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Understanding the Effect of Solvent Structure on Organic Reaction Outcomes when Using Ionic Liquid / Acetonitrile Mixtures

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ABSTRACT: The rate constant for the reaction between hexan-1-amine and 4-methoxybenzaldehyde was determined in ionic liquids containing an imidazolium cation. The effect on the rate constant of increasing the length of the alkyl substituent on the cation was examined in a number of ionic liquid / acetonitrile mixtures. In general it was found that there was no significant effect of changing the alkyl substituent on the rate constant of this process, suggesting that any nano-domains in these mixtures do not have a significant effect on the outcome of this process. A series of SAXS/WAXS experiments were performed on mixtures of the ionic liquid 1-butyl-3-methylimidazolium *bis*(trifluoromethanesulfonyl)imide ([Bmim][N(CF_3SO_2)$_2$]) and acetonitrile; this work indicated that the main structural changes of the mixtures occur by about a 0.2 mole fraction of ionic liquid in the mixture (χ_{IL}). This region where the main changes in the solvent structuring occurs corresponds to the region where the main changes in rate constant and activation parameters occur for S_N2 and condensation reactions previously examined; this is the first time that such a correlation has been observed. To examine the ordering of the solvent about the nucleophile hexan-1-amine, WAXS experiments were performed on a number of [Bmim][N(CF_3SO_2)$_2$] / acetonitrile / hexan-1-amine mixtures, where it was found that some of the patterns featured asymmetric peaks as well as additional peaks not observed in the [Bmim][N(CF_3SO_2)$_2$] / acetonitrile mixtures; this suggests that the addition of hexan-1-amine to the mixture affects the bulk structure of the liquid. The SAXS/WAXS patterns of mixtures of 1-butyl-2,3-dimethylimidazolium *bis*(trifluoromethanesulfonyl)imide ([Bm_2im][N(CF_3SO_2)$_2$]) and acetonitrile were also determined, with the results suggesting that [Bm_2im][N(CF_3SO_2)$_2$] is more ordered than [Bmim][N(CF_3SO_2)$_2$] due to an enhancement in the short-range interactions.

INTRODUCTION

Ionic liquids are salts that generally contain bulky, charge diffuse ions, and the weaker interactions between the components result in these species having lower melting points than typical inorganic salts, with many ionic liquids molten at ambient temperatures.[1-2] These salts are being utilized in many areas, including biomass processing;[3-5] electrochemistry;[6-9] as lubricants;[10-11] and as solvents for organic processes.[2, 12-14] Focusing on the latter, the application of ionic liquids is receiving significant attention due to their low flammability and vapour pressure;[15-18] the ability to tune the physical and chemical properties of the solvent by varying the constituent ions of the salt;[19-21] and the potential to achieve different reaction rates and selectivity when compared to typical molecular solvents.[12-13]

There has been much experimental[12-14, 22] and computational[23-27] work aimed at understanding the origin of the changes in reaction outcome when using an ionic liquid, relative to molecular solvents. It has been repeatedly demonstrated that understanding the interactions that exist between the component ions of ionic liquids and the species along the reaction coordinate is essential to using these solvents rationally,[12-13, 28] with the importance of knowing the magnitude of these interactions recently revealed.[29-32] It has also been demonstrated that the rate constants and selectivities of organic processes are affected by the amount of ionic liquid in the reaction mixture. Typically there are non-linear changes in reaction outcome as the mole fraction of an ionic liquid in a molecular solvent is varied, and the trend observed is different for different reaction types.[22, 29, 31-35]

Previous work has proposed that the structuring of the solvent can also influence reaction outcome.[36-38] As the changes in reaction outcome when using an ionic liquid solvent are often dominated by entropic effects,[13, 22, 28-29, 32, 34, 39-44] it is reasonable to suggest that ordering of the solvent itself is likely to be important. As a representative example, in a study examining the solvolysis of a picolinium salt in a number of ionic liquid / molecular solvent mixtures[36-38] it was concluded that the rate constant was affected by the 'pseudo-encapsulation' of reagents in the polar domain of the solvent. It was suggested that this aggregation of the polar reagents in the polar domain of the solvent increased the effective reagent concentration, and hence the rate constant was increased. It was proposed that for ionic liquids containing a longer alkyl substituent on the cation there is a larger non-polar domain, relative to an ionic liquid featuring a cation with a shorter alkyl chain, resulting in a comparatively smaller polar domain and an increased effective concentration of the polar reagents. This resulted in larger rate constants in ionic liquids featuring a longer alkyl substituent.[37]

Other work has suggested that the extent of ordering of the solvent can affect reaction outcome through changing the entropy of activation of a process. This is exemplified by previous work examining both bimolecular nucleophilic substitution (S_N2) processes[22, 28, 34, 40-42, 44] and related condensation reactions;[29-30, 43] it was found that the main interaction affecting reaction outcome was between the ionic liquid cation and the nucleophile. Disruption of this interaction on forming the transition state complex resulted in an enthalpic cost and a more significant entropic benefit, resulting in an increased rate constant relative to acetonitrile. When moving from low to high mole fractions of ionic liquid in the reaction mixture (χ_{IL}), the entropic benefit due to the breaking of this cation – nucleophile interaction remains comparable.[29, 34] It was proposed that the entropic advantage of removing the coordination of the nucleophile becomes less significant as the ordering in the solvent itself increases with increasing χ_{IL}, therefore the entropic effect plateaus at higher χ_{IL}.[29, 32, 34]

Overall, the structuring of an ionic liquid solvent has been proposed to affect reaction outcome through two mechanisms: 1) the nanostructural heterogeneity of the solvent drives aggregation of solutes into either the polar or non-polar domain;[37-38] 2) the significant ordering of the ionic liquid reduces the extent of disorder on forming the transition state complex, changing the entropy of activation.[34] To further investigate these phenomena, it was firstly of interest to examine the kinetics of a well-studied organic process in ionic liquids that are known to form nano-domains. The reaction chosen was the condensation reaction between benzaldehyde **1** and hexan-1-amine **2**, as this process has been examined previously in a number of ionic liquids, allowing comparison of the obtained rate data with this previous work.[29-30, 43]

Scheme 1: The condensation reaction between benzaldehyde 1 and hexan-1-amine 2

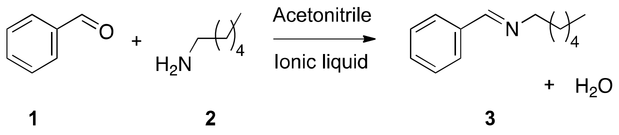
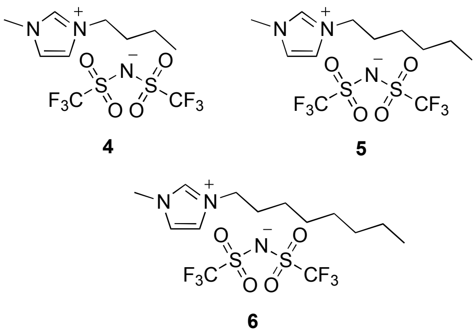


Figure 1: The ionic liquids [Bmim][N(CF_3SO_2)$_2$] 4, [Hmim][N(CF_3SO_2)$_2$] 5 and [Omim][N(CF_3SO_2)$_2$] 6



The reaction between species **1** and **2** has been studied in the ionic liquid 1-butyl-3-methylimidazolium *bis*(trifluoromethanesulfonyl)imide ([Bmim][N(CF_3SO_2)$_2$], **4**);[29] this is a suitable 'parent' ionic liquid as by simply increasing the chain length of the alkyl substituent on the imidazolium cation, the structural heterogeneity of the solvent can be increased.[45] If the rate constant of this process is affected by pseudo-encapsulation of reagents in the different domains, it would be expected that there would be an increase in the rate constant on moving from an ionic liquid with a butyl substituent ([Bmim][N(CF_3SO_2)$_2$] **4**) to one with a hexyl chain ([Hmim][N(CF_3SO_2)$_2$], **5**), and then a further increase on going to the octyl substituted system ([Omim][N(CF_3SO_2)$_2$], **6**), as the non-polar domains will get larger and hence the effective concentration of the reagents in the polar domain will increase.

As mentioned earlier, it has been proposed that as the amount of ionic liquid in the reaction mixture is increased, the solvent becomes more structured and this causes a reduction in the entropic effects observed in ionic liquid solvent effects.[34] To further investigate this concept, the second section of this manuscript focuses on examining the structuring of ionic liquid / molecular solvent mixtures through a series of Small and Wide Angle X-ray Scattering (SAXS and WAXS, respectively) measurements. As ionic liquids are often used in mixtures with a molecular solvent,[22, 29, 31-35] it was of interest to examine how the structuring of the liquid changes, and if nano-domains form, as the solvent composition is varied. A secondary motivation for this work was to investigate the source of the lowered rate constant at around $\chi_{IL} = 0.5$ that has been seen in plots of rate constant for the reaction between benzaldehyde **1** and hexan-1-amine **2** against the proportion of ionic liquid in the reaction mixture.[29] Such a 'dip' in the plots of k_2 against χ_{IL} has also been observed for some S_N2 processes.[32] Recent work has demonstrated that there is a change in the hydrodynamic boundary conditions when transitioning from 'ionic liquid dissolved in acetonitrile' ($\chi_{IL} < 0.4$) to 'acetonitrile dissolved in ionic liquid' ($\chi_{IL} > 0.4$), which is proposed to affect the rate constant at χ_{IL} *ca.* 0.4 and could account for these 'dips' observed.[46] It is possible that changes in the structure of the solvent also contribute to the decrease in the rate constant that is observed at that point.

RESULTS AND DISCUSSION

Kinetic studies

As discussed in the Introduction, previous work has suggested that the partitioning of reagents into the polar and non-polar domains of an ionic liquid solvent can affect reaction outcome due to changes in the effective concentration of the reagents in each domain. Considering this, it was of interest to further examine the ionic liquid solvent effects on the condensation reaction between benzaldehyde **1** and hexan-1-amine **2**, to determine whether such an effect influences the rate constant of this process.

This concept was examined using the ionic liquids [Hmim][N(CF_3SO_2)$_2$] **5** and [Omim][N(CF_3SO_2)$_2$] **6**, as these ionic liquids have been shown to have significant nanoscale structural heterogeneities, with the extent of this nanostructuring being more significant in [Omim][N(CF_3SO_2)$_2$] **6** than [Hmim][N(CF_3SO_2)$_2$] **5**.[45] This data can be compared with previous work examining the effect of [Bmim][N(CF_3SO_2)$_2$] **4** on the rate constant of the reaction of species **1** and **2**; importantly, no significant degree of nanostructure has been observed in the ionic liquid **4**.[45, 47] As such, it could be speculated that if the pseudo-encapsulation of reagents into the polar domains of the ionic liquid solvent affects reaction outcome, the rate constant of the process would be expected to increase on moving from [Bmim][N(CF_3SO_2)$_2$] **4** to [Hmim][N(CF_3SO_2)$_2$] **5** to [Omim][N(CF_3SO_2)$_2$] **6**.

Initially, the rate constants for this process were determined in each of the ionic liquids **5** and **6**, diluted only by reagents,¥ to investigate any changes in the rate constant on changing the salt from the comparatively 'homogenous' [Bmim][N(CF_3SO_2)$_2$] **4** to the more 'heterogeneous' ionic liquids [Hmim][N(CF_3SO_2)$_2$] **5** and [Omim][N(CF_3SO_2)$_2$] **6** (Table 1).

Table 1. Bimolecular rate constants (k_2) for the reaction of benzaldehyde 1 and hexan-1-amine 2 (Scheme 1) in each of the ionic liquids 4-6 at 8 °C

solvent[a]	k_2 / 10^{-3} L mol^{-1} s^{-1} [b]
[Bmim][N(CF_3SO_2)$_2$] **4** (χ_{IL} = 0.97)[29]	6.80 ± 0.20
[Hmim][N(CF_3SO_2)$_2$] **5** (χ_{IL} = 0.96)	2.84 ± 0.10
[Omim][N(CF_3SO_2)$_2$] **6** (χ_{IL} = 0.95)	5.39 ± 0.11

[a] The ionic liquids are diluted only by the reagents **1** and **2**.

[b] Uncertainties quoted represent the standard deviation of three replicates.

It was found that the rate constant in each of the ionic liquids **4-6** were different (Table 1), indicating that changing the length of the alkyl chain on the cation affects the rate constant of the reaction between benzaldehyde **1** and hexan-1-amine **2**. When considering the ionic liquids **4-6** the only difference is the length of the alkyl chain, as such these differences in the rate constant could be due to: a) the pseudo-encapsulation of reagents in the nano-domains of the solvent and/or; b) the increased steric hindrance on the cation as the alkyl chain is increased reduces the extent of cation – nucleophile **2** interactions. Interestingly, there is no correlation between the alkyl chain length and the observed changes in k_2, and the rate constant is highest in [Bmim][N(CF_3SO_2)$_2$] **4**. This is the opposite of what would be expected based on a pseudo-encapsulation model, as the existence of polar and non-polar domains is least prevalent in the ionic liquid **4**.[45]

To probe the microscopic origin of the differences in the rate constant between these ionic liquids further, the activation parameters of the reaction of species **1** and **2** were determined in [Hmim][N(CF_3SO_2)$_2$] **5** and [Omim][N(CF_3SO_2)$_2$] **6** through temperature-dependent kinetic analyses. These data can be compared with the activation parameters in acetonitrile and [Bmim][N(CF_3SO_2)$_2$] **4** which have been determined previously.[29]

It has been previously demonstrated that interactions between the ionic liquid cation and the lone pair on the nucleophile **2** results in an increased enthalpy and entropy of activation, relative to acetonitrile.[29-30, 43] This cation – nucleophile **2** interaction deactivates the nucleophile **2** and thus increases the enthalpy of activation. The increase in disorder that results from the breaking of this interaction on forming the transition state is the origin of the increased entropy of activation, relative to acetonitrile.[29] In [Bmim][N(CF_3SO_2)$_2$] **4** the change in the entropy of activation was more significant than the change in the enthalpy of activation, resulting in an entropically driven rate increase.[29] For [Hmim][N(CF_3SO_2)$_2$] **5**, a similar increase in both activation parameters, relative to acetonitrile, is observed, with the activation parameters in the ionic liquids **4** and **5** being the same within experimental uncertainty (Table 2). While the differences in the rate constant (Table 1) indicate that there must be differences in the activation parameters for these two ionic liquids, clearly the changes are too small to be determined using this methodology. This demonstrates that the effects of nano-domains and increased steric hindrance on the [Hmim]$^+$ cation are not sufficient to change the activation parameters markedly.

Table 2. The activation parameters for the reaction of benzaldehye and hexan-1-amine (Scheme 1) in each of the ionic liquids 4-6

solvent [a]	$\Delta H^\ddagger$ / kJ mol^{-1} [b]	$\Delta S^\ddagger$ / J K^{-1} mol^{-1} [b]
acetonitrile[29]	27.2 ± 2.5	-272.1 ± 8.7
[Bmim][N(CF_3SO_2)$_2$] **4** (χ_{IL} = 0.97)[29]	32.4 ± 1.3	-235.2 ± 4.6
[Hmim][N(CF_3SO_2)$_2$] **5** (χ_{IL} = 0.96)	34.0 ± 1.5	-237.2 ± 5.0
[Omim][N(CF_3SO_2)$_2$] **6** (χ_{IL} = 0.95)	28.7 ± 1.4	-250.4 ± 4.8

[a] The ionic liquids are diluted only by the reagents **1** and **2**.

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

Interestingly, when using [Omim][N(CF_3SO_2)$_2$] **6** as the solvent it was found that there was a decrease in both the enthalpy and entropy of activation of the reaction, relative to both [Bmim][N(CF_3SO_2)$_2$] **4** and [Hmim][N(CF_3SO_2)$_2$] **5** (Table 2). This difference in the activation parameters for the ionic liquids **6**, relative to the salts **4** and **5**, may arise from the partitioning of the polar reagents **1** and **2** into the polar domain in the ionic liquid **6**. Alternatively, this decrease in the activation parameters might be due to the increased alkyl chain length hindering the charged centre on the cation. An increase in the steric hindrance on the [Omim]$^+$ cation, relative to both the [Bmim]$^+$ and [Hmim]$^+$ cations, would result in decreased cation – nucleophile **2** interactions, and hence a reduction in the enthalpic cost and entropic benefit that is associated with this interaction. Such an effect has been demonstrated in previous work examining the effect of changing the steric hindrance on the cation of the solvent for the reaction of species **1** and **2**, although the effect of increasing the *N*-alkyl chain length was not examining in this previous work.[29]

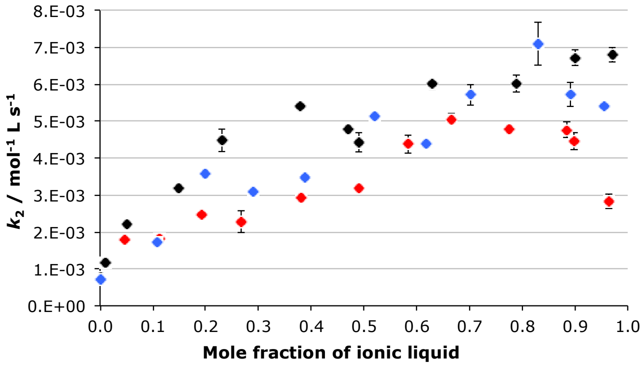
Overall, the lower activation parameters determined in [Omim][N(CF_3SO_2)$_2$] **6**, compared to the ionic liquids **4** and **5**, may arise from: a) pseudo-encapsulation of the reagents into the polar domain; b) decreased cation – nucleophile **2** interaction due to the steric bulk on [Omim]$^+$ cation; or c) a combination of both effects. The extent to which each contribute is difficult to attribute as both effects could affect the activation parameters for the reaction of species **1** and **2**.

The principle outcome from the above work is that for the reaction of species **1** and **2** there is not an increase in k_2 on moving to ionic liquids featuring longer alkyl chains, as might have been expected if the reagents were being preferentially localised in the polar domain of the ionic liquid.[37-38] As such, it is reasonable to suggest that the pseudo-encapsulation of the reagents **1** and **2** into polar domains does not significantly affect the rate constant of this process when using the ionic liquids **4**-**6**.

As it has been widely shown that the amount of ionic liquid present in the reaction mixture affects reaction outcome,[22, 29, 31-35] it was also of interest to determine the rate constant for the reaction of species **1** and **2** in mixtures of either [Hmim][N(CF_3SO_2)$_2$] **5** or [Omim][N(CF_3SO_2)$_2$] **6** and acetonitrile. In previous work examining [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile mixtures it was found that there is a gradual increase in k_2 as the amount of ionic liquid in the reaction mixture was increased, with the most significant increase occurring between χ_{IL} = 0 and 0.2 and a slight decrease in k_2 at χ_{IL} *ca.* 0.5. In this current work it was of interest to determine whether there is a similar trend in k_2 with changing χ_{IL} for the ionic liquids **5** and **6**, and whether there are any 'dips' in these plots as was seen for the [Bmim][N(CF_3SO_2)$_2$] **4** case.[29] As one potential source of this 'dip' observed is that χ_{IL} *ca.* 0.5 is the solvent composition at which the mixture becomes more structured, it might be expected that this effect would be more significant in the ionic liquids **5** and **6** as they have more pronounced nano-structuring.[45]

When using the ionic liquid [Hmim][N(CF_3SO_2)$_2$] **5**, there were a few key differences in the plot of k_2 against χ_{IL} relative to the salt **4** (Chart 1); these were: a) the magnitude of the solvent effect for [Hmim][N(CF_3SO_2)$_2$] **5** is smaller in the range χ_{IL} = 0 to *ca.* 0.5, relative to the trend seen for the salt **4**, with the trend in k_2 comparable for the ionic liquids **4** and **5** between χ_{IL} *ca.* 0.5 and *ca.* 0.8; b) for [Hmim][N(CF_3SO_2)$_2$] **5** there is not a significant dip in the mole fraction dependence plot at χ_{IL} *ca.* 0.5; and c) the rate constant at χ_{IL} *ca.* 0.95 is significantly lower in [Hmim][N(CF_3SO_2)$_2$] **5** than in [Bmim][N(CF_3SO_2)$_2$] **4**, as discussed earlier.

Chart 1: The dependence of k_2 of the reaction of species 1 and 2 (Scheme 1) as the mole fraction of either [Bmim][N(CF_3SO_2)$_2$] 4 (black), [Hmim][N(CF_3SO_2)$_2$] 5 (red) or [Omim][N(CF_3SO_2)$_2$] 6 (blue) in acetonitrile was varied, at 8.1°C.[a]



[a] Uncertainties are reported as the standard deviation of three replicates. It should be noted that some of the error bars fall within the size of the marker.

When using [Omim][N(CF_3SO_2)$_2$] **6** as the ionic liquid, the changes in k_2 for the reaction shown in Scheme 1 with increasing χ_{IL} are similar to that seen for [Hmim][N(CF_3SO_2)$_2$] **5**, although for the salt **6** there appears to be two 'dips' in the plot, one in the region χ_{IL} *ca.* 0.3 to χ_{IL} *ca.* 0.4, and another at χ_{IL} *ca.* 0.6 (Chart 1). There is also a decrease in k_2 on moving to the highest mole fraction of the salt **6** (χ_{IL} *ca.* 0.95), although this decrease in k_2 is not as significant as that seen for [Hmim][N(CF_3SO_2)$_2$] **5**.

As the only difference between the ionic liquids **4**, **5** and **6** is the length of the alkyl chain, the origin of the differences in the trends shown in Chart 1 are likely due to either: a) the existence of nano-domains in the different ionic liquid / acetonitrile mixtures; b) differences in the extent of ordering of the solvent with increasing χ_{IL} for each ionic liquid, which could affect the changes in the entropy of activation; and/or c) changes in the cation – amine **2** interaction due to the different steric hindrance on the cation. It is clear that changing the length of the alkyl chain on the cation affects the rate constant of the reaction between benzaldehyde **1** and hexan-1-amine **2**. However there are no clear correlations between the alkyl chain length and the observed changes in the rate constant. As such, understanding the exact origin of these differences in the plots of the rate constant against ionic liquid concentration is difficult, especially as it is unknown if nano-domains exist in the ionic liquid / acetonitrile mixtures; this will be discussed further in the following section.

SAXS and WAXS measurements

Considering the number of studies that use ionic liquid / molecular solvent mixtures, it was of interest to gain a better understanding of how the properties of the solvent change when using different proportions of an ionic liquid in a molecular solvent. In the kinetic studies presented above for the reaction of species **1** and **2**, it was difficult to attribute the origin of the differences in the plots of k_2 against χ_{IL} for the ionic liquids **4**-**6**. To further investigate the role that solvent structure may have on reaction outcome, we examined the structure of ionic liquid / molecular solvent mixtures to probe whether there is a correlation between solvent structuring and the rate constant for the reaction between species **1** and **2**. As mixtures of [Bmim][N(CF_3SO_2)$_2$] **4** and acetonitrile are commonly used, and there is an anomalous decrease in k_2 at χ_{IL} *ca.* 0.5 that may be due to changes in solvent structure,[29] it was concluded that this system was of most interest to investigate.

Useful methods to examine the bulk structure of liquids include Small and Wide Angle X-ray Scattering (SAXS/WAXS) experiments, where the information obtained from these measurements is interpreted based on Bragg's Law (Equation 1).

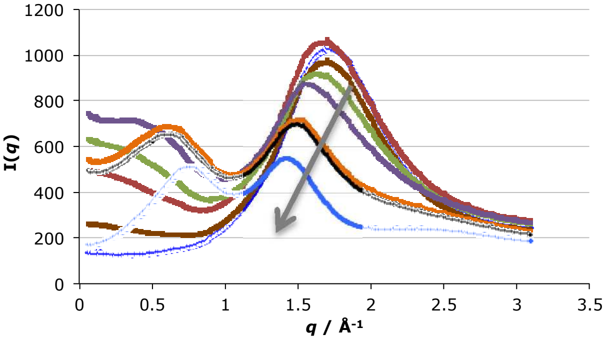
$$d \approx \frac{2\pi}{q_{max}} \qquad (1)$$

SAXS/WAXS techniques have been applied to investigate the extent of nanoscale organisation in many ionic liquids.[48-51] This previous work has mainly focused on neat ionic liquids,[45, 47-48, 52-62] but there have also been investigations on mixtures of ionic liquids and molecular solvents, although they have mainly involved protic ionic liquids.[63-65] Previous SAXS/WAXS measurements of neat ionic liquids have shown that there are three main peaks that tend to be observed in their scattering patterns: at q *ca.* 0.2 - 0.6 Å^{-1} corresponding to polarity alternation and characteristic of nanoscale structural heterogeneity; at q *ca.* 0.9 Å^{-1} due to charge alternation of the ionic components; and at q *ca.* 1.5 Å^{-1} due to correlations between neighbouring atoms, both intra- and inter-molecularly (often termed 'adjacency correlations').[45, 52, 60, 66]

For neat [Bmim][N(CF_3SO_2)$_2$] **4** it has been shown that there is not a significant peak at low *q* values, suggesting that there is not a significant degree of nanostructure in this ionic liquid.[45, 47] Only when moving to ionic liquids that feature a longer alkyl chain (six or more carbon atoms[45]) on the imidazolium cation does a prominent low *q* peak appear. This is a result of the longer alkyl chains driving the formation of polar and non-polar domains, as discussed earlier. It was shown that [Bmim][N(CF_3SO_2)$_2$] **4** does have a peak at *q ca.* 0.9 Å^{-1}, due to charge alternation, and a peak at *q ca.* 1.4 Å^{-1}, due to correlations between neighbouring atoms.[45, 47] There have been no previous studies examining the structure of mixtures of [Bmim][N(CF_3SO_2)$_2$] **4** and acetonitrile.

The SAXS/WAXS patterns of mixtures containing different proportions of [Bmim][N(CF_3SO_2)$_2$] **4** in acetonitrile were measured. Initially the focus was on examining the changes in solvent structure when moving from acetonitrile to mixtures containing small concentrations of the ionic liquid **4**, to determine whether there was aggregation of the ions at very low mole fractions. The results of these experiments are presented as the peak intensity (I) plotted against the scattering vector (*q*) (Chart 2).

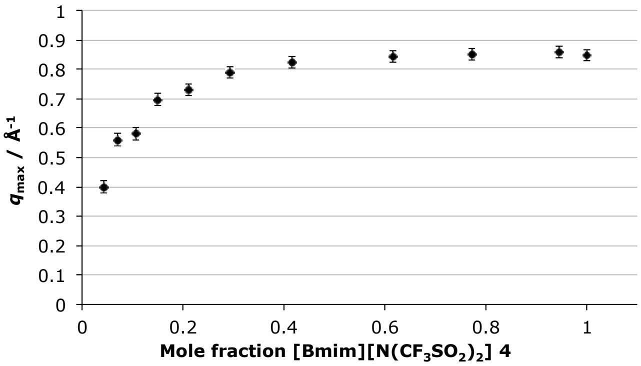
Chart 2: SAXS/WAXS data for the [Bmim][N(CF_3SO_2)$_2$] 4 / acetonitrile mixtures at: χ_{IL} = 0 (dark blue); χ_{IL} = 0.004 (brown); χ_{IL} = 0.009 (red); χ_{IL} = 0.019 (green); χ_{IL} = 0.043 (purple); χ_{IL} = 0.071 (orange), χ_{IL} = 0.106 (black) and χ_{IL} = 0.211 (light blue). The arrow shows the direction of increasing χ_{IL}.



Interestingly, it was found that when moving from neat acetonitrile to mixtures containing low mole fractions of [Bmim][N(CF_3SO_2)$_2$] **4** in acetonitrile a low *q* feature appears (*q ca.* 0.4 Å^{-1}). This feature becomes larger with increasing amounts of [Bmim][N(CF_3SO_2)$_2$] **4** up to χ_{IL} *ca.* 0.04, and above χ_{IL} *ca.* 0.04 this low *q* peaks shifts to higher *q* values (Chart 2). This low *q* feature corresponds to long-range structural heterogeneities in the liquid, and the increasing intensity of this peak suggests that at very low concentrations of [Bmim][N(CF_3SO_2)$_2$] **4** in acetonitrile (χ_{IL} < 0.05) the ionic liquid components are aggregating.

In the range χ_{IL} = 0.04 to 0.21, the peak being considered shifts from *q ca.* 0.4 to 0.78 Å^{-1} and becomes narrower (Chart 2). This shift likely arises from a progression from larger, more diffuse clusters in mixtures containing the lower χ_{IL} to smaller, more defined clusters in mixtures containing higher χ_{IL}, with the peak then lying in the region where peaks due to charge alternation are generally found.[45, 52, 60, 66] Further increases in the amount of ionic liquid **4** in the mixture, from χ_{IL} = 0.21 to 1, result in minimal changes in the position of this lower *q* peak, although it does become narrower and increases in intensity (Chart S1); the narrowing of the peak suggests that this structuring is becoming more defined at higher χ_{IL}. The change in the peak position of the lower *q* peak can be most clearly seen by plotting q_{max} against χ_{IL} (Chart 3), noting that for mixtures containing very low χ_{IL}, that the value of q_{max} could not be accurately determined as the peak is not well defined.

Chart 3: The position of q_{max} for the low *q* peak as the mole fraction of [Bmim][N(CF_3SO_2)$_2$] 4 in acetonitrile was varied.[a]



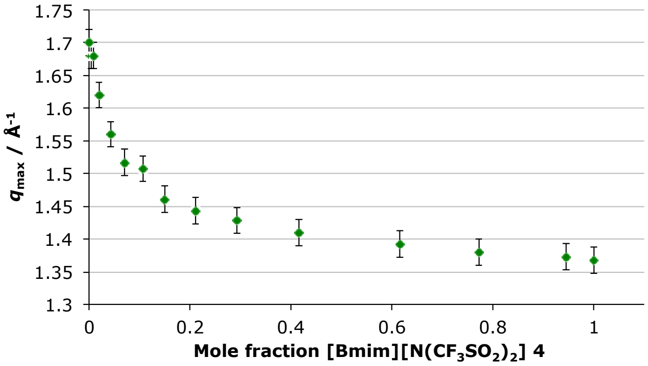
[a] The low *q* peak data for χ_{IL} < 0.043 could not be determined as the peak was not well defined, and the value of q_{max} at χ_{IL} = 0.043 is an estimate as the peak is broad. Uncertainties are reported as ± 0.02 Å^{-1}, which is an estimate of the uncertainty associated with the fitting method used to determine q_{max}.

The most significant change in the position of q_{max} occurs at lower mole fractions of [Bmim][N(CF_3SO_2)$_2$] **4** in acetonitrile (χ_{IL} < 0.2), and with increasing amounts of the salt **4** in the mixture there is little change in the position of this peak (Chart 3). This indicates that for χ_{IL} > 0.2 there is little change in the electrostatic interactions in the solvent mixture, and that the length scale of this intermediate range structuring, due to charge alternation of the ions in the solvent mixture, remains similar when moving from mixtures containing χ_{IL} *ca.* 0.2 to those containing χ_{IL} *ca.* 0.9.

Overall, the changes in the peak position of the low *q* peak suggest that at lower concentrations of [Bmim][N(CF_3SO_2)$_2$] **4** in acetonitrile the component ions cluster together, and then with increasing amounts of the ionic liquid **4** this clustering becomes less significant, and charge alternation starts to become more significant. That is, at very low values of χ_{IL} (< 0.05) there are ionic liquid aggregates, and at higher values of χ_{IL} these aggregates break down and general coulombic, intermediate length scale interactions dominate. This is important as it suggests that for mixtures of [Bmim][N(CF_3SO_2)$_2$] **4** and acetonitrile, structural heterogeneities of significant scale do not form for mixtures containing χ_{IL} > 0.04. Hence it is unlikely that there is trapping of the reagents in either polar or non-polar domains in the [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile solvent mixtures.

The SAXS/WAXS pattern of neat acetonitrile has a single, large peak at *q* = 1.7 Å^{-1}, due to the short-range interactions in the liquid (Chart 2). With increasing amounts of [Bmim][N(CF_3SO_2)$_2$] **4** added to the solvent mixture this peak shifts to lower *q* values (Charts 2 and S1). This trend is best visualised by plotting q_{max} against χ_{IL} (Chart 4), and indicates that the nature of the short-range interactions is becoming less like those in acetonitrile when more ionic liquid **4** is added to the solvent mixture. This wasn't too surprising, as when adding ions to the mixture it would be expected that the solvent structuring would become less like the structuring in acetonitrile and more like the neat ionic liquid **4**.

Chart 4: The position of q_{max} for the high *q* peak as the mole fraction of [Bmim][N(CF_3SO_2)$_2$] 4 in acetonitrile was varied.



[a] Uncertainties are reported as ± 0.02 Å^{-1}, which is an estimate of the uncertainty associated with the fitting method used to determine q_{max}.

The change in the position of the higher *q* peak (Chart 4) suggests that the short-range ordering, due to correlations such as van der Waals' interactions between alkyl chains, exists over a larger length scale when moving to higher concentrations of the salt **4** in acetonitrile. The main changes in the position of this high *q* peak occur when moving from neat acetonitrile to χ_{IL} *ca.* 0.2, in a comparable fashion to that observed for the lower *q* peak (Chart 3).

The trends shown in Charts 3 and 4 indicate that the main structural changes of the mixtures occur before χ_{IL} *ca.* 0.2. This is important, as it suggests that by χ_{IL} *ca.* 0.2 the [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile mixtures are comparable to the neat ionic liquid **4**, according to the SAXS/WAXS data. Such an effect is of particular interest in this work as for both an S_N2 reaction[22, 32, 34] and the condensation reaction between species **1** and **2**[29] examined previously, the main changes in the rate constant and activation parameters in [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile mixtures occurred in the region χ_{IL} = 0 to *ca.* 0.2-0.3. For those cases, the increased rate constant in the ionic liquid was rationalized to be due to interactions between the ionic liquid cation and the nucleophile, where breaking of this interaction on forming the transition state resulted in an enthalpic cost and a more significant entropic benefit, relative to acetonitrile. This current work supports the idea that this trend in k_2 (for example, Chart 1) arises from a reduction in the entropic effect observed at higher χ_{IL} as the solvent becomes more structured. That is, the ordering of the solvent limits the extent of disorder that can occur on forming the transition state complex, causing the entropic benefit to be comparable and therefore there is little change k_2 above χ_{IL} *ca.* 0.2.

Some previous work that is worth considering here is a study examining the structuring of mixtures of protic ionic liquids and water.[64] In those cases there was a significant downward shift in the high *q* peak (*q* = 1.4-1.7 Å^{-1}) when moving from neat water to χ_{IL} *ca.* 0.3, with little change in the position of q_{max} when moving to higher mole fractions of ionic liquid;[64] this is essentially the same trend as that seen in this current work. In that previous work the change in the peak position of the high *q* peak was attributed to a shift from water – water and water – ionic liquid interactions dominating at lower χ_{IL}, to ionic liquid – ionic liquid interactions becoming more prevalent at higher χ_{IL}.[64] The point at which the change in the position of q_{max} became negligible (χ_{IL} *ca.* 0.3) was said to be the point where the intermediate range ionic liquid – ionic liquid interactions dominate, and hence there was little change in the short-range interactions above this point. Such a trend was also seen in another study on mixtures of an ammonium based ionic liquid and water.[63]

Applying this argument to the work completed here suggests that for the [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile mixtures with χ_{IL} above *ca.* 0.2, general ionic liquid – ionic liquid interactions become significant and there is no further change in the ordering within the solvent mixture. It is possible that in the region χ_{IL} 0 to *ca.* 0.2, where the main changes in the short-range acetonitrile – acetonitrile and ionic liquid – acetonitrile interactions occur, that the main changes in the ionic liquid – solute interactions also occur. When moving to χ_{IL} > 0.2, where there was little change in the short-range interactions in the solvent mixture, there might also be expected to be little change in the ionic liquid – solute interactions. This concept is consistent with the minimal changes in the rate constants and activation parameters for both the S_N2[22, 32, 34] and condensation[29] reactions considered in these systems above χ_{IL} *ca.* 0.2.

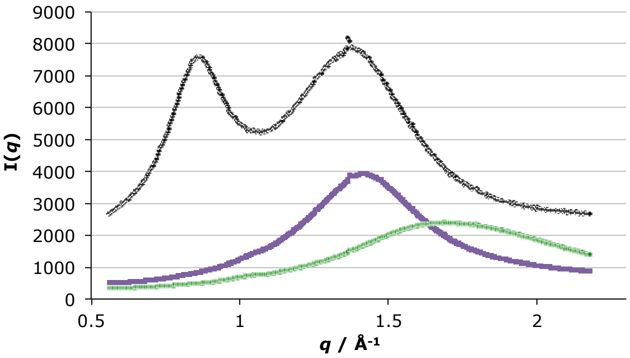
In combination, the SAXS/WAXS studies and the kinetic analyses on the S_N2[22, 34] and condensation[29] reactions suggest that for the [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile mixtures, the region where the main changes in the structuring of the solvent occurs, corresponds to the region where the main changes in rate constant occur. This correlation likely arises from both: a) a reduction in the entropic effects observed above χ_{IL} *ca.* 0.2 as the solvent becomes more structured, and hence the entropic advantage of breaking the cation – nucleophile interaction changes less significantly with proportion of ionic liquid; and b) the main changes in the short-range ionic liquid – nucleophile interactions also occurring between χ_{IL} = 0 and *ca.* 0.2.

The mixtures considered so far have only contained the ionic liquid **4** and the co-solvent acetonitrile, but it was also of interest to see how the bulk structure of the liquid is affected when a reagent is dissolved into the solvent. Ideally, measurements of the bulk structure of systems containing both benzaldehyde **1** and hexan-1-amine **2** dissolved in the solvent mixture (preferably at the concentrations used in reactivity studies) would be carried out, but both being present would result in reaction during the measurements so this was deemed impractical. Considering the importance of the interaction between the ionic liquid cation and the nucleophile **2** demonstrated previously,[29-30, 43] it was concluded that inclusion of this reagent in the solvent mixture was of more interest, particularly to determine if its inclusion would result in changes in the bulk structure of the mixture.

To investigate the structuring of these ternary mixtures, the WAXS patterns of a number of mixtures of [Bmim][$N(CF_3SO_2)_2$] **4** and acetonitrile containing the nucleophile hexan-1-amine **2** (*ca.* 0.1 mol L^{-1}, χ *ca.* 0.03) were measured. As the above section demonstrated that there was no low *q* peak above χ_{IL} *ca.* 0.04, only the higher *q* region was examined in this section. The results of the WAXS experiments are once again presented as the peak intensity (I) plotted against the structure factor (*q*) (Charts S2-4).

The scattering pattern of neat hexan-1-amine **2** has a single peak at *q ca.* 1.4 Å^{-1}, which is in a similar position as the high *q* peak observed for [Bmim][$N(CF_3SO_2)_2$] **4**, while acetonitrile has one broad peak at *q ca.* 1.5-2 Å^{-1} (Chart 5). Generally the determined WAXS patterns for the mixtures of [Bmim][$N(CF_3SO_2)_2$] **4**, acetonitrile and hexan-1-amine **2** (Charts S2-4) were found to have similar peaks at low and high *q* values to those seen for the [Bmim][$N(CF_3SO_2)_2$] **4** and acetonitrile mixtures (Chart 2 and S1). Interestingly, the data for the mixtures containing the amine **2** are much more complicated than those for the mixtures of just [Bmim][$N(CF_3SO_2)_2$] **4** and acetonitrile, with some of the patterns featuring asymmetric peaks as well as additional peaks not observed previously in simple mixtures of salt **4** and acetonitrile. The determined scattering patterns appear to be the sum of several distinct contributions and hence result in a spectrum with poorly defined peaks. As such, simple peak fitting to determine q_{max} was not valid. The peak observed at *q ca.* 1.4 Å^{-1} in neat hexan-1-amine **2** may be present in the mixtures, and could contribute, to some extent, to the complexity of the peak shapes observed.

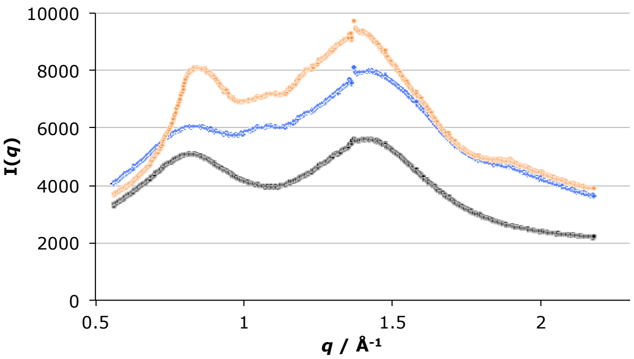
Chart 5: WAXS data for neat [Bmim][$N(CF_3SO_2)_2$] 4 (black), acetonitrile (green) and hexan-1-amine 2 (purple).[a]



[a] The discontinuities observed at *q ca.* 1.4 are an artifact from the detector and should be ignored.

For some, but not all, mixtures containing the ionic liquid **4**, acetonitrile and the amine **2** there is a new peak present in the range *q* = 0.95 to 1.2 Å^{-1} (Charts S2-4). It would seem reasonable to conclude (given other data) that this new peak is due to correlations between the ionic liquid **4**, particularly the cation, and hexan-1-amine **2**. However, it is difficult to attribute the exact nature of this scattering peak as it is only visible in the WAXS data for some proportions of the salt **4** in the mixture. Further, there appears to be no pattern as to when this additional peak is observed. A particularly demonstrative comparison is that between the measured scattering pattern at χ_{IL} = 0.39, which is similar to the WAXS data for the simple [Bmim][$N(CF_3SO_2)_2$] **4** and acetonitrile mixtures described earlier, to the data at χ_{IL} = 0.36 (Chart 6). With only a slight decrease in the ionic liquid **4** concentration, there is a significant change in the scattering pattern, with a much more complex pattern measured at χ_{IL} = 0.36 and a new peak formed at *q ca.* 1.05 Å^{-1}.

Chart 6: WAXS data for mixtures of [Bmim][$N(CF_3SO_2)_2$] 4, acetonitrile and hexan-1-amine 2 (*ca.* 0.1 mol L^{-1}, χ *ca.* 0.03) at χ_{IL} = 0.36 (black) where no new peak is observed, and at χ_{IL} = 0.22 (blue) and χ_{IL} = 0.39 (orange) where an additional peak in the region of *q* = 0.95 to 1.2 Å^{-1} is present.[a]

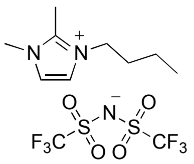


[a] The discontinuities observed at *q ca.* 1.4 are an artifact from the detector and should be ignored.

At this point it is difficult to comment further on the source of this anomalous behavior observed for the mixtures of [Bmim][$N(CF_3SO_2)_2$] **4**, acetonitrile and hexan-1-amine **2**. Despite the relatively limited understanding of these ternary mixtures, the behavior observed clearly demonstrates that addition of hexan-1-amine **2** to the [Bmim][$N(CF_3SO_2)_2$] **4** / acetonitrile mixture affects the bulk structure of the liquid. The formation of an additional peak for only some of the mole fractions examined suggests that predicting how the liquid structure changes on addition of the nucleophile **2** is non-trivial, and these changes in the interactions within the mixtures may be the origin of the ‘dips’ in the mole fraction dependence plots that have been observed previously.

Another ionic liquid that is of particular interest to investigate in terms of its structure is [Bm_2im][$N(CF_3SO_2)_2$] **7** (Figure 2). The effect of this ionic liquid on the rate constant and activation parameters for the reaction of either benzaldehyde **1** or 4-methoxybenzaldehyde and hexan-1-amine **2** has been previously investigated.[29] It was generally found that the ionic liquid **7** affected reaction outcome in a similar manner to when [Bmim][$N(CF_3SO_2)_2$] **4** was used, with identical changes in the rate constant for the reaction between species **1** and **2** as the proportion of the ionic liquid in the reaction mixture was increased.[29] The only difference in the solvent effects observed for ionic liquids **4** and **7** is that the activation parameters determined for the reaction between 4-methoxybenzaldehyde and the amine **2** were slightly lower in [Bm_2im][$N(CF_3SO_2)_2$] **7** than [Bmim][$N(CF_3SO_2)_2$] **4**. This difference in the activation parameters was attributed to the increased steric bulk on the cation of the salt **7**, resulting in reduced cation – hexan-1-amine **2** interactions, and is consistent with previous observations on related processes.[28]

Figure 2: The ionic liquid [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] 7



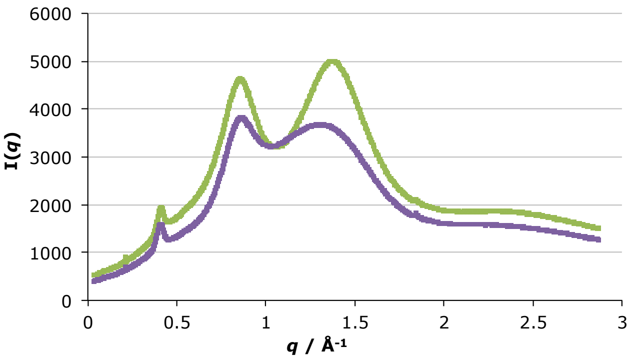
7

While the solvent effects of the ionic liquid **7** on the condensation reactions examined previously were relatively straightforward, this ionic liquid has been previously shown to exhibit some unexpected behaviour. The ionic liquid **7** has a methyl group at the C2 position, rather than the acidic proton that is present in [Bmim][N(CF$_3$SO$_2$)$_2$] **4**. Intuitively, removing this acidic proton would be expected to result in a decrease in the extent of hydrogen bonding of the [Bm$_2$im]$^+$ cation with the [N(CF$_3$SO$_2$)$_2$]$^-$ anion, relative to the [Bmim]$^+$ cation, and therefore result in [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** having a lower viscosity and melting point than [Bmim][N(CF$_3$SO$_2$)$_2$] **4**. Interestingly, the trend is the opposite to what would have been expected, with [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** having a higher viscosity and melting point than the ionic liquid **4**.[67-68] The origin of this phenomenon has been attributed to restricted movement of the ions of [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7**, relative to [Bmim][N(CF$_3$SO$_2$)$_2$] **4**, due to the high potential energy barriers for the different conformers,[69] and a reduction in the number of stable ion-pair conformers (reducing the entropy relative to the salt **4**).[70-71] A decrease in the unoccupied free volume for the ionic liquid **7**[72] and longer lived ion cages in this salt,[73] relative to the ionic liquid **4**, has also been suggested to contribute to the viscosity differences.

Considering this behaviour of [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7**, it was of interest to investigate the structuring of this solvent. As such, the SAXS/WAXS patterns of a number of mixtures of the ionic liquid **7** and acetonitrile were measured, to investigate any differences in the ordering of [Bmim][N(CF$_3$SO$_2$)$_2$] **4** and [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7**. To begin with, the SAXS/WAXS patterns of samples containing a high mole fraction (χ_{IL} = 0.90) of either [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** or [Bmim][N(CF$_3$SO$_2$)$_2$] **4** in acetonitrile were compared (Chart 7). It should be noted that this mole fraction was chosen as when using these ionic liquids as solvents they will always be diluted by reagents, hence, comparing data at χ_{IL} *ca.* 0.9 is of interest.

It was found that for both samples there are two distinct peaks, one at q *ca.* 0.8 Å^{-1} and q *ca.* 1.3 Å^{-1} (Chart 7); these correspond to charge alternation and short-range correlations, respectively, as described earlier. Interestingly, the peaks for the [Bmim][N(CF$_3$SO$_2$)$_2$] **4** case are much sharper than those for [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7**, suggesting that the intermediate and short-range ordering is more defined in the ionic liquid **4** case. The peak at q *ca.* 1.3 Å^{-1} in [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** is particularly broad, which indicates that there are a variety of short-range correlations that exist on similar, but slightly different, length scales.

Chart 7: SAXS/WAXS data for [Bmim][N(CF$_3$SO$_2$)$_2$] 4 in acetonitrile at χ_{IL} = 0.90 (green) and [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] 7 in acetonitrile at χ_{IL} = 0.90 (purple).[a]



[a] The sharp peak at q *ca.* 0.4 is a scattering contribution due to the Kapton tape used to secure the samples and should be ignored.

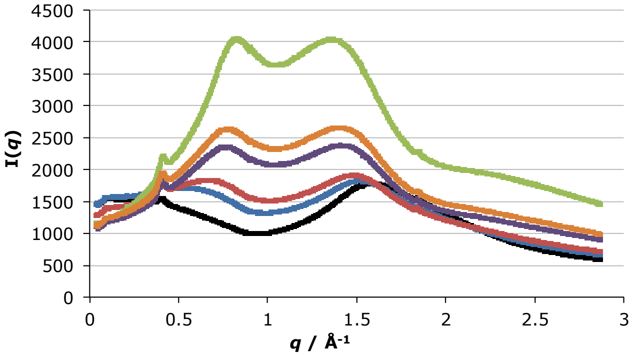
In terms of peak positions, the low q charge alternation peak has q_{max} at a similar position for both ionic liquids, suggesting that the ordering due to charge alternation is comparable for these two ionic liquids. Conversely, q_{max} for the high q peak is shifted to a slightly lower q value for [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7**, compared to [Bmim][N(CF$_3$SO$_2$)$_2$] **4**. This shift to lower q indicates that the length-scale of the ordering is slightly longer for the methylated case **7** than the parent **4**. The increased low q peak intensity suggests that correlations between alkyl chains and other van der Waals' interactions exist over a larger distance for [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7**, relative to the salt **4**, which is in agreement with the increased ordering of this ionic liquid that has been proposed previously.[69-71]

There are two main conclusions from the discussion above: a) the high q peak position shifts to lower q values in [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** relative to to [Bmim][N(CF$_3$SO$_2$)$_2$] **4**; and b) the position of the low q peak is the same for both ionic liquids **7** and **4**. These observations suggest that the increased ordering in [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** compared with [Bmim][N(CF$_3$SO$_2$)$_2$] **4** is due to changes in the short-range correlations rather than changes in the ordering due to charge alternation.

SAXS/WAXS patterns were measured across a range of different mole fractions of [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** in acetonitrile to investigate how the bulk structure of the liquid changes as the amount of the ionic liquid **7** in the mixture is varied. The results of these experiments are presented as the intensity (I) plotted against the structure factor (q) for χ_{IL} = 0.05 to 0.28 (Chart 8) and χ_{IL} = 0.32 to 0.90 (Charts S5-7; included in the ESI as there was little change in the SAXS/WAXS patterns above χ_{IL} *ca.* 0.3).

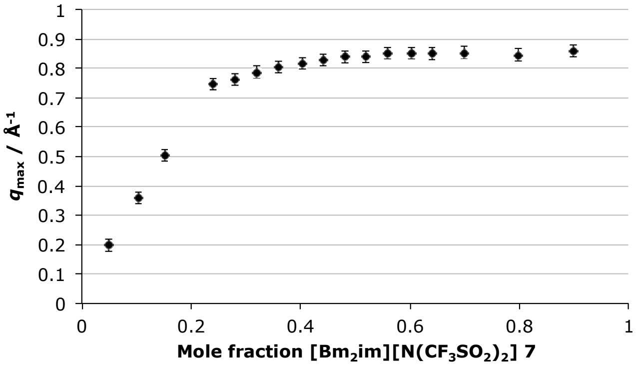
It was observed that with increasing χ_{IL} the low q peak in the SAXS/WAXS data shifted to higher q values (Chart 8 and Charts S5-7), which was analogous to what was observed for mixtures of acetonitrile and [Bmim][N(CF$_3$SO$_2$)$_2$] **4**. This effect for mixtures of acetonitrile and [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** is best seen by plotting the positions of q_{max} for the low q peak against χ_{IL} (Chart 9). The shift of the lower q peak to higher q values with increasing amounts of the ionic liquid **7** indicates that at very low mole fractions of [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** in acetonitrile there is clustering of the ionic liquid components. With increasing χ_{IL} this peak shifts into the region where peaks due to intermediate range ordering are expected, indicating that ordering due to charge alternation becomes prominent for $\chi_{IL} >$ *ca.* 0.2.

Chart 8: The determined SAXS/WAXS patterns for the mixtures of [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] 7 and acetonitrile, at χ_{IL} = 0.050 (black), χ_{IL} = 0.103 (blue), χ_{IL} = 0.151 (red), χ_{IL} = 0.202 (green), χ_{IL} = 0.241 (purple) and χ_{IL} = 0.280 (orange).



^{a} The sharp peak at *q ca.* 0.4 is a scattering contribution due to the Kapton tape used to secure the samples and should be ignored.

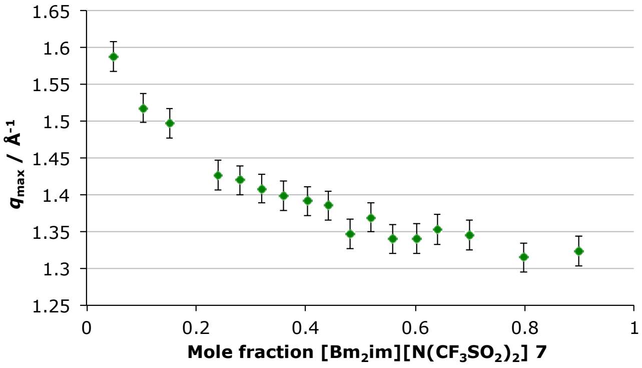
Chart 9: The position of q_{max} for the low *q* peak as the mole fraction of [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] 7 in acetonitrile was varied.^{a}



^{a} Uncertainties are reported as ± 0.02 Å^{-1}, which is an estimate of the uncertainty associated with the fitting method used to determine q_{max}.

The change in the position of the high *q* peak is now going to be considered; it was found that with increasing χ_{IL} the high *q* peak shifted to slightly lower *q* values (Chart 10). This trend suggests that the short-range correlations (such as van der Waals' interactions between alkyl chains) become more prominent and exist over a larger length scale when moving to higher concentrations of the salt **7**. The main changes in the peak position of the high *q* peak occur between χ_{IL} = 0 and *ca.* 0.3-0.4, which indicates that the main changes in the short-range correlations of the [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** / acetonitrile mixtures occurs at $\chi_{IL} <$ *ca.* 0.4. Interestingly, for the salt **7** the decrease in q_{max} is much more gradual with increasing χ_{IL}, than that observed for both the low *q* peak (Chart 9) and the high *q* peak (Chart 4) for the salt **4**. This suggests that for the salt **7** the short-range interactions present at lower χ_{IL} persist on moving to higher χ_{IL}, and that there is a more gradual transition of the short range interactions from being more 'acetonitrile-like' to more 'ionic liquid-like' with increasing χ_{IL}. Additionally, the high *q* peak is much more broad across the mixtures (Chart 8 and Charts S5-7) than that observed for [Bmim][N(CF$_3$SO$_2$)$_2$] **4** (Charts 2 and S1), further suggesting that the short-range correlations in these mixtures exist on similar, but slightly different, length scales.

Chart 10: The position of q_{max} for the high *q* peak as the mole fraction of [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] 7 in acetonitrile was varied.



^{a} Uncertainties are reported as ± 0.02 Å^{-1}, which is an estimate of the uncertainty associated with the fitting method used to determine q_{max}.

Overall, the trends in both the low and high *q* peak position with increasing χ_{IL} for the salt **7** are similar to that seen for the [Bmim][N(CF$_3$SO$_2$)$_2$] **4** / acetonitrile mixtures examined earlier. Once again, this indicates that the main changes in the structure of the solvent occur at lower χ_{IL}. The trends observed for [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** suggests that for $\chi_{IL} <$ *ca.* 0.3-0.4 acetonitrile – acetonitrile and acetonitrile – [Bm$_2$im][N(CF$_3$SO$_2$)$_2$] **7** interactions dominate (more acetonitrile-like), and for $\chi_{IL} >$ *ca.* 0.3-0.4 electrostatic interactions dominate (more ionic liquid-like).

As was discussed earlier, the range of χ_{IL} where the main changes in the solvent structure occurs corresponds to the range of χ_{IL} where the main changes in reaction outcome occur. This is demonstrated by kinetic analyses on the reaction between species **1** and **2** in the ionic liquid **7**, where the most significant changes in the rate constant and activation parameters were found to occur between χ_{IL} = 0 and *ca.* 0.3, with negligible changes in the activation parameters when going to from χ_{IL} *ca.* 0.3 to χ_{IL} *ca.* 0.9.[29] Once again, this effect likely arises from the main both: a) reduced entropic effects above χ_{IL} *ca.* 0.3 as the solvent becomes more structured, and hence the entropic advantage of breaking the cation – nucleophile **2** interaction changes less significantly with proportion of ionic liquid; and b) the main changes in the short-range correlations between the ionic liquid **7** and hexan-1-amine **2** occur between χ_{IL} = 0 and *ca.* 0.3.

CONCLUSIONS

It was found that for the reaction between benzaldehyde **1** and hexan-1-amine **2** there is no correlation between the alkyl chain length on the 1-alkyl-3-methylimidazolium cation of an ionic liquid and the rate constant in that ionic liquid. Additionally, the rate constant was highest in [Bmim][N(CF_3SO_2)$_2$] **4**, the opposite of what would expected from a pseudo-encapsulation model.[37-38] This suggests that the trapping of the reagents **1** and **2** in polar domains is not the only origin of the changes in the rate constant when using the ionic liquids **4**-**6**. When moving from [Bmim][N(CF_3SO_2)$_2$] **4** to [Omim][N(CF_3SO_2)$_2$] **6** there was a decrease in the activation parameters, which could be arise from: a) pseudo-encapsulation of the reagents into the polar domain; b) decreased cation – nucleophile **2** interaction due to the steric bulk on [Omim]$^+$ cation; or c) a combination of both factors. At this point it is difficult to comment on the exact origin of the reduced activation parameters in [Omim][N(CF_3SO_2)$_2$] **6**, relative to the ionic liquid **4** and **5**.

The SAXS/WAXS measurements of both [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile and [B_2mim][N(CF_3SO_2)$_2$] **7** / acetonitrile mixtures indicated that the main changes in solvent structure occur between $\chi_{IL} = 0$ and χ_{IL} *ca.* 0.2-0.3, with little change in structure on moving to higher χ_{IL}. This work, in combination with previous kinetic analyses on S_N2[22, 32, 34] and condensation[29] reactions, highlights that the region where the main changes in the solvent structuring occurs, corresponds to the region where the main changes in rate constant and activation parameters occur; this is the first time that such a correlation has been observed. It is proposed that this correlation arises from two factors; firstly, above χ_{IL} *ca.* 0.2-0.3 there is limited increase in disorder on forming the transition state, as the solvent has become more structured as the proportion of the ionic liquid in the reaction mixture increases. This results in the entropic advantage of breaking the cation – nucleophile interaction reaching a maximum at χ_{IL} *ca.* 0.2-0.3 and, as this is an entropically driven solvent effect, there is limited further increase in k_2 above this point. Secondly, considering previous work,[63-64] it is reasonable to suggest that the main changes in the short-range ionic liquid – nucleophile interactions also occurs between $\chi_{IL} = 0$ and *ca.* 0.2-0.3, and hence the main solvent effects are observed in this region.

On examination of the WAXS patterns of [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile / hexan-1-amine **2** mixtures it was found that some mixtures featured asymmetric peaks as well as additional peaks not observed in the [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile mixtures. This suggests that the addition of hexan-1-amine **2** affects the bulk structure of the mixture. Interestingly, there was no pattern to when this additional peak is observed, suggesting that predicting how the liquid structure changes on addition of the nucleophile **2** to the [Bmim][N(CF_3SO_2)$_2$] **4** / acetonitrile is difficult.

Overall, using an ionic liquid diluted by a molecular solvent is beneficial, both practically (*e.g.* cheaper and less viscous) and from a solvent effect standpoint (similar, or greater, rate enhancement than at higher proportions of the ionic liquid). This current work demonstrates that while the trend in the rate constant with changing χ_{IL} is mainly due to changes in the solvent – solute (and solvent – transition state) interactions along the reaction coordinate, subtle changes in the ordering of the solvent can influence the entropic effects associated with these interactions. In order to be able to predict the effect of a certain ionic liquid / molecular solvent mixture on organic reaction outcomes it is essential to have a good understanding of the origin of the non-linear changes in the rate constant as the solvent composition is varied. This current work highlights the importance of considering the bulk structure of the reaction mixture in this sense.

EXPERIMENTAL

Materials

Benzaldehyde **1** and hexan-1-amine **2** were commercially available, and each was distilled under reduced pressure then stored over 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[74-76] by first treating the corresponding imidazole with either butyl bromide or butyl chloride to afford the intermediate halide salt, which was then treated with lithium *bis*(trifluoromethanesulfonyl)imide to give the required ionic liquid. 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.

Kinetic studies

Kinetic analyses were carried out in solutions containing the benzaldehyde **1** (*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. ^{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 in a 5 mm NMR tube. Results were shown to be reproducible between the different spectrometers.

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 the MestReNova 7.1.1 software. The pseudo-first order rate constants were calculated using integrations of the aldehyde signal in the starting material **1** at δ ca. 10.0, obtained from the processed ^{1}H NMR spectra, by fitting the natural logarithm of the integrations to a linear function using the Microsoft Excel 14.4.3 LINEST function. Bimolecular rate constants (k_2) were obtained from the pseudo-first order constants by dividing by the initial amine **2** concentration in the reaction mixture.

Where appropriate, the activation parameters were then determined through fitting the obtained data using the Microsoft Excel 14.4.3 LINEST function to the bimolecular Eyring equation.[77] Tables containing the exact mole fraction, amine **2** concentration, temperature and rate constants for all the systems described above can be found in the Electronic Supporting Information.

SAXS and WAXS measurements

The small and wide angle X-ray scattering (SAXS/WAXS) experiments were performed on the SAXS/WAXS beamline at the Australian Synchrotron, Victoria, Australia. The *q* range for the SAXS experiments was 0.02 to 0.62 Å^{-1}, and the *q* range for the WAXS experiments was 0.54 to 3 Å^{-1}. The experiments were performed using a one second exposure time at 25 °C. The temperature of the sample holder was regulated using a Huber recirculating water bath. The samples were loaded into 1.5 mm capillaries, which were sealed with silicon rubber to prevent water absorption from the atmosphere. Samples were housed in a 60 sample capillary holder, which was mounted on a three axis sample stage, and the contribution from an empty capillary was subtracted from the scattering profiles. The data acquired was integrated from two dimensions to one dimension and, where relevant, the SAXS and WAXS data were carefully combined to obtain scattering profiles with the *q* range of 0.02 to 3 Å^{-1}. The data was fitted using custom written Matlab code to obtain peak positions, which are not a physically meaningful fit.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthesis and ^{1}H NMR spectra of the ionic liquids, rate constant data and additional charts (PDF)

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Notes

¥ As the amount of ionic liquid present in the reaction mixture has been widely shown to affect reaction outcome, it is important to know the χ_{IL} for each case being considered.

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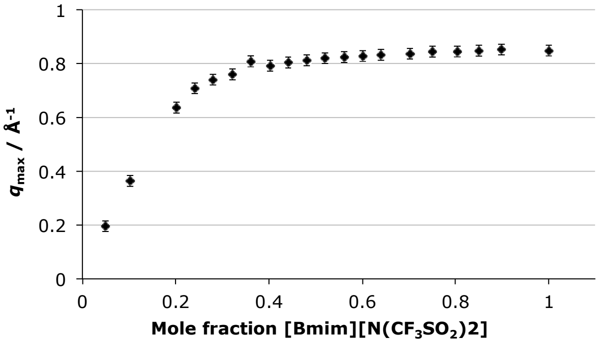
TOC Graphic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0.6
0.4
0.2
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q_{max} / Å^{-1}
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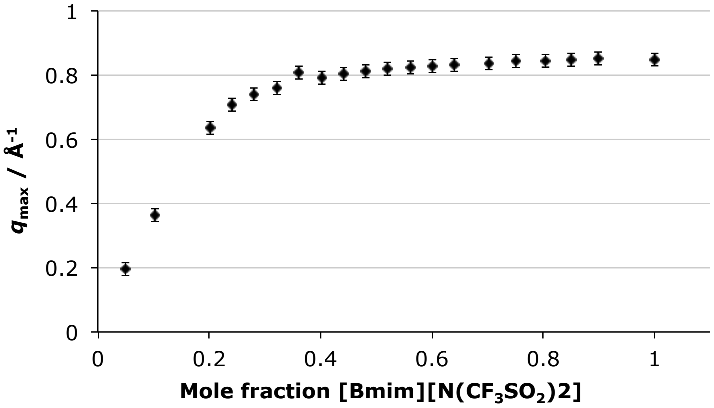
0.2
0.4
0.6
0.8
1
Mole fraction [Bmim][N(CF_3SO_2)2]


1
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0.8
1
Mole fraction [Bmim][N(CF_3SO_2)2]