



# Determination of the Formation Constant of Some Transition Metal Ion- histidine Complexes in Water and Water-dioxane and Evaluation of their Thermodynamic Parameters

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## Authors' contributions

This work was carried out in collaboration between both authors. Author EG designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author EJ managed to do the literature searches and the analyses. Both authors read and approved the final manuscript.

## Article Information

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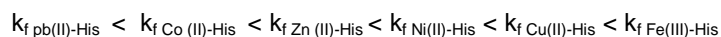
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## ABSTRACT

**Aims:** The formation constants of histidine complexes of Fe (III), Co (II), Ni (II), Cu(II), Zn (II) and Pb (II) at temperatures of 25, 30, 37, 45°C were determined potentiometrically, utilizing modified Bjerrum's method. Potentiometric titrations were carried out in 30% and 70% (v/v); 50% and 50% (v/v) water-dioxane mixtures. Ionic strength of medium was retained at 0.10 M by sodium nitrate. The first and second formation constants were obtained by plotting corrected pH versus concentration of standardized NaOH solution after each addition.

**Results:** The trend for increasing stability in both aqueous solution and in dioxane-water mixtures is as follows:



The effects of dioxane and temperature on the formation constants of histidine complexes were examined. Our findings showed that the formation constants of the complexes increased as the

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dioxane content was raised. The negative values of  $\Delta G^\circ$  are indication of the spontaneity of the reactions.  $\Delta H^\circ$  values are positive conveying the complex formation is an endothermic process.

**Conclusion:** The variations in log of formation constants versus  $1/T$  is linear evidencing that  $\Delta H^\circ_s$  are independent of temperature in temperature range of the study, and increase in entropy are cause of formation of these complexes.

*Keywords: Histidine; metal ion complex; formation constant; water-dioxane mixture.*

## 1. INTRODUCTION

The interaction between metal ions and amino acids which mimics metal-protein reactions is an interesting phenomenon. A disequilibrium in the concentration of metal ions in humans leads to degenerative diseases. Neurodegenerative illnesses which affect different regions of the brain are examples of these dysfunctional interactions [1]. Twenty natural amino acids comprise the building blocks of proteins. One way to understand how well these interactions could occur is evaluation of formation constants of these complexes. Among various methods for determining the formation constant, potentiometry has its own advantages. To evaluate the formation constants of complexes, Pathan [2] has reported an extensive theoretical study on potentiometric titration methods. Potentiometric titration of amino acids in the presents of metal ions is generally used as a method for measuring metal complex formation constants. This technique first described by Bjerrum [3] and has been investigated extensively by numerous researches [4-7]. The determination of formation constants of most amino acid complexes with metal ions have been carried out in aqueous media [8-18]. On the other hand temperature and solvent effects on the stability of the formed complexes have been examined by quite number of researchers [19-29].

A naturally occurring histidine (His) belongs to the group of aromatic and heterocyclic amino acids. It is one of the strongest metal coordinating ligand and plays an important role in the binding of metal ions with proteins [30]. L-Histidine has three potential metal-binding sites, namely the carboxylate oxygen ( $O_{\text{carboxyl}}$ ), the imidazole imido nitrogen ( $N_{\text{im}}$ ) and the amino-nitrogen ( $N_{\text{am}}$ ). The imidazole nitrogen of L-histidine residue often provides the primary means by which the metal ions bind to proteins. The major form of L-histidine at physiological pH is HL. It operates as a precursor of histamine hormone, and adjusts itself to the amounts of metal. L-Histidine is often found as a ligand in metalloenzymes too.

The present study focuses on the i) determination of formation constant of complexes of histidine with Fe (III), Co (II), Ni (II), Zn (II), Cu (II) and Pb (II) metal ions., ii) examination of the nature of the bonding between metal ions and the ligand in solvents mixture of different dielectric constants at different temperature and (iii) evaluation of thermodynamic parameters ( $\Delta G^\circ$ ,  $\Delta H^\circ$ , and  $\Delta S^\circ$ ).

## 2. EXPERIMENTAL

### 2.1 Materials and the Methods

Highly pure histidine, nitrate salt of respective metal ions as reagent grade, dioxane and HCl all were purchased from the Merck, Germany. All of the solutions were made by doubled distilled deionized water (DDW).

A Schott pH meter was standardized by using buffers at pH 7, 4, and 10. The pH values were precise to  $\pm 0.01$  pH units. A 25.00 mL solution mixture was made containing  $5.000 \times 10^{-3}$  M His,  $3.000 \times 10^{-3}$  M metal ion and  $1.690 \times 10^{-2}$  M  $\text{HClO}_4$  and sufficient amount of 0.10 M  $\text{NaNO}_3$  was added to adjust the ionic strength. The solution was poured into a double walled glass reactor, was thermostatted to desired temperatures of 25, 30, 37 and 45°C and then titrated with an accurately standardized NaOH solution. During the experiments the reactor was purged with  $\text{N}_2$ . The pH was corrected and recorded after each addition of titrant in increments of 0.05 mL.

### 2.2 Calibration of the Glass Electrode

Calibration of the combined glass electrode and calomel electrode was performed in both acidic and alkaline regions by titrating a solution of 0.01  $\text{molL}^{-1}$  hydrochloric acid with standard sodium hydroxide prior to each titration to read the hydrogen ion concentration directly. The emf values (E) depend on  $[\text{H}^+]$  according to  $E = E_0 + \text{slog} [\text{H}^+] + J_{\text{H}} [\text{H}^+] + J_{\text{OH}} [\text{OH}^-]$  where  $J_{\text{H}}$  and  $J_{\text{OH}}$  are fitting parameters in acidic and alkaline media in order to correct experimental errors.

These errors arise mainly from the liquid junction and the alkaline and acidic errors of the glass electrode [31].

### 2.3 A Method for the Determination of Formation Constant

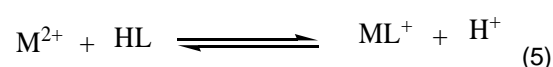
The Bjerrum's pH titration procedure assumes the presence of the reacting species  $H_2L^+$  as amino acid, HL as the monoprotonated amino acid, and  $L^-$  the anion of amino acid.



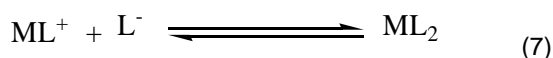
$$K_{a_1} = \frac{[HL][H^+]}{[H_2L^+]} \quad (2)$$



$$K_{a_2} = \frac{[L^-][H^+]}{[HL]} \quad (4)$$



$$K_{f1} = \frac{[ML^+][H^+]}{[M^{2+}][HL]} \quad (6)$$



$$K_{f2} = \frac{[ML_2]}{[ML^+][L^-]} \quad (8)$$

Here  $K_{f1}$  and  $K_{f2}$  are the first and the second stability constants of the complexes. We define  $\bar{n}$  as:

$$\bar{n} = \frac{\text{\# of bond ligands}}{\text{total metal ion concentration}} = \frac{L_{\text{bound}}}{C_M} = \frac{L_{\text{total}} - L_{\text{free}}}{C_M} \quad (9)$$

The concentration of free ligand is the sum of concentration of contained ligand species at different form, i.e.

$$L_{\text{free}} = [H_2L^+] + [HL] + [L^-] \quad (10)$$

The bound ligand concentration ( $L_{\text{bound}}$ ) could then be estimated as:

$$L_{\text{bound}} = L_{\text{total}} - L_{\text{free}} \quad (11)$$

After rearrangement and substitutions we have:

$$\bar{n} = \frac{T_{H_2L^+} - [H_2L^+] - [HL] - [L^-]}{T_{M^{2+}}} \quad (12)$$

$$\text{Then: } \bar{n} = \frac{[ML^+] + 2[ML_2]}{[M^{2+}] + [ML^+] + [ML_2]} \quad (13)$$

According to mass balance relation we have:

$$T_M = [M^{2+}] + [ML^+] + [ML_2] \quad (14)$$

$$T_{HL} = [HL] + [L^-] + [ML^+] + 2[ML_2] \quad (15)$$

$$[ClO_4^-] = T_{HClO_4} + 2 T_M \quad (16)$$

$$[ML^+] + 2[ML_2] = [Na^+] - T_{HClO_4} + [H^+] \quad (17)$$

$$\bar{n} = \frac{[Na^+] - [HClO_4] + [H^+]}{T_M} \quad (18)$$

$$[HL] = \frac{K_a(T_{H_2L^+} - \bar{n}T_M)}{K_a + [H^+]} \quad (19)$$

From plot of  $p_{HL}$  versus  $\bar{n}$  the stability constants could be calculated.

$$K_{f1} = \frac{1}{[HL]_{\bar{n}=\frac{1}{2}}} \quad (20)$$

$$K_{f2} = \frac{1}{[HL]_{\bar{n}=\frac{3}{2}}} \quad (21)$$

All our calculations in this work were executed by GRCbeta computer-program developed in our lab. The software inputs are a) initial volume of solution containing the amino acid, metal ion, and perchloric acid, b) the concentration of perchloric acid, c) the concentration of sodium hydroxide, d) the concentration of amino acid, and e)  $pK_{a1}$  and  $pK_{a2}$  of the amino acid in the specified medium and at desired ionic strength which we found them in literature [32]. After

insertion of the pertinent values, the software plots calculated pH (corrected pH) of the titrand solution versus the concentration of added standardized NaOH, plus drawing two curves, one for a  $\bar{n}=0.5$  and the other for  $\bar{n}=1.5$ . The intersection of the potentiometric titration curve with these two curves produces two points (Fig. 1) whose corresponding pHs will be used to evaluate the respective formation constants of the metallic ion-amino acid complexes. Additionally the software is capable of plotting first and second derivative of d-pH versus  $dV_{\text{NaOH}}$  to clarify the end points. For each potentiometric titration approximately 5-7 mL of standardized sodium hydroxide was used. Thermodynamic study involves evaluating  $\Delta G^\circ$ ,  $\Delta H^\circ$ , and  $\Delta S^\circ$  values. The Gibb's free energy change,  $\Delta G^\circ$ , can be calculated from the equation below:

$$\Delta G^\circ = -RT \ln K_f \quad (22)$$

$$\ln K_f = \frac{-\Delta G^\circ}{RT} \quad (23)$$

By taking the derivative with respect to  $1/T$  from both side of equation (23) we have:

$$\frac{d \ln K_f}{d \frac{1}{T}} = -\frac{1}{R} \left\{ \frac{d}{d \frac{1}{T}} \frac{\Delta G^\circ}{T} \right\} \quad (24)$$

$$\frac{d \ln K_f}{d \frac{1}{T}} = -\frac{1}{R} \left\{ \Delta G^\circ + \frac{d\Delta G^\circ}{T d \frac{1}{T}} \right\} \quad (25)$$

$$\frac{d \ln K_f}{d \frac{1}{T}} = -\frac{1}{R} \left\{ \Delta H^\circ - T\Delta S^\circ + T\Delta S^\circ \right\} = -\frac{\Delta H^\circ}{R} \quad (26)$$

So:

$$\frac{d \log K_f}{d \frac{1}{T}} = -\frac{\Delta H^\circ}{2.303R} \quad (27)$$

Regarding equation (27), the plot of  $\log K_f$  versus  $1/T$  produces straight line with slop equals:

$$\text{slope} = \frac{-\Delta H^\circ}{2.303R} \quad (28)$$

Using Equation (28) enables us to calculate Enthalpy change. For calculating  $\Delta S^\circ$  we have:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (29)$$

Knowing Gibbs free energy and enthalpy changes we can evaluate change in entropy.

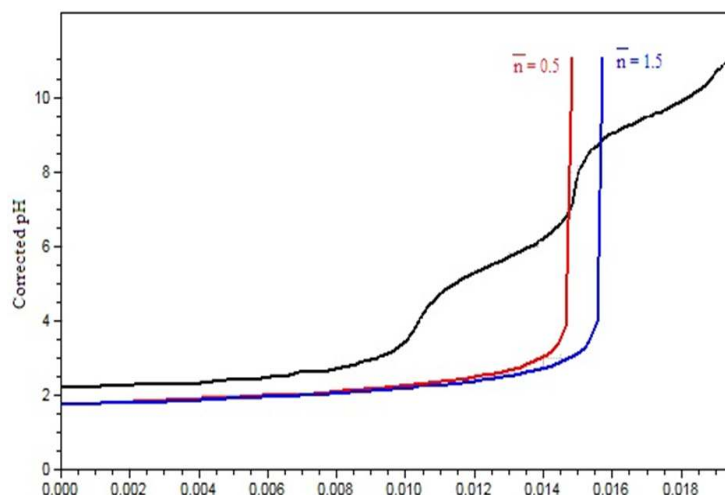


Fig. 1. Plot of corrected pH versus the concentration of added standardized NaOH solution for Zn (II)-His complex in water at 25°C

### 3. RESULTS AND DISCUSSION

Fig. 1 illustrates a potentiometric titration curve for Zn (II)-His complex in water at 25°C. His structure as a potent tridentate ligand has been shown on Fig. 2. The formation constant values of pertinent metal ion-His complexes in water at four different temperatures were exhibited on Table 1. The results indicate that the order of increasing stability is as follows:

$$k_f \text{ Pb(II)-His} < k_f \text{ Co(II)-His} < k_f \text{ Zn(II)-His} < k_f \text{ Ni(II)-His} < k_f \text{ Cu(II)-His} < k_f \text{ Fe(III)-His}$$

In general, it was found that  $K_{f2} < K_{f1}$ . This means that the first formation complex process is stronger than the second process (i.e. attraction between  $M^{2+}$  and  $L^-$  is stronger than  $ML^+$  and  $L^-$ ). Here electrostatic repulsion and steric hindrance between ligands are important factors for the decrease in the stepwise formation constant value of the complex. Table 2 demonstrates the formation constant values of the respective complexes in 50% and 50% (v/v) water-dioxane mixture at temperatures of 25-45°C. Fig. 3 confirms the presence of two nitrogen donor atoms in the copper coordination environment in a square planar arrangement.

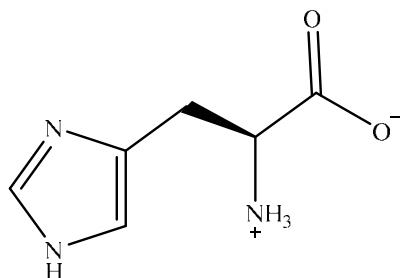


Fig. 2. The structure of histidine

The variation of  $\text{Log } K_{f2}$  versus  $1/T$  for complex of Pb (II)-histidine has been shown in Fig 4. In the similar manner we can plot  $\text{Log } K_{f1}$  and  $\text{Log } K_{f2}$  versus  $1/T$  for the rest of complexes and acquire their  $\Delta H_1$  and  $\Delta H_2$ . Due to systematic approach to examine the formation constants, also it means that for any complex, we are able to evaluate its formation constant at any temperature.

The data in Tables 1 and 2 illustrate that the complexation processes in water and water-dioxane mixtures are endothermic ( $\Delta H > 0$ ) and the temperature increase affects the complexation. Because  $M^{+2}$  exert solvation effect on octahedral structure and ions  $L^-$  and  $M^{+2}$  with

opposite charge could break it, causing  $\Delta H$  and  $\Delta S$  to become positive.

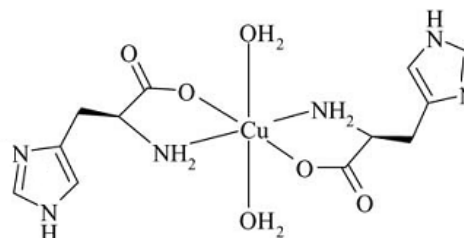


Fig. 3. Histidine complexation with  $\text{Cu}^{+2}$  [34]

Table 3 represents  $\Delta G^\circ_1$  values for the respective His complexes at four different temperatures in water. Table 4 Shows  $\Delta G^\circ_2$  values in different solvents at 25°C. The high negative  $\Delta G^\circ$  values indicate that these complexation processes are spontaneous, thus  $\Delta G^\circ$  values were increased by enhancing the temperature. The results indicate that  $\Delta G^\circ_2 < \Delta G^\circ_1$  and the order of increasing  $-\Delta G^\circ$  is as follows:

$$-\Delta G^\circ_{\text{Pb(II)-His}} < -\Delta G^\circ_{\text{Co(II)-His}} < -\Delta G^\circ_{\text{Zn(II)-His}} < -\Delta G^\circ_{\text{Ni(II)-His}} < -\Delta G^\circ_{\text{Cu(II)-His}} < -\Delta G^\circ_{\text{Fe(III)-His}}$$

Table 5 exhibits  $\Delta H^\circ_1$ ,  $\Delta H^\circ_2$  and  $\Delta S^\circ_2$  all possessing positive values, for those complexes at 25-45°C. Although the process of histidine complexes formation with metal ions have an endothermic nature as a result of the positive  $\Delta H^\circ_1$  and  $\Delta H^\circ_2$  values, we can conclude that the second formation step of complex is highly spontaneous compared to the first formation step.

Regarding using dioxane as a co-solvent, 1,4-dioxane–water mixture is a well-defined solvent. Changes in formation constants upon addition of 1, 4-dioxane to aqueous solution is due to increase in ion-ion interactions resulting from both the decreasing dielectric constant and the change in solvent-ion and solvent-solvent interactions. As the dielectric constant decreases, the ion interaction involving the proton and anionic oxygen on the amino acid decreases to a greater extent than the ion dipole interaction between the proton and the solvent molecules. Co-solvent influences the protonation-deprotonation equilibria in solution by changing the dielectric constant of the medium, which varies the relative contributions of electrostatic and non-electrostatic interactions.

The change in dielectric constant varies the relative contribution of electrostatic and non-electrostatic interactions which in turn vary the magnitudes of formation constants. We found that  $\Delta S^\circ$  values were positive, indicating that these processes could be considered as entropy-favored reactions. This reflects its more spontaneity which can be characterized by its negative  $\Delta G^\circ$  values (i.e., endothermic nature). Therefore, the high negative  $\Delta G^\circ$  values are attributed to the higher contribution of the  $\Delta H^\circ$  term.

We noted that the spontaneity and stability of the complex formations were increased in the following order: Cu (II) > Ni (II) > Zn (II) > Co (II) > Pb (II). This is in a good agreement with the

Irving-Williams order [33]. A simple relation exists between the stability of the formed complexes and the radius,  $r$ , of the unhydrated ion and its valence,  $Z$ . Therefore, the lower stability of the Pb (II) complex with respect to the other studied metal ions complexes is attributed to its larger radius. It can be concluded that Cu (II) complexes are more stable than the other metal ion complexes as a result of the larger ratio of (valance/ radius) and the Jahn-Teller effect. In Fig. 5a plot of  $\log K_{f2}$  of His complexes versus atomic number of the respective metal ions was shown. The trend is consistent with Irving-Williams series except Fe (III) and Zn (II). Table 6 compares our obtained formation constants with literature showing a good agreements.

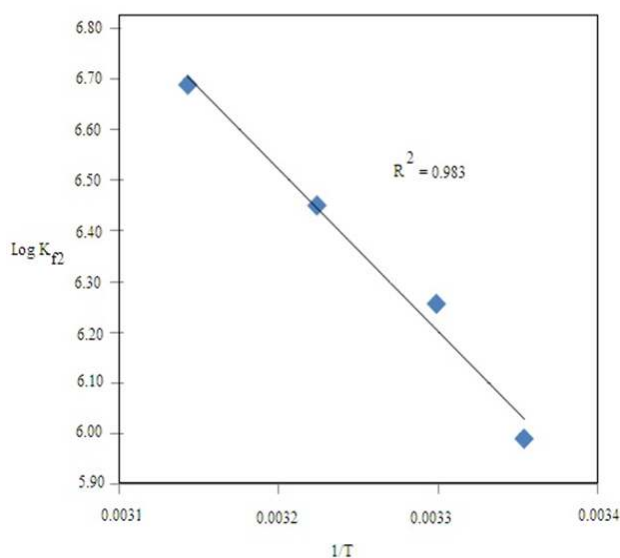


Fig. 4. A Plot of  $\text{Log } K_{f2}$  vs.  $\frac{1}{T}$  for Pb(II)-His complex

Table 1. The Log of the formation constants values for the respective metal- ion His complexes in aqueous solution at different temperatures

Complex	Stability constants	25°C	30°C	37°C	45°C
Fe(III)-His	Log $k_1$	9.91	10.45	10.72	10.93
	Log $k_2$	8.49	9.16	9.22	9.75
Co(II)- His	Log $k_1$	7.15	7.33	7.51	7.91
	Log $k_2$	5.08	5.19	5.36	5.68
Ni(II)- His	Log $k_1$	8.08	8.13	8.21	8.30
	Log $k_2$	6.35	6.54	6.72	7.07
Cu(II)- His	Log $k_1$	8.35	8.43	8.56	8.87
	Log $k_2$	7.49	7.60	7.64	7.73
Zn(II)- His	Log $k_1$	7.36	7.49	7.52	7.65
	Log $k_2$	7.08	7.08	6.32	6.57
Pb(II)- His	Log $k_1$	5.99	6.26	6.45	6.69
	Log $k_2$	3.54	3.73	3.95	4.26

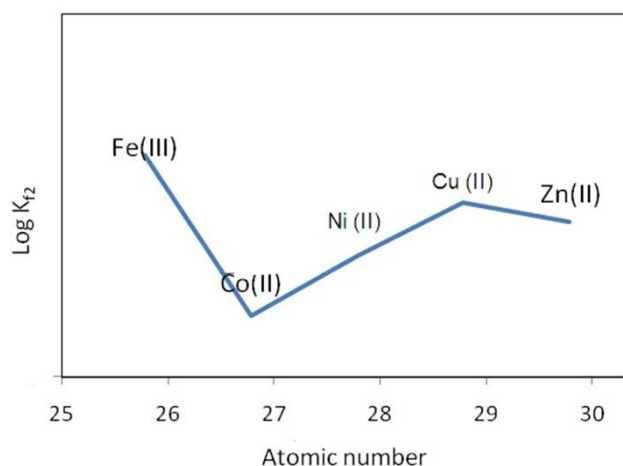


Fig. 5. Plot of LogK<sub>f2</sub> (second formation constant) of His complexes versus atomic number of their respective metal ions

Table 2. The Log of the formation constants values for the pertinent metal ion His complexes in 50% (v/v) and 50% (v/v) water-dioxane mixture at different temperatures

Complex	Stability constants	25°C	30°C	37°C	45°C
Fe(III)-His	Log k <sub>1</sub>	10.75	11.21	11.37	11.90
	Log k <sub>2</sub>	9.77	10.17	10.39	10.54
Co(II)- His	Log k <sub>1</sub>	8.98	9.48	9.56	9.60
	Log k <sub>2</sub>	7.99	8.29	8.52	8.63
Ni(II)- His	Log k <sub>1</sub>	9.01	9.64	9.96	10.05
	Log k <sub>2</sub>	8.17	8.31	8.60	8.75
Cu(II)- His	Log k <sub>1</sub>	9.77	10.52	10.75	10.99
	Log k <sub>2</sub>	9.31	9.76	9.86	9.95
Zn(II)- His	Log k <sub>1</sub>	7.84	8.49	8.85	9.39
	Log k <sub>2</sub>	5.58	6.02	6.33	7.05
Pb(II)- His	Log k <sub>1</sub>	7.45	7.50	7.78	7.82
	Log k <sub>2</sub>	4.04	4.20	4.35	4.59

Table 3. -ΔG<sub>1</sub> values for respective His complexes in water at temperatures of 25-45°C

Complexes	-ΔG <sub>1</sub> (KJ.mol <sup>-1</sup> )			
	25°C	30°C	37°C	45°C
Fe (III)-His	56.55	60.66	63.66	66.8
Co (II)-His	40.85	42.53	44.64	48.18
Ni (II)-His	46.10	47.18	48.73	50.59
Cu (II)-His	47.64	48.95	50.84	54.12
Zn (II)-His	42.04	34.92	44.66	46.65
Pb (II)-His	34.19	36.31	38.30	40.74

Table 4. ΔG<sub>2</sub> values for respective His complexes in different solvents at 25°C

Complex	-ΔG <sub>2</sub> values in KJmol <sup>-1</sup>		
	Water	30%and- 70%(v/v)water-dioxane	50% and-50%(v/v)water-dioxane
Fe(III)-His	48.49	51.42	55.77
Co (II)-His	29.03	46.14	45.63
Ni (II)-His	36.27	46.80	51.41
Cu (II)-His	42.78	52.99	61.37
Zn (II)-His	32.12	27.38	44.76
Pb (II)-His	20.18	29.82	25.47

**Table 5. Enthalpy and entropy changes values for respective His complexes in water at four different temperatures**

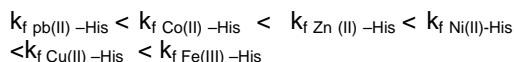
Complexes	$\Delta H_1$ (KJ.mol <sup>-1</sup> )	$\Delta H_2$ (KJ.mol <sup>-1</sup> )	$\Delta S_2$ (J.k <sup>-1</sup> mol <sup>-1</sup> )T (°C)			
			25	30	37	45
Fe (III)-His	87.98	101.36	502.6	503.4	505.3	509.7
Co (II)-His	66.88	53.50	275.2	275.9	276.8	276.9
Ni (II)-His	20.77	63.66	325.4	334.0	335.9	335.6
Cu (II)-His	53.52	66.34	356.6	360.2	364.5	366.0
Zn (II)-His	24.26	154.6	611.9	617.9	619.6	654.3
Pb (II)-His	61.23	65.00	285.2	285.7	285.8	285.9

**Table 6. Comparison between our obtained formation constants of His complexes in water at 25°C with the literature, in parenthesis [35]**

	Co (II)-His	Ni (II)-His	Cu (II)-His	Zn (II)-His	Pb (II)-His
log K <sub>f1</sub>	7.155 (6.860)	8.076 (8.670)	8.346 (10.16)	7.365 (6.510)	5.990 (5.950)
log K <sub>f2</sub>	5.085 (5.390)	6.354 (6.830)	7.494 (7.950)	7.084 (5.500)	3.536 (4.150)

#### 4. CONCLUSION

In this study a systematic approach was made to examine the interaction of some transition metals ions with histidine in water and water dioxane mixtures at different temperatures. The trend for increase in stability of the respective complexes both in water and water-dioxane mixture is as follows:



Our results shows that as the temperature rises, or the percentage of dioxane in the solvent mixture augments, formation constant increases, The Gibbs free energy change is negative correlating to the spontaneity of the complex formation.  $\Delta H^\circ$  values are positive conveying the endothermicity of the reactions. The variations in log of formation constants versus 1/T is linear evidencing that  $\Delta H^\circ_s$  are independent of temperature in temperature range of the study, and increase in entropy are cause of formation of these complexes.

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#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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