Potentiometric study of stability constant of binary and ternary complexes of Enalapril with transition metal ions in aqueous solution

Ammar Qasem[1,3], Mazahar Farooqui[1,2] and Sayyed Hussain[3]

[1]*P. G. & Research Centre, Maulana Azad College, Aurangabad, (M. S)*
[2]*Dr. Rafiq Zakaria College for Women, Aurangabad, (M. S)*
[3]*Sir Sayyed College of Arts, Commerce & Science, Aurangabad, (M. S)*

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ABSTRACT

Mixed ligand stability constants of Co(II),Ni(II),Cu(II) and Zn(II) complexes with enalapril drugs (L_P) and Glycine (L_S) have been determined pH metrically at room temperature and 0.01 M ionic Strength (NaClO$_4$) in aqueous solution. The formation of various possible species has been evaluated by computer program and discussed in terms of various relative stability parameters. The ternary complexes shows, stability order as
$\Delta logk$ = 1:1:1 Co(II)>Ni (II)>Cu(II))>Zn(II)
1:1:2 Ni(II)~ Zn(II)>Co(II)>Cu(II)

Keywords: Stability constant, ternary, binary, metal ions, amino acid.
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INTRODUCTION

The complexes are the compounds forming coordinate bonds between electron pair donor as the ligand and electron pair acceptors as the metal atoms or ions. The number of electron pairs donated to the metal is known as its coordination number and thereby many complexes exists which exhibit coordination number of two, four or six. In order for a pair of electrons to be donated from ligand to a metal ion, there must be an empty (d) orbital on the metal ion to accept the pair of electrons. The electron configuration is (d) because the (s) and (p) orbitals are empty and can be hybridized to give a set of empty (sp) hybrid orbital. This set of hybrid orbitals could accommodate pairs of electrons donated by ligand. In a complex, a central atom or ion is coordinated by one or more molecules or ions (ligands) which act as Lewis base, forming coordinate bonds with the central atom or ion; the latter acts as a Lewis acid. Atoms in the ligands that are directly bonded to the central atom or ion are donor atoms [1]. Divalent metal ions such as copper, nickel and cobalt metal ions are known essential metals in the human body for maintaining health. Although they have beneficial effects in humans, these ions can be toxic if over-accumulated in the human body. To prevent certain diseases caused by metal poisoning and to reduce the concentration of metal ions in blood and urine in the body, the coordination chemistry of some chelating agents of such metals or recently known ligand therapy has been studied extensively [2]. Metal ligand complexes are made up of am central metal ion and ligands in addition to the solvent molecules required to make up the coordination sphere of the metal ion such metal ion ligand complexes are quite common in biological and analytical systems. Thus understanding of the significance of metal ions in biological systems may unravel the mysteries surrounding the protein-substrate interactions and the control mechanisms that determine the coordination and coordination tendency of the metal ions bound at the active sites of many enzymes in enzyme-metal ion-substrate reactions. Apart from this, the formation of mixed-ligand complexes is also important in understanding the behavior of pollutants in natural waters, considering the high affinity of ion for donor atoms like oxygen and nitrogen etc[3]. Enalapril is a prodrug that contains an ester group that is hydrolyzed by esterases to enalaprilat an angiotensin-converting enzyme inhibitor. Enalapril displays very little hydrolysis in human plasma but rapid hydrolysis in rat plasma [4]. Enalapril is used to treat hypertension, symptomatic heart failure, and asymptomatic left ventricular dysfunction. It has been

proven to protect the function of the kidneys in hypertension, heart failure, and diabetes, and may be used in the absence of hypertension for its kidney protective effects.

Structure of Enalapril   Structure of glycine
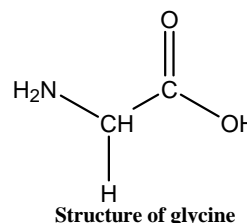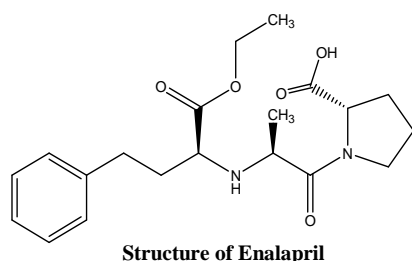
EXPERIMENTAL SECTION

All the chemicals and reagents used were of AR grade. Potentiometric titrations were carried out in aqueous solution at room temperature and ionic strength 0.01M ($NaClO_4$) against 0.2 M NaOH, using glass electronics pH meter with an accuracy of± 0.01 pH. This protonation constant of the ligands and the formation constants of the binary complexes were determined under the same experimental conditions. For this, solutions containing metal ions and the ligands in the ratio 1:1 and 1:2 (M2+:L) have been titrated against standard alkali. The values have been refined using a computer program. The values of the protonation constants of the ligands and the formation constants of binary complexes are in close agreement. These values were used as constants in calculating the formation constants of the ternary complexes. The formation constants of the ternary complexes were determined by the titration of aqueous solutions (50 ml) of the reactants of concentrations 0.002M and 0.001M in ratios M2+:L_P:L_S =1:1:1 and 1:1:2, against carbonate-free NaOH. Titrations of each set were carried out twice to check the reproducibility of the data. Formation constants were refined using the SCOGS computer program [5]. The values of the protonation and the formation constants of the binary and ternary complexes and the $\Delta \log K$ values have been presented in Tables 1 and 2

Potentiometric Procedure: In the study of binary and ternary chelates by the potentiometric titration technique. The following sets were prepared in the standard:

(1)Free $HClO_4$.
(2)Free $HClO_4$ + Ligand (L_P)
(3)Free $HClO_4$ +Ligand (L_P) +Metal ion
(4)Free $HClO_4$ + Ligand (L_S)
(5) Free $HClO_4$ +Ligand (L_S) +Metal ion (M).
(6) Free $HClO_4$ +Ligand (L_P) +Ligand (L_S) +Metal ion (M).

In general, an experimental run involves collecting equilibrium data points throughout the entire pH range, between 2.0 and 10.50 as a function of milliliter standard sodium hydroxide, the pH measurement method for investigating the dependency of complexation to pH for calculating protonation constants of medicinal compounds and glycine, and stability constants of respective complexes with metal ions was carried out according to Irving-Rossetti expression. In a typical experiment, a solution containing about 0.01 mmol of ligands (drugs) was placed in the cell. The required amounts of NaClO4 (from 0.1M stock solution), HClO4 (from 0.2 M stock solution) were added. Finally the required amount of doubly distilled water was added to the cell to a total volume of 50 ml. The second solution contains the same amounts of component plus about 0.01mmol of each metal ions and doubly distilled water was added to the same total volume. The potentiometric study carried out at the metal: ligand molar ratios of 1:1, 1:2 for binary systems. The ternary system contains the same amounts of component plus glycine and doubly distilled water was added to the same total volume, the potentiometric study carried out at the metal: drug: amino acid molar ratios of 1:1:1, 1:1:2 for ternary systems.

RESULTS AND DISCUSSION

Binary complexes: The proton ligand stability constants (pK) are shown in **Table [1]** and metal ligand stability constants (logK) of Co(II), Ni(II), Cu(II) and Zn(II) transition metal ions with **Enalapril** and glycine have been determined for the purpose of comparison with those of ternary systems by using Calvin Bjerrum titration techniques as modified by Irving and Rossotti [6].The n⁻A values ranges between 0.2 to 0.8 and 1.2 to 1.8 indicates the presence of only two pK in drug and is due to the dissociation of carboxylic group present and amino group. The pk_1 2.00 for 1:1 and 2.96 for 1:2 metal ligand ratio is because of carboxylic group and the $pk_2$10.04 for 1:1 and 9.51 for 1:2 metal ligand ratio is because of amino group, this suggest the formation of 1:1 and 1:2 complexes. The

stability constants of transition metal complexes obtained follows the usual natural order (Irving William natural order) of stability [7].

Mixed ligand complexes: The formation of 1:1:1, 1:1:2 and mixed ligand complexes (MLpLs) were identified by the pH of precipitation of ML_p, ML_s, and ML_pL_s titration curves which suggest the higher value of pH of precipitation of ternary system than corresponding binary systems [8].The nature of mixed ligand titration curves indicates that complex formation takes place in the pH range of 2.30 to 8.00 in most of the systems. There was no any solid phase formed during the course of titrations [9]. The relative stability of binary and ternary complexes were explained in terms of $\Delta \log K$, KL_P, KL_S and Kr values as and shown in Table 2

$$Kr = \beta^2_{111}/(\beta_{20}. \beta_{02})$$

$$KL_p = \beta_{111}/K_{10}$$

$$KL_s = \beta_{111}/K_{01}$$

$$\Delta \log K = \log \beta_{111} - \log K_{10} - \log K_{01}$$

The mixed ligand stability constants of $Cu(II)L_PL_S$ and $Ni(II)L_PL_S$ systems shows higher stability whereas low stability of Co(II) and Zn (II) ternary systems of(1:1:1),(1:1:2). The values can be given as:

$\log \beta_{111}$ Cu(II)>Ni(II)>Zn (II)>Co(II)

$\log \beta_{112}$ Cu(II)>Ni(II)>Zn (II)~Co(II)

The comparison of $\log \beta_{111}$ with $\log \beta_{20}$ and $\log \beta_{02}$ of these systems reveals the preferential formation of ternary complexes binary systems [10]. The positive values of K_{Lp} and K_{Ls} indicate less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands. The positive values of Kr also support the extra stability of mixed ligand complexes which may be attributed to the interactions outside the coordinated sphere such as the formation of hydrogen bonding between coordinated ligands, charge neutralization, chelate effect and electrostatic interactions between non coordinated charge groups of ligands. The negative values of $\Delta \log K$ suggests the formation of ternary complexes but less stable having destabilized nature of complexes which has been valid for N and O donors [11]. The positive value of $\Delta \log K$ in some cases is attributed to the extra stability of ternary complexes. If $\Delta \log K$ is positive, it indicates that ternary complexes are more stable than binary. And the negative values of $\Delta \log K$ indicates favorable binary complexation composed to ternary hence, Cu(II) in 1:1:2 shows negative $\Delta \log K_1$ therefore binary complex of Cu(II) one strong than ternary complexes. If $\Delta \log K$ is more than or equal to 0.6, the geometry of complex may be octahedral only in the case Cu(II) at 1:1:2 ratio the $\Delta \log K$ value is less than 0.6.

Table [1] the proton ligand stability constants

Ratio	ENALAPRIL		GLYCINE	
	pK_1	pK_2	pK_1	pK_2
1:1	2.00	10.04	2.39	9.46
1:2	2.96	9.51	2.9	9.22

Table [2] Parameter based on some relationship between formations of mixed ligand complexes of Enalapril as primary ligand and Glycine as secondary ligand

| Parameter	1:1:1				1:1:2			
	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
$\log k_{10}$	3.44	4.79	4.00	4.80	4.02	4.26	7.19	4.36
$\log k_{01}$	4.19	3.82	8.04	4.65	4.65	5.02	8.28	4.56
$\log \beta_{20}$	3.44	4.79	4.00	4.80	4.02	4.26	7.19	4.36
$\log \beta_{02}$	4.19	3.82	8.04	4.65	4.65	5.02	8.28	4.56
$\log \beta_{111}$	9.88	10.71	13.54	10.21				
$\log \beta_{112}$					10.42	10.78	15.07	10.42
K_r	1.29	2.49	2.25	2.16	2.40	2.32	1.95	2.34
K_{Lp}	2.87	2.23	3.38	2.13	2.59	2.53	2.09	2.39
K_{Ls}	2.36	2.8	1.68	2.19	2.24	2.15	1.82	2.28
$\Delta \log K$	2.25	2.1	1.5	0.76	0.75	1.5	-0.4	1.5
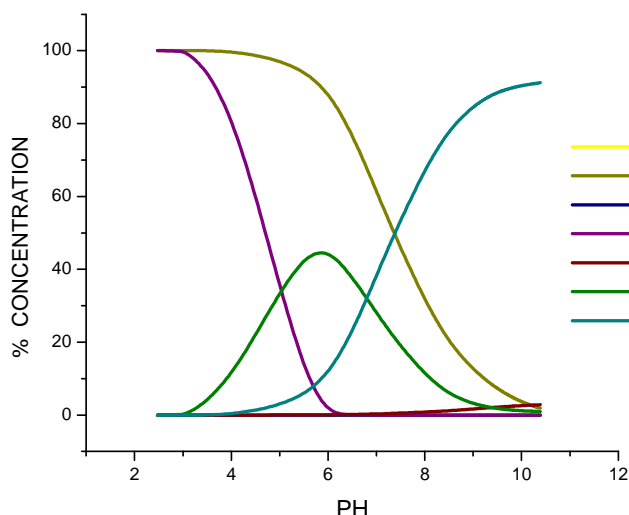
(a) Co(II)-glycine-enalapril
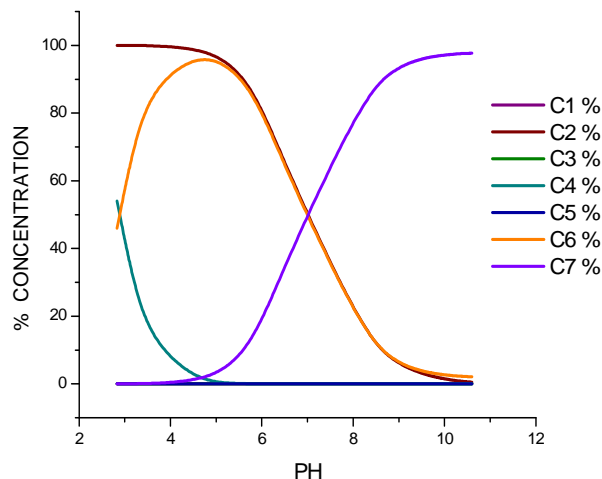
(b) Cu(II)-glycine-enalapril
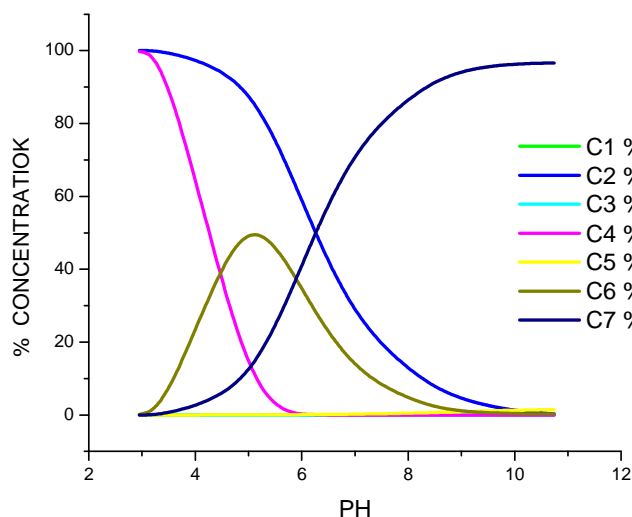
(c) Ni(II)-glycine-enalapril
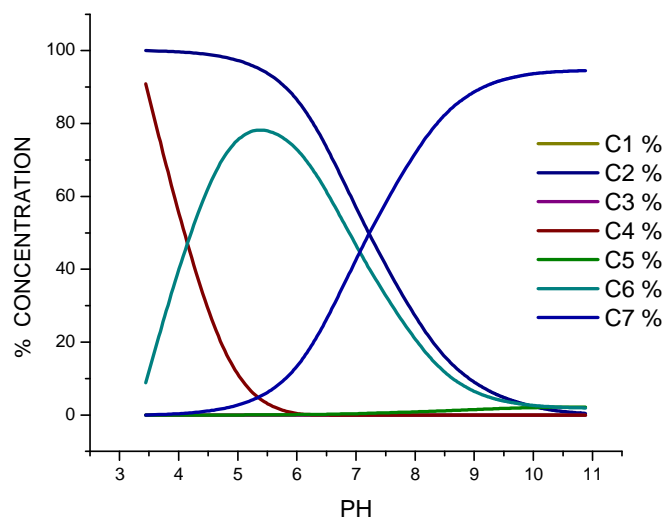
(d) Zn(II)-glycine - enalapril

CONCLUSION

1. Stability of mixed ligand complexes is mainly affected by the characteristics of approaching secondary ligand.
2. The negative values of ΔlogK suggest the formation of ternary complexes but less stable having destabilized nature of complexes and positive value of ΔlogK in some cases is attributed to the extra stability of ternary complexes.
3. If Δlog*K* is positive, it indicates that ternary complexes are more stable than binary.
4. The positive values of Kr also support the extra stability of mixed ligand complexes which may be attributed to the interactions outside the coordinated sphere.
5. The species distribution curve shows the formation of ternary complexes and deprotonation of amino groups.

The species Distribution Curves: The species Distribution Curves for ternary complexes are show in fig a to d. It is absorbed that for **(a) Co(II)-glycine-enalapril** complexes start at(pH 8.75 – 8.19) and **(b) Cu(II)-glycine-enalapril** complexes start at (pH 8.26 – 8.61) and **(c) Ni(II)-glycine-enalapril** complexes start at (pH 8.31 – 9.05) and **(d) Zn(II)-glycine-enalapril** complexes start at (pH 8.86 – 8.77).

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