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Mixed Ligand Stability Constant of Cu(II) Ion complex with Antibiotic Drug and Phenyl Alanine in 40% V/V Alcohol Water Medium

B K. Magare [1*]

1. UG and PG Department of Chemistry, Shivaji Arts, Commerce and Science College, Kannad, Dist. Aurangabad (M.S.) India - 431103. [Email: bkmraj75@gmail.com]

Mixed ligand stability constant of copper complexes with piperacillin (antibiotic) drug and phenyl alanine amino acid have been studied pH metrically in 40% v/v ethyl alcohol water medium at 27 ^{0}C temperature and 0.1 M ionic strength. The equilibrium constant of copper ternary complexes have been correlated with ΔlogK, K_L, K_R and K_r stability related parameters. The percentage concentrations of various possible species with pH were determined by using computer program and possible equilibria were predicted.

Keyword: Equilibria, ternary, drug, amino acids, ionic strength, stability constants.

1. Introduction

The coordination chemistry has played a vital role in the solution equilibria [1]. It plays an important role in the medicinal, analytical, environmental and biological sciences.The stability constants of metal complexes with drugs have been determined so as to know the proper dose of drugs and their effect with all other components of blood streams [2]. The stability of complexes plays a major role in their biological and chemical activity. These have important to measure the metal ligand selectivity in complex media [3]. Researcher has shown that the metal complexes of drugs are more potent than drugs [4]. The detoxification of metal poisoning has overcome due to formation of stable complexes with chelating agents like drugs [5]. The numbers of transition metal complexes are involved in storage, transport, and detoxification and catalytic processes [6]. The coordination behaviours of drug with metal enzymes determine the effectiveness in extra cellular fluid pH condition.

Phenyl alanine is an aromatic, essential, glycogenic amino acid which forms hormones like adrenaline, noradrenaline and melanin pigments in metabolism. It plays a vital role in all aspect of cell structure and function [7]. It is used in food technology and industry.

Piperacillin is an extended spectrum beta-lactam antibiotic of the ureidopenicillin class. It is normally used together with abeta-lactamase inhibitor, notably in the combination with tazobactam. The structures of piperacilin drug and phenyl alanine amino acid were shown in Figure 1 and 2 respectively.

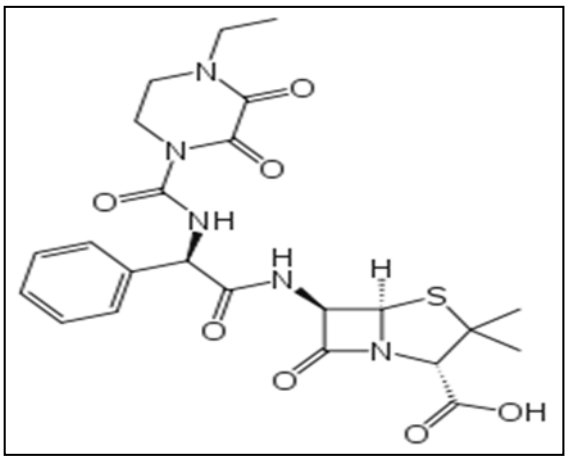

Fig 1: Structure of Piperacillin

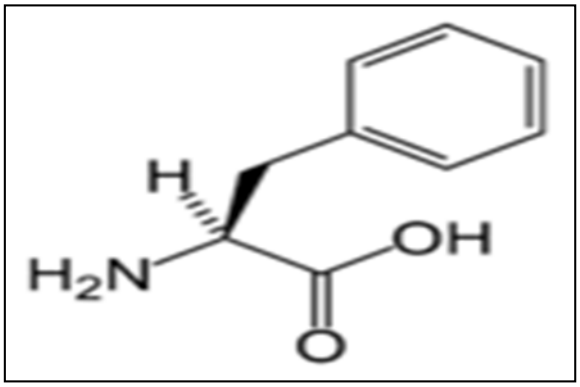

Fig 2: Structure of Phenylalanine

The present paper deals with study of mixed ligand complexes of Cu(II) metal ions with piperacillin(L) drugs and phenylalanine(R)amino acid in 40% v/v ethanol water organo-aqueous medium at 27 ^{0}C temperature and 0.1M ionic strength ($NaClO_4$).

2. Results and Discussion

2.1 Binary complexes

The proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of binary complexes of piperacillin and phenyl alanine were determined by using Irving and Rossotti methods in 40% v/v ethyl alcohol water medium. These stability constants of piperacillin and amino acid were used to determine stability constants of ternary complexes. The deviation of metal titration curves from ligand curve indicates the formation of binary complex.

2.2 Mixed ligand complexes

The ternary copper complexes of piperacilin drug and alanine, glycine, and phenyl alanine amino acids were studied in 40% v/v alcohol water medium at 0.1 M ionic strength. The stability constants of ternary complexes and related parameters like ΔlogK, K_L, K_R and K_r were represented in Table 1.0. In ternary system piperacillin (L_1) the drugs was used as a primary ligand and phenylalanine (R) amino acids were used as a secondary ligand.

2.3 Formation of ternary complexes

The formation of ternary complexes was confirmed with precipitation of 1:1:1 MLR system at higher pH than binary systems. [8] It was also confirmed by drawing composite curve [9]. The nature of mixed ligand titration curves indicates that complex formation takes place in the pH range of 3.30 to 8.00. There was no any solid phase formed during the course of titrations.

2.4 Stability of ternary copper complexes of piperacilin (L_1) drug and amino acids

The logβ values (Table 1.0) of binary and ternary shows that secondary ligands has higher values of stability constants than corresponding ternary ligands which may be attributed to the bidentate nature of secondary ligands .

Table 1.0: Equilibrium constantand related stability parameters of ternary complex of Cu (II) ion with Piperacillin (L) drug and Phenyl alanine(R) Amino acid.

Amino Acid	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	ΔlogK
Phenyl Alanine(R)	11.18	3.31	16.70	7.88	1.80	1.12	-1.51

The stability of mixed ligand complexes of CuLR systems were measured in terms of various parameters like ΔlogK, K_L, K_R and Kr values which explain relative stability of binary and ternary complexes as

$$Kr = \beta^2_{111}/(\beta_{20}.\beta_{02})$$
$$K_L = \beta_{111}/K_{10}$$
$$K_R = \beta_{111}/K_{01}$$

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

The positive values of K_L and K_R indicates that the more stability of ternary complexes over corresponding binary complexes [10]. The Kr values indicate the formation of extra stable ternary complexes [11]. It suggests that there is a strong bonding with secondary ligands. The negative value of ΔlogK shows the formation of ternary complex with destabilised nature of

complex. The negative values of ΔlogK also suggests that secondary ligand forms more stable complex with hydrated metal ion than ML species [12]. This may be attributed to bidentate nature or outer sphere interactions [13].

2.5 Distribution of various complex species with pH

The number of species formed in the solution, their concentrations and possible equilibria has its own significance in dealing with biological, medicinal and environmental problems [14-15]. The percentage distribution of free metal, free ligands FL and FR with corresponding pH and percentage distribution of species of ternary systems were explained with the help of species distribution curves. The species distribution curves were obtained by plotting percentage concentration versus pH of these species and shown in Figure 3.0 and 4.0.

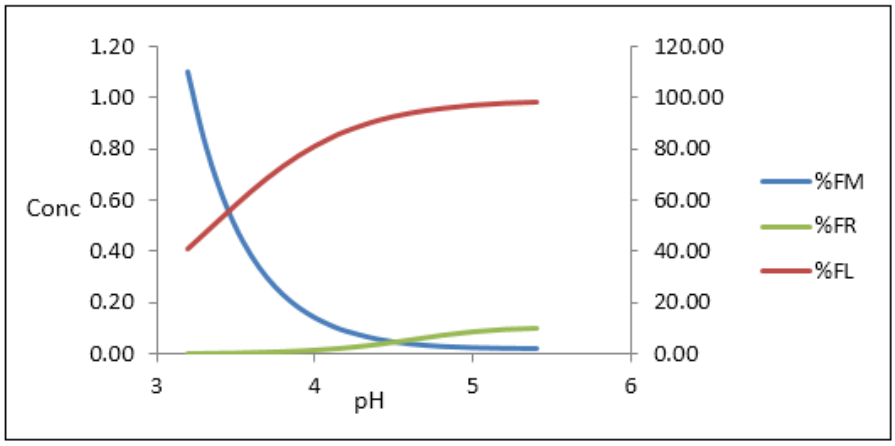

Fig 3: Species distribution diagram of free metal and free ligand(CuLR)

The species distribution curves of (Figure 3.0) free metal, free ligands (FL and FR) species shows that the percentage concentration of free metal decrease with increase in pH and percentage concentration of free ligands FL and FR increases with increase in pH. The concentration of free ligand FL is more than that of free ligand FR at higher pH.

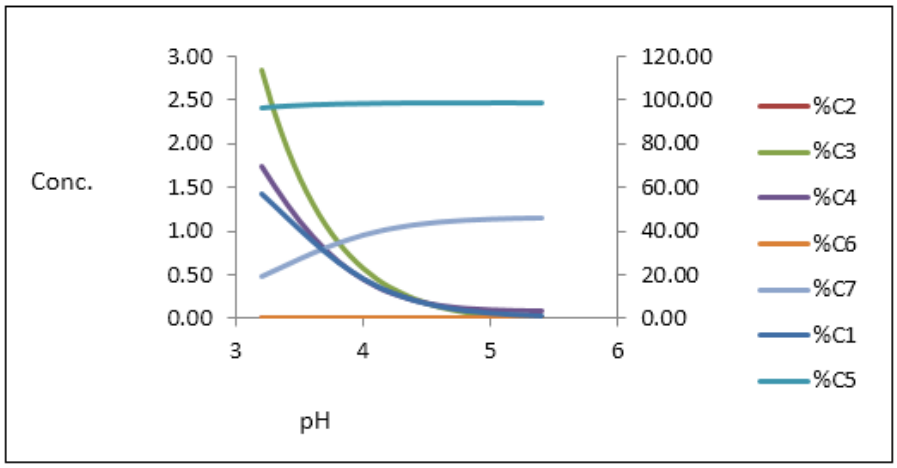

Fig 4: Species distribution diagram of various species of CuLR system

Species distribution diagram of various species shows thatthe curve C_1, C_3 and C_4decreases with increase in pH due to dissociation of species.
The curve C_5 indicate the maximum formation of CuR binary species as the pH increases. It may be one of the reason for the poor formation of ternary complexes. It can be possible by following equilibrium as

$$C_5 = Cu + R \rightleftharpoons CuR \quad \text{.....(6)}$$

Species distribution diagram of different species (Figure 4.0, C7 curve) shows that percentage formation of ternary complex is very poor (1.15 at 5.4 pH).This may be attributed to aromatic nature of ligands and steric effect.

$$Cu + L + R \rightleftharpoons CuLR \quad \text{.....(1)}$$

$$CuR_2 + CuL \rightleftharpoons CuLR + CuR \quad \text{.....(2)}$$

3. Materials and solutions

3.1 Chemicals

All the chemicals used in the present study were A.R. grade. The metals were used as nitrates. Pure drugs were procured as a gift sample. The pure samples of amino acids were obtained from Sd Fine Ltd. Mumbai.

3.2 Solutions

The solutions of all reagents were prepared in double glass distilled water having 6.80-6.90 pH. The solution of drug was prepared in pure alcohol [16]. The fresh solution of NaOH was used as a titrant for pH titrations. It was standardized with oxalic acid [17]. The 1.0 M $NaClO_4$ solution was used to maintain the 0.1 M ionic strength by taking requisite amount of sodium perchlorate solution. The metal solutions were standardized by usual procedure [18].

3.3 Digital pH meter

The digital pH meter [Elico model LI 120; inbuilt temperature compensation and 0.0 to 14 pH range with an accuracy of ± 0.01 pH Unit] in conjunction with combined glass electrode were used for pH measurements and experiments were carried out at 27 ^{0}C temperature and inert atmosphere by maintaining 0.1 M ionic strength ($NaClO_4$) in aqueous solution. The pH meter was calibrated before every set of titrations by using 4.00 and 9.00 pH standard buffer solutions. All the necessary precautions were taken for smooth working of electrode [19].

3.4 General titration procedure:

The Calvin Bjerrum pH titration techniques as modified by Irving Rossotti were applied to determine the equilibrium constants of 1:1:1 ternary complex [20]. Titration procedure involves following steps:

1) Free acid ($HClO_4$) +$NaClO_4$ ..... (A)

2) Free acid (HClO4) + $NaClO_4$+ primary ligand…… (A+L)

3) Free acid (HClO4) + $NaClO_4$+ primary ligand + metal…… (A+L+M)

4) Free acid (HClO4) + $NaClO_4$+ secondary ligand……. (A+R)

5) Free acid ($HClO_4$) + $NaClO_4$+ secondary ligand+ metal…… (A+R+M)

6) Free acid ($HClO_4$) + $NaClO_4$+ primary ligand + secondary ligand+ metal……... (A+L+R+M)

The above thermostatic mixtures were titrated with standard NaOH solution. The total volume of solution was kept at 50 ml by the adding distilled water.

3.5 Calculations

The proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of binary complexes of piperacilin and amino acids were determined with the help of computer (MS Office, Excel) by using Irving and Rossotti methods. It is used to calculate stability constants of ternary complexes. The equilibrium constants

of ternary complexes along with concentrations various species formed during complexation were directly obtained as output of 'SCOGS' computer program [21] which employs non-linear least square approach.

4. Conclusions

(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 complex.
(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.
(5) The percentage formation of ternary complexes is less due to the formation of CuR species.

5. Acknowledgement

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