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Effect of Temperature on Stability Constants of Transition Metal Complexes with Ethambutol Hydrochloride Drug in Aqueous Medium

B. K. Magare[1], B. K. Magar[2] and M. B. Ubale[3]

[1-2]Shivaji Arts, Commerce and Science College Kannad, Dist. Aurangabad, (M.S.) India
[3]Vasantrao Naik Mahavidhyalaya Aurangabad, (M. S.)India

Abstract:- *P^H metric study of transition metal complexes of Co(II), Ni(II), Cu(II) and Zn(II) transition metal ions with ethambutol hydrochloride drug (L) has been carried out at 300K, 310K and 320K temperature and 0.1 M ionic strength($NaClO_4$) in aqueous solution. Proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of metal complexes were determined by using Calvin and Bjerrum as modified by Irving and Rossetti methods at various temperatures. The thermodynamic parameter ΔG, ΔH and ΔS were calculated from values of stability constant at different temperatures. The LogK of metal complexes decreases with increase in temperature. The negative values of thermodynamic parameters show formation of complexes.*

Keywords: thermodynamic parameter, transition metal, ethambutol hydrochloride, and stability constant

1. INTRODUCTION

The complexes of metal ions with ligand plays vital role in biological systems. The metal complexes with drugs are essential to understand proper dose of drug[1], In addition, it is paramount to know the complex physiological process and mode of action drugs and their impact on circulatory systems[2]. The formation of metal complexes depends on metal ligand selectivity in complex media. The stability constant of metal complexes with drugs are important to measure the metal ligand selectivity in terms of relative strength of metal ligand bonds[3-4]. The metal complexes of drugs are found to more potent than drugs[5]. It plays a vital role in transportation, metabolism detoxification and catalytic process. The study of complexes of drugs attracts many researchers because of its tremendous application in medicinal study. The literature survey reveals that the very few researchers had worked on the study of binary complexes of transition metal ions with drugs to know the complexations-[6-10].

The ethambutol hydrochloride drug (L) [Chemical name of drug is 2, 2'ethylenediamine-di-butanol hydrochloride] is an anti-tubercular drug[11].It inhibits the transfer of mycolic acids into cell wall of tubercle bacillus and is effectively used against actively growing micro organism of Genus mycobacterium. It has an antibiotic with bacteriostatic, antimicrobial and antitubercular properties ethambutol interferes with the biosynthesis of arabinogalactan, a major polysaccharide of the mycobacterial cell wall. It inhibits the polymerization of cell wall arabinan of arabinogalactan and lipoarabinomannan by blocking arabinosyl transferases and induces the accumulation of D-arabinofuranosyl-P-decaprenol, an intermediate in arabinan biosynthesis[12]and structure is shown in Figure 1.

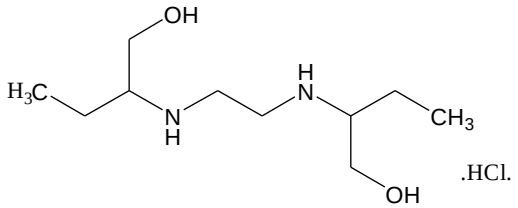

Figure 1: Structure of ethambutol hydrochloride drug (L).

2. EXPERIMENTAL

2.1 Chemicals and solutions

All the chemical reagents used in the present investigation were research grade. The solutions of chemicals 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 per chlorate ($NaClO_4$) solutions was prepared to maintain the 0.1 M ionic strength of the solutions by taking requisite amount of sodium per chlorate. The metal nitrates were used to prepare the metal solutions and were standardized by usual procedure[13].

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[14]. The experiments were carried out at different temperatures (±1.0 ^{0}C) temperature and 0.1M ionic strength ($NaClO_4$) 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[15].

2.3 Titration procedure

The binary stability constants of transition metal complexes were determined by using Calvin Bjerrum pH titration techniques as modified by Irving and Rossotti[16]. The titration procedure involves following steps:

1) Free acid($HClO_4$) + $NaClO_4$ (A)

2) Free acid($HClO_4$) + $NaClO_4$+ primary ligand (A+L)

3) Free acid($HClO_4$) + $NaClO_4$+ primary ligand+ metal (A+L+M)

These three sets were titrated separately with standard sodium hydroxide solution at 300K, 310 K and 320K temperature. 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 observed pH were plotted against volume of alkali added to have three titration curves. Then it is used to calculate n_A,n and pL . The proton ligand stability constants (pKa) and metal ligand stability constants (LogK) of binary complexes were determined from n_A, n and pL by using Irving and Rossotti methods by half integral as well as point wise calculation methods with the help of MS office Excel program as direct output .

3. RESULTS AND DISCUSSION

3.1 Proton ligand stability constant (pKa)

The pKa values of ethambutol HCl were determined by point wise and half integral methods. The values of pH at n_A=0.5 and n_A =1.5 correspond to pK_1 and pK_2 respectively. The values of n_A from 0.2 to 0.8 were used for pK_2 and values from 1.2 to 1.8 were used for pK_1 calculation.

Ethambutol HCl shows only one pKa (6.48) due to secondary amino (=NH) group. The ligand curve shows higher pH than acid curve and lies above the acid curve indicates the deprotonation of that amino group. The highest valu**es** of n^-_A range 0.2 to 1.0, which indicates the presence of only pK_2.

3.2 Metal ligand stability constants

The displacement of metal titration curves with respect to ligand titration curve along volume axis indicates the formation of complex species. The LogK values were determined by pointwise calculation method as well as half integral method[17].The pKa, LogK and logβ values were enlisted in **Table 1.0.**

Table: 1.0

pKa , LogK and logβ values of transition metal ions with ethambutol HCl(L).

Medium: water; **μ**=0.1 M ($NaClO_4$); **Temperature**: =300K (T_1), 310K (T_2), 320K (T_3)

Metal ions	**Stability constants**	**ETB(L)**		
		T_1(300K)	**T_2(**310K)	**T_3(**320K)
	pKa_1	-	-	-

-	pKa_2	6.47	6.20	6.02
Co(II)	$LogK_1$	4.62	4.43	4.30
	$LogK_2$	-	-	-
	logβ	**4 .62**	**4.43**	**4.30**
Ni(II)	$LogK_1$	4.68	4.47	4.33
	$LogK_2$	- -	-	-
	logβ	**4.68**	**4.47**	**4.33**
Cu(II)	$LogK_1$	5.17	4.97	4.74
	$LogK_2$	4.82	4.61	4.40
	logβ	**9.99**	**9.58**	**9.14**
Zn(II)	$LogK_1$	3.67	3.45	3.20
	$LogK_2$	3.12	2.94	2.73
	logβ	**6.79**	**6.39**	**5.93**

The order of stability of transition metal complexes with ethambutol HCl drugs in the present study are as follows:

L : Co(II)< Ni(II)< Cu(II) >Zn(II)

The plots of LogK versus atomic number, atomic radii were plotted and it is observed that the complexes of drug follow the Irving William natural order of stability[18]. The low values of LogK in drug indicate ionic interactions whereas high LogK values of drug may be attributed to covalent interactions[19-20].

3.3 Thermodynamic parameters

The Gibb's free energy change, enthalpy change and entropy change for the formation of metal complexes were determined by using proton ligand stability constant(pKa) and metal ligand stability constant (LogKa) and shown in table 2. The change in free energy of the ligands is calculated by using following equation.The Gibb's free energy change(ΔG)have been determined by using following equation

$\Delta G = -2.303\ RT \log K$ ……..(1)

The values of ΔH were calculated by plotting graph between

logKa Vs 1/T ($\ln K = -\Delta H/RT + \Delta S/R$)……..(2)

The slope of straightline is equal to $-\Delta H/R$ and Intercept is $\Delta S/R$.

The entropy change (Δ S) were determined by following equation

$\Delta S = (\Delta H - \Delta G)/T$ ……..(3)

Table2: Thermodynamic parameters of transition metal complexes with ligand ethambutolHCl.

Metals/ Ligand	-ΔG(KJ/mol)			ΔH(KJ/mol)	ΔS(J/mol)		
Temp	300K	310K	320K		300K	310K	320K
ETB	pKa_{1}-	-	-	-	-	-	-
	pKa_2 37.16	36.80	36.88	-41.41	-14.16	-14.88	-14.15
Co(II)	$LogK_1$ 26.53	26.29	25.86	-29.47	-9.765	-10.23	-9.75
	$LogK_2$-	-	-	-	-	-	-
Ni(II)	$LogK_1$ 26.88	26.53	26.53	-32.23	-17.80	-18.36	-17.79
	$LogK_2$ -	-	-	-	-	-	-
Cu(II)	$LogK_1$ 29.69	29.50	29.04	- 39.48	-32.61	-32.20	-32.62

	$LogK_2$ 27.67	27.36	26.96	- 38.58	-32.61	-32.20	-32.62
Zn(II)	$LogK_1$ 21.08	20.48	19.61	- 43.16	-73.58	-73.16	-73.60
	$LogK_2$ 17.92	17.45	16.72	-35.81	-59.61	-59.21	-59.62

The effect of temperature shows that there is decrease of pKa values with increase in temperature which is attributed to the liberation of protons becomes easier at higher temperature[21]. The values of metal-ligand stability constant (logKa) decreases with increase in temperature. This reveals that the complex formation is exothermic and favorable at lower temperature[22].The negative values of ΔG of complexation indicate the complex formation process is spontaneous[23]. The negative enthalpy changes (ΔH) values for all the metal complexes suggest that the metal-ligand bonds are fairly strong[24]. A negative value of ΔS may be due to the increased order asa result of the solvation process.

4. CONCLUSION

The highest valu**es** of n^-_A range between 0.2 to 1.0, which indicate the presence of only pK_2. The low values of LogK of metal complexes indicate that there are ionic interactions. The pKa and logKavalues decrease with increase in temperature.The negative values of ΔG,ΔH andΔS of complexation processes indicate that the process is spontaneous, exothermic entropicallyunfavorable. The greater stability of Cu^{2+} complexes is produced by the well-knownJahn–Teller effect.

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