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Potentiometric studies of the Zinc (II) complexes with some medicinal compounds and glycine in aqueous solution

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ABSTRACT

The possibility of occurrence of biological relevant ciprofloxacin.HCl, pantoprazole sodium, gabapentin, chloramphenicol, ceftriaxone sodium, atenolol as medicinal drugs, and glycine as amino acid interactions was investigated in ternary systems involving medicinal compounds (drugs) and glycine as amino acid. The study was done in solution using potentiometry. The stability constants of the ternary complexes as well as the binary ones were potentiomtrically determined (T =298K, μ=0.01M, NaClO4).The order of the stability constants of ternary complexes was Zn (II)-Gabapentin-Glycine, Zn(II)-glycine-atenolol, Zn (II) - glycine-ciprofloxacin.HCl, Zn (II)-chloramphenicol-glycine , Zn(II)-glycine- ceftriaxone sodium and Zn (II) - pantoprazole sodium-glycine. ΔlogK showed that when L= medicinal compounds, the ternary complexes are less stable than the binary ones. Suggesting that no interaction occurs between the ligands in the ternary complexes. The concentration distribution of various species formed in solution was evaluated.

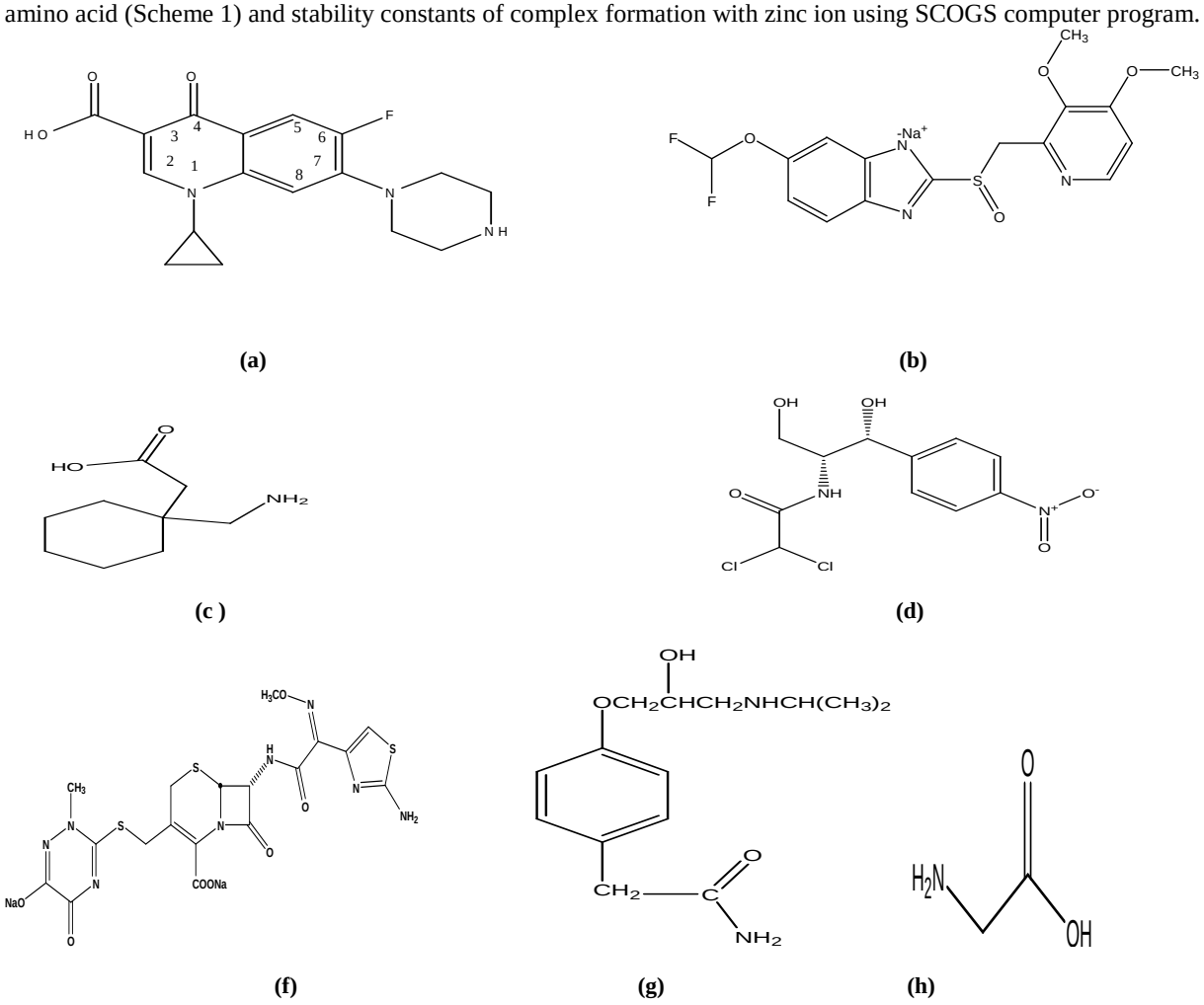
Keywords: Glycine, medicinal compounds, complexes, Zinc (II), pH-metric, SCOGS.

INTRODUCTION

The interactions of transition metals have partial covalent character and involve the d-orbitals of the divalent and the p -orbitals of nitrogen, sulfur, and oxygen ligands from the protein. The formation of a coordination bond in complexes of transition metals can be considered as a transfer of a lone electron pair from the coordinated group or ligand to the metal ion. Whereas zinc prefers tetrahedral binding sites in proteins [1]. Zinc, always occurring as a divalent cation [zinc (II)] in biological systems, is the second most abundant transition metal following iron [2]. In an adult human body, for example, there 2–3 g of zinc in total, while the content of copper is only 250 mg [3]. More interestingly, large amounts of zinc (II) are likely to concentrate in nerve tissues (0.1–0.5 mM for brain tissue). Although the majority of biological zinc ions are tightly sequestered by proteins, the presence of “free zinc pools” in certain cells may still be possible. Though the low concentration delayed the recognition of its importance [4], zinc (II) ions are well known to play diverse roles in biological processes. The most important and best known role for zinc is as a structural cofactor in metalloproteins. Over the last half a century, hundreds of zinc proteins possessing one or more zinc stabilized motifs have been identified and classified into several major families [5]. It has been postulated that the synaptically released zinc (II) modulates the excitability of the brain through the accommodation of amino acid receptors. During the process, zinc (II) ions not only functions as a conventional synaptic neurotransmitter or neuromodulator for the presynaptic neuron [6], but also as a transmembrane neural signal to

traverse the postsynaptic neuron [7]. Currently, there is great interest in heavy-metal pollution and in the design of improved drugs for removing them from plasma. However, before any new pharmaceutical is marketed, it is prudent to know as much as possible about the molecular chemistry of its mode of action. This involves the knowledge of the product of ligand metabolism, the selectivity of the ligand for the pollutant cations with respect to the essential metal ions, the major species present at physiological pH values, the extent to which the ligand and its complexes partition in a cell membrane and the structures of the complexes formed[8].

It is well known that proton transfer plays an important role in the reactions such as complexation, acid–base catalyzing and enzymatic reaction [9] in aqueous solution. The stability constants can be of significance in order to predict different chemical processes such as isolation, extraction, or preconcentration methods [10,11]. Thus, the accurate determination of acidity and stability constants values are fundamental to understanding the behavior of ligands and their interaction with metal ions in aqueous solution. Potentiometric titration is accepted as a powerful and simple electroanalytical technique for determination of stability constants. The determination of stability constants is an important process for many branches of chemistry [12]. Developments in the field of computation of equilibrium constants from experimental data were reviewed a few years ago [13,14]. Since that time, many more programs have been published, mainly so as to be able to use microcomputers for the computations. The purpose of this work was to calculate the protonation constants of ciprofloxacin.HCl, pantoprazole sodium, gabapentin, chloramphenicol, ceftriaxone sodium, atenolol as medicinal drugs, and glycine as amino acid (Scheme 1) and stability constants of complex formation with zinc ion using SCOGS computer program.



Scheme 1. Chemical structure
(a)ciprofloxacin.HCl (b) pantoprazole sodium(c) gabapentin (d) chloramphenicol
(f) ceftriaxone sodium (g) atenolol (h) glycine

MATERIALS AND METHODS

Medicinal compounds were procured from Dr. Zahed Zaheer assistant professor (Y.B. Chavan College of pharmacy) and NaOH, $NaClO_4$, $HClO_4$, zinc nitrate and glycine were of A.R grade. The solutions used in the potentiometric titrations were prepared in double distilled water. The NaOH (0.2M) solution was standardized against oxalic acid solution (0.1M) and the standard alkali solution was again used for standardization of $HClO_4$. The metal salt solutions were also standardized using EDTA titrations [15]. The ligands of medicinal compounds are soluble in double distilled water. The pH meter was calibrated before each titration with standard buffer solutions of 4.00, 7.00, and 9.2. The pH-meter (ELICO, L1-120) was used with a combined glass electrode assembly.

Potentiometric procedure

In the study of binary and ternary chelates by the potentiometric titration technique. The procedure employed for the potentiometric pH measurements have been described in details :

(1)Free $HClO_4$.
(2)Free $HClO_4$ + Ligand (L_P).
(3)Free $HClO_4$ +Ligand (L_P) +Metal ion.
(4)Free $HClO_4$ + Ligand (L_S).
(5) Free $HClO_4$ +Ligand (L_S) +Metal ion (M).
(6) Free $HClO_4$ +Ligand (L_P) +Ligand (L_S) +Metal ion (M).

In general, an experimental run involves collecting equilibrium data points throughout the entire pH range, between 2.0 and 11.50 as a function of millilitre standard sodium hydroxide, the pH measurement method for investigating the dependency of complexation to pH for calculating protonation constants of medicinal compounds and glycine, and stability constants of respective complexes with zinc was carried out according to Irving-Rossotti expression [16]. In a typical experiment, a solution containing about 0.01 mmol of ligands (drugs) was placed in the cell. The required amount of $NaClO_4$ (from a 0.1M stock solution), $HClO_4$ (from a0.2 M stock solution) were added. Finally, the required amount of doubly distilled deionized water was added to the cell to a total volume of 50 ml. The second solution contains the same amounts of component plus about 0.01mmol of each metal ions including $Zn2^+$ and doubly distilled deionized water was added to the same total volume. The potentiometric study carried out at the metal: ligand molar ratios of 1:1 for binary systems. The ternary system contains the same amounts of component plus glycine and doubly distilled deionized water was added to the same total volume, the potentiometric study carried out at the metal: drug: amino acid molar ratios of 1:1:1 for ternary systems.

RESULTS AND DISCUSSION

***Binary complexes*:**

The proton ligand stability constants of ligands ($\log pK_1^H$ and $\log pK_2^H$) as shown in Table (1) were determined by pointwise methods and half integral methods, and metal ligand stability constants (logK) of Zn (II)metal ion with medicinal compounds and glycine have been determined by pointwise methods and half integral methods as suggested by Irving and Rossotti. The stability constant of binary complex of atenolol show high stability of Zn (II)-atenolol and low stability constant of Zn (II)-pantoprazole sodium and the stability of Ciprofloxacin.HCl, gabapentin, ceftriaxone and chloramphenicol with Zn (II) metal ion as shown in Table (2) for the purpose of comparison with those of ternary systems by using Calvin Bjerrum titration techniques as modified by Irving and Rossotti [17]. The n^- A values ranges between 0.2 to 0.8 and 1.2 to 1.8 indicates the presence of only one $\log p K_1^H$ in drug and is due to the dissociation of carboxylic group present. The complexes of drug suggest the formation of 1:1complexe.

Mixed ligand complexes:

The stability of ternary complexes may be evaluated by the following equilibrium:

$$pM+qH+ rL_P+sL_S \rightleftharpoons MpHqL_PrL_Ss \quad (1)$$

Where M is the metal ion, H is the proton, L_P and L_S are the ligands. The global stability constant for the ternary complexes [18] may be represented as following:

$$log\beta_{pqrs} = [M_pH_qL_{P_r}L_{S_s}]/[M]^p[H]^q[L_P]^r[L_S]^s \quad (2)$$

It is also possible to define the stability constants for ternary complexes in relation to their binary ones [18], represented by the equilibria (3) and (4):

$M+L_S \rightleftharpoons ML_S$ $\quad K^M_{ML_S} = [ML_S]/[M][L_S]$ (3)

$ML_P+L_S \rightleftharpoons ML_PL_S$ $\quad K^{ML_P}_{ML_PL_S} = [ML_PL_S]/[ML_P][L_S]$ (4)

The difference between the stability of the ternary and binary complexes shows the tendency of the formation of ternary species [18]. This could be expressed by Eq. (5):

$$\Delta\log K = \log K^{ML_P}_{ML_PL_S} - logK^M_{ML_S} = \log K^{ML_S}_{ML_SL_P} - logK^M_{ML_P} \quad (5)$$

Or Eq. (6): $\Delta\log K = \log\beta_{111} - (log\beta_{20} + log\beta_{02}$ (6)

$KL_P = \beta111/\log K10$ $\quad KL_S = \beta111/\log K01$ (7)

$Kr = \beta^2111/\beta20.\beta\,02$ (8)

A statistical evaluation of ternary complexes formation may be calculated using:

$$\beta_{111} = 2\sqrt{\beta_{01}}\sqrt{\beta_{10}} \quad (9)$$

$$\beta_{01stat} = \log 2 + 1/2\log\beta_{20} + 1/2\log\beta_{02} \quad (10)$$

The difference between the constant from experimental data and those calculated statistically indicates the possibility of ligand–ligand interaction. Another parameter, percent Relative Stabilisation [19] (% R.S.) to quantify the stability of a ternary complex may be defined as: $(\%R.S) = [(logK^{ML_P}_{ML_PL_S} - logK^M_{ML_P}/logK^M_{ML_P})]X100$ (11)

The formation of 1:1:1 mixed ligand complexes (ML_PL_S) were identified by the pH of precipitation of ML_P, ML_S, and ML_PL_S titration curves which suggest the higher value of pH of precipitation of ternary system than corresponding binary systems[20].

Table1.Protonation constants of ligands

Ligands	pK^H_1	pK^H_2
glycine	2.29	10.01
Ciprofloxacin.HCl	2.14	3.26
pantoprazole sodium	5.5	11.19
gabapentin	3.43	10.04
chloramphenicol	-----	11.44
ceftriaxone sodium	3.15	10.7
atenolol	2.76	9.56

It has been also confirmed by drawing composite curve. The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of ΔlogK, Kr, KLp and KLs values, and shown in Table (2) along with stability constants of ternary systems of Zn (II) transition metal ion. The mixed ligand stability constants of Zn(II)LpLs systems shows higher stability of gabapentin whereas low stability of Zn(II) ternary systems of

(1:1:1) of pantoprazole sodium. The comparison of logβ111 with logβ20 and logβ02 of these systems reveals the preferential formation of ternary complexes binary systems [21]. The low positive values of KLp and KLs indicate less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands. The positive values of Kr but less which indicates lower stability of ternary complexes, results of present investigations shows the stability constants of ternary complex formed are less stable [22].The negative values of ΔlogK values suggests the formation of ternary complexes but less stable having destabilized nature of complexes which has been reported in O in coordination of glycine.

Table2. Parameter based on some relationship between formations of mixed ligand complexes of Zn (II) with medicinal compounds (drugs) and glycine

Ligand/parameter	$logk_{10}$	$logk_{01}$	$log\beta_{20}$	$log\beta_{02}$	$log\beta_{111}$	K_r	K_{LP}	K_{LS}	ΔlogK	% R.S
Ciprofloxacin.HCl	5.85	3.99	5.85	3.99	10.29	2.09	1.76	2.58	0.45	-95.6
pantoprazole sodium	3.73	5.85	3.73	5.85	9.07	1.89	2.43	1.55	-0.51	-94.7
gabapentin	5.40	5.85	5.40	5.85	11.32	2.01	2.10	1.93	0.06	-94.1
chloramphenicol	5.01	5.85	5.01	5.85	9.95	1.83	1.99	1.70	-0.91	-95.1
ceftriaxone sodium	4.48	5.85	4.48	5.85	9.24	1.79	2.06	1.58	-1.09	-95.2
atenolol	5.85	5.92	5.85	5.92	10.32	1.75	1.76	1.74	-1.45	-95.5

Species distribution curves:

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

$C_1=HL_P \rightleftharpoons H+L_P$ (1a)

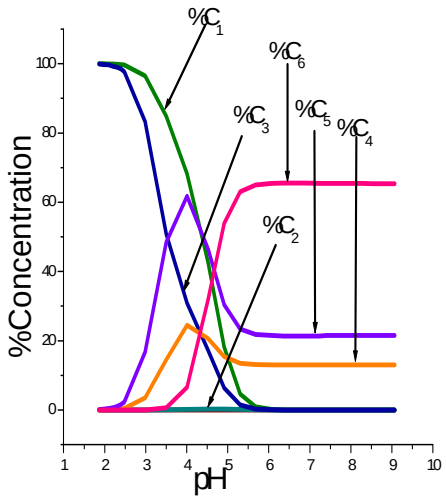
$C_2=H_2L_S \rightleftharpoons HL_S+H$ (2a)

$C_3=HL_S \rightleftharpoons H+L_S$ (2b)

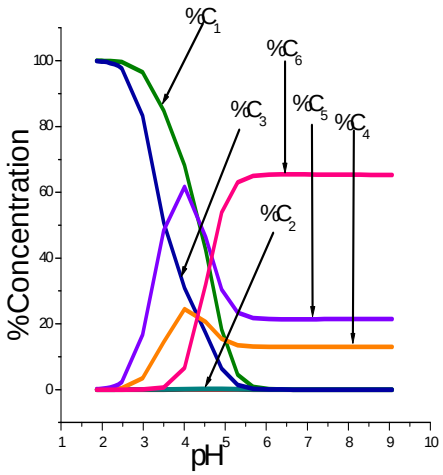
$C_4= M(II) +L_P \rightleftharpoons ML_P$ (3a)

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

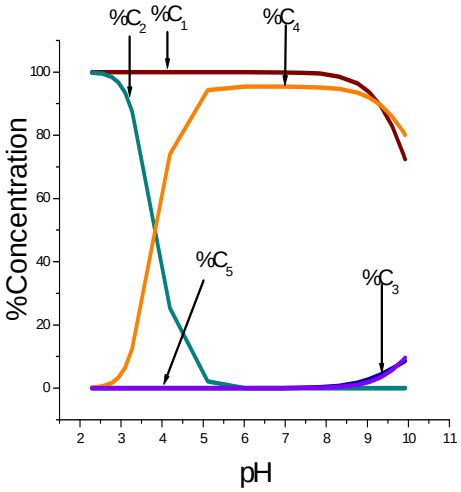
$C_6= M(II)+L_P+L_S \rightleftharpoons ML_PL_S$ (5)

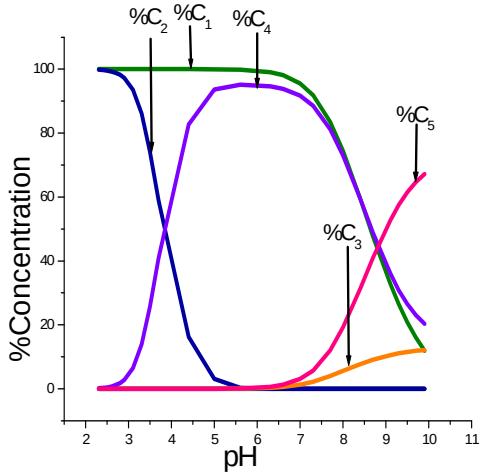


(a) Zn(II)-glycine-atenolol

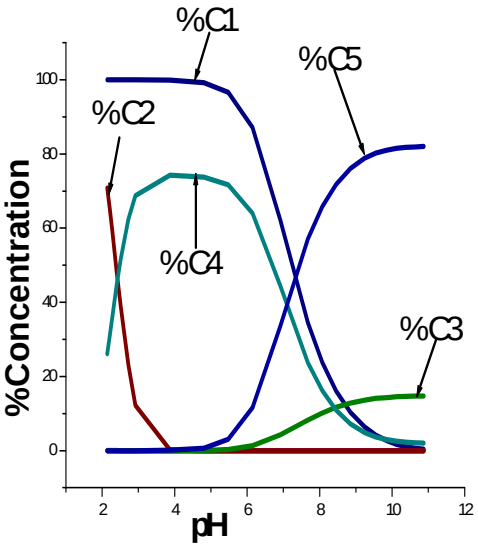


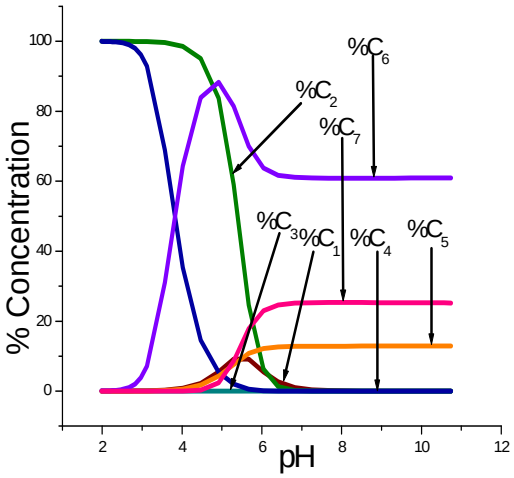
(b) Zn(II)-glycine- ceftriaxone sodium





(C) Zn (II)-chloramphenicol-glycine
(d) Zn (II)-Gabapentin-Glycine





(f) Zn (II) - glycine-ciprofloxacin.HCl **(h) Zn (II) - pantoprazole sodium-glycine**

The model of species for this ternary system that was used in SCOGS program includes all the species as well as the hydrolysis constants of Zn (II). The stability constants of the binary complexes were refined separately using the titration data of these systems in a 1:1 ligand: Zn (II) ratio in the same conditions of temperature and ionic strength. As they were in good agreement with reported value [23, 24], they were fixed, and consequently, only ternary species were refined in the ternary model of the species. The titration data from 1:1:1 Zn (II): LP: LS metal: ligands ratio were not considered for the calculations because they were quite similar to those from 1:1 Zn (II): glycine system, indicating the difficulty of ternary complexes analysis or potentiometric detection in solution when the two ligands are present in the same concentration. The species distribution curves of metal ions(II)L_PL_S systems were obtained by plotting percentage concentration of various possible species formed during complexation versus pH of solution as shown in Fig.(1) as representative graphs. It can be seen that concentration of Zn(II)-glycine-atenolol according to (a), increases in the range of (pH 3.54 : 5.32) whereas increase the percentage of ternary complex from 0.49% to 62.97%, the concentration of Zn(II)-glycine- ceftriaxone sodium according to (b), increase in the

range of (pH 7.55: 9.53) whereas increase the percentage of ternary complex from 2.29% to 14.41%, in the same ways ,the concentration of Zn (II)-chloramphenicol-glycine according to (c), increase in the range of (pH 9.12 : 9.88)whereas increase the percentage of ternary complex from 2.29% to 9.40% , the concentration of Zn (II)-Gabapentin-Glycine according to (d), increase in the range of (pH 7.03:9.88) whereas increase the percentage of his complex from 3.70% to 66.55%, in the same ways, the concentration of Zn(II)-glycine-ciprofloxacin.HCl according to (f), increase in the range of (pH 5.49: 9)whereas increase the percentage of ternary complex from 3.34% to 77.26% and the concentration of Zn(II)- pantoprazole sodium- glycine according to (h), increase in the range of (pH 2.88:4.50) whereas increase the percentage of ternary complex from 2.98% to 83.69% . From these percentages of different medicinal compounds with glycine as amino acid and Zn (II) as metal ions, we can see that, the percentage of metal ligand complex take different percentages and that depend on pH and ligand. the maximum percentage of the formation of ternary complex (83.69%) 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.

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