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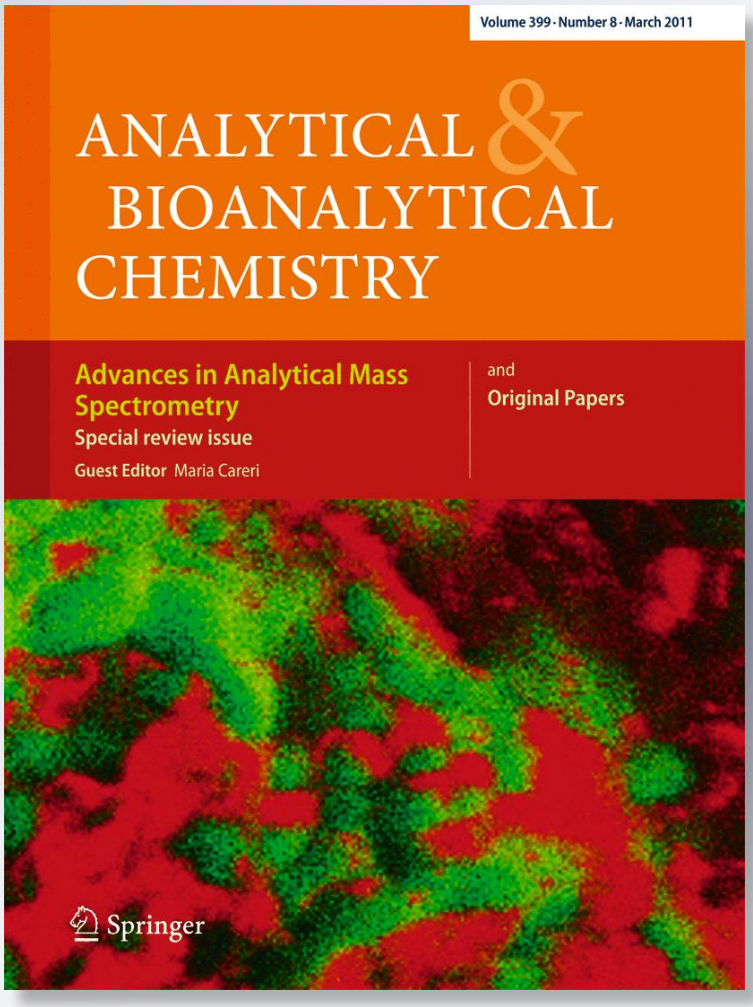

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ORIGINAL PAPER

Predicting the partitioning of biological compounds between room-temperature ionic liquids and water by means of the solvation-parameter model

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Abstract The partition coefficients, $P_{IL/w}$, for different probe molecules as well as for compounds of biological interest between the room-temperature ionic liquids (RTILs) 1-butyl-3-methylimidazolium hexafluorophosphate, [BMIM][PF_6], 1-hexyl-3-methylimidazolium hexafluorophosphate, [HMIM][PF_6], 1-octyl-3-methylimidazolium tetrafluoroborate, [OMIM][BF_4] and water were accurately measured. [BMIM][PF_6] and [OMIM][BF_4] were synthesized by adapting a procedure from the literature to a simpler, single-vessel and faster methodology, with a much lesser consumption of organic solvent. We employed the solvation-parameter model to elucidate the general chemical interactions involved in RTIL/water partitioning. With this purpose, we have selected different solute descriptor parameters that measure polarity, polarizability, hydrogen-bond–donor and hydrogen-bond–acceptor interactions, and cavity formation for a set of specifically selected probe molecules (the *training set*). The obtained multiparametric equations were used to predict the partition coefficients for compounds not present in the training set (the *test set*), most being of biological interest. Partial solubility of the ionic liquid in water (and water into the ionic liquid) was taken into account to explain the obtained results. This fact has not been deeply considered up to date. Solute descriptors were obtained from the literature, when available, or else calculated through commercial software. An excellent agreement between calculated and experimental log $P_{IL/w}$ values was obtained, which demonstrated that the resulting multiparametric equations are robust and allow predicting partitioning for any organic molecule in the biphasic systems studied.

Keywords Ionic liquids · Partition coefficients · Liquid–liquid extraction · Solvation-parameter model · RTIL synthesis

Introduction

Solvent extraction is one of the most widely used sample-preparation techniques for chromatographic analysis. Typical solvent-extraction methods are based on contacting the sample (usually in an aqueous medium) with an immiscible organic solvent able to selectively extract (if possible) the analyte of interest. The extraction efficiency will depend on the partition coefficient between the two phases, among other experimental variables. Organic solvents, however, are often toxic and flammable, and most of their physicochemical properties, such as polarity, cannot be changed. In recent years, room-temperature ionic liquids (RTILs) became an alternative to those solvents in analytical chemistry to overcome the mentioned difficulties since they are considered environmentally benign (green solvents) as a result of their potential low toxicity, negligible vapor pressure, high thermal stability, low flammability, and capability of dissolving a wide range of organic and

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inorganic compounds [1–3]. Depending on the combination of the cation and the anion, the ionic liquid obtained can be either liquid at room temperature or not, with physicochemical properties (polarity, density, viscosity, water miscibility) that can be varied and adjustable [4, 5]. Molecular interactions between ionic liquids and ionic or ionizable compounds can be not only dispersive, dipolar, or hydrogen-bonding in nature, as occurs with typical organic solvents, but also coulombic ones.

One of the most successful models for understanding partitioning processes (among other free-energy-related physicochemical or biological phenomena) at the molecular level is the *Solvation-Parameter Model* (SP model) developed by Abraham et al. [6, 7]. This model can be placed within the framework of the *Linear Solvation-Energy Relationships* hypothesis (LSER), since a multiparametric linear equation relates an appropriate form of the property under study (in this work, the ionic liquid–water-partition coefficient, $P_{IL/w}$) and several independent solute parameters, each one reflecting a different type of solute–solvent interaction. The model (Eq. 1) uses different *solute descriptors* corresponding to a set of solutes (the *training set*) to explain how a given solute property can affect the parameter under study.

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

where 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 overall and effective hydrogen-bond acidity and basicity; V is the McGowan characteristic volume, which parameter accounts for the necessary energy to form the cavity within the solvent for accommodating the solute; and E is an excess molar refraction, the parameter which in turn accounts for polarizability interactions with electron-donor groups. The intercept, c, and the regression coefficients s, a, b, v, and e are obtained from multivariable, simultaneous, least-squares regressions [8–10].

The available partition data between RTILs and water for organic compounds are very limited, and in some reports, the experimental procedure to obtain the partition coefficients is not clearly explained. For example, partition coefficients should be clearly specified to have come either from one partition experiment, from several partitions at different concentrations, or from replicates. The most extensive data set for partition coefficients is available for the biphasic systems formed by the ionic liquids 1-butylammonium-3-methylimidazolium hexafluorphosphate, 1-butyl-3-methylimidazolium hexafluorphosphate, or 1-octyl-3-methylimidazolium hexafluorphosphate and water or heptanes [5, 11–14]. Most of the compounds tested, however, are either structurally simple or volatile—and thus analyzable by gas chromatography—but polar, hydrophobic or high molecular weight compounds were not included. By using such compounds, several $P_{IL/W}$ were obtained indirectly (hypothetical values) by measuring the gas-to-RTIL and gas-to-water-partition coefficients [15]. Thus, the mutual mixing of water and the RTIL phases that affect partition are not considered. The partition mechanism is fundamental for gaining an understanding of the sequestering from the aqueous to the ionic-liquid (IL) phase of analytes—such as occurs in the extraction of polyaromatic hydrocarbons and phenols—and their concomitant enrichment for further analysis [3, 16].

In this work, the partition coefficients, $P_{IL/w,}$ for several critically selected and chemically diverse probe molecules (the *training set*) between three different RTILs (1-butyl-3-methylimidazolium hexafluorophosphate, [BMIM][PF_6]; 1-hexyl-3-methylimidazolium hexafluorophosphate, [HMIM][PF_6]; or 1-octyl-3-methylimidazolium tetrafluoroborate, [OMIM][BF_4]) and water were precisely determined at room temperature. After synthesizing [BMIM][PF_6] and [OMIM][BF_4] by adapting a procedure from the literature to a simpler and faster methodology with much less consumption of organic solvent, we performed multiple linear regressions between log $P_{IL/w}$ and the corresponding solute descriptors for the training set. We interpreted the LSER regression coefficients as a function of the different intermolecular interactions involved in the partition process, taking into account the ionic-liquid structure and the mutual mixing between water and the different RTILs. In order to evaluate the robustness and predictive capability of the SP model for future extractions of several compounds of biological or toxicological interest, we used a set of molecules structurally different to those of the training set (the *test set*). The solute descriptors for these compounds had been obtained from the literature or else calculated by means of the ADME Boxes algorithm.

Experimental

Chemicals

1-hexyl-3-methylimidazolium hexafluorphosphate ([HMIM][PF_6]) was purchased from Fluka, Buchs, Germany, (purity≥ 97.0%). 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) and 1-octyl-3-methylimidazolium tetrafluoroborate ([OMIM][BF_4]) were synthesized in our laboratory (see Section "Synthesis of RTILs"). Reagents were of analytical grade or better: 1-bromobutane, 98.0% (Riedel-de-Haën, Seelze, Germany), sodium hexafluorphosphate, 98.0% (Aldrich, Wisconsin, USA), 1-methylimidazole, ≥99.0%

(Merck, Hohenbrunn, Germany), tetrafluoroboric acid, 48.0% (*w*/*v*) in water (Sigma-Aldrich, St. Louis, USA), 1-bromoctane, 99.0% (Aldrich, WI, USA), hydrochloric acid, (Merck, Buenos Aires, Argentina), phosphoric acid (Merck, Hohenbrunn, Germany), sodium hydroxide (Analar, Poole, England), and methanol High Performance Liquid Chromatography (HPLC) (J. T. Baker, Edo. de Mexico, Mexico). Solutions were prepared with MilliQ® water. Solutes were from Sigma-Aldrich, St. Louis, USA (thiourea, acetanilide, thymine, catechol, benzamide, acetophenone, 4-hydroxybenzoic acid, 2,6-dimethylbenzoic acid, 4-nitrophenol, o-hydroxyethylresorcinol, acetaminophen, fenbufen, suprofen, ketoprofen, ibuprofen, fenoprofen, flurbiprofen, propranolol, cortisone, hydrocortisone, and ß-estradiol); Fluka, Buchs, Germany (*p*-toluidine, *m*-toloudine, *o*-toloudine); Merck, Hohenbrunn, Germany (4-nitroaniline, aniline, 3,4-dichloroaniline, 3-chloroaniline, 4-chloroaniline); Riedel-de Haën, Seelze, Germany (phenol); Carlo Erba Reagents, Milano, Italy (3-nitroaniline); Industria Química Bonaerense, Buenos Aires, Argentina (1,4-benzoquinone, 2-naphthol, resorcinol); Científica Central Jacobo Rapoport, Buenos Aires, Argentina (benzoic acid); Roche, Buenos Aires, Argentina (benznidazole); Bayer, Buenos Aires, Argentina (nifurtimox); ANMAT, Buenos Aires, Argentina (metronidazole); and Bagó, Buenos Aires, Argentina (caffeine).

Equipment

We utilized an HP 1100 liquid chromatograph equipped with a binary pump, a thermostat-controlled column compartment, degasser, and variable-wavelength detector connected to a Data Apex CSW (Data Apex, Czech Republic) workstation and containing a 75×4.6-mm ID (3.5 μm) Zorbax Eclipse XDB-C18 column (Agilent) to separate and quantify the different compounds. Methanol-buffered phosphate (pH 2.70; 25 mM) was used as the mobile phase. Different percentages of methanol were used for isocratic elution depending on the compounds, which later were grouped into different categories according to their retention times. All mobile phases were filtered through 0.22-μm nylon membranes (Osmonics-Magna) for organic solvents and 0.45-μm cellulose-nitrate ones (Micron Separations) for aqueous phases. The detector was set at 254 nm, at which wavelength the RTILs studied have no significant absorbance.

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

^{1}H NMR spectra of the RTILs in $(CD_3)_2C{=}0$ were recorded with a Varian Mercury Plus spectrometer operating at 4.7T. The typical spectral conditions were as follows: spectral width, 3,201 Hz; acquisition time, 4.09 s; and 8–16 scans per spectrum. The digital resolution was 0.39 Hz per point. Deuterium from the solvent was used as the lock and trimethylsilane as the internal standard. Sample concentration was 20 mg mL^{-1}. Measurements were performed at 25 °C. ^{13}C-proton-decoupled and gated-decoupled spectra were recorded with the same spectrometer from $(CD_3)_2C{=}0$ solutions at 25 °C. The spectral conditions were the following: spectral width, 10,559 Hz; acquisition times, 1.303 s; and 512 or 1,000 scans per spectrum. The concentration was 40 mg mL^{-1} and the digital resolution 1.29 Hz per point. A standard one-dimensional ^{1}H-NMR spectrum and ^{13}C spectrum with broad-band proton decoupling were run for each sample, supplemented by two-dimensional gradient-selected COSY and multiplicity-edited HSQC experiments for selected samples to help with the assignment of signals. All two-dimensional spectra were recorded with the same spectrometer.

Materials and methods

Synthesis of RTILs

Organic-synthesis procedures from the literature ordinarily require several days and multiple steps plus large excesses of alkylhalides and organic solvents as reaction media [17]. In this work, however, fast, single-vessel, and very efficient solvent-free methodologies for preparing extremely pure [OMIM][BF_4] and [BMIm][PF_6] were performed as follow:

1-octyl-3-methylimidazolium tetrafluoroborate, [OMIm][BF_4]

1-Methylimidazole (0.05 mol), 1-bromoctane (0.05 mol), and sodium tetrafluoroborate (0.05 mol) were stirred under an argon atmosphere in a two-necked flask with a reflux condenser at 80 °C for 3.5 h. Upon completion of the reaction, the mixture was diluted with 50 mL of acetonitrile to precipitate the NaBr salt. The solution was filtered through a pad of celite to remove the residual inorganic halide and finally concentrated in vacuo. A pale yellow liquid with a yield of 89% was obtained. The absence of Br^- was checked by reaction with aqueous $AgNO_3$. The [OMIM][BF_4] was then further dried under high vacuum at 70 °C for 7 h. No water was detected by ^{1}H NMR spectroscopy afterwards. The ^{1}H, ^{13}C, gCOSY, and gHSQC NMR spectra of the [OMIM][BF_4] were in full agreement with its structure (see Electronic Supplementary Material, Figure S1)

1-Butyl-3-methylimidazolium hexafluorophosphate, [BMIM][PF$_6$]

1-Methylimidazole (0.05 mol), 1-bromobutane (0.05 mol), and potassium hexafluorophosphate (0.05 mol) were stirred under an argon atmosphere in a two-necked flask with a reflux condenser at 80 °C for 3.5 h. Next, 10 ml of deionized water was added, and the [BMIM][PF$_6$] layer was separated from the water phase and washed first with fresh deionized water (4×15 mL) and then with diethyl ether (3x15 mL) to yield [BMIM][PF$_6$]. The absence of bromide was checked by reaction with aqueous $AgNO_3$. The IL was dried in vacuo at 120 °C for 2 h to give a pale yellow liquid in a 92% yield. The ^{1}H, ^{13}C, gCOSY, and gHSQC NMR spectra of the [BMIM][BF$_4$] were in full agreement with its structure (see Electronic Supplementary Material, Figure S1).

Procedure to obtain the partition coefficients

Partitions were performed at four different concentration levels, each one in triplicate, at 25.00±0.05 °C. The partition coefficients, $P_{IL/w}$, were obtained from plots of C_{IL} (=C_i−C_w) vs. C_w (Eq. 2) by calculating the slope of the least-squared linear regressions.

$$P_{IL/w} = (C_i - C_w)/C_w \quad (2)$$

with C_w and C_i being the solute concentration at equilibrium in the water phase and the initial concentration in water, respectively.

The experimental procedure was as follows: A known amount of the solute (concentration range, 1 to 100 μmol dm^{-3} depending on the solubility) was dissolved in 10 mL of deionized water. Solutes with an acidic group (e. g., phenolic and carboxylic acids) were prepared in HCl at pH 2.00 to maintain the undissociated form of the molecule, and saturated aqueous solutions of each RTIL were prepared in 1.5 mL Eppendorf tubes. Since measuring a given volume of RTILs is difficult because of their high viscosity, different amounts between 20–50 mg were weighed with exactitude. From corresponding density of each RTIL at room temperature, its volume was determined. The phase ratio was maintained at V_w/V_{ILs}=10 to use the minimum possible volume of the IL because of its high cost. The phases were manually mixed for several seconds and then vortexed for 24 h, centrifuged at 7,500×*g* for 15 min to effect phase separation, and finally immersed in a water bath at 25.00±0.05 °C for a half an hour. Since more prolonged contact times between both phases and lengthier equilibration periods in the water bath had no effect on the partition coefficients measured, the experimental variables given were regarded as the equilibrium conditions. Finally, a 5-μL aliquant of the aqueous phase was injected into the HPLC column. Solute concentrations in the water phase, C_w, after extraction, were determined from calibration plots obtained from stock solutions (1–100 μmol L^{-1}) for each compound dissolved in MilliQ water. Five microliters of standard solutions at four different concentrations were injected in triplicate. For the partition coefficients of very hydrophobic solutes—such as 2-naphtol, flurbiprofen, ketoprofen, and ß-estradiol—for which no chromatographic peak was observed in the aqueous phase, 5 μL of the RTIL phase was injected after prior dilution with 25 μL of methanol.

Solute-parameter calculations and multivariable least-squared regressions

Solute parameters were calculated by means of the ADME Boxes 5.0 Software (ACD/Labs/Pharma Algorithms Inc., Toronto, Canada). Multivariable least-squared regressions were performed with Microsoft Office Excel 2007.

Results and discussion

Experimental $P_{IL/w}$ values

The partition coefficients, $P_{IL/w}$, obtained from linear regression between C_{IL} and C_W at different initial concentrations in the aqueous phase (*cf.* Section "Procedure to obtain the partition coefficients") together with the regression coefficients are summarized in Table 1 for the training set and in Table 2 for the test set. The characteristics of these two families of compounds are elaborated in Sections "Building the solvation-parameter model" and "Evaluation of the LSER models: residual analysis and prediction of log $P_{IL/w}$ for the test set". Since compounds of the test set are not easily recognized as can be for the training set, their chemical structures are given in the Electronic Supplementary Material (Figure S2). Table 1 shows that partition coefficients for most of the solutes follow the order: [BMIm][PF$_6$]<[HMIm][PF$_6$]<[OMIm][BF$_4$]. This ordering can be attributed to the stronger dispersive interactions between the organic compounds and the longer alkyl chains of the RTIL. For compounds that are not phenols or carboxylic acids (e.g., acetophenone, dichloroaniline), the $P_{IL/w}$ is higher for [HMIm][PF$_6$] than for [OMIm][BF$_4$]. Nevertheless, better extractions in [OMIm][BF$_4$] were obtained for the remaining compounds, mostly phenols and carboxylic acids, when the BF_4^- anion was present. Although an especially strong hydrogen-bonding between this anion and the phenols had already been observed [18], the degree of water solubility in [OMIm][BF$_4$] is higher than that in [HMIm][PF$_6$] (Table 3),

Table 1 Solute descriptors and partition coefficients, $P_{IL/w}$, for the "training set" of solutes in the different ionic liquids

Compounds	Solute descriptors						[BMIm][PF_6]			[HMIm][PF_6]			[OMIm][BF_4]		
	E	*S*	*A*	*B*[a]	*V*	log $P_{oct/w}$	$P_{IL/w}$	*SD*	R^2	$P_{IL/w}$	*SD*	R^2	$P_{IL/w}$	*SD*	R^2
4-Hydroxibenzoic acid^{++}	0.930	0.90	0.81	0.56	0.9904	0.565*	0.99	0.08	0.998	–	–	–	5.2	0.3	0.988
2,6-Dimethylbenzoic acid^{++}	0.730	0.90	0.59	0.57	1.2135	2.616*	1.65	0.03	0.987	1.66	0.07	0.995	5.1	0.2	0.995
Benzoic acid^{++}	0.730	0.90	0.59	0.40	0.9317	1.870**	–	–	–	1.35	0.02	0.990	4.9	0.3	0.990
Phenol^{+}	0.805	0.89	0.60	0.30	0.7751	1.460**	–	–	–	1.68	0.04	0.994	4.28	0.04	0.986
4-Nitrophenol^{++}	1.070	1.72	0.82	0.26	0.9493	1.910**	3.7	0.2	0.990	3.3	0.1	0.996	12.9	0.8	0.990
Resorcinol^{++}	0.980	1.11	1.09	0.52	0.8338	0.800**	0.33	0.04	0.984	0.20	0.03	0.995	1.90	0.06	0.985
Catechol^{+}	0.970	1.10	0.88	0.47	0.8338	0.880**	–	–	–	0.36	0.08	0.997	2.3	0.1	0.986
2-Naphtol^{+}	1.520	1.08	0.61	0.40	1.1441	2.700**	39	4	0.987	50	9	0.968	178	35	0.959
o-Hydroxyethylresorcinol^{++}	1.070	1.20	0.73	0.92	1.1743	0.745*	0.25	0.05	0.989	0.20	0.04	0.991	1.15	0.05	0.991
1,4-Benzoquinone^{++}	0.750	0.55	0.00	0.81	0.7908	0.590*	0.85	0.02	0.998	0.89	0.03	0.989	0.78	0.05	0.991
Acetophenone^{+}	0.818	1.01	0.00	0.48	1.0139	1.580**	18.4	0.9	0.991	31.6	0.6	0.992	12.91	0.09	0.987
Benzamide^{+}	0.990	1.50	0.49	0.67	0.9728	0.640**	0.431	0.0045	0.992	0.47	0.04	0.990	1.11	0.05	0.990
Acetanilide^{+}	0.870	1.36	0.46	0.67	1.1137	1.160**	1.49	0.05	0.986	2.08	0.06	0.990	3.1	0.1	0.996
Caffeine^{+}	1.500	1.60	0.00	1.28	1.3632	−0.278*	0.17	0.03	0.987	–	–	–	0.27	0.03	0.977
Thymine^{++}	0.800	1.00	0.44	1.03	0.8925	−0.599*	0.03	0.02	0.989	0.04	0.02	0.996	0.11	0.03	0.989
Thiourea^{+}	0.840	0.82	0.77	0.87	0.5696	−1.087*	0.04	0.02	0.991	–	–	–	0.07	0.01	0.984
p-Toluidine^{++}	0.923	0.95	0.23	0.52	0.9571	1.574*	4.4	0.2	0.982	6.4	0.2	0.979	–	–	–
m-Toloudine^{++}	0.946	0.95	0.23	0.55	0.9571	1.574*	4.4	0.3	0.971	6.5	0.2	0.983	–	–	–
o-Toluidine^{+}	0.970	0.90	0.23	0.59	0.9571	1.574*	4.1	0.4	0.994	5.2	0.6	0.990	–	–	–
Aniline^{+}	0.955	0.96	0.26	0.50	0.8162	0.928*	2.47	0.04	0.992	2.05	0.03	0.980	–	–	–
3-Nitroaniline^{+}	1.200	1.71	0.40	0.35	0.9904	1.370**	12.1	0.5	0.981	14.1	0.4	0.980	14.1	0.4	0.996
4-Nitroaniline^{+}	1.220	1.91	0.42	0.35	0.9904	1.390**	14.8	0.9	0.997	32	2	0.983	22.2	0.5	0.987
4-Chloroaniline^{+}	1.060	1.10	0.30	0.35	0.9390	1.434*	24	1	0.987	31	2	0.985	–	–	–
3-Chloroaniline^{+}	1.050	1.10	0.30	0.36	0.9390	1.604*	–	–	–	–	–	–	8.9	0.4	0.985
3,4-Dichloroaniline^{++}	1.160	1.24	0.35	0.25	1.0610	2.133*	44	2	0.983	70	3	0.980	55	1	0.987

Solute descriptors obtained from [31] (+) or from ADME BOXES 5.0 (++)

The log $P_{oct/w}$ values were obtained from ADME BOXES 5.0 (*) or from [32] (**)

[a] The B^{o} was used for molecules containing nitrogen atoms

Table 2 Solute descriptors and partition coefficients, $P_{IL/w}$, for the "test set" of solutes in the different ionic liquids

Compounds	Solute descriptors						[BMIm][PF_6]			[HMIm][PF_6]			[OMIm][BF_4]		
	E	*S*	*A*	*B*[a]	*V*	*log* $P_{Oct/w}$[b]	$P_{IL/w}$	*SD*	R^2	$P_{IL/w}$	*SD*	R^2	$P_{IL/w}$	*SD*	R^2
Fenbufen^{++}	1.780	1.8	0.62	1.05	1.9779	3.521	2.52	0.01	0.995	71.3	0.7	0.995	53.0	0.4	0.995
Ibuprofen^{++}	0.730	0.59	0.59	0.81	1.7771	4.425	2.71	0.01	0.997	6.16	0.03	0.998	27.8	0.2	0.996
Suprofen^{++}	1.510	1.89	0.57	0.81	1.9026	3.383	7.96	0.06	0.990	82.8	0.7	0.996	76.1	0.6	0.996
Ketoprofen^{++}	1.650	2.26	0.55	0.89	1.9779	3.407	4.90	0.03	0.994	123.2	0.3	0.999	80.1	0.2	0.999
Fenoprofen^{++}	1.390	1.63	0.57	0.78	1.8800	3.607	8.7	0.1	0.976	97.8	0.6	0.998	85	1	0.988
Flurbiprofen^{++}	1.500	1.51	0.57	0.58	1.8389	4.296	59.5	0.3	0.995	487	4	0.997	303.1	0.9	0.999
Acetaminophen^{++}	1.060	1.63	1.04	0.86	1.1724	0.149	0.0595	0.0008	0.965	0.0683	0.0007	0.995	0.538	0.006	0.991
β-Estradiol^{++}	1.800	1.77	0.86	1.1	2.1988	3.761	2.024	0.007	0.998	41.9	0.2	0.999	67.3	0.6	0.994
Nifurtimox^{++}	1.310	2.20	0.00	1.44	1.8848	0.712	0.1097	0.0004	0.998	7.22	0.07	0.995	0.655	0.003	0.998
Metronidazole^{++}	1.050	1.6	0.18	1.03	1.1919	0.454	0.1526	0.0006	0.997	1.196	0.002	0.999	0.544	0.004	0.995
Benznidazole^{++}	1.780	2.88	0.26	1.23	1.8565	0.887	0.360	0.002	0.995	28.1	0.2	0.997	4.30	0.05	0.990
Propranolol^{++}	1.880	1.43	0.17	1.42	2.1480	3.091	1.744	0.005	0.998	98.0	0.3	0.999	27.4	0.2	0.996
Cortisone^{+}	1.960	3.50	0.36	1.87	2.7546	1.860	0.0238	0.0001	0.996	26.8	0.4	0.988	2.26	0.04	0.974
Hydrocortisone^{+}	2.030	3.49	0.71	1.90	2.7975	2.243	0.01429	0.00006	0.996	7.82	0.05	0.998	2.49	0.02	0.994

Solute descriptors obtained from [31] (+) or from ADME BOXES 5.0 (++)

[a] The B^o parameter was used for molecules containing nitrogen atoms

[b] The log $P_{oct/w}$ values were obtained from ADME BOXES 5.0

Table 3 Solubilities and solvent parameters of the RTILs studied, [BMIm][BF_4], and water (E_T^N: normalized polarity parameter of Dimroth–Reichardt; solvent parameters of polarity–polarizability, π^*; hydrogen-bond donor, α; and hydrogen-bond acceptor, β, of Kamlet–Taft)

	Water in RTIL solubility (wt.%)	RTIL in water solubility (wt.%)	E_T^N [c]	π^* [c]	α[c]	β[c]
[BMIm][PF_6]	2.0±0.3[a]	2.3±0.2[a]	0.669	1.032	0.634	0.207
[HMIm][PF_6]	0.75[b]	0.88[b]	–	–	–	–
[OMIm][BF_4]	1.8±0.5[a]	10.8±0.5[a]	0.63	–	–	–
[BMIm][BF_4]	–	–	0.576	1.083	0.402	0.363
Water	–	–	1.00	1.33	1.12	0.14

[a] Data from 33

[b] Data from 34

[c] Data from 25

which can increase solubility of those hydrogen-bond donor compounds.

The compounds of the test set (Table 2), most of which are carboxylic acids, have higher partition coefficients in [HMIm][PF_6] than in [OMIm][BF_4]. This difference could be attributed to the higher hydrophobicity of these compounds as compared with those of the training set, which is reflected both in the higher molar volume, V (compare Table 2 vs. Table 1) and in the higher polarizability of the PF_6^- anion compared with the BF_4^- [18, 19]. Thus, solubilities of hydrophobic organic compounds in RTILs with the PF_6^- anion will be higher than in those with the BF_4^-, and this difference will be magnified if the organic compound has a significant hydrophobic core. This result explains the importance of hydrophobicity in the extraction mechanism for these neutral or neutralized molecules, as had been previously observed [18].

As can be seen from Table 2, the partition coefficient in [HMIm][PF_6] can be 1.15 times higher than in [BMIm][PF_6] for a hydrophilic molecule such as acetaminophen or 1,165 times higher for a more hydrophobic molecule such as cortisone. Insufficient partition coefficients are available in the literature for the compounds partitioned in the RTIL/water systems studied in this work. Most of those molecules were gaseous or very volatile since the quantification methodology originally had been GC [20] or phenols and amino acids [18, 19], among others. The values of $P_{IL/W}$ for a given compound in a given RTIL obtained from the literature are very diverse. The $P_{IL/W}$ values obtained in this study and from the literature for [BMIM][PF_6]/water are depicted in Table 4. The partition values are similar in some investigations but very different in others. Several conditions can explain those divergences: (1) the quality of data from the literature, influence which was also pointed out by Poole and Poole [1], and (2) the experimental procedures to obtain the partition coefficients, whose steps are not always clearly specified—i.e., if $P_{IL/W}$ had been obtained by performing one or more replicates at just one or at several initial concentration levels.

The transfer of analytes from the aqueous phase to the IL phase is generally believed to involve a partitioning mechanism similar to the one that occurs in traditional organic solvents. Figure 1 compares the log $P_{IL/w}$ vs. the corresponding log $P_{oct/w}$ values in the octanol/water, a known reference system used to measure the hydrophobicity of a given molecule [21]. The $P_{oct/w}$ was obtained from the literature for most of the solutes of the training set (Fig. 1a–c) or calculated with the software ADME Boxes for the test set (Fig. 1d–f). That most of points in the figure lie below the unitary-slope line (dashed line) indicates that the octanol/water system has a better extracting power than the RTIL/water systems studied here. In contrast, that the correlation between both biphasic systems is not good implies that the partition mechanism for the RTIL/water systems is different from that of octanol/water. Huddleston et al. [5], upon determining the partition coefficients between [BMIM][PF_6] and water for 19 different organic compounds, found a good correlation between log $P_{IL/w}$ and log $P_{o/w}$, thus demonstrating that the partitioning mechanism is similar in both systems. Nevertheless, the $P_{o/w}$ values were higher by approximately one order of magnitude than the $P_{IL/w}$ in [BMIM][PF_6]. This difference has been observed in our own experiments for certain compounds of the training set, though for some compounds of the test set (in general, the compounds more hydrophobic than those of the training set), the difference is up to four orders of magnitude. Figure 1 also shows that compounds containing acidic functional groups (e.g., the carboxyl or phenol moieties) partitioned less into the IL phase than into octanol, while amines are better or equally extracted into the organic phase (i.e., with the points being closer to the dotted line). A similar conclusion was obtained by Carda-Broch et al. [13], who studied the partitioning behavior of 38 compounds in [BMIM][PF_6]/water and octanol/water. This

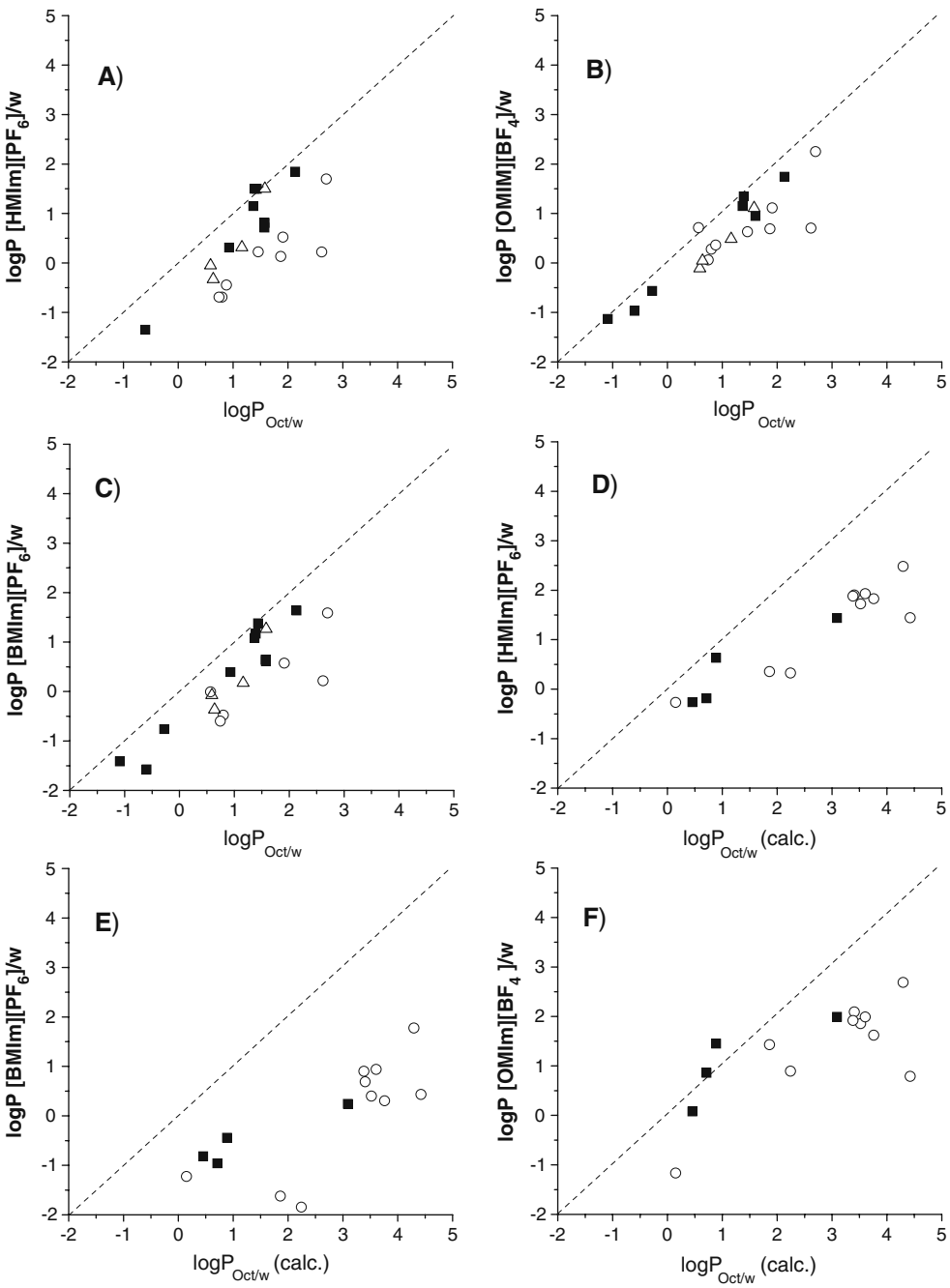

Fig. 1 Relationship between partition coefficients in RTIL/w vs. octanol/water systems. *Dotted line* means equal partition mechanism, (*filled square*) amines, (*empty circle*) carboxylic acids, (*empty triangle*) neutral compounds. Training set: plots **a**, **b** and **c**; Test set: plots **d**, **e** and **f**

behavior was attributed by them to the lower basicity of the ILs compared with octanol.

Building the solvation-parameter model

The SP Model (Eq. 1) had been previously used to determine the LSER coefficients or system constants for the [BMIM][PF_6]/water and [HMIM][PF_6]/water systems [13, 22] by using a direct contact between the RTIL and water. When the partition coefficients from several studies were combined, however, the model obtained was poor [23]. This shortcoming was attributed to the quality of the data obtained from the literature, as mentioned above [1]. The system constants obtained by Carda-Broch et al. [13] were based on only 12 solutes, and for these compounds, a high cross-correlation existed between the E and S descriptors (r=0.85). The results of the work of Abraham et al. [22] made more chemical sense than the earlier one, but no indication was found in the paper as to how the LSER coefficients had been obtained.

Several requirements need to be met to achieve a universally applicable LSER model, i.e., one with stable

Table 4 Comparison between $P_{IL/w}$ values in [BMIm][PF_6] obtained in this work and several reported in the literature

Compound	Ref. 13	Ref. 5	Ref. 22	This work
Aniline	0.33	0.20	–	2.47
Benzamide	4.7	–	0.63	0.43
Benzoic acid	53	~10[a]	0.6	1.25
4-Hydroxybenzoic acid	2.3	~20[a]	–	0.99

[a] These values were estimated from the plot shown in the reference cited

LSER coefficients (1) that are not dependent on the type of solutes selected in the training set; (2) that give chemical information apart from constituting mere regression constants; and (3) that are able to predict partition coefficients with satisfactory precision. Vitha and Carr [24], in a very clear and useful review, have established and summarized a series of recommendations for the design, analysis, and interpretation of an LSER model to be statistically valid and the information obtained to make chemical sense. First, the solutes that form the training set must span a wide range of solute parameters or, in other words, they must be chemically diverse. In this regard, the ranges for the training set selected in this study are: 0.7 to 1.5, 0.5 to 1.9, 0 to 1.9, 0.2 to 1.3, and 0.5 to 1.2 for the E, S, A, B, and V solute descriptors, respectively (Table 1). Second, the property to be studied should span at least one order of magnitude. This requisite is accomplished by selecting solutes with very different chemical properties (hydrophobicities, polarities). Thus, the log $P_{IL/w}$ values span almost five orders of magnitude (*cf.* Table 1). Third, the descriptors must not exhibit significant covariance. Typically, correlation coefficients higher than 0.5 or 0.6 are regarded as indicative of quite strong covariance, while values as high as 0.7 or 0.8 are patently unacceptable. In contrast, the covariance was virtually nonexistent for the training set chosen in the experiments reported here (see Figure S3 in Electronic Supplementary Material). Fourth, because at least four parameters per descriptor are necessary and thus at least 20 solutes must be included in the training set, we used between 20 and 21 solutes for this work. The fulfillment of all four of these requirements is hardly straightforward in studies like the present where chemically diverse solutes need to be retained in the HPLC stationary phase and also partitioned into both phases in amounts sufficiently detectable to be properly quantified (i.e., compounds neither too hydrophobic nor too hydrophilic) since only a reproducible $P_{IL/W}$ value different from zero or infinity is of any use.

The LSER coefficients from Eq. 1 obtained by multiple linear regressions between the log $P_{IL/w}$ for the three RTILs studied and the training-set–solute parameters are shown in Table 5 "Experimental coefficients". Good regression coefficients and standard deviations were obtained in all instances. The coefficients closely resemble those typically obtained for RPLC stationary phases containing C18 or C8 groups used with aqueous mobile phases [10] since the two most influential intermolecular interactions affecting the partition process are the hydrogen-bond acceptor affinity (*negative* **b** term) of the solute and the term that considers both dispersion interactions and cavity formation (*positive* **v** term). The main difference with RPLC chromatographic systems is the **e**-system constant, which factor is quite significant. For comparison with a well-known biphasic system containing a typical organic solvent, Table 5 "Oct/w*" also shows the LSER coefficients for the octanol/water combination. These constants are quite different from the LSER coefficients obtained in this work, thus confirming that the partition mechanism is highly different, as mentioned in Section "Experimental $P_{IL/w}$ values". RTILs, like water, are polar as well as hydrogen-bond–donor and hydrogen-bond–acceptor solvents [1, 25] and can thus

Table 5 LSER coefficients for partitions between RTILs/water and octanol/water at 25 °C: "experimental coefficients" obtained from the "training set" in this work; "calculated coefficients" calculated from the ion-specific model of ref. [30]; "Oct/w coefficients (Oct/w*)" obtained from [22] for the octanol/water system

Experimental coefficients									
Ionic liquid	*v*	*b*	*a*	*s*	*e*	*c*	*N*	SD	R^2
[BMIm][PF_6]	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]	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][BF_4]	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
Calculated coefficients									
[BMIm][PF_6]	3.15	−4.58	−1.31	0.70	0.18	−0.12			
[HMIm][PF_6]	3.44	−4.95	−1.15	0.82	−0.13	−0.13			
[OMIm][BF_4]	3.59	−4.38	−0.48	0.01	0.23	−0.09			
Oct/w*	3.81	−3.46	0.034	−1.05	0.56	0.088			

donate H bonds through the H atom at the C2 of the imidazolium ring [25].

The obtained LSER coefficients from Eq. 1 are not merely regression constants but also contain chemical information about the relative magnitude of each interaction between both phases since those coefficients reflect the difference in the complementary property for each solute parameter as follows: [8, 10]

$$\log P_{\mathrm{IL/w}} = c + s'(s_{\mathbf{IL}} - s_{\mathbf{w}})S + a'(b_{\mathbf{IL}} - b_{\mathbf{w}})A + b'(a_{\mathbf{IL}} - a_{\mathbf{w}})B + v'(v_{\mathbf{IL}} - v_{\mathbf{w}})V + e'(e_{\mathbf{IL}} - e_{\mathbf{w}})E \quad (3)$$

where the subscripts IL and w denote the water-saturated ionic-liquid phase and the ionic-liquid-saturated water phase, respectively. The nomenclature was adapted to this work from [10]. The coefficients s', a', b', v', and e' are fitting parameters. Reta et al. [10] suggested that the $M(v_s - v_m)V_2$ term can be dissected into at least two components, a cavity term and a dispersive one:

$$vV = M(v_{\mathrm{IL}} - v_{\mathrm{w}})V = M_1(s_{\mathrm{w}} - s_{\mathrm{IL}})V + M_2(D_{\mathrm{IL}} - D_{\mathrm{w}})V \quad (4)$$

Here, σ denotes a measure of the cohesive-energy density of forming a hole in a solvent, while D is a dispersion parameter representing the susceptibility of the solvent to engage in London interactions. Based on the solubility-parameter considerations, σ can be taken as the square of Hildebrand solubility parameter (δ_H^2) [10]. Unfortunately, these values are not yet known for RTILs. Table 3 shows the normalized solvent parameter of Dimroth–Reichardt, E_T^N together with the solvent parameters of Kamlet–Taft π^*, α and β (when available) that correspond to the polarity–polarizability, hydrogen-bond–acceptor, and hydrogen-bond–donor interactions for the three RTILs studied and for [BMIm][BF_4] (for comparison). These solvent parameters will help clarify the LSER coefficients obtained from Eq. 1 in the following discussion:

- The v coefficient. It is positive and high. According to the SP model, this property indicates that the RTILs are less cohesive ($\sigma_w > \sigma_{IL}$ in Eq. 4) and more polarizable than water ($D_{\mathbf{IL}} > D_{\mathbf{w}}$), a conclusion that would be consistent with chemical intuition. The low cohesion of the RTILs compared with that of organic solvents of similar polarity had already been observed by Poole [16]. The magnitude of v increases with the alkyl chain attached to the imidazolium ring, but for [OMIM][BF_4] the small decrease in magnitude could be a result of the less polarizable anion BF_4^-.
- The b coefficient. It is negative and high. This property indicates that the RTIL phase is less acidic than the water phase ($a_{\mathbf{IL}} < a_{\mathbf{w}}$ in Eq. 3). This feature is in agreement with the Kamlet–Taft α parameter for these ILs, whose values are between 0.4 to 0.6 (Table 3) [25, 26] because of the presence of the H atom attached to the C2 of the imidazolium ring. The high magnitude of b would mean that the acidity is much lower than that of water, a conclusion which is likewise in agreement with chemical intuition. The smaller b coefficient for [OMIM][BF_4] as compared with the other two RTILs can be attributed to the higher acidity of the RTIL phase since the amount of water dissolved is much higher than with the other two RTILs (*cf.* Table 3) as a result of the higher hydrophilic character of the anion [19, 27]. Thus, $a_{\mathbf{IL}}$ is more similar to $a_{\mathbf{w}}$ for [OMIM][BF_4].
- The a coefficient. It is negative, indicating that the RTIL phases are less avid hydrogen-bond acceptors than the water phase ($b_{\mathbf{IL}} < b_{\mathbf{w}}$ in Eq. 3). This conclusion is consistent with the lower basicity of the RTILs studied in this work compared with that of water, at least for the RTILs containing the PF_6^- anion (*cf.* the parameter β of Kamlet–Taft in Table 5). Nevertheless, the mutual solubilities of the RTILs containing the PF_6^- anion and water should give an almost zero a coefficient since the β values for the two phases are quite similar. In contrast, the a coefficient is much smaller for [OMIM][BF_4] than for the other two RTILs, for both of which that coefficient is high and similar. This difference is consistent with the lower basicity of the PF_6^- anion compared with that of BF_4^- (i.e., with a lower charge-to-radius ratio). In fact, β value in Table 3 is higher for [BMIM][BF_4] than for [BMIM][PF_6]; the longer alkyl chain for the former RTIL should not change the hydrogen-bonding capacity. The IL [OMIM][BF_4] is the one that dissolves the most water (higher $b_{\mathbf{IL}}$), as we said before. This property could explain the smaller a coefficient for [OMIM][BF_4] ($b_{\mathbf{IL}}$ is more similar to $b_{\mathbf{w}}$) although the extent of the difference in value compared with the a coefficients of the other two RTILs are not in a direct relationship to the β parameters of the pure RTILs, according to values in Table 3.
- The s coefficient. It is small, indicative of the high polarity of the RTIL phase as compared with the aqueous phase ($s_{\mathbf{IL}}$ close to $s_{\mathbf{w}}$ in Eq. 3), as has already been reported [1]. The value is also negative, a characteristic which is in agreement with the lower polarity of the RTILs compared with that of water (*cf.* the differences in their respective polarity–polarizability

parameters π* in Table 3), as also occurs with typical organic solvents. The same conclusions were obtained by C.F. Poole [16]—namely that polarity of RTILs encompasses the same range as occupied by most polar and nonionic liquids. The negative sign of the *s* coefficient, however, is not in agreement with conclusions drawn by Abraham et al. [22]. Those authors obtained positive *s* coefficients, indicating that the polarity of RTILs should be higher than that of water. A key difference is that the *s* coefficients reported in [22] were obtained from direct measurements in which the RTIL and aqueous phases were in direct contact and thus, the mutual solubility of those two phases and consequent changes in polarity could not be taken into account. Table 3, in fact, reveals that the polarity of [BMIM][PF_6] is almost the same as that of water.

– The *e* coefficient. It is quite high and positive, indicating that the polarizability is higher for the RTIL phase than for the water phase ($e_{IL} > e_w$ in Eq. 3), a finding which is reasonable from a chemical standpoint. In this instance, the polarizability resulting from the lone pair of electrons on the N atoms of the cation should be low so that this parameter probably reflects the electrons of the anion. Upon comparison of the two RTILs with the same anion in these experiments, the cation with the longer alkyl chain evinces a higher polarizability. Therefore, some type of compensatory effect appears to be occurring between the [BMIm][PF_6] and [OMIm][BF_4] since the PF_6^- anion is more polarizable than the BF_4^-.

Evaluation of the LSER models: residual analysis and prediction of log $P_{IL/w}$ for the test set

The quality of the multiple linear regressions obtained is not evaluated by simply the regression coefficients and accompanying standard deviations because curve overfitting or additional parameters could improve the regressions without having any chemical meaning for the obtained LSER coefficients. Two procedures to evaluate the SP model [24] are: (1) the prediction of the log $P_{IL/w}$ values from the equations obtained by means of a separate test of solutes that are chemically different from the training set, a group which is called the test set, and (2) a less obvious procedure consisting in the so-called *residual* analysis. This last test is made by plotting the differences between the experimental and calculated log $P_{IL/w}$ values (residuals) for each solute vs. a number assigned to each solute in a systematic way (Fig. 2). This type of plot is useful to detect some possible outlier values in the regression, which points could indicate either a degree of experimental error or a different chemical interaction between that compound and the biphasic system not modeled by Eq. 1. If deviations of this type are present, they usually are not quite visible in the prediction of log $P_{IL/w}$. The residual plots of Fig. 2 demonstrate that no systematic error or specific chemical interaction is present since the residuals are randomly distributed around zero. In contrast, a calculation of log $P_{IL/w}$ values for the test set

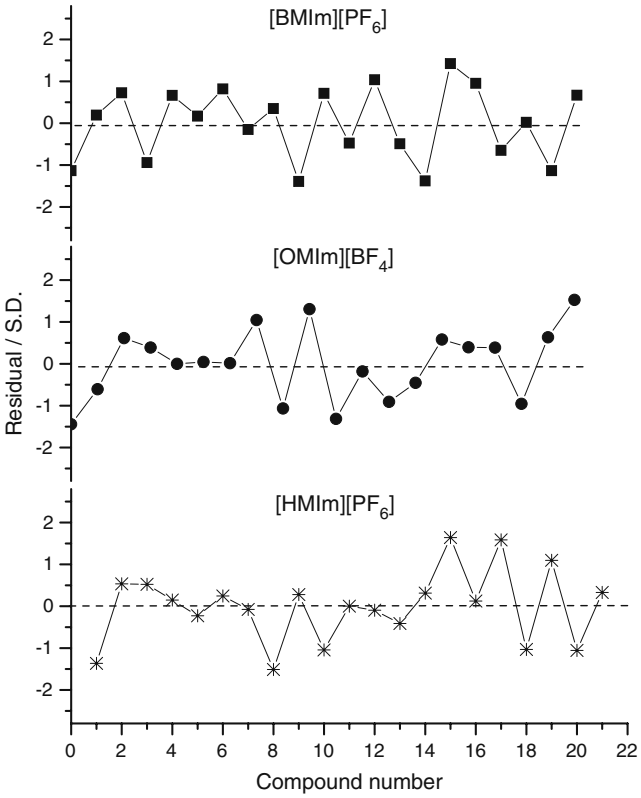

Fig. 2 Normalized residuals (residuals divided by the standard deviation) for regressions of Eq. 1 between the log $P_{IL/w}$ and solute parameters for the three studied RTILs

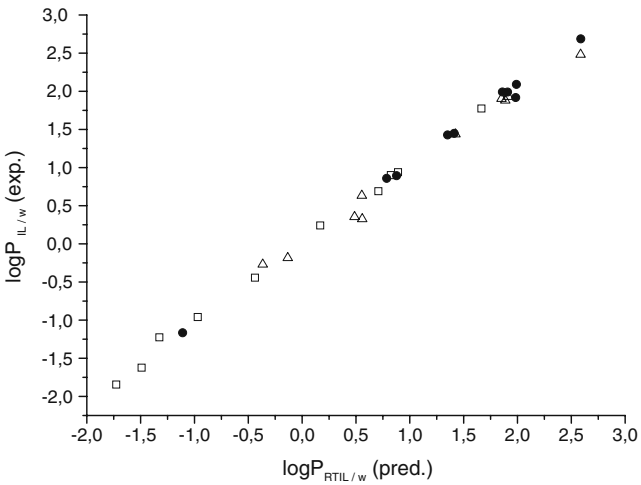

Fig. 3 Experimental vs. predicted (by Eq. 1) log $P_{IL/W}$ values for the "test set" in the three studied RTILs. [BMIM][PF_6] (*empty square*); [HMIM][PF_6] (*filled circle*); [OMIM][BF_4] (*empty square*)

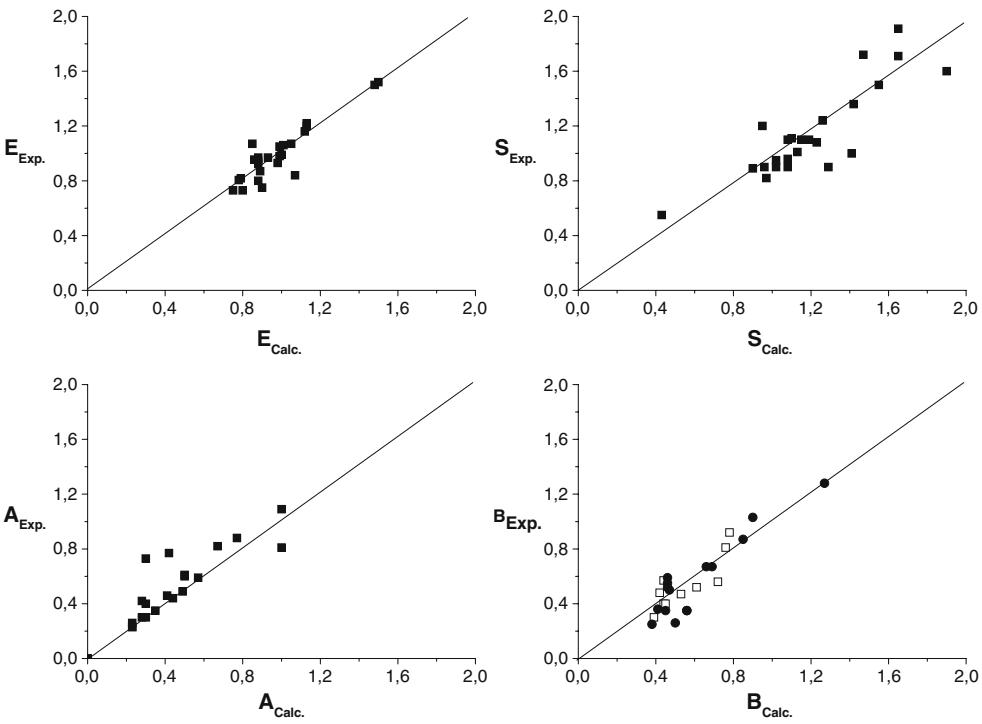

Fig. 4 Experimental vs. calculated (by the ADME Boxes algorithm) solute parameters for the training set

from Eq. 1 is the most straightforward way to indicate the predictive ability of the SP Model. 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 through the use of the solute parameters from the literature when available [6, 7] or by calculations made with the ADME Boxes software. In Fig. 4, it is shown that the solute parameters calculated by this software enabled satisfactory estimations of the empirically generated parameters. The molar volume, *V*, however, is not shown in that figure since the program calculates this parameter through the McGowan algorithm, as is routinely done in the literature for the empirical parameters. The predictions of log $P_{IL/w}$ are quite good since the standard deviations are

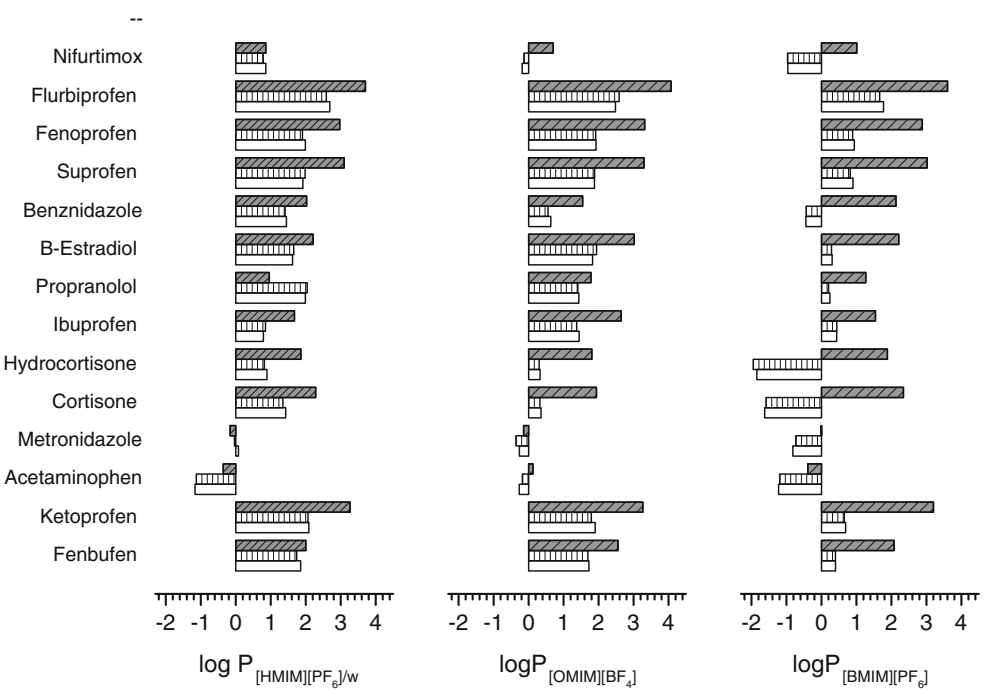

Fig. 5 Comparison of the partition coefficients for the "test set": Experimental values, ▭; calculated in this work from Eq. 1, ▥; calculated by obtaining the LSER coefficients from the "ion-specific model" [30], ▨

low (SD=0.095 for [OMIM][BF_4], 0.065 for [BMIM][PF_6], and 0.072 for [HMIM][PF_6]), indicating that the LSER coefficients are chemically significant and that the SP Model generated in this work is therefore robust and suitable for predicting partition coefficients. The regression equations obtained will be used in future studies to predict the extraction efficiencies of analytes of biological or toxicological interest by using the three studied RTILs.

Comparison of log $P_{IL/w}$ calculated from LSER coefficients obtained from the literature

In order to establish the SP model that is the objective of these investigations, the biphasic systems must first be *calibrated*, i.e., the LSER coefficients must be found by experimentally measuring the partition coefficients of a specific training set for each RTIL. Another approach to obtaining the LSER coefficients for a given RTIL is to use the so-called "*ion-specific model"* [28, 29], which was derived from the SP model of Abraham. These authors split each coefficient into cation-specific and anion-specific LSER coefficients or system constants. This procedure allows the combination of any of the cations and any of the anions that have been characterized to obtain the LSER coefficients for a given RTIL, even when it has not yet been synthesized. In this manner, a need for direct calibration is avoided. Those authors, however, obtained the LSER coefficients indirectly from a training set consisting of volatile molecules analyzable by gas chromatography by combining gas-to-RTIL partition coefficients with water-to-gas partition coefficients. This procedure obviously does not consider the mutual mixing of the RTIL and water. Figure 5, constructed from the LSER coefficients of Table 5, summarizes the experimental and predicted log $P_{IL/w}$ values for our test set. The predicted log $P_{IL/w}$ values were calculated by using the LSER coefficients of Table 5 "Experimental coefficients" obtained by direct calibration in this work and of Table 5 "Calculated coefficients" calculated from the "ion-specific model" coefficients for the corresponding RTILs from [30]. All the partition coefficients calculated from the ion-specific model for these polar and hydrophobic molecules are much higher than the experimental values, probably as a result of the lack of considerations about the mutual-mixing problem mentioned above. If no water was solubilized in the organic phase, the partition coefficients for the neutral or non-ionized organic molecules studied would be higher. The tendency of the *v* coefficient in the ion-specific model is to increase from [BMIM][PF_6] to [OMIM][BF_4], independently of the anion, i.e., as the alkyl chain of the imidazolium ring becomes longer. Clearly, the experimental values of *v* obtained in this work increase from [BMIM][PF_6] to [HMIM][PF_6], but there is a small decrease from [HMIM][PF_6] to [OMIM][BF_4] due to the higher hydrophilicity of the BF_4^- anion.

Conclusions

Partition coefficients at room temperature for several critically selected probe molecules (the "training set") as well as compounds of biological interest (the "test set") between three different RTILs and water were accurately determined. The log $P_{IL/w}$ values for the training set were used in the solvation-parameter model to calibrate the biphasic systems. The system constants obtained (LSER coefficients) allowed an elucidation of the molecular interactions responsible for the partitioning of organic compounds into the RTILs. The LSER equations used also allowed a successful prediction of the partitioning of a series of polar and hydrophobic molecules chemically diverse and different to those of the training set. A comparison of the experimental log $P_{IL/w}$ values with those calculated from the system constants obtained in this work or from the literature (e.g., the ion-specific model) indicated that a direct calibration by partitioning the training-set solutes in the biphasic systems RTIL/water allowed better predictions to be made. This capability could result from the mutual solubilities of water in RTIL and RTIL in water, compatibility which decreases the LSER coefficients relative to those obtained indirectly through the ion-specific model. The good experimental predictions of the partition coefficients also validate the solute parameters calculated by the software used. Finally, an improved, fast methodology with minimum consumption of organic solvent to synthesize two of the ILs studied was proposed.

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