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Towards solvent-controlled reactivity in ionic liquids*

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Abstract: Ionic liquids are frequently touted as alternatives to traditional molecular solvents but are limited in their applicability as the outcome of reactions may be altered on moving from a molecular to an ionic solvent. This manuscript summarizes our progress towards a predictive framework through understanding how ionic solvents affect organic processes, with an emphasis on how these findings might be applied. Particularly, we will consider the importance of the mole fraction of the ionic liquid used, including some hitherto undisclosed results, as well as the importance of understanding the key interactions of the solvent with the components along the reaction coordinate.

Keywords: ionic liquids; reaction control; reaction mechanisms; solvation; solvent effects.

INTRODUCTION

Much has been made of the potential of ionic liquids as alternatives to "traditional" molecular solvents (for a recent, and very comprehensive, review see Hallett and Welton [1]). Whilst crystallization is typically frustrated by the nature of ionic constituents [2–6], resulting in their molten state below 100 °C [7], the electrostatic interactions between the components of the ionic liquid result in negligible vapor pressures [2,8]. However, their application is limited by the current lack of understanding as to how ionic liquids affect reaction outcome [9].

The archetypal example of this comes from the work of Seddon et al. [10], who considered nitration of toluene **1** (Scheme 1), which gives a mixture of regioisomeric nitration products **2** under standard conditions in molecular solvent. When the reaction is carried out in a halide-based imidazolium salt, halogenation products **3** are observed. This can be rationalized in terms of reactivity of anionic component of the solvent. This type of reactivity change—further exemplified by increased rates of acid and base-catalyzed process in ionic liquids by protic cations (for examples, see [11,12]) and basic anions (for examples, see [13,14]), respectively—does not rely on solvation properties of the ionic liquid and will not be discussed further.

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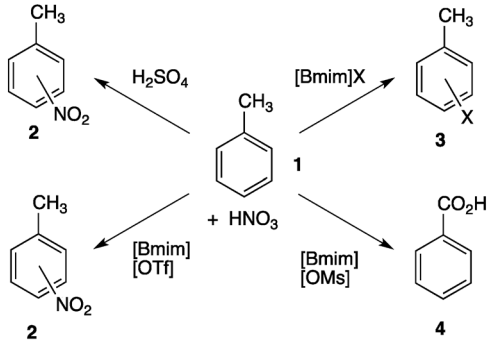


Scheme 1 Variation of the outcome of the reaction between toluene **1** and nitric acid in sulfuric acid in a series of ionic liquids [10].

When the reaction between nitric acid and toluene **1** is carried out in the ionic liquid 1-butyl-3-methylimidazolium ("bmim") triflate, a significant rate increase is observed, along with an increase in the proportion of the *para* isomer in the mixture **2**. On changing the anion of the ionic liquid to the mesylate, oxidation rather than nitration was observed with the acid **4** being isolated. In each case, the reaction outcome was not readily rationalized, let alone predicted. If these solvent effects could be understood and predicted, there is significant opportunity to control reaction outcome using ionic liquids, in a fashion analogous to that currently used for molecular solvents [15].

Two criticisms that may be levelled at the use of ionic liquids need to be raised here. The first is whether or not the term "ionic liquid" truly describes the solvation environment in the mixture used; frequently, the ionic liquid is significantly diluted by either a cosolvent or large concentrations of reagents (examples range from the early work on Diels–Alder reactions [16] through to recent studies on phosphorodiamidite synthesis [17], though it is worth noting that in the latter example the authors carefully highlighted the mole fraction of ionic liquid used). Given the formula weight of ionic liquids is large, this often leads to mixtures that are less than 50 % ionic liquid by mole!

The second point to note is that there are many, many ionic liquids—it is considered that there are thousands of simple ionic liquids alone, before systems containing more than just two components are even considered [18]. Whether solvation in ionic liquids, and hence the nature of ionic liquid effects, can be generalized remains an open question.

In this article, both of these points will be considered in a more positive light. It will be shown that a reaction outcome might be controlled by changing the proportion of the ionic liquid present, and the implications of this control will be discussed. Further, by understanding the microscopic origin of the solvent effects for a given ionic liquid, the underlying interactions might be tailored by changing the structure of the solvent components, thus allowing manipulation of reaction outcomes.[a]

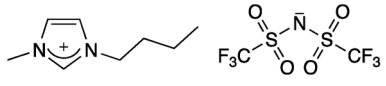
PART 1: SOLVENT OR ELECTROLYTE—AND DOES IT REALLY MATTER?

As mentioned above, the solvents that reactions are carried out in are often more than just an ionic liquid. Diluted by everything from a cosolvent through to the reagents themselves, the solvent environments can vary from that comparable to a neat ionic liquid through to (effectively) a dilute salt solution. To a certain extent, the composition of the mixture does not matter provided it is known and reported—solvent control of reaction outcome can still be achieved.

The fashion in which changing the mole fraction of ionic liquid affects reaction outcome will vary depending on the reaction type. By understanding this variation, the appropriate amounts of ionic liquid may be added to give the desired reaction outcome.

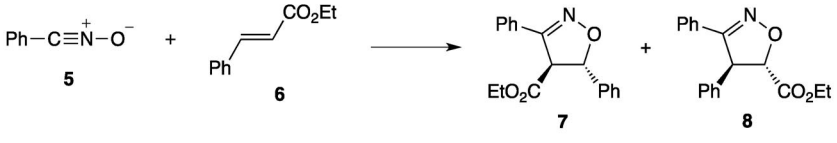
Throughout the arguments below, it is important to recognize that the ionic liquid is (typically) significantly more massive than any other component in the reaction mixture. As such, mole fractions provide a better manner by which to understand the nature of the solvent, rather than simply using the concentration of reagents. Further, it is important to note that while reactions reported in the literature might appear to be carried out in a predominantly ionic liquid medium, due to the different molecular volumes of the species present, reaction mixtures typically need to be >80 % ionic liquid by volume to have a χ_{IL} >0.5.

While, as discussed above, there are numerous ionic liquids, the bulk of the results discussed here will focus on a single representative example. Bmim *bis*(trifluoromethanesulfonyl)imide ([Bmim][$N(CF_3SO_2)_2$]) is widely used in the literature as it is readily prepared [19] free of impurities that can dramatically affect physical properties of [20], and reaction outcomes in [21], ionic liquids. Further, this particular ionic liquid has excellent chemical and thermal stabilities [22], and, unlike the corresponding ionic liquids with hexafluorophosphate and tetrafluoroborate anions, the $[N(CF_3SO_2)_2]^-$ anion does not decompose to generate hydrogen fluoride [23].



[Bmim][$N(CF_3SO_2)_2$]

Consider the four examples below, which demonstrate the dependency of reaction outcome on ionic liquid mole fraction for four representative reactions. The regioselectivity of nitrile oxide cycloadditions, including that shown in Scheme 2, has previously been shown to be increased on moving from one of a range of molecular solvents to a series of bmim-based ionic liquids [24].[b] The difference in such selectivity enhancement, as the solvent is changed from acetonitrile to [Bmim][$N(CF_3SO_2)_2$], is shown in Fig. 1 and is relatively straightforward—the greater the amount of ionic liquid in the solvent mixture, the greater the observed selectivity [25]. Although the trend is not linear as the mole fraction of ionic liquid increases, a simple outcome of this result is that increasing the proportion of ionic liquid present increases the selectivity of the process.



Scheme 2 The reaction of nitrile oxide **5** with cinnamate **6** to give the regioisomeric products **7** and **8**.

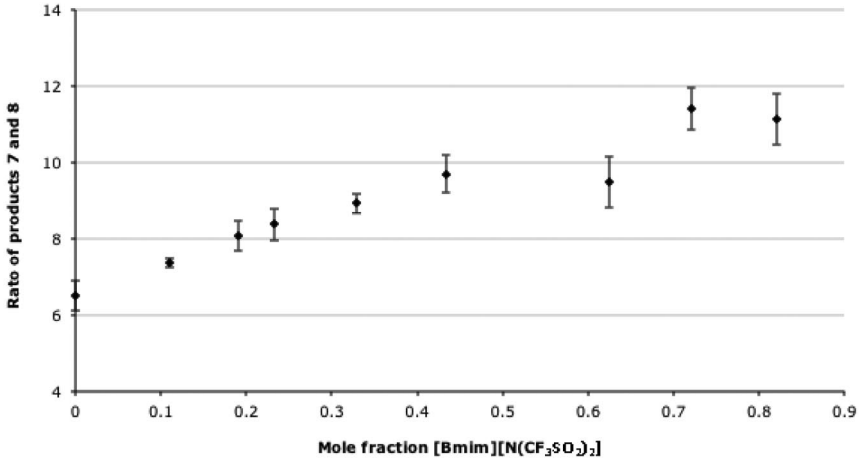
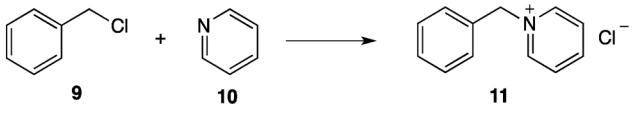


Fig. 1 The ratio of the products **7** and **8** from reaction of the nitrile oxide **5** with the cinnamate **6** in [Bmim][N(CF_3SO_2)$_2$]/acetonitrile mixtures. Note that errors are standard deviations of at least three replicate measurements [25].

The rate constant for the bimolecular substitution process shown in Scheme 3 is dependent on the mole fraction of ionic liquid present as outlined in Fig. 2 [26]. On increasing the proportion of the ionic liquid [Bmim][N(CF_3SO_2)$_2$], the rate constant was observed to increase to a maximum at χ_{IL} ca. 0.66, after which there was little change with additional ionic liquid.



Scheme 3 The reaction of benzyl chloride **9** and pyridine **10** to give the salt **11**, which proceeds solely through a bimolecular reaction mechanism [27].

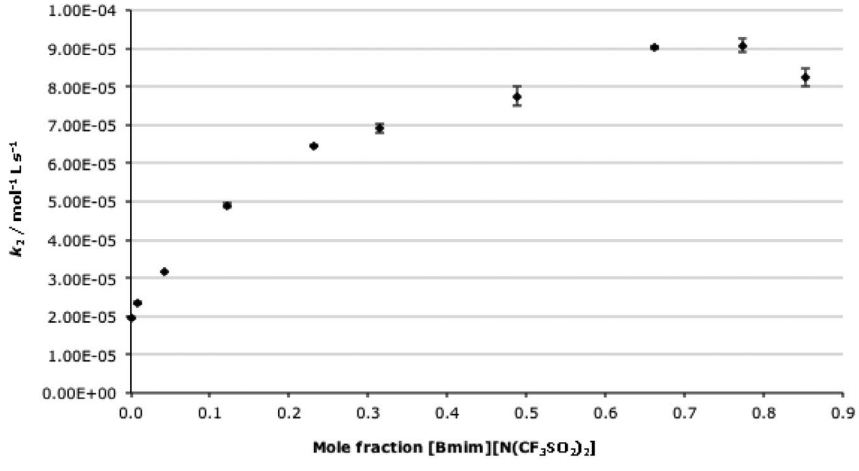


Fig. 2 The bimolecular rate constant for the reaction of the chloride **9** with pyridine **10** in [Bmim][N(CF_3SO_2)$_2$]/acetonitrile mixtures. Note that errors are standard deviations of at least three replicate measurements [26].

This second case demonstrates that it may not be necessary to use solely an ionic liquid as the solvent to get the preferred outcome, be it either the maximum selectivity or (as is the case here) the maximum rate. There may be situations where addition of a small amount of molecular solvent might be beneficial for other reasons (such as cost, viscosity of mixture, or ease of product isolation) and the reaction outcome will be little changed, or even slightly enhanced.[c]

In both of the cases outlined above, the general effect on either selectivity or rate constant increased with increasing proportion of ionic liquid. This is not always the case, as demonstrated in Figs. 3 and 4, for the rate constants of bimolecular substitution at a phosphorus center (Scheme 4) [28] and a unimolecular substitution at a tertiary carbon (Scheme 5) [29], respectively. In both of these cases, there is an initial increase in the rate constant on addition of the ionic liquid [Bmim][$N(CF_3SO_2)_2$] to the reaction mixture and a subsequent significant decrease at higher mole fractions.[d] In the case of the

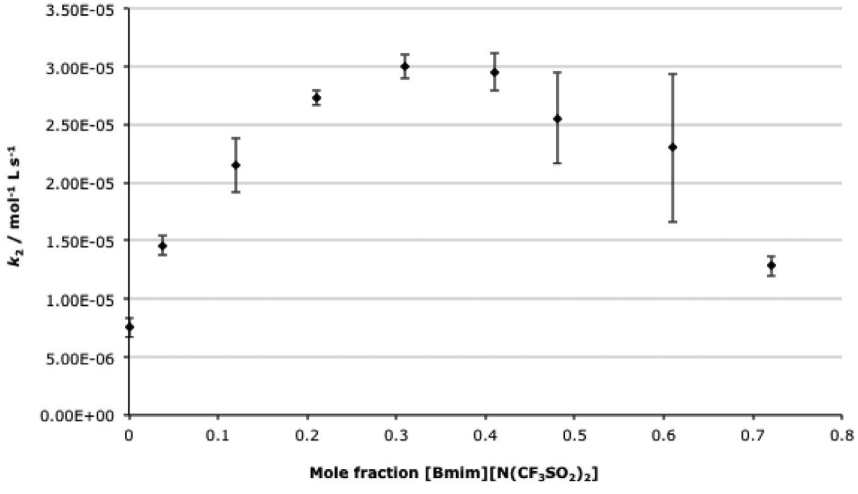


Fig. 3 The bimolecular rate constant for the reaction of deuterated ethanol with the phosphate ester **12** in [Bmim][$N(CF_3SO_2)_2$]/C_2D_5OD mixtures. Note that errors are standard deviations of at least three replicate measurements [26].

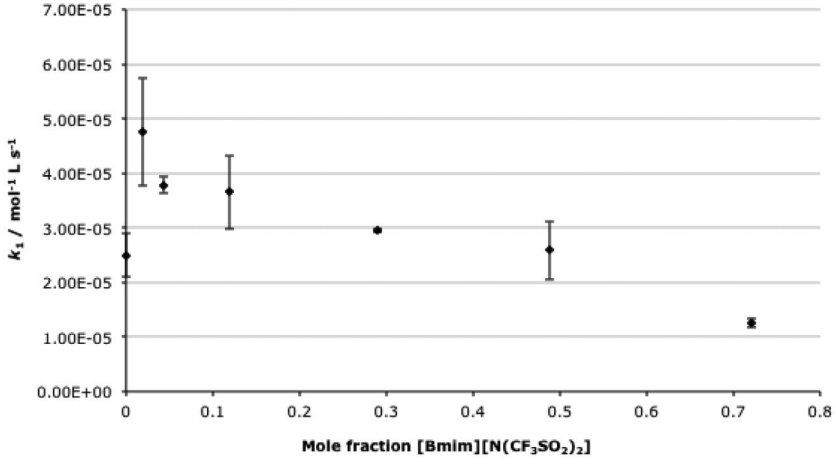
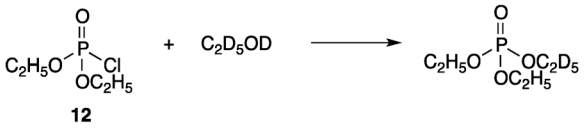
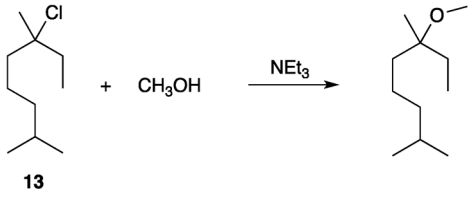


Fig. 4 The unimolecular rate constant for the methanolysis of the chloride **13** in [Bmim][$N(CF_3SO_2)_2$]/methanol mixtures. Note that errors are standard deviations of at least three replicate measurements [29].



Scheme 4 The reaction of deuterated ethanol with the phosphate derivative **12** [28].[e]



Scheme 5 Methanolysis of the alkyl chloride **13** [30].

phosphate ester **12**, maximum rate enhancement occurs at χ_{IL} ca. 0.3, while the greatest rate enhancement occurs at very low χ_{IL} in the chloride **13**.[f]

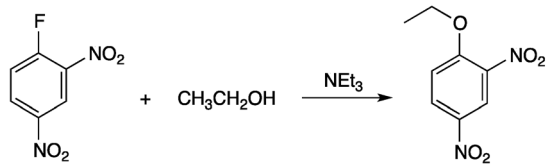
While both of these examples demonstrate situations where the best outcome is achieved with a mixed molecular and ionic solvent system, the methanolysis of chloride **13** presents an intriguing case. At very high mole fractions of the ionic liquid the rate constant of reaction is smaller than in neat molecular solvent, meaning that by appropriate choice of ionic liquid mole fraction the rate constant can be manipulated either up or down, relative to the molecular solvent [29].

A comparison of Figs. 2 and 4 presents what is likely the most interesting potential application of dependence on mole fraction of ionic liquid. If a reaction can proceed through two competing pathways that have differing mole fraction dependence, then an appropriate mole fraction of ionic liquid could be chosen to favor one process at the expense of other. Clearly (at this stage) this is limited to situations where the ionic liquid mole fraction dependence of reaction outcome is either known (e.g., the situations described above) or where it can be estimated based on similarities to other well-described systems (based on the extent of charge development, volumes of activation, and the like). However, if the origin of the effects might be understood, the application of ionic liquids to control reaction outcome could be extended further.

PART 2: MANIPULATING MICROSCOPIC INTERACTIONS—PLAYING MIX & MATCH WITH IONS

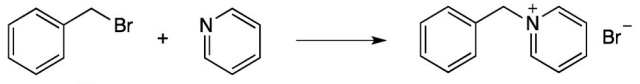
The above discussions on ionic liquid effects across a range of mole fractions are entirely empirical, and, to a certain extent, the use of such empirical knowledge on its own is reasonable. However, if the origin of the effects could be rationalized then there is the potential to manipulate the solvent to give the desired outcomes for an extended range of systems.

By considering the changes in activation parameters on moving from a molecular solvent to an ionic liquid, in conjunction with molecular dynamics simulations, the microscopic interactions responsible for the solvent effects can be inferred. This type of analysis is exemplified by three substitution reactions that we have examined—the unimolecular process in Scheme 5, the aromatic substitution reaction shown in Scheme 6, and the bimolecular process shown in Scheme 7.[g] The effects of moving from molecular solvents to the ionic liquid bmim *bis*(triflouromethanesulfonimide) (at the mole fraction shown) on the activation parameters of the reactions are summarized in Table 1.



14 **15**

Scheme 6 Nucleophilic aromatic substitution of the activated aromatic **14** with ethanol.



16 **10** **17**

Scheme 7 Menschutkin-type reaction, giving the salt **17** from pyridine **10** and the bromide **16**.

Table 1 Changes in the activation parameters for processes shown in Schemes 5 [31], 6 [32], and 7 [27] on moving from a molecular solvent to the ionic liquid [Bmim][$N(CF_3SO_2)_2$]. Uncertainties quoted are standard deviations.

Reaction	$\Delta(\Delta H^{\ddagger})$/kJ mol^{-1}	$\Delta(\Delta S^{\ddagger})$/J K^{-1} mol^{-1}
Methanolysis of chloride **13**, methanol to χ_{IL} ca. 0.5 [31]	–54 ± 7	–172 ± 20
Ethanolysis of fluoride **14**, ethanol to χ_{IL} ca. 0.6 [32]	0.9 ± 0.6	22 ± 2
Pyridine **10** and the bromide **16**, acetonitrile to χ_{IL} ca. 0.9 [27]	6.5 ± 1.6	29 ± 6

The effect of moving from a molecular solvent to an ionic liquid is distinctly different in each of the three cases highlighted. The decrease in the enthalpy of activation in the case of the first-order substitution of the chloride **13** suggests a stabilization of the transition state relative to the starting material **13**, which is consistent with interaction of the ionic liquid components with the incipient charges [31]. Such stabilization requires significant ordering of the solvent, as is consistent with the large decrease in the activation entropy observed; at the mole fraction of ionic liquid considered, these components counteract each other and the rate constant is the same as in neat molecular solvent [29]. Molecular dynamics simulations show this ordering of the components of the ionic liquid around the intermediate (as a model for the transition state) and demonstrate that the key interaction is, not surprisingly, between the cation and the incipient charge on the chlorine atom, presumably due to the accessibility of the charged center [31].

For the nucleophilic aromatic substitution outlined in Scheme 6, the effect of the ionic liquid on both of the activation parameters is not the same as in the unimolecular case; there is an increase in both (albeit very small in the case of the enthalpy of activation) [32]. That is, the rate enhancement observed in this example is due to an entropic effect. Given that the transition state in this case also involves charge development, it seems unlikely that the interactions between the solvent components and the transition state would decrease on moving to an ionic liquid. As such, the origin of these changes is a relatively increased extent of interaction of the solvent with the starting materials.[g] In this case, molecular dynamics simulations [32] show little ordering of the components of the ionic liquid around the nucleophile ethanol but significant ordering about the starting material **14** (Fig. 5). The ordering decreases on moving to the intermediate, though from the probability distributions shown in Fig. 5 it is not entirely clear which interactions have the greatest influence on the change in activation parameters observed. Examining the radial distribution functions (particularly the position of the first local maxima), however, is more instructive as there is little change in the ordering of the cation on moving to the intermediate but a significant decrease in ordering is observed in the case of the anion. These observa-

tions suggest that the key interaction of the activated aromatic **14**, which is disrupted on reaction occurring, is with the anionic component of the ionic liquid.

In the case of the Menschutkin-type generation of the salt **17**, the effect of the ionic liquid on both parameters is the opposite to the unimolecular case; both parameters increase on moving from a molecular solvent to an ionic liquid [27]. The rate enhancement observed is thus a result of the enthalpic cost being outweighed by an entropic benefit. As for the nucleophilic aromatic substitution, since there is charge development, the most likely explanation for the observations is increased ordering about the starting materials but, unlike both previous examples, this reaction is concerted. As such, there is not a readily modeled intermediate that can be treated with molecular dynamics allowing inference of interactions in the transition state. Modeling the transition state is problematic; it is likely that the position of the transition state along the reaction coordinate will be modified from that calculated in either gas phase or molecular solvent by interactions with the ions. Calculation and subsequent parameterization of an appropriate transition state for use in MD simulation requires special approaches that are not yet well developed for discrete ionic systems and are thus nontrivial. As such, no comparisons with the transition state were made, but potential key interactions in the starting material could be identified.

Whilst the key interactions between the components of the ionic liquid could be observed, molecular dynamics simulations (Fig. 6) could not distinguish the origin of the activation parameter changes; whether it was either interaction with the delocalized π-systems in each of the starting materials (as had been used to account for solubility of aromatic systems in ionic liquids [33,34]), an interaction with the nucleophilic nitrogen center of the pyridine **10** (suggested in other kinetic studies [35]), or a combination of both that result in the rate acceleration [36].

In order to determine which of the interactions are pertinent to the reaction outcome, the delocalized π-systems were systematically removed from both the electrophile **16** and nucleophile **17**, and the reactions of these modified substrates were examined [36].[i] The effects on activation parameters of moving from a molecular solvent to an ionic liquid were the same—an increase in both enthalpy and entropy of activation—on removing the delocalized π-system from either one or both of the reagents. This indicates that the relevant interactions in this case are between the cation of the ionic liquid and the nucleophilic nitrogen center.

Having an understanding of the microscopic interactions allows consideration of how the components of the ionic liquid might be manipulated to change the reaction outcome. Consider the cases where the key interaction is between a component along the reaction coordinate and the cation of the ionic liquid (e.g., the unimolecular and bimolecular substitution processes above). By changing the extent of this interaction—by modifying the cation—the effect may be either increased or decreased. Similarly for cases such as the aromatic substitution process where interactions with the anion seem to be most significant, modifying the anion may be used to control reaction outcome by altering these interactions.[j]

The above section highlights that it is also necessary to understand the sites of interaction on the ionic component, such that these can be modified. Ideally, organizational profiles, akin to those shown in Figs. 5 and 6, of a given component of the reaction mixture about the cation would be available. However, the requirement to model an infinitely dilute solution (such that the reagents do not change the nature of the solvent) makes obtaining such profiles computationally prohibitive. Thus, it must be inferred from indirect methods, such as organization profiles of the anion about the cation of an ionic liquid from simulation studies and chemical shift data in NMR spectroscopy [37,38].

In the cases above, the ionic liquid was based on the $[Bmim]^+$ cation. The nature of interactions of components along a reaction coordinate with this cation is not clear. While the C2-H atom of imidazolium cations has been observed in the literature to be the strongest site for interactions with electron-rich species [37,38], it is not clear whether a directional interaction akin to a hydrogen bond or a more generalized electrostatic interaction dominates.

Our preliminary studies use the effect of $[Bmim][N(CF_3SO_2)_2]$ on the reaction outlined in Scheme 7 as the starting point, and examine the effects of systematically varying the cation using every-

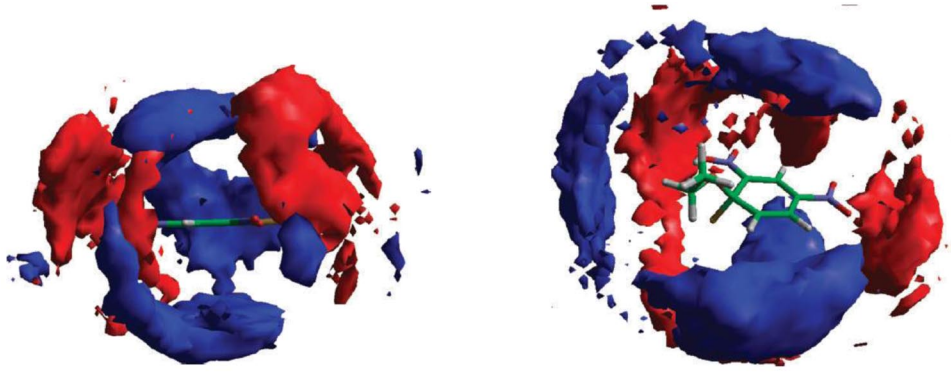


Fig. 5 Coordination around the starting material, 1-fluoro-2,4-dinitrobenzene **14** (left), and the corresponding Meisenheimer intermediate **15** (right), showing anion interactions (blue, cut-off 0.005) above and below the aromatic ring, and cation interactions (red, cut-off 0.005) with electronegative substituents. Originally published in Yau et al. [32]. Reproduced by permission of the PCCP Owner Societies.

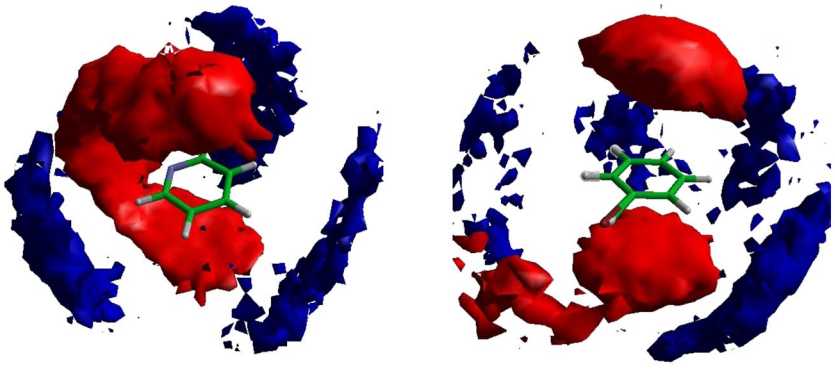


Fig. 6 Coordination about pyridine **10** (left) and the bromide **16** (right) showing cation interactions (red, cut-off 0.005) both above and below the aromatic rings and with the nitrogen center of the nucleophile **10**, and anion interactions (blue, cut-off 0.005) in distinct bands about the equator. Based on material originally presented in Yau et al. [36]. Reproduced by permission of The Royal Society of Chemistry.

thing from simple methyl substitutions to moving to a hindered tetralkylammonium salt [39]. These results show that quite dramatic changes to the cation have little effect on the observed rate enhancements providing the charge is accessible. This is consistent with some previous literature [35], suggesting that the interaction in this case is a generalized electrostatic one rather than directional. Importantly, it increases the generality of the findings of the ionic liquid effect on this system and demonstrates what is required to interfere with the dominant substrate–cation interactions.

It is worth noting that it may not always be possible to determine activation parameters readily (exemplified by the nitrile oxide cycloaddition shown in Scheme 2, where dimerization of the starting material **5** complicates kinetic studies [24]) and, in some cases, the activation parameters may not prove enlightening (which can be seen in the case of azide-alkyne cycloadditions [21]). Similarly, molecular dynamics simulations either may not sufficiently differentiate between possible interactions or, as discussed above, may be limited in terms of addressing key interactions in a transition-state complex. In such cases it may be possible to reasonably suggest the microscopic interactions of the ionic liquid effects based on other experimental evidence. For example, the increased selectivities and rates observed in the cycloaddition reactions described above [21,24] might be reasonably attributed to the

cohesive pressure between components of the solution; this is supported by similar effects in related salt solutions [40] along with the mole fraction dependency [25]. In cases such as these, modifying the anion and cation to increase the interactions between components of the ionic liquid,[k] and hence the internal pressure of solvation in the system, would be anticipated to increase the magnitude of the ionic liquid effects.

Before concluding, it is worth raising a point that follows from the arguments above. Given the effects of ionic liquids can be attributed to electrostatic interactions of the component ions, are these just an extension of "salt effects"? The simple answer to that question is "Yes!", and this is supported by the fact that in several examples described above, along with others, the addition of a "typical" (solid) salt has the same effect in terms of the outcome of the process *and* on the activation parameters for the process [21,31,40]. The more detailed answer highlights that the origin of the effects is the same but any comparison must be moderated by two points. Firstly, the charge density on ionic liquids is, necessarily to ensure a liquid state, quite diffuse, which means that the interactions with components along the reaction coordinate will differ from those with the components of a "typical" salt. Secondly, despite the large molecular weight, the fact that the ionic liquid can be used as a solvent means that the mole fraction present in the reaction mixture can be much greater than cases with a "typical" salt, where solubility issues become important. As such, ionic liquids offer solvent-based reaction control in mole fraction regimes not accessible for simple salts (above and beyond any potential advantages of replacing molecular solvents).

CONCLUSIONS

Reaction outcome can be controlled using an ionic liquid, as has been shown above. In its simplest sense, by knowing the dependency of reaction outcome on the mole fraction of ionic liquid in the reaction mixture, the best outcome can be achieved by choosing the appropriate solvent proportions. In its more complicated sense, an understanding of the interactions that determine ionic liquid effects on reaction outcome may allow ionic liquids to be tailored to affect a process in a desired fashion. Either way, there is significant potential for solvent control of reaction outcomes using ionic liquids.

NOTES

[a]Throughout this article, reaction outcomes only will be discussed. Methods of isolation of products from the reaction mixture, which might be said to be complicated by the nonvolatile nature of the ionic solvent, will not be covered.

[b]Qualitatively, on addition of ionic liquid, the rate of the cycloaddition process outlined in Scheme 2 also increases but this is complicated by the concurrent increase in the rate of the dimerization of the starting material **5**, which is generated in situ from the corresponding chloroaldoxime [24].

[c]As highlighted above, the large molecular volumes (due to the sheer size) of the ionic liquids means that the moving from χ_{IL} 0.90 to 0.50 typically only changes volume fraction of ionic liquid from ca. 0.95 to ca. 0.85. Thus, in these cases only a very small amount of molecular solvent can be added without significantly changing the reaction outcome.

[d]It is perhaps not surprising that other properties, particularly physical, of ionic liquid mixtures vary with mole fraction of the ionic component in a similar fashion; see, for example, the outcomes of dielectric relaxation spectroscopy [41].

[e]Deuterated ethanol was used to facilitate ready monitoring of reaction progress.

[f]It is worth noting that in the examples above the solvent is also the nucleophile, so, while the rate constant changes, the biggest effect on the rate is solvent concentration. However, the same trend has also been observed in other solvents [28].

[g]This is very similar to the process outlined in Scheme 2; similar effects on activation parameters were observed on modification of the electrophile with different leaving groups, along with a range of substituents on the aromatic ring [27].

[h]No such interaction was observed in the unimolecular case outlined in Scheme 5 [31].

[i]The nucleophilic nitrogen center, being inherent to the necessary reactivity of the substrate **16**, could not be removed.

[j]It should be highlighted that any modification of either component of the ionic liquid will not only alter any interactions with components of the mixture involved in the reaction, but will also alter interactions with the counterion of the ionic liquid. This may, in turn, change the interaction of the counterion with components along the reaction pathway and may need to be taken into account when considering the effects of changing ionic liquid components on reaction outcome.

[k]Without turning the ionic liquid into an ionic solid, of course.

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