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## Formation of Transition Metal Complexes Carrying Medicinal Drugs: Thermodynamic Study

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**Abstract:** Stability constant of Isoniazid and Imipramine Hydrochloride drugs with transition metal ions Fe, Co, Ni, Cu, Zn and Cd have been determined by 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<sub>4</sub>. 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 thermodynamic parameters such as, Gibb's free energy change ( $\Delta G$ ), entropy change ( $\Delta S$ ) and enthalpy change ( $\Delta H$ ) 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, Isoniazid drug, Imipramine Hydrochloride drug, pH meter, Thermodynamic parameter.

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## INTRODUCTION

The metal complexes involving medicinal drugs are receiving more attention because of their vital role in Analytical Chemistry, Coordination Chemistry, catalysis, metalloproteins and metalloenzymes. 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. 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 medicinal drugs Isoniazid (ISO) and Imipramine Hydrochloride (IMP).

Isoniazidis an antibiotic drug used primarily as a tuberculostatic. The IUPAC name of ISO is Pyridine-4-carbohydrazide. ISO (Laniazid, Nydrazid) also known as isonicotinyl hydrazine, is an organic compound that is the first-line medication in prevention and treatment of tuberculosis. ISO is a prodrug and must be activated by a bacterial catalase peroxidase enzyme that in *M. tuberculosis* is called KatG. A range of radicals are produced by KatG activation of isoniazid, including nitric oxide, which has also been shown to be important in the action of another antimycobacterial prodrug. ISO reaches therapeutic concentrations in serum, cerebrospinal fluid, and within caseous granulomas. It is metabolized in the liver via acetylation. 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 relaxants and has a significant analgesic effect and thus is very useful in some pain conditions.

Imipramine Hydrochloride (IMP) is an antidepressant drug having IUPAC name is 3-(5,6-dihydrobenzo[b][1]benzazepin-11-yl)-N,N-dimethylpropan-1-amine. In continuation of our earlier work with complexation of medicinal drugs such as Metformin Hydrochloride<sup>1,2</sup>, Isoniazid<sup>3</sup>, Adenosine<sup>4</sup>, Imipramine Hydrochloride<sup>5</sup> and Oxytetracycline Hydrochloride<sup>6</sup>. It was thought of interest to study the effect of temperature on thermodynamic parameters such as Gibb's free energy change  $\Delta G$ , enthalpy change  $\Delta H$  and entropy change  $\Delta S$  of complexes of Isoniazid (ISO) and Imipramine Hydrochloride (IMP) drug with transition metal ions  $Fe^{3+}$ ,  $Cu^{2+}$ ,  $Zn^{2+}$ ,  $Ni^{2+}$ ,  $Co^{2+}$  and  $Cd^{2+}$  using the pH metric titration technique in 20% (v/v) ethanol-water mixture at constant ionic strength of 0.1M  $NaClO_4$ .

## EXPERIMENTAL SECTION

**Materials and Solution:** For the present investigation, Isoniazid (ISO) and Imipramine Hydrochloride (IMP) used as ligand. The Isoniazid and Imipramine Hydrochloride drugs are obtained as a gift sample from a reputed pharmaceutical industry is soluble in double distilled  $CO_2$  free water. All the chemicals used were of high grade of purity (AR Grade). 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 titration<sup>7</sup>.

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  $\pm 0.1^\circ C$  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  $\pm 0.01$  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 (total volume 50 ml) and titrated pH metrically against standard NaOH solution at temperature 25°C, 35°C and 45°C.

(A) HClO<sub>4</sub> (2ml) + NaClO<sub>4</sub> (5ml) + C<sub>2</sub>H<sub>5</sub>OH (10ml)

(B) HClO<sub>4</sub> (2ml) + Drug (10ml) + NaClO<sub>4</sub> (5ml) + C<sub>2</sub>H<sub>5</sub>OH (10ml)

(C) HClO<sub>4</sub> (2ml) + Drug (10ml) + Metal solution (2ml) + NaClO<sub>4</sub> (5ml) + C<sub>2</sub>H<sub>5</sub>OH (10ml)

**Determination of the thermodynamic parameters:** The thermodynamic parameters such as Gibb's free energy change ( $\Delta G$ ), entropy change ( $\Delta S$ ) and enthalpy change ( $\Delta H$ ) for formation of complexes were determined. The change in Gibb's free energy ( $\Delta G$ ) of the ligands is calculated by using the following equation.

$$\Delta G = -2.303RT \log K$$

Where R (ideal gas constant) = 8.314 JK<sup>-1</sup>mol<sup>-1</sup>, K is the dissociation constant for the ligand or the stability constant of the complex and T is absolute temperature in Kelvin.

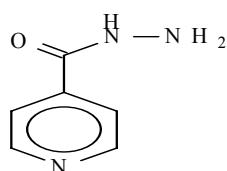
The change in enthalpy ( $\Delta H$ ) is calculated by plotting  $\log K$  vs  $1/T$

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

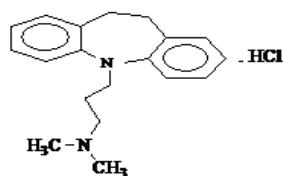
$$\text{Slope} = -\frac{\Delta H}{2.303R}$$

The evaluation of changes in entropy ( $\Delta S$ ) is done by the following equation.

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



**Figure 1:** Isoniazid (Molecular formula C<sub>6</sub>H<sub>7</sub>N<sub>3</sub>O)



**Figure 2:** Imipramine Hydrochloride (Molecular formula C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>Cl)

**Table-1:** Proton-ligand and metal-ligand stability constant of ISO drug.

Temp.	pK <sub>1</sub>	pK <sub>2</sub>	logK	Fe <sup>3+</sup>	Co <sup>2+</sup>	Ni <sup>2+</sup>	Cu <sup>2+</sup>	Zn <sup>2+</sup>	Cd <sup>2+</sup>
25 °C	3.19	10.66	logK <sub>1</sub>	12.14	5.415	5.595	9.011	5.891	5.273
			logK <sub>2</sub>	10.50	4.370	4.710	7.522	4.954	4.229
35 °C	3.11	10.39	logK <sub>1</sub>	11.80	5.150	5.330	8.739	5.626	4.999
			logK <sub>2</sub>	10.19	4.115	4.574	7.118	4.735	3.983
45 °C	2.80	10.21	logK <sub>1</sub>	11.37	4.963	5.154	8.524	5.448	4.773
			logK <sub>2</sub>	9.90	3.939	4.405	6.915	4.517	3.776

**Table-2:** Proton-ligand and metal-ligand stability constant of IMP drug.

Temp.	pKa	logK	Fe <sup>3+</sup>	Co <sup>2+</sup>	Ni <sup>2+</sup>	Cu <sup>2+</sup>	Zn <sup>2+</sup>	Cd <sup>2+</sup>
25 °C	9.062	logK <sub>1</sub>	9.608	3.363	3.422	5.529	4.289	5.213
		logK <sub>2</sub>	9.190	3.076	3.115	5.128	3.663	4.141
35 °C	8.967	logK <sub>1</sub>	9.514	3.292	3.346	5.426	4.197	3.329
		logK <sub>2</sub>	9.089	3.011	3.061	5.003	3.580	3.050
45 °C	8.854	logK <sub>1</sub>	9.399	3.205	3.258	5.320	4.088	3.241
		logK <sub>2</sub>	8.980	2.940	3.003	4.922	3.484	2.992

**Table-3:** Thermodynamic parameters of ISOcomplex 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 <sup>3+</sup>	ΔG <sub>1</sub> =69.27	69.59	69.23	ΔH <sub>1</sub> =60.81	ΔS <sub>1</sub> =0.028	0.028	0.027
	ΔG <sub>2</sub> =59.91	60.12	60.30	ΔH <sub>2</sub> =54.12	ΔS <sub>2</sub> =0.019	0.019	0.019
Co <sup>2+</sup>	ΔG <sub>1</sub> =30.90	30.37	30.22	ΔH <sub>1</sub> =41.02	ΔS <sub>1</sub> = - 0.034	- 0.035	- 0.034
	ΔG <sub>2</sub> =24.94	24.27	23.98	ΔH <sub>2</sub> =39.17	ΔS <sub>2</sub> = - 0.048	- 0.048	- 0.048
Ni <sup>2+</sup>	ΔG <sub>1</sub> =31.92	31.43	31.38	ΔH <sub>1</sub> =39.99	ΔS <sub>1</sub> = - 0.027	- 0.028	- 0.027
	ΔG <sub>2</sub> =26.87	26.98	26.82	ΔH <sub>2</sub> =27.66	ΔS <sub>2</sub> = - 0.003	- 0.002	- 0.026
Cu <sup>2+</sup>	ΔG <sub>1</sub> =51.41	51.54	51.90	ΔH <sub>1</sub> =44.21	ΔS <sub>1</sub> =0.024	0.024	0.024
	ΔG <sub>2</sub> =42.92	41.98	42.11	ΔH <sub>2</sub> =45.87	ΔS <sub>2</sub> = - 0.010	- 0.013	- 0.012
Zn <sup>2+</sup>	ΔG <sub>1</sub> =33.61	33.17	33.17	ΔH <sub>1</sub> =40.20	ΔS <sub>1</sub> = - 0.022	- 0.023	- 0.022
	ΔG <sub>2</sub> =28.27	27.93	27.50	ΔH <sub>2</sub> =39.65	ΔS <sub>2</sub> = - 0.038	- 0.038	- 0.038
Cd <sup>2+</sup>	ΔG <sub>1</sub> =30.10	29.48	29.06	ΔH <sub>1</sub> =45.40	ΔS <sub>1</sub> = - 0.051	- 0.052	- 0.051
	ΔG <sub>2</sub> =24.13	23.49	22.99	ΔH <sub>2</sub> =41.12	ΔS <sub>2</sub> = -0.057	-0.057	-0.057

**Table-4:** Thermodynamic parameters of IMPcomplexes 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 <sup>3+</sup>	ΔG <sub>1</sub> =54.82	56.10	57.23	ΔH <sub>1</sub> =18.97	ΔS <sub>1</sub> = 0.120	0.121	0.120
	ΔG <sub>2</sub> =52.43	53.60	54.68	ΔH <sub>2</sub> =18.99	ΔS <sub>2</sub> = 0.112	0.112	0.112
Co <sup>2+</sup>	ΔG <sub>1</sub> =19.19	19.41	19.51	ΔH <sub>1</sub> =14.38	ΔS <sub>1</sub> = 0.016	0.016	0.016
	ΔG <sub>2</sub> =17.55	17.76	17.90	ΔH <sub>2</sub> =12.35	ΔS <sub>2</sub> = 0.017	0.018	0.017
Ni <sup>2+</sup>	ΔG <sub>1</sub> =19.52	19.73	19.83	ΔH <sub>1</sub> =14.92	ΔS <sub>1</sub> = 0.015	0.016	0.015
	ΔG <sub>2</sub> =17.77	18.05	18.28	ΔH <sub>2</sub> =10.11	ΔS <sub>2</sub> = 0.026	0.026	0.025
Cu <sup>2+</sup>	ΔG <sub>1</sub> =31.54	32.00	32.39	ΔH <sub>1</sub> =18.89	ΔS <sub>1</sub> = 0.042	0.043	0.042
	ΔG <sub>2</sub> =29.26	29.51	29.97	ΔH <sub>2</sub> =18.74	ΔS <sub>2</sub> = 0.035	0.035	0.035
Zn <sup>2+</sup>	ΔG <sub>1</sub> =24.47	24.75	24.89	ΔH <sub>1</sub> =18.25	ΔS <sub>1</sub> = 0.021	0.021	0.020
	ΔG <sub>2</sub> =20.90	21.11	21.21	ΔH <sub>2</sub> =16.23	ΔS <sub>2</sub> = 0.016	0.016	0.016
Cd <sup>2+</sup>	ΔG <sub>1</sub> =29.74	19.63	19.73	ΔH <sub>1</sub> =15.02	ΔS <sub>1</sub> = 0.049	0.015	0.015
	ΔG <sub>2</sub> =23.62	17.98	18.22	ΔH <sub>2</sub> =10.08	ΔS <sub>2</sub> = 0.045	0.026	0.025

## EXPERIMENTAL RESULTS AND DISCUSSION

The results obtained are analyzed by the computer programme and the stability constant values are calculated. Isoniazid drug shows two pKa values due to two dissociable protons. The pK<sub>1</sub> (3.19) value can be assigned to the substituted amide (-CONHR) group which is near to the pK value of nicotinamide. The low value of pK<sub>1</sub> may be attributed to the weak basic nature of amide group. The pK<sub>2</sub> (10.66) value is assigned to the (R-NH-NH<sub>2</sub>) group which is attributed to the deprotonation of primary amino group. Imipramine hydrochloride drug shows only one pKa values. The protonation constant 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 ligand.<sup>8</sup>

The proton ligand stability constant pKa of ISO and IMP drug is determined by point wise calculation method as suggested by Irving and Rossotti. Metal ligand stability constant logK of transition metal ions with ISO and IMP 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  $\bar{n}_A$  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 decrease with increase in temperature, i.e. the acidity of the ligands increases.<sup>9</sup> 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.<sup>10</sup> These values have no sharp behavior with temperature showing the independent nature of the reactions with respect to temperature.<sup>11</sup> 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<sup>12</sup> 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.<sup>13</sup> The positive value of  $\Delta S$  is considered to be the principal driving force for the formation of respective complex species. More positive values of  $\Delta S$  may result due to an increase in the number of particles after the reaction and is responsible for giving more negative values of  $\Delta G$ .<sup>14</sup> According to Martell and Calvin<sup>15</sup> positive entropy effects was predicted towards an increase in the number of particles after the reaction. This positive  $\Delta S$  is responsible to give more negative  $\Delta G$ . The high positive values of  $\Delta S$  in some cases indicate that the entropy effect is predominant over enthalpy effect. The positive  $\Delta S$  values for some metal complexes indicated that the formation of these complexes was entropy favored, while negative  $\Delta S$  values for some metal complexes suggesting a highly solvated metal complexes.<sup>16</sup>

The order of stability constants for ISO complexes was as follows:  $\text{Fe}^{3+} > \text{Cu}^{2+} > \text{Zn}^{2+} > \text{Ni}^{2+} > \text{Co}^{2+} > \text{Cd}^{2+}$  and for IMP complexes was as follows:  $\text{Fe}^{3+} > \text{Cu}^{2+} > \text{Zn}^{2+} > \text{Ni}^{2+} > \text{Cd}^{2+} > \text{Co}^{2+}$

## CONCLUSION

The transition metal ion forms 1:1 and 1:2 complexes with ISO and IMP drug. The metal-ligand stability constant  $\log K$  decreases with an increase in temperature. The negative values of change in entropy ( $\Delta H$ ) for the complexation suggest that all the complication reactions are exothermic, favorable at lower temperature. The negative change in free energy ( $\Delta G$ ) values indicates that both dissociation of the ligand and the complexation process are spontaneous. The negative change in entropy ( $\Delta S$ ) values indicated a highly solvated metal complex while positive  $\Delta S$  values for some metal complexes indicated that the formation of these complexes was entropy favored.

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