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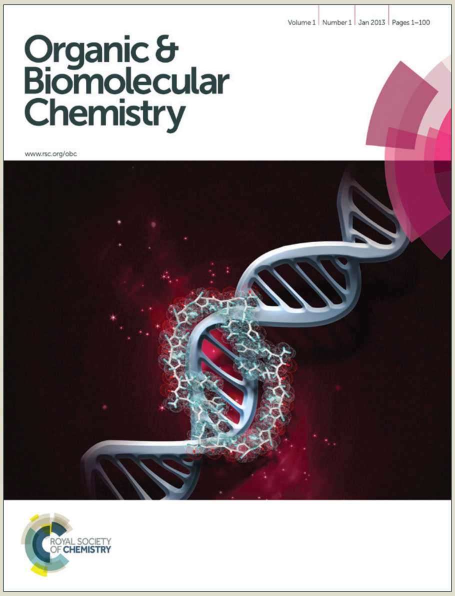

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Developing principles for predicting ionic liquid effects on reaction outcome. A demonstration using a simple condensation reaction

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The effects of a series of ionic liquids, with systematic variations in the cation, on the condensation of an alkyl amine with an aromatic aldehyde were investigated, and the outcomes compared with those predicted based on related reactions. The addition of ionic liquids increased the observed rate constant; the mole fraction dependence of this increase was qualitatively consistent with predictions. Temperature-dependent kinetic analyses were used to demonstrate that the microscopic origins of the effects were as forecast, though the relative weighting of enthalpic and entropic contributions was dependent on the salt used.

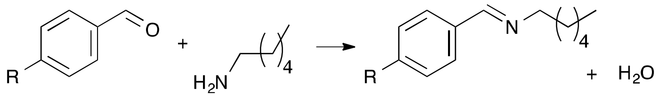
Introduction

Ionic liquids, which are arbitrarily defined as salts with melting points below 100 °C,[1] have potential as alternatives to traditional solvents. Their low vapour pressure[2-4] and lack of flammability,[4] along with the prospect of recycling,[5] makes them potential safe and more environmentally-friendly alternatives to molecular solvents. Further, with reaction outcomes varying in ionic liquids compared to molecular solvents, many reactions proceed more readily and/or more selectively in ionic liquids.[6-15]

This last point can be an obstacle to the use of ionic liquids as solvents; the reaction outcome can change compared to that for a molecular solvent in ways that are difficult to predict.[16] This lack of understanding is hindering the application of these solvents; what is required is the ability to predict (even if qualitatively) the effect on reaction outcome of using a given proportion of a given ionic liquid. This is significant, as it would allow the ionic liquid, and its proportion in the reaction mixture, to be chosen such that it most beneficially affects reaction outcome, for example, in terms of increased reaction rate or selectivity.

Our research group has been systematically investigating the effect ionic liquids have on organic reaction outcomes,[17-27] particularly focussing on well-understood organic substitution processes.[6, 7, 22-28] The information gathered has allowed the differing effects that ionic liquids have on reaction outcome to be rationalised by considering the nature of the process (particularly, charge development in the transition state and the nature of the starting materials),[6, 7, 22-26, 28] the proportion of the ionic liquid in the reaction mixture[7, 22] and the components of the ionic liquid itself.[21, 26, 27]

The work described herein sought to take this rationalisation an extra step; to be able to predict the effects of ionic liquids, of different types and across a range of proportions in molecular solvent, on an organic process. The reaction chosen was the condensation of an aromatic aldehyde **1** and an amine **2**, to give the corresponding imine. There has been some investigation into the effect that an ionic liquid has on the outcome of this reaction type, particularly in the use of ionic liquids as effective solvents for the synthesis of aromatic heterocycles,[29] however, no kinetic studies have been carried out. Having a bimolecular rate determining step with some charge development in the transition state,[30] and involving a nitrogen nucleophile, it was reasoned that the information gathered previously on bimolecular substitution processes[6, 7, 25] could be used to develop principles to qualitatively predict changes in reaction outcome for this case. This manuscript describes such predictions, analyses their efficacy and considers the importance of being able to rationally choose a solvent to control reaction outcome.



1a R = H
1b R = OMe

2

3a R = H
3b R = OMe

Scheme 1 The condensation of a benzaldehyde **1** with an amine **2** to give the corresponding imine **3**.

Experimental

Benzaldehyde **1a**, 4-methoxybenzaldehyde **1b** and hexan-1-amine **2** were commercially available, and each was distilled under reduced pressure then stored with molecular sieves at 253 K prior to use. Analytical grade deuterated acetonitrile was dried over molecular sieves for at least 48 h prior to use. The ionic liquids **4-7** were prepared with reference to literature methods[31-33] by first treating the corresponding imidazole or pyrrolidine with butyl bromide to afford the intermediate bromide salt, which was then treated with lithium *bis*(trifluoromethanesulfonyl)imide to give the required ionic liquid. The ionic liquid **8** was prepared from the commercially available tetraoctylammonium bromide, once again through treatment with lithium *bis*(trifluoromethanesulfonyl)imide. All ionic liquids were dried to constant weight at 70°C under reduced pressure immediately before use, and were found to have <0.1% water using Karl Fischer titration methodology.

^{1}H NMR kinetics experiments were carried out on either a Bruker Avance III 400, Bruker Avance III 500 or Bruker Avance III 600 spectrometer with either a BBFO or TBI probe using *ca*. 0.5 mL of reaction mixture (details below) in a 5 mm NMR tube. Results were shown to be reproducible between the different spectrometers.

Kinetic analyses were carried out in solutions containing one of the benzaldehydes **1a** or **1b** (*ca*. 0.02 mol L^{-1}) and the amine **2** (*ca*. 0.25 mol L^{-1}) at a given temperature and specific mole fraction of the ionic liquid, with the remaining solvent being made up by deuterated acetonitrile. For all reactions the prepared NMR samples were stored in liquid nitrogen prior to analysis. In each case the reaction was monitored *in situ* using ^{1}H NMR spectroscopy with the spectrometer being set to the desired temperature for the duration of the reaction.

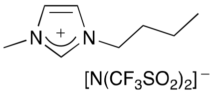
All reactions were followed until more than 95% of the starting material **1** was consumed, and all kinetic analyses were performed in triplicate. NMR spectra were processed using either the Bruker TOPSPIN 1.3 software or the MestReNova 7.1.1 software. The rate constants for the reactions were calculated by fitting the normalised integrations, for the aldehyde signal in in the starting material **1** at δ *ca*. 10.0, obtained from the processed ^{1}H NMR spectra to either an exponential function in GraphPad Prism, or the natural logarithm of the integrations fitted to a linear function using the LINEST function in Microsoft Excel. The pseudo-first order rate constants obtained through each method were the same, and were converted to the corresponding bimolecular rate constants. The activation parameters were then determined using the bimolecular Eyring equation.[34] Tables containing the exact mole fraction, amine **2** concentration, temperature and rate constants for all the systems described below can be found in the Electronic Supporting Information.

Results and discussion

As with previous studies,[6, 7, 22-28] NMR spectroscopy was used to follow the progress of the reaction. The use of this method circumvents any issues with work-up of the reaction mixture (such as selective extraction of components of the reaction mixture[17]) and the reaction shown in Scheme 1 proceeds at a rate that allows convenient application of this analytical technique. The reaction proceeds to completion under (pseudo) first order kinetics in all cases considered. The reactions were not carried out under 'infinitely-dilute' conditions with respect to the reagents, which generally constitute a mole fraction of *ca*. 0.05 of the solution. No deviation from first order kinetics due to changing solvent composition was observed; this indicates that the nature of the solvent does not change significantly as the reaction proceeds (see ESI).

Initially, it was of interest to consider how an ionic liquid may affect the reaction of **1a** and **2** by carefully considering any interactions between the ionic liquid and the species along the reaction pathway. It was judged that, based on precedent from bimolecular substitution processes,[6, 7, 25, 26] while interactions with both the starting materials and the transition state need to be considered, the limited amount of charge development in the transition state means that the key interaction will be between the cation of the ionic liquid and the lone pair on the nitrogen centre of the nucleophile **2**;§ the cation of the ionic liquid will order about, and stabilise, this reagent. Analogous to that observed previously, it was predicted that this would result in an increased rate constant due to an entropic benefit that is partially offset by an enthalpic cost, arising from a greater degree of ordering about the starting materials relative to the transition state.[25] It was also anticipated that the rate constant would continue to increase as the proportion of an ionic liquid in the reaction mixture was increased.[7]

Initially, to allow direct comparison with previous work,[7] the effect of the ionic liquid 1-butyl-3-methylimidazolium *bis*(trifluoromethanesulfonyl)imide ([Bmim][N(CF_3SO_2)$_2$], **4**) on the condensation of compounds **1a** and **2** was considered in reaction mixtures across a range of different mole fractions of the ionic liquid **4** in acetonitrile (Fig. 1).



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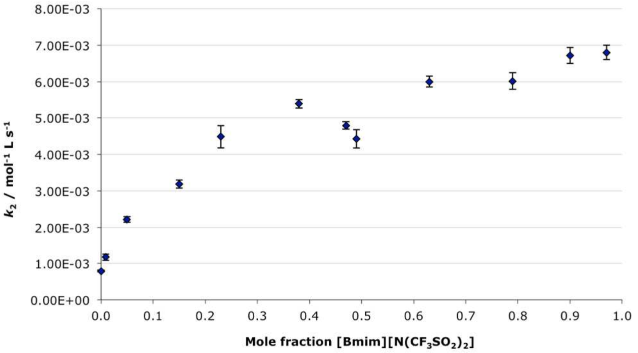


Fig. 1 The bimolecular rate constants for the reaction between benzaldehyde **1a** and the amine **2** in different mole fractions of [Bmim][N(CF_3SO_2)$_2$] **4** in acetonitrile, at 282 K. Uncertainties are reported as the standard deviation of three replicates.

The dependence of the bimolecular rate constant of the reaction shown in Scheme 1 (R = H) with changing proportion of the ionic liquid **4** follows a trend comparable to that previously reported for the reaction of pyridine with benzyl chloride.[7] In both cases, there is a gradual increase in the rate constant with increasing amounts of the ionic liquid **4** in the solvent mixture, with an asymptote approached as the proportion of the solvent **4** approached maximum. It is interesting to note that for the condensation reaction shown in Scheme 1 (R = H) there is a slight decrease in the rate constant at *ca.* χ_{IL} 0.5; this 'dip' in the mole fraction dependence plot has been observed previously;[7] currently the source of this decreased rate constant is unknown and it is being further investigated.

The similarity between the mole fraction dependence of the rate constants for a bimolecular substitution reaction and the condensation reaction shown in Scheme 1 is consistent with them being affected in a similar manner by the ionic liquid **4**. However, it is should be noted that the enhancement in the rate constant is larger in the case described here; *ca*. 8-fold compared to *ca.* 4-fold for the substitution process.[7] The activation parameters for the reaction between species **1a** and **2**, at a series of different mole fractions of the ionic liquid **4** in acetonitrile were determined through temperature dependent kinetic analyses to allow the source of the rate enhancement to be confirmed, and to allow further comparison with previous studies (Table 1).

Table 1 Activation parameters for the reaction between the benzaldehyde **1a** and the amine **2** in mixtures of [Bmim][N(CF_3SO_2)$_2$] 4 in acetonitrile at the mole fraction specified.

χ_{IL}	$\Delta H^{\ddagger}$ / kJ mol^{-1} [a]	$\Delta S^{\ddagger}$ / J K^{-1} mol^{-1} [a]
0	27.2 ± 2.5	-272.1 ± 8.6
0.23	34.5 ± 0.5	-233.2 ± 1.7
0.50	32.4 ± 0.8	-237.0 ± 2.8
0.97	32.4 ± 1.3	-235.2 ± 4.6

[a] Uncertainties quoted are from the fit of the linear regression.

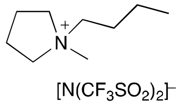
Initially, a key point to note is that the values of the activation parameters in acetonitrile are what would be expected for this type of reaction; a positive enthalpy of activation with a large negative entropy of activation consistent with the two species **1a** and **2** coming together in the transition state.

As can be seen from the data in Table 1, when changing the composition of the solvent from acetonitrile to the ionic liquid **4** there is an increase in the enthalpy of activation for the reaction shown in Scheme 1 (R = H) - an enthalpic cost - as well as an increase in the entropy of activation - an entropic benefit. Once again, direct comparison with previous studies shows that the trend is the same as was seen for the reaction of benzyl chloride with pyridine,[7] and is consistent with the interaction between the cation of the ionic liquid and the nucleophile dominating reaction outcome.[25] This highlights that not only do both reactions experience a comparable dependence of rate constant on the proportion of ionic liquid **4** in the reaction mixture, but the source of the rate constant increase for both cases is the same.

Also worthy of note is that the effects of the ionic liquid **4** on the activation parameters are greater at lower mole fractions (below χ_{IL} *ca.* 0.25); there is a significant change in the activation parameters when moving from acetonitrile to χ_{IL} 0.23, yet when moving from χ_{IL} 0.23 to 0.50 and to 0.97 the activation parameters do not change significantly. This is reflected in the mole fraction dependence plot (Fig. 1) where there is a more substantial change in the rate constants at lower mole fractions, with the change becoming less significant at higher concentrations of ionic liquid **4** in acetonitrile. This suggests that the interactions responsible for the rate increase are principally present at low mole fractions of ionic liquid **4**, and increasing the proportion of ionic liquid does not significantly increase the probability of these interactions.

The most important point to take from the above section is that the effect of the ionic liquid was as forecast based on previous work on bimolecular substitution processes, highlighting the idea that by carefully considering the likely interactions between the ionic liquid and the reagents along the reaction coordinate it *is* possible to predict the effect, even if qualitatively, that an ionic liquid will have on reaction outcome.

Given the expected – and demonstrated – importance of the interaction between the cation of the ionic liquid **4** and the nucleophilic nitrogen on the amine **2**, it was anticipated that varying the extent of charge localisation and accessibility on the cation of the ionic liquid would have a significant effect on reaction outcome. This idea builds on previous work[26] on the reaction between benzyl bromide and pyridine**,** where the effect that a range of ionic liquids containing cations with different extents of charge localization and steric hindrance about the positive charge were investigated. It was found that the more accessible the charge was, the more the rate constant was increased; while it could be generally concluded that the rate enhancements are a result of increased interactions with the nucleophile, due to the similarity of the activation parameters between ionic liquids it was difficult to conclusively state the microscopic origin. For the reaction between benzaldehydes **1** and the amine **2** it was anticipated that there would be an analogous trend when altering the cation, yet it was expected that the effect of such would be more marked due to the nature of the nucleophile; this will be discussed in more detail below.



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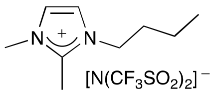

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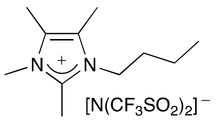

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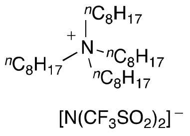

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The ionic liquids **5-8** were considered as, while they have a common anion, the cations cover a range of charge localisation and accessibility. The pyrrolidinium derivative **5** ([Bmpy][N(CF_3SO_2)$_2$]) has comparable steric requirements[26] to the parent ionic liquid **4**, but is electronically different as there is no delocalisation of the positive charge on the nitrogen centre; the [Bmpy]$^+$ cation has a more charge dense positive centre than the [Bmim]$^+$ cation.[35] This case allows the effect of electronics to be investigated; it was anticipated that the extent of interaction with the nitrogen lone pair would be larger for [Bmpy][N(CF_3SO_2)$_2$] **5**, and hence a larger associated enthalpy and entropy of activation would result. The ionic liquids **6** ([Bm_2im][N(CF_3SO_2)$_2$]) and **7** ([Bm_4im][N(CF_3SO_2)$_2$]) have methylated cations, so on moving from solvent **5** to **6** to **7**, whilst the electronic nature of the cation remains comparable, there is the opportunity to examine the increased degree of steric hindrance (which was expected to decrease the interactions between the ionic liquid cation and the nitrogen of the nucleophile **2**). Finally, the tetraoctylammonium (*bis*(trifluoromethanesulfonyl)imide ([TOA][N(CF_3SO_2)$_2$], **8**) ionic liquid, while it has a localised positive charge on the nitrogen, this is inaccessible so interactions between the cation and the amine **2** would be greatly reduced; likely resulting in a lowered enthalpic cost.

As the interaction being considered at length is that between the cation of the ionic liquid and the nucleophile **2**, an interesting point to consider is the accessibility of the nitrogen lone pair itself; hexan-1-amine **2** is sterically less demanding than pyridine, the nucleophile used in the previously studied substitution cases that relate directly to the reaction investigated here.[6, 7, 25-27] Considering the importance of the charge accessibility of the ionic liquid cation shown previously,[26]£ it was reasonable to suggest that the accessibility of the nitrogen lone pair will also have an effect. Given the rationale above, it was anticipated that the reaction between benzaldehyde **1a** and the amine **2,** involving a nucleophile that is smaller and has a more accessible lone pair, will be more affected by the accessibility of the charge on the cation of the ionic liquid than the previous substitution cases.¢ Therefore it was predicted that there would be a more substantial change in the activation parameters for the reaction shown in Scheme 1 across the different ionic liquids **5-8** than that seen previously for the reaction between benzyl bromide and pyridine, allowing the microscopic origin of any changes in rate to be more conclusively demonstrated.[6, 26]

The effect of each of the ionic liquids **5-8** on the condensation of compounds **1a** and **2** was considered in analogous fashion to the case with the ionic liquid **4,** in reaction mixtures across a range of different mole fractions of each of the salts **5-7** in acetonitrile (Fig. 2). Where possible, activation parameters for this reaction were determined in different mole fractions of each of the ionic liquids in acetonitrile (Tables 2-4).

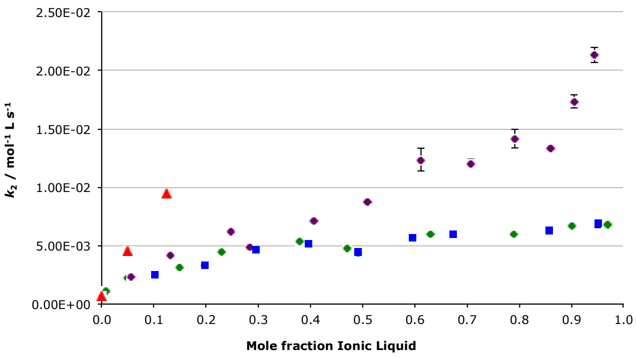

Fig. 2 The bimolecular rate constants for the reaction between benzaldehyde **1a** and the amine **2** in different mole fractions of either [Bmim][N(CF_3SO_2)$_2$] **4** (◆), [Bmpy][N(CF_3SO_2)$_2$] (◆), [Bm_2im][N(CF_3SO_2)$_2$] (■), and [Bm_4im][N(CF_3SO_2)$_2$] (▲) in acetonitrile, at 282 K. Uncertainties are reported as the standard deviation of three replicates.

Table 2 Activation parameters for the reaction between the benzaldehyde **1a** and the amine **2** in mixtures of [Bmpy][N(CF_3SO_2)$_2$] **5** in acetonitrile at the mole fraction specified.

χ_{IL}	$\Delta H^{\ddagger}$ / kJ mol$^{-1\,a}$	$\Delta S^{\ddagger}$ / J K^{-1} mol$^{-1\,a}$
0	27.2 ± 2.5	-272.1 ± 8.6
0.24	37.3 ± 0.6	-218.7 ± 2.4
0.94	45.3 ± 1.7	-180.2 ± 6.2

[a] Uncertainties quoted are from the fit of the linear regression

Table 3 Activation parameters for the reaction between the benzaldehyde **1a** and the amine **2** in mixtures of [Bm_2im][N(CF_3SO_2)$_2$] **6** in acetonitrile at the mole fraction specified.

χ_{IL}	$\Delta H^{\ddagger}$ / kJ mol$^{-1\,a}$	$\Delta S^{\ddagger}$ / J K^{-1} mol$^{-1\,a}$
0	27.2 ± 2.5	-272.1 ± 8.6
0.20	34.1 ± 0.8	-234.9 ± 2.7
0.95	32.3 ± 1.1	-235.2 ± 4.1

[a] Uncertainties quoted are from the fit of the linear regression.

Table 4 Activation parameters for the reaction between the benzaldehyde **1a** and hexyl amine **2** in acetonitrile and in [TOA][N(CF_3SO_2)$_2$] **8** at the mole fraction specified.

χ_{IL}	$\Delta H^{\ddagger}$ / kJ mol$^{-1\,a}$	$\Delta S^{\ddagger}$ / J K^{-1} mol$^{-1\,a}$
0	27.2 ± 2.5	-272.1 ± 8.6
0.87	30.8 ± 3.7	-254.1 ± 11.8

[a] Uncertainties quoted are from the fit of the linear regression.

Firstly, the effect of addition of the ionic liquid [Bmpy][N(CF_3SO_2)$_2$] **5**, containing a relatively charge dense cation, will be discussed. As detailed in Table 2, there is a substantial increase in both the enthalpy and entropy of activation on addition of the salt **5**. Importantly, as was predicted, the change in each of the activation parameters is greater in this case than on addition of [Bmim][N(CF_3SO_2)$_2$] **4**. The more charge dense cation of the ionic liquid **5** results in a greater interaction with the nucleophile **2** than was the case with the [Bmim][N(CF_3SO_2)$_2$] **4** - this is reflected in an increase in the enthalpy of activation ($\Delta(\Delta H^{\ddagger})$ = 13.1 ± 2.1 kJ mol^{-1} ¶) and the entropy of activation (($\Delta(\Delta S^{\ddagger})$ = 55.2 ± 7.7 kJ mol^{-1} ¶)

when moving from $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4** to $\mathrm{[Bmpy][N(CF_3SO_2)_2]}$ **5** (at χ_{IL} 0.97 and 0.94, respectively).

When the pyrrolidinium salt **5** was used as a solvent, the enthalpic cost was offset by a more substantial increase in the entropy of activation resulting in an overall increase in the rate constant when compared to both the acetonitrile and $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4** cases; at χ_{IL} 0.94 of ionic liquid **5** and 282 K, the rate constant is 28 times larger than that in acetonitrile, compared to *ca*. 9-fold increase at χ_{IL} 0.94 for $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4**.

Interestingly, unlike the $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4** case, where the activation parameters changed little above χ_{IL} *c.a.* 0.2, for the pyrrolidinium case **5** both the enthalpy and entropy of activation progressively increased when moving from acetonitrile to χ_{IL} 0.24 to 0.94. This is reflected in Fig. 2 where the rate constant for the process outlined in Scheme 1 (R = H) continues to increase as the mole fraction of the ionic liquid **5** in the reaction mixture increases; this is different to the $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4** case where the rate constant approaches a maximum value at higher mole fractions. This suggests that, in contrast to that described for the imidazolium salt **4**, increasing the proportion of the ionic liquid **5** *does* significantly increase the probability of these interactions.

In summary, as predicted, $\mathrm{[Bmpy][N(CF_3SO_2)_2]}$ **4** has a greater effect on the reaction shown in Scheme 1 (R = H) than $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4**. This is demonstrated by both the increased activation parameters and rate constant, arising from the more charge dense nature of the $\mathrm{[Bmpy]^+}$ cation allowing it to interact more strongly with the nitrogen lone pair on the amine **2**.

The next ionic liquid of interest is $\mathrm{[Bm_2im][N(CF_3SO_2)_2]}$ **6**; this ionic liquid is comparable to the parent $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4** but is slightly more hindered about the positive charge due to methyl substitution at the C2 position, as demonstrated using molecular dynamics simulations.[26, 36] Whilst this might be expected to result in a decreased interaction between the amine **2** and the $\mathrm{[Bm_2im]^+}$ cation relative to the $\mathrm{[Bmim]^+}$ cation, previous experience with the reaction of benzyl bromide and pyridine suggests that the interaction is not directional and that such changes are unlikely to substantially affect reaction outcome.[26]

It was found that the activation parameters at both χ_{IL} *ca.* 0.2 and 0.95 of $\mathrm{[Bm_2im][N(CF_3SO_2)_2]}$ **6** were the same within uncertainty as those for the $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4** case at the same mole fractions. The trend in the mole fraction dependence of the rate constant of the reaction was also identical in each of the ionic liquids **4** and **6**, suggesting that both these ionic liquids have the same effect on the reaction between species **1a** and **2**. This is consistent with what was predicted based on previous examples involving bimolecular substitution mechanisms, and demonstrates that the methyl substituent is not bulky enough to significantly affect interactions between the cation of the ionic liquid and the nucleophile **2** for the reaction between **1a** and **2**, and that these interactions are not directional.

$\mathrm{[Bm_4im][N(CF_3SO_2)_2]}$ **7** was the last of the imidazolium-based ionic liquids considered; the $\mathrm{[Bm_4im]^+}$ cation is more sterically hindered than the cations considered previously. Given this, it was expected that there would be a decrease in the interaction of the nucleophile **2** with the cation of the ionic liquid and hence a decrease in the entropy and enthalpy of activation on changing the ionic liquid from $\mathrm{[Bmim][N(CF_3SO_2)_2]}$ **4** to $\mathrm{[Bm_4im][N(CF_3SO_2)_2]}$ **7**. The balance of these changes (and hence the effect on the rate constant of the reaction) could not be anticipated.

Practical limitations restricted the mole fraction of the ionic liquid **7** that could be used; it is a solid at room temperature[21],€ and has comparatively low solubility in acetonitrile at 282 K. At the mole fractions of the salt **7** that were investigated, the rate constant for the reaction was faster than any of the cases already described. No attempt was made to determine the microscopic basis of these changes at this stage.

The final ionic liquid considered was $\mathrm{[TOA][N(CF_3SO_2)_2]}$ **8**; this ionic liquid has the most sterically hindered cationic centre in the series considered. As such, it was anticipated that the interaction between the nucleophile **2** and the cation of the ionic liquid **8** would be greatly reduced relative to the other ionic liquid cases, and that both the activation parameters and rate constant for this case would lie closest to the acetonitrile case.

Note that no dependence of the rate constant on mole fraction of ionic liquid was able to be determined in the $\mathrm{[TOA][N(CF_3SO_2)_2]}$ **8** case as it is barely soluble in acetonitrile; data presented in Table 4 shows activation parameters for the χ_{IL} 0.87 case, which contains only the ionic liquid **8** diluted by reagents.

Considering the data in Table 4, it is important to note that the uncertainties in the rate constants, and hence the activation parameters determined, are the largest seen in these studies. This is because the ionic liquid **8** is a solid at room temperature, which complicates the sample preparation. Unfortunately, given the larger uncertainties, no difference between the activation parameters for the $\mathrm{[TOA][N(CF_3SO_2)_2]}$ **8** case and either acetonitrile, or the cases with the ionic liquids **4** and **6**, can be distinguished.

While the data presented above clearly demonstrates the outcome of the reaction between benzaldehyde **1a** and the amine **2** in ionic liquids is qualitatively predictable, its application is somewhat limited. The relatively fast rates meant that low temperatures were required to practically follow the kinetic analyses which, in turn, brings about problems with the solid nature of the ionic liquids **7** and **8** (limiting the data that could be obtained and introducing greater uncertainties). Given these salts were of particular interest, an alternative reaction was sought that could be followed readily at temperatures above 305 K, where they would both be liquid. It would also be useful to determine the rate constant at a common temperature in acetonitrile and each of the ionic liquids **4-8**, so that a more direct comparison of the rate constants could be made.

The reaction chosen was of *p*-methoxybenzaldehyde **1b** and the amine **2**, as while the methoxy substituent would slow the reaction down substantially relative to the unsubstituted case, it was anticipated that the interactions of the solvent with the substrates (and hence the effect of ionic liquids on the reaction) would be similar to the unsubstituted case. The focus was on obtaining the activation parameters for this reaction in acetonitrile and all five ionic liquids **4-8** at the highest mole fraction possible (diluted only by reagents) and at a common temperature. The results of this section are summarised in Figure 3, which presents the observed rate data as an Eyring plot, and Table 5, which contains the activation parameters determined from that Eyring plot and relative rate constant data.

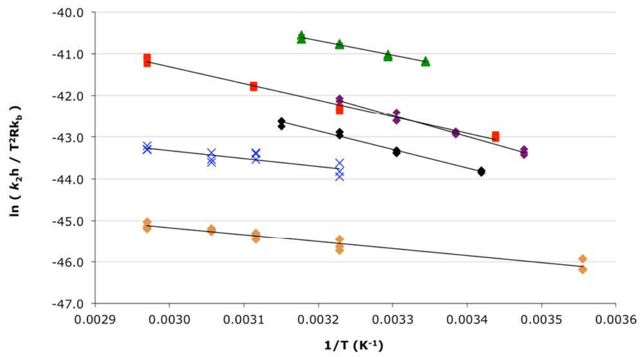

Fig. 3 The bimolecular Eyring plot, from which the activation parameters in Table 5 were determined, for the reaction between methoxybenzaldehyde **1b** and the amine **2** in either acetonitrile (◆) or one of the ionic liquids [Bmpy][N(CF_3SO_2)$_2$] **4** (◆), [Bmim][N(CF_3SO_2)$_2$] **5** (◆), [Bm$_2$im][N(CF_3SO_2)$_2$] **6** (■), [Bm$_4$im][N(CF_3SO_2)$_2$] **7** (▲) and [TOA][N(CF_3SO_2)$_2$] **8** (×). In all cases, the ionic liquid was only diluted by reagents **1b** and **2** (mole fractions outlined in Table 5).

Table 5 The activation parameters for the reaction between 4-methoxybenzaldehyde **1b** and the amine **2** in either acetonitrile or one of the ionic liquids **4-8**, at the mole fractions specified.

Solvent	χ_{IL} ^{b}	$\Delta H^‡$ / kJ mol^{-1} ^{a}	$\Delta S^‡$ / J K^{-1} mol^{-1} ^{a}	k_{rel} ^{c}
acetonitrile	-	14.2 ± 1.0	-333.1 ± 3.3	1
[TOA][N(CF_3SO_2)$_2$] **8**	0.87	15.8 ± 3.2	-313 ± 10	5 ± 2
[Bm$_4$im][N(CF_3SO_2)$_2$] **7**	0.94	28.8 ± 1.4	-246.1 ± 4.6	130 ± 20
[Bm$_2$im][N(CF_3SO_2)$_2$] **6**	0.95	33.3 ± 1.3	-243.4 ± 4.0	26 ± 5
[Bmim][N(CF_3SO_2)$_2$] **4**	0.93	36.8 ± 1.5	-238.5 ± 5.0	15 ± 3
[Bmpy][N(CF_3SO_2)$_2$] **5**	0.93	41.9 ± 1.9	-214.8 ± 6.5	33 ± 6

[a] Uncertainties quoted are from the fit of the linear regression.
[b] The ionic liquid was only diluted by the reagents **1b** and **2**
[c] Measured at 310 K. The values shown represent the rate constant relative to acetonitrile and the uncertainties are based on the standard deviation of triplicate rate measurements, compounded by division.

Initially it is useful to consider the relative rate constants in each of the solvents. At the common temperature (310 K, Table 5 though it is clear from Fig. 3 also), the rate constant increases as the solvent changes in the order acetonitrile < [TOA][N(CF_3SO_2)$_2$] **8** < [Bmim][N(CF_3SO_2)$_2$] **4** < [Bm$_2$im][N(CF_3SO_2)$_2$] **6** = [Bmpy][N(CF_3SO_2)$_2$] < [Bm$_4$im][N(CF_3SO_2)$_2$] **7**. This is interesting because this does not parallel the expected order of increasing interactions between the cation of the ionic liquid and the nucleophile **2** based on consideration of previous cases. As such, consideration of the activation parameters is important.

The activation parameters follow a more consistent trend with the expected interactions between the cation of the solvent and the amine **2**. It was anticipated that the more accessible and charge dense the cation, the greater its interaction with the nitrogen lone pair on the amine **2**, and hence the larger the enthalpy of activation. Similarly, it was expected that the activation entropy would become less negative; the greater the extent of interaction of the cation with the amine **2**, the larger the associated entropic benefit on going to the transition state. On moving down Table 5 the steric hindrance about the cation decreases (in the order [TOA][N(CF_3SO_2)$_2$] **8**, [Bm$_4$im][N(CF_3SO_2)$_2$], **7** [Bm$_2$im][N(CF_3SO_2)$_2$] **6** and then [Bmim][N(CF_3SO_2)$_2$] **4**), and for the final ionic liquid [Bmpy][N(CF_3SO_2)$_2$] there is an increase in the charge localisation on the nitrogen centre.[21, 26] Following this same order there is a gradual increase in the enthalpy of activation, reflecting the trend we predicted! The corresponding entropy of activation also supports this trend, although the entropy of activation is comparable for the imidazolium based ionic liquids **4**, **6** and **7**, this will be discussed in more detail below. Overall, the effect that the ionic liquid has on the activation parameters for this reaction is directly related to the steric and electronic nature of the cation.

The above analysis demonstrates that the key factor responsible for the rate enhancement observed in a particular ionic liquid, is the *relative* magnitude of the effects on the two activation parameters, as both parameters change in the same direction on moving to an ionic liquid solvent. Such enthalpy-entropy compensation has been reported for other ionic liquid effects previously.[6, 7, 18, 20, 21, 23-27]

For the ionic liquids [TOA][N(CF_3SO_2)$_2$] **8**, [Bmim][N(CF_3SO_2)$_2$]) **4** and [Bmpy][N(CF_3SO_2)$_2$] **5** the relative changes in activation enthalpy and entropy are similar and hence the relative rate constants determined follow the order predicted. For the C2-methylated ionic liquid **6**, in comparison to the parent case **4**, there is a small decrease in enthalpy whilst the entropy is unchanged. This suggests that the extent of *order* in solution is unaffected by the addition of a methyl group, despite a decrease in the extent of *interaction* between the cation and the nucleophile **2**. This is consistent with previous studies[36-40] suggesting that entropy in C2-methylated imidazolium systems is more significant than in the parent imidazolium cases; in that case it was used to rationalise the relative melting points of ionic liquids.[36] This effect is even more marked in the ionic liquid **7** case, where the entropy of activation is the same as in the solvents **4** and **6**, but the activation enthalpy is lower still. This, once again, suggests that the extent of organisation is more significant than expected, and that there is a greater degree of ordering about the starting materials than is anticipated based on the extent of interaction.

The observed order of rate constants; [Bmim][N(CF_3SO_2)$_2$] **4** < [Bm$_2$im][N(CF_3SO_2)$_2$] **6**] < [Bm$_4$im][N(CF_3SO_2)$_2$] **7;** can now be rationalised by considering this balance between the activation parameters. As the entropy remains the same for all three cases, it is the enthalpic effect that is key for the imidazolium based ionic liquids; with a lessened extent of interaction with the amine **2** there is a smaller associated enthalpic cost, resulting in increasing rate constants for the more hindered cations.

It is interesting to note that the differentiation between the effects on activation parameters of each of the ionic liquids **4**, **6** and **7** is the first time that the steric nature of the additional methyl groups on the cation is demonstrated; in previous cases[26] any differences were not readily apparent. In this case, the larger differences in ionic liquid effects are likely the result of a less hindered nucleophile, such that the effects of addition of methyl groups to the cation can be more easily distinguished.

Conclusions

The effect of a series of ionic liquids on an addition reaction was predicted, based on an understanding of how ionic liquids affect reaction outcomes gained from previous studies. Whilst qualitative, this prediction was particularly accurate in forecasting the dependence of the rate constant on the mole fraction of ionic liquid present in the reaction mixture. In all the cases considered, the rate of reaction increased on addition of an ionic liquid to the reaction mixture.

The microscopic origin of the observed rate enhancements were also as predicted; an enthalpic cost associated with a greater degree of interaction of the nucleophile **2** with the cation of the solvent was offset (and overcome) by the increase in disorder on moving to the transition state. Further, the effect of ionic liquids on the activation enthalpy was exactly in line with that predicted based on the accessibility and localisation of the charge on the cation. Importantly, differentiation between the effects of ionic liquids **4**, **6** and **7**, with variously methylated cations, was possible for the first time, showing that there was a small decrease in interactions based on the steric effects of the methyl group.

The importance of the relative balance of enthalpic and entropic contributions was highlighted by the consistency in the entropy of activation of the reaction in the series of imidazolium ionic liquids with methylated cations; this did not parallel the enthalpy of activation. This demonstrates that other ordering effects need to be considered (as is consistent with the 'anomalous' melting points of C2-methylated imidazolium salts). This demonstrates a limitation in the method for predicting reaction outcome, the dramatic rate enhancement observed for the reaction on moving to the ionic liquid with the tetramethylated cation was much greater than would have been anticipated; it otherwise performed admirably, with the relative rate enhancements for the other ionic liquids as anticipated.

The effectiveness of the predictive principles put forward here demonstrates that an ionic liquid can be rationally chosen to affect the outcome of such a process in the desired fashion. This is significant as such a predictive framework has not been put forward previously, and reduces the need for screening a range of solvents. There is also clearly the potential to apply this technique to ionic liquid solvent effects on a range of reaction types.

Importantly, the success of the principles presented also allows other factors to be taken into account. For example, addition of a small amount of molecular solvent may be useful if there is negligible difference in rate on changing the mole fraction of ionic liquid, but this addition is useful in another way (such as ease of mixing through reduced viscosity). Similarly, if two ionic liquids have the same or similar effects on reaction outcome, other factors (such as cost) may be considered. Overall, this enhances the utility of ionic liquids as solvents with the ability to control reaction outcome.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Representative fits from which rate constants were determined, mole fraction dependent rate constant data on which the plots in Figures 1 and 2 are based; temperature dependent kinetic data on which Figure 3 is based and from which the activation parameters shown in Tables 1-5 are derived; summaries of activation parameter data presented. See DOI: 10.1039/b000000x/

§ There is also the potential for interaction of the cation of the ionic liquid with lone pairs on the oxygen of the electrophile **1a**. This may stabilise the intermediate relative to the starting material and lead to a decrease in the enthalpy of activation. This, however, is not based on precedent from previous examples.

$ As discussed in the footnote above, there is the potential that the cation may coordinate to the oxygen of the electrophile and decrease the enthalpy of activation. This is not observed, meaning that any effects of coordination at this site are outweighed by coordination to the nucleophile.

£ It might be anticipated based on this argument that the ionic liquid **4** would have a larger effect on the activation parameters for the process shown in Scheme 1 (R = H) than for the substitution reactions described previously. Whilst this is likely given the greater rate increase observed for the condensation reactions described here, the changes in activation parameters ($\Delta(\Delta H^{\ddagger})$ and $\Delta(\Delta S^{\ddagger})$) are the same within the rather larger compounded uncertainties.

¢ Note that in the substitution case, molecular dynamics simulations demonstrated that there are alternate sites of interaction of the nucleophile pyridine with the cation of the ionic liquid,[26] which would not affect reaction progress in the same way. The absence of such competing sites may also enhance the effects of an ionic liquid on the reaction.

¶ Uncertainties quoted are compounded from the individual fits of the linear regression.

€ Although initially reported in the literature to be a liquid at room temperature[41], it was subsequently isolated as a low m.p. (31-32°C) solid.[21]

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