

Equilibrium Studies on Mixed Ligand Complexes of Drug Ethambutol Hydrochloride with Nickel and Cobalt Metal Ions and Amino Acids

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Abstract: Stability constants of mixed ligand ternary complexes of Co(II) and Ni(II), transition metal ions with ethambutol hydrochloride drug (L) and a series of four amino acids(R) have been determined pH metrically at 30°C temperature and 0.1 M ionic strength (NaClO₄) in aqueous solution. The formation of various possible species has been evaluated by computer program and discussed in terms of different relative stability parameters.

Keywords: Mixed ligand complex, transition metal, ethambutol hydrochloride, drug, amino acids, and ionic strength

1. Introduction

The coordination chemistry has played a vital role in the field of medicinal and biological sciences[1]. 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[2].The complexes of drugs are more potent than drug [3]. The studies of complex equilibria of metal ions with drugs help to elucidate the mechanism of action of drugs[4]. The role of transition metal ions and their complexes are involved in metabolism, transportation, and catalytic processes in the systems [5]. Amino acids are the basic structural unit of proteins and played paramount role in the cell structure and functions. They are essential for growth and metabolism processes.

The ethambutol hydrochloride drug (L) [Chemical name of drug is 2,2'ethylenediamine-di-butanol hydrochloride] is an ant tubercular drug that inhibits the transfer of mycolic acids into cell wall of tubercle bacillus [6] and is effectively used against actively growing micro-organism of Genus mycobacterium and structure is shown in Figure 1.

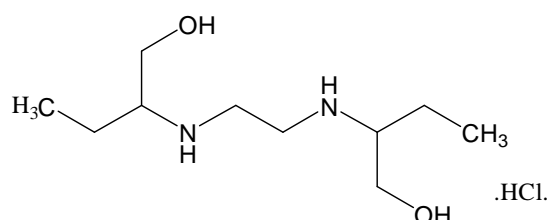


Figure 1: Structure of ethambutol hydrochloride drug (L).

The literature survey reveals that very limited work of binary and ternary complexes of transition metal ions with drugs and amino acids have been reported [7-10].Hence the present paper deals with the systematic study of stability constants of binary and ternary complexes of Co(II), Ni(II)metal ions with ethambutol hydrochloride drug(L) and alanine, glycine, isoleucine and phenylalanine four amino acids (R).

2. Experimental

2.1 Materials and solutions

All the chemical reagents used in the present investigation were Analar grade.The solutions of reagents 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 of cobalt and nickel metal were used to prepare the metal solutions andwere standardized by usual procedure [11].

2.2 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 procedure [12]. The experiments were carried out at 30 °C(±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 electrode [13].

2.3 Titration procedure

Proton ligand stability constant, metal ligand stability constantand mixed ligand stability constants of transition metal ions were determined by using Calvin Bjerrum pH titration techniques as modified by Irving and Rossotti[14]. The titration procedure involves following steps:

- 1) Free acid(HClO₄) + NaClO₄ (A)
- 2) Free acid(HClO₄) + NaClO₄+ primary ligand (A+L)
- 3) Free acid(HClO₄) + NaClO₄+ primary ligand+ metal (A+L+M)
- 4) Free acid(HClO₄) + NaClO₄+ secondary ligand (A+R)

5) Free acid (HClO₄) + NaClO₄ + secondary ligand + metal (A+R+M)

6) Free acid(HClO₄) + NaClO₄ + primary ligand + secondary ligand + metal (A+L+R+M)

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

2.4 Calculations

The proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of binary complexes were determined by using Irving and Rossotti 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' computer program [15] which employs non linear least square approach. ΔLogK , K_r , K_L and K_R values were determined from respective equations.

3. Results and Discussion

3.1 Binary complexes

The proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of binary complexes of drug and four amino acids 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 complexes. It is shown in **Table 1**.

Table 1: Proton and metal ligand stability constants of ethambutol HCl and Amino acids

Ligands	K ₁ ^H	K ₂ ^H	Co(II)		Ni(II)	
			LogK ₁	LogK ₂	LogK ₁	LogK ₂
Ethambutol HCl	6.48	-	4.62	-	4.68	-
Alanine(R ₁)	2.30	9.69	7.80	4.31	9.86	5.41
Glycine(R ₂)	2.36	9.57	8.47	4.61	10.57	5.79
Isoleucine(R ₃)	2.25	9.62	7.73	4.32	9.72	5.40
Phenyl alanine(R ₄)	2.21	9.18	7.57	4.03	9.58	5.15

The highest values of n^- (average number of ligands bound per metal atom) for Alanine, glycine, isoleucine and phenyl alanine amino acids are around 2.0 indicates the formation of 1:1 and 1:2 binary complexes. The Ethambutol HCl forms only 1:1 binary complexes. The order of stability of binary complexes of transition metal ions with drug(L) follows the natural order[Co(II)<Ni(II)] of Irving and Williams series[16] which has been reported by various of researchers[17-18]. The low values of stability constants suggest the ionic interactions [16].

3.2 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 systems [19].

3.3 Stability of mixed ligand complexes

In Co(II)LR system, glycine amino acid shows highest value whereas alanine shows lowest ternary stability constant value among all amino acids. The Ni(II) LR system glycine shows high stability constants values and phenylalanine shows low value.

Among the present cobalt and nickel transition metal complexes with drug(L) and four amino acids Co(II)LR(alanine) system shows low value whereas The Ni(II) LR(glycine) system shows high stability constants values 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.

These variations may be attributed to steric, inductive effects and the increasing side chain of amino acids would result 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 ΔLogK , K_r , K_L and K_R values which are defined by equations:

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

$$K_r = \beta_{111}^2 / \beta_{20} \cdot \beta_{02}$$

$$K_L = \beta_{111} / \log K_{10}$$

$$K_R = \beta_{111} / \log K_{01}$$

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

Table 2: Stability constants of ternary complexes of Co(II) with ethambutol-HCl (L) and amino acids and their relative parameters

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	ΔlogK
Alanine(R ₁)	8.66	6.09	12.11	2.57	0.86	0.95	-5.23
Glycine(R ₂)	12.82	6.09	13.08	6.73	4.35	1.34	-1.74
Isoleucine(R ₃)	12.81	6.09	12.05	6.72	5.08	1.41	-1.01
Phenyl alanine(R ₄)	12.10	6.09	11.60	6.01	4.53	1.37	-1.56

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

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	ΔlogK
Alanine(R ₁)	12.97	6.97	15.27	9.35	3.11	1.17	-0.51
Glycine(R ₂)	13.69	6.97	16.36	10.07	3.12	1.17	-0.50
Isoleucine(R ₃)	13.08	6.97	15.12	9.46	3.36	1.18	-0.26
Phenyl alanine(R ₄)	11.17	6.97	14.73	7.55	1.59	1.03	-2.03

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 [20]. 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 K_r 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 ligands[21]. The negative values of ΔLogK suggests the formation of ternary complexes but less stable having

destabilized nature of complexes which has been reported in N and O donors [22]. The positive value of $\Delta\log K$ in some cases is attributed to the extra stability of ternary complexes.

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