ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Solution Studies on Ternary Copper Complexes of Piperacillin Drug with Alanine and Glycine Amino Acids

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ABSTRACT

Solution studies on ternary copper complexes of piperacillin drug with alanine and glycine amino acids have been studied pH metrically in 40% v/v ethyl alcohol water media at 27^0C temperature and 0.1 M ionic strength. The stability constants of copper ternary complexes of piperacillin with alanine and glycine amino acids have evaluated by using 'SCOGS' computer program. It is correlated with ΔlogK, K_L, K_R and Kr stability related parameters. The percentage concentrations of various possible species with pH have been determined and possible solution equilibria has predicted. The mixed ligand complex formation has affected by preferential formation of binary complexes of secondary ligand.

Keywords: piperacillin, equilibria, ternary, amino acids, ionic strength, stability constants.

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ISSN: 0975-8585

INTRODUCTION

The solution study of metal complexes has played a vital role in the medicinal, analytical, environmental and biological sciences [1]. The stability constants of metal complexes with drugs are important to know the proper dose of drugs and their adverse effect with all other components of blood streams [2]. The stability of complexes plays a major role in elucidation of mechanism of drug action. The acute action of drug and their complex formation in complex media is depend on metal ligands selectivity and stability constants [3]. The study of metal complexes with drugs shows that they are more potent than drugs [4]. The drug forms harmless stable complexes during the detoxification of metal poisoning [5]. Most of transition metal complexes are involved in storage, transport, and catalytic processes [6-7]. The effectiveness of any molecule as a drug depends on its coordination behaviours, body temperature and extra cellular fluid pH condition.

Piperacillin is an extended spectrum beta-lactam antibiotic of the ureidopenicillin class[8]. It is normally used together with a beta-lactamase inhibitor, notably in the combination with tazobactam. The structures of piperacillin drug and alanine and glycine amino acids were shown in Figure 1 ,2 and 3 respectively.

Figure 1: Structure of Piperacillin

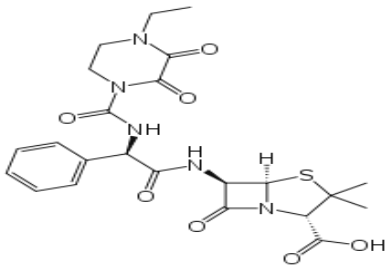


Figure 2: Structure of Alanine

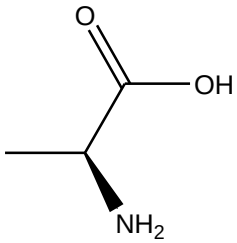
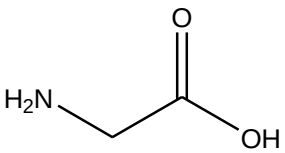


Figure 3: Structure of Glycine



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The alanine is a non essential glycogenic amino acid plays key role in glucose – alanine cycle between tissue and liver [9]. The glycine is a neutral,aliphatic non esstential glycogenic amino acid and play an important role in haeme synthesis[10].It acts as a inhibitory neurotransmitter in central nervous system in spinal cord, brain stem and retina[11]. The copper is essential in iron absorptions, and transportation [12]. It also controls neurotransmitters, pigmentations, hormones.

The present paper deals with study of mixed ligand complexes of Cu(II) metal ions with piperacillin (L_1) drug and alanine(R_1) and glycine(R_2) amino acids in 40% v/v ethyl alcohol water organo-aqueous medium at 27^0C temperature and 0.1M ionic strength($NaClO_4$).

MATERIALS AND METHODS

Chemicals

All the chemicals and reagents used in the present study were analytical grade. Pure piperacillin drug were obtained as a gift sample. The pure samples of amino acids were purchased from SD Fine Ltd. Mumbai. The metals are used as nitrates.

Solutions

The solutions of reagents were prepared in double glass distilled water having 6.80-6.90 pH. The solution of drug was prepared in pure alcohol [13]. The NaOH solution was prepared in double distilled water and fresh solution was used as a titrant for pH titrations. It is standardized with oxalic acid [14]. The 1.0 M $NaClO_4$ solutions were prepared to maintain the 0.1 M ionic strength of the titration solutions by taking requisite amount of sodium perchlorate. The metal solutions were standardized by usual procedure [15].
The Calvin Bjerrum pH titration techniques as modified by Irving Rossotti were applied to determine the equilibrium constants of 1:1:1 ternary complexes [16] .

EXPERIMENTAL

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. The experiments were carried out at 27^0C temperature and inert atmosphere by maintaining 0.1M ionic strength ($NaClO_4$) in organo - aqueous medium. 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 [17].

Titration procedure:

Titration procedure involves following steps:

ISSN: 0975-8585

1) Free acid ($HClO_4$)+ $NaClO_4$ (A)
2) Free acid ($HClO_4$)+ $NaClO_4$+ primary ligand (A+L)
3) Free acid ($HClO_4$) + $NaClO_4$+ primary ligand+ metal (A+L+M)
4) Free acid ($HClO_4$) + $NaClO_4$+ 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 requisite amount of distilled water and pure alcohol.

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 in Excel MS office 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 [18] which employs non linear least square approach.

RESULTS AND DISCUSSION

Binary complexes

The proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of binary complexes of piperacilin and three amino acids were determined by using Irving and Rossotti methods for the comparison with these of ternary systems. These stability constants of piperacilin and amino acids were used to determine stability constants of ternary complexes. The deviation of metal titration curves from ligand curve indicates the formation of binary complex.

Mixed ligand complexes

The ternary copper complexes of piperacillin drug with alanine and glycine amino acids were studied in 40% v/v ethyl alcohol water medium at 0.1 M ionic strength. The stability constants of ternary complexes and ΔlogK, K_L, K_R and K_r related parameters were represented in **Table 1.0.**

Formation of ternary complexes

The formations of ternary complexes were identified from pH of precipitation of complexes and nature of ternary graph. The pH of precipitation of 1:1:1 MLR system was found more than that of binary systems [19]. It was confirmed by drawing composite curves [20]. The nature of mixed ligand titration curves indicates that complex formation takes place in the pH range of 3.30 to 8.00 in most of the systems. There was no any solid phase formed during the course of titrations.

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

The equilibrium constants (Table 1) of binary and ternary complexes 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. The relative stability of binary and ternary complexes were explained in terms of ΔlogK, K_L, K_R and Kr values as

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

Table 1: Equilibrium constants and relative parameters of mixed ligand complexes of Cu(II) with Piperacillin(L_1) drug and Amino acids

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	ΔlogK
Alanine(R_1)	11.65	3.31	16.65	8.34	2.05	1.17	-1.25
Glycine(R_2)	11.51	3.31	15.76	8.20	2.30	1.21	-1.00

The positive values of K_L and K_R indicates that the more stability of ternary complexes over corresponding binary 1:1 complexes [21]. The positive values of Kr indicate the formation of extra stable ternary complexes [22]. Negative values of ΔlogK show the formation of ternary complexes with destabilised nature of complex. The negative values ofΔlogK also suggests that secondary ligand forms more stable complex with hydrated metal ion than ML species [23]. The ternary complexes of copper with piperacillin and two amino acids show following order of stability as

$$\beta_{111} = \text{Ala} > \text{Gly}.$$

This may be attributed to the aliphatic nature of alanine and electron donating effect of methyl group [24].

Distribution of various complex species with pH

The equilibrium constant of binary and ternary complexes are not much use unless the distribution of various possible species at different pH are known .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[25-26]. The percentage distribution of free metal, free ligands [FL and FR] and various species with corresponding pH were explained with the help of species distribution diagram. The species distribution diagram were obtained by plotting percentage concentration versus pH and shown in Figure 4 and 7. The Figure 4.0 and 6.0 of FM,FL and FR 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 species distribution curve of these species is evident that concentration of free ligand FL is more than free ligand FR at higher

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pH. Species distribution diagram of CuL_1R_1 system (Figure 5) shows that percentage formation of ternary complex species is 5.91 % at 5.4 pH.

Figure 4: Species Distribution Diagram of free metal and ligand(CuL_1R_1)

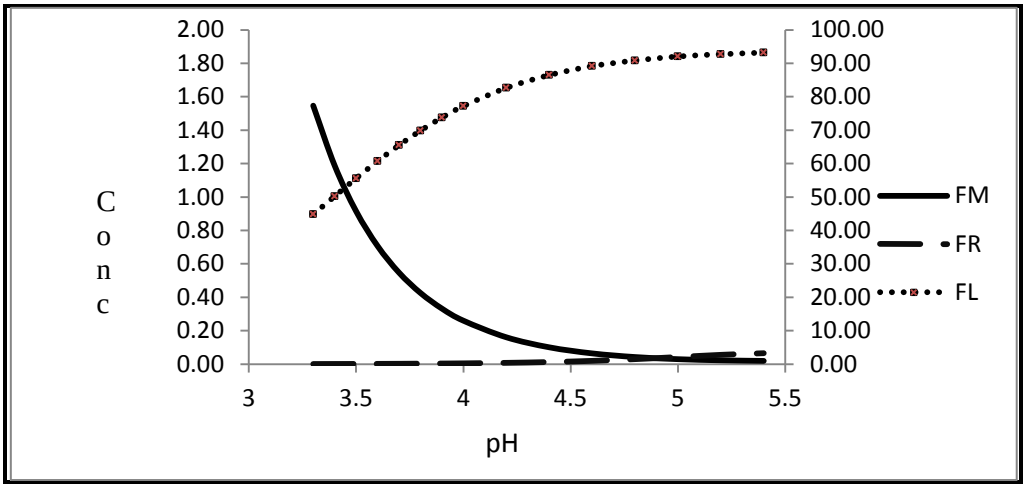

Figure5: Species distribution curve of various species CuL_1R_1

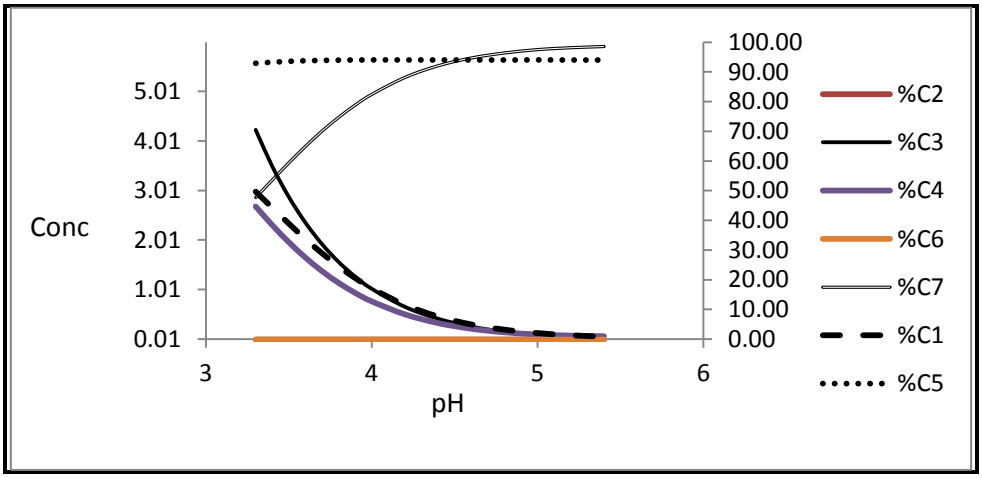

Figure 6: Species Distribution Diagram of free metal and ligand(CuL_1R_2)

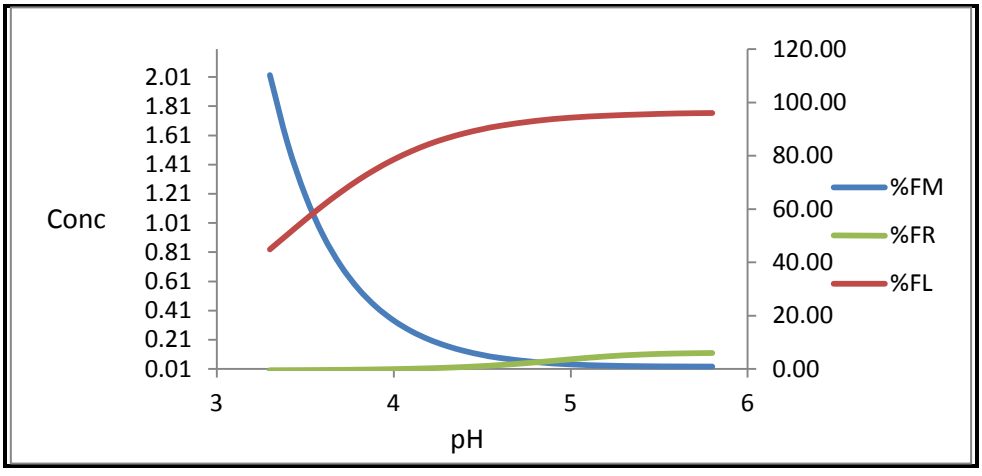

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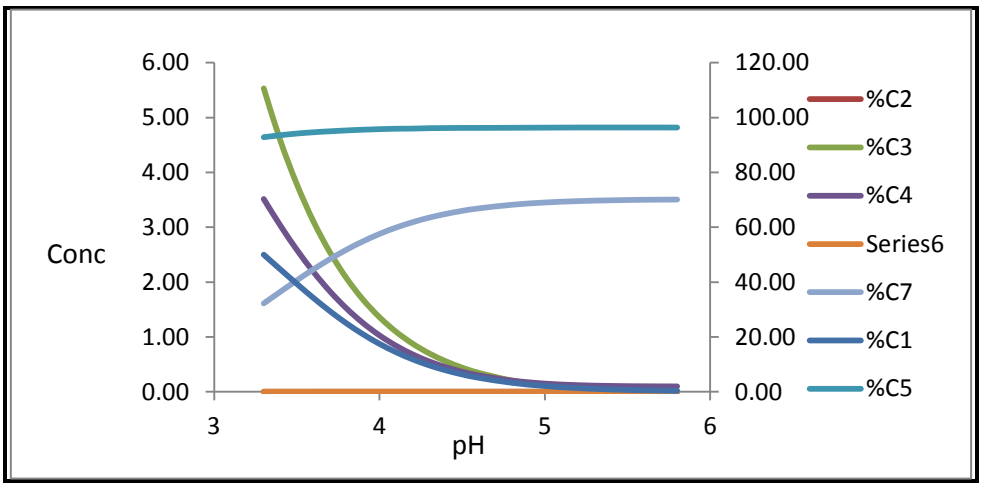
Figure 7: Species distribution curve (pH vs %C)CuL_1R_2



Species distribution curves (Figure 7) of CuL_1R_2 system of various species shows that percentage formation of ternary species is 3.49 % at 5.4 pH by following equilibriums.

$$Cu + L + R \rightleftharpoons CuLR \quad \text{.....(1)}$$
$$CuR_2 + CuL \rightleftharpoons CuLR + CuR \quad \text{.....(2)}$$

It indicates that the percentage formation of (**CuL_1R_1**) species is higher than **CuL_1R_2**. This may be attributed to electron donating effect of methyl group of secondary ligand. The curves C_1, C_3 and C_4 indicate that there is decrease in percentage with increase in pH due to following equilibria as

$$C_1 = HL \rightleftharpoons L + H \quad \text{..... (3)}$$
$$C_3 = HR \rightleftharpoons R + H \quad \text{.....(4)}$$
$$C_4 = Cu + L \rightleftharpoons CuL \quad \text{..... (5)}$$

The curve C_5 indicates the maximum formation of CuR binary species as the pH increases.

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

These affect on formation of ternary complex species.

CONCLUSIONS

- Stability of mixed ligand complexes is mainly affected by the characteristics of approaching secondary ligand.
- The negative values of ΔLogK suggests the formation of ternary complexes but less stable having destabilized nature of complex.
- 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.
- The species distribution curve shows the formation of ternary complexes.

- The percentage formation of ternary complexes is less due to the formation of CuR species.

ACKNOWLEDGEMENT

One of the authors Dr. B. K. Magare, department of chemistry, Shivaji Arts, Commerce and Science College Kannad is very much thankful to the UGC (WRO) Pune for providing financial assistance.

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