

Manipulating Solute Nucleophilicity with Room Temperature Ionic Liquids

Lorna Crowhurst, N. Llewellyn Lancaster, Juan M. Pérez Arlandis, and Tom Welton*

Contribution from the Department of Chemistry, Imperial College London,
South Kensington Campus, London SW7 2AZ, United Kingdom

Received June 2, 2004; E-mail: t.welton@imperial.ac.uk

Abstract: In this work we report the effect of ionic liquids on a class of charge-neutral nucleophiles. We have studied the reactions of ⁿbutylamine, di-ⁿbutylamine, and tri-ⁿbutylamine with methyl *p*-nitrobenzene-sulfonate in [bmpy][N(Tf)₂], [bmpy][OTf], and [bmim][OTf] (bmpy = 1-butyl-1-methylpyrrolidinium; bmim = 1-butyl-3-methylimidazolium) and compared their reactivities, *k*₂, to those for the same reactions in the molecular solvents dichloromethane and acetonitrile. It was shown that all of the amines are more nucleophilic in the ionic liquids than in the molecular solvents studied in this work. Comparison is also made with the effect of ionic liquids on the reactivity of chloride ions, which are deactivated in ionic liquids. The Eyring activation parameters revealed that changes in the activation entropies are largely responsible for the effects seen. This can be explained in part by the differing hydrogen-bonding properties, as shown by the Kamlet–Taft solvent parameters, of each of these solvents and the formation of hydrogen bonds between the solvents and the nucleophiles.

Introduction

Ionic liquids are defined as materials that are composed entirely of cations and anions and that melt at or below 100 °C.¹ They have been used as solvents in a great number of reactions of various classes.² They continue to excite interest for a number of reasons. The first arises from the claim that ionic liquids are environmentally benign solvents, particularly because they have very low vapor pressures under ambient conditions. Second, that they might provide improved reactivities in a number of chemical processes. Third, the fact that a wide range of cations and anions can be employed gives chemists the potential to design the solvent to have specific properties. Hence, the determination of solvent properties of ionic liquids is an important area of research.³

It is the effect that the ionic liquid might have on chemical processes and how such effects can be related to other measurable solvent properties that our recent research effort has addressed. We are attempting to answer a number of ques-

tions: primarily, which reactions can be predicted to be accelerated or decelerated when an ionic liquid is used rather than a molecular solvent, and in which of these cases is the identity of the particular ionic liquid used important.

We have previously reported quantitative kinetic studies of nucleophilic substitutions by halides in a range of ionic liquids, showing the effect of both cation and anion variation.⁴ This body of work shows very clearly that halide nucleophilicity is not enhanced in ionic liquids, as has been claimed elsewhere,⁵ but rather is reduced relative to that observed in molecular solvents. By comparing the kinetic data obtained against empirical solvent polarity measurements,^{3c,6} it became apparent that this could be understood by the application of the classical Hughes–Ingold predictions^{7,8} of solvent polarity on reaction rates combined with an analysis of hydrogen-bonding effects, solvent property studies having revealed that all of the ionic liquids used were “polar” and could be good H-bond donors and/or acceptors (these latter properties were greatly affected

- (1) (a) Zhao, H.; Malhotra, S. V. *Aldrichimica Acta* **2002**, 35, 75 (b) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A* **2002**, 182, 419. (c) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, 74, 157. (d) Sheldon, R. *Chem. Commun.* **2001**, 2399. (e) Gordon, C. M. *Appl. Catal. A* **2001**, 222, 101. (f) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, 39, 3772. (g) Welton, T. *Chem. Rev.* **1999**, 99, 2071.
- (2) *Ionic Liquids in Synthesis*; Welton, T., Wasserscheid, P., Eds.; VCH–Wiley: Weinheim, Germany, 2002.
- (3) For examples see (a) Znamenskiy, V.; Kobrak, M. N. *J. Phys. Chem. B* **2004**, 108, 1072. (b) Huddleston, J. G.; Broker, G. A.; Willauer, H. D.; Rogers, R. D. In *Ionic Liquids: Industrial Applications for Green Chemistry*; ACS Symposium Series 818; American Chemical Society: Washington, DC, 2002. (c) Anderson, J. L.; Ding, J.; Welton, T.; Armstrong, D. W. *J. Am. Chem. Soc.* **2002**, 124, 14247. (d) Dzyuba, S. V.; Bartsch, R. A. *Tetrahedron Lett.* **2002**, 43, 4657. (e) Muldoon, M. J.; Gordon, C. M.; Dunkin, I. R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 433. (f) Aki, S. N. V. K.; Brennecke, J. F.; Samanta, A. *Chem. Commun.* **2001**, 413. (g) Carmichael, A. J.; Seddon, K. R. *J. Phys. Org. Chem.* **2000**, 13, 591. (h) Poole, S. K.; Shetty, P. H.; Poole, C. F. *Anal. Chim. Acta* **1989**, 218, 241.
- (4) (a) Lancaster, N. L.; Welton, T. *J. Org. Chem.* **2004**, 69, 5986. (b) Lancaster, N. L.; Salter, P. A.; Welton, T.; Young, G. B. *J. Org. Chem.* **2002**, 67, 8855. (c) Lancaster, N. L.; Welton, T.; Young, G. B. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2267.
- (5) Examples of works that claim increased halide nucleophilicity in ionic liquids include (a) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* **2002**, 124, 10278–10279. (b) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, 68, 4281–4285.
- (6) (a) Fredlake, C. P.; Muldoon, M. J.; Aki, S. N. V. K.; Welton, T.; Brennecke, J. F. *Phys. Chem. Chem. Phys.* **2004**, 3280. (b) Crowhurst, L.; Mawdsley, P. R.; Perez-Arlandis, J. M.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2003**, 5, 2790.
- (7) (a) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Bell: London, 1969. (b) Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1935**, 244. (c) Hughes, E. D. *Trans. Faraday Soc.* **1941**, 37, 603. (d) Hughes, E. D.; Ingold, C. K. *Trans. Faraday Soc.* **1941**, 37, 657. (e) Cooper, K. A.; Dhar, M. L.; Hughes, E. D.; Ingold, C. K.; MacNulty, B. J.; Woolf, L. I. *J. Chem. Soc.* **1948**, 2043.
- (8) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH (U.K.) Ltd.: Cambridge, U.K., 1998.

by the identities of both the cation and anion). The Hughes–Ingold approach to these S_N2 reactions accurately predicted the effect of using an ionic liquid, while the hydrogen-bonding considerations explained the differences observed between the ionic liquids.

The Hughes–Ingold rules also predict that when two charge-neutral compounds react to form two charged products via a charge-separated activated complex (e.g., an S_N2 mechanism), the effect of increased solvent polarity is to increase the rate of reaction. For this reason, a study of amine nucleophilicity in ionic liquids and molecular solvents was made, with the same substrate as in our previous work. It is this work that we report here.

As stated above, a great number of reactions have been studied in ionic liquids. However, there have been rather few quantitative studies of the effects of ionic liquids on reactions and reaction mechanisms. Chiappe et al. have made kinetic and mechanistic studies of nucleophilic substitutions⁹ as well as investigating electrophilic substitution reactions.¹⁰ Some other reactions^{11,12} have also been studied in depth in ionic liquids, thus allowing quantitative comparison against the same reactions in molecular solvents.

A recent quantitative study by Skrzypczak and Neta¹³ shows very clearly that the rate of reaction of 1,2-dimethylimidazole with benzyl bromide (also an S_N2 reaction) increased dramatically in ionic liquids compared to a range of polar protic and aprotic molecular solvents. That the use of an ionic liquid enhances the nucleophilicity of water has also recently been proposed.¹⁴ Although this account only gave qualitative data, it demonstrated that the yield of the substitution product after unit time is greatest where the solvent is an ionic liquid. Both of these results are in accordance with Hughes–Ingold predictions.

Results and Discussion

Initial Studies in Ionic Liquid. Some concern has been expressed about the reactivity of the 1-butyl-3-methylimidazolium cation, [bmim]⁺, with strong bases.¹⁵ Initial studies of amine nucleophilicity in [bmim][PF₆] suggested that the amines were sufficiently basic to remove a proton from the cationic ring. However, our data clearly indicated that the problem was not general for all [bmim]⁺ ionic liquids but, within the set that we used, specific to [bmim][PF₆]. Nonetheless, the ionic liquids used in this study were mainly based on the [bmpy] cation ([bmpy]⁺ = 1-butyl-1-methylpyrrolidinium), whose saturated alkyl groups certainly cannot be deprotonated by the amines. The reaction studied was that of methyl *p*-nitrobenzenesulfonate with a series of amines, as illustrated in Scheme 1.

The substrate has a λ_{\max} at 253 nm while the *p*-nitrobenzenesulfonate ion product has a λ_{\max} at 275 nm. The progress

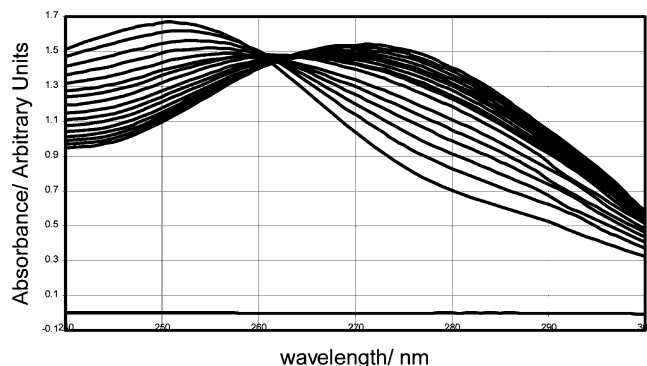
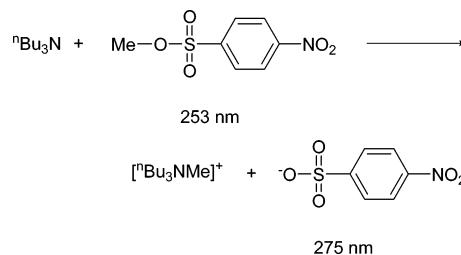
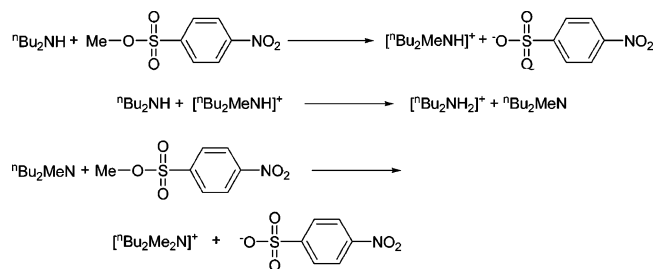


Figure 1. Reaction of tri-*n*-butylamine (4.20×10^{-6} mol) with methyl *p*-nitrobenzenesulfonate.

Scheme 1. Reaction of Tri-*n*-butylamine with Methyl *p*-Nitrobenzenesulfonate



Scheme 2. Potential Dialkylation of Di-*n*-butylamine with Methyl *p*-Nitrobenzenesulfonate



of each reaction was monitored in situ by UV/vis spectroscopy, with an excess of the amine. In each reaction it was possible to record absorbance values at 253 and 275 nm; an isosbestic point was always observed. The reactions in the ionic liquids were studied by adding the amine by microliter syringe to a known mass of the ionic liquid and adding to this an aliquot of the substrate in a small volume of dichloromethane. It was assumed that, as in the study of halide nucleophilicity,⁴ this small amount of dichloromethane would not have a significant effect on the reaction. UV/vis spectra were recorded periodically over the course of the reaction and were combined as in Figure 1.

The data were treated as described elsewhere^{4c} with a least-squares fitting procedure to determine the *pseudo*-first-order rate constant k_{obs} values. A plot of k_{obs} against initial nucleophile concentration allowed calculation of the second-order rate constant for the reaction.

Another potential concern is the possible overalkylation of the primary or secondary amines (for example, Scheme 2). However, no evidence was seen for this process in the reactions studied, be it in the mass spectra of the postreaction mixtures or indeed as a deviation of the kinetics from the model described above. This is likely to be the consequence of the large excess of the amines used rather than any effect of the ionic liquids.

- (9) Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* **2003**, *68*, 6710.
 (10) (a) Chiappe, C.; Conte, V.; Pieraccini, D. *Eur. J. Org. Chem.* **2002**, 2831.
 (b) Chiappe, C.; Capraro, D.; Conte, V.; Pieraccini, D. *Org. Lett.* **2001**, *3*, 1061.
 (11) (a) Owens, G. S.; Abu Omar, M. M. *J. Mol. Catal. A* **2002**, *187*, 215. (b) Aggarwal, A.; Lancaster, N. L.; Sethi, A. R.; Welton, T. *Green Chem.* **2002**, *4*, 517.
 (12) (a) Swiderski, K.; McLean, A.; Gordon, C. M.; Vaughan, D. H. *Chem. Commun.* **2004**, 590. (b) McLean, A. J.; Muldoon, M. J.; Gordon, C. M.; Dunkin, I. R. *Chem. Commun.* **2002**, 1880. (c) Grodkowski, J.; Neta, P.; Wishart, J. F. *J. Phys. Chem. A* **2003**, *107*, 9794 and references therein. (d) Skrzypczak, A.; Neta, P. *J. Phys. Chem. A* **2003**, *107*, 7800.
 (13) Skrzypczak, A.; Neta, P. *Int. J. Chem. Kinet.* **2004**, *36*, 253–258.
 (14) Kim, D. W.; Hong, D. J.; Seo, J. W.; Kim, H. S.; Kim, H. K.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2004**, *69*, 3186.
 (15) Aggarwal, V. K.; Emme, I.; Mereu, A. *Chem. Commun.* **2002**, 1612.

Table 1. Kamlet–Taft Properties of Some Solvents and the Relative Nucleophilicities of ⁿButylamines within Them at 25 °C^a

solvent	$k_2, \text{M}^{-1} \text{s}^{-1}$				Kamlet–Taft parameters ^b		
	ⁿ BuNH ₂	ⁿ Bu ₂ NH	ⁿ Bu ₃ N	Cl ⁻	π^*	a	b
[bmpy][N(Tf) ₂]	0.358 (0.007)	0.493 (0.002)	0.103 (0.015)	0.0391 ^{4b} (0.0026)	0.954	0.427	0.252
[bmpy][OTf]	0.922 (0.005)	1.04 (0.03)	0.523 (0.031)		1.017 ^b	0.396 ^b	0.461 ^b
[bmim][OTf]	0.500 (0.016)	0.541 (0.005)	0.0529 (0.0022)	0.0197 ^{4b} (0.0023)	1.006 ^b	0.625 ^b	0.489 ^b
CH ₃ CN	0.155 (0.003)	0.182 (0.001)	0.0257 (0.0002)		0.799	0.350	0.370
H ₂ O ¹⁶	0.0547	0.0665 ^c	0.0205 ^d		1.33	1.12	0.14
CH ₂ Cl ₂	0.0165 (0.0001)	0.0454 (0.0002)	0.0200 (0.0005)	1.07 ^{e,17} 0.12 ^{f,17}	0.791	0.042	-0.014

^a Standard deviations in parentheses. ^b This work. ^c Amine was ⁿPr₂NH. ^d Amine was Et₃N. ^e Free ion; [Bu₄N]Cl at 22 °C. ^f Ion pair; [Bu₄N]Cl at 22 °C.

The data for the reactions of the three ⁿbutylamines with methyl *p*-nitrobenzenesulfonate in a variety of ionic liquids, acetonitrile, and dichloromethane are available as Supporting Information. In [bmpy][N(Tf)₂], the data show that the order of amine nucleophilicity for the series of ⁿbutylamines is as found in polar molecular solvents. That is, the order of nucleophilicity decreases in the order 2° > 1° > 3° amine. All of the values of k_2 calculated are of the same order of magnitude. It should be noted that tri-ⁿbutylamine was only sparingly soluble in the ionic liquid, giving a larger uncertainty in the value of k_2 calculated.

The reactions of the ⁿbutylamines with methyl *p*-nitrobenzenesulfonate were also studied in [bmpy][OTf]. The order of amine nucleophilicity in [bmpy][OTf] was identical to that in [bmpy][N(Tf)₂] and polar molecular solvents, but the relative nucleophilicities were different. The 1° and 2° amines displayed similar nucleophilicities (with k_2 of 0.922 and 1.04 M⁻¹ s⁻¹, respectively), and di-ⁿbutylamine was only twice as nucleophilic as tri-ⁿbutylamine (compared to almost 5× in [bmpy][N(Tf)₂]). Again it is noted that the tri-ⁿbutylamine was not very soluble in the ionic liquid.

The reactions of the ⁿbutylamines with methyl *p*-nitrobenzenesulfonate were also studied in [bmim][OTf], allowing comparison against the reactions in [bmpy][N(Tf)₂] and [bmpy][OTf]. It is noted that the ⁿbutylamines show the same order of nucleophilicity as in the [bmpy]⁺ ionic liquids and polar molecular solvents, with ⁿBu₂NH being the most nucleophilic and ⁿBu₃N the least. Again the nucleophilicities of the 1° and 2° amine are very similar, with k_2 values of 0.500 and 0.541 M⁻¹ s⁻¹, respectively, but here the tri-ⁿbutylamine was found to be an order of magnitude less nucleophilic.

Finally, the reaction of the amines with methyl *p*-nitrobenzenesulfonate was studied in acetonitrile and in dichloromethane at 25 °C. In acetonitrile the order of ⁿbutylamine nucleophilicity is 2° > 1° > 3°, as expected in a polar solvent. In fact the 1° and 2° ⁿbutylamines are similarly nucleophilic in this solvent and approximately 5× more nucleophilic than tri-ⁿbutylamine. In dichloromethane the order of amine nucleophilicity was ⁿBu₂NH > ⁿBu₃N > ⁿBuNH₂. It is noted that the 1° and 3° ⁿbutylamines were of similar nucleophilicity, and all three displayed k_2 values of the same order of magnitude.

The values of k_2 , determined as described above, have been collected into Table 1 and compared to the k_2 values for the reaction of Cl⁻ with the same substrate, where available. Additionally the Kamlet–Taft parameter values are included. A study of the reaction of methyl *p*-nitrobenzenesulfonate with

amines in aqueous solution¹⁶ has also been made, and these data are also shown. It is noted that the reactions of all of the ⁿbutylamines are faster in the ionic liquids than those of Cl⁻ in the same ionic liquid, whereas the reverse is true in dichloromethane.

When the reactions in the [bmpy]⁺ ionic liquids are compared, it is clear that all of the reactions are faster in [bmpy][OTf]. It is also clear that the nucleophilicity of the tri-ⁿbutylamine shows the most relative enhancement. The rates of the reactions of the 1° and 2° amines in acetonitrile are comparable to (though slower than) those observed in the ionic liquids. However, the reaction of the 3° amine is much slower in acetonitrile than in the ionic liquids. All of the reactions in water and in dichloromethane are an order of magnitude slower.

The reactions in [bmim][OTf] show a slightly different result than those obtained in the [bmpy]⁺ ionic liquids. While the order of nucleophilicity is the same and the values of k_2 for ⁿBuNH₂ and ⁿBu₂NH are similar to those obtained in the [bmpy]⁺ ionic liquids, ⁿBu₃N behaves very differently, giving a k_2 value that is lower by an order of magnitude. This result shows that ⁿBu₃N is only slightly more nucleophilic in [bmim][OTf] than in the molecular solvents employed in this work.

Effects of Solvent Properties on Reaction Rates. The Hughes–Ingold rules, which describe the effect of solvents on reaction rates, are essentially qualitative and rely on a rather vague, generalized idea of solvent polarity. For molecular solvents, polarities are commonly expressed in terms of their dielectric constants, implying an electrostatic model of solvation. However, because these values do not always correlate to observed experimental data, a range of empirical measures of solvent polarity have been devised. These include parameters to describe H-bond acidity (α), H-bond basicity (β), and dipolarity/polarizability effects (π^*) as developed by Kamlet and Taft.¹⁸ We have used these and other parameters in studies of the interaction of solutes with ionic liquid solvents.^{3c,6}

It can be seen that when ⁿBu₃N is considered in the solvents dichloromethane, acetonitrile, and [bmpy][N(Tf)₂], k_2 increases with increasing π^* ; that is, the reaction rate is very similar in dichloromethane and acetonitrile and considerably faster in the

(16) Bunting, J. W.; Mason, J. M.; Heo, C. K. *M. J. Chem. Soc., Perkin Trans. 2* **1994**, 2291.

(17) Alluni, S.; Pero, A.; Reichenbach, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1747.

(18) (a) Kamlet, M. J.; Addoud, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 6027. (b) Yokoyama, T.; Taft, R. W.; Kamlet, M. J. *J. Am. Chem. Soc.* **1976**, *98*, 3233. (c) Taft, R. W.; Kamlet, M. J. *J. Am. Chem. Soc.* **1976**, *98*, 2886. (d) Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 377.

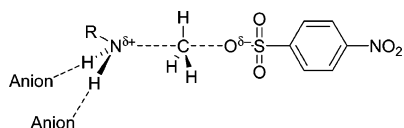


Figure 2. Ionic liquid anion hydrogen-bonding with the emerging ammonium ion in the activated complex for reaction of ${}^n\text{BuNH}_2$ with methyl *p*-nitrobenzenesulfonate.

ionic liquid. This is entirely consistent with the Hughes–Ingold approach, with the caveat that π^* best represents their generalized notion of polarity. Water does not fit this trend and will be discussed separately. We have shown⁶ that all of the ionic liquids that we have studied have high π^* values, with little variation between them. Therefore, one would predict that using an ionic liquid should always lead to an increased rate for this and similar reactions.

As with the halides, this crude Hughes–Ingold approach describes well the effect of using an ionic liquid, as opposed to a molecular solvent, but gives no insight into how changing the ions of the ionic liquid can exert an influence. Also, the rather more dramatic increases in the rates of the reactions of ${}^n\text{Bu}_2\text{NH}$ ($\times 10.9$) and ${}^n\text{BuNH}_2$ ($\times 21.7$) as the solvent is changed from dichloromethane to the ionic liquids require further explanation. Water, acetonitrile, and the ionic liquids can act as hydrogen-bond acceptors, with the $[\text{OTf}]^-$ ionic liquids being the strongest (high β), whereas dichloromethane cannot. Analysis of the activated complexes for the reactions of ${}^n\text{Bu}_2\text{NH}$ and ${}^n\text{BuNH}_2$ shows that as the amine attacks the carbon of the substrate, the amine begins to develop positive charge. This will lead any protons bound to the nitrogen to become stronger hydrogen-bond donors.¹⁹ Therefore a hydrogen-bond-accepting solvent will preferentially stabilize the activated complex with respect to the reagents and increase the rate of the reaction, by interacting with these protons (Figure 2). This effect is greater when more protons are bound to the nitrogen, as can be seen in the relative increases in k_2 for ${}^n\text{BuNH}_2$ and ${}^n\text{Bu}_2\text{NH}$.

While this model holds well for the 1° and 2° amines, it completely fails to explain the dramatic increase in k_2 for the reaction of tri-*n*-butylamine as it is transferred from $[\text{bmpy}][\text{N}(\text{Tf})_2\text{N}]$ to $[\text{bmpy}][\text{OTf}]$. We will return to this in the discussion of the Eyring activation parameters for the reactions.

The hydrogen-bond donor properties of the solvents (α) can also be seen to have an important impact on the reactions. As the hydrogen-bond donor ability of the ionic liquids is increased, the nucleophilicity of the amines is noticeably reduced, particularly for ${}^n\text{Bu}_3\text{N}$. It is this effect that leads to the seemingly anomalous behavior of water as a solvent for these reactions. Since water has the highest π^* value of all of the solvents investigated and can act as a hydrogen-bond acceptor, one would expect that it would greatly accelerate the reactions studied, but it does not. Water is a strong hydrogen-bond donor (high α), whereas $[\text{bmim}][\text{OTf}]$ is a moderate hydrogen-bond donor, acetonitrile and $[\text{bmpy}][\text{N}(\text{Tf})_2]$ are only weak hydrogen-bond donors, and dichloromethane does not hydrogen-bond-donate at all. Although a hydrogen-bond donor can interact with the emerging *p*-nitrobenzenesulfonate anion, it will also hydrogen-bond directly to the lone pair of the nitrogen, which is, of course, the nucleophilic site. The deactivation of the nucleophile and

the activation of the leaving group are always in competition and the outcome of the reaction depends on the chemical nature of the reactants.²⁰ Clearly, in these reactions the deactivation of the amines is dominant and hydrogen-bond-donor solvents should be avoided.

The data for the reactions of chloride with the same substrate in each solvent are provided where available. These confirm that, in the ionic liquids, the increase in the reactivity of the neutral nucleophiles and the decrease in the reactivity of charged ones is pronounced enough to lead to an inversion of reactivity between dichloromethane and the ionic liquids.

Eyring Activation Parameters. To understand the unexpectedly high k_2 for the reaction of ${}^n\text{Bu}_3\text{N}$ in $[\text{bmpy}][\text{OTf}]$, we needed to gain further information on the reactions in the ionic liquid and the molecular solvents. Therefore, the effect of temperature on reaction rate was also studied in order to determine the activation parameters, with $[\text{bmpy}][\text{N}(\text{Tf})_2]$, $[\text{bmpy}][\text{OTf}]$, $[\text{bmim}][\text{OTf}]$, acetonitrile, and dichloromethane as solvents. The full set of data for the reactions in $[\text{bmpy}][\text{N}(\text{Tf})_2]$ are available in the Supporting Information. As in our previous work, given that there was a linear dependence of k_{obs} on $[\text{amine}]_0$ at 25 °C, with negligible intercept, the values of k_2 were determined from one value of $[\text{amine}]_0$ only at each temperature. From these data, the activation enthalpy and entropy of each reaction was calculated by use of the Eyring equation. These values, along with the corresponding ΔG^\ddagger values (at 298 K), have also been tabulated.

In the same way, the reactions of the *n*-butylamines in $[\text{bmpy}][\text{OTf}]$ and in $[\text{bmim}][\text{OTf}]$ were studied at varied temperatures. To gain a direct comparison, the effect of temperature on the reactions in dichloromethane and in acetonitrile were studied and analyzed in exactly the same way as in the ionic liquid. Again these results are given in the Supporting Information.

The activation parameters for the reaction of each of the amines with methyl *p*-nitrobenzenesulfonate in each solvent are summarized in Table 2.

In $[\text{bmpy}][\text{N}(\text{Tf})_2]$, ΔH^\ddagger for the reaction of the amines with methyl *p*-nitrobenzenesulfonate was in the range 34–43 kJ mol⁻¹ and ΔS^\ddagger was in the range -111 to -141 J K⁻¹ mol⁻¹. This compares to the values for the reaction of $[\text{bmpy}]\text{Cl}$ with the same substrate in the same solvent (ΔH^\ddagger 68.5 kJ mol⁻¹ and ΔS^\ddagger -43.9 J K⁻¹ mol⁻¹). That the enthalpic barrier to reaction in ionic liquids is lower for neutral than for charged nucleophiles is again entirely consistent with a Hughes–Ingold interpretation. However, the entropic barrier to reaction for these amines is considerably higher than for the halides.

The values of ΔH^\ddagger in $[\text{bmpy}][\text{OTf}]$ are similar for the 1° and 2° amines (38.5 and 37.2 kJ mol⁻¹, respectively) and close to the values seen for the reactions of the amines in $[\text{bmpy}][\text{N}(\text{Tf})_2]$. However, ΔH^\ddagger for tri-*n*-butylamine is much higher than for the 1° and 2° amines in $[\text{bmpy}][\text{OTf}]$ and for tri-*n*-butylamine in $[\text{bmpy}][\text{N}(\text{Tf})_2]$. In the same way, the activation entropies for the 1° and 2° amines in $[\text{bmpy}][\text{OTf}]$ are similar to those observed in the $[\text{N}(\text{Tf})_2]^-$ ionic liquid, while the entropic barrier for the reaction of the tri-*n*-butylamine is unusually low (-51.5 J K⁻¹ mol⁻¹).

The reactions of *n*-butylamines were studied in $[\text{bmim}][\text{OTf}]$. Although the value of ΔH^\ddagger for ${}^n\text{Bu}_3\text{N}$ in this ionic liquid (50.4

(19) van Mourik, T.; van Duijneveldt, F. B. *J. Mol. Struct. (THEOCHEM)* **1995**, *341*, 63.

(20) Auriel, M.; de Hoffmann, E. *J. Chem. Soc., Perkin Trans. 2* **1979**, 325.

Table 2. Summary of Activation Parameters for the Reaction of Methyl *p*-Nitrobenzenesulfonate with ⁿButylamines

solvent	nucleophile	ΔH^\ddagger , kJ mol ⁻¹	ΔS^\ddagger , J K ⁻¹ mol ⁻¹	$T\Delta S^\ddagger_{298K}$, kJ mol ⁻¹	ΔG^\ddagger_{298K} , kJ mol ⁻¹
[bmpy][N(Tf) ₂]	ⁿ BuNH ₂	38.6 (0.8)	-120 (3)	-35.8 (0.9)	74.4 (1.7)
	ⁿ Bu ₂ NH	42.5 (4.4)	-111 (15)	-33.1 (4.5)	75.6 (8.9)
	ⁿ Bu ₃ N	34.3 (7.4)	-141 (25)	-42.0 (7.5)	76.3 (14.9)
	Cl ⁻ ^{4b}	68.5 (1.8)	-43.9 (6.0)	-13.1 (1.8)	81.6 (3.6)
[bmpy][OTf]	ⁿ BuNH ₂	38.5 (2.3)	-116 (8)	-34.6 (2.4)	73.1 (6.5)
	ⁿ Bu ₂ NH	37.2 (2.5)	-120 (9)	-35.8 (2.7)	72.9 (6.8)
	ⁿ Bu ₃ N	59.4 (2.0)	-51.5 (6.7)	-15.4 (2.0)	74.8 (3.8)
[bmim][OTf]	ⁿ BuNH ₂	41.2 (1.4)	-113 (5)	-33.7 (1.5)	74.8 (5.5)
	ⁿ Bu ₂ NH	43.4 (0.6)	-105 (2)	-31.3 (0.6)	74.6 (4.4)
	ⁿ Bu ₃ N	50.4 (4.3)	-100 (14)	-29.8 (4.2)	80.2 (7.8)
	Cl ⁻ ^{4a}	71.8 (6.9)	-33.8 (6.9)	-10.1 (2.1)	81.9 (9.0)
CH ₃ CN	ⁿ BuNH ₂	40.0 (2.2)	-126 (8)	-37.6 (2.4)	77.6 (4.6)
	ⁿ Bu ₂ NH	37.5 (2.4)	-133 (8)	-39.6 (2.4)	77.1 (4.8)
	ⁿ Bu ₃ N	35.7 (0.8)	-155 (4)	-46.2 (1.2)	81.9 (2.0)
CH ₂ Cl ₂	ⁿ BuNH ₂	35.0 (6.8)	-162 (23)	-48.3 (6.9)	83.3 (13.7)
	ⁿ Bu ₂ NH	32.6 (3.1)	-161 (11)	-48.0 (3.3)	80.6 (6.4)
	ⁿ Bu ₃ N	34.5 (2.2)	-161 (8)	-48.0 (2.4)	82.5 (4.6)

kJ mol⁻¹) remains higher than for the 1° and 2° amines, ΔS^\ddagger (-100 J K⁻¹ mol⁻¹) is similar to the values for the 1° and 2° amines.

The values of ΔH^\ddagger for the reactions of the amines with methyl *p*-nitrobenzenesulfonate in dichloromethane were in the range 32.6–35.0 kJ mol⁻¹, while ΔS^\ddagger was ca. -161 J K⁻¹ mol⁻¹. These values can be compared to those obtained for the reaction of Cl⁻, both as free ion ($\Delta H^\ddagger = 54.4$ kJ mol⁻¹, $\Delta S^\ddagger = -58.6$ J K⁻¹ mol⁻¹) and as ion pair ($\Delta H^\ddagger = 79.5$ kJ mol⁻¹, $\Delta S^\ddagger = 7.9$ J K⁻¹ mol⁻¹), where the counterion was [Bu₄N]⁺. Just as in [bmpy][N(Tf)₂], the enthalpic barrier is lower and the entropic barrier is higher for the reactions of the neutral nucleophiles than the charged nucleophiles in this solvent.

In acetonitrile, the values of ΔH^\ddagger for the reactions of the amines with methyl *p*-nitrobenzenesulfonate were in the range 35.7–40.0 kJ mol⁻¹ for all of the amines. However, the values of ΔS^\ddagger were similar for the 1° and 2° amines (-126 and -135 J K⁻¹ mol⁻¹) while the value for the 3° amine is -155 J K⁻¹ mol⁻¹. It is clear that the activation enthalpy for each amine is not much affected by this solvent but the activation entropy is. This has an impact on the activation free energy and hence on k_2 .

Examination of ΔG^\ddagger_{298K} shows that the total activation energy barriers to these reactions are lower in the ionic liquids than the reactions of the same amine in the molecular solvents (as predicted by the relative k_2 values). It is necessary to examine why this is so.

The data show that the activation enthalpies for the reactions of the 1° and 2° amines are not very sensitive to the solvent used, within the range studied. However, in all cases ΔH^\ddagger for the amines is greater in the ionic liquids than in dichloromethane. The values of ΔH^\ddagger for Bu₃N show considerably greater variation { $\Delta H^\ddagger = 34.3$ kJ mol⁻¹ in [bmpy][N(Tf)₂], 59.4 kJ mol⁻¹ in [bmpy][OTf]} and are generally higher in the ionic liquids than in dichloromethane. Clearly the reason for the reaction being so favorable does not lie in the activation enthalpy.

The largest differences come in the values of ΔS^\ddagger , which need to be explained.

As associative processes, S_N2 reactions have large negative activation entropies. This loss can be compensated for, to a greater or lesser extent, by the reorganization of the solvent around the reacting species. Although a polar solvent with respect to π^* , dichloromethane is neither a hydrogen-bond

acceptor nor donor and has no scope for specific interactions with any of the amines. Hence ΔS^\ddagger is large and invariant for all three of the amines.

Polarity studies showed that the ionic liquid is capable of acting both as a H-bond donor (property of the cation) and/or as a H-bond acceptor (property of anion), as can the 1° and 2° amines; Bu₃N can only act as a hydrogen-bond acceptor. Hence, a number of potential interactions must be considered: anion-amine (for 1° and 2° amines), cation-amine (for all amines), and cation-anion. Additionally, the possibility of activated complex-anion (for 1° and 2° amines) must be considered. No activated complex-cation or methyl *p*-nitrobenzenesulfonate-ion interactions are expected to be significant in the activation process.

The measurement of the Kamlet-Taft parameters uses the aniline dyes 4-nitroaniline and *N,N*-diethyl-4-nitroaniline and clearly demonstrates that the amine functionality of the 4-nitroaniline strongly hydrogen-bonds to the anion of the ionic liquids. Little other data has been published on the interactions of amines with ionic liquids. However, analogies can be drawn with the water, alcohols, and ethers. Water has been demonstrated to form strong interactions with the anions of a wide range of ionic liquids.²¹ Theoretical estimations²² of the strengths of interactions of water, methanol, and dimethyl ether with a 1,3-dimethylimidazolium chloride ionic liquid have been made. While these cannot be used quantitatively, qualitative interpretations should be possible. It is particularly interesting to note that an inverse relationship was found between the strength of the interaction with the anion and that of the interaction with the cation, this behavior being driven by the OH-anion hydrogen bond. This leads to an expectation that BuNH₂ and Bu₂NH will preferentially associate with a hydrogen-bond-accepting anion and will have a much weaker association with the cation. Since the amines' protons are developing positive charge during the activation process, this interaction is strengthened and leads to an increase in the negative activation entropy.

It is clear from the ΔS^\ddagger values for the reactions of the 1° and 2° amines that as the ionic liquid cation-anion attraction increases, the activation entropy for the reaction becomes less

(21) Cammarata, L.; Kazarian, S. G.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2001**, *3*, 5192.

(22) Hanke, C. G.; Atamas, N. A.; Lynden-Bell, R. M. *Green Chem.* **2002**, *4*, 107.

negative. This suggests that the loss in entropy as the starting materials come together is being partly compensated by a concomitant disruption of the ionic liquid structure, with the effect increasing in importance as the ions are more associated in the first place. That is, the formation of a charge-separated activated complex from neutral starting materials, despite the introduction of the possibility of interaction through Coulombic forces, leads to a disruption of the ionic liquid structure. This is, at first sight, counterintuitive.

The data for ${}^n\text{Bu}_3\text{N}$ suggests a more complex and changing situation. In $[\text{bmpy}][\text{N}(\text{Tf})_2]$ ΔH^\ddagger is similar, but slightly lower, and ΔS^\ddagger is higher than for the 1° and 2° amines. Also, ΔH^\ddagger is, within error, the same as that in CH_2Cl_2 , while ΔS^\ddagger is only slightly less negative. This suggests that the starting materials are well dispersed throughout the ionic liquid and that there are few changes in ionic liquid–solute or cation–anion interactions during the activation process. In $[\text{bmim}][\text{OTf}]$, however, ΔS^\ddagger for ${}^n\text{Bu}_3\text{N}$ is the lowest of the amines and ΔH^\ddagger is the highest. Here the principal interaction between ${}^n\text{Bu}_3\text{N}$ and the ionic liquid is a hydrogen bond to the cation. Unlike the NH---anion hydrogen bond, which strengthens during the activation process, this interaction must be broken for the ${}^n\text{Bu}_3\text{N}$ to act as a nucleophile. This provides a dissociative contribution to the process, so reducing ΔS^\ddagger and increasing ΔH^\ddagger . This is, indeed, what we observe.

The reaction of ${}^n\text{Bu}_3\text{N}$ in $[\text{bmpy}][\text{OTf}]$ provides unexpected results. One would predict that this reaction should be somewhere intermediate between the reactions in $[\text{bmpy}][\text{N}(\text{Tf})_2]$ and $[\text{bmim}][\text{OTf}]$. However, this is definitely not the case. The rate of this reaction is much greater than expected. The most striking of the data is the exceptionally low value of ΔS^\ddagger ($-51.5 \text{ J K}^{-1} \text{ mol}^{-1}$). ${}^n\text{Bu}_3\text{N}$ is not capable of hydrogen-bonding to the ionic liquid anion. $[\text{bmpy}]^+$ is only a weak hydrogen-bond donor and, unlike $[\text{bmim}]^+$, does not hydrogen-bond to the ${}^n\text{Bu}_3\text{N}$. In the absence of these interactions, the Coulombic attraction of the ionic liquid ions dominates the system and their association is not disrupted by the neutral starting materials. There are now three possibilities that need to be considered:

(1) The neutral starting materials interact sufficiently to form a loosely associated complex before the reaction occurs, therefore making the activation process less negative. However, this would be expected to also show in the activation enthalpy of the reaction.

(2) The inability of the starting materials to disrupt the Coulombic attraction of the ions leaves them with a restricted volume in which to move, so reducing ΔS^\ddagger , a solvophobic effect.

(3) Since the activated complex is a species containing both δ^+ and δ^- moieties, it is capable of interacting with the ionic liquid ions. In so doing, it disrupts the interionic interactions and causes the local structure of the ionic liquid to break down. This leads to an increase in entropy and a less negative ΔS^\ddagger . It also accounts for the increase in ΔH^\ddagger .

Given the high dilutions used in this work, the most likely explanation is a combination of 2 and 3 above.

We can now test this model against other data in the literature. Neta's study¹³ showed that the rate of the reaction of 1,2-dimethylimidazole with benzyl bromide increased in ionic liquids compared to a range of polar protic and aprotic molecular solvents. This is entirely in accord with our results. As a tertiary

amine, 1,2-dimethylimidazole would be expected to behave in the ionic liquids in a manner similar to ${}^n\text{Bu}_3\text{N}$. Although they did not measure activation parameters nor could they compare to the Kamlet–Taft solvent parameters for ionic liquids, we can compare our k_2 data with theirs. On changing solvent from acetonitrile to $[\text{bmpy}][\text{N}(\text{Tf})_2]$ they found an approximate doubling in k_2 (1.2×10^{-3} and $2.3 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$, respectively). This is slightly less than, but of the same order of magnitude as, the increase in k_2 that we see in our reaction. The second-order rate constant k_2 for the reaction in $[\text{bmim}][\text{N}(\text{Tf})_2]$ is much lower than in $[\text{bmpy}][\text{N}(\text{Tf})_2]$ and only slightly greater than in acetonitrile. This is in complete accord with our results. Although they did not use a triflate ionic liquid, they have a number of examples where they have used ionic liquids with the $[\text{N}(\text{Tf})_2]^-$ and $[\text{BF}_4]^-$ anions with common cations. While not quite as strong a hydrogen-bond acceptor as $[\text{OTf}]^-$, tetrafluoroborate is considerably more basic than $[\text{N}(\text{Tf})_2]^-$. In all cases the reaction is faster in the $[\text{BF}_4]^-$ ionic liquid than in its $[\text{N}(\text{Tf})_2]^-$ counterpart. Again, this is in complete agreement with our results and with our model of the changing ionic liquid–solute interactions during the reaction process. Hence, although their analysis of the effect of the solvent properties of the set of molecular solvents that they used leads them to conclude that the rate of the reaction was only dependent upon α and π^* , in the ionic liquids β is clearly playing an important role in the ionic liquids.

Recently Chi has reported nucleophilic substitutions by water and alcohols in ionic liquids.¹⁴ It is not possible to interpret their data (yields at different times) quantitatively, and the reactions are very slow. However, these reactions were favored in the ionic liquids compared to molecular solvents.

Conclusion

The rates of reactions where the starting materials are charge-neutral and the formation of the activated complex involves the development of charges will be accelerated by the use of an ionic liquid solvent. This is an extension of the Hughes–Ingold rule (devised for molecular solvents) to ionic liquids, showing them to be highly polar solvents. Where the formation of hydrogen bonds between a nucleophile and the anion of an ionic liquid is possible, the reaction will be further accelerated. This can be manipulated by increasing the hydrogen-bond acceptor ability of the anion (care will be required to ensure that the anion does not become sufficiently nucleophilic that it competes in the reaction). The formation of hydrogen bonds between the nucleophile and the cation will reduce its reactivity and should be avoided. When there is no opportunity for the nucleophile to hydrogen-bond to either the anion or cation of the ionic liquid, other effects such as the self-association of the ionic liquid may become important.

Experimental Section

General. All amines were distilled from KOH before use. Dichloromethane and acetonitrile were distilled from standard drying agents. All preparations and reactions were performed with standard Schlenk techniques under a nitrogen atmosphere. The preparations of the ionic liquids and their precursors have been previously described²¹ and are reproduced in the electronic Supporting Information. NMR spectra were recorded on a JEOL GSX-270 or a Bruker AM-500 spectrometer.

Kinetic Studies. The reactions were studied by adding methyl *p*-nitrobenzenesulfonate in dichloromethane ($4.7 \times 10^{-7} \text{ mol}$ in

0.1 cm³) to a solution of amine in a known mass of ionic liquid (ca. 1.5 cm³) in a UV quartz cuvette (0.5 cm path length) at known time. All reactions were studied for at least 6 half-lives.

The reactions in molecular solvents were performed by following a similar procedure, but the substrate was introduced in the same solvent as was being studied.

Acknowledgment. We thank the Leverhulme Trust for the provision of a fellowship (N.L.L.) and Kodak and the EPSRC

and GSK for the provision of studentships (J.M.P.A. and L.C., respectively).

Supporting Information Available: Synthetic details and characterization data for the ionic liquids and their precursors (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA046757Y