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STABILITY CONSTANTS OF TERNARY COMPLEXES OF DRUGS AND AMINO ACIDS

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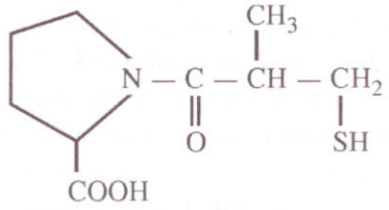
ABSTRACT

The formation constant of the ternary complexes (CuRL), where R = drugs of 2s–1–(3 mercapto–2–methylpropionyl)–L–proline i.e. Captopril (or) 4–[2–hydroxyl–3–(1–methyl ethylamino) propoxy] benzene acetamide i.e. Atenolol and L = amino acids–glycine, alanine, leucine, phenyl alanine, serine, threonine, valine, methionine were determined by potentiometric titrations in 50% (v/v) ethanol–water medium at 30°C and μ = 0. 1M $NaClO_4$ using the SCOGS computer programs. The stability of the ternary complexes is attributed to the possible hydrogen bonding between two ligands through water molecules.

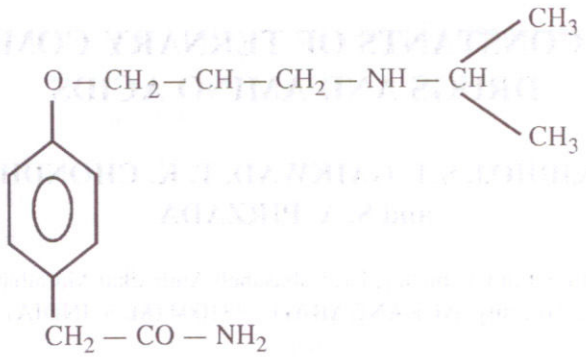
Key words: Formation constant, Ternary complexes, Captropril, Atenolol, Amino acids.

INTRODUCTION

Captopril, a sulpha drug is powerful angiotensin converting enzyme inhibitor and is most widely used in treatment of arterial hypertension[1]. It is assumed that the physiological action of captropril is connected with its ability to bound copper (II) and to transport it across cell membranes. Similar assumption for relation between captopril bonding with Zn (II), Cu (II) and the side effects of the drug was already discussed by other[2 – 5].



Atenolol is β–adrenoceptor blocking agent. Its principle effect is to reduce cardiac activity by diminishing β–adrenoceptor stimulations. This property is used in treatment of angina to reduce oxygen consumption and increase the exercise tolerance of the heart.



Ligands containing oxygen, nitrogen and sulphur donors are used as the chelates of heavy metals. The increase in affinity of Cu (II) towards sulphur containing ligands was attributed towards the reduced steric hinderance and increased polarization of the sulphur atom[6–8]. The complexes of Cd (II), Cu (II) and Ni (II) with methylene bisthiopropionic acid were studied by Tiwary et al.[9] and IR spectra showed that the coordination takes place through both; sulphur and carboxylic groups of the ligands. The complexes of thiocarboxylic acids are interesting because they have both sulphur and oxygen as potential donors. Metal complexes of monothiocarboxylic acid[10–13] and dithiocarboxylic acid[14] have been studied extensively. Cefola et al.[15] have also shown that the stability of some transition elements decreases as the stability group changes from –SH to – OH to $-NH_2$.

EXPERIMENTAL

All reagents used were of A.R. grade and all the solutions were prepared in doubly distilled water and standardized by usual procedure[16]. The titrations were carried out using a digital pH meter [Elico model LI–120] in conjunction with combined electrode. All titrations were carried out at 30 ± 0.1°C. For the determination of formation constants of the ternary complexes, the following sets of solutions were prepared and titrated against standard alkali solutions.

0.008M $HClO_4$, 0.002M ligand R, 0.002M ligand L, 0.002M $M(ClO_4)_2$, and 0.1M $NaClO_4$ solutions were prepared. The proton ligands formation constant of the drugs H_2R and HR and the formation constants of binary complexes CuR and CuR_2 were determined in 50% (v/v) aqueous ethanol at 30°C and μ = 0.1M $NaClO_4$. Concentration of total metal, total ligands, free metal, free ligands and various possible species that are formed during the complexion is calculated using SCOGS computer program[17–18] (charges on species have been omitted for simplicity). In case of amino acids, proton ligand formation constants and metal ligand formation constants were also refined under identical conditions. The values given in Table 1 are in agreement with those reported earlier[18–20]. These refined values were used as fixed parameter for the refinement of the formation constants of mixed ligand complexes CuRL. The set of solution ($50cm^3$) having Cu : R : L in 1 : 1 : 1 ratio were prepared and titrated against

standard carbonate free NaOH solution. The titrations of each set were carried out twice to check the reproducibility of the data.

Table 1. Proton–ligand and metal–ligand ternary constants at 30 ± 0.1°C in 50% (v/v) ethanol–water medium, μ = 0.1M $NaClO_4$

(a) Proton ligand stability constants

Ligand	P^{k2}	P^{k1}	Log k2	Log k2
Captopril (R1)	10.68	3.85	5.00	9.76
Atenolol (R2)	–	9.00	–	5.12
Glycine (L1)	9.63	3.10	7.82	8.98
Alanine (L2)	9.90	3.32	7.71	9.65
Leucine (L3)	9.70	3.58	6.71	9.18
Phenyl alanine (L4)	9.18	3.10	7.27	8.47
Serine (L5)	9.20	3.25	8.00	9.60
Theronine (L6)	8.56	2.99	7.84	8.81
Methionine (L7)	9.30	3.28	6.98	8.64

(b) Stability constant of ternary complexes

L	Captopril (R1)		Atenolol (R2)	
	Log $\beta^{M\,MRL}$	Δ Log K_M	Log $\beta^{M\,MRL}$	Δ Log K_M
Glycine	18.25	–0.48	13.10	–0.99
Alanine	19.26	–1.34	15.97	0.00
Leucine	18.95	0.01	13.68	–0.61
Phenyl alanine	17.24	–0.98	12.34	–1.24
Serine	19.37	–0.01	1370	–1.01
Theronine	16.82	–1.74	12.36	–1.56
Methionine	17.40	–0.99	11.77	–1.98

RESULTS AND DISCUSSION

The formation constant for the binary copper (II) with drugs and amino acid were computed. In captopril, bridging nature of mercapto sulphur under present experimental condition such as polynuclear complex species have been found to be absent. The Log β values obtained suggest that the ligands bind the metal through the mercapto group. The lower p^k of

–COOH group than any saturated aliphatic acid is because of the amide group present near the carboxylic group having a tendency of electron withdrawal by mesomeric effect. Slight enhancement in the dissociation constant (p^{K_2}) can be justified of partial steric hindrance associated with mercapto group.

The only one p^K observed for atenolol can be attributed to the dissociation of conjugated acid formed by the interaction of secondary amine and perchloric acid, which is used as a medium of titrating mixture. However the observed p^K is somehow lower than that of dimethylamine. This is because of steric hindrance and no inductive field effect is operative. The – OH group present in the structure is alcoholic and its expected p^K value is about 18.0, which cannot be determined by this technique. So the ligand shows only one p^K, which is the association constant of –NH group. The amino group present in this structure is so neutral that it can not dissociate.

The stability of mixed ligand complexes is mainly governed by the characteristics of the approaching secondary ligand. The stability therefore depends mainly on the ring size, which offsets the overall basicity of the secondary ligand. It can be inferred that the stability of complex depends much more on the length and spatial configuration of the chelate ring than on the acidity of complexing agent.

Only 1 : 1 : 1 ternary mixture have been used in this study to ensure the exclusive formation of the simplest ternary complex MRL. Considering the p^K values of the ligand and hydrolytic constant of the M^{2+} ions, the following species have been considered to exist in the complextion equilibria.

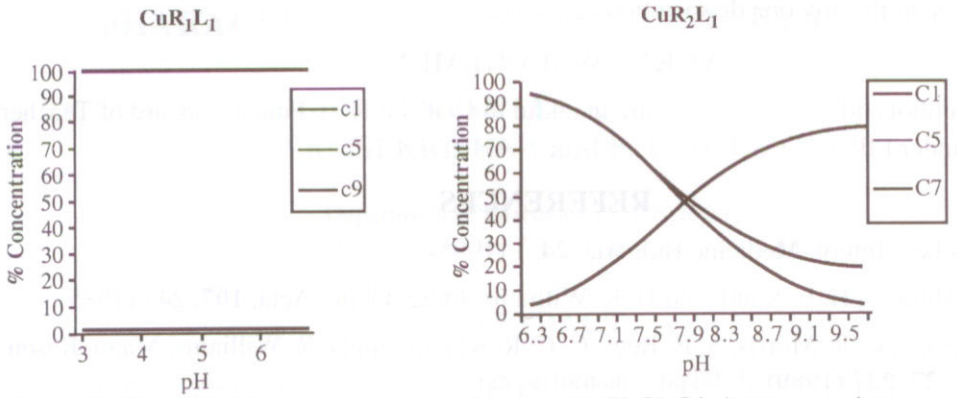
M^{2+}, RH_2, RH, R^{2-}, $M(OH)^+$, $M(OH)_2$, M(A), ML^{2+}, M(A) (OH), M(L) (OH), M(A), (L) and M(A) (L) (OH)

The stability constant of Log K^M MR, Log K^M ML, log β^M MAL (Table 1) and the speciation curves (Fig.1) were obtained as computer outputs. Complex formation equilibria have been elucidated on the basis of speciation curves. The stability of ternary MRL complex formation was generally characterised on the basis of ΔLog K^M values calculated using relation[1].

$$\Delta \text{ Log } K^M \Leftrightarrow \text{ Log } \beta^M_{MRL} - \text{ Log } K^M_{MR} - \text{ Log } K^M_{ML} \qquad ...(1)$$

Examination of the speciation curves (Fig.1a) of Cu–R_1–L system with L amino acids R_1= captopril, indicate the formation of CuRL complexes to considerably high extent i.e. 100% from the beginning of titration and is constant through out the pH range which is shown by parallel line to x–axis. The concentration of MR and ML are negligible in the entire pH range. It indicates that the formation of ternary complex may entirely take place by the following possible reaction.

$$M + L + R \Leftrightarrow MLR$$



Species C2,C3,C4,C7,C8 have very low concentration, so the curves of these species are approx. on X-axis

Species C2,C3,C4,C6 have very low concentration, so the curves of these species are obtained.

Fig. 1. Speciation Diagram

The negative values of Δ LogK (Table–1b) reveals the preferential formation of ternary complexes over binary complexes of both: primary as well as secondary ligands.

Similar nature of speciation curves was observed for other amino acids also.

In CuR_2L system, where R_2 = atenolol and L = amino acids, the species distribution diagram 1b shows that the concentration of primary Ligand HR and that of MR species is 95% each at the initial pH which decreases sharply with increasing pH. It is seen that the concentration of CuLR species increases sharply to 80% in the same pH range. This is the clear indication of the formation of ternary complex entirely in the reaction MR + L ⇔ MRL. Possibility of formation of ternary complex by other reaction is negligible since the concentration of other species is negligibly small. The Δ Log K values for these complexes are also negative indicative of ternary complexes. The possibility of formation of ternary complex seems negligible by other reaction. This is because the percentage concentration of all other species is negligibly small. Similar trend was observed for other amino acids.

Stability of binary MR, ML and ternary MRL complexes fall in expected order. Trends in log β^M MAL values were found to be same as that of log K^M ML values. However as expected, Δ Log K_M values were less negative or positive. This may be attributed to the π–acidic character of drugs and O–N coordination of the amino acid. The stability of mixed ligand complex is found to be less than that of binary complexes. The stability constants of ternary complex were found to be greater in R_1 and R_2. This trend can be justified on the basis of ring size of chelate and structure. The high stability of R_1 chelate may be due to extra stabilization of five

membered chelate ring and also because, it is a sulpha drug. The low stabilisation of complex of R_2 may be due to its only one dissociation constant.

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