Water Solubility Trends in Ionic Liquids: QSPR Model vs. Molecular Dynamics

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KEYWORDS.

Ionic Liquids; water; Quantitative Structure-Property Relationship; Molecular Dynamics; Morpholinium; Pyrrolidinium.

ABSTRACT

The knowledge of the water solubility in ionic liquids (ILs) is an important property with an impact on the design of many physical and chemical processes, like the purification of organic compounds or the establishment of decontamination procedures. The development of methods to predict or establish solubility trends in ILs is, therefore, extremely relevant, as it may avoid expensive and time-consuming experimental procedures. In this work, we compare results of water solubility in ILs predicted by a Quantitative-Structure-Property Relationship (QSPR) model with trends found using aggregation studies in molecular dynamics (MD) simulation results. This study was performed for ILs combining the cations 1-butyl-1-methylpyrrolidinium and 1-butyl-1-methylmorpholinium, with the anions bis(pentafluoroethylsulfonyl)imide ($BETI^-$), trifluoromethanesulfonate (TF^-), and tetrafluoroborate (BF_4^-). Both methods indicated that, at 298.15 K, the water solubility in ILs was almost independent of the investigated cations. However, if the ionic liquid is composed of a hydrophobic anion, a slight increase in the mixability of the IL with water may be observed if the cation can form H-bonds. The QSPR model indicated the hydrophobic $BETI^-$ anion leads to solubilities ($x_{H2O} \sim 0.33$) approximately half of those predicted when the cations are combined with TF^- and BF_4^- anions ($x_{H2O} \sim 0.60$). The MD results suggested that this difference is essentially related to the ability of the water molecules to interact with the anion (AN). This interaction involves the formation of networks of molecules, where H_2O is completely solvated by the anion. These structures difficult the formation of interactions between water molecules, which are responsible for their segregation from solution and, therefore, to liquid-liquid phase separation. For the investigated ILs, the MD

data also suggests that the solubility trends are inversely proportional to the number of “isolated” anions relative to ···AN–H_2O–AN–H_2O··· networks.

INTRODUCTION

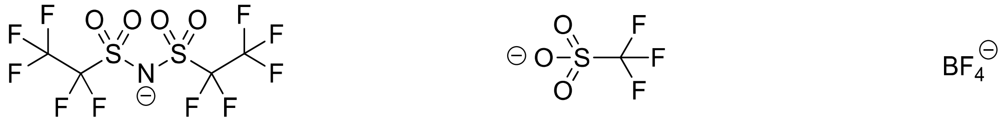
During the last decades, ionic liquids (ILs) have attracted significant research due to their potential use in diverse applications, which include, for example, liquid-liquid extractions,[1-4] carbon dioxide capture,[5,6] and as electrolytes.[7,8] The versatility of these substances rises from the interchangeability of both cations and anions that compose the ILs, allowing tunning the properties of the liquids with an application in view.[9] For this, it is important to predict the properties of newly design substances, speeding up development processes. In this scope, the solubility of water is one of the most important characteristics to be evaluated since (*i*) ILs are known to be highly hygroscopic substances and (*ii*) many processes may require a significant mixability range between water and the IL (e.g., purification of water-soluble molecules and design of decontamination processes).[10-12] Thus, methods that may be able to predict or establish water solubility trends in ILs are in demand.

In a recent publication, a Quantitative-Structure-Property Relationship (QSPR) model was proposed for predicting the solubility of water in ILs.[13] QSPR approach can be described as an application of data analysis and statistics for the development of models capable of effective quantitative prediction of compound properties or biological activities based on their structures.[14] Model development is based on three key elements: (*i*) a dataset providing both compounds chemical structures and experimental values of their biological activity or property; (*ii*) molecular descriptors needed for mathematical representation of structures; (*iii*) machine-learning algorithms for determination of the relationship between structures and activity.

The goal of the QSPR modeling is to predict the property (e.g., solubility) of new compounds that were not a part of the training or validation sets during model development. If a model is good and the new compound prediction is within the model applicability domain, then the prediction is a reliably theoretical estimate of the property for the examined compound. The strength of the QSPR approach is that it only needs to know the structure of a substance to perform predictions. The calculations usually take little time and numerous compounds can be predicted within one batch. It is worth mentioning, that the QSPR model does not simulate the solubilization process itself.

Although the computation of solubility values from molecular dynamics (MD) simulations is a non-trivial process, this theoretical approach has proved valuable in the rationalization of mixability trends.[15-17] Unlike QSPR, this method provides a molecular view of the interaction between the molecules in solution, enabling a physical explanation of the experimentally observed liquid-liquid phase diagrams. One approaches to investigate solubility trends involves the search for aggregation patterns of molecules in solution, and how these networks (or their absence) may suggest that liquid-liquid phase separation is likely to occur.[15,16] For example, if we consider the formation of water aggregates in an IL, a high probability of finding aggregates composed of many molecules of water may suggest that, most likely, the interaction between water and the IL is inefficient, and a liquid-liquid phase separation may be eminent. In turn, a high probability of finding “isolated” water molecules may suggest a favorable interaction with the IL (most often the anion), indicating that the solubility limit may be far from the composition of the investigated system.[15,16] Thus, the comparison of molecular aggregation patterns obtained for solutions with the same composition, where, e.g., the cation or anion are systematically modified, can provide information about the relative solubility trends for the investigated ILs.[15]

The QSPR model and the MD methods involve, therefore, significant different theoretical approaches (data mining vs. molecular trajectory analysis). It is interesting, therefore, to evaluate how predictions of solubility trends made by the two methods would agree for a series of ILs. In addition, since the QSPR model allows the easy and fast prediction of solubility data, enables the systematic study of families of ILs for which experimental data is not available, for comparison with MD data. Thus, in this work, combinations of 1-butyl-1-methylpyrrolidinium ($C_4C_1PY^+$) and 1-butyl-1-methylmorpholinium ($C_4C_1MO^+$) with bis(pentafluoroethylsulfonyl)imide ($BETI^-$), trifluoromethanesulfonate (TF^-), and tetrafluoroborate (BF_4^-), were investigated (Figure 1). This selection aimed to study (*i*) how changes in ammonium-based cations in terms of their ability to form hydrogen bonds (H-bonds), and (*ii*) anions with different hydrophobic and hydrophilic properties, influence the solubility of water in ILs.



Bis(pentafluoroethylsulfonyl)imide ($BETI^-$)

Trifluoromethanesulfonate (TF^-)

Tetrafluoroborate (BF_4^-)

1-butyl-1-methylmorpholinium ($C_4C_1MO^+$)

1-butyl-1-methylpyrrolidinium ($C_4C_1PY^+$)

Figure 1. Molecular structures of the ionic liquids ions combined in this work for evaluations of solubility trends.

METHODS

QSPR Approach. The datasets for the development and validation of the QSPR models for predicting water solubility in ILs from the previous article were used to find ILs with either very high or very low capacity to solubilize water.[13] The definition of high solubilizing capacity is as follows: the IL must be present in either test or external test of the ChSi water in the IL model and it must have a weight fraction of water ≥ 0.1, both for experimental and predicted values. The low solubilizing capacity was defined as the weight fraction of water in IL < 0.01.

The ChSi is a Random Forest regression model[18] that uses ChemAxon cxcalc[19] and Simplex representation of molecular structure (SiRMS) descriptors.[20] Solubility values of the model are predicted as the cubic root of the weight fraction of water in ILs, which were then converted to molar fraction. More information about model specifications may be found elsewhere.[13]

Four ILs satisfied the criteria for high solubilizing capacity: 1-methyl-3-octylimidazolium tetrafluoroborate, 1-octyl-3-methylimidazolium trifluoromethanesulfonate, 1-butyl-1-methylpyrrolidinium tricyanomethanide, 1-butyl-1-methylmorpholinium tricyanomethanide. These ILs are composed of 3 types of cations and 3 types of anions, with 4 combinations explored and the other 5 combinations not previously observed or predicted (see Table S1 given as supporting information). Since imidazolium based ILs are studied relatively well, it was decided to focus on unexplored combinations of morpholinium and pyrrolidinium. As for low solubilizing capacity, the number of ILs that satisfy the criteria was so high that it was only decided to select one anion for the comparison, namely BETI$^-$ (Figure 1). The cation side chains were standardized to be 1-butyl-1methyl residue, to cancel out its impact on the solubility. As a results, the solubility of water in 6 ILs were predicted by the QSPR model:

$[C_4C_1MO][BETI]$, $[C_4C_1MO][BF_4]$, $[C_4C_1MO][BETI]$, $[C_4C_1PY][TF]$, $[C_4C_1PY][BF_4]$, and $[C_4C_1PY][BETI]$. The chemical structure of the ILs was encoded in SMILES format and standardized according to the procedure previously described.[13] QSPR prediction was done for a temperature of 298 K and an implicit atmospheric pressure of 1 bar.

Molecular Dynamics (MD) Simulations. All simulations were performed using GROMACS 2019.4.[21] The initial system configuration was obtained by a random distribution of 500 ion pairs of ionic liquid with 167 water molecules inside a simulation box with $\rho = 0.2$ g·cm^{-3}, to produce solutions with $x_{H2O} = 0.25$. This concentration was selected to avoid the simulation of metastable phases, as it corresponds to a mole fraction ~10% smaller than the lower solubility value predicted by the QSPR model (see below). Before the production runs, the starting configurations were equilibrated by performing several 5 ns simulations, where the temperature, T, and pressure, p, of the system were varied as follows: (*i*) $T = 400$ K; $p = 100$ bar; (*ii*) $T = 298$ K; $p = 100$ bar; (*iii*) $T = 298$ K; $p = 1$ bar. The final step was repeated several times to obtain a constant system density and internal energy. The system temperature and pressure were controlled by employing a Nose-Hover thermostat (relaxation time constant of 5 ps), and a Parrinello-Rahman barostat (relaxation time of 20 ps; compressibility of 4.5×10^{-5}), respectively. After equilibration, a production stage of 40 ns was made at $T = 298$ K and $p = 1$ bar, recording the system configuration every 100 ps for analysis. A cutoff distance of 1.5 nm was used in all calculations and the particle-mesh Ewald technique was used to account for interactions beyond this limit. A timestep of 2 fs was used in all MD runs. The input files for the simulations were prepared using Packmol[22] and DLPGEN 3.0,[23] and the trajectory analysis was made using the software package AGGREGATES.[24] For the aggregation studies it was considered that two molecules belong to the same aggregate (are in contact with each other) if: (*i*) the distance between two adjacent water oxygen atoms are closer than 3.5 Å; (*ii*) the distance between the oxygen atom of a water molecule and the center of mass of $BF4^-$ and TF^- are smaller than 4.6 Å and 5.5 Å, respectively; and (*iii*) if the distance between the nitrogen atom of $BETI^-$ and the oxygen atom of water are smaller than 6.0 Å. The previous connectivity criteria were established following the procedures previously described.[25]

The force field selected for the simulations was based on the CL&P[26,27] and SPC/E[28] parametrizations for the ILs and water molecules, respectively. The water model used in the simulations was selected based on previous works, which suggested that these models can accurately capture the structure of IL aqueous solutions.[17,29] Since the CL&P force field does not include morpholinium cation, a new parametrization was developed for this ion. For this: (*i*) both van der Waals and intermolecular potential functions were borrowed from the OPLS-AA force field;[30] (*ii*) the atomic point charges were computed by the ChelpG[31] methodology at the MP2/aug-cc-pVDZ[32-37] level of theory using Gaussian 09,[38] ensuring that the obtained distribution was compatible with the CL&P model.[39] The final parameterization is given as supporting information, and all input files are available for download elsewhere.[40]

RESULTS AND DISCUSSION

The obtained results for QSPR models are shown in Table 1. The predicted data for the $C4C1PY^+$ and $C_4C_1MO^+$ based ILs present similar solubilities when combined with the same anion. This suggests that the oxygen atom in the morpholinium cation, which could facilitate the solubilization of water molecules via hydrogen bonds formation, has little influence on water's solubility of the IL, particularly when the cation is combined with the hydrophilic anions BF_4^- and TF^-. This conclusion is in line with previous experimental and theoretical results found for other ionic liquids, which suggests that the solubility of water in ILs is largely influenced by the interaction of the anion with water.[41-43] In addition and as expected, the data in Table 1 shows that the ILs containing the hydrophobic $BETI^-$ anion have the smaller predicted solubility.

To the best of our knowledge, no experimental water solubility data is available for the investigated ILs. Thus, it would be interesting to compare the results in Table 1 by an independent method. It is difficult to use MD simulation methods to quantitively compute the solubility of water. Still, several studies demonstrated this methodology may be used to rationalize solubility trends from the analysis of the molecular aggregation patterns in solution.[15-17] Thus, in this work, MD simulation data was explored as a qualitative approach for comparison with the QSPR results.

Table 1. Solubility of water predicted by the QSPR model for different cations–anions combinations. Data in water molar fractions.

	$BETI^-$	BF_4^-	TF^-
$C_4C_1PY^+$	0.31	0.60	0.61
$C_4C_1MO^+$	0.36	0.59	0.61

The solubility trends were initially evaluated by studying the ability of water (W) to form molecular networks. Figure 2 shows the probability of finding clusters containing a given number of water molecules in the investigated mixtures. As mentioned above, all MD runs were performed for solutions with a water molar fraction of $x_{H2O} = 0.25$, by placing 500 ion pairs and 167 water molecules in the simulation boxes. The obtained results for the pyrrolidinium-based ILs revealed that, in [C_4C_1PY][BETI], water tends to form larger structures than in [C_4C_1PY][BF_4] and [C_4C_1PY][TF] (Figure 2). This suggests a larger tendency of water to segregate from the solution in the earlier case. Also, the probability of finding water molecules in the simulation box completely solvated by [C_4C_1PY][BETI] ("aggregates" of size one) is only 25 %. In contrast, in the case of [C_4C_1PY][BF_4] and [C_4C_1PY][TF], 55 % and 65 % of the water molecules are in "structures" where they do not contact with each other. This suggests more favorable IL-W interactions in the latter cases. Thus, in line with the predicted solubility data in Table 1, the MD results suggest that [C_4C_1PY][BETI] must have the lower solubility of these three compounds. In turn, the aggregates of water in [C_4C_1PY][BF_4] and [C_4C_1PY][TF], show similar probability distributions, suggesting similar water solubilities in these two ILs, as concluded from the QSPR values. Similar conclusions are obtained from the probability distributions obtained for the morpholinium based ILs (Figure 2), where, for example, the probability of finding "aggregates" composed by only one water molecule varies as [C_4C_1MO][BETI] (34%) < [C_4C_1MO][BF_4] (60%) < [C_4C_1MO][TF] (66%).

From the analysis of Figure 2, it is also possible to conclude that the aggregation patterns of

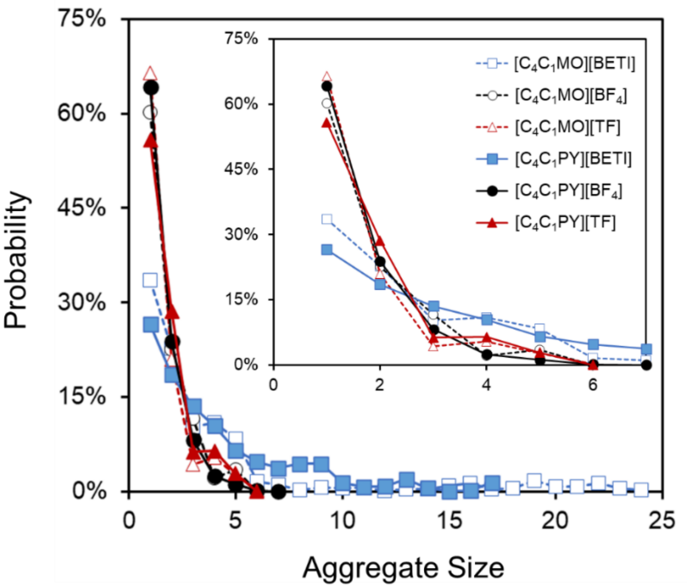


Figure 2. Probability of finding aggregates of water with a given size, measured as the number of water molecules in the structure. All results were obtained for solutions with a molar fraction of x_{H2O} = 0.25 in pyrrolidinium (C_4C_1PY; closed symbols and solid lines), and morpholinium-based (C_4C_1MO; open symbols and dash lines) ionic liquids.

water are almost independent of the cation, reinforcing the idea that the solubility in the investigated substances is primarily influenced by the interaction of water with the anion. Previous DFT and spectroscopic studies, where several imidazolium and (protic) ammonium-based cations were mixed with different anions, suggested that the ability to form H-bonds with the anion is crucial for the mixability of an IL with a solvent.[42,44-48] Thus, it could be expected that two ILs containing cations with and without capabilities to form hydrogen bonds could also impact the amount of water that is tolerated in the mixture. In fact, a recent study has shown that it is possible to significantly improve the mixability of bistriflimide-based ionic liquids with alcohols and water by modifying the polar alkyl chain of the cation with hydroxyl groups.[49] Still, as can be observed in table 1, the combination of $C_4C_1PY^+$ or $C_4C_1Mo^+$ with the hydrophilic BF_4^- and TF^- has apparently little impact on the IL mixability with water. Only when the cations are combined with the hydrophobic $BETI^-$ anion, a slight water solubility increase is noted with $C_4C_1Mo^+$ (x_{H2O} = 0.36) relative to $C_4C_1PY^+$ (x_{H2O} = 0.31). This suggests that the ability of the cation to form H-bonds is only important when is combined with a hydrophobic anion. The analysis of the radial distribution functions computed between the oxygen atom of the morpholinium cation and the oxygen atoms of the water molecules, Figure 3, supports this hypothesis. As can be observed in this image, only in the case of $[C_4C_1MO][BETI]$, a relevant probability of finding the two oxygen atoms at close distances (2.85 Å) is observed, suggesting the formation of some hydrogen bonds in this mixture.

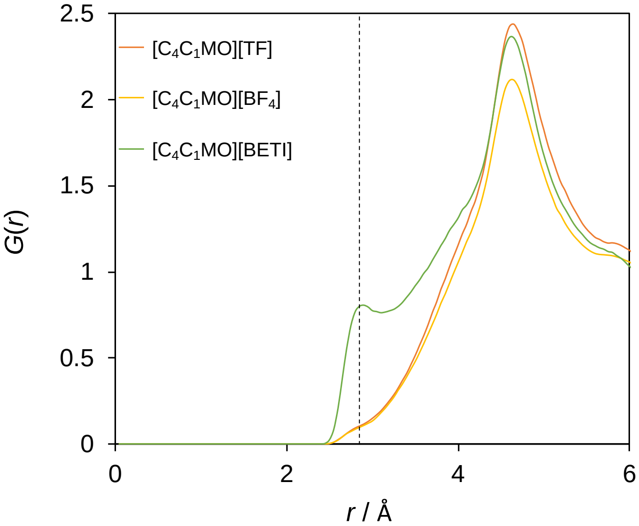
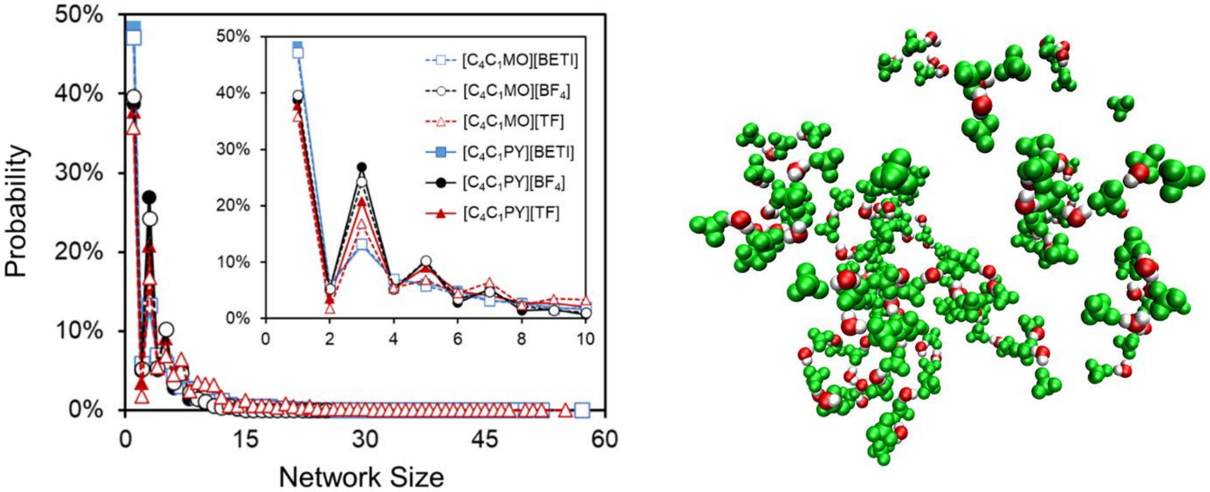


Figure 3. Radial distribution functions computed between the oxygen atom of the morpholinium cation and the oxygen atoms of the water molecules, in the presence of different anions. The vertical dash line denotes the oxygen-oxygen distance of 2.85 Å, which is compatible with the formation of hydrogen bonds.

To further understand the structure of these mixtures, the interaction between the anions and water was also studied. For this, the MD trajectories were analyzed for networks of anions (AN) in alternating positions with water molecules (W), to form structures of the type AN-W-AN-W.[24] Since the systems have the same composition, for each series containing the same cation, any difference in solubility will necessarily reflect changes in the interactions between the anions and water. The obtained results are given in Figure 4a. The analysis of this figure shows that most of AN and W do not contact each other (networks of size 1). This is due to the excess of anions in the simulation box relative to water, so that, more than 98% of these "isolated" molecules were found to be anions. In turn, in all cases, only a small number of aggregates correspond to dimeric units, and the percentage significantly grows for aggregates containing three molecules. Figure 4a also shows that the formation of aggregates composed of an odd number of molecules is always more likely than one of similar size but with an even number of units. Combining this information with the data in Figure 2, i.e., a significant number of water molecules are isolated from each other, suggests that the water molecules are likely to be surrounded by two anions in a sandwich-like structure. This type of organization can be easily observed in Figure 4b. Thus, for example, the large probability of finding trimers in solution reflects the formation of structures composed of two anions surrounding one water molecule. The fact that $BETI^-$ containing ILs present the lowest probability for the formation of this type of structure proposes, therefore, a less favorable interaction between this anion and water, which can limit the solubility of water in the corresponding ILs. It is interesting to note in Figure 4a that in the ILs mixtures with the anions $BETI^-$ and TF^-, larger AN-W networks can be noticed than in the mixtures containing BF_4^-. This could suggest a favorable interaction between water and $BETI^-$ and TF^-, than with



(a) (b)

Figure 4. (a) Probability of finding networks of anions and water molecules in alternating positions, as a function of the number of elements in the structure. (b) Snapshot of the BF_4^- (in green) and water (in red and white) molecules networks in the simulation box of a mixture of [C_4C_1MO][BF_4] with H_2O (for simplicity, all cations and all anions not in contact with water molecules were removed from the image). All results correspond to solutions with a molar fraction of water $x_{H2O} = 0.25$.

BF_4^-, in disagreement with the data in Table 1. Still, the probability of finding networks with more than 15 elements is smaller than 0.01 %. Thus, since these networks are only rarely observed during the simulation, likely, they do not have a significant impact on the average properties of the solutions.

The data in Figure 4a also shows that the number of anions that do not contact with water molecules and vice-versa ("Networks" with only one element), varies in order: (*i*) [C_4C_1PY][BETI] (47%) >> [C_4C_1PY][BF_4] (39%) > [C_4C_1PY][TF] (36%); and (*ii*)

$[C_4C_1MO][BETI]$ (48%) >> $[C_4C_1MO][BF_4]$ (39%) > $[C_4C_1MO][TF]$ (38%). These trends are inversely related to the predicted solubility data in Table 1: (*i*) $x_{H2O}([C_4C_1PY][BETI]) = 0.31 \ll x_{H2O}([C_4C_1PY][BF_4]) = 0.60 < x_{H2O}([C_4C_1PY][TF]) = 0.61$; (*ii*) $x_{H2O}([C_4C_1MO][BETI]) = 0.36 \ll x_{H2O}([C_4C_1MO][BF_4]) = 0.59 < x_{H2O}([C_4C_1MO][TF]) = 0.61$. These results suggest that, if simulation data obtained for solutions of ILs with the same molar fractions are analyzed in terms of the probability of finding isolated anions from water molecules, the obtained result may be used in a qualitative evaluation of water solubility trends in ILs.

CONCLUSIONS

The solubility of water in six ionic liquids was investigated in this work by using two different theoretical approaches: a QSPR model and MD simulation results. From a qualitative point of view, a good agreement between the two methods was found.

ILs composed by cations with ($[C_4C_1MO]^+$) and without ($[C_4C_1PY]^+$) hydrogen bonding formation abilities were investigated in this work, to evaluate how this capability may be used to modify the water solubility in ILs. The predicted values by the QSPR model shown that, when the previous cations are combined with the same anion, the solubilities of the resultant ILs do not change significantly. However, when combined with a hydrophobic anion, a slight increase in the mixability of the IL with water may be observed if the cation can form H-bonds.

A significant effect was found in the mixability of water with the ILs when the anions in the mixture were exchanged. The MD results proposed that the water solubility trend was inversely related to the number of anions that do not contact the water molecules. This behavior was attributed to the ability of the anions to separate water molecules from each other, preventing their segregation from solution. As a result, from the comparison of mixtures with the same composition, the smaller the number of “isolated” anions, the larger the number of water molecules that can be included in the investigated ionic liquids.

ASSOCIATED CONTENT

Supporting Information. Section 1: ion type combinations considered for the QSPR Model. Section 2: details of the force field of the 1-butyl-1-methylmorpholinium cations developed in this work. Table S1 with the ion type combinations studied for the QSPR Model. Table S2 with the force field parameters developed for 1-butyl-1-methylmorpholinium. Figure S1 with the labeling scheme used in the development of the 1-butyl-1-methylmorpholinium cation force field.

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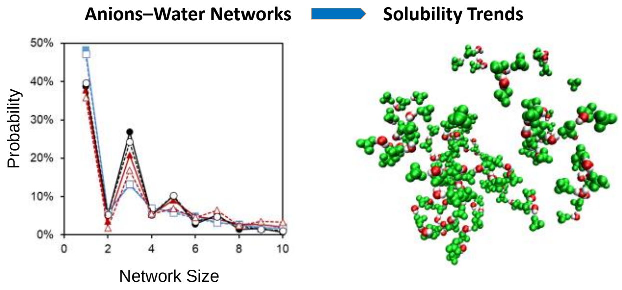
TOC Graphic


Anions–Water Networks
Solubility Trends
50%
40%
30%
20%
10%
0%
Probability
0
2
4
6
8
10
Network Size