Studies of Complexation of Transition Metal Ions With Benazepril Drug in Aqueous Media: Thermodynamic Aspect

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Abstract :

Stability constant of Benazepril hydrochloride 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. The 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: ***Fe^{3+} > Cu^{2+} > Cd^{2+}> Co^{2+} > Zn^{2+} > Ni^{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.

Keywords: stability constant, transition metal ions, Benazepril, pH metry, thermodynamic parameter etc.

Introduction:

Metal complexes of drugs play a central role in the development of coordination chemistry. Most of the d-block elements form complexes. For the present investigation, we have selected drug Benazepril hydrochloride, (3-[(1-ethoxy carbonyl- 3 -phenyl-(1*S*)-propyl)-amino]- 2, 3, 4, 5 -tetrahydro- 2 –oxo - 1- (3*S*) -benazepine-1-acetic acid hydrochloride), is a prodrug type angiotensin-converting enzyme (ACE) inhibitor, which is proved effective in treating congestive heart failure and hypertension. The family of ACE inhibitors inhibits the angiotensin-converting enzyme, which is involved in the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a potent direct vasoconstrictor effect. ACE inhibitors may reduce the degradation of bradykinin. It is used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebro vascular disease.

In continuation of our earlier work [1-29] and after literature survey it was thought of interest to study the effect of temperature on thermodynamic parameters such as Gibb's free energy change ΔG, enthalpy change ΔH and entropy change ΔS of complexes of Benazepril hydrochloride 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.

Materials and Methods:

Transition metal, NaOH, $NaClO_4$, $HClO_4$ are 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 and standard alkali solution was again used for standardization of $HClO_4$. The measurements were made at temperatures 300K, 310K & 320K in 20% (v/v) ethanol-water mixture at ionic strength (0.1M $NaClO_4$). Water thermostat is used to maintain the temperature constant. The pH measurement was made using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode. The instrument was calibrated at pH 9.18, 7.00 and 4.00 using the standard buffer solutions.

To calculate the protonation constant of the ligand and the formation constant of the complexes in 20% (v/v) ethanol-water mixture with different metal ions the following sets of solutions were prepared (total volume 50 ml) and titrated pH metrically against standard NaOH solution at temperature 300K, 310K & 320K.

i. Free Acid $HClO_4$
ii. Free Acid $HClO_4$ + Ligand (Benazepril)
iii. Free Acid $HClO_4$ + Ligand (Benazepril) + Metal solution

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 thermodynamic parameters such as Gibb's free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) for formation of complexes were determined. The change in Gibb's free energy (ΔG) of the ligands is calculated by using the following equation.

$\Delta G = -2.303RT \log K$ Where R (ideal gas constant) = 8.314 $JK^{-1}mol^{-1}$,

K is the dissociation constant for the ligand or the stability 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 = $-\frac{\Delta H}{2.303R}$

The evaluation of changes in entropy (ΔS) is done by the equation: $\Delta S = \frac{(\Delta H - \Delta G)}{T}$

Results and Discussion: Benazepril Hydrochloride is antihypertensive drug. Its structural form shows one carboxylic group one secondary amine and one nitrogen in heptacyclic ring. Apart from these groups drug also contains two carbonyl groups one is cyclic and another is exocyclic one. Out of these groups -COOH is dominating one. It has been an established fact that carboxylate group is most co-ordinating group. Benazepril hydrochloride under experimental conditions shows only one pKa value (3.6486) corresponding to -COOH group in the acidic range. This indicates deprotonation of functional group other than -COOH does not take place.

The proton ligand stability constant (pKa) of Benazepril drug is determined by point wise calculation method as suggested by Irving & Rossoti. Metal ligand stability constant (logK) transition metal ions with Benazepril drug (ligand) were calculated by point wise and half integral method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed. For the present investigation we have studied the stability constant of divalent transition metal ions except iron which is trivalent. Since we got $\bar{n}_A$ between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 complex formations. The proton-ligand stability constants pKa values decreases with increase in temperature, i.e. the acidity of the ligands increases. This suggested that liberation of protons becomes easier at higher temperature.

The negative ΔG values indicate that both dissociation of the ligand and the complexation process are spontaneous. These values have no sharp behavior with temperature showing the independent nature of the reactions with respect to temperature. A decreases in metal-ligand stability constant (logK) with an increase in temperature and the negative values of enthalpy change (ΔH) for the complexation suggests that all the complexation reactions are exothermic, favorable at lower temperature and the metal-ligand binding process is enthalpy driven and metal-ligand bonds are fairly strong. The changes in entropy (ΔS) values are all negative; the complexation has an unfavorable change of entropy. An extensive solvation of metal chelates in aqueous-

organic medium for all the transition metal complexes may also be responsible for the negative ΔS values. The order of stability constants for these metal complexes was as follows:

Fe^{3+} > Cu^{2+} > Cd^{2+}> Co^{2+} > Zn^{2+} > Ni^{2+}

The ratio of $logK_1$/ $logK_2$ is positive and greater than one in all cases .This implies that there is little or no steric hindrance to ligand molecule.

Conclusion: The transition metal ions forms 1:1 and 1:2 complexes with with Benazepril 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 complexes.

Table 1. Proton-ligand and metal-ligand stability constant of Benazepril drug.

Temp	pKa	logK	Fe^{3+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}
300K	3.6486	$logK_1$	4.0343	2.9307	2.7270	3.3414	2.8581	2.9483
		$logK_2$	3.7293	2.8569	2.6955	2.9836	2.7614	2.8977
310K	3.3780	$logK_1$	3.8670	2.8728	2.6805	3.1642	2.7697	2.8787
		$logK_2$	3.5139	2.8314	2.6422	2.9309	2.7210	2.8350
320K	3.1070	$logK_1$	3.6325	2.8384	2.6490	3.0157	2.7134	2.8362
		$logK_2$	3.3192	2.8029	2.6050	2.8980	2.6810	2.8052

Table 2. Thermodynamic parameters of Benazepril 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 =23.01	22.80	22.12	ΔH_1=51.14	ΔS_1 = 94.4	92.0	91.3
	ΔG_2 =21.27	20.72	20.21	ΔH_2=34.21	ΔS_2 = 43.4	43.8	44.0
Co^{2+}	ΔG_1= 16.72	16.94	17.28	ΔH_1=22.10	ΔS_1 = 18.0	16.7	15.1
	ΔG_2= 16.30	16.69	17.06	ΔH_2=21.03	ΔS_2 = 15.9	14.1	12.5

Ni^{2+}	ΔG_1= 15.56	15.81	16.13	ΔH_1=28.54	ΔS_1 = 43.6	41.3	39.0
	ΔG_2= 15.38	15.58	15.86	ΔH_2=24.42	ΔS_2 = 30.4	28.7	26.9
Cu^{2+}	ΔG_1 =19.06	18.66	18.36	ΔH_1=24.78	ΔS_1 = 19.2	19.9	20.2
	ΔG_2 =17.02	17.28	17.64	ΔH_2=34.67	ΔS_2 = 59.2	56.5	53.6
Zn^{2+}	ΔG_1 =16.31	16.33	16.52	ΔH_1=22.08	ΔS_1 = 19.4	18.7	17.5
	ΔG_2 =15.75	16.04	16.32	ΔH_2=19.70	ΔS_2 = 13.2	11.9	10.6
Cd^{2+}	ΔG_1 =16.82	16.98	17.26	ΔH_1=22.93	ΔS_1 = 20.5	19.3	17.8
	ΔG_2 =16.53	16.72	17.08	ΔH_2=23.25	ΔS_2 = 22.6	21.2	19.4

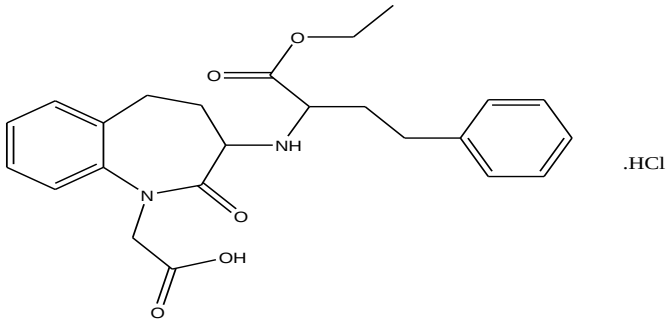

Figure: Benazepril hydrochloride {molecular formula $C_{24}H_{29}N_2O_5Cl$}

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