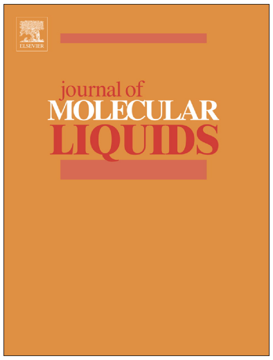

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PII: S0167-7322(18)34648-8
DOI: https://doi.org/10.1016/j.molliq.2019.01.030
Reference: MOLLIQ 10261

To appear in: *Journal of Molecular Liquids*

Received date: 9 September 2018
Revised date: 9 November 2018
Accepted date: 6 January 2019

Please cite this article as: Hemayat Shekaari, Mohammed Taghi Zafarani-Moattar, Seyyedeh Narjes Mirheydari , Study of interactions between l-alanine and 1-octyl-3-methylimidazolium salicylate or 1-octyl-3-methylimidazolium ibuprofenate using the thermophysical properties at T = 298.15 K. Molliq (2019), https://doi.org/10.1016/j.molliq.2019.01.030

Study of interactions between L-alanine and 1-octyl-3-methylimidazolium salicylate or 1-octyl-3-methylimidazolium ibuprofenate using the thermophysical properties at *T*= 298.15 K

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Abstract

The effect of 1-octyl-3-methylimidazolium salicylate, [OMIm][Sal] and 1-octyl-3-methylimidazolium ibuprofenate, [OMIm][Ibu] as an active pharmaceutical ingredient ionic liquids (API-IL) on the solvation properties of aqueous L-alanine solutions have been investigated by thermophysical properties determination. The partial molar volume of transfer ($\Delta_{tra}V_{\varphi}^{0}$), partial molar isentropic compressibility of transfer ($\Delta_{tra}\kappa_{\varphi}^{0}$), viscosity *B*-coefficients of transfer ($\Delta_{\mathrm{tra}}B$), ion association constant (K_A) and molar refraction (R_D) quantities have been determined using the measured density, viscosity, speed of sound, electrical conductance and refractive index data. The results showed that the ion-polar and polar-polar interactions between API-ILs and L-alanine are dominant.

Keywords: 1-Octyl-3-methylimidazolium salicylate; 1-Octyl-3-methylimidazolium ibuprofenate; Partial molar volume of transfer; Viscosity *B*-coefficient; Molar conductivity.

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1. Introduction

Salicylic acid and ibuprofen are the active pharmaceutical ingredients (API) with low water solubility which limits their therapeutic applications [1]. In the new solubility improvement approach, the active pharmaceutical ingredient (API) are combined with the second generation of ionic liquid (ILs) and the third generation of ionic liquids namely API-IL have been created [2, 3]. This form of API presents the improved solubility, drug delivery, and bioavailability due to the hydrophophilicity and hydrophobicity nature [4-7]. In recent years, Viau and Pinto et al. [8, 9] introduced the 1-butyl-3-methylimidazolium ibuprofenate and salicylate as a new gel for drug delivery with excellent properties [8, 9].

To design and improve the biotechnological processes, the information about the molecular mechanism interactions existing between pharmaceutically active ionic liquid form and biomolecules is required [10-12]. Proteins as a complicated biomolecule are composed of the amino acid units, therefore studying of the amino acids is easier than protein [13, 14]. In this respect, the thermophysical properties (i.e., the volumetric and transport properties) of amino acid in the presence of API-IL give us the useful information about the solute-solvent and solute-solute interactions.

In recent years, some authors reported the thermodynamic properties of the mixtures containing amino acid and the first generation of ionic liquid in the aqueous media at different temperatures [15-20]. For the first time, shekaari et al. [20-22] have examined the effect of the active pharmaceutical ingredient in the ionic liquids form (API-ILs), 1-butyl-3-methylimidazolium salicylate and ibuprofenate on the thermodynamic properties of the amino acid aqueous solutions, glycine and L-alanine. Results showed that dominant interactions between these amino acids and API-IL are the ion-polar and polar-polar interactions.

The present work is a continuation of our systematic thermodynamic studies of ternary systems (amino acid + API-IL + water) [20-22]. In this study, the measured density, speed of sound, viscosity, electrical conductance and refractive index data for L-alanine in the presence of aqueous solutions of 1-octyl-3-methylimidazolium salicylate, [OMIm][Sal] and 1-octyl-3-methylimidazolium ibuprofenate, [OMIm][Ibu] were reported at T= 298.15 K and atmospheric pressure. The measured data were used to compute the partial molar volume of transfer $\Delta_{tra}V_{\varphi}^{0}$, partial molar isentropic compressibility of transfer $\Delta_{tra}\kappa_{\varphi}^{0}$, viscosity B-coefficients, ion association constants (K_A) and molar refraction R_D.

2. Experimental

2.1 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 μS cm^{-1} at 298.15 K.

2.2 Synthesis of ionic liquid

The two new API-ILs, 1-octyl-3-methylimidazolium salicylate, [OMIm][Sal] and 1-octyl-3-methylimidazolium ibuprofenate, [OMIm][Ibu] (see the structure of API-IL in Fig. 1) were prepared from the 1-octyl-3-methylimidazolium chloride [OMIm][Cl] and sodium salicylate and sodium ibuprofenate, respectively. 1-octyl-3-methylimidazolium chloride was synthesized and purified according to the standard methods reported in the references [23-27]. The water content of prepared ionic liquid, [OMIm][Cl] by Karl Fischer method was less than 0.05% in mass fraction. Characterization of the ionic liquid by ^{1}HNMR spectroscopy showed good agreement as compared with the literature and confirmed the absence of any significant impurities [26]. The purity of prepared ionic liquid was 98% in mass fraction. To synthesize the 1-octyl-3-methylimidazolium salicylate ionic liquid [OMIm][Sal], (0.4 mol) sodium salicylate was dissolved in dried acetonitrile and added slowly to (0.4 mol) [OMIm][Cl] dissolved in a minimum amount of dried acetonitrile. The resulting mixture was stirred at room temperature overnight then the rotary evaporator at 350 K and then reduced pressure was used to extract the water in the mixture. The resulting mixture was subsequently dissolved in a large amount of dichloromethane to observe white precipitate containing sodium chloride. The white precipitate was then filtered and this process was continued until no white solid 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 procedure for synthesis of 1-octyl-3-methylimidazolium ibuprofenate, [OMIm][Ibu] is similar to [OMIm][Ibu] and the only difference is applying the ethanol as solvent and heating at 353.15 K for 3 h at the beginning of the reaction. The water content of the [OMIm][Sal] and [OMIm][Ibu] determined using coulometric Karl Fischer titrator (Metrohm 756 KF) was approximately 0.1% in mass fraction. The ^{1}H NMR (Brucker Av-400) spectroscopy was applied to characterize the prepared API-ILs (see Fig. S1 and S2).

2.3 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 at atmospheric pressure were applied to calibrate the instrument [28]. The temperature was kept constant within ±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 ms^{-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 was controlled the temperature. The calibration of capillary was performed by the manufacturer using viscosity standard fluids. Before each experiment, the calibration of the instrument was checked by distillated water at specific temperature. The evaluated experimental uncertainty of the viscosity measurements was less than 0.015 mPa·s.

Measurement of the electrical conductivities, κ were performed by a conductivity meter (Metrohm model 712, Switzerland) with the accuracy of ± 0.5%. The instrument was calibrated using the measurement specific electrical conductivities of the KCl solution with 0.01 molality. For measuring 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, $\Lambda = \frac{1000\kappa}{c}$, where κ and c are the specific electrical conductance 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.

3. Experimental results and discussion

3.1 Volumetric properties

To study the hydration layer volume surrounding the amino acid and existing the interactions in the studied systems, calculation of the apparent molar volume V_φ using the measured density is an appropriate approach. So, the density *d* of L-alanine in the aqueous solutions of [OMIm][Sal] (0.0974, 0.2012 and 0.2988) mol·kg^{-1} and [OMIm][Ibu] (0.1101, 0.2001 and 0.2889) mol·kg^{-1} were measured and reported in Table 2. As can be seen in this table, the densities increase with the solute (L-alanine) as well as with the cosolute ([OMIm][Sal], [OMIm][Ibu]) concentrations. The measured densities were used to calculate the apparent molar volumes:

$$V_\varphi = \frac{M}{d} - \left[\frac{1000\,(d - d_0)}{mdd_0}\right] \tag{1}$$

where *m* and *M* is the molality and molar mass of the amino acid and d_0, *d* are the densities of the solvent ([OMIm][Sal], [OMIm][Ibu] + water) and ternary solutions. Table 2 reports the values of V_ϕ for the studied solutions. Since the amino acid and (API-IL + water) were considered as solute and solvent, respectively, the V_φ related to the amino acid was correlated using the following equation:

$$V_\varphi = V_\varphi^0 + S_v m \tag{2}$$

where V_φ° is the standard partial molar volume and S_v is an experimental parameter. Table 2 listed the evaluated values of V_φ° and S_v accompanied with their standard deviation $\sigma(V_\varphi)$ derived by least squares fitting of the V_φ values by Eq. 2. (2).

The extent of the interaction between L-alanine and [OMIm][Sal] or [OMIm][Ibu] can be evaluated from the hydration number n_H using the following equation:

$$n_H = \frac{V_\varphi^\circ(\text{elect})}{V_E^\circ - V_B^\circ} \tag{3}$$

where the value of $(V_E^\circ - V_B^\circ)$ for electrolytes at T= 298.15 K is 3.0 $\text{cm}^3 \cdot \text{mol}^{-1}$ and $V_\varphi^\circ(\text{elect})$ is the molar volume of electrostrictive water and can be obtained by the following relation [29,30]:

$$V_\varphi^\circ(\text{elect}) = V_\varphi^\circ - V_\varphi^\circ(\text{int}) \tag{4}$$

where $V_\varphi^\circ(\text{int})$ is the intrinsic partial molar volume which originates from the hydration of the amino acid zwitterions. Combining of the volume from Vander-Waals and packing effects can obtain the $V_\varphi^\circ(\text{int})$ term from the following relation [31]:

$$V_\varphi^\circ(\text{int}) = \frac{0.7}{0.634} V_\varphi^\circ(\text{cryst}) \tag{5}$$

where $V_\varphi^\circ(\text{cryst}) = \frac{M}{d\,(\text{cryst})}$ is the molar volume of the crystal which was computed using the densities of the amino acid (crystal form) supposed by Berlin and Pallansch at 298.15 K [32]. Table 3 gives the calculated n_H values for the studied solutions. The n_H values for L-alanine in the aqueous solutions of [OMIm][Ibu] are less than in [OMIm][Sal] which indicate the stronger interactions between API-IL and zwitterion forms of L-alanine. At the high concentration of API-IL, the water molecular structure around the amino acid are disrupted and the water molecules release to the bulk and therefore the hydration number decrease.

Another suitable parameter to determine the extent of the interactions is the partial molar volume of transfer calculated using the relation [33]:

$$\Delta_{tra} V_\varphi^\circ = V_\varphi^\circ \text{ (API-IL + water)} - V_\phi^{\,0} \text{ (in water)} \tag{6}$$

The data for the binary systems, L-alanine in water used in the calculations were taken from the earlier published data [21]. The calculated values of $\Delta_{tra} V_\varphi^\circ$ for the studied solutions given in Table 3 are positive and increase with an increase in the APIL concentrations. The observed positive values $\Delta_{tra}V_{\varphi}^{\circ}$ indicate the strong ion–zwitterion interactions between API-IL and L-alanine. According to the co-sphere overlap model, the contribution of solute-solute interactions is negligible and hence the information about the solute-solvent interactions is obtained. The types of the interactions between L-alanine and API-ILs can 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 $\Delta_{tra}V_{\varphi}^{\circ}$ values while the effective contribution of the ion–polar and polar-polar interactions are positive. The obtained $\Delta_{tra}V_{\varphi}^{\circ}$ values presented in Table 4 and Fig. 2 for [OMIm][Ibu] are greater than [OMIm][Ibu] and increase with the API-IL concentration increment. This phenomenon suggests the stronger interactions between the zwitterionic center of L-alanine and the ions of [OMIm][Sal] and [OMIm][Ibu] which result in a decrease in the solvation layer volume [34].

3.2 Ultrasonic properties

Table 2 reports the measured speed of sound values for the studied solutions (L-alanine + [OMIm][Sal], [OMIm][Ibu] + water). The isentropic compressibility $\kappa_s(\mathrm{Pa}^{-1})$ was calculated using the Laplace–Newton's equation as follows;

$$\kappa_s = \frac{1}{du^2} \tag{7}$$

The following equation was used to calculate the apparent molar isentropic compressibility κ_{φ} for understanding the solvent structure around the amino acid as well as in bulk;

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

where κ_{s0} and κ_s are the isentropic compressibility of the solvent (aqueous solutions of [OMIm][Sal] and [OMIm][Ibu]) and ternary solutions (L-alanine in the aqueous solutions of [OMIm][Sal] and [OMIm][Ibu]), respectively and definition of the other parameters are same as for the V_{φ}. The obtained κ_{φ} values for the studied solutions were presented in Table 3. The apparent molar isentropic compressibility of L-alanine in the solutions of ([OMIm][Sal], [OMIm][Ibu] + water) with 0.3 molality at T= 298.15 K was presented in Fig. 3. As can be seen from Table 3 and Fig. 3, the κ_{φ} values increase with an increase in the [OMIm][Sal] and [OMIm][Ibu] concentrations which means the increase in the API-IL-amino acid interactions and release of the water molecules from the solvation layer to the bulk.

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:

$$\kappa_{\varphi}=\kappa_{\varphi}^{\circ}+S_k m \tag{9}$$

where S_k, m are the experimental slope and the molality of L-alanine in the solutions, respectively. The obtained κ_{φ}^{0}, S_k values for the studied solutions accompanied with the standard deviation $\sigma(\kappa_{\varphi})$ are given in Table 4. As shown in Table 4, the κ_{φ}^{0} values increase with increase in API-IL concentrations. This phenomenon suggest the strong interactions between API-ILs and L-alanine which result in the formation of more compressible solvation layer [35, 36].

The partial molar isentropic compressibility of transfer $\Delta_{tra}\kappa_{\varphi}^{0}$ from water to the aqueous solutions of [OMIm][Sal] and [OMIm][Ibu] was calculated using the following relation:

$$\Delta_{tra}\kappa_{\varphi}^{\circ} = \kappa_{\varphi}^{\circ}(\text{aqueous API} - \text{IL}) - \kappa_{\varphi}^{\circ}(\text{water}) \tag{10}$$

Table 4 represents the obtained $\Delta_{tra}\kappa_{\varphi}^{0}$ values for investigated solutions which increase with the API-IL concentration. The positive values of the $\Delta_{tra}\kappa_{\varphi}^{0}$ declare the dominance of the ion-polar and polar-polar interactions between the head charged groups (NH_3^+ and COO^-) of L-alanine and the ions of [OMIm][Sal] and [OMIm][Ibu] which they are more favorable at the high concentration of API-IL [36].

3.3 Pair and triplet interaction coefficients

McMillan and Mayer [35] theory developed by Friedman and Krishnan, [37] offered a simple method for calculation of the interaction coefficients between two or more solute molecules. In this regard, the two following relations were applied to evaluate the partial molar volume of transfer and partial molar isentropic compressibility of transfer:

$$\Delta_{tra}V_{\varphi}^{\circ} = 2V_{\text{AB}}\, m + 3V_{\text{ABB}}\, m^2 \tag{11}$$

$$\Delta_{tra}\kappa_{\varphi}^{\circ} = 2\kappa_{\text{AB}} m + 3\kappa_{\text{ABB}} m^2 \tag{12}$$

where *A* denotes amino acid, *B* denotes [OMIm][Sal] and [OMIm][Ibu] and m_{B} is the molality of L-alanine in the aqueous solutions of API-IL. The pair and triplet interaction coefficients express the corresponding parameters V_{AB}, V_{ABB} for volume and, κ_{AB}, κ_{ABB} for compressibility. These evaluated pair 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 API-IL and L-alanine in the solutions are mostly pairwise [38].

3.4 Viscometric properties

The measured viscosities η of (L-alanine + [OMIm][Sal] water) and (L-alanine + [OMIm][Ibu] + water) with several modalities of ([OMIm][Sal] + water) and ([OMIm][Ibu] + water) were presented in Table 2. Viscosity *B*-coefficients is one of the other parameters which are used to study the solute-solvent interactions. Jones-Dole equation represents the variation of the relative viscosity $\eta_r = \frac{\eta}{\eta_0}$ of the amino acid in the aqueous solutions of API-IL [39]

$$\eta_r = 1 + Ac^{1/2} + Bc \tag{13}$$

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:

$$\eta_r = 1 + Bc \tag{14}$$

where in Eq. (14) η and η_0 are the viscosity of the solutions (L-alanine in the aqueous solution of [OMIm][Sal] and [OMIm][Ibu]) and solvents ([OMIm][Sal] + water) and ([OMIm][Ibu] + water), respectively, *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. Table 3 listed the calculated viscosity *B*-coefficients and $\sigma(\eta)$ of the studied solutions. The size, shape, structure and charge of solute molecules originated from the solute-solvent interactions effect on the viscosity *B*-coefficient values [40]. The high positive values of the viscosity *B*-coefficients in the [OMIm][Ibu] solution compared to [OMIm][Sal] is illustrative of the greater kosmotropic effect of [OMIm][Ibu] on the solution [40]

The following relation presents the variation of *B*-coefficients $\Delta_{tra}B$ from water to the aqueous [OMIm][Sal] and [OMIm][Ibu] solutions:

$\Delta_{tra}B$ = *B*-coefficients in (API-IL + water) – *B*-coefficients (in water) (15)

The viscosity *B*-coefficients of L-alanine in the API-IL solutions are higher than in water and therefore the $\Delta_{tra}B$ values are positive and increase with an increase in the API-IL concentration. The presented $\Delta_{tra}B$ values of L-alanine in the solutions of ([OMIm][Sal], [OMIm][Ibu] + water) in Fig. 4. are higher for [OMIm][Ibu]. It can be interpreted as the stronger interaction between [OMIm][Ibu] and zwitterions of L-alanine rather than [OMIm][Sal].

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

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

where $(\bar{V}_1^0 = \sum \frac{x_i M_i}{\rho})$ is the mean volume of the solvent and $(\bar{V}_2^0 = V_{\varphi}^0)$ is the standard partial molar volume of the pure solute. The terms $\bar{V}_1^0$, x_i, M_i and *d* are the molar volume of the pure solvent, mole fraction, molar masses and density of the solvent ([OMIm][Sal] + water) and ([OMIm][Ibu] + water), respectively. Eyring's simple model was used for calculation of the free energy of activation per mole of the solvent $\Delta\mu_1^{\circ\neq}$ and $\Delta\mu_2^{\circ\neq}$ as follow:

$$\Delta\mu_1^{\circ\neq} = \Delta G_1^{\circ\neq} = RT \ln \frac{\eta_1 V_1^{\circ}}{hN_A} \tag{17}$$

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

where h is the Planck's constant, N_A is the Avogadro number, η_1 is the viscosity of the solvent and the other symbols have their usual meanings. Table 3 presents the calculated values of $\Delta\mu_1^{\circ\neq}$ and $\Delta\mu_2^{\circ\neq}$. It is clear that the values of $\Delta\mu_2^{\circ\neq}$ are positive and more significant than $\Delta\mu_1^{\circ\neq}$ for both API-IL solutions which indicate the stronger interactions between solute (L-alanine) and solvents ([OMIm][Sal] + water) and ([OMIm][Ibu] + water) in the ground state compared to the transition state. The values of $\Delta\mu_2^{\circ\neq}$ increase with an increase in the concentration of API-IL solutions up to 0.3 mol·kg^{-1}. The higher values of $\Delta\mu_2^{\circ\neq}$ for L-alanine in the [OMIm][Ibu] solutions suggests that the transfer from ground state to the transition state requires more energy than in [OMIm][Sal] [40, 41].

3.5 Conductometric properties

Another appropriate way to interpret the possible ions interactions is the molar conductivity and ion association of API-IL. In this respect, the molar conductivity data for [OMIm][Sal] and [OMIm][Ibu] in the aqueous solution of L-alanine were determined. The values of molar conductivity, Λ for [OMIm][Sal] and [OMIm][Ibu] in water and in the aqueous solutions of the L-alanine were computed using $\Lambda = \frac{1000\kappa}{C}$ (see Table 4). The molar conductivity of [OMIm][Sal] and [OMIm][Ibu] in the aqueous solutions of L-alanine with 0.5 molality was plotted in Fig. 5. As can be seen from this table 4 and Fig. 5, the values of Λ decrease by the API-IL concentration increment due to ionic atmosphere effects. In fact, in more concentrated solutions, the ion pairing is responsible for the observed decrease in molar conductivities. The Onsager model was used to estimate the initial guess of limiting molar conductivity Λ_0 and ion association constant K_A for the low concentration Chemical Model (lcCM) to calculate the real

Λ_0 and K_A of the API-ILs in the studied solutions. The following set equations present the lcCM model:

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

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

$$\ln\gamma_\pm = \frac{\kappa q}{1+\kappa R} \tag{21}$$

$$\kappa^2 = \frac{16000N_A z^2 e^2 \alpha c}{\varepsilon_0 \varepsilon K_B T} \tag{22}$$

$$q = \frac{z_+ z_- e^2}{8\pi\varepsilon_0\varepsilon kT} \tag{23}$$

in which, Λ_0 is the molar conductivity at infinite dilution, (1-α) is the fraction of oppositely charged ions acting as ion pairs, $\gamma_\pm$ 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 [42]. The parameter R represents the center-to-center distance between the ions in the formed ion pairs in the solutions. The evaluated Λ_0, K_A and R for the studied API-ILs in water and the aqueous L-alanine solutions were listed in Table 5. From this table, the values of Λ_0 decrease with an increase in the L-alanine concentration which indicates the low mobility of the solvated ions by (COO^- /NH_3^+) zwitterionic centers with large radii and increase the viscosity of medium with the addition of L-alanine. The lower values of Λ and Λ_0 in the solutions of [OMIm][Ibu] relative to [OMIm][Sal] indicate the more ion solvation of [OMIm][Ibu] by (COO^- /NH_3^+) zwitterions centers of L-alanine [22]. Moreover the K_A values of the API-IL decrease with L-alanine concentration which relate to the strong interaction of ions with zwitterions and reduced the ion-pair formation in the concentrated solutions. The lower values of K_A in the solutions of [OMIm][Ibu] compared to [OMIm][Sal] may be indicative of the stronger interactions between (COO^- /NH_3^+) of zwitterions and ions of [OMIm][Ibu].

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].

To eliminate the effect of viscosity on the ionic mobility, the Walden product was calculated. As the conductivity of the ions at infinite dilution only depends on their mobility, the product of the viscosity of the solvent by the ion conductivity is independent of the solvent nature [45]. The smaller $\Lambda_0\eta_0$ values in L-alanine solutions may be attributed to the large effective radius of ions (due to the high association of API-IL). Table 5 represents the calculated Walden product ($\Lambda_0\eta_0$) of the [BMIm][Sal] and [BMIm][Ibu] in the L-alanine solution.

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

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

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.

3.6 Diffusion Coefficients Walden products of ions

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

$$D_{AB}^{\circ} = \frac{RT}{F^2} \frac{|z_+||z_-|}{|z_+ z_-|} \frac{\lambda_0^+ \lambda_0^-}{\lambda_0^+ + \lambda_0^-} \tag{25}$$

where D_{AB}^0 is the diffusion coefficient of API-IL (A) in water (B) at infinite dilution in m^2 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 is the limiting molar conductivities of the cation and anion in S m^2 mol^{-1}, respectively. Table 5 presents the calculated D_{AB}^0 values of [OMIm][Sal] and [OMIm][Ibu] in water. The following relation determines the ionic limiting molar conductivity values of the individual ions:

$$\Lambda_0 = z_+ \lambda_0^+ + z_- \lambda_0^- \tag{26}$$

The ionic limiting molar conductivity of the λ_0^+ in water for [OMIm]$^+$ was obtained from literature [45]. Subsequently, Eq. (27) was used to calculate the limiting molar conductivity of the λ_0^- (see in Table 5).

The diffusion coefficient [47,48] of the individual ions are calculated by the following relation:

$$D_{ion}^{\circ} = \frac{RT\lambda_0}{|z_{ion}|F^2} \tag{27}$$

Table 6 lists the obtained values of the diffusion coefficient D_{ion}^0 and limiting molar conductivity λ_0 of the ions. The D_{ion}^0 and λ_0 of the cation in [OMIm][Sal] are lower than the anion while this trend is vice versa for the [OMIm][Ibu] which is related to the low mobility o ibuprofenate anion rather than salicylate.

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.

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

The calculated values of r_s for the ions are collected in Table 5. The Walden Product [49] has been obtained from the following relation:

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

Where r_s is obtained by Eq. (28). As all other terms of Eq. (29) are constants, Walden Product ($\lambda_0\eta$) vary if r_s changes. This equation reveals that there is an inverse relationship between the effective hydrodynamic radius of an ion and its Walden product ($\lambda_0\eta$).

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 relation:

$$t_\pm = \frac{\lambda_0}{\Lambda_0} \tag{30}$$

The symbols t_+ and t_- are usually used to express the transport numbers of cation and anion, respectively. Table 6 gives the calculated values of t_+ and t_-.

The standard Gibbs free energy (ΔG_A°) of the ion-association process was obtained using the ion association constants. Tables 5 presents the calculated values of the ΔG_A° value for the ion association process of API-IL in water and L-alanine solutions which exhibit the negative values of ΔG_A°. The large negative values of the ΔG_A° for the [OMIm][Sal] solutions indicates the more spontaneously and feasibility of the ion association process in this API-IL compared to [OMIm][Ibu].

3.7 Refractometric properties

Experimental refractive index data n_D for (L-alanine + [OMIm][Sal], [OMIm][Ibu] + water) with several molality of ([OMIm][Sal] + water) and ([OMIm][Ibu] + water) are reported in Table 2. The molar refraction R_D is calculated using Lorentz-Lorentz equation [46]:

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

where x_i, M_i and d are the mole fraction and molar mass of components and density of the solutions, respectively. Table 2 reports the calculated molar refractions of the investigated solutions. Moreover, Fig.6 presents the molar refraction of ternary (L-alanine + [OMIm][Sal], [OMIm][Ibu] + water). As observed in Table 2, the R_D values increase with an increase in the API-IL concentration. As the molecule structure is more complicated, the electron cloud becomes more distributed, and the polarizability of the molecule is intensified.

5. Conclusion

The effect of two active pharmaceutical ingredient based ionic liquids (API-IL), 1-octyl-3-methylimidazolium salicylate ([OMIM][Sal]) and 1-octyl-3-methylimidazolium ibuprofenate ([OMIm][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 volumes of transfer $\Delta_{tra}V_{\varphi}^{0}$, partial molar isentropic compressibilities of transfer $\Delta_{tra}\kappa_{\varphi}^{\circ}$ and viscosity B-coefficients of transfer indicate that the ion–polar and polar-polar interactions between L-alanine and API-ILs are dominant and according to the V_{AB} and κ_{AB} values the pairwise interactions are more preferred. The more significant values of $\Delta\mu_2^{\circ\neq}$ for [OMIm][Ibu] than [OMIm][Sal] show the more effective structure making ability of L-alanine in this API-IL which strengthens with the addition of the API-IL. The low concentration Chemical Model (lcCM) model was used to evaluate the ion association constant (K_A), limiting molar conductivity (Λ_0) and distance parameter (R). The lower values of Λ_0 with the addition of L-alanine to the aqueous [OMIm][Sal] and [OMIm][Ibu] solutions indicate the low mobility of the solvated ions by (COO^- /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^0 for [OMIm][Sal] in the L-alanine solutions compared to the [OMIm][Ibu] solutions suggest the more spontaneously of the ion association process of this API-IL.

Acknowledgment

The authors wish to thank financial support from the graduate council of the University of Tabriz.

References

[1] H.A. Favre, W.H. Powell, Nomenclature of organic chemistry: IUPAC recommendations and preferred names, Royal Society of Chemistry 2013.

[2] J.L. Shamshina, P.S. Barber, R.D. Rogers, Ionic liquids in drug delivery, Expert Opin. Drug Deliv. 10 (2013) 1367-1381.

[3] R. Ferraz, L.C. Branco, C. Prudêncio, J.P. Noronha, Ž. Petrovski, Ionic liquids as active pharmaceutical ingredients, Chem. Med. Chem. 6 (2011) 975-985.

[4] M. Moniruzzaman, M. Goto, Ionic Liquids: Future Solvents and Reagents for Pharmaceuticals, J. Chem. Eng. Japan, 44 (2011) 370-381.

[5] M. Geppi, S. Guccione, G. Mollica, R. Pignatello, C.A. Veracini, Molecular properties of ibuprofen and its solid dispersions with eudragit RL100 studied by solid-state nuclear magnetic resonance, Pharm. Res. 22 (2005) 1544-1555.

[6] B. Bittner, R.J. Mountfield, Intravenous administration of poorly soluble new drug entities in early drug discovery: the potential impact of formulation on pharmacokinetic parameters, Curr. Opin. Drug Discov. Devel. 5 (2002) 59-71.

[7] B. Bittner, R.J. Mountfield, Formulations and related activities for the oral administration of poorly water-soluble compounds in early discovery animal studies: An overview of frequently applied approaches. Part 1, Drugs made in Germany, 45 (2002) 18-24.

[8] P.C. Pinto, D.M. Ribeiro, A.M. Azevedo, V.D. Justina, E. Cunha, K. Bica, M. Vasiloiu, S. Reis, M.L.M. Saraiva, Active pharmaceutical ingredients based on salicylate ionic liquids: insights into the evaluation of pharmaceutical profiles, New J. Chem. 37 (2013) 4095-4102.

[9] L. Viau, C. Tourné-Péteilh, J.-M. Devoisselle, A. Vioux, Ionogels as drug delivery system: one-step sol–gel synthesis using imidazolium ibuprofenate ionic liquid, Chem. Comm. 46 (2010) 228-230.

[10] W.P. Jencks, Catalysis in chemistry and enzymology, Courier Corporation1987.

[11] P.H. Von Hippel, T. Schleich, Ion effects on the solution structure of biological macromolecules, Acc. Chem. Res. 2 (1969) 257-265.

[12] D.B. Northrop, F.B. Simpson, New concepts in bioorganic chemistry beyond enzyme kinetics: Direct determination of mechanisms by stopped-flow mass spectrometry, Bioorg. Medicinal Chem. 5 (1997) 641-644.

[13] A. Hvidt, P. Westh, Different views on the stability of protein conformations and hydrophobic Effects, J. Solution Chem. 27 (1998) 395-402.

[14] R.J. Lavrich, C.R. Torok, M.J. Tubergen, Effect of the bulky side chain on the backbone structure of the amino acid derivative valinamide, J. Phys. Chem. A 106 (2002) 8013-8018.

[15] R. Gaba, A. Pal, D. Sharma, K. Sharma, Solvation behavior of glycine and diglycine in aqueous 1-butyl-3-methylimidazolium chloride ionic liquid solutions at different temperatures, J. Mol. Liq. 220 (2016) 954-960.

[16] H. Shekaari, F. Jebali, Densities and electrical conductances of amino acids + ionic liquid ([Hmim] Br) + H_2O mixtures at 298.15 K, Fluid Phase Equilib. 295 (2010) 68-75.

[17] H. Shekaari, F. Jebali, Volumetric and conductometric studies of some amino acids in aqueous ionic liquid, 1-hexyl-3-methylimidazolium chloride solutions at 298.15 K, Phys. Chem. Liq. 49 (2011) 572-587.

[18] H. Kumar, C. Chadha, A. Verma, M. Singla, Synthesis and study of interactions of ionic liquid 1-methyl-3-pentylimidazolium bromide with amino acids at different temperatures, J. Mol. Liq. 242 (2017) 560-570.

[19] S.K. Sharma, G. Singh, R. Kataria, H. Kumar, S. Sharma, Investigations on molecular interaction of some amino acids with the drug levofloxacin in aqueous solution by volumetric and acoustic methods at different temperatures, J. Chem. Thermodyn.105 (2017) 94-104.

[20] H. Shekaari, M.T. Zafarani-Moattar, S.N. Mirheydari, Effect of 1-Butyl-3-methylimidazolium ibuprofenate as an active pharmaceutical ingredient ionic Liquid (API-IL) on the thermodynamic properties of glycine and l-alanine in aqueous solutions at different temperatures, J. Solution Chem. 45 (2016) 624-663.

[21] H. Shekaari, M.T. Zafarani-Moattar, S.N. Mirheydari, Thermodynamic properties of 1-butyl-3-methylimidazolium salicylate as an active pharmaceutical ingredient ionic liquid (API-IL) in aqueous solutions of glycine and L-alanine at T=(288.15–318.15) K, Thermochim. Acta, 637 (2016) 51-68.

[22] H. Shekaari, M.T. Zafarani-Moattar, S.N. Mirheydari, Conductometric analysis of 1-butyl-3-methylimidazolium ibuprofenate as an active pharmaceutical ingredient ionic liquid (API-IL) in the aqueous amino acids solutions, J. Chem. Thermodyn. 103 (2016) 165-175.

[23] M. Vraneš, S. Armaković, A. Tot, S. Papović, N. Zec, S. Armaković, N. Banić, B. Abramović, S. Gadžurić, Structuring of water in the new generation ionic liquid– Comparative experimental and theoretical study, J. Chem.Thermodyn. 93 (2016) 164-171.

[24] P. Bonhôte, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram, M. Grätzel, Hydrophobic, highly conductive ambient-temperature molten salts, Inorg. Chem. 35 (1996) 1168-1178.

[25] P.-Y. Chen, Y.-T. Chang, Voltammetric study and electrodeposition of copper in 1-butyl-3-methylimidazolium salicylate ionic liquid, Electrochim. Acta, 75 (2012) 339-346.

[26] T. Welton, Room-temperature ionic liquids. Solvents for synthesis and catalysis, Chem. Rev. 99 (1999) 2071-2084.

[27] K.S. Egorova, M.M. Seitkalieva, A.V. Posvyatenko, V.N. Khrustalev, V.P. Ananikov, Cytotoxic activity of salicylic acid-containing drug models with ionic and covalent binding, ACS Med. Chem. Lett. 6 (2015) 1099.

[28] T.J. Fortin, A. Laesecke, M. Freund, S. Outcalt, Advanced calibration, adjustment, and operation of a density and sound speed analyzer, J. Chem. Thermodyn. 57 (2013) 276-285.

[29] S.K. Sharma, G. Singh, H. Kumar, R. Kataria, Densities, sound speed, and viscosities of Some amino acids with aqueous tetra-butyl ammonium iodide solutions at different temperatures, J. Chem. Eng. Data, 60 (2015) 2600-2611.

[30] E. Berlin, M. Pallansch, Densities of several proteins and L-amino acids in the dry state, J. Phys. Chem. 72 (1968) 1887-1889.

[31] A. Pal, H. Kumar, R. Maan, H.K. Sharma, Solute–solvent interactions of glycine, l-alanine, and l-valine in aqueous 1-methyl-3-octylimidazolium chloride ionic liquid solutions in the temperature interval (288.15–308.15) K, Thermochim. Acta, 590 (2014) 127-137.

[32] H. Hertz, F. Franks, Water: A comprehensive treatise, by F. Franks, Plenum Press, New York, 3 (1973).

[33] A.K. Mishra, J.C. Ahluwalia, Apparent molal volumes of amino acids, N-acetylamino acids, and peptides in aqueous solutions, J. Phys. Chem. 88 (1984) 86-92.

[34] H. Kumar, K. Kaur, Volumetric, compressibility and UV spectral studies on interactions of amino acids with aqueous solutions of potassium dihydrogen phosphate at different temperatures, J. Solution Chem. 42 (2013) 592-614.

[35] W.G. McMillan Jr, J.E. Mayer, The statistical thermodynamics of multicomponent systems, J. Chem. Phys. 13 (1945) 276-305.

[36] C. Krishnan, H.L. Friedman, Enthalpies of alkyl sulfonates in water, heavy water, and water-alcohol mixtures and the interaction of water with methylene groups, J. Solution Chem. 2 (1973) 37-51.

[37] H. Kumar, M. Singla, R. Jindal, Viscometric measurements of dipeptides of alanine in aqueous solutions of antibacterial drug ampicillin at different temperatures, J. Mol. Liq. 191 (2014) 183-188.

[38] A. Boruń, A. Bald, Ionic association and conductance of [emim][BF_4] and [bmim][BF_4] in 1-butanol in a wide range of temperature, J. Chem. Thermodyn. 96 (2016) 175-180.

[39] M.J. Iqbal, M.A. Chaudhry, Volumetric and viscometrics of antidepressant drugs in aqueous medium at different temperatures, J. Chem. Eng. Data 54 (2009) 2772-2776.

[40] T. Shedlovsky, The computation of ionization constants and limiting conductance values from conductivity measurements, J. Franklin Inst. 225 (1938) 739-743.

[41] J.M. Barthel, H. Krienke, W. Kunz, Physical chemistry of electrolyte solutions: Modern aspects, Springer Science & Business Media(1998).

[42] K.S. Pitzer, Electrolyte theory: improvements since Debye and Hückel, Acc. Chem. Res.;(United States), 10 (1977).

[43] R. Robinson, R. Stokes, Electrolyte Solutions, Butterworths Scientific Publications, London, 1959.

[44] H. Wang, J. Wang, S. Zhang, Y. Pei, K. Zhuo, Ionic association of the ionic liquids [C_4mim][BF_4],[C_4mim][PF_6], and [$C_n$mim]Br in molecular solvents, Chem. Phys. Chem. 10 (2009) 2516-2523.

[45] A.N. Soriano, A.M. Agapito, L.J.L.I. Lagumbay, A.R. Caparanga, M.-H. Li, Diffusion coefficients of aqueous ionic liquid solutions at infinite dilution determined from electrolytic conductivity measurements, J. Taiwan Inst. Chem. Eng. 42 (2011) 258-264.

[46] M. Tjahjono, M. Garland, On the determination of partial molar volumes, partial molar refractions, mean electronic polarizabilities and effective molecular radii from rilute multi-component data alone using response surface models, J. Solution Chem. 36 (2007) 221-236.

[47] R. Robinson, R. Stokes, Solutions of electrolytes and diffusion in liquids, Annu. Rev. Phys. Chem. 8 (1957) 37-54.

[48] W.C. Su, C.H. Chou, D.S.H. Wong, M.H. Li, Diffusion coefficients and conductivities of alkylimidazolium tetrafluoroborates and hexafluorophosphates, Fluid Phase Equilib. 252 (2007) 74-78.

[49] I.V. Voroshylova, S.R. Smaga, E.V. Lukinova, V.V. Chaban, O.N. Kalugin, Conductivity and association of imidazolium and pyridinium based ionic liquids in methanol, J. Mol. Liq. 203 (2015) 7-15.

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	-	-
[OMIm][Sal]	This work	Synthesized	-	Rotary/ evaporator and vacuum	>0.97	^{1}HNMR
[OMIm][Ibu]	This work	Synthesized	-	Rotary/ evaporator and vacuum	>0.97	^{1}HNMR
N-methylimidazole	7-47-616	Merck	>0.99	None	-	-
1-Chlorooctae	111-85-3	Merck	0.99	None	-	-
Sodium salicylate	54-21-7	Merck	≥0.995	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	-	-

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 [OMIm][Sal] and [OMIm][Ibu] at T = 298.15 K and 0.0868 MPa.[a]

$^b m$/ mol·kg^{-1}	$10^{-3} d$/ kg·m^{-3}	$10^6 V_\varphi$/ m^3·mol^{-1}	u / m·s^{-1}	$10^{14} \kappa_\varphi$ / m^3·mol^{-1}·Pa^{-1}	η/ mPa·s	n_D	$10^6 R_D$ / m^3·mol^{-1}
L-alanine in $m_{\text{API-IL}}$ ([OMIm][Sal] + water)							
$m_{\text{API-IL}}$= 0.0974 mol·kg^{-1}							
0.0000	1.000224		1506.38		1.154	1.3386	3.876
0.0993	1.003019	60.77	1512.76	-2.31	1.187	1.3401	3.912
0.1493	1.004415	60.75	1515.97	-2.31	1.204	1.3408	3.927
0.1974	1.005754	60.73	1519.02	-2.29	1.219	1.3415	3.942
0.2527	1.007286	60.71	1522.52	-2.27	1.237	1.3423	3.960
0.2960	1.008476	60.71	1525.25	-2.26	1.249	1.3429	3.973
0.3383	1.009632	60.70	1527.85	-2.24	1.264	1.3435	3.986
0.3978	1.011254	60.69	1531.53	-2.22	1.282	1.3443	4.004
0.4461	1.012565	60.67	1534.59	-2.21	1.298	1.3450	4.020
$m_{\text{API-IL}}$= 0.2012 mol·kg^{-1}							
0.0000	1.004246		1514.88		1.386	1.3440	4.034
0.0993	1.006984	61.21	1521.10	-2.10	1.428	1.3454	4.082
0.1493	1.008349	61.21	1524.22	-2.09	1.449	1.3462	4.099
0.1974	1.009657	61.20	1527.20	-2.07	1.468	1.3469	4.115
0.2527	1.011154	61.19	1530.64	-2.06	1.493	1.3477	4.133
0.2960	1.012318	61.19	1533.36	-2.06	1.511	1.3483	4.147
0.3383	1.013448	61.18	1535.95	-2.05	1.529	1.3489	4.161
0.3978	1.015032	61.17	1539.62	-2.04	1.557	1.3498	4.181
0.4461	1.016309	61.17	1542.63	-2.03	1.578	1.3504	4.195
$m_{\text{API-IL}}$= 0.2980 mol·kg^{-1}							
0.0000	1.008029		1522.25		1.568	1.3488	4.189
0.0985	1.010725	61.27	1528.38	-2.00	1.620	1.3503	4.262
0.1512	1.012157	61.26	1531.66	-1.99	1.648	1.3512	4.281
0.1970	1.013395	61.25	1534.51	-1.99	1.675	1.3519	4.297
0.2537	1.014917	61.24	1538.02	-1.98	1.706	1.3529	4.318
0.2857	1.015773	61.24	1540.02	-1.98	1.725	1.3534	4.329
0.3493	1.017464	61.23	1543.96	-1.97	1.763	1.3545	4.353
0.3852	1.018413	61.22	1546.18	-1.96	1.785	1.3551	4.366
0.4408	1.019877	61.21	1549.58	-1.95	1.815	1.3560	4.385
L-alanine in $m_{\text{API-IL}}$ ([OMIm][Ibu] + water)							
$m_{\text{API-IL}}$= 0.1101 mol·kg^{-1}							
0.0000	0.997665		1505.96		1.429	1.3408	4.939
0.0988	1.000421	61.12	1511.99	-2.12	1.479	1.3423	3.978
0.1493	1.001808	61.17	1515.18	-2.15	1.507	1.3432	3.996
0.2057	1.003343	61.22	1518.92	-2.21	1.539	1.3442	4.016
0.2728	1.005147	61.28	1523.56	-2.29	1.576	1.3453	4.039
0.3403	1.006947	61.33	1528.40	-2.35	1.615	1.3464	4.062
0.3854	1.008131	61.37	1531.73	-2.39	1.644	1.3472	4.078
0.4378	1.009511	61.39	1535.53	-2.42	1.677	1.3481	4.096
$m_{\text{API-IL}}$= 0.2001 mol·kg^{-1}							
0.0000	0.998173		1512.36		1.832	1.3465	4.132

0.0974	1.000864	61.35	1517.81	-1.77	1.911	1.3487	4.197
0.1458	1.002192	61.34	1520.67	-1.83	1.951	1.3498	4.217
0.1999	1.003666	61.33	1523.94	-1.88	1.999	1.3510	4.240
0.2509	1.005048	61.33	1527.14	-1.93	2.041	1.3521	4.261
0.2935	1.006196	61.33	1529.87	-1.96	2.079	1.3530	4.278
0.3434	1.007532	61.32	1533.16	-2.01	2.117	1.3541	4.299
0.3939	1.008880	61.31	1536.51	-2.05	2.157	1.3552	4.320
0.4472	1.010342	61.33			2.202		
$m_{\text{API-IL}}$= 0.2889 mol·kg^{-1}							
0.0000	0.998651		1518.22		2.241	1.3517	4.332
0.1012	1.001375	62.06	1523.74	-1.60	2.353	1.3529	4.429
0.1406	1.002434	62.00	1525.98	-1.64	2.397	1.3534	4.445
0.1952	1.003903	61.91	1529.15	-1.69	2.457	1.3541	4.467
0.2476	1.005305	61.85	1532.23	-1.72	2.507	1.3548	4.488
0.3016	1.006744	61.81	1535.52	-1.76	2.571	1.3555	4.509
0.3779	1.008759	61.77	1540.36	-1.83	2.652	1.3565	4.540
0.4511	1.010698	61.69	1545.08	-1.88	2.733	1.3575	4.570

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[a] Standard uncertainties u are, u (T) = 0.01 K, u (d) = 0.3 kg m^{-3}, speed of sound u (u) = 0.5, u (□) = 0.015 mPa.s, u (n_D) = 0.002 and u(P) = 0.01 MPa. The estimated uncertainty are, u_c ($V_{□}$) = 0.05·10^{-6} m^3.mol^{-1}, u_c (□$_{□}$) = 0.02·10^{-14} m^{3}mol^{-1}.Pa^{-1} and u_c (R_D) = 0.003.

[b] Relative standard uncertainties u_r for molalities of API-IL and amino acids are u_r ($m_{\text{API-IL}}$) = 0.02 and u_r (m) = 0.005, respectively, where $m_{\text{API-IL}}$ is the molal concentration of API-IL in water.

Table 3. The values of standard apparent molar volume (V_φ°), experimental slope (S_v), standard deviation (σ (V_φ)), transfer volume ($\Delta_{tra}V_\varphi^\circ$), hydration number ($n_H$), pair ($V_{AB}$) and triplet ($V_{ABB}$) interaction coefficients, partial apparent molar isentropic compressibility (κ_φ°) the experimental slope (S_κ), standard deviation (σ(κ_φ)), partial molar isentropic compressibility of transfer ($\Delta_{tra}\kappa_\varphi^\circ$), pair ($\kappa_{AB}$) and triplet ($\kappa_{ABB}$) interaction coefficients, 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 ($\Delta_{tra}B$), of L-alanine in the aqueous solutions of [OMIm][Sal] and [OMIm][Ibu] at *T* = 298.15 K and 0.0868 MPa.

	L-Alanine in m_{API-IL} ([OMIm][Sal] + water)			L-Alanine in m_{API-IL} ([OMIm][Ibu] + water)		
$^a m_{API-IL}$ / mol·kg^{-1}	0.0974	0.2012	0.2980	0.1101	0.2001	0.2889
$10^6 V_\varphi^\circ$/m^3·mol^{-1}	60.79 ± 0.008	61.23 ± 0.001	61.29 ± 0.001	61.05 ± 0.011	61.36 ± 0.003	62.13 ± 0.023
$10^6 S_v$ / m^3·mol^{-2}·kg	-0.27 ± 0.023	-0.14 ± 0.004	-0.18 ± 0.003	0.82 ± 0.039	-0.11 ± 0.009	-1.02 ± 0.082
10^6 σ(V_φ)	0.01	0.01	0.01	0.01	0.01	0.03
$10^6 \Delta_{tra}V_\varphi^\circ$/ m^3·mol^{-1}	0.82	1.26	1.32	1.08	1.39	2.16
n_H	3.32	3.19	3.17	3.24	3.15	2.91
$10^6 V_{AB}$/ m^3·mol^{-2}·kg		5.10			4.50	
$10^6 V_{ABB}$/ m^3·mol^{-3}·kg^2		-6.48			-1.99	
$10^{14} \kappa_\varphi^\circ$ /m^3·mol^{-1}·Pa^{-1}	-2.35 ± 0.01	-2.11 ± 0.00	-2.01 ± 0.00	-2.02 ± 0.01	-1.70 ± 0.02	-1.53 ± 0.01
$10^{14} S_\kappa$ /m^3·mol^{-2}·kg·Pa^{-1}	0.31 ± 0.02	0.19 ± 0.01	0.14 ± 0.01	-0.95 ± 0.04	-0.85 ± 0.06	-0.79 ± 0.02
10^{14} σ(κ_φ)	0.01	0.01	0.01	0.01	0.01	0.01
$10^{14} \Delta_{tra}\kappa_\varphi^\circ$/ m^3·mol^{-1}·Pa^{-1}	0.31	0.54	0.64	0.63	0.95	1.13
$10^{14} \kappa_{AB}$/m^3·mol^{-2}·kg·Pa^{-1}		1.86			-1.75	
$10^{14} \kappa_{ABB}$/ m^3·mol^{-3}·kg^2·Pa^{-1}		3.40			-3.34	
B/ dm^3·mol^{-1}	0.281 ± 0.002	0.306 ± 0.003	0.351 ± 0.003	0.386 ± 0.005	0.454 ± 0.003	0.483 ± 0.004
$\Delta\mu_1^{\circ\#}$/ kJ·mol^{-1}	9.88	10.40	10.77	10.43	11.14	11.69
$\Delta\mu_2^{\circ\#}$/ kJ·mol^{-1}	52.99	49.95	60.67	67.26	74.53	77.25
$\Delta_{tra} B$/ dm^3·mol^{-1}	0.024	0.049	0.094	0.129	0.197	0.226

Table 4. The values of molar electrical conductivity (Λ) of the API-ILs, [OMIm][Sal] and [OMIm][Ibu] in water and in the aqueous solutions of L-alanine as a function of API-IL concentration at T = 298.15 K and 0.0868 MPa[a].

^{b}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}	c / mol·m^{-3}	$10^4\Lambda$/ S·m^2·mol^{-1}
			[OMIm][Sal]				
m_{Ala} = 0.0 mol·kg^{-1c}		m_{Ala} = 0.1 mol·kg^{-1}		m_{Ala} = 0.3 mol·kg^{-1}		m_{Ala} = 0.5 mol·kg^{-1}	
0.0599	67.46	0.0851	63.91	0.1015	60.73	0.0913	57.55
0.1239	66.56	0.1474	63.34	0.1719	60.00	0.1389	57.23
0.1829	65.61	0.2229	62.67	0.2541	59.12	0.217	56.82
0.2435	64.85	0.2993	62.04	0.3413	58.36	0.2848	56.36
0.3078	64.05	0.3649	61.47	0.4464	57.58	0.3612	56.10
0.3746	63.50	0.4443	60.98	0.5414	56.89	0.452	55.62
0.4537	62.96	0.5249	60.38	0.6465	56.18	0.5459	55.23
0.5388	62.40	0.6088	59.92	0.7479	55.57	0.6279	54.79
0.6319	61.85	0.6951	59.37	0.8262	55.10	0.7177	54.35
0.7107	61.22	0.7762	58.90	0.9028	54.72	0.7901	53.99
0.7727	60.89	0.8569	58.51	0.9943	54.36	0.892	53.53
0.8601	60.33	0.9547	57.98	1.0366	54.11	0.9935	53.10
0.9267	59.95	1.0350	57.59			1.0818	52.73
1.0003	59.55					1.1890	52.32
1.0722	59.15					1.2918	51.95
1.1517	58.93					1.4116	51.54
			[OMIm][Ibu]				
m_{Ala} = 0.0 mol·kg^{-1c}		m_{Ala} = 0.1 mol·kg^{-1}		m_{Ala} = 0.3 mol·kg^{-1}		m_{Ala} = 0.5 mol·kg^{-1}	
0.1194	45.85	0.1176	43.93	0.1044	39.85	0.1285	36.78
0.1867	45.31	0.1819	43.64	0.1581	39.48	0.2252	36.32
0.2455	44.98	0.2358	43.38	0.2171	39.20	0.2772	36.10
0.3199	44.45	0.2907	43.16	0.2681	38.95	0.3305	35.85
0.3832	44.01	0.3475	42.98	0.3640	38.61	0.3886	35.61
0.4442	43.70	0.4026	42.83	0.4363	38.36	0.4568	35.36
0.4996	43.47	0.4608	42.56	0.4983	38.13	0.5032	35.15
0.5433	43.16	0.5209	42.45	0.5655	37.88	0.5455	35.01
0.6031	42.80	0.5697	42.24	0.6360	37.68	0.5975	34.78
0.6488	42.45	0.6173	42.07	0.7114	37.50	0.6427	34.60
0.7089	42.16	0.6669	41.90	0.7618	37.39	0.7024	34.40
0.7525	41.89	0.7989	41.40	0.8414	37.23	0.8262	33.93
0.8156	41.55	0.8471	41.31				
0.8731	41.36	0.9009	41.16				

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[a] Standard uncertainties u are, u (Λ) = 3×10^{-6} S m^2 mol^{-1} and u (T)= 0.01 K.

[b] Relative 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.

Table 5. The values of ion association constant (K_A), of limiting molar conductivity (Λ_0), distance parameter (R), standard deviation ($\sigma(\Lambda)$), Walden product ($\Lambda_0\eta$) and standard free Gibbs energy of ion-pairing formation (ΔG_A°) of [OMIm][Sal] and [OMIm][Ibu] in water and in the aqueous solutions of L-alanine and ionic limiting molar conductivity (λ_0), Walden product ($\lambda_0\eta$), Stoke's radius (r_s), diffusion coefficient (D_{ion}^0), and transport number ($t_\pm$) of the ions $[OMIm]^+$, $[Sal]^-$ and $[Ibu]^-$ of [OMIm][Sal] and [OMIm][Ibu] in water at T = 298.15 K and 0.0868 MPa[a].

m_{Ala}/ mol·kg^{-1}	[a] K_A / dm^3·mol^{-1}	$10^4 \Lambda_0$ / S·cm^2·mol^{-1}	$10^{10} R$ / m	$\sigma(\Lambda)$	$10^4 \Lambda_0\eta$ / S·cm^2·mPa·s·mol^{-1}	ΔG_A° / kJ·mol^{-1}
			[OMIm][Sal] in m_{Ala} (L-alanine + water)			
0.0	42.45	67.40 ± 0.22	50.40	0.34	60.32	-9.29
0.1	32.61	64.52 ± 0.07	49.49	0.11	58.70	-8.64
0.3	22.68	61.40 ± 0.12	52.69	0.19	58.64	-7.74
0.5	15.371	58.16 ± 0.04	48.20	0.05	58.21	-6.77
			[OMIm][Ibu] in m_{Ala} (L-alanine + water)			
0.0	23.70	46.74 ± 0.03	54.26	0.05	41.82	-7.85
0.1	19.37	44.47 ± 0.03	46.62	0.04	40.47	-7.35
0.3	17.41	40.25 ± 0.07	48.80	0.12	38.44	-7.08
0.5	14.11	37.44 ± 0.01	52.23	0.01	37.48	-6.56
ions	$10^4 \lambda_0$ / 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}	$t_\pm$	
			[OMIm][Sal] in water			
$[OMIm]^+$	32.2[a]	31.50	2.85	8.57	0.478	
$[Sal]^-$	35.2	28.82	2.60	9.37	0.522	
			[OMIm][Ibu] in water			
$[OMIm]^+$	32.2[a]	28.82	2.85	8.57	0.689	
$[Ibu]^-$	14.54	13.01	6.31	3.87	0.311	

[a] The estimated uncertainties for u (K_A) = 0.2 dm^3 mol^{-1}, u (10^4 Λ_0) = 0.04 S m^2 mol^{-1} and u (T) = 0.01 K.

[b] The λ_0 values of the cation were taken directly from Ref. [45].

Fig. Captions

Fig. 1. The structure of (a) 1-octyl-3-methylimidazolium salicylate ([OMIm][Sal]) and (b) 1-octyl-3-methylimidazolium ibuprofenate ([OMIm][Ibu]).

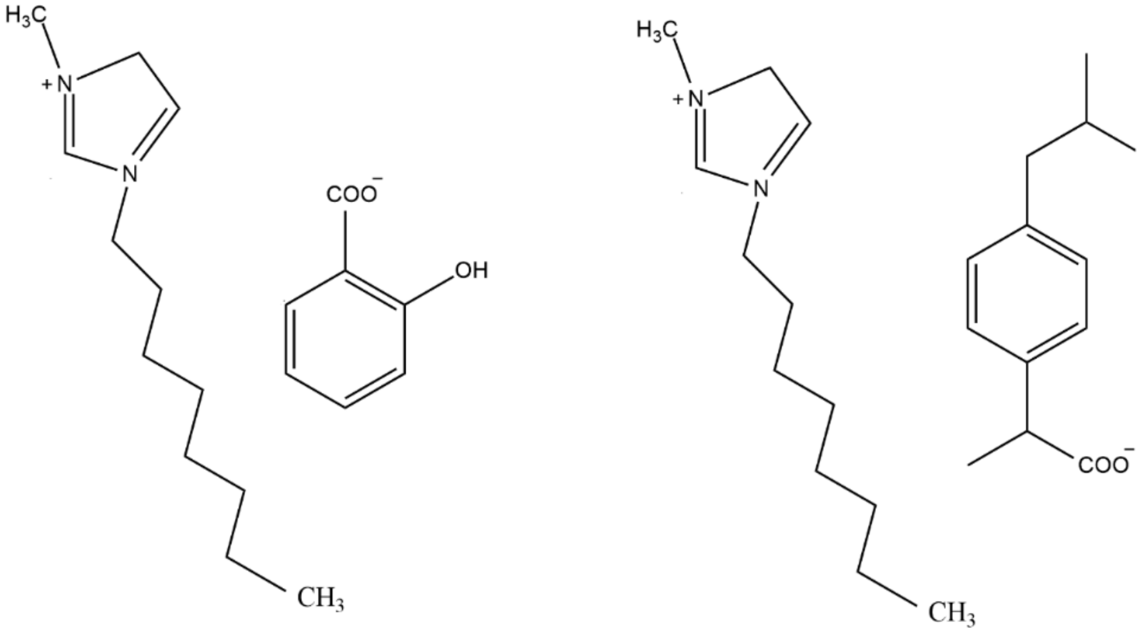
Fig. 2. The partial molar volume of transfers of L-alanine in the solutions of ([OMIm][Sal] (●), ([OMIm][Ibu] (■) + water) with several molalities at *T*= 298.15 K.

Fig. 3. The apparent molar isentropic compressibility of L-alanine in the solutions of ([OMIm][Sal] (●), [OMIm][Ibu] (■) + water) with 0.3 molality at *T*= 298.15 K.

Fig. 4. The *B*-coefficient viscosity of transfer for L-alanine in the solutions of ([OMIm][Sal] (●), [OMIm][Ibu] (■) + water) with several molalities at *T*= 298.15 K.

Fig. 5. The molar conductivity of [OMIm][Sal] (●) and [OMIm][Ibu] (■) in the aqueous solutions of L-alanine with 0.5 molality at *T*= 298.15 K.

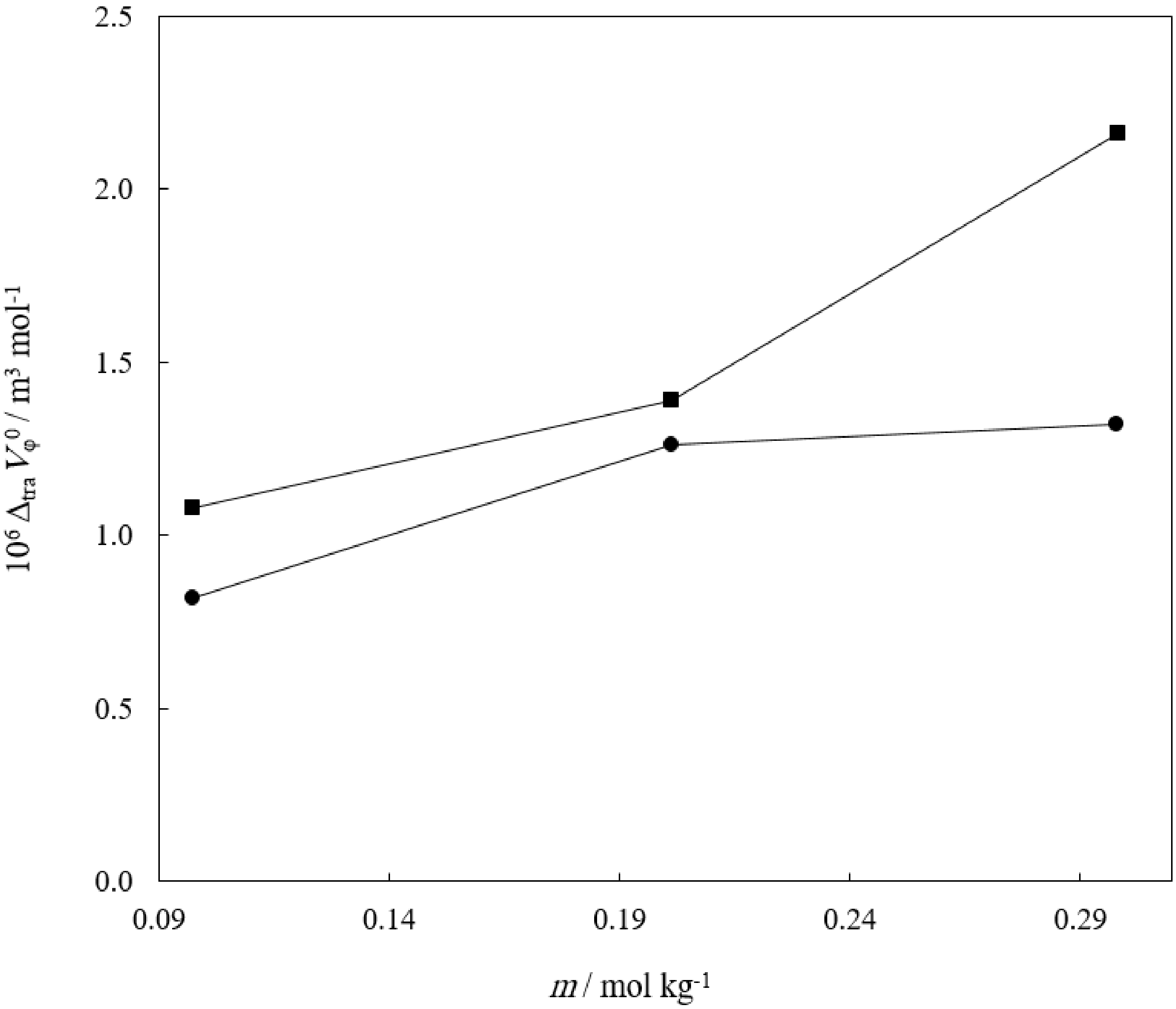
Fig. 6. The molar refraction of ternary (L-alanine + [OMIm][Sal] (●) , [OMIm][Ibu] (■) + water) with 0.3 molality ([OMIm][Sal], [OMIm][Ibu] + water) of at *T*= 298.15 K.



(a)

(b)

Fig. 1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1.5
1.0
0.5
0.0
0.09
0.14
0.19
0.24
0.29
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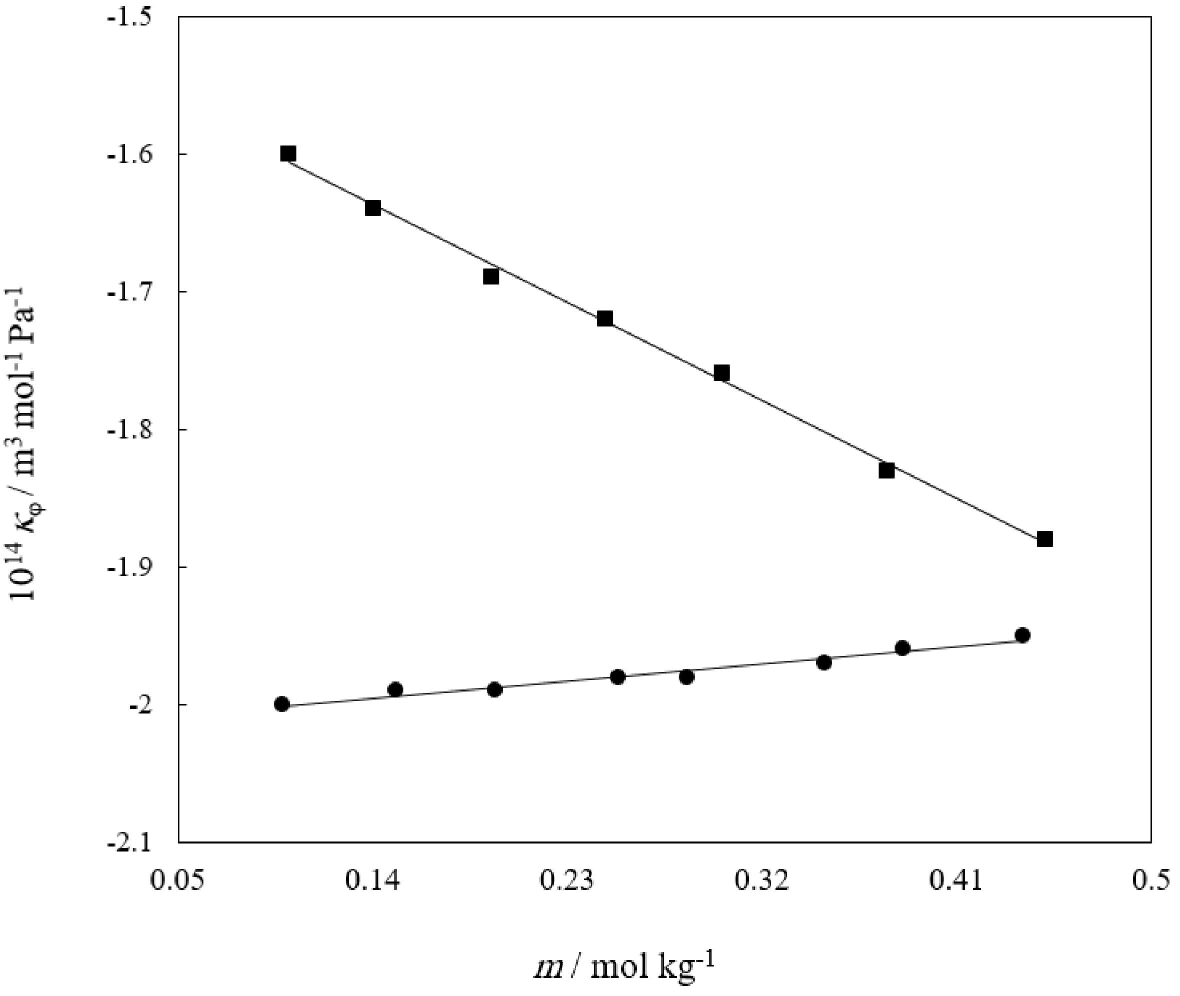
m / mol kg^{-1}

Fig. 2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-1.6
-1.7
-1.8
-1.9
-2
-2.1
0.05
0.14
0.23
0.32
0.41
0.5
$10^{14}\,\kappa_{\varphi}$ / m^3 mol^{-1} Pa^{-1}
m / mol kg^{-1}

Fig. 3

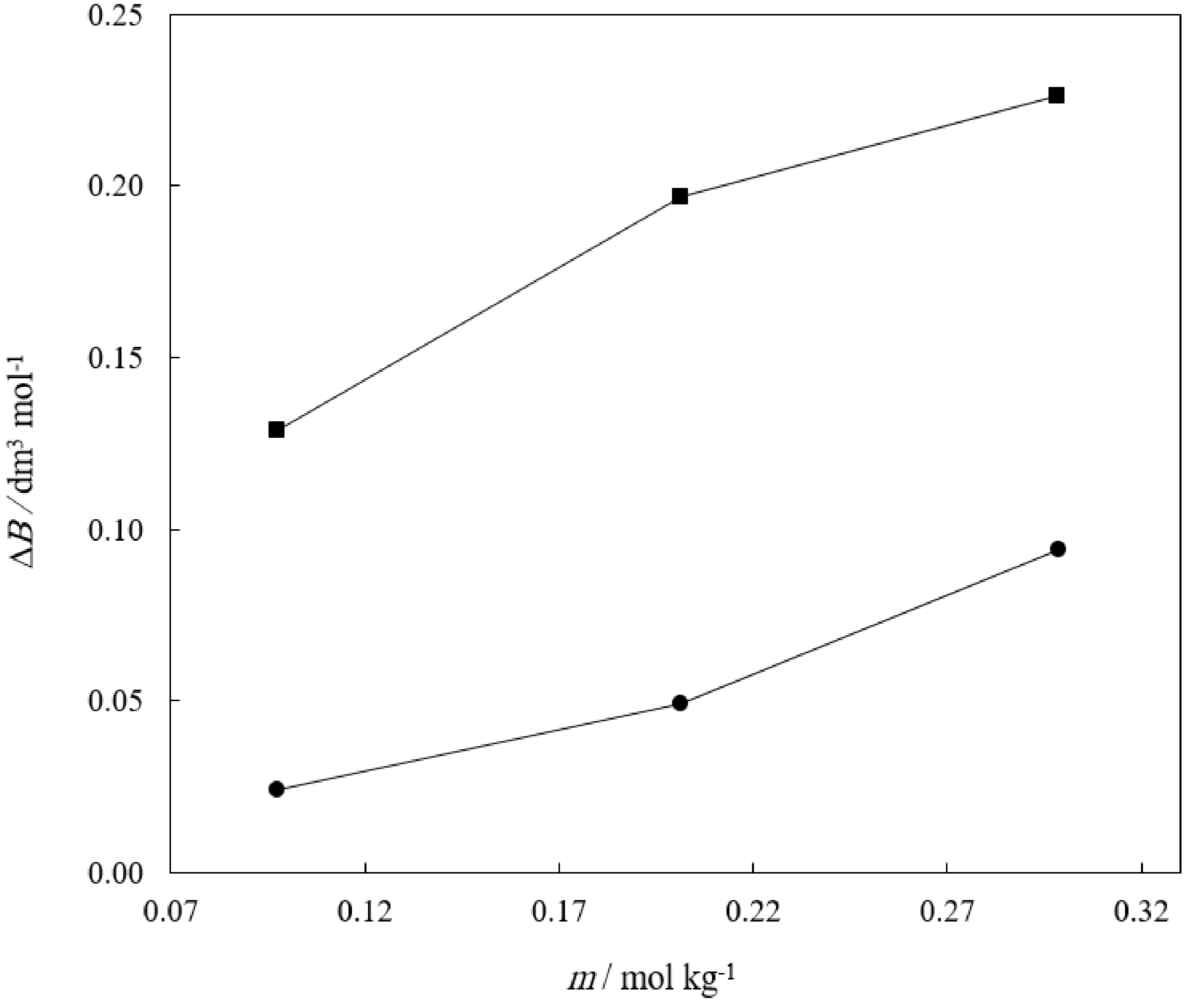
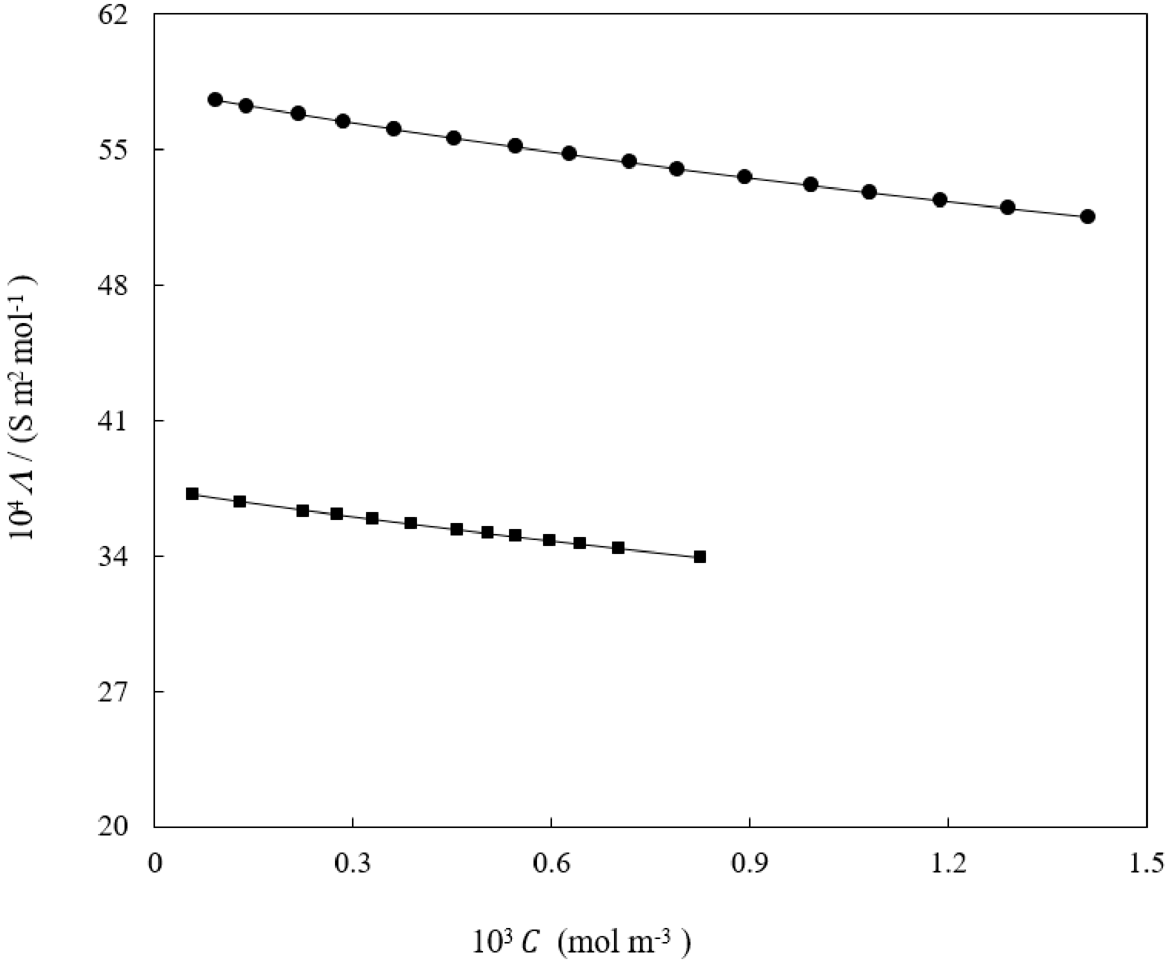

0.25
0.20
0.15
0.10
0.05
0.00
0.07
0.12
0.17
0.22
0.27
0.32
ΔB / dm³ mol⁻¹
m / mol kg⁻¹

Fig. 4



62
55
48
41
34
27
20
0
0.3
0.6
0.9
1.2
1.5
$10^4 \Lambda$ / (S m^2 mol^{-1})
10^3 C (mol m^{-3})

Fig. 5

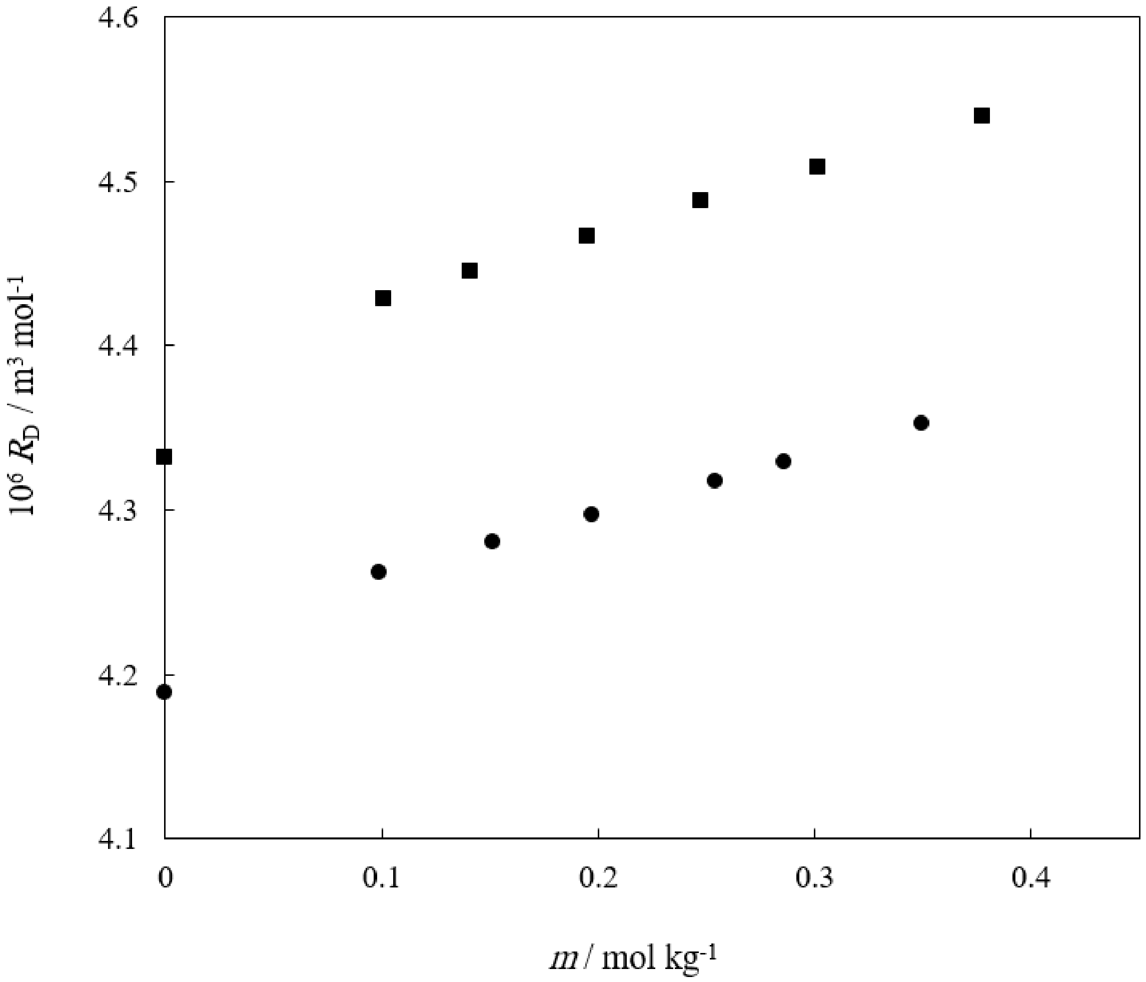


Fig. 6

Highlights

- Two new API-ILs, [OMIm][Sal] and [OMIm][Ibu] were synthesized.
- Thermophysical properties of L-alanine in the presence of API-ILs were determined.
- The $\Delta_{tra}V_{\varphi}^{0}$, $\Delta_{tra}\kappa_{\varphi}^{0}$, $\Delta_{\mathrm{tra}}B$, K_A and R_{D} quantities were calculated using the measured data.
- The dominant types of the interactions between L-alanine and API-ILs were resulted.