Halide anion solvation and recognition by a macrotricyclic tetraammonium host in an ionic liquid: a molecular dynamics study†

Alain Chaumont and Georges Wipff*

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We report a molecular dynamics study of halide anions X^- and their inclusion complexes $X^- \subset L^{4+}$ with a macrotricyclic tetrahedral host L^{4+} built from four quaternary ammonium sites, in an ionic liquid (IL) based on the 1-butyl-3-methylimidazolium (BMI^+) cation and the PF_6^- anion. The "dry" and "humid" forms of the $[BMI][PF_6]$ IL are compared, showing the importance of IL ions in the "dry" IL and, in some cases, of water molecules in the "humid" IL. In the "dry" IL the F^-, Cl^-, Br^- and I^- uncomplexed halides are surrounded by 4–5 BMI^+ cations whose binding mode evolves from hydrogen bonding to facial coordination along this series. Solvent humidity has the largest impact on the solvation of F^- whose first shell BMI^+ cations are all displaced by H_2O molecules, while the first solvation shell of Cl^-, Br^- and I^- comprises 3–4 BMI^+ cations plus *ca.* 4 H_2O molecules. The solvation of the L^{4+} host and of its $X^- \subset L^{4+}$ complex mainly involves PF_6^- anions in the "dry" IL, and additional H_2O molecules in the "humid" IL. The question of anion binding selectivity is addressed by free energy perturbation calculations which predict that, in the "dry" liquid, F^- is preferred over Cl^-, Br^- and I^-, which contrasts with the aqueous solution where L^{4+} is selective for Cl^-. In the "humid" liquid however, there is no F^-/Cl^- discrimination, showing the importance of "small amounts" of water on the complexation selectivity.

Introduction

There is growing interest in room temperature ionic liquids (ILs) as "green solvents" for ion complexation and extraction from aqueous phases.[1–5] Indeed, ILs based on hydrophobic ions such as alkylimidazolium$^+$ and PF_6^- (Fig. 1) are not miscible with water and can be used for liquid–liquid extraction purposes, generally using traditional extractant molecules, like crown ethers or calixarenes to extract alkali cations, or phosphoryl containing molecules to extract uranyl or trivalent lanthanide cations.[6–10] These ILs display fascinating solvation properties.[11–13] Like classical organic solvents, they dissolve hydrophobic species (*e.g.* extractant molecules and their complexes, or small solvent molecules like benzene or CO_2)[14,15] and, like water, they can solubilize the complexes of hard metallic cations (*e.g.* uranyl or lanthanide salts) as well.[16–20]

To our knowledge, no studies have focused so far on anion extraction or complexation in ILs. Generally speaking, even in classical solvents, anion complexation is a more difficult task, compared to cation complexation, due to the restricted choice of binding sites (generally proton donors in hydrogen bonds, or Lewis acids), with marked pH and environment effects.[21] An interesting class of anion receptors was developed by F. Schmidtchen who synthesized tricyclic host molecules of tetrahedral topology, possessing four quaternary ammonium bridgeheads delineating with their $(CH_2)_n$ connectors a "spherical" cavity into which halides (*e.g.* I^- when $n = 6$) can be complexed with high efficiency and selectivity.[22] Smaller hosts ($n < 6$) turned out to be selective for smaller halides in aqueous solution.[23] In such systems, the driving force for complexation stems from the positive potential created by the ammonium at the center of the host, and selectivity depends on the host–guest complementarity and on the solvent. This important class of anion receptors has been investigated by computer modeling studies in aqueous solution and at the water–oil interface.[24,25] So far, to our knowledge, it has not been investigated in ionic liquids. We felt that this should be an interesting candidate, first because the partners involved in the recognition process may be components of IL. The quaternary ammonium sites of the host are potential cationic constituents of ILs, and should be soluble in these media. It is thus interesting to analyze how the host and its complexes are solvated by the IL. Furthermore, the guests (halide anions) can also be present in ILs, either as impurities in the case of Cl^- remaining after the IL synthesis (typically, after mixing of the HPF_6 acid with the imidazolium chloride), or as the main anionic constituent (*e.g.* imidazolium chloride liquids) of the liquid. So far, the solvation of halide anions has not been described in hydrophobic ILs. Most theoretical studies were of molecular dynamics (MD) type and focused on ILs with Cl^- as anionic component,[26–31] or as ligand of metallic ions (*e.g.* $EuCl_n^{3-n}$ ions).[32–34] There are also quantum mechanics (QM) studies on the interactions between halide anions and

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Laboratoire MSM, Institut de Chimie, UMR CNRS 7177, Université Louis Pasteur, 4, rue B. Pascal, 67 000 Strasbourg, France. E-mail: wipff@chimie.u-strasbg.fr

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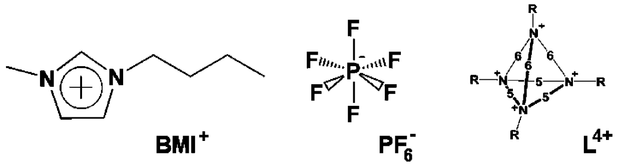

Fig. 1 Schematic representation of the IL constituents and of the L^{4+} host.

imidazolium cations in the gas phase[35,36] as well as Car–Parrinello (CP-MD) simulations on the dimethylimidazolium chloride IL.[37] Note that the search for molecules capable to selectively complex, and eventually remove, halide impurities from IL is by itself an interesting topic with possible technological applications.

In this paper, we focus on the L^{4+} tetrahedral host which possesses one [555] face delineated by three $N(CH_2)_5N$ chains and three larger [566] faces delineated by one $N(CH_2)_5N$ and two $N(CH_2)_6N$ chains, and four N^+–Me substituents at the bridgeheads (Fig. 1). Experimentally, L^{4+} selectively complexes Cl^- in aqueous solution[23] and the corresponding inclusion complex has been characterized by X-ray crystallography in the solid state.[38] The complexation of F^- to I^- anions by L^{4+} has also been studied by simulations in the gas phase and in aqueous solution.[24] Here, its inclusion complexes with halides (F^- to I^-) are simulated in the [BMI][PF_6] liquid, for which a dry form (no water at all) and a humid form (with a 1 : 1 ratio of IL ions and H_2O molecules) are compared. The [BMI][PF_6] IL is indeed hygroscopic and may contain up to 0.26 molar fraction of water,[39] and this amount may still increase in the presence of hydrophilic species, like the simulated halides or their complexes that are, in fact, soluble in water. We want to investigate how the BMI^+ cations and PF_6^- anions of the IL interact with the different partners involved in the complexation process: the free halides, the free L^{4+} host, and their inclusion complex, noted $X^- \subset L^{4+}$. A charged solute should be preferentially surrounded by solvent ions of opposite sign, but the corresponding coordination numbers, and possible contributions of other ions, remain to be assessed. Water is an important competitive ligand, and it is important to investigate how it perturbs the first solvation shell of these solutes. Beyond structural features, we also want to gain insights into the energetics of anion solvation and complexation in the IL. Insights will be obtained from the analysis of the solute–IL interaction energies, and from the calculation of relative free energies of solvation and of complexation of the halides by L^{4+}, obtained *via* free energy perturbation calculations.

Methods

Empirical representation of the potential energy and force field parameters

The systems were simulated by classical molecular dynamics (MD) using the modified AMBER 7.0 software[40] in which the potential energy U is described by a sum of bond, angle and dihedral deformation energies and pairwise additive 1–6–12 (electrostatic + van der Waals) interactions between non bonded atoms: eqn (1):

$$U = \sum_{\text{bonds}} k_b(b-b_0)^2 + \sum_{\text{angles}} k_\theta(\theta-\theta_0)^2 + \sum_{\text{dihedrals}}\sum_n V_n(1+\cos(n\varphi-\gamma)) + \sum_{i<j}\left[\frac{q_iq_j}{R_{ij}} - 2\varepsilon_{ij}\left(\frac{R^*_{ij}}{R_{ij}}\right)^6 + \varepsilon_{ij}\left(\frac{R^*_{ij}}{R_{ij}}\right)^{12}\right] \quad (1)$$

Cross terms in van der Waals interactions were constructed using the Lorentz–Berthelot rules. The BMI^+ ion parameters were taken from ref. 41 while those of PF_6^- are from the OPLS force field[42] and have been tested on the pure liquid properties. Atomic charges and AMBER atom types of the L^{4+} host, taken from ref. 25, are summarized in Fig. S1.† The van der Waals parameters of the halide anions $R_F{}^* = 1.850$; $R_{Cl}{}^* = 2.495$; $R_{Br}{}^* = 2.679$; $R_I{}^* = 3.005$ Å and $\varepsilon_F = 0.200$; $\varepsilon_{Cl} = 0.107$; $\varepsilon_{Br} = 0.0858$; $\varepsilon_I = 0.0522$ kcal mol^{-1}) were those from Berny *et al.*, fitted from FEP calculations on their hydration energies[43] starting from Cl^-.[44] Water was described by the TIP3P model.[45] The 1–4 van der Waals interactions were scaled down by a factor of 2.0 and the 1–4 coulombic interactions were scaled down by 1.2, as recommended by Cornell *et al.*[46] The solutions were simulated with 3D-periodic boundary conditions. Non bonded interactions were calculated with a 12 Å atom based cut-off, calculating the long-range electrostatics by using the Ewald summation method (Particle–particle Mesh Ewald approximation).[47]

Molecular dynamics

The MD simulations were performed at 400 K in order to better sample the different configurations of the solutions. The temperature T was monitored by coupling the system to a thermal bath using the Berendsen algorithm[48] with a relaxation time of 0.2 ps. In the (NPT) simulations, the pressure P was similarly coupled to a barostat with a relaxation time of 0.2 ps. All C–H bonds were constrained with SHAKE, using the Verlet leapfrog algorithm with a time step of 2 fs to integrate the equations of motion.

We first equilibrated "cubic" boxes of the pure liquid, containing either 200 BMI^+ cations and 200 PF_6^- anions for the "dry" form or 200 BMI^+, 200 PF_6^- and 200 H_2O molecules for its "humid" form. This was achieved by repeated sequences of (i) heating the system at 500 K at constant volume for 0.5 ns, followed by (ii) 0.5 ns of dynamics at 300 K and a constant pressure of 1 atm and (iii) 1 ns of dynamics at 300 K and constant volume. The final box was simulated in the (NVT) ensemble for 2 ns at 300 K. The density of the "dry" liquid was 1.33 kg dm^{-3}, in reasonable agreement with the experimental value of 1.36 kg dm^{-3},[49,50] while the density of the humid liquid was 1.32 kg dm^{-3}. We then immersed the different solutes in the "dry" and "humid" liquids, while removing BMI^+ or PF_6^- solvent ions to maintain the box neutral when necessary. The characteristics of the simulated systems are summarized in Table 1. After 1000 steps of energy minimization, 100 ps of dynamics were performed with fixed solutes (BELLY option of AMBER) in order to allow the solvent to relax around the solute. This was followed by 150 ps

Table 1 Characteristics of the simulated systems

	Dry [BMI][PF$_6$]				Humid [BMI][PF$_6$]				
	BMI$^+$	PF$_6^-$	Box size/Å	Time/ns	BMI$^+$	PF$_6^-$	H$_2$O	Box size/Å	Time/ns
F$^-$	200	199	41.5 × 41.5 × 41.5	2	200	199	200	42.6 × 42.6 × 42.6	2
Cl$^-$	200	199	41.5 × 41.5 × 41.5	2	200	199	200	42.6 × 42.6 × 42.6	2
Br$^-$	200	199	41.5 × 41.5 × 41.5	2	200	199	200	42.5 × 42.5 × 42.5	2
I$^-$	200	199	41.5 × 41.5 × 41.5	2	200	199	200	42.5 × 42.5 × 42.5	2
L^{4+}	200	204	41.9 × 41.9 × 41.9	2	200	204	200	42.7 × 42.7 × 42.7	2
F$^-$ ⊂ L^{4+}	200	203	41.7 × 41.7 × 41.7	2	200	203	200	42.8 × 42.8 × 42.8	2
Cl$^-$ ⊂ L^{4+}	200	203	41.7 × 41.7 × 41.7	2	200	203	200	42.8 × 42.8 × 42.8	2
Br$^-$ ⊂ L^{4+}	200	203	41.7 × 41.7 × 41.7	2	200	203	200	42.8 × 42.8 × 42.8	2
I$^-$ ⊂ L^{4+}	200	203	41.7 × 41.7 × 41.7	2	200	203	200	42.8 × 42.8 × 42.8	2

of dynamics at 400 K and a pressure of 1 atm, and by a production step of at least 2 ns at constant volume.

Analysis

The results were analyzed by visual inspection at the computer graphics systems using our DRAW and MDS software.[51] The solute-solvent interaction energies E_{solv} were calculated with a 17 Å + RF cutoff, and averaged over the last 0.2 ns of dynamics. Insights into energy components were obtained from the average interactions between selected groups (cations, anions, water and ionic liquid). The average structure of the solvent around the center of mass of the different solutes was characterized by the radial distribution function (RDFs) of the anions (F_{PF_6} atoms and P_{PF_6} atoms), cations (H_{BMI} protons of the imidazolium ring and CM_{BMI} center of mass of the imidazolium ring) or water during the last 0.2 ns. The snapshots presented here were drawn with the VMD software.[52]

Free energy calculations

The changes in free energies of solvation Δ*G* from one anion to the other were obtained by free energy perturbation calculation using the thermodynamic perturbation method using the thermodynamics integration TI technique based on eqn (2):[53]

$$\Delta G = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda \mathrm{d}\lambda \qquad (2)$$

The transformation of one anion to the other (*i.e.* from $\lambda = 0$ to $\lambda = 1$) was achieved *via* hybrid potential energy $U(\lambda)$ calculated using a linear combination of the R^*, ε parameters of the initial anion ($\lambda = 1$) and the final anion ($\lambda = 0$) [eqn (3)]:

$$R_\lambda{}^* = \lambda R^*_{\lambda=1} + (1-\lambda)\, R^*_{\lambda=0} \text{ and } \varepsilon_\lambda = \lambda\varepsilon_{\lambda=1} + (1-\lambda)\,\varepsilon_{\lambda=0} \quad (3)$$

The mutation was achieved in 51 steps, *i.e.* with increments Δλ of 0.02. At each λ, we performed 5 ps of equilibration followed by 5 ps of data collection, and the changes of free energy Δ*G* were averaged from independent mutations of one anion to the other (λ_1 to λ_2) and *vice versa* (λ_2 to λ_1), starting in each case after 1 ns of MD equilibration.

Potential of mean force calculations

We calculated the potential of mean force (PMF)[53] corresponding to the free energy profile for anion dissociation as a function of its position, using the same protocol as in aqueous solution,[24] moving stepwise from the state C (complex $X^- \subset$ **L**$^{4+}$) to the state UC (uncomplexed $X^-\cdots\cdot$**L**$^{4+}$ system). The change in free energy was obtained by the TI technique.

The transformation of states C to UC was achieved in 101 steps, *i.e.* with increments Δλ of 0.01, corresponding to 0.1 Å each. At each λ, we performed 4 ps of equilibration followed by 6 ps of data collection, and the changes of free energy Δ*G* were averaged from the forward and backward cumulated values.

Results

We first describe the solvation of the uncomplexed halide anions (F$^-$, Cl$^-$, Br$^-$ and I$^-$) in the "dry" and "humid" forms of the [BMI][PF$_6$] liquid. This will be followed by the solvation of the L^{4+} host and of its chloride inclusion complex (Cl$^-$ ⊂ L^{4+}) in the "dry" and "humid" forms of the liquid. Finally we address the question of halide anion recognition and complexation by L^{4+} in [BMI][PF$_6$].

Solvation of the halide anions (F$^-$, Cl$^-$, Br$^-$ and I$^-$) in the "dry" and "humid" [BMI][PF$_6$] ionic liquids

The solvent structure around the halide anions X$^-$ (F$^-$, Cl$^-$, Br$^-$ and I$^-$) is characterized by the RDFs of the P_{PF_6}, H_{BMI}, CM_{BMI}, H_{H_2O} and O_{H_2O} atoms around X$^-$ (see Fig. 2 and 3 and Table 2), and by average X$^-$–solvent interaction energies (Table 3).

The RDFs show that in the "dry" [BMI][PF$_6$] the first solvation shell of all halides is exclusively formed of BMI$^+$ cations. Each halide is surrounded by about 4–5 BMI$^+$ cations whose orientations depend on the halide size. The BMI$^+$ cations are generally hydrogen bonded to F$^-$ *via* one proton of the imidazolium ring, but mainly display facial interaction with the other halide anions. As a result, there are different arrangements of butyl chains, as seen from the RDF of their terminal (C$_4$) carbon atom (Fig. S2):† the number of C$_4$ atoms in the first shell of X$^-$ increases with the size of the anion (from 0 for F$^-$, to 1.4 for Cl$^-$, 1.8 for Br$^-$, and 3.1 for I$^-$), indicating some hydrophobic character of the biggest anions. Behind this first peak one finds a second shell, which comprises 5–6 solvent anions up to 8 Å.

Solvent humidity strongly influences the solvation of F$^-$, as all BMI$^+$ that coordinated to F$^-$ in the "dry" solvent have been displaced by *ca.* 5.5 H$_2$O molecules. The first shell of the other anions (Cl$^-$, Br$^-$ and I$^-$) is less affected by humidity, as

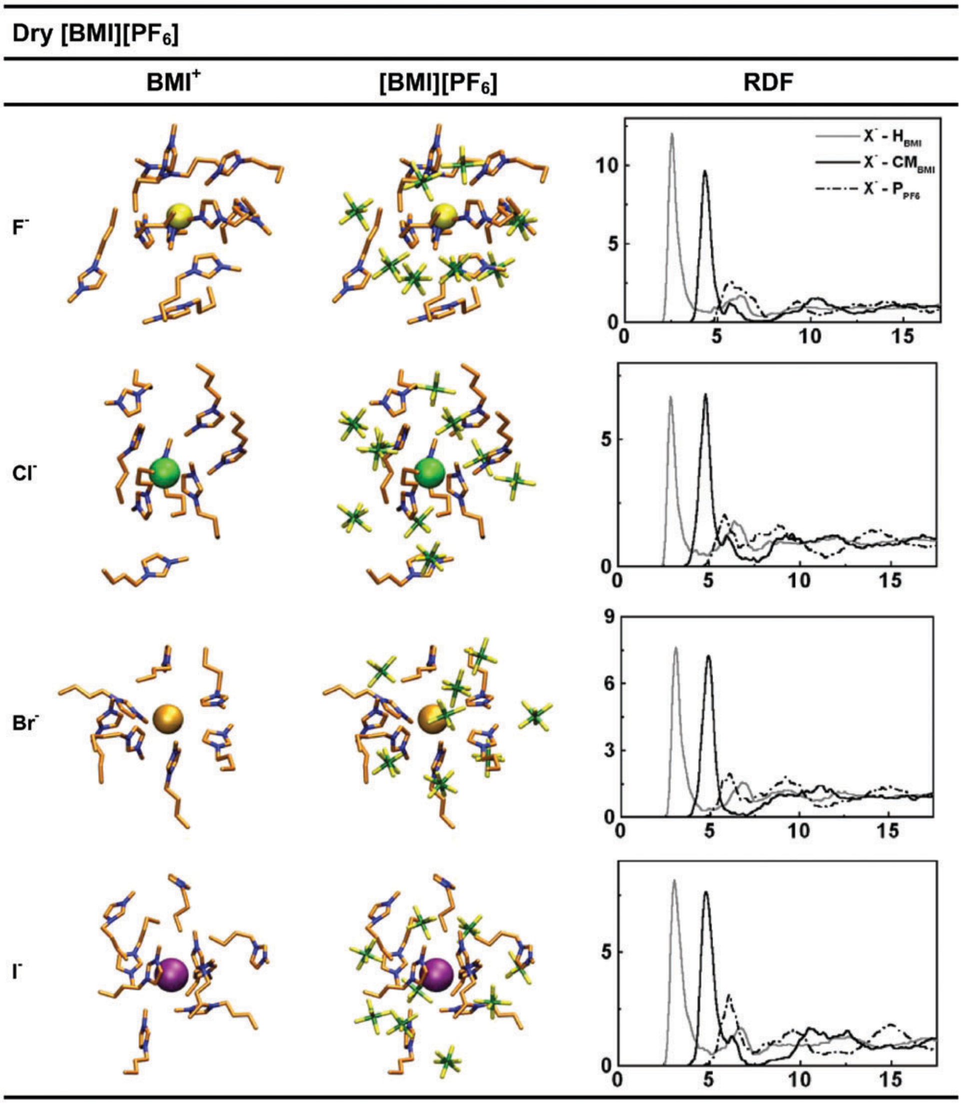

Fig. 2 X^- in "dry" [BMI][PF_6]: radial distribution functions of the imidazolium cation and PF_6^- anion around the X^- anions.

it is composed of a mixture of 3–4 BMI^+ cations and *ca.* 4 H_2O molecules. The average distances between X^- anions and water protons (H_{H_2O}) are *ca.* 0.6–1.0 Å shorter then the corresponding distances between X^- and H_{BMI} protons, indicating that X^- forms stronger hydrogen bonds with H_2O than with BMI^+ molecules. Furthermore, when compared to those in the "dry" IL, the average X^-–H_{BMI} distances are *ca.* 0.1 Å longer and the first solvent RDF peaks are broader, which shows that humidity weakens the interactions between X^- and the first shell BMI^+ cations. Humidity also modifies the second solvation shell, which is formed exclusively of PF_6^- anions in the "dry" liquid, and of a mixture of solvent anions, cations and water molecules in the humid IL.

In both dry and humid [BMI][PF_6] liquids the X^-–IL interaction energies E_{solv} decrease when X^- gets bigger (Table 3). In the dry liquid, this stems from the fact that the attractions with the BMI^+ cations decrease more rapidly than the repulsions with PF_6^- anions. In the "humid" liquid, however, the difference between these energy components ($\Delta \approx -70$ kcal mol^{-1}) remains quasi-constant from F^- to I^- and the drop in "solvation energies" ΔE_{solv} along this series is due to decreased interactions with water molecules. Finally the comparison of "solvation energies" of a given halide in the "dry" *versus* "humid" forms of the IL ($\Delta E_{solv} \approx -70$ kcal mol^{-1} for F^- and -10 kcal mol^{-1} for Cl^-, Br^- and I^-) shows that halides are better solvated by the "humid" then by the "dry" IL.

The L^{4+} host and its halide complexes in "dry" and "humid" forms of the [BMI][PF_6] liquid

Solvation of L^{4+} and its $X^- \subset L^{4+}$ complexes. In the "dry" [BMI][PF_6], each face of the L^{4+} tetrahedral host is solvated by one PF_6^- anion, pointing one F-atom towards the center of the face. As the host possesses three larger [566] faces and one smaller [555] face this leads to the appearance of two peaks, integrating for 3 and for 1 anions, respectively in the RDF (Fig. 4). There is a third peak which corresponds to PF_6^-

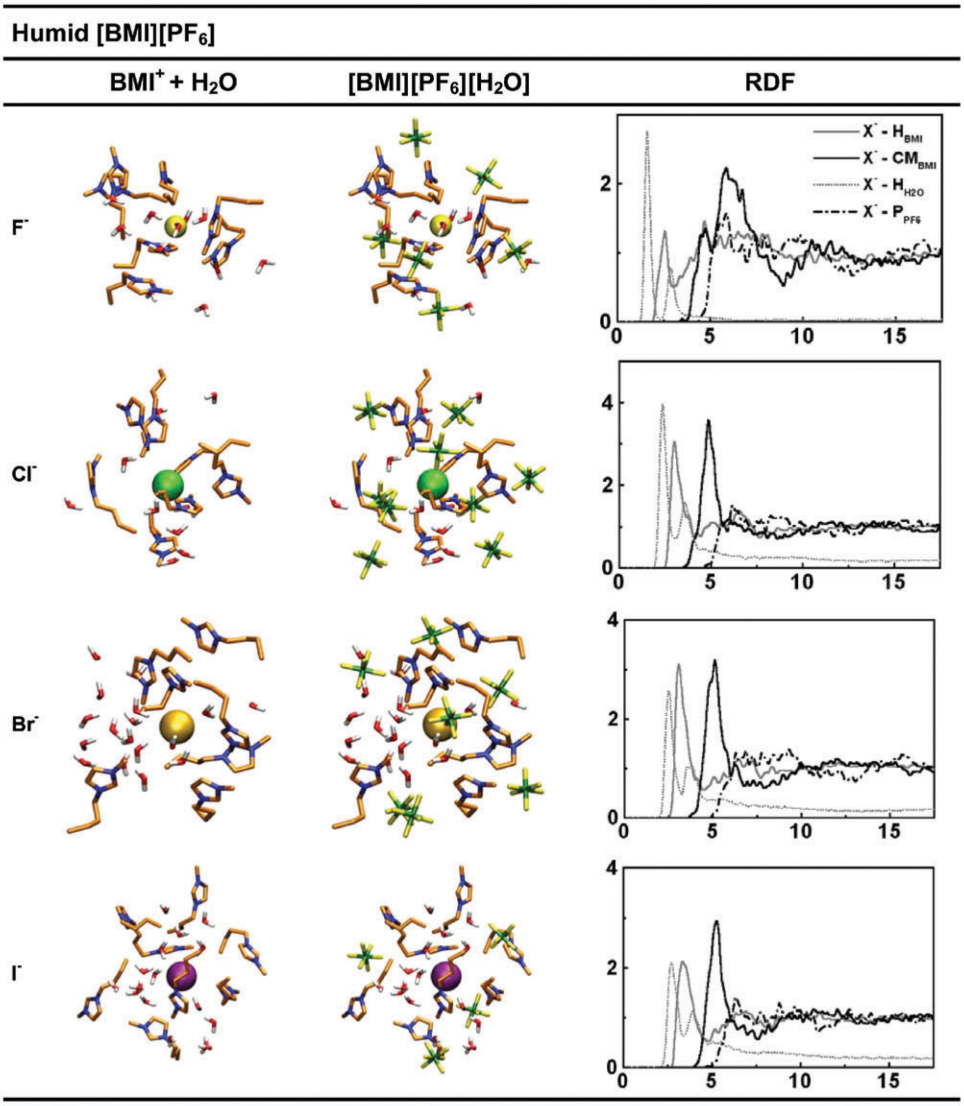

Fig. 3 X^- in "humid" [BMI][PF_6]: radial distribution function of the imidazolium cation and PF_6^- anion around the X^- anions.

anions solvating the ammonium bridgeheads of L^{4+}, each being surrounded by 2–3 PF_6^- anions. Looking now at the cation RDF indicates that the first solvation shell formed by PF_6^- anions is embedded in a cage formed of BMI^+ cations. The broad peak comes from BMI^+ cations interacting with facial PF_6^- anions and from more remote BMI^+ cations interacting with the PF_6^- sitting around the bridgeheads of the host.

The solvation patterns of the $Cl^- \subset L^{4+}$ complex (Fig. 4) markedly differ from those of L^{4+}, as there are no more facial PF_6^- anions, due to repulsive interactions with the complexed Cl^-, and the PF_6^- anions sit further away from L^{4+} as can be seen from the solvent RDF. The complex is solvated by about 15 PF_6^- anions up to 11 Å, embedded in a second shell formed of *ca.* 36 BMI^+ cations.

When L^{4+} is simulated in the "humid" [BMI][PF_6] liquid, one only finds one PF_6^- solvent peak in the RDF, which comes from one PF_6^- anion at each of its three [566] faces, while the PF_6^- anion that was on the [555] face has been replaced by an H_2O molecule. This molecule dynamically exchanges between the face of L^{4+} and its cavity where it remains for about 200 ps. Such water exchange did not occur when L^{4+} was simulated in pure water.[25] In the humid IL, this first shell is surrounded by a shell of BMI^+ cations, as in the dry IL. Around the $Cl^- \subset L^{4+}$ complex one no longer finds PF_6^- anions in the facial positions but all solvate the four ammonium heads. At the center of the faces one finds the C_4-chain of an imidazolium cation which sits in between three PF_6^- anions.

Halide anion recognition by L^{4+} in "dry" and "humid" [BMI][PF_6]. In order to address the question of anion binding selectivity of the tetrahedral host in the "dry" and "humid" [BMI][PF_6] we first equilibrated the different $X^- \subset L^{4+}$ (X^- = F^-, Cl^-, Br^- and I^-) complexes in the two forms of the [BMI][PF_6] liquid. Contrary to what was observed in water,[24] the F^- anion dissociated neither in the "dry" nor in the "humid" [BMI][PF_6] liquid, and hence free energy calculations

Table 2 Halide anions X^- in "dry" and "humid" [BMI][PF_6]: Characteristics of the first peak of the radial distribution functions. Coordination number (CN) (first line) and distances (Å) of the first maximum and minimum (second line). Average taken over the last 0.2 ns

	Dry [BMI][PF_6]			Humid [BMI][PF_6]			
	P_{PF_6}	H_{BMI}	CM_{BMI}	H_{BMI}	CM_{BMI}	H_{H_2O}	O_{H_2O}
F^-	6.1	5.2	4.8	0.5	0.8	5.4	5.5
	(5.70; 8.05)	(2.55; 3.25)	(4.30; 5.35)	(2.60; 2.85)	(4.75; 5.05)	(1.55; 2.30)	(2.55; 3.25)
Cl^-	2.6	4.1	4.2	3.4	2.5	3.3	3.9
	(5.85; 6.70)	(2.90; 3.95)	(4.75; 5.60)	(3.05; 4.45)	(4.90; 5.60)	(2.40; 2.80)	(3.25; 4.15)
Br^-	2.7	5.6	4.8	3.1	2.9	3.3	3.4
	(6.10; 6.75)	(3.05; 4.15)	(4.85; 5.85)	(3.05; 4.50)	(5.15; 6.00)	(2.50; 3.20)	(3.40; 4.10)
I^-	3.3	4.0	4.5	3.3	3.7	3.6	4.2
	(6.35; 7.40)	(3.25; 4.50)	(5.30; 6.10)	(3.35; 4.85)	(5.20; 7.00)	(2.70; 3.35)	(3.55; 4.50)

Table 3 Anions X^- in dry and humid [BMI][PF_6]: average interaction energies and fluctuations (kcal mol^{-1}) between X^- and the liquid

Dry IL

	BMI^+	PF_6^-	IL
F^-	−612 (9)	487 (8)	−125 (9)
Cl^-	−589 (10)	482 (9)	−107 (8)
Br^-	−575 (11)	477 (9)	−97 (8)
I^-	−550 (9)	460 (8)	−90 (8)

Humid IL

	BMI^+	PF_6^-	H_2O	IL
F^-	−513 (16)	445 (12)	−125 (17)	−194 (11)
Cl^-	−502 (15)	430 (13)	−48 (15)	−120 (9)
Br^-	−502 (15)	429 (18)	−36 (11)	−109 (10)
I^-	−475 (16)	409 (15)	−32 (13)	−98 (9)

were performed including also this anion.

$$\begin{tikzcd}
X^- + L^{4+} \arrow[r, "\Delta G_1"] \arrow[d, "\Delta G_3"'] & X^- \subset L^{4+} \arrow[d, "\Delta G_4"] \\
Y^- + L^{4+} \arrow[r, "\Delta G_2"] & Y^- \subset L^{4+}
\end{tikzcd}$$

The calculation of the complexation selectivity $\Delta\Delta G_c$ of L^{4+} in IL was based on the thermodynamic cycle shown. According to this cycle $\Delta\Delta G_C = \Delta G_1 - \Delta G_2$ (by definition) $= \Delta G_3 - \Delta G_4$ (computed "alchemical" route), where ΔG_3 is the free energy difference of two "free" anions in IL, and ΔG_4 is the free energy difference of two anion complexes in IL. A summary of all values is given in Table 4, showing that the hysteresis is generally small, typically 1 kcal mol^{-1}, or less.

In the "dry" IL, the calculated ΔG_3 differences in free energies of solvation are positive for F^-/Cl^- (17.0 kcal mol^{-1}), Cl^-/Br^- (4.3 kcal mol^{-1}) and Br^-/I^- (6.6 kcal mol^{-1}), indicating that the order of solvation energies is the same as in water, also following the X^-–IL interaction energies E_{solv} reported above. However, these ΔG_3 energies are smaller in the IL than in water (29.9 kcal mol^{-1} for F^-/Cl^-, 6.2 kcal mol^{-1} for Cl^-/Br^- and 8.9 for Br^-/I^-).[54] Similar trends have been observed for trivalent lanthanide cations[55] and for alkali cations.[56] In the "humid" solution, the ΔG_3 energies are larger than in the dry liquid (25.7 kcal mol^{-1} for F^-/Cl^-, 5.3 kcal mol^{-1} for Cl^-/Br^- respectively, 8.0 for Br^-/I^-), thereby approaching the corresponding values in pure water.

In both "dry" and "humid" solutions, the ΔG_4 changes in free energies for the $X^- \subset L^{4+}$ complexes also increase in the order: $F^- < Cl^- < Br^- < I^-$, following the same trends in IL solution as in the gas phase or in water.[24] According to the energy component analysis, this is also the order of decreasing host–guest interactions (see Table 5). As the anionic guest gets bigger, the coulombic component becomes less attractive and van der Waals repulsions increase; see Table 6). Thus, in the "dry" liquid, the ΔG_4 values for Cl^-/Br^- (11.7 kcal mol^{-1}) and Br^-/I^- (24 kcal mol^{-1}) are somewhat larger than those calculated in water (10.2 kcal mol^{-1} and 21.2 kcal mol^{-1}, respectively).[24] When the solution becomes humid, however, the ΔG_4 values (11.0 kcal mol^{-1} and 23.3 kcal mol^{-1}) come close to those in water. There is one exception with the F^-/Cl^- pair for which ΔG_4 increases (from 24.3 kcal mol^{-1} in the "dry" to 26.1 kcal mol^{-1} in the "humid" liquid), due to a change in binding mode. In the "humid" solvent F^- sits no longer at the center of the host's cavity but in a facial position where it interacts more strongly with H_2O molecules. The resulting $\Delta\Delta G_C$ energies indicate that in the "dry" IL, L^{4+} prefers F^-, with a selectivity order $I^- < Br^- < Cl^- < F^-$ whereas in the "humid" IL there is no clear preference for F^- or Cl^-, both being however preferred over I^- and Br^- by L^{4+}.

Halide anion complexation by L^{4+} in "dry" [BMI][PF_6]. The above results are based on the hypothesis that the $X^- \subset L^{4+}$ complexes indeed form in solution. That this should be the case is supported by the results of the PMF calculations of the decomplexation of Cl^- *versus* F^- in the dry IL solution. As reaction coordinate, we used the $N\cdots X^-$ distance d (see Fig. 5) between X^- and the nitrogen bridgehead which is opposite to the largest face [566], delineated by one C_5 and two C_6 chains. This distance was increased linearly as a function of a λ parameter from d_c (complexed state C; $\lambda = 1$) to $d_{uc} = d_c + 10$ Å (uncomplexed state UC; $\lambda = 0$): $d_\lambda = \lambda d_c + (1 - \lambda)d_{uc}$. For a given complex, d_c was obtained from the last set of MD equilibration (*ca.* 4.2 Å). The resulting $\Delta G(d)$ curves (Fig. 5) show that as the anion moves from the center of the cage of L^{4+} to a facial coordination ($d \approx 7.8$ Å), ΔG increases markedly, by up to *ca.* 110 and 75 kcal mol^{-1}, respectively for Cl^- and F^-. This is due to the loss of host–guest interactions and to poor solvation, due to antagonistic contributions of the solvent PF_6^- anions (attracted by L^{4+}) and BMI^+ cations (attracted by X^-). When the dissociation proceeds further, $\Delta G(d)$ decreases somewhat, due to better solvation of the partners. At 15 Å, however, $\Delta G(d)$ still amounts to $\approx$100

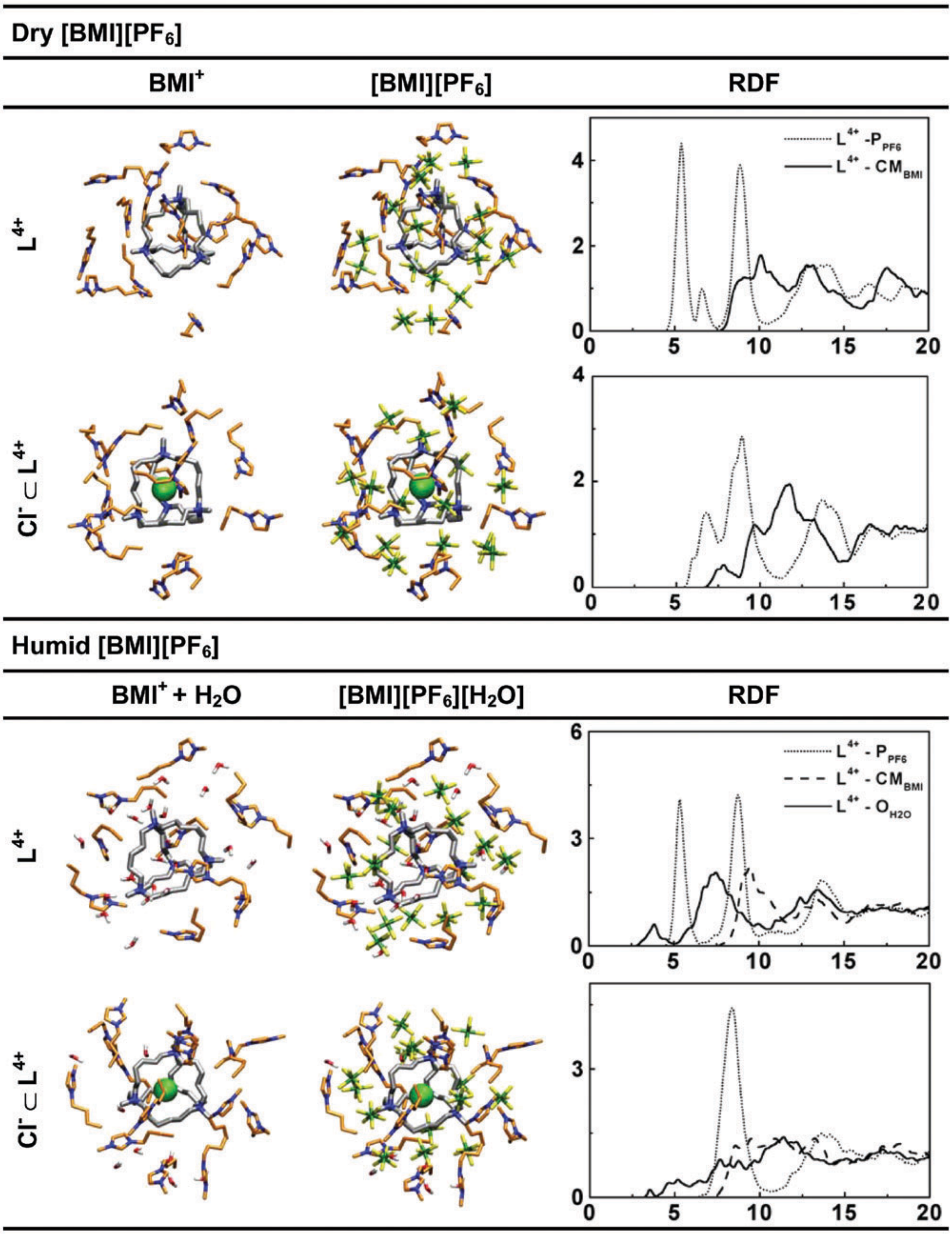

Fig. 4 L^{4+} and its $Cl^- \subset L^{4+}$ complex in the "dry" and "humid" $[BMI][PF_6]$: radial distribution functions of the imidazolium cation and PF_6^- anion around X^-.

kcal mol^{-1} for Cl^- and 115 kcal mol^{-1} for F^-, indicating that the dissociation of both anions is highly disfavored. When compared to the PMFs previously reported in water,[24] note that the PMFs in the IL have been obtained with enhanced sampling, *i.e.* with 100, instead of 50 windows, and at 400 K, instead of 300 K. The results have to be examined with care and considered as qualitative, given the viscous character of the IL and slow relaxation of the IL when the anion decomplexes. They clearly indicate however that the complexes should be stable, and more stable in the IL than in water where the energy barriers for dissociation (*ca.* 20 kcal mol^{-1} for the two anions) and $\Delta G(d)$ at 14 Å ($\approx$5 kcal mol^{-1} for Cl^- and -5 kcal mol^{-1} for F^-) are much smaller.

Conclusions

We report a molecular dynamics study of the solvation of halide anions and of their complexation by a macrotricyclic host L^{4+} in the "hydrophobic" $[BMI][PF_6]$ ionic liquid, comparing the dry *versus* humid forms of the IL. The force field used assumes that the interactions are mainly electrostatic and steric in nature, without explicit representation of electronic reorganization effects. Although charge transfer and polarization effects are far from being negligible,[37,38] the MD results obtained with 1–6–12 potentials for neat imidazolium-based ILs[27,30,57,58] and their solutions,[59,60] as well as the comparison of MD *versus* QM calculated Cl^-/L^{4+} interaction energies[24,25]

Table 4 Free energy changes (kcal mol^{-1}) upon X^- to Y^- mutations and Y^- to X^- mutations (in brackets) for the free ions (ΔG_3) and their L^{4+} complexes (ΔG_4) in dry and humid [BMF][PF_6] solution

$X^- \rightarrow Y^-$ Dry IL	ΔG_3	ΔG_4	$\Delta\Delta G_C$
$F^- \rightarrow Cl^-$	17.4 (−16.6)	25.0 (−23.6)	−7.6 (7.0)
$Cl^- \rightarrow Br^-$	4.3 (−4.4)	11.7 (−11.8)	−7.4 (7.4)
$Br^- \rightarrow I^-$	7.7 (−5.4)	24.8 (−23.2)	−17.1 (17.8)
Humid IL			
$F^- \rightarrow Cl^-$	25.6 (−25.9)	26.7 (−25.2)	−0.9 (−0.7)
$Cl^- \rightarrow Br^-$	5.1 (−5.5)	11.0 (−11.0)	−5.9 (5.5)
$Br^- \rightarrow I^-$	8.4 (−7.6)	23.3 (−21.9)	−14.9 (14.3)

show that the empirical representation of the energy is reasonable.

Concerning the free X^- halides, their solvation is fully analogous (but "symmetrical") to what was found for metallic cations (from monovalent alkali[56] to trivalent lanthanides),[32,33,55,58] *i.e.* with onion-type alternation of solvent shells. Their first shell is fully cationic (BMI^+ cations only), and it is surrounded by a PF_6^- shell in the dry IL. Note that when the anion gets bigger than I^-, its first shell may comprise some solvent anions as well.[61] The onion-type solvation of halides may have important consequences as far as the reaction kinetics with Lewis acids or positively charged species A^{n+} is concerned, because as the latter approaches from X^-, it is difficult to find a continuous pathway for insertion into the first shell, due to repulsion with the IL cations in the first shell. The same problem occurs from the A^{n+} side, which hints at important equilibration problems due to slow diffusion and high kinetic barriers when such ions have to meet and/or react in dry ionic liquids. "Small amounts of water" may play a critical role in ion pairing, due to the important solvation contribution of water (up to 100%, in the case of F^-) in the first solvation shell. Such water molecules may act as relays between the bulk IL and the first solvent shell of the ionic solute. Furthermore, "humidity" is known to enhance the diffusion of ions in the ILs,[62] also facilitating the reaction between ions in the liquids.

Table 5 $X^- \subset L^{4+}$ complexes in dry and humid [BMI][PF_6] solutions. Average interaction energies and fluctuations (kcal mol^{-1}) between X^-, L^{4+}, and the IL components

Dry IL

	L^{4+}	BMI^+	PF_6^-	Total
F^-	−223 (3)	−340 (6)	451 (8)	−111 (7)
Cl^-	−201 (2)	−352 (6)	458 (7)	−94 (6)
Br^-	−185 (2)	−348 (7)	443 (9)	−89 (6)
I^-	−175 (3)	−361 (7)	457 (7)	−79 (7)

Humid IL

	L^{4+}	BMI^+	PF_6^-	H_2O	Total
F^-	−217 (4)	−340 (8)	446 (10)	-14 (9)	−124 (9)
Cl^-	−200 (2)	−320 (9)	415 (12)	1 (7)	−104 (6)
Br^-	−189 (3)	−328 (7)	416 (9)	3 (5)	−98 (7)
I^-	−176 (3)	−333 (8)	430 (13)	3 (11)	−76 (8)

Table 6 $X^- \subset L^{4+}$ complexes in dry [BMI][PF_6] solution: average host–guest interaction energies (kcal mol^{-1}) and their van der Waals and electrostatic components

	F^-	Cl^-	Br^-	I^-
van der Waals	−1 (2)	11 (2)	19 (3)	29(4)
EEL	−222 (3)	−212 (2)	−203 (2)	−204 (2)
Total	−223 (3)	−201 (2)	−185 (2)	−175 (3)

The solvation of the tetra-charged L^{4+} host is also more or less onion-type, with alternation of PF_6^- anions in the first shell, and BMI^+ cations in the second shell in dry conditions, also likely leading to high kinetic barriers for anion inclusion into the host's cavity. Again, the process should be facilitated by water, which may provide a continuous assistance when the halide approaches to the host prior inclusion. Thus, in liquid–liquid extraction conditions, where the host–guest recognition occurs in a water-rich interfacial domain, as well as in the case of anion complexation in a monophasic IL phase, water should facilitate the anion capture by the host. In fully dry conditions, however, the complexation equilibrium is expected to be far reaching. Similar kinetic problems have been recently pointed out in the case of a lanthanide salt dissolution in various ILs, showing that the systems (and especially the [BMI][PF_6] solutions) were not at thermodynamic equilibrium after two days, and that the extent of ion reaction followed the viscosity of the IL.[34]

Concerning the anion binding selectivity, the calculations show the importance of (de)solvation forces. According to the free energy calculations, the energy cost for desolvating X^- prior to complexation is highest for F^- and lowest for I^- in the IL, as in water. The binding selectivity thus stems from a compromise between strong host–guest attractions and (de)solvation energies, thus favouring F^- in the dry IL. In the humid IL, there should be no F^-/Cl^- selectivity, however, but these anions should form stronger complexes than Br^- or I^-.

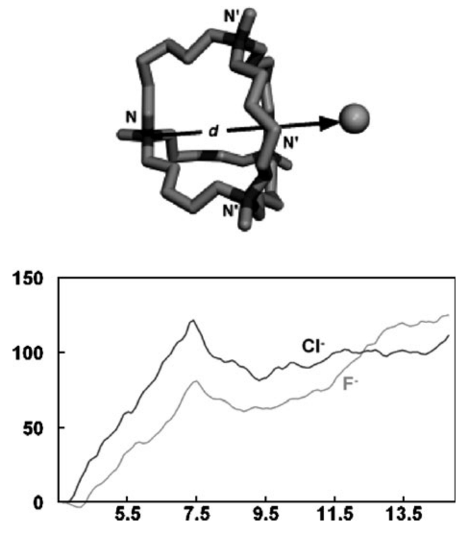

Fig. 5 *Top*: Definition of the "reaction coordinate" *d* used to monitor the decomplexation of X^- from the $Cl^- \subset L^{4+}$ complex. *Bottom*: Change in $\Delta G(d)$ (in kcal mol^{-1}) upon dissociation of F^- (grey) and Cl^- (black) from their inclusion complexes in the dry IL solution.

We note that water, useful from the kinetic point of view, may be detrimental as far as the binding selectivity is concerned. We hope that these simulation predictions will stimulate experimental studies (including thermodynamic analysis) and further theoretical investigations aiming at a better understanding of the dual solvation properties of hydrophobic ILs.

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