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Stability Constants of Mixed Ligand Complexes of Cu(II) and Atenolol with L-Methionine/L-Cysteine/L-Penicillamine and S-Methyl-L-Cysteine

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Chemical equilibrium studies have been investigated pH metrically in 20% (v/v) ethanol-water mixture in I = 0.1 M $NaClO_4$ at a temperature of 25 degrees for an interaction between Cu (II) and atenolol, (2-[4-[2-hydroxy-3-(propan-2-ylamino) propoxy]phenyl]acetamide, (A) and amino acids, (L):L-methionine, L-cysteine, L-penicillamine and S-methyl-L-cysteine (S). The results of potentiometric titrations were used to infer 1:1:1 ternary complexes, 1:1 and 1:2 binary complexes formation. Conclusively, in ternary complexes that involve amino acids, atenolol is the primary ligand. The stability constants of the complexes were determined based on computer analysis of potentiometric results using the HYPERQUAD program. The relative stability of ternary complexes as compared to that of corresponding binary amino acids complexes can be quantitatively expressed in terms of Δ log K and % R.S. The speciation diagrams of various complex species were evaluated as a function of pH.

Keywords: Potentiometric titration; Stability constants; Ternary complexes; Drug; amino acids.

1. INTRODUCTION

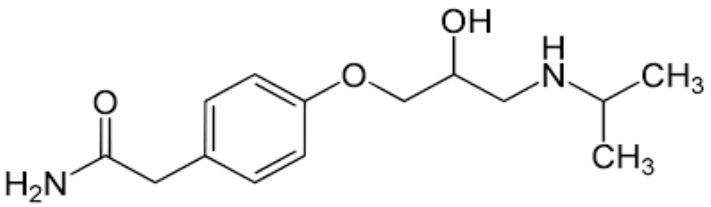
Atenolol Fig. 1 (A) is a beta-blocker used mainly as a treatment for Hypertension and Angina Pectoris [1]. Its mechanism of action is the blockage of beta-adrenergic receptors found on blood vessels and the heart; consequently inhibiting the action of the hormone adrenaline (epinephrine), which reduces heart strain and lowers blood pressure. Atenolol displays major pharmacological action when the functional group Amine is charged at physiological pH. Lately, metal-related biological processes have been affected by complexation [2-4]. In addition to their use to aid diagnosis, metals with therapeutic

properties have been used to treat chronic illnesses, such as rheumatoid arthritis, cardiovascular diseases, inflammatory diseases and diabetes [5,6]. The hydroxy-amino groups make Atenolol qualify as a chelating ligand, which allows a five-membered ring to be formed [7,8]. Additionally, equilibrium data are of great significance in understanding beta-blockers and their activity in vivo. The study of transition metal ions containing amino acids and their complexation has been of great interest to scientists [9–11]. Information regarding the strategies used by biological systems alongside their stability and specificity to enhance factors in biotechnological applications are provided by ternary complex models [12]. Furthermore, two distinct bio-ligands and metal ions that form a ternary complex can be an example of biochemical reactions mediated by metal ions and of a substrate–metal ion–enzyme interaction [13]. Drugs' mechanism of action are determined by referring to complex metal ion equilibrium studies [14], Moreover, drug efficiency is determined by multiple elements, such as the administration route, drug adsorption, drug distribution and elimination. This paper investigates a reactions of Atenolol (A) and Cu(I1) ion with amino acids that contain L-penicillamine, L-methionine, L-cysteine and S-methyl-L-cysteine in 20% v/v ethanol-water medium at a temperature of 25°C and ionic strength of I = 0.1M ($NaClO_4$). The difference between ternary complexes' stability and the stability of binary complexes was addressed in terms of the parameters *%R.S* and *Δlog K*. Additionally, species distribution diagrams are discussed as pH functions.

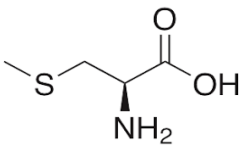
2. EXPERIMENTAL

2.1. Materials

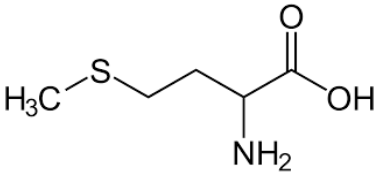
Sigma-Aldrich provided Atenolol, amino acids (L-methionine (M), L-cysteine (C), L-penicillamine (P) and S-methyl-L-cysteine), mercaptoethylamine and $CuCl_2 \cdot 2H_2O$. The compounds, which had a purity range of 99–99.9%, were not purified after arrival. Figure 1 shows the structure of a number of ligands studied in this paper.



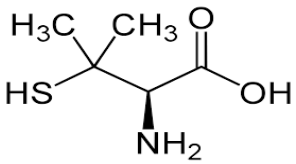
Atenolol (A)



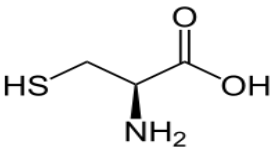
L-methionine



S-methyl-L-cysteine



L-penicillamine



L-cysteine

Figure 1. Structure of ligands.

2.2. Measurements

The preparation and titration of the studied solutions (v = 40 ml) was against 0.05M of NaOH and a $NaClO_4$ (0.1M) and amino acid and drug ligands (0.005M) – containing solution (v = 40 ml) allowed the determination of amino acids' and Atenolol's constant of protonation. A solution (v = 40 ml) that contains $NaClO_4$ in 1:1 and 1:2 ratios (0.1M), drug and amino acid ligands (0.015M) and Cu (II) ion (0.005M) was used to determine the constants of stability of binary complexes and the constants of stability of ternary complexes were estimated using a solution (v = 40 ml) that contains NaClO4 in 1:1:1 ratio (0.1M), Cu (II) ion (0.005M), drug (0.005M), amino acids (0.005M). $HClO_4$ solution was added to all titrations to ensure they were protonated at the start of the process. Using a Griffin pH J-300-010 G Digital pH meter, all titrations were performed at room temperature in a double-walled cell. In order to calibrate the electrode before pH measurements, standard buffer solutions with a pH of 4.008 and 6.865 were used.

2.3. Calculations

The equations of general equilibrium representing amino acids (L), Cu (II) ion and Atenolol (A) and complexation is shown below:

$$l(Cu) + p(A) + q(L) + r\,(H) \rightleftharpoons (Cu)_l\,(A)_p\,(L)_q\,(H)_r \quad (1)$$

$$\beta_{lpqr} = \frac{[Cu_l A_p L_q H_r]}{[Cu]^l\,[A]^p [L]^q\,[H]^r} \quad (2)$$

H-atoms, Atenolol, amino acids and Cu (II) ion coefficients are (r, p, q and l), in that order. HYPERQUAD is a program employed to obtain the constants of stability of ternary and binary complexes; in addition to its role in determining the ligands' constants of protonation constants [15]. HySS is a program used to obtain pH values, which were placed against plotted species percentage concentrations to produce species distribution curves [16].

3. RESULTS AND DISCUSSION

In a water-ethanol solution (20% v/v), with 0.1 M $NaClO_4$ ionic strength and at a temperature of 25 °C, both constants of formation of binary complexes and constants of protonation of the ligands were found. Table 1 shows the estimated values determined in this paper, which agree with previously recorded values [17-19].

3.1. Stability constants of binary and ternary complexes

The titration process involving amino acids (L) and Atenolol (A) constitutes two stages in which Cu (II) ion is absent and present. In comparison to the free ligand curve, the Cu (II) complex titration curve is lowered, which implies that hydrogen ion release is linked with the formation of a complex. Figure 2 displays the potentiometric titration curves of the binary system Cu (II)-Atenolol. Table (1) shows the constants of stability of the complexes.

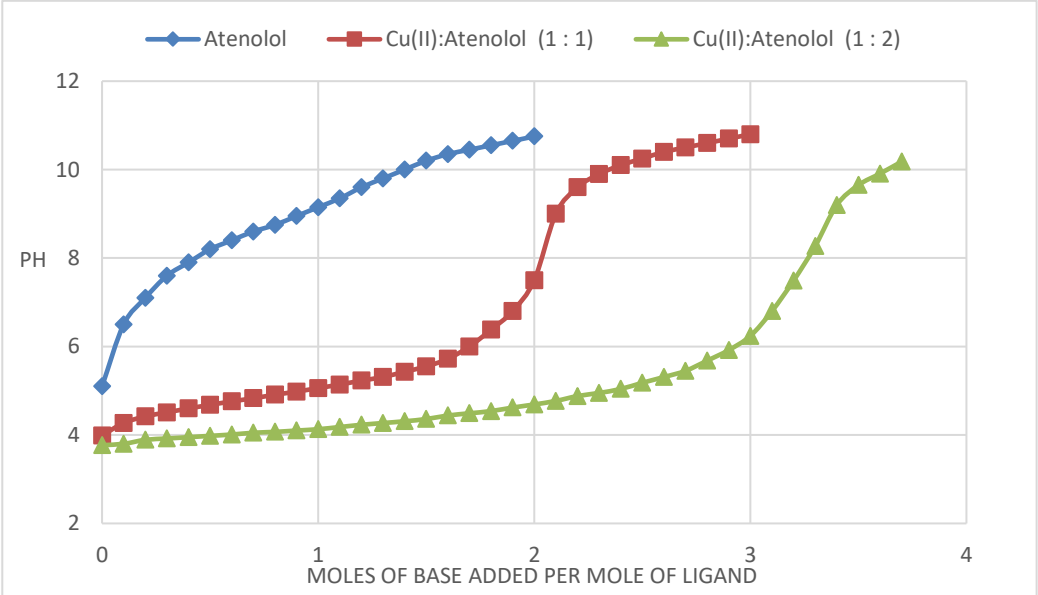


Figure 2. Potentiometric titration curve of Cu(II)- Atenolol (A) system in 20% E—80% water [Temp. = 25°C and I = 0.1 M $NaClO_4$].

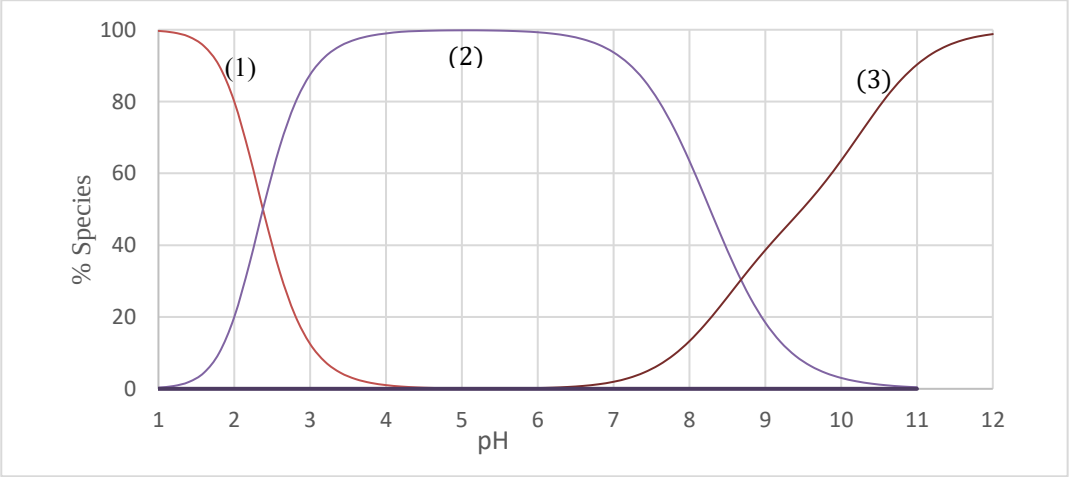


Figure 3. The pH of Cu(II)-Atenolol (A) and the species distribution related to its function in 20% E—80% water [Temp. = 25°C and I = 0.1 M $NaClO_4$]. Species: (1) Cu(II) ; (2) Cu(II)A; (3) Cu(II)A2

The model containing Cu(A)2 and Cu(A) species, which consist of five-membered chelate rings formed by the donor set –NH and –OH, has the best statistical fit for the binary system of Cu(II)-

Atenolol. Fig. 3 presents the Cu (II)-A system diagram of species distribution. The strong affinity between the amino group, which has a displaced proton that leads to complexation, and Cu (II) results in the early formation of Cu (A).

$\log K^{Cu(A)}_{Cu(A)(L)} (= \log\beta^{Cu}_{Cu(A)(L)} - \log K^{Cu}_{Cu(A)})$ and $\log K^{Cu(L)}_{Cu(A)(L)} (= \log\beta^{Cu}_{Cu(A)(L)} - \log K^{Cu}_{Cu(L)})$ constants were estimated in Table 2 and a comparison between them took place to determine the primary and secondary ligand; in addition to the ligand responsible for forming mixed ligand complexes. In all systems, the primary ligand is Atenolol and the secondary ligands are the amino acids.

The chelate ring containing five members allows S-methylcysteine to form a complex that is more stable (1110) than the less favorable methionine, which has a chelate ring of six members.

Table 1. Proton ligand formation constant and stability constants of their binary complexes in 20% E—80% water [Temp. = 25°C and *I* = 0.1 M $NaClO_4$].

System	l	p	q	r[a]	log β[b]
Atenolol	0	1	0	1	9.56(0.02)
	0	1	0	2	11.34(0.02)
	1	1	0	0	3.03(0.01)
	1	2	0	0	8.15(0.03)
L-Methionine	1	1	0	0	9.29 (0.01)
	1	2	0	0	11.26(0.02)
	1	0	1	0	6.77(0.03)
	1	0	2	0	12.23(0.02)
S-Methyl-L-Cysteine	1	1	0	0	7.28(0.01)
	1	2	0	0	11.22(0.02)
	1	0	1	0	7.80(0.01)
L-Cysteine	1	1	0	0	9.32(0.01)
	1	2	0	0	17.73(0.02)
	1	0	1	0	8.33(0.01)
	1	0	2	0	14.03(0.01)
	1	0	1	1	17.50(0.02)
L-Penicillamine	1	1	0	0	9.15(0.01)
	1	2	0	0	16.78(0.02)
	1	0	1	0	10.45(0.03)
	1	0	2	0	19.52(0.05)
	1	0	1	1	21.89(0.05)
Mercaptoethylamine	1	1	0	0	10.15(0.01)
	1	2	0	0	17.23(0.01)
	1	0	1	0	19.21(0.03)
	1	0	2	0	18.52(0.05)
	1	0	1	1	23.89(0.05)

[a] *p*, *l*, r and q are stoichiometric coefficients that correspond to A, Cu(II), H^+ and L. [b] standard deviations are given in parentheses.

The binding sites of the tridentate ligand L-Cysteine\L-Penicillamine are carboxylate, thiol and amino groups. The complexes' constants of stability agree with mercaptoethylamine, which has sulfhydryl and amino groups as the binding sites as seen in Table 2. Therefore, the penicillamine and cysteine are forming a ligand with the Cu (II) ion by the deprotonated-sulfhydryl group and the amino group, which is found in literature [20].

Cysteine and penicillamine systems' pH titration data shows the formation of protonated CuALH (1111) and the corresponding CuALH (1111), which is a protonated species. Acid dissociation constants (pK^H = log β_{1111} − log $\beta_{1110)}$ of the protonated ternary complexes obtained from mercaptoethylamine, cysteine and penicillamine are 6.19, 6.52 7.78, respectively. These estimated values in this research are lower than those of previous reports [20], which indicates the possible involvement of –SH and $[–NH_3]^+$ groups in forming complexes.

Table 2. Stability constants of binary and ternary complexes in 20% E—80% water [Temp. = 25°C and I = 0.1 M $NaClO_4$].

System	l	p	q	r[a]	log β[b]	$\log K^{Cu(A)}_{Cu(A)(L)}$	$\log K^{Cu(L)}_{Cu(A)(L)}$	Δ logK	% R.S[c].
Cu(II)-A- L-Methionine	1	1	1	0	8.33(0.02)	5.30	1.56	-1.47	-21.71
Cu(II)-A- S-Methyl-L-Cysteine	1	1	1	0	9.28(0.01)	6.25	1.48	-1.55	-19.87
Cu(II)-A- L-Cysteine	1	1	1	0	10.50(0.01)	7.47	2.17	-0.86	-10.32
	1	1	1	1	17.02(0.02)				
Cu(II)-A- L-Penicillamine	1	1	1	0	10.91(0.01)	7.88	1.46	-1.57	-16.61
	1	1	1	1	18.69(0.02)				
Cu(II)-A- Mercaptoethylamine	1	1	1	0	10.10(0.01)	7.07	1.52	-2.14	-23.24
	1	1	1	1	16.29(0.01)				

[a] *p*, *l*, r and q are stoichiometric coefficients that correspond to A, Cu(II), H^+ and L. [b] standard deviations are given in parentheses. [c] the percentage relative stabilization value.

By HySS computer program, the increase in pH was followed by an increase in complex concentration in all species distribution curves allowing the formation of the complex to prevail in physiological pH. The favored complex species at low pH values are protonated ternary complex species. Penicillamine, which is the representative amino acid, has a species distribution that is shown in Fig. 4.

Ternary complexes relative stability with respect to the corresponding binary analogs can be articulated quantitatively in terms of Δlog K and % R.S parameters as follows:

$$\Delta\, logK = logK^{CuA}_{Cu(A)L} - \left(logK^{Cu}_{Cu(L)}\right) \quad (3)$$

$$= logK^{CuL}_{Cu(A)L} - \left(logK^{Cu}_{Cu(A)}\right) \quad (4)$$

For all systems, the parameter Δ log K is negative (Table 2), showing the formation of a complex with free Cu(II) ion by the amino acid and that is more stable than the Cu(II)-A complex, which was noted

statistically as additional coordination positions were present to bind the secondary ligand to the Cu(II) ion instead of the Cu(II)-A complex [21].

% RS (percent relative stabilization) is used to determine the quantity of ternary complex stability and is expressed as [22]:

$$\% \text{ R.S} = \left[\frac{\left(log\, K^{Cu(A)}_{Cu(P)L} - log\beta^{Cu}_{Cu(L)}\right)}{log\beta^{Cu}_{Cu(L)}}\right] \times 100 \quad (5)$$

(percent relative stabilization)

Negative % R.S. values correspond to the values of Δ log K listed in Table 2, which can be linked to the fact that binary Cu(II)-atenolol complexes have stability that is higher than that of ternary complexes associated with amino acids.

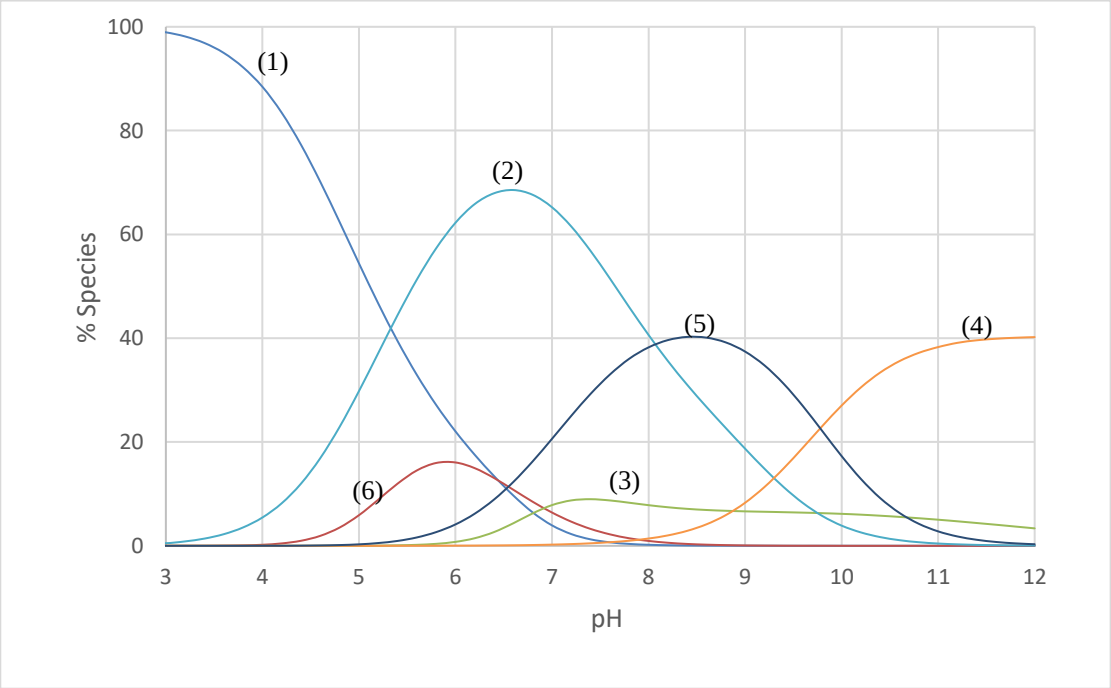


Figure 4. The pH of Cu(II)-A-penicillamine and the species distribution related to its function in 20% E—80% water [Temp. = 25°C and I = 0.1 M $NaClO_4$]; Species: (1) Cu(II); (2) Cu(II)A; (3) Cu(II)L; (4) Cu(II)L2; (5) Cu(II)- A- L; (6) Cu(II)- A- LH

4. CONCLUSION

Current investigations discuss ternary and binary complexes of Cu(II) and their formation equilibria with the involvement of amino acids and atenolol (A). The formation of ternary complexes is achieved by a step-by-step procedure, while amino acid ligation follows the binding of Cu (II) to atenolol. The concentration distribution of complexes was assessed and the stability constants were determined. The more negative Δ log K value suggests that there is steric hindrance in the ternary complex formation due to the bulkiness of drug.

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