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Solubility and solvation energetics of L-histidine in aqueous NaCl/KCl electrolyte media

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ABSTRACT

This article describes the solubility etiquette of an important amino acid L-histidine in chloro aqueous solutions of alkali metals (Na, K) under equilibrium saturated conditions through an analytical gravimetric technique at equidistant temperatures. Different thermodynamic parameters along with transfer Gibbs energies under standard conditions were estimated using theoretical methods and experimental solubilities. The way of surrounding by solvent molecules of solute L-histidine in the used media is discussed based on different modes of interactions occurring during solvation. The experimental section describes that the L-histidine solubility enhances in an aqueous KCl solution rather than in NaCl solution. The drop down in L-histidine solubility with moving up electrolyte concentrations at a certain temperature is caused by the salting-out effect. For the studied amino acid, the salting out effect is more pronounced in NaCl electrolyte at any temperature. Amino acid shows higher solubility with rising temperature in both electrolytes' solutions. The current study suggests that the physical properties of NaCl and KCl and the size of the L-histidine molecules are two crucial factors for the chemical stability of the protein building unit.

1. Introduction

Several crucial biological activities are controlled by amino acids such as nutrient storage, transportation, neurotransmitter production etc. The importance of amino acids is scattered in many other fields like, food [1], pharmaceuticals [2,3] and cosmetic industries [4,5] and chemical industries [6]. Particularly, the studies are done in various electrolytic environments in the aqueous and non-aqueous solvent systems [7,8].Thermodynamics of two properties viz. equilibrium solubility and solvation thermodynamics of various organic bio-molecules have been quite attractive studies for a long time. The importance of solubility and thermodynamic parameters in determining the crystallization and stability behaviours of biomolecules has been firmly established. The study of solvation thermodynamics assists to understand the separation technology of proteins from their natural sources. Due to these factors, it has become extremely important to compile information on learning about the solvable properties of amino acids in various solvent-based systems, and in recent years, this subject has been particularly attractive for research [9–12]. The investigation of solvation thermodynamics was also noticed in various temperatures, polarity, pH and ionic nature of the experimental solvent [13,14].

Extensive studies have been conducted to gain a deeper understanding of the solvation nature of histidine, an essential amino acid, within complex solution systems such as hydrophobic and hydrophilic environments. These investigations often involve examining the three-dimensional histidine framework under a microscope [15–17]. The solubilities of amino acids swap in their equilibrium conditions significantly depending on the physical features of used electrolyte media

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[18–22]. The experimental electrolytes have an interesting tendency to alter the conformation as well as direction of the present solute L-histidine molecule. These changes are highly effective to influence various thermodynamic properties such as hydrophilic-hydrophobic and dipole–dipole interactions. These interactions play a significant role in biological phenomena, as supported by studies [23–25]. Recently, there has been a growing trend in the study of larger bio-organic molecules, such as amino acids, within complex solutions comprising water and various salts such as NaCl and KCl [19,20,22]. Amino acids contain charged groups such as amino ($–NH_3^+$) and carboxyl ($–COO^-$) groups, as well as polar groups like hydroxyl (–OH) and amide ($–CONH_2$) groups. NaCl and KCl solutions provide ions (Na^+, K^+, Cl^-) that can interact with these charged groups through electrostatic interactions. The solvation of amino acids by these ions can influence the overall charge distribution and electrostatic interactions within proteins. This, in turn, affects protein–protein interactions, enzyme activity, and other biological processes. NaCl and KCl solutions have osmotic properties, which mean they can exert osmotic pressure on biological systems. In biochemical research, NaCl and KCl are commonly used in various chromatographic techniques for protein purification. Previously we studied several essential and no essential amino acids, their solubility in pure water, pure non-aqueous and binary solutions, and the effect of solvation thermodynamics [22,26–28]. Therefore, the current investigations aim to attempt the understanding the role of ionic groups $–NH_3^+$ and $–COO^-$ and the present hydrophobic group in L-histidine on their solvation abilities in the present aqueous electrolytes system at equidistant temperature. Since in human physiology the aqueous solution contained NaCl and KCl, and hence the solvation chemistry of amino acids in NaCl and KCl solutions is essential for understanding protein stability, electrostatic interactions, osmotic pressure, and protein purification and many more [29–31]. These factors have significant implications in biological systems, biochemical research, and various applications in biotechnology and pharmaceutical industries. Here, L-histidine is chosen as our study topic as a new amino acid for understanding its nature in pure water and chloroaqueous solutions of alkali metal (Na, K). The solvation chemistry in the experimental media may alter due to the presence of cyclic structure and concerning the side chain. These factors have significant implications in biological systems, biochemical research, and various applications in biotechnology and pharmaceutical industries. Hence, the current study would serve as a significant contribution to the field of solution chemistry and thermodynamics.

2. Experimental

2.1. Chemicals and purifications

Initially, the solute amino acid, L-histidine (>99.0 %, Sigma Aldrich) was dried in an entirely devoid desiccator below its melting point for 15 days. Temperature controlled oven was employed for 7 days to take out absorbed moisture completely by maintaining the temperature at 380.15 K to obtain properly dry NaCl and KCl (>99 % E. Merck, India) then kept it in a desiccator for 5 h and cooled it down. For all experimental solutions, triple-distilled water with a conductivity of 0.9 μs/cm was employed. The detailed specifications of the chemicals are summarized in Table 1.

2.2. Preparations of saturated solutions

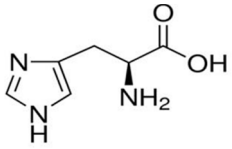
NaCl/KCl solutions were carefully prepared by dissolving particular amounts of NaCl and KCl, carefully measured to have a maximum relative uncertainty in molality ($u_r(m)$) of 0.01 $mol \cdot kg^{-1}$. These solutions were created in the desired volumes of triple-distilled water to achieve concentrations of 0.00, 0.50, 1.00, 1.50, 2.00, and 2.50 $mol \cdot kg^{-1}$, respectively. We utilized a systronic four-digit digital balance for weighing the substances. For our study, six sets of saturated aqueous NaCl and KCl solutions (with predetermined concentrations) were prepared at five equally spaced temperatures ranging from 288.15 to 308.15 K. These mixtures were continuously agitated throughout the day to achieve stability.

To create saturated solutions of L-histidine, an excess amount was added to these prepared solvent mixtures. The mixture was then placed in tightly sealed glass containers to ensure homogeneity. To measure the solubility of L-histidine, approximately 10 mL of each solvent mixture was taken in stoppered glass tubes and shaken until saturated solutions were obtained. The tubes were partially filled with these solutions to ensure proper mixing of L-histidine. The solutions were then placed in a thermostat set at the desired temperatures with an accuracy of 0.10 K. Three sets of equilibrium solutions containing solutes and electrolytes were prepared at the designated experimental temperature, and the solutions were continuously stirred for over 24 h, if necessary, to reach equilibrium. Subsequently, aliquots of the saturated solutions were transferred to stoppered conical flasks, and the solubility was measured using the gravimetric method. The solution was considered to have reached saturation or equilibrium when the concentrations measured at 2-day intervals showed good agreement. A detailed flow chart of the experimental procedure is provided in the supplementary section as Scheme S1.

2.3. Quantitative measurement of solubility of L-histidine

Gravimetric analysis [9,32] an error-free systematic procedure for measuring the soluble L-histidine in present chloro aqueous solvent systems, is employed in the current study. Initially, each saturated solution was permitted to stabilize and equilibrate the undissolved L-histidine for 6 h. After that 5 mL of the upper level of each liquid was separated with the help of a dried pipette and filtered by using a 0.22 μm HPLC disposable filter. The percolated matter was weighed quickly after transferring it into a glass vessel. To get crystals of L-histidine, the

Table 1
Specification of chemical samples.

Chemical Name	Chemical Structure	Source	Initial Purity[a] (fraction)	Drying of reagents & purification of water
L-histidine		Sigma Aldrich	(99.0 % (mass)	drying in a dehydrator with silica gel
Water	H_2O			distillation
Sodium Chloride	NaCl	E. Merck, India	99.0 % (mass)	Oven dried
Potassium Chloride	KCl	E. Merck, India	99.0 % (mass)	Oven dried

[a] Stated by the supplier.

filtrate was evaporated to dry completely at 420.15 K in a hot air oven. Then the temperature was dropped down in a desiccator containing silica gel as dehydrator for 24 h to overcome water absorption and then L-histidine was weighed. The process was performed repeatedly until moving to a constant weight. Atomic absorption spectroscopy helps us to conclude the absence of adsorption or degradation occurring.

The accuracy in determining the solvable capabilities of histidine also attains in higher-concentration environments. In an electrolytic mixture, we dissolved L-histidine at various concentrations and measured the solubility from the each mixture. The estimation revealed a maximum solubility variation of approximately 0.005 mol kg^{-1}. This observation led to the conclusion that the amino acid solute, L-histidine, did not precipitate or adsorb any significant amount of electrolyte during the process.

Another important study that is X-ray powder diffraction study was also performed to justify the pure solid-phase of L-histidine before and after the experiments. That means there are no perceptible differences between the XRD patterns before and after the experiments. The detail of XRD study is cited in Supplementary Section and pattern is shown in Figure S1.

3. Theoretical section

Simple mathematical calculations are plainly taken to calculate the solubility of L-histidine in this study [33,34]. The concentration of the utilised electrolytes in the solution was taken into account when calculating the presence of L-histidine. If the electrolyte is 'm' molal concentration of electrolyte solution then $W_1 = (M \times m \times 5)/1000$ g is the weight of the electrolyte in 5 mL solution, where M = molecular weight of electrolyte.

Whereas mass of solid-L-histidine $(W) = (W_3\text{-}W_2\text{-}W_1)$ g; where W_2 g = the mass of vacant glass vessel; total weight of vessel + dried electrolyte + solid L-histidine = W_3 g. If total weight of vessel with 5 mL amino acid saturated electrolyte solution is W_4 g then the weight of actual evaporated water is W_w g = W_4–W_3. Hence the actual solubility of L-histidine could be calculated as $W_{l\text{-histidine}} = (W/W_w) \times 1000$ g per Kg of water [18].

Table 2 displays the determined saturation solubilities of L-histidine at various temperatures in aqueous Na and in K chloride electrolytes solutions. The repeated findings were found to agree within 2.5 %.

Like previous studies [35,36] the 'equation (1)'was recognisable to measure the standard Gibbs energies of solutions (ΔG_s^0) at a constant temperature,

$$\Delta G_s^0(i) = -RT\ln S\gamma \approx -RT\ln S \quad (1)$$

L-histidine is comfortably present as zwitterions form in aqueous medium. The activity coefficient becomes an important factor $-RT\ln\gamma$ for $\Delta G_s^0(i)$ probably due to presence of large dipole-dipole interaction. Those issues previously had determined the activity coefficients (γ) of numerous biomolecules like amino acids and dipeptides in aqueous electrolyte solutions [19,37,38]. The researchers have computed the γ as unity for such amino acids at lower concentrations in electrolytes. In this respect, the lesser value of L-histidine mole fraction solubility was calculated using equilibrium saturation solubility, which is shown in Table 2, at various concentrations of aqueous chloride solutions of alkali metals of Na and K. In calculation of Gibbs free energy of solution ($\Delta G_s^0(i)$) there might be a role of activity coefficient (γ) but in the current study we consider activity coefficient (γ) as unity. Furthermore, in the current investigation our most important target is to find the standard total transfer Gibbs energies ($\Delta G_t^0(i)$) of the biomolecules: here for L-histidine in the experimental chloride aqueous solutions. A similar purpose was also revealed in the previous study [39].

Further, $\Delta G_t^0(i)$ is correlated as $\Delta G_t^o(i) = \Delta G_s^0(i) - \Delta G_R^0(i)$; where, $\Delta G_s^0(i)$ and $\Delta G_R^0(i)$ are the concerned free energy of the amino acids in a co-solvent (aqueous NaCl and KCl) and in pure water respectively.

Table 2
Solubility of L-histidine in water and water + NaCl and water + KCl in different composition of NaCl and KCl at different temperatures[#] under atmospheric pressure, p = 0.10 MPa[a].

Molality of salts (m) (mol·kg^{-1})	0.00	0.50	1.00	1.50	2.00	2.50
Solubility of L-histidine in mol·kg^{-1} of water in NaCl + H_2O system						
288.18 K	0.2206 ± 0.0018	0.1867 ± 0.0013	0.1685 ± 0.0018	0.1564 ± 0.0083	0.1365 ± 0.0053	0.1255 ± 0.0023
293.15 K	0.2465 ± 0.0023	0.2102 ± 0.0017	0.1907 ± 0.0031	0.1774 ± 0.0013	0.1550 ± 0.0033	0.1424 ± 0.0040
298.15 K	0.2705 ± 0.0017	0.2320 ± 0.0019	0.2115 ± 0.0016	0.1994 ± 0.0063	0.1790 ± 0.0016	0.1688 ± 0.0018
303.15 K	0.2928 ± 0.0035	0.2554 ± 0.0022	0.2345 ± 0.0042	0.2208 ± 0.0015	0.1988 ± 0.0033	0.1877 ± 0.0032
308.15 K	0.3165 ± 0.0038	0.2870 ± 0.0030	0.2660 ± 0.0072	0.2498 ± 0.0023	0.2340 ± 0.0012	0.2205 ± 0.0044
Solubility of L-histidine in mol·kg^{-1} of water in KCl + H_2O system						
288.18 K	0.2206 ± 0.0018	0.2050 ± 0.0028	0.1922 ± 0.0026	0.1804 ± 0.0022	0.1728 ± 0.0041	0.1636 ± 0.0022
293.15 K	0.2465 ± 0.0023	0.2126 ± 0.0021	0.2019 ± 0.0053	0.1894 ± 0.0043	0.1804 ± 0.0026	0.1716 ± 0.0030
298.15 K	0.2705 ± 0.0017	0.2390 ± 0.0084	0.2250 ± 0.0024	0.2160 ± 0.0027	0.2072 ± 0.0021	0.1995 ± 0.0027
303.15 K	0.2928 ± 0.0035	0.2674 ± 0.0070	0.2552 ± 0.0028	0.2424 ± 0.0030	0.2324 ± 0.0032	0.2244 ± 0.0042
308.15 K	0.3165 ± 0.0038	0.2964 ± 0.0025	0.2842 ± 0.0032	0.2682 ± 0.0048	0.2570 ± 0.0042	0.2490 ± 0.0055

Standard uncertainties u is u(T)= ± 0.10 K (uncertainty in temperature) and u (m) = 0.01 mol·kg^{-1}; $u_r(p)$ [a] = 0.02 MPa. [u_r = relative uncertainties].

Again, $\Delta G_t^0(i)$= -RTln$S_s\gamma_s$ + RTln$S_R\gamma_R$ = -RTln $S_s\gamma_s/S_R\gamma_R$ = -RTlnS_s/S_R – RTlnγ_s/γ_R. Hence the activity coefficient factor, -RTlnγ_s/γ_R ('s' stands for aqueous NaCl and KCl, whereas, 'R' for H_2O), which tends to be negligibly small. Thus the assumption of ignoring the impact or input of activity coefficient in the current study for the estimation of total transfer Gibbs free energy $\Delta G_t^0(i)$ may be reasonable.

The experimentally evaluated free energies for the amino acid,ΔG_s^0 were fixed by the mathematical least square least as given in 'equation (2)' as: [40]

$$\Delta G_s^0 = a + bT + cT\ln T \quad (2)$$

The values of the parameters are tabulated in Table 3 & Table 4. Standard transfer Gibbs free energies ΔG_t^0 of L-histidine in chloro aqueous salts solutions of sodium and potassium were measured at 298.15 K on mole fraction scale via equation. (3),

$$\Delta G_t^0(i) = {}_s\Delta G_{sol}^0(i) - {}_R\Delta G_{sol}^0(i)$$

$$i.e.\ \Delta G_t^0(i) = (a_s - a_R) + (b_s - b_R)T + (c_s - c_R)T\ln T - RT\ln(M_s/M_R) \quad (3)$$

In the equation the subscript 's' for aqueous salt solutions and 'R' stands for the pure solvent (H_2O). The symbols M_R, M_s are the molar masses of water and mixed electrolytes solvent respectively. The results of $\Delta G_t^0(i)$ of L-histidine are estimated and shown in Table 4. The standard uncertainties in finding the results of $\Delta G_t^0(i)$ which are found to be near about 0.044 kJ·mol^{-1}.

Table 3
Standard Gibbs energies of solutions (ΔG_S^0) on molal scale in their respective solubilities of L- histidine in aqueous mixtures of NaCl/KCl at different temperature (K).[#]

288.18 K		293.15 K		298.15 K		303.15 K		308.15 K	
S (mol·kg^{-1})	$\Delta G_s^0(i)$ (kJ•mol^{-1})	S (mol·kg^{-1})	$\Delta G_s^0(i)$ (kJ•mol^{-1})	S (mol·kg^{-1})	$\Delta G_s^0(i)$ (kJ•mol^{-1})	S (mol·kg^{-1})	$\Delta G_s^0(i)$ (kJ•mol^{-1})	S (mol·kg^{-1})	$\Delta G_s^0(i)$ (kJ•mol^{-1})
L- histidine in NaCl + H_2O									
0.2206	3.6208	0.2465	3.4131	0.2705	3.2410	0.2928	3.0957	0.3165	2.9474
0.1867	4.0206	0.2102	3.8014	0.2320	3.6216	0.2554	3.4401	0.2870	3.1980
0.1685	4.2663	0.1907	4.0387	0.2115	3.8509	0.2345	3.6553	0.2660	3.3927
0.1564	4.4448	0.1774	4.2149	0.1994	3.9970	0.2208	3.8070	0.2498	3.5537
0.1365	4.7708	0.1550	4.5438	0.1790	4.2645	0.1988	4.0716	0.2340	3.7211
0.1255	4.9721	0.1424	4.7505	0.1688	4.4099	0.1877	4.2164	0.2205	3.8733
L- histidine in KCl + H_2O									
0.2206	3.6208	0.2465	3.4131	0.2705	3.2410	0.2928	3.0957	0.3165	2.9474
0.2056	3.7895	0.2126	3.7737	0.2390	3.5479	0.2674	3.3244	0.2964	3.1155
0.1922	3.9510	0.2019	3.8996	0.2250	3.6975	0.2552	3.4421	0.2842	3.2231
0.1804	4.1028	0.1894	4.0553	0.2160	3.7987	0.2424	3.5718	0.2682	3.3716
0.1728	4.2059	0.1804	4.1740	0.2072	3.9018	0.2384	3.6137	0.2570	3.4809
0.1636	4.3370	0.1716	4.2959	0.1995	3.9957	0.2244	3.7663	0.2490	3.5619

[#] u(T)= ± 0.10 K (uncertainty in temperature).

Table 4
Coefficients a, b and c, Gibbs Energies $\Delta G_t^0(i)$, and Entropies $T\Delta S_t^0(i)$ of Transfer of L-histidine on mole fraction Scale from H_2O to H_2O – NaCl and H_2O – KCl Mixture at 298.15 K.[#]

Molality (m) (mol·kg^{-1})	a (kJ•mol^{-1})	b (kJ•mol^{-1}•K^{-1})	c (kJ•mol^{-1}•K^{-1})	$\Delta G_t^0(i)$ (kJ•mol^{-1})	$T\Delta S_t^0(i)$ (kJ•mol^{-1})
L-histidine in NaCl + H_2O					
0.0	87.13	−1.6947	0.24806	0.0000	0.0000
0.5	−8.54	0.5019	− 0.08093	0.3293	2.0891
1.0	−22.96	0.8451	− 0.13255	0.4979	2.8909
1.5	7.47	0.1719	−0.03220	0.6362	3.2633
2.0	−61.95	1.7811	−0.27362	0.8455	5.6134
2.5	−27.97	1.0397	−0.16339	0.9865	6.5872
L-histidine in KCl + H_2O					
0.0	87.13	−1.6947	0.24806	0.0000	0.0000
0.5	−180.72	4.3447	−0.65406	0.2628	0.8542
1.0	−161.19	3.9457	−0.59545	0.3283	1.8441
1.5	−124.62	3.1070	−0.46971	0.3767	1.8764
2.0	−94.69	2.4439	−0.37090	0.3954	2.3274
2.5	−113.51	2.8773	−0.43581	0.4710	2.7848

[#] u(T)= ± 0.10 K (uncertainty in temperature).

The results found $\Delta G_t^0(i)$ are publicized in Table 4. It is true that $\Delta G_t^0(i)$ is a complex value that comprises different transfer free energies terms mainly for cavity forming interactions ($\Delta G_{t,cav}^0(i)$), due to dipole–dipole interaction ($\Delta G_{t,d-d}^0(i)$) and for chemical transfer Gibbs energies ($\Delta G_{t,ch}^0(i)$) and structural nature of the solute and solvent molecules. To reduce complexity, unlike the other efforts [37,41], we didn't take the dipole-induced dipole interaction into consideration here.

$\Delta G_t^0(i)$ is represented as below:

$$\Delta G_t^0(i) = \Delta G_{t,cav}^0(i) + \Delta G_{t,d-d}^0(i) + \Delta G_{t,ch}^0(i) \quad (4)$$

The scaled particle theory [3,43–46] is considered here to determine of $\Delta G_{t,cav}^0(i)$. Solute and solvent molecules are supposed to be hard spheres and their diameters are shown in Table S1 (supplementary). By using equation (5), the cavity interaction was measured like the previous studies [42]:

$$\Delta G_{cav}^0(i) = G_C + RT\ln(RT/V_S) \quad (5)$$

here, $G_C = RT[-\ln(1-Z) + \{3X/(1-Z)\}\sigma_x + \{3Y/(1-Z)\}\ \sigma_x^2 + \{9X^2/2(1-Z)^2\}\sigma_x^2]Z = \pi N_A/6V_s(z_R\sigma_R^3 + z_s\sigma_s^3)X = \pi N_A/6V_s(z_R\sigma_R^2 + z_s\sigma_s^2)$ $Y = \pi N_A/6V_s(z_R\sigma_R + z_s\sigma_s)V_s = M_s/d_s$

The respective parameters of the above equations are summarized in Table S1.

The $\Delta G_{t,cav}^0(i)$ means the difference like the equation 6 [42].

$$\Delta G_{t,cav}^0(i) = {}_s\Delta G_t(cav) - {}_R\Delta G_t(cav) = ({}_sG_c - {}_RG_c) + RT\ln(V_R/V_s). \quad (6)$$

In this study $\Delta G_{t,d-d}^0(i)$ determined by the standard Keesom-orientation expression as given in equation 7:

$$\Delta G_{t,d-d}^0(i) = ({}_s\Delta G_{d-d}^0(i) - {}_R\Delta G_{d-d}^0(i)) \quad (7)$$

In solution, ${}_s\Delta G_{d-d}^0(i)$ is presented as:

$${}_s\Delta G_{d-d}^0(i) = -(8\Pi/9)N^2\mu_s^2\mu_x^2\sigma_{s-x}^{-3}(kT)^{-1}V_x^{-1} = A/TV_s;$$
$$where$$
$$A = -(8\Pi/9)N^2\mu_s^2\mu_x^2\sigma_{s-x}^{-3}(k)^{-1} \quad (8)$$
$$and$$
$$V_s = M_s/d_s$$

The symbols- N, μ_s and μ_x mean Avogadro's number, dipole moments of mixed solvent and L-histidine (Table S1) respectively. σ_{s-x} means the total diameter of the area where attractive or repulsive interactions act in between the solvent and amino acid molecules and it is equal to ½($\sigma_s + \sigma_x$) [35]. In this regard, σ_s and σ_x are the hard-sphere diameter of hydrated NaCl/KCl and L-histidine in solvent respectively. To calculate $\Delta G_{t,d-d}^0(i)$ in mole fraction scale we use the term X_{s1} like earlier literature

[8,37] and it is expressed as:

$$X_{s1} = X_s(\mu_s/\sigma_s^3)/(\mu_R/\sigma_R^3) \quad (9)$$

Here X_{s1} means the mole fraction mainly takes part in dipole–dipole interaction.

To get the actual results of $\Delta G^0_{t,ch}(i)$ we subtract $\Delta G^0_{t,cav}(i)$ and $\Delta G^0_{t,d-d}(i)$ from $\Delta G^0_t(i)$ and the results are shown in Table 5.

$$Again,\ \Delta S^0_t(i) = (b_R - b_s) + (c_R - c_S)(1 + \ln T) + R\ln(M_s/M_R) \quad (10)$$

Here 'S' and 'R' stand for aqueous chloride solutions and pure water respectively. On the other hand, M_R and M_s were used for the molar masses of water and aqueous chloride mixed solvents, respectively. The results of $T\Delta S^0_t(i)$ are shown in Table 4 & Table 5. It was found that the uncertainty in measuring the $\Delta S^0_t(i)$ values was about ± 0.26 kJ·K^{-1}mol^{-1}.

$\Delta S^0_{t,d-d}(i)[= ({}_s\Delta S^0_{d-d}(i) - {}_R\Delta S^0_{d-d}(i))]$ was estimated with the help of Keesom Orientation expression [39] and it was given as:

$${}_s\Delta S^0_{d-d}(i) = -\{\delta\, {}_s\Delta G^0_{d-d}(i)/\delta T\}_p$$

$$i.e.\ T\, {}_s\Delta S^0_{d-d}(i) = {}_s\Delta G^0_{d-d}(i)[1 + T\alpha] \quad (11)$$

The isobaric thermal expansibility constant (α) of a solvent was determined by using equation (12) [37].

$$\alpha = \delta(\ln V_s/\delta T)_P = -(\delta \ln d_s/\delta T)_P \quad (12)$$

The change of enthalpy due to the creation of the cavity in aqueous to aqueous chloride mixtures was determined by using equations 13 & 14 [43].

$$\Delta H^0_{t,cav}(i) = {}_s\Delta H^0_{cav}(i) - {}_R\Delta H^0_{cav}(i) \quad (13)$$

$$\Delta H^0_{cav}(i) = (A + H + K + E) \times B \quad (14)$$

Where $A = (\Pi N_A/6V_s) \times (Z_R\sigma_R^3 + Z_S\sigma_S^3)$;$B = \sigma_S RT^2/1 - A$;

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

$X = (\Pi N_A/6V_s) \times (Z_R\sigma_R^2 + Z_S\sigma_S^2)$; And $\Upsilon = (\Pi N_A/6V_s) \times (Z_R\sigma_R + Z_S\sigma_S)$;$\Pi = 22/7$

The values of $\Delta H^0_{t,cav}(i)$ in the current studied system are shown in Table 5.

4. Discussion

4.1. Solubility

The temperature and several physicochemical properties effectively directed the blow of salts on the solubilities of L-histidine. In the present description, we evaluated the solubilities of L-histidine in water-NaCl and water-KCl solvent systems at equally spaced (5 K) five different temperatures. Solubilities of L-histidine at different temperatures in aqueous and aqueous NaCl/KCl solutions with different concentrations (in molality) are shown in Table 2. The variations of solubilities in chloro-aqueous solutions of Na and K at five equidistance temperatures of L-histidine are shown in Figs. 1 and 2. A comparative account of the solubilities of L-histidine in water-NaCl and water-KCl solvent systems at a definite temperature (298.15 K) is shown in Fig. 3.

To verify the uniformity of the present technique to conclude the solubility of L-histidine in pure water and in aqueous Na/K salt solution in different concentration at 298.15 K to 308.15 K are compared with the literature [46–52] (Table S2). The results excellently support with the earlier which supports of our procedure strength. It is to be noted that M. J. Abualreish et al. (2020) [52] have also measured the solubility of L-histidine in few temperatures in some composition of aqueous –Na/K chloride solutions but they have calculated only the transfer Gibbs free energy and entropy to describe the solvation interactions. In our work

Table 5
Gibbs energies of transfer $\Delta G^0_t(i)$, $\Delta G^0_{t,cav}(i)$, $\Delta G^0_{t,d-d}(i)$, $\Delta G^0_{t,ch}(i)$ and enthalpy, $\Delta H^0_{t,cav}(i)$ and entropies of transfer $T\Delta S^0_t(i)$, $T\Delta S^0_{t,cav}(i)$, $T\Delta S^0_{t,d-d}(i)$ and $T\Delta S^0_{t,ch}(i)$ of L-histidine in H_2O + NaCl and H_2O + KCl mixture at 298.15 K[#] in kJ•mol^{-1}.

Molality (m) (mol·kg^{-1})	$\Delta G^0_t(i)$ (kJ•mol^{-1})	$\Delta G^0_{t,cav}(i)$ (kJ•mol^{-1})	$\Delta G^0_{t,d-d}(i)$ (kJ•mol^{-1})	$\Delta G^0_{t,ch}(i)$ (kJ•mol^{-1})	$T\Delta S^0_t(i)$ (kJ•mol^{-1})	$\Delta H^0_{t,cav}(i)$ (kJ•mol^{-1})	$T\Delta S^0_{t,cav}(i)$ (kJ•mol^{-1})	$T\Delta S^0_{t,d-d}(i)$ (kJ•mol^{-1})	$T\Delta S^0_{t,ch}(i)$ (kJ•mol^{-1})
L-histidine NaCl + H_2O									
0.0	0.000	0.000	0.000	0.000	0.0000	0.000	0.000	0.000	0.000
0.5	0.329	0.002	−0.052	0.379	2.0891	−0.004	−0.006	−0.056	2.151
1.0	0.498	−0.003	−0.216	0.717	2.8909	−0.001	0.002	−0.233	3.122
1.5	0.636	−0.010	−0.496	1.142	3.2633	−0.006	0.004	−0.534	3.793
2.0	0.846	−0.019	−0.902	1.767	5.6134	−0.015	0.004	−0.971	6.580
2.5	0.987	−0.030	−1.434	2.451	6.5872	−0.024	0.006	−1.543	8.124
L-histidine in KCl + H_2O									
0.0	0.0000	0.000	0.000	0.000	0.0000	0.000	0.000	0.000	0.000
0.5	0.2628	−0.042	−0.048	0.352	0.8542	0.004	0.046	−0.051	0.859
1.0	0.3283	−0.089	−0.195	0.612	1.8441	0.001	0.090	−0.210	1.964
1.5	0.3767	−0.137	−0.446	0.959	1.8764	−0.006	0.131	−0.480	2.225
2.0	0.3954	−0.187	−0.806	1.389	2.3274	−0.015	0.172	−0.868	3.023
2.5	0.4710	−0.237	−1.256	1.964	2.7848	−0.020	0.217	−1.353	3.921

Diameter of L-histidine 0.528 nm and dipole moment of L-histidine 10.68 D [40]. [#]u(T)= ± 0.10 K (uncertainty in temperature).

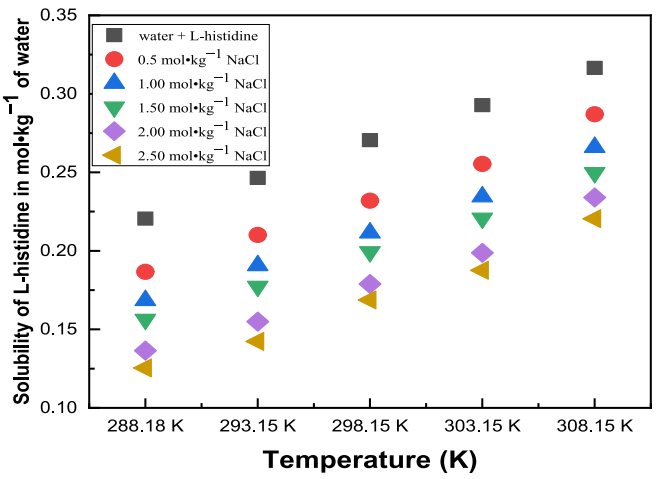


Fig. 1. Solubility of L-histidine in pure water and NaCl-water mixed solutions with variations of temperatures (K).

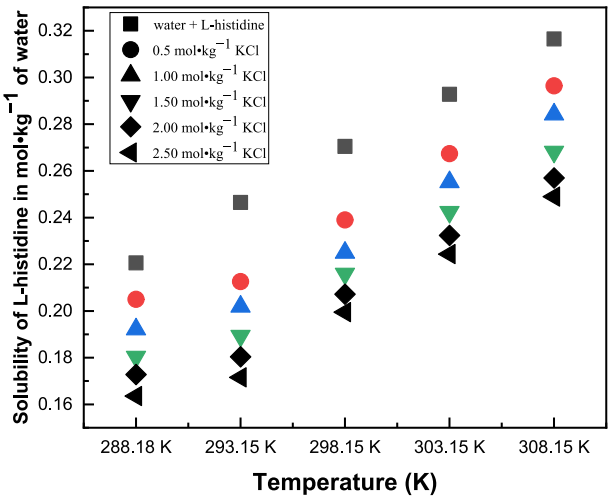


Fig. 2. Solubility of L-histidine in pure water and KCl-water mixed solutions with variations of temperatures (K).

extrapolated the study in terms of chemical transfer energetics and we also calculated theoretically many other thermodynamics parameters like transfer Gibbs free energy for cavity formation interaction, dipole–dipole interactions and many solvation parameters which are very important in solvation chemistry of amino acids.

From all the present experimental data the following observations are evaluated.

a) L-histidine is less soluble in aqueous NaCl/KCl solutions than in just pure water at any concentration (Figs. 1 & 2).
b) For a given concentration, L-histidine becomes more soluble at higher temperatures in both NaCl-H_2O and KCl-H_2O systems (Figs. 1 and 2).
c) With increasing electrolyte concentration at a specific temperature, L-histidine solubility in the two solvent systems indicated diminishes (Figs. 1 and 2).
d) Compared to NaCl-H_2O media, KCl-H_2O media have a higher solubility of L-histidine (Figs. 3 and 4).

The first observation can be clarified by considering the ion–dipole interaction. The aqueous solubility of L-histidine occurs because of ion–dipole interaction between polar H_2O molecules and COO^- and $-NH_3^+$ ion present in L-histidine. The introduction of NaCl/KCl

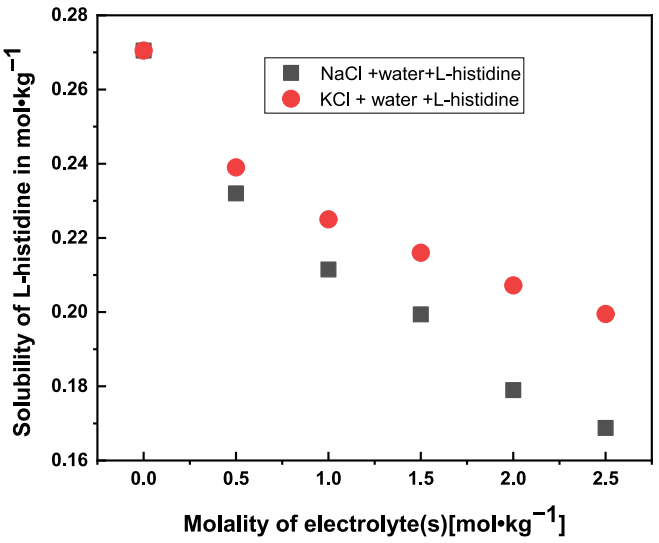


Fig. 3. Comparative solubilities of L-histidine in NaCl + water (black) and KCl + water (red) solvent systems at 298.15 K. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

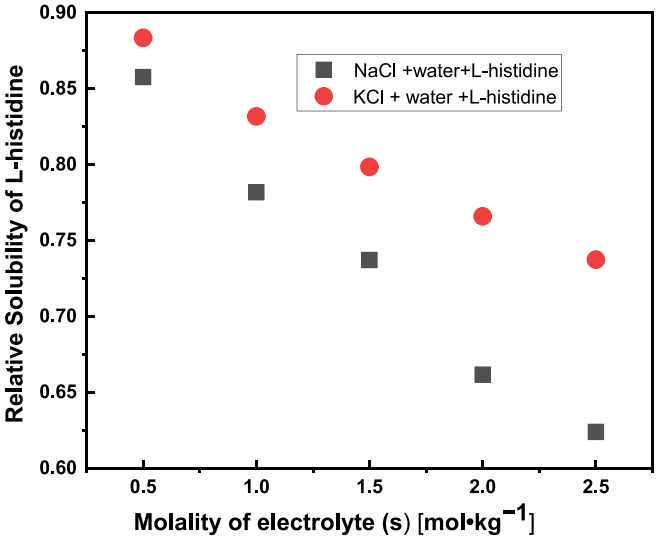
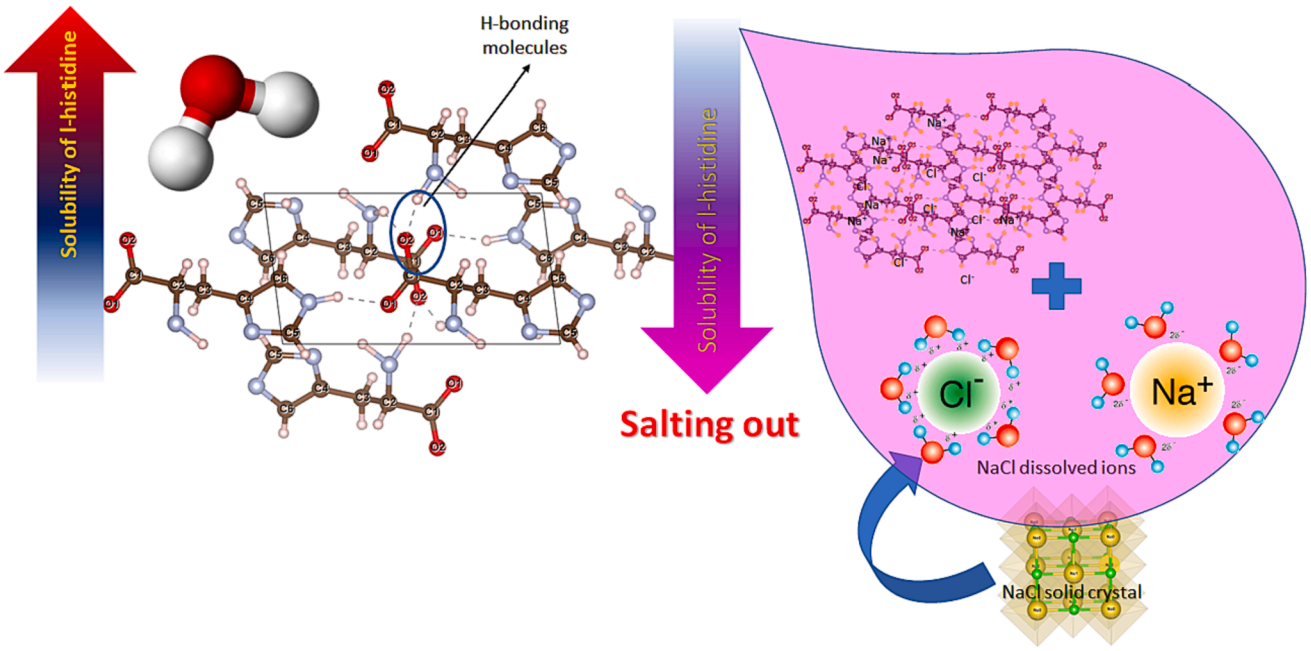


Fig. 4. Relative solubilities of L-histidine in NaCl + water (black) and KCl + water (red) solvent systems at 298.15 K. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

electrolytes in the H_2O molecules leads to ionic interaction between them. This incident enforces the hydrophobic moiety content of L-histidine to separate from the solvent system. Thus, the solubility became lower of L-histidine in the presence of aqueous NaCl/KCl than in pure water (Scheme 1).

The 2nd conclusion might be because of the kinetic motion of the solvent molecule moves up with the rising of temperature. This helps the water molecules to distort the proper ordering with the present L-histidine molecules held by strong intermolecular forces. Therefore L-histidine can now effectively make interaction with solvent molecules and consequently solubility increases.

The 3rd prediction can be described considering the salting in/out effect. The *Ksi* values are negative for both solvent systems (Table 7), which is associated with the effect of salting out. The salting out constant can be determined with the help of the following equation 15: the



Scheme 1. Graphically description of the salting out phenomenon in L-histidine and increased solubility in pure water.

corresponding values which are used are mentioned in Table 6 and Fig. 5 shows the graphical plot.

$$Log(Ss/S_R) = Ksi^{*}m \quad (15)$$

Ksi is a constant and known as Setchenow constants and represents the salting-in or salting-out effects; where, Ss and S_R are the solubilities of L-histidine in aqueous chloride and water, respectively. 'm' is the molality of the electrolyte's solution.

By plotting log *(Ss/S_R)* vs. m (Fig. 5) we evaluated the values of *Ksi*. The slope of the plot of log(Ss/S_R) vs. m (Fig. 5) gives us the exact result of *Ksi* for the solute L-histidine. The finding of *Ksi* values strongly supports the experimentally determined solubility results. The size factor of amino acids is crucial for ion-pair complex formation whereas L-histidine (0.528 nm) has a larger size which cannot form a strong pair complex in aqueous NaCl/KCl solution due to disordered structural arrangement lower the solubility leads to salting out with negative *Ksi* values.

Another interesting effect of proper size can be explained in the 4th conclusion. The unadjusted size of L-histidine and NaCl/KCl systems can hamper the stability and solubility due to an offbeat dispersion interaction as well as H-bonding. Thus, compared with NaCl/water system, KCl/water showed superior dispersion interaction and strong complexation due to the formation of stronger H-bonding with the zwitterionic species of histidine as adjusted size. On moving down the group ionic radius increases and due to this observed salting-out phenomenon of histidine can be discussed. Compared to smaller Na+, larger K + creates a superior ion-pair complex leading to greater solubility also supported by their corresponding '*Ksi*' values given in Table 7.

Table 7
Setchenow constants (salting-out) of L-histidine in aqueous NaCl and KCl solutions at 298.15 K[#].

Amino Acid (L-histidine) K_{si} (salting-in / salting-out) at 298.15 *K*	
NaCl	− 0.0698 ± 0.0036
KCl	− 0.0385 ± 0.0021

[#] u(T)= ± 0.10 K (uncertainty in temperature).

Table 6
Relative Solubility (S_S/S_R) and log (S_S/S_R) of L-histidine in water and water + NaCl and water + KCl in different composition of NaCl and KCl at different temperature under atmospheric pressure, p = 0.1 MPa[a].

Molality (m) (mol·kg^{-1})	**Relative Solubility**									
	Relative solubility (S_S/S_R) 288.15 K	**log (S_S/S_R) at 288.15 K**	**Relative solubility (S_S/S_R) 293.15 K**	**log (S_S/S_R) at 293.15 K**	**Relative solubility (S_S/S_R) 298.15 K**	**log (S_S/S_R) at 298.15 K**	**Relative solubility (S_S/S_R) 303.15 K**	**log (S_S/S_R) at 303.15 K**	**Relative solubility (S_S/S_R) 308.15 K**	**log (S_S/S_R) at 308.15 K**
L-histidine in NaCl + H_2O										
0.5	0.8463	−0.0725	0.8527	−0.0692	0.8577	−0.0667	0.8723	−0.0594	0.9068	−0.0425
1.0	0.7638	−0.1170	0.7736	−0.1115	0.7819	−0.1069	0.8009	−0.0964	0.8404	−0.0755
1.5	0.7090	−0.1494	0.7197	−0.1429	0.7372	−0.1324	0.7541	−0.1226	0.7893	−0.1028
2.0	0.6188	−0.2085	0.6288	−0.2015	0.6617	−0.1793	0.6790	−0.1682	0.7393	−0.1312
2.5	0.5689	−0.2450	0.5777	−0.2383	0.6240	−0.2048	0.6411	−0.1931	0.6967	−0.1570
L-histidine in KCl + H_2O										
0.5	0.9293	−0.0318	0.8625	−0.0642	0.8835	−0.0538	0.9133	−0.0393	0.9364	−0.0285
1.0	0.8712	−0.0593	0.8253	−0.0833	0.8318	−0.0800	0.8716	−0.0596	0.8979	−0.0467
1.5	0.8177	−0.0874	0.7684	−0.1144	0.7985	−0.0977	0.8277	−0.0821	0.8474	−0.0719
2.0	0.7833	−0.1349	0.7318	−0.1356	0.7660	−0.1158	0.7937	−0.1003	0.8120	−0.0904
2.5	0.7416	−0.1298	0.6961	−0.1573	0.7375	−0.1322	0.7664	−0.1099	0.7867	−0.1042

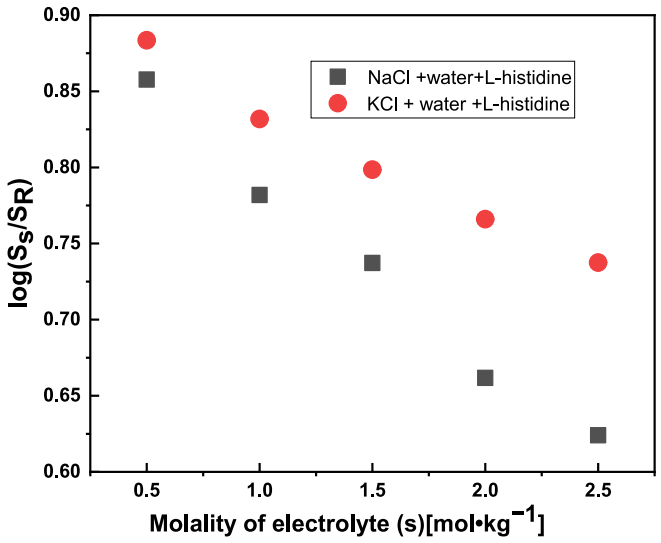


Fig. 5. Plot of logarithm of the ratio of solubilities S_S with and S_R without electrolytes for l-histidine in aqueous electrolyte (NaCl/KCl) mixtures in different composition at 298.15 K.

4.2. Transfer Gibbs free energetics

Fig. 6 and Tables 4 & 5 reveal the total Gibbs energy of transfer $\Delta G_t^0(i)$ for L-histidine in earlier mentioned solvent systems and the following observations are discussed.

a) The Gibbs free energy in a total of transfer $\Delta G_t^0(i)$ values increase with the rise of concentration of both electrolytes (Fig. 6).
b) The rate of increment of the total Gibbs free energy of transfer $\Delta G_t^0(i)$ is more in NaCl-H_2O compared to KCl –H_2O solvent system (Fig. 6).

The variation of $\Delta G_t^0(i)$ mainly depends on $\Delta G_{t,d-d}^0(i)$, $\Delta G_{t,cav}^0(i)$ and free energy owing to different chemical interactions $\Delta G_{t,ch}^0(i)$, such as aquaphobic, aquaholics, acid-base and dispersion collectively and sequentially. The idea of solute–solvent interaction in electrolyte media is the basis for the explanation of the following observations. In this present study, we calculate these values with the help of the least square method by calculating coefficients *a, b*, and *c* (Table 3). In both solvent systems positive increment of $\Delta G_t^0(i)$ value is observed since the lower tendency of forming complexes with electrolytes. This in turn may be due to the presence of hydrocarbon parts in l-histidine. This hydrocarbon part restricts its ability to make interactions with the particular solvent. Consequently, the rise in concentration $\Delta G_t^0(i)$ shows a positive increment. Although two important factors viz. cavity formation and dipole–dipole interactions must contribute to the stability of L-histidine along with considering chemical interactions such as total transferable free energy $\Delta G_t^0(i)$, make $[\Delta G_{t,ch}^0(i)]$ positive enhancement.

Therefore, L-histidine becomes unstable with higher NaCl/KCl concentrations in the aqueous solution system because of these chemical interactions.

The 2nd conclusion can be drawn on the ground of the size factor of the solute and co-solvent molecule. The solute, L-histidine is larger and hence makes stronger solute–solvent interaction with KCl-H_2O solvent system rather than NaCl-H_2O solvent system.

However, transferable Gibbs free energy chemically $[\Delta G_{t,ch}^0(i)]$ control the actual stability of l-histidine moiety majorly in both solvent systems. This function composes of various types of chemical interaction exhibited between solute and solvent like H-bonding, dispersion, hydrophobic interaction etc. This term can be evaluated accurately by subtracting cavity forming $\Delta G_{t,cav}^0(i)$ and dipole–dipole energies $\Delta G_{t,d-d}^0(i)$. All corresponding energy values are shown collectively in Table 5. Fig. 7 shows that this chemical transfer Gibbs free energy.

$[\Delta G_{t,ch}^0(i)]$ values increase for l-histidine in NaCl-H_2O solvent system but a slight decrement in KCl-H_2O solvent system. This indicates the destabilization of l-histidine in NaCl-H_2O media compared to KCl-H_2O medium. This deviation can be explained on the ground of the size factor. On stepping down the group ionic radii gradually enhance due to the addition of new shell that is the rise of the principal quantum number. As a result, L-histidine shows greater capability of forming complexes in KCl-H_2O system than NaCl-H_2O system in an analogous experimental set-up.

4.3. Transfer entropies

Figs. 8 and 9 and Table 5 show the experimental results of total transfer entropies that arising out from the interaction between solvents. To evaluate these values, we considered the least square method to attain a more exact conclusion. Those figures reveal both $[T\Delta S_t^0(i)]$ and

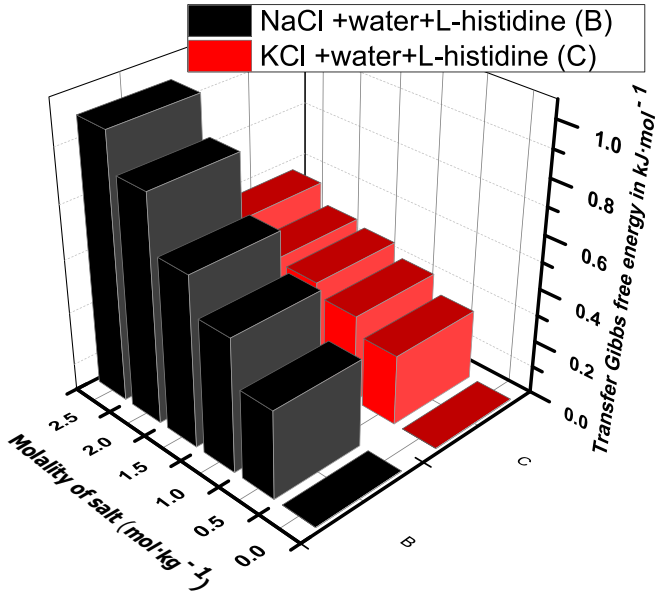


Fig. 6. Variation of transfer Gibbs free energy $(\Delta G_t^0(i))$ in kJ•mol^{-1} for L-histidine in aqueous electrolyte (NaCl/KCl) mixtures in different composition at 298.15 K.

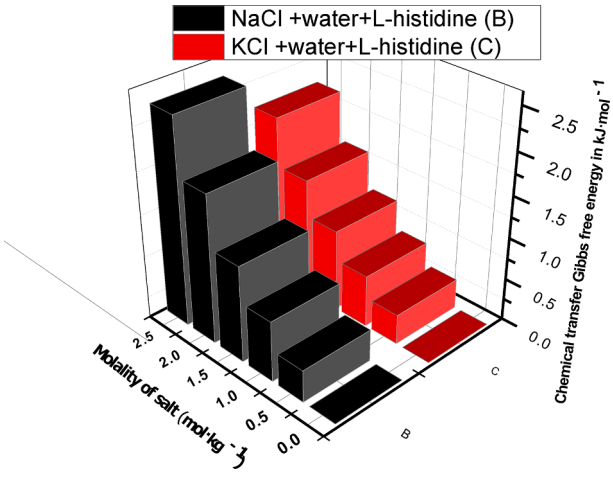


Fig. 7. Variation of chemical transfer Gibbs free energy $(\Delta G_{t,ch}^0(i))$ in kJ•mol^{-1} for L-histidine in aqueous electrolyte (NaCl/KCl) mixtures in different composition at 298.15 K.

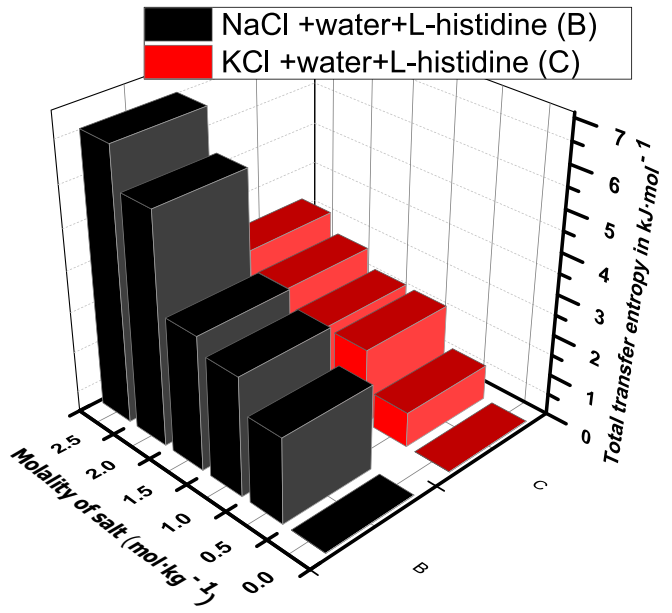


Fig. 8. Variation of transfer entropy ($T\Delta S_t^0(i)$) in kJ•mol^{-1} for L-histidine in aqueous electrolyte (NaCl/KCl) mixtures in different composition at 298.15 K.

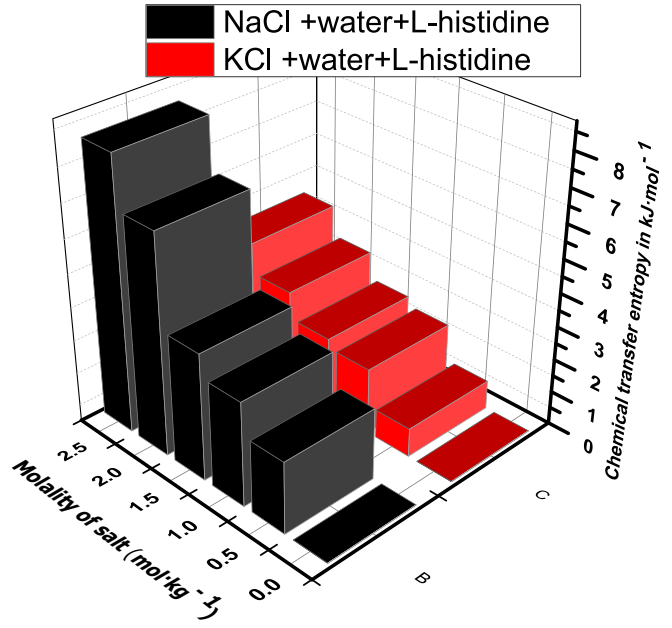


Fig. 9. Variation of chemical transfer entropy ($T\Delta S_{t,ch}^0(i)$) in kJ•mol^{-1} for L-histidine in aqueous electrolyte (NaCl/KCl) mixtures in different composition at 298.15 K.

$T\Delta S_{t,ch}^0(i)$ increase with an increase in the concentration of electrolytes. $T\Delta S_t^0(i)$ is a combined effect of cavity forming transfer entropy $T\Delta S_{t,cav}^0(i)$ and transfer entropy resulting from dipole-dipole interaction $T\Delta S_{t,d-d}^0(i)$ and $T\Delta S_{t,ch}^0(i)$ which is also responsible for other parameters such as hydrophobic, H-bonding interaction etc.

In aqueous histidine, there is the presence of ion–dipole interaction between the zwitterionic ionic form of L-histidine and polar water molecules. But when any electrolyte (here KCl or NaCl) comes in contact with that solution (mean aqueous histidine) ion-ion interaction is predominant between electrolytes ions and zwitterionic form of L-histidine due to stronger ion-ion interaction than ion–dipole interaction. Consequently, in the electrolytic solution, H_2O become free that enhances the entropy of the system, electrolytes also help in crumbling up the H-bonding exhibit between water molecules, resulting in an additional contribution to the rise of gross entropy of the system.

The hydration concept is another explanation to conclude the more ordered value. The smaller Na^+ is highly solvated in water compared to K^+ leading to hydrated Na^+ being more stable. Thus L-histidine interacts more strongly with H_2O in the presence of KCl and therefore, water molecules move less freely in KCl-histidine-water system creating less disordered and resulting in lowering $T\Delta S_t^0(i)$ values in KCl-H_2O system.

5. Conclusion

In this study, solvable capabilities and relevant parameters related to the thermodynamics of l-histidine were evaluated in aqueous and NaCl/KCl-H_2O solvent systems at equidistant temperatures. The experimental conclusion shows that size, salting in/out constant, hydrocarbon part etc influence to a large extent the variations of the measured properties. Several interactions like dipole–dipole, H-bonding etc are also considered as the important factors influencing many properties in this study. Additionally, this study finds that for a certain electrolyte concentration value, L-histidine solubility raises with increasing temperature in both mentioned solvent system and the present amino acid is more stable in KCl-H_2O system rather than NaCl-water system. The solubility data and other related solvation thermodynamics are very needful in the vast region of amino acid research particularly in medicine and drug industry, bio-inorganic and industrial area.

CRediT authorship contribution statement

Avishek Saha: Investigation, Data curation. **Kalachand Mahali:** Investigation, Data curation. **Simanta Kundu:** Investigation, Data curation. **A.M.A. Henaish:** Conceptualization. **Jahangeer Ahmed:** Conceptualization, Methodology. **A.H.S. Rana:** Conceptualization. **Sanjay Roy:** Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2023.123240.

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