PAPER

Ionic liquids: anion effect on the reaction of O,O-diethyl O-(2,4-dinitrophenyl) phosphate triester with piperidine†

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The reactions of O,O-diethyl 2,4-dinitrophenylphosphate triester (**1**) with piperidine in ionic liquids and four conventional organic solvents (COS) were subjected to kinetic and product studies. Analytical techniques (UV-vis and NMR) identified two pathways: nucleophilic attack at the phosphoryl center and at the C-1 aromatic carbon. The nucleophilic rate constants (k_N^T) for these parallel reactions were separated into two terms: k_N^P and k_N^{Ar} for the corresponding electrophilic centers. Both the rate and the selectivities of the reactions are strongly dependent on the nature of the ionic liquid used, and a good correlation with the solvent acceptor capacity to form hydrogen bonds (β) was observed. Remarkably, an exclusive attack at the phosphoryl center was found using [Bmim]DCA, [Bmpyrr]DCA and [Bmpy]DCA as the reaction solvents. In contrast, with [Bmim]PF$_6$ as the reaction solvent, attack at the C-1 aromatic was the main path (94%). These results suggest that ionic liquids can be considered to be designer solvents because by an appropriate choice of the anion it is possible to steer the selectivity of this reaction.

1. Introduction

Ionic liquids (ILs), which are typically composed of organic cations and inorganic anions, have been considered a new class of solvents for many organic reactions. They have attracted considerable attention due to their remarkable properties: negligible vapor pressure, non-flammable and non-corrosive, and can dissolve a significant number of organic species.[1] The current literature describes the successful use of ILs as reaction media in Friedel–Crafts,[2] Diels–Alder,[3] chlorination,[4] enzyme catalysis,[5] polymerization,[6] oxidation[7] and hydrogenation reactions.[8] Among the main advantages reported on the use of ILs as solvents, great improvements in yield, control of product distribution, enhanced rate, ease of product recovery, catalyst immobilization, and the possibility of recycling can be mentioned.[1c] Nevertheless, their application is sometimes limited by uncertainty on how ILs affect the reaction outcome.[9] To understand solute-solvent interactions in these organic salts, solvent parameter such as α, β, $\pi^\star$,[10] and physico-chemical investigations of their complex structures

(from X-ray diffraction to molecular dynamic modeling) have been used.[11]

The multiple cation/anion combinations available for the synthesis of ILs can lead to dramatic changes in the physico-chemical properties of these solvents. This potential has led to ionic liquids being described as "designer solvents". This suggests that for every chemical reaction of interest, it is possible to design a solvent to improve the reaction times and avoid undesired products.[1c,12] Of particular interest is a study of the reactions between toluene and nitric acid, where three completely different products were obtained by using three different ionic liquids.[13] The reactions of pyrrole and other nitrogen heterocycles with various alkyl halides have been found to favor C-alkylation,[14] and in the rearrangement of heterocycles derived from oxadiazole, D'anna et al. reported a large increase in reactivity in going from conventional solvents to ILs.[15] Finally, Kim et al. reported enhanced reactivity and improved selectivity in both the fluorination of 2-(3-methanesulfonyloxypropyl)naphthalene in ([bmim][BF$_4$])[16] and the hydroxylation of 2-(3-bromopropyl)naphthalene.[17] Thus, ILs play crucial roles, such as increasing the rates, reducing the formation of unwanted products and promoting mechanistic changes, as those observed in the aminolysis of some esters, carboxylic acids and phenyl-substituted ethanes. In these cases, the stabilization of the reaction intermediate has been proposed to be responsible for the change in mechanism.[18]

In addition, it is well known that phosphate esters containing both alkyl and aryl substituents can exhibit three reaction pathways for nucleophilic attack: (i) that at the phosphorus center,

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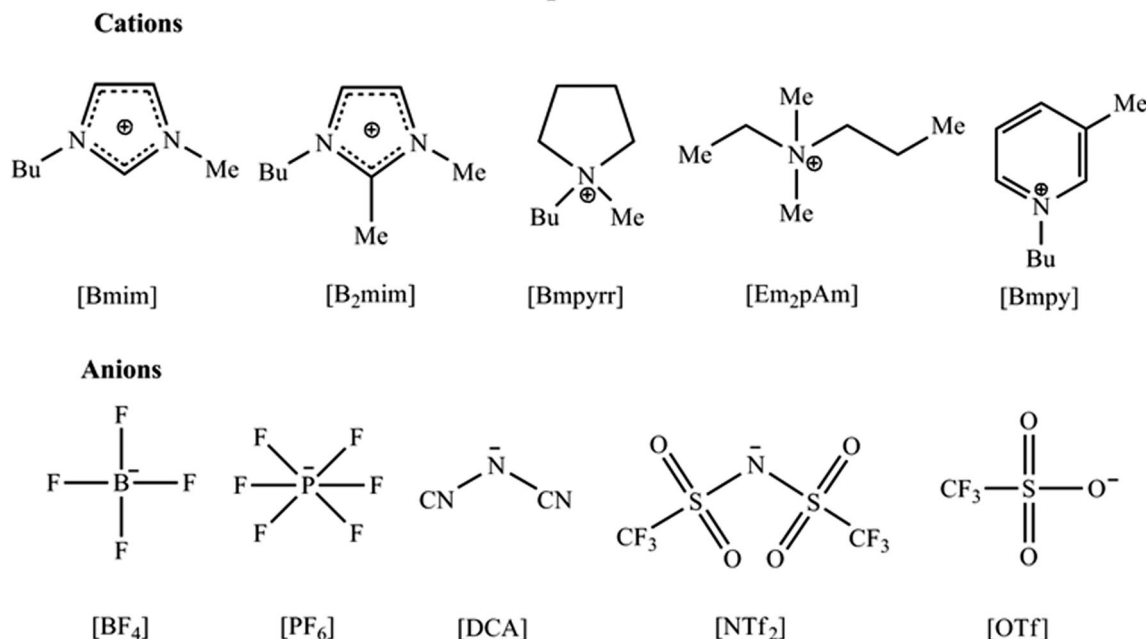
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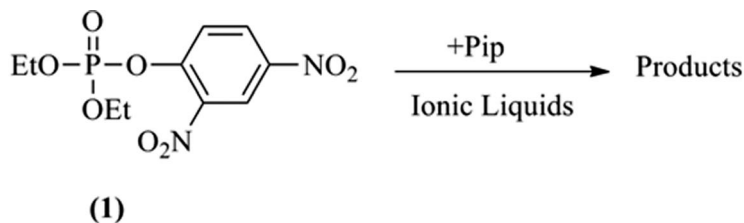
Scheme 1 Schematic representation of the reaction studied and the anions and cations of the ionic liquids used.

$S_N2(P)$,[19] (ii) that at the aromatic moiety, S_NAr,[20] and (iii) that at the aliphatic carbon, $S_N2(C)$.[21] Recently, we have demonstrated that the reaction of paraoxon with piperidine in ILs occurs *via* three simultaneous reaction paths,[22] whereas the same reaction in aqueous solution proceeds with exclusive phosphoryl attack.[19c]

Bearing in mind these precedents, our particular interest is focused on the possibility that ILs may substantially alter the reactivity in parallel nucleophilic substitution reactions of phosphate esters, yielding more than one reaction product. To improve our understanding of the effect of ILs as solvents on rate and product distribution, we examined the reaction of *O,O*-diethyl 2,4-dinitrophenyl phosphate triester (**1**) with piperidine in twelve ionic liquids, as shown in Scheme 1.

The combination of different cations and anions, shown in Scheme 1, provides ILs with different structures and diverse chemical properties, such as hydrogen bonding and hydrogen acidity abilities, which may be important for rationalizing the solvent–substrate interactions in these types of reactions. To compare the results in ILs, we carried out the same reaction in solvents, such as acetonitrile, DMSO and water, under the same experimental conditions, following the kinetic experiments by

UV-vis spectrophotometry and the product analyses by UV–vis and ^{31}P NMR.

2. Results and discussion

2.1 Rates and selectivity

Rate constants for the reaction of **1** with piperidine using ILs and common solvents were determined spectrophotometrically. The rate law for all the reactions studied is given by eqn (1), where P and S represent one of the products and substrate **1**, respectively. First-order rate constants (k_{obsd}) were obtained in the presence of total piperidine excess and are shown in Tables S1 and S2 in ESI.† The plots of k_{obsd} against nucleophile concentration were linear, according to eqn (2), where k_N^T is the nucleophilic rate coefficient.

$$\frac{d[P]}{dt} = k_{obsd}[S] \qquad (1)$$

$$k_{obsd} = k_0 + k_N^T[NH] \qquad (2)$$

All these plots showed a slightly negative intercept when the solvent was an ionic liquid. This behavior was reported before

Table 1 Second-order rate constants (k_N^T) for the reaction of **1** with piperidine in ILs and other solvents, at 25 °C

Solvent	$k_N^{T,b}/M^{-1} s^{-1}$
H_2O	0.66
$EtOH:H_2O$ (50%/v)[a]	0.30
ACN	1.82
DMSO	6.87
[Bmim]BF_4	4.42
[Bmim]PF_6	1.81
[Bmim]DCA	7.80
[Bmim]OTf	4.36
[Bmim]NTf_2	1.24
[Bmpyr]NTf_2	1.45
[Em_2pAm]NTf_2	3.28
[B_2mim]NTf_2	2.95
[B_2mim]BF_4	4.50
[Bmpyr]DCA	7.55
[Bmpyr]OTf	4.35

[a] Ref. 24. [b] Second-order rate constants were reproducible within ±5%.

for ILs derived from imidazole,[23] and was attributed to an acid–base interaction between the acidic imidazolium ion and the amine. The values of k_N^T for the reaction of **1** with piperidine in various solvents are shown in Table 1.

The data in Table 1 show that the k_N^T values in ILs are larger than those found in aqueous solutions, but similar to or lower than those found in DMSO. This result is not surprising because the polarity and structure of DMSO lead to a considerable organization in the liquid state, the same as in ILs.[25] Product studies using UV-vis spectrophotometry show that for the reactions of ILs based on the DCA anion, the reaction is slightly faster and the final spectra correspond to 2,4-dinitrophenoxide

produced as a result of amine attack at the phosphoryl moiety. Conversely, in the other solvents a band near 380 nm was found, suggesting a more complex kinetic behavior.

Fig. 1 shows the ^{31}P NMR spectra obtained for the reaction of **1** with piperidine in [Bmim]BF_4. The figure shows the disappearance of the signal at −7.68 ppm, due to **1**, and the simultaneous appearance of two signals, one at 8.89 and the other at 0.19 ppm, corresponding to O,O-diethyl piperidinophosphate diester (**2a**) and O,O-diethyl phosphate acid (**2b**), respectively, in agreement with Scheme 2. The signals at 0.19 and 8.89 were assigned by comparison with authentic samples of the products obtained by the reactions of piperidine and NaOH with O,O-diethyl chlorophosphate in the same IL, respectively, as shown in Fig. S1 and S2, in ESI.†

The ^{31}P-NMR spectra recorded at the end of the reaction of **1** with piperidine in all the ionic solvents studied and also in other common solvents are shown in Figures S3–S14 in ESI.† The results show similar behavior in most of the solvents studied and that the nucleophilic attack towards the phosphoryl center competes with the attack at the C-1 aromatic carbon, as shown in Scheme 2. Nevertheless, in those ILs that share a common DCA anion, only the signal at 8.89 ppm in the ^{31}P NMR spectra was observed (see Fig. S15–S17, in ESI†). This is in accordance with the exclusive formation of O,O-diethyl piperidinophosphate diester (**2a**); this result is consistent with the UV-vis spectral analysis, which indicates the formation of 2,4-dinitrophenoxide (**3a**).

Integration of the ^{31}P NMR signals of the products formed from piperidine attack on **1** allowed the calculation of the product distribution in the different reaction media. The results
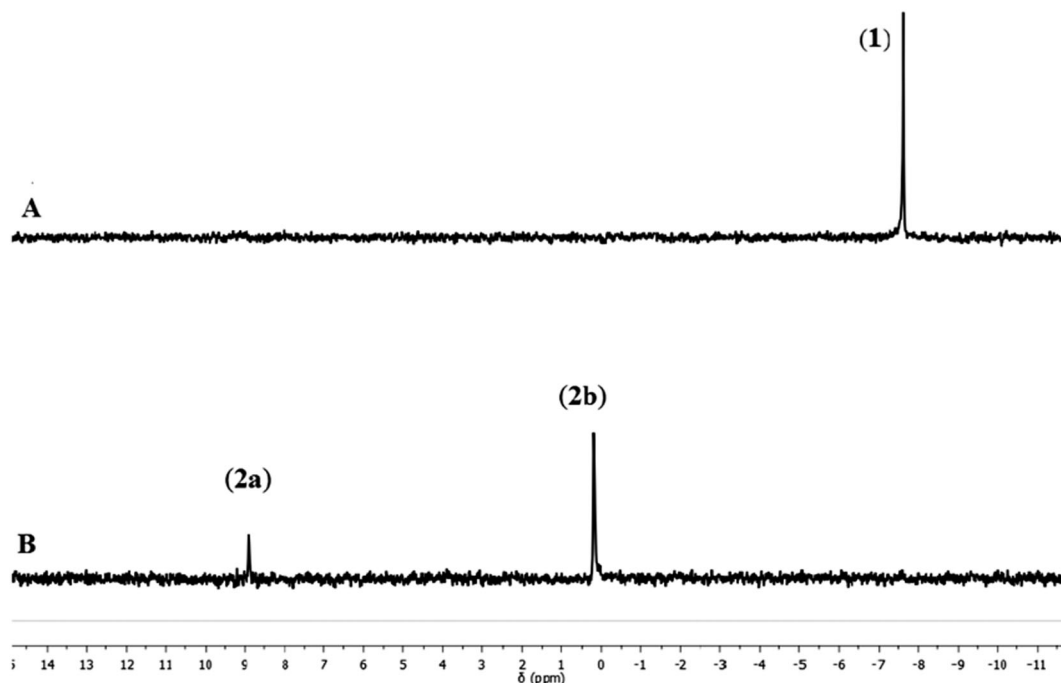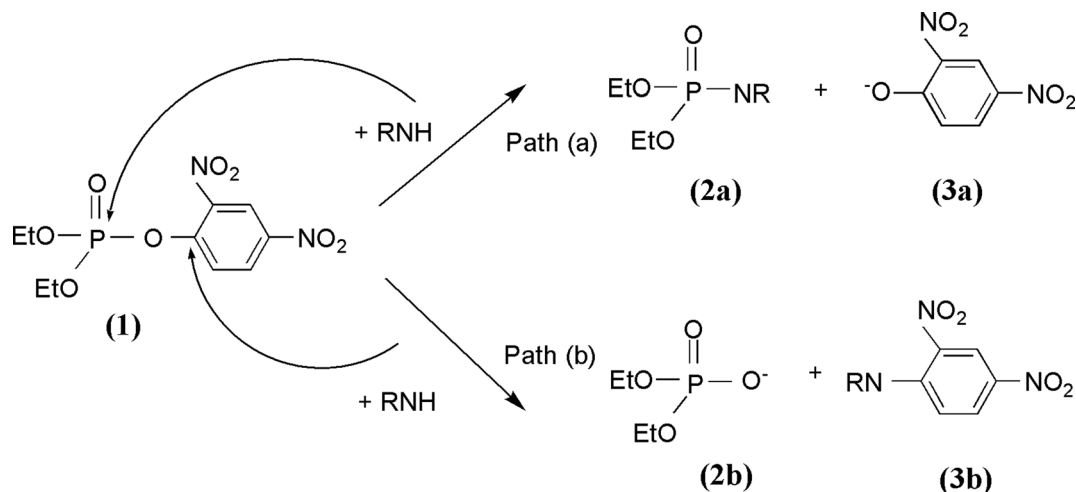

Fig. 1 ^{31}P-NMR spectra obtained for the reaction of **1** (0.4 M) with piperidine (neat) at 25 °C in [Bmim]BF_4 as solvent. (A) Initial time and (B) the end of the reaction.

Scheme 2 Nucleophilic attack of piperidine (RNH) on **1** in ILs, DMSO, ACN and aqueous solutions, by two reactions paths: (a) attack at phosphorus; and (b) attack at the aromatic C-1.
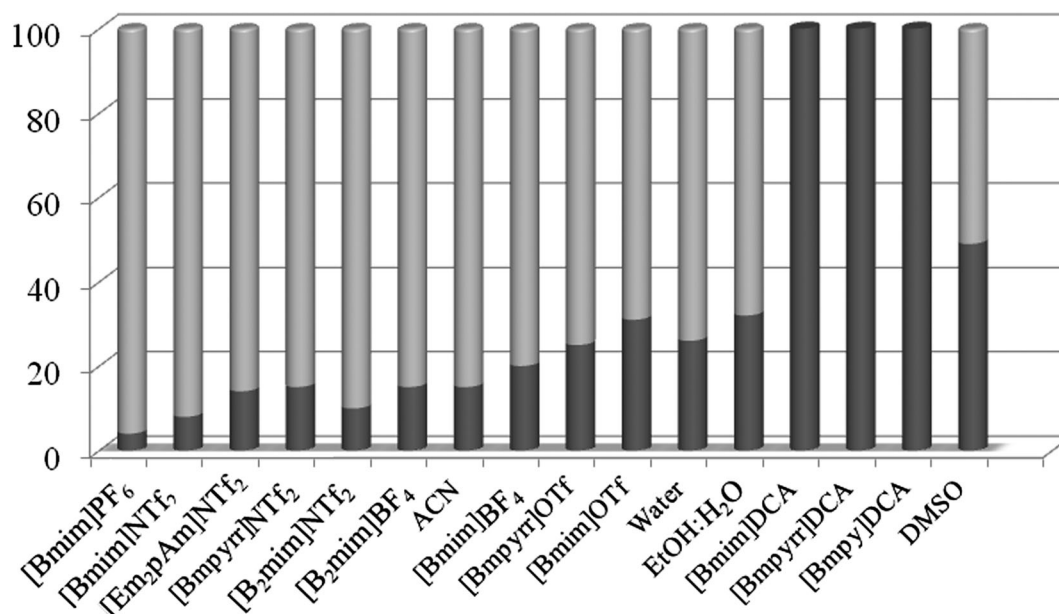
Fig. 2 Nucleophilic attack of piperidine on **1** compared for ILs and other solvents. The dark gray areas represent the $S_N2(P)$ pathway, with attack of piperidine at the phosphorus atom, and the light gray areas represent the S_NAr pathway, with attack at the C-1 aromatic carbon.

are summarized in Table S3 in ESI.† Fig. 2 shows this behavior schematically.

The results agree with previous reports showing that slight modifications in the ILs' cation or anion nature can induce selectivity changes for some reactions.[10c,26] In most of the ILs employed, the $S_N2(Ar)$ pathway (light gray contribution in Fig. 2) is the most important (70–97%), and the results are consistent with those obtained in the degradation of paraoxon in ILs, where S_NAr reactions are favored when ILs are used as solvents.[22] However, an important effect of the solvent on the selectivity of an amine attack is apparent, which changes from 100% attack on the phosphoryl group with [Bmim]DCA, [Bmpyr]DCA and [Bmpy]DCA as solvents, to 94% of attack at the aromatic C-1 in the substrate when [Bmim]PF₆ is the solvent.

These results suggest that ionic liquids can be considered as designer solvents for these reactions because by the appropriate choice of the anion it is possible to control the selectivity of this reaction.

For the parallel reaction shown in Scheme 2, the second-order rate constants k_N^T are the sum of the individual rate constants $k_N^T = k_N^P + k_N^{Ar}$ where k_N^P and k_N^{Ar} are the rate constants for nucleophilic attack at P and at the aromatic C-1, respectively. Using the products distribution shown in Table S3 in the ESI† and the data in Table 1, values of the individual second order rate constants k_N^P and k_N^{Ar} were calculated and are given in Table 2.

Examining the values in Table 2, we can clearly observe the importance of the anion in the rate constant by comparing ILs with a common cation [Bmim], where the k_N^P increases 78 times,

increasing from 0.10 to 7.8 when NTf_2 is replaced by DCA. Nevertheless, when comparing ILs that share a common NTf_2 anion, little difference was found: the k_N^P values increase from 0.1 to 0.46 when [Bmim] is substituted by [Em$_2$pAm], suggesting that the cation has only a minor effect on the rate. These results are in accordance with those of Harper *et al.* for an S_N2 process (Menschutkin reaction), where the change of the IL cation does not affect the outcome of the reaction.[9,27] Nevertheless, this finding cannot be generalized because of the different interactions of the IL with the starting materials and various species along the reaction coordinate.

It is interesting to note that the couples [Bmim]NTf$_2$-[Bmpyrr]-NTf$_2$, [Bmpyrr]OTf-[Bmin]OTf and [B$_2$mim]BF$_4$-[Bmim]BF$_4$ (see Fig. S18, in ESI†) present similar values of k_N^{Ar}, suggesting that the C-1 aromatic attack is mostly affected by the anion, and the change of the cation practically does not affect the reaction rate. Similarly, the effect of the acidity loss due to the blockage of the 2-position of the imidazolium ring[28] shows modest changes in k_N^{Ar}, which may be analyzed by comparing [Bmim]NTf$_2$ with [B$_2$mim]NTf$_2$ (or comparing [Bmim]BF$_4$ with [B$_2$mim]BF$_4$).

Hughes–Ingold theory predicts that an increase in solvent dielectric constant (polarity) would enhance the k_N^P and k_N^{Ar} values. Our results reveal that this is not the case because we found a poor correlation of the rate constant k_N^P and k_N^{Ar} with the polarity parameter $E_T(30)$ (not shown). To rationalize how the individual rate constants depend on the nature of the ILs, we tried to correlate them by using Kamlet–Taft parameters (Table S4, in ESI†). We found a good correlation between $\log k_N^P$ and the hydrogen bond acceptor capacity of the solvent (β), as shown in Fig. 3 ($\log k_N^P = -1.68(0.12) + 3.79(0.29)\beta$; $R = 0.95$). The introduction of α, π^* or both parameters in the fit does not give a better correlation (see Table S5 in ESI†). Conversely, $\log k_N^{Ar}$ does not correlate well with the solvent parameter β, a result that is reasonable because reactions at the phosphorus and aromatic centers proceed with different mechanisms.

By using the data from Table 2, the selectivity of the reaction in each solvent was calculated. The selectivity of the amine attack on the phosphoryl group (f_N^P) is defined by the kinetic
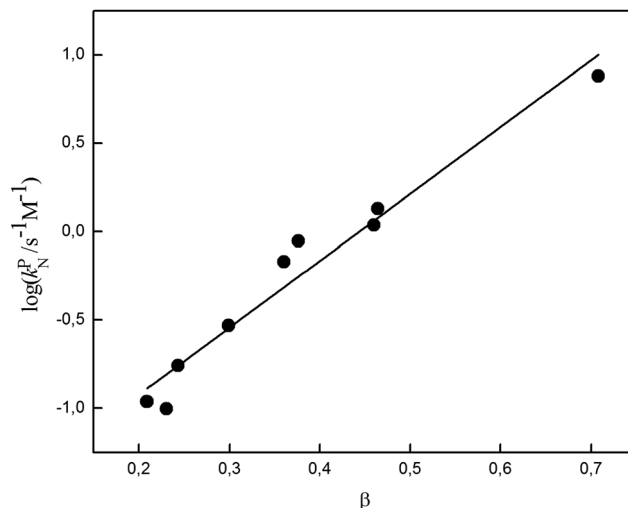

Fig. 3 Correlation between $\log k_N^P$ and the solvent hydrogen bond acceptor capacity (β) for a series of ionic liquids.

parameters: $(f_N^p) = \dfrac{k_N^p}{k_N^p + k_N^{Ar}}$. A treatment based on a multi-parameter regression with respect to Kamlet–Taft solvent descriptors (α, β and π^*) failed when the data from conventional solvents were analyzed together with those from ILs. Nonetheless, a good correlation with the β parameter was obtained; a plot of $\log(f_N^p)$ *vs.* β of the ionic liquids is shown in Fig. 4. ($\log(f_N^p) = -1.62(0.02) + 2.29(0.01)\beta$; $R = 0.96$).

It is noteworthy that the kinetic parameter $\log k_N^P$ presents a linear correlation with β (Fig. 3), while the plot of $\log k_N^{Ar}$ *vs.* β is not linear (Fig. S17, ESI†). This different behavior can be related to the different structures of the intermediates in their corresponding mechanisms. Moreover, the semilog plot of selectivity (obtained either from the kinetic or from the product distribution) against β is linear, showing a dependence even though $\log k_N^{Ar}$ *vs.* β is not linear. This can be explained because the

Table 2 Second-order rate constants for the reactions at the phosphoryl center (k_N^P) and at the C-1 aromatic carbon (k_N^{Ar})

Solvent	$k_N^{P\,b}$/M^{-1} s^{-1}	$k_N^{Ar\,b}$/M^{-1} s^{-1}
H$_2$O	0.17	0.49
EtOH : H$_2$O (50% v/v)^a	0.09	0.21
ACN	0.27	1.55
DMSO	3.37	3.50
[Bmim]BF$_4$	0.88	3.54
[Bmim]PF$_6$	0.11	1.70
[Bmim]DCA	7.80	0
[Bmim]OTf	1.35	3.01
[Bmim]NTf$_2$	0.10	1.14
[Bmpyrr]NTf$_2$	0.17	1.28
[Em2pAm]NTf$_2$	0.46	2.82
[B$_2$mim]NTf$_2$	0.30	2.65
[B$_2$mim]BF$_4$	0.68	3.82
[Bmpyrr]DCA	7.55	0
[Bmpyrr]OTf	1.09	3.26

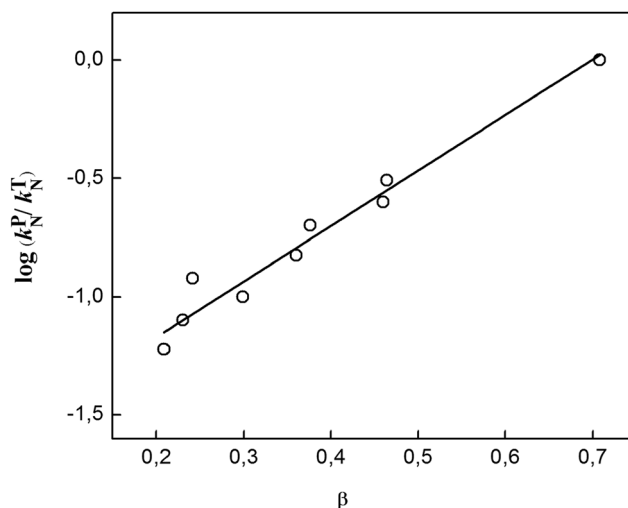^{a} Ref. 24. ^{b} Second-order rate constants were reproducible within ±5%.

Fig. 4 Correlation between $\log(f_N^P)$ and the solvent hydrogen bond acceptor capacity (β) for a series of ionic liquids.

selectivity can be obtained from the kinetics results; however, the selectivity is a thermodynamic property.

In this work, we have demonstrated that the reaction is selective to the phosphoryl group in ILs that share the DCA anion, and the attack at the C-1 aromatic increases as the anion basicity decreases at the point of 94% in $[\text{Bmim}]\text{PF}_6$; probably the design of an IL in which the reaction will be selective to the aromatic attack must contain an anion less basic than PF_6.

It is noteworthy that DMSO has the greatest β value (0.760), higher than any of the ILs used, though attack on the phosphoryl moiety is not 100%. The results suggest that the hydrogen bond acceptor capacity β of the ILs is not the only parameter to be considered and also the structural organization of these solvents[29] should be taken into account. However, there are a lot of studies on how ionic liquids affect reaction outcomes such as reaction rate and selectivity (see ref. 30 and references therein).

3. Conclusions

The reaction of **1** with piperidine in ILs that share the anion DCA is specifically at the phosphoryl group, while in $[\text{Bmim}]\text{PF}_6$ as solvent, the attack at the C-1 aromatic is the main path of the reaction (94%). These results suggest that ionic liquids can be considered to be designer solvents because by an appropriate choice of the anion it is possible to control the selectivity of this reaction.

Good correlations of rate and selectivity with solvent acceptor capacity to form hydrogen bonds (β) are observed for these reactions. In both cases the anion is the most important factor, while the effect of the cation is relatively modest.

4. Experimental section

4.1 Materials

All ionic liquids, piperidine and *O*,*O*-diethyl chlorophosphate were purchased from Aldrich. All ionic liquids were dried before use in a vacuum oven at 70 °C for at least 2 h, and stored in a dryer under nitrogen and over calcium chloride. Water contents determined by Karl–Fischer titration were <200 ppm. Substrate **1** was prepared as described in literature.[31]

4.2 Kinetic measurements

These were performed spectrophotometrically (diode array) in the range of 300–500 nm, by following the appearance of products after at least four half- lives, by means of a Hewlett-Packard 8453 instrument. The reactions were carried out in water, acetonitrile, dimethyl sulfoxide and in twelve different ILs. At least a 10-fold excess of total amine over the substrate was employed. In a typical spectrophotometric measurement, a quartz cuvette (light-path 0.2 cm) containing 500 μL of ionic liquid was thermostated at 25 °C during 10 minutes. Then, a solution of **1** (50 μL, 2×10^{-3} M in ACN) and concentrated amine (10 μL) were added. The spectra were recorded at different reaction times and pseudo-first-order rate coefficients

(k_{obsd}) were found for all reactions. Each sample was made in triplicate. These were obtained by means of the kinetic software of the spectrophotometer, at the wavelength where the greatest absorbance change was observed. The nucleophilic rate constants ($\log k_{\text{N}}^{\text{T}}$) were obtained as the slope of linear plots of k_{obsd} *vs.* free nucleophile concentration. The separation of k_{N}^{T} into k_{N}^{P} (the nucleophilic rate constant for the phosphoryl center) and k_{N}^{Ar} (the nucleophilic rate constant for the C-1 aromatic carbon) was performed considering the quantitative product analysis (see below) and the fact that for parallel reactions $k_{\text{N}}^{\text{T}} = k_{\text{N}}^{\text{P}} + k_{\text{N}}^{\text{Ar}}$.

4.3 Product studies

To determine the products of the studied reactions, ^{31}P-NMR spectra were obtained on an AM-400 instrument in all the solvents used in this study (ILs and COS).

At the end of the reactions of **1** with piperidine in the ILs sharing the DCA anion, the ^{31}P NMR spectra showed only one signal at 8.89 ppm attributed to *O*,*O*-diethyl piperidine phosphate, in comparison with that of the product of the reaction of *O*,*O*-diethyl chlorophosphate with piperidine. Moreover, the UV-vis spectra at the end of the reactions correspond to 2,4-dinitrophenoxide in comparison with an authentic sample.

For the reactions of **1** with piperidine in other solvents, the ^{31}P NMR spectra show 2 signals that correspond to *O*,*O*-diethylamine phosphate and to *O*,*O*-diethyl phosphoric acid, in comparison with authentic samples prepared using *O*,*O*-diethyl chlorophosphate. The ^{31}P NMR signals for the products for the reactions are summarized in Fig. S1–S21 in ESI.† It is noteworthy that the ratio of products was independent of the concentration of **1** and piperidine.

4.4 Selectivity

The selectivity of the amine attack at the phosphoryl group (f_{N}^{p}), that is a thermodynamic property, is defined by the kinetic parameters summarized in Table 2: $(f_{\text{N}}^{\text{p}}) = \dfrac{k_{\text{N}}^{\text{p}}}{k_{\text{N}}^{\text{p}} + k_{\text{N}}^{\text{Ar}}}$ or by using the amounts of obtained products summarized in Table S3 (ESI†) $(f_{\text{N}}^{\text{p}}) = \dfrac{\%\text{S}_{\text{N}}2(\text{P})}{\%\text{S}_{\text{N}}2(\text{P}) + \%\text{S}_{\text{N}}(\text{Ar})}$.

Acknowledgements

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