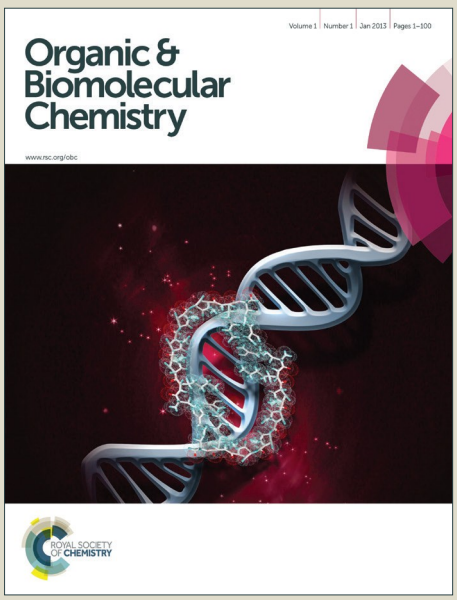
Organic & Biomolecular Chemistry

Accepted Manuscript



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Reaction mechanisms in ionic liquids: Kinetics and mechanism of the reaction of *O*, *O*-diethyl *O*-(2,4-dinitrophenyl) phosphate triester with secondary alicyclic amines

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Abstract

The reactions of *O*,*O*-diethyl 2,4-dinitrophenyl phosphate triester (**1**) with secondary alicyclic (SA) amines in the ionic liquids [Bmim]BF_4 and [Bmim]DCA were subjected to a kinetic study. Eyring plots were obtained for the title reactions in the above ionic liquids (ILs) and also in aqueous ethanol (44 w% ethanol). Two different reaction pathways were observed in Bmim[BF_4]: nucleophilic attack at the phosphoryl center, S_N2(P), and at the C-1 aromatic carbon, S_N(Ar), where the product distribution remained constant and independent of the amine nature. In contrast, in [Bmim]DCA only the S_N2(P) pathway was found. From the kinetic analysis of the S_N2(P) pathway in both ILs, curved upwards plots of k_{obsd} *vs* 1-formylpiperazine concentration were obtained. Based on the kinetic behavior, a change in mechanism of the S_N2(P) pathway is proposed for the aminolysis of **1**, from a concerted process in aqueous ethanol to a stepwise mechanism, through a zwitterionic pentacoordinate intermediate, when [Bmim]BF_4 and [Bmim]DCA are the solvents of the reaction.

Introduction

In the last decade the ionic liquids (ILs) have been considered as an alternative to organic solvents for many reactions. They have remarkable properties such as low volatility, non-flammable, non-corrosive and can dissolve a significant number of organic species.[1-3] At present, there is much literature describing organic reactions where ILs have been successfully used as reaction media.[4-6] Among the main advantages reported on the use of ILs as solvents, it can be mentioned the great improvement in yields, the control of product distribution, enhanced rates, ease of product recovery, catalyst immobilization, and the possibility of recycling once the reaction has finished.[2, 7-8] Nevertheless, information about how the reactions proceed in this ionic media at a molecular level has received less attention.[4, 9-11]

A systematic study of the effect of ILs on the outcome of a number of organic reactions have been developed by Harper et al.[12-15] They have described a set of principles for qualitatively predicting the effect of an IL on the reaction outcome, considering microscopic interactions between the components of the IL and the

starting materials and the transition state (TS). They predict a rate enhancement in those bimolecular reactions involving a charge development in the transition state.[12-15] However, the detailed mechanism of these reactions was not considered by these authors.

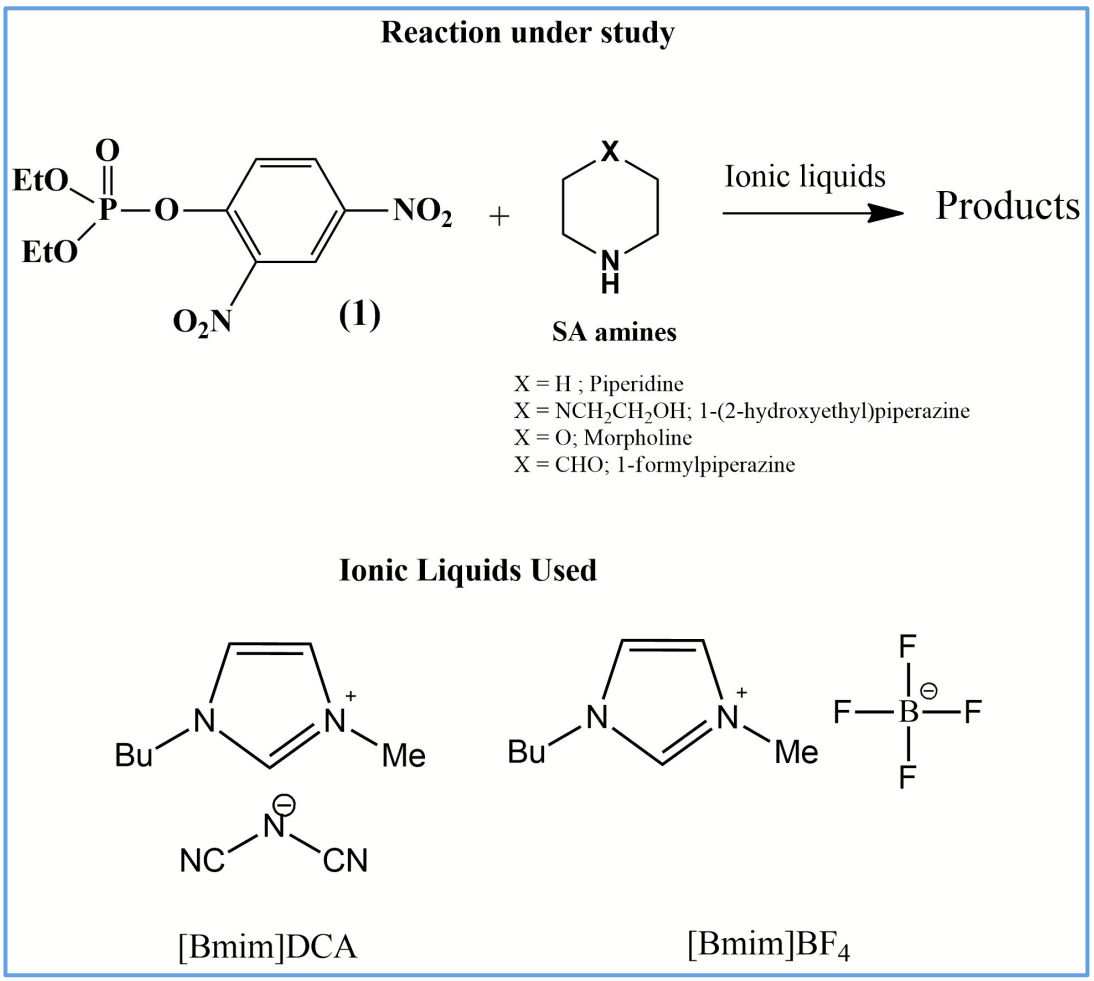
Recently, D´anna and collaborators reported that activation parameters determined for the mononuclear rearrangement reactions of heterocycles are very helpful in order to understand the mechanism of these reactions.[16] They observed changes in activation parameters when ILs are used as solvent in comparison with those found in aqueous solution. These differences were attributed to the solvation of the zwitterionic-like TS by dipole-dipole interactions with the ILs.[16] On the other hand, Chiappe and collaborators have used a Brønsted-type correlation to understand the mechanism of the base-catalyzed enolization reaction of 2-nitrocyclohexanone, using substituted pyridines in several ILs. They found that the β values (β >0.9) for this reaction agree with a mechanism via solvent-stabilized enolate-like TS when ILs are the reaction media.[17]

It is noteworthy that the most used tools to understand the reaction mechanisms are the activation parameters and linear free energy correlations, such as Brønsted plots. Both have been used to shed light to the mechanism of a given reaction when ILs are used as reaction solvent. For example, in the aminolysis of some esters, carboxylic acids and some phenyl-substituted ethanes, an effect of ILs on the stabilization of the reaction intermediate has been reported as responsible for the change in mechanism.[18-19] Furthermore, we have studied the reaction of 4-nitrophenyl acetate with secondary alicyclic (SA) amines in various organic solvents and ILs. A kinetic study at different temperatures was performed in order to obtain kinetic and termodynamic parameters, which were used to clarify the reaction mechanism.[20-21]

On the other hand, the effect of ILs on the nucleophilic sustitutions reactions of phosphoryl center has lately attracted the attention of some researchers. Changes in the rate constants for the ethanolysis of *O*,*O*-diethyl chlorophosphate and the piperidinolysis of *O*,*O*-diethyl 4-nitrophenyl phosphate and *O*,*O*-diethyl 2,4-nitrophenyl phosphate triester have been reported when ILs are the reaction media.[22-24] These studies have concluded that both, the rate constant and product distribution of

these reactions, are strongly dependent on the structure of the anion and cation of the IL. Nevertheless, the mechanism of these reactions was not investigated.

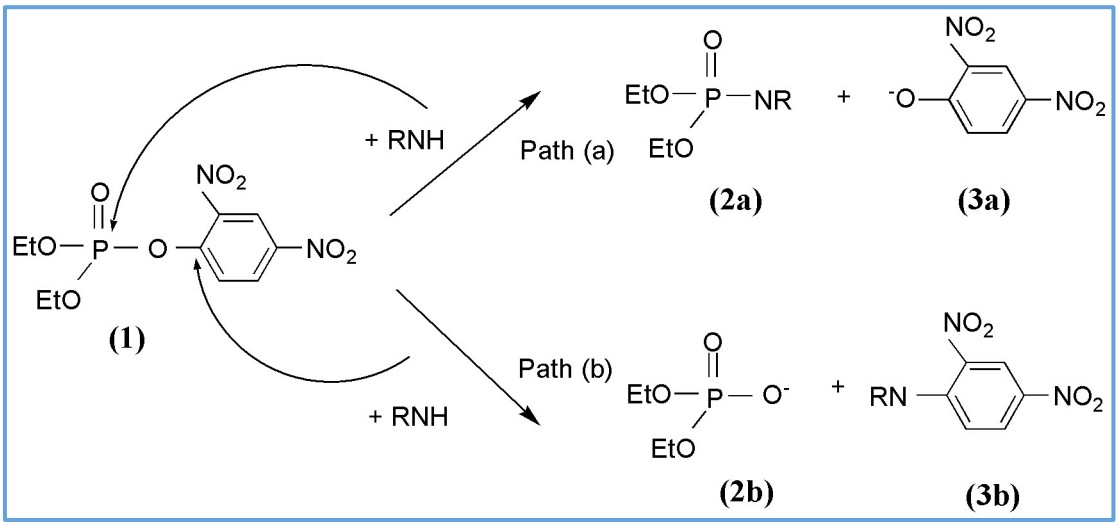
To understand more about the effect of ILs as solvents on the mechanism of nucleophilic substitution reactions of phosphoester compounds, in this work we studied the reaction of *O*,*O*-diethyl 2,4-dinitrophenyl phosphate triester (**1**) with a series of SA amines, which structures are shown in Scheme 1. Firstly we investigated the reaction of **1** with piperidine at several temperatures in order to determine the activation parameters in aqueous ethanol (44 w% ethanol), [Bmim]BF_4 and [Bmim]DCA. Secondly we studied the reaction of **1** with morpholine, 2-(1-hydroxyethyl)piperazine and 1-formylpiperazine in [Bmim]BF_4 and [Bmim]DCA solutions in order to determine the reaction mechanism. We have chosen these SA amines, because they constitute a homogenous series of amines without possible steric effects. The kinetic experiments were followed by UV−vis spectrophotometry and the product analyses by UV−vis and ^{31}P NMR techniques.



Scheme 1: Reaction under study and structures of ionic liquids [Bmim]BF_4 and [Bmim]DCA

Results and Discussion

Recently,[24] we have described a dual nucleophilic attack of piperidine to compound **1** in different ILs: one pathway is the attack toward the phosphoryl center and the other toward the C-1 aromatic carbon, for most of ILs as solvent (including [Bmim]BF_4), as shown in Scheme 2. In contrast, for the same reaction in [Bmim]DCA only the attack at the phosphoryl group was observed, with the formation of the corresponding *O,O*-diethyl piperidinophosphate diester (**2a**) and 2,4-dinitrophenoxide (**3a**) as the only products; therefore, in this IL the path (b) in Scheme 2 does not take place.



Scheme 2: The nucleophilic attack of SA amines (**RNH**) to **1** in some ILs proceeds by two reactions paths: (a) at phosphorus and (b) at the C-1 aromatic carbon.

In this work, the rate constants for the reactions of **1** with SA amines, using [Bmim]BF_4 and [Bmim]DCA as solvents, were determined spectrophotometrically by following the appearance of **3a**. The rate law obtained for the reactions studied is given by eq. 1, where P and S represent the product **3a** and substrate **1**, respectively. For all reactions, pseudo-first-order rate coefficients (k_{obsd}) were obtained (under total amine excess), which are shown in Tables S1 and S2 in Supplementary Information.

According to eq. 2, where (k_N^T) is the total second-order rate constant, the plots of (k_{obsd}) against nucleophile concentration ([NH]) were linear, except those with 1-formylpiperazine, which were curved upwards. The plots always showed a slightly negative intercept. This behavior was reported before in ILs derived from imidazole,[25] which was attributed to an acid–base interaction between the acidic imidazolium ion and the amine.

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

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

In a parallel reaction as that of scheme 2 for the reactions in [Bmim]BF_4, the (k_{obsd}) corresponds to the addition of the pseudo-first-order rate constants of each contribution, as shown in equation 3, where the terms (k_{obsd}^P) and (k_{obsd}^{Ar}) are the individual rate constants for attack at the phosphate and aromatic groups, respectively.

$$\left(k_{obsd}\right) = \left(k_{obsd}^P\right) + \left(k_{obsd}^{Ar}\right) \quad (3)$$

In parallel first-order reactions, the quotient of products is the quotient between the corresponding individual first-order rate constants (equation 4).

$$\left(k_{obsd}^P\right) / \left(k_{obsd}^{Ar}\right) = 2a / 2b \quad (4)$$

Considering that the product distribution (**2a**/**2b**) is 0.25 in the reaction of **1** with all the SA amines used in this study (see ^{31}P-NMR spectra in Figure S1 in the Supplementary Information), the values of the individual pseudo-first-order rate constants were obtained. Similarly obtained were the individual second-order rate constants for attack at phosphoryl center (k_N^P) and at the aromatic C-1 (k_N^{Ar}). The second-order rate constants are given in Table 1. For the same reaction in [Bmim]DCA the (k_N^P) values are equal to (k_N^T) and are also shown in Table1.

It is important to mention that the kinetic discussion in this work only considers the S_N2(P) pathway in both solvents and that in the studied reactions the media contained approximately 10% v/v MeCN (see the experimental part), which means that the molar fraction of the ILs (X_{IL}) is approximately 0.5. Considering that at high concentrations of IL (in binary mixtures with less polar cosolvents) the IL effect as solvent is due to the existence of ionic pairs,[26.] it is expected that in the experimental conditions used in this study the solvent effect may be the same as that of a neat ionic liquid. In addition,

recently results of Harper et al, show that the kinetics and thermodynamic parameters for the ethanolysis of diethyl chlorophosphate do not change significantly in the of 0.3-0.7 X_{IL} range.[22]

Table 1. Nucleophilic rate constants for the reaction of **1** with SA amines in [Bmim]BF_4 and [Bmim]DCA at 25 ºC ±0.1.

	[Bmim]BF_4	**[Bmim]DCA**	
SA amines	$k_N^P / M^{-1}s^{-1}$	$k_N^{Ar} / M^{-1}s^{-1}$	$k_N^P / M^{-1}s^{-1}$
Piperidine	0.890±0.03	3.54±0.13	7.60±0.34
1-(2-Hydroxyethyl)piperazine	0.208±0.01	0.65±0.05	1.50±0.05
Morpholine	0.068±0.002	0.31±0.01	0.55±0.01

Uncertainties quoted represent the standard deviation of at least three replicates.

Plots of (k_{obsd}^P) against amine concentration show first-order kinetics with respect to amine for the reactions of **1** with piperidine, 1-(2-hydroxyethyl)piperazine and morpholine, in [Bmim]BF_4 and in [Bmim]DCA solutions, according to eqn. 2 (see Figure S2 and S3, respectively, in Supplementary Information). Nevertheless, the reaction with 1-formylpiperazine, in both ILs, showed a kinetic behavior according to a second-order polynomial equation, as shown in Figure 1.

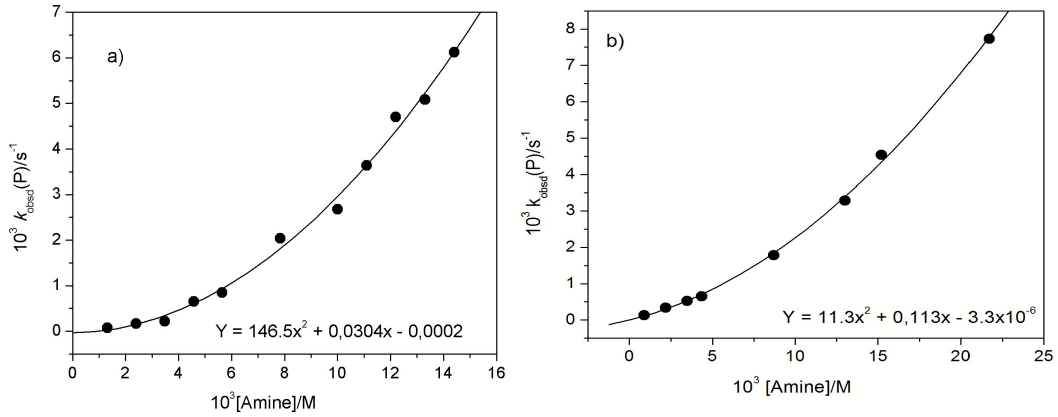
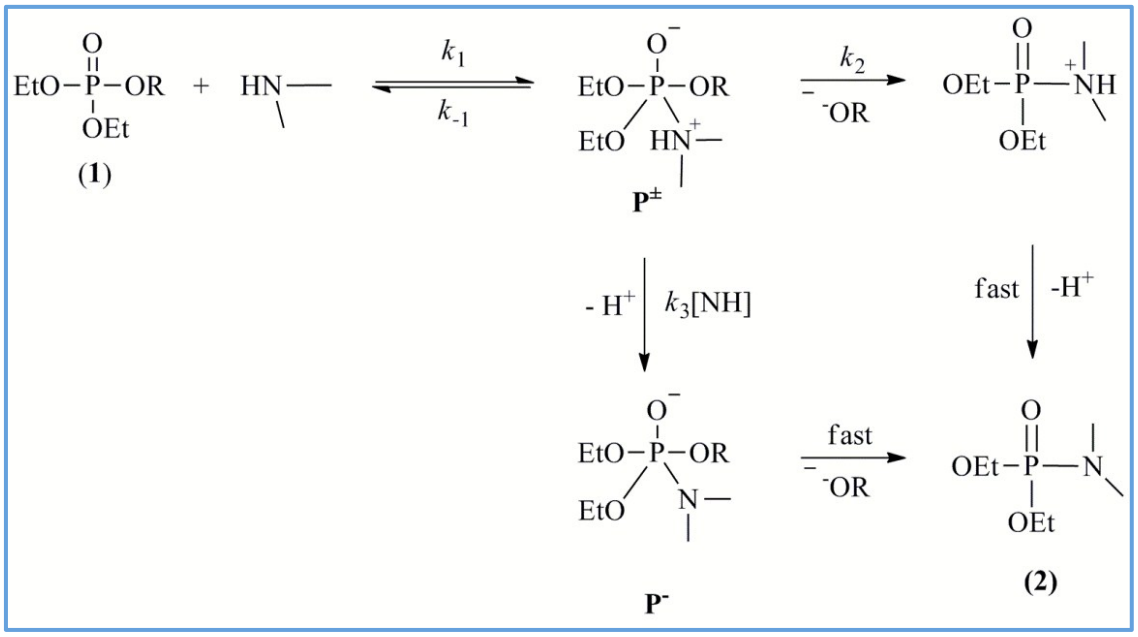


Figure 1. Plots of k_{obsd} vs. [1-formylpiperazine] for the reaction of substrate 1 in a) [Bmim]BF_4 and b) [Bmim]DCA at 25.0 ± 0.1. The line best fits to an order 2 polynomial.

The kinetic behavior of the nucleophilic attack at the phosphoryl moiety by the different SA amines in [Bmim]BF_4 and [Bmim]DCA is consistent with the mechanism described in Scheme 3. In this scheme, the k_3 step is the deprotonation of the zwitterionic pentacoordinate intermediate $\mathbf{P}^{\pm}$ by the amine to give the anionic intermediate $\mathbf{P}^{-}$.



Scheme 3: Stepwise mechanism for the reaction of **1** with SA amines in ILs.

Applying the steady-state condition to the zwitterionic pentacoordinate intermediate $\mathbf{P}^{\pm}$ in Scheme 3, eq. 5 is obtained.

$$k_{obsd} = \frac{k_1(k_2 + k_3[\mathrm{NH}])[\mathrm{NH}]}{k_{-1} + k_2 + k_3[\mathrm{NH}]} \qquad (5)$$

For the reactions of **1** with the three more basic SA amines, where linear plots (k_{obsd}) *vs* [NH] were obtained, $k_{-1} << k_2 + k_3[\mathrm{NH}]$ and eq. 5 reduces to eq. 6; therefore the nucleophilic rate constants k_N in Table 1 correspond to k_1, the formation of the zwitterionic pentacoordinate intermediate $\mathbf{P}^{\pm}$ of Scheme 3.

$$k_{obsd} = k_1[\mathrm{NH}] \qquad (6)$$

For the reactions of **1** with 1-formylpiperazine in [Bmim]BF_4 and [Bmim]DCA, the plots are fitted through a second-order in amine polynomial equation. This can be accounted for by assuming that $k_{-1} >> k_2 + k_3[\mathrm{NH}]$, which is reasonable for a weakly basic amine. In addition, the polynomial equation shows that the second-order in amine term is the most important, i.e $k_2 << k_3[\mathrm{NH}]$. These inequalities reduce eq. 5 to eq. 7, where $K_1 = (k_1/k_{-1})$ is the equilibrium constant for the formation of the intermediate $\mathbf{P}^{\pm}$ in Scheme 3. A linear plot of k_{obsd} *vs*. $[\mathrm{N}]^2$ confirms this result. (See Figure S4 in Supplementary Information).

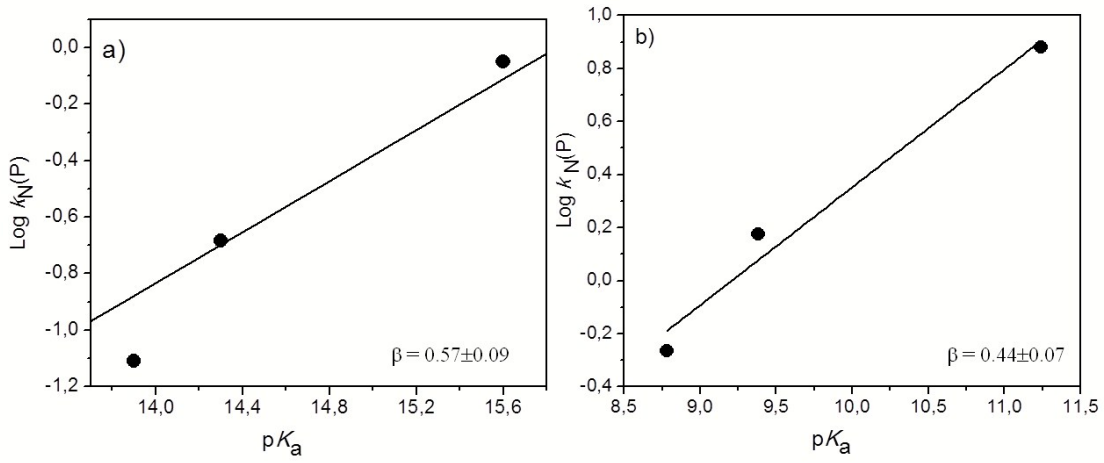
$$k_{obsd} = K_1 k_3[\mathrm{NH}]^2 \qquad (7)$$

The kinetic behavior for the $S_N2(P)$ pathway found in [Bmim]BF_4 and [Bmim]DCA, would indicate a stepwise mechanism proceeding through of a zwiterionic pentacoordinate intermediate $\mathbf{P}^{\pm}$ (Scheme 3).

It is interesting to note that although the k^P_{obsd} against [1-formylpiperazine] plots in ILs are curved up, the same plots in aqueous ethanol solution are linear, at similar concentrations.[27] This can be attributed to a mechanistic change from concerted to

stepwise in going from aqueous ethanol to ILs solvents. In fact, considering the polar character of the zwitterionic intermediate $\mathbf{P}^{\pm}$, this will be more stabilized, by solvation, in a more ionic neighborhood, favoring its formation and, therefore, the stepwise mechanism.

To obtain more information about the effect of ILs on the mechanism of the title reactions, Brønsted plots (log k_N^P *vs* pK_a) were obtained in both ILs. The pK_a values of the conjugate acid of the SA amines were determined in [Bmim]BF_4 by the method described previously by us.[28] Figure 2a shows the linear Brønsted plot for the reactions in [Bmim]BF_4 with a slope value of $\beta = 0.57 \pm 0.09$.



Figures 2: Brønsted plots for the reactions of **1** with SA amines in (a) [Bmim]BF_4 and (b) [Bmim]DCA

On the other hand, in order to obtain the Brønsted-type plot for the reactions in [Bmim]DCA we used the pK_a of the conjugate acid of SA amines determined in water.[29] As discussed in our previous report,[28] we had tried to determine the pK_a of the conjugate acid of SA amines in this IL by a methodology using cyclic voltammetry. But any attempt was infructuous due to the high basicity of the DCA anion, which locks the redox processes, H^+/H_2 and AmH^+/Am. For this reason and taking into

account that a linear relationship was found between the pK_a of the conjugate acid of SA amines in [Bmim]BF_4[20] and in water, (see Figure S5 in Supplementary Information), the Brønsted plot for the title reaction in [Bmim]DCA was drawn by using the pK_a in water (log k_N^P *vs*. p$K_{a(water)}$), Figure 2b. This plot is linear with slope value $\beta = 0.44 \pm 0.07$.

As was mentioned, the k_N values in Table 1 correspond to the k_1 values, therefore the β values correspond to the first step. Considering that the β value describes the development of charge on the nucleophilic atom (N atom) from reactants to the transition state, the Brønsted-type plot has been a very good tool to determine reaction mechanisms in water and in organic solvents.[30] In this study the β values found in both ILs are greater than those described for reactions in aqueous solution where the first step is rate determining (β = 0.1-0.3). However, it is well known that the β values of the reactions of phosphoryl transfer depend on both the nucleophile nature and the alkylation state of the phosphate derivative.[31-33] Therefore, the Brønsted slope values obtained in this work by themselves are not sufficient to support a two-step mechanism for the title reaction.

Taking into account that the mechanism proposed in Scheme 3 proceeds through a zwitterionic pentacoordinate intermediate, $\mathbf{P^{\pm}}$, this should be more stabilized in an IL than in water solution. Therefore, we are prone to accept a change in mechanism of the $S_N2(P)$ pathway for the aminolysis of **1** in ILs, from a concerted in aqueous ethanol to a stepwise, through a $\mathbf{P^{\pm}}$ intermediate, when [Bmim]BF_4 and [Bmim]DCA are the solvents of the reaction.

Finally, by Arrhenius and Eyring plots, the activation parameters of the reaction of **1** with piperidine were obtained in [Bmim]DCA, [Bmim]BF_4 and 44 w% ethanol-water as solvents, at the 20-40ºC range, see Figures S6 – S8 in Supplementary Information . In these experimental conditions the product analysis shows that in [Bmim]BF_4 the relative attack to the phosphoryl center remains constant over the temperature range (20%, see Figure S9 in Supplementary Information). The values of k_{obsd} , k_N^T , k_N^P and

k_N^{Ar} were determined for each temperature in [Bmim]DCA, [Bmim]BF_4 and 44 w% EtOH:H_2O, respectively, and are summarized in Tables S3-S5, in Supplementary Information. With the k_N^P values and using the Eyring equation, the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values, shown in Table 2, were obtained.

Table 2: Activation parameters for the reaction of **1** with piperidine in [Bmim]BF_4, [Bmim]DCA and 44 w% EtOH:H_2O.

Solvent	E_a /kcal mol^{-1}	$\Delta H^{\neq}$/kcal mol^{-1}	$\Delta S^{\neq}$/cal K^{-1}mol^{-1}
[Bmim]BF_4	4.26±0.6	3.65±0.6	-43.7±11
[Bmim]DCA	3.61±0.2	3.01±0.2	-44.1±14
44 w% EtOH:H_2O	13.9 ±1.5	13.5 ±1.5	-14.4 ±2.5

Examination of $\Delta H^{\neq}$ y $\Delta S^{\neq}$ values found in aqueous ethanol compared to those in both ILs shows that the studied reaction is sensitive to the solvent used. The more negative $\Delta S^{\neq}$ values in [Bmim]BF_4 and [Bmim]DCA than in water-ethanol is not surprising since a charge-separated transition state (TS) should be more solvated in ionic media than in aqueous ethanol (44 w% ethanol). This solvation comes together with the solvent rearrangement around the TS, thus the TS becomes more ordered relative to reactants.[19] The $\Delta H^{\neq}$ and $\Delta S^{\neq}$ behavior by changing the molecular solvent to ILs points in the same direction that those described by Harper et al in the ethanolysis reaction of diethyl chlorophosphate, *ie*, the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values decrease on going from water to IL.[22] Nevertheless, these changes in thermodynamic parameters could not be the responsible of the mechanism change, from concerted in aqueous ethanol to stepwise mechanism in both ILs.

Conclusions

For the title reactions, the kinetic behaviour allows to conclude that there is a change in the mechanism from concerted in aqueous ethanol to stepwise in $[Bmim]BF_4$ and [Bmim]DCA. This change could be attributed to a greater stabilization of the zwitterionic pentacoordinate intermediate $\mathbf{P}^{\pm}$ (Scheme 3) in an IL than in aqueous ethanol.

From Arrhenius and Eyring plots the activation parameters were obtained ($\Delta H^{\neq}$ and $\Delta S^{\neq}$). These values decrease on going from water to IL. Nevertheless, these changes in thermodynamic parameters could not be the responsible of the mechanism change, from concerted in aqueous ethanol to stepwise mechanism in both ILs.

The more negative $\Delta S^{\neq}$ value in $[Bmim]BF_4$ and [Bmim]DCA found in this study, could be due to a charge-separated TS, which should be more solvated in ionic media than in aqueous solution.

Experimental Section

Materials. $[Bmim]BF_4$ and [Bmim]DCA and SA amines were purchased from Aldrich. The ILs were dried before use in vacuum oven at 70°C over night, 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.[34]

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 concentration of substrate **1** on the cell was 1.8×10^{-4} M, whilst the range concentrations of SA amines were 9×10^{-4} to 2.2×10^{-2} M. The spectra were recorded at different reaction times and pseudo-first-order rate coefficients (k_{obsd}) were found for all reactions (See kinetic details in Supplementary Information)

The activation parameters were determined at the same experimental conditions as above, at the 20-40ºC temperature range, by using Arrhenius and Eyring equations. In

these experimental conditions the product analysis shows that in [Bmim]BF_4 the relative attack at the phosphoryl center remains constant within the temperature range (20%, see Figure S9 in Supplementary Information).

Product Studies. In order 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.

At the end of the reactions of **1** with piperidine, 1-(2-hydroxyethyl)piperazine, morpholine and 1-formylpiperazine in BmimDCA, the ^{31}P NMR spectra show only one signal at 8.89 ppm, attributed to *O*,*O*-diethyl piperidine phosphate,[23] Also, the UV-vis spectra at the end of the reactions corresponded to 2,4-dinitrophenoxide, by comparison with an authentic sample.

For the reactions of **1** with the SA amines in Bmim[BF_4], the ^{31}P NMR spectra show two signals: one corresponding to *O*,*O*-diethyl amine phosphate and the other assigned to *O*,*O*-diethyl phosphoric acid.[23] In these experimental conditions the product analysis shows that in the aminolysis of **1** in [Bmim]BF_4 the relative attack at the phosphoryl center remains constant, at 20%, for all SA amines (see Figure S1 in Supplementary Information).

Acknowledgments. This work was supported by project ICM-MINECON, RC-130006 - CILIS Chile, and FONDECYT, grant 1130065.

†Electronic Supplementary Information (ESI) available:

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