSION

#### Binary complexes:

Drug enalapril maleate has amine and carboxyl groups which are successively deprotonated at pH 3.02 and 5.45 respectively. The observed value (Fig. 2) is lower than any saturated aliphatic acid and higher than any amino group present in the structure. The five member ring of the drug molecule can also be compared with pyrrolidine molecule which has a pK value 3.11. The observed value (Table 1) in drug is slightly less because of the carbonyl group present near the amine group which has a tendency of electron withdrawal by mesomeric effect which makes carbonyl group more acidic. This effect is also observed for the second pK i.e. deprotonation of secondary amine.

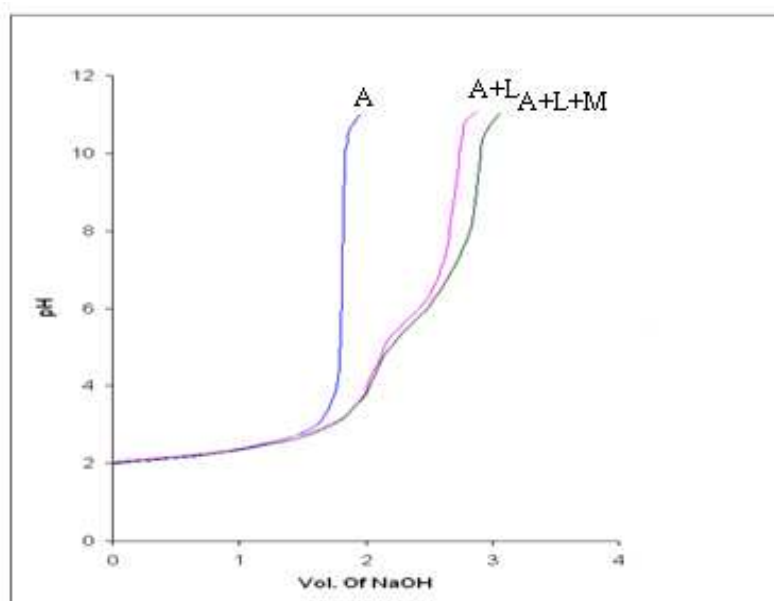


Fig. 2 Potentiometric titration curve

The interaction of metal ions with a base is similar to the neutralization reaction as metal ions like hydrogen ion act as Lewis acids. Therefore more basic ligand form more stable complexes. The charge distribution in the ligand and size and charge of the metal ion influence the stability of metal complexes. The copper metal forms 1:1 and 1:2 complexes with drug and amino acids.

Table 1

Ligand	pK <sub>1</sub>	pK <sub>2</sub>	LogK <sub>1</sub>	LogK <sub>2</sub>
Enalpril Maleate(L)	3.02	5.44	3.12	2.76
Alanine	2.30	9.69	8.13	
Glycine	2.36	9.57	8.15	
Isoleucine	2.25	9.62	8.40	
Phenyl Alanine	2.21	9.18	7.86	
Serine	2.13	9.06	7.89	
Valine	2.26	9.49	8.11	
Tryptophan	2.35	9.33	8.29	
Glutamic acid	2.18	4.20	7.87	

The proton ligand and metal ligand stability constant of enalpril maleate and amino acids with Cu(II) in aqueous medium at temp. 27±0.1°C and ionic strength  $\mu=0.1\text{M NaClO}_4$ .

### Mixed ligand complexes:

The stability of mixed ligand complexes is mainly governed by the characteristics of approaching secondary ligand. The stability therefore depends on the ring size which affects overall basicity of the secondary ligand. It can be inferred that the stability of the complex depends more on the length and spatial configuration of the chelate ring. At the pH of secondary ligand complex combination, the formation of mixed ligand can be represented by equilibria (1) and (2).



(Charges are omitted for simplicity)

Only 1:1:1 ternary complex formation is considered have been to ensure the formation of the simplest ternary complex MLR. Considering the pK values of the ligands and hydrolytic constants of  $\text{M}^{2+}$  ions the following species have been considered to exist in the complexation equilibria, viz.  $\text{M}^{2+}$ ,  $\text{LH}^{2+}$ ,  $\text{LH}$ ,  $\text{L}^{2-}$ ,  $\text{M}(\text{OH})_2$ ,  $\text{ML}(\text{OH})$ ,  $\text{ML}$ ,  $\text{R}^{2+}$ ,  $\text{MR}(\text{OH})$ ,  $\text{R}^{2-}$ ,  $\text{MLR}(\text{OH})$  etc.

The stability constants  $\log K_{\text{ML}}^{\text{m}}$ ,  $\log K_{\text{MR}}^{\text{m}}$ ,  $\log \beta_{\text{MLR}}^{\text{m}}$  were obtained as computer output. Complex formation equilibria have been elucidated on the basis of species distribution curves. Stability of ternary MLR complexes was characterized on the basis of  $\Delta \log K$  value [8-14] calculated using equation (3).

The relative stabilities of mixed ligand complex can be quantitatively expressed in terms of  $\Delta \log K$ ,  $K_{\text{r}}$ ,  $K_{\text{L}}$  and  $K_{\text{R}}$  values which are defined by equations

$$\Delta \log K = \log \beta_{111} - \log \beta_{10} - \log \beta_{01} \quad (3)$$

$$K_{\text{r}} = \beta_{111}^2 / \beta_{20} \beta_{02} \quad (4)$$

$$K_{\text{R}} = \beta_{111} / \log K_{01} \quad (5)$$

$$K_{\text{L}} = \beta_{111} / \log K_{10} \quad (6)$$

In the ternary system, the mixed ligand titration curve shows that percentage of free metal in concentration decreases with increase in pH. In CuLR system mixed ligand titration curve coincided up to pH ~ 2.75 and then deviates. The concentration of CuLR increases upto the pH~7.75 and then blue coloured precipitation was formed. The primary ligand enalpril maleate (L) individually forms 1:1 and 1:2 complexes where as secondary ligand forms 1:1 complex with  $\text{Cu}^{\text{II}}$ .

The species distribution curves of CuLR system were obtained by plotting percentage concentration of various possible species formed during complexation versus pH of solution. It can be observed that the concentration for the formation of drug (L) and amino acid (R) represented by  $C_1$  and  $C_3$  shows continuous decrease with increase in pH which indicate that the formation of Cu(II)-enalpril maleate-glycine (R) represented by  $C_8$ . The concentration of these species increases with increase in pH which the confirm formation of ternary complex.

Ternary complex of Cu<sup>II</sup> with enalpril maleate (L) and amino acids (R) shows following types of equilibria.



(Charges are omitted for brevity)

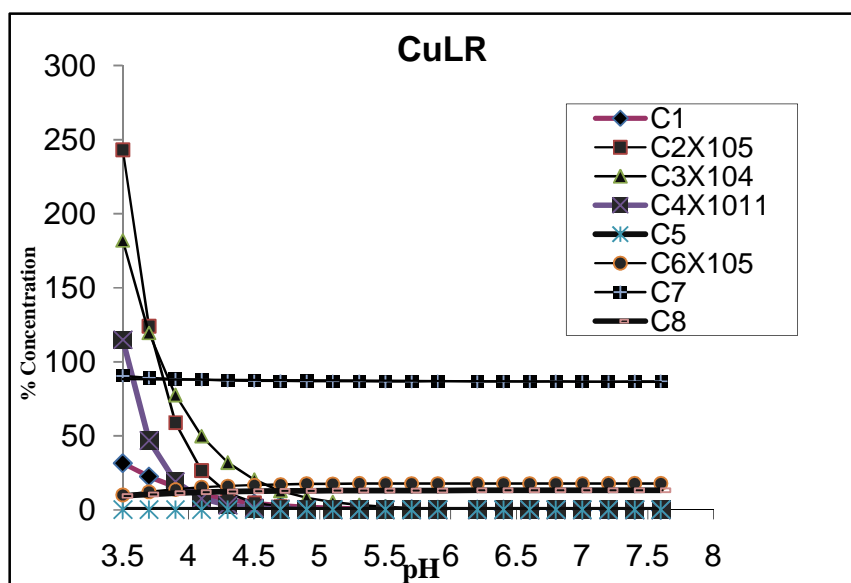


Fig. 3 Species distribution curve

Table. 2

Amino Acids	$\beta_{111}$	$\beta_{20}$	$\beta_{02}$	$K_L$	$K_R$	$K_r$	$\Delta \log K$
Alanine	10.55	5.72	8.13	7.59	2.42	1.52	-0.53
Glycine	10.11	5.72	8.15	7.15	1.96	1.45	-1.00
Isoleucine	9.59	5.72	8.40	6.63	1.15	1.35	-1.80
Phenyl Alanine	9.03	5.72	7.86	6.06	1.17	1.33	-1.79
Serine	9.82	5.72	7.89	6.86	1.93	1.44	-1.02
Valine	10.99	5.72	8.11	8.03	2.88	1.59	-0.07
Tryptophan	10.25	5.72	8.29	7.28	1.96	1.46	-1.00
Glutamic acid	9.32	5.72	7.87	6.36	1.45	1.37	-1.50

From the species distribution curves (Fig. 3) the formation of CuR is nearly 90% at pH 3.5 and represented by reaction (4a). The ternary species CuLR shows (Table-2) a considerably low percentage of CuLR i.e. 10% at pH 3.5. The constancy of ternary species distribution curve during the entire pH range shows the formation of ternary complex CuLR take place by reaction (5a).

Parameter based on some relationship between formation of mixed ligand complexes of Cu(II) with enalapril maleate(L) and amino acids (R) (1:1:1) in aqueous medium at temp.  $27 \pm 0.1^\circ\text{C}$  and  $I=0.1 \text{ M NaClO}_4$ .

### CONCLUSION

The low value of  $K_L$  and  $K_R$  shows stabilization of ternary complexes over the binary complexes of primary and secondary ligands. The positive values of  $K_L$ ,  $K_R$  and  $K_f$  shows the stability of the mixed ligand complexes however these constant are less stable than the considering binary complexes hence negative value of  $\Delta \log K$ . The order of stability of ternary complexes of  $\text{Cu}^{\text{II}}$  with respect to secondary ligands is Enalapril maleate = Valine < Alanine < Tryptophan < Glycine < Serine < Glutamic acid < Isolucine < phenyl alanine.

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