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Der Chemica Sinica, 2011, 2 (2):158-164

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Solution Behavior of Copper Complexes with Antibacterial Drugs and Amino Acids

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ABSTRACT

Mixed ligand stability constants of copper complexes with antibacterial drugs (L) and a series of eight amino acids(R) have been determined pH metrically at 27^0C temperature and 0.1 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.

Keywords: Ternary complex, stability constant, transition metal, drug, ionic strength.

INTRODUCTION

The complex formation has played a vitol role in the field of medicinal and biological sciences[1]. The Literature survey reveals that over the last decade there has been tremendous attention towards studies on metal complex formation using drugs as ligands[2-5] . The main attempt of this work is to know the proper mechanism of action of drugs and lower side effects[6]. The stability constant of metal complexes with drugs are useful to know the proper dose of drug and their effect with all other components of blood stream as well as to measure the strength of metal ligand bonds [7].The complexes of drugs has higher efficacy than parent drugs[8]. The studies of complex equilibria of metal ions with drugs are useful in elucidating the mechanism of action of drugs [9]. The role of transition metal ions and their complexes are involved in metabolism , transportation, and catalytic processes in the systems[10] and amino acids are the basic structural unit of proteins and played main role in the cell structure and functions[11].

Isoniazid(L_1) is used an antitubercular drug for the treatment of tuberculosis(tuberculocidal, antimycobactarial agent)[12].Chemical name of isoniazid is pyridine-4-carboxylic acid hydrazide or Isonicotinic acid.

Pyrazinamide(L_2) is also known as pyrazine carbonamide or pyrazinoic acid amide or pyrazine carbonyl amide[12]. It is an antitubercular (antibacterial) drug, and structures are shown in Figures 1and 2.

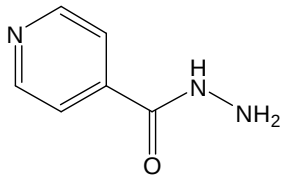


Figure 1: structure of Isoniazid(L_1);

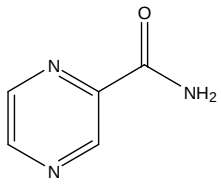


Figure 2: structure of Pyrazinamide (L_2).

The present paper explains the systematic study of mixed ligand stability constants of ternary complexes of, Cu(II) transition metal ions with isoniazid and pyrazinamide, as (antitubercular) antibacterial drugs (L) and a series of eight amino acids (R).

MATERIALS AND METHODS

Materials and solutions

All the chemical reagents used in the present investigation were Analar grade. The solutions of reagents were prepared in CO_2 free doubled distilled water having 6.80-6.90 pH. The NaOH solution was standardized with oxalic acid, kept in pyrex vessel and used as a titrant for pH titrations as well as standardizations of perchloric acids. The 1.0 M $NaClO_4$ solutions were prepared to maintain the 0.1 M ionic strength of the solutions by taking requisite amount of sodium per chlorate. The metal nitrates were used to prepare the metal solutions and were standardized by usual procedure [13] .

Apparatus

The digital pH meter [Elico model LI 120; inbuilt temperature compensation and 0.0 -14 pH range with an accuracy of 0.01 pH Unit.] in conjunction with combined electrode were used for pH measurements. The glassware's used in the present experiment were borosil glass quality and standardized as per standard procedure [14]. The experiments were carried out at 27^0C(±1.0 ^{0}C) temperature and 0.1M ionic strength ($NaClO_4$) in aqueous solution. The pH meter was calibrated before every set of titrations by using 4.00(potassium hydrogen phthalate) and 9.00(borax) pH standard buffer solutions. All the necessary precautions were taken for smooth working of electrode [15].

Titration procedure

The mixed ligand stability constants of transition metal complexes were determined by using Calvin Bjerrum pH titration techniques as modified by Irving Rossotti[16] and titration procedure involves following steps :

1) Free acid + $NaClO_4$ (A)
2) Free acid + $NaClO_4$+ primary ligand (A+L)
3) Free acid + $NaClO_4$+ primary ligand+ metal (A+L+M)
4) Free acid + $NaClO_4$+ secondary ligand (A+R)
5) Free acid + $NaClO_4$+ secondary ligand+ metal (A+R+M)
6) Free acid + $NaClO_4$+ primary ligand + secondary ligand+ metal (A+L+R+M)

The above thermostatic mixtures were titrated with a carbonate free 0.1M NaOH solution. The total volume of solution was kept constant at 50 ml by the adding distilled water.

Calculations

The proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of binary complexes were determined by using Irving and Rossotti methods and stability constants of ternary complexes, concentrations of metal ions, ligands free metals, free ligands and various possible species that are formed during complexation were directly obtained as output of 'SCOGS'computer program [17] which employs non linear least square approach. The species distribution curves were obtained as computer output.

RESULTS AND DISCUSSION

Binary complexes

The proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of binary complexes were determined by using Irving and Rossotti methods for the comparison with these of ternary systems. The deviation of metal titration curves from ligand curve indicates the formation of binary complex. The highest values of n^- are around 2.0 in isoniazid drug indicates the formation of 1:1 and 1:2 binary complexes whereas in pyrazinamide drug it is around one hence 1:1 binary complex formation.

Mixed ligand complexes

The formation of 1:1:1 ternary complex (MLR) were identified qualitatively by the pH of precipitation of ML, MR, and MLR titration curves which indicates the higher value of pH of precipitation of ternary system than corresponding binary systems [18]. It has been also confirmed by drawing composite curve(C).

Table 1 Parameter based on some relationship between formation of mixed ligand complexes of Cu(II) with L_4 drug and Amino acids

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	Δlogk
Alanine	16.52	16.67	8.11	7.62	8.41	1.33	-0.49
Glycine	15.75	16.67	8.16	6.85	7.59	1.27	-1.31
Isoleucine	17.04	16.67	8.41	8.14	8.63	1.36	-0.27
Phenyl alanine	16.77	16.67	7.87	7.87	8.90	1.37	0.00
Serine	14.28	16.67	7.88	5.38	6.40	1.16	-2.50
Valine	16.99	16.67	8.12	8.09	8.87	1.37	-0.03
Methionine	14.73	16.67	8.31	5.83	6.42	1.18	-2.48
Glutamic acid	15.72	16.67	7.87	6.82	7.85	1.28	-1.05

Stability of mixed ligand complexes

The mixed ligand stability constant of isoniazid has higher values than pyrazinamide and among copper complexes of isoniazid and eight aminoacids, isoleucine complexes has high value and serine has low value of stability. In pyrazinamide copper complexes with eight amino acids , isoleucine has high value and glutamic acid has low value. These variations may be attributed to steric, inductive effects and the increasing side chain of amino acids would results in more strain in bending leads to the low values of stability as well as an aliphatic nature of amino acids.The

stability constants and relative parameters of these mixed ligand complexes are enlisted in Table 1 and 2.

Table 2 Parameter based on some relationship between formation of mixed ligand complexes of Cu(II) with L_5 drug and Amino acids

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	Δlogk
Alanine	10.34	2.77	8.11	7.57	2.23	1.90	-0.54
Glycine	10.43	2.77	8.16	7.66	2.27	1.91	-0.50
Isoleucine	11.90	2.77	8.41	9.13	3.49	2.13	0.72
Phenyl alanine	10.63	2.77	7.87	7.86	2.76	2.00	-0.01
Serine	10.16	2.77	7.88	7.39	2.28	1.91	-0.49
Valine	10.82	2.77	8.12	8.05	2.70	1.99	-0.07
Methionine	10.58	2.77	8.31	7.81	2.27	1.91	-0.50
Glutamic acid	9.85	2.77	7.87	7.08	1.98	1.85	-0.79

The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of ΔLogK, K_r, K_L and K_R values which are expressed by equations:

$$\Delta LogK = log\beta_{111} - logK_{10} - logK_{01}$$
$$K_r = \beta^2_{111} / \beta_{20} . \beta_{02}$$
$$K_L = \beta_{111} / logK_{10}$$
$$K_R = \beta_{111} / logK_{01}$$

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 [19]. The low values of K_L and K_R indicates the more stability of ternary complexes with respect to binary complexes of primary and secondary ligands. The positive values of Kr also supports the extra stability of mixed ligand complexes which may be attributed to the interactions outside the coordinated sphere such as formation of hydrogen bonding between coordinated ligands, charge neutralization, chelate effect and electrostatic interactions between non coordinated charge group of ligands[20].The negative values of ΔLogK suggests the formation of ternary complexes but less stable having destabilized nature of complexes which has been valid for N and O donors[21]. The positive value of ΔLogK in some cases is attributed to the extra stability of ternary complexes.

Species distribution curves

The concentration of various species formed in the complex formation process were directly obtained as a computer outputs and the species distribution curves of Cu(II)LR_8 systems of both ligands were constructed by plotting percentage concentration of various possible species formed versus pH of solution during complexation.

In Cu (II)L_1R_8 ternary system of isoniazid and glutamic acid, primary ligand forms 1:1 and 1:2 binary complexes whereas secondary ligands forms only 1:1 binary complexes with copper. The species distribution diagram of free metal (M), free ligands L and R shows that there is slowly decrease in percentage concentration of free metal ions with increase in pH and percentage concentration of both ligands increases with increase in pH of solution. The percentage formation of FR is high than FL as shown in Figure 3.

The species distribution curve of various possible species of Cu(II)L_1R_8 system(Figure:4) shows that(97.94) percentages of ternary complexes(CuLR) were formed at 6.00 pH. It also indicates that the percentage concentration of HL and CuR_2 decreases as the percentage concentration of ternary complex (CuLR) species increases with increase in pH and possible equilibria can be expressed by the equation as:

$$CuR_2 + CuL \rightleftharpoons CuLR + CuR$$
$$Cu + L+R \rightleftharpoons CuLR$$

In Cu (II)L_2R_8 ternary system of pyrazinamide and glutamic acid, primary and secondary ligands forms 1:1 binary complexes.

The species distribution curve in Figure 5.00 shows that concentration of free metal slightly decreases with increase in pH and free ligand (FL) concentration increases up to 94% at 6.00 pH which are very high as compared to free ligand FR.

The percentage concentration of various possible species were shown in Figure 6.00 where curves indicates that the concentration of HL decreases from 80% to 0.077% at 6.0 pH and CuR species decreases from 98% to 94% at 6.0 pH which are much less hence somewhat linear curve. The formation of mixed ligand complex takes place but very low percentage (5.55%) and is shown in Figure 6.00 and possible equilibria of CuLR species is expressed as:

$$CuL + CuR \rightleftharpoons CuLR + Cu$$

Figure: 3 Species distribution curve of Cu(II)L_1R_8 system (pH versus % conc. of free metal and free ligands)

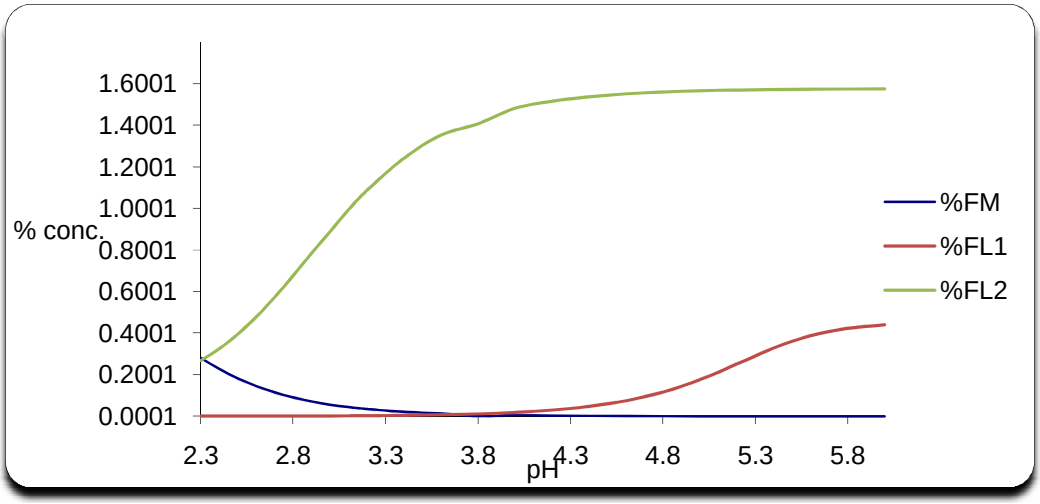


Figure: 4 Species distribution curve of Cu(II)L_1R_8 system (pH versus % conc. of various possible species)

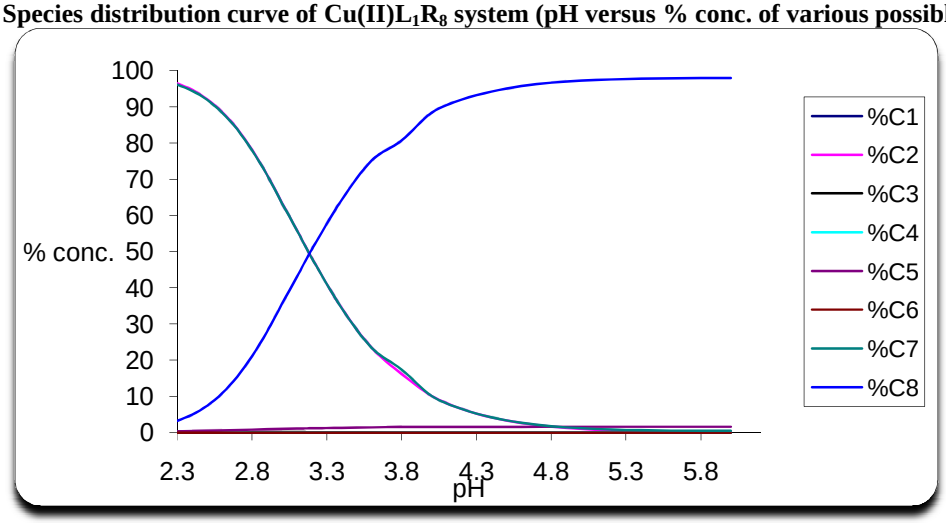


Figure: 5 Species distribution curve of Cu(II)L_2R_8 (pH versus % conc. of free metal and free ligands)

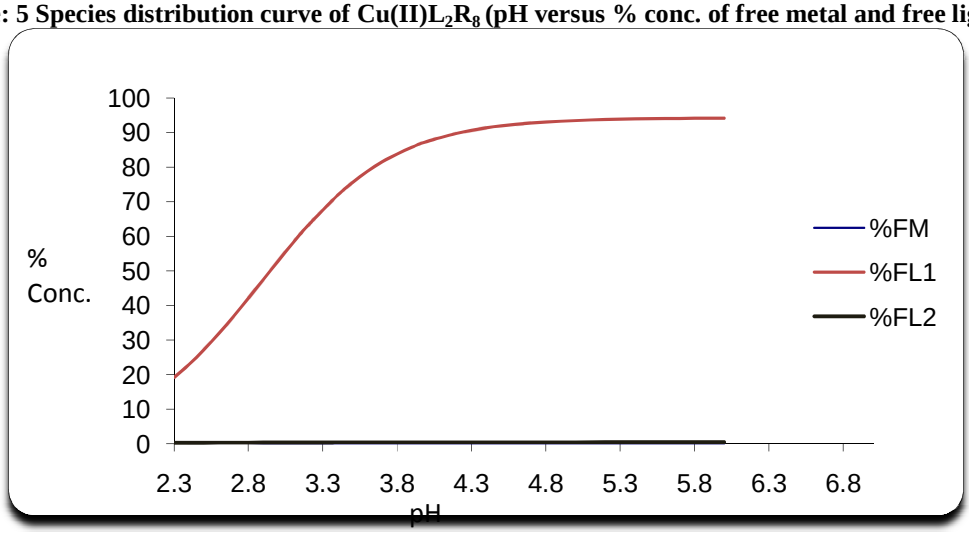
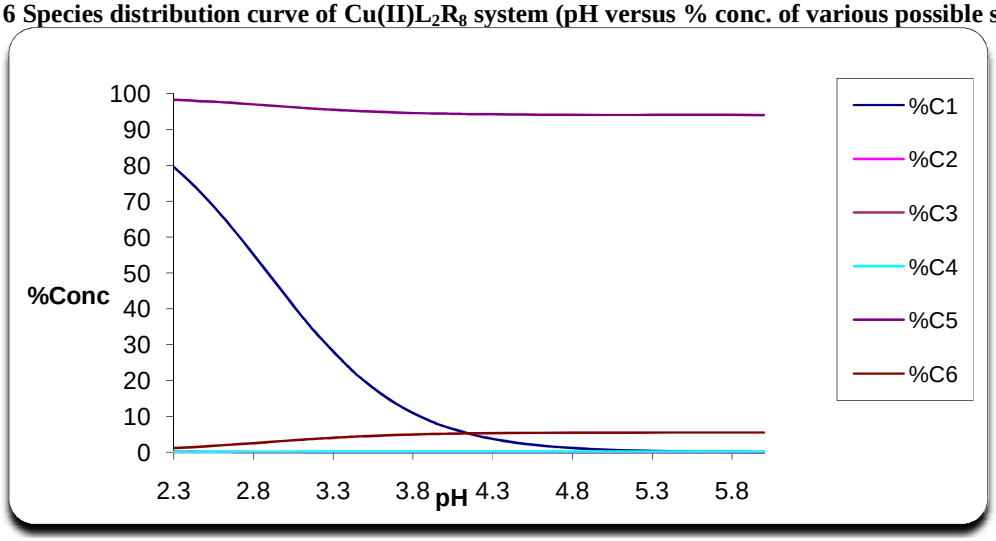


Figure: 6 Species distribution curve of Cu(II)L_2R_8 system (pH versus % conc. of various possible species)



CONCLUSION

(1) Stability of mixed ligand complexes is mainly affected by the characteristics of approaching secondary ligand. (2) The negative values of ΔLogK suggests the formation of ternary complexes but less stable having destabilized nature of complexes and positive value of ΔLogK in some cases is attributed to the extra stability of ternary complexes. (3) The positive values of Kr also support the extra stability of mixed ligand complexes which may be attributed to the interactions outside the coordinated sphere. (4) The species distribution curve shows the formation of ternary complexes and deprotonation of amino groups.

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