Anal Bioanal Chem
DOI 10.1007/s00216-014-8264-z

RESEARCH PAPER

Partition coefficients of organic compounds between water and imidazolium-, pyridinium-, and phosphonium-based ionic liquids

Juan M. Padró · Rocío B. Pellegrino Vidal · Mario Reta

Received: 9 September 2014 / Revised: 3 October 2014 / Accepted: 8 October 2014

Abstract The partition coefficients, $P_{IL/w}$, of several compounds, some of them of biological and pharmacological interest, between water and room-temperature ionic liquids based on the imidazolium, pyridinium, and phosphonium cations, namely 1-octyl-3-methylimidazolium hexafluorophosphate, *N*-octylpyridinium tetrafluorophosphate, trihexyl(tetradecyl)phosphonium chloride, trihexyl(tetradecyl)phosphonium bromide, trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)imide, and trihexyl(tetradecyl)phosphonium dicyanamide, were accurately measured. In this way, we extended our database of partition coefficients in room-temperature ionic liquids previously reported. We employed the *solvation parameter model* with different probe molecules (the *training set*) to elucidate the chemical interactions involved in the partition process and discussed the most relevant differences among the three types of ionic liquids. The multiparametric equations obtained with the aforementioned model were used to predict the partition coefficients for compounds (the *test set*) not present in the training set, most being of biological and pharmacological interest. An excellent agreement between calculated and experimental log $P_{IL/w}$ values was obtained. Thus, the obtained equations can be used to predict, a priori, the extraction efficiency for any compound using these ionic liquids as extraction solvents in liquid-liquid extractions.

Keywords Nitrogen-based ionic liquids · Phosphonium-based ionic liquids · Partition coefficients · Liquid-liquid extraction

Introduction

At present, room-temperature ionic liquids (RTILs) are close to be considered as conventional solvents for liquid-liquid extractions in sample preparation, although their use compared with typical organic solvents is still much lower [1]. The use of ionic liquids in different areas of analytical chemistry, particularly the RTILs, has increased considerably in recent years. This is because these solvents have several characteristics that are different to those of the typical organic solvents, such as unique solubilization properties, low or none vapor pressure, no flammability, and the possibility to modify their physical properties through the proper selection of the cation and anion [2, 3].

Although the lack of toxicity for the majority of the RTILs has not been completely demonstrated, they are invoked as "green" or "environmentally friendly solvents" [4–6]. The density of the RTILs can be higher or lower than that of typical aqueous solutions which conditions the experimental design if an extractant of this type is going to be used in liquid-liquid extractions (LLEs). RTILs denser than water will remain as the bottom phase, and after extraction, the aqueous phase must be carefully separated from the ionic liquid. If it is viscous enough, the aqueous phase can be discarded by just inverting the test tube, since the ionic liquid usually remains to be stuck to the tube wall. If the RTIL is less dense than water or the aqueous sample matrix, it will remain as the top phase and the extraction is direct. As a counterpart, due to the typical high viscosities of the RTILs, a dilution with solvents such as methanol or acetonitrile can be necessary before injection into the HPLC column, which decreases the enrichment factor.

Electronic supplementary material The online version of this article (doi:10.1007/s00216-014-8264-z) contains supplementary material, which is available to authorized users.

J. M. Padró · R. B. Pellegrino Vidal · M. Reta (✉)
Laboratorio de Investigación y Desarrollo de Métodos Analíticos (LIDMA), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, 49 y 115, 1900 La Plata, Argentina
e-mail: mreta@quimica.unlp.edu.ar

Published online: 19 October 2014

Although phosphonium-based RTILs (PB-RTILs) have been known and synthesized for years, they have been more or less *neglected* in the literature compared to their imidazolium- or pyrrolidinium-based counterparts [7]. PB-RTILs are made of tetraalkylphosphonium cations with different anions and can have some additional advantages compared to the nitrogen-based RTILs (NB-RTILs), such as very high thermal and chemical stability and higher solvation properties. There are about 20 different types of PB-RTILs commercially available. Cytec Industries Inc. sells phosphonium salts under the Cyphos® trade name [6, 8]. The use of PB-RTILs in liquid-liquid extractions has been scarcely reported in the literature [9, 10].

In our previous paper [7], we have used the *solvation parameter model* (SPM) to elucidate the molecular interactions involved in the partition process for analytes of very different chemical nature between imidazolium-based RTILs and water, as well as to predict liquid-liquid partitioning of molecules of biological interest, which should be useful to obtain high recoveries and enrichment factors for any analyte (neutral at the working pH) using those studied RTILs as extractants.

The SPM relates the logarithm of some free energy-related physicochemical property, in this case the RTIL-water partition coefficient, $P_{IL/w}$, and several independent solute parameters or descriptors, each one reflecting a different type of solute-solvent interaction (Eq. 1). Thus, since a solvation process (relative solubility of the analyte in a biphasic system) is involved, the SPM is considered as a linear solvation energy relationship (LSER).

$$\log P_{IL/w} = \log C_{IL}/C_w = \mathbf{c} + \mathbf{sS} + \mathbf{aA} + \mathbf{bB} + \mathbf{vV} + \mathbf{eE} \qquad (1)$$

Here C_{IL} and C_w are the analyte concentrations in the RTIL and aqueous phases, respectively, and the solute descriptors are as follows: **S** is the solute dipolarity/polarizability; **A** and **B** are the respective solute parameters which represent the hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) capacity; **V**, the molar volume, accounts for both the necessary energy to form the cavity within the solvent to fit the solute and, also, the dispersive interactions, and **E**, the excess molar refraction, accounts for interactions with electron donor groups. The intercept, **c**, and the regression coefficients, **s**, **a**, **b**, **v**, and **e** (LSER coefficients), are obtained from multivariable, simultaneous, least-square regressions [7, 11]. These coefficients contain chemical information since they reflect the *difference between the RTIL phase and the aqueous phase* in the complementary property to each solute parameter, as discussed later [12].

Partition coefficient data between RTILs and water for organic compounds are very limited in the literature. The most extensive data set available corresponds to the biphasic systems formed by the ionic liquids 1-hexyl-3-methylimidazolium hexafluorophosphate, 1-butyl-3-methylimidazolium hexafluorophosphate, 1-octyl-3-methylimidazolium hexafluorophosphate, and 1-octyl-3-methylimidazolium tetrafluoroborate in contact with water or heptane [7, 13–17].

In this work, the partition coefficients, $P_{IL/w}$, for several critically selected and chemically diverse probe molecules (the *training set*) between different NB-RTILs and PB-RTILs, namely 1-octyl-3-methylimidazolium hexafluorophosphate [OMIM][PF_6], *N*-octylpyridinium tetrafluoroborate [OPy][BF_4], trihexyl(tetradecyl)phosphonium chloride [$(C_6)_3C_{14}P$][Cl], trihexyl(tetradecyl)phosphonium bromide [$(C_6)_3C_{14}P$][Br], trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)imide [$(C_6)_3C_{14}P$][NTf_2], and trihexyl(tetradecyl)phosphonium dicyanamide [$(C_6)_3C_{14}P$][$N(CN)_2$] (c.f. Fig. 1), were accurately measured at room temperature. Multiple linear regressions between log $P_{IL/w}$ and the corresponding solute descriptors for the training set were performed. In order to evaluate the robustness and predictive capability of the model to be used with extraction purposes, we used a set of molecules of biological or pharmacological interest, structurally different from those of the training set called the *test set*. The main goal of this work is to use in the future the obtained LSER equations to predict extraction efficiency for any compound using the studied ionic liquids as extraction solvents in liquid-liquid extractions.

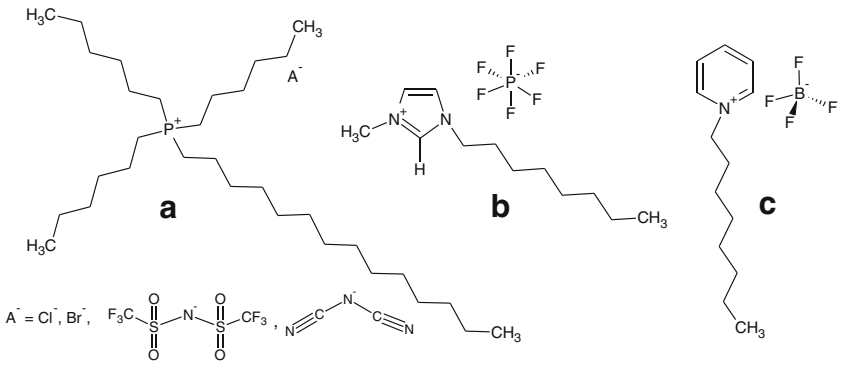

Fig. 1 Chemical structures of the studied RTILs. (**a**) $(C_6)_3C_{14}P^+$ cation with different anions, A^-=Cl^-, Br^-, $N(CN)_2^-$, and NTf_2^-, and (**b**) [OMIM][PF_6]; (**c**) [OPy][BF_4]

Experimental

Chemicals and materials

$[(C_6)_3C_{14}P][Cl]$ (Cyphos® IL 101), $[(C_6)_3C_{14}P][Br]$ (Cyphos® IL 102), $[(C_6)_3C_{14}P][N(CN)_2]$ (Cyphos® IL 105), and $[(C_6)_3C_{14}P][NTf_2]$ (Cyphos® IL 109) were provided by Cytec Industries Inc. (NJ, USA). $[OPy][BF_4]$ and $[OMIM][PF_6]$ were synthesized in our laboratory by adapting a procedure from references [18] and [7], respectively. Reagents were of analytical grade or better as follows: sodium hexafluorophosphate, 98.0 % (Aldrich, WI, USA); 1-methylimidazole, ≥99.0 % (Merck, Hohenbrunn, Germany); pyridine, 99.0 % (Sigma-Aldrich, St. Louis, USA); tetrafluoroboric acid, 48.0 % (*w*/*v*) in water (Sigma-Aldrich, St. Louis, USA); 1-bromooctane, 99.0 % (Aldrich, WI, USA); hydrochloric acid and sodium sulfate anhydrous (Merck, Buenos Aires, Argentina); phosphoric acid (Merck, Hohenbrunn, Germany); sodium hydroxide (Analar, Poole, England); potassium hydroxide (Analar, Poole, England); and methanol and dichloromethane HPLC grade (J.T.Baker, Edo. de Mexico, Mexico). Solutions were prepared with Milli-Q® water. Solutes were from Sigma-Aldrich, St. Louis, USA (thiourea, acetanilide, thymine, catechol, benzamide, acetophenone, 2-nitroaniline, 4-hydroxybenzoic acid, 2,6-dimethylbenzoic acid, *p*-nitrophenol, *o*-hydroxyethylresorcinol, 2,6-dichlorophenol, 2,4,6-trichlorophenol, *o*-nitrophenol, 4-nitrotoluene, 2-nitrotoluene, 3-nitrotoluene, 4-methylanisole, 2-methylanisole, 3-methylanisole, 4-chlorotoluene, *o*-tolualdehyde, *m*-tolualdehyde, benzonitrile, chlorobenzene, nitrobenzene, 2,4-dinitrofluorobenzene, acetaminophen, suprofen, ketoprofen, ibuprofen, fenoprofen, propranolol, cortisone, hydrocortisone, benzoin, indoprofen); Fluka, Buchs, Switzerland (benzaldehyde, *p*-tolualdehyde); Merck, Hohenbrunn, Germany (4-nitroaniline, benzene, *m*-nitrophenol, *p*-dimethylaminobenzaldehyde); Carlo Erba Reagents, Milano, Italy (4-nitrobenzoic acid); Industria Química Bonaerense, Buenos Aires, Argentina (1,4-benzoquinone, 2-naphthol, resorcinol); Riedel-de Haën, Seelze, Germany (phenol); Científica Central Jacobo Rapoport, Buenos Aires, Argentina (benzoic acid); BDH Chemicals Ltd., Poole, England (1,3,5-trinitrobenzene); Roche, Buenos Aires, Argentina (benznidazole); Bayer, Leverkusen, Germany (nifurtimox); ANMAT, Buenos Aires, Argentina (metronidazole); and Bagó, Buenos Aires, Argentina (caffeine).

The micropipettes were purchased from Eppendorf, Hamburg, Germany. The solutions were filtered using a micromate interchangeable syringe (Popper & Sons, Inc., New Hyde Park, NY, USA) with 0.22-μm cellulose nitrate membrane filters.

Equipment

An Agilent 1100 liquid chromatograph equipped with a binary pump, a thermostat-controlled column compartment, a degasser, and a variable wavelength detector connected to a Data Apex CSW (Data Apex, Czech Republic) workstation and a 75×4.6 mm ID (3.5 μm) Zorbax Eclipse XDB-C18 column (Agilent) were used to separate and quantify the different compounds. Methanol:buffered phosphate (pH 2.70; 25 mM) was used as the mobile phase. The methanol was previously filtered through 0.22-μm nylon membranes (Osmonics Magna), while the aqueous phase was filtered with 0.22-μm cellulose nitrate membranes (Micron Separations). The detector was set at wavelengths where the used RTILs show no significant absorbance: 254 nm for $[(C_6)_3C_{14}P][Cl]$, $[(C_6)_3C_{14}P][Br]$, $[(C_6)_3C_{14}P][NTf_2]$, and $[OMIM][PF_6]$ and 300 nm for $[(C_6)_3C_{14}P][N(CN)_2]$ and $[OPy][BF_4]$.

An Eppendorf 5417 C/R centrifuge operating at 14,000 rpm was used for phase separation. A thermostat-controlled bath (Lauda T) maintained at 25.00±0.05 °C was employed for the partitioning experiments, a Vortex Genie 2 (Scientific Industries, USA) mixer allowed thorough mixture of the aqueous and the RTIL phases, and a combined glass Metrohm electrode in a commercial Accumet AR 25 pH/mV/Ion Meter (Fisher Scientific) pH meter was applied for pH measurements.

Procedure to obtain the partition coefficients

The experimental procedure for the determination of the partition coefficients was done like in the previously published work [7], using solutions of known concentrations of the analytes in 0.01 M hydrochloric acid (pH 2). Solute concentrations in the water phase after extraction were determined from calibration plots obtained by injecting, in triplicate, 5 μL of the standard solutions of each compound dissolved in 0.01 M hydrochloric acid at four different concentrations in the range of 1–100 μmol L^{-1}.

Purification of the RTILs

The imidazolium-based RTILs were obtained and purified as previously reported in reference [7], and the pyridinium-based RTIL was obtained as in reference [18]. The PB-RTILs were washed as follows: a mixture of the ionic liquid and dichloromethane (DCM) (1:4) was washed with different aliquots of 1 ml of 10^{-4} M KOH, shaken, and centrifuged for 10 min at 4,200 rpm to separate the two phases. The first five contacts were done with the alkaline solution, and the five final contacts were done with 1 ml Milli-Q water until neutrality. The absence of the RTIL anions coming from the original reactives was checked by reaction with aqueous $AgNO_3$. Then, solid anhydrous Na_2SO_4 was added to eliminate traces of water; the

mixtures were shaken for 15 min and filtered through a Whatman® 40 filter paper. The DCM layer was then concentrated on a rotary evaporator and dried under vacuum at 50 °C for 48 h.

Solute parameter calculations and multivariable least-square regressions

Solute parameters not available in the literature were calculated by means of the ADME Boxes 5.0 software (ACD/Labs/Pharma Algorithms, Inc., Toronto, Canada). pK_a values not available in the literature were calculated using the software MarvinSketch 5.5.0.1, 2011, ChemAxon. Multivariable least-square regressions were performed using Microsoft Office Excel 2007.

Results and discussion

Experimental $P_{IL/w}$ values

Partition coefficients, $P_{IL/w}$, were obtained from linear regressions between the analyte concentrations in the RTIL phase, C_{IL}, vs. the aqueous phase, C_W, after the equilibrium is reached for solutions with different initial concentrations, as described in our previous paper [7] (see "Procedure to obtain the partition coefficients"). In Table 1, we gathered the $P_{IL/w}$ values for the training set and the test set, together with the confidence intervals corresponding to three replicates. Since the solute parameters (experimental or calculated) to be used in the solvation parameter model (next section) correspond to the neutral form of the molecule, we decided to perform the partition at pH 2 at which value all molecules (including phenols and carboxylic) of Table 1 are neutral. Also, working at the same pH with the same buffer for all molecules assures the same experimental conditions for all the $P_{IL/w}$ values determined. In Table 1, the pK_a values of all studied compounds are shown.

For almost all the compounds, partition coefficients with $[(C_6)_3C_{14}P][Cl]$ and $[(C_6)_3C_{14}P][Br]$ are higher than those for the other RTILs. The high solubilization power of the PB-RTILs can be attributed to the strong van der Waals interactions with the four long alkyl chains they have. Thus, these ionic liquids could be considered very good candidates for liquid-liquid extractions.

In Table 2, we compared all the $P_{IL/w}$ values for the test set obtained with NB-RTILs, those used in this work and the ones from the previous work [7]. It is observed that partition coefficients for RTILs with the anion $[PF_6]^-$ increase drastically as the alkyl chain of the imidazolium ring grows in the order butyl, hexyl, octyl. This trend could be attributed to an increasing solubilization of the analytes due to van der Waals (dispersive) interactions with those alkyl substituents in the imidazolium ring. The free energy of transfer of a given compound from an aqueous phase to an organic phase, in this case an ionic liquid, can be written as $\Delta G_{tr} = -RT \log P_{IL/w}$. If the main reason for the observed partitioning is the increment in dispersive interactions, the log $P_{IL/w}$ should be correlated with the number of carbon atoms of the alkyl chain. In Table 3, the obtained linear regressions between log $P_{IL/w}$ and the number of carbon atoms are observed. It can be observed that, in general, good or very good regression coefficients are obtained, which means that the partition to the RTIL phase increases mainly due to the dispersive interactions of the analytes with the ionic liquid.

Analyzing the data for the cation $[OMIM]^+$ combined with both $[PF_6]^-$ and $[BF_4]^-$, it comes to view that the partition coefficients are higher for the former anion. This observation was already made in our previous paper [7], and it was attributed to the higher hydrophobic nature of the $[PF_6]^-$ anion due to its higher size-to-charge ratio as compared with the $[BF_4]^-$ anion, which favors dispersive interactions with the organic compounds. Also, for most compounds, partition coefficients for the $[OPy]^+$ cation are much higher than those for the $[OMIM]^+$ cation with the same $[BF_4]^-$ anion.

It is worth pointing out that although the partition coefficients for the test set in $[OMIM][PF_6]$ are very high, in PB-RTILs, these are, in general, higher. For some compounds, the transfer to the RTIL phase was virtually complete since no chromatographic peak was detected in the aqueous phase after partitioning. Again, the highest partition coefficients are obtained with $[(C_6)_3C_{14}P][Br]$, although with $[(C_6)_3C_{14}P][N(CN)_2]$, $[(C_6)_3C_{14}P][Cl]$, and $[OMIM][PF_6]$, the transfer of the several compounds to the ionic liquid phase is very significant.

Compounds of the test set have higher partition coefficients than those for the training set (c.f. Table 1) for the same RTILs, which could be due to the higher hydrophobicity of those group of molecules which have higher molar volume as reflected by the **V** solute parameter (see Electronic Supplementary Material (ESM) Table S1).

Solvation parameter model

The solvation parameter model (SPM) (Eq. 1) has been previously used to both predict partitioning and to interpret the LSER coefficients and, thus, to elucidate the chemical interactions present in the biphasic systems $[BMIM][PF_6]$/water and $[HMIM][PF_6]$/water [13]. In our previous work [7], we obtained partition coefficients, $P_{IL/w}$, for several compounds, some of biological or pharmacological interest, between three different RTILs ($[BMIM][PF_6]$, $[HMIM][PF_6]$, and $[OMIM][BF_4]$) and water at room temperature. We also used the SPM to study these biphasic systems to both predict partitioning and to chemically interpret the LSER coefficients

Table 1 Partition coefficients, $P_{IL/w}$, for the *training set* and the *test set* for the different ionic liquids at 25 °C and their pK_a values

Compounds		pK_a[a]	$P_{IL/w}$					
			[OMIM][PF_6]	[OPy][BF_4]	[$(C_6)_3C_{14}P$][Cl]	[$(C_6)_3C_{14}P$][Br]	[$(C_6)_3C_{14}P$][$N(CN)_2$]	[$(C_6)_3C_{14}P$][NTf_2]
Training set								
1	4-Nitroaniline	0.997	18.0 (±0.1)	28 (±2)	NM	NM	72.1 (±0.5)	20.1 (±0.3)
2	2-Nitroaniline	−0.287		199 (±20)			199 (±5)	
3	Thymine	0.5[b]	0.13 (±0.03)	0.11 (±0.02)	0.73 (±0.04)	0.49 (±0.06)	0.002 (±0.001)	0.15 (±0.03)
4	Thiourea	−0.96[b]	~0	NM	0.63 (±0.04)	0.50 (±0.04)	NM	~0
5	Benzamide	−1.2[b]	0.42 (±0.01)	NM	3.8 (±0.3)	2.4 (±0.1)	0.20 (±0.02)	0.12 (±0.01)
6	Acetanilide	0.5[b]	1.98 (±0.08)	1.43 (±0.08)	26 (±1)	30 (±1)	0.50 (±0.02)	0.89 (±0.04)
7	Caffeine	0.61[b]	0.39 (±0.03)	0.32 (±0.01)	0.51 (±0.07)	0.41 (±0.03)	0.30 (±0.04)	0.22 (±0.03)
8	2,6-Dimethylbenzoic acid	3.362	~0	6.12 (±0.06)	0.36 (±0.04)	~0	0.26 (±0.01)	0.06 (±0.02)
9	Benzoic acid	4.20	1.38 (±0.01)	15.7 (±0.9)	165 (±22)	68 (±6)		0.86 (±0.01)
10	4-Nitrobenzoic acid	3.424		15.8 (±0.3)			27 (±2)	
11	4-Hydroxybenzoic acid	4.200	0.33 (±0.03)	NM	NM	NM	NM	0.28 (±0.04)
12	Phenol	9.97	1.53 (±0.06)		134 (±6)	128 (±4)		1.2 (±0.1)
13	*p*-Nitrophenol	7.143	4.7 (±0.4)	15.7 (±0.9)	NM	952 (±11)	78 (±2)	4.5 (±0.3)
14	*m*-Nitrophenol	8.267	7.0 (±0.3)	21.72 (±0.05)	496 (±17)	1696 (±27)	202 (±2)	7.8 (±0.1)
15	*o*-Nitrophenol	7.222				164 (±6)	55 (±1)	
16	2,6-Dichlorophenol	6.79[c]	4.8 (±0.1)	53 (±4)	542 (±3)	18.7 (±0.1)		14.4 (±0.9)
17	2,4,6-Trichlorophenol	6.42[c]	3.22 (±0.06)		900 (±4)			NM
18	Resorcinol	9.81[c]	0.15 (±0.04)	1.2 (±0.2)	914 (±37)	164 (±6)		0.15 (±0.04)
19	Catechol	9.83[c]	0.27 (±0.01)		NM	439 (±19)		0.14 (±0.04)
20	2-Naphthol	9.94[c]	60 (±1)		NM	NM		56 (±1)
21	*o*-Hydroxyethylresorcinol	9.49[d]	0.27 (±0.07)		43 (±3)	40.3 (±0.3)		0.15 (±0.01)
22	1,4-Benzoquinone	NI	0.20 (±0.03)		5.82 (±0.06)	38.7 (±0.7)		0.18 (±0.1)
23	Acetophenone	NI	20.2 (±0.7)	6.24 (±0.04)	11.1 (±0.1)	11.8 (±0.3)	7.6 (±0.1)	12.1 (±0.1)
24	*o*-Tolualdehyde	NI		11.5 (±0.03)			20.3 (±0.8)	
25	*m*-Tolualdehyde	NI		12.99 (±0.09)				
26	*p*-Tolualdehyde	NI		12.6 (±0.2)			18.3 (±0.9)	
27	Benzaldehyde	NI		5.15 (±0.06)			5.48 (±0.07)	
28	*p*-Dimethylaminobenzaldehyde	NI		11.5 (±0.3)			13.0 (±0.6)	
29	Nitrobenzene	NI	32.16 (±0.08)	17.3 (±0.3)	28 (±1)	39.4 (±0.9)	24 (±2)	33 (±1)
30	4-Nitrotoluene	NI	58 (±3)	56 (±2)	54 (±1)	104 (±1)	121 (±7)	69 (±4)
31	2-Nitrotoluene	NI		124 (±3)	53.6 (±0.3)	101.2 (±0.3)	199 (±20)	
32	3-Nitrotoluene	NI		41.4 (±0.9)	55 (±1)	100.0 (±0.7)	89 (±3)	
33	2,4-Dinitrofluorobenzene	NI		8.2 (±0.4)			21 (±1)	

Table 1 (continued)

Compounds		pK_a[a]	$P_{IL/w}$					
			[OMIM][PF_6]	[OPy][BF_4]	[$(C_6)_3C_{14}P$][Cl]	[$(C_6)_3C_{14}P$][Br]	[$(C_6)_3C_{14}P$][$N(CN)_2$]	[$(C_6)_3C_{14}P$][NTf_2]
34	1,3,5-Trinitrobenzene	NI		50 (±2)			150 (±3)	
35	Benzonitrile	NI	5.9 (±0.3)		11.3 (±0.4)	18 (±1)		14.3 (±0.1)
36	Benzene	NI	3.43 (±0.04)			13.7 (±0.1)		5.8 (±0.4)
37	Chlorobenzene	NI	20 (±1)			108 (±10)		NM
38	4-Chlorotoluene	NI	24.1 (±0.7)		42 (±1)	528 (±17)		136 (±4)
39	3-Methylanisole	NI	79 (±1)		74 (±3)	93 (±1)		95 (±1)
40	4-Methylanisole	NI	80 (±1)		67 (±3)	95 (±7)		100 (±3)
41	2-Methylanisole	NI	108 (±13)		91 (±3)	148 (±6)		153 (±6)
Test set								
1	Indoprofen	4.40[e]	533 (±3)	1008 (±10)	376 (±2)	[3331]	[2963]	16.96 (±0.02)
2	Ibuprofen	4.58[e]	78.8 (±0.9)	55.81 (±0.06)	[20,791]	[7687]	31.11 (±0.02)	8.93 (±0.04)
3	Suprofen	3.9[f]	887 (±6)	849 (±4)	1334 (±11)	[12,416]	[3759]	58.72 (±0.06)
4	Ketoprofen	4.47[e]	1053 (±11)	853 (±10)	831 (±7)	[9825]	[3962]	74.12 (±0.06)
5	Fenoprofen	4.5[b]	697 (±5)	749 (±5)	[3785]	[14,398]	[2851]	50.6 (±0.8)
6	Acetaminophen	9.5[b]	0.125 (±0.003)	0.84 (±0.02)	35.13 (±0.06)	136 (±2)	0.192 (±0.002)	0.07 (±0.01)
7	Benzoin	12.62[d]	224 (±2)	236 (±3)	73.82 (±0.07)	154 (±2)	331 (±5)	13.92 (±0.05)
8	Cortisone	12.58[d]	633 (±4)	123 (±2)	23.76 (±0.03)	652 (±5)	17.45 (±0.05)	22.82 (±0.06)
9	Hydrocortisone	12.58[d]	322 (±2)	155 (±2)	105 (±2)	(3215)	19.32 (±0.08)	6.92 (±0.03)
10	Benznidazole	14.40[d]	93 (±1)	51.8 (±0.7)	3.00 (±0.04)	60.3 (±0.7)	25.76 (±0.08)	9.77 (±0.03)
11	Propranolol	9.47[g]	603 (±8)	1493 (±13)	220 (±2)	156 (±2)	973 (±7)	5.47 (±0.05)
12	Nifurtimox	0.42[d]	22.32 (±0.06)	4.72 (±0.06)	2.35 (±0.03)	6.16 (±0.05)	0.24 (±0.02)	3.58 (±0.03)
13	Metronidazole	2.5[h]	0.672 (±0.002)	0.81 (±0.03)	0.772 (±0.001)	1.64 (±0.02)	0.0512 (±0.0004)	0.37 (±0.02)

Values in brackets correspond to the calculated $P_{IL/W}$ values from Eq. 1 since the partition coefficients could not be experimentally determined due to the very low solute concentration in the aqueous phase

NM non-measurable due to co-elution of the RTIL or non-detected in the aqueous phase, *NI* non-ionizable compound

[a] Values from reference [27]

[b] Data from reference [31]

[c] Data from reference [28]

[d] Calculated using MarvinSketch 5.5.0.1, 2011, ChemAxon (http://www.chemaxon.com)

[e] Data from reference [29]

[f] Data from reference [30]

[g] Data from reference [32]

[h] Data from reference [33]

Table 2 Comparison of the experimental partition coefficients for the *test set* in the different ionic liquids at 25 °C with values taken from the literature

Compounds	[BMIM][PF_6][a]	[HMIM][PF_6][a]	[OMIM][PF_6]	[OMIM][BF_4][a]	[OPy][BF_4]
Ibuprofen	2.71	6.16	78.8	27.8	55.81
Suprofen	7.96	82.8	887	76.1	849.7
Ketoprofen	4.90	123.2	1053	80.1	853.1
Fenoprofen	8.5	97.8	697	85	749.12
Acetaminophen	0.0595	0.0683	0.125	0.538	0.84
Cortisone	0.0238	26.8	633	2.26	123.2
Hydrocortisone	0.01429	7.82	322	2.49	155.9
Benznidazole	0.360	0.995	93	430	51.8
Propranolol	1.744	98.0	603	27.4	1493.3
Nifurtimox	0.1097	7.22	22.32	0.655	4.72
Metronidazole	0.1526	1.196	6.72	0.544	0.81

[a] Data from reference [7]

obtained. Requirements to use the SPM are clearly described in the review of Vitha and Carr [19], which were summarized in our previous work. Briefly, the requirements to obtain robust LSER coefficients and, thus, precise predicted values are as follows: (i) at least four solutes for each solute parameter must be included in Eq. 1 (at least 20 solutes for the five types of solute parameters that the model considers), (ii) no correlation or covariance between solute parameters is required, and (iii) a wide range of solute parameters or descriptor values as well as log $P_{IL/w}$ values. All these requirements are fulfilled in this work. In ESM Table S2, the covariance matrices for the descriptors of the training set are shown. It can be observed that no covariance is present since the coefficients of determination between the different parameters are lower than 0.36 in all cases. The LSER coefficients (or system constants) of Eq. 1 together with the standard deviation and coefficients of the determinations for the NB-RTILs and PB-RTILs studied, as well as for the three previously reported NB-RTILs, are shown in Table 4. Good coefficients of determination and standard deviations for the LSER equations corresponding to the different biphasic systems were obtained. For both the NB-RTILs and the PB-RTILs, the two most influential intermolecular interactions affecting the partition process are the hydrogen bond acceptor (HBA) capacity (*negative* **b** term) of the solute and the cavity dispersion term (*positive* **v** term). For the analysis shown below, it is important to consider that the LSER coefficients of Eq. 1 reflect the differences between the RTIL phase and aqueous phase in polarity-polarizability (**s** coefficient), HBA (**b** coefficient), HBD (**a** coefficient), cohesion-dispersion interactions (**v** coefficient), and polarizability interactions with electron donor groups (**e** coefficient).

Table 3 Linear regressions between the log $P_{IL/w}$ values for the RTILs [BMIM][PF_6], [HMIM][PF_6], and [OMIM][PF_6] vs. the number of carbon atoms (n=4, 6, and 8) of the imidazolium ring alkyl chain

Compounds	Linear regression	R^2
Ibuprofen	$y=-1.16+0.37x$	0.919
Suprofen	$y=-1.15+0.51x$	1.000
Ketoprofen	$y=-1.56+0.58x$	0.987
Fenoprofen	$y=-0.95+0.48x$	0.996
Acetaminophen	$y=-1.58+0.08x$	0.884
Cortisone	$y=-5.77+1.11x$	0.954
Hydrocortisone	$y=-6.01+1.09x$	0.978
Benznidazole	$y=-3.11+0.60x$	0.882
Propranolol	$y=-2.14+0.63x$	0.954
Nifurtimox	$y=-3.05+0.58x$	0.901
Metronidazole	$y=-2.44+0.41x$	0.997

– The **v** coefficient reflects the ability of the ionic liquid (IL) phase relative to the water (w) phase to interact through dispersive (D) and cohesive (σ) interactions. The **v** coefficient in Eq. 1 can be dissected using the formula $M(\mathbf{v}_{IL}-\mathbf{v}_w)=M_1(\sigma_w-\sigma_{IL})+M_2(D_{IL}-D_w)$ [7]. As can be observed in Table 4, it is positive and large in all cases. According to the SPM, this property indicates that the RTILs are less cohesive and more polarizable than water.

  For the three RTILs with the anion $[PF_6]^-$ (c.f. Table 4), the **v** coefficient increases with the alkyl chain of the cation. This can be attributed to the stronger dispersive interactions with the analyte and, simultaneously, to the decreasing of cohesivity, as could be reflected by the Hildebrand solubility parameter. It can be observed that the **v** coefficient for [OPy][BF_4] is larger than that for [OMIM][BF_4]. Since both have the same anion, this means that the cohesivity is lower for the $[OPy]^+$ cation as compared to the $[OMIM]^+$ or that the dispersive interactions are larger. This last observation is in agreement with the higher amount of carbon atoms of the $[OPy]^+$ cation.

Table 4 LSER coefficients of Eq. 1 at 25 °C

Ionic liquids	**v**	**b**	**a**	**s**	**e**	**c**	N	SD	R^2
Anion: hexafluorophosphate $[PF_6]^-$									
[BMIM][PF_6][a]	1.3±0.3	−3.3±0.1	−1.2±0.1	−0.5±0.1	1.0±0.2	0.9±0.3	21	0.1602	0.97740
[HMIM][PF_6][a]	2.1±0.3	−2.9±0.2	−1.8±0.1	−0.2±0.1	1.4±0.2	−0.3±0.3	21	0.1647	0.97354
[OMIM][PF_6]	3.5±0.3	−3.4±0.2	−1.5±0.1	−0.2±0.1	1.0±0.2	−1.4±0.3	25	0.1638	0.97491
Anion: tetrafluoroborate $[BF_4]^-$									
[OMIM][BF_4][a]	1.9±0.3	−2.8±0.2	−0.3±0.2	−0.5±0.2	1.2±0.3	−0.1±0.3	20	0.1982	0.95956
[OPy][BF_4]	2.5±0.3	−2.7±0.2	−0.3±0.1	−0.7±0.2	2.2±0.4	−1.4±0.4	20	0.1432	0.96727
Cation: trihexyl(tetradecyl)phosphonium $[(C_6)_3C_{14}P]^+$									
[$(C_6)_3C_{14}P$][Cl]	3.5±0.4	−2.6±0.2	1.5±0.2	−1.1±0.2	–	0.0±0.4	20	0.1921	0.95611
[$(C_6)_3C_{14}P$][Br]	3.6±0.3	−3.5±0.1	1.8±0.1	−0.2±0.1	–	−0.6±0.2	20	0.1291	0.98711
[$(C_6)_3C_{14}P$][$N(CN)_2$]	3.5±0.6	−5.3±0.2	−0.4±0.2	−0.8±0.2	3.5±0.4	−2.2±0.4	20	0.1578	0.98879
[$(C_6)_3C_{14}P$][NTf_2]	2.7±0.4	−3.5±0.2	−1.5±0.1	0.4±0.1	–	−0.4±0.4	21	0.1868	0.97487

[a] Data from reference [7]

Comparing the two NB-RTILs with the same cation, it can be seen from Table 4 that the **v** coefficient for [OMIM][BF_4] is lower than that for [OMIM][PF_6]. From the solubility parameters in Table 4, that LSER coefficient should be higher for the latter RTIL, for which the δ_H value is higher than that for the [OMIM][BF_4]. Thus, dispersive interactions seem to be predominating in this case probably because the anion $[PF_6]^-$ is more polarizable than the $[BF_4]^-$.

As can be seen from Table 4, similar or larger **v** coefficients for the PB-RTILs compared to NB-RTILs were obtained. This could be attributed to the strong dispersive interactions that can be established with the four long alkyl chains present in PB-RTILs (c.f. Fig. 1). This observation is also in agreement with the lower δ_H values for [$(C_6)_3C_{14}P$][Cl] and [$(C_6)_3C_{14}P$][NTf_2] as compared with the NB-RTILs, which at room temperature, are 19.9 and 18.7 $MPa^{1/2}$ [20], while, e.g., for [BMIM][PF_6], the value is 29.9 $MPa^{1/2}$ and, for [OMIM][PF_6], 27.8 $MPa^{1/2}$ [21].

- The **b** coefficient reflects the interactions between the solute as HBA and the medium as HBD and can be written as $\mathbf{a}_{IL}$-$\mathbf{a}_w$ [7]. The **b** coefficient is negative and large in all cases, indicating that the RTIL phase is much less acidic than the water phase. This result was expected since water is a very strong HBD solvent and the PB-RTILs have no acidic hydrogen atoms, while the imidazolium-based RTILs are weaker HBD solvents than water due to the presence of the H atom attached to the C2 of the imidazolium ring. While the Kamlet-Taft HBD solvent parameter, α, for water is 1.17 [22], the corresponding values for some of the studied NB-RTILs are between 0.4 and 0.6 [23]. Thus, even when the mutual solubility of water and the RTILs increase in some extent the $\mathbf{a}_{IL}$ term and decrease the $\mathbf{a}_w$ term, the difference is still negative.
- The **a** coefficient reflects the interactions between the solute as HBD and the medium as HBA. This coefficient can be written as $\mathbf{b}_{IL}$-$\mathbf{b}_w$ [7]. These LSER coefficients are negative for all NB-RTILs meaning that the ionic liquid phase has less HBA capacity compared to water.

For the NB-RTILs containing the $[PF_6]^-$ anion, the **a** coefficient is large as compared to those containing the $[BF_4]^-$anion. Since **a** coefficient is negative, this means that the HBA capacity for those RTILs is lower than the RTILs containing the $[BF_4]^-$ anion. The lower electron density of the $[PF_6]^-$ anion compared to the smaller $[BF_4]^-$ anion could explain this behavior.

PB cations cannot accept a hydrogen bond. Thus, HBA capacity for PB-RTILs is also attributed only to the anion. The **a** coefficient is positive and large for [$(C_6)_3C_{14}P$][Cl] and [$(C_6)_3C_{14}P$][Br], which can be due to the high HBA capacity of the Cl^- and Br^- anions as a consequence of its high electron density, which makes the $\mathbf{b}_{IL}$ term much higher than the $\mathbf{b}_w$ term. However, the **a** coefficient is negative for [$(C_6)_3C_{14}P$][$N(CN)_2$] and [$(C_6)_3C_{14}P$][NTf_2] since the two anions of these RTILs have much less electron density as compared with Cl^- and Br^-, which makes them weaker HBA.

Since the **a** coefficient reflects the HBA capacity, a comparison of the different anions can be made independently of the RTIL type. Thus, an arrangement from the weakest to the strongest HBA species (smaller to the larger $\mathbf{b}_{IL}$ term) can be made for the studied RTILs: $[PF_6]^-$ and $[NTf_2]^-$<$[BF_4]^-$ and $[N(CN)_2]^-$<Cl^- and Br^-. Since all anions have the same charge, this order is in agreement with the decreasing size, i.e., chloride and bromide anions have the strongest HBA capacity which makes the $\mathbf{b}_{IL}$ term larger and, thus, the **a** coefficient lower than that for the other anions.

- The **s** coefficient reflects the polarity-polarizability interactions between the biphasic system and the solute, and it can be written as $\mathbf{s}_{IL}$-$\mathbf{s}_w$ [7]. Except for

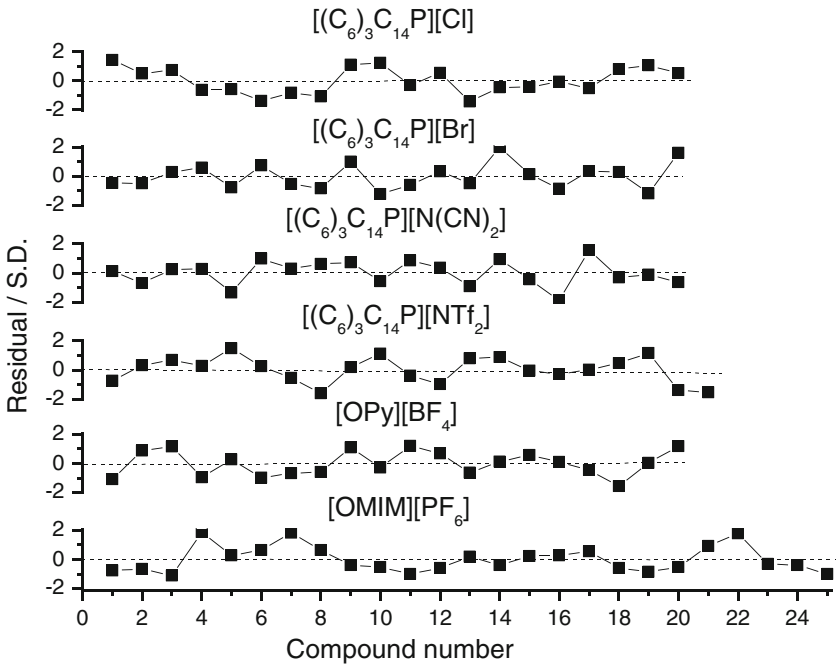

Fig. 2 Normalized residuals (difference between predicted and experimental log $P_{IL/w}$ values divided by the respective standard deviation) corresponding to Eq. 1 for the six studied RTILs

$[(C_6)_3C_{14}P][NTf_2]$, the **s** coefficient is quite small and negative, indicating that the polarity of the RTIL phase is a little smaller than the polarity of the aqueous phase, even when those solvents are ionic compounds. This observation is in agreement with previous results for other RTILs [1] and with the *associated solvents*' characteristic attributed to them [24]. As occurs with the other LSER coefficients, the mutual solubility RTIL-water can increase the actual polarity of the RTIL phase, while in some extent, it can decrease the actual polarity of the water, and the result can be a small negative coefficient or even positive.

– The **e** coefficient reflects the polarizability interactions between the medium and the solute through π and non-bonding electrons, and it can be written as $\mathbf{e}_{IL}$-$\mathbf{e}_w$ [7]. The **e** coefficient in Table 4 is quite high and positive for the NB-RTILs and $[(C_6)_3C_{14}P][N(CN)_2]$, indicating that the polarizability is higher for the RTIL phase than for the water phase. For the NB-RTILs, the **e** coefficients reflect the polarizability due to the π electrons of the cations, while for the $[(C_6)_3C_{14}P][N(CN)_2]$, it reflects the polarizability due to the π electrons of the anion (no free electron pairs neither π electrons are present in any phosphonium cation).

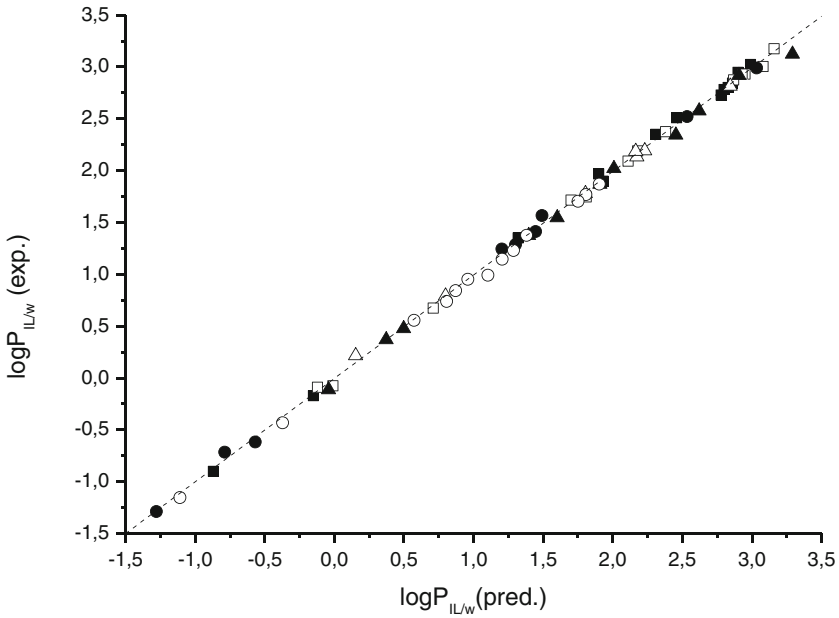

Fig. 3 Experimental vs. predicted log $P_{IL/w}$ values for the test set corresponding to the six studied RTILs: $[OMIM][PF_6]$ (*filled square*), $[OPy][BF_4]$ (*empty square*), $[(C_6)_3C_{14}P][Cl]$ (*filled triangle*), $[(C_6)_3C_{14}P][Br]$ (*empty triangle*), $[(C_6)_3C_{14}P][N(CN)_2]$ (*filled circle*), and $[(C_6)_3C_{14}P][NTf_2]$ (*empty circle*)

Evaluation of the SPM

As it was discussed in our previous work, the regression coefficients and standard deviations are not enough parameters for the quality evaluation of the multiple linear regressions obtained. Thus, we made *residual plots* (differences between the calculated and experimental log $P_{IL/w}$ values vs. the solute number) to detect some possible outliers in the regressions and to assure that the values are randomly distributed around 0 (i.e., no overfitting or non-modelled interactions are present). The residual plots (Fig. 2) demonstrate that systematic errors or specific chemical interactions are absent in the SPM.

The other quality test, and a more direct proof, for the LSER equations obtained, is the prediction of the log $P_{IL/w}$ values for a separate set of solutes, the test set, different from the training set. Figure 3 depicts a plot of the experimental vs. the calculated log $P_{IL/w}$ values for the test set. The calculated partition coefficients were obtained using the solute parameters from the literature when available [25, 26] or the ADME Boxes software. It has to be considered that some of the test compounds are out of the descriptor space since, e.g., the molar volumes of profens and steroids are much higher than the values for the training set. Thus, for those compounds, the predictions of log $P_{IL/w}$ values constitute an extrapolation, even though the calculated values are very good, as can be observed in Fig. 3, and the standard deviations are very low (SD=0.0397 for [OMIM][PF_6], 0.0364 for [OPy][BF_4], 0.0551 for [$(C_6)_3C_{14}P$][Cl], 0.1085 for [$(C_6)_3C_{14}P$][Br], 0.0511 for [$(C_6)_3C_{14}P$][$N(CN)_2$], and 0.0295 for [$(C_6)_3C_{14}P$][NTf_2]). This indicates that the LSER coefficients are chemically significant and that the SPM generated is therefore robust. Thus, the LSER coefficients obtained in this work for the different studied RTILs, as well as the corresponding values for other RTILs obtained in our previous work, are useful to predict together with Eq. 1, partition coefficient RTIL-water for any neutral compound. As a consequence, we have a new methodology that is useful in the sample preparation, not based on the much more tedious *trial-and-error* procedure, to select the most appropriate RTIL to extract a given compound from an aqueous matrix that can assure a high recovery factor. Just five solute descriptors are necessary for the solute to be extracted, which if are not available from the literature, and they can be easily calculated with the ADME Boxes software.

Conclusions

Partition coefficients at room temperature for several critically selected probe molecules as well as for compounds of biological and pharmacological interest between different nitrogen- and phosphonium-based room-temperature ionic liquids and water were accurately determined. The log $P_{IL/w}$ values for several compounds selected as a calibration set (the training set) were used together with the solvation parameter model to find the calibration coefficients of the multiparametric equations for the different biphasic systems, which allowed to elucidate the molecular interactions responsible for the partitioning of organic compounds of very different chemical nature (the test set). For both the NB-RTILs and the PB-RTILs, the two most influential intermolecular interactions affecting the partition process are the HBA capacity of the solute and the cavity dispersion term. The sign and magnitude of the different LSER coefficients are in quite well agreement with their chemical structures and physicochemical properties, considering the mutual solubility of the ionic liquid with water. The multiparametric linear equations obtained also allowed a precise prediction of partition coefficients of the test set used to set up the model, even when some of the test solutes have molar volumes out of the prediction range established by the calibration set. Thus, those equations can be used to predict which will be the most appropriate ionic liquid to be used in a given liquid-liquid extraction for any compound, allowing to obtain high extraction recoveries from a given aqueous sample.

Acknowledgments Financial support from the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and Agencia Nacional de Promoción Científica y Técnica (ANPCYT) is gratefully acknowledged. M. Reta is a scientific member of CONICET and a Professor of Analytical Chemistry at the Universidad Nacional de La Plata (Argentina). J.M. Padró is a research fellow of CONICET, and R. Pellegrino Vidal is a research fellow of Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CIC-PBA), Argentina. The authors want to thank all of these scientific organizations.

References

1. Poole CF, Poole SK (2010) Extraction of organic compounds with room temperature ionic liquids. J Chromatogr A 1217:2268–2286
2. Huddleston JG, Visser AE, Reichert WM et al (2001) Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation. Green Chem 3:156–164
3. Sun P, Armstrong DW (2010) Ionic liquids in analytical chemistry. Anal Chim Acta 661:1–16
4. Xu X, Su R, Zhao X et al (2011) Ionic liquid-based microwave-assisted dispersive liquid-liquid microextraction and derivatization of sulfonamides in river water, honey, milk, and animal plasma. Anal Chim Acta 707:92–99
5. Stojanovic A, Morgenbesser C, Kogelnig D, Krachler R KB (2011) Quaternary ammonium and phosphonium ionic liquids in chemical and environmental engineering. Ion. Liq. Theory, Prop. New Approaches
6. Fraser KJ, MacFarlane DR (2009) Phosphonium-based ionic liquids: an overview. Aust J Chem 62:309–321
7. Padró JM, Ponzinibbio A, Agudelo Mesa LB, Reta M (2011) Predicting the partitioning of biological compounds between room-

temperature ionic liquids and water by means of the solvation-parameter model. Anal Bioanal Chem 399:2807–2820
8. Stojanovic A, Morgenbesser C, Kogelnig D, et al. (2003) Quaternary ammonium and phosphonium ionic liquids in chemical and environmental engineering. Ion. Liq. Theory, Prop. New Approaches (Chapter 26)
9. Yao C, Pitner WR, Anderson JL (2009) Ionic liquids containing the tris(pentafluoroethyl)trifluorophosphate anion: a new class of highly selective and ultra hydrophobic solvents for the extraction of polycyclic aromatic hydrocarbons using single drop microextraction. Anal Chem 81:5054–5063
10. Cascon HR, Choudhari SK, Nisola GM et al (2011) Partitioning of butanol and other fermentation broth components in phosphonium and ammonium-based ionic liquids and their toxicity to solventogenic clostridia. Sep Purif Technol 78:164–174
11. Reta M, Carr PW, Sadek PC, Rutan SC (1999) Comparative study of hydrocarbon, fluorocarbon, and aromatic bonded RP-HPLC stationary phases by linear solvation energy relationships. Anal Chem 71: 3484–3496
12. Gotta J, Keunchkarian S, Castells C, Reta M (2012) Predicting retention in reverse-phase liquid chromatography at different mobile phase compositions and temperatures by using the solvation parameter model. J Sep Sci 35:2699–2709
13. Abraham MH, Zissimos AM, Huddleston JG et al (2003) Some novel liquid partitioning systems: water-ionic liquids and aqueous biphasic systems. Ind Eng Chem Res 42:413–418
14. Berthod A, Carda-Broch S (2003) A new class of solvents for CCC: the room temperature ionic liquids. J Liq Chromatogr Relat Technol 26:1493–1508
15. Carda-Broch S, Berthod A, Armstrong DW (2003) Solvent properties of the 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid. Anal Bioanal Chem 375:191–199
16. Poole CF (2007) Applications of ionic liquids in extraction, chromatography, and electrophoresis. Adv Chromatogr 45:89–124
17. Acree WE, Grubbs LM (2012) Analytical applications of ionic liquids. Encycl. Anal. Chem. John Wiley Sons, Ltd
18. Fang D, Gong K, Shi Q-RQ-R et al (2008) A green and novel procedure for the preparation of ionic liquid. J Fluor Chem 129: 108–111
19. Vitha M, Carr PW (2006) The chemical interpretation and practice of linear solvation energy relationships in chromatography. J Chromatogr A 1126:143–194
20. Kilaru PK, Scovazzo P (2007) Correlations of low-pressure carbon dioxide and hydrocarbon solubilities in imidazolium-, phosphonium-, and ammonium-based room-temperature ionic liquids. Part 2. Using activation energy of viscosity. Ind Eng Chem Res 47:910–919
21. Marciniak A (2010) The solubility parameters of ionic liquids. Int J Mol Sci 11:1973–1990
22. Marcus Y (1993) The properties of organic liquids that are relevant to their use as solvating solvents. Chem Soc Rev 22:409–416
23. Crowhurst L, Mawdsley PR, Perez-Arlandis JM et al (2003) Solvent-solute interactions in ionic liquids. Phys Chem Chem Phys 5:2790–2794
24. Greaves TL, Drummond CJ (2013) Solvent nanostructure, the solvophobic effect and amphiphile self-assembly in ionic liquids. Chem Soc Rev 42:1096–1120
25. Abraham MH, Grellier PL, Prior DV et al (1990) Hydrogen bonding. Part 10. Scale of solute hydrogen-bond basicity using log *K* values for complexation in tetrachloromethane. J Chem Soc Perkin Trans 2: 521–529
26. Abraham MH, Berthelot M, Laurence C, Taylor PJ (1998) Analysis of hydrogen-bond complexation constants in 1,1,1-trichloroethane: the α2 Hβ2 H relationship. J Chem Soc Perkin Trans 2:187–191
27. Christensen JJ, Hansen LD, Izzat R (1976) Handbook of proton ionization heats and related thermodynamic quantities. John Wiley & Sons, Inc. 269
28. Hanai T, Koizumi K, Kinoshita T et al (1997) Prediction of pK(a) values of phenolic and nitrogen-containing compounds by computational chemical analysis compared to those measured by liquid chromatography. J Chromatogr A 762:55–61
29. González AG, Herrador MA (1997) Ionization constants of water insoluble arylpropionic acids in aqueous *N*,*N*-dimethylformamide mixtures from potentiometric pH-titrations. Anal Chim Acta 356: 253–258
30. Fillet M, Bechet I, Piette V, Crommen J (1999) Separation of non-steroidal anti-inflammatory drugs by capillary electrophoresis using nonaqueous electrolytes. Electrophoresis 20:1907–1915
31. Block JH, Beale JMJ (2010) Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry, 12th edn. 1010
32. Fuguet E, Ràfols C, Rosés M (2011) A fast high throughput method for the determination of acidity constants by capillary electrophoresis. 3. Basic internal standards. J Chromatogr A 1218:3928–3934
33. Gholivand MB, Torkashvand M (2011) A novel high selective and sensitive metronidazole voltammetric sensor based on a molecularly imprinted polymer-carbon paste electrode. Talanta 84:905–912