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Comparative chemical transfer Gibbs free energy related to solvation of amino acid, L-Histidine in aqueous mixtures of *N*, *N*-Dimethylformamide and Protic Glycerol at 298.15 K

S. Roy[1], K. Mahali[2] and B. K. Dolui[*3]

[1]*Department of Chemistry, Shibpur Dinobundhoo Institution (college), Howrah-2, W.B, India.*
[2]*Department of Chemistry, University of Kalyani, Nadia, W.B, India-741235.*
[3*]*Department of Chemistry, Visva-Bharati, Santiniketan, W.B, India-731235.*

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Abstract

In this article we are reporting the solubilities of L-histidine in aqueous dipolar aprotic *N*, *N*-dimethylformamide at 298.15 K using 'isothermal saturation' method. The standard transfer Gibbs energy, $\Delta G_t^0(i)$ and cavity forming enthalpy of transfer, $\Delta H_{t,cav}^0(i)$ for the species (i) i.e. L-histidine, have been evaluated. Here also detail theoretical calculations of cavity forming transfer Gibbs free energy, $\Delta G_{t,cav}^0(i)$, dipole-dipole interaction effects, $\Delta G_{t,d-d}^0(i)$ have been carried out taking the literature values. The chemical effects of the transfer Gibbs energies of L-histidine, $\Delta G_{t,ch}^0(i)$ have been obtained by subtracting the cavity effects, $\Delta G_{t,cav}^0(i)$, (estimated by the scaled particle theory) and dipole-dipole interaction effects, $\Delta G_{t,d-d}^0(i)$ (calculated by the Keesom orientation expression) from the $\Delta G_t^0(i)$. In this article a comparative study between aqueous protic and dipolar aprotic solvent, i.e. water-glycerol and water-DMF mixed solvent systems respectively, is presented to discuss about their solvating characteristics as well as stabilizing capacity for the amino acid, L-histidine as well as biomolecules.

Keywords: L-histidine, *N*, *N*-dimethylformamide, hydrophilic hydration, acidity-basicity, transfer energetics.

Contents

***Corresponding author**
B. K. Dolui
Department of Chemistry
Visva-Bharati, Santiniketan,
W.B, India-731235.
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1. Introduction

Amino acids are the biomolecules. These are building block of proteins. The amino acids are not only important in protein formation, but also important due to their applications in chemical, pharmaceutical, food and cosmetics industries. The solubility studies of these biomolecules in different solvents systems, such as aquo-organic, non-aqueous and aqueous electrolyte solutions are very important. This type of studies may help in the understanding of the solubility behaviour of other biomolecules. L-histidine ($C_6H_9N_3O_2$) is an aromatic amino acid which is an essential in human body [1] and other mammals. It is a structural unit of many proteins. However its biochemical behavior and solvation thermodynamics in complex aqueous mixtures in living systems are still incompletely revealed. On the other hand extraction of proteins from the natural sources and the denaturation process is also essential for dissolution and purification of protein.

That is why for better understanding of the effect of complex aqueous mixtures on the thermodynamic properties of amino acids are of vital importance because these studies give valuable information regarding the thermodynamic properties such as solute-solvent, solvent-solvent, acid-base and hydrophilic / hydrophobic interactions in different solvent systems. This type of study also gives the valuable knowledge about the protein folding and unfolding processes [2, 3]. Therefore an attempt is made in this article to know about the solvation thermodynamics of L-histidine in aqueous mixture of dipolar aprotic *N, N*-dimethylformamide at 298.15 K. The measurement of solubility and evaluated thermodynamic parameters of L-histidine in such aquo-organic solvent systems will be helpful to enrich chemical, biochemical and pharmaceutical and industrial sciences in future.

2. Experimental

2.1 Chemicals and purifications

L-Histidine [> 95 %, Sigma Aldrich] was used after drying in vacuum desiccators for 7 days. *N, N*-dimethyl formamide (DMF) (LR, BDH) was purified [8] first by distilling under reduced pressure in N_2 atmosphere and preserving the distillate over dry K_2CO_3 (E Merck) for a week. The solvent was then decanted off and treated with pure P_2O_5 (Riedel) and finally distilled under reduced pressure. The water content of the solvent was determined by Karl-Fisher titration and found to be less than 0.02-mol·dm^{-3}. Triple distilled water was used for the whole experiment.

2.2 Experimental method

N, N-dimethylformamide aqueous solutions were prepared by weight from triply distilled water. Solubility measurements were performed with isothermal saturation method. Mixture of the amino acid and the solvent were placed in the 50 mL glass hermetic cell and stirred with a magnetic stirrer usually for 12 h. The temperature inside the cell was maintained equal to 298.15 K with a low-cum-high temperature thermostat which is capable of registering temperatures having an accuracy of ±0.02 K. thermostat. Four or five milliliters of the liquid content was quickly taken up with a thermostatted syringe, filtered at 298.15 K on a glass filter and weighed in a 50 mL glass hermetic cell by a Mettler balance having a precision of ±0.001 mg and highly diluted by an appropriate solvent for a spectrophotometric control of the solute content in a saturated solution. The absorption band at 210 nm was chosen for all water-*N,N*-dimethylformamide mol fractions studied. Spectrophotometric measurements were repeated with 5-7 times, and the mean value of the absorbance coefficient was selected to compute solubility values.

3. Results and Discussion

Solvent parameters of *N, N*-dimethylformamide-water solvent system are listed in Table 1. The solubilities (S) of L-histidine (on molal scale) are listed in Table 2. The molal solubilities in the aqueous-DMF as well as in water are used to compute standard free energies of transfer $\Delta G_t^0(m)$ using the equation 1 [7].

$$\Delta G_t^0(m) = RT \ln(S_R / S_s) \quad (1)$$

Where the subscripts R and s are for water and aqueous-DMF respectively. It is assumed that the ratio of activity coefficients of the amino acid in these solvents mixtures is unity. Standard transfer free energies in mole fraction scale, $\Delta G_t^{0,c}(i)$ is calculated by the equation 2.

$$\Delta G_t^{0,c}(i) = \Delta G_t^0(m) - RT \ln(M_s / M_R) \quad (2)$$

where M_s and M_R refer to the molar mass of cosolvent (DMF) and reference solvent (water) respectively. $\Delta G_t^0(i)$ are listed in Table 2. Now $\Delta G_t^0(i)$ may be ascribed as the sum of the following terms (assuming dipole-induced dipole term to be negligible) [8],

$$\Delta G_t^0(i) = \Delta G_{t,cav}^0(i) + \Delta G_{t,d-d}^0(i) + \Delta G_{t,ch}^0(i) \quad (3)$$

Where $\Delta G^0_{t,cav}(i)$ stands for the transfer free energy contribution of the cavity effect involving the creation of cavities for the species in water and aquo-organic solvents and $\Delta G^0_{t,d-d}(i)$ stands for the dipole-dipole interaction effect involving interaction between dipolar zwitter-ionic amino acid and solvent molecules. While $\Delta G^0_{t,ch}(i)$ includes all other effects such as those arising from acid-base or short range dispersion interaction, hydrophilic (H_lH) or hydrophobic (H_bH) hydration and structural effects. $\Delta G^0_{t,cav}(i)$ values were computed by the use of scaled particle theory [9, 10] assuming the solutes and solvent molecules as equivalent hard sphere models as dictated by their respective diameters. (vide Table 2)
The equations [7, 17] used for cavity calculation are as follows:

$$\Delta G^0_{cav}(i) = G_C + RT\ln(RT/V_S) \quad \text{Where} \tag{4}$$

$$G_C = RT[-\ln(1-Z) + \{3X/(1-Z)\}\pm_x + \{3Y/(1-Z)\}\pm_x^2 + \{9X^2/4(1-Z)^2\}\pm_x^2]$$
$$Z = ®N_A/6V_s(z_R\pm_R^3 + z_s\pm_s^3)$$
$$X = ®N_A/6V_s(z_R\pm_R^2 + z_s\pm_s^2)$$
$$Y = ®N_A/6V_s(z_R\pm_R + z_s\pm_s)$$
$$V_s = \mathrm{M}_s/d_s$$

In this expression N_A is Avogadro's number, z_R and z_s are the mole fraction of water and DMF respectively. '$\pm_x$', '$\pm_R$' and '$\pm_s$' are the hard sphere diameters of amino acid L-histidine, water and hard sphere diameter of co-solvent respectively. 'M_s' for molar mass of the solvent and 'd_s' stands for molar density of the solvent, glycerol. Finally $\Delta G^0_{t,cav}(i)$ represents the difference ${}_s\Delta G_t(cav) - {}_R\Delta G_t(cav) = ({}_sG_c - {}_RG_c) + RT\ln(V_R/V_s)$.

For the calculation of $\Delta G^0_{t,cav}(i)$ the required solvent parameters are taken from Table 1.

Here $\Delta G^0_{t,d-d}(i)$ was calculated as per equation 5.

$$\Delta G^0_{t,d-d}(i) = ({}_s\Delta G^0_{d-d}(i) - {}_R\Delta G^0_{d-d}(i)) \tag{5}$$

by means of Keesom orientation expression [11]. And for ${}_s\Delta G^0_{d-d}(i)$ in a solvent, ''s', is given as follows:

$$_s\Delta G^0_{d-d}(i) = -(8\Pi/9)N^2\ll_s^2\ll_x^2\pm_{s-x}^{-3}(kT)^{-1}V_x^{-1} = A/TV_s;$$
$$where A = -(8\Pi/9)N^2\ll_s^2\ll_x^2\pm_{s-x}^{-3}(k)^{-1} \tag{6}$$
$$and$$
$$V_s = M_s/d_s$$

Here N stands for Avogadro's number, $\ll_s$ and $\ll_x$ are the dipole moment of solvent and amino acid molecules, respectively, (Table 2.), $\pm_{s-x}$ is the distance at which the attractive and repulsive interactions between the solvent and solute molecules are equal and is generally equal to $½(\pm_s + \pm_x)$, where, $\pm_s$ and $\pm_x$ are the hard sphere diameter of solvent and solute molecules respectively. And $\ll_s$ and $\pm_s$ for such mixed binary solvent system are computed with the variation of mole fraction of the co-solvent as done by Graziano [12]. Following Kim *et al*. [13] and Marcus [11] in order to get $\Delta G^0_{t,d-d}(i)$ term on mole fraction scale the quantity was again multiplied by the term X_{s1}, [18],

where, $X_{s1} = X_s(\ll_s/\pm_s^3)/(\ll_R/\pm_R^3)$ (7)

this is the real mole fraction contribution due to dipole-dipole interaction [11].

Now, the values $\Delta G^0_{t,cav}(i)$ and $\Delta G^0_{t,d-d}(i)$ are subtracted from $\Delta G^0_t(i)$ to get $\Delta G^0_{t,ch}(i)$ of amino acid and all these values are shown in Table 2 . The values of $\Delta G^0_t(i)$ and $\Delta G^0_{t,ch}(i)$ are illustrated in Fig. 1 and 4.

The enthalpy change due cavity forming interaction in water to aqueous *N*, *N*-dimethylformamide mixtures is measured by the equation-

$$\Delta H^0_{t,cav}(i) = {}_s\Delta H^0_{cav}(i) - {}_R\Delta H^0_{cav}(i) \quad (8)$$

$$\Delta H^0_{cav}(i) = (\mathrm{A}+\mathrm{H}+\mathrm{K}+\mathrm{E})\times \mathrm{B} \quad (9)$$

where $\mathrm{A} = (\Pi N_A / 6V_s)\times(Z_R \pm_R{}^3 + Z_S \pm_S{}^3)$; $B = \pm_S RT^2/1-A$;

$H = \pm_x \times 3Y/1-A$; $K = \pm_x \times 3X/1-A$; $E = 9\pm_x{}^2 \times X^2/(1-A)^2$;

$X = (\Pi N_A / 6V_s)\times(Z_R \pm_R{}^2 + Z_S \pm_S{}^2)$; and $Y = (\Pi N_A / 6V_s)\times(Z_R \pm_R + Z_S \pm_S)$; $\Pi = 22/7$

The variations of $\Delta H^0_{t,cav}(i)$ values in kJ·mol^{-1} are shown in Figure 5.

Table 1. Values of solvent parameters (Mole fraction of DMF (zs), water ((zR), mean mol. weight (MS), density (ds), Molar volume (Vs), solvent diameter $\pm_s$, $\pm_{s-x}$, «$_s$ and isothermal expansibility constant (α) and Dielectric constant (D) of the H2O+ DMF system at 298.15 K

Mole fraction of DMF (z_s)	Mole fraction of water (z_R)	Molar mass (M_S)	10^3 d$_s$ (kg m^{-3})	Molar Volume (V_s)	$\pm_s$ (nm)	σ_{s-x} (nm)	Dipole Moment of cosolvent ($\ll_s$)	Dielectric constant (D)	α (x 10^{-3})
0.00	1.00	18.015	0.99708	18.068	0.274	0.401	1.831	78.40	0.257*
0.01	0.99	18.566	0.99655	18.630	0.276	0.402	1.851	77.98	0.265
0.02	0.98	19.118	0.99602	19.194	0.278	0.403	1.871	77.57	0.272
0.03	0.97	19.669	0.99549	19.758	0.281	0.405	1.891	77.15	0.279
0.05	0.95	20.771	0.99443	20.887	0.285	0.407	1.930	76.32	0.295
0.07	0.93	21.874	0.99336	22.020	0.289	0.409	1.970	75.48	0.309
0.09	0.91	22.976	0.99230	23.154	0.294	0.411	2.010	74.65	0.325
0.11	0.89	24.079	0.99124	24.292	0.299	0.414	2.049	73.81	0.339

Table 2. Gibbs energies of transfer i.e. , and of L-histidine from water to DMF in different compositions at 298.15 K (on mole fraction scale in kJ•mol–1).

Mole Fraction of DMF	Solubility (mol·kg^{-1})	$\Delta G^0_t(i)$ (kJ·mol^{-1})	$\Delta G^0_{t,cav}(i)$ (kJ·mol^{-1})	$\Delta G^0_{t,dd}(i)$ (kJ·mol^{-1})	$\Delta G^0_{t,ch}(i)$ (kJ·mol^{-1})	$\Delta H^0_{t,cav}(i)$ (kJ·mol^{-1})$^-$
0.00	4.30±0.02[a] (4.34©)[b]	0	0	0	0	0
0.01	3.95±0.01 [a]	0.136	-0.270	-0.011	0.417	-0.152
0.02	3.41±0.02 [a]	0.428	-0.526	-0.044	0.998	-0.302
0.03	3.03±0.01 [a]	0.649	-0.767	-0.078	1.494	-0.433
0.05	2.60±0.02 [a]	0.894	-1.220	-0.227	2.341	-0.632
0.07	1.93±0.01 [a]	1.505	-1.620	-0.451	3.576	-0.814
0.09	1.63±0.01 [a]	1.802	-1.990	-0.736	4.528	-0.936
0.11	1.28±0.01 [a]	2.285	-2.340	-1.010	5.635	-1.049

The required diameter and other solvent parameters of DMF and its aqueous mixtures are taken from Ref. [8, 11] The required diameter of histidine, as given in Ref [14]. Dipole-moment values of histidine and DMF are 10.68 D and 3.82 D and taken from reference [15], [8] respectively.. [a] The errors are given as standard deviation of the average in a series of 5-7 measurements. [b] Reference value taken from literature.

Figure 1 represent the variation of $\Delta G_t^0(i)$ histidine in kJ·mol^{-1} with mole fraction of *N*, *N*-dimethylformamide. It represents that of $\Delta G_t^0(i)$ value of histidine become increasingly positive. Positive value of this factor signifies the instability of L-histidine in water-DMF system

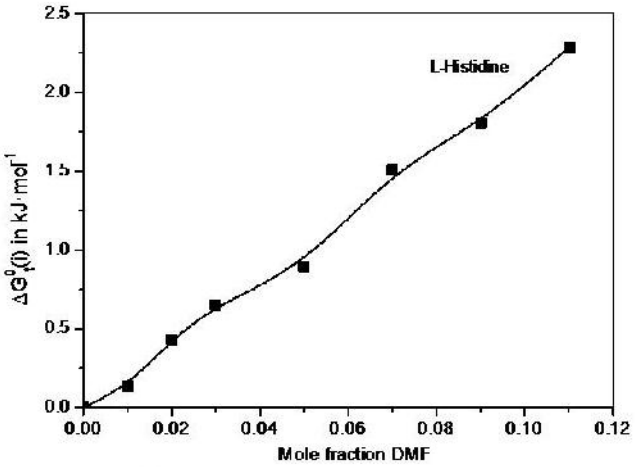

Fig 1. Variation of $\Delta G^0_t(i)$ in kJ·mol^{-1} of L-Histidine in aqueous mixtures of DMF at 298.15K

On the other hand unlike $\Delta G_t^0(i)$, $\Delta G_{t,cav}^0(i)$ value (theoretically calculated) for this amino acid become progressively negative both the solvents i.e. water + glycerol and water + DMF (Fig. 2), therefore stability of histidine is due to creation of cavity after transforming from water to cosolvents is favorable. More negative values of $\Delta G_{t,cav}^0(i)$ indicates that it is easy to create a cavity in water + DMF than water + glycerol. Here $\Delta G_{t,cav}^0(i)$ values are guided by hard sphere diameter of solute and solvent and density of the solvent mixtures. The hard-sphere diameter and number density of DMF is greater than that of glycerol and during transfer to aqueous DMF these parameters leads to favorable $\Delta G_{t,cav}^0(i)$ value.

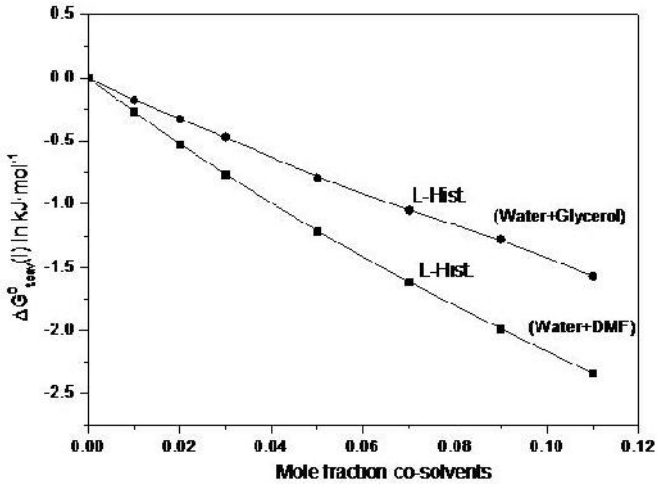

Fig 2. Variation of $G^0_{t,cav}(i)$ in kJ·mol^{-1} of L-histidine in aqueous mixtures of DMF/Glycerol at 298.15 K

In Fig 3, $\Delta G_{t,d-d}^0(i)$ values are increasingly negative for L-histidine in aqueous DMF solvent mixture and $\Delta G_{t,d-d}^0(i)$ value shows increasingly positive for L-histidine in aqueous glycerol solvent system.Here $\Delta G_{t,d-d}^0(i)$ values, which are obtained after subtraction of ${}_R\Delta G_{d-d}^0(i)$ from ${}_s\Delta G_{d-d}^0(i)$. $\Delta G_{t,d-d}^0(i)$ values depend on dipole-moment of solute i.e. amino acid, histidine (10.68D) [15, 19] and co-solvents i.e. DMF (3.82D) [8, 9, 11] and glycerol (2.56 D) [11, 19]. It is also decreased with the increase of hard-sphere diameter of solute and co-solvent.

During transfer from water to water- DMF mixtures these parameters altogether lead to $\Delta G^0_{t,d-d}(i)$ values for histidine an decreasing nature and from water to glycerol shows a increasing nature.

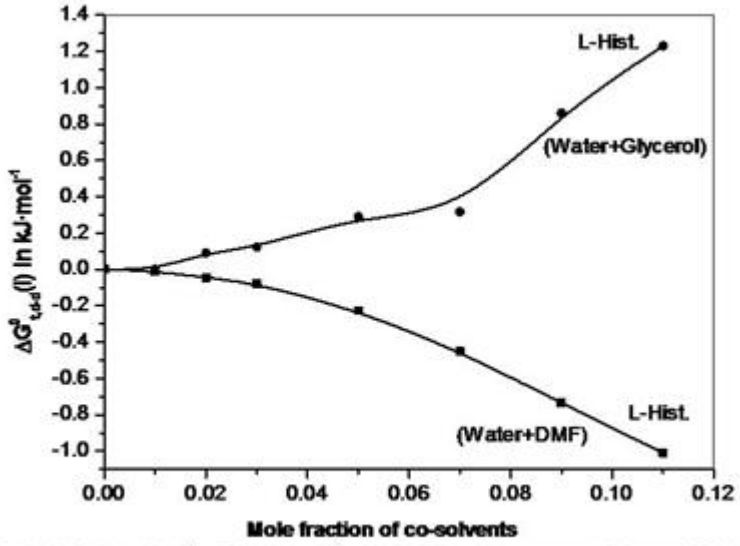

Fig 3. Variation of $\Delta G^0_{t,d-d}(i)$ in kJ·mol^{-1} of L-histidine in aqueous mixtures of DMF and Glycerol at 298.15 K

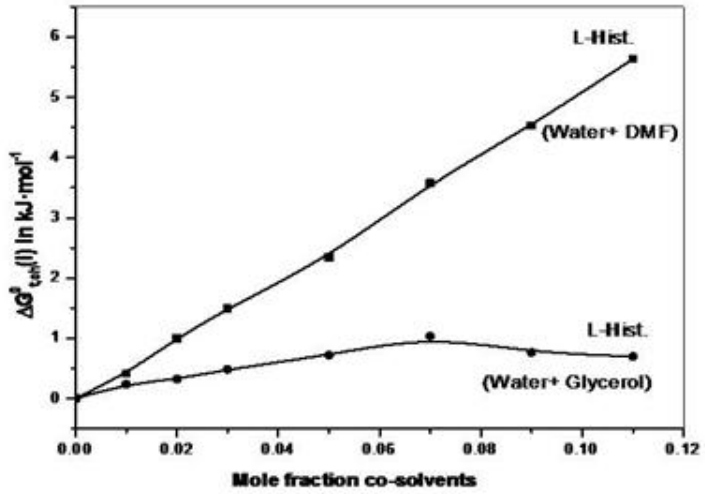

Fig 4. Variation of $\Delta G^0_{t,ch}(i)$ in kJ·mol^{-1} of L-histidine in aqueous mixtures of DMF/Glycerol at 298.15 K

As we know, $\Delta G^0_t(i) = \Delta G^0_{t,cav}(i) + \Delta G^0_{t,d-d}(i) + \Delta G^0_{t,ch}(i)$, ignoring dipole-induced dipole interaction, and the chemical contributions of free energy of solvation, $\Delta G^0_{t,ch}(i)$ can be obtained by subtracting $\Delta G^0_{t,cav}(i)$ & $\Delta G^0_{t,d-d}(i)$ from $\Delta G^0_t(i)$. Here in such solute-solvent system the involved chemical interactions may be different types; i.e. acid-base type interaction, H-bonding interaction, hydrophilic hydration, hard-soft interaction, dispersion interaction, etc.

Figure 4 represent the variation of $\Delta G^0_{t,ch}(i)$ of L-histidine in water-DMF and water-glycerol solvents systems. The nature of variation of the curve indicates that histidine becomes destabilized upto about 0.07 mole fraction of glycerol and then in higher content of glycerol, it becomes stabilized. The maxima at about 0.07 mole fraction of glycerol may be due to the breakdown of extensive hydrogen bonding between hydrophilic head of amino acid, L-histidine and protic water molecules with the introduction of glycerol molecules. In the higher concentration of glycerol $\Delta G^0_{t,ch}(i)$ value become decreasing in nature which reveals that amino acid, L-histidine is more stable in

mixed solvent system than in pure water. Here this may be due to a labile complex formation between L-histidine and glycerol molecules through multiple hydrogen bond formation. The nature of variation of the $\Delta G^{0}_{t,ch}(i)$ value shows a positively increasing order for the zwitter-ion structure of L-histidine in aqueous solution of water-DMF, indicates destabilization of the amino acid, L-histidine. This reflects that there is no formation of labile complex between the amino acid and DMF molecules. In the concentration of DMF the formation of dimeric form is increased which resist to interact between the solute and solvent molecules and hence the stability of the amino acid, L-histidine in water-DMF solvent system.

Figure 5 shows the enthalpy transfer $\Delta H^{0}_{t,cav}(i)$ values due to cavity forming interaction progressively negative (Table 2).

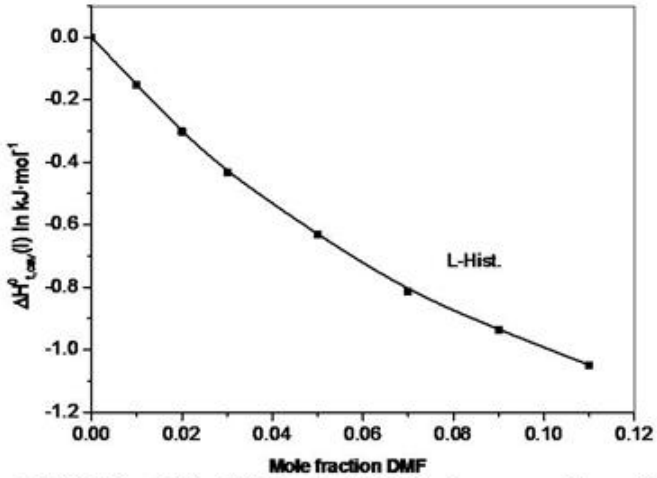

Fig 5. Variation of $\Delta H^{0}_{t,cav}(i)$ in kJ·mol^{-1} of L-histidine in aqueous mixtures of DMF at 298.15 K

4. Conclusion

The transfer chemical Gibbs free energy values indicate that hydrophilic heterocyclic amino acid; L-histidine becomes destabilized in aqueous dipolar aprotic *N, N*-dimethylformamide solvent system and stabilized in aqueous glycerol solvent system. The stability of this amino acid in this mixed solvent system (water + glycerol) is mainly due the complex formation through hydrogen bonding between hydrophilic heads of L-histidine and glycerol molecules.

5. Acknowledgement

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