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Ionic Liquids: Anion effect on the reaction of *O*, *O*-diethyl *O*-(2,4-dinitrophenyl) phosphate triester with piperidine.

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Abstract

The reactions of *O,O*-diethyl 2,4-dinitrophenylphosphate triester (**1**) with piperidine in ionic liquids and four conventional organic solvent (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 the 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 the ionic liquids can be considered as designer solvents, since 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 as a new class of solvents for many organic reactions. They have attracted much 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 can be mentioned great improvements in yield, control of product distribution, enhanced rate, ease of product recovery, catalyst immobilization, and the possibility of recycling.[1c] Nevertheless, their application is

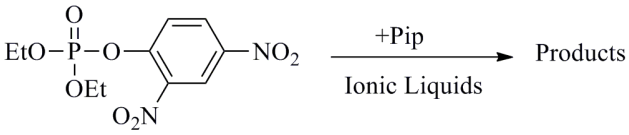
sometimes limited by uncertainty on how ILs affect the reaction outcome.[9] In order to understand solute-solvent interactions in these organic salts, both empirical treatments of solvents, such as that developed by Kamlet and Taft[10] and physico-chemical investigations of their complex structures (from 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 physicochemical 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 should be possible to design a solvent in order 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 oxadiazol, 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][BF4])[16] and the hydroxylation of 2-(3-bromopropyl)naphthalene.[17] Thus, ILs play crucial roles, such as increasing 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]

On the other hand, 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, $S_N2(P)$,[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 react *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 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, see Scheme 1.

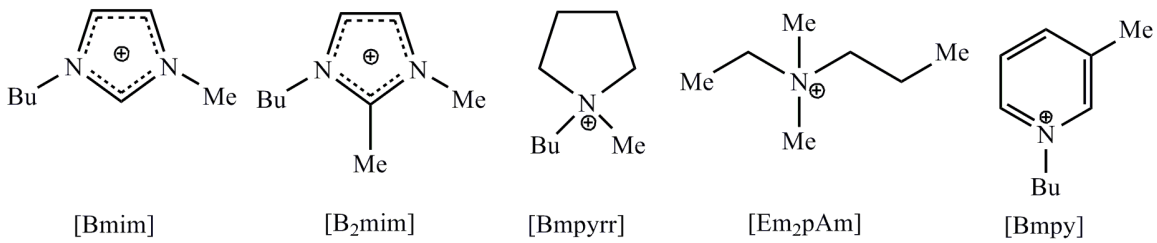
The combination of different cations and anions, shown in Scheme 1, provides ILs with different structures and diverse chemical properties, such as hydrogen bond and hydrogen acidity abilities, which may be important for rationalizing the solvent-substrate interactions in these types of reactions. To 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.



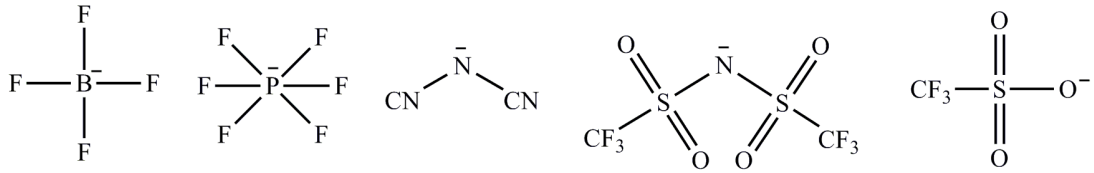
(1)

Ionic Liquids used

Cations



Anions



Scheme 1: Schematic Representation of the Reaction Studied and the Anions and Cations of the Ionic Liquids Used

2. Results and Discussion

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 eq. 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 Supplementary Information. The plots of k_{obsd} against nucleophile concentration were linear, according to eq. 2, where k_N^T is the nucleophilic rate coefficient.

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

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

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

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

Solvent	$k_N^T / M^{-1}s^{-1}$ **
H_2O	0.66
EtOH:H_2O (50% /v)*	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
[Bmpyrr]NTf_2	1.45
[Em_2pAm]NTf_2	3.28
[B_2mim]NTf_2	2.95
[B_2mim]BF_4	4.50
[Bmpyrr]DCA	7.55
[Bmpyrr]OTf	4.35

*ref 24; **Second-order rate constants were reproducible within a ± 5%

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 corresponds 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.

Figure 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 Figures S1 and S2, in Supplementary Information.

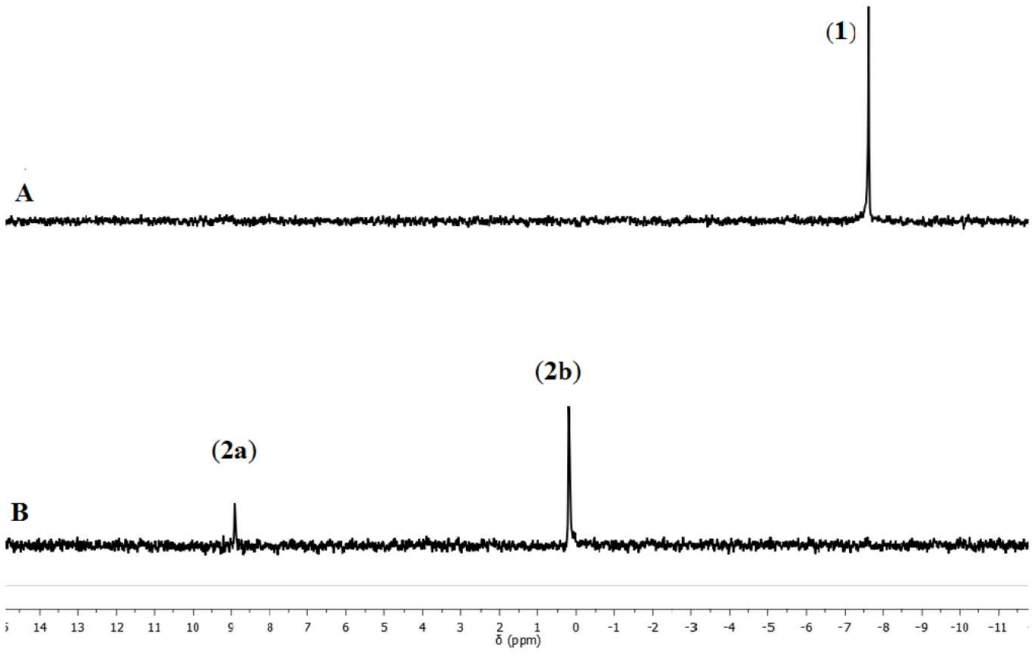
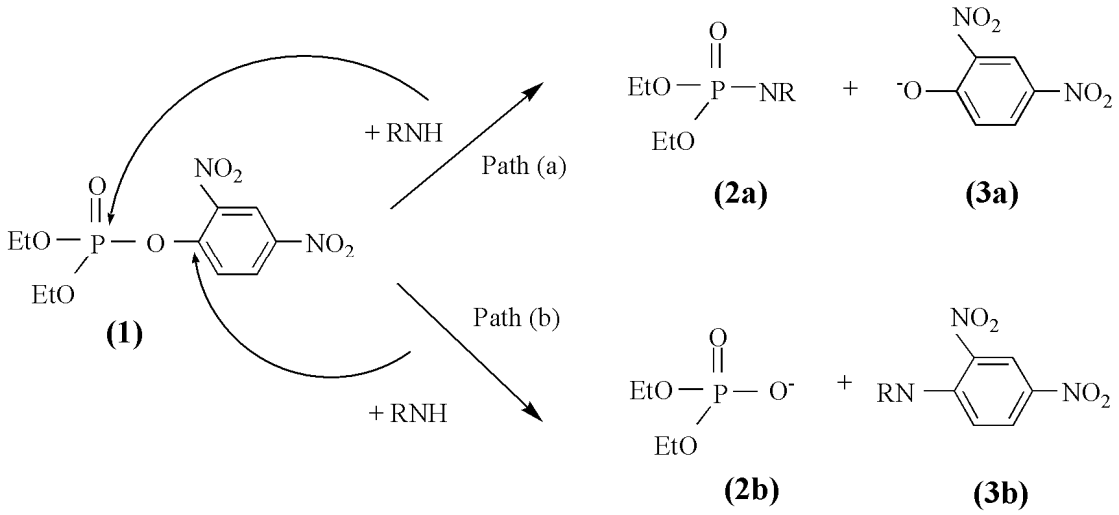


Figure 1. ^{31}P-NMR spectra obtained for the reaction of **1** (0.4 M) with piperidine (neat) at 25 ºC in [Bmim]BF_4 as solvent. (**A**) Initial time and (**B**) the end of the reaction.

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 Supplementary Information. The results show similar behavior in most of the solvents studied and that nucleophilic attack towards the phosphoryl center competes with 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 Figures S15-S17, in Supplementary Information). This is in accordance with the exclusive formation of *O,O*-diethyl piperidinophosphate diester (**2a),** a result consistent with the UV-vis spectral analysis, which indicates the formation of 2,4-dinitrophenoxide (**3a**).



Scheme 2: Nucleophilic attack of piperidine (RNH) to **1** in ILs, DMSO, ACN and aqueous solutions, by two reactions paths: (a) attack at phosphorus; and (b) attack at the aromatic C-1.

Integration of the ^{31}P NMR signals of the products formed from piperidine attack to **1** allowed to calculate the product distribution in the different reaction media. The results are summarized in Table S3 in Supplementary Information. Figure 2 shows this behavior schematically.

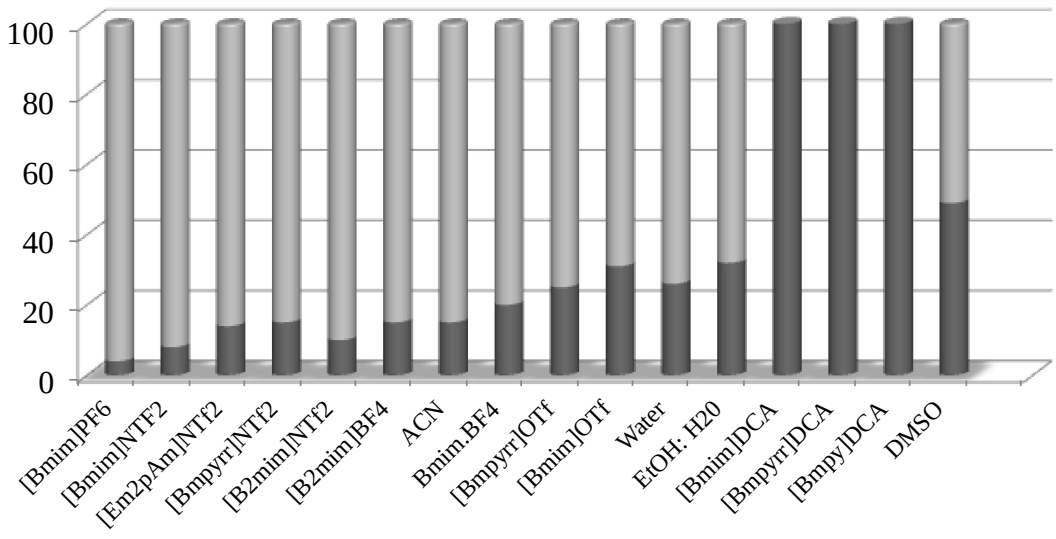


Figure 2: Nucleophilic attack of piperidine to **1** compared for ILs and other solvents. The dark gray areas represent the $S_N2(P)$ pathway, with attack of piperidine at the phosphorus atom, and the light gray areas represent the S_NAr pathway, with attack at the C-1 aromatic carbon.

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 Figure 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 amine attack is apparent, which changes from 100% attack on the phosphoryl group with [Bmim]DCA, [Bmpyrr]DCA and [Bmpy]DCA as solvents, to 94 % of attack at the aromatic C-1 in the substrate when $[Bmim]PF_6$ is the solvent. These results suggest that ionic liquids can be considered as designer solvents for these reactions, since by 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 Supplementary Information 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.

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	$k_N^P / M^{-1}s^{-1}$**	$k_N^{Ar} / M^{-1}s^{-1}$**
H_2O	0.17	0.49
EtOH:H_2O (50% v/v)*	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_2mim]NTf_2	0.30	2.65
[B_2mim]BF_4	0.68	3.82
[Bmpyrr]DCA	7.55	0
[Bmpyrr]OTf	1.09	3.26

*ref 24; **Second-order rate constants were reproducible within a ± 5%

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_2pAm], 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_2mim]BF_4 - [Bmim]BF_4 (see Figure S18, in Supplementary Information), 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_2mim]NTf_2 (or comparing [Bmim]BF_4 with [B_2mim]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 since we found a poor correlation of the rate constant k_N^P and k_N^{Ar} with the 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 Supplementary Information). We found a good correlation between $\log k_N^P$ and the hydrogen bond acceptor capacity of the solvent (β), as shown in Figure 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 Supplementary Information). Conversely, $\log k_N^{Ar}$ does not correlate well with the solvent parameter β, a result that is reasonable since reactions at the phosphorus and aromatic centers proceed with different mechanisms.

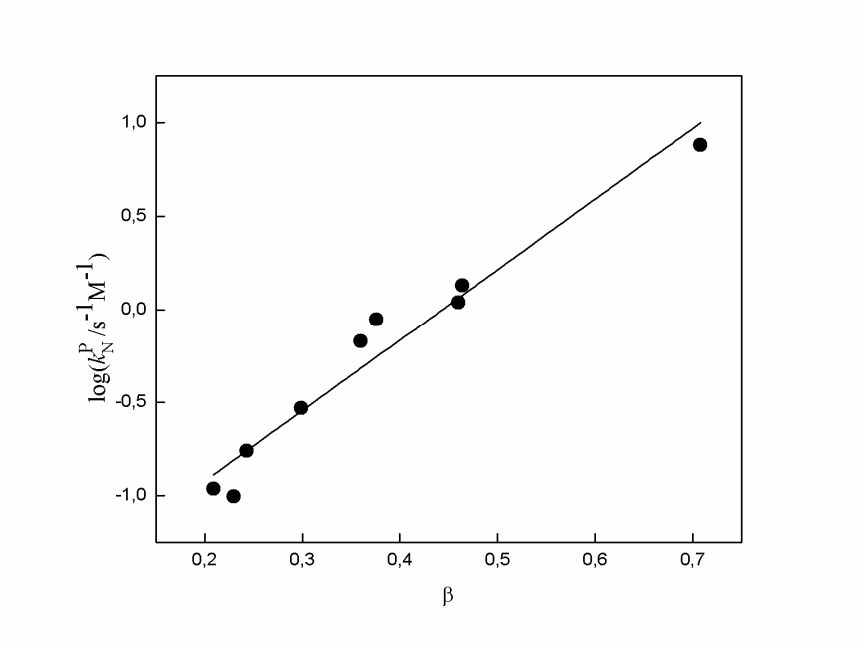


Figure 3: Correlation between log k_N^P and the solvent hydrogen bond acceptor capacity (β) for a series of ionic liquids.

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 $\left(f_N^p\right)$ is defined by the kinetic parameters: $\left(f_N^p\right)=\frac{k_N^P}{k_N^P+k_N^{Ar}}$. A treatment based on a multiparameter 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 $\log\left(f_N^p\right)$ vs β of the ionic liquids is shown in Figure 4. $(\log(f_N^P)=-1.62(0.02)+2.29(0.01)\beta;\mathrm{R}=0.96)$

It is noteworthy that the kinetic parameter log k_N^P presents a linear correlation with β (figure 3) while the plot of log k_N^{Ar} vs. β is not linear (figure S17). This different behavior can be related to

the different structures of the intermediates in their corresponding mechanisms. On the other hand, 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 selectivity can be obtained from the kinetics results, whereas 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 [Bmim]PF_6 ; probably the design of a IL in which the reaction be selective to the aromatic attack must contain an anion less basic than PF_6.

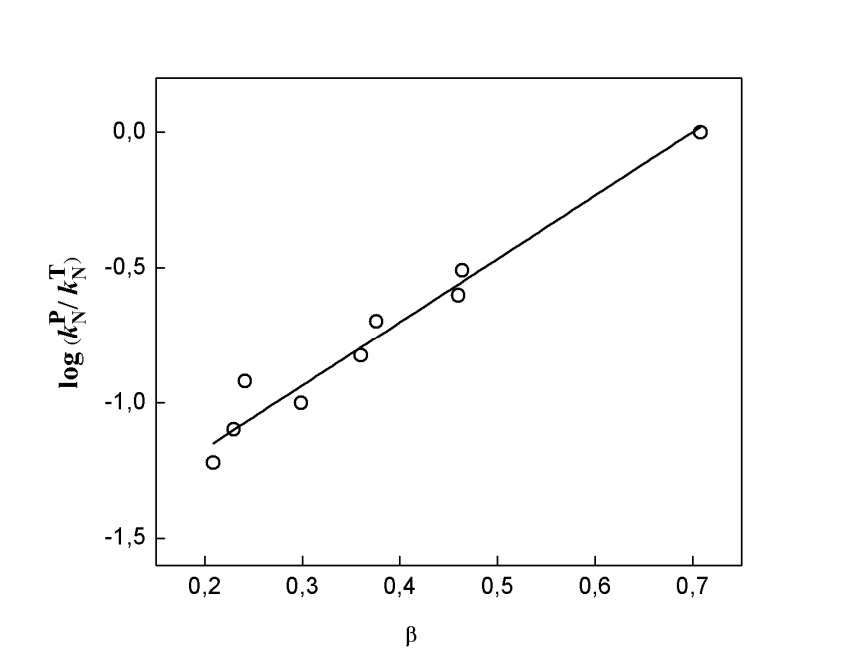


Figure 4. Correlation between $\log\left(f_N^p\right)$ and the solvent hydrogen bond acceptor capacity (β) for a series of ionic liquids

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. On other side, there are a lot of studies on how ionic liquids affect reaction outcomes, such as reaction rate and selectivity (see reference 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 [Bmim]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 as designer solvents, since 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 on vacuum oven at 70°C for at least 2 h, stored in a dryer under nitrogen and over calcium chloride. Water contents determined by Karl-Fisher 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 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, dimethylsulfoxide 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 uL, $2x10^{-3}$ M in ACN) and concentrated amine (10µL) 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 (k_N^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) an the fact that for parallel reactions $k_N^T = k_N^P + k_N^{Ar}$.

4.3 Product Studies. To determine the products of the studied reactions, ^{31}P-NMR spectra were obtained on a 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 those ILs sharing the DCA anion, the ^{31}P NMR spectra show only one signal at 8.89 ppm attributed to *O,O*-diethyl piperidine phosphate, by comparison with that of the product of the reaction of *O,O*-diethyl chlorophosphate with piperidine. Also, the UV-vis spectra at the end of the reactions correspond to 2,4-dinitrophenoxide by 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*-dietyl phosphoric acid, by comparison with authentic samples prepared using *O,O*-diethyl chlorophosphate. The ^{31}P NMR signals for the products for the reactions are summarized in Figures S1-S21 in Supplementary Information. 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 thermodynamical property, is defined by the kinetic parameters summarized in table 2:

$\left(f_N^p\right)=\frac{k_N^P}{k_N^P+k_N^{Ar}}$ or by using the amounts of obtained products summarized in table S3

$(f_N^P)=\frac{\%\ S_N2(P)}{\%\ S_N2(P)+\%\ S_N(Ar)}$.

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†Electronic Supplementary Information (ESI) available:

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