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Solvent effect on a model S_NAr reaction in ionic liquid/water mixtures at different compositions†

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The reaction of phenyl 2,4,6-trinitrophenyl ether and piperidine was kinetically evaluated in $BMIMBF_4$/water mixtures as the reaction media. This study shows the dramatic effect of the mixture composition on the reacting pair and its reaction rate, highlighting two strongly demarcated zones. The first one, rich in water, is characterized by strong variations in the rate coefficient values, suggesting the presence of preferential solvent effects in the aqueous phase. The second zone shows high rate coefficient values independent of the composition of the solvent mixture, suggesting predominant "anion" solvent effects. These results were validated using fluorescence spectroscopy and the Kamlet–Taft parameter.

Introduction

In the last few decades, the hydrogen bond (HB) effect has been a subject of active discussion in nucleophilic aromatic substitution (S_NAr) reactions.[1–3] Bernasconi *et al.* explained the reactivity trends based on the existence of an intramolecular HB between the hydrogen atom of a nucleophile and the *o*-NO_2 group of a substrate (electrophile).[4] Recently, this HB effect was followed along an intrinsic reaction coordinate (IRC) profile showing that it promotes the activation of both the electrophile and the nucleophile.[5] HB complexes in the transition state (TS) structures of a reaction enhance the reactivity of the reacting pair by diminishing the activation barriers.[1,5,6] This effect will be present in electrophiles without NO_2-groups in their structures and involved in S_NAr reactions.[7] On the other hand, the HB effect could be involved in solute–solvent interactions playing a key role in the chemical reactivity beyond the stabilization of species along the potential energy surface (PES). These specific interactions could produce catalytic effects and/or changes in the rate determining step (RDS) of reaction mechanisms.[8] Note that, in this context, the solute is considered as the reacting pair. Solute–solvent interactions are much more complex in solvent mixtures than in pure solvents. Therefore, the study of solvent mixtures opens up the possibility to evaluate: (i) preferential solvation and/or iso-solvation phenomena;[8–10] (ii) properties and structural changes and (iii) catalysis. Preferential solvation is defined as the difference between the local and bulk composition of solutes with respect to the composition of solvents in a binary mixture.[8,10,11–14] Iso-solvation has been introduced as a concept describing the composition of a mixture in which the solute under consideration is solvated, approximately, by an equal number of co-solvent molecules in the solvent mixture.[15–17] To date, studies based on mixtures of solvents have been broadly published. These works involve mixtures of: (i) conventional solvents (CS),[8–10,18] (ii) CS/ionic liquids[19,20] and (iii) ionic liquids.[21–23]

Ionic liquids are salts with a low melting point, usually liquids at room temperature (RTILs).[24,25] RTILs are technological materials that provide an alternative to CSs for both scientific and industrial purposes, taking advantage of their potential as novel reaction media.[24–26] The presence of water or CS in RTILs can modify their physical and chemical properties. For instance: density, vapour pressure, viscosity, electrical conductivity, solvation and solubility properties. RTILs are hygroscopic and they can absorb water from the atmosphere.[27,28] Seddon *et al.*[29] pioneered the study of the effect of impurities and additives in RTILs based on imidazolium cations. They evidenced a change in the properties of these RTILs with the molar fraction of added water. The relevant role of HBs in RTIL/water mixtures and their involvement in the structural changes produced when the RTILs were mixed with a co-solvent were also reported by Seddon *et al.*[28] Linden-Bell *et al.*[30] showed by molecular dynamics simulations that, in mixtures of water/dialkylimidazolium RTILs, low quantities of water behave as small and independent clusters, while in mixtures with high quantities of water, a continuous water network appeared, thereby changing the properties of the mixtures. Fazio *et al.*[31] performed a complete experimental analysis on RTIL/water mixtures, showing that: (i) in the presence of low quantities of water in the mixtures, these water molecules established interactions with the anionic moiety of the RTIL, weakening the polar network produced by the cation–anion interactions of the RTIL and building some clusters

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embedded in the polar network. Note that this effect occurs prior to saturation of the sites of the anion available for establishing HBs with the water molecules; (ii) high quantities of water caused local aggregation of the water molecules inside the polar network because of the gradual loss of cation–anion interactions in the RTIL, producing a saturation of the sites on the anionic moiety available to establish a HB and displacing the cationic moiety. This effect produces repulsive interactions between the cation moieties, weakening the structural network of the RTIL, allowing water–anion moiety and water–water interactions by HBs.

The aforementioned studies led us to analyse the solvation effects based on the reactivity of the reacting pair expressed in terms of the nucleophilic rate coefficients for a S_NAr reaction in a range of aqueous mixtures of 1-butyl-3-methyl imidazolium tetrafluoroborate ($BMIMBF_4$). A S_NAr reaction involves a nucleophilic addition followed by elimination of a leaving group (LG) and it requires the presence of at least one strong electron-withdrawing substituent[1] in the ring of the electrophile to stabilize the intermediate, called the Meisenheimer Complex (MC).[4,7,8,32] The first step of the reaction mechanism corresponds to the formation of a MC. In the second step, the LG detaches after an intramolecular proton transfer (RLPT) from the nucleophile (see more details ahead).[10,32] The studied S_NAr reaction in this work takes place between phenyl 2,4,6-trinitrophenyl ether (PTNPE) and piperidine, as depicted in Scheme 1. This reaction was revisited from a previous work, where piperidine was the only amine of a series of secondary alicyclic amines sensitive to solvation effects in ethanol/water mixtures, establishing a specific electrophilic solvation by the water molecules of the mixtures.[10] The main goals of this work are: (i) to determine the relevance of the HB on the studied reaction at several RTIL/water compositions and its relationship with catalytic processes or solvation phenomena; (ii) to determine the behaviour of each composition using probes in order to sense the micro-domains in the studied solvent mixtures and its effect on the reaction mechanisms, solvent effects or catalytic processes for the studied reaction.

Results and discussion

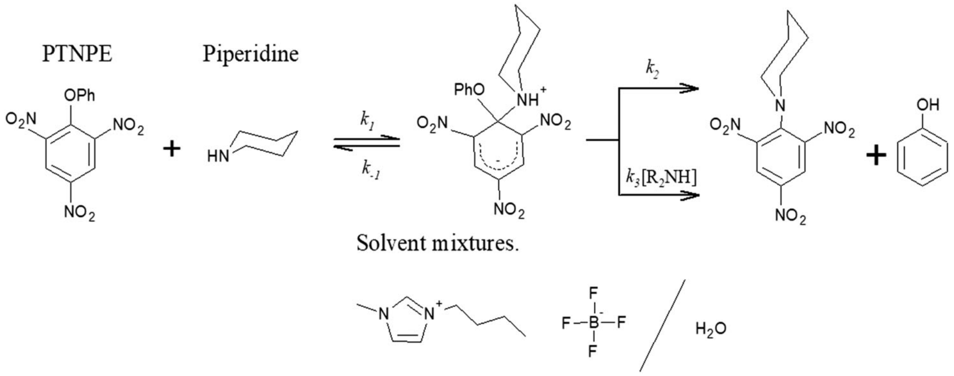
In ethanol/water mixtures, the studied reaction followed a stepwise mechanism, where the loss of a proton from the MC is the rate determining step (*i.e.*, RLPT mechanism) instead of the expulsion of the LG, followed by a dual secondary step: catalyzed and non-catalyzed routes (see Scheme 2).[10] Under the experimental conditions of the studied reaction, a single product named 1-(2,4,6-trinitrophenyl)piperidine was obtained and monitored by UV-vis spectrophotometry. The plots of k_{obs} *vs.* free piperidine concentration for the studied reaction in the mixtures of $BMIMBF_4$ with water were in accordance with a RLPT mechanism. More details are given in Tables S1–S7 in the ESI.† These plots were in accordance with a second order polynomial equation (eqn (2)) derived from eqn (1), assuming that $k_2 + k_3[N_F] \ll k_{-1}$, where $K_1 = k_1/k_{-1}$.

$$k_{\text{obs}} = \frac{k_1k_2[N_F] + k_1k_3[N_F]^2}{k_{-1} + k_2 + k_3[N_F]} \tag{1}$$

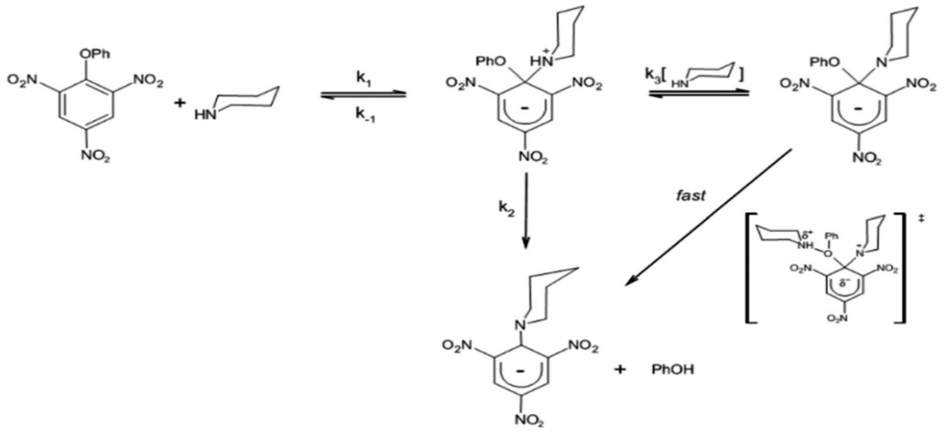
$$k_{\text{obs}} = K_1k_2[N]_F + K_1k_3[N]_F{}^2 \tag{2}$$

The kinetic data were fitted with eqn (2). The resulting curves are shown in Fig. S1–S7 in the ESI.† According to Scheme 2, the reaction proceeds through two intermediates (MC1 and MC2) corresponding to a zwitterionic adduct and its deprotonated form, respectively. Table 1 summarizes all the kinetic data determined at different compositions of $BMIMBF_4$/water in each mixture. Note that the contribution of the non-catalyzed route is negligible (to promote the LG departure) and K_1k_3 constants bear all the kinetic weight (to favor the stabilization of MC2). This result may be traced to the presence of a second molecule of amine that could establish a more favorable interaction with MC1 compared to that of the solvent molecules. Then, the plot of $k_{\text{obs}}/[N]_F$ *vs.* $[N]_F$ is linear if the reaction proceeds as in Scheme 2.[33] Therefore, all the kinetic data for the $BMIMBF_4$/water mixtures follow the catalyzed route, thereby highlighting the key role of the HB interaction between the amine and the solvent.[10]

Fig. 1 shows the relationships between the kinetic data (K_1k_3) and the composition of the solvent mixtures expressed in molar fraction (χ) of $BMIMBF_4$ in the mixtures. This figure shows two strongly demarcated zones. The first one is a zone rich in water in the range of compositions between 0 to 0.2 molar fraction, characterized by strong variations in the rate coefficient values in this narrow range of compositions, suggesting the beginning of a preferential solvation process.[8,10] The second zone



Scheme 1 General mechanism of the studied S_NAr reaction between phenyl 2,4,6-trinitrophenyl ether and piperidine in $BMIMBF_4$/water mixtures.



Scheme 2 RLPT mechanism of the reaction between piperidine and phenyl 2,4,6-trinitrophenyl ether in the studied mixtures.

Table 1 Values of K_1k_2 and K_1k_3 for the studied reaction of each $BMIMBF_4$/water mixture at 25 °C

$\chi_{BmimBF4}$	K_1k_2 (M^{-1} s^{-1})	K_1k_3 (M^{-1} s^{-2})
0.000	1.75 ± 0.19	240.53 ± 10.93
0.030	0	661.29 ± 67.22
0.086	0	752.58 ± 48.71
0.150	0	1006.1 ± 84.60
0.220	1.73 ± 0.86	1162.55 ± 97.91
0.540	0	1186.3 ± 92.40
0.790	0	1209.9 ± 22.46
1.000	0.20 ± 0.33	1293.81 ± 99.90

The values accompanying K_1k_2 and K_1k_3 correspond to the error associated with the intercept and slope, respectively, to obtain these values. More details are given in the ESI.

associated with this figure corresponds to a plateau, suggesting that the rate coefficient values are independent of the composition of the solvent mixture. The response obtained at $\chi \leq 0.2$ suggests that the anionic moiety is establishing a HB interaction with the amine, promoting the strength of the nucleophile and improving the reactivity of the studied substrate. This fact also suggests that in this composition range, preferential solvation is taking place upon addition of $BMIMBF_4$. The second zone, $\chi \geq 0.2$, shows a catalytic effect exerted by the RTIL. However, the rate coefficient values are in a narrow range of variation.

In order to find an explanation for the observed kinetic behavior and its relationship with the preferential solvation proposed in the zone close to $\chi \leq 0.2$, a complete study of basicity based on the Kamlet–Taft (KT) model was performed.[34,35] More details are given in Table S8 in the ESI.† Fig. 2 shows the relationship between β and $\chi BMIMBF_4$. The β parameter of the KT model is related to the ability of the solvent to accept a HB. Note that in the first part of Fig. 2, there is an improvement in the β values. After $\chi \geq 0.2$, the parameter β shows high values that are practically constant and close to those obtained for pure $BMIMBF_4$. Note that Fig. 2 shows a similar trend to Fig. 1. However, the second experiment is related only to the environment, it does not contemplate the reacting pair. This fact suggests a competition between the water molecules and the RTIL anion moiety to establish a HB. As shown in Fig. (1 and 2) and considering $\chi \leq 0.2$, this bond promotes the ability of the oxygen atom of the water molecules to link the hydrogen atom of the amine, enhancing the strength of the nucleophile, which is observed through the increase in the rate coefficients and the increased β values, respectively. However, if the amount of RTIL

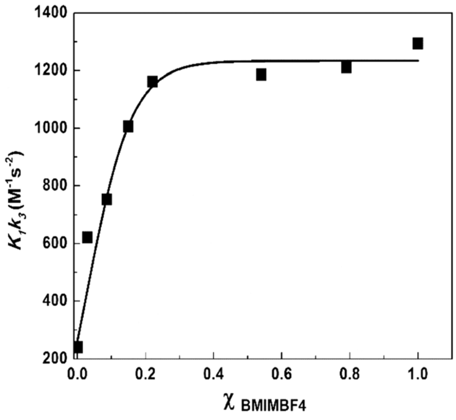


Fig. 1 Plot of K_1k_3 *vs.* molar fraction with to respect $BMIMBF_4$ in $BMIMBF_4$/water mixtures.

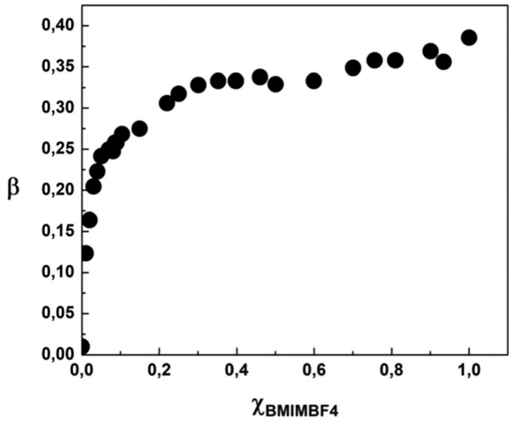


Fig. 2 Plot of K_1k_3 *vs.* the parameter β of Kamlet–Taft at different compositions of the $BMIMBF_4$/water mixtures.

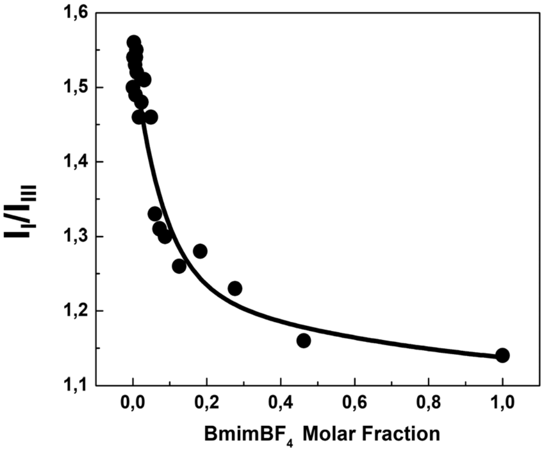
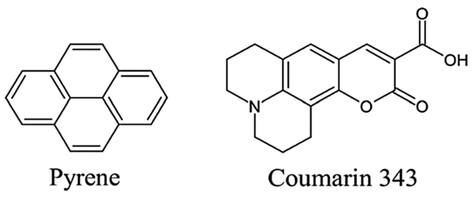


Fig. 3 Relationship between the I_1/I_3 emission intensity ratio and the composition of $BMIMBF_4$ in the $BMIMBF_4$/water solvent mixtures.

increases in the mixtures ($\chi \geq 0.2$), the effect is constant due to a lower degree of freedom of the water molecules to bond the amine and the saturation of the anionic sites by the RTIL cations.

Based on the previous analysis, a second goal was contemplated in this work in order to analyze the features of each microenvironment given by the composition of the solvent mixtures, specifically close to borderline compositions ($0.2 \leq \chi \geq 0.2$). Fig. 3 shows the relationship between the pyrene I_1/I_3 emission intensity ratio and the $BMIMBF_4$ composition in the solvent mixtures. See details in Table S9 in the ESI.† Pyrene (Py) is one of the most used fluorescent probes for the characterization of polarity[36] in both homogeneous and heterogeneous environments (Scheme 3 shows the chemical structure of pyrene). The polarity scale based on Py fluorescence is defined by the I_1/I_3 emission intensity ratio, where I_1 corresponds to the $S_1(\nu = 0)$-$S_0(\nu = 0)$ transition, which undergoes an increase in its intensity in polar environments, and I_3, associated with the $S_1(\nu = 0)S_0(\nu = 1)$ transition, insensitive to polarity, derived from the hyperfine structure of Py fluorescence spectra.[36]

The change in the I_1/I_3 ratio observed in Fig. 3 ranges from 1.55 (pure water) followed by a steep decrease to a value of 1.28 at a molar fraction of $BMIMBF_4$ close to 0.2. Note that at $\chi \leq 0.2$, the polarity of the mixtures diminishes dramatically (0.30 u.e.) with the addition of the RTIL, in accordance with the decrease in the water content of the mixture. Beyond $\chi \geq 0.2$, the variation in the I_1/I_3 emission intensity ratio is negligible (0.05 u.e.), reaching a value of 1.15 in pure $BMIMBF_4$, equivalent to the polarity evaluated in ethanol (I_1/I_3 = 1.10) in accordance with previous reports that show the polarity of the RTILs becoming close to that shown by alcohols.[37] The kinetic response is in accordance with the polarity study, suggesting that close to χ = 0.2, there is a borderline regime, where the properties of the mixtures are different or change. For instance, $\chi \leq 0.2$ is attributable to reaction media with high degrees of freedom that are more susceptible to establishing a HB. On the other hand, $\chi \geq 0.2$ suggests minor possibilities to establish a HB with compositions rich in $BMIMBF_4$. Note that in each extreme zone, the probabilities of interactions are: $H_2O(H)$–BF_4^- and $BMIM^+$–BF_4^-, respectively, highlighting the key role of the anion moiety of the RTIL in each mixture. In order to analyze the anion effect (BF_4^-) on the polarity of the mixtures, experiments based on the absorbance change of coumarin 343 (C343) in $BMIMBF_4$ and pure water and solutions at different concentrations of $NaBF_4$ in water were carried out. Scheme 3 shows the chemical structure of C343 and data are given in Table S10 in the ESI.† In the first step of this experiment, the whole range of $BMIMBF_4$/water mixtures studied was considered. However, each χ showed the same absorption wavelength, except for very high diluted mixtures. See Table S11 in the ESI.† This fact might suggest that: (i) the composition of the solvation shell close to the probe will not correlate linearly with the composition of the solvent bulk or/and (ii) the anionic moiety of the RTIL will be associated with an anion-rich solvation shell surrounding the probe. In order to evaluate specific interactions between C343 and the BF_4^- moiety, UV/vis absorption analysis of C343 in aqueous solutions of $NaBF_4$ was carried out. Fig. 4 shows the absorption maxima of C343 as a function of the ratio between the C343 and $NaBF_4$ concentrations. C343 belongs to a family of 7-aminocoumarin derivatives[38] that has been used extensively as laser dyes and in studies regarding solvation dynamics in different media.[39] The most important properties associated with C343 are: rigidity, strong radiative rates, solubility in aqueous and organic media and high solvatochromism where its absorption and emission spectra display strong dependence



Scheme 3 Structures of pyrene and coumarin 343.

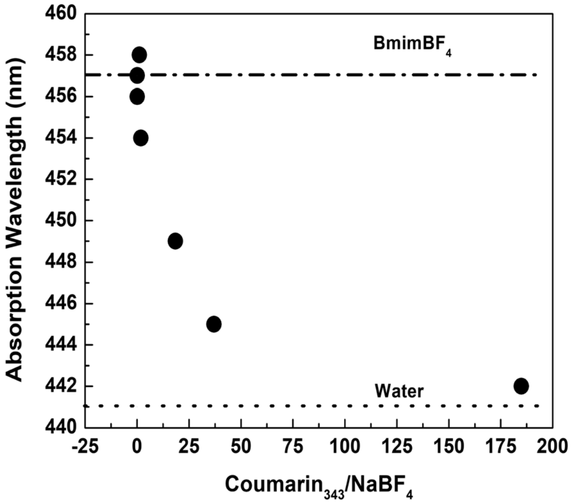


Fig. 4 Absorption maxima of coumarin 343 as a function of the ratio between the probe and $NaBF_4$ concentrations. The segmented lines indicate the maximum absorption wavelength of the probe measured in water and $BMIMBF_4$, respectively.

on the environment.[37,38] The solvatochromic behaviour of C343 is influenced by the Kamlet–Taft parameters denoted by: (i) partial polarizability (π^*) and (ii) high sensitivity to β. This sensitivity of the C343 molecule towards the β parameter is increased upon its excitation due to a weakened intramolecular HB established between the carboxylic and ester groups of C343.[40] Fig. 4 shows the maximum absorbance wavelength (λ_{abs}) for pure $BMIMBF_4$ at 457 nm, while that in pure water is observed at 441 nm. Based on the relationship between C343 and the β parameter, it is possible to analyse the micro-environments produced by the compositions of the mixtures.

Note that in Fig. 4, at high concentrations of $NaBF_4$ in water (lower C343/$NaBF_4$ ratios), the probe senses a similar polarity to that of a pure RTIL. The absorption spectra of C343 at these ratios show an important shift towards longer absorption wavelengths. At a ratio of C343/$NaBF_4$ equal to 1.1, the wavelength of the absorption maximum (458 nm) matches the one measured for pure $BMIMBF_4$ (457 nm). This result enhances the influence of the "anion effect" on the solvation shell. Inversely, decreasing concentrations of $NaBF_4$ readily approximate to the value of C343 in water. This fact could be attributed to the ionization state of the carboxyl moiety of C343. Note that in aqueous media, the absorption maxima of C343 at pH values of 7.0 and 2.0 are reported at 431 nm and 452 nm (see Fig. S8 in ESI†), respectively. This bathochromic shift shows a relationship with the values measured in water and pure $BMIMBF_4$, respectively. This fact could indicate that protonated C343 would prioritize $BMIM^+$–BF_4^- interactions while $H_2O(H)$–BF_4^- interactions would be relevant for non-protonated C343. The analysis is in accordance with the kinetic results, where we found that the larger increase in the rate coefficient values is achieved at low compositions of $BMIMBF_4$ ($\chi \leq 0.2$). This result is in agreement with the proposed preferential solvation exerted in the first part of the mixture compositions, where the anionic moiety of $BMIMBF_4$ might be located on the first solvation shell surrounding the reacting pair. At $\chi \geq 0.2$, a catalytic effect mediated by the anion of the RTIL in the mixture is observed. This fact enhances the "anion effect" on the reaction promoted by the anion moiety that improves the reactivity of the reacting pair.[24]

Experimental

Kinetic measurements

Kinetic measurement was carried out spectrophotometrically (300–550 nm range) by means of a diode array spectrophotometer in the mixtures of ionic liquid/water at 25 ± 0.1 °C. The reactions, studied under an excess of amine over the substrate, were started by injecting a substrate stock solution in acetonitrile into the amine solution in a RTIL–water mixture (1000 μL in the spectrophotometric cell). Under these conditions, pseudo first order rate coefficients (k_{obs}) were found. The experimental data are listed in Tables S1–S10 and Fig. S1–S8 in the ESI.†

Product study

The presence of 1-(2,4,6-trinitrophenyl)piperidine was determined as a product of the reactions spectrophotometrically by comparing the UV-visible spectra at the end of the reactions with those of authentic samples under the same conditions.

Determination of Kamlet–Taft parameters

The solvent parameters were measured by injecting the binary mixtures of IL (950 μL) into a quartz cuvette of 1.0 cm optical path with the probes (4-nitroaniline, and *N*,*N*-diethyl-4-nitroaniline) previously prepared in acetone (50 μL of a stock solution of the probes was evaporated to dryness for 30 minutes). The concentration of the stock solution was 1.6×10^{-3} M. All the solutions were thermostated at 25 ± 0.1 °C.

Coumarin 343 UV-vis spectrophotometry and pyrene steady state fluorescence measurements

Aliquots from freshly prepared stock solutions of C343 dissolved in ethanol were added to pure water, vacuum dried $BMIMBF_4$ as well as $NaBF_4$ aqueous solutions, incorporated into amber glass vials. The resulting solutions were placed into a rotary evaporator and further treated with a stream of nitrogen in order to remove the ethanol used to dissolve the probe. C343 absorbance was measured on an Agilent 8453 UV-vis spectrometer using 1 cm path quartz cells. Similarly, fluorescence measurements were carried out by using pyrene as the fluorescent probe, and adding an adequate volume of a stock solution of pyrene (dissolved in methanol) to water, vacuum dried $BMIMBF_4$ and mixtures of these solvents, in order to achieve a final pyrene concentration of 1 μM. The removal of methanol from the solutions was performed using the same procedure used for the C343 solutions. Pyrene fluorescence spectra were recorded using a Perkin Elmer LS-55 fluorescence spectrometer, at an excitation wavelength of 340 nm, and the final spectrum considered for each measurement corresponds to the average of 20 collected spectra.

Materials

The ionic liquid used was purchased from Merck, and used as received. Specifications are as follows: purity (HPLC) >98%; identity (NMR) passed test; halides (IC) <0.1%; water (KF) <0.1%. The substrate, phenyl 2,4,6-trinitrophenyl ether was prepared by the method described in ref. 10. Pyrene, coumarin 343, and the reaction product, 1-(2,4,6-trinitrophenyl)piperidine were acquired from Sigma Aldrich and used without further treatment.

Conclusions

A complete experimental study on the S_NAr reaction in a series of mixtures of $BMIMBF_4$/water has been presented. This reaction was selected as a model system because its kinetics in EtOH/water is well documented in the literature. The main outcomes of the present study are the solvation phenomena of this reaction in mixtures of $BMIMBF_4$/water at different compositions. The results showed that in the studied range of compositions, a borderline can be located in the range of compositions close to 0.2. Before this value, interesting results indicate that the added RTIL promotes the reactivity of the studied substrate.

This fact is attributable to the preferential solvation produced by the $H_2O(H)–BF_4^-$ interaction through the HB. This bond promotes the ability of the oxygen atom of the water molecule to link the hydrogen atom of the amine, enhancing the strength of the nucleophile, which is indicated through the increase in the rate coefficients. After this value, the rate coefficients remain approximately constant. However, in this range of compositions, a catalytic effect is exerted by the anion of the RTIL over the studied reaction, where the predominant interactions are between the anion and cation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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