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The Partitioning Behavior of Tyramine and 2-Methoxyphenethylamine in a Room Temperature Ionic Liquid–Water System Compared to Traditional Organic–Water System

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Abstract: Ionic liquids have been proposed as replacements for volatile organic solvents (VOSs) by a range of authors, due to their very low vapor pressure, ability to dissolve a range of organic, inorganic, and organometallic compounds, immiscibility with water, and ability to form biphasic systems depending on the choice of cation/anion combination making up the ionic liquid. In this study the room temperature ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] was synthesized and a range of physical properties including the interfacial tension, viscosity, and density determined. The distribution of tyramine and 2-methoxyphenethylamine (MPEA) as a function of pH was determined for the [bmim][PF_6] system. This was compared to distribution data obtained for these solutes in conventional organic

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solvent/water systems: xylene/tributylphosphate (TBP)/water and xylene/Benzyl alcohol (BA)/water.

Keywords: 1-Butyl-3-methylimidazolium hexafluorophosphate, ionic liquid, organic solvents, physical properties, Tyramine, 2-methoxyphenethylamine, Solvent extraction

INTRODUCTION

Many industries, including the pharmaceutical industry, utilize organic solvents to facilitate separation, purification, and concentration of natural products or compounds of interest. In the insecticide industry, methanol is used for the extraction of pyrethrum (1); in the fragrance industry, hexane is used to extract essential oils (2), and in the extraction of estrogens, organic solvents such as ethyl acetate, acetone, tetrahydrofuran, acetonitrile, and cyclohexanol are used (3). However, increasing environmental and occupational health and safety concerns have prompted a search for new, benign solvents in the hope of replacing the highly volatile and toxic compounds currently in use.

Room temperature ionic liquids (RTILs) that consist of organic cations and inorganic anions are being explored as potential environmentally benign solvents (4–6). Their negligible vapor pressure (7) is of interest as this would significantly reduce the risk for operators and losses due to solvent evaporation. 1-Butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] has been successfully used for the extraction of erythromycin-A and for the *Rhodococcus* R312 catalyzed biotransformation of 1,3-dicyanobenzene (1,3-DCB) in a liquid–liquid two-phase system (6). It has also been studied with water as a biphasic extraction system involving partitioning of charged and uncharged aryl moieties as compared to their partitioning in traditional organic solvent-water system (8). 1-alkyl-3-methylimidazolium hexafluorophosphate ([$C_n$mim][PF6], n = 4, 6, 8) RTILs have also been investigated for the extraction of Na^+, Cs^+ and Sr^{2+} from aqueous solutions, in the hope of reducing the use of large quantities of volatile organic solvents (VOSs) in the hydrometallurgy industry (9).

There are many ionic liquid systems, depending on the combination of cation and anion. Cations such as 1,3-dialkylimidazolium, alkylpyridinium or tetraalkylammonium can pair up with anions such as hexafluorophosphate, tetrafluoroborate, or bis(trifluoromethylsulfonyl)imide, which are only a few examples, to form different ionic liquids. Varying the alkyl substituents in the cation that is paired to any particular anion would yet again introduce other ionic liquids. Physical properties such as viscosity, density, melting point, and water miscibility alter, depending on the combination of cation and anion (10).

In this work, 1-butyl-3-methylimidazolium hexafluorophosphate [bmim] [PF_6] was chosen for investigation because it was initially reported to be water immiscible (11, 12) (since this study was undertaken water solubilities of up to 2.3 wt% (13) have been reported), liquid at room temperature (14, 15), stable (15–17), and less expensive than other water immiscible ionic liquids (18). Some researchers have since then shown that this material is unstable in water (19, 20) and this paper will present further results on the instability of this particular RTIL. The aim of this work is to also measure the distribution ratio of tyramine and 2-methoxyphenethylamine (MPEA) in the [bmim][PF_6]/water system and compare the data with conventional systems such as xylene/TBP and xylene/BA.

EXPERIMENTAL SECTION

Tyramine (99% pure) and 2-methoxyphenethylamine (MPEA) (98% pure), anhydrous methanol (99.8% pure) from Sigma–Aldrich were used as received in this work. Chemicals used for the synthesis of [bmim][PF_6] were either AR grade or HPLC grade and were also obtained from Sigma–Aldrich, except for the high-purity nitrogen from BOC and silver nitrate from MERCK. Xylene, tributylphosphate (TBP) and benzyl alcohol (BA) were all LR grade from MERCK. Hydranal®-Composite 5 from Riedel-de Haën was used as received.

The 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] was synthesized by the method described by Marsh (21). The RTIL was washed several times with water, to reduce the chloride content. It was confirmed that no precipitation, i.e., AgCl, formed on adding $AgNO_3$ to the final wash water. The purity of the precursor [bmim][Cl] and final product [bmim][PF_6] was confirmed by ^{1}H (399.75 MHz) and ^{13}C NMR (100.52 MHz) analyses. ^{19}F NMR (376.14 MHz) analysis was also carried out for the final product. Degradation of the RTIL was determined by measuring the fluoride content of water that is continuously in contact with the IL. Readings were taken in triplicate, once a week for 7 weeks. Prior to measurements, the electrode (Model 96–09 Fluoride ionplus Sure–Flow®) was calibrated using Total Ionic Strength Adjustment Buffer (TISAB) II with 1,2-cyclohexane diaminetetraacetic acid (CDTA) and fluoride standard solutions made up by diluting the ORION Fluoride Standard 100 ppm NaF solution. The meter used was a Model EA940 Multi-Channel Benchtop Meter and the filling solution for the electrode was a double junction reference electrode outer fill solution (Catalog No. 900003).

A Karl Fischer titrator (Metrohm 701 KF Titrino, Switzerland) was used with Hydranal®-Composite 5 and anhydrous methanol for the titrations to determine the water content of [bmim][PF_6], xylene/TBP (1:1v/v) and xylene/BA (1:1v/v). The IL content in water was determined by first vigorously agitating equal volumes of [bmim][PF_6] and water for 24 h, followed by the separation and weighing of the two phases. After evaporating as much water as possible from the aqueous phase, the small amount of IL left behind was placed under vacuum for further drying until no bubbles were observed. This was then weighed again to determine the IL content that had transferred to the aqueous phase.

Densities were determined directly from the pycnometer volume and the mass of the sample. Interfacial tensions were measured using the First Ten Ångstrom (FTÅ200) instrument (USA), which was operated with the FTÅ Video Drop Shape Software, and viscosities were determined at 21°C using the Rheometric Scientific SR5 rheometer.

The distribution ratios were obtained by performing shake-up tests, which involved the mixing of equal volumes of the aqueous phase containing the solute and the solvent on an orbital shaker (OM6 Orbital Mixer, Ratek Instrument Pty. Ltd., Australia) at 130 rpm until the system reached equilibrium (3–4 h). These experiments were performed at 21 ± 1°C. After separation of the two phases, the aqueous phase was analyzed using HPLC. The equipment consisted of Waters Model 590 pump, Waters 712 WISP injector, Waters M-490 programmable multi-wavelength detector and Varian 4270 integrator. The column used was Waters Symmetry® C_{18} 5 μL 3.9 × 150 mm and the sonicator for degassing the mobile phase was a Soniclean 120HT. Mobile phase was made up of Milli-Q water, acetonitrile (HPLC grade from EM Science), glacial acetic acid (HPLC grade from Science Supply), trifluoroacetic acid (100% HiPerSolve from MERCK), and ammonium acetate (AR grade 98.0% pure from MERCK). Water was distilled and deionized using a Milli-Q water filtration system from Millipore. All chemicals were used as received without further purification. The flow rate for the mobile phase was 1 mL/min and detection for both tyramine and MPEA was at 280 nm. The solute in the solvent from all systems was back-extracted into 10% v/v glacial acetic acid in one wash, which was then analyzed quantitatively by HPLC.

RESULTS AND DISCUSSION

The physical properties of [bmim][PF_6], xylene/TBP and xylene/BA are presented in Table 1. The ^{1}H NMR spectra confirmed the cation in the precursor [bmim][Cl] and final product [bmim][PF_6] and showed that there was no or very limited amount of residual water in the ionic liquid. ^{19}F NMR was also used to confirm [bmim][PF_6]. The chemical shifts from these NMR analyses were in agreement with Huddleston (22). NMR, however, does not detect trace levels of chlorine anion (23), and Seddon et al. (11) drew attention to the fact that low concentrations of chloride in the ionic liquids could increase the viscosity significantly. Therefore to ensure chloride contamination was essentially negligible or minimal in the final product, $AgNO_3$ was added in the last wash of the synthesis to ensure that no visible precipitate (AgCl) was present. It has, however, been reported that a chloride content of 1–6% w/w is present in the ionic liquid if the preparation method involves

Table 1. Physical properties of [bmim][PF_6], xylene/TBP, and xylene/BA systems (all results were obtained from experiments conducted at 20 ± 1°C)

Physical property	[bmim][PF_6]	Xylene/TBP	Xylene/BA
Density (g/mL)	1.353 ± 0.015 1.34[a] 1.3727[b]	0.910 ± 0.003	0.943 ± 0.013
Viscosity (cP)	312[†] 330[c] 319[d] 293[e]	1.85[‡]	1.61[‡]
Interfacial tension (mN/m)	10.6	13.3	7.2
Water content after synthesis (wt.%)	0.17 ± 0.01 0.15[f]	0.05 ± 0.01	0.55 ± 0.01
Water content after equilibrating with water (wt.%)	2.04 ± 0.02 2.0[g] 2.3[h] 1.5[i]	1.72 ± 0.03	2.59 ± 0.06
Maximum distribution ratio (tyramine as solute) (D_{max})	0.53 (pH 9.40)	1.07 (pH 10.07)	3.16 (pH 9.88)
*Distribution ratio (MPEA as solute) (D)@ ~ pH 12.5 ± 0.2	14.6	15.3	349

[a] Reference (40).

[b] Reference Fine Chemicals in UK (40).

[c] Reference (41), obtained at 20°C.

[d] Reference (26); no temperature was reported, but authors noted that the value was susceptible to change due to the presence of adsorbed moisture from the air which can significantly decrease the viscosity.

[e] Reference (6); obtained at 30°C.

[f] Reference (14).

[g] Reference (21).

[h] Reference (13).

[i] Reference (11).

*D_{max} cannot be determined when MPEA is the solute for the pH range studied.

[†] Cone and plate (Since [bmim][PF_6] was much more viscous that VOSs, it was possible to avoid using bob and cup, which required a lot more of sample to obtain accurate measurements.)

[‡] Bob and cup

metathesis from the corresponding chloride prescursor (23). Hence, even though AgCl precipitate was not observed in the final wash, there still may be trace levels of chloride anions, and as Marcus (24) pointed out for any material, absolute purity is difficult to achieve.

In liquid–liquid extraction systems, high interfacial tension is desired as it enhances coalescence and reduces loss of the aqueous phase in the solvent and vice versa. Comparing the three systems, xylene/TBP had the highest interfacial tension (13.3 mN/m) followed by [bmim][PF_6] (10.6 mN/m) then xylene/BA (7.2 mN/m), which implied that phase separation between xylene/TBP and water would occur quickest. The viscosity of [bmim][PF_6] was approximately 200 times that of xylene/TBP (1.61 cP) and xylene/BA (1.85 cP), which made the IL more difficult to handle.

It was important to determine the water content of the samples since water can effectively change the physical and chemical properties of the solvents (11, 24–27), especially in the case of [bmim][PF_6] because of its hygroscopicity. It was also necessary to know the solubility of the solvents in the aqueous phase because if the solubility was high there would be limitations to the extraction of solutes in the solvent phase. Hence, mutual solubilities were considered in these studies. In comparison to Anthony et al. (2.0 wt.%@25°C) (13) and Marsh et al. (2.7 wt.%@18°C) (21) the solubility of [bmim][PF_6] in water obtained was 2.2 wt.%@21°C, which was reasonable considering the difference in temperature conditions. The VOSs were virtually insoluble in water except for benzyl alcohol which on its own had a solubility of 4 wt.% (28). The water content in the IL was found to be 0.17 wt.% after synthesis, but after saturation the water content increased to 2.04 wt.%. The water content of saturated ionic liquid was in agreement with Marsh et al. (21), but about 0.5 wt.% higher than Seddon et al. (11) and 0.3 wt.% lower than Anthony et al. (13). To obtain the water content of saturated ionic liquid, it was necessary to vigorously agitate the ionic liquid and water phases for several hours in order to achieve equilibrium before measurement. Anthony and coworkers (13) mentioned that even stirring the two phases for 24 h without interrupting the interphase would be insufficient to reach equilibrium. Hence, the relatively small difference (~0.24 wt.%) between Anthony's group and ours confirms that at equilibrium [bmim][PF_6] can absorb about 2.0 wt.% water. Similar to the ionic liquid, the two organic systems also increased in water content after saturation. However, there was no indication that the water in these organics would cause any instability to the solvents. Several researchers (9, 19, 20, 29) observed that [bmim][PF_6] was unstable in the presence of water or nitric acid. Out of interest, we investigated its instability by measuring the fluoride concentration of the aqueous phase for both washed and unwashed samples of [bmim][PF_6] using a fluoride electrode and discovered that the fluoride concentration increased over time (Fig. 1). This confirmed that when [bmim][PF_6] remained in contact with water, it was unstable.

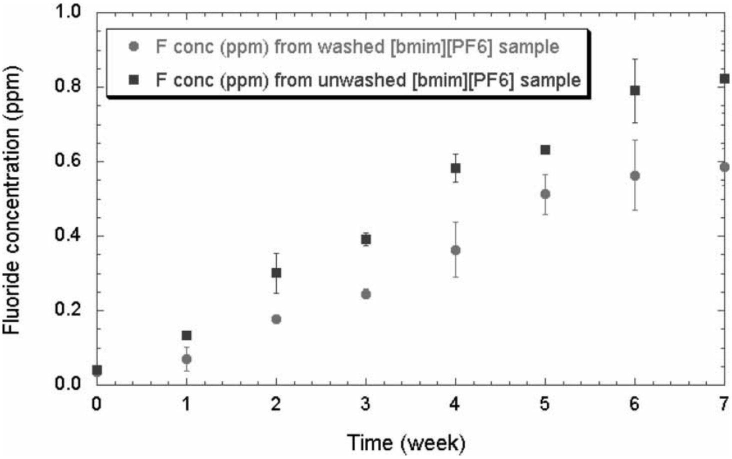

Figure 1. Fluoride concentration in water, which had been continuously shaken with washed and unwashed [bmim][PF_6] samples over time.

The partitioning behavior of tyramine and MPEA as a function of pH was determined in the three different liquid–liquid systems, and this was expressed in terms of distribution ratios (D). Distribution ratio is defined as follows:

$$D = \frac{\text{Concentration of solute in solvent phase } (C_s)}{\text{Concentration of solute in aqueous phase } (C_a)}$$

Tyramine and MPEA (see Figs. 2 and 3 for structures) were used as solutes because they are representative of compounds used in some of the natural products industries. The systems studied were (1) [bmim][PF_6], (2) xylene/TBP, and (3) xylene/BA as the nonaqueous phase and water, sometimes with small amounts of sodium hydroxide or hydrochloric acid as the aqueous phase. The results are summarized in Figs. 2 and 3 and Table 1.

In the organic systems using tyramine as solute, the maximum distribution ratio, $D_{max} \approx 1.07$ in xylene/TBP and $D_{max} \approx 3.16$ in xylene/BA, occurred at about pH 10. In [bmim][PF_6], $D_{max} \approx 0.53$ was displayed at around pH 9. In both xylene/TBP and xylene/BA systems, the distribution ratio decreased to essentially zero in pHs below 7 and pHs above 13. This was due to tyramine having two ionizable groups, an amine group and a phenolic group. Various researchers have determined the pK values of p-tyramine. There are a few discrepancies with the pK values assigned to their respective amine and phenolic groups amongst the various authors. Despite the conflicting designation of pK values to the groups, both values remain relatively close for example, 9.3 and 10.9 (30), 9.77 or 9.53 (depending on method), and 10.78 (31), 9.37 and 10.70 (32), 9.74 and 10.53 (33), 9.3 and 10.9 (34). When the pH is 9.3 or lower and 10.7 or higher the tyramine molecule is

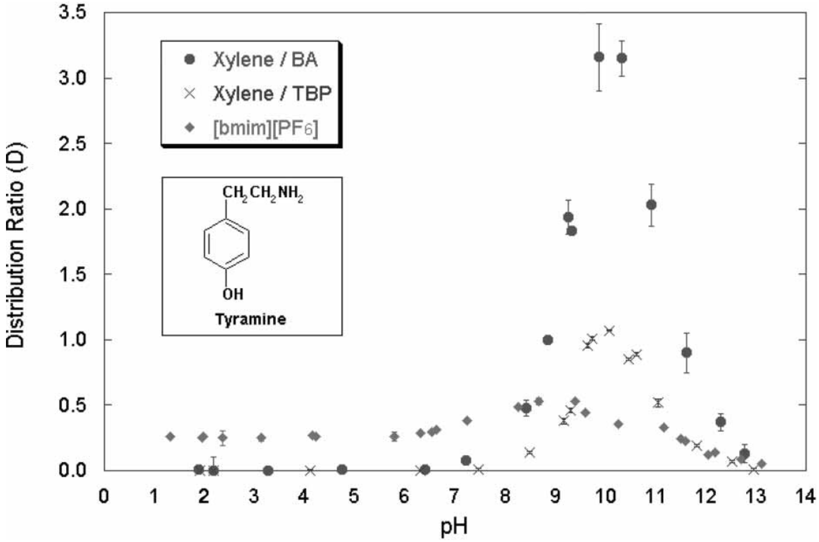

Figure 2. Distribution ratio vs. pH with tyramine as solute in [bmim][PF_6]/water, xylene/TBP/water and xylene/BA/water systems.

ionized, and thus has a high solubility in the aqueous phase, resulting in decreasing distribution ratios on either side of pH 10.

The inability to load tyramine appreciably into [bmim][PF_6], and the tendency for tyramine to remain dissolved in [bmim][PF_6] at pH < 7, make the ionic liquid unsuitable for extracting tyramine. The distribution ratios remained at ~0.27 at pH < 7, indicating that at acidic pHs it is possible that there was a cation–exchange occurring in which the positively charged tyramine molecule partitioned into the IL and the dialkylimdazolim [bmim]$^+$ into the aqueous phase, a mechanism that has been suggested in literature (35–37). In this mechanism the counter ion in the aqueous phase at these lower pHs would be the chloride anion from the HCl added for pH adjustment. In addition to ion-exchange considerations, studies (9, 38) have shown that in the presence of acids such as HNO_3, leaching of [bmim]$^+$ to the aqueous phase can occur, especially at high concentrations (8M). However, Visser and coworkers (9) have reported that the use of HCl resulted in no detection of [bmim]$^+$ in the aqueous phase, even at a concentration of 8M. Hence, we can assume that using HCl (0.05 M) for pH adjustments in our studies would cause minimal leaching.

Figure 1 shows a comparison of all the solvent systems using tyramine as solute. The error bars in the plots from Fig. 2 were obtained from triplicate HPLC readings for each of the shake-up tests for the varying pHs. When a few of the experiments were repeated for the VOS systems with back extraction, the error ranged from 1.1–3.2%.

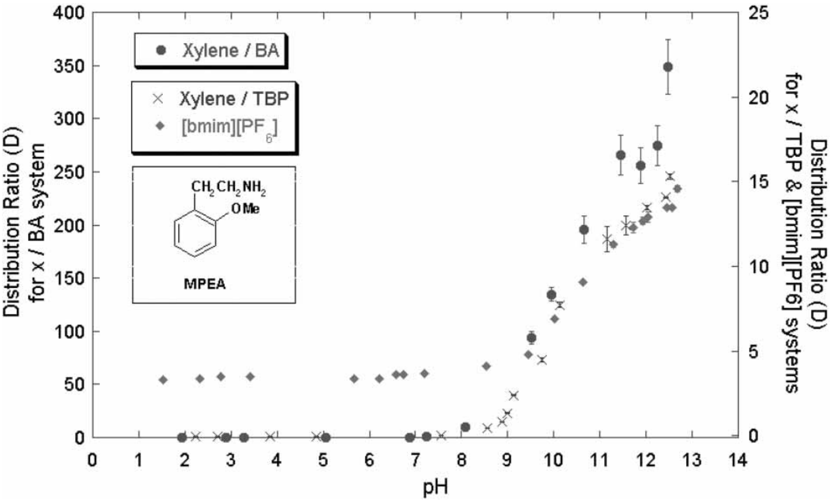

Figure 3. Distribution ratio vs. pH with MPEA as solute in [bmim][PF_6]/water, xylene/TBP/water and xylene/BA/water systems.

Similarly, when MPEA was used as a solute, some partitioned in the ionic liquid in the acidic pHs. However, since MPEA has only one ionizable group, as pH increased MPEA became less ionized and partitioned into the nonaqueous phase. The pK value of MPEA is reported as 10.20 at 25°C (33). Hence, with all systems studied, MPEA displayed increasing distribution ratios as pH increased, especially when $pH > pK \sim 10$. From Fig. 3, it can be observed that regardless of pH in the [bmim][PF_6] system, MPEA cannot be completely back extracted into the aqueous phase with only one wash because of its solubility in the ionic liquid at $pH < 7$, similar to the possible cation-exchange mechanism as mentioned for the tyramine solute. Hence, several washing stages will be necessary to recover the MPEA from any loaded in the ionic liquid system, compared to the VOS systems.

Using either tyramine or MPEA as the solute, the following systems seemed most effective for solvent extraction in decreasing order: xylene/BA > xylene/TBP > [bmim][PF_6]. Generally these systems displayed higher distribution ratios for MPEA than tyramine. Stripping of tyramine and MPEA from xylene/BA and xylene/TBP systems were attained with a 0.1–7.4% error in the material balance.

CONCLUSION

In this work, the low distribution ratios obtained from [bmim][PF_6] for extracting tyramine and MPEA from aqueous solution suggest that it is not ideal for replacing the VOSs. Also, the high viscosity of the ionic liquid as compared to the VOSs, makes it difficult to handle. Modifying the anion counterpart in the ionic liquid to say, bis((trifluoromethyl)sulfonyl)imide [Tf_2N], would reduce the solvent viscosity (39), which might increase its potential as a solvent extractant. However, an investigation to lower viscosity ionic liquids is required to confirm this. The instability of [bmim][PF_6] when contacted with water as reported by various researchers (9, 19, 29) is also of concern since it produces volatiles such as HF, POF_3, which can etch or dissolve glassware and corrode equipment. Studies into other ionic liquids that are immiscible with water but remain stable are essential if these nonvolatile, nonflammable liquids are to be used for liquid–liquid extraction processes.

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REFERENCES

1. Istudor, V., Gard, C.E. (1997) Extraction of Pyrthrins from Pyrethrum Flowers. Romania Patent RO 112153, June 30.
2. Rajeswara Rao, B.R., Kaul, P.N., Syamasundar, K.V., and Ramesh, S. (2002) Water Soluble Fractions of Rose—Scented Geranium (*Pelargonium* Species) Essential Oil. *Bioresource Technology*, 84 (3): 243–246.
3. Wang, R.Y.C., Ho, Y., Lee, S.-L. (2001) Process for Extracting Estrogens from Pregant Mare Urine. US Patent WO 01/27134 A1, April 19.
4. Chauvin, Y. and Olivier-Bourbigou, H. (1995) Nonaqueous Ionic Liquids as Reaction Solvents. *CHEMTECH*, 25 (9): 26–30.
5. Fremantle, M. (1998) Designer Solvents—Ionic Liquids May Boost Clean Technology Development. *Chemical and Engineering News*, March 30: 30–37.
6. Cull, S.G., Holbrey, J.D., Vargas-Mora, V., Seddon, K.R., and Lye, G.J. (2000) Room—Temperature Ionic Liquids as Replacements for Organic Solvents in Multiphase Bioprocess Operations. *Biotechnol. Bioeng.*, 69: 277–233.
7. Gordon, C.M. and McCluskey, A. (1999) Ionic Liquid: A Convenient Solvent for Environmentally Friendly Allylation Reactions with Tetraallylstannane. *Chem. Commun.*, (15): 1431–1432.
8. Huddleston, J.G., Willauer, H.D., Swatloski, R.P., Visser, A.E., and Rogers, R.D. (1998) Room Temperature Ionic Liquids as Novel Media for 'Clean' Liquid–Liquid Extraction. *Chem. Commun.*, (16): 1765–1766.
9. Visser, A.E., Swatloski, R.P., Reichert, W.M., Griffin, S.T., and Rogers, R.D. (2000) Traditional Extractants in Nontraditional Solvents: Groups 1 and 2 Extraction by Crown Ethers in Room—Temperature Ionic Liquids. *Ind. Eng. Chem. Res.*, 39: 3596–3604.

10. Muldoon, M.J., Gordon, C.M., and Dunkin, I.R. (2001) Investigations of Solvent–Solute Interactions in Room Temperature Ionic Liquids Using Solvatochromic Dyes. *J. Chem. Soc., Perkin Trans. 2*, 4: 433–435.
11. Seddon, R.R., Stark, A., and Torres, M.-J. (2000) Influence of Chloride, Water, and Organic Solvents on the Physical Properties of Ionic Liquids. *Pure Appl. Chem.*, 72 (12): 2275–2287.
12. Earle, M.J., McCormac, P.B., and Seddon, K.R. (2000) The First High Yield Green Route to a Pharmaceutical in a Room Temperature Ionic Liquid. *Green Chemistry*, 2 (6): 261–262.
13. Anthony, J.L., Maginn, E.J., and Brennecke, J.F. (2001) Solution Thermodynamics of Imadazolium—Based Ionic Liquids and Water. *J. Phys. Chem.*, 105: 2879–2885.
14. Blanchard, L.A., Gu, Z., and Brennecke, J.F. (2001) High-pressure Phase Behavior of Ionic Liquid/CO_2 Systems. *J. Phys. Chem. B*, 105 (12): 2437–2444.
15. Freemantle, M. (1999) Ionic Liquids Prove Increasingly Versatile. *Chemical and Engineering News*, January 4: 23–24.
16. Fuller, J., Carlin, R.T., and Osteryoung, R.A. (1997) The Room Temperature Ionic Liquid 1-Ethyl-3-Methylimidazolium Tetrafluoroborate: Electrochemical Couples and Physical Properties. *J. Electrochem. Soc.*, 144 (11): 3881–3886.
17. Schröder, U., Wadhawan, J.D., Compton, R.G., Marken, F., Suarez, P.A.Z., Consorti, C.S., de Souza, R.F., and Dupont, J. (2000) Water–Induced Accelerated Ion Diffusion: Voltammetric Studies in 1-Methyl-3-[2,6-(S)-Dimethylocten-2-yl]imidazolium Tetrafluoroborate, 1-Butyl-3-Methylimidazolium Tetrafluoroborate and Hexafluorophosphate Ionic Liquids. *New J. Chem.*, 24 (12): 1009–1015.
18. Visser, A.F., Swatloski, R.P., Reichert, W.M., Mayton, R., Sheff, S., Wierzbicki, A., Davis, J.H., Jr., and Rogers, R.D. (2001) Task-Specific Ionic Liquids for the Extraction of Metal Ions from Aqueous Solutions. *Chem. Commun.*, 1: 135–136.
19. Swatloski, R.P., Holbrey, J.D., and Rogers, R.D. (2003) Ionic Liquids Are Not Always Green: Hydrolysis of 1-Butyl-3-Methylimidazolium Hexafluorophosphate. *Green Chemistry*, 5: 361–363.
20. Gubicza, L., Nemestóthy, N., Fráter, T., and Bélafi-Bakó, K. (2003) Enzymatic Esterification in Ionic Liquids as Replacements for Conventional Solvents—a Review. *Green Chemistry*, 5 (2): 236–239.
21. Marsh, K.N., Deev, A., Wu, A.C.-T., Tran, E., and Klamt, A. (2002) Room Temperature Ionic Liquids as Replacements for Conventional Solvents—a Review. *Korean J. Chem. Eng.*, 19 (3): 357–362.
22. Huddleston, J.G., Visser, A.E., Reichert, W.M., Willauer, H.D., Broker, G.A., and Rogers, R.D. (2001) Characterization and Comparison of Hydrophilic and Hydrophobic Room Temperature Ionic Liquids Incorporating the Imidazolium Cation. *Green Chemistry*, 3: 156–164.
23. Carda-Broch, S., Berthod, A., and Armstrong, D.W. (2003) Solvent Properties of the 1-Butyl-3-Methylimidazolium Hexafluorophosphate Ionic Liquid. *Anal. Bioanal. Chem.*, 375 (2): 191–199.
24. Marcus, Y. (1998) *The Properties of Solvents*; John Wiley & Sons: Chichester; Vol. 4.
25. Cammarata, L., Kazarian, S.G., Salter, P.A., and Welton, T. (2001) Molecular of Some Electrogenerated Organic Cation Radicals in Room—Temperature Ionic Liquids. *Phys. Chem. Chem. Phys.*, 3 (32): 5192–5200.

26. Lagrost, C., Carrié, D., Vaultier, M., and Hapiot, P. (2003) Reactivities of Some Electrogenerated Organic Cation Radicals in Room—Temperature Ionic Liquids: Toward an Alternative to Volatile Organic Solvents? *J. Phys. Chem. A*, 107 (5): 745–752.
27. Wasserscheid, P. and Keim, W. (2000) Ionic Liquids—New Solutions for Transiton Metal Catalysis. *Angew. Chem. Int. Ed.*, 39 (21): 3772–3789.
28. Perry, R.H. and Green, D.W. (1997) *Perry's Chemical Engineers' Handbook*, 7th Ed.; McGrawHill: New York, Chap. 2.
29. Holbrey, J.D., Turner, M.B., and Rogers, R.D. (2002) Selection of Ionic Liquids for Green Chemical Applications, 244th National Meeting of the American Chemical Society, Boston, Massachusetts, Aug 18–22, 2002; American Chemical Society: Washington, DC; ACS Symposium Series 856.
30. Ogston, A.G. (1936) Some Dissociation Constants. *Journal of the Chemical Society*, 1713.
31. Lewis, G.P. (1654) The Importance of Ionization in the Activity of Sympathomimetic Amines. *Brit. J. Pharmacol.*, 9: 488–493.
32. Riegelman, S., Strait, L.A., and Fischer, E.Z. (1962) Acid Dissociation Constants of Phenylalkanotamines. *Journal of Pharmaceutical Sciences*, 51: 129–133.
33. Kappe, T. and Armstrong, M.D. (1965) Ultraviolet Absorption Spectra and Apparent Acidic Dissociation Constants of Some Phenolic Amines. *J. Med. Chem.*, 8 (3): 369–374.
34. Dean, J.A. (1992) In *Lange's Handbook of Chemistry*. Nalven, G.F. and Smith, S.M., eds.; McGraw Hill, Inc.: New York, 8.19–8.55.
35. Dietz, M.L., Dzielawa, J.A., Laszak, I., Young, B.A., and Jensen, M.P. (2003) Influence of Solvent Structural Variations on the Mechanism of Facilitated Ion Transfer into Room—Temperature Ionic Liquids. *Green Chemistry*, 5 (6): 682–685.
36. Jensen, M.P., Dzielawa, J.A., Rickert, P., and Dietz, M.L. (2002) Exafs Investigations of the Mechanism of Facilitated Ion Tranfer into a Room—Temperature Ionic Liquid. *Journal of the America Society*, 124 (36): 10664–10665.
37. Smirnova, S.V., Torocheshnikova, I.I., Formanovsky, A.A., and Pletnev, I.V. (2004) Solvent Extraction of Amino Acids into a Room Temperature Ionic Liquid with Dicyclohexano-18-Crown-6. *Anal. Bioanal. Chem.*, 378 (5): 1369–1375.
38. Visser, A.E., Swatloski, R.P., Griffin, S.T., Hartman, D.H., and Rogers, R.D. (2001) Liquid/Liquid Extraction of Metal Ions in Room Temperature Ionic Liquids. *Sep. Sci. Technol.*, 36 (5&6): 785–804.
39. Bonhôte, P., Dias, A.-P., Armand, M., Papageorgiou, N., Kalyanasundaram, K., and Grätzel, M. (1996) Hydrophobic, Highly Conductive Ambient—Temperature Molten Salts. *Inorg. Chem.*, 35 (5): 1168–1178.
40. Fadeev, A.G. and Meagher, M.M. (2001) Opportunities for Ionic Liquids in Recovery of Biofuels. *Chem. Commun.*, 3: 295–296.
41. Gordon, C.M. and McLean, A.J. (2000) Photoelectron Transfer from Excited–State Ruthenium (II) Tris(Bipyridyl) to Methylviologen in an Ionic Liquid. *Chem. Commun.*, 15: 1395–1396.