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Substitution reactions in ionic liquids. A kinetic study

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Abstract—The rate of the substitution reaction of (*R*)-3-chloro-3,7-dimethyloctane (**1**) with either methanol or benzyl alcohol in mixtures containing the ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$] was monitored using ^{35}Cl NMR spectroscopy. The enantiomeric excess of the product, (*S*)-3-methoxy-3,7-dimethyloctane (**2a**), was analyzed using chiral gas chromatography. This product showed a decreasing enantiomeric excess with increasing concentration of ionic liquid. The rate of reaction of substrate **1** in each case varied with the concentration of the ionic liquid. Polarity measurements of the solvent mixtures were undertaken by standard methods, which are compared both to each other and to the observed rates. Solvent reorganization and selective solvation are also each proposed as contributing to the difference in the observed rates of reaction.
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Ionic liquids have attracted considerable attention in recent years due to their unique properties, such as lack of measurable vapour pressure.[1] These properties have led to a variety of successful applications, ranging from industrial processes to green chemistry.[2,3] However, many processes carried out in ionic liquids proceed very differently when compared to those in traditional organic solvents. Examples include changes in the rates and the selectivities of Diels–Alder reactions[4] and changes in the reactivity of organometallic catalysts.[3] While there are numerous reports of such differences, limited work has been done to explain these observations.[5,6] To understand the effects of ionic liquids on organic reactions, a simple nucleophilic substitution was targeted; the solvolysis of 3-chloro-3,7-dimethyloctane (**1**) is in either methanol or benzyl alcohol containing the ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$] (Fig. 1).

While previous studies of this solvolysis reaction by Müller et al.[7] and Takeuchi et al.[8] investigated the cause of the significant amounts of inversion seen for the process, our study focused on the effects of the ionic liquid on the rate of the solvolysis reaction and the enantiomeric excess of the product **2a**. This is a particularly useful system, as it allows the study of the rate of the formation of the carbocation without
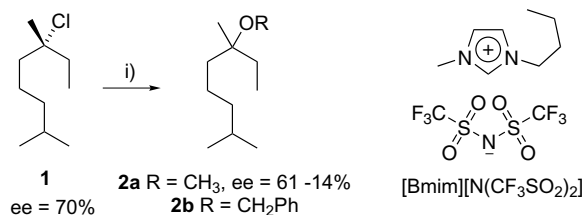

Figure 1. Solvolysis of the linalool derivative **1** to give an ether: (i) ROH, NEt$_3$, [Bmim][N(CF$_3$SO$_2$)$_2$].

the need to consider the nucleophilicity of the nucleophile.[5] Since ionic liquids are involatile, the reaction mixture cannot be directly analyzed using gas chromatography. Any attempts to remove the ionic liquid through flash chromatography would likely alter the mixture composition, leading to inaccurate results. Heteronuclear magnetic resonance spectroscopy investigating a range of nuclei was examined and ^{35}Cl NMR spectroscopy proved to be a practical method based on the preliminary experiments. This method is consistent with the conductivity and titrimetric methods developed by Takeuchi et al.[9]

A drawback that may affect the use of ^{35}Cl NMR spectroscopy, and is evident with the conductivity and the titrimetric methods, is that it cannot distinguish between events, which may release chloride. The two avenues for chloride release in this case are the formation of the carbocation and the elimination of hydrogen chloride to form alkenes. Given that the second possibility
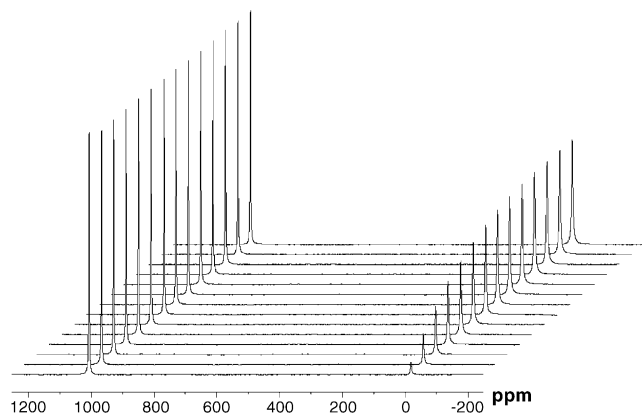
Figure 2. Stacked plots of ^{35}Cl NMR spectra of the solvolysis of chloride **1** in 12.5% by volume [Bmim][N(CF$_3$SO$_2$)$_2$] in methanol from a Bruker DMX500 spectrometer operating at ca. 49 MHz and 313 K. The first spectrum was that acquired after 28 min and each subsequent spectrum occurs in increments of 110 min. The signal at ca. δ 0 corresponds to chloride and the signal at ca. δ 1000 to sodium perchlorate, an external standard.

Figure 3. The extent of inversion of configuration on formation of the product **2a** in [Bmim][N(CF$_3$SO$_2$)$_2$]/methanol mixtures. Note that errors are standard deviations and that each point is the mean of multiple (3+) samples.

Table 1. Data presented in Figure 3

Mole fraction of ionic liquid	Extent of inversion (%)
0	88 ± 2
0.019	70 ± 1
0.043	57 ± 2
0.12	57 ± 5
0.49	39 ± 2
0.72	25 ± 7

(i.e., elimination) is a second order reaction, based on the accumulated data, which include the use of alternative bases,[7] this can be discounted because no significant deviation from first order kinetics was observed.

In each kinetic run, a sample of chloride **1** (ca. 50 mg) was dissolved in a mixture of [Bmim][N(CF$_3$SO$_2$)$_2$] and methanol (ca. 3.5 mL) followed by addition of a base. For these series of experiments, triethylamine (ca. 0.1 mL) was used. The sample was held at 313 K and a ^{35}Cl NMR spectrum was acquired every 28 min (Fig. 2). The signal due to the chloride anion at ca. δ 0 was integrated against a sodium perchlorate external standard at ca. δ 1000. Correlating this integration with time allowed the first order rate constants for the release of chloride in each case to be determined. The reaction mixtures were then each treated with ruthenium tetraoxide, generated in situ from ruthenium(III) chloride and sodium periodate, to give the corresponding formate.[7] Any ionic liquid present was removed by passing the mixture through a pad of silica. The eluant was concentrated and analyzed using chiral gas chromatography to determine the enantiomeric excess of the product **2a** in each case. This allowed the extent of inversion in the substitution reaction to be calculated.

It should be noted that both the ^{1}H NMR and the GC analyses of the final reaction mixtures indicated the presence of alkenes. It is not possible to estimate the proportion of these elimination products that form directly from the carbocation intermediate and that which forms subsequently from either ether **2a** or formate **2b**. However, in each case the elimination was similar to that reported previously, being ca. 50%.[7]

Müller et al.[7] found that the solvolysis of chloride **1** in methanol proceeded with 78% inversion of configuration in the methanol case. This was attributed to the ion pairing of the carbocation and the chloride anion intermedi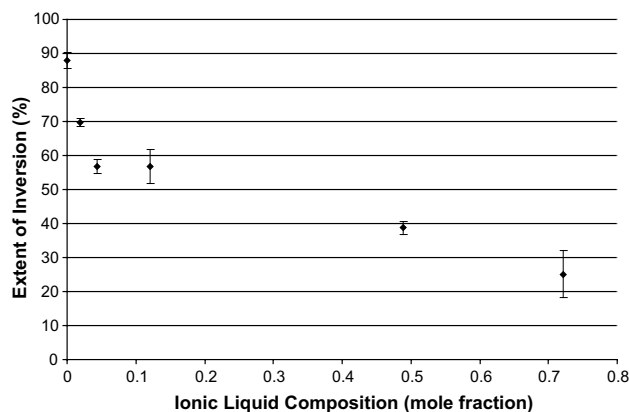ates. The effect of the concentration of ionic liquid on this process is shown in Figure 3 and in Table 1. Though it was found that the extent of inversion was larger than reported, the key point is that the extent of inversion drops markedly, from ca. 90% in neat methanol to ca. 25% in ca. $X = 0.7$ ionic liquid. This is consistent with the ionic liquid disrupting the ion pairing in solution, thus allowing the nucleophile to attack from either face of the carbocation. These results suggested that the ionic liquid is acting as a polar non-nucleophilic solvent, and would thus promote racemization of the chloride **1**,[10] which was found to be the case.

The rate constant data calculated from the ^{35}Cl NMR spectra show an initial increase with increasing ionic liquid concentration, followed by a decrease in the rate of chloride release (Fig. 4, Table 2). The origin of this trend is not immediately apparent, particularly the initial increase. Initially, the polarity of the system was considered, as changing the polarity of the solvent might be expected to change the stability of the ion paired intermediates and hence the rate of reaction. Thus, two methods that have been used previously to measure solvent polarity in ionic liquids were investigated; keto-enol tautomerism[11] and the use of a solvatochromic dye.[12]

The solvatochromic dye Nile Red was used to investigate the polarity of [Bmim][N(CF$_3$SO$_2$)$_2$]/methanol mixtures (Fig. 5, Table 2). An increase in the wavelength of maximum absorption corresponds to an increase in polarity.[13] In addition, the extent of keto-enol tautomerism of pentane-2,4-dione has been shown to correlate
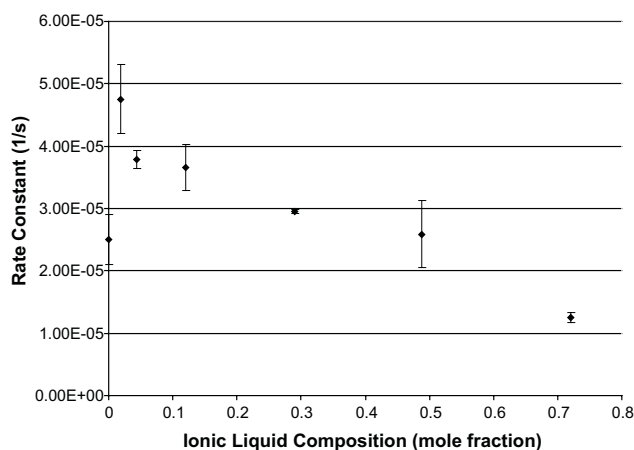
Figure 4. The rate constant for the formation of chloride anion from chloride **1** in [Bmim][N(CF$_3$SO$_2$)$_2$]/methanol mixtures at 313 K. Note that errors are standard deviations and that each point is the mean of multiple (3+) samples.

Table 2. Data presented in Figures 4 and 5

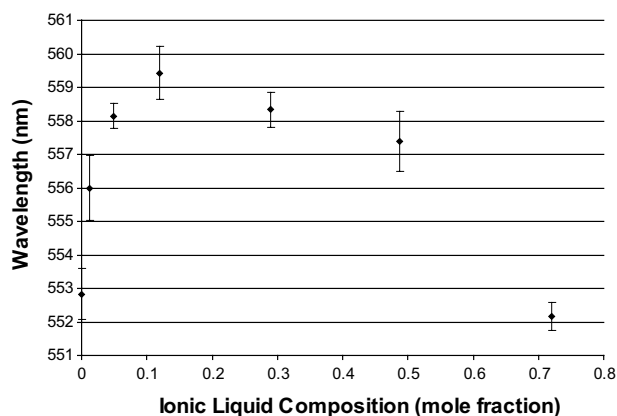| Mole fraction of ionic liquid	Rate constant (s^{-1})	Wavelength (nm)
0	$(2.5 \pm 0.4) \times 10^{-5}$	552.8 ± 0.8
0.019	$(4.8 \pm 0.6) \times 10^{-5}$	556 ± 1
0.043	$(3.8 \pm 0.1) \times 10^{-5}$	558.1 ± 0.4
0.12	$(3.7 \pm 0.4) \times 10^{-5}$	559.4 ± 0.8
0.29	$(2.95 \pm 0.03) \times 10^{-5}$	558.3 ± 0.5
0.49	$(2.6 \pm 0.5) \times 10^{-5}$	557.4 ± 0.9
0.72	$(1.26 \pm 0.08) \times 10^{-5}$	552.2 ± 0.4

Figure 5. The wavelength of maximum absorption of Nile Red in [Bmim][N(CF$_3$SO$_2$)$_2$]/methanol mixtures. Note that errors are standard deviations and that each point is the mean of six samples.

with the polarity of the solvent, with a greater enol content being noted for more polar solvents.[11] The variation of enol content of this diketone, as measured using the appropriate signals in the corresponding ^{1}H NMR spectra of 5% v/v samples, with ionic liquid concentration is shown as in Figure 6 and Table 3.

The most striking point to arise from these two measurements of solvent polarity is that they do not correlate
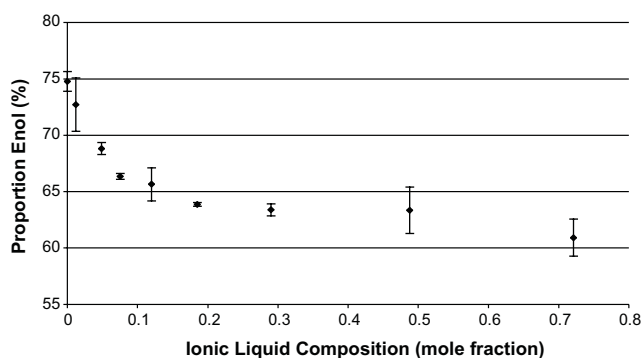

Figure 6. The extent of enol formation, determined using ^{1}H NMR spectroscopy, in dilute solutions of pentane-2,4-dione in [Bmim]-[N(CF$_3$SO$_2$)$_2$]/methanol mixtures. Note that errors are standard deviations and that each point is the mean of three samples.

Table 3. Data presented in Figure 6

Mole fraction of ionic liquid	Proportion enol (%)
0	74.8 ± 0.9
0.019	73 ± 2
0.043	68.9 ± 0.5
0.076	66.4 ± 0.3
0.12	66 ± 1
0.19	63.9 ± 0.2
0.29	63.4 ± 0.6
0.49	63 ± 2
0.72	61 ± 2

well with each other. However, the Nile Red results predict an initial increase in the rate of chloride **1** solvolysis with increasing ionic liquid concentration followed by a decrease, which is consistent with that observed. These results illustrate two important points. Firstly, a single parameter measure of polarity is evidently not sufficient in this case. It has been shown that a model using multiple solvent probes is effective for categorizing ionic liquids, which are able to act as polar solvents for polar solutes as well as non-polar solvents for non-polar solutes.[14] Perhaps this is also more appropriate for mixed solvent systems containing ionic liquids. The second point is that the components of a solution involved in the solvation of the probe molecules may not be representative of the overall composition of the solutions. This 'selective solvation' will, clearly, vary with the nature of the probe molecule.

While there are obvious drawbacks with the use of empirical polarity probes, it is clear that in this case the general trend follows the polarity scale predicted using the solvatochromic dye. This was tested further by repeating the above rate studies replacing methanol with benzyl alcohol (Fig. 7), along with repeating the solvatochromic dye measurements (Fig. 8). The solvolysis of the chloro compound **1** in benzyl alcohol exhibited similar trends to those observed in methanol. Comparison of the observed trends with the polarity data obtained using the solvatochromic dye once again showed a reasonable correlation, with an initial increase in both the polarity and rate of solvolysis with
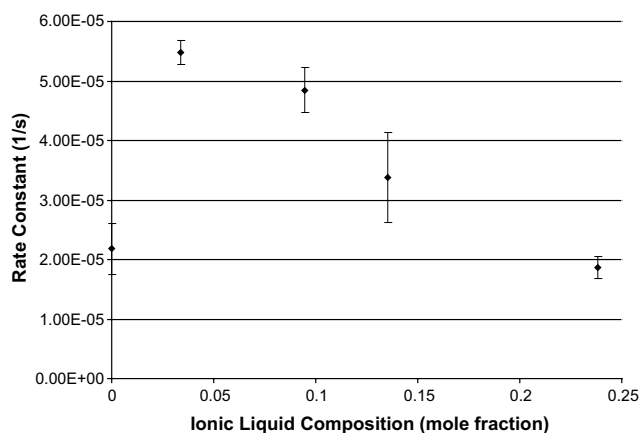
Figure 7. The rate constant for the formation of chloride anion from the chloride **1** in [Bmim][N(CF$_3$SO$_2$)$_2$]/benzyl alcohol mixtures at 313 K. Note that errors are standard deviations and that each point is the mean of multiple (2+) samples.
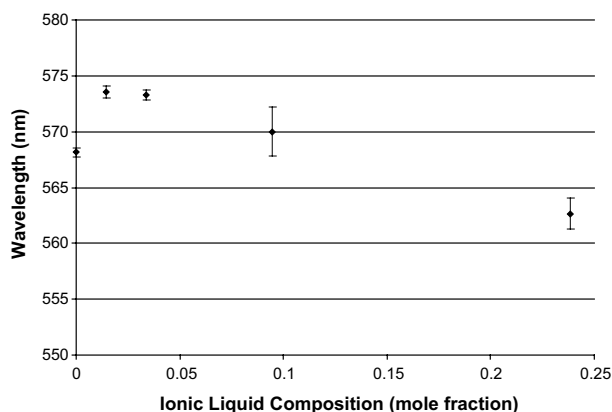

Figure 8. The wavelength of maximum absorption of Nile Red in [BMIM][N(CF$_3$SO$_2$)$_2$]/benzyl alcohol mixtures. Note that errors are standard deviations and that each point is the mean of six samples.

Table 4. Data presented in Figures 7 and 8

Mole fraction of ionic liquid	Rate constant (s^{-1})	Wavelength (nm)
0	$(2.2 \pm 0.4) \times 10^{-5}$	568.2 ± 0.4
0.015	—	573.6 ± 0.5
0.034	$(5.5 \pm 0.2) \times 10^{-5}$	573.3 ± 0.5
0.094	$(4.8 \pm 0.4) \times 10^{-5}$	570 ± 2
0.14	$(3.4 \pm 0.8) \times 10^{-5}$	—
0.24	$(1.9 \pm 0.2) \times 10^{-5}$	562 ± 1

increasing concentration of the ionic liquid, followed by a decrease (Table 4).

However, a closer inspection reveals the frailties of this method. If a methanol and a benzyl alcohol mixture containing a similar mole fraction of ionic liquid are compared, inconsistencies become apparent. For instance, the polarity data for the mixtures with ca. $X = 0.1$ of ionic liquid: the Nile Red data suggests that the benzyl alcohol case should have the higher rate con-

stant but this was not observed, rather the rate constants were similar.

It is important to consider what additional factors might be influencing the rates of reaction. One is selective solvation (as described for the probe molecules above) that may result in the solvation of the transition state leading to the chloride anion not being representative of the bulk solvent mixture. However, with the observed acidity of the Bmim cation[15] it is not immediately apparent, which solvent would be more effective at solvating the transition state.

Another consideration is the reorganization of the solvent required on formation of the transition state. Molecular dynamics simulations have demonstrated, perhaps not surprisingly, that the largest interactions in solutions containing ionic liquids are between ions.[16] This suggests that the energy required for any solvent reorganization would increase with ionic liquid concentration. This may account for the difference in the relative rates predicted by the Nile Red polarity data and the observed rates.

We are currently conducting molecular dynamics simulations, which have been shown previously to be effective for the examination of the nature of solute–ionic liquid mixtures,[17] in order to examine each of these effects.

In conclusion, based on these results, the ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$] does not significantly effect the formation of the intermediate species in the solvolysis of chloride **1**. Work done on similar acyclic systems by Takeuchi et al.[8] found that a change from methanol to ethanol led to a rate of change of an order of magnitude while the largest change observed in the cases here is only approximately a factor of three. At the same time, substitution reactions performed in ionic liquids cannot be rationalized simply using the polarity of the mixtures, the empirical measure of which may vary with the probe used. While the general trend correlates well with polarities as measured using the solvatochromic dye Nile Red, other factors, including selective solvation and the energies required for solvent reorganization need to be considered and are currently being examined. It is important to note that while the ionic liquid does not increase the rate of formation of the charged intermediate species, it does disrupt the ion pairing in solution. A natural extension of the work is to study the effects of a chiral ionic liquid, where the chirality may be based on the cation, anion or both, on the solvolysis reaction.

Acknowledgements

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