



Thermodynamics of the Complexation of Imipramine Hydrochloride Drug with Lanthanide

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Abstract: pH metry is one of the most convenient and successful technique employed for metal complex equilibrium measurements. In the present work we investigate the stability constant of Imipramine Hydrochloride drug with lanthanide metal ions La^{3+} , Ce^{3+} , Nd^{3+} , Sm^{3+} , Gd^{3+} , Tb^{3+} and Dy^{3+} using p^H metric titration technique in 20% (v/v) ethanol-water mixture at three different temperatures (25 °C, 35 °C & 45 °C) and at an ionic strength of 0.1M NaClO_4 . The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine metal-ligand stability constant ($\log K$) values. It is observed that a lanthanide metal ion forms 1:1 and 1:2 complexes. The trend in the formation constants for lanthanide metal ions follows the order: $\text{La}^{3+} < \text{Ce}^{3+} < \text{Nd}^{3+} < \text{Sm}^{3+} > \text{Gd}^{3+} < \text{Tb}^{3+} < \text{Dy}^{3+}$ and 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 calculated. The formations of metal complexes were found to be spontaneous and exothermic in nature.

Key Words: pH metry, Stability Constant, Lanthanide metal ions, Imipramine Hydrochloride drug, Thermodynamic parameter.

I. Introduction

The coordination chemistry of metal ion in aqueous solution is the vast field of investigation¹. Drugs have various functional groups present in its structure. They can bind to metal ions present in human body². Metal complexes of drugs are found to be more potent than parent drugs. It has been found that numbers of drugs are known to inhibit protein synthesis in bacteria by causing misreading of the genetic code³. 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. Recently, there is great interest in heavy-metal pollution and in the design of improved drugs for removing them from plasma. However, before any new pharmaceutical is marketed, it is prudent to know as much as possible about the molecular chemistry of its mode of action. This involves the knowledge of the product of ligand metabolism, the selectivity of the ligand for the pollutant cations with respect to the essential metal ions, the major species present at physiological pH values, the extent to which the ligand and its complexes partition in a cell membrane and the structures of the complexes formed⁴. It is well known that proton transfer plays an important role in the reactions such as complexation, acid-base catalyzing and enzymatic reaction⁵ in aqueous solution. The stability constants can be of significance in order to predict different chemical processes such as isolation, extraction, or preconcentration methods^{6,7}. Thus, the accurate determination of acidity and stability constants values are fundamental to understanding the behavior of ligands and their interaction with metal ions in aqueous solution. 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 chemistry⁸. Most of the f-block elements form complexes. There are different kinds of ligand used for complexation. For the present investigation, we selected antidepressant drug Imipramine Hydrochloride (IMP), having molecular formula $\text{C}_{19}\text{H}_{25}\text{N}_2\text{Cl}$ and IUPAC name is 3-(5,6-dihydrobenzo[b][1]benzazepin-11-yl)-N,N-dimethylpropan-1-amine. IMP is a tricyclic antidepressive analgesics agent, adrenergic uptake inhibitors and norepinephrine reuptake inhibitors. IMP is mainly used in the treatment of major depression and enuresis (inability to control urination). It has also evaluated for use in panic disorder. IMP is a tertiary amine affects numerous neurotransmitter systems known to be involved in the etiology of depression, anxiety ADHD, enuresis and numerous other mental and physical conditions. IMP is similar in structure to some muscle relaxations and has a significant analgesic effect and thus is very useful in some pain conditions. Literature

survey reveals that a very few researchers have done such type of work using medicinal drug as a ligand⁹⁻¹⁵. The detail study of complex under identical set of experimental condition is still lacking. Therefore we decide to study the effect of temperature on thermodynamic parameters ΔG , ΔH and ΔS of complexes of IMP drug with lanthanide metal ions La^{3+} , Ce^{3+} , Nd^{3+} , Sm^{3+} , Gd^{3+} , Tb^{3+} and Dy^{3+} by using pH metric titration technique in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M NaClO_4 .

II. Experimental Section

Materials and Solution:

All the chemicals used were of high grade of purity. The pure drug IMP obtained as a gift sample from a reputed pharmaceutical industry is soluble in double distilled 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 HClO_4 . The metal salt solutions were also standardized using EDTA titration¹⁶. 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 NaClO_4 . 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 minute before titration. The pH measurement were 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) HClO_4 (A)

(B) $\text{HClO}_4 + \text{IMP}$ (A + L)

(C) $\text{HClO}_4 + \text{IMP} + \text{Metal}$ (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 were potentiometrically titrated against the standard alkali at temperature 298K, 308K and 318K.

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 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 ligand 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. Imipramine Hydrochloride

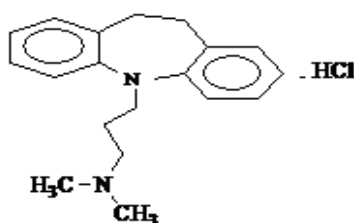
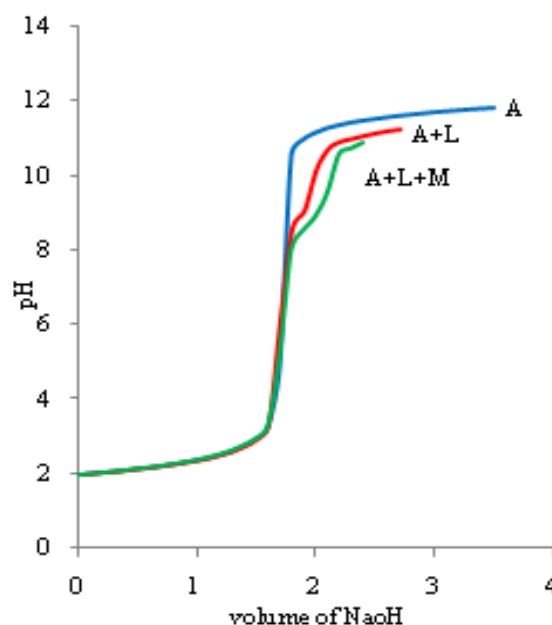
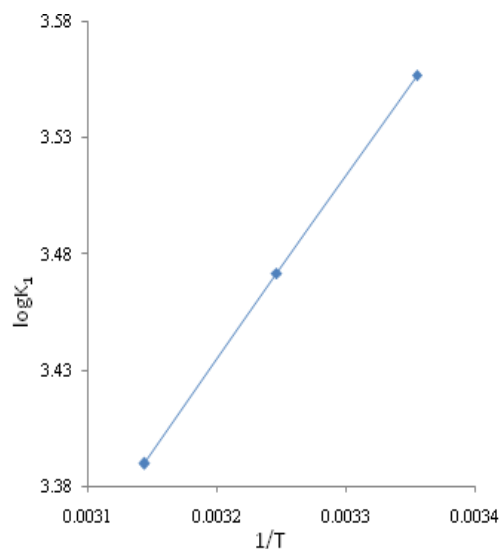
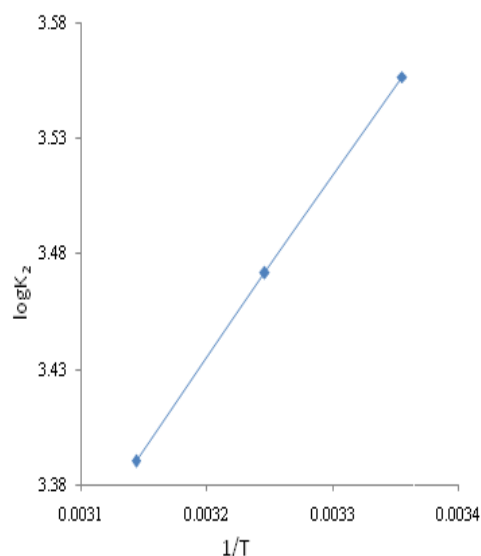


Figure 2. The pH metric titration curve for Ce (III)-IMP**Table 1. Proton-ligand and metal-ligand stability constant of IMP drug.**

Temperature	pKa	logK	La ³⁺	Ce ³⁺	Nd ³⁺	Sm ³⁺	Gd ³⁺	Tb ³⁺	Dy ³⁺
25 °C	9.062	logK ₁	5.232	5.427	5.914	6.042	5.510	5.776	5.831
		logK ₂	3.419	3.557	4.429	4.601	3.764	4.390	4.494
35 °C	8.967	logK ₁	5.152	5.332	5.82	5.947	5.416	5.674	5.736
		logK ₂	3.345	3.485	4.328	4.508	3.657	4.299	4.388
45 °C	8.854	logK ₁	5.025	5.191	5.681	5.752	5.294	5.568	5.622
		logK ₂	3.200	3.390	4.138	4.403	3.430	4.179	4.292

Table 2. Thermodynamic parameters of IMP complexes formation with lanthanide metal ions.

Metal ions	- ΔG			- ΔH	ΔS			
	(KJ/mol)				(KJ/mol)	(KJ/mol)		
	25 °C	35 °C	45 °C			25 °C	35 °C	45 °C
La ³⁺	ΔG ₁ =29.85	30.38	30.6	ΔH ₁ =18.75	ΔS ₁ = 0.037	0.038	0.037	
	ΔG ₂ =19.51	19.79	19.48	ΔH ₂ =19.87	ΔS ₂ =-0.001	-0.001	-0.001	
Ce ³⁺	ΔG ₁ =30.96	31.44	31.6	ΔH ₁ =21.39	ΔS ₁ = 0.032	0.033	0.032	
	ΔG ₂ =20.29	20.55	20.64	ΔH ₂ =15.10	ΔS ₂ = 0.017	0.018	0.017	
Nd ³⁺	ΔG ₁ =33.75	34.32	34.59	ΔH ₁ =21.15	ΔS ₁ = 0.042	0.043	0.042	
	ΔG ₂ =25.27	25.52	25.19	ΔH ₂ =26.46	ΔS ₂ =-0.004	-0.003	-0.004	
Sm ³⁺	ΔG ₁ =34.47	35.07	35.02	ΔH ₁ =26.25	ΔS ₁ = 0.028	0.029	0.028	
	ΔG ₂ =26.25	26.59	26.81	ΔH ₂ =17.95	ΔS ₂ = 0.028	0.028	0.028	
Gd ³⁺	ΔG ₁ =31.44	31.94	32.23	ΔH ₁ =19.91	ΔS ₁ = 0.039	0.04	0.039	
	ΔG ₂ =21.47	21.56	20.88	ΔH ₂ =24.53	ΔS ₂ =-0.010	-0.009	-0.011	
Tb ³⁺	ΔG ₁ =32.96	33.46	33.9	ΔH ₁ =18.89	ΔS ₁ = 0.047	0.047	0.047	
	ΔG ₂ =25.05	25.35	25.44	ΔH ₂ =19.19	ΔS ₂ = 0.019	0.02	0.019	
Dy ³⁺	ΔG=33.27	33.83	34.23	ΔH ₁ =18.89	ΔS ₁ = 0.048	0.048	0.048	
	ΔG ₂ =33.27	25.88	26.13	ΔH ₂ =18.37	ΔS ₂ = 0.024	0.024	0.024	

Figure 3. Plot of $\log K_1$ Vs $1/T$ for Ce (III)-IMPFigure 4. Plot of $\log K_2$ Vs $1/T$ for Ce (III)-IMP

IV. Experimental Result and Discussion

Imipramine hydrochloride drug shows only one pK_a values. The protonation constant pK_a for IMP obtained under the experimental condition is 9.062. This is due to presence of two tertiary amine nitrogen. Out of these two, the terminal of tertiary amino group might have been involved in the complexation. The dimethyl ammonium group is considered to be the most basic functional group of any ligand¹⁷. The proton ligand stability constant pK_a of IMP drug is determined by point wise calculation method as suggested by Irving and Rossotti. Metal ligand stability constant $\log K$ of lanthanide metal ions with IMP drug 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 trivalent lanthanide metal ions. 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 decreases with increase in temperature, i.e. the acidity of the ligands increases¹⁸. 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 spontaneous¹⁹. These values have no sharp behavior with temperature showing the independent nature of the reactions with respect to temperature²⁰. A decreases 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 driven²¹ and metal-ligand bonds are fairly strong. Positive entropy changes accompanying a given reaction are due to the release of bound water molecules from the metal chelates. During 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 increases²². 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 number of particles after the reaction and is responsible for giving more negative values of ΔG ²³.

According to Martell and Calvin²⁴ 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 complexes²⁵. The order of stability constants for these metal complexes was as follows:

$La^{3+} < Ce^{3+} < Nd^{3+} < Sm^{3+} > Gd^{3+} < Tb^{3+} < Dy^{3+}$ and shows a break at gadolinium.

V. Conclusion

The lanthanide (rare earth) metal ion forms 1:1 and 1:2 complexes with IMP drug. The metal-ligand stability constant $\log K$ 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 Gibbs's free energy (ΔG) values indicates that both dissociation of the ligand and the complexation process are spontaneous. The positive change in entropy (ΔS) values indicated that the formation of these complexes was entropy favored and negative ΔS values for some metal complexes suggesting a highly solvated metal complexes.

References

- [1] H. Singel, *Metal ions in Biological System*, vols. 1-34, ed. H. Singel, Marcel Dekker, New York, 1971-1997.
- [2] A.L. Lehninger, *Physical Rev*, 30, 393, 1950.
- [3] M.S. Nair and M.A. Neelkantan, *Indian J. Chem. Sect. A*, 38, 578, 1999.
- [4] S. Monica, I. Daniela and M. Ledi, *J. Inorg. Biochem*, 78, 355, 2000.
- [5] I. Ando, K. Ujimoto and H. Kurihara, *Bull. Chem. Soc. Japan*, 55, 713, 1982.
- [6] E.A. Gracia and D.B. Gomis, *Mikrochem. Acta*, 124, 179, 1996.
- [7] S. Cao and M.J. Zhang, *Trace Microprobe Tech*, 17, 157, 1999.
- [8] R.J. Motekatis and A.E. Martell, *The determination and use of stability constants*, VCH, New York, 1988.
- [9] M. N. Valeria, C. Guido, P. Tiziana, D. Martina and R. Maurizio, *J. Inorg. Biochem*, 102, 684, 2008.
- [10] M. Omar, El-Roudi, A. Samir and Abdel-Latif, *J. Chem. Eng. Data*, 49, 1193, 2004.
- [11] F. Khan and A. Khanam, *Port. Electrochim. Acta*, 27, 87, 2009.
- [12] E.H. El-Mossalamy, *Port. Electrochim. Acta*, 27, 143, 2009.
- [13] M.S. Parihar and F. Khan, *Ecletica Quimica*, 33, 1, 2008.
- [14] A. Vyas and R.P. Mathur, *J. Rare Earths*, 27, 457, 2009.
- [15] L. Jain, S. Jangid, H. Singh and R.K. Mehta, *J. Ind. Inst. Sci*, 72, 495, 1992.
- [16] G.H. Jaffery, J. Basset, J. Mendham and R.C. Denney, *Vogel's Textbook of Quantitative Chemical Analysis*, 5th edition, Long man group UK limited, 1978.
- [17] N. P. Marta, El. Mansour, M. Hadi and P. Gabor, *J. Pharm. Biomed. Ana*, 14, 1025, 1996.
- [18] A.A. El-Bindary, A.Z. El-Sonbati, E.H. El-Mosalamy and R.M. Ahmed *Chem. Pap.* 57, 255, 2003.
- [19] M.F. El-Sherbiny *Chem. Pap.* 59, 332, 2005.
- [20] H.M. Abd Erbary, H.A. Shehata, M.A.F. El Arab, A.A. Mohamed and M.M. Emara *J. Ind. Chem. Soc.* 73, 25, 1996.
- [21] Y. Sharmeli and R. Lonibala, *J. Chem. Eng. Data*, 54, 28, 2009.
- [22] R. Shakru, S. Kumar, V. Kumar and Shivraj, *J. Adv. Scient. Rec.* 2, 58, 2011.
- [23] U.S.A. Nair and G.H. Nancollas, *J. Chem. Soc.* 255, 4367, 1961.
- [24] A.E. Martell and M. Calvin, *Chemistry of metal chelate compounds*. Prentice Hall, New Jersey, p150, 1952.
- [25] D. T. Promila and R. Lonibala, *J. Chem. Eng. Data*, 55, 1166, 2010.

Acknowledgments

Authors thankful to Principal, Dr. Mohd. Ilyas Fazil, Principal, Dr. Maqdoom Farooqui, Entire management of Milliyya College, Beed (MS) and Maulana Azad College, Aurangabad (MS), for providing all necessary research facilities.