

## Computing the NMR Spectrum of a Bulk Ionic Liquid Phase by QM/MM Methods

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The dependence of  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts of 1-butyl-3-methylimidazolium ([bmim])-based room-temperature ionic liquids on the counteranion ( $[\text{BF}_4]$ ,  $[\text{MeSO}_4]$ ) is investigated experimentally and computationally. The local structure of the ionic liquids is investigated by means of DFT calculations of the structure of ion pairs and molecular dynamics simulations. Clusters extracted from the simulation runs are used to calculate  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts by means of QM/MM methods with various partition schemes. Proton H2 of the imidazolium ring is the most sensitive to the counteranion; its chemical shift is strongly dependent on subtle details of the arrangement of the two closest anions. It is shown that a correct spacing of signals can be attained by including the two anions closest to C2 and H2 in the QM layer.

The unique solvent properties of ionic liquids (ILs) have become a common topic of research in pure and applied chemistry.<sup>1</sup> However, the relationship between such properties and structure is still poorly understood; all evidence points to an extremely complex structure with unique features that involve both the local arrangement of constituent ions and their dynamics.<sup>2,3</sup>

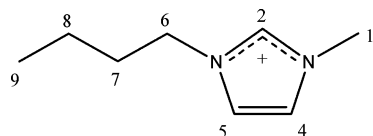
ILs based on a 1,3-disubstituted imidazolium cation (especially 1-butyl-3-methylimidazolium, [bmim]; Scheme 1) have been studied extensively by molecular dynamics (MD) simulations,<sup>2–7</sup> NMR,<sup>8–10</sup> and quantum-chemical calculations.<sup>11–14</sup>

NMR spectroscopy is an established technique for probing solvation phenomena, particularly through the influence of the environment on chemical shifts and relaxation rates,<sup>15</sup> and is therefore a natural avenue of investigation of ionic liquids.

The  $^1\text{H}$  NMR spectra of [bmim] ILs with various anions show small but easily measurable chemical shift variations.<sup>16</sup> These changes occur mostly at H2 (for which there is ample consensus of being involved in a HB-type interaction with the anion<sup>17</sup>) but are detectable for the other ring protons (H4 and H5) too, whereas the signals of the *N*-alkyl groups are quite constant. Thus, in a series of [bmim]-based ILs with different counterions<sup>18</sup> H2 is deshielded by 0.79 ppm upon going from  $[\text{PF}_6]$  to  $[\text{MeSO}_4]$  as the counterion; however, these variations ( $\delta_{\text{H2}}$  decreasing as  $[\text{MeSO}_4] > [\text{BF}_4] > [\text{Tf}_2\text{N}] > [\text{PF}_6]$ ) do not follow a clearly recognizable trend.<sup>16</sup> For protons H4,5 (which differ by less than 0.1 ppm for any given IL), the anion effect,  $\Delta\delta$ , is 0.5 ppm and follows a different pattern than H2. For *N*-alkyl protons (H6, H10),  $\Delta\delta$  is much smaller (0.2 ppm), and for H7–H9 changes are minimal ( $\Delta\delta < 0.02$  ppm).

$^{13}\text{C}$  chemical shifts are relatively less sensitive to the anion,<sup>15</sup> with a maximum  $\Delta\delta$  of 1.4 ppm at C2 and only 0.5 ppm at the other sites. Very small changes (0.2 ppm) have been observed at  $^{15}\text{N}$ .<sup>19</sup>

## SCHEME 1. Structure and Numbering of the 1-Butyl-3-methylimidazolium Cation [bmim]



DFT methods have shown a remarkable ability to predict the NMR parameters of molecular systems.<sup>20</sup> It has also been shown that in many cases success can be attained only by going “beyond static molecules”,<sup>21–23</sup> that is, dealing not only with the species of interest but also with the environment and its dynamics. For liquid phases as complex as ionic liquids this approach seems mandatory.

Hence, one is naturally led to wonder whether it is possible to predict the small changes induced by different anions. In this Communication we will show that this objective can be accomplished, provided that the IL is modeled by an extended system far beyond a simple ion pair, and its dynamic averaging is taken into account.

A DFT calculation of the chemical shifts of isolated [bmim] (see the Experimental Section) leads to the correct order of all  $^1\text{H}$  and  $^{13}\text{C}$  signals (however, for H4,5 the experimental difference is smaller than the achievable resolution, currently around 0.1 ppm).<sup>24</sup> These data confirm the known predictive power of DFT calculations but, of course, do not provide any information on the anion effect; thus, the objective of this work is to reproduce computationally the anion effect on the spacing of signals, rather than their ordering as has been done for complex natural substances.<sup>24</sup> Given the notoriously small range encompassed by  $^1\text{H}$  shifts, this is a severe benchmark for the performance of DFT methods. We will assess the quality of the various levels of calculation comparing the mean absolute errors (MAE), with  $\text{MAE} = (\sum_n |\delta_{\text{calcd}} - \delta_{\text{exptl}}|)/n$ . Because the value of  $\sigma_{\text{TMS}}$  is uncertain (see the Experimental Section), we compute MAEs for chemical shifts relative to H9 or C9, which

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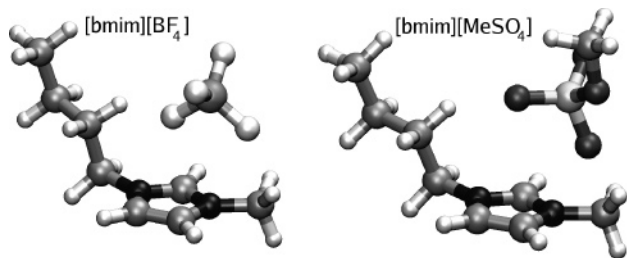
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**TABLE 1: Performance of QM/MM Methods in the Calculation of  $^1\text{H}$  and  $^{13}\text{C}$  Chemical Shifts.**

level	$\text{BF}_4$				$\text{MeSO}_4$			
	$\delta_{\text{H2}}^a$	MAE <sup>b</sup>	$\delta_{\text{C2}}^a$	MAE <sup>b</sup>	$\delta_{\text{H2}}^a$	MAE <sup>b</sup>	$\delta_{\text{C2}}^a$	MAE <sup>b</sup>
isol	6.62	0.42	122.4	3.7		0.60		3.9
ion pair	13.31	1.22	140.6	4.0	11.37	0.73	138.2	3.9
A	6.57	0.39	121.3	2.4				
B	7.38	0.22	126.5	1.3				
C	7.00	0.18	123.1	1.4	7.17	0.25	124.3	1.5
D	6.97	0.21	124.0	1.4				
E	7.45	0.12	124.9	1.5	7.84	0.20	125.4	1.3
exptl	7.83		123.9		8.38		124.1	

<sup>a</sup> Relative to H9 or C9 (ppm). <sup>b</sup> Mean absolute error (ppm) of all chemical shifts.

**Figure 1.** DFT-optimized geometry of the ion pairs. Some geometrical parameters are reported in Table S4.**Figure 2.** Spatial distribution function of the probability of finding the center of mass of  $[\text{BF}_4]$  at a given point around  $[\text{bmim}]$ . Light and dark isodensity contours correspond to a probability density of 2.5 and 9.9, respectively.

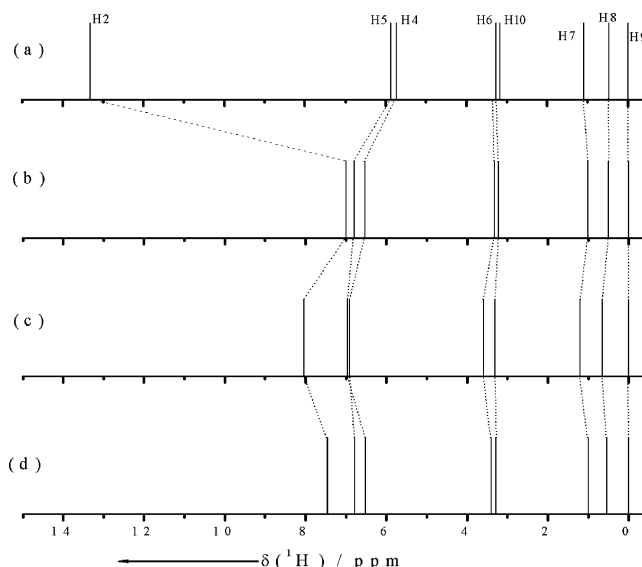
are the most shielded signals and least affected by anion (Table 1) so that  $\delta_{\text{calcd}} = \sigma_{\text{H9/C9}} - \sigma$ .

The simplest option for taking the anion into account is to consider an ion pair (Figure 1). The optimized geometries of  $[\text{bmim}][\text{BF}_4]$ ,  $[\text{bmim}][\text{MeSO}_4]$ , and  $[\text{bmim}][\text{PF}_6]$  feature the anion facing the C2–H2 bond with the F or O atoms involved in hydrogen bonds with H2, even starting from widely different initial geometries.<sup>11</sup> In the case of  $[\text{Tf}_2\text{N}]$ , the anion lies almost in the ring plane.

Interaction with a single anion causes a large deshielding of H2 and C2 and an incorrect anion effect ( $[\text{BF}_4] > [\text{MeSO}_4]$ ); the MAE is even larger than that for the isolated cation (Table 1).

This suggests that  $[\text{bmim}]$   $^1\text{H}$  shifts are affected by the local structure of the liquid to an extent that goes beyond the immediate, static surroundings of each proton. To deal with long-range and dynamic effects, we have run MD simulations of  $[\text{bmim}][\text{BF}_4]$  and  $[\text{bmim}][\text{MeSO}_4]$  and performed QM/MM calculations of NMR properties. This choice was dictated by the large anion effect observed for these two ILs and by the availability of suitable force fields.

The arrangement of anions around the cation is best visualized by a spatial distribution function (SDF) (Figure 2). Two lobes of high probability are close to H2, roughly at  $\pm 45^\circ$  with respect

**Figure 3.**  $^1\text{H}$  stick spectra of  $[\text{bmim}][\text{BF}_4]$ : (a) Ion pair; (b) level C; (c) experimental; (d) level E. Dotted lines connect equivalent sites. Chemical shifts are referred to H9.

to the imidazolium plane, each corresponding to one anion. H4,5 are faced by a lobe in the plane of the imidazolium ring.<sup>5,6</sup>

There are important differences between the cation–anion arrangement in the liquid and in the ion pairs. (a) The average distance between C2 and the anion center of mass is 3.8 Å in the liquid and 3.0–3.5 Å in the ion pairs. This effect is due to the enhanced attraction of the two ions in vacuum; an attempted optimization of  $[\text{bmim}] \cdot 2[\text{BF}_4]$  starting from a configuration close to that obtained from the SDF failed to locate a minimum close to it, owing to the strong repulsion of the two anions. (b) In the liquid phase two anions, rather than one, are close to H2. These effects call for caution when gas-phase structures are used to interpret liquid-phase data.

From the final configuration of the simulation, we extracted clusters for QM/MM calculations<sup>25</sup> of  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts according to the following partition schemes, where H and L indicate the high (QM) and low (MM) layers. The QM layer was modeled by B3LYP/cc-pVTZ<sup>24</sup> and the MM layer by means of point charges as in the force field used in the simulation;  $[\text{bmim}]$  was always in the QM layer. (A):  $[\text{bmim}]$  only (i.e., conformationally averaged); (B–D): surrounding ions (L) up to a cutoff of 6.0, 7.8, or 10.0 Å from the center of the imidazolium ring; (E): the two anions closest to C2 (H) plus surrounding ions (L) up to a cutoff of 7.8 Å. Calculations were performed at levels A–E for  $[\text{bmim}][\text{BF}_4]$ , and only at levels C and E for  $[\text{bmim}][\text{MeSO}_4]$ . The performance of each level was again assessed by the respective MAEs (Table 1). Even at level A the MAE is smaller than for the ion pair, and decreases further along B–D. For  $^1\text{H}$ , level E leads to the minimum MAE in both cases, although the ordering of H4,5 is incorrect. The results are best appreciated by stick spectra (Figure 3). For  $^{13}\text{C}$  trends are similar except that partition scheme E, tailored for H2, is not particularly good for C2.

In conclusion, even the relatively minor anion effect on the chemical shift of the H2 ring proton of  $[\text{bmim}]$  can be modeled by means of a hybrid MD-QM/MM approach where the cation and the two anions closest to H2 are dealt with at the DFT level; ion pairs are not reliable models. The remaining minor discrepancies are likely to arise from the need to use geometries based on molecular mechanics.

This accomplishment is significant in several respects: within the domain of IL chemistry, this capability measures our ability

to model ionic-liquid phases, and highlights the importance of long-range effects for understanding their behavior; more generally, it portrays the outstanding accuracy in the theoretical modeling of complex systems that can currently be achieved.

## Experimental Section

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra have been recorded as described previously.<sup>16</sup> Signal assignment, particularly of H4/5, was done by HSQC and HMBC.

Geometry optimizations of isolated ions and ion pairs were run at the B3LYP/6-31G(d,p) level and checked by vibrational analysis; coordinates are reported in the Supporting Information. NMR shielding constants ( $\sigma$ ) have been calculated at the B3LYP/cc-pVTZ level. Calculated chemical shifts are expressed by  $\delta_{\text{calcd}} = \sigma_{\text{ref}} - \sigma$ , where  $\sigma_{\text{ref}}$  is the shielding constant of H9 or C9. Because determining  $\sigma_{\text{TMS}}$  in ionic liquids would require an additional set of simulations with the appropriate force field, one can estimate  $\sigma_{\text{TMS}}$  from the linear fitting  $\delta_{\text{calcd}} = a + b\delta_{\text{exptl}}$  and  $\sigma_{\text{TMS}} = a/b$  (Table S6) from which chemical shifts can be referred to TMS. Gaussian 03 was used for DFT and QM/MM calculations.<sup>26</sup>

MD simulations were performed using MOSCITO<sup>27</sup> on a 125 ion-pair box; force fields<sup>4,28,29</sup> and simulation details<sup>7</sup> have been reported. For calculations (C), we averaged the shielding constants from all 125 clusters in the final configuration; for the other calculations, only 70 clusters were considered because the shieldings had converged already.

Experimental and calculated results are detailed in the Supporting Information (Tables S1–6, Figures S1–9).

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**Supporting Information Available:** Experimental NMR spectra in graphical and tabular form, optimized geometries and Cartesian coordinates of ion pairs, radial and spatial distribution functions, and calculated chemical shifts and stick spectra at all theoretical levels. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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