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Thermodynamic Study of the formation of transition metal ion complexes carrying medicinal drug in mixed solvent media

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Abstract: *Stability constant of Labetalol drug with transition metal ions Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Cd^{2+} using a pH metric titration technique in 20%(v/v) ethanol-water mixture at three different temperatures 300K, 310K & 320K at an ionic strength of 0.1M $NaClO_4$ were studied. Calvin-Bjerrum method as adopted by Irving-Rossotti has been employed to determine metal-ligand stability constant logK values. The trend in the formation constants for transition metal ions follows the order* $\boldsymbol{Fe^{3+} > Cu^{2+} > Zn^{2+} > Cd^{2+} > Ni^{2+} > Co^{2+}}$*.The thermodynamic parameters such as, Gibb's free energy change ΔG, entropy change ΔS and enthalpy change ΔH associated with the complexation reactions were calculated.*

Key Word*: transition metals, Labetalol, stability constant, pH metry, thermodynamic parameter etc.*

I. Introduction

For the present investigation, we selected Labetalol hydrochloride (LBT). It is chemically described as 5-[1-Hydroxy-2-(1-methyl-3-henyl propyl amino) ethyl] salicylamide hydrochloride. LBT (mixed α- and β-adreno receptor blocking agent) is considered as one of the major therapeutic drugs for the treatment of hypertension and also used to induce hypotension during surgery as it reduces blood pressure more rapidly than other beta blockers. The drug is quite sensitive, even a small dose of the drug gives sufficient blockage, thus indicating that the drug is very much confined to the cardio protective effects. It is used in the treatment of patients with angina pectoris with and without co-existing hypertension. LBT is also one of the well-known doping agents in sports and hence, it has been banned for Olympic players by International Olympic Committee.

In continuation of our earlier work with complexation of medicinal drugs[01-14] and after literature survey it was thought of interest to study effect of temperature on thermodynamic parameters such as Gibb's free energy change ΔG, enthalpy change ΔH and entropy change ΔS of complexes of Labetalol drug with transition metal ions Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Cd^{2+} using pH metrically in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$.

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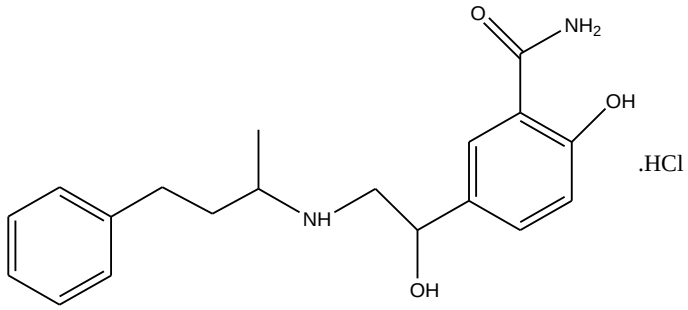

Figure 1: *Labetalol hydrochloride (molecular formula $C_{19}H_{25}N_2O_3Cl$)*

II. Material And Methods

NaOH, NaClO4, HClO4, metal salts were of AR grade. Labetaloldrug is soluble in 20% (v/v) ethanol-water mixture. The solutions used in the pH metric titration were prepared in double distilled water. NaOH solution was standardized against oxalic acid solution and standard alkali solution was again used for standardization of HClO4. The metal salt solutions were also standardized using EDTA titration. The measurements were made at three temperatures 300K, 310K and 320K in 20% (v/v) ethanol-water mixture at ionic strength 0.1M NaClO4. Water thermostat is used to maintain the temperature constant. pH measurement was made using Elico L1-120pH meter in conjunction with glass and reference calomel electrode. The instrument was calibrated at pH 7.00 and 4.00 using standard buffer solutions.

For evaluating the protonation constant of the ligand and the formation constant of the complexes in 20 % (v/v) ethanol-water mixture with different metal ions we prepare the following sets of solutions.

(A) HClO4 (A)
(B) HClO4+Labetalol (A+ L)
(C) HClO4+ Labetalol + Metal (A+ L+ M)

The above-mentioned sets prepared by keeping M:L ratio, the concentration of perchloric acid and sodium perchlorate were kept constant for all sets. The volume of every mixture was made up to 50ml with double distilled water and the reaction solution were pH metrically titrated against the standard alkali at three temperatures 300K, 310K and 320K.

Thermodynamic parameters such as Gibb's free energy change ΔG, entropy change ΔS and enthalpy change ΔH for formation of complexes were determined. Gibb's free energy change ΔG of the ligands is calculated by using the equation:

ΔG = −2.303RT logK, Where R is ideal gas constant (8.314 JK-1mol-1),
K is the dissociation constant for the ligand or thestability constant of the complex and
T is absolute temperature in Kelvin.
The change in enthalpy (ΔH) is calculated by plotting logK vs 1/T
The equation utilized for the calculation of changes in enthalpy is as Slope = - ΔH/2.303R
The evaluation of changes in entropy (ΔS) is done by the equation: ΔS =((ΔH-ΔG))/T

Table 1: Proton-ligand and metal-ligand stability constant of Labetalol drug in 20% (v/v) ethanol-water medium {Metal to ligand ratio =1:5}

pKa	Log K	Fe^{3+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}
7.7424	$logK_1$	4.2816	2.8805	3.0615	4.1402	3.2344	3.2704
	$logK_2$	4.1452	2.7794	2.8846	4.0566	2.9832	2.8020
	log β	8.4268	5.6599	5.9461	8.1968	6.2176	6.0724

Table 2: Proton-ligand and metal-ligand stability constant of Labetalol drug in 20% (v/v) ethanol-water medium {Metal to ligand ratio =1:1}

pKa	Log K	Fe^{3+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}
7.7424	$logK_1$	4.8920	3.8464	3.6727	4.7510	3.7286	3.5579
	$logK_2$	- - - -	- - - -	- - - -	- - - -	- - - -	- - - -
	log β	4.8920	3.8464	3.6727	4.7510	3.7286	3.5579

Table 3: Proton-ligand and metal-ligand stability constant of Labetalol drug

Temperature	pKa	Log K	Fe^{3+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}
300K	7.7424	$logK_1$	4.2816	2.8805	3.0615	4.1402	3.2344	3.2704
		$logK_2$	4.1452	2.7794	2.8846	4.0566	2.9832	2.8020
310K	7.5906	$logK_1$	4.1712	2.7812	2.9582	4.0344	3.1262	3.1682
		$logK_2$	4.0361	2.6698	2.7758	3.9468	2.8686	2.6822
320K	7.4116	$logK_1$	4.0604	2.6702	2.8452	3.9208	3.0128	3.0544
		$logK_2$	3.9262	2.5528	2.6592	3.8342	2.7688	2.5718

Table 4: Thermodynamic parameters of Labetalol complexes formation with metal ions.

Metal ions	- ΔG (KJ/mol)			-ΔH (KJ/mol)	ΔS (J/mol)		
	300K	310K	320K		300K	310K	320K
Fe^{3+}	ΔG_1 =24.43	23.80	23.95	ΔH_1=20.32	ΔS_1 = 13.8	11.7	11.8
	ΔG_2 =23.65	23.03	23.15	ΔH_2=20.12	ΔS_2 = 11.8	9.8	9.8
Co^{2+}	ΔG_1= 16.44	15.87	15.75	ΔH_1=19.31	ΔS_1 = -9.7	-11.6	-11.6
	ΔG_2= 15.86	15.23	15.06	ΔH_2=20.81	ΔS_2 = -16.6	-18.7	-18.7
Ni^{2+}	ΔG_1= 17.47	16.88	16.78	ΔH_1=19.86	ΔS_1 = -8.0	-10.0	-10.0
	ΔG_2= 16.46	15.83	15.68	ΔH_2=20.70	ΔS_2 = -14.2	-16.3	-16.3
Cu^{2+}	ΔG_1 =23.62	23.02	23.12	ΔH_1=20.15	ΔS_1 = 11.6	9.6	9.6
	ΔG_2 =23.15	22.52	22.61	ΔH_2=20.43	ΔS_2 = 9.1	7.0	7.1
Zn^{2+}	ΔG_1 =18.45	17.84	17.77	ΔH_1=20.36	ΔS_1 = -6.4	-8.5	-8.4
	ΔG_2 =17.02	16.37	16.33	ΔH_2=19.72	ΔS_2 = -9.0	-11.2	-11.0
Cd^{2+}	ΔG_1 =18.66	18.08	18.01	ΔH_1=19.84	ΔS_1 = -3.9	-5.9	-5.9
	ΔG_2 =15.99	15.30	15.23	ΔH_2=20.25	ΔS_2 = -14.3	-16.6	-16.3

III. Result

Labetalol Hydrochloride(C19H25N2O3Cl) is antihypertensive drug. The structural form shows that it contains primary amine group and secondary amine group. Along with these amino groups drug also contains two hydroxyl groups out of which one is phenolic -OH and other is cyclic -OH group. It also contains one carbonyl group. The labetalol under experimental conditions shows only one protonation constant in the basic range. Instead of hydroxyl groups, carbonyl group and secondary amino group, nitrogen of primary amino group might be involved in the process of protonation. The lower value of pKa (7.7429) is attributed to strong electron withdrawing effect of carbonyl group present nearer to -NH2 group.

The proton ligand stability constant pKa of Labetalol is determined by point wise calculation method as suggested by Irving and Rossoti. Metal ligand stability constant logK of transition metal ions with Labetalol drug were calculated by point wise and half-integral method of Calvin-Bjerrum as adopted by Irving -Rossotti.

The order of stability constants for these metal complexes was as follows:

Fe3+>Cu2+> Zn2+> Cd2+ >Ni2+> Co2+ {Metal to ligand ratio=1:5}and

Fe3+>Cu2+> Co2+ > Zn2+> Ni2+> Cd2+ {Metal to ligand ratio=1:1}

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The above stabilities of metal complexes with ligand are similar to the observations made by several research workers and are in accordance with Irving and Williams order. In the present metal ions, trivalent Iron has highest stability while divalent copper has available d orbital with low energy hence show maximum stability whereas it decreases in zinc complexes due to the lack of vacant d orbital having low energy. This natural order is particularly valid for nitrogen and oxygen donor ligands, irrespective of nature of ligands. Extra stability of divalent copper complex is attributed to unique electronic configuration of Cu (II) and John-Teller effect.

Negative ΔG values indicate that both dissociation of the ligand and complexation process are spontaneous. These values have no sharp behavior with temperature showing the independent nature of the reactions with respect to temperature. A decrease in metal-ligand stability constant logK with increase in temperature and negative values of enthalpy change ΔH for complexation suggests that all the complexation reactions are exothermic, favorable at lower temperature and metal-ligand binding process is enthalpy driven and metal-ligand bonds are fairly strong. The positive entropy changes ΔS accompanying a given reaction are due to the release of bound water molecules from the metal chelates. The positive value of ΔS is considered to be principal driving force for the formation of respective complex species. According to Martell and Calvin positive entropy effects was predicted towards an increase in the number of particles after the reaction and positive ΔS is responsible to give more negative ΔG. The positive values of ΔS in some cases indicate that entropy effect is predominant over enthalpy effect. The positive ΔS values for some metal complexes indicated the formation of these complexes was entropy favored, while negative ΔS values for some metal complexes suggesting a highly solvated metal complexes.

IV. Conclusion

In the present investigation, stability constants of transition metal complexes with Labetalol drug at 1:5 and 1:1 metal-ligand ratio were studied at 300K. It is found that stability constant of transition metal complexes when metal-ligand ratio 1:5 is greater than those of transition metal complexes when metal-ligand ratio is 1:1. This indicates that at higher concentration of ligand more stable complexes are formed.

The transition metal ions forms 1:1 and 1:2 complexes with Labetalol drug. The negative ΔG values indicates that both dissociation of the ligand and the complexation process are spontaneous. The negative values of enthalpy change ΔH for the complexation suggests that all the complexation reactions are exothermic, favorable at lower temperature. The negative change in entropy ΔS values indicated a highly solvated metal complex, while positive ΔS values for some metal complexes indicated that the formation of these complexes was entropy favored.

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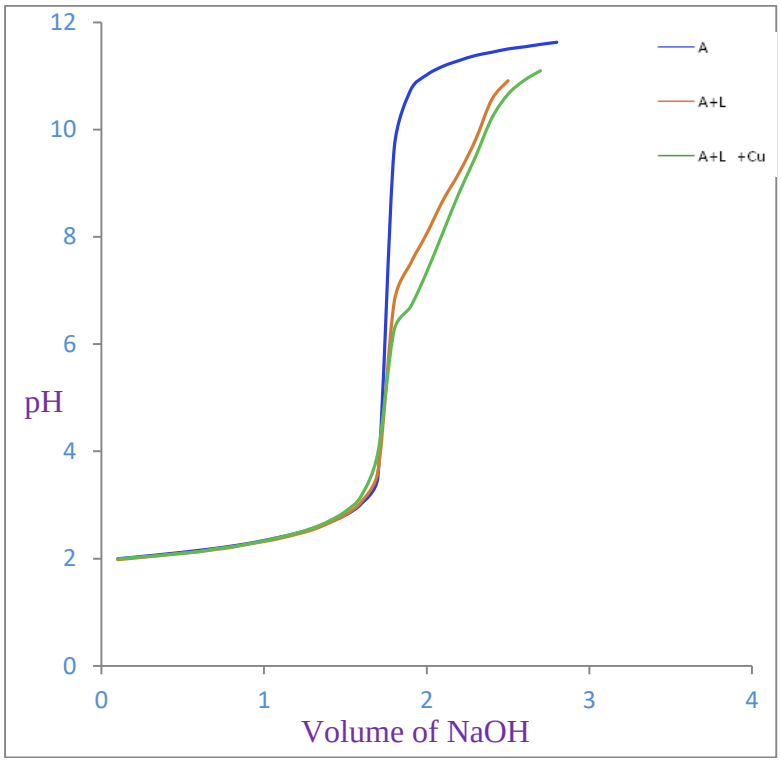

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Figure 2: The pH metric titration curve for Cu (II)- Labetalol

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