



Stability Constants of Mixed-Ligand Complexes of Cu(II) with Oxprenolol HCl as Pharmaceutical Ligand and Some Biologically Active Ligands

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The oxprenolol-Cu(II) complexes have been used as DNA constituents (L) and antihypertensive drug. In this study, the formation constants of these complexes, which formed in H₂O/MeOH (80:20) solution and their concentration distributions were assessed at ionic strength of 0.1 mol/L NaClO₄ at 25 °C. Stability constants and the values of $\Delta \log K$ for the targeted complexes have also been evaluated depending on pH meter.

Keywords: Oxprenolol HCl, Mixed-ligand, Stability constants, Potentiometric titration.

INTRODUCTION

Sarkar [1] discussed the therapeutic problems for using of chelating agents in treatment of Wilson's diseases due to Cu(II) toxicity. In order to design a drug from small organic ligands for inactivate of a metalloenzyme, a widespread studies on matrix metalloproteinases have been established [2,3]. Because the enzymes containing zinc lead to various diseases like cancer and arthritis, many drug improvement approaches interested in an inhibition of zinc active site. Definitely, the variety of structures and catalytic characters of enzymatic zinc, make it an attractive objective [4,5]. Albert [6] revealed that there is a drugs whose role is to kill cells act as chemotherapeutic agents and drugs whose achievement must be basically reversible and/or short-lived acting by a pharmacodynamic mechanism. The differences between these two drug types in addition to the recent and future uses must be study and covered [6]. Various studies revealed the great consideration for importance role of the metal complex formation using drugs and ligands in the therapeutic and biological field in the last decade [7-11]. Literature survey demonstrations that in order to recognize the suitable dose of drugs, drug effects on all blood stream components and to determine the metal ligand bonds strength, a stability constant of metal-drugs complexes must be estimated [12]. The drugs complexes has advanced value than parent drugs [13]. With the purpose of interpreting the action mechanism of drugs, the studies of metal ion-drugs complex equilibria is essential [14]. In this work, a potentiometric pH titration results were used to determine the stability constant of both

ternary and binary complexes, Cu(II)-oxprenolol (as primary ligands) and Cu(II)-DNA constituents (as secondary ligands), at 25 °C and 0.1 M of NaClO₄, respectively. Furthermore, species distribution in solution within a wide range of pH was also assessed. The chemical structure of oxprenolol HCl (Oxp) was depicted in Fig. 1.

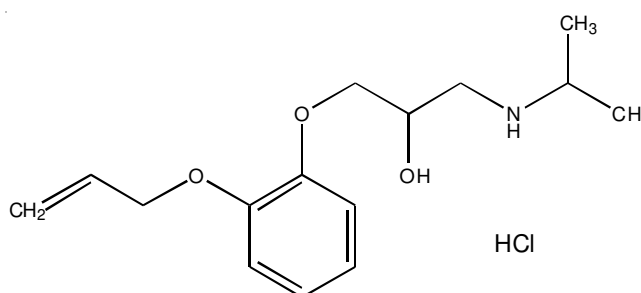


Fig. 1. Structure of oxprenolol HCl

EXPERIMENTAL

All the reagents used were of AR grade. Oxprenolol HCl was purchased by Sigma Chem. Company. DNA unit components investigated are inosine, thymine, uracil, adenine, uridine and thymidine. These materials were provided by BDH-Biochemicals Ltd. EDTA titrations was used for standardization of Cu(ClO₄)₂ stock solution [15]. A prepared solution of sodium hydroxide (carbonate free) was standardized with potassium hydrogen phthalate solution. An adjusted ionic

strength of 0.1 mol/L of all solutions was attained by addition of NaClO₄.

A Griffin pH J-300-010 G Digital pH meter was used for potentiometric titrations in a double-walled glass vessel. Before the pH measurements started, a calibrated electrode was prepared using buffer solutions at pHs (4 and 10) and the temperature was fixed at 25 ± 0.1 °C by flowing water from a constant temperature water bath through the jacket. In order to measure the p[H] of the free [H⁺], the pH results were corrected by titrating an identified concentration of standard HCl solution with standard NaOH solution using the same experimental conditions. The pK_w was evaluated using methanol-water (20 %) solutions at ionic strength equal 0.1 mol/L to be 13.78 (0.05). A magnetic stirrer was used for solution stirring and all titrations were achieved in triplicate. For studying both of the formation constant of possibly binary or ternary complexes formed and the acid dissociation constants of the ligands, three mixture solutions were prepared and titrated potentiometrically with 0.05 mol/L NaOH solution.

(A) 40 mL of a solution containing 0.005 mol/L ligands and 0.1 mol/L NaClO₄.

(B) 40 mL of a solution containing 0.005 mol/L Cu(II) solution, 0.01 mol/L oxprenolol HCl or L and 0.1 mol/L NaClO₄.

(C) 40 mL of a solution containing 0.005 mol/L Cu(II) solution, 0.005 mol/L (oxprenolol HCl), 0.005 mol/L (L) and 0.1 M mol/L NaClO₄.

Titration of mixture (A) gave the protonation constants of oxprenolol HCl (or L). While the formation constants of Cu(II)-Oxp and Cu(II)-L complexes were determined by titration of mixture (B) and titration of mixture (C) provided the stability constants of the mixed-ligand complexes. Before titrations started, all titrated solutions were fully protonated by adding of HClO₄ solution. By studying of several possible conformation simulations for the system, the stability and stoichiometric constants of the complex species formed in aqueous solution were evaluated. Both of the complex formation and dissociation constants were measured using the computer program HYPERQUD [16]. Whereas the computer program HYSS was used to determine the speciation as a function of pH [17].

RESULTS AND DISCUSSION

By using the potentiometric titration data, the acid-base equilibrium constants of the ligands, the formation constants of the ternary complexes and the formation constants of the Cu(II)-Oxp and Cu(II)-L complexes were evaluated in 20 % methanol-water (v/v) solution at 25 °C and ionic strength 0.1 M NaClO₄ and the results are given in (Tables 1 and 2).

Acidity constants: Perrin [18] has reported the acid dissociation constants of the DNA units in aqueous solution. The stability constants of the corresponding ternary and binary complexes in methanol-water solution (20 %) were determined by the proton dissociation constants of the ligands; which have been redetermined using the same experimental conditions. Table-1 shows that the pK_a values of the ligands in MeOH/H₂O solutions are higher than those testified in only water. This can be explained because the ligand donor group's basicity

TABLE-1
DISSOCIATION CONSTANTS OF THE LIGANDS AND
STABILITY CONSTANTS OF Cu(II) COMPLEXES OF BINARY
SYSTEMS AT 25 °C AND mol L⁻¹ IONIC STRENGTH

System	l	p	q ^a	log β ^b
[Cu(H ₂ O) ₄] ²⁺	1	0	-1	-7.44 (0.03)
	1	0	-2	15.09 (0.02)
Oxprenolol HCl	0	1	1	9.15 (0.02)
	1	1	0	7.26 (0.02)
	1	2	0	10.36 (0.01)
	1	1	-1	-2.55 (0.04)
	1	1	-2	9.64 (0.03)
Uracil	0	1	1	8.89 (0.04)
	1	1	0	4.63 (0.02)
Uridine	0	1	1	8.89 (0.03)
	1	1	0	4.66 (0.01)
Thymine	0	1	1	9.56 (0.02)
	1	1	0	5.62 (0.03)
Thymidine	0	1	1	9.04 (0.02)
	1	1	0	5.73 (0.01)
Inosine	0	1	1	8.32 (0.01)
	1	1	0	4.21 (0.04)
	1	2	0	9.34 (0.01)
	1	1	1	11.56 (0.03)
Adenine	0	1	1	9.38 (0.01)
	0	1	2	13.78 (0.02)
	1	1	0	5.54 (0.01)

^aThe values l, p and q are the stoichiometric coefficients corresponding to Cu(II), oxprenolol HCl or DNA units and H⁺, respectively.

^bStandard deviations are given in parentheses.

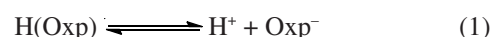
TABLE-2
FORMATION CONSTANTS OF Cu(II) COMPLEXES OF
TERNARY SYSTEMS AT 25 °C mol L⁻¹ IONIC STRENGTH

System	l	p	q	r ^a	log β ^b	Δ log
Uracil	1	1	1	0	11.76 (0.01)	-0.13
Uridine	1	1	1	0	11.83 (0.01)	-0.09
Thymine	1	1	1	0	12.09 (0.01)	-1.79
Thymidine	1	1	1	0	12.21 (0.01)	-0.78
Inosine	1	1	1	0	11.34 (0.02)	-0.13
	1	1	1	1	16.33 (0.02)	
Adenine	1	1	1	0	12.43 (0.05)	-0.37

^aThe values l, p, q and r are the stoichiometric coefficients corresponding to Cu(II), oxprenolol HCl, DNA units and H⁺, respectively.

^bStandard deviations are given in parentheses.

in methanol is higher than in water solutions. The calculated acid dissociation constant (pK_a) values of the investigated oxprenolol HCl ligand are given in Table-1. The oxprenolol HCl ligand can form a negatively charged anion since it has at least one site that can reversibly disassociate a proton, so oxprenolol HCl can release one proton from amine group according following deprotonation equilibria:



The pK_a value of protonated oxprenolol HCl equal of 9.15, this means that it is mainly present in the ionized form at a physiologic pH.

Copper(II) complex formation constants of oxprenolol HCl: The titration procedure was performed for oxprenolol HCl alone and for oxprenolol HCl in presence of Cu(II). The titration results reveal that the Cu(II)-Oxp complex curve is dropped than that of the free oxprenolol HCl curve. This means that Cu(II) complex formation was carried out by displacement

of protons. In order to determine the formation constant, the potentiometric results was fitted based on promising composition simulations. The Cu(Oxp) and Cu(Oxp)₂ complexes were found to be the model with superlative statistical acceptable and oxprenolol HCl acts as a bidentate fashion over the amino nitrogen and hydroxyl oxygen. The concentration distribution for Cu(Oxp) complex system is given in Fig. 2. The Cu(Oxp) species concentration increases as pH increase, attaining a maximum concentration of 92.7 % at pH (4.8). For more increase in pH values, the Cu(Oxp) species concentration need to be decreased, while the Cu(Oxp)₂ species concentration increased.

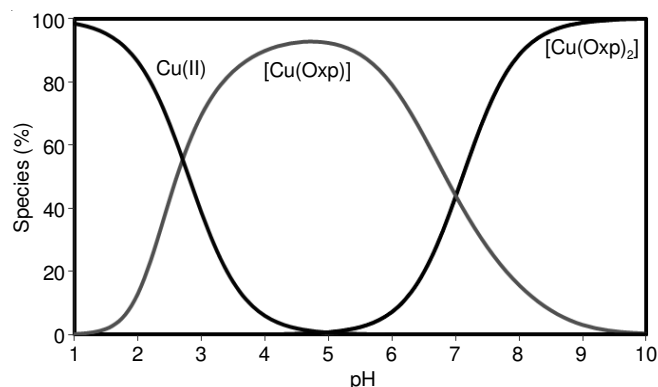
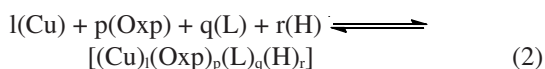


Fig. 2. Concentration distribution of various species as a function of pH in the Cu(II)-Oxp system.

Ternary Cu(II) complex formation equilibria: There are two mechanisms for the ternary complex formation may carry on, by a simultaneous or a stepwise mechanisms depending on the chelating potential of oxprenolol HCl and other ligands. The formation constants of the 1:1 Cu (II) complexes with oxprenolol HCl and those of DNA units, cited in Table-2, are of the same order. Consequently, the ligation of oxprenolol HCl and DNA units (L) will proceed simultaneously. The titration data of the ternary complexes with oxprenolol HCl and DNA units fit satisfactorily with formation of the species: [Cu(Oxp)], [Cu(L)] and [Cu(Oxp)(L)]. Mixed-ligand complex formation by simultaneous mechanism may be established by relating the experimental titration data points, the theoretical curve depending on the formation constants calculated. The good fit obtained is indicative of the validity of the complex formation model. The general four components equilibrium can be written as follows (charges are omitted for simplicity):



$$\beta_{l p q r} = \frac{[\text{Cu}_l \text{Oxp}_p \text{L}_q \text{H}_r]}{[\text{Cu}]^l [\text{Oxp}]^p [\text{L}]^q [\text{H}]^r} \quad (3)$$

The pH range of the solution is affected the complex formation as in an inosine compound which has two donor sites, N₁ and N₇, if the pH range is acidic, the metal ion is bonded to N₇ while N₁ left in protonated form. As pH value increase, the binding in the complex formation slowly changed from N₇-binding to N₁ binding [19,20]. The results revealed that inosine can form the complexes 110 and 111 (Table-2,

Fig. 3). While the complexes species distribution is schemed as a function of pH. Corresponding to the N₇ coordinated complex and acidic pH region, the species 111 is formed and the N₁ nitrogen is still in protonated form. The pK_a of the protonated form ($\log \beta_{111} - \log \beta_{110}$) extents to 4.99.

Due to the higher basicity of the N₃ site of thymidine and thymine which result from the inductive effect of the extra electron-donating methyl group, thymidine and thymine complexes are more stable than those of uridine and uracil.

For changing the deprotonating from N(1) and N(9) sites, acid-base equilibria of adenine in the protonated form (H₂L⁺) used. Existing of Cu(Oxp)(L) species in adenine, make the mixed-ligand titration of adenine is the best model, notably by Hodgson, discussed the addition of adenine to a metal center and both solid complex and solution studies which have indicated that N(9) is the ligating site [21].

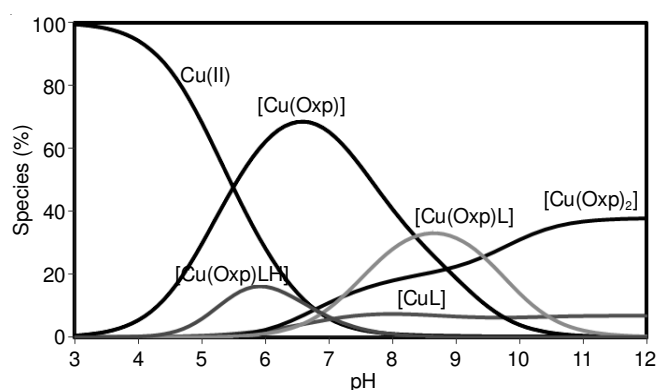


Fig. 3. Concentration distribution of various species as a function of pH in the Cu(II)-Oxp-inosine system

For indication of the relative stability for the ternary complexes formed by simultaneous mechanism, the $\Delta \log K$ values are used, comparing to corresponding binary complexes, which can be calculated by eqn. 4:

$$\Delta \log K = \log \beta_{\text{Cu(Oxp)L}}^{\text{Cu(Oxp)}} - (\log \beta_{\text{Cu(Oxp)}}^{\text{Cu}} + \log \beta_{\text{Cu(L)}}^{\text{Cu}}) \quad (4)$$

Because of the higher stability of the binary complexes, the value of the $\Delta \log K$ is negative and this lead to reduce in steric hindrance, number of coordination sites, difference in bond type, geometrical structure and electronic consideration [22,23].

Studies of species distribution: Species distribution curves have been plotted as a function of pH using HYSS program at I = 0.10 M NaClO₄ and T = 25 °C in order to clarify the equilibria nature and to estimate the stability constant calculated of Cu(II)-Oxp-DNA constituents (L) ternary complexes [17].

As pH values increase, the ternary complexes concentration increase in all of the species distributions. The complex reached to the maximum concentration (about 30 %) at a pH about 9 is the ternary complexes formed with DNA constituents.

Conclusion

In this study, the formation equilibria of Cu(II), (oxprenolol HCl) and DNA constituents has been estimated. The results reveal that the complexes are formed by simultaneous mechanism. Consequently, the (Cu(II)-Oxp) and (Cu(II)- DNA

unites) complexes formation constants have been found to be of the same demand. Both of the concentration distribution and the stability constants of complexes in solution have been evaluated. Studying the pH-ranges of different systems, obviously show that the ternary complexes concentration increases as pH value increase. Reducing the steric hindrance electronic and the number of coordination sites can be reached by the negative value of $\Delta \log K$ due to the higher stability of its binary complexes.

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