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Mixed ligand complexes of zinc metal ion with antibacterial drug Isoniazid and some amino acids in aqueous solution

Shailendrasingh Thakur,

S. A. Peerzade,

A. J. Khan,

R. L. Ware,
Department of Chemistry,
Milliya College, Beed .

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Abstract: The stability constant of the mixed ligand complexes of zinc(II) ion with antibacterial drug Isoniazid (ISO) as primary ligand and the amino acids viz. glycine, DL-alanine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-â-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 $NaClO_4$. 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.

Introduction:

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. In continuation of earlier work with complexation of antibacterial drug[1-4], we study ternary complexes of zinc metal ion with antibacterial drug Isoniazid (ISO) as primary ligand and eight amino acids as secondary ligands in 20% (v/v) ethanol-water medium at 25 °C and at an ionic strength of 0.1 M $NaClO_4$.

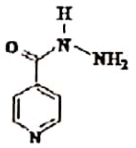


Figure 1: Isoniazid (molecular formula $C_6H_7N_3O$)

Experimental: i. Materials and Solution:

The ligand Isoniazid is soluble in double distilled water. NaOH, $NaClO_4$, $HClO_4$ & metal salts were of AR grade. The solutions used in the pH metric 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 $HClO_4$. 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 $NaClO_4$ strength. Thermostat was used to maintain the temperature constant. The pH measurement 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.

ii. pH metric 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)$HClO_4$ (A)

(iv)$HClO_4$+Amino acid (A+R)

(ii)$HClO_4$+Drug (A+L)

(v)$HClO_4$+ Amino acid + Metal (A+R+M)

(iii)$HClO_4$+Drug+Metal (A+L+M)

(vi)$HClO_4$+Drug+Amino acid +Metal (A+L+R+M)

The above mentioned sets prepared by keeping M: L: R ratio, the concentration of perchloric acid & sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made upto 50 ml with double distilled water. The test solutions were magnetically stirred, NaOH was added stepwise and pH reading was recorded until stable values 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. 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 and metal-ligand stability constant of Isoniazid drug and amino acids with zinc (II) at 0.1M ionic strength in 20% (v/v) ethanol-water medium

Ligands	Proton-ligand stability constant		metal-ligand stability constant	
	PK_1	PK_2	$logK_1$	$logK_2$
Isoniazid	3.192	10.657	5.891	4.954
Glycine	2.472	9.582	5.525	4.239
DL-Alanine	2.364	9.658	4.492	3.561
Glutamic acid	2.501	4.416	2.921	2.744
DL-Isoleucine	2.654	9.624	6.960	5.071
DL-Methionine	2.303	9.079	4.883	3.655
DL-β-Phenyl alanine	2.255	9.174	4.863	4.056
DL-Serine	2.344	8.983	4.644	3.476
DL-Valine	2.488	9.501	5.149	4.175

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

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	?logk
Glycine	11.4146	10.8451	9.7634	5.5234	5.8899	1.1078	-0.0013
DL -Alanine	9.8818	10.8451	8.0529	3.9906	5.3898	1.0458	-0.5014
Glutamic acid	8.0617	10.8451	5.6647	2.1705	5.1407	0.9766	-0.7505
DL -Isoleucine	11.5998	10.8451	12.029	5.7086	4.6401	1.0142	-1.2511
DL -Methionine	10.2737	10.8451	8.538	4.3825	5.3906	1.0601	-0.5006
DL-β-Phenyl alanine	10.7527	10.8451	8.918	4.8615	5.8902	1.0882	-0.001
DL -Serine	10.5329	10.8451	8.1205	4.6417	5.8886	1.1107	-0.0026
DL -Valine	10.0395	10.8451	9.3243	4.1483	4.8901	0.9955	-1.0011

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 Zn (II) transition metal complexes with Isoniazid drug is calculated by using Calvin Bjerrum titration techniques as adopted by Irving and Rossotti.

Titration curves were obtained for different sets. During titration no precipate was formed indicating that there is no tendency to form hydroxo complexes. 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 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. The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of "logK, Kr, K_L and K_R values which are defined by equations:

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

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

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

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

Where

β_{111} is the equilibrium constant of ternary system.

β_{20} is the overall stability constant of primary complexs.

β_{02} is the overall stability constant of secondary complexs.

The equilibrium constants β_{111} of ternary systems of Zn(II) transition metal ion and relative stability parameters are shows in **Table**

2. The ternary complexes of zinc metal ions with DL-isoleucine shows higher values of stability whereas glutamic acid ternary complexes shows low values of stability. This may be attributed to the aliphatic nature of secondary ligand, steric effect and chelation formation. The order of stability of equilibrium constants β_{111} of ternary systems of Zn(II) transition metal ion with respect of secondary ligand is

ISO: isoleucine >glycine >β-phenyl alanine >serine> methionine> valine >alanine >glutamic

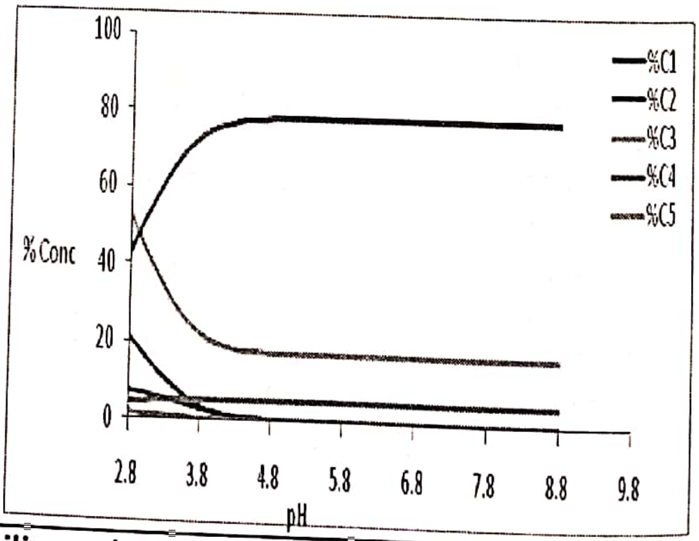
The comparison of β_{111} with β_{20} and β_{02} of these systems reveals the preferential formation of ternary complexes over binary complexes. The low positive values of K_L and K_R indicates less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands. The Kr values are positive but less, which indicates lower stability of ternary complexes. 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 non coordinated charge groups of ligands. The negative values of ΔlogK 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 ΔlogK 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.

Thompson and Lorass pointed out that more negative ΔlogK value of ternary complexes is due to the electrostatic repulsion between the negative charge on the ligand and amino acids. In solution, ternary complex forms as the titration curve run below the Zn(II)-drug titration curve. So, it is evident that the entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Zn(II)-drug complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Zn(II) metal ion and thus reduces the stability of ternary complexes.

iii. Species distribution curves:

The species distribution curves of Zn(II)LR systems were obtained by plotting percentage concentration of various possible species formed during complexation versus pH of solution as shown in figure. In Zn(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 Zn (II)LR system shows the formation of mixed ligand complexes. The concentration for the formation of drug (L) and HR represented by C_1 and C_2 show continuous decrease with increasing pH. The concentration of C_6 species continuously increases, confirm the formation of ternary complexes Zn (II)LR.

Figure: Species distribution curve of Zn (II)- ISO- isoleucine system



References:

1. SV Thakur, Mazahar Farooqui, SD Naikwade, *Asian J Biochemical & Pharma Res.,*3(3): 34-43, 2013.

2. SV Thakur, Mazahar Farooqui, SD Naikwade, *Int J Pharm Tech Res.,* 5(4): 1508-1515, 2013.

3. Shailendrasingh Thakur, MA Sakhare, Mazahar Farooqui, SD Naikwade, *J Basic & Applied sci.,* 10(1): 48-51, 2013.

4. Shailendrasingh Thakur, SD Naikwade, Mazahar Farooqui, *J Medicinal Chem & Drug discovery,* 107-118, 2015.

5. SV Thakur, Mazahar Farooqui, SD Naikwade, *J Chem & Phrm res.,4(9): 4412-4416, 2012.*

6. SV Thakur, Mazahar Farooqui, SD Naikwade, *Int J Res Inorg Chem,* 1(4): 5-7, 2012.

7. SV Thakur, Mazahar Farooqui, SD Naikwade, *J Chem Bio Phy Sci.* 4(1): 1-6, 2014.

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