

**Mixed ligand complexes of cobalt (II) metal ion with Isoniazid drugs and some amino acids**Shailendrasingh Thakur<sup>1\*</sup>, M.A.Sakhare<sup>2</sup>, Mazahar Farooqui<sup>3</sup> & S.D. Naikwade<sup>4</sup><sup>1</sup>Department of Chemistry, Milliya College, Beed.<sup>2</sup>Department of Chemistry, Balbhim College, Beed.<sup>3</sup>Department of Chemistry, Dr. Rafiq Zakaria College for women, Aurangabad.<sup>4</sup>Principal, Mrs. K.S.K. College, Beed (MS) India.

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**ABSTRACT**

The stability constant of the mixed ligand complexes of cobalt (II) metal ion with antibacterial drug Isoniazid as primary ligand and the eight amino acids viz. glycine, DL-alanine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-β-phenyl alanine, DL-serine and DL-valine as secondary ligands were determined pH metrically in 20% (v/v) ethanol-water medium at 25°C and at an ionic strength of 0.1 M NaClO<sub>4</sub>. The formation of complex species has been evaluated by SCOGS computer program and discussed in terms of various relative stability parameters. **Keywords:** Stability constant, Isoniazid drug, amino acids, pH metry, mixed ligand complexes, ionic strength.

**1. INTRODUCTION**

The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity. Metal Complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc. Amino acids are the structural unit of proteins. These are essential constituents of all living cells and contain one or more amino and carboxylic groups and have good coordination sites for the metal complexation. After literature survey [1-5] & in continuation of our earlier work with complexation of antibacterial drugs [6-7], we study ternary complexes of cobalt metal ion with antibacterial drug Isoniazid (ISO) as primary ligand and a series of eight amino acids viz. glycine, DL-alanine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-β-phenyl alanine, DL-serine and DL-valine as secondary ligands in 20% (v/v) ethanol-water medium at 25°C and at an ionic strength of 0.1 M NaClO<sub>4</sub>.

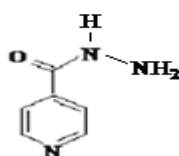


Figure 1: Isoniazid (molecular formula C<sub>6</sub>H<sub>7</sub>N<sub>3</sub>O)

**2. EXPERIMENTAL**

**Materials and Solution:** The ligand ISO is soluble in double distilled water. NaOH, NaClO<sub>4</sub>, HClO<sub>4</sub> & metal salts were of AR grade. The solutions used in the potentiometric titration were prepared in double distilled water. The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of HClO<sub>4</sub>. The metal salt solutions were also standardized using EDTA titration. All the measurements were made at 25°C in 20% ethanol-water mixture at 0.1M NaClO<sub>4</sub> strength. The pH measurements were made using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode. The pH-meter was adjusted with buffer of pH 4.00, 7.00 and 9.18.

**Potentiometric procedure:** For evaluating the protonation constant of the ligand & the formation constant of the complexes in 20% ethanol-water mixture with different metal ions, we prepared the following six sets of solutions.

- (i) HClO<sub>4</sub> (A)
- (ii) HClO<sub>4</sub> + Drug (A + L)
- (iii) HClO<sub>4</sub> + Drug + Metal (A + L+ M)
- (iv) HClO<sub>4</sub> + Amino acid (A + R)
- (v) HClO<sub>4</sub> + Amino acid + Metal (A+ R + M)
- (vi) HClO<sub>4</sub> + Drug + Amino acid + Metal (A + L + R + M)

The above mentioned sets prepared by keeping M:L: Rratio, the concentration of perchloric acid & sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made upto 50ml with double distilled water. The test solutions were magnetically stirred, NaOH was added stepwise and pH reading was recorded until stable values, within  $\pm 0.002$  pH units were obtained. Graphs were obtained by plotting pH vs volume of NaOH added. These data were used to determine the pKa of ligands and logK values of metal complexes of primary and secondary ligands. The equilibrium constants of ternary complexes were calculated by using SCOGS program[8].The total concentrations of metal ions, free metals, free ligands and various possible species that are formed during complexation were obtained as computer output of program.

**Table 1: Proton-ligand stability constant & metal-ligand stability constant of Isoniazid & amino acids with Co (II) at 0.1M ionic strength in 20% (v/v) ethanol-water medium**

<i>Ligands</i>	<i>Proton-ligand stability constant</i>		<i>metal-ligand stability constant</i>	
	<i>PK<sub>1</sub></i>	<i>PK<sub>2</sub></i>	<i>logK<sub>1</sub></i>	<i>logK<sub>2</sub></i>
Isoniazid	3.192	10.657	5.415	4.370
Glycine	2.472	9.582	5.034	3.786
DL -Alanine	2.364	9.658	3.753	2.999
Glutamic acid	2.501	4.416	2.859	2.697
DL -Isoleucine	2.654	9.624	4.406	3.158
DL -Methionine	2.303	9.079	4.798	3.395
DL-β-Phenyl alanine	2.255	9.174	4.441	3.408
DL -Serine	2.344	8.983	4.173	2.942
DL -Valine	2.488	9.501	4.578	3.368

**Table 2: Parameters based on some relationship between formations of mixed ligand complexes of Co (II) with ISO drug and amino acids.**

<i>Amino Acids</i>	<i>β<sub>111</sub></i>	<i>β<sub>20</sub></i>	<i>β<sub>02</sub></i>	<i>K<sub>L</sub></i>	<i>K<sub>R</sub></i>	<i>K<sub>r</sub></i>	<i>Δlogk</i>
Glycine	9.4470	9.7855	8.8197	4.0318	4.4135	1.0155	-1.0017
DL -Alanine	8.1669	9.7855	6.7515	2.7517	4.4141	0.9877	-1.0011
Glutamic acid	8.2725	9.7855	5.5557	2.8573	5.4133	1.0785	-0.0019
DL -Isoleucine	9.5708	9.7855	7.5639	4.1556	5.1646	1.1033	-0.2506
DL -Methionine	8.7058	9.7855	8.1934	3.2906	3.9078	0.9684	-1.5074
DL-β-Phenyl alanine	9.6068	9.7855	7.8488	4.1916	5.1659	1.0896	-0.2493
DL -Serine	9.0893	9.7855	7.1152	3.6741	4.9159	1.0756	-0.4993
DL -Valine	9.7220	9.7855	7.9456	4.3068	5.1440	1.0966	-0.2712

### 3. RESULT AND DISCUSSION

*i. Binary complex:* The proton ligand stability constants (pKa) of drug and amino acids were calculated by point wise and half integral method. The metal ligand stability constant (logK) of Co (II) transition metal complexes with ISO drug were calculated by using Calvin Bjerrum titration techniques as adopted by Irving and Rossotti [9].

Titration curves were obtained for different sets. The mean value the average number of protons associated with the ligand  $\bar{n}_A$ , at different pH values were calculated. The pKa values were determined from  $\bar{n}_A$ . Similarly  $\bar{n}$  i.e metal ligand formation number, which can be defined as average number of ligand molecules co-ordinated to the metal ions, were also obtained using Irving & Rossotti method. The  $\bar{n}$  values obtained between 0.2 to 0.8 indicates 1:1 complexation and when  $\bar{n}$  lies in between 1.2 to 1.8 indicate 1:2 complexation. The values of proton ligand stability constants (pKa) and metal ligand stability constant (logK) are represented in **Table 1**.

*ii. Mixed ligand complexes:* The formation of 1:1:1 mixed ligand complex were identified by the pH of precipitation of ML, MR, and MLR titration curves. These curves indicate the higher value of pH of precipitation of ternary system than corresponding binary systems [10]. The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of  $\Delta\log K$ ,  $K_r$ ,  $K_L$ , and  $K_R$  values which are defined by equations:

$$\Delta\log K = \log\beta_{111} - (\log K_{10} + \log K_{01}) \quad (1)$$

$$K_r = \frac{\beta_{111}^2}{(\beta_{20}\beta_{02})} \quad (2)$$

$$K_L = \frac{\beta_{111}}{\log K_{10}} \quad (3)$$

$$K_R = \frac{\beta_{111}}{\log K_{01}} \quad (4)$$

Where  $\beta_{111}$  is the equilibrium constant of ternary system.

$\beta_{20}$  is the overall stability constant of primary complexes.

$\beta_{02}$  is the overall stability constant of secondary complexes.

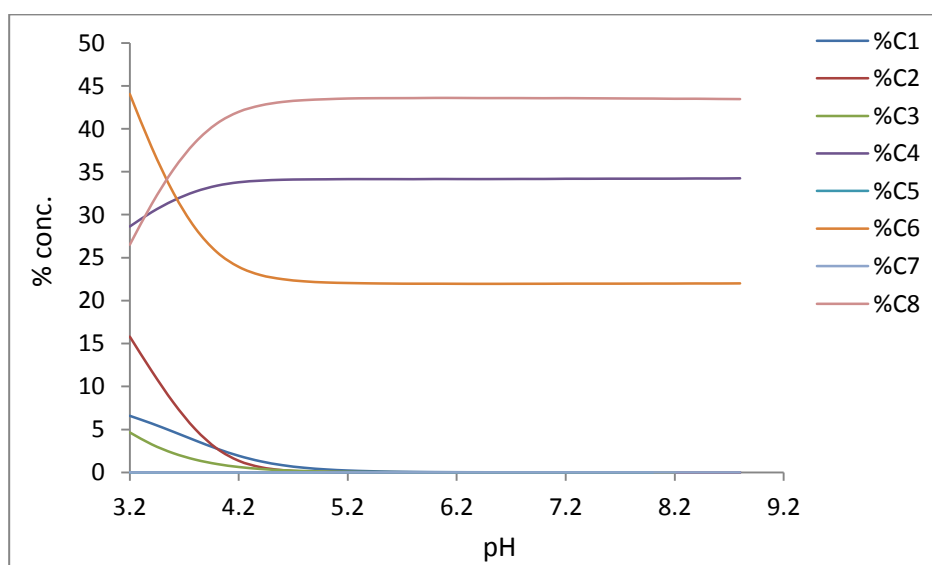
The equilibrium constants  $\beta_{111}$  of ternary systems of Co(II) transition metal ion and relative stability parameters are shown in **Table 2**. The order of stability of equilibrium constants  $\beta_{111}$  of ternary systems of Co (II) transition metal ion with respect of secondary ligand ISO is

valine >  $\beta$ -phenyl alanine > isoleucine > glycine > serine > methionine > glutamic acid > alanine.

The comparison of  $\beta_{111}$  with  $\beta_{20}$  and  $\beta_{02}$  of these systems reveals the preferential formation of ternary complexes over binary complexes [11]. The low positive values of  $K_L$  and  $K_R$  indicate less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands. The  $K_r$  values are positive but less, which indicates lower stability of ternary complexes [12]. This 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 noncoordinated charge group of ligands [12]. The negative values of  $\Delta\log K$  have been found in all systems, which show the formation of ternary complex but less stable and

destabilized nature of complexes which has been reported in N and O coordination of amino acids. The negative value of  $\Delta \log K$  does not mean that the complex is not formed. The negative value may be due to the higher stability of its binary complexes, reduced number of coordination sites, steric hindrance, electronic consideration, difference in bond type, geometrical structure etc.

**iii. Species distribution curves:** The species distribution curves of Co(II)LR systems were obtained by plotting percentage concentration of various possible species formed during complexation versus pH of solution as shown in **figure 2**. In all Co(II)LR ternary systems, primary as well as secondary ligands forms 1:1 and 1:2 binary complexes. The species distribution curves of free metal (M), free ligands L and R indicates that there is a slowly decrease in concentration of free metal ions with increase in pH whereas increase in concentration of ligands with pH and indicates higher percentage concentration of FL than FR. The species distribution diagram of various possible species of Co(II)LR system shows the formation of mixed ligand complexes. The concentration for the formation of drug (L) and HR continuous decrease with increasing pH. The concentration of MLR species continuously increases, confirm the formation of ternary complexes Co (II)LR.



**Figure 2: Co (II)-ISO- glycine**

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