



Study of mixed ligand complexes of copper (II) with enalapril maleate as primary ligand and some peptides as secondary ligand

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ABSTRACT

Interaction of mixed ligand complexes of copper(II) with enalapril maleate and four peptides viz. glycil-glycine, alanine-glycine, glycil-glycil-glycine and glycil-leucine have been determined by pH metric measurements in aqueous solutions at 27°C in 0.1M NaClO₄. The mixed ligand complex formation constants of complex species have been evaluated using computer program (SCOGS).

Keywords: Mixed ligand complexes, enalapril maleate, $\Delta \log K$ etc.

INTRODUCTION

Enalapril maleate is a pro-drug without direct biological activity which is rapidly absorbed after oral administration. It 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]. Mixed ligand complex formation equilibria of biological metal ions with drugs, amino acids and peptide provided useful models of relevance to the enzymatic systems. Many of these mixed ligand complexes are suitable for mimicking the role of metal ions in the active site of metalloenzymes studying the drug designing [5], detoxification mechanism and studying the toxic effects of metal ions. With a view to study the effect of drug, its chelating position and modes of coordination with peptide (-CONH-) linkage, we describe in this paper, the results of an equilibrium study on the mixed ligand complex formation of Cu^{II} with drug enalapril maleate with four peptides viz. glycil-glycine, alanine-glycine, glycil-glycil-glycine and glycil-leucine in aqueous solution at constant ionic strength(I=0.1M NaClO₄) at 27°C. Stability constants of the mixed ligand complexes have been correlated with the possible modes of coordination of enalapril maleate i.e. COOH and NH₂,

MATERIALS AND METHODS

All the reagents used were of A.R grade and all solutions were invariably prepared in double distilled water and standardized by usual procedures [6]. The titrations were carried out using a digital pH meter [Elico model LI-120] in junction with combine electrode. All titrations have carried out at 27°C. For the determination of formation constants of ternary complexes, following solutions were prepared, 0.008M perchloric acid, 0.002M primary ligand (drug), 0.002M secondary ligands (peptides), 0.002M metal solutions and the ionic strength was maintained using 0.1M sodium perchlorate. The titration 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 constants are calculated using SCOGS program. 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 carboxyl and amine groups which are successively deprotonated at pH 3.02 and 5.45 respectively. The observed value (Fig. 1) is lower than any saturated aliphatic acid and higher than any amino group present in the structure (Fig. 2). The five membered 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. 1 Potentiometric titration curve.

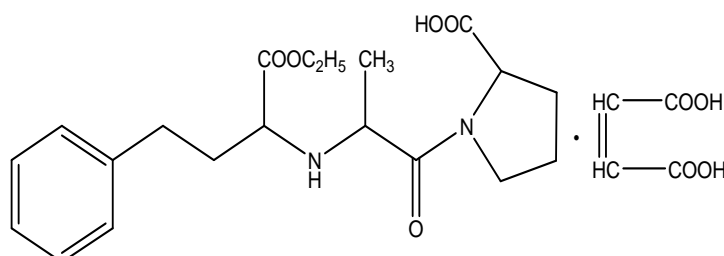
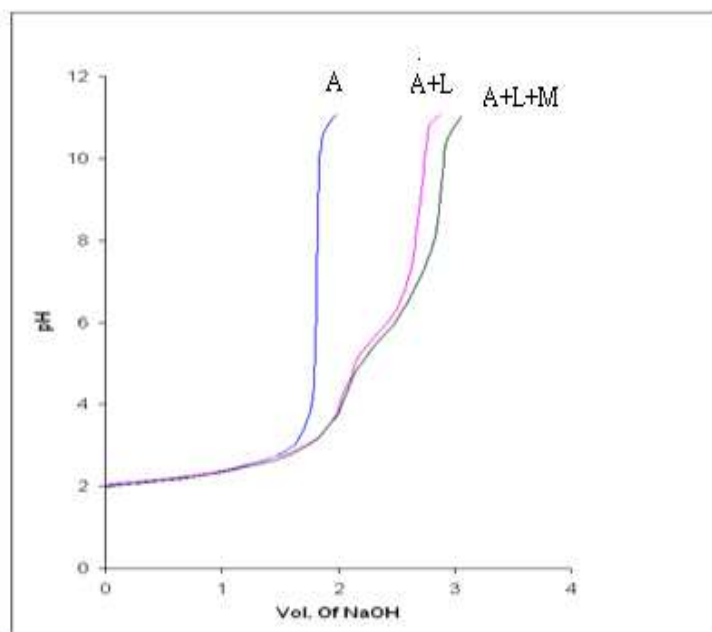


Fig. 2 Structure of (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline (enalpril maleate)]

Table-1: The proton ligand and metal ligand stability constant of enalapril maleate and peptides with Cu(II) in aqueous medium at 27°C and ionic strength $\mu=0.1\text{M NaClO}_4$.

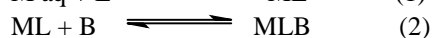
| Ligand | pK ₁ | pK ₂ | LogK ₁ | LogK ₂ |
|-----------------------|-----------------|-----------------|-------------------|-------------------|
| Enalapril maleate | 3.02 | 5.44 | 3.12 | 2.76 |
| Glycyl-glycine | 3.13 | 8.07 | 5.50 | - |
| Alanine-glycine | 3.07 | 8.12 | 5.41 | - |
| Glycyl-glycyl-glycine | 3.20 | 7.89 | 9.69 | 5.08 |
| Glycyl-leucine | 3.09 | 8.14 | 5.93 | - |

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 ligands form more stable complexes. The charge distribution on the ligand, size and charge of the metal ion influence the stability of metal complexes. The copper^{II} forms 1:1 and 1:2 complexes with drug and peptides.

Mixed ligand complexes:

The stability of mixed ligand complexes is mainly governed by the characteristics of approaching secondary ligands. 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 combination, the formation of mixed ligand complex can be represented by equilibria (1) and (2).



(Charges are omitted for simplicity)

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

The stability constants $\log K_{ML}^m$, $\log K_{MB}^m$, $\log \beta_{MLB}^m$ were obtained as computer output. Complex formation equilibrium have been elucidated on the basis of species distribution curves. Stability of ternary complexes MLB was characterized on the basis of $\Delta \log K$ value [5, 8-21] calculated using equation (3).

The relative stabilities of mixed ligand complexes can be quantitatively expressed in terms of $\Delta \log K$, K_r , K_L and K_B values which are defined by equations

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

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

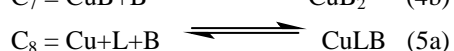
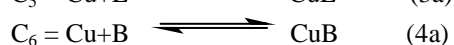
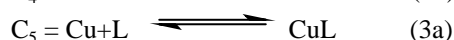
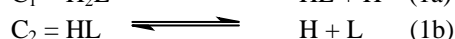
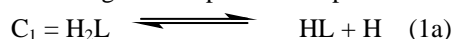
$$K_B = \beta_{111} / \log K_{01} \quad (5)$$

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

In CuLB system in the primary ligand enalapril maleate (L) and secondary ligand peptides (B) both forms 1:1 and 1:2 complex with Cu^{II} .

The species distribution curves of Cu LB 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 peptides (B) represented by C_1 and C_3 shows continuous decrease with increase in pH which indicate that the formation of mixed ligand complex i.e. Cu(II)-enalpril maleate –peptides (B) represented by C_8 . The concentration of these species increases with increase in pH which confirms the formation of mixed ligand complex.

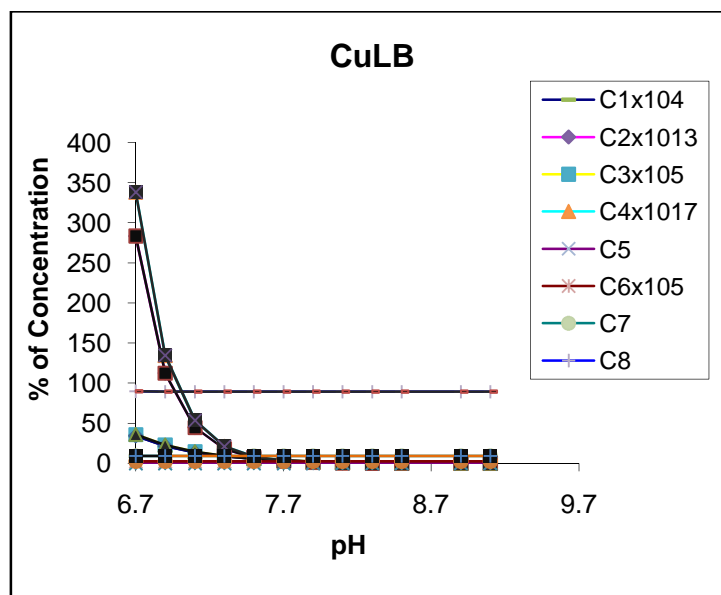
Mixed ligand complex of enalapril maleate (L) with peptide (B) shows following types of equilibria.



(Charges are omitted for brevity)

From the species distribution curves (Fig. 3) the formation of CuLB is 90% and percentage of formation of CuB_2 is 10% which remains constant throughout the pH range shown by parallel line to the X- axis. The constant value of ternary species distribution curve during the entire pH range shows the formation of ternary complex CuLB take place by reaction (5a). The positive values (Table 2) of K_L , K_B , K_r and $\Delta \log K$ support the enhanced stability of the mixed ligand complexes.

Fig. 3 Species distribution curves



CONCLUSION

The formation of CuLB is more preferred over the formation of binary species. The positive value of $\Delta \log K$ indicates stable nature of complexes. The order of stability of ternary complexes of Cu (II) with respect of secondary ligand peptides is Enalapril Maleate = Glycyl-glycyl-glycine < Glycyl-Lucine < Alanine-glycine < Glycyl-glycine

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