Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(8):59-63

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Mixed-ligand complex formation of cadmium (II) with some amino acids and drug efavirenz

Ramesh L. Ware[1], Shoeb Peerzade[1], S. D. Naikwade[2] and Mazahar Farooqui[3]

[1]Department of Chemistry, Milliya College Beed (MS), India
[2]Mrs. K. S. K. College, Beed (MS), India
[3]Post -graduate and Research Center, Maulana Azad College, Aurangabad (MS), India

---

ABSTRACT

Formation of binary and ternary complexes of Cd (II) metal ion with Efavirenz as a primary ligand and some amino acids (DL-alanine, glycine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-β-phenyl alanine, DL-serine and DL-valine) as secondary ligands was studied by the potentiometric technique at 27±0.1°C in 20% (v/v) ethanol-water medium and at 0.1M ($NaClO_4$) ionic strength. Proton ligand (pK) and metal-ligand (logK) stability constant were determined by using Calvin Bjerrum titration technique as modified by Irving & Rossotti. The stability constants of these 1:1:1 ternary complex have been evaluated by the computational methods. ΔlogK values reveal that ternary complexes are less favoured than binary complexes.

Key word: Stability constant, ΔlogK, Medicinal drug and mixed ligand complexes.

INTRODUCTION

The formation of complexes, in aqueous solutions is a matter of great importance not only in inorganic but also in analytical, biochemistry and other scientific and industrial field [1-2]. Metal ions can induce toxicity in humans and plant. Classic examples being heavy metal poisons such as mercury, lead and Cadmium. Even essential metal ions can be toxic when present in excess or beyond certain threshold concentrations [3] .One way for treatment of metal toxicity involves chelation therapy, in which metal-specific chelating agents are administrated as drug to complex and facilitate excretion of unwanted excess element.

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used as a part of highly active anti-retroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV-1) [4]. It is never used alone and is always given in combination with other drugs. It is a white to slightly pink crystalline powder and it is soluble in various organic solvents but insoluble in water. It is chemically (4*S*)-6-chloro-(cyclopropylethynyl)-1, 4-dihydro-4- (trifluoromethyl) - 2H-3, 1-benzoxazin-2-one (Fig.1). Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 RT [5-7].

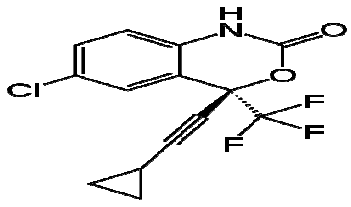

Fig1: Efavirenz (molecular formula $C_{14}H_9ClF_3NO_2$)

The survey of literature reveals that no work has been reported on complex tendencies of drug Efavirenz with transition metal ion cadmium (II) in ethanol-water solution. We are reporting in the present paper ,the result of potentiometric studies on the mixed ligand complexes of Cd(II) with drug efavirenz and some amino acids viz. DL-alanine, glycine, L-glutamic acid, DL-isoleucine, DL-methionine, DL-β-phenyl alanine, DL-serine and DL-valine as a ligands. Amino acids comprise the building blocks of proteins and are chemical species necessary for performing a massive quantity of biological functions, as exemplified by the part of enzymes [8].The work is aimed to establish the various equilibria that exist in solution, and to determine the dissociation constant of free ligand and stability constant of binary and ternary complexes (1:1:1) in 20% (v/v) ethanol-water medium at 27 ^{O}C and at fixed ionic strength 0.1M. Although aqua-organic solvent mixtures are of little interest, since these media are not present in human body, these systems are studied for comparison.

EXPERIMENTAL SECTION

Drug sample of Efavirenz is A. R. grade was obtained from pharma industries and used as received. Stock solutions of ligands were prepared by dissolving an accurate amount in ethanol solvent. The solutions used in the potentiometric titrations were prepared in carbonate free double distilled water. All chemicals used were AnalaR grade or of high purity. Metal ion solution was prepared by dissolving metal nitrate (Sigma-Aldrich) in Carbonate free double distilled water and standardized by EDTA [9]. Carbonate free sodium hydroxide solution was prepared by dissolving the Analar pellets in water and the solution was standardized [10]. The stock solution of perchloric acid was prepared and used after standardization [11]. Ethanol was purified as described in literature [12]. All the measurements were made at 27°C in 20% ethanol-water mixture at 0.1 M $NaClO_4$ strength. The measurement of pH 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. Purified nitrogen was bubbled through the solution to maintain an inert atmosphere. Efficient stirring of the solution was achieved with a magnetic stirrer.

The experimental procedure: In the study of binary and ternary chelates by the potentiometric titration technique. The following sets were prepared in the standard:

(i) $HC1O_4$ (A)
(ii) $HC1O_4$ + Drug (A+L)
(iii) $HC1O_4$ + Drug + Metal (A+ L+ M)
(iv) $HC1O_4$ +Amino acid (A+ R)
(v) $HC1O_4$ + Amino acid + Metal (A+ R+ M)
(vi) $HC1O_4$ + Drug + Amino acid + Metal (A+L+ R+ M)

Against standard sodium hydroxide, the ionic strength of solutions was maintained constant by adding appropriate amount of (0.1M) Sodium perchlorate solution. The titrations were carried out at 27 °C in an inert atmosphere by bubbling oxygen free nitrogen gas through an assembly containing the electrode to expel out CO_2. The pH meter readings in 20% (v/v) ethanol-water were corrected by method of Vanuitert and Hass [13].Graphs were obtained by plotting pH versus volume of NaOH added. These data were used to determine the pKa of ligand and logK values of metal complexes with ligands. The stability constant of ternary complexes were determined by computational programme "SCOGS" [14] to minimize the standard derivation.

RESULTS AND DISCUSSION

Binary metal complexes:
The protonation constant pK_2 of drug efavirenz and pK_1, pK_2 of amino acids and their metal-ligand formation constants ($LogK_1$ and $LogK_2$) with Cd (II) have been determined for the purpose of comparison with those of ternary systems by using Calvin Bjerrum titration techniques as modified by Irving and Rossotti [15] (Table No.1). Titration curves were obtained by plotting pH versus volume of NaOH added. Analysis of complexed ligand curve indicates that the addition of metal ion to the free ligand solution shifts buffer region of the ligand to lower pH value. This shows complexation reaction proceeds by release of proton from ligand. The complexes are quite stable as there is no precipitation during titration. The ligand efavirenz and amino acids forms 1:1 and 1:2 binary complexes with Cd (II) metal ion.

TABLE: PROTON-LIGAND AND METAL-LIGAND STABILITY CONSTANT OF EFAVIRENZ DRUG AND AMINO ACIDS WITH CD (II) AT 0.1M IONIC STRENGTH IN 20 %(V/V) ETHANOL-WATER MEDIUM

Ligand	Proton-ligand stability constant		Metal-ligand stability constant		
	pK_1	pK_2	$logK_1$	$logK_2$	logβ
Efavirenz	……	10.7206	4.7295	3.9432	8.6727
DL-alanine	2.5336	9.8082	4.2567	3.0844	7.3411
Glycene	2.5660	9.7850	4.5527	3.0878	7.6405
L-glutamic acid	2.2732	4.4116	2.8519	2.8266	5.6785
DL-isoleucine	2.5141	9.7599	4.3226	3.2796	7.6022
DL-methionine	2.0793	9.3410	3.8005	3.0706	6.8711
DL-β-phenylalanine	2.2552	9.0546	4.0265	3.3512	7.3777
DL-serine	2.1152	9.1066	4.4659	3.6178	8.0837
DL-valine	2.5923	9.6759	4.1585	3.2113	7.3698

Ternary metal complexes

Complexes in which metal ion has two or more types of ligands in its coordinating sphere are called as mixed ligand complexes. The study of ternary complexes in solution provides simpler models for more complicated biochemical reactions [16-19]. Only 1:1:1 ternary complex have been used in this study to ensure the exclusive formation of the simplest ternary complex MLR. The relative stabilities of the binary and ternary complexes are quantitatively expressed in terms of β_{111}, β_{20}, β_{02}, K_L, K_R, K_r and logK values which are presented in Table No.2. The comparison of β_{111}, β_{20}, β_{02} of this system shows preferential formation of ternary complexes over binary complex of primary as well as secondary ligand. The considerably low positive value of K_L and K_R indicate less stability of ternary complex with respect to that of primary and secondary ligands. The Kr value of this complex is positive but less which indicate lower stability of ternary complex.

It is worthy to mention that negative ΔlogK values (Table 2) imply that the ternary complexes are less stable than the binary ones, and therefore can be used to indicate that no interaction occurs between the ligands in the ternary complexes. However, this behavior does not mean that the complex is not formed. In this regards, the negative value may be interpreted in terms of higher stability of the binary complexes and/or reduced number of coordination sites in the ligand. Other electronic and structural factors such as sterric hindrance [20-21], bond type, and geometrical configuration are also expected to have an effect on ΔlogK values.

The Efavirenz and amino acids acting as ligand form 1:1 and 1:2 complexes with Cd (II). It is evident from the figure of the percentage concentration species Cd (II) - drug amino acids system that the percentage distribution curves of free metal decreases sharply with increasing pH. This indicates involvement of metal ion in the complex formation process. The maximum percentage of the formation of ternary complexes is less than that of binary complexes; this indicates that the ternary complex is less stable as compared to binary complex. In ternary systems of Cd (II) LR (1:1:1), the mixed ligand complex of Cd (II) LR_2 (R== Glycine) is more stable where as mixed ligand complex of Cd(II) LR_3(R=Glutamic acid) shows less stability. The order of stability of ternary systems of Cd (II) transition metal ion with respect of amino acids for efavirenz is-

Topiramate: gly > ser > isoleu > ala> val > met > β - phe ala> glu acid.

TABLE-2: PARAMETERS BASED ON SOME RELATIONSHIP BETWEEN FORMATIONS OF MIXED LIGAND COMPLEXES OF CD (II) WITH EFAVIRENZ (L_5) DRUG IN PRESENCE OF AMINO ACID (1:1:1 SYSTEM)

Amino Acid	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	ΔlogK
DL-Alanine	8.2080	8.6727	7.3411	3.4785	3.9513	1.025116	-0.7782
Glycine	9.2809	8.6727	7.6405	4.5514	4.7282	1.137839	-0.0013
Glutamic acid	6.5741	8.6727	5.6785	1.8446	3.7222	0.916174	-1.0073
DL-Isoleucine	9.0509	8.6727	7.6022	4.3214	4.7283	1.112253	-0.0012
DL-Methionine	8.0201	8.6727	6.8711	3.2906	4.2196	1.031936	-0.5099
DL-β-Phenyl alanine	7.738	8.6727	7.3777	3.0085	3.7115	0.964213	-1.018
DL-Serine	9.191	8.6727	8.0837	4.4615	4.7251	1.097014	-0.0044
DL-Valine	8.1332	8.6727	7.3698	3.4037	3.9747	1.013957	-0.7548

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

C_1=HL $\rightleftharpoons$ H+L (1a)

C_2=H_2R $\rightleftharpoons$ HR+H (2a)

C_3 = HR $\rightleftharpoons$ H + R (2b)

$C_4 = Cu + L \rightleftharpoons CuL$ (3a)

$C_5 = Cu + R \rightleftharpoons CuR$ (4a)

$C_6 = CuR + R \rightleftharpoons CuR2$ (4b)

$C_7 = Cu + L + R \rightleftharpoons CuLR$ (5)

The species distribution curves of Cu (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 Cu (II) LR ternary systems, primary as well as secondary ligand 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, which confirms the involvement of metal ion in the complexation process. Percentage concentration of free ligands FL1 and FL2 increases with increase of pH and this increase may be due to dissociation of ligand present in the system.

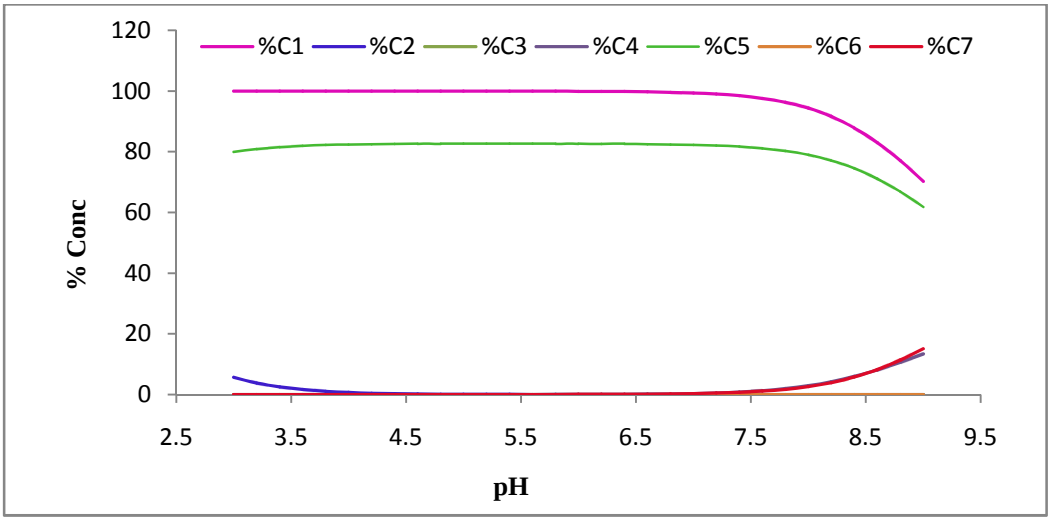

FIGURE 2: SPECIES DISTRIBUTION CURVE OF CD (II) LR_8 SYSTEM (PH VERSUS CONC. OF VARIOUS POSSIBLE SPECIES)

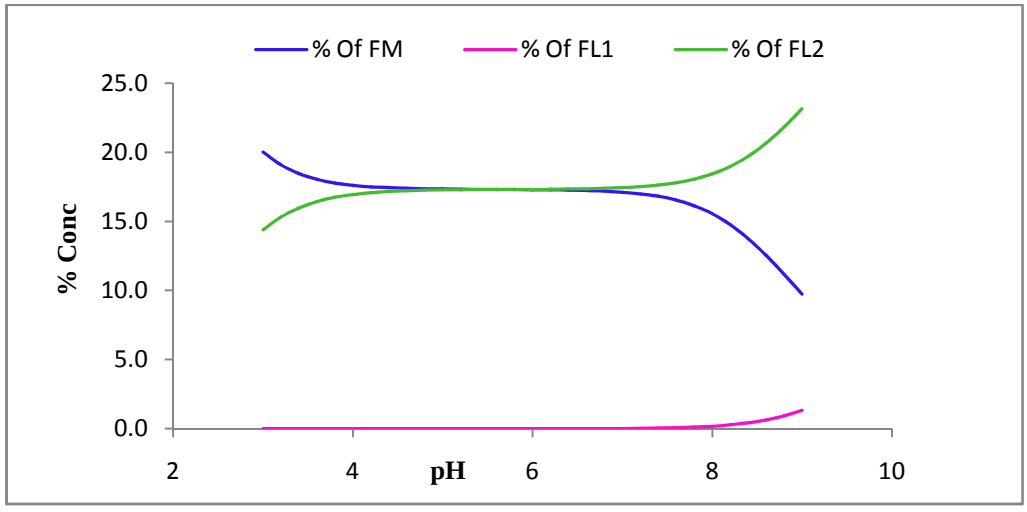

FIGURE 3: PERCENTAGE DISTRIBUTION CURVE FOR CD (II) LR_8 SYSTEM

REFERENCES

[1] Martell, A.E., Motekaitis R.J. in "The Determination and Use of stability constants".2nd Ed; VCH Publishers, NY, **1992**

[2] Bell C. F. in "Principles and Metal Chelation",Oxford University Press,**1977**

[3]S. Sudharsan, P. Seedevi, P. Ramasamy, N. Subhapradha, S. Vairamani and A. Shanmugam, *Journal of Chemical and Pharmaceutical Research*, **2012**, 4(9):4240-4244

[4] http://www.drugbank.ca/drug/DB00625
[5] Indian pharmacopoeia, The Indian pharmacopoeia commission, Ghazianad, **2007**, volume I & II, p.477-480, 1071-1073.
[6] Mottat CA, Osserton MD and Widdop B. Clarke's analysis of drugs and poisons, 3rd edition, Pharmaceutical press, **2004**;968.
[7] Rao BU, Nikalje AP. *African Journal of Pharmacy and Pharmacology* **2009**, 3(12), 643-650.
[8] Sutha Shobana, Jeyaprakash Dharmaraja, Ponnurangam Kamatchi and Shanmugaperumal Selvaraj, *Journal of Chemical and Pharmaceutical Research*, **2012**, 4(12):4995-5004
[9] Welcher, F.J., The Analytical uses of EDTA,Von Nostrand, perinceton, NJ, **1965**.
[10] Vogel, A.I., A Text Book of Quantitative Inorganic Analysis, 4th ed.; Pergamon Green and Co.Ltd., London, **1978**.
[11] Vogel, A.I., A Text Book of QuantitativeChemical Analysis, 6th ed.; Pearson, **2003**.
[12] Vogel A.I., "A Text Book of Practical Organic Chemistry", Pergamon Green and Co.Ltd., London (**1956**)
[13] B. C. Khade, P. M. Deore and B. R. Arbad , *Acta sciencia Indica* , **2007**, 33 (2), 235.
[14] M. J. Lozano and J. Borras, *J. Inorg. Biochem*. **1987**, 31, 187.
[15] Irving H.M. and Rossotti H.S., *J. Chem. Soc*. (**1954**) 2904.
[16] Ahmed Eid Fazary, Mohamed Taha, and Yi-Hsu Ju, *J. Chem. Eng. Data*, **2009**, 54, 35–42.
[17] Sigel H., Metal ions in biological systems, Marcel Dekker, New York, 2, **1973**, 63.
[18] Wellman K.M., Mecca T.G., Mungall W., Hare C.R., *J. Am. Chem. Soc*., **1968**, 90, 8057.
[19] LeussingD.L., *Talanta*, **1964**, 11(2), 189-201.
[20] M.M.Shoukry, M. Mohamed, M.R. Shehata and A.M. Mohmoud, *Mikrochim. Acta*, **1998**,129, 107
[21] M.M. Shoukry, M.E. Khair and R.G. Khalid, *Transition Met. Chem*.,**1997**, 22, 465.