ORIGINAL ARTICLE

Potentiometric study of atenolol as hypertension drug with Co(II), Ni(II), Cu(II) and Zn(II) transition metal ions in aqueous solution

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Abstract Binary and ternary complexes of Co(II), Ni(II), Cu(II) and Zn(II) with atenolol as hypertension drug and glycine 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.

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1. Introduction

Knowledge of the physicochemical properties of a drug compound, e.g. its acid–base properties is important in the optimization stage of a drug development project. Commonly dissociation constants of drug compounds are determined by techniques such as titration by potentiometric in aqueous solution. Potentiometric titrimetry in aqueous solutions is the most precise method for the determination of equilibrium constants. Stability constant values can also be predicted by computational methods. These techniques have certain advantages, for example calculations can be performed on large virtual compound libraries. Still, erroneous data are often predicted for complex and flexible drug compounds containing several functional groups. Furthermore, these calculations are based on parameters in databases containing experimental data from the literature. Hence, sufficient data for new types of compounds, to give accurate predictions (Shokrollahi et al., 2008) may be missing (Ornskov et al., 2003). Recently, complexation has often been used to influence biological processes that are metal dependent, at the same time; many drugs behave as ligands, coordinating biometals such as Co(II), Ni(II), Cu(II) and Zn(II) which affects their homeostasis. It can be assumed, therefore, that the action of at least some of the drugs used in the treatment of metal-dependent diseases can be explained on these grounds (Bontchev et al., 2000). Arterial hypertension represents a good example of this type, being sensitive to the copper and zinc concentration levels (Sultana et al., 2008). The β-blockers are among the drugs most widely used in the

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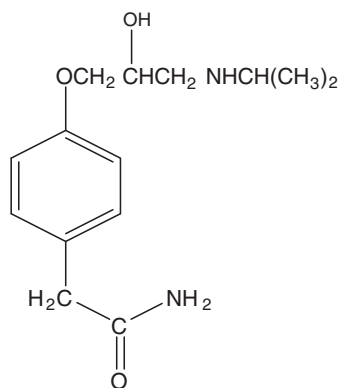Peer review under responsibility of King Saud University.

Figure 1 Atenolol: 2-[4-(2-Hydroxy-3-isopropylamino-propoxy)-cyclohexa-1, 2, 3, 5-tetraenyl] acetamide.

Figure 3 Binuclear complex of atenolol. $R_1 = CH_2OC_6H_4[CH_2C(O)NH_2]^{-4}$; $R_2 = CHMe_2$.

treatment of various cardiovascular disorders, such as angina pectoris, cardiac arrhythmia and hypertension (Martinez et al., 2000), and for that reason we have initiated a study on their complexation with copper and zinc. This paper deals with the ligand–ligand interactions of Co(II), Ni (II), Cu(II) and Zn(II) ternary complexes involving atenolol and glycine because, glycine is an inhibitory neurotransmitter in central nervous system, especially in the spinal cord, brain stem, and retina. In the formation of the ternary complex ML_PL_S, where primary ligand (L_P) and secondary ligand (L_S) and atenolol sometimes behavior as primary ligand (L_P) and sometimes as secondary ligand, depend on proton ligand stability constant of ligand, and glycine as essential amino acid behaves as a uni-negative bidentate ligand with N and O donor sites and coordinated to the metal ions via *N*-amine group and deprotonated carboxylic oxygen. It was, therefore, thought of interest to study the formation constants of ternary complexes of the type [M-primary ligand (L_P)–secondary ligand (L_S)] and to compare with the values of various complexes. Atenolol (RS)-4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide (Fig. 1) is a typical β-blocker, having a prolonged effect. The atenolol molecules are coordinated to metal ions (II) forming, consequently, the complexes $[Cu–(HAt)]^{2+}$ and $[Cu–(HAt)_2]^{2+}$, where atenolol acts as a bidentate (–OH, –NH) neutral ligand. The addition of the next two undissociated ligands HAt leads to the formation of the mononuclear $[Cu–(HAt)_2]^{2+}$ complex, where HAt in the axial position is coordinated as a monodentate ligand. On the basis of all data obtained the following structures are
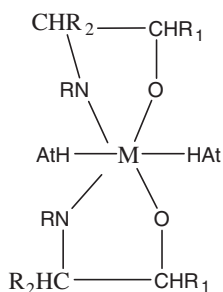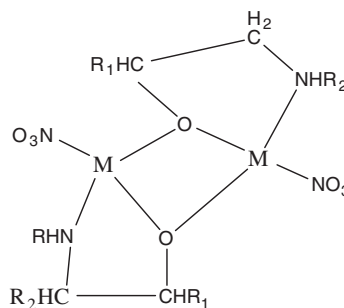
suggested for the mononuclear (Fig. 2) and binuclear (Fig. 3) complexes, respectively, atenolol a good chelating ligand, allowing the formation of a five-membered ring. The properties of atenolol are: chemical formula ($C_{14}H_{22}N_2O_3$), molecular weight = 266.3, melting point = 146° to 148°, sparingly soluble in water and isopropanol; freely soluble in methanol; soluble in acetic acid and dimethyl-sulfoxide; very slightly soluble in acetone and dioxane; practically insoluble in acetonitrile, ethyl-acetate, and chloroform, yellow–brown solid.

2. Experimental

All the reagents used were of AR grade. Potentiometric titrations were carried out in aqueous solution at room temperature and ionic strength 0.01 M ($NaClO_4$) 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 (M^{2+}: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 0.002 M and 0.001 M in ratios M^{2+}:L_P:L_S = 1:1:1 and 1:1:2, 1:2:1 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 (Gaizer, 1979; Gans et al., 1996; Berthon, 1995). 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.

3. Results and discussion

3.1. Binary complexes

The proton ligand stability constants (pK) and metal ligand stability constants (log K) of binary complexes were determined by using Irving and Rossotti methods for comparison

Figure 2 Mononuclear complex of atenolol.

Table 1 The proton ligand stability constants.

Ratio	Atenolol		Glycine	
	pK_1	pK_2	pK_1	pK_2
1:1	2.76	9.56	2.29	10.01
1:2	4.24	10.70		9.91

with those of the ternary systems. The deviation of metal titration curves from ligand curve indicates the formation of binary complex. The highest values of n^- being around 2.0 in atenolol drug indicates the formation of 1:1 and 1:2 binary complexes whereas in atenolol drug it is around 1 hence the 1:1 binary complex formation.

3.2. Mixed ligand complexes

In the formation of the ternary complex ML_PL_S, $\Delta \log K$ and percent relative stabilization (% R.S.) (Khalil and Radalla, 1998) to quantify the stability of a ternary complex represent the difference in the tendency of the ligand to bind to the free metal ion and the metal ion already is bound to another ligand, which is represented as follows:

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

$$K_r = \beta_{111}^2 / \beta_{20} \cdot \beta_{02}$$

$$K_{L_p} = \beta_{111} / \log K_{10}$$

$$K_{L_s} = \beta_{111} / \log K_{01}$$

$$R.S.\% = \{(\log K_{ML_PL_S} - \log K_{ML_P}^M / \log K_{ML_P}^M) \times 100$$

From statistical considerations, it is expected that $\Delta \log K$ should be negative, but variations are observed, dependent on the nature of the metal ion and the ligand. The formations of 1:1:1, 1:1:2 and 1:2:1 ternary complex (ML_PL_S) were identified qualitatively by the pH of precipitation of ML_P, ML_S, and ML_PL_S titration curves which indicate the higher value of the pH of precipitation of ternary system than that of the corresponding binary systems.

4. Stability of mixed ligand complexes

The mixed ligand stability constant (Sigel, 1975) of atenolol and among metal ions complexes of glycine, Co(II)–glycine–atenolol (1:1:2) complexes have high value and Zn(II)–atenolol–glycine (1:1:2) complexes have low value of stability. The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of $\Delta \log K$, K_r, K_{L_P} and K_{L_S} values. The comparison of β_{111} with β_{20} and β_{02} of these systems reveals the preferential formation of ternary complexes over the binary systems (Ammar et al., 2011). The low values of K_{L_P} and K_{L_S} indicate the high stability of ternary complexes with respect to binary complexes of primary and secondary ligands. The positive values of K_r 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 group of ligands .The negative values of $\Delta \log K$ suggest the formation of ternary complexes but are less stable having the destabilized nature of complexes which have been valid for N and O donors. The positive value of $\Delta \log K$ in some cases is attributed to the extra stability of ternary complexes. The formation of binary complexes with transition metal ions indicates the low stability of copper (1:1) complexes which may be one of the reasons to fewer occurrences of cobalt complexes in the biological systems Table 1.

The ternary complexes indicate the highest stability of cobalt complex of (1:1:2) ratio and low stability of zinc complex of (1:1:2) ration which is commonly true in the 3d series of present transition metal ions. The values of % R.S. have been calculated (Table 2). For all systems, the parameter % R.S. is negative. This may be attributed to the higher stability of binary M(II)–atenolol complexes than those corresponding to the ternary systems involving carboxylic acids. Negative values of % R.S. agree with the $\Delta \log K$ values.

5. Species distribution curves

According to the result given by SCOGS computer program, the concentration of different species distributed are as follows:

Table 2 Parameters based on some relationship between formations of mixed ligand complexes of primary ligand and secondary ligand.

Parameters	1:1:1				1:1:2				1:2:1			
	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
$\log K_{10}$	4.79	5.87	8.18	5.85	3.66	3.66	3.68	3.67	4.3	5.65	8.07	4.18
$\log K_{20}$					3.94	3.65	3.78	4.22	4.67	5.45	7.85	4.42
$\log K_{01}$	4.54	4.46	3.67	5.92	4.79	5.87	8.18	5.85	4.54	4.46	3.67	5.92
$\log \beta_{20}$	4.79	5.87	8.18	5.85	7.6	7.31	7.46	7.6	8.97	11.1	15.92	8.6
$\log \beta_{02}$	4.54	4.46	3.67	5.92	4.79	5.87	8.18	4.79	8.97	4.46	3.67	8.6
$\log \beta_{111}$	9.05	9.21	9.01	10.32								
$\log \beta_{112}$					10.77	9.37	8.87	7.84				
$\log \beta_{121}$									9.57	10.64	10.29	9.21
K_r	1.94	1.78	1.52	1.75	1.74	1.42	1.13	1.74	1.07	1.37	1.05	1.07
K_{L_P}	1.89	1.57	1.10	1.76	2.94	2.56	2.35	2.94	2.23	1.88	1.28	2.20
K_{L_S}	1.99	2.07	2.46	1.74	2.25	1.60	1.08	2.25	2.11	2.39	2.80	1.56
$\Delta \log K$	−0.28	−1.12	−2.84	−1.45	2.32	−0.16	−25.2	2.32	0.73	0.53	−1.45	−0.89
% R.S.	−95.7	−96.7	−99.2	−95.5	−92.9	−94.3	−94.8	−95.8	−94.7	-95.0	−97.8	−95.0
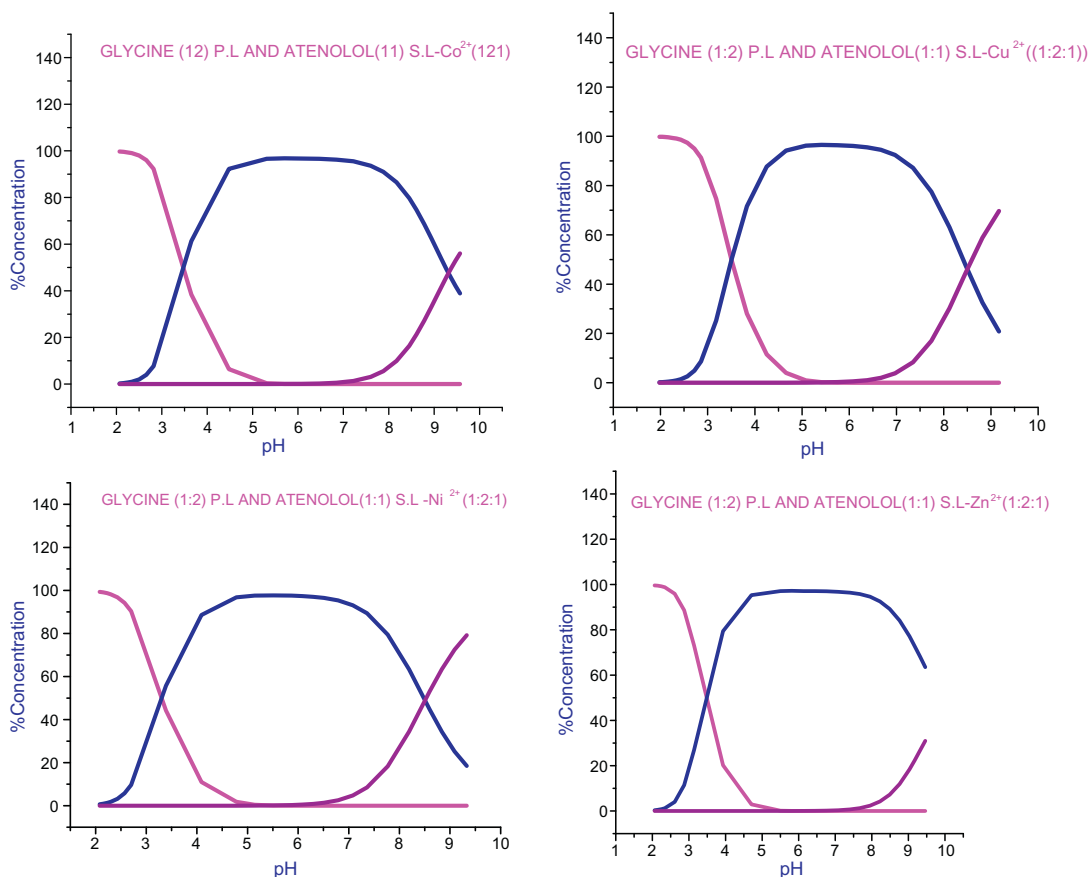
Figure 4   Glycine (1:2) as primary ligand and atenolol (1:1) as secondary ligand (1:2:1).

$$C_1 = HL_P \rightleftharpoons H + L_P \tag{1a}$$

$$C_2 = H_2L_S \rightleftharpoons HL_S + H \tag{2a}$$

$$C_3 = HL_S \rightleftharpoons H + L_S \tag{2b}$$

$$C_4 = M(II) + L_P \rightleftharpoons ML_P \tag{3a}$$

$$C_5 = M(II) + L_S \rightleftharpoons ML_S \tag{4a}$$

$$C_6 = M(II) + L_P + L_S \rightleftharpoons ML_PL_S \tag{5}$$

.The species distribution curve shows the formation of ternary complexes shown in Fig. 4 considered in different systems was as follows: HL_P, H_2L_P, HL_S, H_2L_S, ML_P, ML_S, ML_{2S}, ML_PL_S. The Species distribution curves of metal ions(II) L_PL_S systems were obtained by plotting percentage concentration (90%) of various possible species formed during complexation versus pH of solution as shown in Fig. 4 as representative graphs. It can be seen that the concentration of metal ion (L_PL_S) which increases in the range of pH 2.5:7.5 and decreases in the range of pH 7.5:9.5 too confirms the formation of ternary complexes, the maximum percentage of the formation of ternary complex is more than that of metal ion binary complex. This indicates that the ternary complex is more stable as compared to ML_S binary complex and more stable than ML_P binary complex.

6. Conclusion

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 and positive value of $\Delta \log K$ in some cases is attributed to the extra stability of the ternary complexes. The positive values of K_r also support the extra stability of mixed ligand complexes which may be attributed to the interactions outside the coordinated sphere. The species distribution curve shows the formation of ternary complexes and deprotonation of amino groups.

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