

Equilibrium studies on mixed ligand complexes of Copper (II) metal ion with some antihypertension drugs and amino acids

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Abstract: The equilibrium studies of the mixed ligand complexes of Copper(II) ion with antihypertension drugs Labetalol hydrochloride, Lisinopril hydrochloride and Benazepril hydrochloride as primary ligand and the eight aminoacids viz. DL-alanine, glycine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-β-phenyl alanine, DL-serine and DL-valine as secondary ligands were determined pH metrically in 20% (v/v) ethanol-water medium at 27°C and at an ionic strength of 0.1 M NaClO₄. ΔlogK values reveal that ternary complexes are less favoured than binary complexes, the antihypertension drug used in the present study co-ordinate through NH₂ and COOH group. The calculations of stability constants have been made using computer programme "SCOGG" and discussed in terms of various relative stability parameters.

Keywords: Equilibrium studies, antihypertension drugs, ΔlogK, mixed ligand complexes.

I. Introduction

As drug has various functional groups which can bind to receptor or enzyme or metal ions present in the body, they can conform many type of complexes and can enhance the activity of drug. The metal complexes of drugs play an important role in drug action and metabolism [1, 2]. Metal complexes of drugs are found to be more potent than parent drugs. Metal complexes are widely used in various fields, such as biological processes, pharmaceuticals, analytical processes, separation techniques etc [3-5]. Labetalol hydrochloride [2-Hydroxy-5-{1-hydroxy-2-[(4-phenylbutan-2-yl) amino] ethyl} benzamide] is sympatholytic, andrenergic alpha-antagonists and antihypertensive agent. Labetalol is used parenterally for immediate reduction in blood pressure in severe hypertension, for the control of blood pressure in patients with pheochromocytoma and pregnant women with preeclampsia, and to produce controlled hypotension during anesthesia to reduce bleeding resulting from surgical procedures. Lisinopril hydrochloride (2S)-1-[(2S)-6-amino-2-[[[(1S)-1-carboxy-3-phenylpropyl] amino] hexanoyl] pyrrolidine-2-carboxylic acid is an angiotension-converting enzyme inhibitor, antihypertensive agent, cardiotonic agent. It is used for the treatment of hypertension and symptomatic congestive heart failure. May be used to slow the progression of renal disease in hypertensive patients with diabetes mellitus. Benazepril hydrochloride is an angiotension-converting enzyme inhibitor, antihypertensive agent. It is used to treat high blood pressure (hypertension), congestive heart failure, and chronic renal failure. Amino acids and their metal complexes are equally important compounds; since they have frequent utilization in both biological and chemical applications [6-7]. They are the structural units of proteins. These are essential constituents of all living cells and contain one or more amino and carboxylic groups and have good coordination sites for the metal complexation.

Survey of literature reveals that no work has been reported on complex tendencies of Cu (II) ion with antihypertention drugs and amino acids in ethanol-water solution.[8-22] Therefore for the present investigation, we investigated ternary complexation of Cu(II) ion with antihypertension drugs Labetalol hydrochloride(Lab), Lisinopril hydrochloride (Lis) and Benazepril hydrochloride (Ben) as primary ligand and a series of eight amino acids viz DL-alanine (Ala), glycine (Gly), L-glutamic acid (Glu-acid), DL-isoleucine (Iso), DL-methionine (Met), DL- β-phenyl alanine (Phe), DL-serine (Ser) and DL-valine (Val) as secondary ligands in 20% (v/v) ethanol-water medium at 27°C and at an ionic strength of 0.1 M NaClO₄.

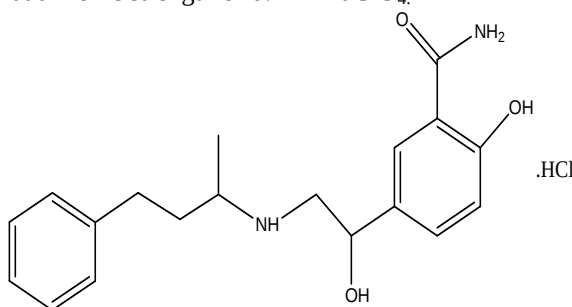


FIG: 1 LABETALOL HYDROCHLORIDE

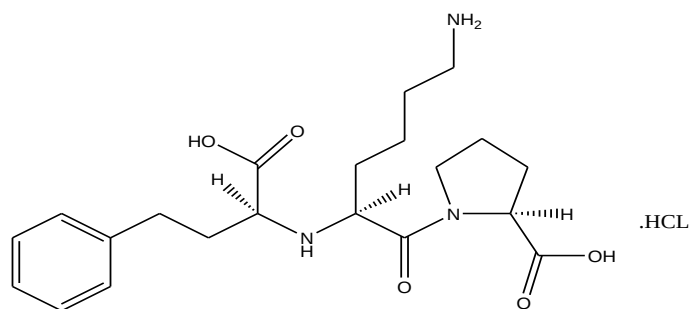


FIG: 2 LISINOPRIL HYDROCHLORIDE

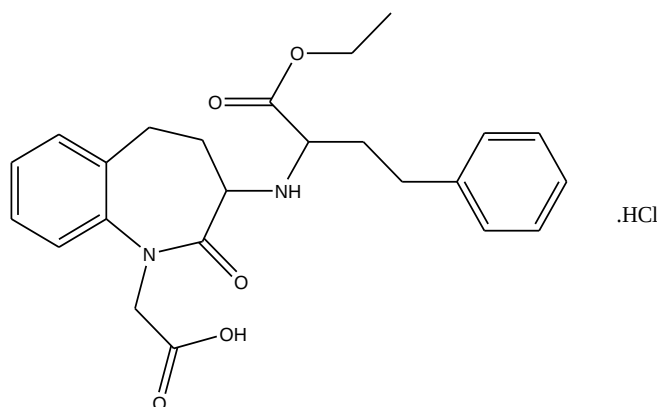


FIG: 3 BENAZEPRIL HYDROCHLORIDE

II. MATERIALS AND METHODS

Drug sample of Labetalol hydrochloride (Lab), Lisinopril hydrochloride (Lis) and Benazepril hydrochloride (Ben) in pure form were obtained from pharma industries and used as received. Ethanol was purified as described in literature [23]. The solutions used in the potentiometric titrations were prepared in carbonate free double distilled water. All chemicals used were AnalaR grade. The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of HClO_4 . The metal salt solution was also standardized using EDTA titration [24]. All the measurements were made at 27°C in 20% ethanol-water mixture at 0.1 M NaClO_4 strength. The thermostat model SL-131 (Adar Dutt and Co (India) Pvt. Ltd. Mumbai) was used to maintain the temperature constant. The measurement of pH was recorded using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode (reading accuracy ± 0.01). The pH-meter was adjusted with buffer of pH 4.00, 7.00 and 9.18. Purified nitrogen was bubbled through the solution to maintain an inert atmosphere. Efficient stirring of the solution was achieved with a magnetic stirrer.

The experimental procedure: In the study of binary and ternary chelates by the potentiometric titration technique, the following sets were prepared in the standard:

- (i) HClO_4 (A)
- (ii) HClO_4 + Drug (A+L)
- (iii) HClO_4 + Drug + Metal (A+ L+ M)
- (iv) HClO_4 + Amino acid (A+ R)
- (v) HClO_4 + Amino acid + Metal (A+ R+ M)
- (vi) HClO_4 + Drug + Amino acid + Metal (A+L+ R+ M)

Against standard sodium hydroxide, the ionic strength of solutions was maintained constant by adding appropriate amount of (0.1M) Sodium perchlorate solution. The titration were carried out at 27°C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrode to expel out CO_2 . pH meter reading in 20% (v/v) ethanol-water were corrected by method of Vanuiter and Hass [25]. Graphs were obtained by plotting pH versus volume of NaOH added. These data were used to determine the pK_a of ligand and $\log K$ values of metal complexes of primary and secondary ligand. (Table-1) The equilibrium constant of ternary complexes were determined by computational programme "SCOGS" [26] to minimize the standard derivation.

Table1: Proton-ligand stability constant and metal-ligand stability constant of anti hypertension drugs and amino acids with Cu (II) at 0.1M ionic strength in 20% (v/v) ethanol-water medium.

Ligands	proton-ligand stability constant		Metal-ligand stability constant	
	pK ₁	pK ₂	logK ₁	logK ₂
Labetalol hydrochloride(L ₁)		7.7424	4.1402	4.0566
Lisinopril hydrochloride(L ₂)	3.3224	7.5328	7.7890	4.5435
Benazepril hydrochloride(L ₃)		3.6436	3.3414	2.9836
DL-alanine	2.5336	9.8082	8.2808	6.9970
Glycine	2.5660	9.7850	8.9278	7.6977
L-glutamic acid	2.2732	4.4116	4.0564	3.4113
DL-isoleucine	2.5141	9.7599	9.3618	7.7585
DL-methionine	2.0793	9.3410	8.5045	7.1715
DL-β-phenylalanine	2.2552	9.0546	8.1655	7.1612
DL-serine	2.1152	9.1066	8.3817	7.1235
DL-valine	2.5923	9.6759	9.0102	7.5889

Table 2: Parameters based on some relationship between formations of mixed ligand complexes of Cu (II) with lab (L₁) drug in presence of amino acid (1:1:1 system)

Amino Acid	β ₁₁₁	β ₂₀	β ₀₂	K _L	K _R	K _r	ΔlogK
DL-alanine	11.4196	8.1968	15.2778	7.2794	3.1388	0.972932	-1.0014
Glycine	13.0656	8.1968	16.6255	8.9254	4.1378	1.052731	-0.0024
L-glutamic acid	6.1953	8.1968	7.4677	2.0551	2.1389	0.790999	-2.0013
DL-isoleucine	12.9985	8.1968	17.1203	8.8583	3.6367	1.026855	-0.5035
DL-methionine	12.3939	8.1968	15.676	8.2537	3.8894	1.038328	-0.2508
DL-β-phenylalanine	11.5543	8.1968	15.3267	7.4141	3.3888	0.982362	-0.7514
DL-serine	11.9922	8.1968	15.5052	7.852	3.6105	1.011915	-0.5297
DL-valine	13.1497	8.1968	16.5991	9.0095	4.1395	1.060635	-0.0007

Table 3: Parameters based on some relationship between formations of mixed ligand complexes of Cu (II) with lis (L₂) drug in presence of amino acid (1:1:1 system)

Amino Acid	β ₁₁₁	β ₂₀	β ₀₂	K _L	K _R	K _r	ΔlogK
DL-alanine	15.3195	12.3325	15.2778	7.5305	7.0387	1.109695	-0.7503
Glycine	15.7148	12.3325	16.6255	7.9258	6.787	1.085351	-1.002
L-glutamic acid	10.8428	12.3325	7.4677	3.0538	6.7864	1.095221	-1.0026
DL-isoleucine	17.1499	12.3325	17.1203	9.3609	7.7881	1.164568	-0.0009
DL-methionine	16.2904	12.3325	15.676	8.5014	7.7859	1.163247	-0.0031
DL-β-phenylalanine	14.9539	12.3325	15.3267	7.1649	6.7884	1.081297	-1.0006
DL-serine	14.6706	12.3325	15.5052	6.8816	6.2889	1.054009	-1.5001
DL-valine	15.7953	12.3325	16.5991	8.0063	6.7851	1.091906	-1.0039

Table 4: Parameters based on some relationship between formations of mixed ligand complexes of Cu (II) with Ben (L₃) drug in presence of amino acid (1:1:1 system)

Amino Acid	β ₁₁₁	β ₂₀	β ₀₂	K _L	K _R	K _r	ΔlogK
DL-alanine	10.6212	6.325	15.2778	7.2798	2.3404	0.983317	-1.001
Glycine	11.5151	6.325	16.6255	8.1737	2.5873	1.003473	-0.7541
L-glutamic acid	7.3962	6.325	7.4677	4.0548	3.3398	1.07248	-0.0016
DL-isoleucine	11.4499	6.325	17.1203	8.1085	2.0881	0.976733	-1.2533
DL-methionine	11.0947	6.325	15.676	7.7533	2.5902	1.008563	-0.7512
DL-β-phenylalanine	10.2553	6.325	15.3267	6.9139	2.0898	0.947297	-1.2516
DL-serine	11.7225	6.325	15.5052	8.3811	3.3408	1.073971	-0.0006
DL-valine	11.6012	6.325	16.5991	8.2598	2.591	1.01214	-0.7504

III. Results and Discussion

Binary complex: The proton ligand stability constants (pK) and metal ligand stability constants (logK) of binary complexes were calculated by using Calvin Bjerrum titration techniques as adopted by Irving and Rossotti [27]. All metal ions depress the titration curve of the free ligand by the release of the protons according to the abilities of the metal ions to bind to the ligand [28], indicate the formation of binary complex. During titration no precipitate was formed indicating that there is no tendency to form hydroxo complexes. For all the three primary ligand (drugs), $\bar{n}$ values obtained are between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 complex formation. The order of $\log K_1 > \log K_2$ is commonly observed. The reason is statistical effect, statistically co-ordination of a second molecule is difficult with compare to the first due to availability of less number of co-ordinating sites on the metal ion for the second ligand. The stability constants of transition metal complexes obtained follows the usual natural order (Irving William natural order) of stability [29].

Mixed ligand complexes: The formation of 1: 1: 1 mixed ligand complex were identified by the pH of precipitation of ML, MR, and MLR titration curves. These curves indicate the higher value of pH of precipitation of ternary system than corresponding binary systems [30]. The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of $\Delta \log K$, K_r , K_L , and K_R values which are represented by equations:

$$\Delta \log K = \beta_{111} - (\log K_{10} + \log K_{01}) \quad (1)$$

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

$$K_L = \frac{\beta_{111}}{\log K_{10}} \quad (3)$$

$$K_R = \frac{\beta_{111}}{\log K_{01}} \quad (4)$$

Where β_{111} is the equilibrium constant of ternary system.

β_{20} is the overall stability constant of primary complexes.

β_{02} is the overall stability constant of secondary complexes.

The primary ligands (drugs) and secondary ligands (amino acids) form 1:1 and 1:2 complexes with Cu (II). It is evident from the figure of the percentage concentration species Cu (II) - drug amino acids system that the percentage distribution curves of free metal decreases sharply with increasing pH. This indicates involvement of metal ion in the complex formation process.

The relative stabilities of the binary and ternary complexes are quantitatively expressed in term of β_{111} , β_{20} , β_{02} , K_L , K_R , K_r and $\Delta \log K$ value which are represented in table 2-4. In the present investigation, the comparison of β_{111} with β_{20} and β_{02} these systems reveal the preferential formation of ternary complexes over binary systems [31]. The low positive values of K_L and K_R indicate less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands. The positive values of K_r but less which indicates lower stability of ternary complexes, results of present investigations shows the stability constants of ternary complex formed are less stable [32]. The negative values of $\Delta \log K$ suggests the formation of ternary complexes but less stable having destabilized nature of complexes which has been reported in N and O in coordination of amino acids [33]. The negative value of $\Delta \log K$ does not mean that the complex is not formed. The negative value may be due to the higher stability of its binary complexes, reduced number of coordination sites, steric hindrance [34-35], electronic consideration [36-37] difference in bond type, geometrical structure etc.

Thompson and Lorass pointed out that more negative $\Delta \log K$ value of ternary complexes is due to the electrostatic repulsion between the negative charge on the ligand and amino acids. Steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand coordinates with the metal ion in the lower pH range and form 1:1 and 1:2 complex. In solution, ternary complex forms as the titration curve run below the Cu (II)-drug titration curve. So, it is evident that the entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Cu (II)-drug complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Cu (II) metal ion and thus reduces the stability of ternary complexes.

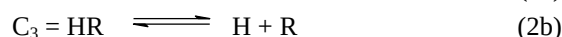
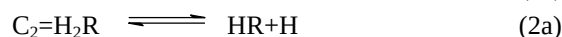
The order of stability of equilibrium constants β_{111} of ternary systems of Cu (II) transition metal ion with respect of secondary ligand is

Lab: val > gly > isoleu > met > ser > β - phe ala > ala > glu acid.

Lis: isoleu > met > val > gly > ala > β -phe ala > ser > glu acid.

Ben: ser > val > gly > isoleu > met > ala > β -phe ala > glu acid.

Species distribution curves: According to the result given by SCOGS computer programme, the concentration of different species distributed are as follows:



The species distribution curves of Cu (II) LR systems were obtained by plotting percentage concentration of various possible species formed during complexation versus pH of solution as shown in figure (4a-c). In all Cu (II) LR ternary systems, primary as well as secondary ligand forms 1:1 and 1:2 binary complexes. The species distribution curves of free metal (M), free ligands L and R indicates that there is a slowly decrease in concentration of free metal ions with increase in pH whereas increase in concentration of ligands with increase in pH and indicates higher percentage concentration of FL than FR. The species distribution diagram of various possible species of Cu (II) LR system shows the formation of mixed ligand complexes. The concentration for the formation of drug (L) and HR continuously decreases with increasing pH. The concentration of MLR species continuously increases, confirm the formation of ternary complexes Cu (II) LR.

**Figure: Species distribution curve of cu (II) LR₈ System
(pH versus % conc. of various possible species)**

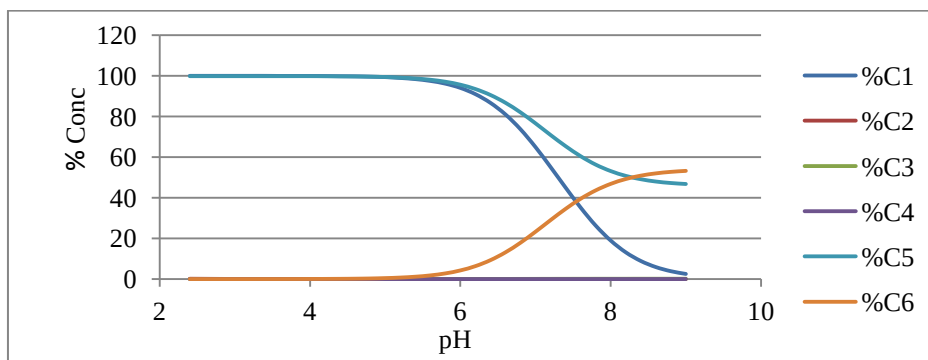


Fig 4a: cu (II)-Lab-DL-Val

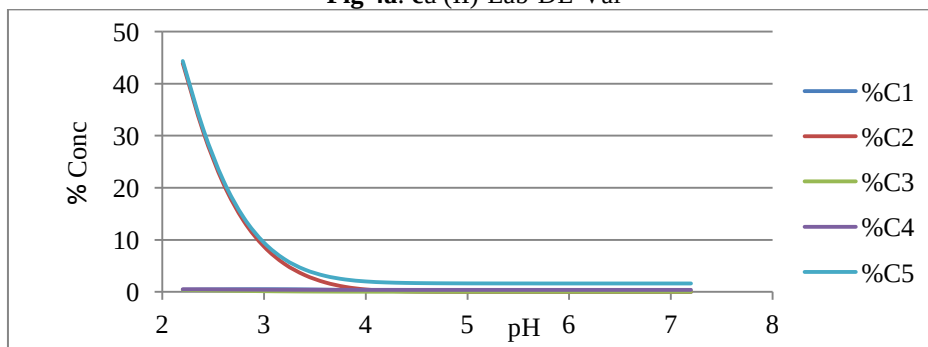


Fig 4b: cu (II)-Lis-DL-Val.

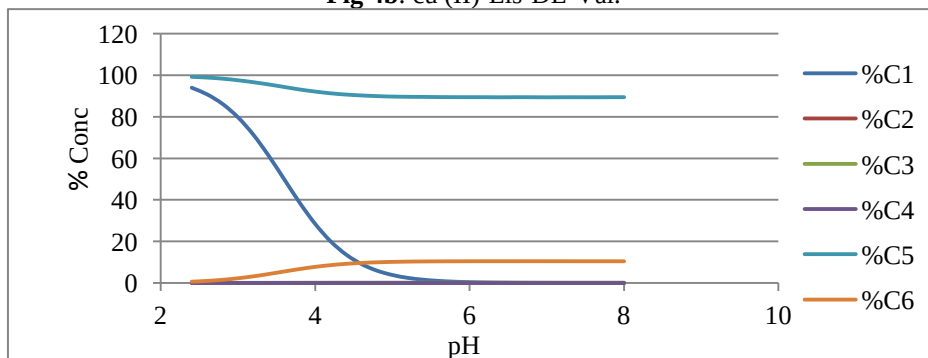


Fig 4c: cu (II)-Ben-DL-Val.

IV. Conclusion

The values of n for all primary ligand (drugs) and amino acid lies between 0.2 to 0.8 and 1.2 to 1.8 which indicate 1:1 and 1:2 complexes are formed by all the ligands with transition metal ions. The order of $\log K_1 > \log K_2$ is commonly observed. The stability constants of transition metal complexes obtained follows the usual natural order (Irving William natural order) of stability.

Stability of mixed ligand complexes is mainly affected by the characteristics of the approaching secondary ligand. The negative values of $\Delta \log K$ suggests the formation of ternary complexes that are less stable having the destabilized nature of complexes. The low positive values of K_L and K_R indicate less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands. The positive values of K_r but less which indicates lower stability of ternary complexes. The species distribution curve shows the formation of ternary complexes and deprotonation of amino groups.

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