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The Dependence of Ionic Liquid Solvent Effects on the Nucleophilic Heteroatom in S_NAr Reactions. Highlighting the Potential for Control of Selectivity

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Nucleophilic aromatic substitution (S_NAr) reactions of 1-fluoro-4-nitrobenzene using similar nitrogen and sulfur nucleophiles were studied through extensive kinetic analysis in mixtures containing ionic liquids. The interactions of the ionic liquid components with the starting materials and transition state for each process were investigated in an attempt to construct a broad predictive framework for how ionic liquids affect reaction outcome. It was found that, based on the activation parameters, the microscopic interactions and thus the ionic liquid solvent effect were different for each of the nucleophiles considered. The results from this study suggest that it may be possible to rationally select a given ionic liquid mixture to selectively control reaction outcome of an S_NAr reaction where multiple nucleophiles are present.

Introduction

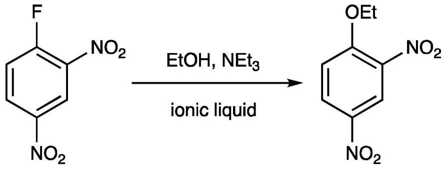
Ionic liquids are salts with low melting points (conventionally defined as being below 100 °C)[1] due to the bulky charge diffuse nature of their constituent ions that results in irregular, disrupted packing. The physicochemical properties (*i.e.* melting point, viscosity, density, *etc.*) of ionic liquids can be easily varied by changing the cation and anion combination, leading to ionic liquids being deemed as 'designer solvents'.[2] Ionic liquids have been used in a range of applications including but not limited to: bioprocessing,[3] electrolytes for batteries,[4] applications involving carbon dioxide[5] and as solvents for synthetic processes.[1c,6]

Given the versatile nature of ionic liquids and the ability to selectively tune their physical properties for a given purpose, ideally it should be possible to select a specific ionic liquid as a solvent for a given reaction. In order to do so, the effects of ionic liquids on the outcome of the reaction in question need to be understood. Much work has been undertaken investigating the effects ionic liquids have when used as solvents for a range of reactions,[7] particularly on understanding specific interactions between the ionic liquid solvent and species along the reaction coordinate across a range of solvent compositions.[6,8]

A focus of some of these studies has been to investigate how varying the substrates affects the interactions of the components of the ionic liquid with species along the reaction coordinate and thus the outcome of the observed ionic liquid solvent effect. Particularly, the effect of varying the nature of the electrophile in condensation and bimolecular nucleophilic substitution reactions has been considered.[6,9] In both cases, it was noted that the balance of interactions in solution changed, significantly affecting reaction outcome.

This study focuses on understanding how varying the nature of the nucleophile affects the ionic liquid solvent effects observed for nucleophilic aromatic substitution (S_NAr) reactions. Previous studies have investigated the S_NAr reaction between ethanol and 1-fluoro-2,4-dinitrobenzene **1** (Scheme 1) in mixtures containing one of a range of different ionic liquids.[10] In those studies, the key interactions responsible for rate constant enhancement were shown to vary with the proportion of the ionic liquid added,[10c,d] although at all solvent compositions containing an ionic liquid an increase in the rate constant was observed compared to the ethanol case.

Changing the nucleophilic heteroatom will likely change the interactions between the nucleophile and the components of any ionic liquid in the reaction mixture, and hence the reaction outcome. For a nitrogen nucleophile, interactions between the nitrogen lone pair and the ionic liquid cation are likely; these interactions have previously been shown to be key in determining ionic liquid solvent effects in both condensation and S_N2 processes.[6,11] The effect of moving to a sulphur nucleophile is less clear (as equivalent studies with sulphur species have not been carried out), however, the interactions would be expected to vary from the other cases considered. Additionally, on varying the heteroatom, the nature of the transition state of the



1 **2**

Scheme 1. The nucleophilic aromatic substitution reaction between 1-fluoro-2,4-dinitrobenzene **1** and ethanol to give the benzene **2** which has been previously studied in mixtures of an ionic liquid and ethanol.[10]

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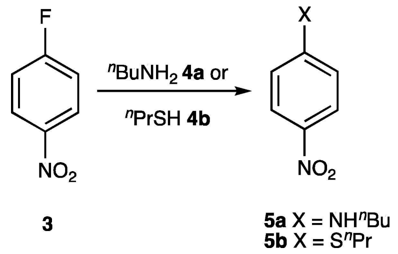


Scheme 2. The nucleophilic aromatic substitution reaction between 1-fluoro-4-nitrobenzene **3** and one of the nucleophiles **4a** and **4b** to give the corresponding adducts **5**.

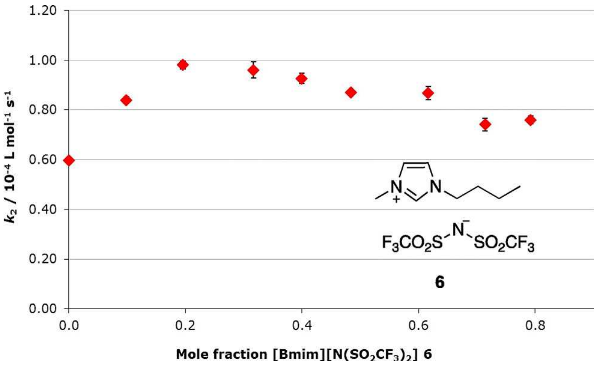


Figure 1. The bimolecular rate constants for the reaction between 1-butylamine **4a** and the benzene **3** in different proportions of the ionic liquid [Bmim][N(SO$_2$CF$_3$)$_2$] **6** in acetonitrile at 51.0 °C. Uncertainties are reported as the standard deviation of triplicate results with some uncertainties falling within the size of the markers used.[15]

initial addition step will vary (in, for example, the extent of charge development), which will affect interactions involving that species.

With the above in mind, it is clearly of interest to evaluate which of the aforementioned microscopic interactions is dominant (or if multiple interactions are responsible for the overall solvent effect) when different nucleophiles are considered. It is also of interest to see if these interactions can be rationally varied (through changing the nature of the ionic liquid and the proportion of the salt in the reaction mixture) and exploited to control reaction outcome. To this end, the reaction between 1-fluoro-4-nitrobenzene **3**[12] and either 1-butylamine **4a** or 1-propanethiol **4b** in mixtures containing an ionic liquid have been examined (Scheme 2).

Results and Discussion

Effects of Ionic Liquids on an S$_N$Ar Reaction Involving a Nitrogen Nucleophile

Initially this study focused on how changing from an oxygen nucleophile to a nitrogen nucleophile would affect ionic liquid solvent effects on an S$_N$Ar process. 1-Butylamine **4a** was chosen as it is similar in chemical structure to the oxygen nucleophile studied previously,[10] with a boiling point that allows for practical solution-phase kinetics. The electrophile **3**, was chosen instead of the 1-fluoro-2,4-dinitrobenzene **1** used in the previous studies[10] as removal of the *ortho* nitro group allowed measurement of the rate constant over a practical time interval. However removal of the *ortho* group can affect the S$_N$Ar mechanism and associated solvent effects;[13] this will be taken into consideration in the discussion to follow. Acetonitrile was used in these studies as the molecular solvent (*cf.* ethanol previously). It was not expected that this change would affect the observation of ionic liquid solvent effects, based on the minimal differences seen in related substitution processes with significant charge build-up in the transition state.[14]

The bimolecular rate constants of the reaction of 1-butylamine **4a** with the benzene **3** were determined across a range of solvent compositions of 1-butyl-3-methylimidazolium *bis*(trifluoromethanesulfonyl)imide ([Bmim][N(SO$_2$CF$_3$)$_2$], **6**) in acetonitrile (Figure 1). [Bmim][N(SO$_2$CF$_3$)$_2$] **6** was selected as it is the ionic liquid that has been examined in the relevant studies on the previous S$_N$Ar reaction[10] as well as the aforementioned bimolecular processes,[6] allowing the most direct comparisons to be made.

There was a two-fold increase in the rate constant on changing the proportion of the ionic liquid **6** in the reaction mixture from $\chi_6 = 0$ to $\chi_6 \approx 0.2$. On increasing the amount of ionic liquid **6** from $\chi_6 \approx 0.2$ upwards, the rate constant decreases with increasing proportions of the salt **6** in the reaction mixture. However, for all solvent compositions containing the salt **6** the observed rated constant is greater than in acetonitrile.

This trend in the mole fraction dependence of the rate constant is markedly different from the case for the reaction shown in Scheme 1 where an oxygen rather than nitrogen nucleophile was used, where the bimolecular rate constant continued to increase as the amount of ionic liquid in the reaction mixture increased.[10b–d] Instead, the observed trend is more akin to what has been reported for bimolecular processes involving nitrogen nucleophiles, suggesting that the dominant interaction(s) driving the ionic liquid solvent effects in these systems may be the same.

To investigate the interactions responsible for the observed solvent effects, temperature dependent kinetic studies were undertaken by measuring the rate constant across a range of temperatures and analysing the data using a bimolecular Eyring plot[16] (see Figure S6 in the Supporting Information). The solvent compositions chosen for this study were: acetonitrile ($\chi_6 = 0$), an intermediate solvent composition by which the majority of the rate enhancement observed has occurred ($\chi_6 \approx 0.2$) and the case where the ionic liquid **6** is diluted by reagents only ($\chi_6 \approx 0.8$).

From the activation parameters presented in Table 1 there is an increase in both the enthalpy and entropy of activation on changing the solvent composition from $\chi_6 = 0$ to $\chi_6 \approx 0.2$, though the changes are small compared to those seen in other cases.[6,9b] At the temperatures considered, the variation of the entropy change dominates, accounting for the rate constant enhancement observed.

These activation parameters suggest that the dominant interaction causing the rate constant enhancement at $\chi_6 \approx 0.2$

Table 1. Activation parameters for the reaction between 1-butylamine **4a** and the benzene **3** in mixtures of [Bmim][$N(SO_2CF_3)_2$] **6** in acetonitrile. Uncertainties reported are propagated from the linear regression.

χ_6	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
0	40.6 ± 1.0	−267 ± 3
0.19	47.0 ± 1.8	−243 ± 6
0.80	42.9 ± 1.1	−260 ± 3

(relative to $\chi_6 = 0$) is between the components of the ionic liquid **6** and the starting materials; there is a greater interaction of the solvent, with, and organisation of the solvent about, the starting materials. (It is considered that destabilisation of, and a lesser degree of ordering about, the transition state is unlikely given the charged nature of both the ionic liquid **6** and the transition state.) This trend in the activation parameters is consistent with previous observations of the ionic liquid solvent effect where addition of a nitrogen nucleophile is involved in the rate determining step.[6,9b,17]

For the previously studied S_NAr reaction involving ethanol as the nucleophile (Scheme 1) the same trend in the activation parameters (an increase) was observed on addition of small amounts of ionic liquid in the reaction mixture ($\chi_6 < 0.5$).[10b–d] Those changes in activation parameters were also attributed to ionic liquid-starting material interactions, particularly the anion of the ionic liquid interacting with the electrophile **3**.[10d] With the data presented thus far it is difficult to isolate the particular starting material(s) involved in this case where there is a nitrogen nucleophile.

The trend in the activation parameters shown in Table 1 between $\chi_6 \approx 0.2$ and $\chi_6 \approx 0.8$ is the opposite to that observed at lower proportions of salt **6** in the reaction mixture; both parameters decrease. Overall, on moving from acetonitrile ($\chi_6 = 0$) to ionic liquid diluted only by reagents ($\chi_6 \approx 0.8$), there are marginal increases in both parameters.

A decrease in activation parameters is characteristic of either a reduction in the interactions between the ionic liquid **6** and the starting materials (which seems unlikely) or an increase in the stabilising interaction between the ionic liquid **6** and the transition state (which seems more reasonable, particularly given the charged nature of all species involved). This analysis suggests that in this reaction at high proportions of the salt **6** in the reaction mixture, the interaction of the components of the ionic liquid with the transition state become more significant relative to the interactions with the starting material (which dominate at low mole fractions of the salt **6**) such that, at the highest concentration of salt **6** used, there is almost a balance of these interactions.

It is worth contrasting these interactions with observations in the literature. For bimolecular processes involving a nitrogen nucleophile,[6] the key interaction between the ionic liquid cation and the nitrogen nucleophile does not change significantly above a low proportion of salt in the reaction mixture. Such an effect is consistent with the changes observed here. For the S_NAr reaction shown in Scheme 1 involving an oxygen nucleophile, at low proportions of added salt, starting material-ionic liquid interactions dominate, while at high proportions of ionic liquid, interactions with the transition state dominate.[10c,d] As such, the interactions implicit from the activation parameters (and the resulting rate constants) for an S_NAr process involving a nitrogen nucleophile are consistent with a combination of the previously observed ionic liquid effects.

In an attempt to further understand the ionic liquid-starting material interactions observed in the S_NAr reaction discussed above, the mole fraction dependence of the rate constant and temperature dependent kinetic studies conducted above were carried out with an ionic liquid containing a different cation; tetraoctylammonium *bis*(trifluoromethanesulfonyl)imide ([TOA][$N(SO_2CF_3)_2$], **7**). The $[TOA]^+$ cation has a particularly hindered charge centre and this ionic liquid has been used previously to observe the effects of minimising potential interactions with the cation of an ionic liquid.[6,10b–d,18] The hindered nature of the charged centre of $[TOA]^+$ also means that the anion of the ionic liquid would be expected to associate less with the cation and thus be more available to interact with species along the reaction coordinate. (The anionic component of the salt has been seen previously to dominate the effects of ionic liquids on this type of reaction.[8]) Both of these considerations shall be taken into account in the discussion below.

The dependence of the bimolecular rate constant for the reaction between 1-butylamine **4a** and the benzene **3** on the proportion of the ionic liquid [TOA][$N(SO_2CF_3)_2$] **7** in acetonitrile is depicted in Figure 2. The trend observed is broadly similar to the trend in the [Bmim][$N(SO_2CF_3)_2$] **6** case but several key differences must be noted. First of all, the maximum rate constant enhancement observed is smaller (*ca.* 25% *cf.* 70% above). Secondly, the downward trend in rate constant at higher proportions of the salt **7** in the reaction mixture results in rate constants the same as in acetonitrile. Immediately clear is that changing the cation of the ionic liquid changes the reaction outcome, likely as a result of changing the microscopic interactions involving the cation of the ionic liquid.

To better understand the interactions of the ionic liquid [TOA][$N(SO_2CF_3)_2$] **7** in the S_NAr reaction shown in Scheme 2, the activation parameters at specific solvent compositions were

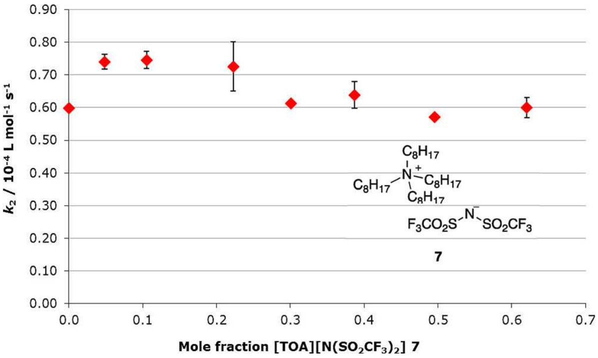


Figure 2. The bimolecular rate constants for the reaction between 1-butylamine **4a** and the benzene **3** in different proportions of the ionic liquid [TOA][$N(SO_2CF_3)_2$] **7** in acetonitrile at 51.0 °C. Uncertainties are reported as the standard deviation of triplicate results with some uncertainties falling within the size of the markers used.

Table 2. Activation parameters for the reaction between 1-butylamine **4a** and the benzene **3** in mixtures of [TOA][N(SO_2CF_3)$_2$] **7** in acetonitrile. Uncertainties reported are propagated from the linear regression.

χ_7	$\Delta H^{\neq}$/kJ mol^{-1}	$\Delta S^{\neq}$/J K^{-1} mol^{-1}
0[a]	40.6 ± 1.0	−267 ± 3
0.11	45.7 ± 1.1	−249 ± 3
0.62	47.6 ± 0.9	−245 ± 3

[a] Reproduced from Table 1 above for ease of comparison.

determined using the same methodology as described above (Eyring plots can be found in the Supporting Information, Figure S7). The solvent compositions chosen were: $\chi_7 = 0$ (acetonitrile, reproduced from above), $\chi_7 \approx 0.1$ (where the greatest rate enhancement was observed) and $\chi_7 \approx 0.6$ (where the ionic liquid **7** is diluted by reagents only). The data are presented in Table 2.

On changing the solvent composition from $\chi_7 = 0$ to $\chi_7 \approx 0.1$ there is an increase in both the enthalpy and entropy of activation. As discussed above, this trend in the activation parameters is likely due to increased interaction of the ionic liquid **7** with, and ordering of the ionic liquid **7** about, the starting materials. Given the sterically hindered charged centre on the cation of [TOA][N(SO_2CF_3)$_2$] **7** (compared to [Bmim][N(SO_2CF_3)$_2$] **6**), in this case the dominant interaction resulting in the change in the rate constant is likely the anion of the salt **7** interacting with, and organising about, the electrophile **3**.

Importantly, these data do not suggest a lack of interaction between the cation of [Bmim][N(SO_2CF_3)$_2$] **6** and the starting materials of the process. Whilst interactions between the cation and the nucleophile are not implicit from the activation parameter data (which in any case are based on small rate constant changes), understanding gained from previous examples,[6,10b,c] along with the reduced rate constant enhancement observed relative to the imidazolium salt **6** case, does suggest interactions between the nucleophile and the cation of the salt occur.

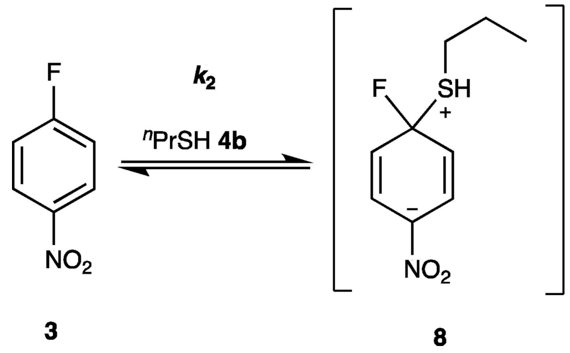
No change in the activation parameters was observed on changing the solvent composition from $\chi_7 \approx 0.1$ to $\chi_7 \approx 0.6$ suggesting that there is little change in the balance of interactions within the [TOA][N(SO_2CF_3)$_2$] **7** system on changing the concentration of the salt. Whether or not the magnitude of each of the possible interactions has changed is unclear based on these data alone.[19] When the same salt was used in the related aromatic substitution involving an oxygen nucleophile (Scheme 1),[10b,c] there was a decrease in both activation parameters relative to the molecular solvent case indicating that the dominant interaction was of the ionic liquid **7** with the transition state of the process; changing the nature of the anion of the salt also implied that it was involved in these interactions.[10d] The difference in this case may be due to the nature of the transition state, though this seems less likely than potential additional anion-starting material interactions possible between the amine **4a** and the anion. This idea is supported further by considering that the magnitude of the change in the enthalpy of activation from $\chi_7 = 0$ to $\chi_7 \approx 0.6$ compared to $\chi_7 \approx 0.1$ to $\chi_7 \approx 0.6$ is *ca.* 2 kJ mol^{-1} greater suggesting more starting material-ionic liquid interactions are occurring at the highest mole fraction of the salt **7** considered.

Overall, the work in this section shows that for S_NAr reactions containing a nitrogen nucleophile, ionic liquid-starting material interactions are responsible for the changes in reaction outcome across all proportions of the salt **7** considered (*cf.* ionic liquid-transition state interactions at high salt concentrations in the case of oxygen nucleophiles).[10c,d] Whilst specific sites of interactions are difficult to isolate, those involving both the cation and anion are implied.

Effects of Ionic Liquids on an S_NAr Reaction Involving a Sulphur Nucleophile

To further expand upon our understanding of ionic liquid solvent effects on S_NAr reactions it was thought that examination of a sulphur nucleophile would be of interest, particularly given their prevalence. As such, the reaction between the electrophile **3** and 1-propanethiol **4b** (Scheme 2) was considered. The benzene **3** was chosen as the electrophile for this system to allow direct comparison with the amine **4a** S_NAr reaction discussed in the previous section. The differences between the electrophile used in this work and the previous ethanol system have been discussed above and the same considerations shall be made for the thiol **4b** system as was done for the amine **4a** system. 1-Propanethiol **4b** was chosen as the nucleophile for similar reasons as the amine **4a**; the boiling point of the thiol **4b** made solution-phase kinetics practical and was closest to that of the amine **4a**. Moreover, the molecular weight of amine **4a** and thiol **4b** are the similar thus ensuring that the diffusion of these species are comparable. Also, variation of carbon chain length by one unit (*i.e.* from propyl to butyl) has been shown to not significantly impact nucleophilicity.[6,20] It was necessary to add triethylamine, a non-nucleophilic base, to the thiol **4b** system for the reaction to proceed whilst this was not necessary for the amine **4a** system. Given the difference in pK_a values of the thiol **4b** and triethylamine the addition of base to this system is not expected to significantly alter the nucleophilicity of the thiol **4b**.[21]

In initial studies on this system, it was immediately apparent that, even in an excess of the nucleophile **4b**, the reaction did not follow pseudo first order kinetics. This is not unusual, having been observed previously for other S_NAr reactions[8c,d,13c,d,18,22] and simply means that the initial bimolecular addition step of the S_NAr mechanism is not rate determining. Modelling of the observed data included many possible mechanisms for the sulphur-containing S_NAr reaction in question, with each model systematically increasing in complexity (a discussion of this process is included in the Supporting Information). The model that was eventually used fits the observed data to multiple steps, but importantly allows determination of the bimolecular rate constant for the first step of the reaction, nucleophilic addition of species **4b** to the



Scheme 3. The initial, reversible nucleophilic attack step for the aromatic substitution reaction between 1-propanethiol **4b** and 1-fluoro-4-nitrobenzene **3** to obtain the Meisenheimer complex **8**.

electrophile **3** (Scheme 3), allowing direct comparison with previous work.

With this model in hand, the dependence of the rate constant for the reaction of the nucleophile **4b** to the electrophile **3** on the proportion of [Bmim][N(SO$_2$CF$_3$)$_2$] **6** (again chosen to allow comparison with previously) present in the reaction mixture was, investigated. These data are presented in Figure 3. Equivalent plots for the other rate constants determined are available in the Supporting Information (Figures S8-S15).

The trend in rate constant is markedly different to that seen for the nitrogen nucleophile **4a** cases. There is a monotonic, though not linear, increase in the rate constant as the amount of [Bmim][N(SO$_2$CF$_3$)$_2$] **6** in the reaction mixture increases. The rate constant observed at $\chi_6 \approx 0.8$ is nearly 40 times greater than that observed for the acetonitrile ($\chi_6 = 0$) case. These trends in the mole fraction dependence of the rate constant are perhaps more similar to those seen previously for the S$_N$Ar reaction of ethanol shown in Scheme 1, in that case an approximately exponential increase in rate constant by up to *ca.* 120 times was observed.[10b–d]

To further understand the interactions causing the ionic liquid solvent effects observed for the thiol **4b** system in [Bmim][N(SO$_2$CF$_3$)$_2$] **6**, activation parameters were determined at key solvent compositions in a similar manner to that for the amine **4a** system discussed earlier. The mole fractions chosen were: the molecular solvent acetonitrile ($\chi_6 = 0$), a case to allow direct comparison with the amine **4a** system studied above ($\chi_6 \approx 0.2$), an intermediate proportion of ionic liquid **6** to allow direct comparison with the previously studied ethanol system ($\chi_6 \approx 0.5$) and the case where the ionic liquid **6** is diluted by reagents only ($\chi_6 \approx 0.8$). The data are presented in Table 3. It should be noted that activation discussion as to their implications can be found in the Supporting Information (Figures S16–S23 and Tables S21, S23, S25, S27, S29, S31 and S33).

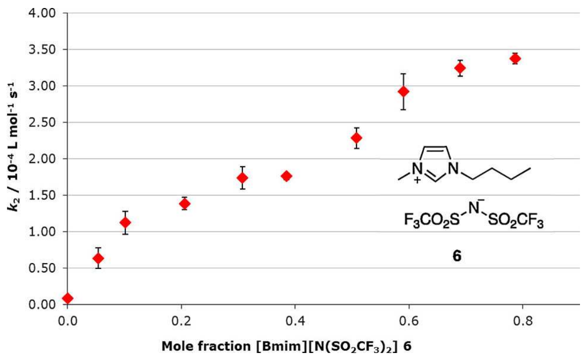


Figure 3. The bimolecular rate constants for the reaction between 1-propanethiol **4b** and the benzene **3** in different proportions of the ionic liquid [Bmim][N(SO$_2$CF$_3$)$_2$] **6** in acetonitrile at 51.0 °C. Uncertainties are reported as the standard deviation of triplicate results with some uncertainties falling within the size of the markers used.

Table 3. Activation parameters for the initial nucleophilic addition step of the reaction between 1-propanethiol **4b** and the benzene **3** in mixtures of [Bmim][N(SO$_2$CF$_3$)$_2$] **6** in acetonitrile. Uncertainties reported are propagated from the linear regression.

χ_6	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
0	40.0 ± 1.6	-285 ± 5
0.20	22.3 ± 2.4	-317 ± 7
0.50	39.7 ± 2.6	-258 ± 8
0.79	62.1 ± 2.8	-186 ± 8

On changing from $\chi_6 = 0$ to $\chi_6 \approx 0.2$ in the reaction mixture there is a decrease in both activation parameters that, as discussed above, suggests ionic liquid-transition state interactions are principally responsible for the rate constant enhancement observed. As the solvent composition changes from $\chi_6 \approx 0.2$ to $\chi_6 \approx 0.5$ and from $\chi_6 \approx 0.5$ to $\chi_6 \approx 0.8$ there is an increase in both the enthalpy and entropy of activation, suggesting interaction of the ionic liquid **6** with the starting materials is the dominant interaction in determining the rate constant increases as the amount of ionic liquid in the reaction mixture increases beyond $\chi_6 \approx 0.2$.

This trend in the activation parameters, and therefore microscopic interactions, for the thiol **4b** system is the opposite to what is observed for both the amine **4a** case above and the previously studied ethanol S$_N$Ar reactions.[10b,c,23] In both the amine **4a** and ethanol studies there was an increase in the enthalpy and entropy of activation at low-intermediate proportions of [Bmim][N(SO$_2$CF$_3$)$_2$] **6** in the reaction mixture ($\chi_6 \approx 0.2$ and $\chi_6 \approx 0.5$, respectively) due to ionic liquid-starting material interactions. At the higher mole fractions of [Bmim][N(SO$_2$CF$_3$)$_2$] **6** ionic liquid-transition state interactions were observed and were the dominant interaction in the ethanol system.[10b,c,23] The magnitude of the changes in the activation parameters are also significantly greater than those for the aforementioned S$_N$Ar reactions suggesting that the changes in interactions in the thiol **4b** system are more significant than the other systems. The potential interactions for the thiol **4b** system are similar to those discussed for the amine **4a** system; the ionic liquid could interact with the electrophile **3**, the nucleophile **4b**, and/or the transition state.

A benefit of the more complex kinetic model for the thiol **4b** reaction is that, as mentioned above, activation parameters were obtainable for all steps of the reaction and therefore enthalpy and entropy profiles for the reaction are obtainable across a range of solvent compositions by considering the differences in the activation parameters determined for each step. This can provide additional information about the interactions present in the thiol **4b** system, an advantage over the previously studied S_NAr systems. The full enthalpy and entropy profiles at each solvent composition can be found in the Supporting Information (Figures S25–S28). Only the initial nucleophilic addition step shall be discussed here as it is the only direct comparison that can be made with both the amine **4a** system discussed above and the previously studied ethanol system.[10,23] The enthalpy profiles for this step are presented in Figure 4 below.

The following discussion will focus on comparing how the nature of the transition state changes in an effort to understand the microscopic interactions in solution as the proportion of the ionic liquid **6** in the reaction mixture is varied. From the enthalpy profiles, the transition state changes from a very 'early' (or reactant-like) transition state at $\chi_6 \approx 0.2$ (relative to $\chi_6 = 0$) to an increasingly 'late' (or product-like) transition state at $\chi_6 \approx 0.5$ and then a truly 'late' transition state at $\chi_6 \approx 0.8$. That is, the transition state goes from resembling the starting materials to more closely emulating the charged Meisenheimer complex. At a low proportion of the salt **6** in the reaction mixture ($\chi_6 \approx 0.2$) the activation parameters suggest that ionic liquid-transition state interactions dominate; the ionic liquid is stabilising the transition state resulting in it being more 'reactant-like'. As the amount of ionic liquid in the reaction mixture increases, a greater degree of charge development in the transition state would be better stabilised, explaining why the transition state becomes 'later' at higher proportions of the salt **6**. However, if the ionic liquid **6** interacts more favourably with the starting materials in this system, as suggested by the activation parameters, the magnitude of ionic liquid-starting material interactions would increase relative to ionic liquid-transition state interactions when the transition state is comparatively 'late' as it would no longer resemble the starting materials at higher proportions of the salt **6** in the reaction mixture.

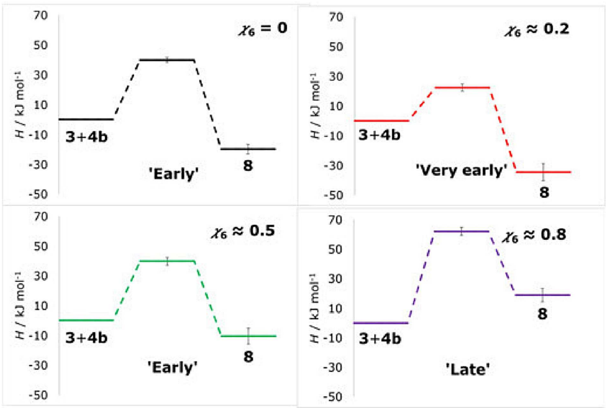


Figure 4. The enthalpy profile for the first step of the reaction between 1-propanethiol **4b** and the benzene **3** in different proportions of the ionic liquid [Bmim][N(SO_2CF_3)$_2$] **6** in acetonitrile. The mole fractions of the ionic liquid **6** are: $\chi_6 = 0$ (black, top left), $\chi_6 \approx 0.2$ (red, top right), $\chi_6 \approx 0.5$ (green, bottom left) and $\chi_6 \approx 0.8$ (purple, bottom right). Uncertainties are propagated from the uncertainties in the enthalpy of activation reported in Table 3 and S21.

In an effort to further understand the ionic liquid interactions in solution, the reaction between the thiol **4b** and the benzene **3** was also examined in the ionic liquid [TOA][N(SO_2CF_3)$_2$] **7**, for the same reasons as outlined above in the amine case. The dependence of the bimolecular rate constant for the nucleophilic addition of the thiol **4b** onto the benzene **3** on the proportion of the ionic liquid [TOA][N(SO_2CF_3)$_2$] **7** in the reaction mixture was initially investigated (Figure 5).

It should be noted immediately that the complex kinetics observed in acetonitrile and mixtures containing the salt **6** for this reaction were not seen in mixtures containing the salt **7**, rather first order kinetics were observed in the presence of an excess of the thiol **4b**. Whilst the origin of this change is not clear, it both greatly simplified analysis and suggests that there is a distinct difference in solvent interactions when using [TOA][N(SO_2CF_3)$_2$] **7** compared to [Bmim][N(SO_2CF_3)$_2$] **6**. Such observations are not unusual for S_NAr reactions; it has been well documented that changing the nature of the solvent can affect the observed reaction outcome by changing, for example, the rate determining step.[13d,24]

The first thing to note from the data shown in Figure 5 is that there is a decrease in the rate constant as the proportion of [TOA][N(SO_2CF_3)$_2$] **7** in the reaction mixture increases with the rate constant at $\chi_7 \approx 0.6$ being *ca.* 20% of that observed in acetonitrile ($\chi_7 = 0$). This trend is opposite to that observed for the other S_NAr systems discussed in this work and also the previously studied ethanol reaction.[10b–d,23] This difference in the trend of the rate constant with the amount of ionic liquid **7** in the reaction mixture is another indication that the balance of the interactions of the salt **7** with species along the reaction coordinate are likely different from those observed in the other S_NAr reactions considered.

Once again, temperature dependent kinetic studies were undertaken in an analogous manner to those discussed earlier in this work. The solvent compositions chosen were: $\chi_7 = 0$ (acetonitrile, reproduced from above), $\chi_7 \approx 0.2$ (to allow direct comparison with the amine **4a** and the [Bmim][(N(SO_2CF_3)$_2$] **6**

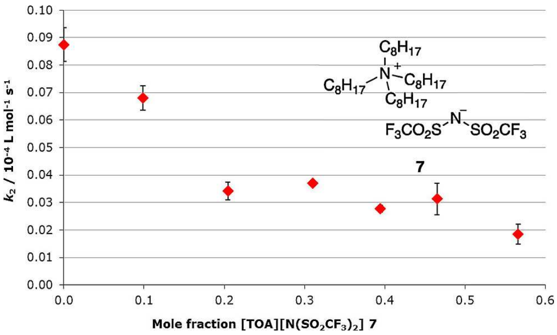


Figure 5. The bimolecular rate constants for the reaction between 1-propanethiol **4b** and the benzene **3** in different proportions of the ionic liquid [TOA][N(SO_2CF_3)$_2$] **7** in acetonitrile at 51.0 °C. Uncertainties are reported as the standard deviation of triplicate results with some uncertainties falling within the size of the markers used.

thiol **4b** case above) and $\chi_7 \approx 0.6$ (the case where the ionic liquid **7** is diluted by reagents only). The activation parameters determined can be found in Table 4 below and the corresponding Eyring plots in the Supporting Information (Figure S24).

From the data presented in Table 4 when changing the solvent from $\chi_7 = 0$ to $\chi_7 \approx 0.2$ there is no measurable difference in the activation parameters. Given that there is a corresponding change in the rate constant (albeit small in absolute terms), this suggests any changes in the interactions as the solvent system changes are too small to measure using this methodology. There is then an increase in both activation parameters upon going from $\chi_7 = 0$ to $\chi_7 \approx 0.6$ and $\chi_7 \approx 0.2$ to $\chi_7 \approx 0.6$. As discussed early, an increase in both the enthalpy and entropy of activation in these systems are likely due to increased interaction and organisation of the ionic liquid **7** about the starting materials.

Table 4. Activation parameters for the reaction between 1-propanethiol **4b** and the benzene **3** in mixtures of [TOA][N(SO$_2$CF$_3$)$_2$] **7** in acetonitrile. Uncertainties reported are propagated from the linear regression.

χ_7	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
0[a]	40.0 ± 1.6	-285 ± 5
0.20	39.9 ± 2.1	-282 ± 7
0.59	62.6 ± 4.2	-228 ± 13

[a] Reproduced from Table 3 above for ease of comparison.

The key difference in terms of interactions observed on addition of each of the salts **6** and **7** is that no ionic liquid-transition state interactions are observed when using [TOA][N(SO$_2$CF$_3$)$_2$] **7** as the solvent. This observation suggests that the cation of the ionic liquid is important in the ionic liquid-transition state interactions observed in S$_N$Ar reactions involving a thiol nucleophile. This lack of ionic liquid-transition state interaction could also explain the solvent effect on the complexity of the kinetics; no interactions with the transition state suggest similar limited interactions with the Meisenheimer complex that would result in a (relatively) high energy intermediate such that all subsequent reactions proceed quickly and the first step is rate determining. This outcome contrasts with the significant stabilisation of the intermediate in acetonitrile and the ionic liquid **6** (Figure 4), resulting in a much more complicated mechanism.

In the [TOA][N(SO$_2$CF$_3$)$_2$] **7** solvent system there was a decrease of the rate constant at all solvent compositions. This change can be attributed to strong interaction of the ionic liquid **7** with the starting materials suggested by the activation parameter data. In this case, the data highlight the importance of interactions involving the anion of the ionic liquid, likely with the electrophile as has been previously observed where ethanol was the nucleophile.[10,23]

It has been shown that for an S$_N$Ar reaction involving a thiol nucleophile, the complexity of the mechanism is very solvent dependent and this dependence is due to differing degrees of stabilisation of (particularly) the Meisenheimer complex. The accessibility of the charged centre of the cation of an ionic liquid is important for ionic liquid-transition state interaction whereas the key ionic liquid-starting material interaction is between the anion of the ionic liquid and the starting materials, presumably, the electrophile **3**.

Conclusion

From this study it is clear that the solvent effects of an ionic liquid on an S$_N$Ar reaction will change depending on the nature of the nucleophile and the amount and nature of the ionic liquid used.

For nitrogen nucleophiles, rate constant enhancement is small and little change is seen after initial addition of a small amount of ionic liquid. This outcome is similar to those observed previously in ionic liquids for bimolecular processes involving a nitrogen nucleophile.[6] The cation of the ionic liquid appears important for nucleophile interactions, as has been previously noted, and this opens up the possibility to rationally choose ionic liquids to favour this reaction in a method akin to previously for related systems.[6,25]

Where a sulphur nucleophile was used in an S$_N$Ar reaction, the rate determining step was shown to be highly solvent dependent. Importantly, in terms of the ionic liquid used, interactions with the cation of the ionic liquid are key in influencing this dependence. Once more, changing the cation dramatically changed the solvent effect and rational selection of an ionic liquid to control reaction outcome is a possibility.

Significantly, the observed solvent effects of addition of ionic liquids to reactions involving each of these nucleophile types differ based on the amount of ionic liquid added (and the type of ionic liquid). Thus, there is the potential to use this knowledge to control reaction outcome when multiple nucleophiles are present in a synthetic setting. For instance, in an S$_N$Ar reaction where oxygen, nitrogen and sulphur nucleophiles are competing for the same electrophile, the order of reactivity might be controlled through rational selection of an ionic liquid allowing predictable and selective control of reaction outcome. Preliminary studies suggest that selectivity for either the nitrogen **5a** and sulphur **5b** products of the reaction depicted in Scheme 2 can be controlled through choice of either acetonitrile or the ionic liquid **6** as solvents, respectively (see the Supporting Information for further details, Figures S31 & S32).

Experimental Section

1-Fluoro-4-nitrobenzene **3** was commercially available and was used without further purification. The following reagents were purified according to literature methods.[26] Triethylamine and 1-butylamine **4a** were distilled and stored over activated molecular sieves at −20 °C. 1-Propanethiol **4b** was distilled and stored over activated molecular sieves at room temperature. Acetonitrile was dried by stirring over potassium carbonate for 24 h before distillation. The ionic liquid [Bmim][N(SO$_2$CF$_3$)$_2$] **6** was prepared according to literature methodology;[27] 1-bromobutane was added to 1-methylimidazole, both distilled prior to use, to yield the bromide precursor salt. The bromide salt then underwent a salt methathesis reaction with lithium *bis*(trifluoromethanesulfonyl) imide to afford the desired ionic liquid. [TOA][$N(SO_2CF_3)_2$] **7** was also prepared through the same salt metathesis reaction of the appropriate bromide precursor salt. Both ionic liquids **6** and **7** were dried under reduced pressure ($<$0.1 mbar) at room temperature until a constant pressure reading was obtained and $<$200 ppm water was detected using Karl-Fischer titrimetry. Ion chromatography determined $<$1% bromide content in the ionic liquids **6** and **7** confirming the absence of the bromide salt precursor. Full experimental detail for these preparations can be found in the Supporting Information.

All reactions were monitored *via* ^{1}H NMR spectroscopy using either a Bruker Avance III 400, 500 or 600 NMR spectrometer equipped with either a BBO, BBFO or TBI probe with results proving to be reproducible regardless of the spectrometer or probe used.

Reaction progress was monitored following signals corresponding to depletion of the electrophile **3** at *ca.* 7.4 and 8.4 ppm and signals corresponding to formation of the aromatic product **5a** at *ca.* 6.8 and 8.0 ppm for the amine **4a** reaction and signals corresponding to formation of the aromatic product **5b** at *ca.* 7.8 and 8.2 ppm for the thiol **4b** reaction. For the determination of the dependence of the rate constant on the proportion of ionic liquid in the reaction mixture, stock solutions were prepared containing the benzene **3** and the nucleophile (amine **4a** or thiol **4b** in a 12-fold excess, relative to the benzene **3**) in differing amounts of the ionic liquid **6** and **7** in acetonitrile. For the thiol **4b** reaction it was necessary to add a base, triethylamine (*ca.* 2 times equivalents, relative to the benzene **3**) to the reaction mixture Kinetic samples were stored at $-20\,^{\circ}$C prior to use with *ca.* 0.5 mL of the reaction mixture in a 5 mm NMR tube. These reactions were monitored either *in situ* or were placed in a water bath at the selected temperature with spectra recorded periodically until $>$90% conversion of the starting material **3** was observed. For the thiol **4b** reaction in [TOA][$N(SO_2CF_3)_2$] **7** initial rate methodology was employed (*i.e.* reaction progress monitored until 8–10% completion).[28] The temperature dependence of the rate constants were determined in an analogous manner to that described above at four temperatures across a range of 30 °C. By fitting these data to the appropriate Eyring equation[16] using the LINEST function in Microsoft Excel the activation parameters were determined.

Additional details for the kinetic analyses including temperatures, rate constants, equations used to determine the rate constants and composition of stock solutions (masses, concentrations of reagents and mole fraction of ionic liquid), rate equations and derivations can be found in the Supporting Information.[29]

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Conflict of Interest

The authors declare no conflict of interest.

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