

Thermodynamic Study of L-alanine in Aqueous Solutions of 1-Hexyl-3-Methylimidazolium Ibuprofenate as an Active Pharmaceutical Ingredient Ionic Liquid (API-IL)

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In this study, density, viscosity, speed of sound, electrical conductivity and refractive index data are presented for L-alanine in the aqueous solutions of 1-hexyl-3-methylimidazolium ibuprofenate at $T = 298.15$ K. Using the measured data, partial molar volume of transfer ($\Delta_{tra}V_{\phi}^0$), partial molar isentropic compressibility of transfer ($\Delta_{tra}K_{\phi}^0$), viscosity B -coefficient of transfer ($\Delta_{tra}B$), ion association constant (K_A) and molar refraction (R_D) quantities were calculated. The obtained parameters provide the information about the solvation properties of aqueous solutions of L-alanine in the presence of [HMIm][Ibu]. The positive values of $\Delta_{tra}V_{\phi}^0$, $\Delta_{tra}K_{\phi}^0$ and $\Delta_{tra}B$ are indicative of the ion-polar and polar-polar interactions between [HMIm][Ibu] and L-alanine. In addition, decreasing the K_A values with addition of L-alanine to the [HMIm][Ibu] solutions suggests that the ion pair formation do not proceed spontaneously at higher concentrations of amino acid.

Keywords: 1-Hexyl-3-methylimidazolium ibuprofenate, The Partial molar volume of transfer, Viscosity B -coefficient, Molar conductivity

INTRODUCTION

In recent years, the combination of active pharmaceutical ingredient (API) with the second generation of ionic liquid (IL) has created the third generation of ionic liquid namely API-IL [1-3]. This new form of API presents the improved solubility, drug delivery, and bioavailability due to its hydrophobicity and hydrophilicity nature [4-7]. Viau and Pinto *et al.* [8,9] introduced the two new synthesized API-ILs, 1-butyl-3-methylimidazolium ibuprofenate and salicylate as new gels for drug delivery with excellent properties.

Recently, some references have reported the thermodynamic properties of the mixtures containing amino acid and first generation of ionic liquid in aqueous media at different temperatures [10-15]. For the first time, shekaari *et al.* [15-17] investigated the effect of the active

pharmaceutical ingredients in the ionic liquids form (API-ILs), 1-butyl-3-methylimidazolium salicylate and ibuprofenate on the thermodynamic properties of glycine, and L-alanine in aqueous media. The obtained results showed that the dominant interactions between the studied amino acid and API-IL are the ion-polar and polar-polar interactions.

The present work is a continuation of our systematic thermodynamic studies of the ternary systems (amino acid + API-IL + water) [15-18]. In this research, the effect of the synthesized API-IL, 1-hexyl-3-methylimidazolium ibuprofenate, [HMIm][Ibu] on the thermodynamic properties of L-alanine solutions was studied. These properties provide the information about the molecular mechanism interactions between API-IL and the studied amino acid which are useful for designing and improving the biotechnological processes [19-22]. To this end, the density, speed of sound, viscosity, electrical conductivity and refractive index data of L-alanine in the aqueous

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solutions of 1-hexyl-3-methylimidazolium ibuprofenate, [HMIm][Ibu] were measured at $T = 298.15$ K and atmospheric pressure. The measured data were used to compute the partial molar volume of transfer $\Delta_{tr}V_{\phi}^0$, partial molar isentropic compressibility of transfer $\Delta_{tr}\kappa_{\phi}^0$, viscosity B -coefficients, ion association constants K_A , molar refraction R_D , and other calculated parameters are used to describe the solute-solute and solute-solvent interactions.

MATERIALS AND METHODS

Materials

Table 1 gives the provenance, CAS number, purity in mass fraction and analysis method of the used materials. The double distilled deionized water was used with a specific conductivity less than $1 \mu\text{s cm}^{-1}$ at 298.15 K.

Synthesis of Ionic Liquid

The new API-IL, 1-hexyl-3-methylimidazolium ibuprofenate, [HMIm][Ibu] (see the structure in Fig. 1) was prepared from 1-hexyl-3-methylimidazolium chloride [HMIm][Cl] and sodium ibuprofenate [Na][Ibu], respectively. [HMIm][Ibu] was synthesized and purified according to the standard methods reported in the literature [23-27]. The water content of prepared ionic liquid, [HMIm][Cl], using the Karl Fischer method was less than 0.05% in mass fraction. Characterization of the ionic liquid by ^1H NMR spectroscopy as compared with the literature confirmed the absence of any significant impurities [26]. The purity of prepared ionic liquid was 98% in mass fraction.

To synthesize the 1-hexyl-3-methylimidazolium ibuprofenate ionic liquid [HMIm][Ibu], (0.4 mol) [Na][Ibu] was dissolved in dried ethanol and added slowly to (0.4 mol) [HMIm][Cl] dissolved in a minimum amount of dried acetonitrile. In the first reaction, the temperature of the mixture was slowly increased to 353.15 K for 3 h. Then, the temperature was reduced to the room temperature and stirred overnight. Then, the solvent was extracted using the rotary evaporator at 350 K and reduced pressure. The resulting mixture was subsequently dissolved in a large amount of dichloromethane to observe white precipitate containing sodium chloride. The white precipitate was then

frequently filtered up to the point that no white solid was observed with the addition of dichloromethane [23,25]. The silver test confirmed the lack of sodium chloride. The obtained product (a yellowish solid) was further evaporated at 343.15 K by rotary evaporator [26]. The water content of the [HMIm][Ibu] determined using coulometric Karl Fischer titrator (Metrohm 756 KF) was approximately 0.1% in mass fraction. The ^1H NMR (Bruker Av-400) spectroscopy was applied to characterize the prepared API-IL, and its chemical shifts are:

The ^1H NMR (400 MHz, CDCl_3) of [HMIm][Ibu]: 10.80 (1H, s); 7.35 (2H, d); 7.33 (1H, d); 7.02 (1H, d); 6.99 (2H, d); 4.22 (2H, t); 3.83 (3H, s); 3.62 (1H, q); 2.38 (2H, d); 1.76 (3H, m); 1.47 (3H, d); 1.18-1.29 (6H, m); 0.85-0.89 (9H).

Apparatus and Procedure

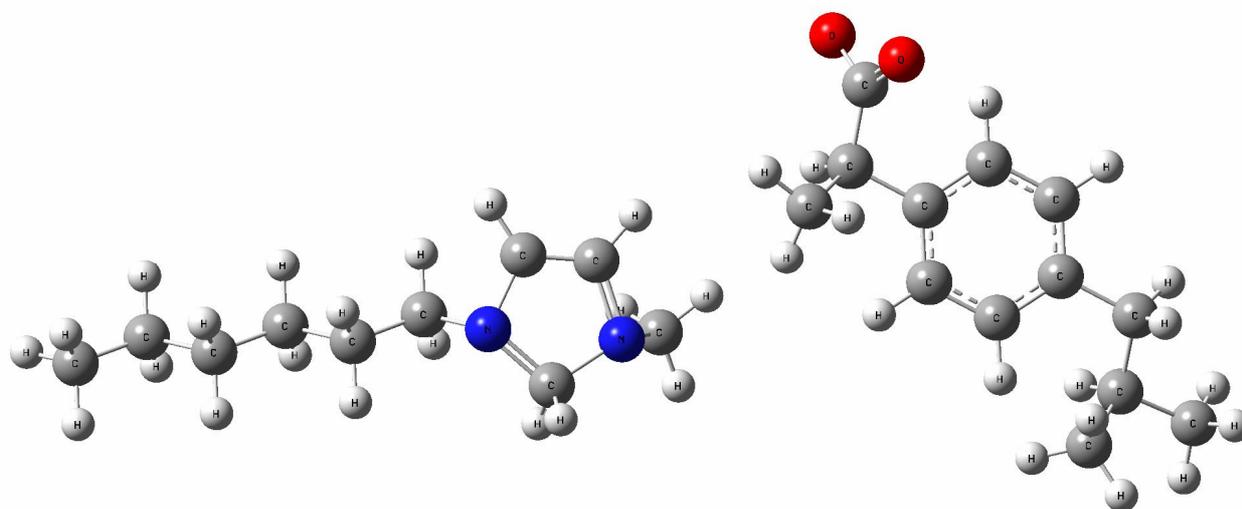
The density d and speed of sound u of the solutions were measured by vibrating tube densimeter, Anton Paar, DSA 5000. Distilled deionized and degassed water as well as dried air were applied to calibrate the instrument [28]. The temperature was kept constant within $\pm 10^{-3}$ K using the Peltier technique embedded in densimeter. The experimental uncertainty of density and speed of sound measurements were less than 0.3 kg m^{-3} and 0.5 m s^{-1} , respectively.

Anton Paar Rolling-ball viscometer Lovis 2000 M/ME was also applied to measure the viscosity of the solutions. The Peltier technique built in the thermostat controlled the temperature. The evaluated experimental uncertainty of the viscosity measurements was less than 0.015 mPa s .

The specific electrical conductivities, κ were measured by a conductivity meter (Metrohm model 712, Switzerland) with the accuracy of $\pm 0.5\%$. The instrument was calibrated using the measurement of specific electrical conductivities of the KCl solution with 0.01 molality. To measure the κ values, the weighed drop of pure API-IL was added into the cell container of the conductivity meter with 60 ml capacity which was agitating using a magnetic stirrer. The temperature was fixed by circulation of water from thermostatically adjusted bath around the cell with an uncertainty ± 0.02 K. The molar conductivity (Λ) values of the solutions were computed using the relation,

Table 1. A Sample Description of the Used Chemicals

Chemical name	CAS No.	Supplier	Initial mass fraction purity	Purification method	Final mass fraction purity	Analysis method
L-alanine	56-41-7	Merck	> 0.99	None	-	-
[HMIm][Ibu]	This work	Synthesized	-	Rotary/evaporator and vacuum	0.98	¹ H NMR
N-methylimidazole	7-47-616	Merck	> 0.99	None	-	-
1-Chlorohexane	544-10-5	Merck	≥ 0.98	None	-	-
Sodium ibuprofen	31121-93-4	Sigma aldrich	≥ 0.98	None	-	-
Ethyl acetate	6-78-14	Merck	> 0.998	None	-	-
Dichloromethane	75-09-2	Fluka	≥ 0.999	None	-	-

**Fig. 1.** The structure of 1-hexyl-3-methylimidazolium ibuprofenate ([HMIm][Ibu]).

$\Lambda = 1000\kappa/c$, where κ and c are the specific electrical conductivity and the molarity of the solutions, respectively.

Refractive indices n_D of the solutions were measured by a digital refractometer (ATAGO-DRA1, Japan) with an uncertainty of ± 0.002 . The temperature was kept constant using a circulating bath thermostat (Cooling Bath 490, Iran) with the thermal stability of ± 0.01 K.

Volumetric Properties

The density d of the solutions were used to calculate the apparent molar volumes:

$$V_\phi = \frac{M}{d} - \left[\frac{1000(d - d_0)}{md_0} \right] \quad (1)$$

where m and M are the molality and molar mass of L-alanine, and d_0 , d are the densities of the solvent ([HMIm][Ibu] + water) and ternary solutions. The calculated values of V_ϕ was correlated by the following equation:

$$V_\phi = V_\phi^0 + S_v m \quad (2)$$

where V_ϕ^0 is the standard partial molar volume and S_v is an experimental parameter. The extent of the interaction between L-alanine and [HMIm][Ibu] can be evaluated from the hydration number n_H using the following equation [29]:

$$n_H = \frac{V_\phi^0(\text{elect})}{V_E^0 - V_B^0} \quad (3)$$

where $V_\phi^0(\text{elect})$ is the molar volume of electrostrictive water, and V_B^0 is the molar volume of the bulk water. The value of $(V_E^0 - V_B^0) \approx 3.0 \text{ cm}^3 \text{ mol}^{-1}$ is for electrolytes at 298.15 K, and the $V_\phi^0(\text{elect})$ values were obtained by [30]:

$$V_\phi^0(\text{elect}) = V_\phi^0 - V_\phi^0(\text{int}) \quad (4)$$

where $V_\phi^0(\text{int})$ is the intrinsic partial molar volume which originates from the hydration of L-alanine zwitterions. The $V_\phi^0(\text{int})$ term is obtained from the combination of the volume from van der Waals and packing effects from the following equation [31]:

$$V_\phi^0(\text{int}) = \frac{0.7}{0.634} V_\phi^0(\text{cryst}) \quad (5)$$

where $V_\phi^0(\text{cryst}) = \frac{M}{d(\text{cryst})}$ is the molar volume of the crystal

computed using the densities of the amino acid (crystal form) supposed by Berlin and Pallansch at 298.15 K [32].

Another suitable parameter to determine the extent of the interactions existing in the studied system is the partial molar volume of transfer calculated through Eq. (6) [33]:

$$\Delta_{tra} V_\phi^0 = V_\phi^0([\text{HMIm}][\text{Ibu}] + \text{water}) - V_\phi^0(\text{in water}) \quad (6)$$

The data for the binary systems, L-alanine water, used

in the calculations were taken from the earlier published data [15,16].

Ultrasonic Properties

The measured speed of the sound values for the studied solutions was used to calculate the $\kappa_s(\text{Pa}^{-1})$ through the Laplace-Newton's equation as follows,

$$\kappa_s = \frac{1}{du^2} \quad (7)$$

The following equation was used to calculate the apparent molar isentropic compressibility κ_ϕ [34] for understanding the solvent structure around the amino acid as well as in bulk,

$$\kappa_\phi = \frac{(\kappa_s d_0 - \kappa_{s0} d)}{m d d_0} + \kappa_s \frac{M}{d} \quad (8)$$

where κ_{s0} and κ_s are the isentropic compressibilities of the solvent (aqueous solutions of [HMIm][Ibu]) and ternary solutions (L-alanine in the aqueous solutions of [HMIm][Ibu]), respectively.

The partial apparent molar isentropic compressibility κ_ϕ^0 value can be calculated from the extrapolation of the apparent molar isentropic compressibility κ_ϕ to an infinite dilution using the following linear equation:

$$\kappa_\phi = \kappa_\phi^0 + S_k m$$

where S_k , m are the experimental slope and the molality of L-alanine in the solutions, respectively. The partial molar isentropic compressibility of transfer $\Delta_{tra} \kappa_\phi^0$ of L-alanine from water to the aqueous solutions of [HMIm][Ibu] was calculated using the following equation:

$$\Delta_{tra} \kappa_\phi^0 = \kappa_\phi^0([\text{HMIm}][\text{Br}] + \text{water}) - \kappa_\phi^0(\text{water}) \quad (10)$$

The positive values of $\Delta_{tra} \kappa_\phi^0$ supports the dominant role of the ion-polar and polar-polar interactions, and negative values indicate the ion-nonpolar and nonpolar-nonpolar interactions [33,34].

Pair and Triplet Interaction Coefficients

McMillan and Mayer [35] theory developed by Friedman and Krishnan [36], suggests a simple method for calculation of the interaction coefficients between two or more solute molecules. In this regard, the following two equations were applied to evaluate the partial molar volume of transfer and partial molar isentropic compressibility of transfer:

$$\Delta_{tra}V_{\phi}^0 = 2V_{AB}m_{API-IL} + 3V_{ABB}m_{API-IL}^2 \quad (11)$$

$$\Delta_{tra}\kappa_{\phi}^0 = 2\kappa_{AB}m_{API-IL} + 3\kappa_{ABB}m_{API-IL}^2 \quad (12)$$

where A denotes L-alanine, B denotes [HMIm][Ibu] and m_{API-IL} is the molality of [HMIm][Ibu] in water.

Viscometric Properties

Viscosity B -coefficients is one of the other parameters used to study the solute-solvent interactions. In this regard, the Jones-Dole equation represents the variation of the relative viscosity $\eta_r = \eta/\eta_0$ of the amino acid in the aqueous solutions of API-IL [37,38].

$$\eta_r = 1 + Ac^{1/2} + Bc \quad (13)$$

The A -coefficient (also called Falkenhagen coefficient, indicating the solute-solute interactions) can be theoretically calculated but are usually small (negligible for nonelectrolytes). The viscosity B -coefficients essentially illustrate the solute-solvent interactions. In fact, by neglecting the A -coefficient in Eq. (14), it is simplified to the following equation:

$$\eta_r = 1 + Bc \quad (14)$$

where η and η_0 are the viscosities of the solutions (L-alanine

in the aqueous solution of [HMIm][Ibu] and solvent ([HMIm][Ibu] + water), respectively, and c is the molar concentration of L-alanine in the studied solutions. The slope of the linear plot of $(\eta_r - 1)$ vs. c using the least square method was used to calculate the viscosity B -coefficients.

The following relation presents the variation of B -

coefficients, $\Delta_{tra}B$, from water to the aqueous [HMIm][Ibu] solutions:

$$\Delta_{tra}B = B\text{-coefficients} ([HMIm][Ibu] + \text{water}) - B\text{-coefficients} (\text{water}) \quad (15)$$

Feakins and co-worker analyzed the viscosity data bases on the transition state treatment of the relative viscosity. The following relation gives the viscosity B -coefficient regarding this theory:

$$B = (\bar{V}_1^0 - \bar{V}_2^0) + \bar{V}_1^0 \left(\frac{\Delta\mu_2^{\circ\ddagger} - \Delta\mu_1^{\circ\ddagger}}{RT} \right) \quad (16)$$

where $(\bar{V}_1^0 = \sum \frac{x_i M_i}{\rho})$ is the mean volume of the solvent and $(\bar{V}_2^0 = V_{\phi}^0)$ is the standard partial molar volume of the pure solute. The terms \bar{V}_1^0 , x_i , M_i and ρ are the molar volume of the pure solvent, mole fraction, molar mass and density of the solvent ([HMIm][Ibu] + water), respectively. Eyring's simple model was used to calculate the free energy of activation per mole of the solvent $\Delta\mu_1^{\circ\ddagger}$ and $\Delta\mu_2^{\circ\ddagger}$ as follows:

$$\Delta\mu_1^{\circ\ddagger} = \Delta G_1^{\circ\ddagger} = RT \ln \frac{\eta_1 V_1^0}{h N_A} \quad (17)$$

$$\Delta\mu_2^{\circ\ddagger} = \Delta\mu_1^{\circ\ddagger} + \frac{RT}{V_1^0} [B - (\bar{V}_1^0 - \bar{V}_2^0)] \quad (18)$$

where h is the Planck's constant, N_A is the Avogadro number, η_0 is the viscosity of the solvent and the other symbols have their usual meanings. Table 3 presents the calculated values of $\Delta\mu_1^{\circ\ddagger}$ and $\Delta\mu_2^{\circ\ddagger}$ [38,39].

Conductometric Properties

Another appropriate way to interpret the possible ionic interactions are the molar conductivity and ion association of API-IL. In this respect, the molar conductivity data for [HMIm][Ibu] in the aqueous solution of L-alanine was determined.

The Onsager model was used to estimate the initial guess of limiting molar conductivity Λ_0 and ion association constant K_A . The low concentration Chemical Model

(lcCM) was used to calculate the real Λ_0 and K_A of the API-IL in the studied solutions [39,40]. The following equations represent the lcCM model:

$$\Lambda = \alpha[\Lambda_0 - S(c\alpha)^{1/2} + Ec\alpha \ln(c\alpha) + J_1c\alpha + J_2(c\alpha)^{3/2}] \quad (19)$$

$$K_A = \frac{1-\alpha}{\alpha^2 c \gamma_{\pm}^2} \quad (20)$$

$$\ln \gamma_{\pm} = \frac{\kappa q}{1 + \kappa R} \quad (21)$$

$$\kappa^2 = \frac{16000 N_A z^2 e^2 \alpha c}{\epsilon_0 \epsilon K_B T} \quad (22)$$

$$q = \frac{z_+ z_- e^2}{8\pi \epsilon_0 \epsilon k T} \quad (23)$$

in which Λ_0 is the molar conductivity at infinite dilution, $(1-\alpha)$ is the fraction of oppositely charged ions acting as ion pairs, γ_{\pm} is the corresponding mean activity coefficient of the free ions, κ is the Debye parameter, e is the electronic charge, z is the ionic charge, ϵ_0 is the permittivity of vacuum, ϵ is the dielectric constant of the solvent, and the other symbols have their usual meanings. The required coefficients E , J_1 , and J_2 for calculations were taken from the literature [41]. The parameter R represents the center-to-center distance between the ions in the formed ion pairs in the solutions [42-44].

To eliminate the effect of viscosity on the ionic mobility, the Walden product $\Lambda_0 \eta_0$ was calculated. As the conductivity of the ions at infinite dilution only depends on their mobility and the product of the viscosity of the solvent by the ion conductivity is independent of the solvent nature [44,45].

The standard deviations of the experimental molar conductivities (Λ) and the calculated ones (Λ_{cal}) were computed as follows:

$$\sigma(\Lambda) = \left[\frac{\sum (\Lambda - \Lambda_{cal})^2}{n-p} \right]^{1/2} \quad (24)$$

where n and p show the number of experimental data and

parameters, respectively. Table 5 lists the calculated standard deviations of electrical conductivity using lcCM model.

Diffusion Coefficients and Walden Products of Ions

Diffusion coefficients of the API-IL at infinite dilution were calculated using their molar conductivities by the Nernst-Haskell equation [46] as follows:

$$D_{AB}^0 = \frac{RT}{F^2} \frac{|z_+||z_-|}{|z_+z_-|} \frac{\lambda_0^+ \lambda_0^-}{\lambda_0^+ + \lambda_0^-} \quad (25)$$

where D_{AB}^0 is the diffusion coefficient of API-IL (A) in water (B) at infinite dilution in $\text{m}^2 \text{s}^{-1}$, F is the Faraday's constant, z^+ and z^- are the charge numbers of the cation and anion, λ_0^+ and λ_0^- are the limiting molar conductivities of the cation and anion in $\text{S m}^2 \text{mol}^{-1}$, respectively. Equation 26 determines the ionic limiting molar conductivity values of the individual ions:

$$\Lambda_0 = z_+ \lambda_0^+ + z_- \lambda_0^- \quad (26)$$

The ionic limiting molar conductivity λ_0^+ in water was obtained from the literature [45]. The diffusion coefficients of the individual ions are also calculated using the following equation [47,48]:

$$D_{ion}^0 = \frac{RT\lambda_0}{|z_{ion}|F^2} \quad (27)$$

The D_{ion}^0 and η values of the pure water were used to evaluate the Stoke's radius (r_s) or effective hydrodynamic radius of the ions which is closely related to solute mobility and affected by not only size but also the solvent.

$$r_s = \frac{kT}{6\pi\eta D_{ion}^0} \quad (28)$$

Replacing Eq. (28) in Eq. (27) and its rearrangement results in the following relation [49]:

$$\lambda_0 \eta = \frac{k|z_{ion}|F^2}{6\pi R r_s} \quad (29)$$

This equation reveals that there is an inverse relationship between the effective hydrodynamic radius of an ion and its Walden product ($\lambda_0\eta$). Since all parameters in the right hand of Eq. (29) except r_s are constant, the Walden product must vary only if the r_s value changes.

The ion transport number, called the transference number, is the contribution of an ion to the total molar conductivity of the solution. This parameter can be determined according to the following equation:

$$t_{\pm} = \frac{\lambda_0}{A_0} \quad (30)$$

The symbols t_+ and t_- are usually used to express the transport numbers of cation and anion, respectively.

The standard Gibbs free energy (ΔG_A°) of the ion-association process was obtained using the ion association constants.

Refractometric Properties

Experimental refractive index data n_D for (L-alanine + [HMIm][Ibu] + water) solutions was used to calculate the molar refraction R_D the using Lorentz-Lorenz equation [46]:

$$R_D = \left[\frac{n_D - 1}{n_D^2 + 2} \right] \left(\sum_{i=1}^3 \frac{x_i M_i}{d} \right) \quad (31)$$

where x_i , M_i and d are the mole fraction and molar mass of the components, and density of the solutions, respectively.

RESULTS AND DISCUSSION

Volumetric Properties

The density d of L-alanine in the aqueous solutions of [HMIm][Ibu] (0.1085, 0.1963 and 0.2946) mol kg⁻¹ were measured, and are reported in Table 2. As can be seen in this table, the densities increase with the solute (L-alanine) as well as with the co-solute ([HMIm][Ibu]) concentrations.

Table 2 reports the values of V_ϕ for the studied solutions. Moreover, Fig. 2 shows the apparent molar volume of L-alanine in the aqueous solutions of [HMIm][Ibu] with several molalities of [HMIm][Ibu] which

increases with an increase in the [HMIm][Ibu] concentration. This phenomenon might be due to the expansion of the hydration layer surrounding the L-alanine zwitterions. Table 3 lists the evaluated values of V_ϕ^0 , S_v , and their corresponding standard deviation $\sigma(V_\phi)$ derived from the least squares fitting of the V_ϕ values by Eq. (2).

Table 3 gives also the calculated n_H values of L-alanine in the aqueous solutions of [HMIm][Ibu] which are reduced with increase in the API-IL concentration. At the high concentration of API-IL, the molecular structure of water around the amino acid are disrupted and they are released to the bulk, and therefore, the hydration number decreases.

The calculated values of $\Delta_{tra}V_\phi^0$ for the studied solutions, given in Table 3, are positive and increase with an increase in the [HMIm][Ibu] concentrations. The observed positive values $\Delta_{tra}V_\phi^0$ indicate the ion-polar and polar-polar interactions between [HMIm][Ibu] and L-alanine. According to the co-sphere overlap model, the contribution of the solute-solute interactions is negligible, and hence the information about the solute-solvent interactions can be obtained. The nature of the interactions between L-alanine and [HMIm][Ibu] may be categorized as: (i) ion-polar interactions, (ii) polar-polar interactions, (iii) ion-nonpolar interactions, and (iv) nonpolar-nonpolar interactions.

Based on the co-sphere overlap model, the ion-nonpolar and nonpolar-nonpolar interactions have a negative effect contribution on the $\Delta_{tra}V_\phi^0$ values while the effective contribution of the ion-polar and polar-polar interactions are positive. The strong attractive interaction cause to increase the hydration layer volume of L-alanine in the solutions while the repulsive interaction reduce these layer and therefore V_ϕ^0 . The obtained $\Delta_{tra}V_\phi^0$ values presented in Table 3. By increasing in the [HMIm][Ibu] concentration, the $\Delta_{tra}V_\phi^0$ values increase which suggests the stronger interactions between the zwitterionic center of L-alanine and the ions of [HMIm][Ibu] at higher concentration of API-IL [33,34].

Ultrasonic Properties

Table 2 reports the speed of sound values, u , and κ_ϕ values measured for the studied solutions (L-alanine +

Table 2. The Values of Density (d), Apparent Molar Volume (V_ϕ), Speed of Sound (u), Apparent Molar Isentropic Compressibility (κ_ϕ), Viscosity (η), Refractive Index (n_D) and Molar Refraction (R_D) of L-alanine in the Aqueous Solutions of [HMIIm][Ibu] at $T = 298.15$ K and 0.0868 MPa^a

m^b (mol kg ⁻¹)	$10^{-3}d$ (Kg m ⁻³)	$10^6 V_\phi$ (m ³ mol ⁻¹)	u (m s ⁻¹)	$10^{14} \kappa_\phi$ (m ³ mol ⁻¹ Pa ⁻¹)	η (mPa s)	n_D	$10^6 R_D$ (m ³ mol ⁻¹)
L-Alanine in ([HMIIm][Ibu] + water)							
$m_{\text{API-IL}} = 0.1085$ mol kg ⁻¹							
0.0000	0.998270		1511.21		1.128	1.3407	3.923
0.1008	1.001114	60.76	1517.32	-2.10	1.159	1.3426	3.964
0.1480	1.002432	60.78	1520.21	-2.10	1.173	1.3433	3.979
0.2001	1.003871	60.82	1523.35	-2.08	1.189	1.3441	3.996
0.2474	1.005166	60.86	1526.20	-2.07	1.202	1.3448	4.012
0.2983	1.006549	60.89	1529.29	-2.06	1.219	1.3455	4.027
0.3492	1.007919	60.93	1532.38	-2.05	1.234	1.3463	4.044
0.3983	1.009235	60.95	1535.31	-2.04	1.247	1.3470	4.060
0.4669	1.011061	60.97	1539.46	-2.03	1.267	1.3481	4.083
$m_{\text{API-IL}} = 0.1963$ mol kg ⁻¹							
0.0000	0.999121		1520.62		1.346	1.3456	4.099
0.0990	1.001888	61.00	1526.17	-1.76	1.384	1.3468	4.150
0.1507	1.003318	61.02	1529.12	-1.78	1.402	1.3475	4.166
0.2026	1.004741	61.04	1532.15	-1.80	1.421	1.3481	4.181
0.2490	1.006008	61.04	1534.92	-1.82	1.440	1.3487	4.196
0.2985	1.007351	61.05	1537.90	-1.84	1.455	1.3493	4.211
0.3634	1.009096	61.06	1541.89	-1.87	1.474	1.3501	4.231
0.3965	1.009980	61.07	1543.94	-1.88	1.492	1.3505	4.241
0.4437	1.011230	61.09	1546.90	-1.89	1.511	1.3511	4.255
$m_{\text{API-IL}} = 0.2946$ mol kg ⁻¹							
0.0000	1.000105		1528.48		1.551	1.3508	4.289
0.1413	1.003999	61.29	1536.34	-1.67	1.613	1.3527	4.396
0.1685	1.004735	61.32	1537.90	-1.68	1.624	1.3531	4.408
0.1986	1.005555	61.31	1539.66	-1.70	1.637	1.3535	4.420
0.2509	1.006959	61.35	1542.69	-1.71	1.660	1.3543	4.442
0.2962	1.008168	61.37	1545.35	-1.72	1.679	1.355	4.461
0.3471	1.009504	61.43	1548.41	-1.73	1.702	1.3557	4.482
0.3965	1.010801	61.45	1551.31	-1.74	1.723	1.3564	4.502
0.4402	1.011951	61.45	1553.92	-1.74	1.743	1.3571	4.521

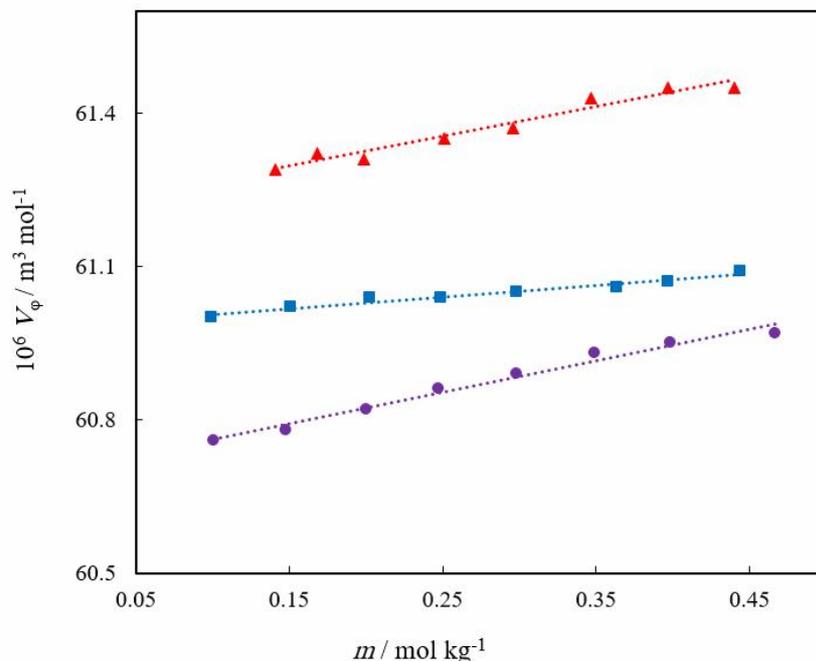


Fig. 2. The apparent molar volume of L-alanine in the solutions of ([HMIm][Ibu] + water) with 0.1 (●), 0.2 (■) and 0.3 (▲) molalities at $T = 298.15 \text{ K}$.

[HMIm][Ibu] + water). As seen in this table, the u values increase as the ionic liquid concentration increases. The apparent molar isentropic compressibilities of L-alanine in the solutions of [HMIm][Ibu] with different molalities are presented in Fig. 3. Based on Table 2 and Fig. 3, the κ_ϕ values increase with an increase in the [HMIm][Ibu] concentrations indicating an increase in the API-IL-amino acid interactions and release of the water molecules from the solvation layer to the bulk.

The obtained κ_ϕ^0 , S_κ , $\Delta_{tra}\kappa_\phi^0$ values for the studied solutions in addition to the standard deviation $\sigma(\kappa_\phi)$ are given in Table 3. As can be in this table, the κ_ϕ^0 values increase with an increase in the [HMIm][Ibu] concentrations. This phenomenon suggests the strong interactions between API-IL and L-alanine because of more compressibility of the hydration layer [35,36]. The positive values of the $\Delta_{tra}\kappa_\phi^0$ support the dominance of the ion-polar and polar-polar interactions between the head charged groups (NH_3^+ and COO^-) of L-alanine and ions of

[HMIm][Ibu] which are more favorable at the high concentration of API-IL [33,39].

Pair and Triplet Interaction Coefficients

The evaluated pairwise interaction coefficients V_{AB} and κ_{AB} are positive, while triplet interaction coefficients V_{ABB} and κ_{ABB} are negative for the studied systems (see Table 3). The positive values of V_{AB} and κ_{AB} predict that the frequent interactions between [HMIm][Ibu] and L-alanine in the solutions are mostly pairwise [38].

Viscometric Properties

The measured viscosities η of (L-alanine + [HMIm][Ibu] + water) with several molalities of ([HMIm][Ibu] + water) were listed in Table 2. The viscosities of (L-alanine + [HMIm][Ibu] + water) solutions with several molalities were presented in Fig. 4. In this figure, the viscosities increase with an increase in the concentration of [MHIm][Ibu] as well as L-alanine.

The slope of the linear plot of $(\eta_r - 1)$ vs. c using the least square method was used to calculate the viscosity B -

Table 3. The Values of Standard Apparent Molar Volume, V_{ϕ}^0 , Experimental Slope, S_v , Transfer Volume $\Delta_{tra}V_{\phi}^0$, Partial Molar Isentropic Compressibility κ_{ϕ}^0 , Partial Molar Isentropic Compressibility of Transfer $\Delta_{tra}\kappa_{\phi}^0$, Hydration Number n_H Viscosity B -coefficient (B), Free Energy of Activation per Mole of Solvent ($\Delta\mu_1^{\circ\#}$) and the Solute ($\Delta\mu_2^{\circ\#}$), Viscosity B -coefficients of Transfer ($\Delta_{tra}B$), Pair (V_{AB} and κ_{AB}) and Triplet (V_{ABB} and κ_{ABB}) Interaction Coefficients of L-alanine in the Aqueous Solutions of [HMIm][Ibu] at $T = 298.15$ K and 0.0868 MPa

m_{API-IL} (mol kg ⁻¹) ^a	$10^6 V_{\phi}^0$ (m ³ mol ⁻¹)	$10^6 S_v$ (m ³ mol ⁻² kg)	$10^6 \sigma(V_{\phi})$	$10^6 \Delta_{tra}V_{\phi}^0$ (m ³ mol ⁻¹)	n_H
0.1085	60.69 ± 0.012	0.63 ± 0.034	0.01	0.72	3.35
0.1963	60.98 ± 0.005	0.23 ± 0.015	0.01	1.01	3.26
0.2946	61.21 ± 0.018	0.57 ± 0.005	0.02	1.24	3.19
m_{API-IL} (mol kg ⁻¹) ^a	$10^{14} \kappa_{\phi}^0$ (m ³ mol ⁻¹ Pa ⁻¹)	$10^{14} S_{\kappa}$ (m ³ mol ⁻² kg Pa ⁻¹)	$10^{14} \sigma(\kappa_{\phi})$	$10^{14} \Delta_{tra}\kappa_{\phi}^0$ (m ³ mol ⁻¹ Pa ⁻¹)	
0.1085	-2.02 ± 0.01	-0.95 ± 0.04	0.01	0.63	
0.1963	-1.70 ± 0.02	-0.85 ± 0.06	0.01	0.95	
0.2946	-1.53 ± 0.01	-0.79 ± 0.02	0.00	1.13	
m_{API-IL} (mol kg ⁻¹) ^a	B (dm ³ mol ⁻¹)	$\Delta\mu_1^{\circ\#}$ (kJ mol ⁻¹)	$\Delta\mu_2^{\circ\#}$ (kJ mol ⁻¹)	$\Delta_{tra}B$ (dm ³ mol ⁻¹)	
0.1085	0.267 ± 0.002	9.84	50.86	0.010	
0.1963	0.273 ± 0.001	10.35	50.86	0.016	
0.2946	0.280 ± 0.001	10.78	50.86	0.023	
	$10^6 V_{AB}$ (m ³ mol ⁻² kg)	$10^6 V_{ABB}$ (m ³ mol ⁻³ kg ²)	$10^{14} \kappa_{AB}$ (m ³ mol ⁻² kg Pa ⁻¹)	$10^{14} \kappa_{ABB}$ (m ³ mol ⁻³ kg ² Pa ⁻¹)	
	3.82	-3.92	3.24	-3.37	

coefficients. Table 3 lists the calculated viscosity B -coefficients and $\sigma(\eta)$ of the studied solutions [33,37,39]. The viscosity B -coefficients of L-alanine in the [HMIm][Ibu] solutions are higher than those in water, and therefore, the $\Delta_{tra}B$ values are positive and increase with an increase in the API-IL concentration. This trend confirms the stronger interaction between solute-co-solute rather than solute-water.

Table 3 presents the calculated values of $\Delta\mu_1^{\circ\#}$ and $\Delta\mu_2^{\circ\#}$. It is clear that the values of $\Delta\mu_2^{\circ\#}$ are positive and

more significant than $\Delta\mu_1^{\circ\#}$ for both API-IL solutions which indicate the stronger interactions between solute (L-alanine) and solvent ([HMIm][Ibu] + water) in the ground state compared to that in the transition state. In fact, more energy is required to flow the ternary mixtures of (L-alanine + [HMIm][Ibu] + water) rather than ([HMIm][Ibu] + water) mixtures. The values of $\Delta\mu_2^{\circ\#}$ increase with an increase in the concentration of API-IL solutions up to 0.3 mol kg⁻¹ [35-37].

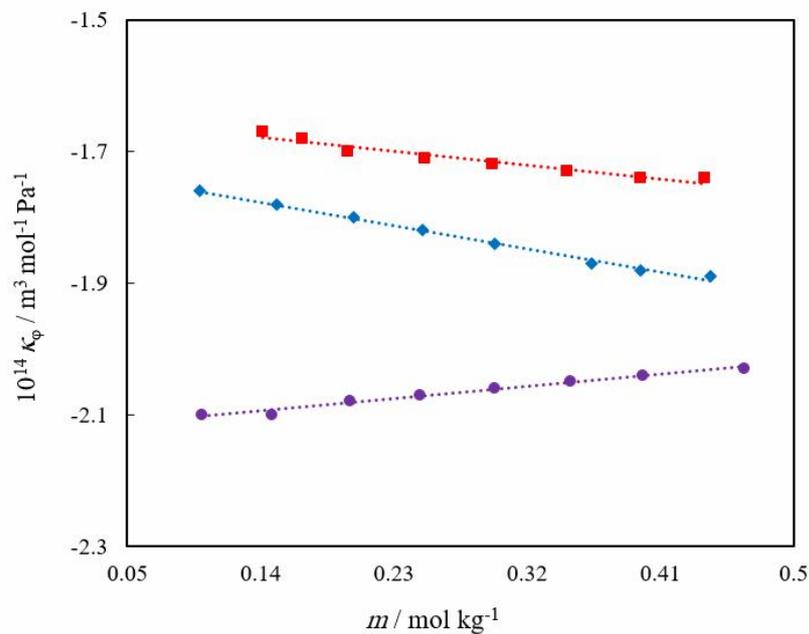


Fig. 3. The apparent molar isentropic compressibility of L-alanine in the solutions of ([HMIm][Ibu] + water) with 0.1 (●), 0.2 (◆) and 0.3 (■) molalities at $T = 298.15 \text{ K}$.

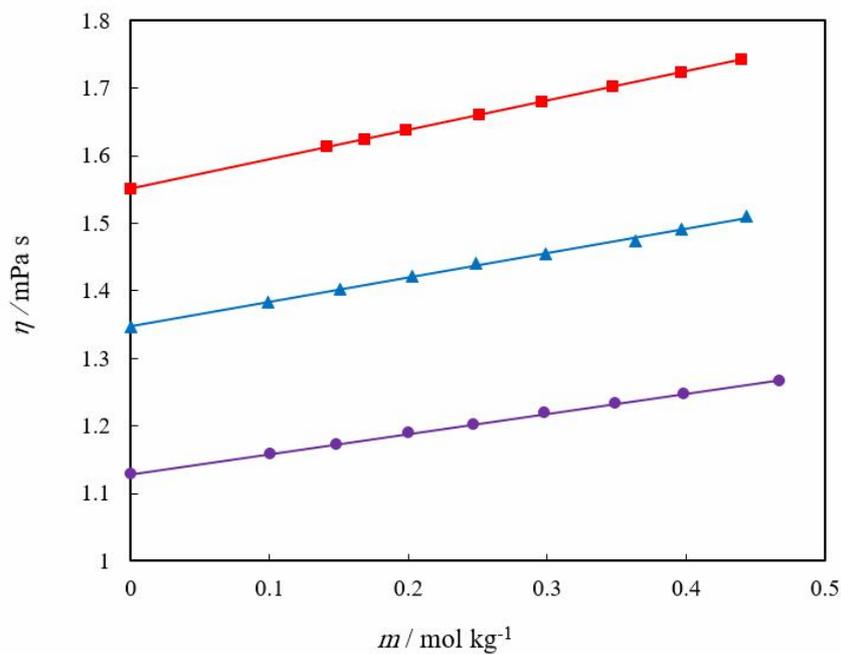


Fig. 4. The viscosity of (L-alanine + HMIm)[Ibu] + water) solutions with 0.1 (●), 0.2 (▲) and 0.3 (■) molalities at $T = 298.15 \text{ K}$.

Table 4. The Values of Molar Electrical Conductivity (Λ) of the [HMIm][Ibu] in Water and in the Aqueous Solutions of L-alanine as a Function of [HMIm][Ibu] Concentration at $T = 298.15$ K and 0.087 MPa^a

c (mol m ⁻³) ^b	$10^4 \Lambda$ (s m ² mol ⁻¹)	c (mol m ⁻³)	$10^4 \Lambda$ (s m ² mol ⁻¹)	c (mol m ⁻³)	$10^4 \Lambda$ (s m ² mol ⁻¹)	c (mol m ⁻³)	$10^4 \Lambda$ (s m ² mol ⁻¹)
[HMIm][Ibu]							
$m_{\text{Ala}} = 0.0$ (mol kg ⁻¹) ^c		$m_{\text{Ala}} = 0.1$ (mol kg ⁻¹)		$m_{\text{Ala}} = 0.3$ (mol kg ⁻¹)		$m_{\text{Ala}} = 0.5$ (mol kg ⁻¹)	
0.0627	53.79	0.0917	51.63	0.0691	46.88	0.0569	45.14
0.1251	53.21	0.1510	51.07	0.1362	46.45	0.1378	44.71
0.1850	52.52	0.2149	50.41	0.2066	46.05	0.2072	44.37
0.2617	51.91	0.2737	49.86	0.3055	45.55	0.2821	43.99
0.3319	51.09	0.3513	49.18	0.3783	45.06	0.3659	43.61
0.4034	50.40	0.4212	48.61	0.4815	44.60	0.4483	43.20
0.4699	49.69	0.4919	48.12	0.5743	44.11	0.5493	42.78
0.5524	48.90	0.5625	47.65	0.6456	43.78	0.6444	42.33
0.6376	48.12	0.6533	47.01	0.7046	43.45	0.7494	41.89
0.7259	47.36	0.7305	46.51	0.7828	43.15	0.8358	41.55
0.7833	46.83	0.7923	46.12	0.8829	42.66	0.9315	41.16
0.8380	46.30	0.8543	45.77	0.9797	42.22	1.0551	40.73
0.9021	45.95	0.9287	45.24	1.0735	41.79	1.0970	40.56
0.9550	45.47	1.0114	44.82	1.1719	41.43	0.0569	45.14
1.0667	44.74	1.0678	44.51	1.3079	40.93	0.1378	44.70

^aStandard uncertainties u are: $u(\Lambda) = 3 \times 10^{-6} \text{ s m}^2 \text{ mol}^{-1}$ and $u(T) = 0.01 \text{ K}$. ^bRelative standard uncertainties u_r for molarities of AP-IL is $u_r(c) = 0.004$. ^c m_{Ala} is the molal concentration of L-alanine in water.

Conductometric Properties

The values of molar conductivity, Λ , for [HMIm][Ibu] in water and in the aqueous L-alanine solutions are presented in Table 4 and compared in Fig. 5. As can be seen, the values of Λ decrease with an increment in the API-IL concentration due to ionic atmosphere effects. In fact, in more concentrated solutions, the ion pairing is responsible for the observed decrease in molar conductivities in addition to increase in the viscosity.

The evaluated Λ_0 , K_A and R values of the [HMIm][Ibu] in water and the aqueous L-alanine solutions are listed in Table 5. From this table, the values of Λ_0 decrease with an increase in the L-alanine concentration indicating the low mobility of the solvated ions by $(\text{COO}^-/\text{NH}_3^+)$ zwitterionic centers with large radii and increase in the viscosity of medium with the addition of L-alanine [22]. Moreover, decreased K_A values of API-IL with L-alanine concentration proposed the strong interaction of ions with zwitterions of

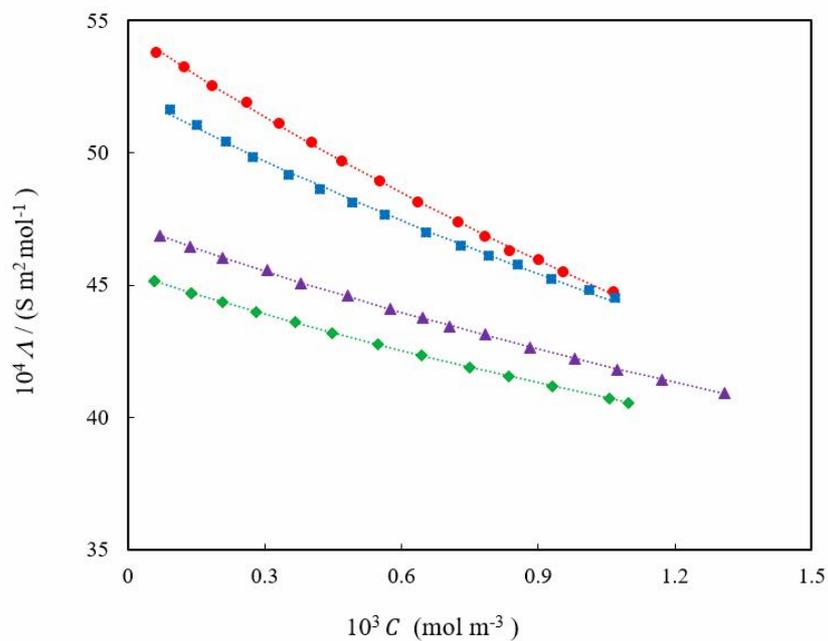


Fig. 5. The molar conductivity of [HMIm][Ibu] in water (●) and aqueous solutions of L-alanine with 0.1 (■), 0.3 (▲) and 0.5 (◆) molalities at $T = 298.15$ K.

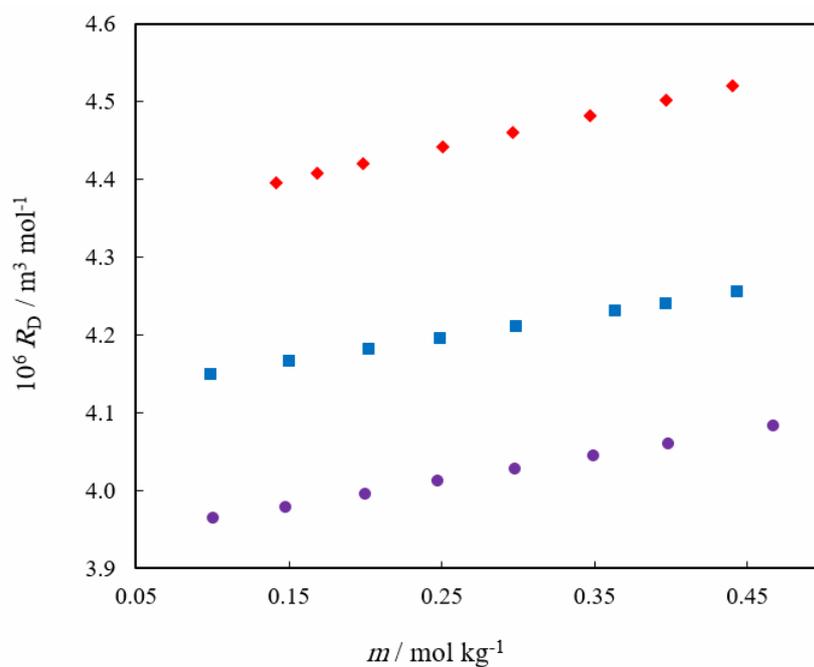


Fig. 6. The molar refraction of ternary mixtures of (L-alanine + [HMIm][Ibu] + water) with 0.1 (●), 0.2 (■) and 0.3 (◆) molalities of ([HMIm][Ibu] + water) at $T = 298.15$ K.

Table 5. The Values of Limiting Molar Conductivity (Λ_0), Walden Product ($\Lambda_0\eta$), Ion Association Constant (K_A), Standard Free Gibbs Energy of Ion-pairing Formation (ΔG_A^0), Distance Parameter (R) and Standard Deviation ($\sigma(\Lambda)$) of [HMIm][Ibu] in the Aqueous Solutions of L-alanine, and the Values of the Ionic Limiting Molar Conductivity (λ_0), Walden Product ($\lambda_0\eta$), Stoke's Radius (r_s), Diffusion Coefficient (D_{ion}^0) and Transport Number (t) of [HMIm]⁺ and [Ibu]⁻ for [HMIm][Ibu] in Water at $T = 298.15$ K and 0.087 MPa^a

m_{AA} (mol kg ⁻¹)	K_A (dm ³ mol ⁻¹) ^a	$10^4 \Lambda_0$ (s cm ² mol ⁻¹) ^a	$10^{10} R$ (m)	$\sigma(\Lambda)$	$10^4 \Lambda_0\eta$ (s cm ² mPa s mol ⁻¹)	ΔG_A^0 (kJ mol ⁻¹)
[HMIm][Ibu] in (L-alanine + water)						
0.1	21.99	52.34 ± 0.01	56.35	0.11	47.63	-7.66
0.3	18.21	47.36 ± 0.02	51.83	0.03	45.23	-7.19
0.5	14.84	45.52 ± 0.01	50.79	0.02	45.56	-6.69
Ions	$10^4 r_s$ (s m ² mol ⁻¹)	$10^4 \Lambda_0\eta$ (s cm ² mPa s mol ⁻¹)	$10^{10} r_s$ (m)	$10^{10} D_{ion}^0$ (m ² s ⁻¹)	t	ΔG_A^0 (kJ mol ⁻¹)
[HMIm][Ibu] in water						
[HMIm] ⁺	35.4 ^b	31.46	2.61	9.43	0.647	-8.52
[Ibu] ⁻	19.30	17.16	4.78	5.14	0.353	

^aThe estimated uncertainties for $u(K_A) = 0.2$ dm³ mol⁻¹, $u(10^4 \Lambda_0) = 0.04$ s m² mol⁻¹ and $u(T) = 0.01$ K. ^bThe λ_0 values of the cations were taken directly from Ref. [45].

amino acid and reduced the ion-pair formation in the concentrated solutions. The parameter R represents the maximum center-to-center distance between the ions or separated ion pairs in the solvent. The values of the distance parameter (R) have no meaningful trend [43,44].

Table 5 represents the calculated Walden product ($\Lambda_0\eta$) and standard deviations of electrical conductivity using lcCM model of the [HMIm][Ibu] in the aqueous L-alanine solution [45]. As seen in this table, the $\Lambda_0\eta$ values decrease by an increase in the API-IL concentration suggesting that the mobility of ionic liquid increases regardless of the viscosity of solution [44].

Diffusion Coefficients Walden Products of Ions

Table 5 presents the calculated values of D_{AB}^0 , λ_0 , D_{ion}^0 , r_s , $\lambda_0\eta$, ΔG_A^0 , t_+ , and t_- of [HMIm][Ibu] in water. As seen in

this table, the λ_0^+ is bigger than λ_0^- which means that the effect of cation on Λ_0 is more than that of anion. This point is also concluded by the larger value of r_s and smaller value of D_{ion}^0 and t for anion compared to cation. As seen in Table 5, the negative values are obtained for ΔG_A^0 in the ion association process of API-IL in water and L-alanine solutions. The large negative values of ΔG_A^0 for the [HMIm][Ibu] solutions indicate the more spontaneously and feasibility of the ion association process in this API-IL compared to [HMIm][Ibu] [17,44].

Refractometric Properties

Experimental refractive index data n_D and the calculated molar refractions R_D for (L-alanine + [HMIm][Ibu] + water) solutions with several molalities of ([HMIm][Ibu] + water) are reported in Table 2 and shown in Fig. 6. As observed in

this table, the R_D values increase with an increase in the API-IL concentration. As the molecular structure is more complicated, the electron cloud becomes more distributed, and the polarizability of the molecule is intensified.

CONCLUSIONS

The effect of active pharmaceutical ingredient based ionic liquid (API-IL), 1-hexyl-3-methylimidazolium ibuprofenate ([HMIm][Ibu]), on the volumetric, compressibility, viscometric, electrical conductivity and refractometric properties of L-alanine have been studied at $T = 298.15$ K. The positive values of partial molar volume of transfer $\Delta_{tra}V_\phi^0$, partial molar isentropic compressibility of transfer $\Delta_{tra}\kappa_\phi^0$, and viscosity B -coefficient of transfer indicate that the ion-polar and polar-polar interactions between L-alanine and [HMIm][Ibu] are dominant and according to the V_{AB} and κ_{AB} values which the pairwise interactions are more preferred. The low concentration Chemical Model (lcCM) model was used to evaluate the ion association constant (K_A), limiting molar conductivity (A_0), and distance parameter (R). The lower values of A_0 for [HMIm][Ibu] with the addition of L-alanine to the solution indicate the low mobility of the solvated ions by ($\text{COO}^-/\text{NH}_3^+$) zwitterionic centers with large radii and increase in the viscosity of the medium. From the thermodynamic data analysis, the more negative values of ΔG_A° for [HMIm][Ibu] in the L-alanine solutions with the addition of L-alanine concentration suggest the spontaneous ion-association process in this API-IL.

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