

# An analytical view of ionic liquids

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Within the last decade, ionic liquids have come to the fore as environmentally-responsible designer solvents. But what are ionic liquids and what can they offer the analytical scientist? This article addresses these questions and chronicles recent progress made in the application of ionic liquids toward analytical problem-solving. While further progress is required before ionic liquids become mainstream analytical solvents, results to date commend their use in various modes of chemical analysis. It is our aim that the findings reported herein draw other researchers into this area and encourage the increased application of ionic liquids in this manner.

## What (and what good) are ionic liquids?

Against a backdrop of increasing legislative and social pressure and an increasingly “green”-conscious industrial community, researchers have begun to explore more eco-friendly, innovative, and sustainable chemistry in earnest. An important recent addition to this class of green solvents, one receiving serious consideration with the promise of benefits both environmental and technological, is ionic liquids. The term ionic liquid (IL) is currently used to describe a broad class of low-melting semi-organic salts or salt mixtures which have appreciable liquid range. Composed entirely of ions, they are (in this sense alone) phenomenological analogs of classical metallic molten salts such as sodium chloride (NaCl, common table salt). Although an arbitrary divide, there is considerable consensus that such salts must melt at or below 100 °C to qualify as ILs. In reality, hundreds of ILs that are molten at or below room temperature have been reported and one that remains liquid down to −96 °C is known. Compare this to NaCl which has a melting point of about 800 °C. Truly, as molten salts go they are the benchmark version of Dante’s *Inferno*.

Although to the uninitiated ILs may appear to have enjoyed overnight success, this is not entirely the case. In fact, the haloaluminate molten salts, originally conceived as lower-temperature electrolyte alternatives in thermal batteries, are the ancestors of the modern day IL. As Wilkes put it, ‘it all started with a

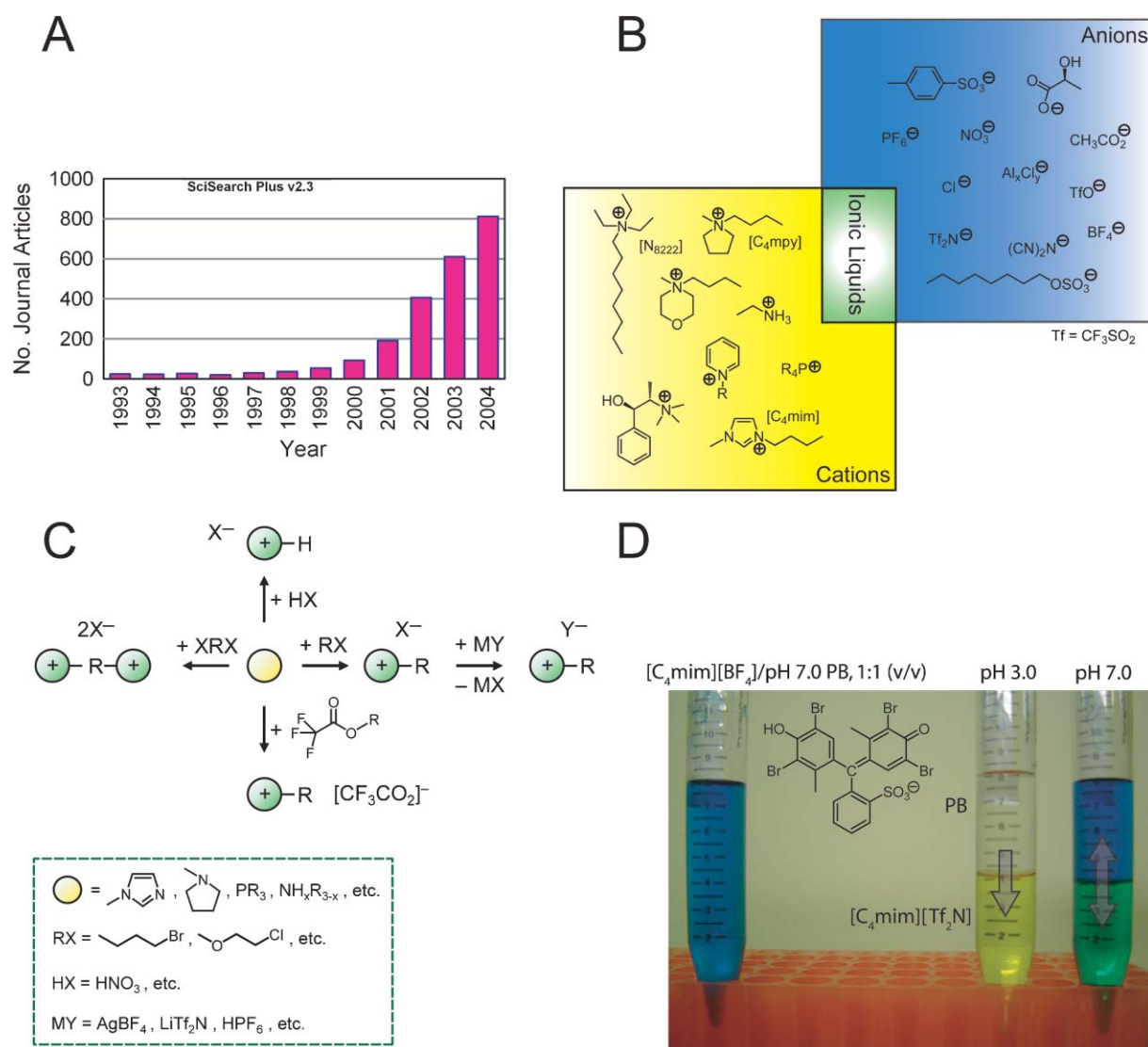
battery that was too hot to handle’.<sup>1</sup> Unfortunately, the requirement that haloaluminates be handled under essentially anhydrous conditions due to their extreme reactivity towards water ultimately limited their usefulness. With the advent of relatively air- and moisture-stable ILs in the early nineties, their use quickly expanded into many other fields, but particularly as solvents for synthesis and catalysis, both biphasic and homogeneous. As Fig. 1A illustrates, beginning about 1998, the field of ILs experienced a rapid growth phase in publication rate. Indeed, in the chemical world they became front page news around that time and all indications are that these trends will continue.

This renewed interest hinges largely on the fact that these second-generation ILs offer the unique properties of earlier molten salts combined with ease of handling and without the stability and incompatibility issues associated with the chloroaluminate anions. Their most often cited attribute, and an essential component of their being green, is their minimal vapor pressure even at elevated temperatures which offers advantages such as ease of containment, product recovery, and recycle. Other pertinent properties include high intrinsic ionic conductivity, nonflammability, thermal and oxidative stability, a wide electrochemical window (often in excess of 5 V), broad liquid range, excellent heat transfer properties, and efficient absorption/transfer of microwaves. This latter property has led to expeditious “solvent-free” microwave assisted IL preparation routes.

Notably, the inherent synthetic flexibility afforded by pairing different cations with any of a growing number of anions provides the possibility for “fine-tuning” certain IL solvent properties to the particular task at hand. The considerable variation within this general framework is such that conservative estimates of the number of *practical* ILs that can be easily prepared from relatively inexpensive materials reach the tens of thousands although, in theory, some 10 trillion combinations are possible for these “modular” solvents. Solvent features subject to such tailoring include melting point, water-miscibility, viscosity, polarity, acid/base character, and coordinating ability.<sup>1,2</sup> Accordingly, ILs have been appropriately described as “designer solvents”.

In this review, the shorthand notation adopted to describe IL cations follows the following examples where subscripts refer to the number of carbons in the alkyl chain: 1-butyl-3-methylimidazolium, [C<sub>4</sub>mim]; *N*-butyl-*N*-methylpyrrolidinium, [C<sub>4</sub>mpy]; *n*-ihexyltriethylammonium, [N<sub>6222</sub>]; see Fig. 1B. Anions discussed herein include: hexafluorophosphate, [PF<sub>6</sub>]; tetrafluoroborate, [BF<sub>4</sub>]; bis-(trifluoromethanesulfonyl)imide, [Tf<sub>2</sub>N]. Accordingly, [C<sub>4</sub>mim][PF<sub>6</sub>] denotes the IL 1-butyl-3-methylimidazolium hexafluorophosphate.

As summarized in Fig. 1C, the typical preparation of an IL initially involves a quaternization reaction such as the alkylation of a 1-alkylimidazole by a haloalkane. This step is generally followed by an acid–base neutralization or metathesis of the resulting halide salt



**Fig. 1** Bar chart showing the growth in the number of IL journal articles appearing annually during the last decade; compiled using SciSearch Plus v2.2 (A). Representative cations and anions used as building blocks in IL formulation (B). Summary of general pathways for IL synthesis including a halide-free route employing a fluorinated ester; see text for description (C). Photograph showing a homogeneous [bmim][BF<sub>4</sub>]/water mixture (left) and a two-phase water/[bmim][Tf<sub>2</sub>N] system containing water buffered to pH 3.0 and 7.0 (right); solutions are dyed with the pH indicator dye bromocresol green whose paraquinoidal form is shown (D).

with a Group 1A metal, ammonium, or silver salt of the desired anion to afford the IL, together with a stoichiometric amount of by-product (HX or MX, respectively) which must subsequently be removed. To date, the most commonly studied systems consist of a bulky, asymmetrically-substituted N-containing cation with varying heteroatom functionality paired with a charge-diffuse (poorly-coordinating) anion. So far, many classes of cation have been explored, particularly 1-alkyl-3-methylimidazolium, *N*-alkylpyridinium, *N*-methyl-*N*-alkylpyrrolidinium, and tetraalkylammonium types. This list is by no means exhaustive and

other classes like phosphonium salts are finding greater utility daily. It should also be noted that ILs of various types are increasingly commercially available. On the anionic side, an assortment of inorganic or organic species have been used such as [PF<sub>6</sub>]<sup>-</sup>, [BF<sub>4</sub>]<sup>-</sup>, [(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]<sup>-</sup>, [(C<sub>2</sub>F<sub>5</sub>SO<sub>2</sub>)<sub>2</sub>N]<sup>-</sup>, [CF<sub>3</sub>SO<sub>3</sub>]<sup>-</sup>, [(C<sub>2</sub>F<sub>5</sub>)<sub>3</sub>PF<sub>3</sub>]<sup>-</sup>, [CF<sub>3</sub>CO<sub>2</sub>]<sup>-</sup>, [NiCl<sub>3</sub>]<sup>-</sup>, [SCN]<sup>-</sup>, and [(CN)<sub>2</sub>N]<sup>-</sup>. In general, a more lipophilic IL may be generated by employing a charge-diffuse anion and/or increasing alkyl substitution on the cation. Of particular relevance here, we note that the miscibility of ILs in water is, to a large extent,

dictated by the anion used and two- and three-phase systems with water and/or conventional organic solvents are possible. For example, as shown in Fig. 1D, [C<sub>4</sub>mim][BF<sub>4</sub>] is water-miscible at room temperature whereas [C<sub>4</sub>mim][Tf<sub>2</sub>N] forms a biphasic system with water.

Early on, the potential of ILs as viable reaction media to replace less desirable organic solvents was recognized. A decade after they were first prepared, emphasis began to include a variety of other areas as well. Only recently have ILs captured the imagination and interest of the analytical community. However,

the last few years have been witness to significant innovation in analytical separations, mass spectrometry, electrochemistry, spectroscopy, and chemical sensors based on the application of ILs. We project a highly promising future for ILs as enabling solvents and materials in analysis. Truly, the wonder years may be just around the corner with the full extent of their analytical potential only just beginning to surface.

## Analytical extractions and separations

### Liquid/liquid extraction and liquid-phase microextraction

In 1998, the Rogers group first reported the use of an ionic liquid as an alternative to traditional volatile organic solvents for two-phase liquid/liquid separations.<sup>3</sup> Using a radiotracer assay, these authors found that the distribution coefficients ( $D$ ) of several  $^{14}\text{C}$ -labeled aromatic amines, carboxylic acids and other simple, substituted benzenes in a  $[\text{C}_4\text{mim}][\text{PF}_6]/\text{water}$  two-phase system were correlated with, and roughly an order of magnitude lower than, the corresponding 1-octanol/water partition coefficients ( $P$ ), an oft-cited empirical measure of solute hydrophobicity. As expected,  $D$  was highly dependent upon the pH of the aqueous contacting phase and often a change in phase preference was observed between solutes in their neutral and charged/ionized forms making possible the adoption of forward/backward extraction steps. An illustration of the pH-modulated partitioning of a colorimetric dye in the water/ $[\text{C}_4\text{mim}][\text{Tf}_2\text{N}]$  system is provided in Fig. 1D.

Task-specific ionic liquids (TSILs, a term coined by Prof. J. H. Davis) for heavy metal ion extraction from aqueous media were later reported by Davis and co-workers.<sup>4</sup> By appending thioether, thiourea or urea metal-binding functionality onto an imidazolium cation, TSILs that both form a biphasic system with water and function as ligating agents for  $\text{Hg}^{2+}$  and  $\text{Cd}^{2+}$  extraction were created. Distribution ratios measured for contacting equal volumes of the conventional IL  $[\text{C}_4\text{mim}][\text{PF}_6]$  with water (0.84 for  $\text{Hg}^{2+}$  and 0.03 for  $\text{Cd}^{2+}$ ) indicated that these metal ions were largely retained in the

aqueous phase, clearly due to their preference for hydration. In comparison, when mixed with an equal mass of  $[\text{C}_4\text{mim}][\text{PF}_6]$  as an inexpensive diluent, one of the thiourea TSILs gave  $D$  values near 700 ( $\text{Hg}^{2+}$ ) and 300 ( $\text{Cd}^{2+}$ ) at neutral pH, an improvement of roughly 3 and 4 orders of magnitude, respectively. Many paths forward for heavy metal detection and remediation can be envisaged based on these TSILs.

Very recently, Liu *et al.*<sup>5</sup> showed that ILs have excellent potential as solvents for both single drop direct-immersion and headspace liquid-phase microextraction (LPME). Using EPA priority polycyclic aromatic hydrocarbons (PAHs) as model analytes in water, the authors found that the ILs  $[\text{C}_6\text{mim}][\text{PF}_6]$  and  $[\text{C}_8\text{mim}][\text{PF}_6]$  both outperformed 1-octanol in direct-immersion LPME with an average enrichment factor of 93 ( $n = 12$ ) for a 30 min extraction using a 3  $\mu\text{L}$  droplet of  $[\text{C}_8\text{mim}][\text{PF}_6]$  (see Fig. 2A). The higher extraction efficiency was attributed, at least in part, to improved droplet stability (survival) in aqueous media. Interestingly, in the extraction of naphthalene, a relatively volatile PAH, the enrichment factor for headspace LPME was nearly 3-fold higher than in direct-immersion mode.

### Gas chromatography

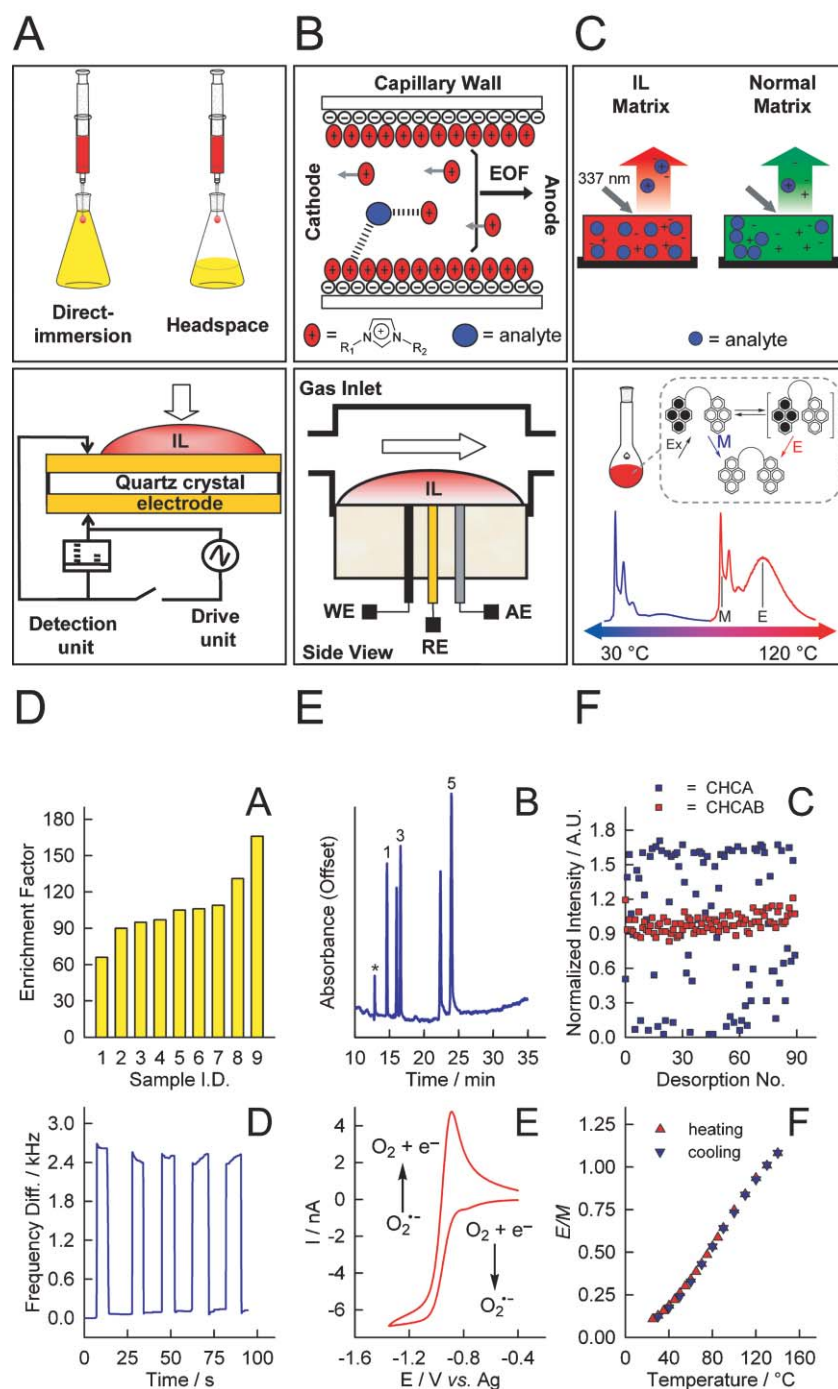
The most popular application of ILs in the field of analytical chemistry has been in the area of analytical separations. For an excellent introduction to this topic, see the recent review by Stalcup and Cabovska.<sup>6</sup> ILs are among the most complex solvents possible and are able to participate in a host of varied solvation interactions with many types of functionality. As a result, when employed as stationary phases in gas-liquid chromatography (GLC), ILs exhibit a unique dual-nature behavior that can be exploited to separate complex mixtures of both polar and nonpolar compounds. Dispersive interactions with an aliphatic- or aromatic-substituted cation and hydrogen bonding, primarily between the IL anion and proton-donating analytes (alcohols, diols, phenols), both play roles in the overall selectivity and retention mechanism. However, while ILs possess several essential features of a good liquid stationary phase (*i.e.*, high

viscosity, high thermal stability, low vapor pressure, and wetting ability toward common column supports such as fused-silica capillary tubing), some probe solutes were tenaciously retained (some acids and bases) and either had long retention times, relatively high peak asymmetry factors (tailing is often observed for alcohols and carboxylic acids), poor peak efficiencies, or did not elute at all (*e.g.*, alkylamines). Moreover, common ILs also exhibit some column bleed at lower temperatures than conventional stationary phases (below 200  $^{\circ}\text{C}$ ), possibly due to partial thermal decomposition or slight volatilization.<sup>6,7</sup>

In response to these shortcomings of the more “conventional” IL GLC stationary phases, Anderson and Armstrong have engineered two new triflate ILs based on an imidazolium cation sporting a bulky benzyl or 4-methoxyphenyl aromatic group.<sup>7</sup> Designed to provide efficient separation with very low column bleed, these new ILs have decomposition temperatures up to 260  $^{\circ}\text{C}$  as well as improved retention behavior and symmetrical peak shapes. The new IL stationary phases were found to be particularly well suited for the separation of linear alkanes and isomeric compounds including alcohols, sulfoxides, PAHs, and polychlorinated biphenyls. In some cases, faster separations, reversal of elution order, improved peak shapes, or greater selectivity were observed compared with a commercial DB-17 methylphenyl polysiloxane GLC stationary phase.

### Liquid chromatography

Several groups have reported using ILs as mobile phase modifiers or running electrolytes to improve liquid chromatographic (LC) separations. For example, the surface acidity of residual silanol groups in silica-based chemically-bonded or endcapped stationary phases has been associated with a host of undesirable “silanophilic” interactions (pronounced peak tailing, and irreproducible or excessively long retention times, for example), particularly when separating basic compounds. Zhang *et al.*<sup>8</sup> have explored the use of 0.054–0.869 vol% 1-alkyl-3-methylimidazolium  $[\text{BF}_4]^-$  or  $[\text{Cl}]^-$  ILs as aqueous mobile phase additives in the separation of the three



**Fig. 2** Select analytical applications of ionic liquids. Liquid-phase microextraction of PAHs from water using a  $[C_8mim][PF_6]$  micro-droplet. Lower: Samples 1–9 denote the following PAHs: benzo[a]pyrene, acenaphthene, acenaphthylene, fluorene, anthracene, fluoranthene, pyrene, phenanthrene, naphthalene; see ref. 5 (A).  $[C_2mim][BF_4]$  as a running electrolyte in the CE analysis of polyphenols. Lower: Representative electropherogram for the separation of polyphenol standards. The asterisk denotes the EOF marker and peaks 2 and 3 are the diastereomeric pair (–)-epicatechin and (+)-catechin; see ref. 13 (B). ILs as ionic MALDI-MS matrixes. Lower: Normalized  $[M + H]^+$  ion intensities for MALDI-MS analysis of human angiotensin II at random positions across a matrix droplet using CHCA (shown in blue) compared with the ionic matrix CHCAB (red); see ref. 18 (C). QCM detection of organic vapors using an IL-coated quartz crystal. Lower: A typical frequency response curve for cycling between acetone-saturated air and dry air using a  $[C_2mim][BF_4]$ -modified QCM device; see ref. 19 (D). Electrochemical detection of gases in IL. Lower: Cyclic voltammogram of the  $O_2/O_2^{\cdot-}$  redox couple in  $[N_{6222}][Tf_2N]$  at a 5  $\mu m$  radius gold microdisk electrode,  $v = 500 \text{ mV s}^{-1}$ ; see ref. 20 (E). IL-based optical thermometry. Lower: Reversible, hysteresis-free ratiometric response of a luminescent thermometer based on 1,3-bis(1-pyrenyl)propane cyclization within  $[C_4mpy][Tf_2N]$ ; see ref. 25 (F).



catecholamines epinephrine, norepinephrine, and dopamine by reversed-phase high-performance liquid chromatography (HPLC). These authors suggested that the improved peak symmetry and excellent calibration curve linearity ( $r \geq 0.9998$  for concentrations from *ca.* 3–950  $\mu\text{g mL}^{-1}$ ) arose chiefly from reduced silanol activity as a result of adsorption of IL components on the octadecyl (C18) stationary phase surface.

Kaliszan and co-workers have also reported using dialkylimidazolium  $[\text{BF}_4]^-$  ILs as alternative adsorbable silanol blocking agents with suppression potencies far exceeding those of standard mobile phase additives such as  $\text{NH}_4\text{OH}$ , triethylamine, or dimethyloctylamine.<sup>9</sup> In this work, it was shown that 0.5–1.5 vol%  $[\text{C}_2\text{mim}][\text{BF}_4]$ , for example, added to the mobile phase allowed for both normal phase (*i.e.*, underivatized silica) and C18 reversed-phase thin-layer chromatographic (TLC) separations of 8 strongly basic drugs, including four phenothiazines, all of which otherwise did not elute using neat acetonitrile as the mobile phase. Free silanol passivation followed a Langmuir adsorption isotherm and retention parameters ( $R_M$ ) for basic drug elution on C18 TLC plates with water/acetonitrile mixtures containing 3.0 vol%  $[\text{C}_2\text{mim}][\text{BF}_4]$  were linear in eluent composition (*i.e.*, classical Snyder–Soczewiński behavior). The latter behavior is a consequence of removing spurious effects resulting from uncontrolled, mutual attractions between surface silanols and basic analytes. As a result, chromatographic lipophilicity parameters,  $\log k_w$ , determined by gradient HPLC for a series of 13 basic drugs in the presence of 1.5 vol%  $[\text{C}_2\text{mim}][\text{BF}_4]$  with a water/methanol mobile phase were reasonably linear in  $\log P$ , contributing to a rational optimization of separation conditions.

Recently, Berthod and Carda-Broch have discussed the prospects for using ILs as either support-free stationary or mobile phases in countercurrent chromatography (CCC).<sup>10</sup> Although no actual studies with CCC apparatus were undertaken due to material limitations, some useful data were compiled including  $[\text{C}_4\text{mim}][\text{PF}_6]/\text{water}$  and  $[\text{C}_4\text{mim}][\text{PF}_6]/n\text{-heptane}$  distribution coefficients for a host of substituted aromatics, and ternary phase diagrams

for  $[\text{C}_4\text{mim}][\text{PF}_6]/\text{water} + \text{acetonitrile}$ , methanol, ethanol, 1-propanol, and 2-propanol mixtures. The authors conclude that while the high viscosities of the pure ILs formulated to date preclude their direct use as a liquid phase in CCC at room temperature (viscosities for neat ILs generally span the 50–400 cP range at 20 °C), several ternary organic solvent/IL/water mixtures apparently have suitably low viscosities using typical CCC instrument tubing bore.

### Capillary electrophoresis

Several research groups have reported on the utility of ILs as mobile phase or run buffer modifiers, dynamic or supported coatings on the capillary wall, or the background electrolyte in capillary electrophoresis (CE) or non-aqueous capillary electrophoresis (NACE) separations.<sup>11–16</sup> In the first example, Vaher *et al.*<sup>11</sup> used 0.5–8.5  $\text{mg mL}^{-1}$   $[\text{C}_4\text{mim}][\text{X}]$ , where  $\text{X} = \text{PF}_6^-$ ,  $\text{CH}_3\text{CO}_2^-$ , or  $\text{CF}_3\text{CO}_2^-$ , as the electrolyte in acetonitrile to enable the NACE separation of five poorly water-soluble biological stains and to reveal the existence of several minor impurities in one of the dyes. No separation was observed in neat acetonitrile. Later work by the same authors extended this methodology to the NACE resolution of a variety of carboxylic acids and phenols including the baseline separation of the three dihydroxybenzene positional isomers hydroquinone, resorcinol, and pyrocatechol.<sup>12</sup> In both reports, the authors invoke heteroconjugation between the analyte and the anionic portion of the IL to explain the observed separation. This is accordant to the observation that the anion generally has a greater effect on the hydrogen bond basicity of an IL as compared to the cation.

Recently, Stalcup and co-workers have reported a simple and highly reproducible ( $\approx 2\%$  RSD for migration times,  $n = 3$ ) aqueous CE method for the separation and identification of polyphenolic compounds isolated from grape seed extracts using 50–300 mM  $[\text{C}_2\text{mim}]$  or  $[\text{C}_4\text{mim}]$  ILs as running electrolytes.<sup>13</sup> The 1-alkyl-3-methylimidazolium cation of the IL was found to coat the 50  $\mu\text{m}$  id bare fused-silica capillary imparting the surface with a pH-independent

(permanent) positive charge and reversing the electroosmotic flow (EOF) in the anodic direction (Fig. 2B). The separation mechanism apparently relies on the weak association ( $K_{\text{app}} \approx 5 \text{ M}^{-1}$ ) of free imidazolium cation migrating away from the detector with the phenolic analyte in the bulk. Interestingly, however, no separations were obtained with the  $[\text{CF}_3\text{SO}_3]^-$  or  $[\text{NO}_3]^-$  salts.

Dynamic coating with 1-alkyl-3-methylimidazolium ILs was also found to address the problem of protein adherence to the capillary wall.<sup>14</sup> We note that, as a rule-of-thumb, protein will resist adsorption onto a surface if the association constant of the protein–surface interaction is reduced below  $10^3 \text{ M}^{-1}$ . In the study by Ou and co-workers,<sup>14</sup> elution with 30–110 mM aqueous  $[\text{C}_2\text{mim}][\text{BF}_4]$ , for example, led to a surface charge reversal on the capillary wall and efficient ( $0.92\text{--}1.20 \times 10^5$  plates) and reproducible baseline separation of a mixture of the basic proteins lysozyme (pI 11.0), cytochrome *c* (pI 10.7), trypsinogen (pI 8.7), and  $\alpha$ -chymotrypsinogen A (pI 9.2). These basic proteins not only experience electrostatic repulsion from the treated silica surface at near-neutral pH but the trends in effective electrophoretic mobility of proteins and the magnitude of the EOF as functions of  $[\text{C}_2\text{mim}][\text{BF}_4]$  concentration further suggest some degree of association between the dissolved protein and  $[\text{C}_2\text{mim}]^+$ . No separation was observed for the  $[\text{SO}_4]^-$  anion, in line with the strong mutual affinity mediated by hydrogen bonding between the C-2 proton of the imidazolium cation and oxygen-containing anions as proposed by Stalcup and co-workers earlier.<sup>13</sup>

A “supported” IL formed *via* covalent immobilization of the decyl-imidazolium moiety on the inner wall of a silica capillary has shown promise in DNA separations. In the presence of 2% hydroxyethylcellulose in buffer as sieving matrix, Qin and Li showed that IL-functionalized capillaries result in faster separations of a  $\Phi\text{X174}$  DNA-Hae III digest (this standard contains 11 fragments ranging in size from 72 to 1353 bp) compared with a polyacrylamide-coated capillary.<sup>15</sup> The shortened analysis time arises because the anodic EOF moves co-directionally with the negatively-charged DNA fragments. Importantly,

and in contrast to chemisorption-coated capillaries which deteriorate after multiple runs, the silanized capillary surface has a lifetime of at least 96 h with no significant decrease in performance. We note that by eliminating the presence of a nonvolatile electrolyte, this approach is also well suited for hyphenation with electrospray mass spectrometry (ESI-MS).

The Warner group has recently explored using 1-alkyl-3-methylimidazolium ILs as polymeric pseudostationary phase modifiers in micellar electrokinetic chromatography (MEKC).<sup>16</sup> Addition of low levels (1–3 mM) of either [C<sub>2</sub>mim][BF<sub>4</sub>] or [C<sub>4</sub>mim][BF<sub>4</sub>] to background electrolyte solutions containing the polymeric surfactant poly(sodium *N*-undecylelinic sulfate) were shown to improve the resolution and peak efficiency in the separation of 8 alkyl aryl ketones and 7 chlorophenols. When combined with the chiral surfactant poly(sodium oleyl-L-leucylvalinate), these ILs also facilitated the baseline resolution of the *R*(+) and *S*(–) enantiomers of three pairs of chiral binaphthyl derivatives, in a single mixture. Again, ILs containing [CF<sub>3</sub>SO<sub>3</sub>]<sup>–</sup> or [Cl]<sup>–</sup> proved ineffective.

## An unorthodox matrix for analysis

### Matrix-assisted laser desorption/ionization

The application of ILs as replacements for the conventional liquid or solid matrixes in matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) has also been recently recognized. A shortcoming of the so-called “dried-drop” method used with such a matrix is the considerable degree of heterogeneity (incongruities) resulting in poor reproducibility and making necessary the tedious search for “hot spots” that give acceptable signal. Indeed, as many as half of the locations examined within a solid matrix produce no signal. In the continued search for alternative approaches, Armstrong and co-workers have reported several dozen ionic matrixes formed by neutralization of the commonly used solid acidic matrixes  $\alpha$ -cyano-4-hydroxycinnamic acid (CHCA) and sinapinic acid (SA).<sup>17</sup>

Although the ILs evaluated in this study invariably showed good analyte dissolution, excellent high-vacuum ( $10^{-7}$ – $10^{-8}$  mbar) stability, and strong absorption at the desired wavelength (337 nm), they varied widely in their ability to promote gas-phase analyte ion formation. Many, including more conventional ILs such as [C<sub>4</sub>mim][PF<sub>6</sub>] or [C<sub>4</sub>mim][BF<sub>4</sub>], produced no MALDI signals for any of the solutes tested (bradykinin, human insulin, equine skeletal apomyoglobin, PEG 2000). While much higher laser intensities were typically needed to produce results comparable to those found for conventional solid matrixes, it was always possible to identify an ionic matrix that outperformed its parent solid matrix (CHCA or SA) and produced higher ion peak intensities and equivalent or lower detection limits. The most significant criterion for an effective ionic MALDI matrix was that the cation must contain an acidic proton.

In addition, the ionic matrixes have a number of key advantages to the analyst. They readily formed homogeneous solutions with all of the analytes studied and gave much improved shot-to-shot reproducibility. In addition, because of diffusion and liquid matrix flow, ionic matrixes are “self-healing” and can endure a high number of repetitive desorptions making repeat analysis feasible. Even after several hundred consecutive laser shots to the same locus on an ionic matrix, no signal depletion occurred as was the case with a solid matrix.

The performance of the ILs 2,5-dihydroxybenzoic acid butylamine (DHBB),  $\alpha$ -cyano-4-hydroxycinnamic acid butylamine (CHCAB), and 3,5-dimethoxycinnamic acid triethylamine (SinTri) as new ionic MALDI matrixes was investigated in detail by Mank *et al.*<sup>18</sup> Compared with the traditional MALDI matrixes CHCA and 2,5-dihydroxybenzoic acid (DHB), these authors observed somewhat lower sensitivities for the ionic matrixes. They attribute this behavior to the fact that under their preparation conditions, *i.e.*, IL/ethanol/sample solution (1 : 1 : 2, v/v/v), minimal sample pre-concentration occurs resulting in a lower final analyte concentration as compared to the dried-droplet approach.

As with Armstrong and co-workers,<sup>17</sup> however, Mank *et al.*<sup>18</sup> reported that ionic matrixes were a promising solution to the unsatisfying variability of signal intensities at different desorption points across the surface of a dried-droplet prepared from the solid matrixes CHCA and DHB. That is, because no crystallization occurs, the use of ionic matrixes obviates the time-consuming manual search for “hot spots” in order to yield acceptable signal-to-noise ratios or even an analyte signal at all. The improved shot-to-shot reproducibility for the ionic matrix CHCAB relative to CHCA is shown in Fig. 2C using human angiotensin II as a test analyte. The associated relative standard deviations (RSD) of the MALDI-MS signal are *ca.* 8 and 60%, respectively, showing the marked enhancement in reproducibility for the IL MALDI matrix. The individual ionic matrixes have unique strengths as well. The ionic matrix CHCAB almost completely suppressed alkali adduct formation ([M + Na]<sup>+</sup>, [M + 2Na – H]<sup>+</sup>, and [M + 3Na – 2H]<sup>+</sup>) resulting in cleaner spectra containing mainly the pseudomolecular ion [M + H]<sup>+</sup>. In comparison, DHBB was found to be much more tolerant to very high sample concentrations (*e.g.*, 87 mM maltoheptaose or 25 mM PEG 2000) and, despite the higher laser fluence required relative to solid DHB, was associated with softer desorptions (reduced fragmentation) of monosialylated glycans and bovine ganglioside GM1. Alternatively, SinTri proved to be the best choice for analyzing high molecular weight proteins such as monoclonal mouse IgG (150 kDa).

Overall, ionic matrixes appear poised to offer a general approach to *quantitative* and high-throughput MALDI-MS analysis in areas such as proteomics and quality control in the food industry. One can also envision several other possibilities such as direct interfacing with liquid separation techniques from preparative LC to  $\mu$ -TAS chips.

### Quartz crystal microbalance sensors and electroanalysis

In recent work, Dai and co-workers modified the upper gold electrode of a 6 MHz AT-cut quartz crystal with a thin film of 1-alkyl-3-methylimidazolium [Tf<sub>2</sub>N]<sup>–</sup> or [BF<sub>4</sub>]<sup>–</sup> toward the

construction of a quartz crystal microbalance (QCM) vapor-sensing device.<sup>19</sup> In this work, exposure of the membrane-free IL-coated crystal to a flow of organic vapor gave a fully reversible and reproducible change in the QCM oscillating frequency, with a response time of a few seconds (a steady-state response was typically observed within 2 s) and a frequency increase that was strongly dependent on both the analyte in question and the IL used to coat the electrode. Fig. 2D shows a typical temporal frequency response to repeated exposure to acetone-saturated air for a QCM device modified with a sorbent layer of [C<sub>2</sub>mim][BF<sub>4</sub>]. The sensory response was ascribed to a sharp decrease in the viscosity (and, to a lesser extent, the density) of the IL film contacting the electrode, induced by sorption of organic vapor and giving rise to a frequency shift of the resonator. The active layer can easily be regenerated by purging the system with an inert gas or *in vacuo* and recycling of the QCM element is afforded by rinsing with a suitable solvent such as MeCN.

Having come to prominence in the form of haloaluminate molten salts explored as alternative electrochemical solvents in the battery industry, it is only fitting that the electrochemical utility of second-generation ILs remains a current focus of research.<sup>20</sup> As electrochemically-robust solvents, the additional potential range offered by these non-aqueous media may be exploited to study the direct oxidation or reduction of species whose solution-phase electrochemistry has so far remained inaccessible. Although the electrode material and the presence of electroactive impurities (such as residual halide) can narrow the observed range, a 4.5–6.0 V potential window is typical for a non-haloaluminate IL, regardless of the reference electrode used. In general, the cathodic limit is more variable and depends on the identity of the cation; *e.g.*, substitution at the C-2 carbon of an imidazolium ring improves the cathodic threshold.

Given their entirely ionic composition, which eliminates the need for added supporting electrolyte, the intrinsic conductivity and negligible vapor pressure of ILs suggest their use in the development of stable electrochemical sensors for gaseous analytes such as oxygen, carbon

dioxide, ammonia, and sulfur dioxide. So far, the majority of effort in this area has centered on the electrochemical investigation of oxygen in ILs.<sup>20–23</sup> For instance, the one-electron reduction of oxygen to superoxide radical (O<sub>2</sub><sup>•−</sup>) was studied in [C<sub>4</sub>mim][PF<sub>6</sub>] by AlNashef *et al.*<sup>21</sup> In this report, O<sub>2</sub><sup>•−</sup> generated *in-situ* was found to be stable at glassy-carbon or platinum mesh electrodes and the increased cathodic peak current coupled with the decreased peak current for the reverse scan observed in the presence of CO<sub>2</sub> were consistent with the irreversible formation of peroxydicarbonate ion, C<sub>2</sub>O<sub>6</sub><sup>2−</sup>, a putative reagent for follow-on carboxylation (*e.g.*, the conversion of amines into carbamates).

More recently, Compton and co-workers proposed an amperometric gas sensor consisting of a two-electrode cell design whereby the surface of a gold working microelectrode is modified with a thin layer of IL which serves as a nonvolatile electrolyte, eliminating the need for a gas-permeable membrane to separate the sample and the internal electrolyte layer.<sup>22</sup> For [Tf<sub>2</sub>N]-based ILs, the response times required to reach 90% of the steady-state current (*t*<sub>90</sub>) following a step change in oxygen concentration fell in the 10–50 ms range, for a 5 μm thickness IL layer. The diffusion coefficients for oxygen are about an order of magnitude lower than in traditional aprotic media [*D*/10<sup>−6</sup> cm<sup>2</sup> s<sup>−1</sup> = 2.5 and 21.0 in [C<sub>2</sub>mim][Tf<sub>2</sub>N] and DMSO, respectively], resulting in an increased *t*<sub>90</sub> and limiting the attainable steady-state current. While these effects conspire to prevent any significant advantage over previously reported membrane-independent microelectrode designs (*t*<sub>90</sub> ~ 5 ms), the response times are still adequate for many real-world applications. Notably, such sensors have potential for operation in extreme environments, such as high temperature and pressure, where traditional solvents quickly volatilize or degrade, with important implications for gas exhaust/combustion analysis, fermentation monitoring, and air-quality control.

In related work, the Ohsaka group developed a porous polyethylene membrane-coated oxygen sensor incorporating [C<sub>2</sub>mim][BF<sub>4</sub>].<sup>23</sup> Potential-step

chronoamperometric experiments conducted as a function of vol% O<sub>2</sub> revealed that, in addition to the transient oxidation and reduction currents, the steady-state cathodic current was suitable for the determination of O<sub>2</sub> concentration in a gas mixture.

As electrochemical solvents, ILs can also produce distinctive voltammetry.<sup>20,23</sup> This is illustrated in Fig. 2E (lower) where both steady-state and transient behavior is observed in a single cycle. In this example, the shape of the forward wave for reduction of O<sub>2</sub> in [N<sub>6222</sub>][Tf<sub>2</sub>N] is dictated by radial diffusion to the electrode surface and shows steady-state behavior. Owing to the large disparity in the diffusion coefficients for the two oxygen species [*D*(O<sub>2</sub>) = 1.5 × 10<sup>−6</sup> cm<sup>2</sup> s<sup>−1</sup>, *D*(O<sub>2</sub><sup>•−</sup>) = 4.5 × 10<sup>−8</sup> cm<sup>2</sup> s<sup>−1</sup>],<sup>20</sup> the reoxidation of the O<sub>2</sub><sup>•−</sup> formed contains a significant contribution from linear diffusion giving rise to a strongly peak-shaped reverse wave.

### Optical sensors/optrodes

In one of the few reports to explore ILs as media for developing optical sensors, Pandey and co-workers showed that nitromethane selectively quenched the emission of alternant PAHs in [C<sub>4</sub>mim][PF<sub>6</sub>] following simple Stern–Volmer behavior.<sup>24</sup> The luminescence of nonalternant PAHs containing a five-membered ring, exemplified by fluoranthene, was not quenched. These results suggest that ILs may find use in other areas of environmental analysis as well.

No molecular solvent, except perhaps some liquid polymers, can match the liquid range of ILs (*i.e.*, 300 °C in some cases). Toward this, Baker *et al.*<sup>25</sup> recently described a novel class of luminescent molecular thermometer based on the intramolecular *excited-state dimer* (excimer) formation/dissociation of a 1,*n*-bis(aryl)alkane luminophore dissolved in [C<sub>4</sub>mpy][Tf<sub>2</sub>N]. Owing to the modulation in the solvent's absolute viscosity, the thermometer displays a completely reversible and ratiometric optical response to temperature with a useful operational range of at least 25–140 °C and an average imprecision below 0.35 °C for *T* ≤ 100 °C (Fig. 2F).

Not only has the introduction of ILs opened up new potential for chemical analysis but the field of



analytical chemistry has also reciprocated by contributing to a molecular-level view of solvation within neat ILs and IL/liquid mixtures. For example, while beyond the scope of this review, among others, the groups of Bright,<sup>26</sup> Maroncelli,<sup>27</sup> and Sarkar,<sup>28</sup> have used picosecond time-resolved fluorescence spectroscopy to probe the kinetics of solvent relaxation surrounding dipolar fluorescent probes dissolved in ILs such as [C<sub>4</sub>mim][PF<sub>6</sub>].

### Outlook and neglected issues

Whether ILs will have lasting and far-reaching industrial consequences remains an open question. However, as we hope this Education makes clear, the adoption of ILs as solvents by forward-thinking analytical chemists has already led to some intriguing benefits in chemical analysis. We suspect that ILs will find an increasing number of applications in analytical chemistry, however, a number of important issues and concerns should be raised.

First, there has been a tendency in the field to blindly regard ILs as inherently “green”, however, as with any other property the toxicity will depend on the exact ionic composition and is subject to some control. It should also be pointed out that their non-volatile nature is a relatively small component of their being green. With regard to their greenness, it should be noted that the class of polychlorinated biphenyls (PCBs) was once considered completely safe. Additional research aimed at issues of considerable practical importance such as their toxicology, environmental fate, bioaccumulation/biodegradation, thermal and chemical stability, life cycle assessment, and recovery/recycling and disposal limitations is needed. This being said, while most analytical uses of ILs are not predicated on their being green *per se*, several outstanding issues ancillary to their being green (e.g., purity, stability, high cost, limited information on their properties) are certain to impact upon their anticipated utility for chemical analysis. For example, the hydrolytic stability of ILs, particularly given their hygroscopicity, assumes key practical importance.<sup>29</sup>

In the beginning of this Education we remarked how deliberate variation in the

solvent properties of ILs was possible through different ion pairings. How then does one select the best IL for a particular analytical application? Although the flexibility of these “designer solvents” promises to suit the needs of the analyst, a clarification of these design rules is still awaited. Further to this, owing to the sheer number of different cation/anion combinations that could in principle be synthesized, amassing anything closely resembling a complete or reliable database of their various physico-chemical properties is no small undertaking. As the nature of interactions with different solutes comes under study, the purity of ILs is also an area of increasing interest. Depending on the volumes and purity required for a given application, a cost analysis compared with existing technologies will also be required. Finally, in order to improve mass transport through these media for some uses, application of microwaves, heat, or sonication may prove necessary. As a result, the stabilities of ILs under these various conditions need to be assessed.

While it will likely be some time before ILs are assimilated into the analytical chemist's normal repertoire, exciting developments seem certain along the way. From an analytical viewpoint, TSILs with built-in functionality such as cations or anions incorporating polymerizable, photo-reactive (e.g., photo-isomerizable, photo-cleavable), or chelating side chains as well as chiral, liquid crystalline, and amphiphilic ILs are noteworthy. The application of ILs in chemical analysis is poised to receive heightened attention during the next decade with the prospect for exciting and unforeseen benefits. In addition to their potential to broaden or even revolutionize the range of analytical approaches currently available, the use of ILs may also be expected to receive increased attention in the areas of homeland security, biomedicine, nanophotonics, and forensics. As a final thought, given the demonstration that ILs can act as agents for effectively stabilizing proteins at elevated temperatures,<sup>30</sup> we presage that the elaboration of biosensors incorporating ILs will be a particularly fertile area for exploration.

### Where to find more information

In addition to two edited volumes on the subject,<sup>1,2</sup> papers collected from the trilogy of American Chemical Society (ACS) National Meeting ionic liquid symposia held in San Diego (April 1–5, 2001), Boston (August 18–22, 2002), and New York (September 7–11, 2003), all co-organized by Robin D. Rogers (Center for Green Manufacturing, University of Alabama) and Kenneth R. Seddon (QUILL, Queen's University of Belfast), should also be considered essential reading.<sup>31</sup> In addition, *Chemical Communications* and *Green Chemistry* have been popular repositories for IL papers. Finally, several journal topical issues devoted to ILs have appeared recently in *Green Chemistry*,<sup>32</sup> *Australian Journal of Chemistry*,<sup>33</sup> and *Journal of Molecular Catalysis A*.<sup>34</sup>

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