SMU
Sikkim Manipal University

Manipal
INSPIRED BY LIFE

I2OR

SMU Medical Journal

SIS
Scientific Indexing Services

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 Lewis Acidic Ionic Liquids for Medical Use

**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;
zenabheydari.pebdani@yahoo.com;
Mobile: +98 936 253 6131.

Manuscript received : 30.05.2015
Manuscript accepted: 23.06.2015

## Abstract

Drug Ionic Liquids (ILs) have been broadly studied in Medicine and Industrials 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. We investigated functions of temperature, densities ($\rho$), dynamic viscosities ($\eta$), surface tension ($\sigma$), ionic conductivity ($\kappa$), refractive indices ($n_D$), and thermal conductivity ($\lambda$) for the binary systems of the DMSO with ionic liquids as pharmaceutical salts over the whole composition range at temperature from 298.15 to 363.15K under atmospheric pressure. The ILs investigated in this study comprised $[Bu_3NBn]Cl\text{-}2(MCl_m)$, ($MCl_m$= $AlCl_3$, $CuCl_2$, $FeCl_3$, $SnCl_4$, $ZnCl_2$) which we synthesized in our laboratory. By using TLC, CHNS, FT-IR and Mass Spectroscopy, the temperature influence on the thermophysical properties on the new series of room-temperature ionic liquids (RTILs) prepared and characterized. Thermo-gravimetric analysis (TGA) confirmed that ILs are stable at the temperature range of 400–800ºC. We used the Hammett method ($H_o$) which is a common and effective way to evaluate the acidity of Lewis acids. Also densities, dynamic viscosities, surface tensions, ionic conductivities, refractive indices and thermal conductivity deviations, and dynamic viscosity deviations for the binary systems with DMSO were fitted to a Vogel-Fulcher-Tammann (VFT) equation.

***Keywords:*** Ionic liquids, Medical Chemistry, Pharmaceutical Salts, Physical and Thermophysical properties, DMSO, Molecular interactions.

***Abbreviations:*** (LAILs) Lewis Acidic Ionic Liquids; (RTILs) Room Temperature Ionic Liquids; (APIs) Active Pharmaceutical Ingredients; (VOC) Volatile Organic Compounds, (DMSO) Di Methyl Sulfoxide.

## Introduction

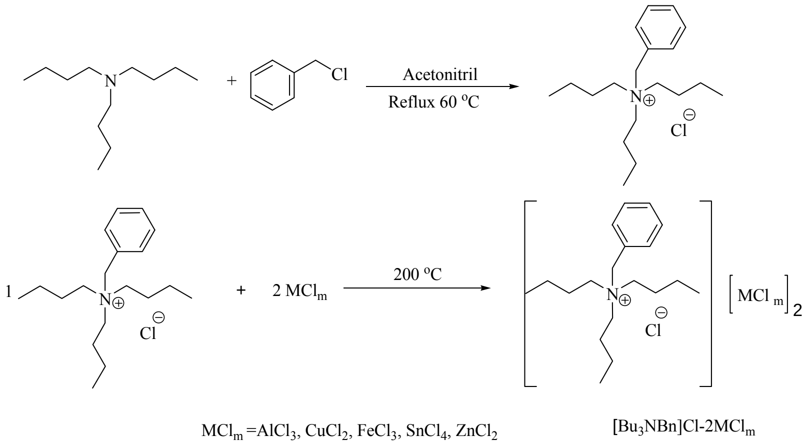
Design and synthesis of pharmaceutically acceptable salts is one of the main aspects of drug development. Almost half of all drugs used in medicine are administered as salts [1], it is undoubtedly experiencing a series of challenges such as ILs and biomedical application to improve surface on the iron oxide nanoparticles is useful for biomedical applications such as like magnetic resonance imaging (MRI), furthermore, the interaction with bimolecular such as DNA was found [2]. Owing to many well-known drawbacks such as low solubility, polymorphic conversion and low bioavailability, administration of solid form of many drugs is one of the current challenges [3]. A large effort has been made to use ionic liquids (ILs) as alternatives for usual molecular solvents used in organic synthesis and catalytic reactions [4]. They complement the family of “green solvents” including water and supercritical fluids. Among all factors, room temperature ionic liquids are the only materials containing ionic species having a melting point lower than 298 K. Ionic liquids display many interesting properties such as slight vapour pressure, low melting point, and large liquid range. However, flexibility of their physico-chemical properties is the only solvent specificity which makes them attractive in this regard. Most of the studies on ILs are based on $[Bu_3NBn]$ Cl-2($AlCl_3$), $[Bu_3NBn]$ Cl-2($CuCl_2$), $[Bu_3NBn]$Cl-2($FeCl_3$), $[Bu_3NBn]$Cl-2($SnCl_4$) and $[Bu_3NBn]$Cl-2($ZnCl_2$). It has recently been suggested that ILs can be used as solvents in chemical reactions [5-7], multiphase bioprocess operations [8] and liquid–liquid separations [9,10], electrolytes for batteries and fuel cells[11], stationary phases in gas chromatography [12-15], mobile phase additives in liquid chromatography[16-18] and electrolyte additives in capillary electrophoresis (CE) [17-26]. However, finding of their physical-chemistry properties revealed a direct relation with their purity level, temperature dependence of density, dynamic viscosity, conductivity, surface tension, refractive index, and thermal conductivity. Among all of the known ionic liquids, those series with asymmetric quaternary ammonium cations are assumed to be the most promising for battery electrolyte use. These ILs show a wider electrochemical window, especially along with cathodic direction, andimidazoliumcation-based ionic liquids [27-29]. On the other hand, quaternary ammonium-based ionic liquids have the drawback of low ionic conductivity at $10^{-3}$ S $cm^{-1}$ or lower. Indeed, salts based on small quaternary ammonium cations are solid at room temperature [30]. In contrast, increasing the cation size decreases cation mobility, and mixing of cations is expected to lower the melting point of the salt as reported by Sun et al [31]. Despite of the interesting features and practical importance of ILs, there are fewliterature reports on the accurate measurements of many of their basic physical and chemical properties at various temperatures [32-35]. Here, we report the results of our studies on the physical, electrochemical, thermodynamic and transport properties of $[Bu_3NBn]Cl$-$2(AlCl_3)$, $[Bu_3NBn]Cl$-$2(CuCl_2)$, $[Bu_3NBn]Cl$-$2(FeCl_3)$ and $[Bu_3NBn]Cl$-$2(SnCl_4)$, $[Bu_3NBn]Cl$-$2(ZnCl_2)$. Figure 1 shows molecular structures of five ILs. Density, viscosity, thermal stability, surface tension, refractive index, conductivity and thermal conductivity are among the physical properties of these five ILs that accurately measured at atmospheric pressure and several different temperatures. The densities measured as a function of the temperature from 298.15 to 363.15 K. Also, we measured the Hammett parameter ($H_o$) which is a common measure to evaluate the acidity of Lewis acids we used for RTILs [36]. Because of its wide use in applied chemistry and participation in biological processes, the highly polar self-associated and aprotic solvents such as dimethylsulfoxide (DMSO) ($\mu$= 4.06 Debye) [34] was chosen [36, 37]. If used as a reaction medium, DMSO behaves as a multitalented organic liquid with a special solvent power to promote a chemical reaction. It also behaves as an effective solvent to accelerate a reaction brought by another reagent. Because of its high dielectric constant value ($\varepsilon$ = 46.45 at 298.15 K), indeed, it has been used as a solvent for polymerization reactions displacement reactions [38]. In liquid DMSO, the computer molecular dynamics (MD) simulations suggest that the weak H-bonds C–H···O S are formed [39 - 41].

## Materials and methods

### *Preparation of ionic liquids*

*Materials:* Chemicals of analytical grade were used for the synthesis of the ILs. Tributylamine and DMSO were purchased from the Sigma-Aldrich (with >99 % purity), and salts such as $AlCl_3$, $CuCl_2$, $FeCl_3$, $SnCl_4$, $ZnCl_2$ were purchased from Merck. The purity of the ILs was further confirmed by FT-IR and Mass- spectroscopy and elemental analysis. The RTILs were prepared from the corresponding chlorides according to the procedures reported in literature [42].

*Synthesis of ILs:* $[Bu_3NBn]Cl$-$2(AlCl_3)$, $[Bu_3NBn]Cl$-$2(CuCl_2)$, $[Bu_3NBn]Cl$-$2(FeCl_3)$,$[Bu_3NBn]Cl$-$2(SnCl_4)$ and $[Bu_3NBn]Cl$-$2(ZnCl_2)$. First, tri-butyl Ammine Chloride and benzencholorid was added in 1:1 ratio to a round-bottom flask. Then Acetonitril was added and stirred thoroughly, and finally anhydrous $MCl_m$ was added in 1:2 molar ratio to an oil path under protecting dry nitrogen in stages forming a liquid. The mixture was stirred at room temperature for 30 min and then was heated to 80°C. Since chlorometallic ionic liquid easily reacts with moisture, it was required to be kept in desiccators [43]. Yield reaction 64%, Scheme (1).



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

**$[Bu_3NBn]Cl\text{-}2(AlCl_3)$;** FT-IR (NaCl): *ν*= 3325-3294, 2962-2534, 1638-1380, 843-610, cm$^{-1}$.Mass Spectroscopy (T=230 ºC, EI=70 eV): *m/z*= 591, 552, 236, 185, 142, 100, 91, 57.

**$[Bu_3NBn]Cl\text{-}2(CuCl_2)$;** FT-IR (NaCl):*ν* = 3036-3388, 2962-2874, 2309-2359, 1378-1478, cm$^{-1}$. Mass Spectroscopy (T=230 ºC, EI=70 eV): *m/z*= 753, 677, 616, 571, 466, 447, 428, 409, 396, 360, 351, 332, 309, 285, 188, 126, 84, 57.

**$[Bu_3NBn]Cl\text{-}2(FeCl_3)$;** FT-IR (NaCl): *ν* =3782-3384, 2967-2874, 1998-1825, 1477-1370, 878-702, cm$^{-1}$. Mass Spectroscopy (T=230 ºC, EI=70 eV): *m/z*= 474, 459, 369, 313, 285, 239, 210, 185, 176, 142, 91, 58.

**$[Bu_3NBn]Cl\text{-}2(SnCl_2)$;** FT-IR (NaCl): *ν* =3526-3420, 2965-2876, 2380-2309, 1679-1375, 846-701, cm$^{-1}$. Mass Spectroscopy (T=230 ºC, EI=70 eV): *m/z*= 690, 573, 260, 225, 155, 142, 120, 91, 58.

**$[Bu_3NBn]Cl\text{-}2(ZnCl_2)$;** FT-IR (NaCl): *ν* =3092-3037, 2964-2742, 1969-1624, 1497-1348, 1031, 865-701, cm$^{-1}$. Mass Spectroscopy (T=230 ºC, EI=70 eV): *m/z*= 654, 626, 598, 535, 507, 190, 176, 142, 100, 91, 57.

## Results and discussions

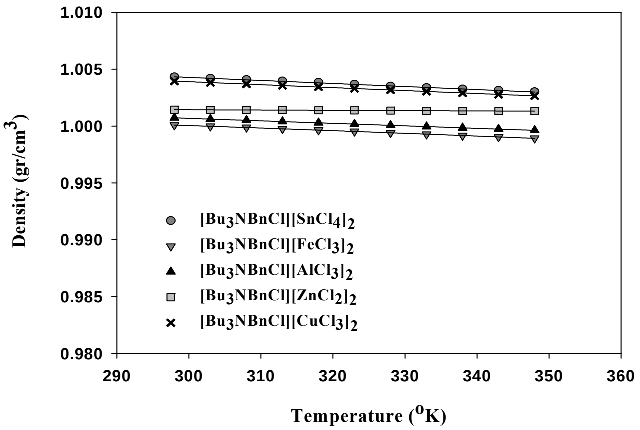
### *Determination of water content*

The ionic liquids samples were dried and degassed under vacuum ($10^{-3}$ bar) at 85 °C during 3 h, at the beginning. After this treatment, the mass fraction of water determined by coulometricKarl–Fischer titration using a Metrohm 756 KF Coulometer with a Hydranal®Coulomat AG reagent. Defined water content was very low at $(50 \pm 10) \times 10^{-3}$w/w, and therefore disregarded in the measurements.

### *Density*

Density was measured in a 25 ml pyknometer. In general, density precisions are ±0.0005 g cm$^{-3}$. 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 can be well correlated by the linear regression ($r^2 > 0.999$).

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



The temperature-dependent densities ($\rho$), refractive indices ($n_D$), surface tension ($\sigma$) and thermal conductivity (K) values were fitted by the method of least squares using the following equations (1) [44].

$$z = A_\circ + A_1 T(K) + A_2 T^2 (K)^2 \tag{1}$$

Where fitting parameters B and A are related on the coefficient of volume expansion (gcm$^{-3}$ K$^{-1}$) and extrapolated density at 0K (gcm$^{-3}$), respectively and T is the temperature (K). The adjustable parameters of Eq. (2) for the density of these ILs are summarized in Table 1.

**Table.1**Fitting Parameters of Equation 1 and Standard Deviations, SD, of the Density ($\rho$) ILs**.**

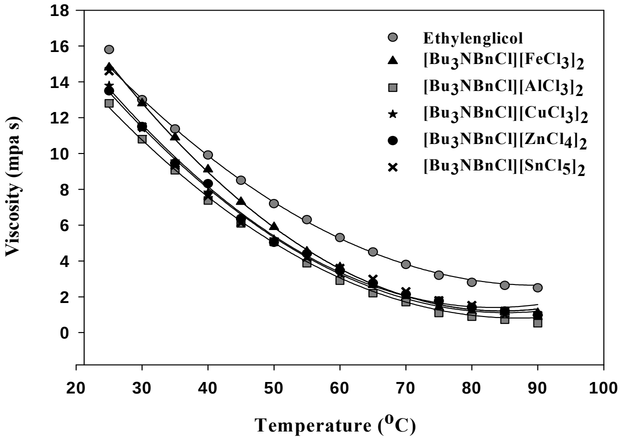
$$\rho = A_\circ + A_1 T(K) + A_2 T^2 (K)^2$$

| ILs | $A_\circ (g\,cm^{-3})$ | $A_1 (g\,cm^{-3} K^{-1}) \times 10^{-2}$ | $A_2 (g\,cm^{-3} K^{-2})$ | $SD \times 10^{-4}$ | $(\Delta\rho/\rho) \times 100$ |
|---|---|---|---|---|---|
| [Bu$_3$NBn][Al$_2$Cl$_7$] | 1.0073 | -2.2000 | 1.5701 | 1.6583 | 1.0232 |
| [Bu$_3$NBn][Cu$_2$Cl$_5$] | 1.0117 | -2.6000 | -6.7742 | 6.6332 | 1.0033 |
| [Bu$_3$NBn][Fe$_2$Cl$_7$] | 1.0028 | -3.1773 | -4.1119 | 3.8799 | 0.9995 |
| [Bu$_3$NBn][Sn$_2$Cl$_9$] | 1.0118 | -2.3716 | -4.6620 | 4.4374 | 1.0037 |
| [Bu$_3$NBn][Zn$_2$Cl$_5$] | 1.0022 | -2.6000 | -8.6318 | 4.3116 | 1.0014 |

*Viscosity*

ILs showed no deviation from Newtonian behaviour in the investigated temperature range in viscosity measurements. Kinematic viscosities were measured using a LVDV-IPRIME model viscometer made of Brookfield Co and capillary tube deepen in a thermostat bath with a precision of ±0.01 K. The dynamic viscosities were calculated from the densities with a precision equal to 0.03 mPa·s. All measurements were repeated twice. Sample viscosities were first determined as a function of the temperature during a heating cycle from (298.15 to 363.15) K. Data on viscosity for the ILs at temperatures ranging from (298.15 to 363.15) K. are shown in Fig 2.

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



The temperature dependency of the dynamic viscosity values fit well to the Vogel–Tammann–Fulcher (VTF) equation (2) [45-49].

$$\eta = \eta_{\circ} \exp\left[ B/(T - T_{\circ}) \right] \tag{2}$$

Where $T$ is the absolute 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. Commonly used equation to correlate the variation of viscosity with temperature is the Arrhenius-like law Eq (3) [50-53].

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

Viscosity at initial temperature $\eta_o$ and the activation energy ($Ea$) are characteristics parameters generally adjusted from experimental data. Table 3 lists the parameters for equations with the standard relative deviation (S. D.) Eq (4):

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

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

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

| ILs | $\eta = \eta_\circ \exp\left[B/(T - T_\circ)\right]$ | | | | |
|---|---|---|---|---|---|
| | $\eta_\circ\,(mpas)$ | $B\,(K)$ | $T_\circ\,(K)$ | $SD$ | $(\Delta\eta/\eta)\times 100$ |
| $[Bu_3NBn][Al_2Cl_7]$ | 23.9420 | -0.5309 | 0.0030 | 4.0284 | 4.6514 |
| $[Bu_3NBn][Cu_2Cl_5]$ | 25.7803 | -0.5791 | 0.0034 | 4.1442 | 5.1007 |
| $[Bu_3NBn][Fe_2Cl_7]$ | 29.0771 | -0.6586 | 0.0039 | 4.6741 | 5.6021 |
| $[Bu_3NBn][Sn_2Cl_9]$ | 26.3494 | -0.5989 | 0.0036 | 4.1831 | 5.2036 |
| $[Bu_3NBn][Zn_2Cl_5]$ | 25.9771 | -0.6586 | 1.4286 | 4.0827 | 5.1629 |

*Refractive Index*

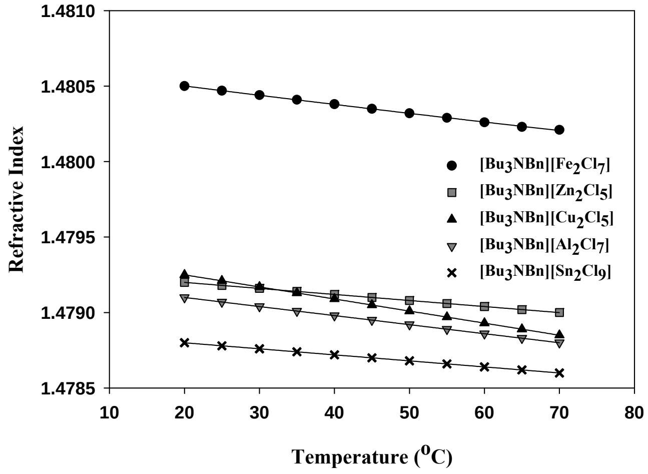
AnAbbe Refractometry Model ATAGO-T3 programmable digital with a measuring accuracy of $(4\times 10^{-5})$ was used to measure the refractive index of various ILs in a temperature range of (298.15 to 363.15) K. The temperature was controlled with an accuracy of (0.05) K. The apparatus was calibrated and checked before each series of measurements using pure organic solvents (ethanol) with known refractive indices [54, 55]. Refractive Indices can be well fitted by Equation (1).

**Table. 3** Fitting Parameters of Equation 1 and Standard Deviations, SD, of the Refractive Index ($n_D$) ILs.

| **ILs** | $n_D = A_\circ + A_1 T\,(K) + A_2 T^2\,(K)^2$ | | | | |
|---|---|---|---|---|---|
| | $A_\circ$ | $A_1(C^{-1})\times 10^{-2}$ | $A_2(C^{-2})$ | $SD\times 10^{-4}$ | $(\Delta n_D/n_D)\times 100$ |
| $[Bu_3NBn][Al_2Cl_7]$ | 1.4792 | -6.0000 | -1.4293 | 9.9499 | 1.4790 |
| $[Bu_3NBn][Cu_2Cl_5]$ | 1.4794 | -8.0000 | -6.0984 | 1.3226 | 1.4791 |
| $[Bu_3NBn][Fe_2Cl_7]$ | 1.4806 | -6.5385 | -6.9930 | 9.8026 | 1.4804 |
| $[Bu_3NBn][Sn_2Cl_9]$ | 1.4789 | -4.0000 | -7.3833 | 6.6333 | 1.4787 |
| $[Bu_3NBn][Zn_2Cl_5]$ | 1.4793 | -4.0000 | -6.7560 | 6.6333 | 1.4791 |

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

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



*Surface Tension*

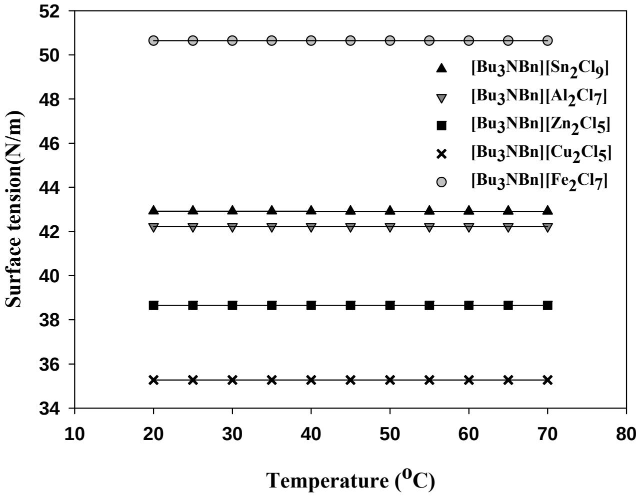
Stalagmometer dope of falling was used for estimated surface tension ILs. The surface tension of the ILs measured as a function of temperature. Fig 4 shows that the experimental data of ILs which decrease with increase in temperature. These values were compared with the data collected from [$Bu_3NBn$][$Fe_2Cl_7$] which has higher surface tension than Lewis ILs. Based on the collected data, it appears that the surface tension slowly decreases with increasing the temperature. The relationship between surface tension and temperature of ILs can be fitting by the Equation (1).

**Table. 4** Fitting Parameters of Equation 1 and Standard Deviations, SD, of the Surface tension ($\sigma$) ILs.

| ILs | $\sigma = A_\circ + A_1 T(K) + A_2 T^2 (K)^2$ | | | | |
|---|---|---|---|---|---|
| | $A_\circ (mN\, s^{-1})$ | $A_1 \times 10^{-2} (mN\, s^{-1})$ | $A_2 (mN\, s^{-1} K)$ | $SD \times 10^{-4}$ | $(\Delta\sigma / \sigma) \times 100$ |
| [$Bu_3NBn$][$Al_2Cl_7$] | 42.2259 | -4.0000 | 3.5157 | 6.6332 | 4.2241 |
| [$Bu_3NBn$][$Cu_2Cl_5$] | 25.2757 | -5.2825 | -9.7902 | 1.0226 | 3.2731 |
| [$Bu_3NBn$][$Fe_2Cl_7$] | 50.6445 | -6.8420 | 6.5268 | 1.0376 | 5.6415 |
| [$Bu_3NBn$][$Sn_2Cl_9$] | 42.918 | -5.2420 | 1.8648 | 5.9391 | 4.9161 |
| [$Bu_3NBn$][$Zn_2Cl_5$] | 38.6589 | -0.0448 | 9.7902 | 1.0226 | 3.6559 |

The synthesized ionic liquids show a weak temperature dependency on the surface tension (Fig 4).

**Figure 4.**Surface tension (σ) as a function of temperature for ILs.



*Thermal conductivity*

The thermal conductivity was measured by using a KD2 thermal property meter (decagon, Canada), which is based on the transient hot wire method. The KD2 meter has a probe with 60 mm length and 0.9 mm diameter, which 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 steadily within the range of±0.1 K. At least five measurements were taken for each temperature to make sure the uncertainty of measurements almost ±2%.

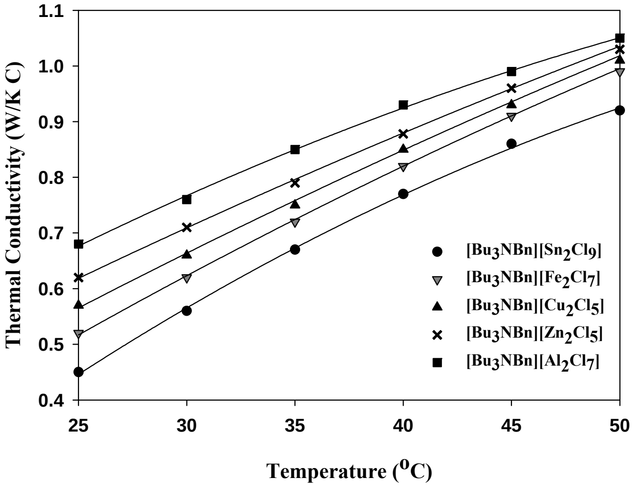
The relationship between thermal conductivity ($\lambda$) and temperature of can be fitting by the Eq (1) and fitting parameters listed in table 5.

**Table. 5** Fitting Parameters of Equation 1 and Standard Deviations, SD, of the Thermal conductivity ($\lambda$) ILs.

| **ILs** | $\lambda = A_0 + A_1 T(K) + A_2 T^2 (K)^2$ | | | | |
|---|---|---|---|---|---|
| | $A_\circ (W / mK)$ | $A_1 (W / mK) \times 10^{-2}$ | $A_2 (W / mK)$ | $SD$ | $(\Delta\lambda / \lambda) \times 100$ |
| $[Bu_3NBn][Al_2Cl_7]$ | 0.1057 | 0.0268 | -0.0002 | 0.1405 | 0.8767 |
| $[Bu_3NBn][Cu_2Cl_5]$ | -0.1686 | -0.0144 | 6.4286 | 0.1663 | 0.7950 |
| $[Bu_3NBn][Fe_2Cl_7]$ | -0.0186 | 0.0222 | -2.8571 | 0.1776 | 0.7633 |
| $[Bu_3NBn][Sn_2Cl_9]$ | -0.3271 | 0.0368 | -0.0002 | 0.1799 | 0.7050 |
| $[Bu_3NBn][Zn_2Cl_5]$ | 0.1877 | 0.01714 | -.1.4286 | 0.1545 | 0.8331 |

Figure 5 shows the thermal conductivity of ILs as a function of temperature.

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



*Electrical Conductivity*

As electrolyte materials, electrical conductivity is one of the most important properties of ILs [35]. The electrical conductivity ($\kappa$) of the ionic liquids was analytically measured with a conductivity meter CTR80 (ZAG-CHEMIE). Using a thermometer, electrical conductivity was measured by complex impedance method under atmosphere for determined temperature.Be using an aqueous 0.02 M KCl aqueous solution, the cell constant was determined by calibration after each sample measurement. The $\kappa$ data for the considered aqueous RTIL systems were measured for temperatures ranging from (298.15 to 348.15) K at normal atmospheric pressure. Table 6 shows 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 Eq (5).

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

The electrical conductivity reveals linear relationship with temperature for all ILs measured. Electrical conductivity ($\kappa$) values were fitted by the method of least squares using the following equations (6) [36].

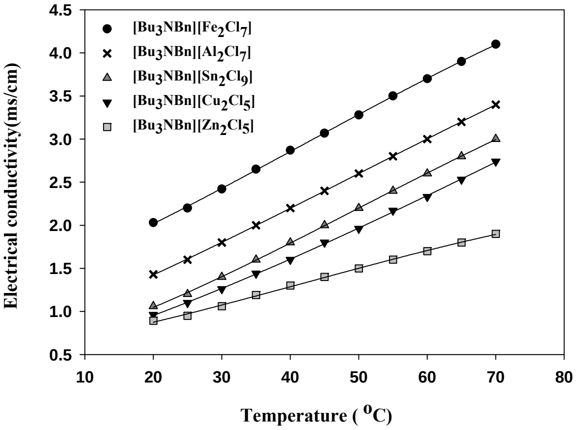
$$\Lambda = \Lambda_{o} + AT(K) + BT^{2}(K)^{2} + CT^{3}(K)^{3} \tag{6}$$

**Table.6** Fitting Parameters of Equation 5 and Standard Deviations, SD, of the Electrical conductivity ($\Lambda$) ILs

| | $\Lambda=\Lambda_o+AT(K)+BT^2(K)^2+CT^3(K)^3$ | | | | | |
|---|---|---|---|---|---|---|
| **ILs** | $\Lambda_o\,(ms\,cm^{-1})$ | $A\,(ms\,cm^{-1}K^{-1})$ | $B\,(ms\,cm^{-1}K^{-2})$ | $C\,(ms\,cm^{-1}K^{-3})$ | $SD$ | $(\Delta\Lambda\,/\,\Lambda)\times 100$ |
| $[Bu_3NBn][Al_2Cl_7]$ | 6.0371 | -0.1120 | 0.0005 | -04.8415 | 0.6588 | 2.4027 |
| $[Bu_3NBn][Cu_2Cl_5]$ | -79.6589 | 0.7109 | -0.0022 | 2.3140 | 0.5930 | 1.8082 |
| $[Bu_3NBn][Fe_2Cl_7]$ | -10.0573 | 0.0176 | 0.0001 | -2.1875 | 0.6966 | 3.0625 |
| $[Bu_3NBn][Sn_2Cl_9]$ | -43.4523 | 0.3440 | -0.0009 | 9.6830 | 0.6545 | 2.0055 |
| $[Bu_3NBn][Zn_2Cl_5]$ | -33.5008 | 0.2711 | -0.0007 | 7.1673 | 0.3435 | 1.3901 |

The plots showing the behaviour of the present κ data for the studied solvent systems: $[Bu_3NBn][Al_2Cl_7]$ + DMSO, $[Bu_3NBn][Cu_2Cl_5]$ + DMSO, $[Bu_3NBn][Fe_2Cl_7]$ + DMSO, $[Bu_3NBn][Sn_2Cl_9]$ + DMSO, $[Bu_3NBn][Zn_2Cl_5]$ + DMSO are shown in Fig 6.

**Figure 6.**Electrical conductivity (κ) as a function of temperature for ILs.



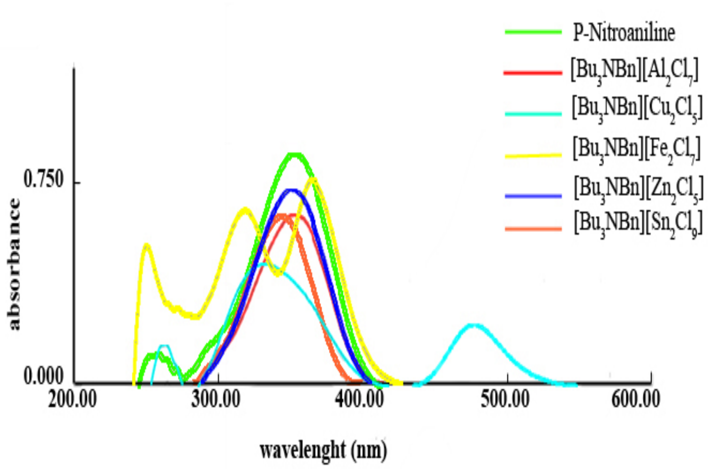
*Determination of $H_o$ values of Lewis acidic ILs*

The Hammett method is a common method to evaluate the acidity of Brönstedacids [43]. It has been shown that the measurement of the acidic scale of these acidic BrönstedILs was conducted on a UV-Vis spectrophotometer with a basic indicator (para-nitroaniline). With increasing the acidic scale of the acidic IL, the absorbance of the unprotonated form of the basic indicator was decreased. Because of its small molar absorptive and its wavelength, the protonated form of the indicator was not observed. Thus, *[I]/[HI]* (I represents the indicator) ratio was determined from the measured absorbance differences after addition of an acidic Brönsted IL. Then, the Hammett function, $H_o$, was calculated by using Equation 7.

$$H_\circ = pK(I)_{aq} + \log([I]/[HI]) \tag{7}$$

This value was regarded as the relative acidity of the IL [19-26], where $pK(I)_{aq}$ was the $pKa$ value of the indicator, *[I]* was the molar concentrations of the unprotonatedand *[HI]* was protonated forms of the indicator determined by UV–visible spectroscopy.

**Figure 7.**UV-Vis absorption spectra of ILs.



With adding an acidic IL, 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. The acidity order of several ILs was obtained with the $H_o$ values which are shown in Table 7:

**Table.7** $H_o$ Values of Ionic Liquids in $CH_2Cl_2$ at Room Temperature.

| ILs | $A_{max}$ | [I]% | [HI]% | $H_o$ |
|---|---|---|---|---|
| Para-nitro aniline | 0.858 | 100 | - | - |
| [Bu$_3$NBn][Al$_2$Cl$_7$] | 0.642 | 74.83 | 25.18 | 1.46 |
| [Bu$_3$NBn][Cu$_2$Cl$_5$] | 0.456 | 53.15 | 46.85 | 1.044 |
| [Bu$_3$NBn][Fe$_2$Cl$_7$] | 0.772 | 89.98 | 10.02 | 1.94 |
| [Bu$_3$NBn][Sn$_2$Cl$_9$] | 0.630 | 73.43 | 26.57 | 1.43 |
| [Bu$_3$NBn][Zn$_2$Cl$_5$] | 0.735 | 85.66 | 14.33 | 1.76 |

With the same concentration of 4-nitroaniline (10 mg/L, $pK(I)_{aq}= pK_a= 0.99$) and Lewis ILs (0.1 mmol/L) in dichloromethane, $H_o$ values of all Lewis ILs were determined. The maximal absorbance of the unprotonated form of the indicator was observed at 350 nm in dichloromethane. After adding Lewis IL, the absorbance of the unprotonated form of the basic indicator decreased (Figure 7 and Table 7). Hammett acidity ($H_o$) of these Lewis ILs was calculated using equations (7) as shown in Figure 7. Calculations suggest that the Hammett acidity ($H_o$) of these ionic liquids follows this order: $[Bu_3NBn][Cu_2Cl_5]$> $[Bu_3NBn][Sn_2Cl_9]$> $[Bu_3NBn][Al_2Cl_7]$> $[Bu_3NBn][Zn_2Cl_5]$> $[Bu_3NBn][Fe_2Cl_7]$.

**Table.8** Experimental value of dynamic viscosities (η), refractive indices (nD), densities ($\rho$), surface tensions (σ), electrical conductivity (κ), thermal conductivity (λ) and thermal decomposition (td) of the Lewis ionic liquids at 25.0 °C.

| ILs | η(mPa.s) | $n_D$ | $\rho$(g/cm$^3$) | σ(N/m) | κ(ms/m) | λ(W/KC) | $t_d$(ºC) |
|---|---|---|---|---|---|---|---|
| $[Bu_3NBn][Al_2Cl_7]$ | 12.8 | 1.4791 | 1.0007 | 42.2249 | 1.6000 | 0.6800 | 129.37 |
| $[Bu_3NBn][Cu_2Cl_5]$ | 13.8 | 1.4792 | 0.0039 | 35.2743 | 1.1000 | 0.5700 | 240.32 |
| $[Bu_3NBn][Fe_2Cl_7]$ | 14.8 | 1.4805 | 0.0001 | 50.6428 | 2.2000 | 0.5200 | 310.59 |
| $[Bu_3NBn][Sn_2Cl_9]$ | 14.6 | 1.4788 | 1.0043 | 42.9167 | 1.2000 | 0.4500 | 147.52 |
| $[Bu_3NBn][Zn_2Cl_5]$ | 13.5 | 1.4792 | 1.0014 | 38.6572 | 0.9500 | 0.6200 | 116.17 |

A comparison between the experimental data for the physical properties of the studied Lewis ILs at 25 °C has also made in Table 8. To the best of our knowledge, no literature data on densities ($\rho$), dynamic viscosities ($\eta$), surface tension ($\sigma$), electrical conductivity ($\kappa$), refractive indices ($n_D$) and thermal conductivity ($\lambda$), were not previously available for five studied ILs. The experimental data for $[Bu_3NBn][Al_2Cl_7]$, $[Bu_3NBn][Cu_2Cl_5]$, $[Bu_3NBn][Fe_2Cl_7]$, $[Bu_3NBn][Sn_2Cl_9]$ and $[Bu_3NBn][Zn_2Cl_5]$ are shown in Table 8.

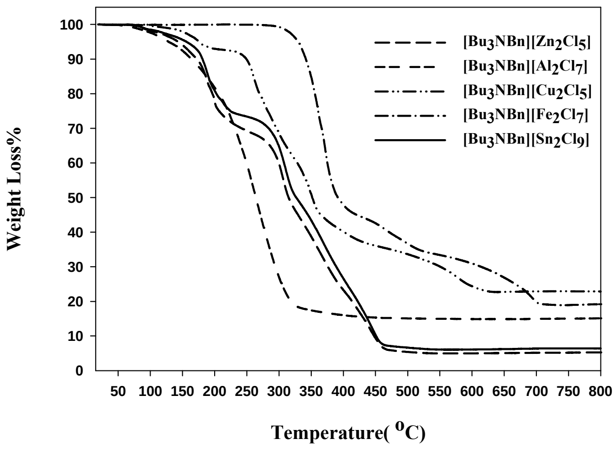
*Thermal properties*

Thermo-gravimetric analysis was applied to evaluate the thermal properties of the Lewis ILs at a heating rate of 10ºC/min, under a nitrogen atmosphere. Figure 8 showsthe respective TGA profiles and the corresponding thermo-analysis data, including the temperatures at which 5% ($T_5$) and 10% ($T_{10}$) degradation occur. Char yield at 800ºC and limiting oxygen index (LOI) based on Van Krevelen and Hoftyzer equation (Equation (8)) is summarized in Table 9 [52, 53].

$$LOI= 17.5+0.4\ CR \qquad (8)$$

Where CR = char yield.

**Figure 8.**TGA thermo-grams of ILs under a nitrogen atmosphere at heating rate of 10 °C/min.



It is evident from our data that the [Bu$_3$NBn][Fe$_2$Cl$_7$] is stable at300ºC and introduction of inorganic particles in IL matrix raised the thermal properties.

**Table.9** Thermal properties of ILs.

| **ILs** | **Decomposition temperature (°C)** | | **Char Yield[%]**[c] | **LOI**[d] |
|---|---|---|---|---|
| | **$T_5$**[a] | **$T_{10}$**[b] | | |
| [Bu$_3$NBn][Al$_2$Cl$_7$] | 128.24 | 158.54 | 15.5 | 23.7 |
| [Bu$_3$NBn][Cu$_2$Cl$_5$] | 176.05 | 244.33 | 22.8 | 26.62 |
| [Bu$_3$NBn][Fe$_2$Cl$_7$] | 329.69 | 339.9 | 19.53 | 25.32 |
| [Bu$_3$NBn][Sn$_2$Cl$_9$] | 156.15 | 180.92 | 6.8 | 20.22 |
| [Bu$_3$NBn][Zn$_2$Cl$_5$] | 143.29 | 172.26 | 5.95 | 19.88 |

[a] Temperature at which 5% weight loss was recorded by TGA at heating rate of 10°C/min under a nitrogen atmosphere.

[b] Temperature at which 10% weight loss was recorded by TGA at heating rate of 10°C/min under a nitrogen atmosphere.

[c] weight percentage of material left undecomposed after TGA analysis at a temperature of 800°C under a nitrogen atmosphere.

[d] Limiting oxygen index (LOI) evaluating char yield at 800°C.

## Conclusion

The unique and useful solvent properties of ionic liquids make them talented alternatives to classic organic solvents for various applications in the pharmaceutical and biotechnology industry. 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 from, ii) easy conversion of APIs into ionic liquids which possess enhanced 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."

We suggest 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.

Physical properties data of the ionic liquids are necessary for every theoretical research and pharmaceutical industrials application. The databases in this respect will support the study and advance of ionic liquids. Here, we have carefully measured several important physical properties of Lewis ionic liquids: $[Bu_3NBn][Al_2Cl_7]$, $[Bu_3NBn][Cu_2Cl_5]$, $[Bu_3NBn][Fe_2Cl_7]$, $[Bu_3NBn][Sn_2Cl_9]$ and $[Bu_3NBn][Zn_2Cl_5]$ over a wide range of temperature from 298.15 K to 363.15 K. We concluded that much more attention should be paid on the measurement of physicochemical properties of Lewis ionic liquids.

The measured densities, $\rho$, and the dynamic viscosities, $\eta$, for the binary mixtures of $[Bu_3NBn][Fe_2Cl_7]$ with water at $T$ = (298.15 to 363.15) K over the entire composition range are listed in Tables 1 and 2. The densities of all the mixtures with DMSO have almost always decreased 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 Lewis ILs of this study are in agreement with the scarce data from the literature and are well represented by the VTF equation. At the same temperature, $[Bu_3NBn][Fe_2Cl_7]$ have significantly higher viscosity than other Five ILs. Presence of metal atoms perhaps makes the viscosity of this IL higher than other ILs. Since the viscosities of ILs are affect essentially by the Van der Waals interactions and H bonding. Therefore, metal atoms of $[Bu_3NBn][Fe_2Cl_7]$ interactions with atoms H of DMSO and this cause to influence on the physical properties ILs. There is large body of evidence that even low concentrations of chloride in the $[Bu_3NBn][Fe_2Cl_7]$ can substantially raisethe viscosity.

Fig. 5 shows the thermal conductivity of Lewis ILs as a function of temperature, and the thermal conductivity of $[Bu_3NBn][Al_2Cl_7]$ is 0.68 $Wm^{-1}C^{-1}$. This suggests that $[Bu_3NBn][Al_2Cl_7]$ is a fairly poor thermal conductor with the thermal conductivity of roughly the same as water at the room temperature. Electrically conductive Lewis ILs is influence of temperature (does not make sense). Also Thermo-gravimetric analysis was confirmed to evaluate the thermal properties of the Lewis ILs.

## Acknowledgement

Funding support received from the Isfahan University of Technology (IUT), Iran, by (Y.GH) and (A.R.H.) grants.

## References

1. Kummar. V. and Sanjay V. Malhotra, (2009) "Ionic Liquids as Pharmaceutical Salts,A Historical Perspective", Laboratory of synthetic Chemistry, SAIC-Fredrick, Inc., National Cancer Institute at Frederick, 1050 Boyles Street, Fredrick, MD 21702, USA.
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. Moniruzzaman.M,Goto. M"Ionic Liquids: (2011) Future Solvents and Reagents for Pharmaceuticals". J Chem. Eng. Japan.;44:370-381.
4. Wasserscheidt.P, Weldon.T, (2003) "Ionic Liquids in Synthesis", Wiley-VCH, New York.
5. Dupont.J, de Souza.R. F, Suarez.P. A. Z, (2002) Chem. Rev. 102, 3667.
6. Wasserscheidt.P, Keim.W, Angew, (2000) Chem. Int. Ed. 39, 3772.
7. Earle.M .J, SeddonK. R, (2000) Pure Appl. Chem. 72, 1391.
8. Cull.S. G, HolbreyJ. D, Vargas-MoraV, SeddonK. R, LyeG. J,(2000) Biotechnol, Bioeng. 69**,** 227.
9. HuddlestonJ. G, WillauerH. D, SwatloskiR. P, VisserA. E, RogersR.D,(1998) Chem. Commun, 176.
10. FadeevA. G, MeagherM. M, (2001) Chem. Commun,295.
11. VisserA. E, SwatloskiR. P, RogersR. D, (2000) Green Chem.2,1.
12. PacholeF, ButlerH. T, PooleC. F, (1982) Anal. Chem. 54,1938.
13. ArmstrongD.W, AndersenJ. L, DingJ, T. Welton, (2002) J. Am. Chem. Soc. 124 ,14247.
14. BerthodA, HeL, ArmstrongD.W, (2000) Chromatographia. 53,63.
15. HeintzA, KulikovD.W, VerevkinS. P, J. (2002) Chem. Eng. Data. 4, 4789.
16. HeL, ZhangW, ZhaoL, LiuX, JiangS,(2003) J. Chromatogr. A. 399, 1007.
17. KaliszanR, MarszallM. P, MarkuszewskiM. J, BaczekT, PernakJ; (2004) J. Chromatogr. A. 263, 1030.
18. XiaoX, ZhaoL, LiuX, JiangS, (2004) Anal. Chim.Acta. 207,519.
19. YanesE. G, GratzS. R, StalcupA. M, (2000) Analyst. 125,1919.
20. YanesE. G, GratzS. R, BaldwinM. J, RobinsonS. E, StalcupA. M (2001) Anal. Chem. 73, 3838,.
21. Vaher.M, KoelM, KaljurandM,(2001) Chromatographia. 53, S–302.
22. VaherM, KoelM, KaljurandM, (2002) Electrophoresis. 23,426.
23. VaherM, KoelM, KaljurandM, (2002) J. Chromatogr. A. 27, 979.
24. KuldveeR, VaherM, KoelM, KaljurandM, (2003) Electrophoresis. 24,1627.
25. VaherM, KaljurandM, (2003) J. Chromatogr. A. 225, 990,225.

26. MwongelaS. M, NumanA, GillN. L, AgbariaR. A, WarnerI. M (2003) Anal. Chem.75,6089.
27. SakaebeH, MatsumotoH, (2003) Electrochem. Commun.5,594.
28. HowlettP. C, MacFarlaneD. R, HollenkampA. F (2004) Electrochem. Solid-State Lett.7,A97.
29. MatsumotoH, YanagidaM, TanimotoK, NomuraM, KitagawaY, MiyazakiY,(2000) Chem. Lett.922.
30. SunJ, MacFarlaneD. R, ForsythM (1997) Ionics. 3, 356.
31. SunJ, ForsythM, MacFarlaneD. R (1998) J. Phys. Chem. B. 102,8858.
32. PereiroA. B, TojoE, RodríguezA, CanosaJ, TojoJ (2006) J. Chem. Thermodyn. 38,651.
33. PereiroA.B, SantamartaF, TojoE, RodríguezA, TojoJ (2006) J. Chem. Eng. Data. 51,952.
34. PereiroA.B, TojoE, RodríguezA, CanosaJ, TojoJ, (2006) Green Chem. 8,307.
35. PereiroA. B, LegidoJ.L, RodríguezA, J. (2007) Chem. Thermodyn. 39,1168.
36. CoxB. J., JiaS, ZhangZ. C, EkerdtJ. G,(2011) Polymer Degradation and Stability. 96,426e 431.
37. RiddickJ.A, BungerW.B, SakanoT.K,(1986) Organic Solvents, 4th ed., Wiley-InterScience, New York.
38. RadhammaM, VenkatesuP, RaoM.V.P, PrasadD.H.L,(2007) J. Chem. Thermodyn. 39,1661–1666.
39. Radhamma.M, Venkatesu.Hofman.P, T, RaoM.V.P, J. (2007) Fluid Phase Equilib.262,32–36.
40. RaoB.G, SinghU.C, (1990) J. Am. Chem. Soc. 112,3803–3811.
41. VaismanI.I, BerkowitzM.L,(1992) J. Am. Chem. Soc. 114,7889–7896.
42. HajipourA. R, RafieeF, (2010) Organic Preparations and Procedures International. 42,285-362.
43. ZhangR, MengX, LiuZ, MengJ.and XuC,(2008) Ind. Eng. Chem. Res. 47, 8205.
44. PereiroA. B, Verdı´aP, TojoE, and guezA. R, (2007) J. Chem. Eng. Data. 52,377-380.
45. StepniakI, AndrzejewskaE, (2009) Electrochim. Ac. 54,5660.
46. Wilkes, J. S. Properties of ionic liquid solvents for catalysis. (2010) J. Mol.Catal, 32, 577 - 643.
47. Mter K.S. (2004) ChemA. 214. 11–17.
48. OkoturoO. O, VandernootJ. J (2004) J. Electroanal. Chem. 568,167-181.
49. GomezE, GonzalezB, CalvarN, TojoE, DominguezA (2006) J. Chem. Eng. Data. 51,2096–2102.
50. SeddonK. R, StarckA. S, TorresM. J (2004) ACS Symp. Ser., No. 901.
51. WilkesJ. S; J. Mol. Catal. A(2004) Chem. 214,11-17.
52. OkoturoO. O, VandernootJ. J (2004) J. Electroanal. Chem. 568,167-181.
53. YunusN. M, MutalibM. I,AMan Z, BustamM. A, MurugesanT (2010) J. Chem. Thermodyn. 42 491–495.
54. MuhammadA, MutalibM. I. AWilfred, C. D, MurugesanT, ShafeeqA (2008) J. Chem. Thermodyn. 40, 1433–1438.
55. Van KrevelenD. W, HoftyzerP. J.(1976) “Properties of polymers”, Elsevier, Amsterdam.

# 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.

SMU Medical Journal, Volume – 2, No. – 2, July, 2015, PP. 106 – 123.