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Application of Ionic Liquids in Liquid Chromatography

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1. Introduction

Ionic liquids (ILs) are salts formed by a bulky nitrogen- or phosphorous-containing dissymmetrical organic cations such as alkyl-imidazolium, pyridinium or pyrrolidinium, ammonium or phosphonium and a variety of organic anions: triflate, dicyanamide, acetate, trifluoroacetate, trifluoromethylsulfate or inorganic: bromide, chloride, nitrate, perchlorate, chloroaluminate, tetrafluoroborate, or hexafluorophosphate. The number of possible combinations of anion-cation amounts 10^{18} , which makes this class of substances one of the biggest in chemical chest of substances. Properties of ILs depend on their structure. In order to obtain ionic liquid of desirable properties, with the specific melting point, viscosity, density, miscibility with water and organic solvents, one should select appropriate ions. For this reason ionic liquids are often called “designer” solvents.

There are certain common characteristics which definitely distinguish this class of chemical compounds. They have the ability of dissolving inorganic and organic compounds, including enzymes, simultaneously retaining their activity. They are stable chemically and thermally. The difference between the boiling point and of melting is of 300 °C. They possess low vapor pressure, which is why ionic liquids don't produce volatile environmental pollution. The most specific feature of these compounds is the low melting temperature -below 100 °C. If melting point is below room temperature (25 °C), the IL is called room-temperature ionic liquid (RTIL).

ILs found applications as new non-molecular types of solvents with unique properties in different areas of chemistry like organic synthesis, electrochemistry, extraction, spectroscopy and mass spectrometry. The growing interest in ILs has been observed also in chromatographic methods: gas chromatography (GC), capillary electrophoresis (CE) and liquid chromatography (LC). From a point of view of separation techniques, an important property of ILs is a possibility of generating strong donor-acceptor interactions and ability of undergoing coulombian interactions (chromatography), good electrical conduction (capillary electrophoresis), the great viscosity, the surface tension, the thermal stability (gas chromatography), excellent solvent properties (extraction). Worth noting are critical reviews emphasizing specific advantageous of ILs application in chromatographic and electromigration techniques (Buszewski & Studzińska, 2008; Marszał & Kaliszan, 2007; Berthod et al., 2008; Pandey, 2006; Koel, 2005; Stalcup & Cabovska, 2004; Poole, 2007; Sun & Armstrong, 2010; Poole, 2004).

A major problem associated with using ILs, as solvents, in liquid chromatography is their high viscosity, many times bigger than one of methanol or acetonitrile. A completely different situation concerns using ionic liquids as small additives (2-60 mM) to water-organic mobile phases. In such minute concentration, ionic liquids lose their unique properties and they simply become salts. Apart from that, small concentration of the additive doesn't change the eluent viscosity drastically and can be applied in conditions both of high pressure chromatography (HPLC) as well as thin-layer chromatography (TLC). The addition of ionic liquids is particularly beneficial in analysis of basic compounds on the reversed-phase columns obtained on the basis of silica, where silanol interactions were usually a disadvantage. Activity of reducing of silanol interactions through ionic liquids exceeds commonly used tertiary amines as well as bivalent cations, frequently applied for this reason.

Modification of the stationary phase with the help of ILs relies on covalent bonding of silanol groups of silica gel with the cation of an ionic liquid. Obtained phases change its properties into ion-exchanging able to separate inorganic as well as organic ionic analytes.

This review focuses on application of ILs in liquid chromatography (HPLC and TLC), and electromigration techniques. Control of ILs by these techniques is also discussed according to increases of their popularity in industry.

2. Physicochemical properties of ionic liquids

Physicochemical properties of ILs depend on their components. The asymmetric organic cations and large polyatomic anions are responsible for lowering of the lattice energy and finally lowering of the melting point of resulting compound. For instance the melting point of archetypical sodium chloride equals 800 °C. Displacement of sodium by imidazolium cation lowers the melting point ten times. Increasing popularity of ILs in chemical industry is connected with their low vapor pressure, which is lower than the one of water, mercury and nonacosane - least volatile among alkanes. In the room temperature, the pressure achieves non-measurable values thus they appear to be friendly for environment. Besides that, they exhibit a wide range of solubility, viscosity and density depending on the kind of anion and cation in their structure. To find proper composition for exact analytical application, physicochemical properties of almost all existing ILs are collected in data banks available on the following websites: Dortmund Data Bank, Germany (Data Bank of Ionic Liquids, DECHEMA, DETHERM on the WEB, Thermophysical Properties of Pure Substances & Mixtures, <http://www.ddbst.de/new/Default.htm> or another one: NIST Boulder Colorado, USA (Ionic Liquids Database (IL Thermo), Thermodynamics Research Center, National Institute of Standards and Technology, Boulder, CO, USA, <http://ilthermo.boulder.nist.gov/ILThermo/mainmenu.uix>.

One of the advantages of ILs is their high thermal robustness. They possess thermal stability in the range approximately from -40°C to 200°C, which is much wider than other solvents like water, ammonium, acetone, methanol, benzene or nitrobenzene. ILs could be hydrophobic or hydrophilic depending on the properties of their ions. Hydrophilic ILs similarly to regular salts dissociate into ions which are hydrated in aqueous solutions. Ions exerting strong interactions with water molecules cause increase of the structuring of water and they are known as "structure-makers" or 'kosmotropes'. Hydrophobic ions partially or completely immiscible with water which decrease the structuring of water are known as 'chaotropes. meaning disorder-makers'. These terms originated from the Hofmeister series,

which orders the ion abilities of proteins precipitation. Comparing several thermodynamic parameters like the viscosity *B*-coefficients obtained from the Jones-Dole empirical equation, structural entropies (ΔS^0), structural volumes and ion mobility expressed as the limiting Walden product $\Lambda_m\eta$ quantification of the ILs ions kosmotropicity/chaotropicity can be evaluated (Zhao, 2006). According to Zhao investigation, it appears that smaller organic cations including [MMIM]⁺, [EMIM]⁺, [MePy]⁺, [EtPy]⁺ and [Me₄N⁺] are chaotropes, while those of medium size (such as [BuPy]⁺ and [Et₄N⁺] are borderline ions, in turn larger ions such as [BMIM]⁺, [Pr₄N⁺], [Bu₄N⁺], and [Pe₄N⁺] possess kosmotropic properties. The anions can be kosmotropes or chaotropes depending on the position in Hofmeister series of salts. The properties of a modern ILs could be characterized by the following features (Johnson, 2007):viscosity: < 100 cP, dielectric constant: < 30, specific conductivity: < 10 mScm⁻¹, molar conductivity: < 10 Scm² mol⁻¹,electrochemical window > 2V.

Comparing properties of ILs and other liquids according to their molarities and molar conductance, it is clear that modern ILs consist of not only ions but also un-dissociated molecules in a form of ion-pairs. From a point of view of liquid chromatography such properties as viscosity, refractivity, solubility, E_T^N - Reichardt polarity index are the most important. Table 1 contains properties of ILs common in chromatographic techniques.

Symbol	Name	Melting point (°C)	Density (25 °C)	Refrac. index	Visc. (25 °C) (cP)	Sol. in water	E_T^N (×100)
EMIM BF ₄	1-Ethyl-3-methyl imidazolium tetrafluoroborate	6	1.248		66	s	
BMIM BF ₄	1-Butyl-3-methyl imidazolium tetrafluoroborate	−82	1.208	1.429	233	s	67
BMMIM BF ₄	1-Butyl-2,3-dimethyl imidazolium tetrafluoroborate	37	1.2		780	s	
HMIM BF ₄	1-Hexyl-3-methyl imidazolium tetrafluoroborate	−82	1.208		310	p	
OMIM BF ₄	1-Octyl-3-methyl imidazolium tetrafluoroborate	−79	1.11		440	p	54
DMIM BF ₄	1-Decyl-3-methyl imidazolium tetrafluoroborate	−25	1.072		930		63
BMIM PF ₆	1-Butyl-3-methyl imidazolium hexafluorophosphate	10	1.373	1.411	400	18 g L ^{−1}	67
HMIM PF ₆	1-Hexyl-3-methyl imidazolium hexafluorophosphate	−61	1.304		800	n	

OMIM PF ₆	1-Octyl-3-methyl imidazolium hexafluorophosphate	−40	1.2		810	n	
EMIM Cl	1-Ethyl-3-methyl imidazolium chloride	89	1.12*	Solid	Solid	s	
HMIM Cl	1-Hexyl-3-methyl imidazolium chloride	−75	1.05		7500	s	
OMIM Cl	1-Octyl-3-methyl imidazolium chloride	0	1		16,000	s	
(C ₇) ₄ N Cl	Tetraheptyl ammonium chloride	−9	0.882		598	s	
BMIM Cl	1-Butyl-3-methyl imidazolium chloride	65	1.10*	Solid	Solid	s	
BMIM Br	1-Butyl-3-methyl imidazolium bromide					s	
BMIM I	1-Butyl-3-methyl imidazolium iodide	−72			1110		
EMIM Act	1-Ethyl-3-methyl imidazolium acetate	−20	1.03		91	s	
BMIM Act	1-Butyl-3-methyl imidazolium acetate	−20	1.06		525	s	
EA NO ₃	Ethylammonium nitrate	12.5	1.122	1.4537	32	s	95
PA NO ₃	Propylammonium nitrate	4	1.157	1.4561	67	s	92
TBA NO ₃	Tributylammonium nitrate	21.5	0.918	1.4627	640	s	80
EMIM MS	1-Ethyl-3-methyl imidazolium methylsulfate	5	1.24		80	s	
BMIM MS	1-Butyl-3-methyl imidazolium methyl sulfate	−20	1.2		180	s	

Table 1. Physicochemical properties of selected ionic liquids (Berthod et al., 2008).

3. Chromatography

ILs were applied firstly in gas chromatography as new liquid stationary phases owing to their low volatility, high viscosity and non-flammability (Barber et al., 1959). Barber and co-workers proposed GC stationary phases modified with molten stearates of Mn, Co, Ni, Cu, and Zn for separation of alcohols and amines. Later on, GC columns based on ethylammonium nitrate and ethylpyridinium bromide and tetraalkylphosphonium salts were prepared and tested (Pachloec et al., 1982; Pacholec & Poole, 1983). ILs-based stationary phases exhibited selectivity towards polar and hydrogen bond forming analytes. However, they possessed some limitations concerning narrow liquid range, poor thermal

stabilities, poor efficiency and lack of selectivity according to n-hydrocarbons. Since imidazolium ILs: 1-Butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF₆] and chloride [BMIM][Cl] salts started to be coated onto silica capillaries, GC systems have achieved satisfactory efficiency useful for separation either nonpolar or polar compounds (Armstrong et al., 1999; Berthod et al., 2001; Anderson & Armstrong, 2003).

In liquid chromatography, ILs have not been widely applied so far. However, the number of publications dealing with this subject has recently visibly increased. Generally, ILs are too viscous to be used as solvents and exhibit poor transmittance of low-wavelength UV light, worsening detection limits. However, when ILs are diluted, properties characteristic for the neat ones are lost and ILs become common organic salts. Among whole group, only pyridinium and imidazolium hexafluorophosphates or tetrafluoroborates are the most commonly applied in solution as mobile phase modifiers. In this case ILs can play different roles: coating residual silanols, modifying the stationary phase and acting as ion-pairing reagents.

3.1 Thin-layer chromatography

The first paper concerning application of ILs in thin-layer chromatography (TLC) was published by Kaliszan's group (Kaliszan et al., 2004). The imidazolium classes of tetrafluoroborate ILs covering [EMIM] [BF₄], [HxMIM] [BF₄], [Hx-HpOMIM] [BF₄] were tested as mobile phase modifiers in analysis of several basic compounds on an octadecyl bound-silica stationary phase. It appeared that proposed modifiers were more effective in chromatographic separation of chosen basic analytes in comparison to other standard additives such as triethylamine (TEA), dimethyloctylamine (DMOA) or ammonia. Whereas TEA, DMOA and ammonia showed negligible effect on investigated compounds retention, ILs appeared to be the most effective suppressor of attractive interactions between acidic free silanols present on the stationary phase surface and analyzed basic drugs causing drastically retention decreases, improvement of selectivity and spots shape. Effects of investigated additives on chromatographic results are compared in Fig.1.

Dependences of ionic liquid concentration in eluent system versus obtained experimental retardation factors (R_F) exhibit typical Langmuir shapes. Independently on the kind of stationary phase (silica or the octadecyl silica-covered plates), mobile phase composition (pure acetonitrile, water-acetonitrile) and IL used, saturation level was achieved at ca. 0.5% v/v of ionic liquid content in eluent system. Comparison of the effectiveness of investigated silanol screening agents on the basis of reciprocal of retardation factor vs. reciprocal of the additive concentration relationship (Fig.2), proved the most effective adsorption of exemplary ionic liquid [EMIM] [BF₄].

Addition of imidazolium tetrafluoroborates to mobile phase improved also linearity of the classical Snyder-Soczewiński relationship of R_M ($\log 1-R_F/R_F$) versus organic modifier concentration in the mobile phase. This suggests that chromatographic systems modified with ILs could be applied for much more precise determination of chromatographic lipophilicity parameters (R_M^0 , ϕ_0) by extrapolation and interpolation graphical techniques. Using of IL as the mobile phase modifier is useful also in normal-phase TLC systems. Kaliszan and his group (Bączek et al., 2005) described behavior of a homologous series of peptides analysed on a silica support by the use of the eluent system enriched with [EMIM] [BF₄]. It appeared that experimental dependences of the retention coefficient, R_M on the volume percentage of organic modifier in the mobile phase containing ionic liquid were

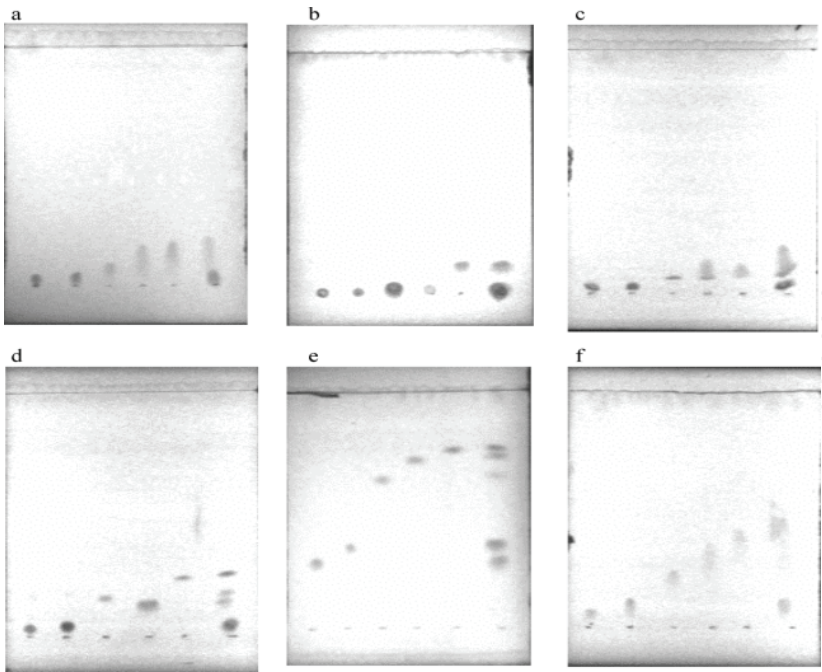


Fig. 1. Chromatograms of thioridazine, trifluoropromazine, phenazoline, naphazoline, tiamenidine and the mixture of the drugs, as spotted from left to right, on RP-18 F254 plates, developed with water-acetonitrile 40:60 v/v eluent either pure or containing 1.5% v/v of various additives: a-no additive; b-NH₄OH; c-DMOA; d-TEA; e-[EMIM][BF₄]; f-buffer of pH 2.87. (Kaliszan et al., 2004).

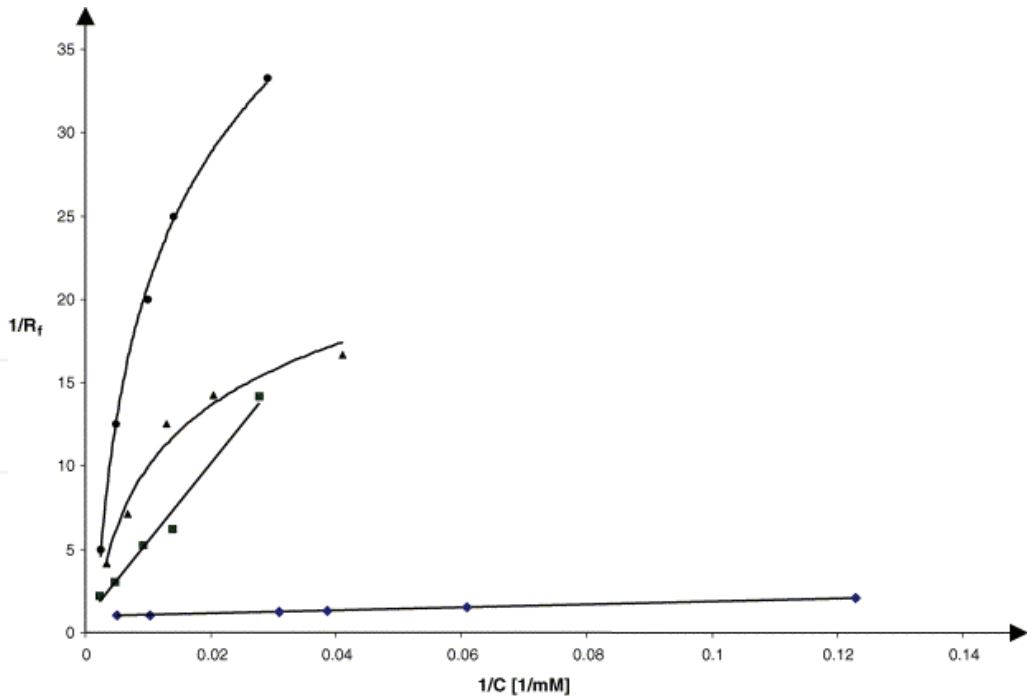


Fig. 2. Plots of reciprocal of retardation factor of tiamenidine on octadecylsilica plates with acetonitrile as eluent vs. the reciprocal of concentration of additive in the mobile phase. Additives are denoted as follows: IL 1 (◆), TEA (◻), DMOA (▲) and NH₄OH (·).(Kaliszan et al., 2004).

nonlinear and could be described with a third-degree polynomial function. Whereas quadratic equation was well fitted to dependences obtained for chromatographic systems without addition of IL.

RTILs were examined also as matrixes for online separation and identification of peptides, proteins, and poly(ethylene glycol) (PEG-2000) with matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS) (Armstrong et al., 2001; Mehl & Hercules, 2000). The method described hybrid TLC-MALDI plates. Authors concluded that tested ILs, owing to good solubilizing properties and vacuum stability, in comparison to other commonly used liquids and solid matrixes, should be further investigated as potential MALDI matrixes.

3.2. High-performance liquid chromatography

3.2.1 Ionic liquids as mobile phase solvents

In the 80s of the last century, Poole et al. (Poole et al., 1986) elaborated on the synthesis of six alkylammonium salts of the general formula $R_{n-a}NH_a^+X^-$, where R = ethyl, propyl, butyl or sec.-butyl, X^- = nitrate or thiocyanate, $n < 4$ and $a = 0, 1, 2$ or 3 . Authors measured their physical properties including melting point, refractive index, UV spectra, miscibility with common organic solvents, aqueous solution pH, density and viscosity and concluded that obtained liquid organic salts forming immiscible solvent pairs with non-polar organic solvents appear to be suitable for liquid–liquid chromatography and liquid–liquid extraction. Some of them, such as the alkylammonium nitrate or the thiocyanate salts mixed with a second solvent of low viscosity such as water, methanol, acetonitrile, tetrahydrofuran and dichloromethane could be used as mobile phases in liquid chromatography. Studies of their solvent properties in microcolumn RPLC demonstrated that the back pressure on the column was too high, in spite of the fact of a small flow of 0.05 ml/min, a small internal diameter of the column (1mm) and the least viscous of ILs applied (Shetty et al., 1987). Additionally, applied aqueous solutions of thiocyanates corroded metal parts of the apparatus and demonstrated poor baseline stability. In turn tetra-n-alkylammonium sulfonates were too basic and caused silica-based columns degradation process. Therefore, the project was abandoned.

A couple of years after that, Waichigo applied a few monoalkylammonium nitrates and acetates adding them, as modifiers, to water in concentrations of 20-60 % using classical C18 columns or the copolymer-styrene-divinylbenzene (Waichigo et al., 2005; Waichigo & Danielson, 2006 a; Waichigo & Danielson, 2006 b; Waichigo et al., 2007). It appears that ethylammonium nitrate possesses similar solvent strength to tetrahydrofuran. Elongation of alkyl chain in ammonium salt structure is connected with increasing of elution strength of IL in chromatographic system. In turn, the solvent strength of ethylammonium acetate is similar to methanol. Waichigo observed the lower number of theoretical plates (20%) and the twice higher back pressure on the column compared with the conventional arrangement of reversed phases and water-organic eluent. One should emphasize it that majority of authors applying alkylammonium salts achieved worse effects comparing with classical RP-HPLC as for: the transparency in UV, viscosities triggering back pressure, worsened efficiency. Taking into account the fact that alkylammonium salts possess the lowest viscosity in comparison to other ILs, it is difficult to expect that they would displace currently applied organic modifiers like methanol or acetonitrile. However, the non-molecular nature of ILs could give meaningful improvement of selectivities (Fig.3)

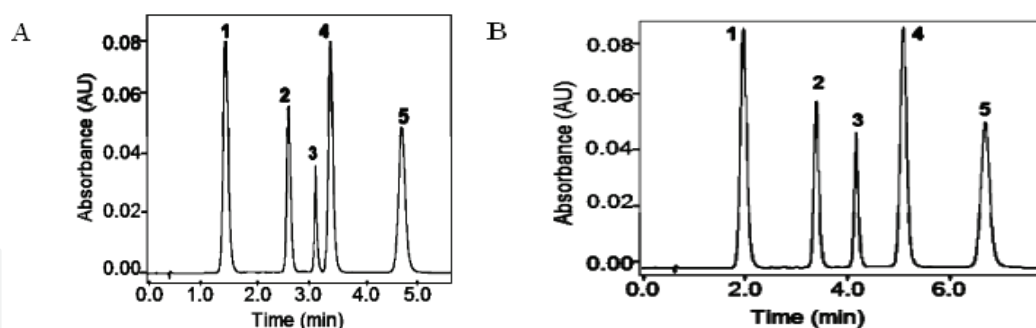


Fig. 3. Chromatogram of 1-ascorbic acid, 2-nicotinic acid, 3-thiamine, 4-pyridoxine, and 5-niacinamide using the Aquasep C8 column with a) 30% methanol-70% water. b) 30% ionic liquid ethylammonium acetate-70% acetate. Flowrate: 1.0 mL min⁻¹. UV detection at 254 nm. (Waichigo et al., 2005).

3.2.2 Ionic liquids as mobile phase modifiers.

ILs were found to be more useful when added to the mobile phase at millimolar concentration, however all their unique properties were lost and they were just salts adjusting the solvent strength. By dilution of IL with water or organic-aqueous solvent or by increasing the column temperature, the viscosity of ionic liquids can be drastically reduced. Several advantages associated with the use of ionic liquids as mobile phase additives should be emphasized. First of all, these compounds don't damage the silica based columns, do not change radically pH of the mobile phase, and could replace the less advantageous alkylamines with aim of silanol screening.

Many papers demonstrate the usefulness of ILs at these conditions in terms of improvement of efficiency and peak symmetry (He et al., 2003; Zhang et al., 2003; Zhang et al., 2004; Marszałł et al., 2005; Marszałł et al., 2006 a; Ruiz-Angel et al., 2006). Fig. 4 presents comparison of prochlorperazine peaks depending on the kind of modifier added to the mobile phase (Flieger, 2009).

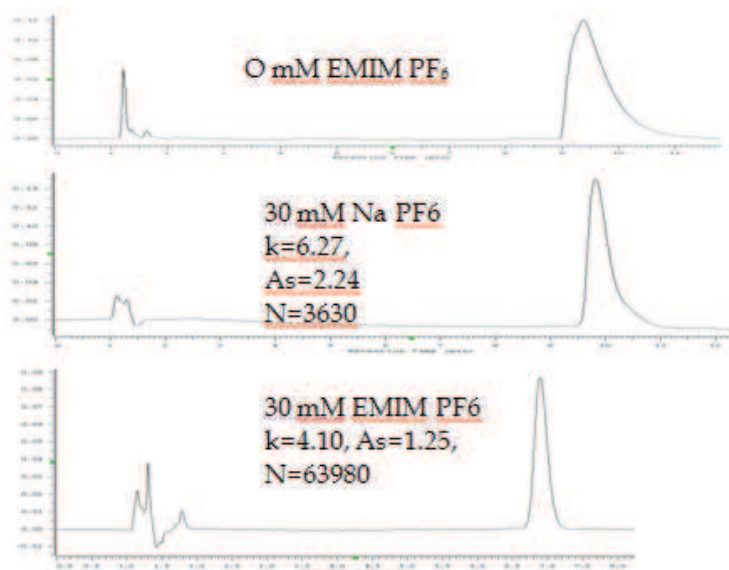


Fig. 4. The effect of different mobile phase additives on chromatographic parameters of prochlorperazine. Eluent: 40% ACN/10mM phosphate buffer (pH 2.8), column: Zorbax Extend-C18 (Flieger, 2009).

To understand the influence of the particular ions of added reagents, the eluent systems containing the following components: ACN/phosphate buffer pH=2.8, ACN/phosphate buffer (pH=2.8)/NaPF₆ and ACN/phosphate buffer (pH=2.8)/[EMIM] [PF₆] were compared. As it can be seen, unacceptable parameters in system containing only organic-aqueous mobile phase acidified by phosphate buffer being a consequence of the ionic nature of the analyte, cause the creation of tailing peaks with not satisfactory symmetry. Addition of chaotropic additive NaPF₆ to the mobile phase improves the peak symmetry and efficiency of the system, nevertheless A_s factor is still out of an acceptable range. The best parameters of peak symmetry and efficiency were obtained for ionic liquid [EMIM] [PF₆] as the mobile phase additive. Change of Na⁺ cation, which is not adsorbed into hydrophobic surface into the enlarged imidazole cation possessing the structure enabling to penetrate the space between the hydrocarbon chains, appears to be the most advantageous.

However, special attention should be devoted to appropriate concentration of IL in the mobile phase to avoid dissymmetry and multiplication of peak as a result of existing analyte in different forms: ion-pair and free protonated base. Fig.5 shows how peaks profile of nortryptiline can be improved according to increasing concentration of [BMIM][PF₆] (Flieger & Czajkowska-Żelazko, 2010).

Improving peak symmetry, efficiency expressed as theoretical plates number and visible in decreasing peaks tailing and reducing band broadening, are connected with changing of the retention mechanism in the presence of ILs in a chromatographic system. Both ions contribute to the retention of analytes. They can affect obtained results either antagonistically or synergistically.

Many authors confirm suppression of silanophilic interaction by ILs which coat the surface and interact with free silanol groups of silica based supports (Marszałł et al., 2006 a; Marszałł et al., 2005; Ruiz-Angel et al., 2006; Flieger, 2009). As new masking agents enabling reduction of deleterious silanol effect, ILs appeared to be more advantageous in comparison to traditional additives like amino quenchers (triethylamine (TEA), dimethyloctylamine (DMOA), cyclohexylamine, quaternary ammonium ions) applied so far for this reason. It was demonstrated that either anions can be adsorbed on hydrophobic stationary phase according to their chaotropicity (Pan et al., 2004; Gritti & Guiochon, 2004) or ionic liquids' cations following their lyotropy related to the lengths of the alkyl chains (Berthod et al., 2005; Zhao, 2006). Ions can also move together with the mobile phase and interact with ionic analytes. Protonated basic analytes could interact with anions creating neutral ion-pairs with longer retention. In this case ion-associated complexes are formed only with that ones exhibiting chaotropic properties (H₂PO₄⁻ < HCOO⁻ < CH₃SO₃⁻ < Cl⁻ < NO₃⁻ < CF₃COO⁻ < BF₄⁻ < ClO₄⁻ < PF₆⁻) (LoBrutto et al., 2001; Flieger, 2006). So far, adsorption of ILs on adsorbent surface and ion-pairing mechanism has been proposed to explain retention mechanism in chromatography applying ILs as modifiers.

Firstly Jiang (Jiang et al., 2004) described addition of 2–50 mM IL to aqueous mobile phases as silanol suppressing agents in the separation of basic and strong hydrophilic analytes ephedrine, catecholamines, and amino acids. Later on Marszałł et al. evaluated the silanol-suppressing potency of ILs (Marszałł et al., 2006 a) applying dual retention model proposed by Nahum and Horvath:

$$\frac{[A]}{k_0 - k} = \frac{1}{k_2 K_A} + \frac{[A]}{k_2} \quad (1)$$

where k_0 indicates retention factor at the absence of any additives and k is the retention factor obtained at the concentration $[A]$ of the silanol suppressor.

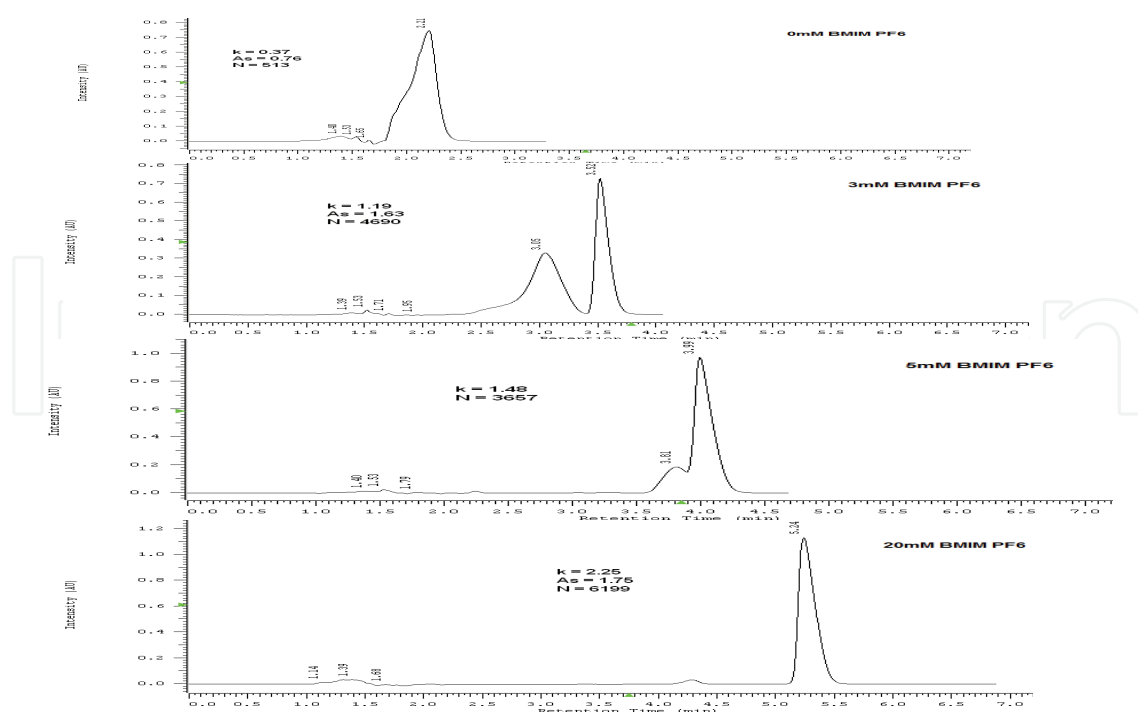


Fig. 5. The effect of different concentration of BMIM PF₆ on retention, peak symmetry and efficiency of nortryptiline. Column: on Zorbax Eclipse- XDB-C18, Eluent system: 40% ACN / 20 mM phosphate buffer pH = 2.9 (Flieger & Czajkowska-Żelazko, 2010).

The effect of different imidazolium based ILs was established on the basis of calculated binding constant of the silanol complex (K_A). It appears that the higher values were obtained for chloride and bromide ionic liquids than for tetrafluoroborates. Additionally, it should be emphasized that observed screening effect was achieved at lower concentration of these additives. Determined stability constant of the silanol complexes together with recommended additive concentration are presented in Table 2.

Advantages connected with suppression of silanophilic interaction appear simultaneously with the changes in analytes' retention factor. The increasing K_A values of alkylimidazolium halides, reflecting the silanol-masking potency, are connected with decreases of the basic analytes retention and selectivity of their separation.

In the light of conducted experiments, it is obvious that the cation of ionic liquid is responsible for the silanol screening effect, whereas the retention factor primarily depends on the properties of its anion. Only more chaotropic character of ILs anion, meaning not only hydrophobic nature but also entirely ion-pairing properties, leads to drastic retention increase. When anion of IL does not create ion-associated complex with analyte in ionic form, decrease in retention is observed. Summarizing, the retention mechanism in chromatographic system modified with ILs additives is complex covering the creation of ion pairs as well as ion exchange and hydrophobic partitions.

Generally, the retention of the basic compounds increases with the increase of the ionic liquids with chaotropic anion concentration in the mobile phase in reversed-phase systems (Flieger, 2009). However, these dependences differ in the shapes especially at their initial sectors. Fig. 6 illustrates the effect of concentration of 1-ethyl-3-methyl-imidazolium hexafluorophosphate [EMIM][PF₆], 1-butyl-3-methyl-imidazolium hexafluorophosphate [BMIM][PF₆] added to acetonitrile-aqueous eluent system on retention of basic compounds

Investigated ionic liquids	Benzyltriethylammonium hydrochloride		Thioridazine hydrochloride		Chlorpromazine hydrochloride	
	$K_A \times 10^{-3}$ [M ⁻¹]	C_A^* [mM]	$K_A \times 10^{-3}$ [M ⁻¹]	C_A^* [mM]	$K_A \times 10^{-3}$ [M ⁻¹]	C_A^* [mM]
[EMIM][BF ₄]	2.15	4.65	7.11	1.41	7.40	1.35
[PMIM][BF ₄]	2.37	4.22	7.67	1.30	8.68	1.15
[BMIM][BF ₄]	2.38	4.20	7.92	1.26	9.45	1.06
[HMIM][BF ₄]	2.71	3.69	9.39	1.07	17.95	0.56
[OMIM][BF ₄]	3.12	3.20	13.52	0.74	18.43	0.54
TEA	1.13	8.86	0.52	19.31	0.61	16.49
[MMIM][MSO ₄]	2.45	4.07	8.53	1.17	14.31	0.69
[EMIM][ESO ₄]	2.61	3.82	6.99	1.43	7.09	1.41
[BMIM][OSO ₄]	1.90	5.26	1.05	9.52	0.94	10.63
[EMIM][Br]	3.57	3.34	10.31	0.96	8.24	1.21
[EMIM][Cl]	2.99	2.80	9.7	1.03	7.90	1.26
[EMIM][Ts]	0.26	38.46	5.44	1.83	6.36	1.57
[BMIM][Br]	2.59	3.86	7.08	1.41	7.05	1.41
[BMIM][Cl]	2.89	3.46	6.54	1.52	6.94	1.43
[OMIM][Cl]	5.58	1.79	13.81	0.72	16.28	0.61

Table 2. Stability constant of the silanol complex, K_A and the recommended additive concentration, C_A^* , in 50:50 v/v acetonitrile/water pH 3 when using 1-alkyl-3-methylimidazolium ionic liquids. (Marszałł et al., 2006a).

belonging to phenothiazine derivatives on an octadecyl bounded-silica stationary phase. This class of isotherms possesses characteristic Langmuir shape related to horizontal orientation of the adsorbate molecules on the adsorbent surface. At higher concentration of ionic liquids, the shape of the isotherms differs, depending on the type of the additive. Quite different are also the concentrations provided to column saturation. The addition of [BMIM] [PF₆] ensures obtaining of the plateau at 2mM, and the shape of this dependence is a typical one of the monolayer adsorption (the basic type of Langmuir adsorption). In case of [EMIM] [PF₆], the shape of the above mentioned dependence suggests the incidence of a multi-layer adsorption. Quite different is the shape of the isotherm for the additive containing anion of a neutral character [BMIM] [Cl]. In this case, retention time of bases decreases with increasing ionic liquid concentration. This effect could be a consequence of repulsion forces between the adsorbed imidazolium cation on the adsorbent surface and protonated analytes.

Xiaohua obtained similar results (Xiaohua et al., 2004) analyzing the series of amines: benzylamine, benzydine, N-ethylaniline, N, N'-dimethylaniline and *k* o-,m-,p-phthalic acids in the presence of [BMIm][BF₄] in the mobile phase. Decreases of basic and acidic compounds retention proved that the part of ionic liquids coat on the reversed-phase surface and simultaneously anion of ionic liquid added does not interact with analytes. Kaliszan and his group also observed the retention decrease of neuroleptic basic drugs on octadecylsilica support and mobile phase comprising acetonitrile: phosphoric buffer (pH 3) 70/30 (v/v) modified with 1-ethyl-3-methylimidazolium tetrafluoroborate and 1,3-dimethylimidazolium methyl sulfate (Marszałł et al., 2005).

Owing to addition of ILs at minute concentration to the mobile phase we can improve also separation selectivity. Xiaohua and co-workers (Xiaohua et al., 2004) showed improvement

of amines mixture separation covering benzylamine, benzydine, N,N-dimethylaniline, N-ethylaniline on C18 column and water with addition of 1-ethyl-3-methylimidazolium tetrafluoroboran as an eluent system.

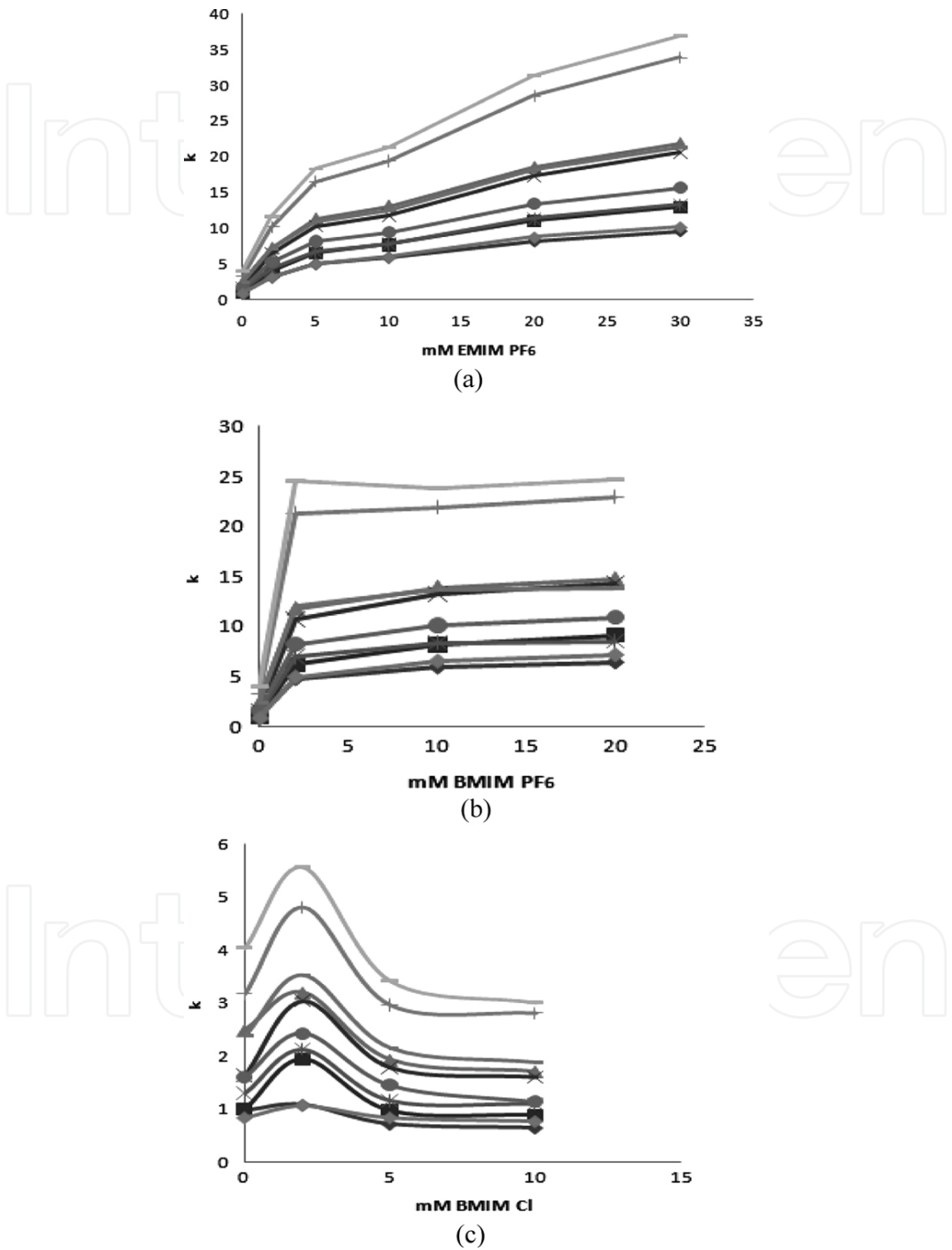


Fig. 6. Experimental retention factor for the investigated neuroleptic drugs vs. concentration of ILs in mobile phase containing 30% ACN/10 mM phosphate buffer (pH=2.8). A-EMIM PF₆, B-BMIM PF₆, C-BMIM Cl. (Flieger, 2009).

In my latest studies, some new aspects devoted to application of ionic liquids as mobile phase modifier were revealed (Flieger & Czajkowska-Żelazko, 2010). Analyzing chosen basic drugs in reversed-phase systems on two columns: Zorbax XDB-C18 and Zorbax SB-Phenyl in acetonitrile aqueous mobile phase acidified and modified with [BMIM] [Cl] or [BMIM][PF₆], visible differences in chromatographic behavior were detected. Fig.7 presents the retention dependences of pindolol on the concentration of investigated ionic liquids in 10% ACN buffered eluent system.

As it could be seen, pindolol shows an increase of retention with increasing concentration of ionic liquid possessing chaotropic anion [PF₆⁻], as a result of ion-pair creation between protonated basic molecule [BH⁺] and the counter-anion [PF₆⁻]. This process achieves saturation level after which ionic liquid concentration does not influence the retention. In turn, the presence of neutral anion [Cl⁻] causes decreasing of retention factor. Moreover, at this graph unexpected retention increase on Zorbax SB-Phenyl at low concentration (1 mM) of [BMIM] [Cl] in 10% ACN mobile phase could be observed. This deviation is the consequence of differences in structure of interphases created in compared systems.

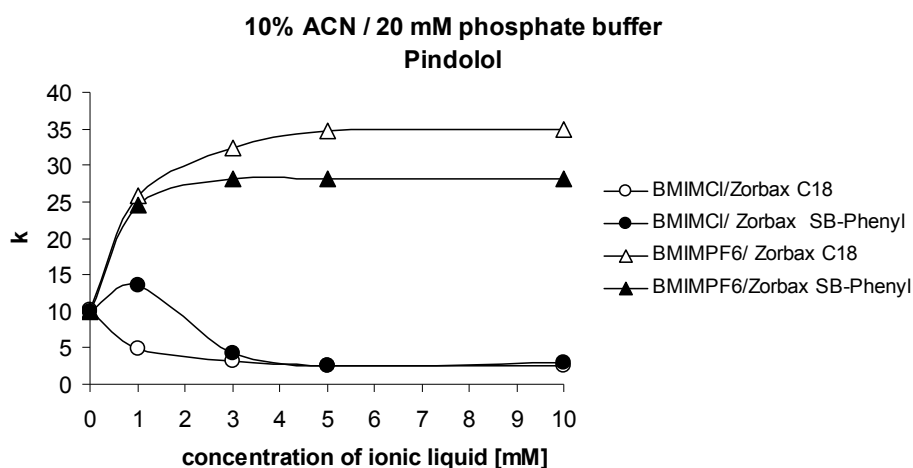
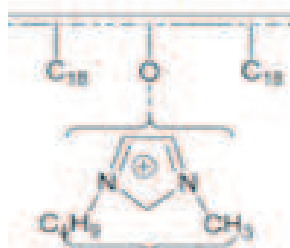


Fig. 7. Experimental retention factors for pindolol versus ionic liquids (1-butyl-3-methyl-imidazolium hexafluorophosphate-[BMIM] [PF₆], 1-butyl-3-methyl-imidazolium chloride-[BMIM] [Cl] concentration in 10% ACN / 20 mM phosphate buffer pH = 2.9 obtained for different hydrophobic columns: Zorbax Eclipse- XDB-C18 and Zorbax SB-Phenyl. Flow rate: 0.9 ml/min., temperature: 20°C, UV detection at 254 nm; sample: 3 µl injection. (Flieger & Czajkowska-Żelazko, in press).

Multilayer of adsorbed acetonitrile molecules forming on the adsorbent surface is a good medium for solubility of ionic liquids as a liophilic species. Assuming that free silanols are in ionized state, the addition of even small amount of ionic liquid (1 mM for Zorbax XDB-C18 or 1-3 mM for Zorbax SB-Phenyl) could be enough to reduce free silanols and to increase of stationary phase hydrophobicity owing to electrostatic interactions occurring accordingly to the following scheme:



This effect could be useful in practice for improvement of separation selectivity by retention enhancement. Fig.8 presents example of improvement of 1,4 benzodiazepine separation by addition of 3 mM [BMIM][Cl] to acetonitrile-water mobile phase on Zorbax SB-Phenyl column.

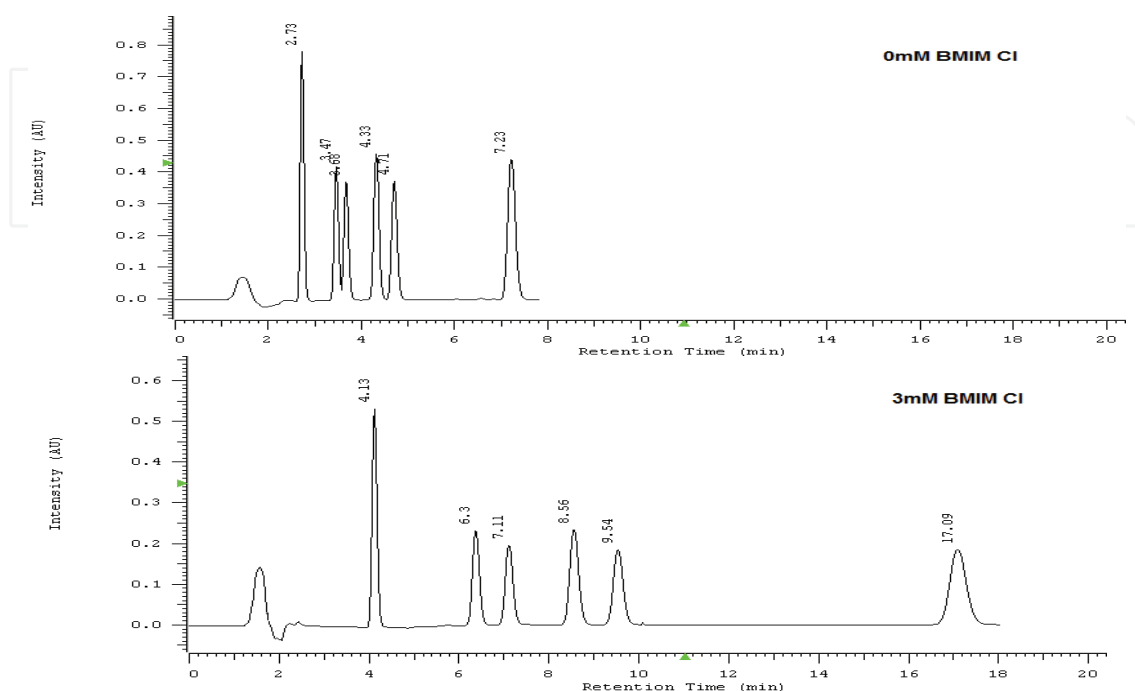
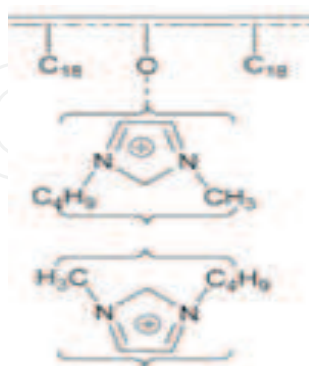


Fig. 8. Separation of 1,4-benzodiazepines mixture on Zorbax SB-Phenyl column and eluent system: 50% ACN / 20 mM phosphate buffer pH = 2.9 with addition of 3 mM [BMIM] [Cl]. For HPLC conditions see Experimental part. The peaks order: dechloridiazepam, oxazepam, lorazepam, nitrazepam, demethyldiazepam, diazepam.

Further increase of [BMIM] [Cl] concentration in the mobile phase causes decrease in retention of protonated amines probably owing to excess adsorption of liophilic ionic liquid cation with polar part oriented toward polar eluent environment in agreement with the following scheme:



According to this scheme, positive charge on the surface is responsible for retention decrease of protonated amines at higher concentration of ionic liquid chloride in the mobile phase. Though, some papers (Hu et al., 2009; Stepnowski et al., 2006) demonstrated adsorption of ILs on hydrophobic surface, nobody has shown before real reflectance of these speculations in retention factor and connection with ILs concentration in the mobile phase.

Addition of ILs to the mobile phase in RP-HPLC systems appears to be especially advantageous for determination of the lipophilicity parameters of ionogenic basic analytes owing to suppression of silanophilic interactions and improvement of linearity of $\log k$ vs. volume fraction of organic modifier in eluent system:

$$\log k = -S\phi + \log k_w \quad (2)$$

where $\log k$ indicates the isocratic capacity factor, ϕ the volume fraction of organic modifier in the mobile phase, $\log k_w$ the retention factor extrapolated to pure water, S the slope of the regression curve.

The correlation between the reference lipophilicity parameter from the n-octanol-water partition system ($\log P_{\text{oct}}$) and chromatographically determined lipophilicity parameters (S , $\log k_w$, ϕ_0) is statistically significant mainly for congeneric group of neutral solutes. Application of ionic liquids additives improved evidently this correlation for compounds exhibiting acid-base behavior. Kaliszan (Kaliszan et al 2004) proposed [EMIM] [BF₄] for this purpose. Fig.9 illustrates improvement of correlations between the chromatographic lipophilicity parameters, $\log k_w$, and $\log P_{\text{oct}}$ obtained for a series of basic drugs by gradient HPLC at the presence of [EMIM] [BF₄] in the mobile phase.

For acid compounds, the mechanism for separation and the effects of ionic liquids appear to be different. Hu et al (Hu et al., 20) applied 1-butyl-3-methylimidazolium chloride [C₄MIM][Cl], 1-octyl-3-methylimidazolium chloride [C₈MIM][Cl], and 1-decyl-3-methylimidazolium chloride [C₁₀MIM][Cl] as mobile phase additives in reversed-phase separation phenoxy acid herbicides and phenols at neutral pH on conventional C18 column. It was demonstrated that [BMIM][Cl], was the most efficient. The retention time of the target

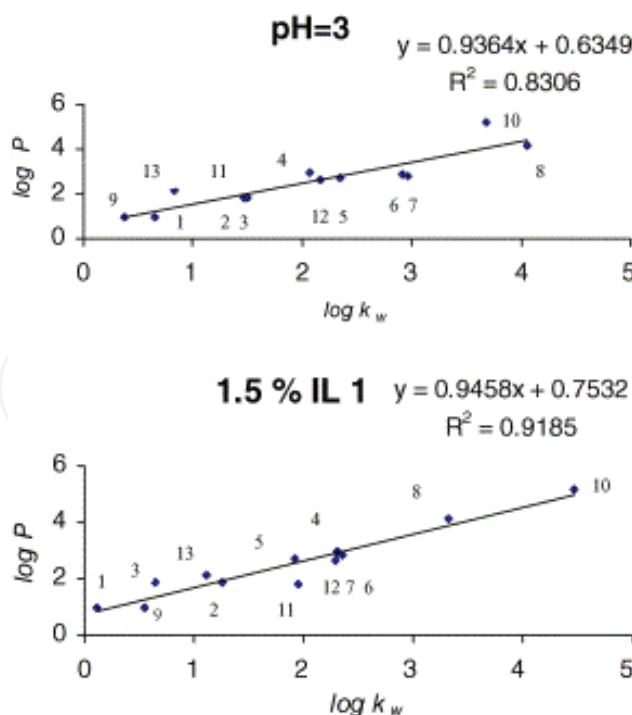


Fig. 9. Relationships between $\log P$ and the lipophilicity parameter $\log k_w$, determined by gradient HPLC with a buffered at pH 2.87 water-methanol eluent not comprising (upper plot) and comprising (bottom plot) 1.5% (v/v) of IL (Kaliszan et al., 2004).

acids was shortened with the increase of the alkyl chain length and the concentrations of ionic liquids. The delocalization of the positive charge on the imidazolium cation, the repulsion between chlorine ions of ionic liquids and the acid compounds, as well as the stereo-hindrance effect are probably responsible for the observed effects.

3.2.3 Ionic liquids as liquid chromatography stationary phases

The newest approach in liquid chromatography is stationary phase modification by the use of ILs. Initial experiments were performed by the dynamic coating of the silica support using alkylammonium nitrate ILs in chlorinated hydrocarbons or ethers in hexane containing up to 75% (v/v) of the polar organic solvent as the mobile phase (Shetty et al. 1990). In this way, ILs formed the so-called supported liquid phases generating liquid-liquid separation mechanism. Obtained biphasic systems were effective for identifying systems for liquid-liquid extraction of complex mixtures and determination of partition coefficients. This method, owing to favorable features including speed, accuracy and minimal consumption of reagents, appears to be suitable in spite of some disadvantages concerning UV absorbance limitations caused by ILs. This idea found application in countercurrent chromatography (CCC) requiring two immiscible liquid phases as separation medium. Berthod et al. (Berthod et al. 2004) constructed biphasic liquid system consisting of water and [BMIM] [PF₆] with addition of acetonitrile reducing viscosity for determination of the distribution constant of various aromatic compounds containing basic, acidic and neutral substituents. A preparative high-speed counter-current chromatography method for isolation and purification of flavonoid compounds from *Oroxylum indicum* was successfully established by using ionic liquids as the modifier of the two-phase solvent system. Two flavonoid compounds including baicalein-7-*O*-diglucoside and baicalein-7-*O*-glucoside were purified from the crude extract of *O. indicum* by using ethyl acetate–water–[BMIM][PF₆] (5:5:0.2, v/v) as two-phase solvent system (Liu et al., 2010).

Liu and his group was among the first who examined new LC stationary phases based on covalently bonded ILs. They immobilized a vinyl-hexylimidazolium tetrafluoroborate IL at the surface of porous silica particles activated with a silane-coupling agent (mercaptopropyl trimethoxysilane). The obtained column was applied for separation of an ephedrine mixture (Jiang et al. 2004). The initial results weren't satisfactory. However, the next study of the same team concerning covalent bonding between silanol groups and the cation of the ILs turned out to be a considerable success (Qiu et al., 2006 a; Qiu et al., 2006 b). Owing to the reaction of silanised with 3-chloropropyltrimethoxysilane gel with imidazolium salt, stationary phase possessing anion-exchanging properties able to separate inorganic as well as organic anions was obtained. A schematic diagram of SilprMim synthesis and separation results is shown in Fig.10 and Fig.11.

Next, Stalcup and co-workers (Sun et al. 2005) received new column thanks to the reaction of silica gel with 1-butyl-3 heptylimidazolium bromide. IL's cation was covalently immobilized through an n-alkyl ether chain. Properties of obtained column were studied under reversed-phase conditions for the separation of a group of neutral aromatic solutes applying the linear solvation energy relationship approach. Retention properties were remarkably similar to conventional phenyl-based stationary phases despite the presence of significant charge on the surface. The slope of the $\log k_{\text{butylimidazolium}}$ versus $\log k_{\text{phenyl}}$ is close to unity (0.958) indicating additionally that residual alkyl linker does not play a large role in the retention process (Fig.12).

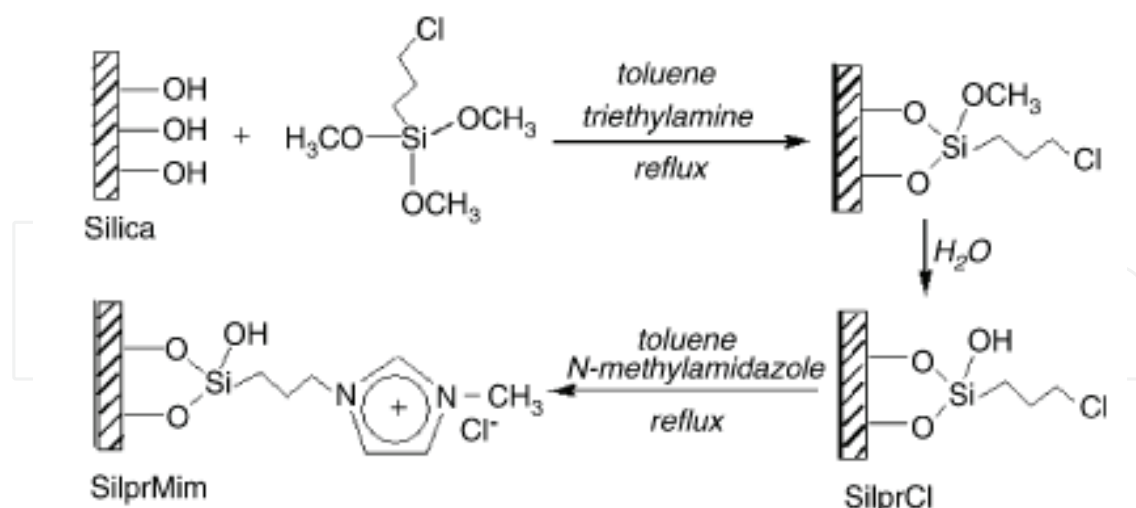


Fig. 10. Preparation of N-methylimidazolium functionalized silica. (Qiu et al. 2006 b)

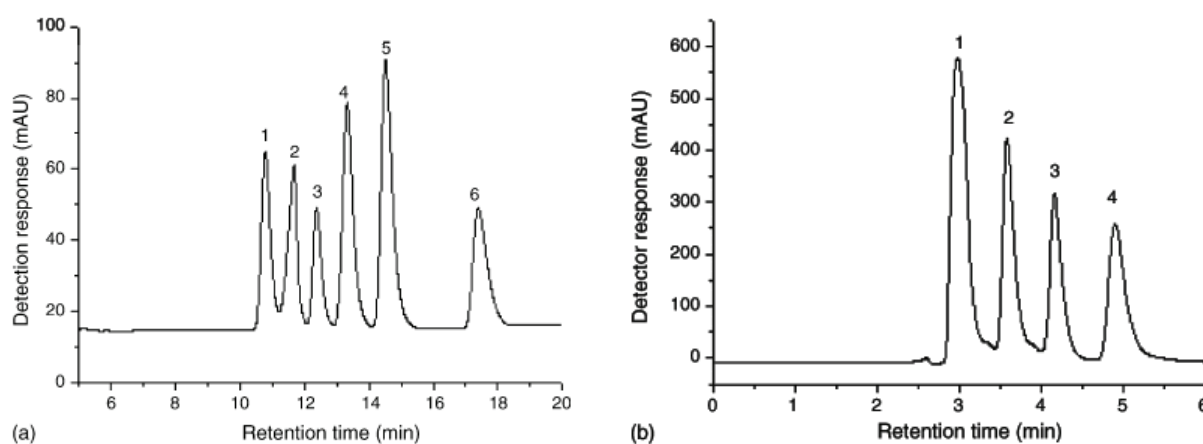


Fig. 11. Chromatogram of separation of test mixture composed of: (a) iodate(1) chloride(2); bromide(3); nitrate(4); iodide(5); thiocyanate(6). Mobile phase $20\text{mmol}^{-1}\text{KH}_2\text{PO}_4$ (pH 4.6); (b) N-ethylaniline(1); N,N-dimethylaniline(2); o-nitroaniline(3); and benzidine(4); - Mobile phase was $50\text{mmol}^{-1}\text{KH}_2\text{PO}_4$ (pH 4.6) (Qiu et al. 2006 b).

Recently, consecutive study describing other stationary phase has been published (Wang et al. 2006). Trimethoxysilane “ionosilane” derivatives of RTILs based on alkylimidazolium bromides were bonded to $3\text{ }\mu\text{m}$ diameter silica particles. The ionic liquid moiety was predominantly attached to the silica surface through two siloxane bonds of the ionosilane derivative. The obtained structure was confirmed by thermogravimetric analysis (TGA) and ^{13}C and ^{29}Si NMR spectroscopies. Properties of the column were studied by using aromatic carboxylic acids as model compounds. It appears that the separation mechanism involves multiple interactions including ion exchange, hydrophobic interaction, and other electrostatic interactions. Authors of the study emphasize it that a clear advantage of the new columns is a possibility of reducing the content of organic solvent in the mobile phase and a diversified selectivity depending on the spatial orientation of bounded ligands (Fig.13).

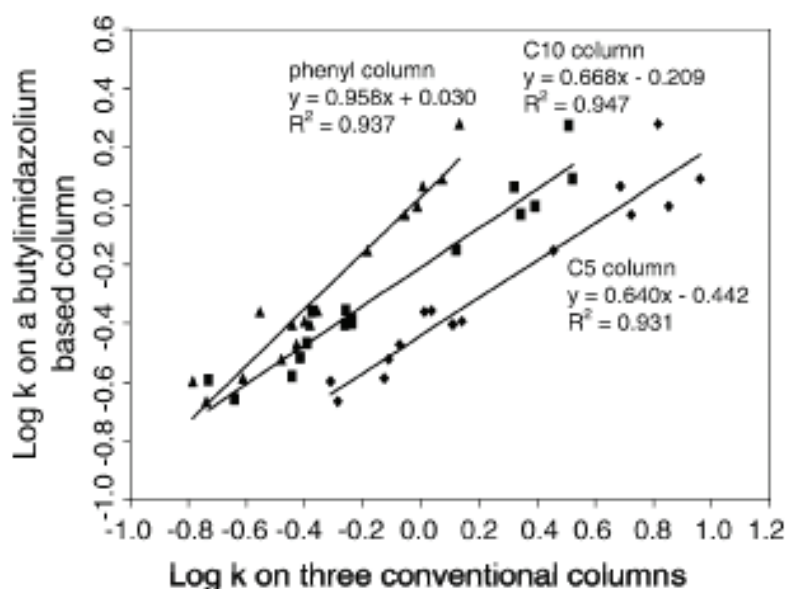


Fig. 12. Plot of $\log k$ obtained using 60% MeOH on the butylimidazolium column versus $\log k$ obtained on conventional aliphatic reversed phase columns under the same mobile phase conditions (Sun et al. 2005).

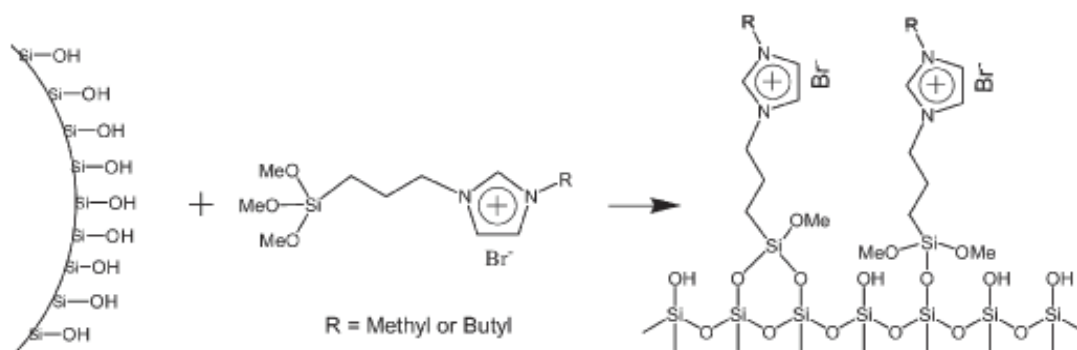


Fig. 13. Schematic procedure of ILs bonded stationary phase synthesis (Wang et al. 2006).

4. Liquid chromatography of ionic liquids

In the recent years, ILs have gained great popularity in chemical industry. Their determination is very important because of high probability of their migration into the environment. Unfortunately, this subject has not been extensively explored so far. There are only several papers dealing with analytical methods suitable for ILs determination. Among them chromatographic techniques, especially reversed-phase liquid chromatography, appear to be the most suitable for analysis of ILs as well as determination of their properties or identifying systems suitable for their liquid-liquid extraction. Different stationary phases such as cholesterol ligands bonded chemically to silica, alkylamide, butyl, octyl, octadecyl, phenyl, aryl, mixed (containing octyl, octadecyl, phenyl, aminopropyl, cyanopropyl) were tested for this purpose (Buszewski et al., 2006). Due to the non-molecular nature of ILs, the retention mechanism is not as simple as the one of molecular species. The retention mechanism combines hydrophobic and ionic interactions (ion-pairing, ion-exchange). In agreement with hydrophobic nature of retention mechanism, retention of ILs increases with

increasing hydrophobicity of the stationary phase. However, for packings containing protonized functional groups, the lowering of the retention factor was observed owing to electrostatic repulsion forces between entities and charged surface. The main interactions, predominant in the case of aryl stationary phase, are dispersive ones and of π - π type.

The best results according to separation selectivity towards ILs were achieved on the butyl and silica monolith with bonded octadecyl groups probably owing to the lowest heterogeneity of these ligands (Buszewski et al., 2006). Routinely, liquid chromatography with the use of an octyl stationary phase could be applied for isolation, identification and quantification of 1-alkyl and 1-aryl-3-methylimidazolium based ILs (Stepnowski et al., 2003). It should be stressed that when a salt is added to the mobile phase, only ILs differing with the cation can be separated (Ruiz-Angel & Berthod, 2006). To improve IL peak shape and enhance retention time, NaPF_6 or NaClO_4 could be added to the mobile phase. These anionic additives, possessing chaotropic properties, form ion-pairs with the IL cations. In turn, mobile phases containing no salts are able to separate ILs differing with the anion. Their elution order depends on the lyotropy of the anions. Berthod investigated eleven 1-alkyl-3-methyl imidazolium ionic liquid salts in reversed phase mode with a Kromasil C_{18} column. It was shown that it is possible to separate different ILs depending on the mobile phase composition. Additionally, working with salt-free mobile phases, fronting peaks for all ILs were observed, associated with the IL/ C_{18} stationary phase interactions responsible for concave isotherms. With mobile phase containing 0.01 M of salt, tailing IL peaks corresponding to convex adsorption isotherms were obtained, as could be seen in Fig.14.

Taking into account the fact that short chain ILs, as the early eluting compounds in reversed-phase systems, are not satisfactorily resolved, Stepnowski and Mroziak (Stepnowski & Mroziak, 2005) applied the SCX stationary phase with strong cation exchange properties. They investigated the chromatographic behavior of 8 ILs: 7 homologues of 1-alkyl-3-methylimidazolium and 4-methyl-*N*-butylpyridinium. Depending on the mobile phase composition, different interactions such as cation exchange, nonspecific hydrophobic interactions, and adsorption affected the retention process. In comparison to the chromatographic behavior of ILs in the classical reversed phase system much higher selectivity of highly hydrophilic compounds was noticed.

In order to take advantage of the potential π - π interactions, an ether-linked phenyl stationary phase with polar endcapping was also proposed in the separation of imidazolium and pyridinium ILs (Stepnowski et al., 2006). With phenyl-bonded phases, very good separations of the cations were achieved however; gradient elution was required to achieve separation at appropriate time (Fig.15). Once again special attention was paid to the short-chain hydrophilic entities, known to be poorly separated on conventional reversed-phase columns. Authors declare the applicability of the proposed method for monitoring degraded cations of 1-butyl-3-methylimidazolium salts obtained in the Fenton process.

The aim of this study was also investigation of the nature of interactions occurring in the chromatographic system. Possible interaction between imidazolium IL and phenyl-bonded stationary phase is illustrated schematically in Fig.16. In case of acetonitrile, which is able to form electrono-donor-acceptor complexes, suppression of π - π interactions between the solute and the aromatic moiety of the stationary phase could be assumed. Thus at higher acetonitrile concentration in the mobile phase only hydrophobic and hydrogen-bonding interactions would be responsible for the separation mode. Recently, Studzińska and Buszewski proved that ILs are bonded much stronger to variety of stationary phase surfaces when pH of mobile phase is less acidic (Studzińska & Buszewski 2010).

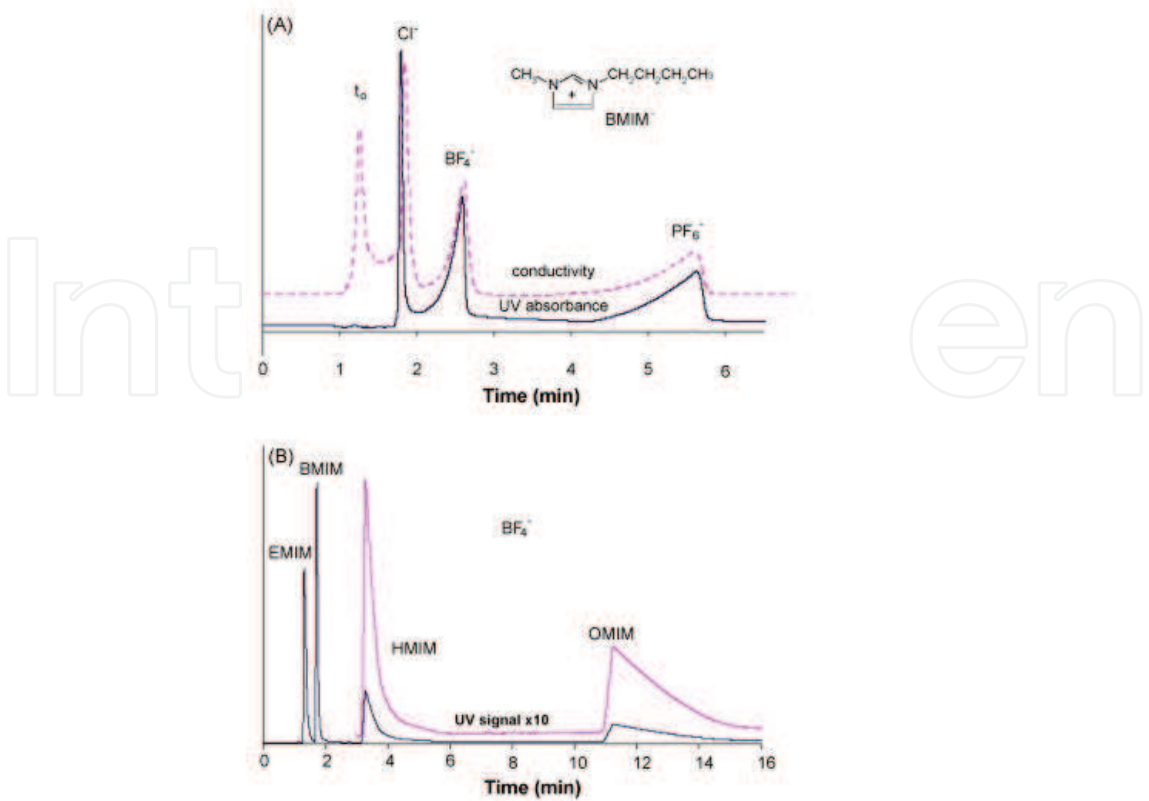


Fig. 14. RPLC separation of ionic liquids. (A) Separation of three BMIM ILs; continuous line: UV 254 nm detection; dotted line: conductimetric detection; salt-free mobile phase: acetonitrile/water 10/90% (v/v), 1 mL/min. (B) Separation of EMIM Cl, BMIM BF_4 , HMIM BF_4 and OMIM PF_6 ; mobile phase: acetonitrile/water 0.01 M NaCl 30/70% (v/v), 1 mL/min; UV detection 254 nm; column Kromasil C_{18} 150 mm \times 4.6 mm i.d. (Ruiz-Angel & Berthod, 2006).

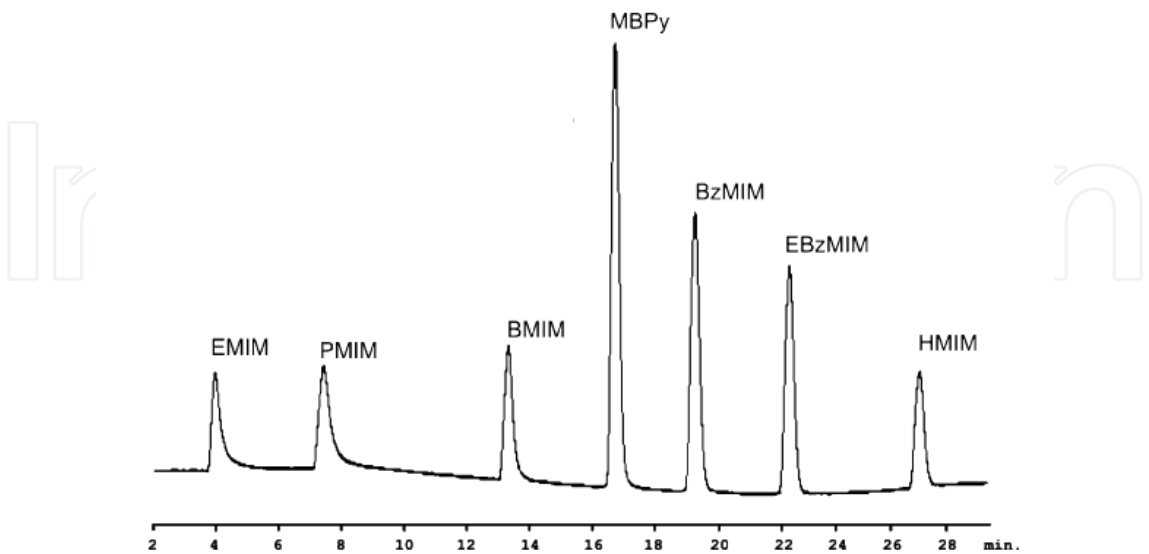


Fig. 15. Gradient separation of selected imidazolium and pyridinium ionic liquids under the conditions investigated. Mobile phase: methanol (2–20%)-water (5mM K_2HPO_4).pH 3.0.Column: Synergi Polar RP (Stepnowski et al., 2006).

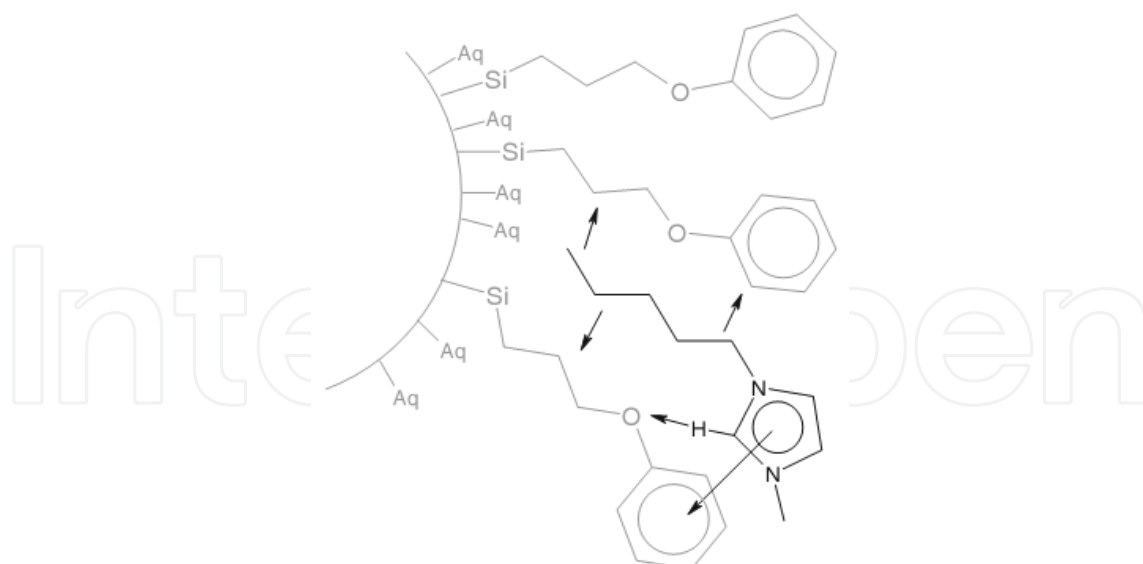


Fig. 16. Possible interactions of imidazolium ionic liquid cation and phenyl-bonded stationary phase. Arrows indicate hydrogen-bonding, hydrophobic and π - π interactions (Stepnowski et al., 2006).

Chromatographic behavior of ionic liquid cations in view of quantitative structure-retention relationship (QSRR) was studied by Molíková and co-workers (Molíková et al., 2010). The most significant QSRR equation between experimentally determined $\log k_w$ values and the structural descriptors of test analytes from molecular modeling (the solvent accessible surface: SAS, the differences in the energies of the highest occupied and the lowest unoccupied molecular orbitals: *diffHL*) was obtained in case of columns with the highest carbon loads and larger specific surface areas, i.e. Symmetry C18 and Symmetry C8. In turn, the column ACE 5 C18 allowed to obtain the best separations of the ILs according to cations kind. As the authors declare, identification of QSRRs can provide the knowledge regarding hydrophobicity and retention mechanism of ILs. It could be further helpful in prediction of their biological effects and the way of these chemicals into the environment.

5. Electromigration techniques.

ILs, due to good electrical conductivity and appropriate viscosity, could be used as electrolytes, additives in the run buffer or reagents for dynamic coating or covalent attachment to the capillary walls in capillary electrophoresis (CE). The main disadvantage of this chromatographic technique is an electroosmotic flow (EOF) provoked by silanol groups on the inner surface of silica capillaries. To reverse this process ILs can be covalently bonded to a fused-silica capillary surface. Qin and Li (Qin & Li, 2002; Qin et al. 2003) covalently bonded propyl methyl imidazolium chloride [PMIM][Cl] to a silica capillary. Due to the positive charge of the bonded moieties and reduction of interaction between analytes and the capillary wall, separation of sildenafil and its metabolites in human serum and DNA analysis with MS detection were possible. The capillary wall modified with 1-ethyl-3-methylimidazolium was used for separation of positively charged inorganic ions: NH_4^+ and K^+ in human urine, the separation of K^+ , Na^+ , Li^+ , Ca^{2+} , Mg^{2+} and Ba^{2+} ions in red wine. The main advantage of those capillaries appears to be increases in the working pH range of the

running buffer with good efficiency and the compatibility with mass spectrometry (Qin & Li, 2002; Qin & Li, 2003; Qin et al., 2003).

Fused-silica capillaries could be chemically modified with an analogue of the imidazole-based IL (1-butyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium tetrafluoroborate) as well as zwitterionic salt (*N*-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazole) (Borissowa et al., 2007).

It appeared that the electroosmotic flow in the capillary coated with an ionic liquid analogue was found to be anodic and dependent on the pH of the separation buffer. Whereas in the case of a zwitterionic capillary, the electroosmotic flow was cathodic and its velocity remained almost constant in the pH range of 4–7. Schematic illustration of ionic liquid bonding to the capillary wall is presented in Fig.17.

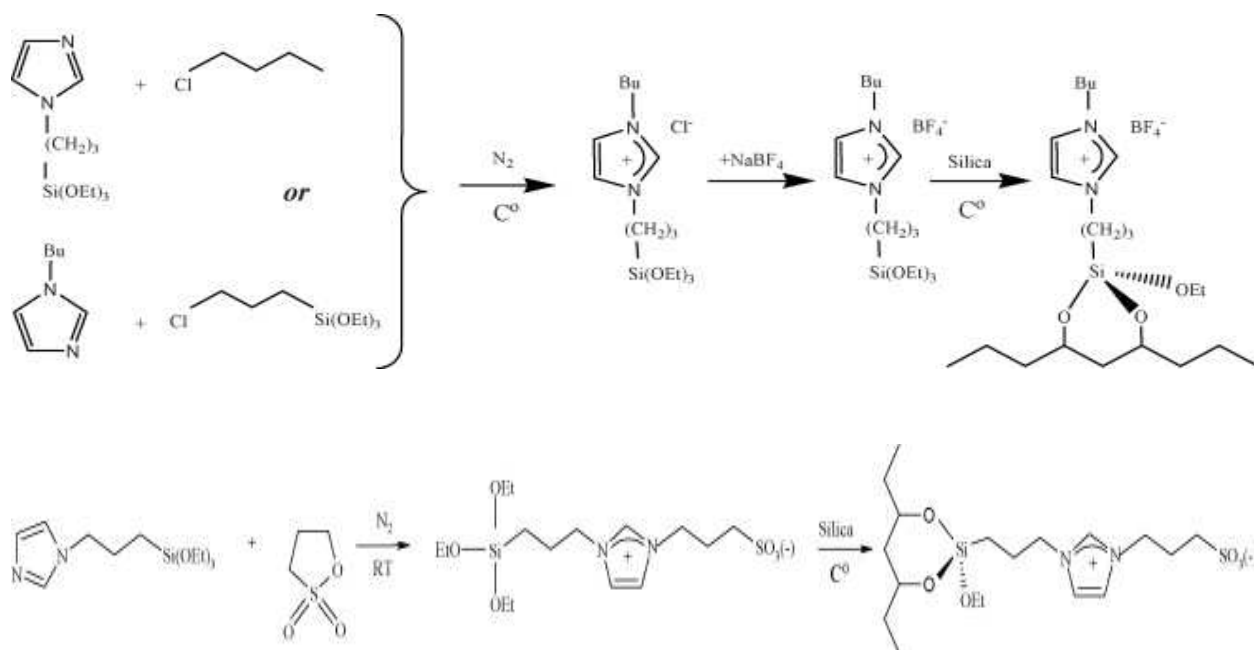


Fig. 17. Scheme representing the IL and zwitterionic salt coating procedure (Borissowa et al., 2007).

ILs could be applied also as background electrolytes in aqueous as well as non-aqueous electrophoresis (NACE). In NACE, the EOF does not change its direction by addition of IL indicating that the dynamic coating process is meaningless. That is why interactions between the solute and ILs ions and significant changes in the electrophoretic mobility are mainly responsible for enhancement of separation selectivity. Effect of ionic liquids on EOF in NACE was monitored by contactless conductivity detection (Seiman et al., 2008). Dialkylimidazolium ILs were used in NACE for separation of water insoluble dyes (Vaher et al., 2000), phenols and aromatic acids (Vaher et al., 2002a), polyphenols (Vaher et al., 2002b).

In turn, ILs used as the electrolytes in aqueous capillary electrophoresis, enable the dynamic coating of the capillaries wall. IL cations, as well as anions, influence the migration behavior of analytes but the resolving power of the system is much more affected by activity of the IL

cation. Analytes can interact either with the ILs cations adsorbed on the capillary wall or with the free IL cations in the electrolyte solution. Not meaningless is the suppression of the EOF and changing electrophoretic properties of capillary wall by IL's cationic molecule. It makes the separation mechanism more complex. Fig.18 illustrates mechanism of polyphenol separation using 1-alkyl-3-methylimidazolium based IL in the background electrolyte (Yanes et al., 2001).

ILs as dynamic coating materials were used for separation of different groups of compounds. For instance, dimethyldinonylammonium bromide was used for determination of carboxylates as copper complexes (Laamanen et al., 2005), 1-alkyl-3-methylimidazolium-based ionic liquids were used as the running electrolytes for separation of acidic and basic proteins (Jiang et al., 2003; Wu et al., 2008) and flavone derivatives (Qi et al., 2006), nicotinic, isonicotinic and picolinic acids (Marszałł et al., 2006 b), monocationic and dicationic phosphonium-based ILs were tested for separation of inorganic and small organic anions (Krizek et al., 2009). Dicationic ion pairing reagent (*N,N'*-dibutyl 1,1'-pentylenedipyrrolidinium) was applied for determination of several anions in the positive mode using CE-ESI-MS method achieving greater sensitivity, in comparison to the direct MS detection in the negative mode (Lin et al., 2009).

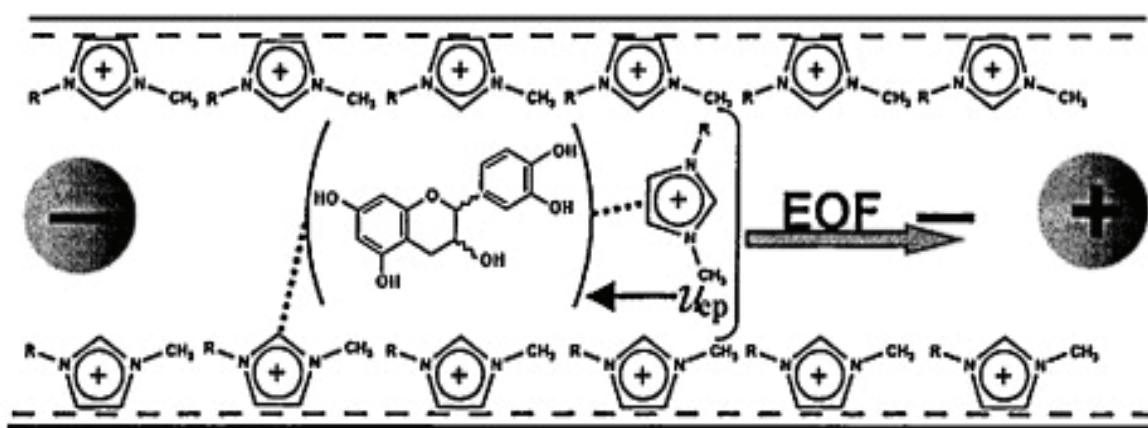


Fig. 18. Mechanism of polyphenols' separation using 1-alkyl-3-methylimidazolium-based ionic liquids. (Yanes et al., 2001).

Separation of both neutral and charged analytes is possible owing to micellar capillary electrophoresis (MCE). In this chromatographic technique, long chain alkylimidazolium ILs could be used as surfactants and short chain ones as modifiers. 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF₄] was added as modifier to the micellar system containing SDS resulting in the complete separation of active components of lignans in medicinal herbs (Tian et al., 2005). As the authors claimed, ILs affected the size and shape of the micelles, altering the separation. Long chain alkylimidazolium ILs added to the aqueous buffer were used as surfactants for separation of neutral methylresorcinol isomers and benzene derivatives (Borissova et al., 2008). 1-Butyl-3-methylimidazolium dodecanesulfonate (BAS) was applied in microchip MCE for the separation of proteins (Xu et al., 2008).

Chiral ILs could be used for enantiomeric separation in electromigration techniques. S-[3-(chloro-2-hydroxypropyl)trimethylammonium] NTf₂ was used as a chiral selector to separate various enantiomeric pharmaceutical compounds in CE (Tran & Mejac, 2008), undecenoxycarbonyl-L-prolyrrolidinol bromide, and undecenoxycarbonyl-L-leucinol bromide to separate enantiomeric acidic analytes were used in MCE (Rizvi & Shamasí 2006). Sometimes ILs chiral selector requires another chiral selector to achieve enantioseparation. For instance, two chiral ILs: (ethyl- and phenylcholine of bis(trifluoromethylsulfonyl)imide) acting synergistically with cyclodextrins were able to improve the enantioselectivity for 2-arylpropionic acids (Francois et al., 2007).

6. Concluding remarks

Growth of ionic liquids applications in analytical chemistry has been observed during the last years. It appears to be reasonable, considering a wide range of their physico-chemical properties. As green solvents they could find many industrial applications in future. That is why elaborating on new sensitive methods of their determination in environmental and industrial samples appears to be a dire must. Taking into account chromatographic techniques the most promising progress connected with good solvent properties of ionic liquids, their low volatility and electrical conductivity, is observed in liquid chromatography as well as electromigration techniques. The next generation of ionic liquids also with chiral properties will be synthesized and will find other applications. Special precaution should be taken as for the toxicity, stability and purity of these reagents. Long term stability devoted especially to ionic liquids containing perfluorinated anions should be taken into account in connection with the degradation products which could damage the silica based adsorbents. Understanding ionic liquids properties in chromatographic system is still unclear. Some authors assume that an ionic liquid should not be used as an alternative to a normal salt because the distinction between liquid and solid is lost in solution and ILs properties become the same as those of organic salts. However, other authors satisfactorily demonstrate special behavior of ionic liquids in chromatographic systems, stressing unique stationary phase modification and advantageous interactions with investigated compounds. Interpretation of the separation mechanisms when ionic liquids are used still appears to be an interest of the scientific forum.

7. References

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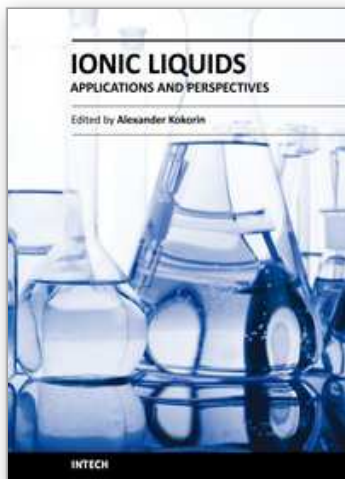
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