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Thermodynamics of the Formation of Trivalent Lanthanide Complexes Carrying Adenosine Drug in Mixed Solvent Media

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The stability constant of Adenosine drug with trivalent lanthanide metal ions La^{3+}, Ce^{3+}, Nd^{3+}, Sm^{3+}, Gd^{3+}, Tb^{3+} and Dy^{3+} using a pH metric titration technique in 20% (v/v) ethanol-water mixture at three different temperatures (25 °C, 35 °C and 45 °C) and at an ionic strength of 0.1M $NaClO_4$ were studied. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine metal-ligand stability constant (logK) values. The trend in the formation constants follows the order: **La^{3+}< Ce^{3+}< Nd^{3+}< Sm^{3+}> Gd^{3+}< Tb^{3+}< Dy^{3+}** and it shows a break at gadolinium. The thermodynamic parameters such as Gibb's free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) associated with the complexation reactions were also calculated. The formation of metal complexes was found to be spontaneous and exothermic in nature.

Keyword: Stability Constant, Lanthanides, Adenosine drug, pH meter, Thermodynamic Parameter.

1. Introduction

The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity. Metal complexes of medicinal drugs have played a central role in the development of coordination chemistry. Metal complexes are widely used in various fields, such as biological processes pharmaceuticals, separation techniques, analytical processes etc [1]. pH metric titration is accepted as a powerful and simple electro analytical technique for determination of stability constants. It is also well known that some medicinal drugs exhibit increased activity when administered as metal complexes. Most of the f-block elements form complexes. There are different kinds of ligands used for complexation. For the present investigation, we have selected Adenosine (ADO) drug, having molecular formula $C_{10}H_{13}N_5O_4$ and IUPAC name is (3R,4S,5R)-2 (6-aminopurin-9-yl) -5-(hydroxymethyl) oxolane-3,4 dials.[1] It is an analgesic, cardiac drug, anti-arrhythmia agents, anti-arrthmic agents and vasodilator agents.

The physical properties of medicinal drugs adenosine is shown below -

(i) Molecular weight = 267.24 g/mol
(ii) Phase = Solid (at STP)
(iii) Melting point = 234 ºC
(iv) Boiling point = 676 ºC
(v) Density = 0.99224 g/cm3
(vi) Solubility = Soluble in water 8230 mg/L or 1.40 e + 01 g/L

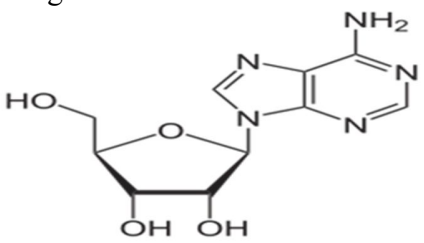

Fig 1: Adenosine

In recent years, there has been an increased interest in the study of the lanthanide complexes. Owing to the unique properties of the lanthanide ions, lanthanides have often been effectively employed as active Ca^{2+} and Mg^{2+} substitutes in many metalloproteins as chiral NMR shift reagents. MRI contrast agents and also luminescent probes of metal binding in biological sytems [2]. Thus keeping the above facts in mind and in continuation of our earlier work with complexation of medicinal drugs such as Adenosine [3], Imipramine Hydrochloride [4], Metformin Hydrochloride [5,6], Isoniazid [7], we have carried out a solution study on the complexation of ADO drug. It was thought of interest to study the effect of temperature on thermodynamic parameters ΔG, ΔH and ΔS of complexes of ADO drug with rare earth metal ions La^{3+}, Ce^{3+}, Nd^{3+}, Sm^{3+}, Gd^{3+}, Tb^{3+} and Dy^{3+} using pH metrically in 20% (v/v) ethanol-water mixture.

2. Experimental

2.1 Materials and Solution

The pure drug Adenosine is soluble in double distilled water. NaOH, $NaClO_4$, $HClO_4$ and all metal salts are of analytical reagent grade. The solutions used in the pH metric titration were prepared in double distilled CO_2 free 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 solutions were also standardized using EDTA titration [8]. All the measurements were made at temperatures 25°C, 35°C, and 45°C in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$. The water thermostat model SL-131, scientific isotemperature refrigerated circulator accurate to ± 0.1 ºC is used to maintain the temperature constant. The solutions were equilibrated in the thermostat for about 15 minutes before titration. The pH measurement was made using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode (reading accuracy ±0.01 pH units). The instrument was calibrated at pH 4.00, 7.00 and 9.18 using the standard buffer solutions.

2.2 pH metric procedures

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 the following sets of solutions were prepared (total volume 50 ml) and titrated pH metrically against standard NaOH solution at three different temperatures 25 °C, 35 °C and 45 °C.

i. Free Acid $HClO_4$ (2ml) + $NaClO_4$ (5ml) + C_2H_5OH (10ml)
ii. Free Acid $HClO_4$ (2ml) + ADO Drug (10ml) + $NaClO_4$ (5ml) + C_2H_5OH (10ml)
iii. Free Acid $HClO_4$ (2ml) + ADO Drug (10ml) + Metal solution (2ml) + $NaClO_4$ (5ml) + C_2H_5OH(10ml)

The above mentioned sets prepared by keeping M: L ratio, the concentration of perchloric acid and sodium perchlorate were kept constant for all sets.

2.3 Determination of the thermodynamic parameters

The thermodynamic parameters such as Gibb's free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) for formation of complexes are 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 is 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 the absolute temperature in Kelvin (K)
The change in enthalpy (ΔH) is calculated by plotting log K vs 1/T
The equation utilized for the calculation of changes in enthalpy (ΔH) is as

$$Slope = -\frac{\Delta H}{2.303R}$$

The evaluation of changes in entropy (ΔS) is done by the following equation.

$$\Delta S = \frac{(\Delta H - \Delta G)}{T}$$

Table 1: Proton-ligand and metal-ligand stability constant of ADO drug in 20 % ethanol-water media.

Temperature	pK_1	pK_2	log K	La^{3+}	Ce^{3+}	Nd^{3+}	Sm^{3+}	Gd^{3+}	Tb^{3+}	Dy^{3+}
25 °C	3.292	11.66	log K_1	6.402	7.094	7.364	8.068	7.891	8.100	8.282
			log K_2	4.689	5.148	5.659	6.786	6.451	7.113	7.309
35 °C	3.082	11.47	log K_1	6.238	6.933	7.200	7.900	7.728	7.937	8.118
			log K_2	4.528	4.986	5.524	6.602	6.288	6.949	7.145
45 °C	2.988	11.28	log K_1	6.030	6.740	7.010	7.714	7.537	7.746	7.928
			log K_2	4.340	4.811	5.278	6.412	6.098	6.759	6.955

Table 2: Thermodynamic parameters of ADO complex formation with lanthanide metal ions in 20% ethanol-water media.

Metal Ions		- ΔG KJMol^{-1}		- ΔH KJMol^{-1}		ΔS KJMol^{-1}	
	25 °C	**35 °C**	**45 °C**		**25 °C**	**35 °C**	**45 °C**
La^{3+}	ΔG_1=36.53	36.79	36.71	ΔH_1=33.70	ΔS_1 =0.009	0.01	0.009
	ΔG_2=26.75	26.7	26.42	ΔH_2=31.65	ΔS_2 =-0.02	-0.016	-0.016
Ce^{3+}	ΔG_1=40.48	40.88	41.04	ΔH_1=32.06	ΔS_1 =0.028	0.029	0.028
	ΔG_2=29.37	29.4	29.3	ΔH_2=30.55	ΔS_2 =-0.01	-0.004	-0.004
Nd^{3+}	ΔG_1=42.02	42.46	42.68	ΔH_1=32.07	ΔS_1 =0.033	0.034	0.033
	ΔG_2=32.29	32.58	32.14	ΔH_2=34.55	ΔS_2 =-0.01	-0.006	-0.008
Sm^{3+}	ΔG_1=46.04	46.59	46.97	ΔH_1=32.11	ΔS_1 = 0.047	0.047	0.047
	ΔG_2=38.72	38.93	39.04	ΔH_2=33.97	ΔS_2 = 0.016	0.016	0.016
Gd^{3+}	ΔG_1=45.03	45.57	45.89	ΔH_1=32.11	ΔS_1 =0.043	0.044	0.043
	ΔG_2=36.81	37.08	37.13	ΔH_2=32.02	ΔS_2 =0.016	0.016	0.016
Tb^{3+}	ΔG_1=46.22	46.8	47.17	ΔH_1=32.05	ΔS_1 =0.047	0.048	0.047
	ΔG_2=40.59	40.98	41.15	ΔH_2=32.12	ΔS_2 =0.028	0.029	0.028
Dy^{3+}	ΔG=47.25	47.87	48.27	ΔH_1=32.10	ΔS_1 =0.051	0.051	0.051
	ΔG_2=41.70	42.14	42.35	ΔH_2=32.07	ΔS_2 =0.032	0.033	0.032

3. Results and Discussion

The results obtained are analyzed by the computer programme and the stability constant values are calculated. Adenosine has N-atom as the binding site. The functional group NH_2 is mostly responsible for complexation, although there are nitrogen atoms present in the coordinate bond formation. ADO contains three OH groups, out of these two are attached to cyclic ring and one is in the side chain. The deprotonation of side chain –OH is easier compared to –OH directly attached to the ring. Hence only one deprotonation in the acidic range (3.292) and the other proton-ligand stability constant (pK_a) in the basic region correspond to $–NH_2$ group only (11.659).

The proton-ligand stability constant (pK_a) of ADO drug is determined by point wise calculation method as suggested by Irving and Rossoti. Metal ligand stability constant (logK) of lanthanide metal ions with ADO drug are

calculated by point wise and half integral method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed . Since we got values of proton-ligand formation number ($\bar{n}_A$) between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 complex formations. The proton-ligand stability constant (pK_a) values decrease with increase in temperature i.e. the acidity of the ligands increases [9]. This suggests that the liberation of protons becomes easier at higher temperature.

The negative ΔG values indicates that both dissociation of the ligand and the complexation process are spontaneous [9]. A decrease 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[2] and metal-ligand bonds are fairly strong. Positive entropy changes (ΔS) accompanying a given reaction are due to the release of bound water molecules from the metal chelates. During the formation of metal chelates, water molecules from the primary hydration sphere of the metal ion are displaced by the chelating ligand. Thus there is an increase in the number of particles in the system i.e. randomness of the system increases [10]. The positive value of ΔS is considered to be the principle driving force for the formation of respective complex species.

According to Martell and Calvin [11] positive entropy effects was predicted towards an increase in the number of particles after the reaction. This positive ΔS is responsible to give more negative ΔG. The high positive values of ΔS in some cases indicate that the entropy effect is predominant over enthalpy effect. The positive ΔS values for some metal complexes indicated that the formation of these complexes was entropy favored, while negative ΔS values for some metal complexes suggesting a highly solvated metal complexes [12]. The order of stability constants for these metal complexes found to be: $La^{3+} < Ce^{3+} < Nd^{3+} < Sm^{3+} > Gd^{3+} < Tb^{3+} < Dy^{3+}$ and it shows a break at gadolinium.

4. Conclusions

The lanthanide metal ion forms 1:1 and 1:2 complexes with ADO drug. The metal-ligand stability constant logK decreases with an increase in temperature and shows a break at gadolinium. The negative values of change in enthalpy (ΔH) for the complexation suggest that all the complexation reactions are exothermic, favorable at lower temperature. The negative change in free energy (ΔG) values indicates that both dissociation of the ligand and the complication process are spontaneous. 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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