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Ionic Liquids in Analytical Chemistry: Fundamentals, Advances, and Perspectives

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Since their initial discovery in 1914, ionic liquids (ILs) have been widely studied in multiple chemistry disciplines. Applications of ILs in analytical chemistry have enjoyed much success and contributed to the rapid evolution of the ionic liquid field. ILs are collectively known as organic salts which possess melting points at or below 100 °C. In most cases, ILs are composed of an organic cation and an organic or inorganic anion. It has been estimated there can be up to 10^{18} possible combinations of ILs, due to the ability to interchange their corresponding cationic/anionic moieties.[1]

A number of ILs exhibit beneficial characteristics, such as high thermal stability, negligible vapor pressure, and nonflammability, in addition to varying viscosities, conductivity, and miscibility in different solvents. This is due to the electrostatic interactions associated with the cation and anion moieties comprised within the ILs, as well as their ability to undergo unique intermolecular interactions with one another. These characteristics can also be finely tuned to meet specific requirements by imparting different functional groups and/or varying the combinations of cations and anions in the ILs. In light of these attributes, ILs are practical for many analytical

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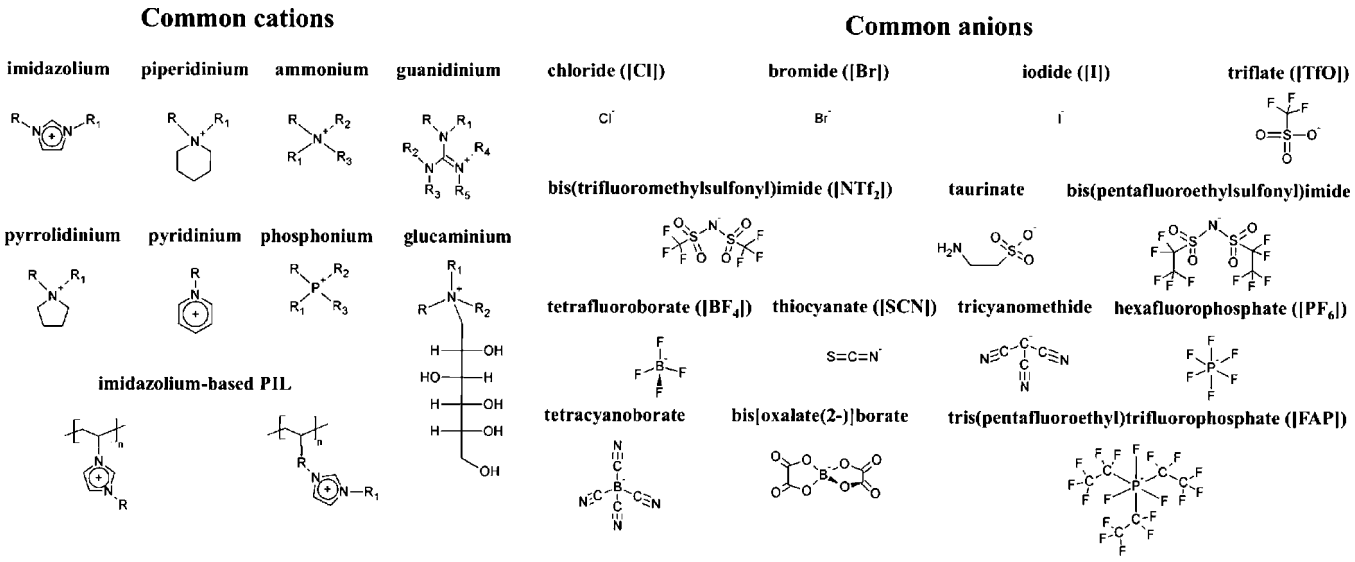

Figure 1. Chemical structures of selected IL and PIL cation/anion pairs commonly employed in techniques and methods within analytical chemistry.

applications and can be an indispensable alternative to traditional organic solvents in many sample preparation techniques. Although the properties of ILs will not be discussed within this Review, the audience is referred to a number of publications which describes the structural relationship of ILs to their physicochemical properties.[2−6]

Aside from the aforementioned properties, ILs can also be engineered to exhibit exceptional selectivity toward specific groups of compounds. For example, imparting polar substituents to an IL can promote dipolar interactions between the IL and polar solutes. Analogously, tailoring long aliphatic alkyl chains to an IL can enhance its ability to undergo dispersion interactions with nonpolar analytes. Overall, the ability to tune the selectivity of ILs can enable high preconcentration of analytes in various sample preparation and detection techniques. On the other hand, when applied as chromatographic stationary phases, ILs can produce excellent separation efficiency and peak capacities.

This Review aims to provide an update to novel applications of ILs in analytical chemistry. Due to the increasing popularity of ILs and the large volume of scientific literature that currently exists, it is not possible to exhaustively cover all previous studies. Therefore, significant advances pertaining to the applications of ILs in sample preparation and extraction, chromatography, capillary electrophoresis, mass spectrometry, and electrochemical sensing within the past two years will be discussed.

IONIC LIQUIDS IN SOLVENT-BASED MICROEXTRACTIONS

Single Drop Microextraction. Single drop microextraction (SDME) is a microscale preconcentration technique developed by Dasgupta and co-workers in the 1990s.[7] Cantwell and co-workers expanded the applicability of SDME by coupling the technique to chromatographic systems.[8] In SDME, a single microdroplet of extraction solvent is exposed to a sample matrix by use of a chromatographic syringe. Extraction can typically be performed in the sample headspace or by direct immersion in the sample solution. Following the extraction step, the microdroplet can be withdrawn back into the syringe and injected to a chromatographic system for analysis. This method is rapid and easy to operate and provides good sensitivity due to the preconcentration of analytes. The application of ILs as extraction solvents, initially reported by Liu and co-workers,[9] provides multiple advantages compared to employing traditional organic solvents as the extraction phase. For convenience, common IL cations and anions previously employed in a number of analytical chemistry fields are shown in Figure 1. Due to their high viscosity and low vapor pressure, ILs enable the formation of large, stable microdroplets that are not prone to evaporation during extraction. This can provide superior analyte extraction capabilities as well as improved analytical precision compared to organic solvents. Additionally, the tunable characteristics of ILs can further increase method sensitivity, leading to better limits of detection (LODs) for trace and ultratrace level analysis.[8−10] The following studies provide a brief update on the recent progress of IL-based SDME in environmental and biological analysis.

IL-SDME in Environmental Applications. IL-SDME has recently been applied in the extraction of analytes in various environmental water samples. For instance, the 1-butyl-3-methylimidazolium hexafluorophosphate ($[C_4MIM][PF_6]$) IL and diethyldithiocarbamate (DDTC) was employed as the extraction solvent and chelating reagent, respectively, in the analysis of copper ions (Cu).[11] The method demonstrated good Cu recovery in both food and water matrixes. Applying an IL-based extraction solvent also significantly improved the overall analytical performance of the technique, compared to using no ILs. Rahmani and co-workers also successfully employed the same IL in the extraction of methylcyclopentadienyl-manganese tricarbonyl in gasoline and water, while Wen et al. recently applied this IL in the analysis of cadmium in rice and waters samples.[12,13] Márquez-Sillero and co-workers reported the analysis of 2,4,6-trichloroanisole in water and wine samples using IL-SDME coupled to ion mobility mass spectrometry (IMS). The 1-hexyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]imide ($[C_6MIM][NTf_2]$) IL was used as an extraction microdroplet in headspace mode, wherein high analyte selectivity and method sensitivity was achieved.[14,15] Four extraction solvents, namely, toluene, *n*-heptane, $[C_6MIM][PF_6]$, and 1-octyl-3-methylimidazolium $[PF_6]$ ($[C_8MIM][PF_6]$) were compared in the automated

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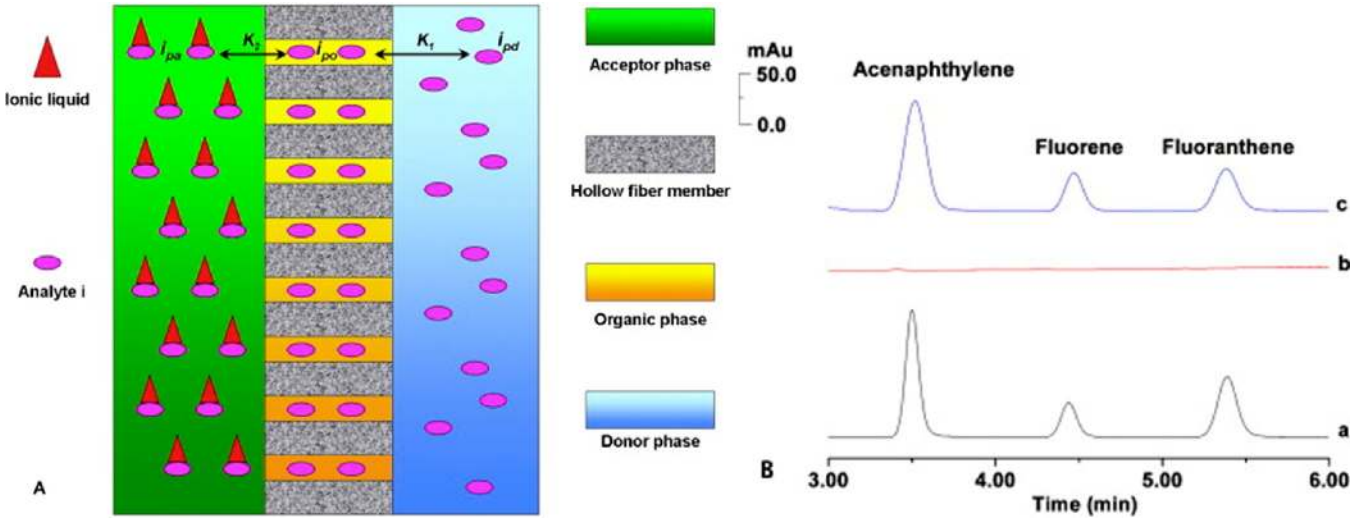

Figure 2. Application of ILs as acceptor-phase additives in HF-LPME. (A) Schematic of HF-LPME employing ILs as additives in the acceptor phase. i_{pd}: analyte in the aqueous donor phase; i_{po}: analyte in the immobilized organic phase; i_{pa}: analyte in the IL-modifed acceptor phase; K_1: ratio of the concentration of analyte *i* in the organic phase with respect to the donor phase under equilibrium; K_2: ratio of the concentration of analyte *i* in the acceptor phase with respect to the organic phase under equilibrium. (B) Extraction comparison of 0.4 μg mL^{-1} neutral analytes, wherein (a) is a direct injection of a 10 μg mL^{-1} standard solution, (b) HF-LPME using no IL additives, and (c) HF-LPME using 4.5 MIL in the acceptor phase. Reprinted from Liu, W.; Wei, Z.; Zhang, Q.; Wu, F.; Lin, Z.; Lu, Q.; Lin, F.; Chen, G.; Zhang, L. *Talanta* **2012**, *88*, 43 (ref 23). Copyright 2012, with permission from Elsevier.

extraction of musk fragrances in environmental water samples.[16] The [C_8MIM][PF_6] IL and toluene provided the highest extraction peak areas; however, the [C_8MIM][PF_6] IL was chosen as a superior solvent since this IL microdroplet exhibited improved stability and yielded significantly better method precision.

IL-SDME in Bioanalytical Applications. IL-SDME was also demonstrated to be highly useful for bioanalytical applications. Pathogenic bacteria were extracted by the [C_4MIM][PF_6] IL impregnated with platinum nanoparticles and characterized by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS).[17] This method showed promising results for the potential analysis of pathogenic organisms in biological samples. IL microdroplets were modified with CdSe/ZnS quantum dots (QDs) for the analysis of trimethylamine (TMA) in fish.[18] The QD-[C_6MIM][PF_6] IL mixture was used to extract volatile TMA from fish samples followed by QD-based fluorimetric detection. Quantification was achieved by observing signal enhancements from pure QD-IL relative to QD-IL containing TMA.

Hollow Fiber Membrane Liquid-Phase Microextraction. Hollow fiber membrane liquid-phase microextraction (HF-LPME) is a solvent preconcentration technique developed by Pedersen-Bjergaard and Rasmussen in the late 1990s.[19] This method employs a porous polymer membrane that enables the permeation of analytes from an aqueous sample solution (donor phase) to an extraction solvent (acceptor phase). Extraction in HF-LPME can be categorized into two different modes, namely, two-phase and three-phase mode. In two-phase mode, the lumen of the hollow fiber is filled with the same organic acceptor phase as those impregnated within its porous walls. On the other hand, the three-phase mode involves the fiber lumen being filled with an aqueous solution while its porous walls are impregnated with a water-immiscible organic solvent. During the extraction step, a solvent-impregnated hollow fiber containing an acceptor phase is immersed into the aqueous sample solution. Analytes can permeate through the porous structure of the membrane wall and subsequently partition in the acceptor phase. Afterward, a syringe can be used to withdraw and inject the acceptor phase to a chromatographic system for analysis. The primary advantages of employing HF-LPME in various analytical procedures include its cost-effectiveness, high throughput, low solvent consumption, and high applicability in complex sample analyses.

Similar to other extraction techniques, a potential drawback to using traditional organic acceptor phases in HF-LPME stems from the volatility, toxicity, and low selectivity of these solvents. To address this issue, Peng and co-workers initially reported the application of ILs in three-phase HF-LPME.[20] The [C_8MIM][PF_6] IL was impregnated in the hollow fiber membrane, while aqueous sodium hydroxide was employed as an acceptor phase, for the HF-LPME of chlorophenols in environmental water samples. The high stability, hydrophobicity, and negligible volatility of the IL contributed to the good extraction efficiency and precision of the method.

ILs as Acceptor Phases in HF-LPME. Ma and co-workers exploited the [C_4MIM][PF_6] IL as an acceptor phase in the IL-HF-LPME of benzene, toluene, ethylbenzene, xylene (BTEX).[21] After extraction, the IL was directly injected to a GC-FID for analysis with no manipulation. Good analytical performance was obtained; however, the GC injector required frequent maintenance due to IL contamination within the GC liner. Ge and co-workers investigated four different ILs, namely, [C_6MIM] tris(pentafluoroethyl)trifluorophosphate ([C_6MIM][FAP]), 1-butyl-1-methylpyrrolidinium [FAP] ([C_4MPL][FAP]), [C_4MIM] phosphate ([C_4MIM][PO_4]), and [C_4MIM][PF_6], as acceptor phases in IL-HF-LPME coupled to HPLC-UV for the analysis of UV filters.[22] High enrichment factors were obtained by using the [C_6MIM][FAP] IL compared to other ILs. Furthermore, the enrichment factors obtained using this method were superior to other microextraction techniques, such as DLLME and SDME.

ILs as Additives in HF-LPME. The water-miscible [C_4MIM][Cl] IL was utilized as an acceptor-phase additive in the three-

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phase HF-LPME of alkaline, acidic, and neutral organic compounds.[23] As shown in Figure 2A, the water-miscible IL was dissolved in the aqueous acceptor phase. As analytes partition from the donor to the acceptor phase, the IL can interact with the analytes and mitigate their back-extraction to the organic phase of the membrane. Using this approach resulted in slightly better extraction performance for alkaline and acidic compounds. On the other hand, as shown in Figure 2B, significant enhancements in extraction efficiency were obtained for neutral organic compounds compared to analogous three-phase HF-LPME systems containing no IL additives. Zeng and co-workers explored a variety of ILs as donor-phase additives for the extraction of Cr (VI) and Cr (III).[24] After a preliminary screening, it was determined that the addition of the $[C_4MIM][BF_4]$ IL, alongside a metal chelating agent (diethyldithiocarbamate (DDTC)), to the donor phase significantly enhanced the extraction of the chromium complexes by up to 3.5-fold. It should be noted that the addition of DDTC to sample could promote the formation of a hydrophobic metal complex, which can easily be extracted by an organic acceptor phase. However, the mechanism describing the extraction enhancements obtained from adding an IL to the donor phase is still unknown. Recently, an automated technique using IL-impregnated HF membranes was also successfully employed for the determination of Cr (VI).[25]

Dispersive Liquid–Liquid Microextraction. Although ILs have been extensively applied in various sample preparation and/or preconcentration techniques, the utilization of ILs as extraction solvents in dispersive liquid–liquid microextraction (DLLME) has generated the most interest and publications within the past two years. Introduced by Rezaee and co-workers in 2006, DLLME is a solvent extraction technique that preconcentrates analytes from an aqueous sample matrix to a water-immiscible extraction phase in the presence of a disperser solvent.[26] During the extraction step, microliter volumes of a hydrophobic organic solvent and a disperser solvent are injected to an aqueous sample solution. The hydrophobic solvent functions as the analyte extraction phase, while the disperser solvent (an organic modifier that is miscible with both the aqueous matrix and the extraction solvent) is used to facilitate the formation of fine microdroplets of the extraction phase in solution. Subsequently, the extraction phase can be recovered by centrifugation and injected to a chromatographic system for analysis. The primary advantages of employing DLLME over traditional liquid–liquid extraction (LLE) techniques are its low solvent consumption, high extraction throughput, and excellent extraction efficiency, which is primarily achieved by the large surface area of the microdroplets formed during extraction.

Zhou and co-workers initially applied hydrophobic ILs as extraction phases in DLLME.[27] Instead of utilizing organic disperser solvents, the formation of IL microdroplets was achieved by the manipulation of the solution temperature. This approach, noted as temperature-controlled IL-DLLME (TC-IL-DLLME), demonstrated high method sensitivity as a result of the selectivity attained from employing ILs as extraction solvents. Additionally, the use of toxic organic solvents during extraction was minimized. Anderson and co-workers developed an in situ IL-DLLME method, wherein a hydrophilic IL is injected to a sample solution as the extraction solvent instead of a hydrophobic IL.[28] Subsequent to the complete dissolution of the hydrophilic IL, an ion-exchange reagent, such as $LiNTf_2$, was added to the solution to promote the metathesis reaction and the subsequent formation of a hydrophobic IL extraction phase. Overall, the in situ IL-DLLME method demonstrated better enrichment factors compared to conventional DLLME due to the formation of smaller microdroplets during extraction. Furthermore, no organic disperser solvents were needed during the extraction step.

The following studies will explore the recent applications of ILs in DLLME. Emphasis will be placed on the applicability of this technique for the analysis of pharmaceutical products, metal ions, and organic environmental pollutants.

Application of IL-DLLME in the Analysis of Pharmaceutical Entities. The TC-IL-DLLME of various isoquinoline alkaloids, namely, berberine, palmatine, jatrorrhizine, and coptisine, were investigated by Wu and co-workers.[29] The $[C_8MIM][PF_6]$ IL was shown to exhibit high selectivity for the alkaloids in the presence of various metals and organic species. Additionally, coupling this extraction method to fluorescence detection provided good method sensitivity and LODs in the subppb range. The same IL was later successfully applied in the ultrasonic-assisted IL-DLLME (UA-IL-DLLME) of various pharmaceutical entities in wastewaters[30] and the conventional IL-DLLME of antichagasic drugs in human plasma, using an organic disperser solvent.[31] A rapid IL-DLLME sampling procedure was developed in the analysis of salmeterol in dried blood spot (DBS).[32] After adding the DBS to a microcentrifugation tube, a conventional IL-DLLME approach, using methanol as a disperser solvent, was employed to extract the salmeterol. The method was proven to be effective for monitoring salmeterol in DBS samples obtained from asthmatic patients. In another example, aminoglycosides in milk samples were quantified using IL-DLLME coupled to HPLC/fluorescence.[33] Dispersion of the extraction phase, namely, the $[C_6MIM][PF_6]$ IL, was achieved by using a nonionic surfactant, Triton X-100. Additionally, derivatization of the analyte via fluorescent labeling was accomplished simultaneously during the extraction step. This method provided competitive performance compared to previous analytical procedures, such as biosensor immunoassays and solid-phase extraction (SPE) coupled to HPLC-ESI-MS/MS.

The analysis of antihypertensives in rat serum was demonstrated by conventional IL-DLLME coupled to HPLC-UV. Excellent method precision and recovery was achieved by using the $[C_4MIM][PF_6]$ IL as the extraction solvent in this study.[34] Recently, Ge and co-workers coupled IL-DLLME to microsolid-phase extraction (μ-SPE) for the determination of tricyclic antidepressants from water samples.[35] The $[C_6MIM]$-[FAP] IL was employed as an extraction phase, and methanol was used as a disperser solvent in this method. During emulsion formation by IL-DLLME, a μ-SPE device, containing zeolite imidazolate frameworks (ZIF), was exposed to the sample solution to back-extract analytes preconcentrated in the IL. Subsequently, the analytes are desorbed from the μ-SPE device and analyzed by HPLC. This technique provided high analyte extraction efficiency since the μ-SPE device is exposed to a large surface area of the IL during the extraction step. In relation to genetic engineering in biopharmaceuticals, Anderson and co-workers recently applied in situ IL-DLLME for the preconcentration of deoxyribonucleic acid (DNA).[36] After screening a number of ILs, it was determined that DNA was best-extracted using the 1-(1,2-dihydroxypropyl)-3-hexadecylimidazolium bromide ($[C_{16}POHIM][Br]$) and *N*,*N*-didecyl-*N*-methyl-D-glucaminium bromide ($[(C_{10})_2NMDG][Br]$) ILs, which provided extraction efficiencies above 97%. On the

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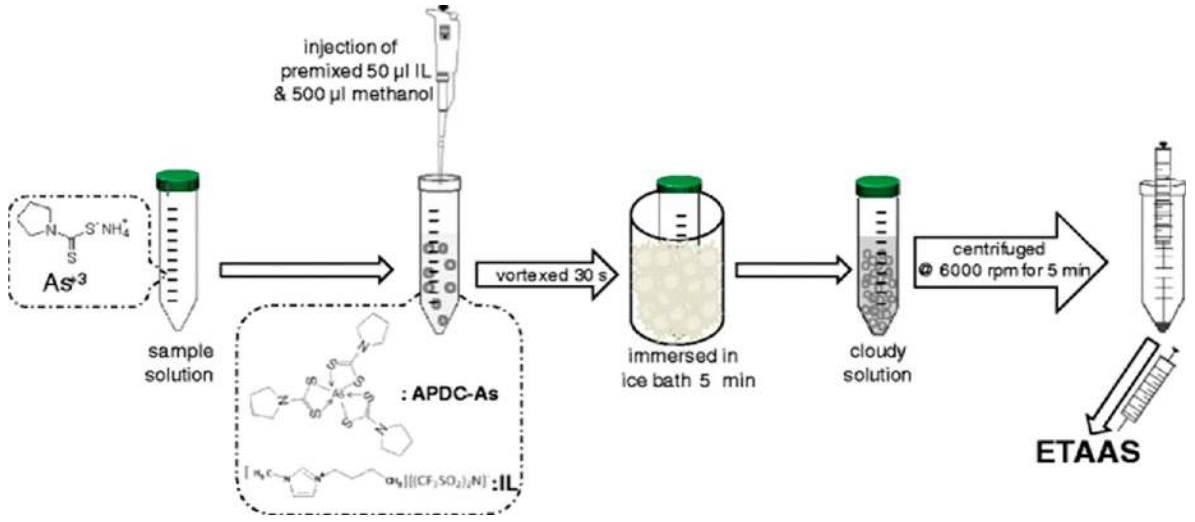

Figure 3. Schematic illustrating the extraction steps involved in the speciation of arsenite and arsenate species by IL-DLLME coupled to ETAAS. Reprinted from Rabieh, S.; Bagheri, M.; Planar-Friedrich, B. *Microchim. Acta* **2013**, *180*, 415 (ref 38), with kind permission from Springer Science and Business Media.

basis of ^{31}P nuclear magnetic resonance (NMR) spectroscopy, it was observed that the DNA and ILs interact favorably through electrostatic and $\pi-\pi$ interactions.

IL-DLLME in the Analysis of Metal Ions. As ILs are not highly suitable for extracting charged metal ions, a metal chelating agent can be injected to the sample solution during extraction to enhance the affinity of the ILs toward the metal species.[37] A schematic representation of this method for the speciation of arsenite and arsenate by electrothermal atomic absorption spectrometry (ETAAS) is shown in Figure 3.[38] Similar approaches using various IL extraction phases and metal complexing agents were successfully employed for the analysis of Cr (III) and (IV),[39,40] Au (III) and Ag (I),[41] As (III) and As (V),[38,42] Pb (II),[43,44] Cd (II),[44] Co (II),[45] and Hg (II).[46] The DLLME of Tl (III) involved utilizing tetradecyl(trihexyl)-phosphonium chloride ($[P_{66614}][Cl]$) as an ion-pairing reagent rather than an extraction phase.[47] Subsequent to forming a $[TlCl_4]$-chlorocomplex by reaction with HCl, the anionic thalium species were ion-paired with the phosphonium IL in solution and were extracted using chloroform. Compared to traditional ion-pairing reagents such as cetyltrimethylammonium bromide (CTAB), trimethyltetradecylammonium bromide (TTAB), and tetrabutylammonium bisulfate, the $[P_{66614}][Cl]$ IL contributed to higher extraction efficiency of the Tl complex. Pressure-assisted IL-DLLME was recently developed for the determination of a vanadium complex in real water samples.[48] The $[C_4MIM][PF_6]$ IL was applied as an extraction phase while pressurized argon was exploited as a dispersive medium during the extraction step. The use of pressurized argon enabled highly efficient dispersion of the selective IL phase and provided superior analytical performance compared to other preconcentration techniques.

Application of IL-DLLME in the Analysis of Organic Environmental Pollutants. Zhang and co-workers compared various IL dispersion strategies for the IL-DLLME of pyrethroid pesticides in honey/water samples.[49] The $[C_8MIM][PF_6]$ IL was dispersed in a honey/water matrix by using a methanol disperser solvent (conventional IL-DLLME), controlling the extraction temperature (TC-IL-DLLME), or applying ultrasonic treatment (UA-IL-DLLME). On the basis of the superior extraction efficiency and good recoveries obtained for all pesticides, UA-IL-DLLME was selected as the optimal IL dispersion strategy in this study. The extraction of pyrethroids was also performed by coupling UA-IL-DLLME with dispersive μ-SPE, wherein magnetic barium ferrite nanoparticles were dispersed into the sample solution to retrieve the IL after extraction.[50] Similarly, magnetic Fe_3O_4 nanoparticles were used to recover the $[C_6MIM][PF_6]$ IL in the IL-DLLME of benzoylurea insecticides.[51]

A hydrophobic IL and a hydrophilic IL was selected as the extraction solvent and disperser solvent, respectively, in the IL/IL-DLLME of triclosan and triclocarban in environmental water.[52] Following a preliminary screening of various hydrophilic and hydrophobic ILs, the $[C_8MIM][PF_6]$ IL was chosen as the extraction phase while the $[C_4MIM][BF_4]$ IL was selected as the disperser solvent. The synergistic effects of both ILs provided wide linear ranges, good method precision, and LODs in the subppb levels. A similar IL/IL-DLLME method was applied for the extraction of sulfonamides in milk powder.[53]

In situ IL-DLLME was compared with conventional IL-DLLME in the extraction of emerging contaminants in water samples.[54] Overall, the in situ IL-DLLME method demonstrated better enrichment factors for all contaminants compared to the conventional IL-DLLME technique employing the same IL. In regards to analyte selectivity, the 1-(6-amino-hexyl)-1-methylpyrrolidinium [FAP] ($[C_6NH_2MPL][FAP]$) IL used in this study exhibited higher enrichment factors in the extraction of tertiary amines compared to other FAP-based ILs. Boron species were extracted from water by in situ IL-DLLME.[55,56] The cis diol functionality, comprised within the carbohydrate moiety of the cation, enabled the selective complexation of boron to the IL. Additionally, the IL was regenerated after extraction by displacing the boron-IL complex using hydrochloric acid. In situ IL-DLLME was also successfully applied in the extraction of phenols, phenylurea pesticides, triazine herbicides, and acaricides.[57−60]

IONIC LIQUIDS IN SORPTION-BASED EXTRACTIONS

Solid-Phase Extraction. Solid-phase extraction is a technique used to extract sample analytes from liquid matrixes.

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Very simply, this sorbent-type extraction method functions by exposing liquid samples to solid supports containing suitable materials that can retain analytes of interest. Subsequently, analytes can be desorbed from the sorbent materials and further analyzed. Similar to other extraction techniques, continuous development in SPE materials revolves around improving the sorbent-to-analyte selectivity and capacity. The exploitation of ILs as sorbents in SPE was first explored by Tian and co-workers in 2009, wherein silica substrates were modified by *N*-methylimidazolium chloride for the extraction of tanshinones.[61] Since then, there have been numerous studies that investigate the potential of ILs as selective sorbents in SPE. A couple recent reviews provide additional insight into the applications and development of ILs in SPE.[62,63] The following sections highlight the recent advancements in IL-SPE and are broadly categorized on the basis of analyte classes and matrix composition.

IL-SPE of Metal Ions in Aqueous Matrixes. Within the past two years, there has been a number of investigations involving the application of ILs in SPE for the analysis of transition metals. The analysis of Pb (II) ions from various environmental water sources has been reported. Within these studies, ILs composed of varying hydrophobicity and polarities were physically adsorbed to silica substrates and applied as selective sorbent phases. The IL-modified SPE silica substrates were demonstrated to provide good recovery of Pb (II).[64−68] Two ILs composed of either imidazolium [Cl] or imidazolium [PF_6] were covalently linked to Merrifield resin and successfully applied as solid substrates for the analysis of Sc (III).[69] The IL-Merrifield resin was further impregnated with Cyanex 923 and the [C_8MIM][PF_6] IL to promote the extraction of Sc (III) via cation exchange. The extraction of trivalent Eu (III) and Am (III) was achieved by impregnating the [C_8MIM][NTf_2] IL extraction phase in Chromosorb-W.[70] Compared to an analogous Chromosorb-W resin impregnated with *n*-dodecane, the IL-impregnated resin exhibited up to 1 order of magnitude higher metal-to-resin weight distribution coefficients for Am (III). Amjadi and co-workers recently reported the application of titanium dioxide (TiO_2) nanoparticles physically coated with 1-hexadecyl-3-methylimidazolium [Br] ([C_{16}MIM][Br]) in the extraction of Ni (II).[71] The IL-modified nanoparticles provided a Ni (II) adsorption capacity of 630 mg g^{-1}, which was superior to nanoparticles immobilized with CTAB. IL-modified magnetic nanoparticles were also reported for the extraction of various heavy metals in human hair and urine.[72] The magnetic nanoparticles were exploited as a robust solid substrate that can easily be separated from the sample solution by an external magnetic field. On the other hand, the methyltrioctylammonium [Cl] IL was employed as a chelate-free extraction phase capable of providing good method sensitivity.

IL-SPE of Organic Compounds in Aqueous Matrixes. A large number of organic compounds can be extracted from aqueous samples by using IL-modified SPE materials. The 1-vinyl-3-butylimidazolium [Cl] ([VC_4IM][Cl]) IL was applied as a functional monomer to produce a molecularly imprinted polymer (MIP) that can selectively extract chlorosulfuron from water samples.[73] Rapid adsorption/desorption kinetics of chlorosulfuron, in addition to low ppb-level detection limits was obtained using the chloride-based IL as the MIP. Similarly, imidazolium [Cl] IL-modified MIPs were applied as SPE sorbents in the extraction of tanshinones from *Salvia miltiorrhiza* Bunge extract and functional drinks.[74] Analyte-to-sorbent hydrogen-bonding interactions played a crucial role in enhancing adsorption selectivity and capacity. This observation was justified by the high selectivity obtained by employing IL-modified MIPs functionalized with a carboxylic acid moiety. Magnetic microspheres covalently bounded with an imidazolium [Cl] IL was successfully applied in the extraction of chlorophenols from environmental water samples.[75] A similar approach using imidazolium [PF_6] bound magnetic nanoparticles was fruitfully employed for the extraction of PAHs in water.[76] Due to their high analyte adsorption capabilities, soft materials such as IL-modified carbon nanotubes (IL-CNTs) can also be used as extraction materials for PAHs.[77] In a similar manner, IL-CNTs were exploited in conjunction with in-line capillary electrophoresis (CE) to analyze nitrophenols at ultratrace levels.[78]

Vidal and co-workers reported the SPE of a variety of organic acids, amines, and aldehydes using silica materials modified with three different imidazolium-based ILs.[79] A side-by-side screening of the analyte-to-sorbent extraction efficiencies revealed the unique selectivity achieved by functionalizing each IL with diverse substituents. Organophosphate pesticides were successfully analyzed using methylimidazolium [PF_6] functionalized silica as the extraction phase in dispersive μ-solid-phase extraction coupled to ultra performance liquid chromatography (UPLC).[80] Compared to an analogous IL-functionalized silica comprising [Cl] anions, IL-modified silica containing the [PF_6] anion provided superior analyte interactions due its enhanced hydrophobicity. The enrichment factors of all organophosphates ranged from 74 to 111 using the proposed method. Methylimidazolium [PF_6] IL-modified gold nanoparticles (GNPs) were exploited as extraction sorbents in the preconcentration and analysis of sulfonylurea herbicides in water.[81] Superior method LODs, LOQs, and recoveries were obtained by using the IL-modified GNPs compared to analogous unmodified nanoparticles and conventional C_{18} sorbents.

IL-SPE of Organic Compounds in Biological Matrixes. There have been increasing reports on the use of IL-modified materials as selective sorbents enabling the analysis of various organic compounds in biological samples. Microspheres composed of IL-based MIPs were applied in the analysis of clenbuterol and clorprenaline from urine samples.[82] The IL-based MIP microspheres provided high selectivity for the two compounds which resulted in low chromatographic background when analyzing the biological samples. An IL-mediated MIP containing the [C_4MIM][PF_6] IL was produced by precipitation polymerization and applied in the SPE of dicofol from different vegetable samples.[83] The IL-mediated MIPs exhibited superior adsorption capacity and selectivity compared to nonmodified MIPs, C_{18}-functionalized sorbents, NH_2-functionalized sorbents, and silica sorbents. Precipitation polymerization, using the [C_4MIM][PF_6] IL as a functional monomer, was also recently applied for the analysis of four Sudan dyes in foodstuff.[84] It was observed that the [C_4MIM][PF_6] IL provided significantly better recovery of all Sudan dyes compared to commercial alumina and C_{18} sorbents. A number of ILs, each possessing different functionalities, was covalently bonded to silica particles for the extraction of oxymatrine from *Sophora flavescens* Ait.[85] Aside from the higher extraction efficiencies obtained compared to conventional sorbents, the IL-modified silica was also capable of separating matrine from oxymatrine as a result of competitive adsorption.

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Ionic Liquids and Polymeric Ionic Liquids in Solid-Phase Microextraction. Solid-phase microextraction (SPME) is a popular sorbent-type extraction technique developed by Pawliszyn in the early 1990s.[86] The preconcentration of analytes in SPME is achieved by exposing a solid substrate coated with a thin sorbent layer to a sample solution, either by headspace or direct immersion mode. Subsequently, the sorbent layer is exposed to high temperatures in the GC injector or different organic solvents in HPLC to rapidly desorb the analytes from the coating for analysis. Unlike SPE, SPME is an equilibrium-based extraction technique. In other words, extractions by SPME are nonexhaustive, thereby allowing for multiple analyses of a single sample and preventing analyte-to-sorbent breakthrough. Additionally, this technique enables the consolidation of sample preparation and sampling into one simple step which can significantly reduce the cost and increase the throughput of an analysis. Owing to their unique characteristics and tunable selectivity, ILs were first applied as SPME sorbent coatings for the analysis of BTEX in paints.[87] Another major advancement was the application of polymeric ionic liquids (PILs) as sorbent coatings, wherein the robustness and reusability of the sorbent phase was significantly enhanced without sacrificing analyte selectivity.[88] Recent reviews provide detailed overviews on the development of IL and PIL sorbent phases in SPME.[89,90] The following sections are arranged on the basis of different IL/PIL sorbent loading strategies developed within the past two years.

IL/PIL Sorbent Coatings Prepared by Physical Dip-Coating. Physical dip coating is a quick and simple strategy for loading a sorbent coating onto a SPME support. To showcase the tunable selectivity and applicability of PIL-based SPME in the analysis of important pharmaceutical impurities, Anderson and co-workers screened a number of dip-coated PIL sorbents composed of different functionalities for the analysis of genotoxic impurities (GTIs) in water.[91] PIL-based sorbent coatings composed of the [Cl] anion provided the highest selectivity for anilines while a glucaminium-based PIL containing alkyl substituents and a benzyl-functionalized PIL, poly(1-4-vinylbenzyl-3-hexadecylimidazolium) [NTf_2] (poly-([$VBC_{16}IM$][NTf_2]), exhibited the highest sensitivities for large aliphatic alkyl halides and aromatics, respectively. The selectivity of various PIL-based coatings was evaluated in coffee aromas, wherein the poly([$VBC_{16}IM$][NTf_2]) coating was highly selective toward aldehydes and acids, and the poly(1-vinyl-3-hexylimidazolium) chloride (poly([VC_6IM][Cl]) sorbent exhibited good selectivity for aromatic alcohols.[92] Recently, two vinylimidazolium-based PIL sorbent coatings containing of a cyclohexanol moiety were synthesized and successfully employed in the analysis of various volatile organic compounds in beer.[93]

PIL-based sorbent coatings can also assist in the extraction of chiral organic compounds. Anderson and co-workers successfully applied a physically coated poly([VC_6IM][NTf_2]) PIL SPME sorbent to investigate the enantiomeric purity of chiral molecules in crude synthetic batches.[94] The PIL-based sorbent coating was used to extract the chiral compounds, while GC (containing a chiral stationary phase) was used to separate and quantify each enantiomer.

IL/PIL Sorbents Prepared by Chemical Bonding to Fiber Support. Even though PIL-based sorbent coatings provided superior robustness, reusability, and stability for SPME compared to ILs, physically coated PILs lacked the mechanical stability needed for extractions in harsh matrix conditions. As a result, various PIL sorbent loading techniques were employed to overcome this drawback. Pang and co-workers developed a chemical bonding technique to immobilize 1-vinyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium [Cl] to a silica-modified steel support.[95] The covalently bound fiber demonstrated good thermal and mechanical stability in addition to providing comparable extraction performance to a commercial polydimethyl siloxane (PDMS) coating. In another study, Zhang and co-workers covalently linked 1-vinyl-3-hexadecylimidazolium [PF_6] to a substrate derivatized with γ-methacryloxypropyltrimethoxysilane via copolymerization.[96] The PIL-bound sorbent coating provided higher extraction efficiency of pyrethroids in vegetables compared to a commercial PDMS coating. Electrochemical deposition was employed to load a [C_4MIM][PF_6] IL-polyaniline composite sorbent on a steel wire.[97] This technique was then applied in the extraction of organochlorine pesticides in various water samples. Aside from providing better analytical performance compared to a commercial PDMS coating and an analgous polyaniline coating, the composite coating exhibited high robustness with thermal stabilities up to 350 °C.

Feng and co-workers covalently bound and polymerized 1-vinyl-3-octylimidazolium [PF_6] ([VC_8IM][PF_6]) to a steel substrate via in situ surface radical chain-transfer polymerization for the analysis of BTEX, phenols, and PAHs in water and soil.[98] The method provided good analytical performance and acceptable precision values after 56 extraction/desorption steps. A PIL-based SPME sorbent composed of a naphthalene sulfonate anion was also fabricated using this technique and applied for the extraction of PAHs in hair spray and nail polish.[99] The sensitivity of the novel aromatic functionalized PIL was superior compared to an anolgous PIL containing a [PF_6] anion. Surface radical chain-transfer polymerization was also employed to covalently link a PIL containing both polymerizable cations and anions, namely, [VC_8IM] *p*-styrenesulfonate, to a stainless steel substrate for the analysis of anilines, phenols, and PAEs in water samples.[100] The double-confined PIL sorbent coating exhibited better resistance to high ionic strength aqueous samples compared to a PIL containing no polymerizable anions.

Sol−gel chemistry has also been employed in multiple occasions to produce thermally stable and covalently linked PIL sorbent coatings that are applicable in both headspace and direct-immersion SPME. An organic/inorganic hybrid IL-silica composite consisting of a benzo-crown ether moiety was developed as a sorbent coating in the extraction of a variety of organic compounds.[101] Enhanced $\pi-\pi$ and hydrogen bonding interactions were achieved by tailoring this substituent to the IL-silica composite. The role of anions in IL-sol gel composites for the extraction of a variety of polar and nonpolar compounds was investigated by Shu and co-workers.[102] The 1-(3-triethoxysilyl propyl)-3-methyl imidazolium [PF_6] ([TESPMIM][PF_6]), [TESPMIM][BF_4], and [TESPMIM]-[NTf_2] IL-sol gel composites showed high resistance to various organic solvents and aqueous solutions with extreme pH conditions. Additionally, the [BF_4], [PF_6], and [NTf_2]-based IL composites were thermally stable up to 285, 300, and 454 °C, respectively. An ultrathermally stable IL-sol gel composite, namely, 1-allyl-3-methylimidazolium [NTf_2]−hydroxy-terminated silicone oil ([AMIM][NTf_2]−OH-TSO), was developed for the extraction of phthalate esters (PAEs) in agricultural plastic films.[103] The high thermal stability of this IL-sol gel composite enabled a thermal desorption temperature of 360 °C

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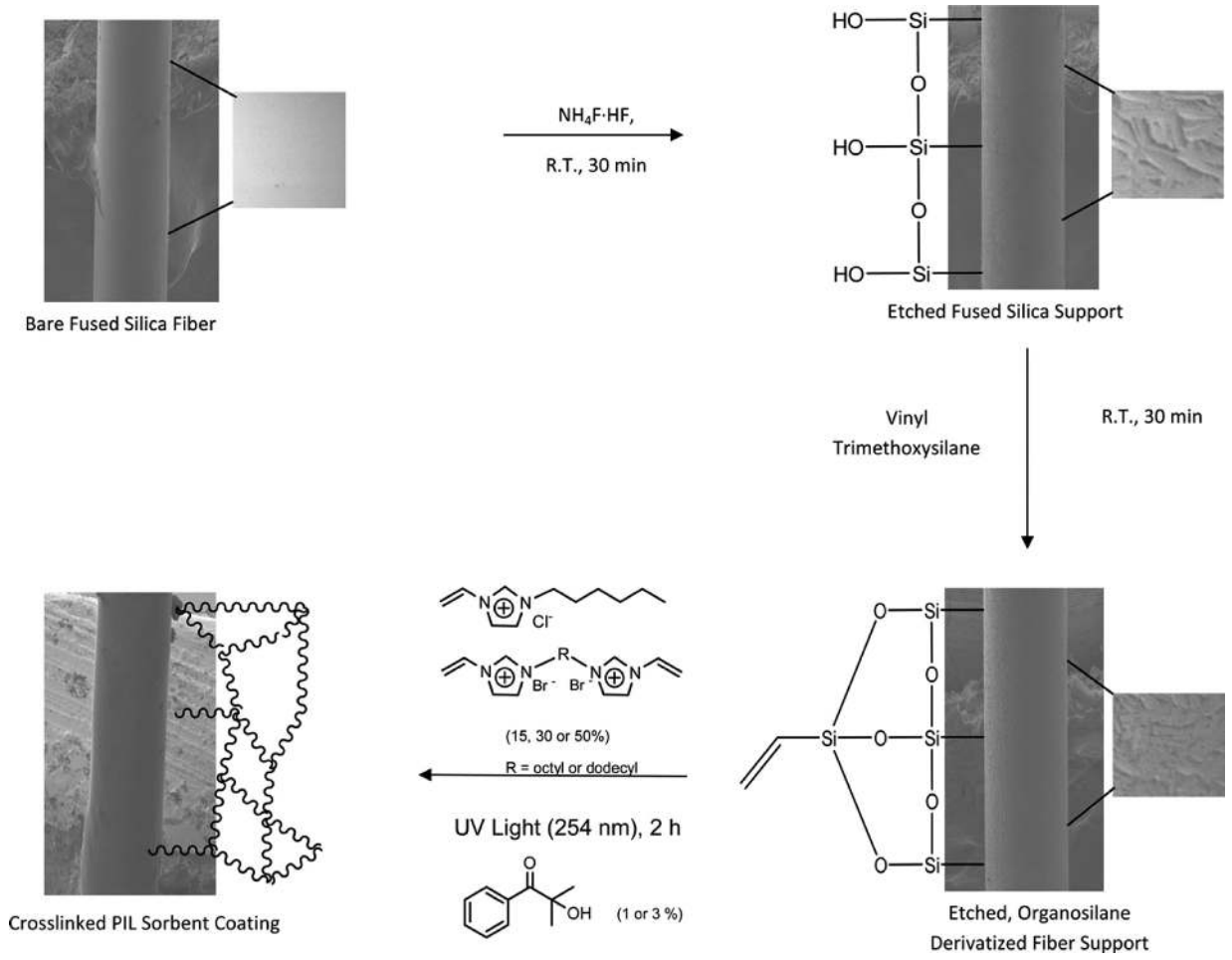

Figure 4. Schematic showing the fabrication procedure of polar cross-linked PIL-based sorbent coatings by "on-fiber" photoinitiated polymerization. Reproduced from ref 108. Copyright 2012 American Chemical Society.

(8 min desorption time), which increased method precision and mitigated analyte carryover effects. The same sorbent loading methodology was recently applied in the analysis organophosphate esters in water samples by Gao and co-workers.[104] ILs not only can be applied as a selective copolymeric sorbent in sol–gel chemistry but also can be used to mediate the production of molecular sol–gel sorbents in hollow fiber SPME (HF-SPME), as demonstrated by Ebrahimi and co-workers.[105,106]

Cross-Linked Copolymeric PIL-Based SPME Sorbent Coatings. IL/PIL composite materials have been shown to provide significant improvements in thermal stability, resistance to matrix composition, and overall robustness for a SPME fiber. Nevertheless, using these materials may alter the unique selectivity gained by using pure IL/PIL sorbent phases. Cross-linked PIL sorbent coatings have recently been developed to address this potential drawback. Feng and co-workers reported the exploitation of covalently bound polar cross-linked PIL sorbent coatings for the headspace extraction of polar compounds.[107] An IL monomer and IL cross-linker composed of bromide anions were copolymerized in situ by AIBN-initiated free radical polymerization while covalent bonded to a derivatized stainless steel support. The cross-linked PIL coating exhibited superior thermal stability and longer fiber lifetimes compared to noncross-linked PIL fibers. Anderson and co-workers further expanded the development and application of polar cross-linked PILs in the analysis of multiple organic compounds from water samples using both headspace and direct immersion SPME.[108] Using UV-initiated photopolymerization, two IL cross-linkers, 1,8-di(3-vinylimidazolium) octane dibromide ($[(VIM)_2C_8]$ 2[Br]) or 1,12-di(3-vinylimidazolium) dodecane dibromide ($[(VIM)_2C_{12}]$ 2[Br]), were copolymerized with an IL monomer, $[VC_6IM][Cl]$, to produce polar cross-linked PIL-based sorbent coatings. A schematic representing the fabrication of the cross-linked copolymeric PIL coating is shown in Figure 4. This coating approach eliminated the need for organic dispersive solvents and increased production throughput since neat IL monomer and cross-linkers were copolymerized on-fiber, while also being chemically linked to an etched and derivatized silica support. The cross-linked PIL-based sorbent coatings also possessed high robustness and fiber lifetimes, even when applied for direct immersion experiments in complex water samples. Recently, the extraction mechanism of both cross-linked and noncross-linked PIL coatings was also investigated.[109] The linearity, sensitivity, and linear range obtained for a model analyte, 1-octanol, were largely unaffected when a high concentration of an interfering species, naphthalene, was added to the sample. This indicated that noncompetitive analyte partitioning was the primary mechanism of extraction for all PIL coatings studied. In a subsequent study, benzyl functionality was imparted to a dicationic IL cross-linker and applied in the analysis of PCBs in milk and seawater.[110] The cross-linker exhibited higher method sensitivity for most polychlorinated biphenyls (PCBs)

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compared to a nonfunctionalized IL counterpart and a PDMS coating, which may be due to enhanced $\pi-\pi$ interactions.

GAS CHROMATOGRAPHY

Over the past decades, gas chromatography (GC) has become the most popular technique for the separation, detection, and identification of volatile and semivolatile analytes in complex samples. Two paramount requirements to obtain separation of analytes involve enhancing the migration rate differences between a pair of chromatographic bands and decreasing the effect of zone spreading.[111,112] Even though there have been major instrumental advances, zone spreading can only be diminished to a certain extent. Hence, in order to effectively enhance peak capacity, the development of new stationary phases for conventional and multidimensional gas chromatographic (MDGC) separations has been extensively reported. ILs have drawn considerable attention as GC stationary phases, due to their unique and tunable selectivity and thermal stability.[113] Unlike conventional PDMS and poly(ethylene glycol) (PEG) stationary phases, ILs are capable of undergoing multiple solvation interactions, thereby imparting unique selectivities toward a wide range of analytes with different functional groups.[114] As a result, the possibilities for engineering new ILs for specific applications are endless.[1] While this section is largely confined to the latest contributions to the field, several excellent reviews describing the most important developments and applications over the past decade are available for the interested reader.[115−123] A broad compendium of studies describing the chromatographic selectivity of several ILs and PILs and their application in GC and MDGC has also been reported.[117,124]

The main limitations of early molten salt-based stationary phases was based on their limited thermal stability, narrow liquid range, and poor chromatographic efficiency.[113] The operating temperatures for most of the ammonium-based molten salts were between 120 and 170 °C with selected salts capable of reaching 200 °C.[124] Hence, over the past decade, ILs have been rigorously engineered to possess different physicochemical properties from the initial molten salts.

The ILs employed today as stationary phases in GC consists mainly of cations such as phosphonium, imidazolium, pyridinium, and pyrrolidinium paired with several inorganic and, more frequently, organic anions. In addition, several monocationic and polycationic ILs, as well as PILs, have been exploited in GC and MDGC. Furthermore, these ILs have been used to disperse different selectors to modify the overall selectivity of stationary phases.

The solvation parameter model, proposed by Abraham and co-workers, has been used to evaluate the strength of the stationary-phase solvation capabilities, namely, the ability of the stationary phase to interact with the analytes through $\pi-\pi$ or $n-\pi$ interactions (e), polarizability/dipolarity (s), hydrogen bond basicity and acidity of the stationary phase (a and b, respectively), and dispersion forces (l).[125] The system constants are determined by the multiple linear regression analysis of the numerous solute descriptors and the retention factor of the probes. For convenience, the system constants of all IL stationary phases discussed within this Review are reported in Table 1.

Phosphonium, Sulfonium, and Guanidinium Ionic Liquid Stationary Phases. Phosphonium-based ILs typically exhibit superior chemical and/or thermal stability compared to those ILs possessing nitrogen-containing cations.[124] A number of studies which display the applications of phosphonium-based ILs as GC stationary phases has been published recently.[126,127] An interesting application of phosphonium-based ILs is the analysis of the residual water in high purity organic solvents. Two of the main challenges that stationary phases face are: (1) water should not degrade or alter the stationary phase and (2) the chromatographic peaks should show good separation efficiency and symmetry.[127,128] Thus, three ILs, namely, trigonal tripropylphosphonium triflate ([TTP][TfO]), bis(3-hydroxyalkylimidazolium)-PEG [TfO], and bis(2,3-dimethylimidazolium)-PEG [TfO], were designed and evaluated.[127] The analytical performance of these columns was compared to that of a commercially available PEG stationary phase. The phosphonium-based IL, [TTP][TfO] IL, provided the best results and displayed unique selectivity toward water. This IL also provided increased resolution, allowing the use of internal standards and enabling quantitation of trace amounts of water in several organic solvents.[127−129] Sulfonium- and guanidinium-based ILs were evaluated as stationary phases, and the retention behavior of various molecules were examined.[126,130−132] The guanidinium-based ILs were shown to operate up to 250 °C without significant loss in efficiency and separation of probe analytes;[132] the sulfonium-based IL, however, exhibited poor thermal stability.[126]

Morpholinium, Piperidinium, Pyrrolidinium, Pyridinium, and Imidazolium Ionic Liquid Stationary Phases. A series of morpholinium-, piperidinium-, pyrrolidinium-, and pyridinium-based ILs have been evaluated as GC stationary phases and characterized by the Abraham parameter solvation model.[114,126,133] In general, the hydrogen bond acidity of nonfunctionalized ILs largely depends on the nature of the cation, which can be regulated by the anion.[114,134,135] Recently, the hydrogen bond basicity of [C_4MPL] paired with thiocyanate, tricyanomethide, tetracyanoborate, and [FAP] anions has been reported.[114] Interestingly, ILs paired with cyano-containing anions exhibited enhanced dipolarity and hydrogen bond basicity, compared to the FAP-based ILs. These solvation characteristics were enhanced with an increase in the number of cyano-moieties.

Twu et al. observed superior hydrogen bond basicity for the *N*-hexyl-4-(*N*′,*N*′-dimethylamino)pyridinium [FAP] IL compared to *N*-hexyl-pyridinium [FAP].[114] This may be due to the enhanced interaction between the tertiary amine moiety of the IL and the hydrogen bond acidic solute. Similarly, introducing hydroxyl functionality to the IL can lead to a 2-fold increase in the hydrogen bond acidity of *N*-hydroxypropylpyridinium [FAP] compared to *N*-hexyl-pyrridinium [FAP] IL.

The solvation properties of a number of FAP-based ILs, namely, 1-methoxyethyl-3-methylimidazolium [FAP], methoxyethyl-dimethyl-ethylammonium [FAP], 1-methoxyethyl-1-methylmorpholinium [FAP], 1-methoxyethyl-1-methyl-piperidinium [FAP], and 1-methoxypropyl-1-methylpiperidinium [FAP], were also evaluated.[114] The dispersive interaction capability of these ILs did not appear to be significantly affected by the cation type. Additionally, the hydrogen bond acidities and basicities of ILs containing imidazolium, ammonium, and morpholinium cations were similar to one another, with the exception of the 1-methoxyethyl-1-methylpiperidinium [FAP] IL.

Several imidazolium-based ILs, with thermal stabilities ranging from 280 to 320 °C, have been previously studied.[114,126,136] One advantage of imidazolium-based ILs over pyridinium- and pyrrolidinium-based ILs is that the latter

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Table 1. Structure, Physicochemical, and Chromatographic Properties of Selected Ionic Liquids[a]

ionic liquid	maximum temperature (°C)	system/phase constants: solvation parameter model: *e*	*s*	*a*	*b*	*l*	temperature (°C)	McReynolds constants	application	reference
Phosphonium-Based ILs										
bis(3-hydroxyalkylimidazolium)-poly(ethylene glycol) [TfO]	–	–	–	–	–	–	–	–		
trigonal tripropylphosphonium [TfO]	–	–	–	–	–	–	–	–	trace analysis of water	127−129
bis(2,3-dimethylimidazolium)-poly(ethylene glycol) [TfO]	–	–	–	–	–	–	–	–		
tetradecyltrihexylphosphonium bis(2,4,4-trimethylpentyl)phosphinate	300	–	–	–	–	–	–	–	analysis of *n*-alkanes, esters, and alcohols	126
Imidazolium-Based ILs										
poly(1-(3-butenyl)-3-(2-cyclohexanol)-imidazolium) [Br]		0.11	1.18	3.11	1.34	0.55	50			
	–	−0.10	0.70	3.00	0.17	0.46	70	–		
		−0.28	0.42	1.67	0.08	0.42	100			
poly(1-(3-butenyl)-3-(2-cyclohexanol)-imidazolium) [NTf_2]		0.21	1.55	1.66	1.78	0.53	50			
	250	0.08	1.45	1.33	1.64	0.51	70	–		
		−0.03	1.21	0.99	1.42	0.50	100			
poly(1-(3-butenyl)-3-(2-cyclohexanol)-imidazolium) [SCN]		0.24	1.40	2.62	0.90	0.57	50			
	200	0.13	1.37	2.41	0.77	0.53	70	–		
		0.11	0.90	2.11	0.43	0.38	100			
poly(1-(3-butenyl)-3-(2-cyclohexanol)-imidazolium) [BF_4]		−0.13	1.37	3.70	0.90	0.69	50			
	220	−0.45	1.19	3.34	0.54	0.58	70	–	analysis of *n*-alkanes, xylenes, ketones, alcohols, amines, and esters	140
		−0.54	1.14	1.95	0.20	0.27	100			
poly(1-allyl-3-(2-cyclohexanol)-imidazolium) [NTf_2]		−0.18	1.24	1.27	1.39	0.74	50			
	250	−0.28	1.22	1.20	0.95	0.63	70	–		
		−0.31	1.07	1.10	0.50	0.56	100			
poly(1-(2-cyclohexanol)-3-(1-octenyl)-imidazolium) [NTf_2]		0.09	1.57	2.14	1.12	0.62	50			
	320	−0.14	1.56	2.06	1.00	0.58	70	–		
		−0.23	1.49	1.39	0.84	0.55	100			
poly(1-(2-cyclohexanol)-3-(4-vinylbenzyl)-imidazolium) [NTf_2]		0.11	1.48	1.41	1.58	0.64	50			
	270	−0.21	0.66	1.02	0.89	0.56	70	–		
		−0.23	0.32	0.99	0.73	0.50	100			
1-(1,2-dimethyl)-3-propylimidazolium [NTf_2]	320	–	–	–	–	–	–	–		
1-(1,2-dimethyl)-3-propylimidazolium [NTf_2]	320	–	–	–	–	–	–	–		
1-butyl-1-methylpyrrolidinium [NTf_2]	300	–	–	–	–	–	–	–	analysis of *n*-alkanes, esters, and alcohols	126
3-methyl-1-propylpyridinium [NTf_2]	300	–	–	–	–	–	–	–		
1-butyl-3-methylimidazolium [BF_4]	280	–	–	–	–	–	–	–		
1,2-dimethyl-3-propylimidazolium [NTf_2]	250[b]	–	–	–	–	–	–	–		
1,2-dimethyl-3-propylimidazolium tris(trifluoromethylsulfonyl) methide	250[b]	0.08	1.59	1.15	0.15	0.36	120	–	analysis of *n*-alkanes, alcohols, esters, phenols, and organic acids	133
1,2-dimethyl-3-(3-cyanopropyl)imidazolium [NTf_2]	250[b]	0.25	1.81	1.25	0.30	0.35	120	–		
1,2-dimethyl-3-(3-hydroxypropyl)imidazolium [NTf_2]	250[b]	0.21	1.50	1.25	0.66	0.34	120	–		

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Table 1. continued

ionic liquid	maximum temperature (°C)	system/phase constants: solvation parameter model: *e*	*s*	*a*	*b*	*l*	temperature (°C)	McReynolds constants	application	reference
Imidazolium-Based ILs										
1-methoxyethyl-3-methylimidazolium [FAP]		0.05	1.96	1.09	0.89	0.53	50			
	–	0.06	1.78	0.86	0.73	0.43	80	–		
		0.06	1.61	0.68	0.65	0.37	110		comparison of several IL-based GC columns	114
1-ethyl-3-methylimidazolium [FAP]		0.17	1.91	0.89	0.89	0.51	50			
	–	0.15	1.74	0.70	0.72	0.42	80	–		
		0.11	1.74	0.64	0.66	0.41	110			
1,9-bis(2,3-dimethylimidazolium)nonane [NTf_2]	250[b]	0.37	1.62	0.00	1.13	0.14	120	–	analysis of *n*-alkanes, alcohols, esters, phenols, and organic acids	133
1,9-bis[3-(3-cyanopropyl)-2-methylimidazolium]nonane [NTf_2]	250[b]	0.35	1.57	0.00	1.22	0.29	120	–		
3,3′,3″,3‴,3⁗,3⁗′-[benzene-1,2,3,4,5,6-hexaylhexakis(methylene)]hexakis[1-(cis-2-hydroxycyclopentyl)-1H-imidazol-3-ium [NTf_2]	–	−0.31	1.15	0.91	1.88	0.41	70			
		−0.16	1.10	0.5	1.28	0.38	100	–		
3,3′,3″,3‴,3⁗,3⁗′-[benzene-1,2,3,4,5,6-hexaylhexakis(methylene)]hexakis[1-(trans-2-hydroxycyclohexyl)-1*H*-imidazol-3-ium [TfO]	–	1.05	1.78	1.71	2.36	0.41	70		analysis of alcohols and aromatic compounds	137
		0.84	0.56	1.15	1.01	0.34	100	–		
3,3′,3″,3‴,3⁗,3⁗′-[benzene-1,2,3,4,5,6-hexaylhexakis(methylene)]hexakis[1-(trans-2-hydroxycyclopentyl)-1*H*-imidazol-3-ium [NTf_2]	–	−0.61	1.31	2.45	1.06	0.51	70			
		−0.05	0.29	2.13	0.59	0.22	100	–		
Pyridinium-Based ILs										
2-methyl-1-propylpyridinium [NTf_2]	250[b]	0.06	1.62	1.19	0.17	0.31	120	–		
3-methyl-1-propylpyridinium [NTf_2]	250[b]	0.07	1.6	1.15	0.15	0.31	120	–		
4-methyl-1-propylpyridinium [NTf_2]	250[b]	0.10	1.57	1.13	0.10	0.32	120	–		
2,6-dimethyl-1-propylpyridinium [NTf_2]	250[b]	0.18	1.70	1.35	0.30	0.37	120	–	analysis of *n*-alkanes, alcohols, esters, phenols, and organic acids	133
3,5-dimethyl-1-propylpyridinium [NTf_2]	250[b]	0.16	1.55	1.11	0.28	0.37	120	–		
1-propyl-2,4,6-trimethylpyridinium [NTf_2]	250[b]	0.28	1.61	1.40	0.59	0.42	120	–		
1,9-bis(4-methylpyridinium)nonane [NTf_2]	250[b]	0.35	1.66	1.25	0.11	0.35	120	–		
1,9-bis(2-methylpyridinium)nonane [NTf_2]	250[b]	0.33	1.74	1.29	0.13	0.35	120	–		
N-hexylpyridinium [FAP]		0.12	1.71	0.73	0.82	0.60	50			
	–	0.24	1.47	0.55	0.79	0.50	80	–		
		0.21	1.39	0.47	0.66	0.42	110			
N-hexyl-4-(*N*′,*N*′-dimethylamino)pyridinium [FAP]		0.24	1.61	0.86	0.57	0.63	50			
	–	0.30	1.44	0.65	0.50	0.54	80	–	comparison of several IL-based GC columns	114
		0.26	1.32	0.50	0.41	0.46	110			
N-hydroxypropylpyridinium [FAP]		0.28	1.76	1.01	1.78	0.50	50			
	–	0.23	1.71	0.84	1.44	0.43	80	–		
		0.13	1.66	0.66	1.20	0.37	110			

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Table 1. continued

ionic liquid	maximum temperature (°C)	system/phase constants: solvation parameter model: *e*	*s*	*a*	*b*	*l*	temperature (°C)	McReynolds constants	application	reference
Ammonium-Based ILs										
methoxyethyl-dimethyl-ethylammonium [FAP]		0.09	1.97	0.91	0.85	0.53	50			
	–	0.13	1.68	0.67	0.76	0.44	80	–		
		0.10	1.62	0.62	0.64	0.37	110		comparison of several IL-based GC columns	114
hexyl-trimethylammonium [NTf_2]		0.00	1.90	2.00	0.45	0.59	50			
	–	0.00	1.73	1.68	0.37	0.48	80	–		
		0.00	1.66	1.49	0.31	0.41	110			
Piperidinium-Based ILs										
1-methoxypropyl-1-methylpiperidinium [FAP]		0.28	1.77	1.25	0.73	0.53	50			
	–	0.23	1.66	0.93	0.67	0.45	80	–		
		0.25	1.46	0.74	0.59	0.37	110		comparison of several IL-based GC columns	114
1-methoxyethyl-1-methylpiperidinium [FAP]		0.16	1.82	0.95	0.58	0.56	50			
	–	0.16	1.65	0.74	0.46	0.46	80	–		
		0.17	1.52	0.58	0.43	0.40	110			
Pyrrolidinium-Based ILs										
1-butyl-1-methylpyrrolidinium [SCN]		0.44	2.21	4.40	0.15	0.54	50			
	–	0.41	2.14	4.10	0.00	0.42	80	–		
		0.51	1.98	3.60	0.10	0.31	110			
1-butyl-1-methylpyrrolidinium tricyanomethide		0.18	2.07	3.17	0.16	0.56	50			
	–	0.28	1.99	2.81	0.24	0.47	80	–		
		0.28	1.82	2.43	0.20	0.39	110			
1-butyl-1-methylpyrrolidinium tetracyanoborate		0.11	1.97	2.25	0.29	0.57	50			
	–	0.22	1.76	1.95	0.34	0.47	80	–	comparison of several IL-based GC columns	114
		0.21	1.67	1.76	0.26	0.40	110			
1-butyl-1-methylpyrrolidinium bis[oxalate(2-)]borate		0.11	2.46	2.45	0.16	0.55	50			
	–	0.16	2.16	2.04	0.18	0.45	80	–		
		0.17	1.97	1.80	0.14	0.38	110			
1-propyl-1-methylpiperidinium [NTf_2]		0.28	1.87	2.11	0.35	0.55	50			
	–	0.30	1.77	1.86	0.26	0.45	80	–		
		0.27	1.63	1.60	0.21	0.39	110			
Guanidinium-Based ILs										
N,N,N′,N′-tetramethyl-*N″,N″*-dioctylguanidinium [NTf_2]	250[b]	−0.23	1.81	1.81	0.00	0.67	70	*X′* = 283,*Y′* = 395, *Z′* = 367, *U′* = 506, *S′* = 397 (120 °C)	separation of alcohols and fatty acid methyl esters	132
		−0.18	1.66	1.54	0.00	0.59	100			
N,N,N′,N′-tetraoctyl-*N″,N″*-dimethylguanidinium [NTf_2]	250[b]	−0.18	1.16	1.50	0.42	0.66	70	*X′* = 209, *Y′* = 302, *Z′* = 275, *U′* = 354, *S′* = 327 (120 °C)		
		−0.09	0.98	1.09	0.35	0.55	100			
Sulfonium-Based ILs										
triethylsulfonium [NTf_2]	200	–	–	–	–	–	–	–	analysis of *n*-alkanes, esters, and alcohols	126
Morpholinium-Based ILs										
1-methoxyethyl-1-methylmorpholinium [FAP]	–	0.10	2.05	1.02	0.86	0.51	50	–	comparison of several IL-based GC columns	114
		0.10	1.87	0.81	0.70	0.42	80			

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Table 1. continued

ionic liquid	maximum temperature (°C)	system/phase constants: solvation parameter model: e	s	a	b	l	temperature (°C)	McReynolds constants	application	reference
Morpholinium-Based ILs										
		0.10	1.71	0.68	0.63	0.35	110			

[a]Abbreviations: [NTf_2], bis[(trifluoromethyl)sulfonyl]imide; [Br], bromide; [PF_6], hexafluorophosphate; [BF_4], tetrafluoroborate; [SCN], thiocyanate; [TfO], triflate; [FAP], tris(pentafluoroethyl)-trifluorophate. [b]No bleed profile was reported.

ILs normally exhibit higher melting points compared to imidazolium-based ILs, thereby decreasing their usefulness as GC stationary phases.[124] It was observed that introducing ether functionality to the IL increased the hydrogen bond basicity of the IL.[114]

Polycationic Ionic Liquid Stationary Phases. One way to increase the liquid range and thermal stability of ILs is by exploiting polycationic ILs.[124] González-Álvarez and co-workers reported the synthesis of seven hexacationic imidazolium-based ILs,[137] most of which exhibited thermal stabilities ranging from 260 to 365 °C. The thermal stability of these polycationic ILs was superior to analogous monocationic ILs and commercially available PEG-based stationary phases.[136,137] In addition, these hexacationic ILs possess similar thermal stabilities compared to other families of dicationic and tricationic ILs.[138,139] As a result, these stationary phases may be an interesting alternative for the characterization of complex samples such as those currently found in aroma and fragrance, metabolomics, lipidomics, and petrochemical derivatives.

Polymeric Ionic Liquid Stationary Phases. Unfortunately, a number of IL-based stationary phases may have a tendency to agglomerate or pool at high temperatures. Consequently, maintaining the homogeneity of the IL coated film throughout the capillary can often be problematic.[124] PIL-based stationary phases have been developed in an effort to circumvent this limitation. Recently, a series of imidazolium-based PILs has been explored as GC stationary phases.[140] These stationary phases exhibited thermal stabilities ranging from 240 to 300 °C. They also displayed high selectivities toward polar analytes, allowing for the separation of fragrances, alcohols, and amines. Good chromatographic resolution of xylene isomers was achieved by employing the poly[3-allyl-1-(2-cyclohexanol)-imidazolium] [NTf_2] as a PIL-based stationary phase.[141,142] Interestingly, poly([VC_8IM]) paired with [NTf_2] and bis[(pentafluoroethyl)sulfonyl]imide also displayed unique selectivities for xylene isomers.

Hybrid Ionic Liquid-Based Stationary Phases. Sun and co-workers and Wei and co-workers reported separately the functionalization of polysiloxane with IL-based moieties.[143,144] Although the authors employed different synthetic routes, they successfully modified the selectivity of these hybrid materials compared to conventional PDMS stationary phases. The reported thermal stabilities for the hybrid [VC_6IM] stationary phase paired with [NTf_2] and [PF_6] anions were approximately 225 and 250 °C, respectively.[144] Methylimidazolium-based hybrids paired with [Cl] and [NTf_2] resulted in phases exhibiting thermal stabilities ranging from 220 to 380 °C, respectively.[143] The latter were successfully used for the resolution of fatty acid methyl esters (FAME) and several PCBs.

ILs have also been applied as a medium for the dispersion of macromolecules, such as cyclodextrins,[145] calixarenes,[146] and CNTs,[147] to yield stationary phases with unique selectivities and thermal stabilities. For chiral separations, the stationary phases consists of chiral ILs or dispersions of the chiral selectors in the bulk IL.[145,148] Recently, Zhao and co-workers reported the dispersion of CNTs in a chiral IL as a GC stationary phase.[147] Introducing CNTs to the bulk of the IL improved the resolution of enantiomers when compared to a neat IL phase.

Applications of Commercial Ionic Liquid Stationary Phases in 1D-GC and MDGC. Multidimensional separation techniques are powerful methods in which two or more

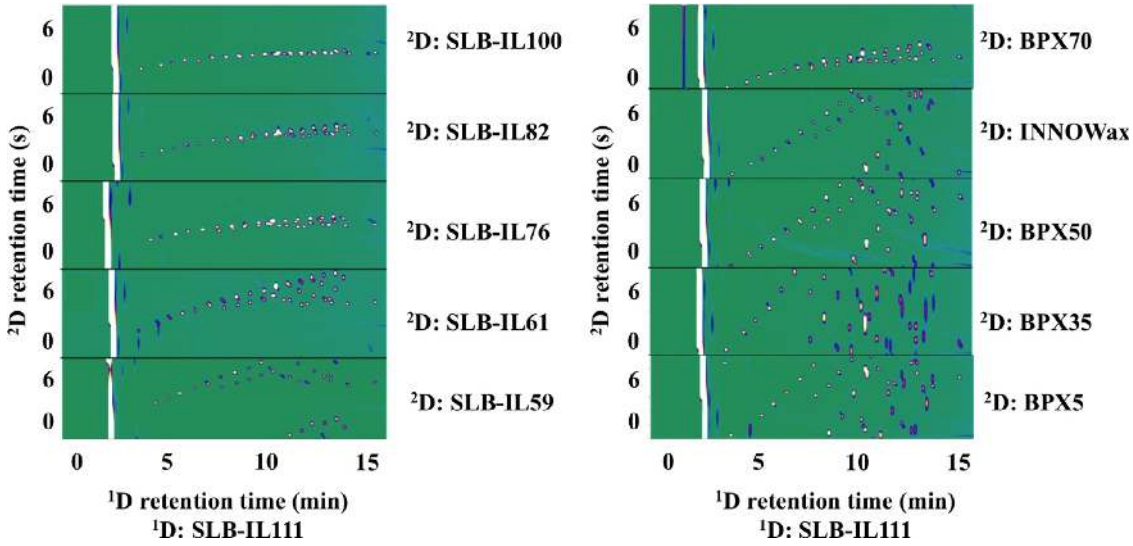

Figure 5. Chromatograms of a fatty acid methyl esters mixture obtained on several combinations of capillary columns by GC×GC-FID. BPX5: 5% phenyl polysilphenylene-siloxane; BPX35: 35% phenyl polysilphenylene-siloxane; BPX50: 50% phenyl polysilphenylene-siloxane; BPX70: 70% cyanopropyl polysilphenylene-siloxane; INNOWax: poly(ethylene glycol); SLB-IL59: 1,12-di(tripropylphosphonium)dodecane [NTf_2]; SLB-IL61: mixture of 1,12-di(tripropylphosphonium)dodecane paired with [NTf_2] and trifluoromethylsulfonate; SLB-IL76: tri-(tripropylphosphoniumhexanamido)triethylamine [NTf_2]; SLB-IL82: 1,12-di(2,3-dimethylimidazolium)dodecane [NTf_2]; SLB-IL100: poly[1,9-di(3-vinylimidazolium)nonane] [NTf_2]; SLB-IL111: 1,5-di(2,3-dimethylimidazolium)pentane [NTf_2]. Reprinted from Nosheen, A.; Mitrevski, B.; Bano, A.; Marriott, P. J. *J. Chromatogr., A* **2013**, *1312*, 118 (ref 169). Copyright 2013, with permission from Elsevier.

independent separative steps are linked together for separation.[149] A typical MDGC separation employs two or more gas chromatographic separations in a sequential fashion.[150] To achieve a significant increment in resolution power, the stationary phases employed often possess different selectivities. Additionally, separation produced in each stage/dimension is maintained, at least in part, so that the resolving power of the composite separation exceeds that of the individual stages.[150] Recently, Marriott and co-workers described the fundamentals of heart-cutting multidimensional gas chromatography,[151] while Seeley and co-workers reported the advances of comprehensive two-dimensional gas chromatography (GC×GC).[150]

At the current time, commercially available IL-based GC stationary phases are commonly rated by their polarity number, determined by the normalized sum of the Kovats retention indices, with respect to the polarity number of poly[1,9-di(3-vinylimidazolium)nonane] [NTf_2] (SLB-IL100).[152,153] A number of commercially available ILs, namely 1,12-di-(tripropylphosphonium)dodecane [NTf_2] (SLB-IL59), 1,12-di(tripropylphosphonium)dodecane [NTF_2] (SLB-IL60), a mixture of 1,12-di(tripropylphosphonium)dodecane paired with [NTf_2] and trifluoromethylsulfonate (SLB-IL61), tri-(tripropylphosphoniumhexanamido)triethylamine [NTf_2] (SLB-IL76), 1,12-di(2,3-dimethylimidazolium)dodecane [NTf_2] (SLB-IL82), SLB-IL100, 1,5-di(2,3-dimethyllimidazolium)pentane [NTf_2] (SLB-IL111), have been used for the analysis of essential oils,[152−154] biological fluids,[155] fuel and petrochemical samples,[156−159] environmental contaminants,[160−163] lipids,[164−169] and other applications.[170]

Mondello and co-workers compared the thermal stability of SLB-IL59 with respect to a standard SupelcoWax 10 [100% PEG] stationary phase by monitoring the first dimension bleed profile by a GC×GC/quadropole mass spectrometry (QMS) system fitted with a loop-modulator.[152] At 280 and 300 °C, the signal intensities from the 1D bleed profile of the IL-based stationary phase were consistently 2 orders of magnitude lower. Subsequently, this stationary phase was successfully employed in the analysis of lemon essential oil by GC/QMS. Compared to SLB-5 [5% phenyl poly(silphenylene-siloxane)] and SupelcoWax 10 phases, the SLB-IL59 significantly improved the resolution of several critical pairs of analytes, namely, neryl acetate/geranial and limonene/β-phellandrene/1,8-cineole, *trans*-sabinene hydrate/linalool and neral/carvone. A preparative three-dimensional heart-cutting gas chromatographic system for the isolation and characterization of a novel compound found in wampee essential oil was recently reported.[154] Separation was performed by employing a combination of Equity-5 [poly(5% diphenyl/95% dimethylsiloxane)], SupelcoWax 10, and SLB-IL59 in the ^{1}D, ^{2}D, and ^{3}D, respectively.

Cagliero and co-workers reported a systematic evaluation of several IL stationary phases, namely, SLB-IL59, SLB-IL60, SLB-IL61, SLB-IL76, SLB-IL82, SLB-IL100, and SLB-IL111, for the analysis of flavor, fragrances, and essential oils by GC.[153] The overall chromatographic performance of the SLB-IL76 stationary phase was the lowest among the evaluated phases, which was in agreement with previous results.[162] Both SLB-IL100 and SLB-IL111 stationary phases displayed the lowest retention factors for nonpolar solutes, such as monoterpene hydrocarbons. Using the SLB-IL61 followed by the SLB-IL60 stationary phase seemed to provide the best chromatographic performance in the analysis of allergens by GC-FID, comparable to the performance of the 14% cyanopropylphenyl/86% dimethylpolysiloxane (OV-1701) phase. The SLB-IL59, SLB-IL60, and SLB-IL61 were the most promising stationary phases in the 1D-GC analysis of essential oils. On the other hand, SLB-IL 60 was the most effective stationary phase for the analysis of low-volatility analytes, such as pesticides.[153] SLB-IL61 and SLB-IL111 were also successfully applied as stationary phases for the analysis of 136 tetra- to octa-polychlorinated dibenzo-*p*-dioxins and dibenzofurans by GC/MS.[162] Additionally, the separation of 196 polychlorinated biphenyl congeners

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by GC×GC-TOFMS employing SLB-IL59 in the second dimension was also reported.[160]

Augusto and co-workers successfully established a source-independent method for the quantitation of biodiesel in mineral diesel blends by GC×GC-FID employing SLB-IL61 in the ^{2}D.[158] Unique selectivities toward FAMEs in mineral diesel were obtained using this technique. SLB-IL82, SLB-IL100, and SLB-IL111 stationary phases were employed in the separation of FAME in complex matrices, such as marine algae and milk fat, by 1D-GC and GC×GC.[164,166,167] Marriott and co-workers examined simultaneously the chromatographic efficiency of two IL-based stationary phases in GC×GC for the analysis of FAMEs from Safflower oil.[169] The combination of SLB-IL111 in the ^{1}D and SLB-IL59 in the ^{2}D provided excellent separation of the FAMEs, when compared to several other stationary phases, as illustrated in Figure 5. A hybrid MDGC system was developed for the analysis of FAMEs in fish oil and milk fat.[171] This integrated instrument can operate as either a heart-cut MDGC-FID or a GC×GC-FID. The nitroterephthalic acid-modified PEG (DB-FFAP) stationary phase and three IL-based stationary phases, namely, SLB-IL76, SLB-IL100, and SLB-IL111, were evaluated in heart-cut MDGC analysis. Enhanced resolution of the C18 FAMEs, including their monounsaturated geometric isomers, was obtained by the IL phases while the same isomers were unresolved by a DB-FFAP phase. The peak capacity for the ^{2}D IL phases was 34, 41, and 42 for SLB-IL76, 100, and 111, respectively. These capacities were superior to the DB-FFAP stationary phase, which showed a peak capacity of 30.

A series of fundamental studies evaluating the retention behavior of several ILs toward specific groups of analytes, such as alkyl phosphates, and FAMEs were reported.[168,172] Schmarr and co-workers studied the retention behavior of deuterated and nondeuterated probe molecules in liquid IL-based and conventional silicone stationary phases.[173] Heavier deuterated isotopic compounds elute earlier than corresponding non-deuterated solutes (inverse isotope effect) in conventional PDMS phase. On the other hand, normal isotope effects, where deuterated solutes are more retained with respect to analogous nondeuterated molecules, were observed in polar IL-based stationary phases, such as SLB-IL100 and SLB-IL111. As for the intermediate polarity IL stationary phases, such as SLB-IL59 and SLB-61, both deuterated and nondeuterated molecules coelute.

It is apparent that IL-based stationary phases exhibiting intermediate polarity, similar to conventional PEG phases, namely, SLB-IL59, SLB-IL60 and SLB-IL61, are suitable for the analysis of volatile and semivolatile analytes possessing a wide range of polarities. These stationary phases can be highly applicable to food chemistry, metabolomics, and fragrance- and aroma-related fields. Highly polar phases, such as SLB-IL100 and SLB-IL111, are most effective for the analysis of high-boiling point analytes commonly encountered in complex lipid samples, fuels, and petrochemical derivatives. The performance of most IL-based stationary phases is now comparable to the traditional polar phases, such as DB-FFAP, OV-1701, and SupelcoWax10. Additionally, the IL phases are also capable of providing higher peak capacity, thereby reducing peak overlap in the analysis of complex samples.

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

Utilization of ILs as HPLC Stationary Phases. The development of new IL-modified LC stationary phases has received much success since their introduction in 2004.[174] The main advantages of employing IL-modified stationary phases stem from the tunability of the ILs, which can consequently change the properties of the stationary phases. Recent studies of IL-modified stationary phases have been summarized by Qiu and co-workers.[175] The development of IL-modified LC stationary phases reported within the past two years will be summarized in this section.

The 1-allyl-3-butylimidazolium bromide ([AC_4IM][Br]) IL was applied for the modification of 3-mercaptopropyltrimethoxysilane-functionalized silica through the surface radical chain-transfer addition reaction.[176] The IL-modified silica stationary phase enabled multiple solvation interactions, including dispersion, $\pi-\pi$, and ion−dipole interactions for the separation of polycyclic aromatic hydrocarbons (PAHs) and dipolar compounds. Superior selectivity was obtained using this stationary phase compared to a conventional octadecylsilica (ODS) stationary phase. The same procedure was also employed to prepare a 1-(2-acryloyloxyundecyl)-3-methylimidazolium bromide ([mC_{11}MIM][Br]) modified silica stationary phase.[177] The synthesis scheme and separation results are shown in Figure 6. The column was successfully applied for multiple chromatographic modes, including ion-exchange, reversed-phase, and hydrophilic interaction chromatography. Additionally, the [mC_{11}MIM][Br] modified column demonstrated better selectivity for the separation of PAHs compared to an ODS phase.

Applications of ILs as HPLC Mobile-Phase Additives. The addition of ILs into conventional mobile phases may result in decreasing the zone broadening and improving chromatographic resolution. This is due to the masking of residual free-silanol groups on the surface of the silica-based stationary phases. Additionally, IL-based additives exhibit minimal influence on the pH of the mobile phase.

Han and co-workers applied a number of 1-alkyl-3-methylimidazolium-based ILs as mobile-phase additives for the separation of β-Lactam antibiotics. The best resolution was obtained when adding 1.0 mM [C_4MIM][BF_4] to the mobile phase.[178] Additionally, the retention factors for the antibiotics were enhanced by increasing the alkyl chain length of the IL. A mobile phase consisting 0.4% (v/v) [C_4IM][Cl], 0.4% (v/v) [C_4MIM][BF_4], and 99.2% (v/v) water was used for the separation of selenium species.[179] Good efficiency and shorter separation times were achieved using the ILs compared to common ion-pair reagents. A similar strategy has also been applied for the separation of alkaloids,[180,181] antiretroviral drugs,[182] nitroaromatic explosives,[183] fangchinoline and tetrandrine,[184] and β-blockers[185] on different stationary phases. An achaotropic salt, $NaPF_6$, and the [C_2MIM][PF_6] IL were compared as mobile-phase additives for the separation of biogenic amines.[186] Excellent separation resolution was achieved when 40 mM of IL was added. However, the LODs of the eluent system modified with $NaPF_6$ was 10 times better compared to systems modified with the IL. The [C_8MIM][BF_4] IL was utilized as a cationic surfactant reagent in the separation of urea derivatives.[187] It was observed that analytes could hydrogen bond with the imidazolium cation of the IL modifier, resulting in improved peak symmetry factors. The

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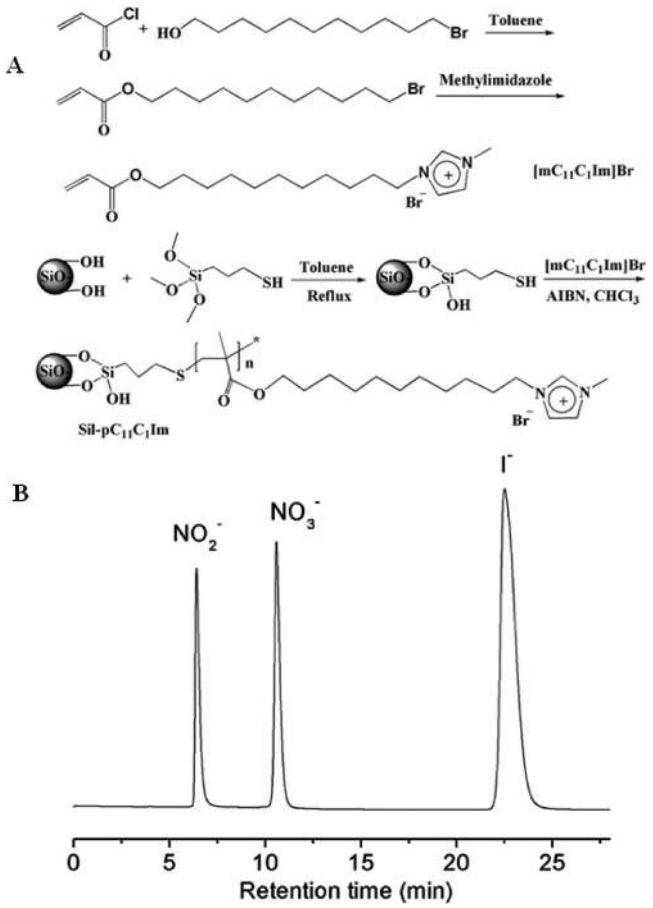

Figure 6. (A) Illustration of the synthesis procedure for fabricating a novel multimode stationary phase (Sil-pC_{11}MIm). (B) Chromatogram showing the separation of inorganic anions including nitrite, nitrate, and iodide. Reproduced from Qiu, H.; Mallik, A. K.; Takafuji, M.; Jiang, S.; Ihara, H. *Analyst* **2012**, *137*, 2553 (ref 177) with permission of The Royal Society of Chemistry.

formation of IL-based micelles also improved the separation selectivity of chloro and methoxy substituted derivatives.

A HPLC electrochemical detector was developed by Jia and co-workers in the analysis of phenolic acids.[188] The [C_4MIM][Br] IL, in addition to gold nanoparticles (GNP), were utilized as additives to enhance the efficiency of the separation. Compared to analogous separations using no IL modifications, the separation times of all analytes were decreased while the separation efficiency and method sensitivity were significantly increased.

Both achiral and chiral ILs have also been employed as mobile-phase additives for the separation of ofloxacin enantiomers by ligand-exchange HPLC.[189] The chiral amino acid IL, namely, [C_4MIM][L-leucine], demonstrated superior enantioseparation efficiency compared to the achiral ILs. Baseline separation of the enantiomers was achieved within 14 min, while the enantioseparation factor was observed to be 1.34. Zhou and co-workers applied isopropylammonium formate (IPAF) as a mobile-phase modifier for the separation of native proteins.[190] A significant enhancement in protein stability was observed when using IPAF as a mobile-phase modifier compared to acetonitrile. All proteins, except for lactate dehydrogenase, maintained their native structures within up to 50% IPAF. On the other hand, the proteins were denatured when using only 10% acetonitrile in the mobile phase. The superior stability of proteins in IPAF can be a result of the strong interaction between the IL and their native structures.

■ CAPILLARY ELECTROPHORESIS (CE)

Due to their high conductivity and tunable miscibility in aqueous solutions, ILs have been used as supporting electrolytes and/or additives to running buffers in CE. The recent application of IL-assisted CE in the analysis of phenols, aromatic acids, metal ions, medicines, enantiomers, and biological materials such as amino acids and proteins has been reviewed by Xu and co-workers.[191] In this section, the recent development of ILs/PILs in capillary electrophoresis will be summarized.

The poly(1-vinyl-3-butylimidazolium) bromide PIL was physically deposited to a silica capillary for applications in CE.[192] The coating enabled the reversal of the electroosmotic flow (EOF) at pH 3.0 to 9.0 while exhibiting high tolerance to organic solvent. In another study, an IL-bonded organic-silica hybrid monolithic column was prepared for capillary electrochromatography (CEC).[193] EOF reversal and better separation efficiency was observed for the IL-bonded column compared to an analogous column without IL modification.

The EOF modulation capability of several ILs composed of phosphonium, sulfonium, cysteinium, ammonium, and guanidinium cations were evaluated by Mendes and co-workers.[194] Phosphonium-based ILs and the trioctyl methylammonium chloride IL demonstrated the strongest ability to reverse the EOF under both acidic and basic conditions. ILs were exploited as background electrolyte (BGE) additives for the CE of neutral carbohydrates.[195] The ILs functioned as both a chromophore for indirect UV detection and as a selector to improve analyte separation. Under optimized conditions, sucrose, glucose, and fructose were fully separated within 7 min. The utilization of PILs as BGE additives was also reported by Zhou and co-workers.[196]

Achiral and chiral additives have also attracted significant attention in chiral separations by CE. A series of achiral ILs was employed as modifiers to cooperate with β-cyclodextrin derivatives for the enantioseparation of three β-blockers.[197] The glycidyltrimethylammonium chloride ([GTMA][Cl]) IL was most effective for improving the enantioseparation of the β-blockers. This indicated a synergistic effect that exists between the IL and β-cyclodextrin derivatives. Two chiral amino acid derivatized ILs were applied in conjunction with β-cyclodextrin derivatives for the separation of naproxen, pranoprofen, and warfarin enantiomers.[198] Significant improvements in enantioseparation, which can be attributed to the participation of the IL in chiral recognition, was obtained for all compounds. A similar synergistic system, using glycogen as a chiral selector, was also recently studied.[199] As shown in Figure 7, significant improvement in the enantioseparation can be observed in the chiral ILs/glycogen synergistic system when compared to the single glycogen separation system. Amino acid derivatized ILs have also been applied as a chiral ligand to coordinate with Zn(II) in the enantioseparation of dansyl amino acids (Dns-D,L-AAs) by chiral ligand exchange capillary electrophoresis (CLE-CE).[200,201] Baseline separation of multiple Dns-D,L-AA pairs was achieved using this method. Yu and co-workers reported the synthesis and application of a chiral IL-functionalized β-cyclodextrin selector, namely, 6-*O*-2-hydroxypropyltrimethylammonium-β-cyclodextrintetrafluoroborate ([HPTMA-β-CD][BF_4]) in CE.[202] Tailoring the IL chiral

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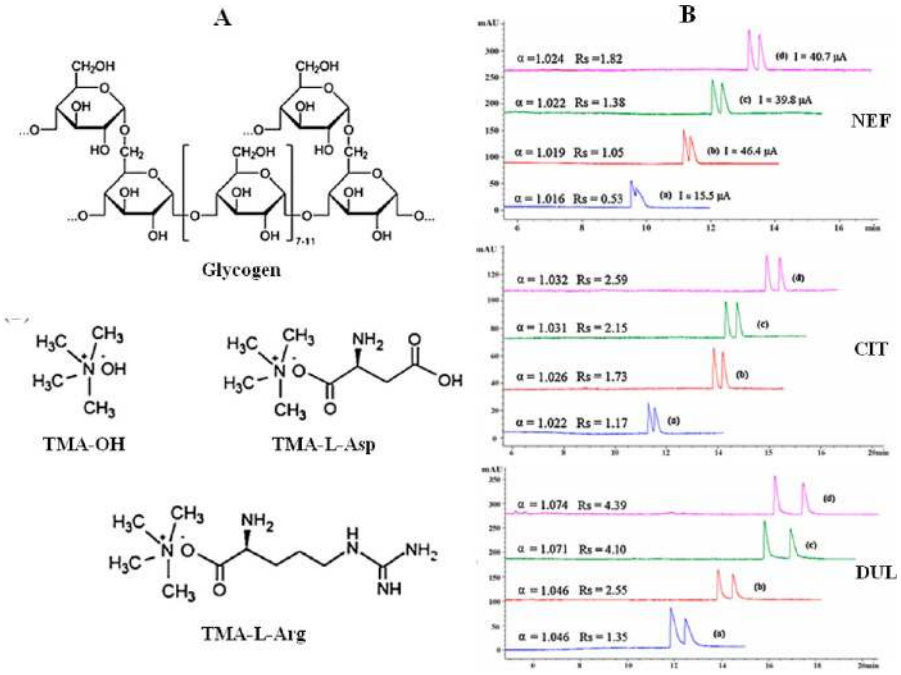

Figure 7. (A) Illustration of the chemical structures of the synthesized chiral additives. (B) Electropherograms of the chiral separations of nefopam hydrochloride (NEF), citalopram hydrobromide (CIT), and duloxetine hydrochloride (DUL). Conditions: (a) 2.5% glycogen; (b) 2.5% glycogen + 60 mM TMA−OH; (c) 2.5% glycogen + 60 mM TMA-L-Asp; (d) 2.5% glycogen + 60 mM TMA-L-Arg. Reprinted from Zhang, Q.; Du, Y. *J. Chromatogr., A* **2013**, *1306*, 97 (ref 199). Copyright 2013, with permission from Elsevier.

selector significantly enhanced the solubility of β-cyclodextrin in the aqueous buffer. Additionally, the [HPTMA-β-CD][BF_4] exhibited better enantioresolution compared to an analogous β-CD selector possessing no IL functionality.

MASS SPECTROMETRY

Ionic Liquids in Matrix-Assisted Laser Desorption Ionization. Since its introduction in 1988, MALDI has become a widespread and powerful source for the production of intact gas-phase ions for a broad range of large, nonvolatile, and/or thermally labile compounds. The matrices employed in MALDI should adhere to specific requirements, such as possessing a strong absorbance at the laser wavelength, low molecular mass, stability under vacuum, ability to promote analyte ionization, and adequate solubility of the analyte.[113,118] Since a number of ILs can accommodate these requirements, they have been successfully employed as MALDI matrices.[203−209]

Many IL-based matrices are composed of cations paired with α-cyano-4-hydroxycinnamate (4-CHCA), 2,5-dihydroxybenzoate (2,5-DHBA), or 3-hydroxypicolinate (3-HPA). Recently, the IL/[4-CHCA] matrices were employed in various forensic investigations,[210,211] polymer analysis,[212] and melamine screening in milk.[213] Novel IL matrices were proposed for the study of intact pathogenic bacterial cells.[214] Tetraalkyl phosphonium-based ILs were prepared and used for a single-step extraction of dyes and analysis by MALDI-TOFMS,[215] while two new ammonium-based ILs paired with 3-oxocoumarate and dihydroxymonooxoacetophenoate were explored as MALDI matrices for the analysis of biodegradable photoluminescent polymers.[216] The dihydroxymonooxoacetophenoate IL provided similar signal intensities and shot-to-shot reproducibility when compared to the analogous [4-CHCA]-based IL matrix.

It is known that IL-based MALDI matrices should possess labile protons to promote ionization, although there appears to be no correlation between the matrix pK_a and the analyte signal.[203] Lately, a method devised to measure the ion yield in MALDI experiments was reported. This metric was applied in an attempt to understand the gas-phase ion formation of preformed ions, such as those formed in ILs versus pure CHCA acid matrices.[217] In another study, Dertinger and co-workers explored the structural role of ILs and their effects on analyte signal enhancements.[218,219]

Matrix-assisted laser desorption ionization in-source decay (MALDI-ISD) can be an alternative approach to determine the sequence of a protein, without the need for enzymatic digestion.[220] It was observed that 2,5-DHBA acid and 1,5-diaminonaphthalene (1,5-DAN) matrices efficiently induced MALDI-ISD fragments, separately. However, the ISD-fragments were suppressed when the RTIL, 1,5-diammoniumnaphthalene [2,5-DHBA], was employed as matrix. Consequently, the use of IL matrices for MALDI-ISD experiments will require additional fundamental studies to improve the induction of ISD fragments.

Ionic Liquids in Atmospheric Pressure Ionization Techniques. The analysis of various organometallic complexes by electrospray ionization mass spectrometry (ESI-MS) is often problematic due to their solubility in protic organic solvents.[221] Nevertheless, a neutral organometallic complex, bis-(triphenylphosphine)palladium II, was successfully analyzed by employing [C_4MIM]-based ILs. The best sensitivities were obtained when employing more hydrophobic anions such as [BF_4], trifluoromethylsulfonate, and heptafluorobutanoate. The analysis of polysaccharides by ESI-MS was recently reported by Chang and co-workers.[222] These analyses were carried out with the use of ILs dissolved in the sample solution. The addition of butylammonium paired with [2,5-DHBA] or [4-CHCA] significantly increased the sensitivity of the method. Additionally, the mass spectra obtained using this approach were also

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greatly simplified, due to a narrower charge distribution window.

ILs have also been applied for enzyme kinetic and inhibition studies. Typical assays used to visualize enzymatic activity depend on the direct measurement of radioactive or fluorescent substrates. Galan and co-workers proposed a task-specific IL that easily attaches and detaches to target-substrates.[223] This facilitated both substrate purification and allowed enzymatic reaction monitoring. The proposed method was demonstrated to be more rapid and sensitive compared to conventional methods. In subsequent reports, the chemical stability of the IL-based probes was enhanced and successfully employed for the measurement of apparent kinetic parameters for enzyme catalyzed transformations with glycosyltransferases.[224,225]

The $[C_4MIM][Br]$ IL was applied as a solvent for the detection of dimethoate in fruit juices by thermal dissociation atmospheric chemical ionization ion trap mass spectrometry.[226] The $[C_4MIM][BF_4]$ IL was also employed as a matrix in the analysis of pharmaceuticals and pesticides by matrix-assisted corona beam ionization.[227] This allowed for the successful and reproducible quantitation of pharmaceuticals and pesticides in synthetic samples.

IONIC LIQUIDS IN ELECTROCHEMICAL SENSING SYSTEMS

Many ILs exhibits wide electrochemical potential windows and good conductivity making them highly useful for various electrochemical applications.[228−230] Since their initial application for electrode modification in 1997,[231] ILs have received much attention as alternative electrolytes in many electrochemical devices. The application of ILs in electrode modification has been reviewed by Opallo and co-workers.[228] A number of IL-modified electrode fabrication techniques, including direct mixing, casting and rubbing, physical adsorption, electro deposition, layer-by-layer approach, sol−gel encapsulation, and sandwich-type assays, was recently described.[229] The application of ILs in electrochemical sensing systems was also summarized by Silvester.[230] The following sections provide a brief update on the application of ILs in electrode modifications within the past two years.

ILs as Surface Modifiers for Electrodes. Electrochemical sensors can be modified by directly applying ILs as droplets or films on the surface of an electrode. Zevenbergen and co-workers employed a gold working electrode covered by a thin layer of the $[C_4MIM][NTf_2]$ IL for the detection of ethylene.[232] An LOD of 760 ppb and a linear response up to 10 ppm was achieved using this IL-modified system. Hu and co-workers exploited the $[C_4MIM][PF_6]$ IL as an electrolyte on paper-based gold electrode arrays (PGEAs) for oxygen sensing.[233] The fabrication of the IL-modified PGEA is illustrated in Figure 8. The resulting sensor exhibited several unique properties including good conductivity, excellent flexibility, and high electrochemical performance. The PGEAs also possessed high method sensitivity in the determination of trace oxygen in a nitrogen atmosphere, wherein a LOD of 0.0075 v/v % (O_2/N_2) was obtained.

The electro-deposition of ILs to the surface of an electrode has also become a popular method for the fabrication of IL-modified electrodes. For example, Pandurangachar and co-workers deposited the 1-butyl-4-methyl-pyridinium $[BF_4]$ ($[BMPY][BF_4]$) IL to the surface of a carbon paste electrode (CPE) by cyclic voltammetry (CV).[234] Excellent electrocatalytic activity for the selective detection of dopamine in the presence of ascorbic acid and uric acid was obtained using this electrode.

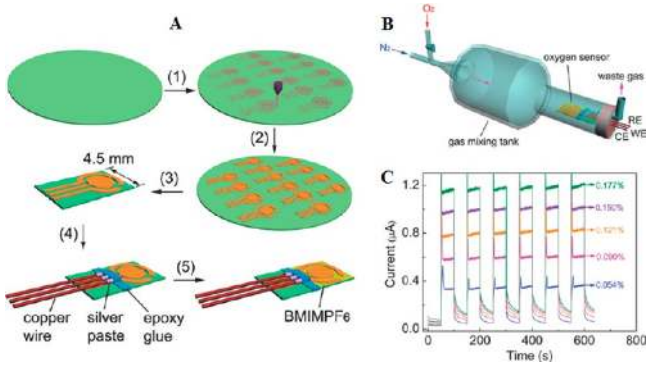

Figure 8. (A) Schematic showing the fabrication of paper-based solid-state electrochemical oxygen sensors. (1) Inkjet printing of GNP patterns on cellulose membranes, (2) growth of GNP patterns into gold electrode arrays, (3) cutting single PGEA, (4) electric connection of a PGEA, and (5) fabrication of oxygen sensor by applying $[BMIM][PF_6]$ onto the PGEA. (B) Illustration of a homemade gas mixing setup for the electrochemical sensing of oxygen. (C) Amperometric responses of oxygen at different concentrations. Reprinted from ref 233. Copyright 2012 American Chemical Society.

IL Composite Electrochemical Sensing Systems. ILs can also be incorporated into different matrixes, such as graphite, graphene, carbonnanotubes, metal nanoparticles, and polymers to form stable composite materials. The mechanical and electrical properties of the IL-based composites can be significantly enhanced by synergistically exploiting and combining the unique physicochemical properties found within each component.

Incorporation of ILs in Carbon-Based Composites in Electrochemical Sensing Systems. Recently, ILs have been applied as an alternative to the nonconducting organic binder, such as paraffin, in carbon paste electrodes.[228] The IL carbon paste composite electrodes (ILCPEs) were prepared by mixing or grinding graphite powder/or carbon nanotubes with ILs to form a uniformly wetted paste. The resulting paste can then be packed firmly into the cavity of an electrode. An *n*-octylpyridinium $[PF_6]$ ($[C_8PY][PF_6]$) modified carbon paste electrode was developed by Ping and co-workers for the evaluation of trace amounts of cadmium and lead in soil samples.[235] Superior electrochemical activity and low ppb-level LODs were obtained using the ILCPE compared to a traditional carbon paste electrode, which employs paraffin oil as a binder. The same ILCPE was applied in the determination of (−)-Epigallocatechin Gallate in tea infusion samples.[236] Various ILCPEs and IL-based carbon nanotube paste electrodes were also utilized for the determination of adenosine-5′-triphosphate (ATP),[237] carbidopa,[238] epinephrine,[239] ascorbic acid,[240] morphine,[241] nitric oxide,[242] and norepinephrine[243] in different sample matrixes. The electrochemical performance of IL-based, graphene-based, and IL-graphene modified carbon electrodes was evaluated by Du and co-workers.[244] Faster redox chemistry and favorable electron-transfer kinetics were observed using the IL-graphene modified carbon electrode compared to the IL-based and graphene-based carbon paste electrode.

Imidazolium-based ILs can form a physical gel when ground with single-walled carbon nanotubes (SWCNTs).[245] The CNT/IL composites typically possess the mechanical, electrical,

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and thermal properties of the CNT, in addition to the conductivity inherent to the ILs. Direct rubbing is a common method for the preparation of a CNT/IL composite sensor. The nanocomposite gel can be fabricated by mixing specific amounts of CNTs (typically lower than 5% w/w) with ILs. After grounding and/or sonication, the gel can be directly applied to the surface of an electrode.[229] Bu and co-workers developed a multiwalled carbon nanotubes (MWCNTs)/IL glassy carbon electrode (GCE) for the simultaneous determination of hydroquinone and catechol.[246] The IL-modified GCE showed well-defined redox waves for both analytes in both CV and DPV. In other studies, an IL-graphene hybrid nanosheet was applied for the rapid detection of trinitrotoluene, wherein subppb level LODs were obtained.[247] In addition, the application of IL-graphene modified electrode in the analysis of metronidazole in pharmaceutical dosage forms has also been reported.[248] Recently, carboxylated-SWNTs (SWCNTs-COO) composed of 3-butyl-1-[3-(*N*-pyrrolyl)propyl]imidazolium cations were synthesized and coated on a GCE.[249] Polymerization of the IL was performed by cyclic voltammetric scanning to produce a PIL/SWCNTs-COO hybrid. The PIL/SWCNTs-COO GCE was applied for the determination of bisphenol A, wherein LODs in the nM range were obtained.

Application of Metal Nanomaterials/IL-Modified Electrodes. Due to their large surface-to-volume ratios and high thermal stability, several metal nanoparticles have been applied in conjunction with ILs as electrodes. Bo and co-workers employed PIL-coated mesoporous carbons (OMCs) as support materials for the deposition and formation of Pt nanoparticles.[250] The PIL provided sufficient binding sites to anchor the metal ion precursors and facilitated the homogeneous formation of ultrafine nanoparticles. The novel electrode also exhibited higher electrocatalytic activity toward hydrogen peroxide (H_2O_2) compared to an analogous Pt/OMCs nanocomposite containing no PIL. Similar methods have also been applied for the electrodeposition of gold nanoparticle[251] and gold–platinum alloy nanoparticles[252] on various substrates.

Application of IL-Based Multicomponent Electrochemical Sensors. Recently, the incorporation of ILs to multicomponent electrochemical sensor systems has enjoyed increasing attention in the analytical community. An IL/CNT modified glassy carbon (GCA) was used to facilitate the electro deposition of Prussian blue (PB) nanoparticles.[253] Incorporating an IL to the system improved the deposition efficiency of PB by 1.8-fold and provided a 2.35-fold enhancement in the electron-transfer rate compared to a non-IL modified PB/CNTs/GCA electrode. Similarly, the production and application of different electrodes, including chitosan/copper/IL,[254] nickel/IL/MWCNTs,[255] stacked graphene platelet nanofibers/IL/chitosan,[256] and manganese oxide nanoparticles/IL/chitosan,[257] have been reported. Different ILs were homogenized with GNPs and CNTs and applied as nonenzymatic glucose sensors.[258] The imidazolium-based IL exhibited better stability and detection sensitivity to glucose compared to tetrabutylammonium, pyrrolidinium, and piperdinium-based ILs. Additionally, the oxidation of glucose was enhanced by appending hydrophilic moieties, such as a sulfonate substituent, to the IL.

Application of IL-Modified Biosensors. Various electrodes including GCA, metal, CPE, and screen-printed electrodes have been applied for the deposition of biological recognition elements. However, conventional electrodes usually suffer from poor production reproducibility and compatibility to biological samples.[229] Due to their biocompatibility, ILs and IL-based composites have been shown to be ideal matrixes for the immobilization and/or encapsulation of biological components in biosensors. Recent developments of IL-based electrochemical biosensing systems have been summarized in a number of review articles.[229,259]

A novel PIL-functionalized graphene material, namely, poly([VC_4IM][Br])-graphene, was synthesized and applied for the detection of glucose.[260] The PIL-based nanocomposite can easily be dispersed in aqueous solution to form a homogeneous colloidal suspension. The surface of the PIL-modified material is also positively charged, which enables the immobilization of negatively charged glucose oxidase (GOD) to the electrode under mild conditions, as shown in Figure 9A.

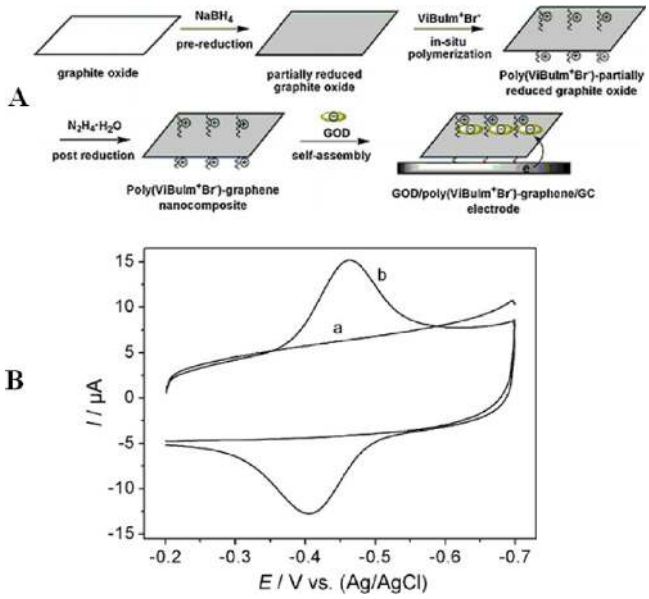

Figure 9. (A) Schematic showing the preparation of GOD/poly([VBIM][Br])-graphene/GC electrode and the direct electron transfer between GOD and GC electrode. (B) Cyclic voltammograms of the poly([VC_4IM][Br])-graphene/GC electrode (a) and GOD/poly([VC_4IM][Br])-graphene/GC electrode (b). Reprinted from Zhang, Q.; Wu, S.; Zhang, L.; Lu, J.; Verproot, F.; Liu, Y.; Xing, Z.; Li, J.; Song, X.-M. *Biosens. Bioelectron.* **2011**, *26*, 2632 (ref 260). Copyright 2011, with permission from Elsevier.

Well-defined redox peaks can be observed after the assembly of GOD to the PIL-modified electrode, as shown in Figure 9B. Additionally, the electrode exhibited excellent sensitivity and stability and a wide linear range for the detection of glucose. Similar strategies were used to immobilize hemoglobin,[260,261] glucose dehydrogenase,[262] GOD,[263] nicotinamide adenine dinucleotide,[264] single-stranded DNA (ssDNA),[265,266] bovine serum albumin (BSA),[267] horseradish peroxidase (HRP),[268,269] carcinoembryonic antigen antibody,[270] laccase and polyphenol oxidase,[271,272] HRP and GOD,[273] and antigoat immunoglobulin Gamma and human dihydrofolate reductase[274] to the surface of IL-modified electrode. The encapsulation of biomolecules, including HRP[275,276] and myoglobin,[277] in IL-modified biochemical sensors has also been reported. An electrochemical DNA biosensor was developed by Gao and co-workers by assembling ssDNA with a Au/IL-CPE.[278] The sensor demonstrated high selectivity for one-base and three-base mismatched ssDNA sequences. Cholesterol oxidase was immobilized onto modified electrodes using a similar approach.[252]

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A graphene/IL/Nafion-modified pyrolytic graphite electrode was developed by Qiu and co-workers to investigate DNA damage by acrylamide (AA) and its metabolites.[279] A layer-by-layer fabrication method was applied by alternately coating HRP and natural double-stranded DNA on the graphene/IL/Nafion-modified electrode. The coexistence of HRP, H_2O_2, and AA catalyzed the transformation of AA to glycidamide. It was determined that, in the presence of H_2O_2, AA could be transformed to glycidamide and induce more severe damage to DNA than AA. Yang and co-workers designed a sandwich-type immunosensor composed of an IL-doped chitosan immobilization matrix.[280] Subsequent to applying the matrix to a GCE, various sensing components were successfully immobilized to the IL-doped matrix. The synergistic effects of all components, in addition to the suitable electrochemical properties of the IL, allowed for the determination of immunoglobulin G at ppt levels. A similar sandwich-type immunosensor, composed of Pd nanoparticles in functionalized SBA-15 (Pd@SBA-15) and the $[C_4MIM][Br]$ IL, has also been developed for the detection of salbutamol.[281] The sensitivity obtained for the IL-modified sandwich-type immunosensor was significantly better than analogous immunosensors containing no ILs.

CONCLUSIONS AND PERSPECTIVES

Owing to their unique physicochemical properties, ILs have been successfully utilized in all major fields within analytical chemistry. In the fields of sample preparation and extraction, ILs were shown to be highly effective extraction phases that can provide superior analyte selectivity and exceptional analytical performance. Furthermore, these contemporary ionic solvents were demonstrated to be powerful alternatives to traditional molecular solvents, which often possess high toxicity and volatility. The versatility of ILs has made them an interesting class of new stationary phases or additives in GC, HPLC, and CEC. In many cases, exploiting task-specific ILs provides unique analyte selectivity and improved chromatographic separation for a number of analyte classes. This is especially true for heart-cutting MDGC and GC×GC, where the selectivity of the second dimension stationary phase is crucial. Select IL stationary phases also exhibited superior thermal stability and high polarity numbers compared to conventional polar stationary phases. ILs have played an important role as buffer additives in CE to improve the separation of numerous pharmaceutical drugs, organic compounds, and biomolecules. Modulation of the EOF can also be achieved by choosing the appropriate IL. With respect to mass spectrometry, ILs are applicable as matrices for MALDI-based techniques. IL-based matrices can be useful alternatives to traditional matrices, providing better shot-to-shot reproducibility and matrix homogeneity, while exhibiting broader solubility windows for many analytes. Novel applications of ILs in electrochemical sensing systems have shown promising results for the detection of various analytes. Additionally, ILs can also be combined with a number of organic/inorganic compounds to yield materials that exhibit enhanced electrocatalytic activity, thermal stability, mechanical stability, and selectivity.

Although ILs have been utilized to enhance numerous analytical processes, further characterization and synthetic optimization is critical for the applicability of these materials. For example, the synthesis of highly pure ILs is vital for many analytical procedures. Impurities often introduce significant background noise in various detection methods and alter the unique selectivity exhibited by the IL in chromatographic/electrophoretic techniques. Similarly, impurities also influence the physicochemical properties of an IL and can detrimentally affect their analytical performance in sample preparation. As a result, effort should be focused on improving synthetic and/or purification methods to produce pure ILs in high yields. Although ILs exhibits negligible vapor pressures at room temperature, which results in virtually no air pollution, improper disposal of these compounds may adversely affect the ecosystem. Therefore, it is important to continue to investigate and monitor the toxicity of ILs and their effects on the surrounding environment.

A promising trend of ILs in analytical chemistry resides on the ability to combine these compounds with other organic/inorganic materials. As demonstrated in current literature, the union between ILs with other materials, such as CNTs, silica, metals, and organic polymers can significantly alter the physicochemical properties of such materials. Many IL-based composites exhibit high thermal and chemical stability, good mechanical strength, suitable electrochemical properties, and enhanced robustness. Therefore, combining ILs with different materials, in addition to synthesizing novel task-specific ILs, can ultimately broaden the usefulness of these compounds within the many interdisciplinary subfields of analytical chemistry.

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Notes

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