



Thermodynamics of the Formation of Transition Metal Complexes Carrying Adenosine Drug in Mixed Solvent System

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Abstract: In the present work we investigate the stability constant of Adenosine drug with transition metal ions Fe, Co, Ni, Cu, Zn, and Cd 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 NaClO₄. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine metal-ligand stability constant logK values. It is observed that transition metal ion forms 1:1 and 1:2 complexes. The trend in the formation constants follows the order: $Fe^{3+} > Cu^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+}$. 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. The formations of metal complexes were found to be spontaneous, exothermic in nature and favorable at lower temperature.

Keywords: Stability Constant, Transition metal, Adenosine drug, pH meter, Thermodynamic parameter.

I. Introduction

Drugs have various functional groups present in its structure, which can bind to metal ions present in the human body. Metal complexes of drugs are found to be more potent than parent drugs. Chemistry of drugs attracts many researchers because of its application in medicinal study. The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity. Metal complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc. Potentiometric titration is accepted as a powerful and simple electro analytical technique for determination of stability constants. The determination of stability constants is an important process for many branches of chemistry. Most of the d-block elements form complexes. There are different kinds of ligand used for complexation. For the present investigation, we have selected Adenosine (ADO) drug, having molecular formula C₁₀H₁₃N₅O₄. It is an analgesic, cardiac drug, anti-arrhythmia agents, anti-arrhythmic agents, vasodilator agents. The IUPAC name of ADO is (3R, 4S, 5R)-2(6-aminopurin-9-yl)-5-(hydroxymethyl) oxolane-3, 4 diol. ADO is used as an initial treatment for the termination of paroxysmal supraventricular tachycardia, including that associated with accessory bypass tracts, and is a drug of choice for terminating stable, narrow-complex supraventricular tachycardias (SVT). Also used as an adjunct to thallous chloride TI 201 myocardial perfusion scintigraphy (thallium stress test) in patients who are unable to exercise adequately, as well as an adjunct to vagal maneuvers and clinical assessment to establish a specific diagnosis of undefined, stable, narrow-complex SVT.

After a review of literature survey¹⁻¹⁰, the detail study of the complex under an identical set of experimental condition is still lacking. 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 Adenosine drug with transition metal ions Fe³⁺, Cu²⁺, Zn²⁺, Ni²⁺, Co²⁺ and Cd²⁺ using the pH metric titration technique in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M NaClO₄.

II. Experimental Section

Materials and Solution:

All the chemicals used were of high grade of purity (AR Grade). The pure drug Adenosine obtained as a gift sample from a reputed pharmaceutical industry is soluble in double distilled CO₂ free water. The solutions used in the potentiometric titration were prepared in double distilled water. The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of HClO₄. The metal salt solutions were also standardized using EDTA titration¹¹. All the measurements were

made at 25 °C, 35 °C and 45 °C in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M NaClO₄. The water thermostat Fisher Scientific Isotemperature Refrigerated Circulator model 9000 accurate to $\pm 0.1^\circ\text{C}$ was 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.

Potentiometric procedure:

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

(A) HClO₄ (A)

(B) HClO₄+ADO (A+ L)

(C) HClO₄+ ADO + Metal (A+ L+ M)

The above mentioned sets prepared by keeping M: L ratio, the concentration of Perchloric acid and sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made up to 50 ml with double distilled water and the reaction solution was potentiometrically titrated against the standard alkali at a temperature 25°C, 35°C and 45°C.

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 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) = $8.314 \text{ JK}^{-1}\text{mol}^{-1}$, K is the dissociation constant for the legend or the stability constant of the complex and T is absolute temperature in Kelvin.

The change in enthalpy (ΔH) is calculated by plotting $\log K$ vs $1/T$

The equation utilized for the calculation of changes in enthalpy is as

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

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

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

Figure 1. The pH metric titration curve for Cu (II)-ADO

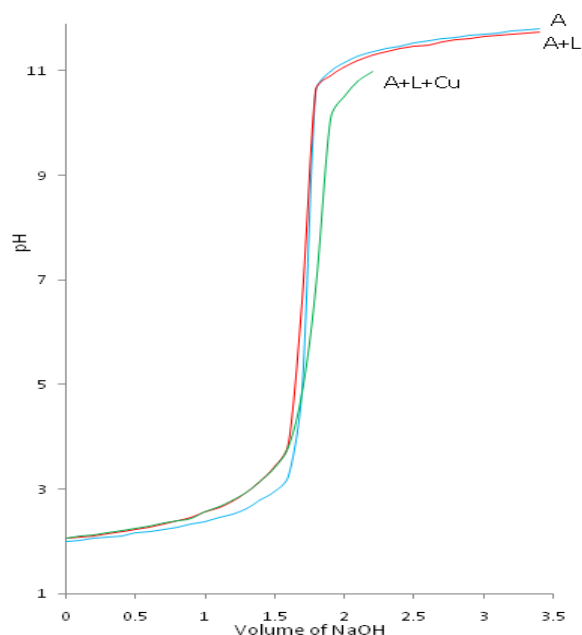
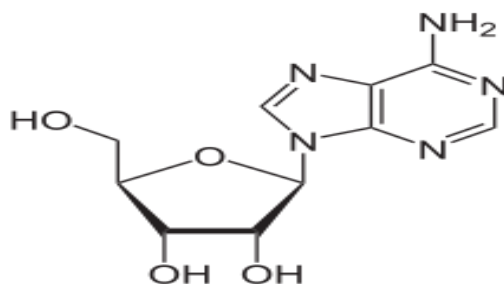
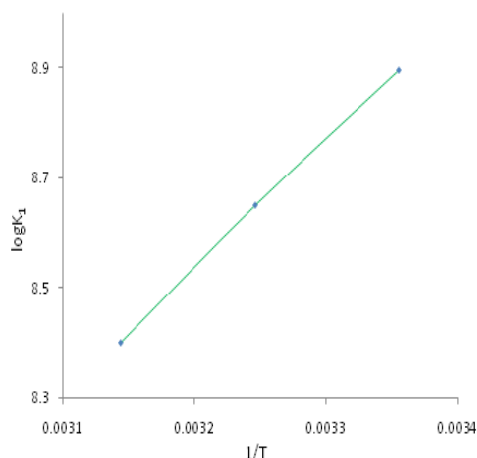
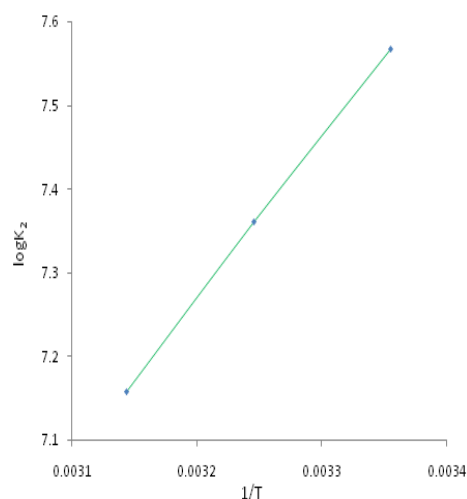


Figure 2. Adenosine**Table 1. Proton-ligand and metal-ligand stability constant of ADO drug.**

Temperature	pK ₁	pK ₂	logK	Fe ³⁺	Co ²⁺	Ni ²⁺	Cu ²⁺	Zn ²⁺	Cd ²⁺
25 °C	3.29	11.66	logK ₁	11.95	5.808	5.977	8.894	7.042	5.704
			logK ₂	10.71	4.906	5.080	7.567	6.361	4.687
35 °C	3.082	11.47	logK ₁	11.63	5.619	5.789	8.671	6.851	5.516
			logK ₂	10.48	4.720	4.893	7.378	6.172	4.502
45 °C	2.988	11.28	logK ₁	11.39	5.430	5.600	8.400	6.682	5.326
			logK ₂	10.27	4.535	4.705	7.158	5.943	4.327

Table 2. Thermodynamic parameters of ADO complex formation with transition metal ions.

Metal Ions	- ΔG KJ/Mol			- ΔH KJ/Mol	ΔS KJ/Mol		
	25 °C	35 °C	45 °C		25 °C	35 °C	45 °C
Fe ³⁺	ΔG ₁ =68.18	68.61	69.37	ΔH ₁ =50.94	ΔS ₁ =0.058	0.057	0.058
	ΔG ₂ =61.10	61.79	62.55	ΔH ₂ =39.41	ΔS ₂ =0.073	0.073	0.073
Co ²⁺	ΔG ₁ =33.14	33.14	33.06	ΔH ₁ =34.31	ΔS ₁ =-0.01	-0.004	-0.004
	ΔG ₂ =27.99	27.84	27.61	ΔH ₂ =33.70	ΔS ₂ =-0.02	-0.019	-0.019
Ni ²⁺	ΔG ₁ =34.10	34.14	34.09	ΔH ₁ =34.23	ΔS ₁ =0.001	-0.001	-0.001
	ΔG ₂ =28.99	28.86	28.65	ΔH ₂ =34.02	ΔS ₂ =-0.02	-0.017	-0.017
Cu ²⁺	ΔG ₁ =50.74	51.14	51.15	ΔH ₁ =44.72	ΔS ₁ =0.020	0.021	0.020
	ΔG ₂ =43.18	43.51	43.58	ΔH ₂ =37.05	ΔS ₂ =0.021	0.021	0.021
Zn ²⁺	ΔG ₁ =40.18	40.40	40.68	ΔH ₁ =32.72	ΔS ₁ =0.025	0.025	0.025
	ΔG ₂ =36.29	36.40	36.18	ΔH ₂ =33.40	ΔS ₂ =0.010	0.010	0.009
Cd ²⁺	ΔG ₁ =32.55	32.53	32.43	ΔH ₁ =34.28	ΔS ₁ =-0.01	-0.006	-0.006
	ΔG ₂ =26.74	26.55	26.34	ΔH ₂ =32.69	ΔS ₂ =-0.02	-0.02	-0.02

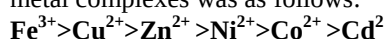
Figure 3. Plot of $\log K_1$ Vs $1/T$ for Cu (II)-ADO**Figure 4. Plot of $\log K_2$ Vs $1/T$ for Cu (II)-ADO**

IV. Experimental Result and Discussion

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 co-ordinate bond formation. ADO contains three OH groups, out of these two are attached to cyclic ring and one is to the side chain. The deprotonation of side chain $-\text{OH}$ is easier compared to $-\text{OH}$ directly attached to the ring. Hence only one deprotonation in the acidic range (3.292) and the other pK_a in the basic region correspond to $-\text{NH}_2$ 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 $\log K$ of transition 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 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 pK_a values decrease with increase in temperature, i.e. the acidity of the ligands increases.¹² 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.¹³ These values have no sharp behavior with temperature showing the independent nature of the reactions with respect to temperature.¹⁴ A decrease in metal-ligand stability constant ($\log K$) 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 driven¹⁵ 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.¹⁶ The positive value of ΔS is considered to be the principal driving force for the formation of respective complex species. More positive values of ΔS may result due to an increase in the number of particles after the reaction and is responsible for giving more negative values of ΔG .¹⁷ According to Martell and Calvin¹⁸ 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.¹⁹ The order of stability constants for these transition metal complexes was as follows:



The ratio of $\log K_1 / \log K_2$ is positive and greater than one in all cases. This implies that there is little or no steric hindrance to ligand molecule.

V. Conclusion

The transition metal ion forms 1:1 and 1:2 complexes with ADO drug. The metal-ligand stability constant $\log K$ decreases with an increase in temperature. The negative values of change in entropy (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 complexation 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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