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# Introduction

Ionic liquids (ILs), frequently defined as salts that melt below 100 °C,<sup>1,2</sup> have often been proposed as attractive 'green' replacements for volatile organic compounds (VOCs).<sup>3,4</sup> Even though questions have been raised as to how green ILs truly are,<sup>4-6</sup> the versatility of such solvents arising from the sheer number of potential cation and anion combinations has meant extensive work has been undertaken to assess their influence on reactions.<sup>7-11</sup> The flexibility of IL choice means that, if the use of IL mixtures is included, the formation of a huge range of potential solvent systems is possible (estimated to be up to 10<sup>18</sup> on the assumption that mixtures of ILs are considered to be 'new' solvent systems).<sup>12</sup> To enable the rational selection of such solvents from such a vast pool, a thorough understanding of the effects of the variation of each component and correspondingly of mixtures of those components is required.

In addition to directly influencing solvent-solute interactions through the choice of cation and anion pair, ILs have

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# Steric, hydrogen-bonding and structural heterogeneity effects on the nucleophilic substitution of *N*-(*p*-fluorophenyldiphenylmethyl)-4-picolinium chloride in ionic liquids†

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The nucleophilic substitution of *N*-(*p*-fluorophenyldiphenylmethyl)-4-picolinium chloride was investigated using water and a range of alcoholic nucleophiles in ionic liquid solvents. The reactivity patterns across the nucleophiles examined could be attributed to steric factors, which mediated the relative nucleophilicities. Reducing the hydrogen-bond acidity of the ionic liquid cation was found to generally increase the rate of reaction, however, the magnitude of this rate effect could be influenced by the steric bulk of the nucleophile and the structural heterogeneity of the ionic liquid. Preferential solvation phenomena in binary mixtures of ionic liquids were examined and suggest that the mechanism behind the hydrogen-bond solvation phenomenon arises from direct cation-mediated, rather than indirect anion-mediated, effects.

been shown to possess an array of interesting structural features that can influence reactivity. One of these is the formation of heterogeneous structures on elongation of the alkyl chain on the IL, with the creation of polar and non-polar domains.<sup>13–16</sup> For imidazolium systems it has been found that ILs, bearing alkyl chains longer than propyl, are capable of forming such heterogeneous structures.<sup>17</sup> ILs are also capable of forming liquid clathrates around aromatic solute molecules, leading to the relatively greater solubility of aromatic compounds relative to aliphatics in these solvents.<sup>18-21</sup> Although the use of such phenomena to account for unusual reaction outcomes in ILs is still in its infancy, recently some examples have emerged implicating such effects in unusual reaction outcomes.<sup>22-24</sup> The consideration of these effects is, therefore, important for the interpretation of any results obtained within IL systems.

Nucleophilic substitution reactions have been investigated within ILs utilising an array of substrates, ranging from  $S_N 1$ substitutions of alkyl chlorides<sup>25–27</sup> and aryl diazonium salts<sup>28,29</sup> to  $S_N 2$  reactions between amines and neutral or charged electrophiles<sup>30–35</sup> or halides and an array of electrophiles.<sup>33,36–41</sup> In these investigations, when multiple ILs were employed, the resultant reactivity could frequently be correlated with solvation parameters through linear solvation energy relationships (LSERs),<sup>42</sup> implying that a combination of microscopic solvation effects could account for the observed behaviour. The most frequently employed parameters for such correlations are those described by Kamlet and Taft. These parameters account for solvation behaviour in terms of the solvent's hydrogen-bond acidity ( $\alpha$ ), hydrogen-bond basicity ( $\beta$ )

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<sup>†</sup>Electronic supplementary information (ESI) available: Full details of the synthesis and characterisation of ILs and reaction products, mole fractions of ILs, LFER details, Kamlet–Taft correlations for ethanol, 1-50 butanol and phenol, preferential solvation data for benzyl alcohol, rate dependence on nucleophile concentration and correlation of hydrogen-bond effect with Charton's steric parameter. See DOI: 10.1039/c30b40105g

and dipolarity/polarisability  $(\pi^*)$ .<sup>43–45</sup> A notable exception is the nucleophilic substitution of a sulfonium salt with halide nucleophiles, where the reactivity could be attributed to the random distribution of ion-pairs within the IL, *i.e.* an 'ILeffect'.<sup>39–41</sup>

Another example of such an 'IL-effect' involves the nucleophilic substitution of N-(p-fluorophenyldiphenylmethyl)-4picolinium chloride ([Ar<sub>3</sub>CPic][Cl]), which was recently shown to be influenced by the structural heterogeneity of the IL.<sup>22</sup> Within that investigation, reaction rate enhancements were observed with increasing IL alkyl chain length. For that reaction system, rate increases were also detected upon reducing the hydrogen-bond acidity of the IL solvent, although only water was examined as a nucleophile.46 Importantly, the magnitude of the rate increase resulting from the structural heterogeneity of the IL was found to be substantially greater than that which could be attributed to hydrogen-bonding effects.<sup>22,46</sup> As the investigation into the interplay between the hydrogen-bonding and structural effects of the solvent was limited in these reports to water being used as a nucleophile, it is necessary to extend this study to a wider range of hydroxylic nucleophiles to develop a more thorough understanding of such solvent effects.

Furthermore, the previous investigations on this reaction system have uncovered several interesting phenomena that have not been fully explored thus far. Firstly, a linear relationship between the rate constant and solvent composition was observed in binary mixtures of 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([BMIM][NTf2]) and 1butyl-2,3-dimethylimidazolium bis(trifluoromethanesulfonyl)imide ([BMMIM][NTf<sub>2</sub>]) for the hydrolysis of [Ar<sub>3</sub>CPic][Cl].<sup>46</sup> This result is in stark contrast to the interaction of Reichardt's dye with these solvent mixtures, where significant preferential solvation was observed. The underlying nature of this discrepancy was not further investigated in the original study. Another unexplained experimental result was that the rate constant for the hydrolysis of [Ar<sub>3</sub>CPic][Cl] in [BMIM][NTf<sub>2</sub>] was significantly lower than anticipated from the fitted kinetic model for the structural heterogeneity of the IL.<sup>22</sup> Interestingly, all the other IL and nucleophile combinations gave an excellent fit to the model suggesting the poor fit discovered for water and [BMIM][NTf<sub>2</sub>] was due to a fundamental difference in solvent behaviour for this specific case. Finally, it was found that using ethanol as a nucleophile compared to water and methanol led to a smaller rate constant,<sup>22</sup> despite an earlier literature report<sup>47</sup> on a closely related reaction finding that the reaction involving ethanol proceeded substantially faster than with water.

To thoroughly explore the issues outlined above, many different nucleophiles have been examined in the present work. Furthermore, the ILs examined as solvents include the combination of 1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([EMIM][NTf<sub>2</sub>]) and [BMIM][NTf<sub>2</sub>] to investigate the consequences of structural heterogeneity, [BMMIM][NTf<sub>2</sub>] to isolate hydrogen-bonding effects and 1-butyl-1-methylpyrrolidinium bis(trifluoromethanesulfonyl)-



Fig. 1 Structure of cations and anion used in this investigation, with the corresponding abbreviations.

 Table 1
 Kamlet–Taft parameters for all ILs investigated, data obtained from ref. 48

Ionic liquid	α	β	$\pi^*$
[EMIM][NTf <sub>2</sub> ]	0.63	0.23	1.00
BMIM NTf2	0.61	0.23	0.99
[BMPyrr][NTf <sub>2</sub> ]	0.43	0.24	0.95
[BMMIM][NTf <sub>2</sub> ]	0.38	0.26	1.02

imide [BMPyrr][NTf<sub>2</sub>] to enable further examination of the hydrogen-bonding effects as well as the determination of whether the aromaticity of the cation has any specific consequences for aromatic nucleophiles. The structures of the cations and the anion used in all the ILs discussed herein are depicted in Fig. 1 with their corresponding Kamlet–Taft parameters detailed in Table 1.

# **Results and discussion**

Scheme 1 outlines the general reaction investigated, including the range of nucleophiles and solvents examined. It should be noted that the mole fraction of IL employed for all reaction systems was always greater than 0.73, so the IL constitutes the bulk of the reaction medium. The precise IL mole fractions for every nucleophile and IL combination are detailed in the ESI.<sup>†</sup> [Ar<sub>3</sub>CPic][Cl] was generated *in situ* from *p*-fluorophenyldiphenylmethyl chloride (FDMC) and the nucleophilic substitution reactions monitored using <sup>19</sup>F{<sup>1</sup>H} NMR, as has previously been reported.<sup>22,46</sup> 4-Picoline was selected as the leaving group for experimental convenience to enable data to be collected



 $\label{eq:scheme 1} \begin{array}{l} \text{Nucleophilic substitution of } [Ar_3CPic][CI] \text{ in a range of } ILs. R = H, \\ \text{Me, Et, 1-Pr, 2-Pr, 1-Bu, Bn and Ph. IL = [EMIM][NTf_2], [BMIM][NTf_2], [BMPyrr]-[NTf_2] and [BMMIM][NTf_2]. \end{array}$ 

 
 Table 2
 Summary of pseudo-first-order rate constants obtained for the nucleophilic substitution of [Ar<sub>3</sub>CPic][CI] at 294.3 K. Reported errors are standard deviations from at least 3 replicate experiments

Rate constants $(10^{-4} \text{ s}^{-1})$					
Nucleophile	[EMIM]- [NTf <sub>2</sub> ]	[BMIM]- [NTf <sub>2</sub> ]	[BMPyrr]- [NTf <sub>2</sub> ]	[BMMIM]- [NTf <sub>2</sub> ]	
H <sub>2</sub> O	$8.7 \pm 0.3$	$10.6 \pm 0.2$	16.1 + 1.0	$18.8 \pm 0.4$	
MeOH	$17.4 \pm 0.2$	$23.9 \pm 1.0$	$28.2 \pm 2.0$	$32.4 \pm 1.4$	
EtOH	$6.4 \pm 0.2$	$8.5 \pm 0.1$	$10.8\pm1.0$	$10.6 \pm 0.2$	
1-PrOH	$6.5 \pm 0.1$	$8.6 \pm 0.7$	$10.5 \pm 1.4$	$11.0\pm0.4$	
1-BuOH	$7.3 \pm 0.4$	$8.9\pm0.6$	$12.9\pm0.3$	$12.1\pm0.7$	
BnOH	$3.0 \pm 0.1$	$4.1 \pm 0.3$	$4.4 \pm 0.3$	$4.8 \pm 0.1$	
PhOH	$2.7 \pm 0.2$	$4.1 \pm 0.5$	$4.0 \pm 0.4$	$3.7 \pm 0.2$	
2-PrOH		$\textbf{0.28} \pm \textbf{0.01}$		$\textbf{0.36} \pm \textbf{0.01}$	

over a reasonable time scale near room temperature. The reaction rate has been previously shown not to depend on the concentration of 4-picoline,<sup>46</sup> nonetheless, the concentration of 4-picoline was maintained at 0.49 M for all reactions. The nucleophile was used in excess, and all reactions monitored gave excellent fits to the integrated first-order rate law. The pseudo-first-order rate constants obtained are summarised in Table 2. The initial nucleophile concentrations in all cases were maintained at 0.515 M, meaning that the pseudo-firstorder rate constants are directly comparable across the range of nucleophiles and ILs. To ascertain the specific dependence of the reaction rate on nucleophile concentration, the concentration of water, methanol and ethanol used for this reaction were varied in [EMIM][NTf<sub>2</sub>] (see ESI<sup>+</sup>). From these results it is apparent that a first order dependence on the nucleophile is observed, demonstrating that the reaction studied is bimolecular, as has been reported previously.22,46

#### Nucleophile effects

The results in Table 2 demonstrate significant variation across the range of nucleophiles. Firstly, upon changing the nucleophile from water to methanol the rate constant increases within every solvent examined, as would be anticipated from the greater nucleophilicity of methanol.<sup>49</sup> When ethanol is employed as a nucleophile, however, the observed rate constant is significantly smaller than that observed for methanol and water, an effect which cannot be attributed to the order of nucleophilicity. Furthermore, as the length of the linear alkyl chain on the nucleophile is extended, no additional kinetic effects are observed with the rate constants for ethanol being consistent with those for 1-propanol and 1-butanol within most solvents.

The electron-withdrawing effect of the aromatic substituent of phenol and benzyl alcohol leads to the reduced nucleophilicity of these species and correspondingly their reduced rate constants relative to the aliphatic alcohols. However, the similarity of such rate constants is surprising given that benzyl alcohol would be expected to be substantially more nucleophilic than phenol.

It is the significant decrease in the rate constant observed for 2-propanol compared with the other nucleophiles in both [BMIM][NTf<sub>2</sub>] and [BMMIM][NTf<sub>2</sub>] that suggests the underlying cause for the apparent rate discrepancies. Since 2-propanol results in rate constants more than an order of magnitude smaller than those of 1-propanol, it is clear that effects other than nucleophilicity are important. It would appear that steric hindrance induced by  $\alpha$ -substituents on the alcohol account for such behaviour and explain the significant reduction in the rate constant for 2-propanol and ethanol. The planarity of the phenyl substituent in phenol could account for the similarity in rate constants between phenol and benzyl alcohol, where the anticipated increased nucleophilicity of benzyl alcohol is offset by its larger effective steric bulk.<sup>50</sup> The greater relative acidity of phenol, however, means that deprotonation by the excess 4-picoline to yield a more nucleophilic phenolate anion cannot be eliminated as an alternative.

Attempts to fit these data to Charton steric parameters<sup>50,51</sup> and the Mayr nucleophilicity parameters<sup>52</sup> resulted in the anticipated correlation. However, the lack of available nucleophilicity data meant that only 5 nucleophiles could be included in each analysis. Consequently, these fits had large standard errors and limited statistical significance ( $0.08 ) for the three parameters fitted. Therefore, these correlations will not be discussed further in the main text, although a more comprehensive analysis can be found in the ESI.<sup>†</sup> It can be safely surmised, however, that the variation of rate constants across the range of nucleophiles arises not only from the order of nucleophilicity, but more significantly from the steric hindrance of the <math>\alpha$ -substituents of the alcohol.

#### Cation effects

From Table 2, it is apparent that varying the solvent leads to significant rate effects for most nucleophiles examined. For all alcohols, with the exception of phenol, the reduction of the hydrogen-bond acidity of the solvent through the use of [BMMIM][NTf<sub>2</sub>] rather than [BMIM][NTf<sub>2</sub>] as a solvent, yielded an increase in the rate constant. To compare the magnitude of this increase, the rate constants obtained in [BMIM][NTf<sub>2</sub>] have been divided by those observed in [BMIM][NTf<sub>2</sub>] for the corresponding nucleophile (Table 3). As the hydrogen-bond acidity is the only significant difference between these ILs, it can be concluded that this ratio is correlated with any 'hydrogen-bond effect' in the reaction.

Upon examination of Table 3, it is evident that hydrogenbonding has a larger effect on water than any of the other

 Table 3
 Ratios of rate constants observed in [BMMIM][NTf<sub>2</sub>] divided by those

 in [BMIM][NTf<sub>2</sub>]. Reported errors are the propagated standard deviations

Nucleophile	$k_{ m BMMIM}/k_{ m BMIM}$	
H <sub>2</sub> O	$1.77\pm0.05$	
MeOH	$1.35\pm0.08$	
EtOH	$1.25\pm0.02$	
PrOH	$1.29\pm0.12$	
BuOH	$1.36\pm0.12$	
BnOH	$1.18\pm0.09$	
PhOH	$0.89\pm0.11$	
2-PrOH	$1.27\pm0.06$	

nucleophiles. This is somewhat counter-intuitive as water should be the weakest hydrogen-bond acceptor, with the exception of phenol. The result implies that in the sterically hindered transition state, interactions between the cation and the nucleophile are somewhat restricted for the alcohols relative to the substantially less hindered water molecule. Alternatively, the observed hydrogen-bond effect may arise from the weaker cation–anion interactions, in turn leading to stronger nucleophile–anion and electrophile–anion interactions. The evidence for or against each of these potential mechanisms will be discussed in more detail within the next section.

As discussed above, it is evident that hydrogen-bonding can account for at least some of the apparent solvent-induced rate behaviour and it is clear (from Table 1) that the  $\alpha$  parameter is the only Kamlet–Taft parameter that varies significantly upon changing the IL cation. Therefore, an attempt to correlate the observed rate constant with the  $\alpha$  parameter of each IL was made. Fig. 2 depicts some representative examples of such correlations and it is apparent that while this fit is appropriate for water, it breaks down significantly for most of the other alcohols.

Notably in all of these correlations except for water, the value for [EMIM][NTf<sub>2</sub>] ( $\alpha = 0.63$ ) is below the trend, suggesting that the discrepancy in the rate constants between [EMIM]-[NTf<sub>2</sub>] and the other ILs examined is likely due to a systematic factor other than hydrogen-bond acidity. This is consistent with the excellent fits to the domain models obtained in our earlier communication for all alcohols except for water,22 implying that such a breakdown in the dependence on hydrogen-bond acidity can be attributed to the structural heterogeneity of the IL. Interestingly, the good correlation observed for water implies that it is sufficiently dissociative in 0.515 M concentrations in [BMIM][NTf<sub>2</sub>], such that the inherent heterogeneity of this IL is affected. The other noteworthy result is that no significant outlier behaviour is observed for [BMPyrr][NTf<sub>2</sub>] with any of the aromatic alcohols, confirming that the solvation of aromatics is not strongly influenced by the aromaticity of the cation itself. This supports the view that the strong interactions between aromatic molecules and ILs reported in the literature result primarily from ion-quadrupole rather than  $\pi$ - $\pi$  interactions.<sup>20,21,53</sup>



**Fig. 2** Linear correlation between the observed pseudo-first-order rate constants and the Kamlet–Taft  $\alpha$  parameter of the IL solvent for (clockwise from top left): water, methanol, 1-propanol and benzyl alcohol. Similar correlations for the other nucleophiles are given in the ESI.†

#### **Preferential solvation**

In addition to the results in the neat ILs; water, methanol, ethanol and 1-butanol were examined in a range of binary [BMIM][NTf<sub>2</sub>]:[BMMIM][NTf<sub>2</sub>] mixtures. These experiments were conducted in an attempt to isolate the origin of the preferential solvation differences observed previously between water as a nucleophile in this reaction system and Reichardt's dye as a solvatochromic probe.<sup>46</sup> It was hypothesised that the difference in size and, hence, rate of diffusion of the two molecules, or the variation in their hydrogen-bond accepting ability. The magnitude of any preferential solvation phenomenon would also yield additional information as to the nature of the hydrogen-bond effect discussed previously.

The rate constants observed in these binary mixtures were fitted to a simple preferential solvation model that models the solvation of the solute molecule (R) as an equilibrium between solvent 1 ( $S_1$ ) and solvent 2 ( $S_2$ ), as outlined in eqn (1). Such a model has been traditionally utilised for the preferential solvation of solvatochromic dyes, however, its utility for representing other preferential solvation phenomena has also been demonstrated.<sup>46,54,55</sup>

$$\mathbf{RS}_1 + \mathbf{S}_2 \rightleftharpoons \mathbf{RS}_2 + \mathbf{S}_1 \tag{1}$$

From eqn (1), by assigning [BMIM][NTf<sub>2</sub>] as S<sub>2</sub> and [BMMIM][NTf<sub>2</sub>] as S<sub>1</sub>, it can be shown that the observed rate constant in binary mixtures of these ILs ( $k_{obs}$ ) can be fitted to the equilibrium constant (K), the individual rate constants in [BMIM][NTf<sub>2</sub>] and [BMMIM][NTf<sub>2</sub>] ( $k_{BMIM}$  and  $k_{BMMIM}$  respectively) and the mole fraction of [BMIM][NTf<sub>2</sub>] ( $x_{BMIM}$ ) through eqn (2).

$$k_{\rm obs} = \frac{K x_{\rm BMIM} (k_{\rm BMIM} - k_{\rm BMMIM})}{1 - x_{\rm BMIM} + K x_{\rm BMIM}} + k_{\rm BMMIM}$$
(2)

The fitted data and equilibrium constants obtained for the nucleophiles water, methanol, ethanol and 1-butanol are depicted in Fig. 3. It is worth noting that the values of *K* obtained from these fits are the inverse of those reported in our earlier publication<sup>46</sup> as  $S_2$  is now assigned to [BMIM]-[NTf<sub>2</sub>]. This modification was employed as it results in values



Fig. 3 Rate constants observed in [BMIM][NTf<sub>2</sub>]: [BMMIM][NTf<sub>2</sub>] binary solvent systems fit to the model described in eqn (2). The solid line represents the fitted model, the dashed line indicating ideal behaviour, *i.e.* no preferential solvation, is provided as a guide to the eye. Fitted K parameters and their standard error are reported.

of K greater than 1 when preferential solvation by the more hydrogen-bond acidic IL occurs. Such an analysis was also attempted for the preferential solvation of benzyl alcohol, however, the small magnitude of the hydrogen-bonding effect and large relative experimental errors precluded a meaningful fit of the model in this case. The data for benzyl alcohol are included in the ESI.<sup>†</sup> Good fits were observed for all other nucleophiles examined, and it appears that all alcohols investigated exhibit some preferential solvation by the more hydrogen-bond acidic [BMIM]<sup>+</sup> cation. Water, on the other hand, is only marginally preferentially solvated and it appears the preference is for solvation by the [BMMIM]<sup>+</sup> cation, although such an effect lies only just outside of experimental error. It does not appear that a significant trend can be observed within the alcohols as such, but it is apparent that methanol is more preferentially solvated than either ethanol or 1-butanol.

The observation that methanol is more strongly preferentially solvated than ethanol disproves the hypothesis regarding molecular size being the main determining factor. That is, the hypothesis that the more rapid diffusion of water within the IL medium resulted in a more fully averaged solvation environment than is observed for more bulky compounds such as Reichardt's dye.<sup>46</sup> In fact, methanol is even more strongly preferentially solvated within this binary solvent system than is Reichardt's dye, despite the dye being both significantly larger and a better hydrogen-bond acceptor.<sup>46</sup> To explain such a discrepancy the origin of the preferential solvation phenomenon needs to be discussed in relation to the specific transition state structure of this reaction (*vide infra*).

#### Consideration of the reaction mechanism

With the foregoing in mind, it is instructive to consider the mechanism of the reaction in more detail. Clearly, a traditional S<sub>N</sub>2 process is unlikely due to the steric hindrance of the *p*-fluorophenyldiphenylmethyl group. Therefore, dissociation of the 4-picoline must precede the nucleophilic attack. As discussed previously, no rate dependence with 4-picoline concentration is observed,<sup>46</sup> indicating the absence of leaving group return. Furthermore, we have found a firstorder dependence on the nucleophile concentration for a range of nucleophiles, illustrating that it is truly a bimolecular process. Collectively these results imply that although 4-picoline dissociation must occur first, nucleophilic attack must proceed prior to the solvent separation of the carbocation and 4-picoline. Correspondingly, the transition state of such a process would be exceptionally congested, resulting in the significant steric dependence observed for the nucleophile. Fig. 4 gives a simplified representation of some potential steric interactions in the transition state.

Such significant steric effects were not observed for the nucleophilic substitution of a comparable pyridinium salt in nitromethane using water and ethanol.<sup>47</sup> The most likely explanation lies with the reduced basicity of the pyridine leaving group used in the earlier study relative to 4-picoline used in the present study. This reduced basicity would decrease the strength of the C–N bond and increase the extent of leaving



**Fig. 4** A simplified structure representing some potential steric interactions in the proposed reaction transition state. The solvent has been omitted for clarity.

group dissociation in the rate determining step. Alternatively, the presence of the bulky  $[NTf_2]^-$  anion in the IL system could contribute to this discrepancy as the interaction of this anion with the  $[Ar_3CPic]^+$  cation would further crowd the transition state compared to the interaction with the substantially smaller chloride anion in nitromethane.

From the preceding discussion, it is apparent that the hydrogen-bond effect has less of an impact on the alcohols than water despite the former, with the exception of phenol, being better hydrogen-bond acceptors. Consequently, two hypotheses have been presented. Firstly, that the steric congestion in the transition state means that alcohols, which are more sterically hindered, are less able to be affected by the solvating cation in the reaction transition state and therefore exhibit a smaller rate enhancement upon reduction of the hydrogen-bond strength of the medium. Alternatively, the 'hydrogen-bond effect' being observed could be a result of reduced cation-anion interactions within the ILs, leading to stronger substrate-anion interactions. As water and alcohols have been established to form strong hydrogen-bonds with the anion in IL systems,<sup>56,57</sup> such an effect could result in increased interactions between the nucleophile and [Ar<sub>3</sub>CPic]<sup>†</sup> cation.

To distinguish between these mechanisms, it is important to consider the preferential solvation of the aliphatic alcohols by [BMIM][NTf<sub>2</sub>] with respect to [BMMIM][NTf<sub>2</sub>]. If the nature of the hydrogen-bond effect were anion-dominated then it would be anticipated that the nucleophiles most capable of hydrogen-bonding to the anion should be most strongly affected. However, water does not exhibit any significant preferential solvation whereas methanol, ethanol and 1-butanol do, implying that a property of these alcohols renders their interaction with [BMIM][NTf<sub>2</sub>] significantly more favourable than with [BMMIM][NTf<sub>2</sub>]. This supports the direct interaction of the cation with the transition state, as anion-directing effects should influence water more strongly, while the stronger hydrogen-bond accepting properties of the alcohols could account for their preferential solvation by [BMIM][NTf<sub>2</sub>]. The observation that the preferential solvation effect is more pronounced for methanol than either ethanol or 1-butanol can potentially be accounted for, at least in part, in terms of sterics

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Fig. 5 Schematic depiction of the potential cation–nucleophile interactions in the transition state for (a) water and (b) an alcohol. The IL anions, explicit O–H bonds and hydrogen-bonding interactions between the nucleophile and 4-picoline have been omitted for clarity.

and the availability of the nucleophilic oxygen for hydrogenbonding interactions with the IL cation. The direct role of the IL cation in the transition state is depicted schematically in Fig. 5.

It is important distinguish between the steric effects being introduced to account separately for the observed trends in nucleophilicity and the hydrogen-bonding effect, as the substituents implicated in these effects are subtly different. In the former case, it is the additional steric bulk of the  $\alpha$ -substituents on the alcohol which reduces the number of allowed conformations of the nucleophile as it approaches the sterically crowded carbocationic centre, thereby reducing the observed reaction rate. In the latter case, the ability of the cation to solvate the nucleophile is dependent upon the sterics of any substituent attached *directly* to the alcoholic group. In fact, a reasonable correlation ( $R^2 = 0.868$ ) can be observed between Charton's  $\nu$  parameter and the observed hydrogen-bond effect (see ESI<sup>†</sup>). This correlation is somewhat biased by the extreme phenol and water  $\nu$  values, as the other alcohols examined possess similar steric parameter values and the magnitude of the hydrogen-bond effect observed for these alcohols was largely within experimental error. Nonetheless, this correlation is consistent with the proposal that the magnitude of the hydrogen-bond effect is predominantly determined by the ability of the solvent to directly interact with the nucleophilic oxygen in the sterically crowded transition state. Collectively, these observations illustrate that the IL cation can have a significant and direct effect on reaction rates, even for similarly charged transition states where such interactions may not be expected.

## Conclusion

The rate of nucleophilic substitution of  $[Ar_3CPic][Cl]$  in a range of ILs has been shown to depend not only on the nucleophilicity, but also the steric bulk of the  $\alpha$ -substituents of the alcohol. In addition, the effect of solvent hydrogen-bond acidity on the rate has been examined and surprisingly suggests that the steric bulk of the substituents on the nucleophile reduces the magnitude of the effect more than the hydrogen-bond basicity of the nucleophile. Furthermore, the ability to exhibit nearly ideal reaction behaviour within binary mixtures of [BMIM][NTf2] and [BMMIM][NTf2] has been shown to be unique to water, with alcohols exhibiting significant preferential solvation behaviour (where such investigations could be conducted), implicating the influence of the IL cation in the transition state of the reaction. Finally, the dependence on the hydrogen-bond acidity of the solvent indicated that the aromaticity of the cation had no specific influence on reaction rates, while structural heterogeneity led to significant disparities between the rates predicted and observed for the alcohols examined. Water was the exception with a good correlation between hydrogen-bond acidity and reaction rate for all the ILs investigated, likely as a result of the partial dissociation of the ions and breakdown of the IL structure. These results will hopefully contribute to a greater understanding of the reaction mechanism of such sterically crowded species and illuminate the effect that IL selection can have on nucleophilic substitution reactions, as well as revealing the influence even relatively small concentrations of water may have on IL structure and reactivity.

### Experimental

### General procedures

[EMIM][NTf<sub>2</sub>], [BMIM][NTf<sub>2</sub>], [BMMIM][NTf<sub>2</sub>], [BMPyrr][NTf<sub>2</sub>] and FDMC were all prepared according to literature procedures or modifications thereof<sup>58,59</sup> and characterised by NMR, ESI-MS and melting point analysis where appropriate. 4-Picoline (Fluka) was passed through activated neutral alumina and stored over 4 Å molecular sieves; methanol, ethanol, 1-propanol, 1-butanol, 2-propanol and benzyl alcohol were dried over calcium hydride, distilled and stored over 3 Å molecular sieves under nitrogen. Phenol was dried and stored *in vacuo* over  $P_2O_5$ . All ILs were dried at 80 °C *in vacuo* for at least 24 h prior to kinetics experiments. Karl-Fischer titration found that this procedure yielded water contents consistently below 200 ppm. In addition, hydrolysis side-products, where they could be detected, never accounted for more than 3% of product formation observed and were typically within the error of integration.

#### **Kinetics experiments**

Solutions of ROH were prepared by mixing known volumes of ROH and IL under a dry nitrogen atmosphere using gas-tight syringes to yield the desired ROH concentration, with the exception of phenol for which a gravimetric method was employed. Volume additivity of these solutions was assumed, as published data for these and closely related systems indicate excess volumes of these binary mixtures would be smaller than the anticipated error from the volumetric methods employed.<sup>60–62</sup> For example, the volume contraction of 1 mL of a 0.55 M methanol in [EMIM][NTf<sub>2</sub>] solution would be less than 0.15  $\mu$ L (*i.e.* the error would be less than 0.015%). All solutions were stirred for at least an hour prior to use to ensure thorough mixing.

For the general kinetics protocol, an NMR tube equipped with a Young's valve was charged with FDMC (15-25 mg, 0.05-0.08 mmol) under a flow of nitrogen. 4-Picoline (50 µL) was added to dissolve the substrate. Approximately 5 minutes before the reaction was to be monitored, the solution was diluted with ionic liquid containing ROH (0.98 mL of 0.55 M ROH) and cooled on ice. The sample was then mixed using a Vortex mixer and the reference capillary (1-bromo-4-fluorobenzene in acetone- $d_6$  (0.50 M)) inserted co-axially. The tube was immediately inserted into the NMR probe which had been pre-cooled to 294.3 K, the temperature of the NMR tube allowed to equilibrate, and <sup>19</sup>F{<sup>1</sup>H} NMR spectra subsequently obtained at that temperature every 65 seconds for 10-40 spectra. For reactions with 2-propanol, the above procedure was followed except a spectrum was obtained every 21 minutes for a total of 37 spectra.

All reactions afforded the anticipated alcohol/ether, as confirmed by either comparison with an independently synthesised compound or isolation of the reaction product. The details and characterisation data for all compounds are given in the ESI.<sup>†</sup>

#### Preferential solvation experiments

IL solutions were prepared by directly weighing dry samples of  $[BMIM][NTf_2]$  and  $[BMMIM][NTf_2]$  in the desired molar ratios. The resultant mixture was further dried and the kinetics experiments conducted using the protocols outlined above.

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