

JOURNAL OF LIQUID CHROMATOGRAPHY & RELATED TECHNOLOGIES®

Vol. 27, No. 7–9, pp. 1443–1459, 2004

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Ionic Liquids in Chromatography and Capillary Electrophoresis

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ABSTRACT

One of the major challenges facing the chemical industry is the development of new, “green” technologies which reduce the environmental impact of manufacturing processes. Ionic liquids are emerging as a promising alternative to traditional organic solvents and are, thus, generating considerable interest in a variety of areas. This review examines some of the unique properties of ionic liquids and their applications in analytical separations.

Key Words: Ionic liquids; Molten salts; Gas chromatography; Liquid chromatography; Capillary electrophoresis; Review.

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INTRODUCTION

Ionic liquids continue to generate considerable interest in “green chemistry”^[1] and have been utilized in a variety of different areas. While the significance of these materials to the separations community, thus far, may have predominantly resided in product isolation and ionic liquid analysis^[2]/regeneration, the unique interactions of these materials suggest that they might also provide interesting opportunities for separation science. One of most intriguing aspects of ionic liquids is that they are comprised of two distinct species—the cation and the anion—and both may play unique yet interdependent roles in retention and separation mechanisms obtainable with these materials.

The main goal of this review is to focus on some of the unique properties and uses of ionic liquids as well as their applications to chromatography and capillary electrophoresis.

PHYSICAL PROPERTIES OF IONIC LIQUIDS

Ionic liquids, sometimes referred to as molten salts, are ionic substances with melting points at or close to room temperature. Typically, these compounds consist of large organic cations, most commonly nitrogen-containing (e.g., 1-ethyl-3-methylimidazolium, tetraalkylammonium) and inorganic anions (e.g., chloride, bromide, tetrafluoroborate, hexafluorophosphate) (Fig. 1).^[3,4] In the case of 1,3-dialkylimidazolium-based ionic liquids, because the nomenclature can become quite cumbersome, it is common to use the first letter of one alkyl substituent followed by the first letter of the second alkyl substituent, followed by “IM” for imidazolium. Thus, the shorthand for 1-butyl-3-methylimidazolium becomes BMIM. Alternatively, BMIM could also be referred to as [C₄MIM][anion].

The melting points, densities, and viscosities for some representative ionic liquids are presented in Table 1. As can be seen even for this limited selection of ionic liquids, the melting points for ionic liquids can encompass a broad range of temperatures. Furthermore, because they are relatively

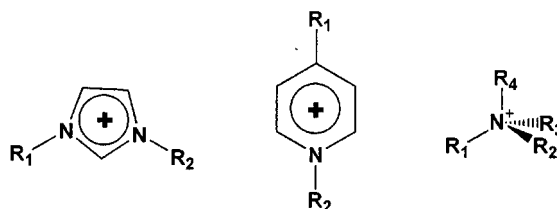
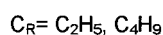
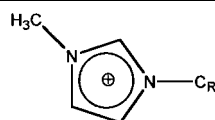


Figure 1. Structures of typical ionic liquid cations.

Table 1. Melting points, densities, and viscosities for representative ionic liquids.

| Ionic liquid | | Melting point (°C) | Viscosity (cP) | Density (g/mL) | References |
|----------------------------------------------------|----------------------|--------------------|----------------|----------------|------------|
| Cation | Anion | | | | |
| [C ₂ mim] | [PF ₆] | 58–60 | | | [10] |
| [C ₂ mim] | [BF ₄] | 15 | 43 (25°C) | | [2,10] |
| [C ₄ mim] | [Cl] | 65 | Solid (20°C) | 1.08 | [10,11] |
| [C ₄ mim] | [PF ₆] | –8 | 312 (20°C) | 1.36 | [10,11] |
| [C ₄ mim] | [AlCl ₄] | 65 | | | [10] |
| [C ₄ mim] | [BF ₄] | –82 _(g) | 233 (20°C) | 1.12 | [10,11] |
| [N(C ₆ H ₁₃) ₄] | [BF ₄] | 89.5–91.5 | | | [19] |
| [EtPy] | [Br] | 110 | | | [17] |

Note: g, glass transition; mim, methylimidazolium.

non-volatile, individual ionic liquids typically may have fairly large thermal operating ranges (e.g., –40 to 200°C).^[5] In addition to their negligible vapor pressure, it is estimated that there are potentially $\sim 10^{18}$ different room temperature ionic liquids^[6] with a wide range of physical and chemical properties. Thus, they encompass a much broader array of solvent properties than conventional organic solvents.

While ionic liquids are considered to be environmentally benign because of their negligible vapor pressure and non-flammability, it should be noted that polychlorinated biphenyls were also once considered “safe”. Very little information is available regarding the toxicity or environmental fate of ionic liquids.^[7] Furthermore, PF₆[–], a common anion found in hydrophobic ionic liquids, is known to be hydrolytically and thermally unstable with HF as a decomposition product.^[8] Thus, their ultimate “greenness” may also be limited by the anion.^[9]

NONCHROMATOGRAPHIC APPLICATIONS OF IONIC LIQUIDS

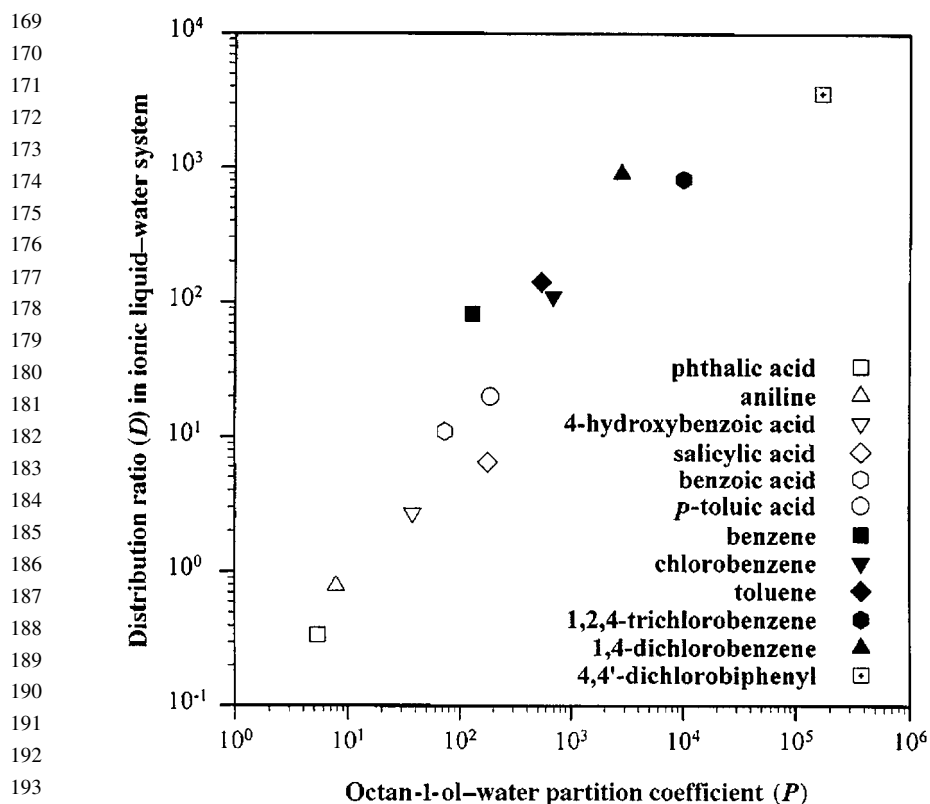
Ionic liquids are being investigated as “green chemistry” replacements^[6] for volatile organic compounds (VOCs) which are traditionally used as

127 solvents^[10] and/or catalysts in a variety of synthetic processes such as
128 Friedel–Crafts reactions,^[11] Diels–Alder reactions,^[5,12] Heck reactions,^[13]
129 and many others. They have been reported to enhance these processes by
130 increasing reaction efficiency, decreasing the use of raw materials thereby
131 decreasing environmental load. For example, in the case of Diels–Alder reac-
132 tions, the use of ionic liquids was reported to provide higher yields, selectiv-
133 ities, and rate enhancement;^[12] for Friedel–Crafts reactions, they provided
134 yields comparable to the best results reported^[11] using conventional organic
135 solvents.

136 Work-up and product isolation in traditional organic synthetic methods
137 usually rely on differences in aqueous-organic partitioning by sequestering
138 the product in an organic phase. Sequestering the product in an organic
139 phase rather than the aqueous phase is usually preferred because the high vola-
140 tility of most organic solvents facilitates isolation of the pure product. The
141 negligible vapor pressure of ionic liquids precludes this approach and compli-
142 cates recovery of nonvolatile products, necessitating extraction into volatile
143 organic solvents, thereby defeating the “green” goal of waste reduction. A
144 promising alternative to product recovery from ionic liquid reaction media
145 is the use of supercritical CO₂. In a pioneering study using supercritical
146 CO₂ to extract a wide range of organic solutes from [BMIM][PF₆], Blanchard
147 and Brennecke^[14] found that while aromatic compounds were generally more
148 soluble in the ionic liquid than aliphatic compounds, all solutes investigated
149 exhibited greater than 95% recovery from the ionic liquid. This approach
150 was adapted to a continuous process in which a catalyst was dissolved in
151 the ionic liquid and supercritical CO₂ acted as a transport vector for both sub-
152 strate and product in the formylation of alkenes.^[15] Brennecke et al. also
153 demonstrated that supercritical CO₂ could be used to “tune” ionic liquid/
154 methanol miscibility.^[16]

155 The viscosity and miscibility of ionic liquids with water or organic sol-
156 vents can be modified by changing the anions or the alkyl chains on the cation.
157 ^[17,18] For example, [BMIM][BF₄] is water miscible while [BMIM][PF₆]
158 is not. Many ionic liquids are immiscible with several organic solvents
159 and/or water, providing alternative two-phase systems for liquid-liquid
160 extraction.^[19] For example, [BMIM][PF₆] was used to extract organic
161 amines (e.g., aniline, bromoaniline), acids (e.g., 2-amino benzoic acid, 3,5-
162 dinitrobenzoic acid), benzene, and other substituted benzenes (e.g., phenol,
163 toluene) from heptane.^[20] Indeed, heptane/water/[BMIM][PF₆] and water/
164 [BMIM][PF₆]/chloroform were shown in this work to form triphasic systems.

165 For liquid–liquid extraction applications, the partition coefficients for
166 [BMIM][PF₆]/water and octanol/water systems for some acids and substi-
167 tuted benzenes appears to correlate, as shown in Fig. 2.^[19] However, another
168 study^[20] examining partitioning between [BMIM][PF₆] and water found



195 **Figure 2.** Correlation of partitioning data between [BMIM][PF₆]-water and octan-
196 1-ol-water biphasic systems.^[19] Source: Reproduced with permission of The
197 Royal Society of Chemistry.

201 that while there was considerable correlation in partitioning behavior in
202 octanol/water and ionic liquid/water partitioning for neutral, amino-aromatic
203 compounds, and compounds with mixed acidic and basic functionality, there
204 was more divergence for acidic compounds in the two systems and pH, not
205 surprisingly, also affected partitioning.

206 Task-specific imidazolium-based ionic liquids that incorporated
207 thioether, thiourea or urea side chains were designed for the extraction of
208 cadmium and mercury ions from aqueous solutions by incorporating ligand
209 groups on the cation that complex with the metal ions.^[21] However, traditional
210 metal chelates could also be extracted from water into ionic liquids.^[22]

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211 The solvation properties of specially designed ionic liquids were also
212 exploited for matrix assisted laser desorption ionization (MALDI) analysis
213 of peptides, proteins and synthetic polymers.^[23,24] Successful ionic liquid
214 matrices for MALDI applications required an acidic proton and were shown
215 to be better than analogous solid matrices in their ability to promote ion
216 formation. In this capacity, ILs offered the homogeneity advantages of liquid
217 matrices while demonstrating vacuum stability comparable or even exceeding
218 those of conventional solid matrices. Indeed, the homogeneity of these ionic
219 liquid matrices is advantageous when compared with solid matrices which
220 require the sampling of several matrix spots with the averaging of the results.

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223 IONIC LIQUIDS IN GAS CHROMATOGRAPHY

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225 Thus far, most of the applications of ionic liquids in analytical separations
226 have been in the area of gas chromatography and most of these studies have
227 focused on characterizing their intermolecular interactions. The application
228 of molten salts in gas chromatography started as a search for polar, thermally
229 stable, and selective stationary phases. Their chemical and physical properties
230 (e.g., nonvolatility, viscosity, polarity) enabled ionic liquid stationary phases
231 to be prepared either by coating the ionic liquid on a solid support or in a capil-
232 lary.^[25-33] Despite their low volatility, it was reported^[34] that most common
233 ionic liquids do exhibit some column bleed below about 200°C and attributed
234 some of this bleed to ionic liquid decomposition.

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242 GENERAL GC TRENDS

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244 One of the most intriguing aspects of the studies using ionic liquids as
245 stationary phases in gas chromatography is that the phases exhibit a “dual”
246 nature.^[32] In a comparison of ionic liquids to squalene and DB-5 GC columns,
247 it was found that non-polar analytes (e.g., paraffins, substituted alkanes, aromatics)
248 were retained and separated on all phases to a similar extent.^[32] Not too surpris-
249 ingly, polar analytes seem to have higher affinity for ionic liquid phases than
250 nonpolar analytes. For instance, on an ethylpyridinium bromide column, the
251 least polar analytes eluted first, followed by analytes with large dipole moments;
252 hydrogen bonding solutes eluted last. Alkylamines did not elute while phenols

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253 had long retention times and poor peak shapes.^[26] Studies on other ionic liquid-
254 based gas chromatographic phases revealed similar trends.^[28,32]
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THE ROLE OF THE CATION

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259 As might be expected, dispersive interactions with the ionic liquid cation
260 seem to play a role in retention.^[29] Several studies have examined the role of
261 alkyl chain length and found that the longer the alkyl chain on the ionic liquid
262 cation, the longer the retention.^[28,29] Similarly, the larger the number of alkyl
263 substituents on the ionic liquid nitrogen, the longer the retention. For example,
264 in a study using alkylammonium thiocyanates, the series of the salts used had
265 an aromatic ring or from one to four alkyl groups on the nitrogen. More sub-
266 stituents on the ionic liquid cation correlated with longer retention for non-
267 polar analytes. In addition, bulky groups on the imidazolium moiety were
268 found to enhance thermal stability of the ionic liquid stationary phase.^[34]
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THE ROLE OF THE ANION

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273 The anion also appears to play significant role in promoting interactions
274 between the analytes and the ionic liquid. For instance, comparing
275 [BMIM][PF₆] and [Cl], it was observed that the chloride salt retained proton
276 donating analytes such as alcohols, diols, and phenols more than the hexa-
277 fluorophosphate salt. In contrast, the hexafluorophosphate salt retained ana-
278 lytes lacking good proton-donor or accepting groups (e.g., aliphatic and
279 aromatic compounds, aldehydes, esters, and ketones) longer than the chloride
280 salt.^[32,34] The results obtained in another study, comparing tetra-*n*-butylam-
281 monium salts with a variety of anions (e.g., picrate, trifluoromethanesulfonate,
282 4-toluenesulfonate, and nitrate), were consistent in that the primary impact of
283 anion type was also for proton donating analytes.^[31]
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**GC RETENTION MODELS OF IONIC LIQUID
STATIONARY PHASES**

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289 In gas chromatography, attempts to describe analyte–stationary phase
290 interactions have relied primarily on McReynold's constants or linear
291 free energy models and have met with varying degrees of success. The
292 McReynold's method uses a selected probe set to describe the relative import-
293 ance of dispersion, orientation, induction, and hydrogen bond donor/acceptor
294 interactions to retention.^[35] Determination of McReynold's constants requires

295 that the retention indices of the probe set relative to *n*-alkanes is determined
296 on the test column. Two issues with the application of McReynold's constants
297 to ionic liquid based GC stationary phases include the overall low retention for
298 *n*-alkanes and the observation that, in general, non-polar analytes seem to
299 interact with the polar stationary phase through adsorption while polar
300 analytes interact through partitioning.^[27,29] Thus, McReynold's constants
301 may not be the best descriptor of stationary phases if more than one sorption
302 process takes place.^[35]

303 Alternatively, the linear free energy approach has also been used to
304 characterize ionic liquids.^[36] This method describes the ability of ionic liquid
305 to interact with π and *n*-electrons, dipolarity, polarizability, hydrogen bond
306 basicity, hydrogen bond acidity, and dispersion forces. The linear free energy
307 approach relates retention of a training set of analytes to various molecular
308 descriptors through:

$$\log K_L = c + rR_2 + s\pi_2^H + a\alpha_2^H + b\beta_2^H + l\log L^{16}$$

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312 where R_2 is an excess molar refraction calculated from the solute's refractive
313 index; π_2^H is the solute dipolarity/polarizability, α_2^H and β_2^H are the solute
314 hydrogen bond acidity and hydrogen bond basicity, and L^{16} is the solute gas-
315 hexadecane partition coefficient at 298 K. These molecular descriptors can be
316 readily obtained for many solutes.^[37] The coefficients (*r*, *s*, *a*, *b*, *l*) are then
317 determined by multiple regression analysis using the retention factors for
318 the training set of solutes for the column being investigated. The magnitude
319 and sign of the various coefficients provide an indication of the relative mag-
320 nitudes of the individual interactions to the overall retention for the stationary
321 phase of interest.^[33] Comparison of coefficients for different phases can pro-
322 vide insight into similarities and/or differences in selectivity and retention
323 mechanisms.

324 In a study investigating 17 different ionic liquid stationary phases, dis-
325 persion, hydrogen bond basicity, and dipolarity were the strongest interactions
326 present for ionic liquids.^[33] The results showed that dispersion forces were
327 similar for an array of ionic liquid cations that included substituted imidazo-
328 lium and alkylammonium ions and could account for the ability of the ionic
329 liquids to distinguish between homologs. Hydrogen bond basicity and dipolar-
330 ity was more variable although the variability of the hydrogen bond basicity
331 seemed to reside predominantly in the anion.^[33] In general, the retention
332 factors for the set of probe solutes on imidazolium based ionic liquid stationary
333 phases were larger than on the alkylammonium based ionic liquid stationary
334 phases

335 Ionic liquid stationary phases in gas chromatography also allowed the
336 determination of activity coefficients for alkenes, alkanes, and other analytes

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337 in ionic liquids. Activity coefficients for different solutes in a variety of ionic
338 liquids^[38,39] suggest that intermolecular interactions between the solute and
339 ionic liquid become stronger when the number of polarizable electrons in
340 double bonds or aromatic rings of the analytes increases, which the authors
341 interpreted as an indicator of the importance of ion-induced dipole interactions
342 to retention. For linear *n*-alcohols and alkanes, activity coefficients increase
343 with increasing chain length while branching in the molecule reduces the
344 activity coefficients. Similar results were also obtained with [HMIM][PF₆].^[40]

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MISCELLANEOUS IONIC LIQUID GC APPLICATIONS

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IONIC LIQUIDS IN LIQUID CHROMATOGRAPHY

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Thus far, the application of ionic liquids in liquid chromatography has been predominantly as mobile phase additives and their applications have been somewhat limited. Many of the most common ionic liquids used in GC (e.g., BMIM-based) are not completely UV transparent at wavelengths at which analytes are usually detected. In addition, ionic liquid viscosities are generally higher than typical HPLC solvents. Indeed, the viscosities of ionic liquids were found to be too high for direct use in centrifugal partition chromatography.^[42] Reduction in mobile phase viscosity can be achieved either by increasing the temperature or by mixing the ionic liquid with another solvent. For a series of alkylammonium ionic liquids, dilution by solvents with

low dielectric constants (e.g., tetrahydrofuran), the viscosity change with increasing organic modifier followed an exponential decline while for high dielectric modifiers (e.g., water, methanol), the viscosity change was found to follow a third order polynomial.^[43]

Arguably, when ionic liquids are diluted or immobilized on a support, they may not possess all the properties of the neat ionic liquids. As mobile phase additives, ionic liquids can play a variety of roles (e.g., coat residual silanols, modify the stationary phase or act as ion-pairing agents). In one study,^[44] using alkylmethylimidazole salts as mobile phase additives, it was shown that for the separation of ephedrine on a reversed phase column, the retention and peak tailing significantly decreased when ionic liquids were present in the mobile phase, presumably because the ionic liquid ions coated residual silanols which reduced the interaction of analytes with residual hydroxyl groups on the silica. The decreased retention times and improved the peak shapes obtained with increased chain length on the cation were attributed to better shielding of the residual silanols.

IONIC LIQUIDS IN CAPILLARY ELECTROPHORESIS

Ionic liquids have been used in capillary electrophoresis for separation of different classes of compounds either as additives in the run buffer, as a dynamic coating on the capillary walls or by covalent attachment to the capillary walls.

Dynamically coating the capillaries, while simultaneously using the ionic liquids as electrolytes, provides sites of interactions for solutes not only on capillary walls but also in bulk solution (Fig. 3). This feature can assist in separation of neutral compounds which otherwise would migrate with electroosmotic flow. For example, using 1-alkyl-3-methylimidazolium (50–400 mM) based ionic liquids as running electrolytes allowed separation of polyphenols

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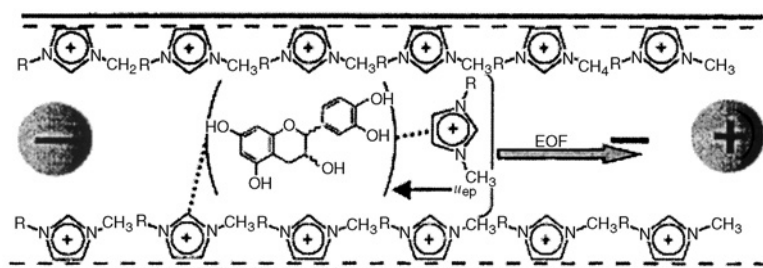


Figure 3. Mechanism of polyphenol CE separation using 1-alkyl-3-methylimidazolium-based ionic liquids in the background electrolyte.^[45]

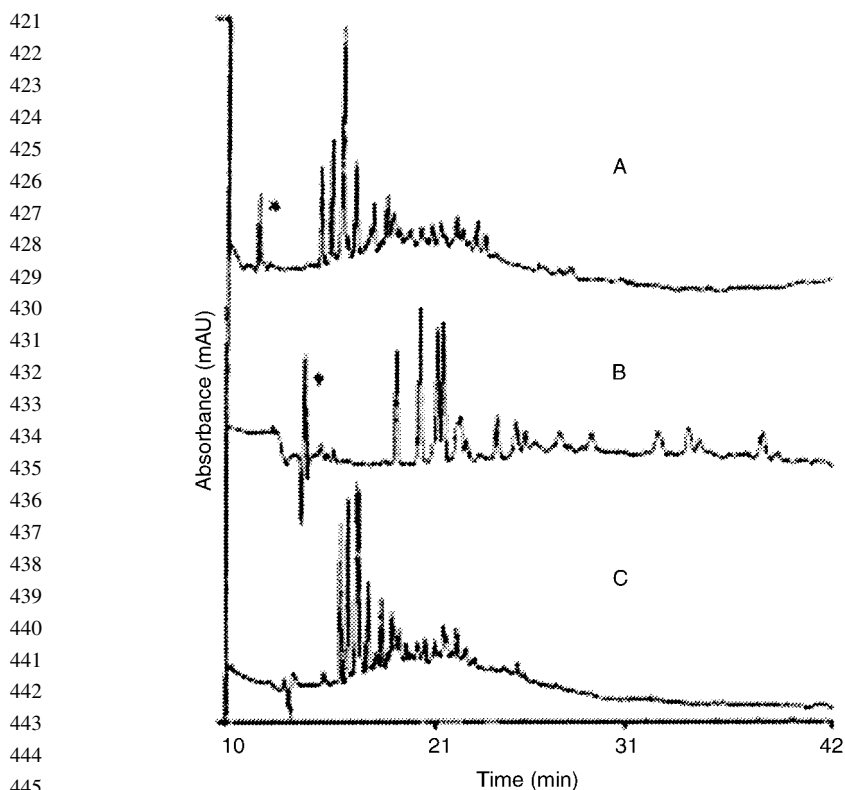


Figure 4. Separation of polyphenols using (A) [EMIM][BF₄], (B) [BMIM][BF₄], and (C) [EMIM][PF₆] [150 mM]; voltage, 16 kV, with anodic detection at 240 nm; (*), nitromethane.^[45]

which were neutral under the electrophoretic conditions used.^[45] The authors attributed the post-EOF migration of the polyphenols under anodic detection to association with the cation of the ionic liquid in the bulk solution or on the capillary walls. In addition, the separation for a mixture of phenols was fairly insensitive to changes in anion but very sensitive to changes in cation (Fig. 4). Similar results for polyphenols were obtained using tetraethylammonium tetrafluoroborate.^[46] Further, NMR studies^[47] indicated that solute/ionic liquid association in aqueous solutions occurred through π - π stacking between monohalophenols and the imidazolium cation.

Dynamic coating of the capillary walls with 1-alkyl-3-methylimidazole also alleviated the wall adsorption usually associated with CE separations

463 of basic proteins.^[48] The authors attributed the improved performance to
464 electrostatic repulsion of the positively charged proteins from capillary
465 walls due to surface charge reversal arising from the presence of the imidazo-
466 lium cations. Increased chain length of the imidazolium alkyl substituent
467 resulted in overall decreased EOF. Warner et al. also found ionic liquids useful
468 at low (e.g., ~1–5 mM) concentrations as substitutes for organic modifiers
469 when using polymeric surfactants.^[49] At these low concentrations, it is
470 unlikely that the ionic liquid is significantly coating the capillary.

471 Apart from the applications to the separations of organic molecules, ionic
472 liquids have been used also for inorganic ion separations. Using [EMIM][OH]
473 with phosphoric acid or acetic acid in the running buffer in a capillary co-
474 valently coated with butylimidazole, improved separation of ammonium
475 and several metal ions without adding any other modifiers. The coating
476 reversed the electroosmotic flow, so that analytes migrated in opposite direc-
477 tion of electroosmotic flow thereby increasing the resolution.^[50]

478 While the use of imidazolium electrolytes has proven useful in CE, the
479 presence of a nonvolatile electrolyte complicates interfacing to mass spec-
480 trometer (MS). Recently, ionic liquids immobilized on capillary walls were
481 found to have some utility in the separation of DNA.^[51] In this work, the imi-
482 dazolium cation's primary role was as an EOF modifier but the DNA was also
483 found to interact electrostatically with the imidazolium cation. The strength of
484 the interaction was found to be dependent on fragment size. In a related
485 study,^[52] the CE-MS separation of sildenafil (Viagra, a purine/pyrimidine/
486 nucleoside analog), from its active major metabolite showed that the immobi-
487 lized imidazolium cation not only engendered a pH-independent EOF but
488 also inhibited analyte/wall association through electrostatic repulsion. Immo-
489 bilization of the ionic liquid cation allowed the advantages associated
490 with the unique ionic liquid properties to be retained (e.g., pH-independent
491 EOF), while simultaneously facilitating interfacing to electrospray mass
492 spectrometry.

493 As noted previously, many ionic liquids are also soluble in organic
494 solvents and have been used in non-aqueous capillary electrophoresis.^[53,54]
495 Ionic liquids also associate with neutral compounds like phenols in
496 acetonitrile or methanol, enabling their separation in CE.^[53,54] In contrast to
497 aqueous CE, the interaction for neutral analytes was attributed to interaction
498 with the anionic part of ionic liquid because the analytes eluted after the
499 neutral marker using normal polarity. The concentrations of ionic liquids
500 used in the run buffers were much lower than in the case of aqueous CE
501 (e.g., ~0.005–0.025 mM). The separation of acids and phenols was attributed
502 to heteroconjugation between the analytes and anions of the ionic liquids.
503 Difficulties were encountered with polyphenols which were not soluble in
504 acetonitrile.^[53,54]

CONCLUSIONS

Ionic liquids are widely applicable in different areas of chromatography and capillary electrophoresis. They provide promising separation interactions for wide variety of compounds from alkanes to aromatics, from polyphenols to proteins, and other biomolecules. Most work to date using ionic liquids has been gas chromatography and in capillary electrophoresis but the emphasis in the GC studies have been on the investigation of physical properties of the analytes and interactions between solvent and solutes. Thus, there are still many opportunities to explore their separation applications in all areas of analytical separations.

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Received December 17, 2003

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Accepted December 30, 2003

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Manuscript 6285

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| CMS ID number (DOI): | 120030611 |
| Article title: | Ionic Liquids in Chromatography and Capillary Electrophoresis |
| Article type: | Research |
| Classification: Category: | |
| Primary subcategory: | |
| Subcategory(ies): | |
| Topic(s): | |
| Key words: | Ionic liquids; Molten salts; Gas chromatography; Liquid chromatography; Capillary electrophoresis; Review |
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| Article data: | Submission date: | |
| | Reviewed date: | 17-Dec-03 |
| | Revision date: | |
| | Accepted date: | 30-Dec-03 |