Research Article

Potentiometric Studies of Ternary Complexes of Cu(II) with Antihypertension Drug Paroxetine HCl and Some Amino Acids

Samar O. Aljazzar*, Reda A. Ammar, Amani S . Alturiqi
Department of Chemistry, College of Science, Princess Nourah bint Abdul Rahman University, Riyadh, Saudi Arabia.
Deanship of Scientific Research, Princess Nourah Bint Abdul Rahman University, Riyadh, Saudi Arabia.
***Corresponding author'sE-mail:** drjazzar1971@hotmail.com

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ABSTRACT

The equilibrium studies of the mixed ligand complexes of Cu (II)ion with anti-hypertension drug paroxetine HCl (PXT) as primary ligand and some amino acids viz. glycine, α- alanine, cysteine, S-methyl cysteine, methionine and histidine as secondary ligands (L)are investigated. The acidity constants of the ligands were determined and used for determining the stability constants of the complexes formed in 50% (v/v) ethanol-water media under the experimental conditions at 25 ºC, *I* = 0.10 mol/L ($NaNO_3$) by using Potentiometric technique. Stability constants of ternary complexes were calculated and various models were refined with HYPERQUAD. The formation and distribution of different species with varying pH were represented in the form of distribution diagrams. The relative stabilities of the mixed ligand complexes were compared with those of the binary complexes.

Keywords: Paroxetine HCl, Amino acids, Stability constant, Potentiometric technique.

INTRODUCTION

Paroxetine, (-)-trans-4-(4-fluorophenyl)-3-(3, 4-methylenedioxy-phenoxymethyl) piperidine hydrochloride, is one of the SSRIs used widely as an antidepressant drug alone, or in combination, with other drugs[1]. Paroxetine is comparable to the tricyclic antidepressants in their clinical efficacy, however, it is safer and has greater acceptance by the patients. Paroxetine is devoid of sedative effect and remarkably safe in overdose also. It is normally used in the treatment of clinical depression, obsessive-compulsive disorder, and panic disorder [2]. 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 [3, 4]. 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.[5-7]. Amino acids and their metal complexes are equally important compounds; since they have frequent utilization in both biological and chemical applications[8, 9]. 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. In the present investigation, the stability constants of Cu(II) complexes with anti-hypertension drug paroxetine HCl and some amino acids were studied in detail by Potentiometric titration method in 50% (v/v) ethanol-water at 25 ºC and *I* = 0.10 mol/L $NaNO_3$. The concentration distribution of the complexes in solution was evaluated.

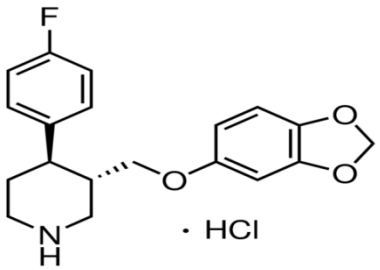

Figure 1: Chemical structure of paroxetine HCl .

MATERIALS AND METHODS

Materials and Reagents

Paroxetine HCl (PXT), Fig.1, glycine, α- Alanine, cysteine, S-methylcysteine, methionine, histidine and related compounds, methylamine, histamine.2HCl, imidazole and mercapto ethylamine were obtained from Sigma Chemical Co. and used without further purification. Stocks solutions of $Cu(NO_3)_2{\cdot}2H_2O$, NaOH, HNO_3 and $NaNO_3$ were prepared from analytical reagent grade chemicals obtained from Merck. The copper content of the solutions was determined accurately by titration with standard ethylene diamine tetra acetic acid (EDTA). Solutions were made up under N_2 atmosphere in decarbonated H_2O. The ionic strength was maintained constant at 0.10 ± 0.01 mol/L with $NaNO_3$ in all titrations which were carried out at 25 ºC. Double distilled water was used for the preparation of solutions. Fresh solutions were prepared at the time of use.

Apparatus and Measuring Techniques

Potentiometric titrations were performed at 25±0.1°C in a double-walled glass vessel using a Griffin pH J-300-010 G Digital pH meter. The electrode was calibrated

with standard buffer solutions (pH4.0 and 10.0) before the pH measurements. The ionic strength was kept constant (0.10 mol/L) using a NaNO3 solution, and a total volume of 40 cm-3 was used for each titration. The pkw of water was calculated at ionic strength of 0.1 mol/L to be 13.87±0.05.

Equilibrium measurements

The acid dissociation constants of the ligands were determined potentiometrically by titrating the ligand (40 ml) solution (1.25×10^{-3} mol/L) of constant ionic strength 0.1 mol/L, adjusted with $NaNO_3$. The stability constants of the binary complexes were determined by titrating 40 ml of a solution mixture of Cu (II) (1.25×10^{-3} mol/L), the ligand (2.5×10^{-3}M mol/L) and 0.1 mol/L $NaNO_3$. The stability constants of mixed ligand complexes were determined by titrating 40 ml of solution containing Cu (II), PXT and amino acids, all of concentration (1.25×10^{-3}mol/L) and 0.1 mol/L $NaNO_3$.

The above solutions were virtually titrated against 0.1 mol/L NaOH. For all the titrations, HNO_3 solution was added, so that they were fully protonated at the beginning of the titrations.

Calculations

The stoichiometries and stability constants of the complex species formed in solution were determined by examining various possible composition models for the systems studied. The overall stability constants β, were determined using the HYPERQUAD program[10], and the speciation as a function of pH using the HYSS program [11].

RESULTS AND DISCUSSION

The logarithm of the protonation constants of the ligands and the log β values of the formation constants of the complexes found in the binary and PXT-containing ternary systems are reported in Table 1.A *pKa* value of PXT 9.2 means that is predominantly present in the ionized form at a physiologic pH. The stability of binary and ternary complexes may be evaluated by the following equilibria (charges were omitted for simplicity):

$$l(Cu)+p(PXT)(orL)+r(H) \rightleftharpoons (Cu)_l(PXT)_p(H)_r(orL) \quad \textbf{(1)}$$

$$l(Cu)+p(PXT)+q(L)+r(H) \rightleftharpoons (Cu)_l(PXT)_p(L)_q(H)_r \quad \textbf{(2)}$$

The stability constant of the binary and ternary complexes may be represented by:

$$\log \beta_{lpr} = \left[Cu_l PXT_p H_r\right]_l \Big/ [Cu]^l [PXT]^p [H]^r \quad (or\ L) \textbf{(3)}$$

$$\log \beta_{lpqr} = \left[Cu_l PXT_p L_q H_r\right] \Big/ [Cu]^l [PXT]^p [L]^q [H]^r \quad \textbf{(4)}$$

Where l, p, q and r are the numbers of Cu(II) ion, paroxetine (PXT), a

Where l, p, q and r are the numbers of Cu (II) ion, paroxetine (PXT), amino acids (L) and proton, respectively, in the complex $[(Cu)_l(PXT)_p(L)_q(H)_r]$.

Binary Cu (II): PXT equilibria

The complex formed between paroxetine HCl (PXT) and Cu (II) was indicated by the metal–ligand titration curve. The titration curve of the Cu (II)- A complex is lowered from that of the free PXT curve, indicating formation of Cu(II) complex by displacement of protons. The formation constants were determined by fitting Potentiometric data on the basis of possible composition models. The selected model with the best statistical fit was found to consist of Cu (PXT) (1100) and $Cu(PXT)_2$ (1200) complexes. The stability constants of their complexes are given in Table (1). The concentration distribution diagram of Cu (II)- PXT system is shown in Fig. 2. The concentration of the 1100species increases with increasing pH, attaining a maximum of 97.4% at pH 7.0. Further increase in pH is accompanied by a decrease in the concentration of the1100species and an increase in the concentration of the 1200 species.

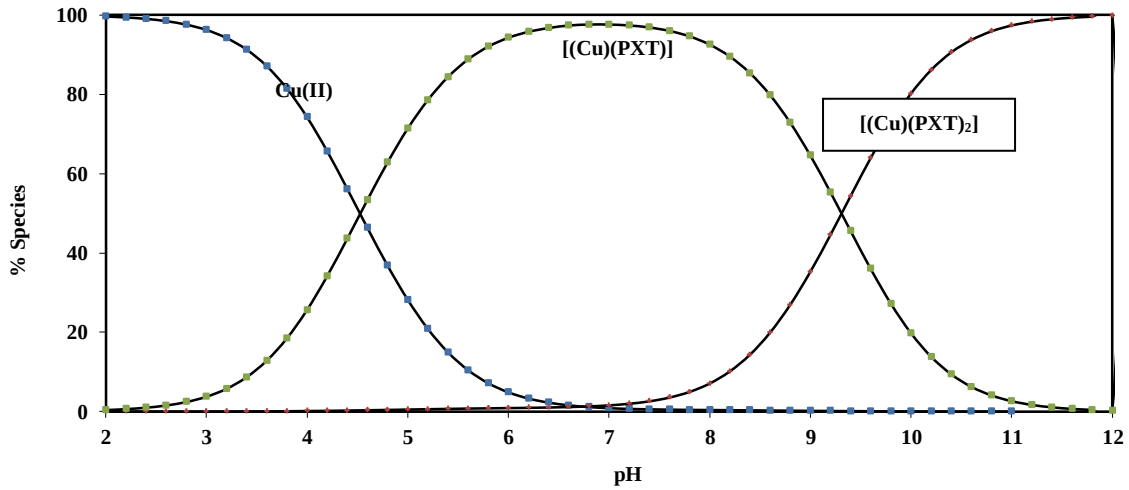

Figure 2: Percentage distribution curves of various species as a function of pH in the binary Cu(II)-PXT systemsat 25 ºC and *I* = 0.10 mol/L $NaNO_3$.

Table 1: Proton-association constants of ligands and formation constant of the binary and ternary complexes of Cu(II) involving paroxetine HCl (PXT) and amino acids (L) at 25°C and 0.1 mol\L ionic strength.

System	l	P	q	ra	log βb	ΔlogK
Paroxetine HCl (PXT)	0	1	0	1	9.20 (0.001)	
	1	1	0	0	8.40 (0.02)	
	1	2	0	0	15.75(0.03)	
Glycine	0	0	1	1	9.60 (0.01)	-0.1
	0	0	1	2	12.33 (0.02)	
	1	0	1	0	8.15 (0.02)	
	1	0	2	0	14.87 (0.04)	
	1	1	1	0	16.45(0.01)	
α- Alanine	0	0	1	1	9.67(0.01)	--0.74
	1	0	1	0	8.79(0.03)	
	1	0	2	0	16.65(0.01)	
	1	1	1	0	16.09(0.01)	
Methionine	0	0	1	1	9.23 (0.02)	-0.81
	0	0	1	2	12.04 (0.04)	
	1	0	1	0	8.72 (0.03)	
	1	0	2	0	14.16 (0.05)	
	1	1	1	0	16.31(0.02)	
S-Methylcysteine	0	0	1	1	8.65 (0.02)	-0.1
	1	0	1	0	8.51 (0.01)	
	1	0	2	0	14.81 (0.02)	
	1	1	1	0	16.81(0.02)	
Histidine	0	0	1	1	9.47 (0.01)	-0.72
	0	0	1	2	15.80 (0.01)	
	0	0	1	3	17.07 (0.04)	
	1	0	1	0	10.44 (0.01)	
	1	0	2	0	18.68 (0.03)	
	1	0	1	1	18.39 (0.02)	
	1	1	1	0	18.12(0.01)	
	1	1	1	1	24.14(0.01)	
Histamine	0	0	1	1	9.88 (0.03)	-0.08
	0	0	1	2	15.94 (0.05)	
	1	0	1	0	9.98 (0.02)	
	1	0	2	0	15.12 (0.05)	
	1	0	1	1	17.34 (0.02)	
	1	1	1	0	18.30(0.01)	
	1	1	1	1	22.01(0.01)	
Imidazole	0	0	1	1	7.41 (0.01)	-2.74
	1	0	1	0	4.12 (0.01)	
	1	0	2	0	7.96(0.02)	
	1	1	1	0	9.78(0.05)	
	1	1	2	0	16.62(0.02)	
Cysteine	0	0	1	1	10.12 (0.02)	-2.66
	0	0	1	2	18.35 (0.03)	
	0	0	1	3	19.20 (0.09)	
	1	0	1	0	13.58 (0.04)	
	1	0	2	0	22.02 (0.06)	
	1	1	1	0	19.32(0.01)	
	1	1	1	1	25.17(0.01)	
Mercapto ethylamine	0	0	1	1	10.03(0.04)	-0.46
	0	0	1	2	18.64(0.02)	
	1	0	1	0	11.87(0.06)	
	1	1	1	0	19.81(0.01)	
	1	1	1	1	24.17(0.02)	

[a] l, p, q and r are the stoichiometric coefficient corresponding to Cu^{2+}, PXT, (amino acids) and H^{+}, respectively. [b] Standard deviations are given in parentheses.

Ternary Complexes

The formation constants of Cu (II) ternary complexes with PXT or L are of the same order of magnitude, Table 1. Consequently the ligation of PXT and L will proceed simultaneously. The titration data of the ternary complexes with PXT and L fit satisfactorily with formation of the species: Cu (PXT), Cu $(PXT)_2Cu$ (L), Cu $(L)_2$, Cu (PXT)(L) and Cu (PXT)(LH). The species distribution curves of Cu-PXT-L systems were obtained by plotting percentage concentration of various possible species formed during complexation versus pH of solution. In all investigated ternary systems, the concentration of the ternary complex increases with increasing pH, thus making the complex formation more favoured in the physiological pH rang. Protonated ternary complex species has been found to be most favoured at lower pH values. The species distribution of cysteine, taken as a representative amino acid, is given in Fig. 3.

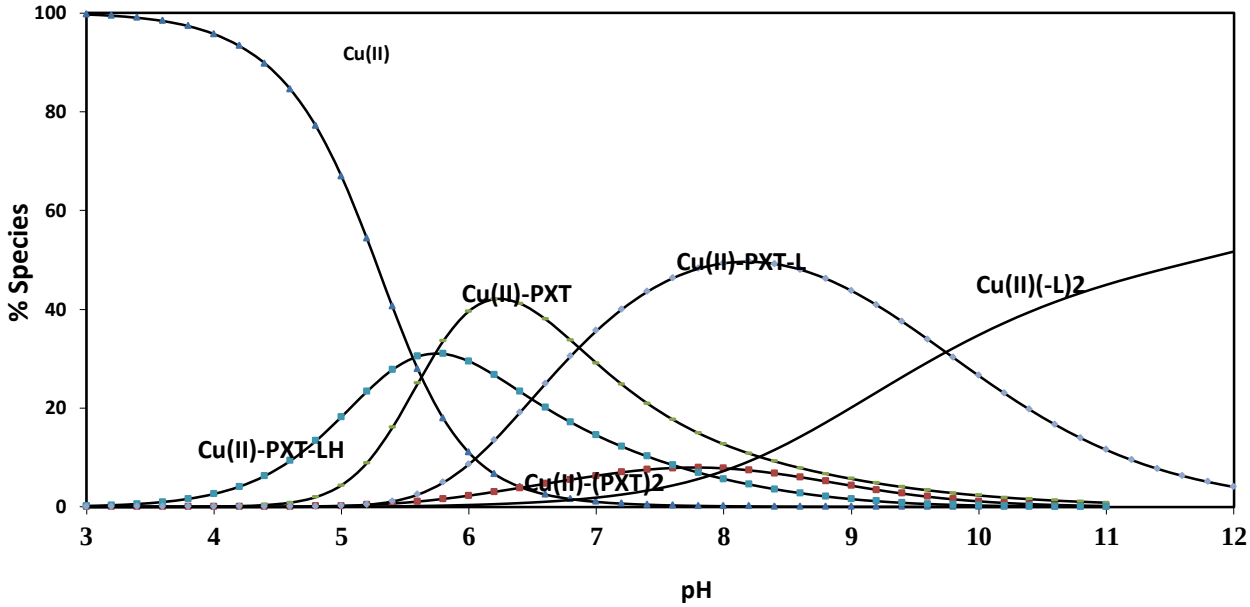

Figure 3: Percentage distribution curves of various species as a function of pH in the ternary Cu (II)-PXT- cysteine system sat 25 ºC and *I* = 0.10 mol/L $NaNO_3$.

A comparison of the overall stability constants of Cu(II)-PXT-L ternary systems, (Table 1) indicates the higher stabilities of the ternary complexes containing histidine or histamine than those of α-amino acids reveals that histidine or histamine interacts with the metal ion by the amino and imidazole nitrogen atoms. *S*-methylcysteine forms a more stable complex than methionine, plausibly due to the fact that the five-membered chelate ring in the former complex is energetically more favoured than six-membered chelate ring in the latter complex.

Cysteine has three binding sites, carboxylic, amino and sulfhydryl groups. It forms the complexes 1110 and 1111. The stability constant of the 1110 complex is in fair agreement with that of mercaptoethylamine, (where the binding sites are the amino and sulfhydryl groups) and higher than those α-amino acids (where the binding sites are the amino and carboxylate groups). This indicates that cysteine interacts with Cu (II) ion by the amino and deprotonated–SH groups. The acid dissociation constants of the protonated complexes are given by the following relation:

$$pK^{H} = \log \beta_{1111} - \log \beta_{1110} \quad (5)$$

The acid dissociation constant obtained for the protonated ternary complex with histidine is 6.02, being lower than that of the protonated amino group NH3+(pKa= 9.47), but closer to that of the protonated imidazole group (pKa= 6.33), suggesting the proton in the protonated complex would be located mainly on the imidazole group.

The Δ log K values are used to indicate the relative stability of the ternary formed through simultaneous mechanism, as compared to those of the corresponding binary complexes can be calculated using Eq. (6)

$$\Delta \log K = \log \beta^{Cu\,(PXT)}_{Cu\,(PXT)L} - (\log \beta^{Cu}_{Cu\,(PXT)} + \log \beta^{Cu}_{Cu\,(L)}) \quad (6)$$

The values of Δlog K for the ternary complexes studied in this paper are listed in Table 1. The theoretical Δ log K value for a distorted-octahedral Cu2+complex is -0.913. The tendency to form ternary complexes was compared with this value, so that if Δ logK is greater than -0.9, this should be taken as an indication that the ternary complex is favored. The Δ log K values of amino acids are less negative than the theoretical value (-0.9). This may be considered as evidence for the occurance of enhanced stabilites involving π back-donation from the negatively charged amino acid to the π-system of the PXT. The Δ log K for the cysteine mixed ligand complex (1110) is more

negative than -0.9. This may be described on the premise that cysteine is a tridentate ligand and that two coordination sites are available in the [Cu (PXT)]+complex.

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