Solvent reorganisation as the driving force for rate changes of Menschutkin reactions in an ionic liquid†

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The effect on the rate of reaction of each of a series of Menschutkin processes on changing from a molecular solvent to an ionic liquid was investigated. In each case, the rate acceleration observed at room temperature could be attributed to the change in the entropy of the system on reaching the transition state, offsetting any enthalpic cost.

Introduction

Ionic liquids, which are typically made up of a bulky organic cation and a charge-diffuse anion,[1–4] are salts which are liquid below 100 °C.[5] The ability to change the nature of the solvent through modification of the components means that a variety of solvent properties are available.[3,4,6,7] Further, since the forces between the components of the solvent are electrostatic, ionic liquids have very low vapour pressures[1,7] and are thus often proposed as alternatives to environmentally damaging organic solvents.[8]

One of the challenges to the widespread application of ionic liquids is that differences in the outcomes of reactions, both in terms of rates and selectivities, are often observed on changing from molecular to ionic solvents, but there has been little investigation of the origin of these changes.[9,§] In order for ionic liquids to become broadly applicable, their effect on reaction outcome needs to be understood in a fashion akin to that available for molecular solvents.[10]

The key difference between molecular solvents and ionic liquids is the significant electrostatic interactions between the components of the liquid. Along with resulting in the low vapour pressures so characteristic of ionic liquids, these electrostatic interactions may result in increased stabilisation of charged species and significant ordering in the solution.

Scheme 1 The Menschutkin reaction between the benzyl bromides **1a–g** and pyridine **2** carried out in either acetonitrile or the ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$].[14]

Our research effort aims to understand the origin of the effects of ionic liquids on organic processes and to examine whether electrostatic interactions between components of the solution might be used to explain the outcomes observed. We have demonstrated the effect of ionic liquid solvents on nitrile oxide cycloadditions,[11] both in terms of rate and regioselectivity, with the changes being attributed to compression of, and hence increased steric demand in, the transition state. We have also examined the S$_N$1 substitution of a tertiary chloride in mixtures containing various proportions of the ionic liquid, 1-butyl-3-methylimidazolium ([Bmim]$^+$) bis(trifluoromethanesulfonyl)imide ([N(CF$_3$SO$_2$)$_2$]$^-$) and shown that the variation in rate observed[12] was the result of enthalpic stabilisation of the incipient charges in the transition state, which was offset by the necessary ordering of the components of the solution.[13]

The work described herein aims to extend our observations on substitution processes by considering the Menschutkin reaction of substituted benzyl bromides and pyridine (Scheme 1).[14] This reaction was chosen because the extent of charge development is less than for the S$_N$1 process and both this and the extent of bond formation and bond breakage in the transition state, whether it is either 'loose' or 'tight',[15] can be varied with the electronic nature of the substituent.

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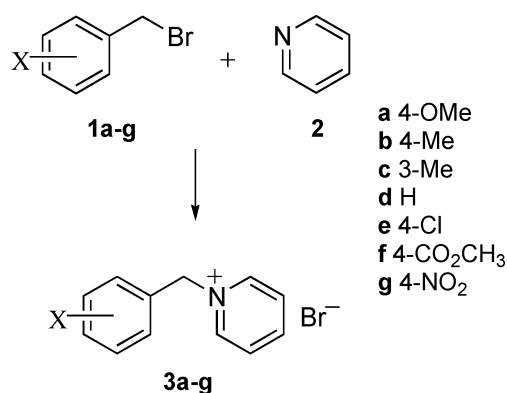
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† Electronic supplementary information (ESI) available: Hammett plot for the reaction shown in Scheme 1 at 300.8 K, second-order rate constants for reactions shown in Scheme 1 at 300.8 K and 311.5 K (acetonitrile) and 278.1 K and 300.8 K ([Bmim][N(CF$_3$SO$_2$)$_2$]), exemplar Eyring plots for the data shown in Tables 2 and 3, second-order rate constants and Eyring plots for the reactions of pyridine with benzyl chloride and with benzyl iodide. See DOI: 10.1039/b909171h

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§ There are specific cases where the reactivity of the components of an ionic liquid,[23] particularly through the use of protic cations[24] and basic anions[25] alters the reaction outcome. These cases do not rely on the fundamental properties of the ionic liquid and will not be referred to further here.

Experimental

The benzyl halides **1a–g**, **4** and **5** were either commercially available or prepared from commercially available starting materials using literature methods.[16] [Bmim][N(CF$_3$SO$_2$)$_2$] was prepared from the corresponding chloride[4] and dried to constant weight over phosphorus pentoxide. Pyridine (**2**) was purified using a literature method[17] and analytical grade acetonitrile was used as received. ^{1}H NMR spectra were recorded either on a Bruker Avance 500 spectrometer (500 MHz), a Bruker Avance 400 spectrometer (400 MHz) or on a Bruker DPX 300 spectrometer (300 MHz) using *ca.* 0.7 mL of reaction mixture (details below) in a 5 mm NMR tube. Results were demonstrated to be independent of the instrument used.

Kinetic analyses of the Menschutkin reactions were carried out in solutions containing the appropriate benzyl halide (*ca.* 0.05 mol L^{-1}) and pyridine **2** (*ca.* 5–20 equiv.) over a range of temperatures between 278 K and 341 K. In each case the reaction was followed using ^{1}H NMR spectroscopy until more than 95% of the starting material was consumed. Spectra were taken at regular intervals during the reaction and at least 20 spectra were obtained for each kinetic run. The extent of reaction was deduced by integration of the signals corresponding to the benzyl protons in the starting materials **1a–g** (*ca.* δ = 4.5) and the products **3a–g** (*ca.* δ = 5.8). From this information, the pseudo first-order rate constants for the reaction of each of the species **1a–g** under these conditions were calculated and, consequently, from the concentration dependence of these values, the second-order rate constants at each temperature were also calculated. The activation parameters were then determined using the bimolecular form of the Eyring equation.[18]

Results and discussion

Initially, the reaction of the benzyl bromides **1a–g** was examined using ^{79}Br NMR spectroscopy[19] by following the formation of a single signal due to the bromide ion in acetonitrile. However, line broadening of the bromide signal in the ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$] made such analysis impractical and thus ^{1}H NMR spectroscopy was used.

The first thing to note is that for each of the substituted bromides **1a–g**, kinetic analysis showed that the reaction proceeded through a bimolecular rate-determining step with no measurable contribution from the corresponding unimolecular process. These second-order rate constants for the Menschutkin reactions at 289.6 K are tabulated below (Table 1) and the Hammett plot given (Fig. 1); the latter represents the first such investigation undertaken in ionic liquid media. Under the conditions used, the mole fraction of ionic liquid present in the reaction mixture was *ca.* $\chi = 0.9$.

From this data, it is clear that the effect of moving from acetonitrile to the ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$] was to increase the rate of reaction of the bromides **1a–g** by 1.5–3 times, with the greater change observed for electron-donating substituents. The Hammett plot is non-linear in each instance, though it is important to note that the data used are the second-order rate constants; that is, the curvature is not due to a change in mechanism from an S$_N$2 to an S$_N$1 process as the substituents become more electron-donating. Rather, the extent of bond formation and bond breakage is comparable for electron-withdrawing substituents. That is, there

Table 1 Second-order rate constants for the reactions described in Scheme 1 at 289.6 K with either acetonitrile or [Bmim][N(CF$_3$SO$_2$)$_2$] as the solvent

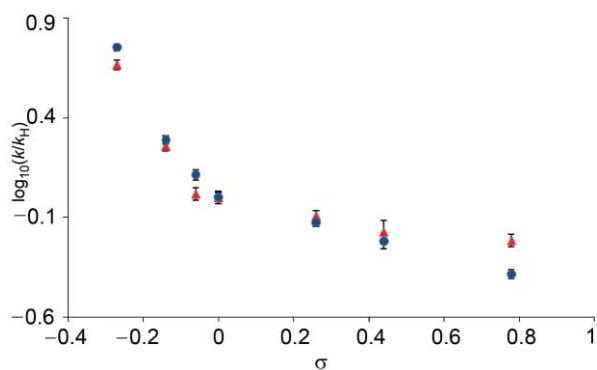|	k_2 (acetonitrile)/ 10^{-4} mol L^{-1} s^{-1} ^{a}	k_2 ([Bmim][N(CF$_3$SO$_2$)$_2$])/ 10^{-4} mol L^{-1} s^{-1} ^{a}
1a	21.0 ± 0.61	53.2 ± 0.82
1b	8.22 ± 0.15	18.3 ± 0.54
1c	4.73 ± 0.25	12.2 ± 0.57
1d	4.55 ± 0.23	9.44 ± 0.35
1e	3.68 ± 0.11	7.05 ± 0.22
1f	3.05 ± 0.38	5.68 ± 0.45
1g	2.76 ± 0.15	3.89 ± 0.12

^{a} Uncertainties quoted are standard deviations.

Fig. 1 Hammett plot for the second-order rate constants for the reaction outlined in Scheme 1 carried out at 289.6 K in either acetonitrile (▲) or the ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$] (●).

is a 'tight' transition state.[15] As the electron-donating ability of the substituent increases, and a positive charge can be more readily stabilised at the benzylic position, preferential bond breaking over bond formation is observed. That is, there is a 'loose' transition state.[15]

The effect of the ionic liquid on the Hammett plot is to increase the slope of the tangent to the curve at any given point; this was consistent across a range of temperatures (see the ESI†). While this indicates an increased charge development on going to the transition state compared to the case in acetonitrile, it is not apparent simply from this data alone whether it is stabilisation of the incipient charges by the components of the ionic liquid which is responsible for the observed rate increases.

The activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were calculated for the reactions of the bromides **1a–g** from the temperature dependent kinetic data using Eyring plots[18] (Tables 2 and 3). In all cases, the observed activation enthalpy is positive and there is little change based on the electronic nature of the substituent. The latter is important as it indicates that while the degree of charge development at the benzylic position in the transition state changes with the electronic nature of the substituent, this is not reflected in the activation enthalpy. Similarly, for both solvent systems there is little change in the entropy of activation with the nature of the substituent, despite marked changes in the nature of the transition state. This is likely to be the result of ordering of the solvent shell as the transition state becomes more 'loose'.

The effect on the activation parameters of changing solvent from acetonitrile to the ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$] are best

Table 2 Activation parameters for the Menschutkin reaction of pyridine **2** with the benzyl bromides **1a–g** in acetonitrile

	$\Delta H^{\ddagger}/\text{kJ mol}^{-1}$ [a]	$\Delta S^{\ddagger}/\text{J K}^{-1}\text{ mol}^{-1}$ [a]
1a	40.9 ± 1.2	-220 ± 4
1b	43.2 ± 1.1	-219 ± 4
1c	42.6 ± 1.3	-226 ± 4
1d	43.4 ± 0.8	-224 ± 3
1e	47.7 ± 1.0	-210 ± 3
1f	50.0 ± 2.8	-205 ± 9
1g	44.2 ± 1.0	-225 ± 3

[a] Uncertainties quoted are standard deviations.

Table 3 Activation parameters for the Menschutkin reaction of pyridine **2** with the benzyl bromides **1a–g** in [Bmim][N(CF$_3$SO$_2$)$_2$]

	$\Delta H^{\ddagger}/\text{kJ mol}^{-1}$ [a]	$\Delta S^{\ddagger}/\text{J K}^{-1}\text{ mol}^{-1}$ [a]
1a	47.7 ± 1.1	-188 ± 4
1b	48.8 ± 0.9	-193 ± 3
1c	53.5 ± 2.0	-181 ± 7
1d	49.9 ± 0.8	-195 ± 3
1e	51.5 ± 1.2	-191 ± 4
1f	53.1 ± 2.1	-187 ± 4
1g	48.7 ± 0.7	-207 ± 2

[a] Uncertainties quoted are standard deviations.

Table 4 Changes in the activation parameters for the Menschutkin reaction of pyridine **2** with the benzyl bromides **1a–g** on going from acetonitrile to [Bmim][N(CF$_3$SO$_2$)$_2$] as the solvent

	$\Delta(\Delta H^{\ddagger})/\text{kJ mol}^{-1}$ [a]	$\Delta(\Delta S^{\ddagger})/\text{J K}^{-1}\text{ mol}^{-1}$ [a]
1a	6.9 ± 1.6	32 ± 5
1b	5.6 ± 1.4	26 ± 5
1c	10.9 ± 2.3	45 ± 8
1d	6.6 ± 1.2	29 ± 4
1e	3.9 ± 1.6	19 ± 5
1f	3.2 ± 3.5	17 ± 12
1g	4.5 ± 1.2	18 ± 4

[a] Uncertainties quoted are standard deviations.

Table 5 Activation parameters for the Menschutkin reaction of pyridine **2** with benzyl chloride **4** in either acetonitrile or [Bmim][N(CF$_3$SO$_2$)$_2$]

	$\Delta H^{\ddagger}/\text{kJ mol}^{-1}$	$\Delta S^{\ddagger}/\text{J K}^{-1}\text{ mol}^{-1}$ [a]
Acetonitrile	62.8 ± 2.4	-203 ± 7
[Bmim][N(CF$_3$SO$_2$)$_2$]	62.7 ± 1.9	-190 ± 6
Difference	-0.1 ± 3.0	13 ± 9

[a] Uncertainties quoted are standard deviations.

Table 6 Activation parameters for the Menschutkin reaction of pyridine **2** with benzyl iodide **5** in either acetonitrile or [Bmim][N(CF$_3$SO$_2$)$_2$]

	$\Delta H^{\ddagger}/\text{kJ mol}^{-1}$	$\Delta S^{\ddagger}/\text{J K}^{-1}\text{ mol}^{-1}$ [a]
Acetonitrile	41.7 ± 0.3	-220 ± 1
[Bmim][N(CF$_3$SO$_2$)$_2$]	51.3 ± 0.3	-186 ± 1
Difference	9.6 ± 0.4	34 ± 1

[a] Uncertainties quoted are standard deviations.

was the leaving group used. As such, kinetic analyses, equivalent to those described above, were carried out for benzyl chloride **4** and benzyl iodide **5** and the activation parameters calculated (Tables 5 and 6).

The first thing to note is that there is a trend in the effect of the ionic liquid on the activation parameters. Both the change in enthalpy of activation ($\Delta H^{\ddagger}$) and the change in the entropy of activation ($\Delta S^{\ddagger}$) increase on going from the chloride **4** to the bromide **1d** to the iodide **5**. This is consistent with a decrease in stabilisation of the incipient charges in the transition state, along with less ordering, relative to the starting material, as the size of the halogen increases and the electronegativity decreases. This can be rationalised by decreased ordering in, and stabilisation of, the transition state as the charge density on the incipient anion decreases.

While the trend in these effects is clear, the most critical observation from this data is that the effect of changing the leaving group was small. Irrespective of the halide used, the rate enhancements observed over the range of temperatures considered on changing the solvent to an ionic liquid are primarily as a result of an increase in the entropy of activation.

It is also worth considering whether the effect of the ionic liquid varies with the electronic nature of the aromatic substrate (and hence the nature of the transition state). The fact that the effect of the ionic liquid on the enthalpy of activation does not change with the nature of the substituent on the aromatic ring suggests that the charge development, which is shown in Fig. 1 to be greater at the benzylic position in an ionic liquid, is not stabilised to a greater extent in [Bmim][N(CF$_3$SO$_2$)$_2$]. This may be the result of a congested transition state where interaction of the cationic reaction centre with the anion of the ionic liquid is restricted. Such congestion would account for the fact that the effect of the ionic liquid is the same for all substituents, though in order to explain the increase in the activation enthalpy it requires that the ionic liquid is less able to interact with the incipient charges than acetonitrile. This is considered unlikely given the significant cation–halogen interactions observed for an S$_N$1 process previously,[13] and the relative accessibility of the incipient negative charge on the halogen atom.

seen in Table 4. The most striking point is that these changes are very different from those which have been observed previously for the substitution of an alkyl chloride that occurs through an S$_N$1 mechanism, where a dramatic enthalpic stabilisation was counterbalanced by an entropic cost.[13] In this case there is very little change in the enthalpy of activation, with the effect ranging from zero, within the limits of the experiment, to *ca.* 11 kJ mol^{-1} in the case of the benzyl bromide **1c**. While the values vary slightly, the key point is that enthalpic effect of the ionic liquid is small and unfavourable in the present case. In contrast, the entropy of activation increases on moving to the ionic liquid and, again, this is observed for all substituents. To reiterate, for the Menschutkin reaction of each of the benzyl bromides **1a–g**, the rate enhancement observed on changing from acetonitrile to an ionic liquid is due to an increase in disorder on going to the transition state. It is worthwhile considering the origin of these changes as they differ so significantly from those observed previously for a process that proceeds through an S$_N$1 mechanism.[13]

One of the potential sources of the differences in the activation parameters between this system and that reported previously[13]

A similar argument also holds with respect to the observed entropies of activation. Whilst the congested transition state might limit the extent to which organisation of the ionic liquid changes with different electron-donating groups, it is still not clear as to why the entropy of activation decreases on going to an ionic liquid; simply considering the transition state, this implies there is less ordering in the ionic liquid case than for acetonitrile, which is considered unlikely for the same reasons outlined above.

Until this point, the interaction of the solvents with the starting materials has not been discussed. In the S_N1 process studied previously[12,13] interactions with the starting material were limited. By comparison, the charge separation in the transition state of the S_N1 process is considerable and the interactions with the ionic solvent significant. In this case, as the reaction proceeds through an S_N2 mechanism, the charge development is not as significant in the transition state and hence the interaction with the solvent might be expected to be less than in the S_N1 case. However, this change would only decrease the magnitude of the entropic effect; the activation entropy would still be expected to be negative. As such, an increased interaction of the solvent with the starting materials is implied.

The introduction of aromatic components to the starting material in the work presented here needs to be considered. Aromatic compounds have anomalously high solubilities in ionic liquids[20] and this has been demonstrated, using molecular dynamics simulations for simple systems, to be due to the interaction of the quadrupole of the aromatic compound with the components of the ionic liquid.[21] Importantly, in these simulations, significant ordering of the components of the solution about the aromatic solute was observed.[21,22]

If there is significant organisation of the solvent about the aromatic starting materials it is likely that this will require significant disruption on going to the transition state. This disruption may simply be a result of bringing the two reactants together but there may also be some contribution from a change in the quadrupole of each aromatic system (as a result of some charge development). Experimental efforts to deconvolute this contribution are currently underway.

Conclusions

The ionic liquid [Bmim][N(CF$_3$SO$_2$)$_2$] accelerates the Menschutkin reaction of benzyl halides with pyridine. The origin of this rate enhancement is an increase in the entropy of activation, which offsets a small increase in the enthalpy of activation, in contrast to the effects on substitution processes reported previously. The rate of reaction has been shown to be independent of the nature of both the aromatic substrate and the leaving group, and is proposed to be governed by the organisation of the ionic liquid about the aromatic starting materials.

Acknowledgements

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