International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.5, No.4, pp 1508-1515, Oct-Dec 2013

Mixed Ligand Complexes Of Cobalt (II) Metal Ion With Medicinal Drugs Metformin, Imipramine And Adenosine In Mixed Solvent System

Shailendrasingh Thakur[1]*, Mazahar Farooqui[2] and S.D. Naikwade[3]

[1]Department of Chemistry, Milliya College Beed (MS) 431122, India.

[2]Post Graduate and Research Center, Maulana Azad College, Aurangabad. (MS) 431003 India.

[3]Mrs. K.S.K. College, Beed (MS) 431122, India.

***Corres. author : svthakur50@yahoo.com, Mob.No.09421345228**

Abstract: The equilibrium studies of the mixed ligand complexes of cobalt (II) ion with medicinal drugs Metformin hydrochloride, Imipramine hydrochloride and Adenosine as primary ligand and the eight aminoacids 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 temperature 25°C and at an ionic strength of 0.1 M $NaClO_4$. The ΔlogK values reveal that ternary complexes are less favored than binary complexes, the medicinal drug used in the present study co-ordinate through NH_2 group. The formation of complex species has been evaluated by SCOGS computer programme and discussed in terms of various relative stability parameters.

Keywords: Stability constant, medicinal drugs, amino acids, pH metry, mixed ligand complexes, ionic strength.

INTRODUCTION

Chemistry of drugs attracts many researchers because of its application in medicinal study. The metal complexes of drugs play an important role in drug action and metabolism. Metal complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc. Metformin Hydrochloride (Mtf) [1,1dimethylbiguanidehydrochloride] is an antidiabetic drug and biguanide antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus. Imipramine Hydrochloride (Imp) is an antidepressant drug. Adenosine (Ado) is an analgesics, cardiac drug, anti-arrhythmia agents, anti-arrthmic agents, vasodilator agents. 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.

Survey of literature reveals that no systematic study of complexes of cobalt ion with antibacterial drugs and amino acids had been reported[1-12]. For the present investigation, we investigated ternary complexesation of cobalt(II) ion with medicinal drugs Metformin hydrochloride(Mtf), Imipramine hydrochloride(Imp) and

Adenosine(Ado) as primary ligand and a series of eight amino acids viz. glycine (Gly), DL-alanine (Ala), L-glutamic acid (Glu-acid), DL-isoleucine (Ile), DL-methionine (Met), DL-β-phenyl alanine (Phe), DL-serine (Ser) and DL-valine (Val) as secondary ligands in 20% (v/v) ethanol-water medium at 25 °C and at an ionic strength of 0.1 M $NaClO_4$.

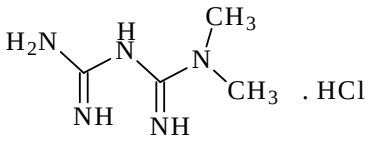

Figure1: *Metformin Hydrochloride (molecular formula $C_4H_{12}ClN_5$)*

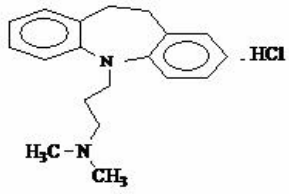

Figure2: *Impramine Hydrochloride (molecular formula $C_{19}H_{25}N_2Cl$)*

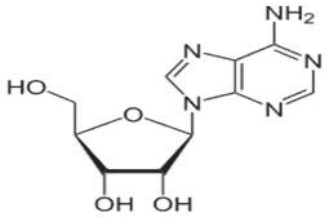

Figure3: *Adenosine (molecular formula $C_{10}H_{13}N_5O_4$)*

EXPERIMENTAL

Materials and Solution: The ligand Mtf, Imp and Ado are water soluble. NaOH, $NaClO_4$, $HClO_4$ and 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 $HClO_4$.The metal salt solution was also standardized using EDTA titration[13]. All the measurements were made at temperature 25 °C in 20% ethanol-water mixture at 0.1M $NaClO_4$ strength. The thermostat model SL-131 (Adar Dutt and Co (India) Pvt. Ltd. Mumbai) was used to maintain the temperature constant. The pH measurement was recorded using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode (reading accuracy ± 0.01). 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% (v/v) ethanol-water mixture with different metal ions, we prepared the following six sets of solutions.

(i) $HClO_4$ (A)

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

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

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

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

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

The above mentioned sets prepared by keeping M: L: R ratio as 1:1:1 and the concentration of perchloric acid and sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made up to 50 ml with double distilled water. The test solutions were magnetically stirred, NaOH was added stepwise and pH reading was recorded until stable values, within ± 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 (Table 1). The equilibrium constants of ternary complexes were calculated by using SCOGS programme[14]. 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 programme.

Table 1: Proton-ligand stability constant and metal-ligand stability constant of antibacterial drugs and amino acids with Co(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	$logK_1$	$logK_2$
Metformin Hydrochloride	2.905	11.101	5.233	4.336
Imipramine Hydrochloride	- - - -	9.062	3.363	3.076
Adenosine	3.292	11.659	5.808	4.906
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 Mtf (L_1) drug and amino acids.

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	$\Delta logk$
Glycine	9.0126	9.5691	8.8197	3.7799	3.9791	0.9802	-1.2536
DL -Alanine	8.2321	9.5691	6.7515	2.9994	4.4793	1.0088	-0.7534
Glutamic acid	6.5911	9.5691	5.5557	1.3584	3.7319	0.8716	-1.5008
DL -Isoleucine	9.6306	9.5691	7.5639	4.3979	5.2244	1.1242	-0.0083
DL -Methionine	10.0286	9.5691	8.1934	4.7959	5.2306	1.1292	-0.0021
DL-β-Phenyl alanine	9.4255	9.5691	7.8488	4.1928	4.9846	1.0823	-0.2481
DL -Serine	8.9061	9.5691	7.1152	3.6734	4.7327	1.0676	-0.5000
DL -Valine	9.3128	9.5691	7.9456	4.0801	4.7348	1.0634	-0.4979

Table 3: Parameters based on some relationship between formations of mixed ligand complexes of Co(II) with Imp (L_2) drug and amino acids.

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	***Δlogk***
Glycine	7.635	6.4393	8.8197	4.2718	2.6015	1.0007	-0.762
DL -Alanine	6.6151	6.4393	6.7515	3.2519	2.8623	1.0030	-0.501
Glutamic acid	5.7202	6.4393	5.5557	2.3570	2.8610	0.9538	-0.502
DL -Isoleucine	7.0153	6.4393	7.5639	3.6521	2.6091	1.0020	-0.754
DL -Methionine	7.1488	6.4393	8.1934	3.7856	2.3508	0.9771	-1.012
DL-β-Phenyl alanine	6.8016	6.4393	7.8488	3.4384	2.3607	0.9521	-1.003
DL -Serine	6.2838	6.4393	7.1152	2.9206	2.1104	0.9272	-1.253
DL -Valine	7.7716	6.4393	7.9456	4.4084	3.1936	1.0805	-0.170

Table 4: Parameters based on some relationship between formations of mixed ligand complexes of Co(II) with Ado (L_3) drug and amino acids.

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	***Δlogk***
Glycine	9.5893	10.7141	8.8197	3.7815	4.5558	0.9818	-1.252
DL -Alanine	9.5488	10.7141	6.7515	3.741	5.796	1.0934	-0.0118
Glutamic acid	7.9153	10.7141	5.5557	2.1075	5.0561	0.973	-0.7517
DL -Isoleucine	9.2123	10.7141	7.5639	3.4045	4.8061	1.008	-1.0017
DL -Methionine	10.1043	10.7141	8.1934	4.2965	5.3063	1.0688	-0.5015
DL-β-Phenyl alanine	9.7467	10.7141	7.8488	3.9389	5.3058	1.0501	-0.502
DL -Serine	8.233	10.7141	7.1152	2.4252	4.0596	0.9235	-1.7482
DL -Valine	9.8846	10.7141	7.9456	4.0768	5.3066	1.0595	-0.5012

RESULTS AND DISCUSSION

a. Binary complex: The proton ligand stability constants *pKa* of drugs 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 medicinal drugs were calculated by using Calvin Bjerrum titration techniques as adopted by Irving and Rossotti[15].

Titration curves were obtained for different sets. All metal ions depress the titration curve of the free ligand by the release of the protons according to the abilities of the metal ions to bind to the ligand[16]. During titration no precipate was formed indicating that there is no tendency to form hydroxo complexes. The stability constants of the formed complexes were investigated in the pH range of 3-6. The mean value the average number of protons associated with the ligand EMBED Equation.DSMT4 $_A$ at different pH values were calculated.

The *pKa* values were determined from EMBED Equation.DSMT4 $_A$ .Similarly EMBED Equation.DSMT4 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 EMBED Equation.DSMT4 values obtained between 0.2 to 0.8 indicates 1:1 complexation and when EMBED Equation.DSMT4 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**. Since we got EMBED Equation.DSMT4 $_A$ between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 complex formation. The order of $logK_1 > logK_2$ is observed. The reason is statistical effect, statistically coordination of a second molecule is difficult when compare to the first due to availability of less number of coordinating sites on the metal ion for the second ligand. Irving and Rossotti have proposed a relation between the stability of the complexes and basicity of the ligand by equation $logK = apK + b$

The relation graph shows a straight line and the value of slope should be unity for a series of closely related ligand. In the present study such relationship do not exists since the medicinal drugs Mtf, Imp and Ado used are of diverse in nature.

***b. 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[17] than corresponding binary systems. The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of $\Delta logK$, K_r, 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 Co(II) transition metal ion and relative stability parameters are shows in Table 2-4. The ternary complexes of cobalt metal ions with Ado-DL-met shows higher values of stability (10.104), whereas Imp-Glu acid ternary complexes shows low values of stability (5.720). This may be attributed to the aliphatic nature of secondary ligand, steric effect and chelation formation. Either back co-ordination or hydrophobic interactions, favored ternary complexations[18]. The order of stability of equilibrium constants β_{111} of ternary systems of Co (II) transition metal ion with respect of secondary ligand is

Mtf: ***met* > *isoleu* > *β-phe ala* > *val* > *gly* > *ser* > *ala* > *glu acid***

Imp: ***val* > *gly* > *met* > *isoleu*> *β-phe ala* > *ala* > *ser*> *glu acid***

Ado: ***met* > *val* > *β-phe ala* > *gly* > *ala* > *isoleu* > *ser*> *glu acid***

The comparison of $\beta_{111}$with β_{20} and β_{02} of these systems reveals the preferential formation of ternary complexes over binary complexes[19]. 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 K_r values are positive but less, which indicates lower stability of ternary complexes[20]. 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[21]. The higher negative values than statistical values (-0.4) found in some system indicates relatively less stable complexes with square planar geometry of ternary complexes. 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. Steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand

coordinates with the metal ion in the lower pH range and form 1:1 and 1:2 complex. In solution, ternary complex forms as the titration curve run below the Co (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 Co (II)-drug complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Co (II) metal ion and thus reduces the stability of ternary complexes.

c. Species distribution curves:

According to the result given by SCOGS computer programme, the concentration of different species distributed are as follows:

$$C_1 = HL \quad \text{(1a)}$$

$$C_2 = H_2R \quad \text{(2a)}$$

$$C_3 = HR \quad \text{(2b)}$$

$$C_4 = Co + L \quad \text{(3a)}$$

$$C_5 = CoL + L \quad \text{(3b)}$$

$$C_6 = Co + R \quad \text{(4a)}$$

$$C_7 = CoR + R \quad \text{(4b)}$$

$$C_8 = Co + L + R \quad \text{(5)}$$

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(4a-c).

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.

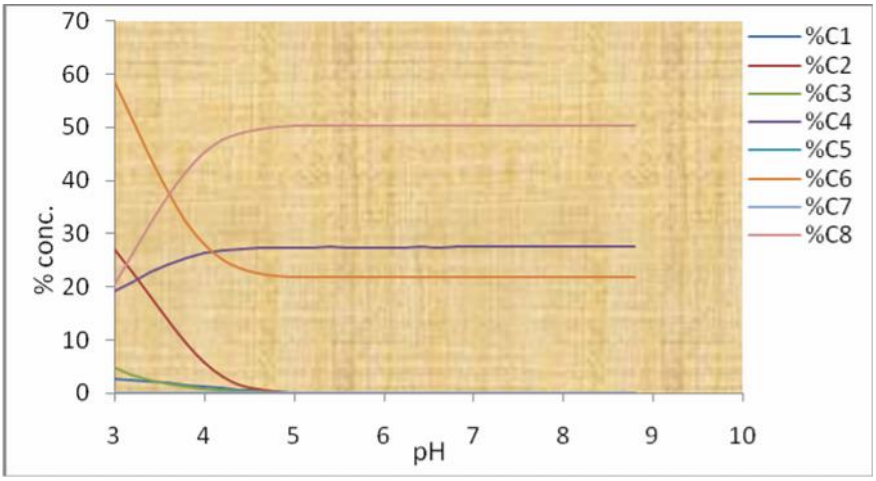

Figure 4a: Species distribution curve of Co (II)-Met- glycine system

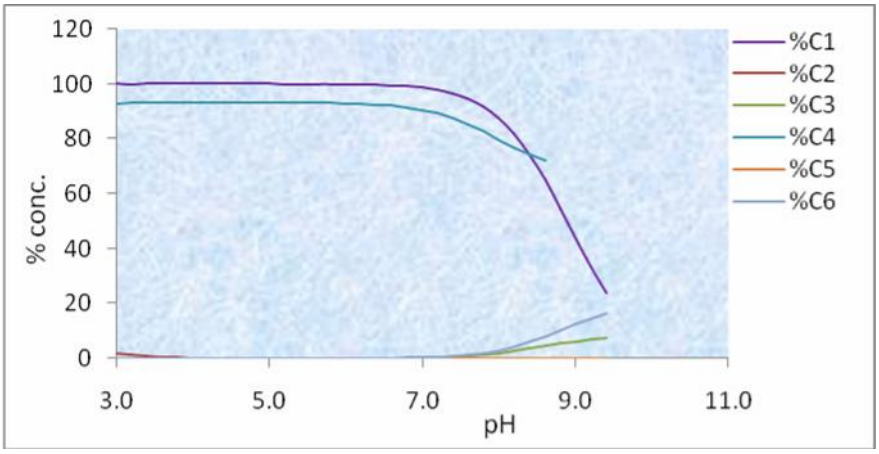

Figure 4b: Species distribution curve of Co (II)-Imp- glycine system

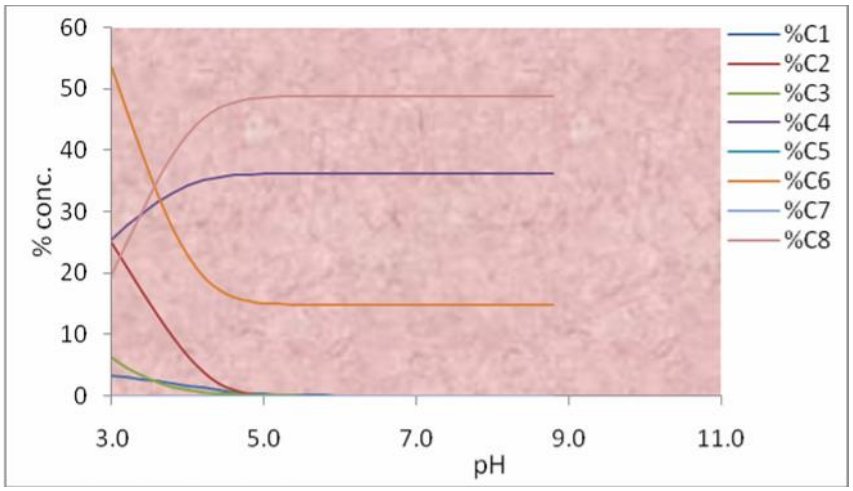

Figure 4c: Species distribution curve of Co (II)-Ado- glycine system

REFERENCES

1. Chaudhari V.T. and Mazahar Farooqui, J Indian Chem. Soc., 2009, 86, 166-167.
2. Mapari A.K. and Mangaonkar K.V., E-Journal of Chem., 2011, 8(2), 859-862.
3. Sevgi Arzik, Ebru Mavioglu Ayan and A.Sedat Celebi, Turk J Chem., 2008, 32, 721-729.
4. Sekhon B.S., Juhi Srivastava, Sarbjit Kaur and Randhawa S.K., J Indian Chem. Soc., 2008, 85, 200-202.
5. Khade B.C., Deore P.M. and Arbad B.R., Int.J.Pharm.Tech Res., 2010, 2 (4), 2168-2173.
6. Nadkarni N.G.and Mangaonkar K.V., E-Journal of Chem., 2011, 8(4), 1911-1915.
7. A.A.Zaid, Mazahar Farooqui and D.M. Janrao, J Chem ,Biolo and Phys Sci., 2012, 2(1), 67-81.
8. A.A Zaid, Mazahar Farooqui and D.M. Janrao, Der Chemica Sinica., 2012, 3(1),64-70.
9. Tuncer Degim,Volkan Zaimoglu,Cemal Akay and Zelihagul Degim, IL Farmaco, 2001, 56, 659-663
10. Mohamed M.Khalil, Mohamed M.El-Deeb and Rehab K.Mahmoud. J.Chem. Eng. Data, 2007, 52, 1571-1579.
11. Khade B.C., Deore P.M. and Arbad B.R., Int.J.Chem.Tech Res., 2010, 2 (2), 1036-1041.
12. Magare B.K. and Ubale M.B., J Chem Bio and Phy.Sci., 2012, 2(1), 108-113.
13. Jaffery G.H., Basset J., Mendham J., Denney R.C.,Vogels textbook of quantitative chemical analysis .5th edition ,Long man ,group UK limited, 1978.
14. Sayce I.G., Talanta, 1988, 15, 1397.
15. Irving H.and Rossotti H.S., J. Chem. Soc., 1954, 2904.

16. Aysegul Golcu, Mehmet Tumer, Havva Demirelli, R. Alan Wheatley; Inorg chim Acta; 2005, 358, 1785.
17. Rao V.M., Latha M.P., Rao T.S. and Rao G.N., J Ind.Chem.Sci., 2006, 83,925.
18. Marta Novak-Pekli, Mansour El-Hadi Mesbah, Gabor Petho; J Pharma. Biomed. Anal., 1996, 14, 1025-1029.
19. Rajbhoj A.S., Gaikwad S.T. and Chondhekar T.K., J. Ind.Chem.Soc., 2007, 84, 987.
20. Sakurai T., Yamauchi O., Nakahara A., Bull.Chem.Soc.,Japan, 1997, 50, 1776.
21. Griesser R. and Sigel H., Helv.Chim.Acta, 1967, 50, 1842.

*****