# Charge Screening in the S_N2 Reaction of Charged Electrophiles and Charged Nucleophiles: An Ionic Liquid Effect

Jason P. Hallett,[†] Charles L. Liotta,[‡] Giuseppe Ranieri,[†] and Tom Welton*,[†]

Department of Chemistry, Imperial College London, South Kensington Campus, London, SW7 2AZ, United Kingdom, and School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia 30332-0400

t.welton@imperial.ac.uk

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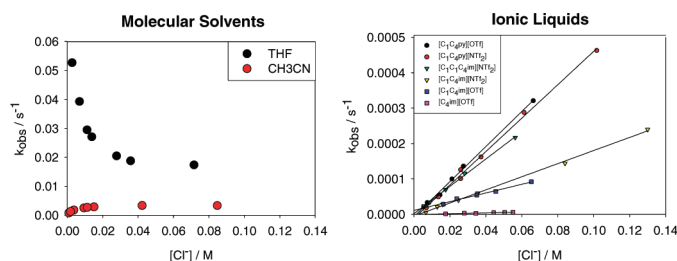
The application of liquids that are salts at room temperature to chemical synthesis has become a hugely exciting field of study. The greatest promise that these ionic liquids hold is that they might offer process advantages, even novel behaviors that cannot be achieved in molecular solvents. We report here that the S_N2 reaction of the trifluoromethanesulfonate and bis(trifluoromethanesulfonyl)imide salts of dimethyl-4-nitrophenylsulfonium ([p-NO$_2$PhS(CH$_3$)$_2$]$^+$[X]$^-$; [X]$^-$ = [CF$_3$SO$_3$]$^-$, [N(CF$_3$SO$_2$)$_2$]$^-$) with chloride ion follow a fundamentally different pathway to when the same salts react in molecular solvents.

Introduction

Since the introduction of air and water stable salts that are liquid at room temperature in 1992,[1] there has been an explosion of interest in the application of these as solvents for chemicals synthesis and processing.[2] In the intervening years at least 8 chemicals processing applications have been brought into use in the chemicals industry.[3] Much of this interest has been centered on their possible use as greener alternatives to conventional molecular solvents, although this remains highly controvesial. Perhaps the greatest potential of these ionic liquids is that they might offer process advantages over molecular solvents or even novel behaviors that cannot be achieved in molecular solvents.

A phenomenon observed in an ionic liquid that arises *because the liquid is composed of ions* and is observed in all ionic liquids (or at least the great majority) and not observed in any molecular liquid could justifiably be called an "ionic liquid effect". In spite of efforts to detect such a phenomenon, detailed quantitative investigations on the effects of ionic liquids on reactions of solutes have repeatedly demonstrated that the results can be correlated with, and hence rationalized in terms of, polarity behaviors originally derived to describe molecular solvents.[4,5] In particular, we have previously reported quantitative kinetic studies of nucleophilic substitutions by halides in reactions with neutral nucleophiles in a range of ionic liquids, showing that both cation and anion variation can change the nucleophilicity of the halide ion.[4] By comparing the kinetic data obtained against empirical solvent polarity measurements,[4] it became apparent that this could be understood by the application of the classical Hughes–Ingold predictions[4] of solvent polarity on reaction rates combined with an analysis of hydrogen-bonding effects, with the ionic liquid acting in the same way as polar molecular solvents. In no reaction did we observe any behavior unique to the ionic liquids, nor in which the ionic liquids were at the extreme of the observed behaviors. Similarly, the reactions of neutral nucleophiles with ionic electrophiles showed no special ionic liquid effect.[5] We report here the reaction of

[†] Imperial College London.
[‡] Georgia Institute of Technology.
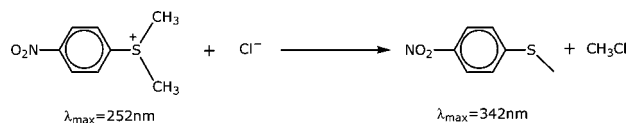(1) Wilkes, J. S.; Zaworotko, M. J. *J. Chem. Soc., Chem. Commun.* **1992**, 965.
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SCHEME 1. The S$_N$2 Reaction of a Chloride Ion with a Sulfonium Center

FIGURE 1. Sample absorbance spectra for a sulfonium salt and its corresponding demethylated sulfide in acetonitrile.

chloride ions with an ionic electrophile, which provides the first demonstration of just such an "ionic liquid effect" on a chemical reaction.

Results and Discussion

The reaction we studied was the S$_N$2 reaction of the tri-fluoromethanesulfonate and bis(trifluoromethanesulfonyl)imide salts of dimethyl-4-nitrophenylsulfonium ([p-NO$_2$PhS(CH$_3$)$_2$]$^+$[X]$^-$; [X]$^-$ = [CF$_3$SO$_3$]$^-$, [N(CF$_3$SO$_2$)$_2$]$^-$) with chloride ion, as shown in Scheme 1. The reactions were assayed by UV spectroscopy, with each substrate having λ_{max} at 252 nm and the demethylated products having a λ_{max} at 342 nm (see Figure 1), well above the cutoff of either the imidazolium (240 nm) or pyrrolidinium (200 nm) based ionic liquids that were used as solvents. The sulfonium salts were synthesized as described in our previous study.[5]

The nucleophilic displacement by chloride ion was studied in several molecular solvents and ionic liquids. The ionic liquids (IL's) chosen were 1-butyl-1-methylpyrrolidinium bis(trifluo-romethanesulfonyl)imide [C$_4$C$_1$py][N(CF$_3$SO$_2$)$_2$], 1-butyl-1-me-thylpyrrolidinium trifluoromethanesulfonate [C$_4$C$_1$py][CF$_3$SO$_3$], 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide [C$_4$C$_1$im][N(CF$_3$SO$_2$)$_2$], 1-butyl-3-methylimidazolium trifluo-romethanesulfonate [C$_4$C$_1$im][CF$_3$SO$_3$], 1-butyl-2-methyl-3-me-thylimidazolium bis(trifluoromethanesulfonyl)imide [C$_4$C$_1$C$_1$im]-[N(CF$_3$SO$_2$)$_2$], and 1-butylimidazolium trifluoromethanesulfonate [C$_4$Him][CF$_3$SO$_3$] and the molecular solvents were dichlorome-thane (CH$_2$Cl$_2$), tetrahydrofuran (THF), acetonitrile (CH$_3$CN), dimethyl sulfoxide (DMSO), acetone, 1-butanol, and propylene carbonate. Due to solubility differences between the two salts in the different solvents used in this study, we were forced to utilize different anions of the sulfonium salt. The trifluo-romethanesulfonate salt was used with acetonitrile, DMSO, propylene carbonate, and the three trifluoromethanesulfonate-based ionic liquids. The bis(trifluoromethanesulfonyl)imide salt was used with acetonitrile, dichloromethane, tetrahydrofuran, 1-butanol, acetone, and the three bis(trifluoromethanesulfo-nyl)imide-based ionic liquids. No rate difference was found between studies involving the two different sulfonium salts in acetonitrile; therefore we have treated the two electrophiles as interchangeable. This is in agreement with a previous study with this electrophile.[5] Both electrophiles were found to be stable in every solvent as no change in UV−vis absorbance was observed in the absence of nucleophile within 24 h. As for the nucleophile cation, tetrahexylammonium chloride was used in acetonitrile, DMSO, propylene carbonate, 1-butanol, acetone, tetrahydrofuran, dichloromethane, [C$_4$C$_1$py][N(CF$_3$SO$_2$)$_2$], [C$_4$C$_1$im][N(CF$_3$SO$_2$)$_2$], and [C$_4$C$_1$C$_1$im][N(CF$_3$SO$_2$)$_2$]. [C$_4$C$_1$im][Cl] was used in ace-tonitrile, dichloromethane, and [C$_4$C$_1$im][CF$_3$SO$_3$]. [C$_4$C$_1$py][Cl] was used in [C$_4$C$_1$py][CF$_3$SO$_3$], [C$_4$Him][Cl] was used in [C$_4$Him][CF$_3$SO$_3$], and [C$_4$C$_1$C$_1$im][Cl] was used in [C$_4$C$_1$C$_1$im]-[N(CF$_3$SO$_2$)$_2$].

This is a bimolecular reaction, which means that the rate is dependent upon the concentrations of both the electrophile and the nucleophile. To quantify the rates of such reactions it is
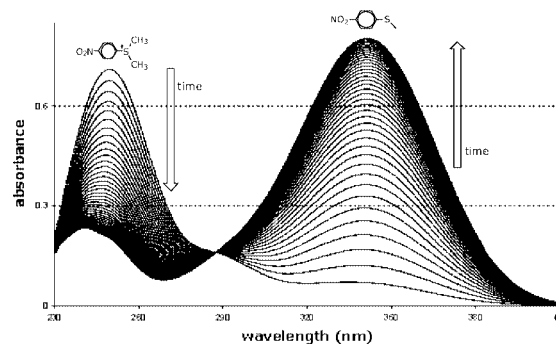
usual to use a large excess of one reagent to give *pseudo*-first-order kinetic behavior, which is a linear dependence of k_{obs} upon nucleophile concentration. This is what was observed in all cases where this reaction was performed in an ionic liquid (see Figure 2) and in no case when the reaction was performed in a molecular solvent (see Figure 2). When the solvent was a polar molecular liquid (CH$_3$CN, dimethyl sulfoxide, 1-butanol, pro-pylene carbonate), nonlinear partial-order kinetics were ob-served. When the solvent used was a relatively nonpolar molecular liquid (tetrahydrofuran, acetone, dichloromethane), a white precipitate was observed and k_{obs} had an apparently negative-order dependence on nucleophile concentration (i.e., as the nucleophile concentration was increased, the observed rate of reaction decreased). This precipitate was isolated and identified as dimethyl-4-nitrophenylsulfonium chloride.

The molecular solution-phase behavior of this type of reaction is well established (Scheme 2).[6] First an ion metathesis reaction occurs to give dimethyl-4-nitrophenylsulfonium chloride. This salt is insoluble in acetone, dichloromethane, and tetrahydrofuran and precipitates from solution. As the concentration of tetra-hexylammonium chloride is increased the equilibrium constant for this metathesis leads to greater formation of dimethyl-4-nitrophenylsulfonium chloride and hence depletion of the electrophile in solution and a slowing of the rate of the reaction (i.e., apparent negative order). When there is sufficient tetra-hexylammonium chloride this leads to effectively complete formation of dimethyl-4-nitrophenylsulfonium chloride and no further effect of increased concentration on the rate of the reaction. This is observed as the leveling off of the k_{obs} (Figure 2). In polar molecular solvents the initial metathesis again leads to the formation of dimethyl-4-nitrophenylsulfonium chloride, but this salt exists as ion pairs in solution. It is the reaction of these ion pairs that is observed in the kinetic experiments (Figure 2). Hence, increasing the concentration of nucleophile increases the rate of reaction, but not in the linear fashion dictated by *pseudo*-first-order conditions. Alternatively, the quaternary ion pair formed can redistribute between a sulfonium−ammonium pair (**I**) and a diammonium quadropolar ion pair (**II**). The diquaternary ammonium quadrupolar ion pair can undergo a monomer−dimer equilibrium shift to complete the reaction cycle. When our (nonlinear) kinetic results are fitted to this model we obtain an excellent correlation, supporting the established mechanism. Finally the reaction was attempted in water and methanol. Unfortunately, the nucleophilic substitution reaction does not take place in these solvents: in both cases no

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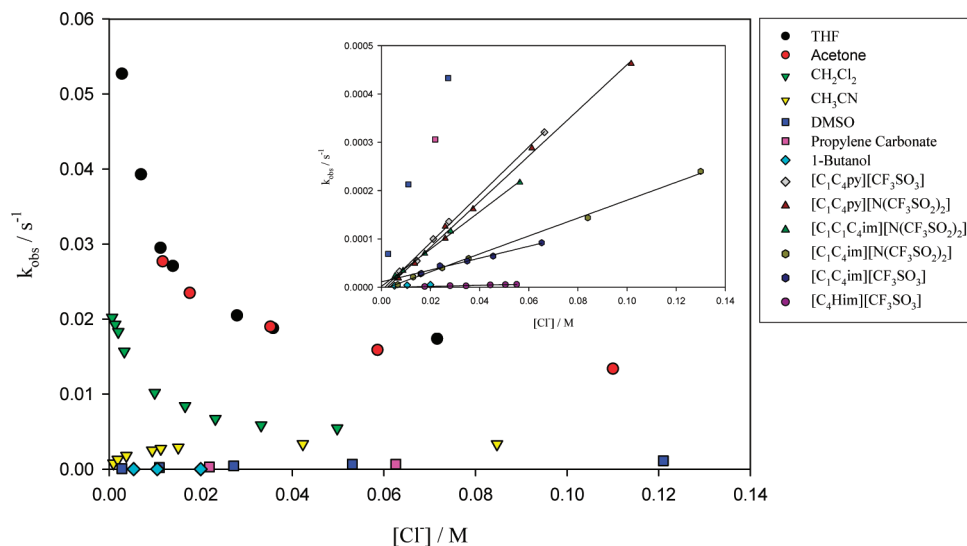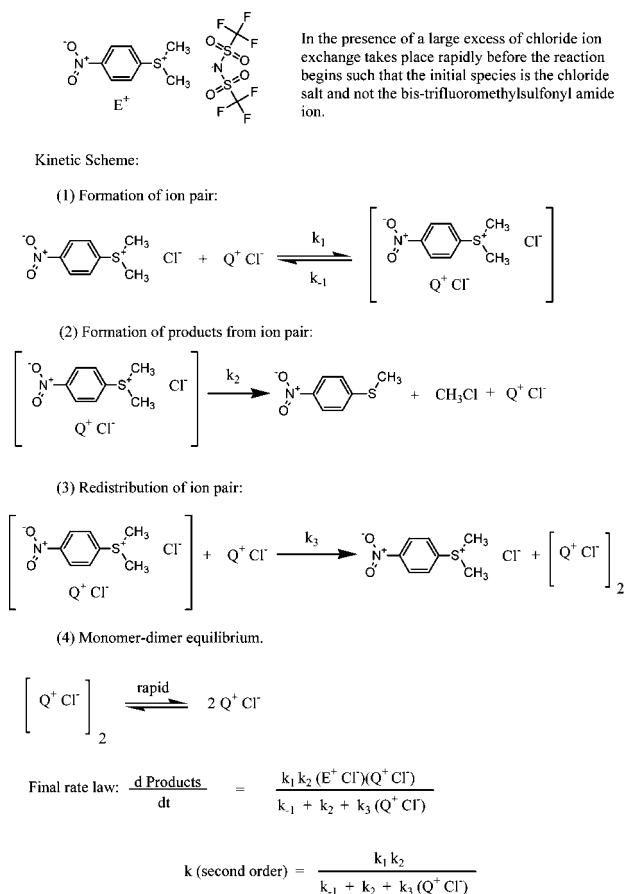
FIGURE 2. Results of the nucleophilic reaction in molecular solvents and ionic liquids. The inset is an enlarged area near the concentration axis.

SCHEME 2.   The S_N2 Mechanism in Molecular Solvents^a

^{a} Q^+ refers to the (quaternary) cation originally associated with the chloride ion.

first-order kinetic behavior for this nucleophilic substitution reaction is seen.

Having established a phenomenon that is only observed in ionic liquids we sought to explain this behavior. The linear kinetic behavior seen in the ionic liquid solutions clearly indicates that the reactions are not progressing via ion pairs, but via free solvated ions.[7] There are two possibilities: the ionic solutes fully dissociate from each other and the dimethyl-4-nitrophenylsulfonium chloride ion pairs do not form or these ion pairs form as they do in the molecular solvents but they do not react in the ionic liquids. In kinetic experiments the slowest step of the fastest reaction is what can be observed. Since all of the molecular solvents that show the solution kinetic results (i.e., DMSO, propylene carbonate, and acetonitrile) are dissociating solvents,[8,9] their solutions of the reagents contain both ion pairs and free solvated ions. That the kinetic behavior is dominated by dimethyl-4-nitrophenylsulfonium chloride ion pairs shows that these ion pairs are considerably more reactive than the free solvated ions. This suggests that the explanation for the linear kinetic behavior is because these ion pairs do not form in the ionic liquids. This is further supported by the low observed rates of the reactions in the ionic liquids.

To further investigate ion-pairing in ionic liquids, the UV spectrum of the salt 1-ethyl-4-(methoxycarbonyl)pyridinium iodide was measured in the same ionic liquids and molecular solvents as used in the kinetic experiments. In molecular solvents these show a well-defined peak arising from an iodide to pyridinium charge transfer absorbance that has been used to define the Kosower Z scale of solvent polarity.[10–12] In no ionic liquid was this absorbance observed in concentrations similar to those used for the reagent in excess in the kinetic experiments. This strongly suggests these ions are no longer associated with one another, but are instead solvated by the

reduction in the sulfonium UV/vis absorbance was observed over a period of 1 week. This is most likely due to these solvents being able to form strong hydrogen bonds with the nucleophile, thus greatly reducing reactivity.[5] In fact, the sulfonium chloride salt could be isolated as a stable species and dissolved in D_2O for NMR analysis without any decomposition products detectable after 1 week. Hence, it is only in ionic liquids that *pseudo*-

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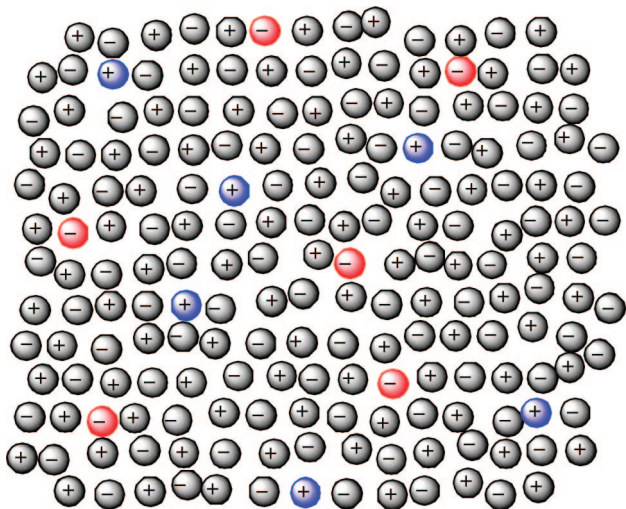
FIGURE 3. The ionic liquid mélange.

ionic liquid ions.[13] Thus the ionic liquids are extremely dissociating solvents (Figure 3).

Ion pairing in solution is driven by the mutual attraction of oppositely charged ions. This attraction is dominated by Coulombic forces and is inversely proportional to the dielectric constant of the solvent. The dielectric constants of some ionic liquids, including $[C_4C_1im][N(CF_3SO_2)_2]$ ($\varepsilon = 11.6$) and $[C_4C_1im][CF_3SO_3]$ ($\varepsilon = 13.2$), have been measured and found to lie in the range $10-15$.[17-19] On this basis it would be expected that the degree of ion pair dissociation in the ionic liquids would be less than that of most of the molecular solvents use here. Clearly this is not the case. In an ionic liquid the solute ions are present in a melange of ions, the majority of which are the solvent. If the solute and solvent cations are of similar dimensions, as is the case in this experiment, then there will be no preferential Coulombic attraction for any particular anion and vice versa. Another way in which this can be expressed is to say that the Coulombic attraction between any two given ions in an ionic liquid solution is highly screened by the other ions in the melange. Thus Coulombic interactions, and consequently the dielectric constant of the solvent, are no longer the driving force for ion pairing of the solute salt. This breaking of the relationship between the degree of dissociation of the solute salt and the dielectric constant of the solvent leads us to characterize these ionic liquids as "super-dissociating" solvents. The consequences of this "super-dissociation" on ion reactivity are rather straightforward. For a molecular solvent to overcome the Coulombic interactions of the ion pairs very strong specific solvation interactions (e.g., strong hydrogen bonding) are required, which greatly reduce the reactivities of the ions. In an ionic liquid, dissociation of the ion pairs is possible without such strong specific solvation interactions, leaving the ions

capable of reacting. Hence, our kinetic experiments in ionic liquids show reaction via dissociated ions, whereas in a strongly dissociating molecular solvent (such as water) no reaction is seen, and in a non-dissociating solvent the reaction is via solvated ion pairs. Of course, the well-established flexibility of ionic liquid design allows that one could be synthesized to interact with the reagent ions sufficiently strongly so as to prevent these from reacting.

Conclusion

In conclusion, we have demonstrated that ionic liquids can be considered to be super-dissociating solvents toward solute salts. This occurs because of the high level of screening of the Coulombic attraction of solute ions provided by the ions of the ionic liquids. In addition, should the solute ions find themselves in close contact the motion of the solvent ions that occurs due to the system being in the liquid state will rapidly disrupt this contact, thus making any such ion pair short-lived. The clear effect of this behavior, which arises because the system is both liquid and ionic (i.e., an ionic liquid), on the reaction of the dimethyl-4-nitrophenylsulfonium and chloride ions is to give a true S_N2 reaction of the free solvated ions rather than the ion-pair mechanism seen in molecular solvents. Hence, this change in mechanism can be called a true "ionic liquid effect".

Finally, there has been some debate about whether solvent systems that are composed of ions in equilibrium with molecular species, e.g., protic ionic liquids,[14,20] reversible ionic liquids,[21,22] eutectic ionic liquids,[23,24] and highly concentrated salt solutions, should be considered as ionic liquids. The ionic liquid effect reported here can be used to characterize an ionic liquid, since any system exhibiting this behavior would be defined as an ionic liquid and any system not displaying this behavior would not be so defined.

Experimental Section

Synthetic Techniques. All syntheses were performed under anaerobic conditions with standard Schlenk techniques. The preparations and spectral data of the ionic liquids have been described elsewhere[25] with the exception of $[C_4Him][OTf]$, which is described below. The preparations of dimethyl-4-nitrophenyl-sulfonium bis(trifluoromethylsulfonyl)imide and dimethyl-4-nitro-phenylsulfonium trifluoromethanesulfonate are also described elsewhere.[5]

Synthesis of 1-Butylimidazolium Trifluoromethanesulfonate, $[C_4Him][OTf]$. A solution of triflic acid (60 g, 0.400 mol) in 200 mL of diethyl ether was carefully added at -70 °C to a solution of 1-butylimidazole (52.0 g, 0.419 mol) in 200 mL of diethyl ether and the mixture was stirred for 2 h at room temperature. Removal of the upper layer from the resulting suspension provides the crude product, which was washed with portions of diethyl ether ($3 \times$ 100 mL), treated with activated charcoal, and filtered through a pad of acidic alumina to give a colorless liquid. Complete removal

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of solvent by means of high vacuum gives a crystalline solid. Mp 30−33 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 11.55 (s, 1H, N−*H*), 8.76 (s, 1H, N−C*H*−N), 7.41 (s, 1H), 7.29 (s, 1H), 4.20 (t, 2H, N−C*H$_2$*CH$_2$CH$_2$CH$_3$), 1.83 (q, 2H, N−CH$_2$C*H$_2$*CH$_2$CH$_3$), 1.32 (sextet, 2H, N−CH$_2$CH$_2$C*H$_2$*CH$_3$), 0.92 (t, 3H, N−CH$_2$CH$_2$CH$_2$-C*H$_3$*); ^{13}C NMR (400 MHz, d_6-DMSO) δ (ppm) 135.3 (N$_2$*C*), 122.0 and 120.1 (N*C*H), 119.6 (q, $^1J_{13C-19F}$ = 317.5 Hz, [OSO$_2$*C*F$_3$]$^-$), 48.4 (N−*C*H$_2$(CH$_2$)$_2$CH$_3$), 31.5 (N−CH$_2$*C*H$_2$CH$_2$CH$_3$), 18.9 (N−(CH$_2$)$_2$*C*H$_2$CH$_3$), 13.2 (N−(CH$_2$)$_3$*C*H$_3$); (FAB$^+$) MS (*m/z*) 399, [(C$_4$Him)2(OTf)]$^+$, 9.38%; 125, [C$_4$Him]$^+$, 100%; (FAB$^-$) MS (*m/z*) 423, [(C$_4$Him)(OTf)$_2$]$^-$, 18.12%; 149, [OTf]$^-$, 100%. Anal. (% calcd, % found): C (35.04, 35.16), H (4.78, 4.69), N (10.21, 10.20).

Kinetic and Analytical Procedures. See our previous publication.[5]

Supporting Information Available: Details of the kinetic model and a sample data fit along with 1D and 2D ^{1}H and ^{13}C NMR spectra of [C$_4$Him][OTf]. This material is available free of charge via the Internet at http://pubs.acs.org.

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