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Stability constants of Cu(II) and Zn(II) Metal complexes with Ethambutol hydrochloride and Alanine, Glycine, Isoleucine and Phenylalanine amino acids

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Abstract : Stability constants of binary and ternary complexes of Cu(II) and Zn(II) transition metal ions with ethambutol hydrochloride drug (L) and alanine, glycine, isoleucine and phenyl alanine amino acids(R) have been determined potentiometrically at 30° C temperature and 0.1 M ionic strength(NaClO₄) in aqueous solution. The formations of complexes were confirmed from deviation of curves. Stability of complexes was discussed in terms of different relative stability parameters.

Keywords : binary, ternarycomplexes, transition metal, ethambutol hydrochloride, amino acids.

Introduction

The coordination chemistry of metal complexes has played a vital role in the field of medicinal and biological sciences¹. The stability of metal complexes with drugs are important to measure its effectiveness. It is useful to know the proper dose of drug and their effect with all other ligands of blood stream as well as to measure the strength of metal ligand bonds². The complexes of drugs are found more effective than drug³. The studies of complex equilibria of metal ions with drugs help to elucidate the mechanism of action of drugs⁴. The role of transition metal ions and their complexes are involved in metabolism, transportation, detoxification and catalytic processes in the systems⁵. Amino acids are the basic structural unit of proteins and played paramount role in the cell structure and functions⁶⁻⁸. It is important to explain the nature and driving forces for the interactions occurring in human body⁹⁻¹¹. It will be helpful to understand the structure activity relationship of an active site of zinc and copper ions.¹²⁻¹⁶

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Experimental

Chemicals and solutions

The ethambutol hydrochloride drug (L) [Chemical name of drug is 2,2'ethylenediamine-di-butanol hydrochloride] is an antitubercular drug that inhibits the transfer of mycolic acids into cell wall of tubercle bacillus¹⁷ and is effectively used against actively growing microorganism of Genus mycobacterium and structure is shown in Figure 1.



Figure 1: Structure of ethambutolhydrochloride drug (L).

The literature survey reveals that very limited work of binary and ternary complexes of transition metal ions with drug ethambutol hydrochloride and amino acids have been reported.¹⁸⁻²¹Hence the present paper deals with the systematic study of stability constants of binary and mixed ligand ternary complexes of Cu(II) and Zn(II) metal ions with ethambutol hydrochloride drug(L) and alanine, glycine, isoleucine and phenyl alanine amino acids (R).

All the chemical reagents used in the present investigation were A.R. grade. The solutions of drug and amino acids were prepared in carbonate free doubled distilled water having 6.80-6.90 pH. The NaOH solution was standardized with oxalic acid and kept in Pyrex vessel. The 1.0 M sodium perchlorate (NaClO₄) 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.²²

Apparatus

The digital pH meter [Elico model LI 120; inbuilt temperature compensation and 1.0 -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 procedure²³. The experiments were carried out at 30°C(\pm 1.0°C) temperature and 0.1M ionic strength (NaClO₄) 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 electrode²⁴.

Titration procedure

The binary and ternary stability constants of transition metal ions were determined by using CalvinBjerrum pH titration techniques as modified by Irving and Rossotti²⁵. The titration procedure involves following steps:

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 a carbonate free standardNaOH 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 andRossotti methods with the help of MS office Excel program. The equilibrium 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' computerprogram²⁶ which employs nonlinear least square approach. The species distribution curves

Results and Discussion

were obtained as computer output.

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^- (average number of ligands bound per metal atom) are around 2.0 except cobalt (1:1 Binary complex) indicates the formation of 1:1 and 1:2 binary complexes. The order of stability of binary complexes of transition metal ions with drug(L) follows the natural order[Cu(II)> Zn(II)] of Irving and Williams series²⁷ which has been reported by various of researchers²⁸⁻²⁹. The low values of stability constants suggest the ionic interactions²⁷. Stability constant of Cu and Zn metal complexes with drug and amino acids are shown in Table 1.

Liganda	K ₁ ^H	K ₂ ^H	Cu(II)		Zn(II)	
Liganus			LogK ₁	LogK ₂	LogK ₁	LogK ₂
EthambutolHCl	6.48	-	5.17	4.86	3.67	3.12
Alanine(R ₁)	2.30	9.69	8.90	-	8.59	4.59
Glycine(R ₂)	2.36	9.57	8.16	-	09.17	4.96
Isoleucine(R ₃)	2.25	9.62	8.41	-	8.48	4.47
Phenyl	2.21	9.18	7.87	-	8.34	4.27
alanine(R ₄)						

Table 1: Stability constant of Cu and Zn metal complexes.

Mixed ligand complexes

The formation of 1:1:1 mixed ligand complexes (MLR) were identified qualitatively by the pH of precipitation of ML, MR, and MLR titration curves. It indicates the higher value of pH of precipitation of ternary system than corresponding binary systems³⁰.

In ternary system of Copper and Zinc metal ions, The $Cu(II) LR_2(glycine)$ system shows high stability constants values among the present copper and zinc transition metal complexes with drug(L) and four amino acids whereas $Zn(II)LR_1(alanine)$ system shows low value which may be attributed to the bonding interaction of amino acids and metal ions. The stability constants and relative parameters of these mixed ligand complexes are enlisted in Table 2 and 3.

Table: 2 Stabi	ility constants of terna	ry complexes of Cu (II)) with ethambutol-HCl	(L)and amino	acids and
their relative	parameters.				

Amino Acids	β ₁₁₁	β ₂₀	β ₀₂	KL	K _R	Kr	∆logK
Alanine(R ₁)	12.32	10.03	8.11	7.15	4.21	1.36	-0.96
Glycine(R ₂)	13.34	10.03	8.16	8.17	5.18	1.47	0.01
Isoleucine(R ₃)	12.94	10.03	8.41	7.77	4.53	1.40	-0.64
Phenyl alanine(R ₄)	13.04	10.03	7.87	7.87	5.17	1.46	0.00

Amino Acids	β ₁₁₁	β ₂₀	β ₀₂	KL	K _R	Kr	∆logK
Alanine(R ₁)	11.76	6.79	13.18	8.09	3.17	1.18	-0.50
Glycine(R ₂)	12.82	6.79	14.13	9.15	3.65	1.23	-0.02
Isoleucine(R ₃)	12.14	6.79	12.95	8.47	3.66	1.23	-0.01
Phenyl alanine(R ₄)	10.99	6.79	12.61	7.32	2.65	1.13	-1.02

Table: 3 Stability constants of ternary complexes of Zn (II) with ethambutol-HCl (L) and amino acids and their relative parameters.

In Cu(II)LR system, the ternary complex with glycine shows high value of stability constant whereas alanine ternary complex shows low value. The glycine ternary complex of Zn(II)LR system shows high value of stability and alanine system shows low value of stability. These variations may be attributed to steric, inductive effects and the increasing side chain of amino acids would results in more strain in bonding leads to the low values of stability as well as an aliphatic nature of amino acids.

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

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

$$\begin{split} K_r &= \beta^2_{111} / \beta_{20.} \beta_{02} \\ K_L &= \beta_{111} / log K_{10} \\ K_R &= \beta_{111} / log K_{01} \end{split}$$

And shown in Table 2 and 3 along with stability constants of ternary systems of Cu(II) and Zn(II) transition metal ions respectively.

The comparison of β_{111} with β_{20} and β_{02} of these systems reveals the preferential formation of ternary complexes over the binarysystems³¹. The low values of K_L and K_R indicate the more stability of ternary complexes with respect to binary complexes of primary and secondary ligands. 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 such as formation of hydrogen bonding between coordinated ligands, charge neutralization, chelate effect and electrostatic interactions between non coordinated charge group of ligands³². The negative values of Δ LogK suggests the formation of ternary complexes but less stable having destabilized nature of complexes which have been reported in N and O donors³³. The positive value of Δ logK 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 and Cu(II)LR systems were constructed by plotting percentage concentration of various possible species formed during complexation versus pH of solution.

The species distribution diagram f free metal (M), free ligands L and R indicates the slowly decrease in percentage concentration of free metal ions with increase in pH and percentage concentration of both ligands increases with increasein pH of solution.

The species distribution curve of various possible species of Cu(II)LR system clearly indicates the formation of ternary complexes(CuLR) which is at pH 6.4. It also shows that very less amount of formation of CuL binary species. The percentage concentration of CuR₂decreases due to the formation of mixed ligand complexes as:

The percentage concentration of HL (C_1) species decreases as the pH increases which indicates the deprotonation of primary ligand as shown in equilibria:

 $HL \leftrightarrow L+H.$

The possible equilibria in the formation of ternary complexes of Copper and Zinc metal ions(M)are as follows:

 $\begin{array}{l} M+L+R \leftrightarrow MLR.\\ MR_2+ML \leftrightarrow MLR +MR\\ ML_2+MR \leftrightarrow MLR +ML \end{array}$

Conclusion

(1)The stability constant of binary complexes with transition metal ions and primary ligand indicates the usual trend in order.

(2) Mixed ligand stability constants of drug indicates high value of ternary complexes with aliphatic amino acids.

(3) The negative values of $\Delta LogK$ suggests the formation of ternary complexes but less stable having destabilized nature of complexes and positive value of $\Delta logK$ in some cases is attributed to the extra stability of ternary complexes.

(4) The positive values of Kr also supports the 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.

(5)The species distribution curve shows the formation of ternary complexes.

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