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Review Article

Application of Ionic Liquids in Liquid Chromatography and Electrodriven Separation

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Ionic liquids (ILs) are salts in the liquid state at ambient temperature, which are nonvolatile, nonflammable with high thermal stability and dissolve easily for a wide range of inorganic and organic materials. As a kind of potential green solvent, they show high efficiency and selectivity in the field of separation research, especially in instrumental analysis. Thus far, ILs have been successfully applied by many related researchers in high-performance liquid chromatography and capillary electrophoresis as chromatographic stationary phases, mobile phase additives or electroosmotic flow modifiers. This paper provides a detailed review of these applications in the study of natural products, foods, drugs and other fine chemicals. Furthermore, the prospects of ILs in liquid chromatographic and electrodriven techniques are discussed.

Introduction

Ionic liquids (ILs) are generally defined as salts that may be liquid at temperatures below 100°C. They are composed of bulky, nonsymmetrical organic cations such as 1-alkyl-3-methylimidazolium, *N*-methylpyrrolidinium, *N*-alkylpyridinium, tetraalkylammonium, tetraalkylphosphonium and numerous different organic or inorganic anions such as hexafluorophosphate $[PF_6]^-$, tetrafluoroborate $[BF_4]^-$, trifluoromethylsulfonate $[CF_3SO_3]^-$, *bis*[(trifluoromethyl)sulfonyl]amide $[(CF_3SO_2)_2N]^-$ (or $[Tf_2N]$), trifluoroethanoate $[CF_3CO_2]^-$, acetate, nitrate and halide. Some ILs are shown in Figure 1. Because the nomenclature can become quite cumbersome, it is common to use the abbreviation. For instance, $[C_nmim]^+$ represents the 1-alkyl-3-methylimidazolium cation, $[C_npy]^+$ represents *N*-alkylpyridinium and $[C_nmpyr]^+$ represents the 1-alkyl-1-methyl pyrrolidinium cation, where the index n represents the number of carbon atoms in the linear alkyl chain. $[P_{wxyz}]^+$ and $[N_{wxyz}]^+$ are used to represent tetraalkylphosphonium and tetraalkylammonium cations, where the indices w, x, y and z indicate the lengths of the corresponding linear alkyl chains. Thus, the abbreviation for 1-butyl-3-methylimidazolium becomes C_4mim and can also be referred to as Bmim.

The physicochemical properties of ILs depend on the type and size of the constituents of both their cations and anions. Because the interionic force between cations and anions in ILs is stronger than ordinary organic solvents but weaker than typical ion crystals, ILs have some specific properties, including high ionic conductivity, wide temperature range as a liquid phase, negligible vapor pressure, good thermal stability, tunable viscosity and miscibility with water and organic solvents, in addition to good solubility for various organic compounds and metal ions (1). These unique properties, especially their very low volatility, make them useful in high-vacuum systems and eliminate many contamination problems. Therefore, ILs are regarded as environmentally friendly and have many advantages over common organic solvents. The combination of various cations and anions can lead to many ILs that provide considerable flexibility in the selection of the most suitable pair for a specific application (2).

ILs have been successfully used in many applications, including catalysis (3, 4), cellulose processing (5), solvent extraction (6, 7), electrolytes in batteries (8), metal deposition (9, 10) and gas treatment (11, 12). ILs have attracted great interest in separation science, especially in chromatographic techniques. They can be used in sample pretreatment like solid-phase microextraction (13), dispersive liquid–liquid microextraction (14, 15), as a suitable gas chromatography (GC) stationary phase coated on a fused silica capillary column (16) or as an additive/stationary phase in high-performance liquid chromatography (HPLC). Meanwhile, ILs are used either as the supporting electrolyte, background electrolyte modifier or as supported coatings of the capillary wall in capillary electrophoresis (CE) and micellar electrokinetic chromatography (MEKC). From 2004 to the present, ILs have been described as separating agents in chromatographic techniques in many reviews. The emphasis in each review is different. In 2005, Liu and Jiang (17) referred to sample preparation and detection; in 2007, Marszall and Kaliszan (18) reviewed ILs used in thin-layer and other chromatographic techniques; in 2009 and 2010, Han *et al.* and Han and Row (19, 20) used ILs as porous and nonporous membrane materials. Stalcup and Cabovska in 2004 (21), Shamsi and Danielson in 2007 (22), Berthod *et al.* in 2008 (23) and Buszewski and Studzinska in 2008 (24) discussed ILs used in chromatography and CE. In the last four years, the applications have grown and evolved, and some new application aspects have been developed, such as the use of ILs in monolithic columns, polymeric ionic liquids and poly(dimethylsiloxane) (PDMS) modification. The primary goal of this review is to focus on some of the unique properties of ILs and their mechanisms and applications in LC (especially reversed-phase LC) and electrodriven separation for natural products, foods, drugs and other fine chemicals. Studies on sample preparation (13–15) are not discussed, because this is outside the scope of this review.

Ionic Liquids in Liquid Chromatography

LC includes several separation modes such as reversed phase (RPLC), normal phase (NPLC), hydrophilic interaction (HILIC), ion pair (IPC), ion exchange (IEC) and some others. RPLC is one of the most popular separation techniques used for almost 90% of chromatographic applications. However, poor performance is usually obtained in the analysis of polar or ionizable compounds

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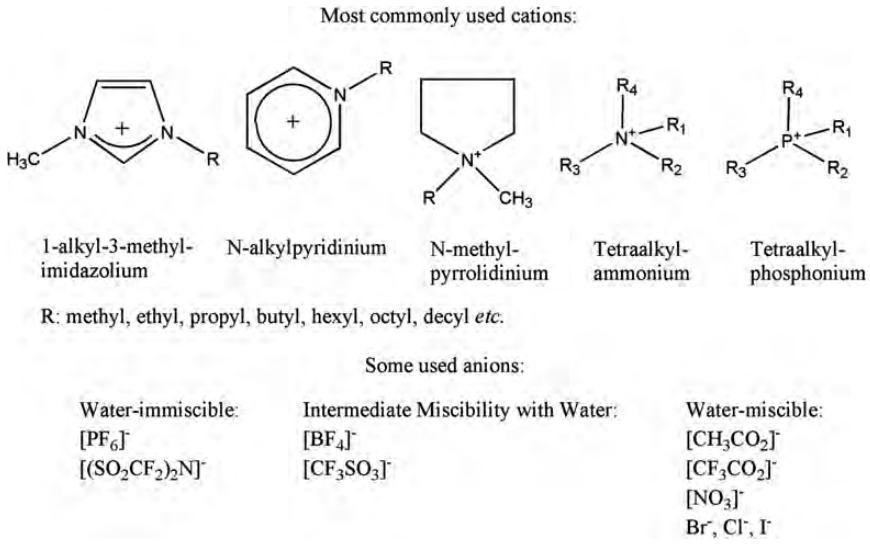

Figure 1. Chemical structures of the common ILs.

owing to the activity of residual silanol groups, which is an interaction between the cationic sites of the compounds with the anionic silanols of the stationary phase. These lead to severe band tailing, band broadening, asymmetric peaks, low efficiency and irreproducible retention in analysis. Two methods can be used to avoid these problems: developing more adaptive adsorbents other than silica or adding solutes to the mobile phase, which can interact with residual silanols. The latter is easy to implement and costs less. The next section will discuss ILs as mobile phase additives and stationary phases in chromatography.

Mobile phase additives

Mechanism

Alkyl amines and other amino quenchers have been demonstrated to be useful silanol-blocking agents. However, these additives are usually ineffective and do not fully remove the detrimental effect of free silanols in the case of strongly basic compounds (25). Even worse, their presence may cause slow equilibration of the chromatographic system when the mobile phases are changed (26). In recent years, the number of studies using ILs as additives to the mobile phase in RPLC has increased dramatically. Interestingly, two major advantages of using ILs as mobile phase additives have been noted. The first is that the replacement of traditional mobile phase additives may produce improved separation efficiency. The second advantage is that ILs have no influence on the pH of the mobile phase, unlike triethylamine (TEA) and other amines. The latter may be much more important.

As mobile phase additives, ILs play various roles, including coating residual silanols to modify the stationary phase and acting as ion-pairing agents (27, 28). It is shown that the cations in ILs are mostly responsible for interaction with the stationary phase silanol groups and the chaotropic character of the anions is responsible for possible ion-pairing with the cationic solutes. According to He *et al.* (29), ILs form a weak bilayer electronic structure (also called dynamic pseudostationary phase) on the surface of the modified silica gel and lead to the competition between imidazolium cations and polar group of analytes for silanol groups (Figure 2). Therefore, ILs can effectively suppress free silanols and improve peak shapes, while also decreasing the retention times of analytes such as bases because of the repulsion between the imidazolium cation and the ionized bases. However, if the analytes are acidic or zwitterionic, the retention times may not be shortened (30). In addition, the change in retention times is related to the concentration of the additive. At the beginning of increasing the concentration of the additive, the concentration of additive on the stationary phase is higher than that in the mobile phase; thus, the retention times increase. When the concentration of the additive is high enough, the retention times decrease when the amount of ILs in the mobile phase increases (31). Polyakova and Row (32) found that the occurrence of multilayer adsorption of the ILs has a substantial effect on the retention of ionized analytes and the realization of an ion-exchange mechanism of retention, in contrast with that for non-dissociated molecules, which is the ordinary mechanism of RPLC, leading to small differences in analyte retention. Other research groups including Xiao *et al.* (33) hypothesized that in addition to the preceding mechanism, the strong hydrogen bonding between the imidazolium cation and its counterion of ILs and solutes would also play an important role. The newest research result from Chul-Woong *et al.* (34) showed that the type of head group, alkyl chain length and further substituents of the cation have a significant influence on the dipolarity/polarizability and the hydrogen-bonding acidity, and that the functionalized groups (hydroxyl, ether and dimethylamino) lead to hydrogen-bonding basicity of the cation.

From the preceding research, the mechanism of ILs as mobile phase additives is still very complicated and further research is needed, especially more quantitative analyses. It would be difficult to find the underlying mechanism concerning the nature of modifiers, for which the adsorption-partition becomes a multiplex mechanism. It is not inconceivable that new separation mechanisms can be made available with ILs (35, 36).

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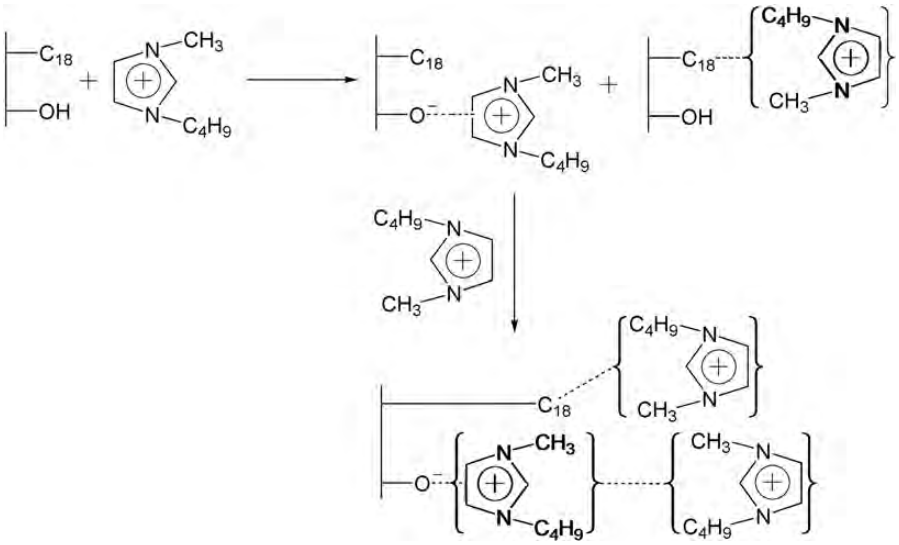

Figure 2. Proposed scheme of interaction for $[C_4mim][BF_4]$ on a modified silica surface. Reproduced from Journal of Chromatography A, 1007, He, Lijun et al., Effect of 1-alkyl-3-methylimidazolium-based ionic liquids as the eluent on the separation of ephedrines by liquid chromatography, 39–45, 2003, with permission from Elsevier BV.

Table I
Applications of ILs as Mobile Phase Additives in HPLC

ILs	Target analytes	Advantages	Reference
$[C_4mim][BF_4]$	Ephedrines		29
$[C_nmin]^+$ $[C_4py]^+$	Catecholamines	Decreased band tailing and broadening, improved resolution	31
Six ILs	Alkaloids		39
$[C_nmim][BF_4]$ [Moim][BF_4] $[N_{2222}][BF_4]$	Fluoroquinolone antibiotic	Improved sensitivity and selectivity, reduction in analysis time	40, 41
$[C_4mim][BF_4]$ $[C_6mim][BF_4]$ $[C_8mim][BF_4]$	β-Lactam antibiotics	Good separation with sharp peaks	42
$[C_nmin][BF_4]$ $[C_4min]$	Cytosine, thymine, adenine, 6-chlorouracil, L-his, L-tyr, L-phe and DL-try	Improved retention and resolution	30
$[C_4mim][PF_6]$	N-carbobenzyloxy-D-phe and D-try		32
$[C_4mim][BF_4]$ $[C_6mim][BF_4]$ [Moim][BF_4]	Six heterocyclic aromatic amines	More favorable than a common additive like TEA	43
$[C_nmin]^+$	AMP, CMP, UMP, GMP and IMP	Simpler and faster than current method	44
$[C_6mim][BF_4]$ $[C_8mim][BF_4]$	Aromatic compounds		45
$[C_4mim][BF_4]$ $[C_2mim][BF_4]$ $[C_2mim][MS]$	5′-IMP, 5′-UMP, 5′-GMP and TMP	Baseline separation of nucleotides without requiring gradient elution	35, 36
(*R*)-*N*, *N*, *N*-trimethyl-2-aminobutanol-*bis*(trifluoromethanesulfon)imidate	Alcohol, amine, acid and amino acid	Enantioselective separation	46
IL-assisted ligand-exchange	Ofloxacin		47

Application

Ruiz-Ángel *et al.* and Fernández-Navarro *et al.* (37, 38) compared ILs with TEA and sodium dodecyl sulfate (SDS) as mobile phase additives in the analysis of a group of β-blockers (acebutolol, alprenolol, labetalol, metoprolol, nadolol, pindolol and propranolol). ILs showed a nice performance and were notably superior to the classic TEA additive for improvements in both efficiency and peak shape. Some applications have been shown in Table I. From these examples, the following conclusion may be drawn: there is no "best" IL. If the basic compounds are polar and lightly retained, a polar IL additive with a strongly chaotropic anion such as $[PF_6]^-$ or $[ClO_4]^-$ is recommended. With less polar and hydrophobic compounds, a less polar IL additive with a cosmotropic anion such as Cl^- is likely a good choice.

At present, many task-specific ionic liquids (TSILs) have been used as mobile additives, especially in enantioselective separation. The separation of chiral compounds is greatly important in both research and industry, particularly in the pharmaceutical industry. After Ding *et al.* (48) presented the first enantiomeric separations using a chiral IL stationary phase in GC, many articles have been reported, but have primarily focused on CE. Chiral ILs are rarely used in LC. In 2006, Yuan *et al.* (46) first used chiral ILs as an effective chiral selector in HPLC. Eight racemates were separated on a C18 column by using (*R*)-*N*, *N*,

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N-trimethyl-2-aminobutanol-*bis*(trifluoromethanesulfon)-imidate as the chiral additive of the mobile phase in HPLC. It showed chiral recognition ability toward alcohol, amine, acid and amino acid enantiomers. Bi *et al.* (47) investigated the effect on chiral separation of ofloxacin by ionic liquid-assisted ligand-exchange HPLC. The method was simple and accurate. These research studies exhibited the potential for the separation and determination of drug enantiomers by using chiral ILs as a new chiral selector in chromatography.

Owing to very high viscosity, inferior ultraviolet (UV) transparency and much higher costs, it is unlikely that any ILs can replace methanol and/or acetonitrile in routine RPLC. However, as mentioned previously, ILs as mobile phase additives can indeed improve analysis results. These aspects can allow the development of more efficient separation processes for RPLC. However, ILs are certainly not the additive of choice with a mass spectrometry (MS) detector. The non-volatility of ILs is responsible for condensation and pollution of ILs in the electron spray or atmospheric pressure ionization sources.

Stationary phase

Another new direction in the application of ILs in LC is as surface-bonded stationary phases (also called surface confined IL: SCIL). Related synthesis methods, mechanisms and performance in separating individual classes of compounds are the focus in this section.

Methods for the synthesis of SCIL

3-Mercaptopropyltrimethoxysilane (MPS), as a silane-coupling agent, was first used to synthesize SCIL in 2004 (49). As is shown in Figure 3A, IL reacted with MPS-modified silica using azodiisobutyronitrile (AIBN) as the initiator via the radical chain transfer addition. Additionally, a considerable number of researchers (50–52) have adopted 3-chloropropyltrimethoxysilane to connect silica gel and ILs (Figure 3B). Some of these SCILs have been used as anion-exchange stationary phases for HPLC (51, 52). Another synthesis route for preparing SCIL is to graft an 8-bromooctyl-1-trichlorosilane linking ligand to the silica substrate (53). The subsequent attachment of IL precursor compounds (methylimidazole, butylimidazole and benzylimidazole) or a zwitterionic IL to the linking ligand leads to the formation of the SCIL phase.

In recent years, a major breakthrough in column technology has been the development of monolithic columns. Monolithic HPLC columns are prepared by a polymerization process from either organic polymers, such as polymethacrylates, polystyrenes or inorganic polymers, such as silica. This technology has many advantages: the columns are easy to make and provide low cost and good stability, and the cost of analysis can be reduced by reusing the monolithic column up to 100 times injections without significant changes in analyte recovery or column backpressure. Zhu *et al.* (54) used *in situ* polymerization technology to synthesize the IL-based monolithic column. The synthesis processes is depicted in Figure 4. In this study, the determination of caffeine and theophylline was used to evaluate the characteristics of the new material; this analysis method showed high sensitivity and the appropriate precision, accuracy and recovery.

Mechanism

Sun *et al.* (55) have worked to understand the complex intermolecular interactions and to investigate the retention mechanism of SCIL. They used linear solvation energy relationships (LSERs) to describe the contribution of individual intermolecular interactions to the retention behavior. As a result, the SCIL stationary phase showed multimodal retention properties, including strong

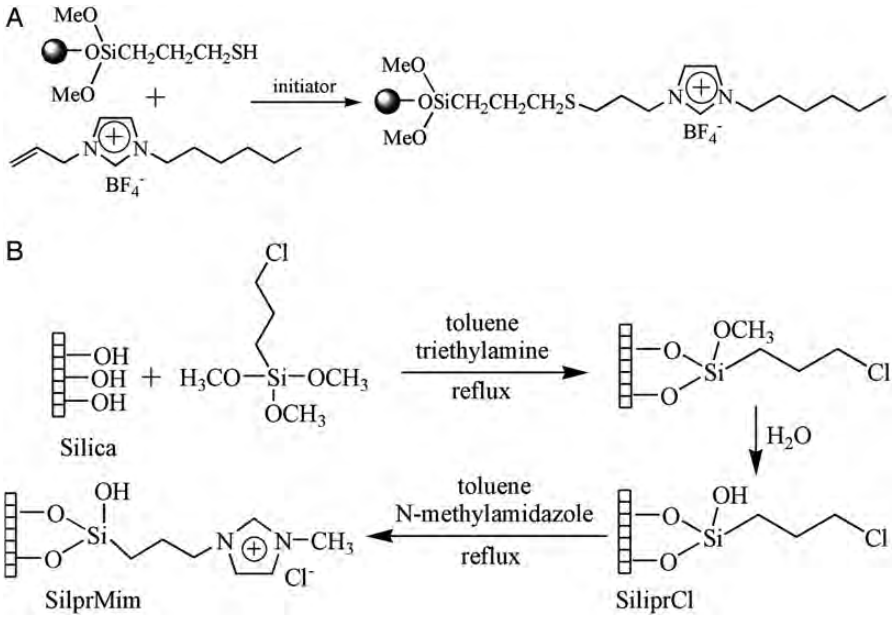

Figure 3. Some methods for preparing SCIL stationary phases. (A) adapted from Chinese Chemical Letters, 15, Liu, S. J. et al., Surface Confined Ionic Liquid—A New Stationary Phase for the Separation of Ephedrines in High-performance Liquid Chromatography, 1060-1062, 2004. (B) reproduced from Journal of Chromatography A, 1103, Qiu, H., Jiang, S. and Liu, X, N-Methylimidazolium anion-exchange stationary phase for high-performance liquid chromatography, 265–270, 2006, with permission from Elsevier BV

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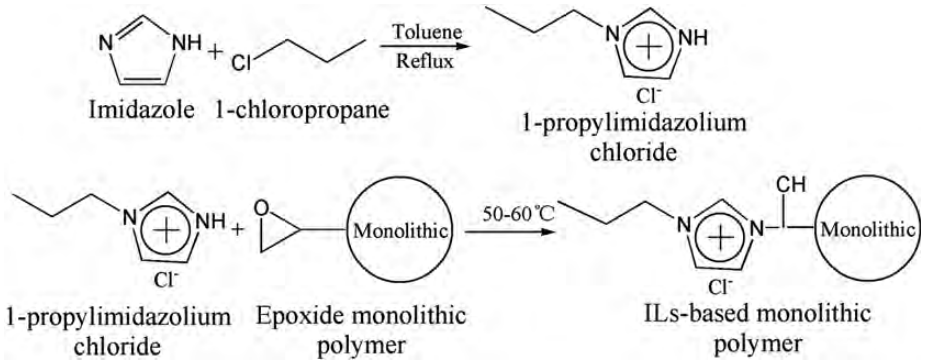

Figure 4. Synthesis processes of ILs and IL-based monolithic column. Adapted from Journal of Applied Polymer Science, 118, Zhu, T., Bi, W. and Row, K. H, A new ionic liquids-based monolithic column for determination of caffeine and theophylline, 3425–3430, 2010

Table II
Applications of SCILs in LC except Enantioseparation

ILs used to modify silica	Target analytes	Advantages	Reference
$[C_n him][BF_4]$	Ephedrines	Retention times were obviously decreased but resolution was improved	49
Imidazole and others	Caffeine, theophylline, theobromine	Deionized water used as mobile phase for separation	50
$[C_n mim]^+$	Amines, nucleotides		51, 52
1-Propylimidazolium-based monolithic column	Caffeine, theophylline	Fast separations and low back-pressure	54
3-Methylimidazolium	Antiretroviral drugs	Gradient drift reduced drastically compared to TEA	62
2-Ethyl-4-methylimidazole chloride	Tanshinone I and IIA in Danshen herb	IL-modified silica is more effective than unmodified silica	63
$[C_4 mim][Br]$	Peptides		64
$[C_1 pim][Br]$	Aromatic carboxylic acids		56
$[C_4 pim][Br]$			

hydrogen bonding, hydrophobic interactions and ion-dipole or ion-induced-dipole and strong ion-pairing effects. This result is the same as that found by other research groups (49, 51, 52, 56). In their next study (57, 58), the previously used C_4mim column was characterized by an LSER approach in both methanol–water and acetonitrile–water mixtures using 28/32 test solutes. A comparison of three conventional RP systems revealed that the retention properties were similar to phenyl phases, which has also been observed by Qiu *et al.* (59). Under RP conditions, the primary interaction contributing to retention is the hydrophobic interaction between solutes and the stationary phase, which is compensated by the hydrogen bonding acidity interaction residing in the mobile phases. To further identify the retention characteristics, the authors employed a commercial quaternary amine silica-based strong anion exchange column to examine the differences and similarities between the SCIL and conventional ion exchange media (60). A significant difference in the hydrophobic and hydrogen bond acceptance interaction properties was obtained from a comparison of the two stationary phases. Furthermore, the results also showed that an important distinction of SCIL or ion exchange phase from alkyl-based phases was the more important effect of ion-dipole interactions. Further research from this group in 2009 suggested that retention on SCIL phases was more profoundly affected by the identity of the anion than by that of the cation (53).

Application

In recent years, the applications of SCIL have increased gradually. Amines, nucleotides, peptides and natural products have been effectively separated (Table II). Additionally, ILs may be custom designed, including the possibility of changing the anions, cations and alkyl chain. This advantage may provide the ability to manipulate the structure of IL-modified silica and, consequently, its properties. Therefore, using ILs in enantioseparation may be very effective. Zhou *et al.* (61) first synthesized four ILs functionalized β-cyclodextrin (β-CD) bonded chiral stationary phases by treating 6-tosyl-β-CD with ILs and bonding to silica gel. Using these new stationary phases in HPLC, the separation was satisfactorily performed. These chiral stationary phase afforded excellent enantioselectivity by using an acetonitrile-based polar organic mobile phase.

One of the advantages of using SCIL stationary phases is that effective separations can be achieved with aqueous mobile phases without organic solvent or containing only very small amounts of the solvent (<1%). This reduces the cost and pollution. Additionally, pure products can be obtained from this method without further separation. If combined with monolithic column technology, the potential environmental benefits and economic incentives of analyzing and separating will greatly promote the development of LC.

Ionic Liquids in Electrodriven Techniques

Capillary electrophoresis

CE is an electrodriven separation method that combines the advantageous features of online detection, high efficiency, low sample consumption, rapid analysis, automation and low cost of capillaries compared to HPLC columns. CE has incredible

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efficiency or ability to separate compounds with similar structures. This is ascribed to electroosmotic flow (EOF). EOF is the solution that moves toward the cathode when a voltage is applied across a tube that has a negatively charged surface (e.g., fused silica capillary) filled with an electrolyte solution. This should not be confused with electrophoretic mobility, which is used to describe the affinity of a molecule for its opposite electrode. Each ion has different electrophoretic mobility, which is based on the charge to mass ratio. Because the EOF of the buffer solution is generally greater than the electrophoretic mobility of the analytes, all analytes are carried along with the buffer solution toward the cathode in an uncoated capillary. Cations migrate quickly, neutral compounds take slightly longer and negatively charged analytes are retained longer in the capillary due to their conflicting electrophoretic mobility. Therefore, both EOF and electrophoretic mobility occurring at the same time and working in opposite directions provide greater resolution than other separation technologies.

The primary variables affecting EOF mobility are zeta potential value, dielectric constant and viscosity of the buffer. The use of buffer additives and/or other modifications of the buffer composition may influence these parameters. Alkylammonium salts were used as EOF modifiers in some early CE studies. Currently, ILs are good candidates as EOF modifiers for their good electrical conductivity. They are also slightly more viscous than organic solvents; therefore, low concentrations may be required for buffer modification to achieve better separation. In the field of CE, ILs can be used as electrolytes, as additives to electrolytes and as covalent coating reagents of the capillary, but the latter is not easy to implement and costs more, so ILs are most often used as electrolytes or additives to electrolytes to modify the capillary. Some applications of ILs in CE have been displayed in Table III.

Electrolytes or additives to electrolytes

When ILs are added to electrolytes, their cations and anions influence the migration behavior of analytes in different ways. The resolving power of the system is more often connected to the activity of IL cations, which play two roles: first, the IL can coat the wall of the capillary to modify the EOF (and can sometimes even reverse the direction of the EOF); second, the analytes interact with the cations on the capillary or free cations in the electrolyte solution (Figure 5). Therefore, once the added amount of IL is perfectly controlled, each ion will have different electrophoretic mobility and the resolution will be greater. Many examples shown in the following have proved this mechanism.

Aqueous capillary electrophoresis

Yanes *et al.* (65) first used tetraalkylammonium-based ILs as the background electrolyte (BGE) for separating phenolic compounds extracted from grape seeds. The same group also used $C_n$mim-based ILs as the BGE (66). The authors found that the sizes of the uncharged polyphenols and the different degrees of association with IL cations provided effective electrophoretic mobility differences for effective separation. Other natural products like aconitine alkaloids and other bioactive constituents have also been successfully separated (67, 68). In addition to ILs, some other additives have been added to aid in separation. Qi *et al.* (69) reported the use of IL used as the running electrolyte in CE with β-CD as a modifier for the separation of an extract of anthraquinones from the Chinese herb *Paedicalyx attopevensis* Pierre ex Pitard.

CE has also become one of the most powerful tools for analyzing a wide variety of peptide and protein mixtures. A key concern in protein separation in traditional CE is the tendency of these molecules to be adsorbed onto the surface of the capillary tubing. The fused-silica tubing has a negatively charged surface due to the presence of silanol groups, which electrostatically attract the positively charged sites of proteins. This seriously impairs the separation efficiency and leads to poor repeatability. Several common optimized approaches have been proved to fail: (i) adjusting the pH or ionic concentration of the BGE may cause protein denaturation; (ii) permanent modification of the capillary by covalent bonding needs a long-term coating operation. Hence, adding additives to electrolytes to modify the capillary by dynamic coating or physical adsorption is particularly attractive due to its versatility and simplicity. Jiang *et al.* (70) used $C_n$mim-based ILs as dynamic coatings of CE to successfully separate basic proteins, such as lysozyme, cytochrome c, trypsinogen and α-chymotrypsinogen A. In addition, polymeric ionic liquids (PILs) have also been applied as additives to electrolytes. Li and colleagues (71, 72) employed poly(1-vinyl-3-butylimidazolium) bromide ([PVBim][Br]) as the dynamic coating additive in CE to separate aromatic acids and proteins, which provided better separation than the normal mode.

Nonaqueous capillary electrophoresis

In the last few years, nonaqueous media has played an important role in electrophoretic separation. Nonaqueous media often competes favorably with aqueous systems in the separation of both charged and uncharged species (73, 74). Nonaqueous capillary electrophoresis (NACE), which is based on the use of the electrolyte solutions prepared from pure organic solvents or their mixtures, offers many attractive features such as alteration of selectivity, improved solubility of hydrophobic compounds and reduced electrophoretic current. Faster separations can be obtained in NACE because of the lower viscosity solution and the higher EOF, and the use of organic solvents makes direct online MS detection feasible. NACE has received considerable attention due to these special advantages; additionally, some water-insoluble compounds cannot be separated in traditional aqueous CE. Meanwhile, ILs possess some attractive properties over conventional organic solvent modifiers, such as good electrical conductivity. Hence, using ILs in NACE may produce better separation effects.

Vaher *et al.* (75) first used dialkylimidazolium ILs as buffer electrolytes to separate water-insoluble dyes in acetonitrile-based NACE. When the C_4mim-based IL was added as an additive, the dyes were well separated. Vaher and coworkers (76, 77) applied $C_n$mim-based ILs in NACE to separate carboxylic acids and phenolic and polyphenolic compounds. They found that the primary mechanism of separation was heteroconjugation between the salt anion and the analyte molecules.

Enantiomeric separation

HPLC and GC are the two most widely used methods for chiral separation. Because of the low sample consumption and rapid analysis, CE has provided an alternative method for chiral separation. However, the number of chiral selectors that are known to be effective in CE is considerably less than the chiral stationary

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Table III
Applications of ILs as Electrolytes or Additives to Electrolytes in CE

ILs	Target analytes	Advantages	Reference
ILs used as electrolytes or additives to electrolytes to modify or dynamically coat the capillary			
$[P_{2222}][BF_4]$	Polyphenols in grape seed extracts	Simple and reliable method, produced good peak resolution and excellent reproducibility migration times	65, 66
$[C_n mim]^+$			
$[C_4mim][BF_4]$	Aconitine, meaconitine and hypaconitine in *Aconitum* plants	Analytical time decreased 4–8 fold and effect of Joule heating was weak	67
$[C_2mim][BF_4]$	Bioactive constituents in opium poppy	Detection was rapid, sensitive, quantitative and reproducible combined with electrochemiluminescence	68
$[C_4mim][BF_4]$	Anthraquinone extracts of Chinese herb *Paedicalyx attopevensis* Pierre ex Pitard	Simple and sensitive method, produced good reproducibility and detection limit, and analysis time was short	69
$[C_n mim]^+$	Basic proteins	Baseline separation, high efficiency and symmetrical peaks obtained	70
[PVBim][Br]	Eight negatively charged aromatic acids, basic proteins	Eliminated adsorption of proteins onto the capillary wall	71, 72
$[C_4mim]^+$	Water-insoluble dyes	Successfully separated the target analyte, which was not resolved with traditional CE methodology	75
$[C_n mim]^+$	Carboxylic acids, phenolic and polyphenolic compounds	Research on the mechanism	76, 77
S-[CHTA][Tf_2N]	Pharmaceutical products: atenolol, propranolol, warfarin, indoprofen, ketoprofen, ibuprofen and flurbiprofen	IL served as both electrolyte and chiral selector	78
[DMP][Tf_2N]	Rabeprazole and omeprazole		79
Ethyl-[Tf_2N]	Anti-inflammatory drugs: 2-arylpropionic acids	Increased separation selectivity and resolution	80
Phenylcholine-[Tf_2N]			
$[C_4mim]^+$	Chlorophenoxy and benzoic acid herbicides	Method offered relatively short analysis times and potential ability to resolve positional isomers	81
$[C_2mim][BF_4]$	Monohalogenated phenols	Research on the mechanism	82
$[N_{2222}][BF_4]$			
Dimethyldinonyl-ammonium bromide	Carboxylates as copper complexes	High separation efficiency	83
$[C_2mim][BF_4]$	Nicotinic acid and its structural isomers	Decreased migration times, improved peak shapes and increased separation performance	84
$[C_n mim]^+$	Five anthraquinone derivatives in Rhubarb species	Simple, rapid technique with high selectivity and much simpler than reported methods	85
$[C_4mim][BF_4]$	Alkaloids (verticine and verticinone) from *Bulbus fritillariae*	Improved limits of detection between 10^2 and 10^4-fold more sensitive than existing analytical methods	86
$[C_4mim][Tf_2N]$	Four arylpropionic acids	Research on the mechanism	87
ILs used as covalent coating reagents of the capillary			
1,3-Dialkylimidazolium-coated capillary, $[C_2mim]+$ as BGE	NH_4^+ ions in human urine; K^+, Na^+, Li^+, Ca^{2+}, Mg^{2+} and Ba^{2+} ions in red wine	Improved working pH range of running buffer with good efficiency; resolution of metal ions improved without addition of modifiers	88
1,3-Dialkylimidazolium-coated capillary	DNA	DNA separation accomplished with shorter analysis time in IL-coated capillary than in polyacrylamide-coated capillary.	89
	Sildenafil and its metabolite UK-103,320(UK)	Enhanced resolution enhanced; connected with MS	90

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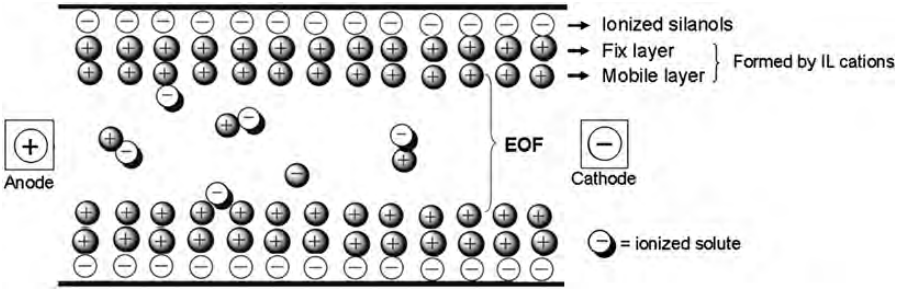

Figure 5. ILs coat the capillary walls to modify the EOF and interact with analytes.

phases available in GC and HPLC. As a consequence, searching for new chiral selectors is an important concern in CE separation. A variety of compounds including CDs, crown ethers, proteins, polysaccharides, macrocyclic antibiotics, chiral micelles and metal chiral ligand complexes can be effectively used as chiral selectors for CE. Unfortunately, when they are used without any other additives, these chiral selectors may not provide adequate selectivity and resolution. In some cases, more than one chiral selector is needed for chiral separation. Therefore, considerable efforts have been made in the last few years to find novel chiral selectors that can offer high selectivity and resolution for enantioseparation by CE. Chiral ILs offer an attractive solution for this problem. When used in CE, a chiral IL can simultaneously serve as an electrolyte and a chiral selector. Tran and Mejac (78) used a chiral IL, *S*-[3-(chloro-2-hydroxypropyl)trimethylammonium]-[*bis*((trifluoromethyl)sulfonyl)amide] (S-[CHTA][Tf_2N]), as a co-electrolyte and a chiral selector for pharmaceutical products. A variety of pharmaceutical products were successfully baseline separated, including atenolol, propranolol, warfarin, indoprofen, ketoprofen, ibuprofen and flurbiprofen. Ma *et al.* (79) used an ephedrine-based IL as the chiral selector to successfully separate rabeprazole and omeprazole by NACE. They found that ion-pair interaction and hydrogen bonding may be responsible for the primary separation mechanism. Francois *et al.* (80) evaluated chiral ILs as additives to CDs for enantiomeric separations by CE. The study was conducted with the anti-inflammatory drugs 2-arylpropionic acids as model compounds. The results showed that these chiral ILs did not present direct enantioselectivity with regard to the model analytes. The influence of chiral ILs in the electrolytes was studied in the presence of classical chiral selectors (di- or trimethyl-β-CD). Although no general trend could be established, an increase in separation selectivity and resolution was observed in some cases, suggesting synergistic effects. Unfortunately, chiral ILs are not commercially available at present, which severely hinders their applications.

Covalent coating reagents of the capillary

Another application of ILs in CE involves covalently coating the capillary wall. The EOF of a bare silica capillary can be reversed by the covalently bonded 1,3-dimethylimidazole (88). Additionally, the utilization of $[C_2mim]^+$ as BGE efficiently increases the working pH range of the running buffer. Capillaries prepared in this way were applied to the separation of NH_4^+ in human urine from K^+ and the separation of K^+, Na^+, Li^+, Ca^{2+}, Mg^{2+} and Ba^{2+} ions in red wine. The resolution of metal ions can be improved with a freshly coated capillary. In another work, the authors reported the use of capillaries coated with ILs for DNA (89) and positively charged drug separation (90).

Micellar electrokinetic chromatography

Mechanism

MEKC is a powerful extension of CE that allows the separation of mixtures of uncharged and/or charged compounds. This technique was developed by Terabe *et al.* in 1984 (91). In MEKC, the surfactant monomers added to an electrolyte solution above the critical micelle concentration (CMC) form aggregates called micelles, which are important as a pseudostationary phase. The separation process is based on differences between the analytes partitioning in a micellar stationary phase and on the results of the electrophoretic mobility of the analytes. The neutral analyte will gain an apparent electrophoretic mobility when it is incorporated into the micelles and will migrate at same velocity as the micelle under electrophoretic conditions. Thus, the neutral and charged solutes with the same charge-to-mass ratio can also be separated (91), because the migration time in MEKC is a function of the electrophoretic velocity of the micelle, the distribution ratio and EOF velocity. A schematic principle of MEKC is shown in Figure 6.

Various kinds of surfactants have been used in MEKC. SDS is the most widely used anionic surfactant. It has a low CMC and provides good selectivity and efficiency. In addition, it is readily available and has the low cost of a pure product. However, there are two problems: (i) SDS has a relatively high CMC and a high Krafft point (16°C), which causes the precipitation of SDS at low temperatures; potassium dodecyl sulfate has a particularly high Krafft point (40°C), therefore, the use of potassiumion as an electrolyte should be avoided when SDS is used (92); (ii) the nucleus of the SDS micelles is strongly hydrophobic. For very hydrophobic compounds, MEKC with SDS is often insufficiently selective because all compounds tend to be almost completely absorbed into the micelles and migrate with the velocity of the micelles (93). Hence, there is a need for other micellar phases. Many different types of surfactants may be used as the pseudostationary phase in MEKC, and the characteristic parameters of typical surfactants have been described in Terabe's review articles (92).

In addition to surfactants, several additives have been developed to improve MEKC separation. They primarily have been used to modify the aqueous phase, but some are incorporated into and concomitantly modify the micelle. The most popular

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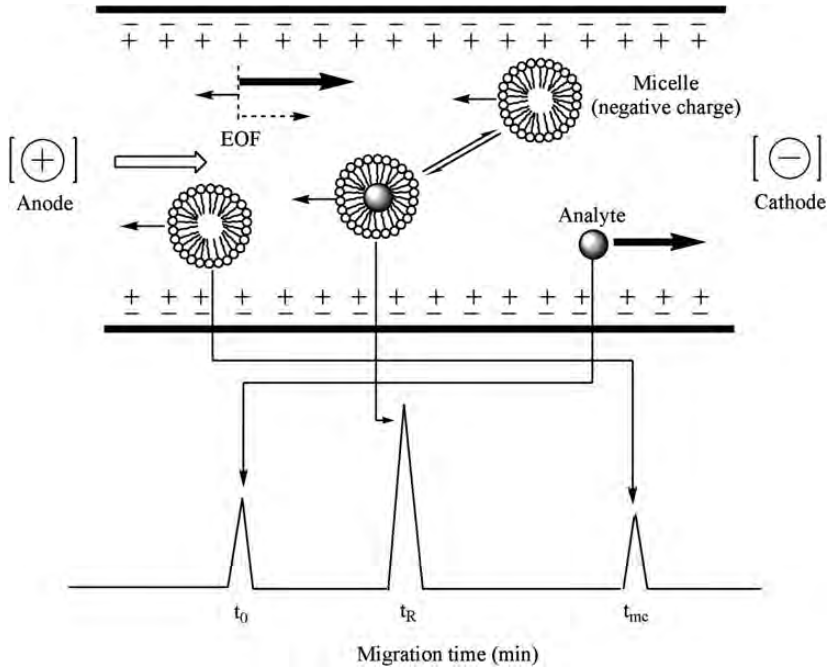

Figure 6. Schematic principle of MEKC with anionic micelle; t_0: migration time of a neutral unretained solute; t_R: retention time in MEKC; t_{mc}: migration time of a micellar aggregate.

additives are organic solvents such as acetonitrile (93), 2-propanol (94) and other organic compounds (95, 96). CD derivatives are probably the next most widely used additives (97, 98), and are particularly useful for the separation of enantiomers. Several additional additives have been reported: crown ether (18-crown-6) (99), ion-pair reagents (100), glucose (101), silver(I) (102), polyelectrolyte complex (103) and metal cations (104).

ILs involve a charged hydrophilic head group and one or more hydrophobic tails; these ILs resemble conventional surfactants (105), and indeed, micelles form in solution when the concentration of ILs exceeds the CMC. Because of their high conductivity, hydrophobicity and solvation, ILs can be used at higher concentrations than organic solvents because they do not destroy the micellar system in MEKC. In recent years, ILs have been applied as surfactants or additives to improve the properties of MEKC-based separations (Table IV).

Application

Schnee *et al.* (106) found that the presence of a [$C_n$mpyr][Br] micellar pseudophase provided highly efficient separation because the interactions of these less hydrophobic surfactants with polar compounds were stronger than a commonly employed surfactant, cetrimonium bromide (CTAB). The magnitudes of the LSER coefficients showed that lipophilicity and hydrogen-bond acidity played the most important roles in MEKC retention. Borissova *et al.* (107) introduced the surfactant [C_{14}mim] into the BGE to successfully separate neutral analytes, such as methylresorcinol isomers and other hydrophobic benzene derivatives. According to these findings, imidazolium and pyrrolidinium-based surfactants appear to have great potential for application in MEKC.

Mwongela *et al.* (108) used polymeric surfactants with ILs as modifiers in MEKC to separate both achiral and chiral compounds. Poly(sodium *N*-undecylelinic sulfate) and poly(sodium oleyl-L-leucylvalinate) were tested as surfactants to separate three types of mixtures (alkyl aryl ketones, phenols and enantiomers of binaphthyl derivatives). Five different ILs were tested as modifiers and [C_4mim][BF_4] worked best. Peak efficiency and elution time were influenced by the concentration of ILs. The migration order of ketones indicated that the more hydrophobic analytes partitioned more to the polymeric pseudophase than to the bulk aqueous phase.

Wang *et al.* (109) combined certain cationic IL-type surfactants, *N*-undecenoxy-carbonyl-L-leucinol bromide (L-UCLB) and 2,3,6-tri-O-methyl-β-CD (TM-β-CD), as a dual chiral selector for MEKC. The enhancement in chiral selectivity and the resolution of two profens (e.g., carprofen and suprofen) were achieved. This is the first study in which the simultaneous enantioseparation of profen drugs was achieved by using a mixture of IL and TM-β-CD as a dual chiral selector. The authors expanded their study by using a competitive inhibition mechanism to investigate the interactions among TM-β-CD, L-UCLB and profens, suggesting that the inhibition observed in chiral separation of profens is a competitive inhibition (110).

In addition to fused silica, PDMS is an attractive polymer material for fabricating fluidic devices in CE and MEKC. It has been used extensively in many applications due to its excellent properties such as optical transparency, flexibility and easy fabrication. However, the porous nature, hydrophobic surface and incompatibility with aqueous separation media, especially the hydrophobic tail adsorbing to protein, have hampered its widening applications. Thus, surface modification is an indispensable prerequisite. Xu *et al.* (111) evaluated MEKC by using PDMS based on one functionalized IL and found excellent performance on the separation of proteins. They found that C_4mim-dodecanesulfonate (BAS) used as a running buffer applied in microchip MEKC significantly enhanced the EOF and resolution efficiency

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Table IV
Some Applications of ILs in MEKC

ILs	Target analytes	Advantage	Reference
$[C_n mpyr][Br]$	Four to six alkyl phenyl ketone homologs	Research on the mechanism	106
$[C_{12}mim]^+$	Isomers of methylresorcinol and benzene derivatives	Baseline separation	107
$[C_{14}mim]^+$			
$[C_6mim][BF_4]$, $[C_2mim][CF_3SO_3]$	Eight alkyl aryl ketones, seven phenols, three chiral binaphthyl derivatives	Successful separations of two achiral mixtures and one chiral mixture	108
$[C_2mim]$			
L-UCLB	Five profen compounds	Resolution values significantly higher than previously reported	109, 110
BAS	Proteins	Eliminated protein adsorption to PDMS surface; achieved well-separated protein mixtures	111
	Proline and hydroxyproline	Significantly improved resolution efficiency; enhanced electrochemiluminescence intensity and column efficiency for negative targets	112
$[C_{16}mim][Br]$	Benzodiazepines	Enhanced separation efficiency and detection sensitivity	113
$[C_{16}mpy][Br]$			
$[C_{16}mIm][Br]$:$[C_{14}mIm][Br]$	Quinol, phloroglucinol, resorcinol, phenol, *p*-cresol and *m*-nitrophenol	Results indicated that $[C_{16}mIm][Br]$ has advantages over $[C_{14}mIm][Br]$ and $C_{16}TAB$	114
$[C_4mim][BF_4]$	Narcotic drugs	Less noisy baselines, low electrophoretic current and satisfactory separation performance	115
$[C_4mim][BF_4]$	Active components of lignans from seeds of *Schisandra* species	$[C_4mim][BF_4]$ found to be an effective additive for improving the separation of lignans, which was impossible with the use of pure SDS	116

Figure 7. Number of publications per year (2002–2012) on the subjects of ILs and LC, and ILs and CE, according to SciFinder Scholar data.

between analytes. BAS not only provided the appropriate ionic strength, but also alleviated the absorption of proteins to the PDMS surface. This is crucial for increasing the functionality of PDMS in MEKC systems.

Conclusion

The rapid growth in interest toward the application of ILs in LC and CE (Figure 7) is reasonable in view of their unique properties. The use of ILs opens new opportunities to solve problems in the difficult separation of different analytes. The almost unlimited number of available ILs allows scientist to design various applications in separation science. At the same time, the use of ILs as green chemical modifiers is recommended instead of the conventional environmentally harmful agents, which are currently widely employed in analytical practices.

Although these fields continue to progress, there are some underlying problems. First, the systematic and mechanistic understanding of IL properties is not adequate; second, the toxicity and long-term stability of ILs can vary widely and must be taken into consideration when ILs are chosen for any project; third, the purity of ILs cannot always be warranted because of the preparing techniques and storage methods. Therefore, precautions should be taken because impurities can affect both the properties of the IL and the application in which it is used. Fourth, commercial suppliers of ILs are few and the prices are still expensive, which will limit their applications to some extent.

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