



**SMU**  
Sikkim Manipal University



**SMU Medical Journal**



ISSN : 2349 – 1604 (Volume – 2, No. 2, July 2015) Research article

Indexed in SIS (USA), ASI (Germany), I2OR (India) and SJIF  
(Morocco) databases  
Impact Factor: 3.835 (SJIF)

## **Studies on Thermophysical Properties of Brönsted Acidic Ionic Liquids for Medical applications**

**Zeinab Heidari Pebdani\***

Pharmaceutical Research Laboratory, Department of Chemistry, Isfahan University of Technology,  
Isfahan 84156, IR Iran, Tel: +98 313 391 3292; fax: +98 313 391 2350.

\*Corresponding Author

E-Mail: zeinabheidari.pebdani@gmail.com;

zenabheidari.pebdani@yahoo.com;

Mobile: +98 936 253 6131.

Manuscript received : 28.05.2015

Manuscript accepted: 20.06.2015

### **Abstract**

Drug Ionic liquids have been widely studied in Medicine for the replacement of VOCs in organic chemistry for the synthesis of biologically active compounds including Active Pharmaceutical Ingredients (APIs). ILs and antimicrobial or antibacterial activity, antibiofilm activity, ILs and antitumor activity, biotechnology and toxicity of ionic liquids, and biomedical applications (use of ILs to boosting MRI), all these are important for Medical applications. To overcome problems pharmaceutical process, ionic liquids (ILs) have been increasingly exploited as solvents and or (co) solvents and or reagents in a wide range of pharmaceutical applications due to their tailor-made chemical, physical and biological properties. The Brönsted Acidic Ionic Liquids (BAILs)  $[\text{Bu}_3\text{NH}]\text{H}_2\text{PO}_4$ ,  $[\text{Bu}_3\text{NH}]\text{HSO}_4$ ,  $[\text{Bu}_3\text{NH}]\text{NO}_3$ ,  $[\text{Bu}_3\text{NH}]\text{Cl}$ , were synthesized and characterized instruments tending: TLC, FT-IR,  $^1\text{H-NMR}$  and elemental analysis. Experimental densities ( $\rho$ ), dynamic viscosities ( $\eta$ ), surface tension ( $\sigma$ ), electrical conductivity ( $\kappa$ ), refractive indices ( $n_D$ ) and thermal conductivity ( $\lambda$ ), that were investigated as a function of temperature under (293.15 to

363.15) K conditions, for binary systems with water ionic liquids at atmospheric pressure. A standard and effective method to evaluate the acidity of Brønsted acids was the Hammett method ( $H_o$ ) which might use them for BAILs,  $pH$  and  $pKa$ . Conjointly, densities, dynamic viscosity, surface tension, ionic conductivity, refractive indices and thermal conductivity deviations, and dynamic viscosity deviations in for the binary systems with water were fitted to a Vogel-Fulcher-Tammann (VFT) equation. The current synthesized ionic liquids show a weak temperature dependency on the physical properties.

**Keywords:** Ionic Liquids, Medical Chemistry, Pharmaceutical Salts, Physical Properties, Temperature dependence, Water, Molecular interactions.

**Abbreviations:** (BAILs) Brønsted Acidic Ionic Liquids; (RTILs) Room temperature ionic liquids, (APIs) Active Pharmaceutical ingredients. (VOCs) Volatile Organic Compounds.

## **Introduction**

Ionic liquids have been broadly studied in Medicine for the replacement of VOCs in organic chemistry for the synthesis of biologically active compounds including APIs. However, the pharmaceutical industry does not appear to take ILs seriously as solvents due to issues of their purity, toxicity, and regulatory approval. But the applications of ILs in pharmaceuticals are not limited only as reaction medium. Though there is no concerned effort of finding applications of ILs in the pharmaceutical arena in recent years, a detailed survey of the literature shows that pharmaceutical salts having properties now termed as ‘ionic liquids’ have existed for a long time [1]. It is undoubtedly experiencing a series of challenges such as ILs and biomedical application to improve surface on the iron oxide nanoparticles is useful for biomedical applications such as like magnetic resonance imaging (MRI), furthermore, the interaction with biomolecular such as DNA was found [2].

Basic ILs exhibited great potential for the replacement of conventional basic catalysts because they are flexible, nonvolatile, noncorrosive, and immiscible with many organic solvents [3]. One of the most principles of green chemistry is that the avoiding using dangerous solvents in chemical synthesis [4, 5], and decrease using pricy toxic solvents and generating risky wastes [6, 7]. In recent years, ionic liquids (ILs) have attracted increasing interest and been with success used in the variability of reactions as environmentally benign solvents and catalysts because of their fairly low viscosities, low vapor pressure, and high thermal and chemical stability [8-12]. Room temperature ionic liquids (RTILs) are novel and new category of substances with high potential to substitute, several ancient organic solvents in reaction and separation processes [13-14]. In spite of their importance and a focus, correct values for several of the fundamental physical-chemistry properties of this ionic liquid are either briefly offer or absent [15].

To devise any process involving ionic liquids on an industrial level, it is essential to understand a series of physical properties including viscosity, density, surface tension, refractive Index, ionic conductivity, thermal conductivity, and so on moreover; the presence of water in the ionic liquid part

will significantly affect their physical properties [16-18]. In spite of the attention-grabbing feature and sensible importance of ILs, there are restricted literature reports for the correct measurements of the many of their elementary physical and chemical properties at many temperatures [19, 20]. So, during this paper we tend to want to report the results of our studies on the physical, thermodynamic and transport properties of BAILs. Properties like dynamic viscosity, density, surface tension, refractive Index, thermal stability, ionic conductivity, thermal conductivity Hammett value ( $H_o$ ) and  $pH$ , for many ionic liquids including,  $[Bu_3NH]H_2PO_4 + water$ ,  $[Bu_3NH]HSO_4 + water$ ,  $[Bu_3NH]NO_3 + water$ , and  $[Bu_3NH]Cl + water$  were determined as a function of the temperature in the range of (293.15, 363.15) K and atmospheric pressure.

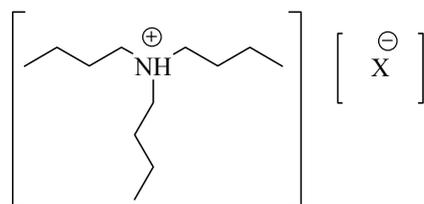
## Materials and methods

### Preparation of ionic liquids

*Materials:* Water used was freshly deionized and distilled before use. Tributylamine was purchased from the Sigma-Aldrich. (With >99 % of purity), Sulfuric Acid (98%) and Nitric Acid (78%) and phosphoric acid (99%) and Choleric acid (37%) were purchased from Merck. The purity of the ILs were confirmed by FT-IR and  $^1H$ -NMR spectroscopy and elemental analysis. The BAILs were prepared from the corresponding chlorides according to the procedures reported in literature [11].

*Synthesis of ILs:*  $[Bu_3NH]H_2PO_4$ ,  $[Bu_3NH]HSO_4$ ,  $[Bu_3NH]NO_3$ ,  $[Bu_3NH]Cl$ . at first, tri-butyl ammine Chloride was added in to a round-bottom flask, dichloromethane was added and stirred thoroughly, and then concentrated Brönsted acids in 1:1 ratio was also added slowly at room temperature for 3 hours under atmosphere. The resulting ionic liquids were dried using rotary evaporated under vacuum conditions. Produce the ionic liquids in 86%. Scheme 1.

**Scheme (1).** preparation of ionic liquids.



X= $H_2PO_4$ ,  $HSO_4$ ,  $NO_3$ , Cl

**$[Bu_3NH]H_2PO_4$** ; FT-IR (NaCl): 3000, 2962, 2875, 2388, 2340, 1472, 1105, 962, 741, 522,  $cm^{-1}$ .  $^1H$ -NMR (400MHz, DMSO-  $d_6$ ):  $\delta$  9.36 (s, 1H, NH), 2.84 (t, 6H, J=7.2,  $CH_2$ ), 1.56 (m, 6H,  $CH_2$ ), 1.27 (m, 6H,  $CH_2$ ), 0.89(m, 9H,  $CH_3$ ) ppm.

**[Bu<sub>3</sub>NH]HSO<sub>4</sub>**; FT-IR (NaCl): 3433, 2938, 2875, 2875, 2801, 2558, 2801, 1381, 1645, 1234, 1041, 853, 740, 582 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400MHz, DMSO- *d*<sub>6</sub>): δ 7.11 (s, 1H), 2.99 (t, 6H, J=7.6, CH<sub>2</sub>), 1.59 (m, 6H, CH<sub>2</sub>), 1.27 (m, 6H, CH<sub>2</sub>), 0.87 (m, 9H, CH<sub>3</sub>) ppm.

**[Bu<sub>3</sub>NH]NO<sub>3</sub>**; FT-IR (NaCl): 3463, 2962, 2875, 2740, 2561, 1742, 1633, 1469, 1294, 1035, 1159, 926, 826, 738, cm<sup>-1</sup>. <sup>1</sup>H-NMR (400MHz, DMSO- *d*<sub>6</sub>): δ 7.00 (s, 1H, NH), 3.02 (t, 6H, J=7.6, CH<sub>2</sub>), 1.56 (m, 6H, CH<sub>2</sub>), 1.34 (m, 6H, CH<sub>2</sub>), 0.89 (m, 9H, CH<sub>3</sub>) ppm.

**[Bu<sub>3</sub>NH]Cl**; FT-IR (NaCl): 3434, 2960, 2524, 1631, 1379, 1105, 1034, 926, 739, 580, 563, cm<sup>-1</sup>. <sup>1</sup>H-NMR (400MHz, DMSO- *d*<sub>6</sub>): δ 9.85 (s, 1H, NH), 2.85 (t, J=7.2, 6H, CH<sub>2</sub>), 1.57 (m, 6H, CH<sub>2</sub>), 1.29 (m, 6H, CH<sub>2</sub>), 0.89 (m, 9H, CH<sub>3</sub>) ppm.

## **Results and discussions**

### *Determination of water content*

Before their use, the ionic liquids samples were dried and degassed under vacuum (10<sup>-3</sup> bar) at 85 °C during 3 hours. After this treatment, the mass fraction of water determined by coulometric Karl–Fischer titration using a Metrohm 756 KF Coulometer with a Hydranal<sup>®</sup> Coulometer AG conductor-chemical agent. Outlined water content (45 ± 10) × 10<sup>-3</sup> w/w that were showed terribly low levels of water, therefore we ignored it's in the measurements.

### *Density*

Density was measured by a 25 ml pycnometer. In general, density precisions are ±0.0005 g cm<sup>-3</sup>. The temperature was maintained using thermostatic bath with a precision of ±0.01 K. All density measurements were repeated at least three times. Densities of the ILs as a function of temperature are shown in Fig. 1. As expected, densities decrease linearly with increasing temperature, and may be correlated by the simple regression ( $r^2 > 0.999$ ).

The temperature-dependent densities ( $\rho$ ), refractive indices ( $n_D$ ), surface tension ( $\sigma$ ) and thermal conductivity ( $\lambda$ ) values were fitted by the method of least squares using the following equations (1) [21-26].

$$z = A_0 + A_1 T (K) + A_2 T^2 (K)^2 \quad (1)$$

Wherever fitting parameters  $A_0$  ( $gcm^{-3}$ ),  $A_1$  ( $gcm^{-3} K^{-1}$ ) and  $A_2$  ( $gcm^{-3} K^{-2}$ ) are associated with temperature and extrapolated density at 0 K, respectively and  $T$  is that the temperature (K). The parameters adjusted to equation (2) For the density of those ILs are summarized in Table 1.

Figure 1. Temperature dependence of density data for the ILs.

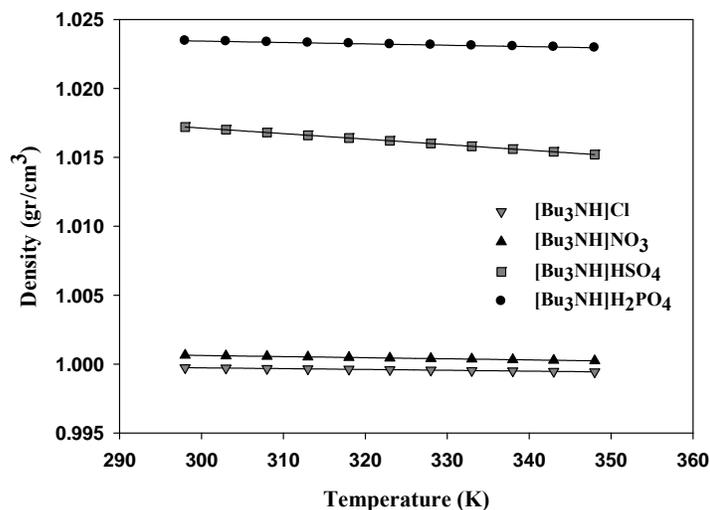


Table 1. Fitting

$$\rho = A_0 + A_1 T (K) + A_2 T^2 (K)^2$$

ILs	$A_0$ ( $g cm^{-3}$ )	$A_1$ ( $g cm^{-3} K^{-1}$ ) $\times 10^{-2}$	$A_2$ ( $g cm^{-3} K^{-2}$ ) $\times 10^{-4}$	$SD \times 10^{-4}$	$(\Delta\rho / \rho) \times 100$
[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	1.0264	-1.0002	-5.7137	1.6583	1.0232
[Bu <sub>3</sub> NH]HSO <sub>4</sub>	1.0291	-4.0000	2.8837	6.6332	1.0162
[Bu <sub>3</sub> NH]NO <sub>3</sub>	1.0007	-6.1538	1.3916	1.0028	0.9996
[Bu <sub>3</sub> NH]Cl	1.0030	-8.0000	5.1021	1.3266	1.0004

### Viscosity

In BAILs measurements viscosity showed no deviation from Newtonian behavior in the investigated temperature vary. Kinematic viscosities were obtained using a LV DV-I PRIME model measuring instrument manufactured from Brookfield Co and capillary tubing deepen in an exceedingly thermo explicit bathtub with a preciseness of  $\pm 0.01$  K. The dynamic viscosities were calculated from the densities with preciseness adequate to 0.03 mPas. All measurements were repeated two occasions. Sample viscosities were first determined as a function of the temperature throughout a heating cycle from (293.15 to 363.15) K. Knowledge on viscosity and density for the ILs at temperatures ranging

from (293.15 to 363.15) K. are shown in Figures 2. The temperature dependency of the dynamic viscosity values match well to the Vogel–Tammann–Fulcher (VTF) equation (2) [23-24].

$$\eta = \eta_o \exp \left[ B / (T - T_o) \right] \tag{2}$$

Wherever T is that the temperature,  $\eta_o$ , B and  $T_o$  are adjustable parameters. The  $\eta_o$  (cP), B (K), and  $T_o$  (K) parameters are given in Table 2. Normally used equation to correlate the variation of viscosity with temperature is the Arrhenius-like law Equation (3) [25- 29].

$$\eta = \eta_o \exp(-Ea / RT) \tag{3}$$

Viscosity at first temperature and the energy of activation (Ea) are characteristics parameters usually adjusted from experimental knowledge. Table 3 lists the parameters for each equation with the standard relative deviation (S. D.) Equation (4):

$$S.D. = \left[ \sum_i^n (z_{exp} - z_{cal})^2 / n \right]^{1/2} \tag{4}$$

Where  $z_{exp}$  and  $z_{cal}$  are the values of the experimental and calculated property, n is that the verity of experimental data of parameters.

**Table 2.** Fitting Parameters of Equation 2 and Standard Deviations, SD, of the Dynamic viscosity ( $\eta$ ) ILs.

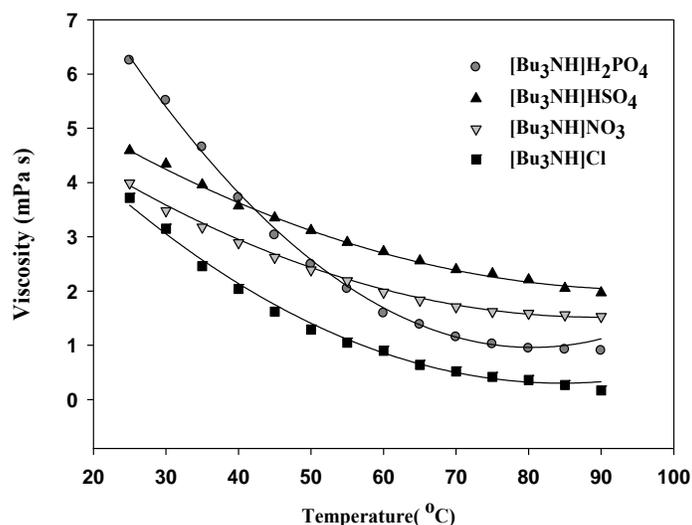
ILs	$\eta = \eta_o \exp \left[ B / (T - T_o) \right]$				
	$\eta_o$ (mpas)	$T_o$ (K)	B (K)	SD	$(\Delta\eta / \eta) \times 100$
[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	12.2363	-0.2302	0.0017	1.8248	2.5421
[Bu <sub>3</sub> NH]HSO <sub>4</sub>	6.6842	-0.0963	0.0005	0.8500	3.0050
[Bu <sub>3</sub> NH]NO <sub>3</sub>	12.2363	-0.2802	0.0017	0.7972	2.3257
[Bu <sub>3</sub> NH]Cl	6.9168	-0.1565	0.0009	1.1275	1.3293

A comparison between the experimental data for the physical properties of the studied ABILs at 25 °C has conjointly created in Table 3. To the most effective of our data, no literature data on densities ( $\rho$ ), dynamic viscosities ( $\eta$ ), surface tension ( $\sigma$ ), electrical conductivity ( $\kappa$ ), refractive indices ( $n_D$ ) and thermal conductivity ( $\lambda$ ), weren't previously available for four studied ILs. As is obvious from Table 3, the experimental data for [Bu<sub>3</sub>NH]H<sub>2</sub>PO<sub>4</sub>, [Bu<sub>3</sub>NH]HSO<sub>4</sub>, [Bu<sub>3</sub>NH]NO<sub>3</sub>, and [Bu<sub>3</sub>NH]Cl.

**Table 3.** Experimental value of dynamic viscosities ( $\eta$ ), refractive indices ( $n_D$ ), densities ( $\rho$ ), surface tensions ( $\sigma$ ), electrical conductivity ( $\kappa$ ), thermal conductivity ( $\lambda$ ) and pKa of the Acidic Brönsted ionic liquids at 25.0 °C.

ILs	$\eta$ (mPa.s)	$n_D$	$\rho$ (g/cm <sup>3</sup> )	$\sigma$ (N/m)	$\kappa$ (ms/m)	$\lambda$ (W/KC)	pKa
[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	6.25	1.3499	1.0235	0.0819	10.8000	0.6700	5.35, 3.35
[Bu <sub>3</sub> NH]HSO <sub>4</sub>	4.59	1.3475	0.0172	0.0860	60.2000	0.5800	6.33, 2.26
[Bu <sub>3</sub> NH]NO <sub>3</sub>	3.99	1.3402	0.9997	0.0968	14.1000	0.5500	2.55
[Bu <sub>3</sub> NH]Cl	3.72	1.3395	1.0006	0.0885	27.4000	0.5100	1.95

**Figure 2.** Dynamic viscosity ( $\eta$ ) as a function of temperature for ILs.



### Refractive Indexes

An Abbe Refractometry Model ATAGO-T3 programmable digital with a measurement accuracy of ( $4 \times 10^{-5}$ ) was used to measure the refractive index of various ILs in a temperature range of (298.15 to 363.15) K. The temperature was controlled with an accuracy of (0.05) K. The equipment was calibrated and checked before every series of measurements using pure organic solvents (ethanol) with well-known refractive indices [30, 31]. Refractive Indices are often well fitted by Equation (1).

### Surface Tension

Stalagmometer dope of falling was used for estimated surface tension ILs. The surface tension of the ILs measured as a function of temperature. The experimental data decrease with increase in temperature which shows at Fig 4. These values were compared with those obtained with [Bu<sub>3</sub>NH]NO<sub>3</sub> has high surface tension than ILs. Supported these data, it seems that the surface tension lowly decreases with will increases temperature. The connection between surface tension and temperature of are often fitting by the Equation (1).

Table .4 Fitting Parameters of Equation 1 and Standard Deviations, SD, of the Refractive Index ( $n_D$ ) ILs.

$$n_D = A_o + A_1 T (K) + A_2 T^2 (K)^2$$

ILs	$A_o$	$A_1 (K^{-1}) \times 10^{-2}$	$A_2 (K^{-2})$	$SD \times 10^{-3}$	$(\Delta n_D / n_D) \times 100$
[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	1.3515	-6.5385	6.9930	9.8026	1.3487
[Bu <sub>3</sub> NH]HSO <sub>4</sub>	1.3490	-6.0013	-4.6620	9.9590	1.3463
[Bu <sub>3</sub> NH]NO <sub>3</sub>	1.3422	-8.0000	1.2472	1.3266	1.3386
[Bu <sub>3</sub> NH]Cl	1.3410	-6.0000	2.6056	9.9499	1.3383

Figure. 3 shows temperature dependence of refractive index for studied ILs have refractive indices >1.4. As it can be seen from Fig 3, for all three ILs, the refractive index decreases linearly with raising temperature.

Figure 3. Refractive Index ( $n_D$ ) as a function of temperature for ILs.

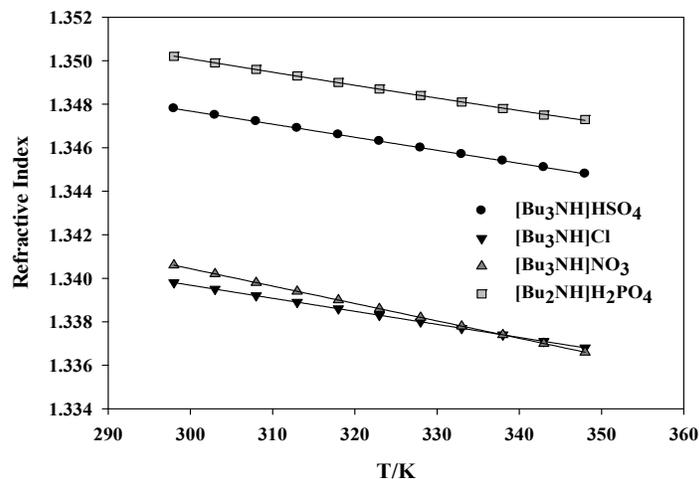


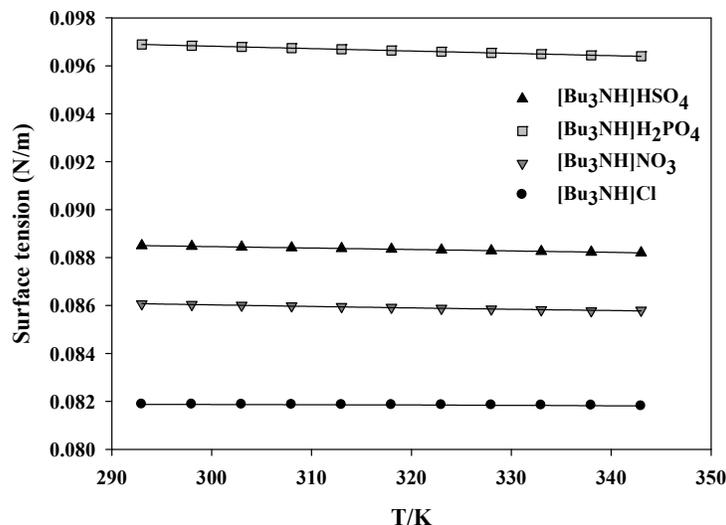
Table 5. Fitting Parameters of Equation 1 and Standard Deviations, SD, of the Surface tension ( $\sigma$ ) ILs.

$$\sigma = A_o + A_1 T (K) + A_2 T^2 (K)^2$$

ILs	$A_o (mN s^{-1})$	$A_1 \times 10^{-2} (mN s^{-1})$	$A_2 (mN s^{-1} K)$	$SD \times 10^{-3}$	$(\Delta \sigma / \sigma) \times 100$
[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	1.3515	-6.5385	6.9930	2.1598	0.0818
[Bu <sub>3</sub> NH]HSO <sub>4</sub>	1.3490	-6.0013	-4.6620	9.9982	0.0859
[Bu <sub>3</sub> NH]NO <sub>3</sub>	1.3422	-8.0000	1.2472	1.6434	0.0966
[Bu <sub>3</sub> NH]Cl	1.3410	-6.0000	2.6056	9.9500	0.0884

The synthesized ionic liquids show a weak temperature dependency on the surface tension Figure 4.

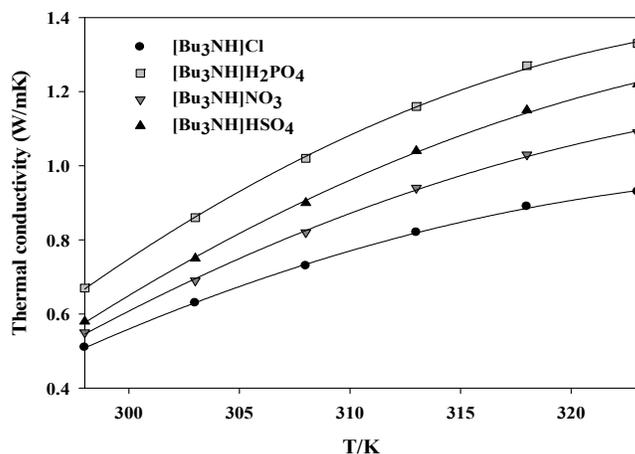
Figure 4. Surface tension ( $\sigma$ ) as a function of temperature for ILs.



*Thermal conductivity*

The thermal conductivity was measured by using a KD2 thermal property meter (decagon, Canada), that relies on the transient hot wire method. The KD2 meter includes a probe with 60 mm length and 0.9 millimeter diameter that integrates in its interior a heating element and a thermo-resistor, and is connected to a microprocessor for controlling and conducting the measurements. The KD2 meter was calibrated by using distilled water and standard ethylene glycol before any set of measurements. In order to study the effect of temperature, a thermostat bath was used, which was able to keep the temperature regularity within the range of  $\pm 0.1$  K. At least five measurements were taken for each temperature to be sure the uncertainty of measurements almost  $\pm 2\%$ . Figure. 5 show the thermal conductivity of ILs as a function of temperature.

Figure 5. Thermal conductivity ( $\lambda$ ) as a function of temperature for ILs.



The relationship between thermal conductivity ( $\lambda$ ) and temperature of are often fitting by the Equation (1) and fitting parameters listed in table 6.

**Table 6.** Fitting Parameters of Equation 1 and Standard Deviations, SD, of the Thermal conductivity ( $\lambda$ ) ILs.

$$\lambda = A_0 + A_1T (K) + A_2T^2 (K)^2$$

ILs	$\lambda = A_0 + A_1T (K) + A_2T^2 (K)^2$				
	$A_0 (W / mK)$	$A_1 (W / mK) \times 10^{-2}$	$A_2 (W / mK)$	SD	$(\Delta\lambda / \lambda) \times 100$
[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	-0.7557	0.0715	-0.0006	0.0125	0.2531
[Bu <sub>3</sub> NH]HSO <sub>4</sub>	-0.6600	0.0609	-0.0005	0.2449	0.9400
[Bu <sub>3</sub> NH]NO <sub>3</sub>	-0.4671	0.0495	-0.0004	0.2071	0.8533
[Bu <sub>3</sub> NH]Cl	-0.3800	0.0448	-0.000	0.1608	0.7517

*Electrical Conductivity*

As electrolyte materials, electrical conductivity is one in every of the foremost main properties of ILs as solution (electrolyte) materials [32]. The electrical conductivity ( $\kappa$ ) of the ionic liquids was analytically measured with a conductivity meter CTR80 (ZAG-CHEMIE). Electrical conductivity was measured by suggests that of the complicated electrical impedance technique, employing a measuring device and using a thermometer, under atmosphere for determined temperature. The cell constant was determined by calibration after each sample measurement using an aqueous 0.02 M KCl aqueous solution. The  $\kappa$  data for the considered aqueous RTIL systems were measured for temperatures ranging from (293.15 to 348.15) K at normal atmospheric pressure. Table 7 presented the obtained  $\kappa$  measurements. Molar conductivity of the ionic liquids  $\Lambda$  ( $m^2Smol^{-1}$ ) was calculated from the ionic conductivity  $\sigma$  ( $Sm^{-1}$ ) and the molar concentration  $C$  ( $kmolm^{-3}$ ) according to the Equation (5).

$$\Lambda = 1000 \left( \frac{\kappa}{C} \right) \tag{5}$$

The electrical conductivity presents linearly behaviour with temperature for all ILs measured. Electrical conductivity ( $\kappa$ ) values were fitted by the strategy of statistical method (least squares) using the following equation (6) [33].

$$\Lambda = \Lambda_0 + AT (K) + BT^2 (K)^2 + CT^3 (K)^3 \tag{6}$$

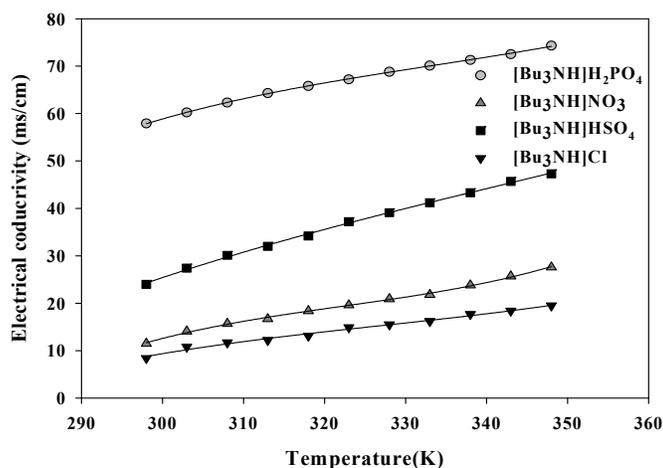
**Table 7.** Fitting Parameters of Equation 5 and Standard Deviations, SD, of the Electrical conductivity ( $\Lambda$ ) ILs.

$$\Lambda = \Lambda_0 + AT(K) + BT^2(K)^2 + CT^3(K)^3$$

ILs	$\Lambda_0 (ms\ cm^{-1})$	$A (ms\ cm^{-1}\ K^{-1})$	$B (ms\ cm^{-1}\ K^{-2})$	$C (ms\ cm^{-1}\ K^{-3})$	SD	$(\Delta\Lambda / \Lambda) \times 100$
[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	0.7212	0.5210	-0.0068	4.6309	3.4696	14.4000
[Bu <sub>3</sub> NH]HSO <sub>4</sub>	48.7594	0.5213	-0.0031	1.2121	5.2367	66.7891
[Bu <sub>3</sub> NH]NO <sub>3</sub>	-3.6261	1.0933	-0.0194	0.0001	4.9628	19.6182
[Bu <sub>3</sub> NH]Cl	11.6469	0.6826	-0.0027	3.8850	7.6316	36.5000

The plots showing the behaviour of the present  $\kappa$  data for the studied solvent systems: [Bu<sub>3</sub>NH][H<sub>2</sub>PO<sub>4</sub>] + H<sub>2</sub>O, [Bu<sub>3</sub>NH][HSO<sub>4</sub>] + H<sub>2</sub>O, [Bu<sub>3</sub>NH][NO<sub>3</sub>] + H<sub>2</sub>O, [Bu<sub>3</sub>NH][Cl] + H<sub>2</sub>O are shown in Figure 6.

**Figure 6.** Electrical conductivity ( $\kappa$ ) as a function of temperature for ILs.



*Acidity*

The acidic scale of the RTILs was measured using a universal pH meter with volume of NaOH indicator and the pKa data of RTILs listed on table 8.

**Table 8.** The pKa data of RTILs at 25°C.

ILs	[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	[Bu <sub>3</sub> NH]HSO <sub>4</sub>	[Bu <sub>3</sub> NH]NO <sub>3</sub>	[Bu <sub>3</sub> NH]Cl
pKa <sub>1</sub>	3.35	2.26	2.55	1.95
pKa <sub>2</sub>	5.35	6.33	-	-

*Determination of  $H_o$  values of Brönsted acidic ILs*

A common and effective way to evaluate the acidity of Brönsted acids was the Hammett method [34, 35]. In reported papers, the measurement of the acidic scale of these acidic Brönsted ILs was conducted on a UV-Vis spectrophotometer with a basic indicator (para-nitroaniline). Increasing the acidic scale of the acidic IL, the absorbance of the unprotonated kind of the fundamental indicator was decreased, wherever because the protonated kind of the indicator wasn't observed because of its little molar absorptive and its wavelength. Thus  $[I]/[HI]$  (I represents the indicator) ratio was determined from the measured absorbance differences after addition of an acidic Brönsted IL, and then the Hammett function,  $H_o$ , was calculated by using Equation 7.

$$H_o = pK(I)_{aq} + \log([I]/[HI]) \quad (7)$$

This value was regarded as the relative acidity of the IL [18]. Where  $pK(I)_{aq}$  was the  $pK_a$  value of the indicator,  $[I]$  and  $[HI]$  were, respectively, the molar concentrations of the unprotonated and protonated forms of the indicator, determined by UV-visible spectroscopy.

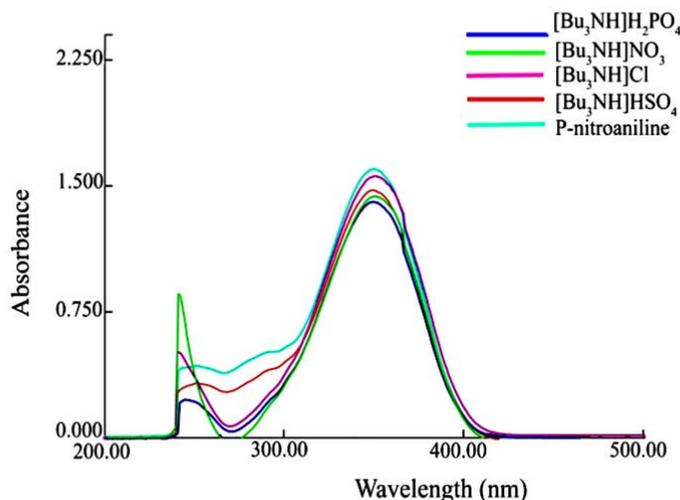
**Table 9.**  $H_o$  Values of Ionic Liquids in  $CH_2Cl_2$  at Room Temperature.

ILs	$A_{max}$	[I]%	[HI]%	$H_o$
Para-nitro aniline	1.602	100	-	-
[Bu <sub>3</sub> NH]H <sub>2</sub> PO <sub>4</sub>	1.409	87.95	12.05	1.85
[Bu <sub>3</sub> NH]HSO <sub>4</sub>	1.467	91.57	8.43	2.03
[Bu <sub>3</sub> NH]NO <sub>3</sub>	1.433	89.45	10.85	1.92
[Bu <sub>3</sub> NH]Cl	1.558	97.25	2.75	2.54

When an acidic IL was added, the absorbance of the unprotonated form of the indicator decreased. The acidities of the four ionic liquids were examined using 4-nitroaniline as indicator in dichloromethane. We got the acidity order of several ILs with the  $H_o$  values that are shown in Table 9.

Under the same concentration of 4-nitroaniline (10 mg/L,  $pK(I)_{aq} = pK_a = 0.99$ ) and BAILs (0.1 mmol/L) in dichloromethane,  $H_o$  values of all BAILs were determined. The maximal absorbance of the unprotonated form of the indicator was observed at 350 nm in dichloromethane. When the BAIL was added, the absorbance of the unprotonated form of the basic indicator decreased (Figure 7 and Table 9).

Figure 7. UV-Vis absorption spectra of ILs.



Hammett acidity ( $H_0$ ) of these BAILs was calculated using equations (7). As shown in Figure 7. Calculations suggest that the Hammett acidity ( $H_0$ ) of these ionic liquids follows this order:  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4] > [\text{Bu}_3\text{NH}][\text{NO}_3] > [\text{Bu}_3\text{NH}][\text{HSO}_4] > [\text{Bu}_3\text{NH}][\text{Cl}]$ .

## Conclusion

The distinctive and useful solvent properties of ionic liquids make them capable alternatives to classic organic solvents for various applications in the pharmaceutical and biotechnology industry. The use of ionic liquids as the active pharmaceutical ingredient offers several potential benefits such as i) the possibility of drug existing in several different crystalline form, ii) easy conversion of APIs into ionic liquids which possess improved solubility and dissolution rates, iii) the potential of novel and more efficient delivery methods, iv) patent protection for each of the new forms of the drug, v) prevention of the difficult issues nearby polymorphism and “polymorphic transformation.”

The research on the combination of two ions (scheme (1)), which are physiologically active in the body since it may help to control the dose in drug combination therapies. Moreover, many drugs cannot be delivered to the desired parts of the body or have poor solubility, and we may potentially overcome these nuisances by formulating these drugs as an ionic liquid. Indeed, a number of issues including but not limited to cost effectiveness, recycling, biodegradability and toxicity should be addressed before ILs industrial applications widely used in pharmaceutical and biotechnological sectors. The development of nontoxic biodegradable ILs and evaluation of their possible applications in pharmaceutical drug development should be emphasized.

Most of the active salts given in tables in the context structurally resemble the class of compounds now known as ‘ionic liquids’. However, it’s only during the last two decades that there have been significant efforts to develop an understanding of the physic-chemical of ILs which has lead to their wide range of applications. Obviously, much more research has to be done to explore their biomedical applications. Perhaps, we should revisit the ‘ionic liquid-like compounds with pharmaceutical and or biological application’ already reported could help the community in designing biologically active and useful ILs. A modular IL strategy has the potential to transform the pharmaceutical industry in ways never expected. This approach can provide a platform for improved activity with new treatment options or even personalized medication. The data of physical properties on ionic liquids are necessary for each theoretical analysis and industrial application such as pharmaceutical.

The databases during this respect will definitely support the study and advance of ionic liquids. So, in this work, we have carefully measured several important physical properties of ionic liquids: tri-butyl ammonium chloride  $[\text{Bu}_3\text{NH}][\text{Cl}]$ , tri-butyl ammonium nitrate  $[\text{Bu}_3\text{NH}][\text{NO}_3]$ , tri-butyl ammonium hydrogen sulfate  $[\text{Bu}_3\text{NH}][\text{HSO}_4]$  and tri-butyl ammonium di-hydrogen phosphate  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  over a wide range of temperature from (293.15 to 363.15 K). Clearly, much more attention should be paid on the measurement of physicochemical properties of ionic liquids.

The measured densities,  $\rho$ , and the dynamic viscosities,  $\eta$ , for the binary mixtures of  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  with water at  $T = (293.15 \text{ to } 363.15) \text{ K}$  over the whole composition range are listed in Tables 1 and 2. As can be seen, the density of all the mixtures always decreases with temperature. A good linear correlation is observed for all compositions ( $r = 1$ ), this result is linear behavior with temperature.

The experimental viscosity results of  $[\text{Bu}_3\text{NH}][\text{Cl}]$ ,  $[\text{Bu}_3\text{NH}][\text{NO}_3]$ ,  $[\text{Bu}_3\text{NH}][\text{HSO}_4]$ ,  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  from this study are in good agreement with the scarce data from the literature and are well represented by the VTF equation. At the same temperature,  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  have high significantly the viscosity of other three ILs. Presence oxygen atoms perhaps make up high viscosity this IL than other ILs. Since the viscosities of ILs are essentially affect by the Van der Waals interactions and H bonding. Therefore, Hydrogen atoms of  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  interactions with atoms oxygen of  $\text{H}_2\text{O}$  and this cause to influence on the physical properties ILs. It shown that the presence of even low concentrations of oxygen in the  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  substantially increases the viscosity.

Figure. 5 show the thermal conductivity of ILs as a function of temperature. It can be seen that the thermal conductivity of  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  is  $0.67 \text{ Wm}^{-1}\text{K}^{-1}$ . This means that  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  is a relatively poor thermal conductor with the thermal conductivity about of that of water at the room temperature. Initially, the temperature-independent thermal conductivity of the  $[\text{Bu}_3\text{NH}][\text{H}_2\text{PO}_4]$  was thought to be due to the in proper method of measurements as the thermal probe and the liquid are electrically conductive. It was also hypothesised that the temperature-independent behaviour is associated with the high viscosity of the ionic liquids.

## **Acknowledgement**

We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR Iran, (Y.GH) and (A.R.H.), grants.

## **References**

1. Wermuth, C. G., Stahl, P. (2002) H., Eds. "Handbook of Pharmaceutical Salts: Properties, Selection, and Use"; Wiley-VCH: Weinheim, Germany, .
2. Nsrita A, Naka K, Chujo Y, (2010)"Preparation of Ionic Liquid- Modified Inorganic Nanoparticles and their Biomedical Application, In: Ionic Liquids as Green Solvents": Progress and Prospects (ACS S symposium Series). Malhotra SV(Ed), Volume 1038, American Chemical Society, Chapter 9, pp 103-114.
3. Hajipour A. R, Rafiee F. (2009)Basic Ionic Liquids. A Short Review. J Iran Chem Soc; 6:647-678.
4. Shen J, Wang H, Liu H, Sun Y and Liu Z. (2008) J. Mol. Catal. A: Chem. 280, 24.
5. Wasserscheid .P, Hal R. v. and Bösmann A (2002) Green Chemistry4, 400–404.
6. Singh .V, Kaur .S, Sapehiyia .V, Singh J. and Kad G. L (2005) Catal. Commun. 6, 57.
7. Earle M. J, McCormac P. B, Seddon K. R, (1999) Green Chem, 1, 23–25.
8. Zhang .R, Meng X, Liu Z, Meng J. and Xu C (2008) Ind. Eng. Chem. Res47, 8205.
9. Hajipour A. R, Rafiee F. and Ruoho A. E (2006) Synth. Commun. 36, 2563.
10. Hajipour A. R, Rafiee F. and Ruoho A. E (2007) Synlett, 7, 1118.
11. Wassercheid P, Welton T, (2003) Eds. Ionic Liquids in Synthesis; Wiley-VCH. p. 364.
12. P. Wassercheid, T. Welton (2003) Eds. Ionic Liquids in Synthesis; Wiley-VCH., 364.
13. Baltus R. E, Counce R. M, Culbertson B. H, Luo H, DePaoli D. W, Dai S, Duckworth D. C (2005) Sep. Sci. Technol. 40, 525-541.
14. Najdanovic-Visak .V, Esperanca J. M. S. S, Rebelo L. P. N, Nunes da Ponte M, Guedes H. J. R, K. R. Seddon. (2002) Szydowski J. 4, 1701-1703.

15. Seddon K. R, Stark A, Torres M. J (2000) *Pure Appl. Chem*72, 2275-2287.
16. Carmichael A. J, Seddon K. R, Red N. (2000) *J. Phys. Org. Chem*, 13, 591- 595.
17. Law G. P. R.(2001) *Chem. Phys. Lett*345, 1-4.
18. Pereiro A. B, Tojo E, Rodríguez A, Canosa J, Tojo J (2006) *J. Chem. Thermodyn*, 38, 651.
19. Pereiro A. B, Santamarta F, Tojo E, Rodríguez A, Tojo J (2006) *J. Chem. Eng. Data*. 51, 952.
20. Pereiro A. B, Tojo E, Rodríguez A, Canosa J, Tojo J (2006) *Green Chem*, 8, 307.
21. Hajipour A. R, Rafiee F (2010) *Organic Preparations and Procedures Inter.*, 42, 285- 362.
22. Pereiro A. B, Verdi´a P, Tojo E, and guez A. R (2007) *J. Chem. Eng. Data*52, 377-380.
23. Stepniak I, Andrzejewska E, (2009) *Electrochim. Acta*. 54, 5660.
24. Wilkes, J. S. (2004) “Properties of ionic liquid solvents for catalysis”. *J. Mol.Catal. A: Chem.*, 214, 11–17.
25. Okoturo O. O, Vandernoot J. J (2004) *J. Electroanal. Chem*568, 167-181.
26. Gomez E, Gonzalez B, Calvar N, Tojo E, Dominguez A (2006) *J. Chem. Eng. Data*. 51, 2096–2102.
27. Seddon K. R, Starck A. S, Torres M. J (2004) *ACS Symp. Ser*No. 901.
28. Wilkes J. S (2004) *J. Mol. Catal. A: Chem*214, 11-17.
29. Okoturo O. O, Vandernoot J. J, J. (2004) *Electroanal. Chem.*, 568, 167-181.
30. Yunus N. M, Mutalib M. I. A, Man Z, Bustam M. A, Murugesan T, J (2010) *Chem. Thermodynamic.*, 42, 491–495.
31. Muhammad A, Mutalib M. I. A, Wilfred C. D, Murugesan T, Shafeeq A (2008) *J. Chem. Thermodynamic.*, 40, 1433–1438.
32. Wu T. Y, Sua S. G, Wangc H. P, Lind Y. C, Gunga S. T, Lina M. W, Suna I. W, J. (2011) *Electrochemical Acta*; 56, 3209–3218, .

33. Wang Y. Y, Li W. and Dai L. Y, Chin(2008) J. Chem.. 26, 1390; Chem. Abstr. 151, 103209, 2008.
34. Seddon .R (2000) Green Chem. 2, 21–23.
35. Welton T, Adams C. J, Earle M. J, K. (1999) Chem. Rev. 99, 2071.

---

### *Authors Column*



**Ms. Zeinab Heidari Pebdani** is presently working as Research Fellow at Medicine Chemistry Division, Isfahan University of Technology and Iranian Biochemistry Research Institute. She has specialization in Biochemistry analyzed important medicinal and synthesis of Drug Ionic Liquids for catalysts in Pharmaceutical Industries and evaluated their different physical chemistry properties. Major Areas of Interest: Design of Drug Ionic Liquids; Synthesize Biocatalyst & Biopolymers, Drug Deliver. She has published research papers, scientific articles in peer reviewed journals and has made significant number of research presentations in various national and international scientific events.