

Organic reactivity in ionic liquids: some mechanistic insights into nucleophilic substitution reactions

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Ionic liquids have been advanced as alternative solvents for organic reactions. In this paper, the principal findings of studies on nucleophilic substitutions in ionic liquids are reviewed. Thus our examination of halides (Cl⁻, Br⁻ and I⁻) in a range of ionic liquids is combined with our study of amine nucleophilicity into a single narrative. There have been a few other quantitative studies of nucleophilic substitutions in ionic liquids, and the results of these studies are also summarised in this work. These data are compared to related reactions in molecular solvents, and used to show where ionic liquids do (and do not) offer advantages over molecular solvents for nucleophilic substitutions.

Keywords: organic reactivity, ionic liquids, nucleophilic substitution reactions

Introduction

Ionic liquids as solvents for synthesis

Ionic liquids have been proposed as alternative solvents for organic reactions. Indeed, they have been employed for a range of reaction types: catalytic; stoichiometric; enzymatic; electrochemical. This is in addition to their use in applications such as batteries, metal polishing and metal extraction. The purpose of this article is not to examine these uses in detail, as such applications have been extensively reviewed in the literature¹ and in text books.²

There are a number of reasons for using ionic liquids; they are “green”; they have properties that can be altered (or “tailored”) by the chemist;³ and they show good thermal and chemical stability. The claim that ionic liquids are green is based on the fact that they are non-volatile and have a very low vapour pressure. Whether this in itself is enough to make an ionic liquid green is a moot point when one considers that they are often constituted of fluorine containing anions; the counter-argument is that, if the ionic liquid can be recycled, then its composition does not matter. The second unknown with ionic liquids is their toxicity. This is an active area of current research.⁴

By definition, ionic liquids are pure compounds, consisting only of cations and anions, which melt at or below 100 °C. It is convenient to invoke a second classification, Room Temperature Ionic Liquid (RTIL). The RTILs all melt at or below 25 °C; all of the ionic liquids considered in detail in this paper are RTILs. Some of the common cations and anions that can be used to form ionic liquids are shown in figure 1. Typical ions used to form ionic liquids are large, of

low symmetry, and are either charge-delocalised or have the charge “shielded” by pendant groups (e.g. [bmpy]⁺).

Solvent properties

Clearly there are a great many variations available to the chemist, and we can expect these variations of cation and anion to affect the solvent properties of the ionic liquids. Since ionic liquids were first used, chemists have asked which solvents ionic liquids are like. Thus the study of solvent properties of ionic liquids is an active area of research. These studies have mainly made use of solvent-solute interactions to estimate the extent of various characteristics of the solvents, such as hydrogen bonding or polarisability. This work was the subject of a recent review.⁵

It should be stated that in order to be confident of the solvent properties measured, one must be confident of the quality of the ionic liquids themselves. Given that the ionic liquid cannot be purified by distillation (for example), this means that care must be taken at each stage of the synthesis. All materials should be purified before use; the intermediates should be recrystallised before use, and the crude ionic liquid can be further treated in order to remove impurities (typically halides and/or amines). If these steps are employed, the ionic liquid will be obtained as an odourless, colourless substance. It is possible to check the quality of the ionic liquids by simple analytical techniques. These include FAB-MS, optical tests and use of silver nitrate to ensure the absence of halide impurities.^{6–9} The use of ¹H NMR is not always appropriate because any halide impurity will not be revealed by this technique.

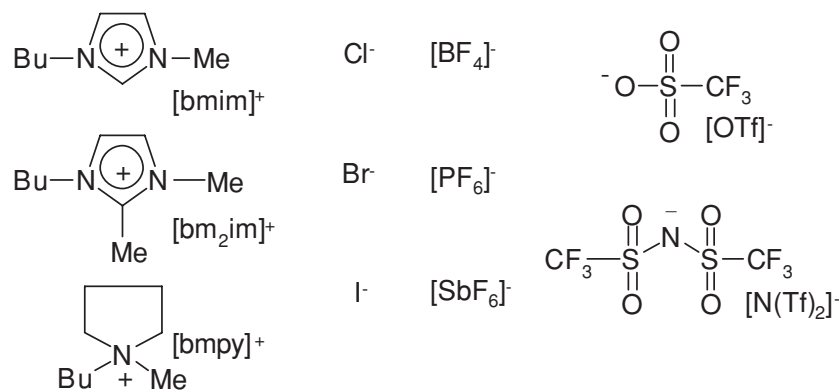
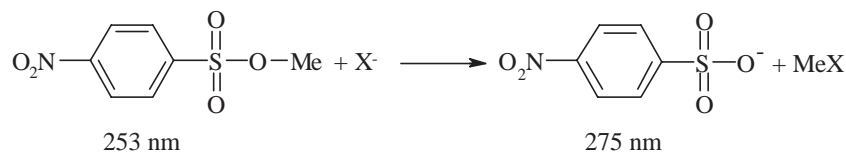


Fig. 1 Cations and anions constituting the ionic liquids described in this report.

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Scheme 1

Organic reactions in ionic liquids

Until recently, little quantitative evidence was available to help the chemist to decide whether these ionic liquids would be of benefit to them for a reaction of interest. In 1999, we began a research program in order to answer this question by studying nucleophilic substitutions in ionic liquids. The main aim was to show which reactions ionic liquids would be good solvents for and to determine whether ionic liquids were a poor solvent choice for others. In the process, we were the first to publish kinetic data for nucleophilic substitutions in ionic liquids. Additionally, we showed that ionic liquids could be prepared to “spectroscopic” quality, such that all of our reactions were monitored *in situ* by UV/vis spectroscopy.

Nucleophilic substitutions by charged nucleophiles

The reaction chosen was that of methyl *p*-nitrobenzenesulfonate with halides as illustrated in Scheme 1. The substrate has an absorbance maximum at 253 nm whilst the product absorbs at 275 nm. Therefore, provided the ionic liquid could be prepared to sufficient optical purity, it would be possible to conduct this investigation by UV/vis spectroscopy. In fact, all of the ionic liquids based on [bmim]⁺ or [bm₂m]⁺ had a UV cut-off of 240 nm and [bmpy]⁺ had a cut-off of 200 nm.⁶⁻⁹

It was by no means clear when we began this project that the ionic liquids would be innocent (or at least innocent enough). For example, one might expect that [OTf]⁻ would act as a nucleophile. In fact it does, but is so poorly nucleophilic in comparison with the halides studied that this was not an

impediment to our work. Our work on halide nucleophilicity can be broken into two parts; the effect of changing the cation and the effect of changing the anion.

Effect of changing the ionic liquid anion

Although a wide variety of reactions have been studied in ionic liquids, the most commonly used ionic liquids remain [bmim][BF₄] and [bmim][PF₆]. And it was with [bmim][BF₄] that we began our investigation of nucleophilic substitutions in ionic liquids.⁶ Sequential plots of absorbance against wavelength at regular time intervals (*e.g.* Fig. 2) reveal peaks due to the substrate and product, plus an isosbestic point indicative of an “A to B” reaction. The source of halide used was such that the cation was identical to that of the ionic liquid (or as close as possible; [emim]Br was used in place of [bmim]Br as the latter was obtained only as a yellow oil). The reactions were studied under *pseudo* first order conditions, using an excess of the nucleophile. A plot of k_{obs} against [nucleophile]₀ allowed determination of the second order rate constant for that nucleophile in that ionic liquid.

Having shown that it was possible to perform this study, a range of ionic liquids based on the [bmim]⁺ cation were used as solvents for this reaction. The values of k_2 are shown in Table 1. Also given are the Kamlet-Taft parameters α , β and π^* .¹² These represent H-bond acidity, H-bond basicity and polarity/polarisability respectively. Comparisons are also made to the same reaction in dichloromethane, where the nucleophile was either the free halide or an ion pair.

The first and most obvious conclusion to draw is that not all ionic liquids are the same. For example, the largest value of k_2 for iodide is achieved in [bmim][OTf] whilst for chloride this is achieved in [bmim][BF₄]. Nor is the order of nucleophilicity identical in each ionic liquid. In [OTf]⁻ and [N(Tf)₂]⁻ chloride is less nucleophilic than bromide; in [PF₆]⁻ chloride is more nucleophilic.

Clearly changing the anion is the cause of this variation. In order to understand this better, it is necessary to consider the likely solvent-solute interactions, and how changing the anion can affect these. The Kamlet-Taft parameters¹² are based on a series of solvent-solute interactions which manifest as solvatochromic effects. There is little effect on changing the anion on the value of α , which is a measure of the cation's ability to be a H-bond donor. This is perhaps due to the fact that in all cases, the probe solute is a better H-bond acceptor than the ionic liquid anion. One would also predict that the halides will be better H-bond acceptors than the ionic liquid

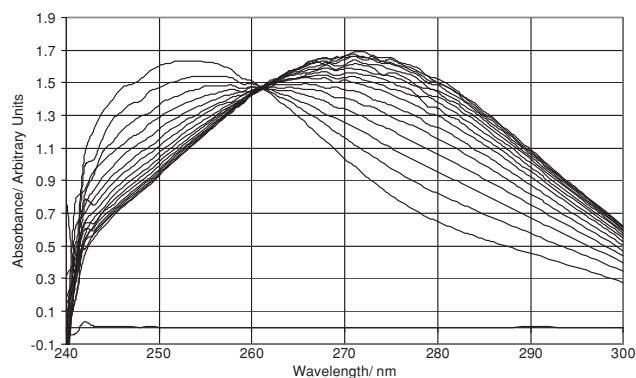


Fig. 2 UV spectra for the reaction of [bmim]Cl with methyl *p*-nitrobenzenesulfonate in [bmim][N(Tf)₂] at 25 °C.

Table 1 Second order rate constants for the reaction of halides with methyl *p*-nitrobenzenesulfonate at 25 °C

Solvent	$k_2 / \text{M}^{-1} \text{s}^{-1}$			Kamlet-Taft parameters ¹⁰		
	Cl ⁻	Br ⁻	I ⁻	α	β	π^*
[bmim][BF ₄]	0.0403	0.0381	0.0538	0.627	0.376	1.047
[bmim][PF ₆]	0.0144	0.0086	0.0278	0.634	0.207	1.032
[bmim][SbF ₆]	0.0115	0.0123	0.0180	0.639	0.146	1.039
[bmim][OTf]	0.0197	0.0314	0.0619	0.625	0.464	1.006
[bmim][N(Tf) ₂]	0.0124	0.0195	0.0232	0.617	0.243	0.984
CH ₂ Cl ₂ (ion pair) ¹¹	0.51	0.42		0.042	-0.014	0.791
CH ₂ Cl ₂ (free ion) ¹¹	1.04	0.46				

Data reproduced from ref. 8.

anions, and therefore that the halides will be most nucleophilic in ionic liquids in which they are least strongly coordinated; *i.e.* those with lowest α . This trend is observed, though imperfectly.

The values of β are more identified with the anion of the ionic liquid. A high value of β shows that the ionic liquid is an excellent H-bond acceptor, and it is in these ionic liquids that the anion will compete best with the nucleophile for H-bonding to the cation. Therefore one would expect the halides to be relatively poorly coordinated, and thus more nucleophilic. This holds true for the reactions of halides in the ionic liquids with highest β ($[\text{BF}_4]^-$ and $[\text{OTf}]^-$). But as with α , there is not a perfect correlation between β and nucleophilicity.

Thus in this set of reactions, though it is possible to show that the ionic liquids do not all behave alike, it is difficult to say *quantitatively* what it is that makes them different.

Effect of changing the ionic liquid cation

The reaction of methyl *p*-nitrobenzenesulfonate with halides was studied in a series of $[\text{N}(\text{Tf})_2]^+$ ionic liquids using $[\text{bmim}]^+$, $[\text{bm}_2\text{im}]^+$ and $[\text{bmpy}]^+$ as cations. The values of k_2 are shown in Table 2.

In these ionic liquids, the values of k_2 are in the same range as earlier (Table 1). However, a closer examination reveals that the values of k_2 for Br^- and I^- are very similar, at about $0.02 \text{ M}^{-1} \text{ s}^{-1}$ in each of the three ionic liquids. The variation in nucleophilicity is only significant for Cl^- .

It is known that $[\text{bmim}]^+$ (and $[\text{bm}_2\text{im}]^+$ to a lesser extent) can form hydrogen bonds with halides.¹³ Recent studies show that cations such as $[\text{bmpy}]^+$ can also act as hydrogen bond donors.¹⁴ Given that (of the halides used) chloride is the best hydrogen bond acceptor, it is reasonable to expect chloride nucleophilicity to be most sensitive to the hydrogen bond donor ability of the ionic liquid.

The table shows that $[\text{bmim}][\text{N}(\text{Tf})_2]$ is the best hydrogen bond donor solvent of the ionic liquids used. Thus it interacts strongly with chloride, which is stabilised, and so chloride reacts most slowly in this ionic liquid. It is also noted that the order of nucleophilicity in this ionic liquid is $\text{Cl}^- < \text{Br}^- < \text{I}^-$. By contrast $[\text{bmpy}][\text{N}(\text{Tf})_2]$ is the poorest hydrogen bond donor. It therefore interacts more weakly with chloride and so chloride reacts more rapidly and changes the order of nucleophilicity such that chloride is the most nucleophilic halide and iodide is the least.

Nucleophilic substitutions by uncharged nucleophiles

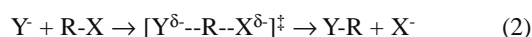
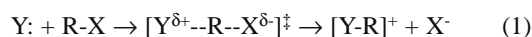
The reactions of $^n\text{BuNH}_2$, $^n\text{Bu}_2\text{NH}$ and $^n\text{Bu}_3\text{N}$ with methyl *p*-nitrobenzenesulfonate in ionic liquids were studied, and compared to the same reactions in some molecular solvents.⁹ The results are shown in Table 3.

In these reactions, all amines reacted faster in the ionic liquids than in the molecular solvents (by an order of magnitude compared to water or dichloromethane). The order of nucleophilicity in ionic liquids was as in water (with k_2 following the trend $2^\circ > 1^\circ > 3^\circ$), and the relative nucleophilicities were also similar.

Hughes–Ingold model of nucleophilic substitutions

The Hughes–Ingold rules offer a qualitative guide to the effect of solvent polarity on reaction rates.^{16,17} The polarity of molecular solvents might often be described by their dielectric constants. However, a range of empirical measurements of solvent polarity have been developed (such as the Kamlet–Taft scale¹² of α , β , π^* introduced above) for the occasions where reaction outcome and dielectric constant do not correlate, or indeed where dielectric constant cannot be measured directly.

The two reaction types examined in this work can be described by equations 1 and 2. In the reactions of charge neutral nucleophiles (Eqn(1)), in the activated complex there is a separation of unlike charge. The Hughes–Ingold prediction is that increasing the polarity of the solvent in this reaction will significantly increase the rate of reaction. By contrast, in Eqn (2) there is dispersal of charge and so the prediction is that increased solvent polarity will cause a reduction of reaction rate.



If we assume that π^* represents a general indication of solvent polarity, then this explains why amines are more nucleophilic in ionic liquids than in dichloromethane or acetonitrile (and halides are more nucleophilic in dichloromethane than in ionic liquids). Thus it can be shown that ionic liquids obey the Hughes–Ingold rules, and that nucleophilic substitutions can be predicted according to our classical understanding of solvent properties. Water does not fully fit this pattern, for reasons that will be discussed later.

Table 2 Second order rate constants for the reaction of halides with methyl *p*-nitrobenzenesulfonate at 25 °C

Solvent	$k_2 / \text{M}^{-1} \text{s}^{-1}$			Kamlet-Taft parameters ¹⁰		
	Cl ⁻	Br ⁻	I ⁻	α	β	π^*
$[\text{bmim}][\text{N}(\text{Tf})_2]$	0.0124	0.0195	0.0232	0.617	0.243	0.984
$[\text{bm}_2\text{im}][\text{N}(\text{Tf})_2]$	0.0296	0.0221	0.0238	0.381	0.239	1.010
$[\text{bmpy}][\text{N}(\text{Tf})_2]$	0.0391	0.0226	0.0188	0.427	0.252	0.954
CH_2Cl_2 (ion pair) ¹¹	0.51	0.42		0.042	-0.014	0.791
CH_2Cl_2 (free ion) ¹¹	1.04	0.46				

Data reproduced from ref. 7.

Table 3 Second order rate constants for the reaction of amines with methyl *p*-nitrobenzenesulfonate at 25 °C

Solvent	$k_2 / \text{M}^{-1} \text{s}^{-1}$			Kamlet-Taft parameters ¹⁰		
	$^n\text{BuNH}_2$	$^n\text{Bu}_2\text{NH}$	$^n\text{Bu}_3\text{N}$	α	β	π^*
$[\text{bmpy}][\text{N}(\text{Tf})_2]$	0.358	0.493	0.103	0.427	0.252	0.954
$[\text{bmpy}][\text{OTf}]$	0.922	1.04	0.523	0.396	0.461	1.017
$[\text{bmim}][\text{OTf}]$	0.500	0.541	0.0529	0.625	0.489	1.006
CH_3CN	0.155	0.182	0.0257	0.350	0.370	0.799
H_2O ¹⁵	0.0547	0.0655 ^a	0.0205 ^b	1.12	0.14	1.33
CH_2Cl_2	0.0165	0.0454	0.0200	0.042	-0.014	0.791

^aAmine was $^n\text{Pr}_2\text{NH}$. ^bAmine was Et_3N . Data reproduced from ref 9.

As we consider the reaction described by Eqn (1), we observe that the high β values show that water, acetonitrile and ionic liquids act as hydrogen bond acceptors, whereas dichloromethane does not. The activated complexes for the reactions of the 1° and 2° amines show that as the amine attacks the carbon centre, the N atom develops a positive charge (and thus increases the H-bond donor ability of the N–H protons). Therefore H-bond acceptor solvents will stabilise the complex rather than the reagent, thus increasing the rate of reaction.

The H-bond donor properties also have an effect; as α increases, amine nucleophilicity decreases and it is this that explains water's behaviour. Water has high π^* and moderate β , so one would expect the amines to react rapidly in this solvent. However, the high α value means that water can form hydrogen bonds not only with the emerging *p*-nitrobenzenesulfonate anion but also with the amine lone pair (which is of course the nucleophilic site).

Before considering the 3° amines, we recognise that further insight into the reactions in ionic liquids is provided by studying the effect of temperature on the second order rate constant, and calculating the activation parameters ΔH^\ddagger and ΔS^\ddagger for these reactions. We should recognise that the Eyring equation relates ΔG^\ddagger to k_2 , such that they are inversely proportional to each other.

Unlike the primary and secondary amines, the tertiary amine can only act as a H-bond acceptor. Therefore the only interaction of interest is the H-bond between the cation of the ionic liquid and the amine. For the amine to act as a nucleophile, this bond must break (in contrast with the primary and secondary amines where there are H-bonding interactions between the anion and the amine proton, which gets stronger as the reaction proceeds). The result is that as one directional interaction forms (a bond between N and C) another breaks (between N and cation). The net result is that the $T\Delta S^\ddagger$ term is smaller for the 3° amines in ionic liquids than for 1° and 2°, thus reducing ΔG^\ddagger . In a recent paper, it has been proposed that the poor solvation of amines by ionic liquids causes an increase in their reactivity.¹⁸

We can now consider the reactions of the charged nucleophiles, and observe that there are some clear trends. The first is that the interaction of ionic liquid cation with the nucleophiles affects the nucleophilicity of the anion. The strength of cation-nucleophile interaction is in turn affected by changing the anion (to a degree), and affected greatly by changing the cation. The greatest effect is observed with anions which are good H-bond acceptors (i.e. chloride); this is most clear in the use of the $[N(Tf)_2]^-$ ionic liquids, where Br and I have similar k_2 values in each ionic liquid. However, it is clear that all of the k_2 values fall within a narrow range (ca 0.01 – 0.06 M⁻¹ s⁻¹) regardless of ionic liquid. In other words, there seems to be a “levelling effect”, where the nucleophiles are actually fairly similar in nucleophilicity.

When comparing the reactions of the halides in ionic liquids and in molecular solvents, we can return to the Hughes–Ingold rules. In this reaction, as the activated complex forms so charge is dispersed, making the complex less stabilised than the reagents (particularly the nucleophile) in “polar” solvents. Thus the prediction is that increased solvent polarity will lead to a reduction of reaction rate. In comparing the reactions in ionic liquids against the same in dichloromethane, we can see that this prediction is obeyed.

Again, we can obtain further information about the reaction mechanism by an examination of the activation parameters. Such an analysis showed (broadly) that the ΔH^\ddagger values in ionic liquids were comparable to the same reaction in dichloromethane (specifically compared to $\Delta H^\ddagger_{\text{ion pair}}$). One would not expect a true ion-pair to form, but an ion-pair picture is more appropriate than a free ion in the ionic liquid solvents.

However, the $T\Delta S^\ddagger$ term presented a much greater barrier to reaction, and the effect on ΔG^\ddagger was sufficient that the reactions in ionic liquids were less favoured. This information allows a tentative reaction mechanism to be proposed, in which the fully coordinated halide dissociates from one (or more) cations and thus becomes available to react. The ΔH^\ddagger values are similar to those seen for the ion pair in dichloromethane because in both cases a cation⁺-X⁻ “bond” breaks as a C–X bond forms. The $T\Delta S^\ddagger$ term can be understood when we consider that the halide goes from being loosely coordinated by a number of cations to forming a directional interaction (i.e. a bond). The result is a large, and negative, change in entropy.

Comparison to other studies of nucleophilicity in ionic liquids

In the literature there are a number of examples of nucleophilic substitutions in ionic liquids, but very few of these studies allow even qualitative comparisons to be made between ionic liquids and molecular solvents. There have been very few examples of kinetic studies of any reactions in ionic liquids. However, it is possible to draw some comparisons between the work described above and other work in ionic liquids. From these accounts we can also make further comparisons between the use of ionic liquids and molecular solvents for nucleophilic substitution reactions.

Neta has studied the reaction between 1,2-dimethylimidazole and benzyl bromide in a range of ionic liquids and molecular solvents.¹⁹ The reactions were faster in ionic liquids than in the molecular solvents, although the range of k_2 values within the ionic liquids was quite narrow. Neta also compared rate constant to some empirical measures of solvent properties, finding that reaction rate was proportional to the E_T^N value of the ionic liquid (but that this could not be extended to plot reaction rates of the reaction in molecular solvents against E_T^N ; the two solvent sets followed different trends). It was possible to relate the rate constant for the reaction in molecular solvents to two parameters: α and π^* . However, such an analysis was not performed with the ionic liquids.

Chi has published an example of nucleophilic substitution on 2-(3-bromopropyl)naphthalene using water as the nucleophile.²⁰ These reactions took many hours, even when performed at 110 °C. However, the data suggest that the reactions were faster in the ionic liquids than in 1,4-dioxane.

In the use of charged nucleophiles, there is less agreement with the Hughes–Ingold prediction, at least on the surface. For example,²¹ Chi claims that nucleophilicity of fluoride is enhanced in ionic liquids compared to molecular solvents (other charged nucleophiles such as CN⁻, MeO⁻ and halides were briefly examined). However, many of these reactions are carried out in the presence of added water at elevated temperatures. As there is no kinetic or mechanistic study, it is not possible to be sure whether enhanced nucleophilicity is being observed, or a change in reaction mechanism. What is beyond doubt is the measured yield after given time, but this in itself does not allow more than speculation about reaction mechanism.

Other work on the use of charged nucleophiles in ionic liquids does fit the Hughes–Ingold prediction. For example Chiappe has studied the reactions of azide and cyanide nucleophiles in ionic liquids.²² In this work, the authors examined the effect of the leaving group on the reaction mechanism (S_N1 for tertiary substrates and S_N2 for primary substrates) and showed how ion-ion interactions affected the reaction mechanism. It is particularly noteworthy that the reactions of secondary substrates showed intermediate behaviour between S_N1 and S_N2; perhaps proceeding through an S_N1 mechanism *via* a preassociation complex.

More recently, Landini and Maia have reported a kinetic study of anion nucleophilicity in ionic liquids.²³ They have used a wide range of nucleophiles, including halides, in two ionic liquids, and compared the results to some molecular solvents. They showed (as predicted) that the reactions were slower in ionic liquids than in (the polar, aprotic solvents) chlorobenzene and dimethylsulfoxide. In fact the rate constants measured in the ionic liquids were of approximately the same order of magnitude as those measured for the same reaction in methanol. In this work, the authors note that in fact the reactivity of the different anions in ionic liquid spans a narrow range. However, the effect of water in the ionic liquid is shown to have a dramatic effect on reaction rate. For example, the value of k_2 is predicted to increase more than 6 fold on going from 30 ppm to 0 ppm of water in the ionic liquid. It should be noted that the water content of the ionic liquids used in this work was, deliberately, quite high (ca 2000 ppm). However, most other studies of nucleophilicity in ionic liquids will have made use of solvents which contained significant (if lower) quantities of water.

There is one significant advantage to using ionic liquids for nucleophilic substitutions (and indeed other organic reactions) and that is the fact that they can be heated to high temperatures without significant solvent degradation. Ionic liquids are very amenable to microwave heating; a phenomenon which has been utilised by Leadbeater in the cyanation of aryl halides.²⁴ The reagent used was either Ni(CN)₂ or NaCN in the presence of NiBr₂. Particularly interesting is that when reactions were carried out using conventional heating, the yield after unit time was lower than was achieved under microwave heating to the same temperature.

Conclusions and outlook

The studies described above mostly point to the same outcome: that it is possible to use the Hughes–Ingold rules as a guide to the result of nucleophilic substitutions in ionic liquids. That is, when one considers the likely ion-ion and ion-dipole interactions that can occur in the ionic liquid (of the solvent with the reagent and activated complex), the results can be understood. This has been illustrated by use of both charged and charge neutral nucleophiles. By the same analysis, it is possible to examine the effect of the leaving group on reaction mechanism.

However, there is a real shortage of published work in the field of nucleophilic substitution (or indeed organic reactions generally) within ionic liquids which allows any conclusions as to the effect of the solvent to be drawn. To perform a reaction in [bmim][BF₄] alone does not, in itself, tell the chemist anything about how ionic liquids as a group might affect that particular reaction. If ionic liquids are to be adopted as reaction media, we must know how they compare against each other, and against molecular solvents.

In order to establish the effect of any solvent on a reaction, it is pre-requisite that some element of the reaction can be fully probed: this might be achieved by looking at product distribution; alternatively yields after unit time might be examined. But by far the most informative technique is the determination of reaction kinetics. By such an approach, one can compare the rate law in different media, and ensure that the mechanism is (or is not) unchanged from that observed in the reference solvent. It is pleasing to see that such studies are now being made; the wider chemistry community will surely benefit from the results of these research programs.

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