

Room-Temperature Ionic Liquids: Solvents for Synthesis and Catalysis. 2

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 Supporting Information

CONTENTS

1. Introduction	3508	6.6.6. Metal Alkyl and Aryl Addition Reactions	3541
2. Preparation	3510	6.7. Acid-Catalyzed Reactions	3542
3. Handling	3511	6.7.1. Electrophilic Aromatic Substitutions	3542
4. Physical Properties	3512	6.7.2. Isobutane Alkylation	3545
5. Solvent–Solute Interactions in Ionic Liquids	3513	6.7.3. Esterification	3546
5.1. Water	3513	6.7.4. Diels–Alder Reactions	3548
5.2. Polarity	3515	6.7.5. Dehydration	3549
5.2.1. Dielectric Constant	3515	6.7.6. Beckmann Rearrangement	3549
5.2.2. Hildebrand Solubility Parameter, δ_H	3516	6.7.7. Ring Closing of Isonitrosoacetanilides	3550
5.2.3. Single-Molecule Spectroscopic Probes	3516	6.7.8. Mannich Reaction	3550
5.2.4. Multiparameter Scales	3519	6.7.9. Glycosylation	3550
5.2.5. Antagonistic Behavior in Hydrogen Bonding	3521	6.7.10. Summary	3550
5.2.6. Apparent Discrepancies between Polarity Measurements in Ionic Liquids	3521	6.8. Base/Nucleophile-Catalyzed Reactions	3550
5.3. Infinite Dilution Activity Coefficients	3522	6.8.1. Aldol Reaction	3550
5.3.1. Activity Coefficients and Solute–Ionic Liquid Interactions	3522	6.8.2. Morita–Baylis–Hillman Reaction	3552
5.3.2. Modeling of γ^∞ Values	3526	6.8.3. Knoevenagel Reaction	3552
5.3.3. Summary	3526	6.8.4. Keto–Enol Tautomerization	3553
6. Ionic Liquid Effects on Stoichiometric Chemical Reactions	3527	6.8.5. Nucleophilic Substitutions	3554
6.1. Energy Transfer	3527	6.8.6. Esterification/Acetylation of Alcohols	3554
6.2. Electron Transfer Reactions	3527	6.8.7. Acid Scavenging	3555
6.3. Acid–Base Reactions	3528	6.8.8. Summary	3555
6.4. Substitutions	3531	7. Transition-Metal-Catalyzed Reactions	3555
6.4.1. Type a S_N2 $Y^- + R-X$ Reaction	3531	7.1. Ionic Liquids as Catalyst Immobilizers	3555
6.4.2. Type b S_N2 $Y + R-X$ Reaction	3533	7.2. Hydrogenations	3556
6.4.3. Type c S_N2 $Y + [R-X]^+$ Reaction	3535	7.3. Oxidations	3559
6.4.4. Type d S_N2 $Y^- + [R-X]^+$ Reaction	3535	7.4. Carbonylations and Hydroformylations	3561
6.4.5. Type e S_N1 $R-X$ Reaction	3536	7.5. Dimerizations	3563
6.4.6. Type f S_N1 $[R-X]^+$ Reaction	3536	7.6. Palladium-Catalyzed Coupling Reactions	3563
6.4.7. Ionizing vs Dissociating Solvents	3536	7.7. Olefin Metathesis	3564
6.4.8. Nucleophilic Aromatic Substitutions	3537	7.8. Summary	3564
6.5. Elimination	3537	8. Overview	3564
6.6. Additions	3538	Author Information	3564
6.6.1. Electrophilic Addition	3538	Biographies	3565
6.6.2. Nucleophilic Addition	3539	Acknowledgment	3565
6.6.3. 1,4-Conjugate Additions	3539	References	3565
6.6.4. Diels–Alder Reactions	3539		
6.6.5. Oxidative Addition	3541		

1. INTRODUCTION

In 1999 *Chemical Reviews* published its first review on the subject of “Room-Temperature Ionic Liquids: Solvents for

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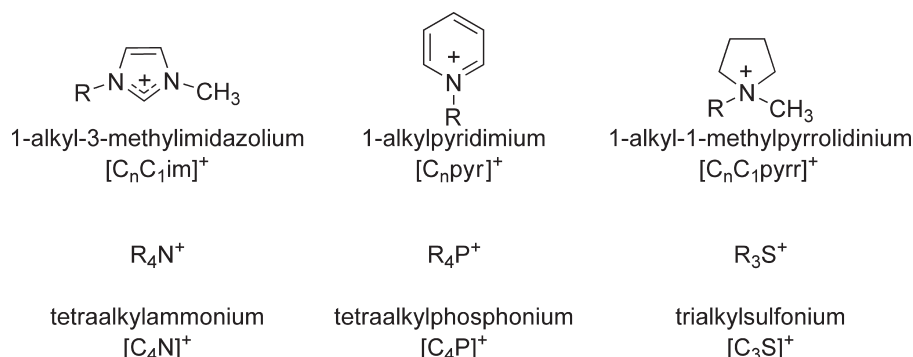


Figure 1. Some commonly used cations for ionic liquids.

Synthesis and Catalysis”.¹ Then the field was dominated by a small number of specialist research groups, and it would have been very unlikely to find a general synthetic chemist considering whether an ionic liquid might be the best possible solvent in which to try a reaction. At that time there were very few chemists who had even heard of ionic liquids. Today, the same chemist is likely to be well aware of the existence of ionic liquids and to know that they are a useful addition to the range of solvents that they might use. There has been an explosion of interest in ionic liquids. There have been well over 6000 papers published in the past 10 years with the phrase “ionic liquid(s)” in the title, and just over half of these have been on the subject of chemical synthesis and/or catalysis in one way or another. Whereas in 1999 it was possible to be truly comprehensive with just 123 references, now it is an impossible task. Therefore, it is important for us to first define the scope of this review.

First, the question of the definition of an “ionic liquid” has been the subject of much debate over the past 10 years. Here we reproduce the note on nomenclature that was used in the original review;¹ we believe that it is still the best approach to this thorny issue: “Room-temperature ionic liquid, nonaqueous ionic liquid, molten salt, liquid organic salt, and fused salt have all been used to describe salts in the liquid phase. With the increase in electronic databases, the use of keywords as search tools is becoming ever more important. While authors are free to choose any name that they wish for their systems, I would suggest that they at least include the term ionic liquid in keyword lists. In this paper, I allow the term ionic liquid to imply that the salt is low melting.”

There are a number of systems for which it is fair to say that they are not composed *solely* of ions when pure that have been described, such as “deep eutectic solvents”² and some protic ionic liquids (depending upon the acid–base equilibrium constant),³ including “Olah’s reagent”.⁴ These will be included in this review when their use meets the criteria below.

This review is designed to update and complement the 1999 paper, with the primary literature surveyed up to the end of 2009, and will follow most of the same format. However, this time we will not separate the halogenoaluminate ionic liquids for special attention. Ionic liquids can be used in many ways. The focus of this review is their use as solvents in synthesis and catalysis. In 1999 it was exciting that a small number of organic and catalytic reactions had been conducted in ionic liquids. The primary conclusion that emerges from there being such a vast literature of the use of ionic liquids (ILs) in synthesis and catalysis is that, providing there is no direct reaction between the ions of the IL and the starting materials, most reactions will “go” in most ionic liquids. With the benefit of

hindsight, it now seems that we were naïve to have found this to be anything other than what we should have expected. Consequently, we will not review papers where this is the sole conclusion of the work. Much of the interest in ionic liquids has centered on their possible use as “green” alternatives to volatile organic solvents.⁵ This claim usually rests on the fact that ionic liquids are generally nonvolatile under ambient conditions. Hence, exposure risk to ionic liquids is much lower than it is for a volatile solvent, and they have no damaging atmospheric photochemistry. This nonvolatility also leads to most ionic liquids being nonflammable under ambient conditions.⁶ These properties were known at the time of the 1999 review and were used to justify interest in the use of ionic liquids then. Hence, we will not include studies in which the advantage claimed for the use of ionic liquids over other solvents rests on these properties alone. There have been many reviews of ionic liquids that can be referred to for information that is outside the scope of this paper. Some of these have focused on particular applications, e.g., analysis,⁷ biocatalysis,⁸ electrochemical devices,⁹ or engineering fluids.¹⁰ Others have concentrated on particular subgroups of ionic liquids, e.g., protic ionic liquids³ or task-specific ionic liquids.¹¹ Catalysis has been particularly well reviewed very recently.¹² Two special journal issues appeared in 2007 containing reviews covering a wide range of subjects in ionic liquid research.¹³ Finally, three books are available.¹⁴ There is also an online, free to users, ionic liquid database.¹⁵ We will not seek to simply rereview these. We will instead concentrate on those studies that have sought to understand how ionic liquids can affect the reactivity of solute materials (e.g., yields, rates, and/or selectivities).

As the number of ionic liquids and the number of research groups working in ionic liquids has proliferated the number of different abbreviations for ionic liquid, ions have done likewise. This has been particularly so for ionic liquid cations. Most abbreviations used in the literature derive from the name of the ion; e.g., [bmim]⁺ and [BMIM]⁺ both refer to the 1-butyl-3-methylimidazolium cation. However, ambiguities rapidly arise; e.g., should [pmim]⁺ refer to the 1-propyl-3-methylimidazolium cation or to the 1-pentyl-3-methylimidazolium cation? To circumvent these problems, we have chosen to use an alphanumeric system to describe the alkyl chains, with an alphabetic abbreviation for the charged center (Figure 1). In this system the 1-butyl-3-methylimidazolium cation becomes [C₄C₁im]⁺. If the alkyl chain is not linear, this can be noted; e.g., the 1-*tert*-butyl-3-methylimidazolium cation becomes [tC₄C₁im]⁺. If the side chain is functionalized, then the type and position of the functional group are noted; e.g., [(HO)⁴C₄C₁im]⁺ denotes that there is an alcohol group on the terminal carbon of the butyl chain. In-chain inclusion of non-carbon atoms can also be shown; e.g., [(C₁OC₂)C₁im]⁺ shows the

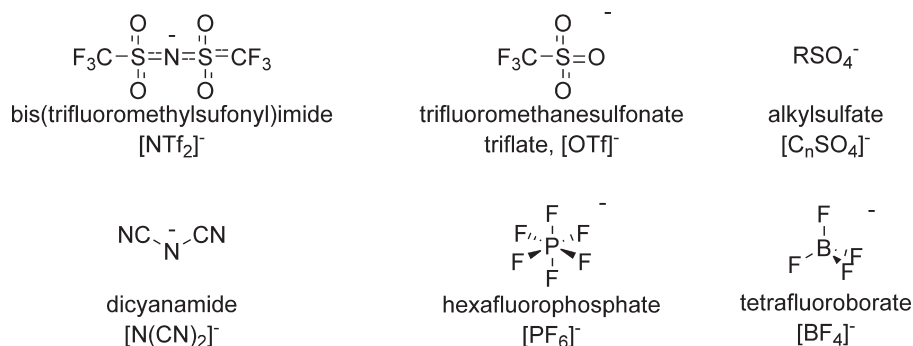
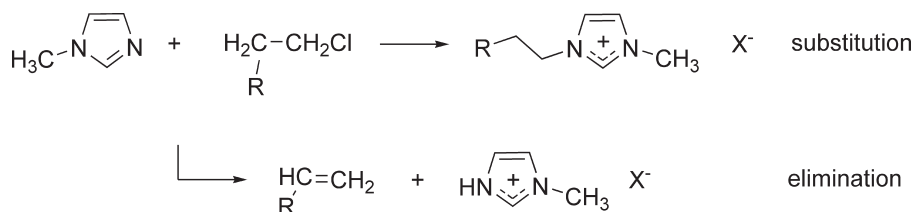


Figure 2. Some commonly used anions for ionic liquids.

Scheme 1



presence of an etheral oxygen in the chain between the second and terminal carbon atoms. Alkyl chains are assumed to be saturated unless noted otherwise; e.g., $[(C_1=C_2)C_1im]^+$ represents 1-allyl-3-methyl-imidazolium cation. For cyclic cations, alkylation is assumed to be on the heteroatom(s) unless otherwise indicated by giving the numerical position of the alkylation on the ring such that 1-butyl-2,3-dimethylimidazolium becomes $[C_4C_1C_1^2im]^+$. Where alkyl chains are present in anions, the same system will be used (Figure 2); e.g., $[C_4OSO_3]^-$ denotes butyl sulfate. No system is perfect, but this one gives the least ambiguity and is the most systematic of those currently in use.

2. PREPARATION

The past 10 years has seen a proliferation of the number of ionic liquids that have been prepared. However, it remains true that the vast majority of ionic liquid cations are based upon alkylated amines, with a smaller number of phosphonium and sulfonium salts used. Consequently, although details vary, there are common themes that reappear in the synthesis of ionic liquids: first alkylation of an amine/phosphine/sulfide to give an intermediate salt, followed by anion exchange to give the ionic liquid. Most ionic liquids cannot be distilled in large quantities. Hence, the ability of synthetic protocols to give high-purity ionic liquids has been an important focus for their selection.¹⁶

Impurities in ionic liquids can come from a number of sources. The first is that they are contained in the starting material. Consequently, it is necessary to purify these before use, typically by distillation from a suitable drying agent in an inert atmosphere. However, when very pure “spectroscopic grade” ionic liquids have been required, prewashing of the starting materials has also been used.^{17,18}

Once the starting materials have been prepared, the alkylation step can then be performed. Throughout this step air and moisture should be rigorously excluded. This nucleophilic substitution is highly exothermic, and this can lead to runaway reactions.^{19,20} Overheating of the reaction solution also leads to greater formation of elimination products from the competing reaction (Scheme 1). Hence, the reaction is usually performed in solution, the reactants are usually

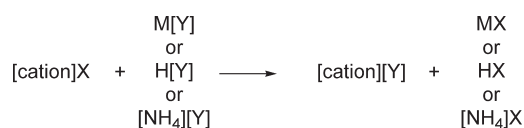
added slowly to prevent hot spots, and there has been a trend in academic laboratories over the years to reduce the temperature and to extend the time of the reaction. A kinetic investigation of the reactions of 1-bromohexane with 1-methylimidazole in 10 different solvents, followed by a linear solvation energy relationship (LSER) analysis, showed that the rate was greatest in dipolar non-hydrogen bond donor solvents.²¹ The corollary of this is, of course, that the same rate of reaction can be achieved at lower temperature.

Microwave heating has also been used for these syntheses.²² Although this allows reactions to be conducted very quickly, the difficulty in controlling the reaction conditions, especially the generation of hot spots, leads to variable quality of the products.²³ Ultrasound has also been used at this stage of the synthesis, with excellent yields being reached more quickly and at lower temperatures than with conventional heating and stirring.²⁴ Here, the authors also reported that the product salts were purer than those made by the conventional method. These results probably arise from the more efficient mixing that is achieved with ultrasound, both leading to faster reaction and preventing the formation of hot spots, particularly later in the reaction when the mixture becomes more viscous. [C₄C₁im]Br has been prepared at a rate of up to 9.3 kg/day in a continuous-flow microreactor, which was shown to be an appreciable improvement over a batch system.¹⁹

Most of the halide salts of cations used in ionic liquids are solid at room temperature, allowing purification of the intermediate salts by recrystallization, most often from acetonitrile; ethyl acetate can be added to aid precipitation of the salt and removal of unreacted starting materials. Finally the salt is dried *in vacuo*.

The ionic liquid can then be prepared by metathesis of the halide salt with a metal or ammonium salt or the conjugate acid of the required anion (Scheme 2). For hydrophobic ionic liquids this can be done in aqueous solution,²⁵ with the product separating during the reaction. The aqueous solution can then be washed with CH_2Cl_2 and the ionic liquid isolated from the CH_2Cl_2 solution to increase the overall yield. Of course, the ionic liquid is not dry at this stage, and any remaining water is removed

Scheme 2



in vacuo. This is usually conducted at elevated temperatures, but care is required because this can lead to decomposition of the ionic liquid.⁶ For hydrophilic ionic liquids the metathesis is usually performed in a water-immiscible organic solvent.²⁶ The resulting mixture is then filtered and the filtrate washed with water to remove any residual halide salt. The greater the miscibility of the product ionic liquid with water, the less effective this process is, leading to either low yields or halide contamination of the ionic liquid.²⁷ The application of ultrasound for the metathesis reaction of $[\text{NH}_4][\text{PF}_6]$ or $[\text{NH}_4][\text{BF}_4]$ with $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ in acetone has been shown to lead to less colored ionic liquids in shorter time than the same reaction with stirring (500 rpm at room temperature).²⁸ The organic solvent is then removed in vacuo. If all of the steps in the synthesis have been performed well, the ionic liquid is then ready for drying and use. However, the ionic liquids are often colored at this stage or contain other impurities, such as unreacted starting materials. These are typically removed by the action of sorbents such as activated charcoal, alumina (usually neutral or acidic), or silica.²⁹ However, concern has recently been expressed that this can leave small amounts of the sorbent material in the ionic liquid.³⁰

The general preparations of ionic liquid as described above form the vast majority of the syntheses described in the literature. The details of the syntheses vary between ionic liquids and research groups and over time and are not always reported in detail. With the exception of the points noted above, it is not at all clear which of the variations reported do provide a synthetic advantage and which are merely the consequences of local custom. For instance, when working on chloroaluminate ionic liquids in the 1980s, one of us noticed that the use of acetone in the cleaning of glassware gave colored ionic liquids, and we have never used it since, preferring instead to use ethanol, regardless of which ionic liquids we are working with at the time.

The metathesis step and subsequent washings and separations cannot always be performed to give an ionic liquid of the required standard, particularly for ionic liquids with more basic anions, so a number of techniques have arisen to avoid this. When the hydroxide salt is available, as with $[(\text{C}_4)_4\text{P}]\text{OH}$, the ionic liquid can be prepared by direct neutralization of an acid.³¹ When it is not available, a solution of it can be generated using an ion exchange column. This has been used for the synthesis of 20 ionic liquids prepared from amino acids.³² An aqueous solution of $[\text{C}_2\text{C}_1\text{im}]\text{Cl}$ was passed down a column of Amberlite IRA400OH resin to generate a dilute aqueous solution of $[\text{C}_2\text{C}_1\text{im}]\text{OH}$, which was then neutralized with an aqueous solution of the amino acid. The water was then removed by freeze-drying. Aqueous solutions of $[\text{C}_2\text{C}_1\text{im}]\text{OH}$ have also been prepared by membrane electrodialysis.^{33,34}

Direct alkylation of an amine/phosphine can also be used to avoid the need for a halide intermediate. For instance, methyl triflate has been reacted with a stoichiometric amount of the 1-alkylimidazole in 1,1,1-trichloromethane to yield the $[\text{C}_n\text{C}_1\text{im}][\text{OTf}]$ ionic liquid.³⁵ This is an exothermic reaction, and methyl triflate is sensitive to moisture, so the reaction must be carried out under anhydrous conditions with cooling of the reaction mixture. Other

sulfonate ionic liquids have been prepared by the direct reaction of alkanesulfonate esters with substituted imidazoles to yield $[\text{C}_n\text{C}_1\text{im}][\text{C}_m\text{SO}_3]$ ($n = 1$ or 4 ; $m = 1, 2$, or 4).³⁶ Several of these were solid at room temperature and could be recrystallized from acetone. The authors then used the $[\text{C}_4\text{C}_1\text{im}][\text{C}_1\text{SO}_3]$ salt to prepare $[\text{C}_4\text{C}_1\text{im}]\text{X}$ {where $\text{X} = [\text{BF}_4], [\text{PF}_6], [\text{PF}_3(\text{CF}_2\text{CF}_3)_3], [\text{OTf}]$, or $[\text{NTf}_2]$ } by metathesis in water followed by extraction with CH_2Cl_2 to give Cl^- -free ionic liquids.

The first alkyl sulfate ionic liquid, $[\text{C}_4\text{C}_1\text{im}][\text{C}_8\text{OSO}_3]$, was prepared by metathesis of $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ and $\text{Na}[\text{C}_8\text{OSO}_3]$ to give a less toxic and “greener” ionic liquid than those available at the time.³⁷ However, dialkyl sulfates and trialkyl phosphates can be used as direct alkylating agents to give alkyl sulfate or dialkyl phosphate salts, respectively.^{38–40} Again care is required when using these direct alkylation routes to avoid overheating of the reaction mixture and the formation of colored or otherwise impure ionic liquids. $[\text{C}_2\text{C}_1\text{im}][\text{C}_m\text{OSO}_3]$ ($m = 1$ or 2) have been converted into salts with longer alkyl chains on the sulfate anions by transesterification with a suitable alcohol.⁴¹ However, this requires the presence of an acid catalyst that can be difficult to remove entirely from the ionic liquid.

In an attempt to alkylate 1-methylimidazole with dimethyl carbonate to give $[\text{C}_1\text{C}_1\text{im}][\text{C}_1\text{CO}_3]$, Rogers et al. formed the zwitterionic 1,2-dimethylimidazolium 2-carboxylate.⁴² Reaction of this salt with strong acid can lead to decarboxylation and formation of the dimethylimidazolium salt of the conjugate base of the acid.⁴³ However, the selectivity problems that arise with this route are significant and difficult to control. Attempts are continuing to alleviate these problems, such as using this route to first generate $[\text{C}_1\text{C}_1\text{im}][\text{HCO}_3]$, which itself can be used as an intermediate for the formation of other salts.⁴⁴ Although promising, this route requires more development before it can be widely applied to the synthesis of a variety of 1,3-dialkylimidazolium salts.

The avoidance of impurities arising from the metathesis reactions has also been attempted by the synthesis of volatile intermediates. 1,3-Dialkylimidazolium salts have been treated with strong base to give the 1,3-dialkylimidazolylenes, which were then distilled and added to acid HX to give $[\text{C}_n\text{C}_m\text{im}]\text{X}$ ionic liquids.⁴⁵ This methodology was subsequently extended to 1,2,3-trialkylimidazolium and trialkylmethylphosphonium salts.⁴⁶ While this technique does avoid halide impurities, it is difficult to perform the addition of the acid precisely and acid impurities can remain in the final ionic liquid.

The importance of Brønsted acids as catalysts in chemical synthesis (see below) led to the preparation of ionic liquids with the cation bearing a $-\text{SO}_3\text{H}$ functional group as the first of the so-called “task-specific ionic liquids”.⁴⁷ The reactions of *N*-butylimidazole or triphenylphosphine with 1,4-butanediol or 1,3-propanediol sulfone led to the zwitterions $[(^-\text{O}_3\text{S})^n\text{C}_n\text{C}_1\text{im}]^+$ or $[(^-\text{O}_3\text{S})^n\text{C}_n\text{PPh}_3]^+$ ($n = 3$ or 4), respectively.⁴⁸ These are then followed by the addition of a strong acid, which protonates the sulfonate group to yield the product ionic liquid. Another group of Brønsted acidic ionic liquids are the protic ionic liquids.³ These are prepared by simple neutralization of the appropriate base with a suitably strong acid and subsequent drying.^{49,50} Of course, BASF’s BASIL (biphasic acid scavenging utilizing ionic liquids) process involves the formation of a protic ionic liquid during a proton abstraction reaction.⁵¹

3. HANDLING

When considering how a material should be handled, two aspects need to be considered, these being possible detrimental effects on the material itself and hazards that the material poses to those exposed to it.

It can fairly be said that it was the publication of a paper titled “Air and water stable 1-ethyl-3-methylimidazolium based ionic liquids” that paved the way for the widespread application of ionic liquids in synthesis and catalysis.²⁵ However, it also led many to believe that there are no problems associated with the use of these ionic liquids in the air. Of course, the likely reactivity of an ionic liquid with the air, principally oxygen and water, is a chemical phenomenon and depends upon the identity of the component ions of the ionic liquid. There is no evidence that being a component of an ionic liquid makes any given ion more reactive to oxygen or water, but there is equally no evidence that it makes these ions any less reactive. Unfortunately, some ionic liquids, such as those containing the ions $[\text{PF}_6]^-$, $[\text{SbF}_6]^-$, $[\text{BF}_4]^-$, and $[\text{C}_n\text{SO}_4]^-$, which were originally described as air and moisture stable, undergo hydrolysis.⁵² In many cases the toxic and corrosive HF is formed.

Even when the ionic liquid components do not react with moisture, failure to protect the ionic liquids from the atmosphere will lead to considerable concentrations of water. The hydrophilicity of the ionic liquids is largely determined by the nature of the anion of the ionic liquid; the more basic the anion, the greater the solubility of water, with a secondary cation effect of shorter alkyl chains or substitution with hydrophilic functional groups leading to greater water solubility.^{26,53} However, even the ionic liquids with the least miscibility with water will contain considerable concentrations if not handled under anhydrous conditions,⁵⁴ and this can lead to dramatic changes in both physical and chemical properties of the solution.⁵⁵ Oxygen has proven to be far less problematic. This is because ionic liquids are rarely made using easily oxidized ions, the solubility of O_2 in most ionic liquids is relatively low,⁵⁶ and it is easily removed by applying even a moderate vacuum.

Of course, although it is important for anyone working with ionic liquids to know how to protect these during handling, it is more important that they are aware of any risks to themselves from the ionic liquids. Alongside the “green” label for ionic liquids came a widely held misconception that all ionic liquids were nontoxic. It is only recently that the study of the toxicity of ionic liquids has come to the fore, and most of this has been applied to gaining an understanding of (eco)toxicity, rather than being directly about risk assessment for those working with ionic liquids.⁵⁷ Furthermore, no single ionic liquid has been studied so completely that it can be claimed to be fully understood with respect to its toxicity. Although several studies have shown a link between the length of alkyl chains on the cations and toxicity, none have used enough ionic liquids to, by themselves, be sure of all structure–toxicity relationships. Attempts have been made to draw results from several studies together to derive sufficiently robust quantitative structure–property relationships (QSPRs) to give some predictive capacity for ionic liquid toxicity. Luis et al.⁵⁸ used their QSPR to develop a group contribution method for estimating the toxicity of ionic liquids to the aquatic organism *Vibrio fischeri*. They showed that the contribution to an ionic liquid’s toxicity increased in the order pyrrolidinium < imidazolium < pyridinium and with increasing length of the alkyl substituents. A subsequent study of *V. fischeri* and *Daphnia magna* showed up to four important factors.⁵⁹ The effect of changing the anion of the ionic liquid was pronounced, but not systematic. For the cations, the presence of an aromatic ring and then the number of heteroatoms in the ring increased the toxicity of the ionic liquid, which is a result different from that of the earlier study. It was shown again that increasing the alkyl chain on the cation increased the toxicity of the ionic liquid, but further methylation of the ring reduced its toxicity. The link between toxicity and alkyl chain length was also

observed in another QSPR study of the human Caco-2 cell line.⁶⁰ This cell line is interesting in that it is a human epithelial [derived from a colon (large intestine) carcinoma] cell line that has been proposed to be a good model for human toxicology studies.

The increasing toxicity of ionic liquids with the increased length of alkyl substituents on cations has been explicitly, if imperfectly, related to the lipophilicity of the resultant ionic liquid, as described either by the octanol/water partition coefficient⁶¹ or by the retention behavior in HPLC.⁶² Ionic liquids with greater lipophilicity are more able to interfere with biological membranes, which can in turn lead either directly to cell breakdown or to the passage of toxic substances to the cell interior and hence greater toxicity.

The claim that ionic liquids are safer solvents has never really rested on a belief that they are composed of nontoxic ions. Rather it has been based on the fact that their insignificant vapor pressures mean that accidental exposure to ionic liquids is far less likely than for volatile organic carbons. Transdermal exposure remains a risk. $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ has been found to be acutely orally toxic in female Fischer 344 rats, with an estimated LD_{50} of 550 mg/kg.⁶³ In the same study, the transdermal toxicity was shown to be more complex. When administered as a concentrated aqueous solution, there were no signs of gross toxicity ($\text{LD}_{50} > 2000$ mg/kg), whereas when administered in a solution in *N,N*-dimethylformamide (DMF), an LD_{50} of between 800 and 2000 mg/kg was found in the female rats, but the LD_{50} was greater than 2000 mg/kg in male rats. Clearly the ability of the salt to cross the skin is an important component of its transdermal toxicity, and this can be increased by the presence of cosolvents. It must be remembered that $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ is a solid at room temperature and could not be administered as a pure liquid. Furthermore, $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ is highly hygroscopic and is difficult to extract from aqueous solution. It has been proposed that suitably lipophilic ions can be used to deliver pharmaceutical counterions transdermally.⁶⁴ This suggests that ionic liquids that are liquid when in contact with skin and particularly those that are lipophilic are more likely to lead to transdermal toxicity.

4. PHYSICAL PROPERTIES

There are many liquid properties that are important to the performance of a reaction solvent; these include the liquid range, heat capacities, viscosities, etc. These properties for ionic liquids have been very well reviewed elsewhere and are not detailed here.^{13–15,65} These properties are controlled by the selection of both the cation and anion. This has led to the concept of ionic liquids being “designer solvents”.⁶⁶ However, for this to be achieved requires not just a post hoc rationalization of the ionic liquids’ properties, but the ability to predict them.

Most people who have worked with ionic liquids for any length of time will have experienced the frustration of making a salt that seems to be little different from a known room-temperature ionic liquid only to discover that it has a melting point much higher than expected. Consequently, the search for the ability to predict the melting points of organic salts has become an important activity. The QSPR approach has had some limited success in this respect. The first attempt at this was to correlate and predict the melting points of organic salts based on the quaternary ammonium cation.⁶⁷ Moderate correlations were found for a set of 75 tetraalkylammonium bromides and for a set of 34 (hydroxyalkyl)trialkylammonium bromides. Descriptors used in the correlations were analyzed to determine which structural features led to lower melting points. These were that asymmetry, due to one or two moderately long chains (e.g., octyl)

with two or three shorter chains (e.g., butyl), gives lower melting points; branching on the longer chains was also predicted to lead to lower melting points, as long as two or more bonds separate the branch points. Since only bromide salts were studied, nothing could be said about the effect of structural change on the anion. However, it was noted that more complex anions would lead to lower melting points.

In a more wide ranging study,⁶⁸ QSPR modeling of the melting point of a total of 717 nitrogen-containing bromide salts was performed using a variety of different techniques and descriptors. It was noted that although the neural network methods used were marginally superior, the differences between the predictive performances of the various methods were small. However, it was concluded that the deviation of predicted and calculated results was sufficiently large that the models could only give general trends rather than accurate predictions of the melting point of a candidate ionic liquid. Much of the problem with generating these QSPRs is with the experimental data. There is the well-known problem that many ionic liquids are glass-forming materials. Consequently, their melting points are difficult to determine, can be dependent upon heating/cooling rates, and give a very broad range of results. Other possible effects arise from many salts having more than one polymorph,⁶⁹ each with different melting points. Also, if more than one polymorph is present in the solid state, this will lead to a lower melting point eutectic. Consequently, achieving the necessary level of control over the experimental conditions to achieve more precise melting point data is unrealistic, and it is unlikely that these data, or precise predictions based upon these data, will be generally available for a wide range of salts. However, notwithstanding the complexities described above, it has been possible to generate some reasonable predictions for small, closely related groups of ionic liquids using parameters such as calculated molecular volumes and/or quantum mechanical calculations.^{70,71}

The upper operating limit of an ionic liquid is given by its thermal decomposition. As a chemical rather than physical phenomenon, decomposition temperatures for ionic liquids are expected to be difficult to predict. This is particularly true given that the kinetics of decomposition reactions need to be considered as well as the thermodynamics. Angell et al.^{50,72} found that the temperature at which the total vapor pressure of a protic ionic liquid reaches 1 atm (boiling) can be predicted by the difference in the pK_a values, in dilute aqueous solution, of the acid and base from which the ionic liquid was made (ΔpK_a). The larger the ΔpK_a , the higher the boiling temperature. The onset of boiling was also shown to be over a small temperature range and so can be used as an estimation of the upper limit of the useful liquid range of the protic ionic liquids. This concept has subsequently been used to design some highly thermally stable protic ionic liquids.⁷³

An attempt to predict the upper end of the liquid range and the thermal decomposition of other ionic liquids has also been made.⁷⁴ Quantum chemical calculations were used to calculate activation energies to predict decomposition mechanisms and rates. It was found that ionic liquids with sufficiently nucleophilic anions decomposed primarily through S_N2 dealkylation of the cation by the anion and that rate constants correlated well with experimental decomposition temperatures. Interestingly, the predicted rate constants gave decomposition temperatures approximately 100 °C below the commonly quoted experimental values, which is in good agreement with studies that have looked at long-term stabilities of ionic liquids.⁶ Ionic liquids with the $[NTf_2]^-$ anion were found to decompose via the elimination of SO_2 from the anion, again in agreement with experimental data.⁷⁵

Molecular volume data have been used to predict a number of physical properties of ionic liquids, namely, densities,^{76–78} surface tensions,^{76,79} and viscosities and conductivities.⁷⁷ Given the potential importance of molecular volume data for predicting physical properties of ionic liquids, it is useful that they have also been the subject of prediction using a variety of methods.^{71,80}

5. SOLVENT–SOLUTE INTERACTIONS IN IONIC LIQUIDS

5.1. Water

The ubiquitous presence of water in even the most well controlled systems singles it out for special consideration as a solute species. At the time of the 1999 review, interest was concentrated on water's reactions with chloroaluminate species and the consequent protic species present in these ionic liquids and their reactivity and superacidity. Since then, concern has moved to the effects that even small amounts of water can have on the properties of the wide range of ionic liquids that do not react with water, such as electrical conductivity,⁸¹ viscosity,⁵⁵ surface tension,⁸² and how the ionic liquid interacts with other solutes,⁸³ even for ionic liquids often described as hydrophobic. In fact, all ionic liquids that have been described to date are hygroscopic and will absorb water from their surroundings.

Early investigations of water miscibility found that the ionic liquids $[C_nC_1im][PF_6]$ ($n = 4, 6, \text{ or } 8$) formed biphasic mixtures with water whereas $[C_nC_1im]Cl$ ($n = 4, 6, \text{ or } 8$) did not.⁸⁴ Furthermore, it was shown that the miscibility of the $[C_nC_1im][PF_6]$ ionic liquids with water decreased as the alkyl chain length increased. The reactivity of the $[PF_6]^-$ ion with water was not considered. $[C_nC_1im][BF_4]$ ($n = 2–5$) has been found to be fully miscible with water at room temperature, whereas for $[C_nC_1im][BF_4]$ ($n = 6–10$) two layers were formed.²⁷ The temperature-dependent behavior of this phenomenon has been used to provide temperature-reversible ionic liquid–water two-phase/one-phase systems for catalysis.⁸⁵ The miscibility of $[PF_6]^-$ ionic liquids with water has been increased by preparing imidazolium cations with ether-functionalized alkyl chains.⁸⁶ For $[C_4C_1im]^+$ ionic liquids the macroscopic phase behavior of ionic liquid–water mixtures has been demonstrated to vary with the anion such that Cl^- , Br^- , $[OTf]^-$, and $[BF_4]^-$ give ionic liquids that mix with water in all compositions, whereas $[C(CN)_3]^-$, $[C_1OC_2OC_2OSO_3]^-$, $[PF_6]^-$, and $[NTf_2]^-$ will phase separate.⁵³ It has also been shown that by using an anion with a suitably long perfluorinated alkyl chain, e.g., nonafluorobutanesulfonate, $[F_4C_4SO_3]^-$, can give an ionic liquid that forms two layers with water, even with protic cations, e.g., $[C_3C_2C_1NH]^+$.⁸⁷ As well as phase separation, complex phase behaviors, such as micelle⁸⁸ and gel⁸⁹ formation, have been observed for ionic liquid–water mixtures.

Octanol–water partition coefficients, K_{OW} , offer a methodology to quantify the hydrophobicity of a compound. These have been measured for a number of imidazolium ionic liquids.⁹⁰ For anions in $[C_4C_1im]^+$ ionic liquids, K_{OW} was found to increase in the order $[OTf]^- < [BF_4]^- < Br^- < [NO_3]^- < Cl^- < [PF_6]^- < [NTf_2]^-$, suggesting that hydrogen bonding to the anion is a significant contribution to the hydrophilicity of the ionic liquid. For $[NTf_2]^-$ ionic liquids, K_{OW} was found to increase with the alkyl chain length, but not with the number of substitutions, of the di- or trisubstituted imidazolium cations. These observations led to the conclusion that hydrogen bonding from the C^2-H of the cation was not a significant contribution to the hydrophilicity of the ionic liquid. This is in direct contrast to the result of a calorimetric study using 1-propanol to study $[C_4C_1C_1^2im]Cl$ and $[C_2C_1im]Cl$ in water.⁹¹ However, it should be noted that these experiments were conducted with very different concentration ranges of ionic liquid in the water.

A puzzling set of results regarding the lack of reactivity of water in some ionic liquid processes have been reported. This is in spite of the fact that hydrolysis reactions in ionic liquids have also been clearly demonstrated.⁹² Water has even been shown to have an increased nucleophilicity in some reactions (see below).⁹³ This lack of expected reactivity of water in ionic liquids was first observed in studies of the oxidation of alcohols using ruthenium⁹⁴ or palladium⁹⁵ catalysts. It is well-known that the presence of water often leads to significant further oxidation of the product aldehydes to acids when primary alcohols are used. This is usually dealt with by the addition of molecular sieves to the reaction mixture. However, in the hydrophilic ionic liquid $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, this was not necessary, and even upon the addition of water, no overoxidation was seen until the amount of water present exceeded that of ionic liquid.⁹⁴ The same lack of overoxidation has also been seen in the TEMPO–CuCl-catalyzed (TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl) oxidation of alcohols to aldehydes.⁹⁶ PCl_3 and POCl_3 have been found to be significantly more hydrolytically stable in the ionic liquids $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$, $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$, and $[\text{C}_2\text{C}_1\text{im}][\text{OTf}]$ than in molecular solvents.⁹⁷ In the $[\text{NTf}_2]^-$ ionic liquids PCl_3 could be stored for days in contact with the air without any hydrolysis. In a recent study of the precipitation of the antimalarial compound artemisinin from ionic liquids by the addition of water as an antisolvent, it was found that the cybotactic region around the artemisinin was more effectively dehydrated by a hydrophilic ionic liquid, $[(\text{HO})^2\text{C}_2(\text{C}_1)_2\text{NH}][\text{C}_2\text{CO}_2]$, than the hydrophobic $[(\text{HO})^2\text{C}_2(\text{C}_1)_3\text{N}][\text{NTf}_2]$.⁹⁸ It is known that ionic liquids can interact strongly with water and that it is possible that hydrated and anhydrous domains can exist in these mixtures (see below), but it is not at all clear how these domains contribute to the effects on the chemistry of water dissolved in ionic liquids. Ionic liquids have even been used as drying agents, such as in the dehydration and breaking of ethanol–water or tetrahydrofuran (THF)–water azeotropes in extractive distillation.⁹⁹

In an attempt to understand the molecular basis for these phenomena, the IR spectra of water in a range of ionic liquids, $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{PF}_6], [\text{SbF}_6], [\text{BF}_4], [\text{ClO}_4], [\text{OTf}], [\text{NTf}_2], [\text{CF}_3\text{CO}_2], \text{or } [\text{NO}_3]\}$, were investigated.²⁶ The spectra showed that the water dissolved in the $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{PF}_6], [\text{SbF}_6], [\text{BF}_4], [\text{ClO}_4], [\text{OTf}], \text{or } [\text{NTf}_2]\}$ ionic liquids was in a symmetric 2:1 complex bound to two anions via H-bonding (Figure 3). In $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{CF}_3\text{CO}_2] \text{ or } [\text{NO}_3]\}$ the spectra of the water were found to indicate the existence of water aggregates or even droplets. The strength of the hydrogen bonding from the water to the anion was found to increase in the order $[\text{PF}_6]^- < [\text{SbF}_6]^- < [\text{BF}_4]^- < [\text{ClO}_4]^- < [\text{OTf}]^- < [\text{NTf}_2]^- < [\text{CF}_3\text{CO}_2]^- < [\text{NO}_3]^-$, which agrees well with other measures of the hydrogen bond acceptor abilities of these ions (see below). This was found to also correlate with the concentrations of water in the ionic liquids in equilibrium with the air. In no case in this study was there spectroscopic evidence for an interaction between the water and the cation of the ionic liquid.

Similar results have been found in other IR studies.¹⁰⁰ In fact, this is so well accepted that the IR spectra of dissolved D_2O have even been suggested as polarity probes for ionic liquids.¹⁰¹ Variable-concentration experiments in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ have shown that, at higher concentrations of water than used in the initial study above, self-association of the water occurs in an anion–water–water–anion chain (Figure 3),¹⁰² with the application of pressure to some degree reversing this.¹⁰³

A recent study of the IR spectra of D_2O in $[\text{C}_2\text{C}_1\text{im}][\text{BF}_4]$ focused more on the changes occurring in the interactions between the ionic liquid's ions.¹⁰⁴ At low concentrations the water begins to break down the three-dimensional structure of

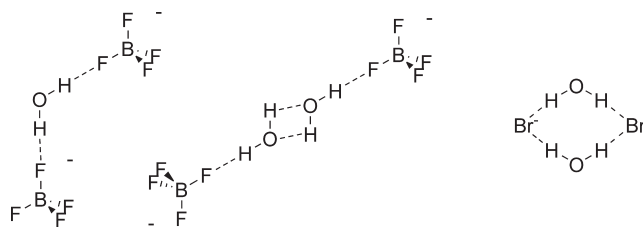


Figure 3. Some observed ionic liquid–water hydrogen-bonded structures: symmetric 2:1 anion–water, anion–water–water–anion chain, and anion–water–anion–water cyclic dimer.

the ionic liquid, which then goes on to form ionic clusters as the concentration of water increases until eventually ion pairs form, which are the dominant species in the aqueous solution (10 mol % ionic liquid). It would seem that the breakup of the ionic liquid into clusters and the self-association of water molecules are occurring in similar concentration ranges. This and other 2D IR experiments have also indicated that some hydrogen bonding between the imidazolium ring protons and the water can also occur, also at higher concentrations of water than used in the original study.^{106,105}

^1H NMR spectra of various concentrations of water in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ have also been studied.¹⁰⁶ Through-space coupling experiments showed that water comes between the anions and the imidazolium ring of the cations, thus loosening the former tight structure and leading to a greater distance between neighboring imidazolium rings. At the same time the formation of hydrophobic domains, where the butyl groups of neighboring cations become closer, was observed. As the concentration of water was increased, distinct interactions between the cation protons and the water could be seen, indicating the formation of hydrogen bonds between them.

The crystal structure of the hemihydrate $[\text{C}_{10}\text{C}_3\text{C}_1\text{N}]\text{Br} \cdot 0.5\text{H}_2\text{O}$ contains isolated water molecules that are hydrogen bonded to two bromide ions ($\text{Br}^- \cdots \text{HOH} \cdots \text{Br}^-$) in the same way as proposed from the IR studies.¹⁰⁷ In the monohydrate $[\text{C}_{10}\text{C}_3\text{C}_1\text{N}]\text{Br} \cdot \text{H}_2\text{O}$, containing twice as much water, cyclic $[(\text{H}_2\text{O})\text{Br}]_2^{2-}$ dimers (Figure 3) are seen.¹⁰⁸ In the crystal structures of $[\text{C}_{18}\text{C}_1\text{im}]\text{Cl} \cdot \text{H}_2\text{O}$, $[\text{C}_{14}\text{C}_1\text{im}]\text{Cl} \cdot \text{H}_2\text{O}$ (polymorph 1), and $[\text{C}_{18}\text{C}_1\text{C}_1\text{im}]\text{Cl} \cdot \text{H}_2\text{O}$ similar $[(\text{H}_2\text{O})\text{Cl}]_2^{2-}$ dimers are seen, but in these structures the water is also hydrogen bonded to the imidazolium ring protons via the water oxygen atoms.¹⁰⁹ However, a second polymorph of $[\text{C}_{14}\text{C}_1\text{im}]\text{Cl} \cdot \text{H}_2\text{O}$ contained the water hydrogen bonded to the Cl^- ions in an infinite chain, again with imidazolium ring $\text{CH} \cdots \text{OH}_2$ hydrogen bonds.

Molecular dynamics (MD) simulations of water in $[\text{C}_1\text{C}_1\text{im}]\text{X}$ $\{\text{X} = \text{Cl} \text{ or } [\text{PF}_6]\}$ showed remarkably little difference in their microscopic properties, in spite of the macroscopic difference of $[\text{C}_1\text{C}_1\text{im}]\text{Cl}$ being miscible with water at all concentrations and $[\text{C}_1\text{C}_1\text{im}][\text{PF}_6]$ forming a biphasic mixture.¹¹⁰ It was shown from the radial and spatial distribution functions around the water molecules that the main interactions with the solvent were two H-bonds formed to two anions. The nearest cation was also close by, but its precise position resulted from the proximity of the water to the anions with which the cation was interacting rather than a direct interaction between the cation and the water. As the concentration of the water was increased, self-association of the water began to be seen, with water clusters and a percolating network of water molecules forming. Subsequent simulations of water– $[\text{C}_n\text{C}_1\text{im}]\text{X}$ $\{n = 2 \text{ or } 4; \text{X} = [\text{BF}_4] \text{ or } [\text{NTf}_2]\}$ mixtures have led to similar conclusions,¹¹¹ although a

more recent study has reported that a cation–water hydrogen bond can be found in water–[C₄C₁im][BF₄] mixtures.¹¹² This study also concluded that the higher concentration clusters of water were composed of linear chains of water molecules. Finally, quantum mechanical (QM) calculations have shown that both cation–water and anion–water hydrogen bonds can be important in determining the structures found in [C₂C₁im]X {X = Cl, Br, [BF₄], or [PF₆]}.¹¹³ A Car–Parrinello QM–MD simulation of a single [C₂C₁im]Cl ion pair dissolved in 60 water molecules found that the ions remain somewhat associated, with the Cl[−] ion lying in the vicinity of the C²–H of the imidazolium ring, even in this relatively dilute system.¹¹⁴

Combining all of the above, a picture in which at low concentrations water is dispersed throughout the ionic liquid as isolated molecules hydrogen bonded to the ionic liquids' anions with a weaker interaction with the cations emerges. This leads to the beginnings of the separation of the oppositely charged ions. As the concentration of water increases in water-miscible ionic liquids, it can begin to self-associate in dimeric structures. For ionic liquids that do not mix fully with water, phase separation occurs at or before this stage. As the concentration of water increases still further, these dimeric structures begin to form chains of molecules, which can percolate through the ionic liquids' structures and cause them to break up into first large, but then smaller, ionic clusters. As the amount of water increases still further, the ionic liquids dissolve to become ion pairs in aqueous solution and eventually free hydrated ions. The precise concentrations at which the different behaviors emerge are very dependent on the anion and to a lesser extent the cation of the ionic liquid.

5.2. Polarity

Most modern discussions of solvents rely on the concept of solvent polarity. Qualitative ideas of polarity are based upon observations such as “like dissolves like” and are well accepted and understood. The currently accepted definition of polarity is that it is the sum of all possible (specific and nonspecific) intermolecular interactions between the solvent and any potential solute, excluding those interactions leading to definite chemical changes (reactions) of the solute.^{115,116} This includes Coulombic interactions, the various dipole interactions, hydrogen-bonding interactions, and electron pair acceptor–electron pair donor acid–base interactions and is both a physical and a chemical phenomenon. Hence, there can be no simple single measure of all of these interactions. There are many empirical solvent polarity scales¹¹⁷ that attempt to give quantitative estimates of solvent polarity, several of which have been applied to ionic liquids. None of these scales are perfect, and all are more or less sensitive to different aspects of polarity. Care is therefore required, since attempts to compare polarities measured by different techniques that are sensitive to different properties of the solvent often only lead to confusion. The test of a solvent polarity scale is its usefulness in explaining and/or predicting changes in solute properties when dissolved in different solvents. There is no useful concept of “right” or “wrong” when comparing these scales; rather the idea that a particular scale is more or less appropriate in a given circumstance is more helpful. However, it is possible to draw some tentative general conclusions.

All ionic liquids are not the same; different combinations of anions and cations lead to solvents with different polarities. No ionic liquids have shown themselves to be “superpolar”; regardless of the method of assessing their polarities, values for ionic liquids come within the range of molecular solvents. Most general measures of overall polarity place ionic liquids in the range of the short to medium alkyl chain length alcohols.

Table 1. Estimated Static Dielectric Constants for Ionic Liquids

ionic liquid	ϵ_r (dielectric spectroscopy) ¹¹⁸	ϵ_r (P_i + CED) ¹¹⁹	ϵ_r (other methods)
[C ₁ NH ₃][HCO ₂]	40.3		
[C ₂ NH ₃][HCO ₂]	30.3		
[C ₄ NH ₃][HCO ₂]	29.2		
[(HO) ² C ₂ NH ₃][HCO ₂]	57.3		
[C ₂ C ₁ im][C ₂ OSO ₄]	27.9	13.5	37–39 ¹⁰¹
[C ₂ NH ₃][NO ₃]	26.2		
[C ₂ C ₁ im][OTf]	15.2	15.8	
[C ₄ C ₁ im][OTf]	13.2	13.5	
[C ₂ C ₁ im][BF ₄]	12.8	14.8	
[C ₄ C ₁ im][BF ₄]	11.7	12.9	
[C ₄ C ₁ im][PF ₆]	11.4	14.0	11.4 ¹²⁰
[C ₆ C ₁ im][PF ₆]	8.9	11.1	
[C ₂ C ₁ im][NTf ₂]	12.25	11.5	<10 ³⁵ 14–16 ¹⁰¹
[C ₃ C ₁ im][NTf ₂]	11.80	10.6	
[C ₄ C ₁ im][NTf ₂]	11.52	9.4	
[C ₅ C ₁ im][NTf ₂]	11.45	7.9	
[C ₂ C ₁ C ₁ ² im][NTf ₂]	11.45		
[C ₂ C ₁ C ₁ ² im][NTf ₂]	11.6		

5.2.1. Dielectric Constant. The dielectric constant (ϵ_r) of the pure liquid is by far the most commonly used polarity scale. Dielectric constants have been measured for most molecular liquids and are widely available in reference texts, including most commercial catalogues. Molecular solvents with $\epsilon_r < 9$ are considered to be nonpolar, those with $9 < \epsilon_r < 15$ are moderately polar, and values in the range $15 < \epsilon_r < 30$ characterize the solvent as polar, but not exceptionally so. Liquids with ϵ_r in excess of 50 are considered to be highly polar. The ubiquity of ϵ_r leads many to treat it as if it is synonymous with polarity. It is not; it is a physical phenomenon that is used as an empirical polarity scale. Estimates of static dielectric constants of ionic liquids have been derived from microwave dielectric spectroscopy (e.g., Table 1).¹¹⁸ Most values found ranged from 9 to 15 depending upon the ionic liquid, characterizing these as moderately polar liquids. However, values in excess of 30 were found for some protic ionic liquids.^{118f} The dielectric constant of the ionic liquids appears to be related to the ability of the ionic liquids to enter into hydrogen bond networks. Hence, for anions the dielectric constant varies such that [HCO₂][−] > [C₂OSO₄][−] ≈ [NO₃][−] >> [OTf][−] > [BF₄][−] > [NTf₂][−] ≈ [PF₆][−], which is the order of the decreasing basicity of the ions, and for cations the order is [(HO)²C₂NH₃]⁺ > [C₂NH₃]⁺ > [C_nC_mim]⁺. The dielectric constant was also found to decrease as the length of the alkyl chain on the cations increased. These effects are similar to the behaviors seen for molecular solvents.

The static dielectric constant has also been estimated from measurements of the speeds of sound, densities, and heats of vaporization (Table 1).¹¹⁹ The speeds of sound and densities provide the basis for the estimation of the cohesive energy densities (CEDs) of the ionic liquids, while the heats of vaporization give the internal pressures (P_i). Together these values then provide the basis for the ϵ_r calculations. Given how different this method of deriving ϵ_r is from dielectric spectroscopy, it is remarkable how well the results agree. However, it should be noted that the only ionic liquid for which a significant difference was found using the two techniques is

$[\text{C}_2\text{C}_1\text{im}][\text{C}_2\text{OSO}_4]$, which is the only ionic liquid from the more polar sets according to microwave spectroscopy that has been tested by both techniques. The trend that, for a given anion, changing the length of the alkyl chain on the imidazolium cation decreases the ϵ_r is seen. However, while a general trend of more basic ions giving higher ϵ_r values is seen, the precise ordering $\{[\text{OTf}]^- > [\text{PF}_6]^- \approx [\text{BF}_4]^- > [\text{NTf}_2]^- \}$ is different from that seen with microwave spectroscopy.

The dielectric constants of some ionic liquids have also been estimated from measurements of the spectra of a number of probes. The band shape of the emission spectrum of pyrenecarboxaldehyde was used to give an upper limit of $\epsilon_r < 10$ for $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$.³⁵ By comparing the spectrum of pyrene with that of 6-propionyl-2-(*N,N*-dimethylamino)naphthalene (PRODAN), Baker et al. deduced a value of $\epsilon_r = 11.4$ for $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$,¹²⁰ the same as that derived from microwave dielectric spectroscopy. The excellent agreement of these completely independent measurements suggests that the values derived from microwave spectroscopy can indeed be relied upon, or at least that these measurements are recording the same behaviors. Good agreements have also been found with values derived from infrared spectra of water and D_2O for $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$, although again there was greater deviation for the values for $[\text{C}_2\text{C}_1\text{im}][\text{C}_2\text{OSO}_4]$.¹⁰¹

5.2.2. Hildebrand Solubility Parameter, δ_H . For any species to be dissolved in a solvent, the molecules or ions of the solvent must first be separated. Similarly, any process that involves a significant change in the molar volume of the solute(s) will involve a change in the separations of the solvent species. The Hildebrand solubility parameter, δ_H , attempts to measure the energy required to do this:¹¹⁵

$$(\delta_H)^2 = \frac{\Delta U_v}{V_m} \approx \frac{\Delta H_v - RT}{V_m} \quad (1)$$

where V_m is the molar volume of the solvent and ΔU_v and ΔH_v are the molar energy and enthalpy of vaporization to a gas of zero pressure.

It was for many years believed that ionic liquids were completely nonvolatile so direct access to the Hildebrand parameter would not be possible. However, this is now known to have been a false assumption.¹²¹ Since this realization, the enthalpies of vaporization have been measured for ionic liquids and δ_H values derived.¹²² For a range of imidazolium, pyrrolidinium, and ammonium ionic liquids, including some with alcohol-functionalized chains, values for δ_H in the range 16.3–26.5 (J cm^{-3})^{1/2} were found, which are of the same order as those found for short to medium chain length alcohols. The values were found to be dependent upon the anion of the ionic liquid, with the values for the bis(heptafluoroethylsulfonylethyl)imide $\{[\text{beti}]^-\}$ ionic liquids being lower than those of the $[\text{NTf}_2]^-$ ion, and to decrease with increasing chain length of the alkyl chains on the cations.

Where comparison is possible, the δ_H values derived from enthalpies of vaporization are slightly lower than those derived from surface tension measurements¹²³ and significantly lower than those derived from viscosities^{124,125} or chemical reactivity.¹²⁶ For molecular solvents a gas of zero pressure consists of isolated molecules and is well approximated to under usual experimental conditions. However, it has been shown that for ionic liquids it is likely that any gas phase is composed of ion pairs and higher order clusters.¹²⁷ It is likely that this would lead to an underestimate for δ_H .

5.2.3. Single-Molecule Spectroscopic Probes. There are many polarity scales that are based upon the measurement of the spectrum of a single probe molecule.^{115,117} This approach has the advantage that the measurements are often simple and can be made

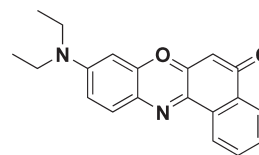


Figure 4. Nile red.

quickly using readily available equipment. However, while the response of the probe to the solvent in which it is dissolved is determined by all possible solvent–probe interactions, there is no reason for there to be an equal contribution from all of these for all probes. Hence, it is important to be as aware as possible of which interactions are likely to have a strong effect on the particular probe used and which have a lesser effect. Since ionic liquids are composed of both anions and cations, either of which may preferentially solvate a particular probe molecule, this requirement is even greater than is usually the case for molecular solvents. In many papers one of these scales is reported for a small number of ionic liquids and then used as a basis to make statements about their overall polarity. None of these polarity scales are capable of delivering this kind of information, except in the vaguest sense. Finally, many of the probes used for such measurements are used in very low concentrations and may be susceptible to preferential solvation by impurities in the ionic liquids, the presence of which can lead to distorted results. However, these problems do not mean that these data are without use, quite the reverse; it just means that care is required when comparing results.

5.2.3.1. Electronic Absorption Spectra. The first solvatochromic dye to be used with a number of ionic liquids was Nile red (Figure 4).¹²⁸ The ionic liquids used were composed of $[\text{C}_n\text{C}_1\text{im}]^+$ cations with $[\text{NO}_2]^-$, $[\text{NO}_3]^-$, $[\text{BF}_4]^-$, $[\text{PF}_6]^-$, and $[\text{NTf}_2]^-$ anions. The values of the energy of the electronic transition, E_{NR} , did not vary greatly and characterized the ionic liquids as being moderately polar liquids, in broad agreement with the ϵ_r values reported above.

The effect of hydrogen bond donation to Nile red from the cation of the ionic liquid can be seen when comparing the E_{NR} values of imidazolium salts protonated on one of the ring nitrogen atoms¹²⁹ with that of the equivalent methyl-substituted salt {e.g., E_{NR} for $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4] = 217.2 \text{ kJ mol}^{-1}$ and E_{NR} for $[\text{C}_4\text{Him}][\text{BF}_4] = 212.5 \text{ kJ mol}^{-1}$ }. This is also seen when comparing the value for $[(\text{C}_{10})_3\text{C}_1\text{P}][\text{NO}_3]$ ($E_{\text{NR}} = 225.8 \text{ kJ mol}^{-1}$) with that of $[\text{C}_8\text{C}_1\text{im}][\text{NO}_3]$ ($E_{\text{NR}} = 217.4 \text{ kJ mol}^{-1}$).¹³⁰ This strong cation effect arises due to the ease of hydrogen bond donation to Nile red. Functionalization of the side chain of the imidazolium cation has also been found to give an increase in the polarity of the resultant ionic liquid, regardless of whether a hydrogen bond donor $\{[(\text{HO})^2\text{C}_2\text{C}_1\text{im}][\text{NTf}_2], E_{\text{NR}} = 211.9 \text{ kJ mol}^{-1}\}$ or hydrogen bond acceptor $\{[(\text{C}_1\text{OC}_2)\text{C}_1\text{im}][\text{NTf}_2], E_{\text{NR}} = 213.5 \text{ kJ mol}^{-1}\}$ is used.¹³¹

The anion also has an effect on the E_{NR} value of the ionic liquids.¹²⁸ The E_{NR} values for several 1-ethylimidazolium ionic liquids have been compared to the pK_a of the conjugate acid of the anion of the ionic liquid.¹²⁰ This study shows a general trend that more basic anions lead to higher E_{NR} (less polar) values for the ionic liquids. This trend is the opposite to that observed for the ϵ_r values reported above (more basic anion = more polar ionic liquid). This shows the complexity of these polarity phenomena and warns against attempts to use any one scale to be a general polarity measure. It is known that in molecular solvents E_{NR} is affected by the ability of the solvent to hydrogen bond donate to the Nile red.¹³² It can be surmised that this dominates any contribution from direct interaction of the ionic liquid (cation) with

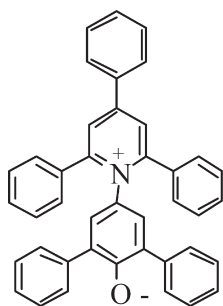


Figure 5. Reichardt's dye.

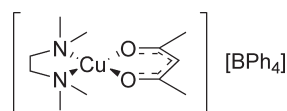
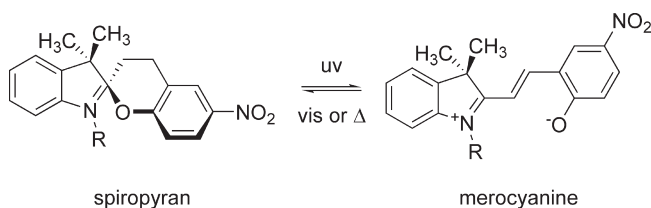
the dye. Hence, the result can largely be attributed to antagonistic behavior of the ionic liquid anions in determining the overall hydrogen-bond-donating properties of the ionic liquids (see below).

The most popular of all of the solvatochromic empirical polarity scales is that based upon the longest wavelength absorption band of Reichardt's dye 2,4,6-triphenylpyridinium *N*-(2,6-diphenylphenoxide) betaine (Figure 5).^{115,133} Reichardt's dye is commercially available and shows one of the largest solvatochromic shifts known (375 nm between diphenyl ether and water). It registers effects arising from the solvent dipolarity, hydrogen bonding, and Lewis acidity, with the greatest contribution coming from the hydrogen bond donor property of the solvent.¹³⁴ Reichardt has collected together the results for the normalized polarity scale, E_T^N , for 82 liquid salts.¹³⁵ Results for the same ionic liquid measured by different groups were shown to vary widely. These measurements are highly sensitive to the presence of impurities, such as water, amines, or chloride ions, and so to the precise preparation of the ionic liquids used. Reichardt notes from the values quoted that most of the measurements are consistent with the ionic liquids containing water from exposure to the air. The results are also sensitive to the precise experimental conditions, such as the temperature at which the measurements are made. Therefore, care is needed when comparing the results of different studies.

The E_T^N values for ionic liquids are dominated by the cations with the general trend $[(C_n)NH_3]^+ \approx [(C_n)_2NH_2]^+ > [(C_n)_3NH]^+ > [C_nC_1im]^+ \approx [C_npyr]^+ > [C_nC_1C_1^2im]^+ > [(C_n)_4N]^+ > [(C_n)_4P]^+$, as would be expected from the hydrogen bond donation capacity of these cations. The highest values are similar to those of highly polar solvents such as water, the lowest are similar to those of polar aprotic solvents, and those of the imidazolium salts are of the same order as those of moderately polar protic solvents. Increasing the alkyl chain length for a given cation type causes a slight decrease in the E_T^N value for the ionic liquid. Functionalizing the alkyl chain leads to increases in the E_T^N value for the ionic liquid,¹³¹ in broad agreement with the Nile red values above.

The role of the anion is less direct. Reichardt's dye does not act as a hydrogen bond donor and cannot report the hydrogen bond acceptor nature of the ionic liquids directly. However, ionic liquids with the same cation but different anions do have different E_T^N values. The degree of this difference varies with the cations. For $[(C_2)_4N]Cl$ and $[(C_2)_4N][NO_3]$ the difference is only 0.006, whereas the difference between $[C_2NH_3]Cl$ and $[C_2NH_3][NO_3]$ is 0.318. Less dramatically, the difference in the values for $[C_8C_1C_1^2im][BF_4]$ and $[C_8C_1C_1^2im][NTf_2]$ is only 0.018, whereas the difference between $[C_4C_1im][BF_4]$ and $[C_4C_1im][NTf_2]$ is 0.031. These results can largely be attributed to antagonistic behavior of the ionic liquid anions in determining the overall hydrogen-bond-donating properties of the ionic liquids (see below).

Scheme 3

Figure 6. $[Cu(acac)(tmen)][BPh_4]$.

The solvatochromism of the longest wavelength absorption of some merocyanine probes (in equilibrium with their spiropyran isomers, Scheme 3) has been used to investigate the polarity of a number of different ionic liquids. Wu et al. compared the changing spectra of a number of these probes $[R = (CH_2)_3CH_3, (CH_2)_7CH_3, (CH_2)_2COOH, (CH_2)_3SO_3H]$ in a variety of carboxylate ionic liquids with Reichardt's $E_T(30)$ scale.¹³⁶ It had previously been shown that the transition energies for these dyes were well correlated with Reichardt's $E_T(30)$ scale in molecular solvents.¹³⁷ This correlation was found to hold well for ionic liquids without strong hydrogen bond acceptor ability ($\beta < 0.9$). Similar results were found for another merocyanine probe ($R = CH_3$).¹³⁸ This suggests that the principle interaction between the ionic liquids and the merocyanine form of the probe is well modeled by the interaction between the ionic liquids and Reichardt's dye. This is most likely due to all of them being zwitterionic compounds with hydrogen bond acceptor phenoxide groups. Indeed, ab initio calculations of the ionic liquid solvated merocyanine isomer ($R = CH_3$) have shown a strong cation interaction with the phenoxide oxygen and only a weak interaction with the anion.¹³⁹ The dye for which this was not true was the one with the $(CH_2)_3SO_3H$ substituent.¹³⁶ For this dye a significant solvatochromic shift was only observed for those ionic liquids with very strong hydrogen bond donation ability. This suggests that the primary hydrogen bond acceptor site for the dye is at the ionized $-SO_3^-$ rather than the phenoxide (which may well be protonated under these conditions). When the ionic liquid anion did have very strong hydrogen bond acceptor ability, no solvatochromism was observed.

The interaction of ionic liquids with the transition-metal complex $[Cu(acac)(tmen)]^+$ (Figure 6) has also been studied.^{140,141} It has been shown that the λ_{max} for the $d \rightarrow d$ band correlates well with the Gutmann donor numbers¹⁴² and is dominated by the nature of the anion of the ionic liquid. The values vary greatly in the order $[C_4C_1im][OTf] (\lambda_{Cu} = 602) > [C_4C_1im][NTf_2] (\lambda_{Cu} = 546) > [C_4C_1im][PF_6] (\lambda_{Cu} = 517)$, which compares to DMF ($\lambda_{Cu} = 602$) $>$ acetone ($\lambda_{Cu} = 569$) $>$ CH_2ClCH_2Cl ($\lambda_{Cu} = 500$). This is counter to the generally held myth that ionic liquids are composed of anions that cannot coordinate to metal centers. Clearly, for this coordinatively unsaturated complex, they do. These values have been used to demonstrate that more Lewis basic ionic liquids can reduce silica particle-particle interactions in colloidal dispersions by giving greater ionic liquid-particle interactions.¹⁴³

5.2.3.2. Vibrational Spectra. The Gutmann acceptor number (AN) is a measure of the ability of the solvent to interact with an

electron pair donor and is traditionally derived from the ^{31}P NMR chemical shift of solutions of triethylphosphine oxide in the solvent.^{115,144} These have not been measured for a wide range of ionic liquids. However, the Raman spectra of diphenylcyclopropane, particularly the $\{\text{C}=\text{C} + \text{C}=\text{O}\}$ mode, have been used to estimate the AN of several ionic liquids.¹⁴⁵ The values were found to vary in the order $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6] (27.7) > [\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{BF}_4] (27.5) > [\text{C}_4\text{C}_1\text{im}][\text{BF}_4] (26.9) = [\text{C}_4\text{C}_1\text{im}]\text{Cl} (26.9) > [\text{C}_4\text{C}_1\text{im}][\text{NTf}_2] (25.2) > [(\text{C}_1\text{OC}_2)(\text{C}_2)_2\text{C}_1\text{N}][\text{BF}_4] (23.9) > [(\text{C}_1\text{OC}_2)(\text{C}_2)_2\text{C}_1\text{N}][\text{NTf}_2] (20.3)$. These values are of the same order as that for CHCl_3 (23.1) and are considerably less than that for methanol (41.5) and the values that the authors estimated using measurements based on Reichardt's dye (ca. 36). While the AN is not the same as the hydrogen bond donor property of the liquid, one might have expected greater agreement for these values (see below). However, the general trend that imidazolium-based ionic liquids have a greater AN than quaternary ammonium salts is in agreement with expectations.

The $\nu_{\text{C}=\text{O}}$ IR stretching frequencies of acetone have been shown to correlate with the AN of a range of solvents.¹⁴⁶ The range of values found in a variety of imidazolium-based ionic liquids was very narrow ($\nu_{\text{C}=\text{O}} = 1706\text{--}1711\text{ cm}^{-1}$), even when the alkyl chain was substituted with $-\text{OH}$ and $-\text{CN}$ groups, and similar to that of polar solvents (both protic and aprotic).¹⁴⁷ Similar results were found for the $\nu_{\text{C}=\text{O}}$ IR stretching frequencies of DMF. When the authors used $\text{Fe}(\text{CO})_5$ as the probe, they noted that the polarity of the ionic liquid decreased with increasing alkyl chain length on the imidazolium cation and that there was also an anion effect, similar to that seen for Reichardt's dye and Nile red.

5.2.3.3. Electron Paramagnetic Resonance. The ^{14}N hyperfine coupling constant of the electron paramagnetic resonance (EPR) spectrum of 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl, a commercially available stable free radical, has been used to measure the polarity of a small number of ionic liquids.¹⁴⁸ The values correlate very well with the $E_{\text{T}}(30)$ scale and so arise from a combination of hydrogen bond donation from the solvent and Coulombic, dipolarity, and polarizability effects. EPR also provides information about the tumbling of the probe solute in a solvent by its effect on the spin relaxation times (τ_{r}). τ_{r} times in the ionic liquids are longer than those in the molecular solvents studied. This was attributed partly to the higher viscosities of the ionic liquids and partly to a hydrogen-bonding interaction between the cation and the nitroxide functionality of the probe molecule. This technique has the advantage that it does not require that the ionic liquid is transparent to UV and visible wavelengths and may be used for colored ionic liquids.

The α -hydroxydiphenylmethyl radical bears a $-\text{OH}$ group, and consequently, its EPR spectra in ionic liquids highlight the importance of the anion in its solvation.¹⁴⁹ The hyperfine coupling constants were found to increase with increasing Gutmann donor number (DN) of the anions, implying the formation of a hydrogen bond between the probe and the ionic liquid. The values ranged from those similar to that of 1,2-dichloroethane ($a_{\text{OH}} = 2.08$) for $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ ($a_{\text{OH}} = 2.03$) to values closer to that of pyridine ($a_{\text{OH}} = 3.25$) for $[\text{C}_4\text{C}_1\text{im}]_2[\text{WO}_4]$ ($a_{\text{OH}} = 3.21$); $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ ($a_{\text{OH}} = 2.28$) had a value similar to that of benzonitrile ($a_{\text{OH}} = 2.27$). As expected, no correlation of the values was found with the Reichardt's dye spectra in the ionic liquids.

5.2.3.4. Fluorescence Spectra. Fluorescence spectra of a number of probe dyes have been used to investigate solvation phenomena in ionic liquids. The spectra of pyrene have generally placed the ionic liquids in the polarity range of moderately polar solvents.^{115,150,151} Although some contribution from solvent hydrogen bond acidity has been noted,¹⁵² the mechanisms by

which spectral changes arise are poorly understood, and it is difficult to draw conclusions in anything other than the most general terms from these measurements. The spectrum of pyrene has been used to compare the microenvironment provided by a supported ionic liquid phase (SILP) to the bulk ionic liquid.¹⁵³ Salts with cations similar to those that give rise to ionic liquids were covalently bound to polymeric resins via the cation. The authors concluded that the functional surfaces of the SILP maintained the same polarity as the equivalent bulk ionic liquids.

The Stokes shift of the fluorescence spectra of PRODAN has been used to estimate the polarity of $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ as being between those of chloroform and acetone.¹¹⁵ Correlations of the fluorescence maxima of PRODAN and coumarin 153 (C153) with $E_{\text{T}}(30)$ values for molecular solvents have been applied to the results found in a number of ionic liquids $\{[\text{C}_2\text{C}_1\text{im}][\text{BF}_4], [\text{C}_4\text{C}_1\text{im}][\text{BF}_4], [\text{C}_2\text{C}_1\text{im}][\text{NTf}_2], [\text{C}_4\text{C}_1\text{im}][\text{NTf}_2], \text{and } [\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]\}$.¹⁵⁴ However, these values were significantly below the values obtained with Reichardt's dye itself.¹³⁵

Time-resolved fluorescence spectra allow the dynamics of solvation in ionic liquids to be probed. The literature reports an ongoing debate. The questions that are at issue include whether the cations and anions of the ionic liquid solvate on different time scales, the relative importance of ion translation as opposed to dielectric relaxation, and what effects the correlated motion of ions has on solvation. On the basis of the fluorescence spectra of PRODAN, C153, and Nile red,¹⁵⁵ Samanta et al. attributed an initial fast component of the solvation to the anion and a longer component to collective motion of both anions and cations. Armstrong et al.¹⁵⁶ have proposed that solvation of C153 is by the cation, which mainly contributes to initial solvation behavior via dipole relaxation. Although neutral, these three dyes all carry electron pair donor sites such as carbonyl groups, and none have any hydrogen-bond-donating sites, which leads one to expect that solvation by the cation is most likely. The observed cation effect on the electronic absorption spectra of Nile red (see above) strongly supports this proposal. Also using C153, Maroncelli et al.¹⁵⁷ noted the similarity between data for some ionic liquids and those for supercooled liquids close to their glass transition. This is a very reasonable description of many ionic liquids at room temperature. The dissimilarity that they observed between imidazolium-based ionic liquids and phosphonium ionic liquids again suggests preferential solvation by the cation and that the polarizability of the delocalized electrons of the imidazolium ring makes an important contribution to initial solvation by these ionic liquids. On the basis of viscosity correlations, they also consider the rotation of the cation to give a significant contribution to the solvation dynamics, which is then followed on a longer time scale by ion translation.

12'-Apo- β -carotenoic 12'-acid (12'CA) is structurally very different from those dyes used above, bearing a carboxylic acid functionality and an extended polyene chain. The lifetime of its intramolecular charge transfer state (τ_1) has been used to investigate a wide range of ionic liquids.¹⁵⁸ In molecular solvents τ_1 has been correlated with a function derived from the static dielectric constant and the refractive index of the solvent, but this did not hold for the ionic liquids. The results are in the range 40–110 ps, which are in the range found for short chain alcohols (e.g., ethanol, 109 ps, and methanol, 49 ps). Comparing the results for the ionic liquids $[\text{Cat}][\text{NTf}_2]$, τ_1 varies in the order $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}]^+ (96\text{ ps}) > [\text{C}_4(\text{C}_1)_3\text{N}]^+ (85\text{ ps}) \approx [\text{C}_4\text{C}_1\text{pyrr}]^+ (83\text{ ps}) > [\text{C}_4\text{C}_1\text{im}]^+ (65\text{ ps}) \approx [(\text{C}_2)_3\text{S}]^+ (64\text{ ps})$. This strongly suggests that interactions between the cation and the 12'CA are an important contributor to the spectral changes. A general, but imperfect, trend of increasing lifetime with increasing

chain length for $[C_nC_{1im}][NTf_2]$ ($n = 2, 3, 4, 6, 8$, or 10) was also observed. For $[C_4C_{1im}][X]$, the trend is less pronounced, $[BF_4]^-$ (71 ps) $>$ $[N(CN)_2]^-$ (67 ps) $>$ $[NTf_2]^-$ (65 ps) $>$ $[PF_6]^-$ (62 ps). The authors reject the idea that these behaviors are due to hydrogen bonding and attribute them to electrostatic interactions between the cations and the probe. However, the results do fit equally well with the widely proposed interpretations of ionic liquid–solute interactions via hydrogen bonding.

Solutions of (S)-(1-methyl-2-pyrrolidinyl)methyl 2(S)-(6-methoxy-2-naphthyl)propionate in tetrabutylphosphonium D- or L-tartrate have shown a 10% difference in the observed fluorescence lifetimes in the two ionic liquids.¹⁵⁹ This chiral discrimination was attributed to subtly different solvent–solute interactions between the two different chiral anions and the chiral solute, giving rise to different activation energies for the fluorescence quenching.

5.2.4. Multiparameter Scales. Given the myriad contributions that make up polarity, it is unsurprising that attempts to describe it with a single number are inadequate to the task of gaining insight into changes in solute behaviors generated by changes of solvent.^{115–117} Multiparameter scales attempt to solve this by using an additional level of sophistication in the description of the solvent.

5.2.4.1. Kamlet–Taft System. Rather than hoping to find a single probe molecule that could act as a somehow generic solute, Kamlet and Taft developed a system of solvent description based upon the comparison of effects on the UV–vis spectra of sets of closely related dyes that were selected to probe particular solvent properties.¹⁶⁰ This system is based upon LSERs (eq 2) composed of the complementary scales of hydrogen bond acidity (α), hydrogen bond basicity (β), and dipolarity/polarizability effects (π^*). Complete sets of Kamlet–Taft parameters have been measured for a number of ionic liquids (Table 2).^{136,141,161,162}

$$(XYZ) = (XYZ)_0 + a\alpha + b\beta + s\pi^* \quad (2)$$

To derive the π^* value, a solvatochromic dye with an absorption maximum in an easily accessible part of the spectrum that has sufficient nonspecific interactions with the solvent, but zero hydrogen bonding, would be required. Unable to find such a probe, Kamlet and Taft originally used seven solvatochromic dyes that have strong and symmetric solvatochromic maxima in an attempt to average out any undesirable specific interactions of any one probe molecule.¹⁶⁰ The data used to calculate π^* values were then expanded, with more solvents investigated and more solvatochromic dyes used. In total, they used 47 dyes to give π^* values to 70 solvents. The new π^* scale was then an average of those derived for all of the solvatochromic dyes, with a normalization between 0 (cyclohexane) and 1 (dimethyl sulfoxide). While using such a large number of dyes allowed anomalies in the original set of dyes to be observed and corrected for, it makes the measurement of π^* impractical when new solvents are made, even more so when an entire new class of solvents are made. Consequently, most authors have reported π^* results for ionic liquids using a single dye. However, care is required when doing so. For instance, it has been shown for the ionic liquid tetrabutylammonium 2-[bis(2-hydroxyethyl)amino]ethanesulfonate that π^* values varied as widely as from 1.41 when *N*-methyl-4-nitroaniline was used as the probe to 0.77 when *N,N*-diethyl-3-nitroaniline was used, with a range of values between these values found for four other dyes.¹⁶³ π^* is not a fundamental physical parameter; hence, it cannot be said that one of the values is right and the others are wrong nor indeed that one is inherently better

Table 2. Kamlet–Taft Parameters Using the Dye Set Reichardt's Dye, *N,N*-Diethyl-4-nitroaniline, and 4-Nitroaniline.^{136,141,163}

salt	π^*	α	β
$[(HO)^2C_2C_{1im}][NTf_2]$	1.08	1.14	0.28
$[(HO)^3C_3C_{1im}][NTf_2]$	1.06	0.91	0.24
$[(HO)^3C_3C_{1im}][CH_3CO_2]$	1.08	0.51	0.99
$[C_4C_{1im}][BF_4]$	1.05	0.63	0.38
$[C_4C_{1im}][OTf]$	1.01	0.63	0.46
$[C_4C_{1im}][SbF_6]$	1.04	0.64	0.15
$[C_4C_{1im}][PF_6]$	1.03	0.63	0.21
$[C_4C_{1im}][NTf_2]$	0.98	0.61	0.24
$[C_4C_{1im}][C_1CO_2]$	1.04	0.43	1.05
$[C_4C_{1im}][O_2CC_2(OH)^2CO_2]$	1.01	0.41	1.00
$\{[C_4C_{1im}][O_2CC_2CO_2]$	1.09	0.39	1.08
$[C_4C_{1im}][NTf_2]$	1.01	0.38	0.24
$[C_4C_{1im}][BF_4]$	1.08	0.40	0.36
$[C_4C_{1im}][NTf_2]$	0.98	0.51	0.29
$[C_8pyr][NTf_2]$	0.99	0.51	0.28
$[C_8C_{1im}][NTf_2]$	0.95	0.48	0.35
$[C_8C_{1im}][NTf_2]$	0.97	0.50	0.33
$[C_8C_{1im}][NTf_2]$	0.97	0.50	0.33
$[C_4C_{1im}][NTf_2]$	0.95	0.43	0.25

than another. Rather, what this does show is that one cannot make direct comparisons of results obtained with different probe molecules nor can one use values derived from different probes together in the analysis of some other solvent phenomenon.

The most widely applied π^* dye in ionic liquids is *N,N*-diethyl-4-nitroaniline.^{136,141,162} As one of the original Kamlet–Taft dyes and a commercially available material, it has also been applied to several hundred molecular solvents. These π^* values were high for all of the ionic liquids investigated, but not beyond the range found in molecular solvents. The π^* values result from measuring the ability of the solvent to induce a dipole in the probe solute and should be expected to incorporate the effect of Coulombic interactions from the ions as well as dipole and polarizability effects. This is reinforced by values for symmetrical quaternary ammonium ionic liquids showing a general trend of lower values for larger cations¹⁶¹ and helps to explain the consistently high values for all of the salts in the studies. The values for imidazolium ionic liquids appear to be consistently higher than those of pyridinium ionic liquids; anion effects are less clear-cut.

As expected, some small differences in the derived π^* values have been found when *N,N*-dimethyl-4-nitroaniline has been used as the probe^{161,164} and similarly when 4-*tert*-butyl-2-(dicyanomethylene)-5-[4-(diethylamino)benzylidene]- Δ^3 -thiazoline has been used.¹⁶⁵ Spange et al. found that the π^* values of their ionic liquids were higher than might be expected on the basis of the dielectric constant (as expressed through the Onsager parameter) and attributed this to the likely high polarizability of the imidazolium cations that they used. However, Kimura et al. further noted that the π^* values showed a reasonable correlation with the molar concentrations of the ionic liquids and concluded that considering the relative charge concentrations of the ionic liquids was a useful way to understand the values.¹⁶⁴

The Kamlet–Taft β values are derived by comparing the spectra of closely related pairs of dyes (Figure 7).¹⁶⁰ Different values are obtained when different dye pairs are used. Again this

does not mean that values derived from one dye set are right and those from another wrong, but it does mean that one cannot make direct comparisons of results obtained with different pairs of probe molecules nor can one use values derived from different pairs together in the analysis of some other phenomenon.

The β values of ionic liquids are primarily controlled by the anions, with basicity increasing as the strength of the conjugate acid of the anion decreases.^{136,141,162} It was also shown that the values can be correlated with the ^1H NMR chemical shift (at fixed concentration in CD_2Cl_2) of the proton at the C^2 position of the imidazolium ring in a number of $[\text{C}_4\text{C}_1\text{im}]^+$ salts.¹⁶⁶ While these general trends are clear, the cations do appear to be playing a role in determining the β values. When the *N,N*-diethyl-4-nitroaniline and 4-nitroaniline pair is used, it is generally true (though not perfectly so) that ionic liquids with the $[\text{NTf}_2]^-$ have lower β values when they have more hydrogen bond donating cations (see Table 2). This is likely to be a consequence of an antagonistic relationship between the ions in determining the overall hydrogen bond acceptor ability of the ionic liquid (see below).

The hydrogen bond donor ability of a solvent is determined by using the spectrum of Reichardt's dye and the π^* value of the solvent. Consequently, it is sensitive to how π^* itself was derived. It has been measured for a number of ionic liquids using π^* derived from *N,N*-diethyl-4-nitroaniline.^{136,141,163} The α value of an ionic liquid is largely determined by the availability of hydrogen bond donor sites on the cation. For the ionic liquids used the general trend OH -substituted imidazolium \gg imidazolium $>$ pyridinium $>$ pyrrolidinium was found. Clearly the addition of a hydrogen-bond-donating functional group to the cation has a significant impact upon the overall ability of the ionic liquid to act as a hydrogen bond donor. Also, comparison of the results for 1-butyl-3-methylimidazolium succinate $\{[\text{C}_4\text{C}_1\text{im}][\text{O}_2\text{CC}_2\text{CO}_2], \alpha = 0.39\}$ with those for 1-butyl-3-methylimidazolium malate $\{[\text{C}_4\text{C}_1\text{im}][\text{O}_2\text{CC}_2(\text{OH})_2\text{CO}_2], \alpha = 0.41\}$, $[\text{C}_4\text{C}_1\text{im}][\text{C}_1\text{CO}_2]$ ($\alpha = 0.43$), and $[\text{C}_4\text{C}_1\text{im}][(\text{HO})\text{C}_1\text{CO}_2]$ ($\alpha = 0.44$) show a similar but much lesser effect of adding the same hydrogen-bond-donating group to the anion.¹³⁶ For both imidazolium and pyridinium ionic liquids, substitution of protons on the ring with methyl groups reduced the α value of the ionic liquid. For the pyridinium ionic liquids it was further shown that the position of the substitution was important, with the ionic liquid methylated at the 2-position of the ring having a lower α value than those with substitution at the 3- or 4-position. It was also found that lengthening the *N*-substituted alkyl chains led to a reduction of the α value. Again there was strong evidence of an antagonistic role for the counterion, with more basic anions leading to lower α values (see below).

When dissolved in a range of solvents, $[\text{Fe}(\text{phen})_2(\text{CN})_2][\text{ClO}_4]$ ($\text{phen} = 1,10\text{-phenanthroline}$) reduces to the neutral complex $\text{Fe}(\text{phen})_2(\text{CN})_2$, the UV-vis spectrum of which has been used as a measure of the ability of the solvent to donate a hydrogen bond.¹⁶⁷ First, the absorption maximum was correlated with the Kamlet-Taft α value for a range of molecular solvents, described as "well-behaved" by the authors. Then this correlation was used to calculate an α value for a range of $[\text{C}_4\text{C}_1\text{im}]^+$ ionic liquids. These values were significantly lower than those found for the directly measured Kamlet-Taft α values and showed a more pronounced antagonistic anion effect than seen for those derived from Reichardt's dye, again with more basic anions leading to ionic liquids with lower α values. This is discussed below.

5.2.4.2. Chromatographic Measurements and the Abraham Model. In a series of papers published throughout the 1980s and beyond, Colin Poole and his co-workers investigated the solvation properties of a wide range of alkylammonium and, to a lesser extent,

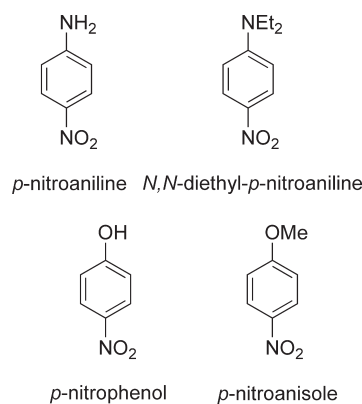


Figure 7. Two dye sets commonly used in conjunction with Reichardt's dye (Figure 5) to produce the Kamlet-Taft parameters.

phosphonium salts using gas chromatography.¹⁶³ More recently, Armstrong et al.¹⁶⁸ and others¹⁶⁹ have taken a similar approach. Ionic liquids were used as stationary phases for gas chromatography, and the retention of a variety of probe compounds was analyzed using Abraham's solvation parameter model:¹⁷⁰

$$\log K_L = c + rR_2 + s\pi_2^H + a\alpha_2^H + b\beta_2^H + l \log L^{16} \quad (3)$$

where K_L is the solute gas-liquid partition coefficient, r is the tendency of the solvent to interact through π - and n -electron pairs (Lewis basicity), s is the contribution from dipole-dipole and dipole-induced dipole interactions (in molecular solvents), a is the hydrogen bond basicity of the solvent and b is its hydrogen bond acidity, and l is how well the solvent will separate members of a homologous series and has contributions from solvent cavity formation and dispersion interactions. Since a wide variety of probe solutes were used, any problems associated with the use of a single probe, which will inevitably have its own specific chemistry, were removed. Differences in the detail of how the measurements were made and the results treated again mean that the results of the two sets of studies cannot be interchanged,¹⁷¹ but they do lead to the same general conclusions. It should be noted that the use of this methodology has been criticized,¹⁷² but also that these criticisms have been convincingly rebutted.¹⁷³

All of the ionic liquids were found to have ranges of values for the various parameters that placed them among the polar aprotic solvents. Particularly, all but a few showed little hydrogen bond acidity. This is in direct contradiction to some of the spectroscopic results detailed above. However, most of the ionic liquids studied have been shown to be hydrogen bond bases. The precise basicity is largely a function of the anion, with halide salts having particularly large basicities and polyatomic, highly fluorinated anion salts having low basicities. Cation effects have been seen with phosphonium ionic liquids having greater basicities than imidazolium ionic liquids with a common anion. The dipolarity terms, s , of the ionic liquids are generally large but sensitive to changes in the ions, particularly anions, of the ionic liquids. However, high values for l , which are usually associated with nonpolar solvents, have also been found. This may help to explain the observations that ionic liquids are good solvents for both polar and nonpolar solutes.

The effect of functionalizing the cation of the ionic liquid has also been investigated by this method. The incorporation of sulfoxides and sulfones in the alkyl chain of some imidazolium ionic liquids led to significant increases in both the hydrogen

bond acidity and basicity of the ionic liquids in comparison to those with simple alkyl chains.¹⁷⁴ A similar effect on the hydrogen bond basicity was found by the inclusion of an ether linkage in a phosphonium ionic liquid.¹⁷⁵

5.2.5. Antagonistic Behavior in Hydrogen Bonding. It has been demonstrated crystallographically^{46,176} and by neutron diffraction,¹⁷⁷ NMR spectroscopy,¹⁷⁸ vibrational spectroscopy,¹⁷⁹ mass spectrometry,¹⁸⁰ and theory¹⁸¹ that hydrogen bonding is an important structure-forming factor in many pure ionic liquids¹⁸² and that the degree of interionic interaction is dependent upon the ions of the ionic liquid. It was first proposed that these interionic hydrogen bonds could have a significant impact upon the ability of ionic liquids to hydrogen bond to solutes to explain the anion effects upon the selectivities observed for some Diels–Alder reactions.¹⁸³ It was proposed that the ability of the ionic liquid to form a hydrogen bond with a solute molecule appears to come from one of the ions, but that competition between the solute and the counterion of the ionic liquid weakens this interaction. This has subsequently been reaffirmed by several of the studies detailed above and by molecular dynamics simulations.¹⁸⁴

Let us first consider hydrogen bond donation by the cation. This can be described in terms of two competing equilibria. The cation may hydrogen bond to the ionic liquid anion:



The cation may also hydrogen bond to the solute:



It can be easily seen that because of the commonality of $[\text{C}^+]$ to both equations, $[\text{C}^+ \cdots \text{solute}]$ arises as a consequence of both K'' and K' . For any given solute, an ionic liquid with a stronger hydrogen-bond-donating cation will lead to a higher value for K'' and a greater $[\text{C}^+ \cdots \text{solute}]$. For the same solute and ionic liquids with the same cation, a greater hydrogen-bond-accepting ability of the ionic liquid anion leads to a larger K' and hence a reduction in $[\text{C}^+ \cdots \text{solute}]$. To summarize, the overall ability of an ionic liquid to donate a hydrogen bond to a solute comes from the ability of the cation to act as a hydrogen bond donor, reduced to some degree by the ability of the ionic liquid anion to act as a hydrogen bond acceptor. In a similar way, the overall ability of an ionic liquid to accept a hydrogen bond from a solute comes from the ability of the anion to act as a hydrogen bond acceptor, reduced to some degree by the ability of the ionic liquid cation to act as a hydrogen bond donor.

5.2.6. Apparent Discrepancies between Polarity Measurements in Ionic Liquids. The use of the dielectric constant estimated by microwave dielectric spectroscopy as a descriptor of the solvent–solute relationship in ionic liquids has received some criticism.¹⁸⁵ This rests on three arguments. The first is that ionic liquid structures are heterogeneous on the nanoscale¹⁸⁶ and that no continuum-based description can capture this level of detail. The second is that the high frequency of the measurements fails to capture the defining feature of ionic liquids—the translation of ions—giving rise to an inadequate description of the ionic liquid.^{185,187} Finally, the dielectric constants for most ionic liquids describe them as considerably less polar than several of the polarity scales described above and fail to explain the outcome of quantitative investigations of reactions in ionic liquids (see below), yet these dielectric

constants do agree with some other measurements described above.^{35,101,119,120}

We suggest that, to explain these apparent contradictions, it is necessary to consider the time scale of the various processes. The highly structured nature of the ionic liquids has important implications for how they interact with solute species, particularly with respect to any solvent reorientation around a solute.^{185,186} For example, 2-amino-7-nitrofluorene exhibits excitation-wavelength-dependent fluorescence spectra in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, and $[\text{C}_2\text{C}_1\text{im}][\text{BF}_4]$, which has been interpreted as the dye molecules occupying distinct nonexchanging (on the time scale of the measurements) environments in these ionic liquids.¹⁸⁸ Undoubtedly, solvent reorganization around a solute in ionic liquids is slower than in most commonplace molecular solvents. A model of solvation in ionic liquids that does not encapsulate ion translation is likely to fit better to measurements that occur on a time scale that is faster than that of ion translation, such as in fluorescence^{35,120} or vibrational spectroscopy,¹⁰¹ than those whose time scale is slower than that of ion translation, such as chemical reactions involving atom or group transfers. Although electronic absorption spectra arise from electronic transitions in molecules that are rapid, their solvatochromism most often arises from interactions of the solvent with the ground state of the probe, which is in equilibrium with its surroundings. Hence, these polarity scales should not be expected to agree with dielectric constants derived from microwave dielectric spectroscopy.

Another area in which there has been some disagreement has been in the estimation of the abilities of ionic liquids to act as hydrogen bond donors. Measurements of the hydrogen bond donor ability of ionic liquids that have used Reichardt's dye have described some ionic liquids as strong hydrogen bond donors. These results agree well with those found for the solvatochromism of merocyanine dyes and with the analysis of many of the reactions described below.¹³⁶ Several other studies of hydrogen bond donor abilities of ionic liquids that have compared their results to these results, including those based upon GC measurements,^{141,168} the UV–vis spectrum of $\text{Fe}(\text{phen})_2(\text{CN})_2$,¹⁶⁷ the fluorescence spectra of PRODAN and coumarin 153 (C153),¹⁵⁴ and the Raman spectrum of diphenylcyclopropane,¹⁴⁶ describe these ionic liquids as considerably poorer hydrogen bond donors. For several of these ionic liquids, not only were the derived values lower, but the relative effects of changing cations or anions were also different. What is immediately clear when comparing across the whole range of measurements is that when the assessment of the hydrogen-bond-donating ability of an ionic liquid is based upon a measurement of the property of a charged probe, the value derived is greater than when a neutral probe is used. This observation can now be used to explain these differences.

The first assumption behind the use of empirical polarity scales to study ionic liquids is that if the response of a particular probe solute, or solutes, is the same as that in some known molecular solvent, then it can be said that the polarities of the ionic liquid and the molecular solvent are the same and that the appropriate value of the parameter can then be assigned to the ionic liquid. To then compare the results of these different scales for ionic liquids carries the second, implicit assumption that the effect of transferring from a molecular solvent to an ionic liquid is the same for all probes. It is unlikely that this would be perfectly true for any potential probe, but there may be some for which this difference is great enough to significantly change the results. Hence, it is important to consider the nature of the solute as well as the solvent.

There is some debate among theoreticians as to whether the interactions between cations and anions in ionic liquids should be considered as Coulombic interactions with overlying hydrogen

bonding or whether they are hydrogen bonds with a significant Coulombic contribution. Nonetheless, both of these views recognize the importance of the Coulombic contribution to interionic interactions in ionic liquids.¹⁸¹ If the solute is charged, then this strong Coulombic component is present in the ionic liquid–solute interaction. If the solute in the ionic liquid is neutral, this Coulombic contribution is absent from the ionic liquid–solute interaction. It is also absent when the solvent is molecular, regardless of whether the solute is charged. Hence, the second assumption above does not hold. The effect of transferring a charged solute from a molecular solvent to an ionic liquid will be very different (greater) than that of transferring a neutral solute, the difference being this extra Coulombic interaction. Consequently, the scales based upon charged solutes will give higher values for ionic liquids than those based upon neutral probes.

When such major differences are found, the question of which approach is “right” usually arises. As stated above, this is not helpful when considering empirical polarity scales, and the question of which is more appropriate in a given set of circumstances is more useful. The review of the literature measurements of ionic liquid polarity above suggests that when using empirical polarity scales to gain insight into ionic liquid effects on solvent-dependent phenomena, it is important to consider the nature of the solute species being investigated. Put simply, phenomena arising from neutral solutes will be better modeled using polarity scales based upon neutral probes, whereas those arising from charged solutes are probably modeled better using polarity scales based upon charged probes.

5.3. Infinite Dilution Activity Coefficients

Infinite dilution activity coefficients (γ^∞) are valuable thermodynamic parameters for the calculation and correlation of various properties important to multicomponent, multiphase systems, such as vapor–liquid and liquid–liquid equilibria. These data are crucial to the evaluation of solvent suitability (via solubility) and the all-important process consideration of evaluating separation approaches (i.e., extraction or distillation). γ^∞ values also provide valuable insight into solvent–solute interactions.

γ^∞ values themselves are a measure of solute–solvent interactions. The “infinite dilution” label indicates that no solute molecule is in an environment where it can interact with another solute molecule. Therefore, all solute–solute interactions have been eliminated. Since these values are activity coefficients, by definition $\gamma = 1$ for an ideal mixture (solvent–solvent interactions). This yields γ^∞ as strictly a measure of solvent–solute interactions. If $\gamma^\infty > 1$ (positive deviation from Raoult’s law), it indicates that the solvent–solute interactions are *less* favorable than the solvent–solvent interactions, and the larger the value, the more unfavorable these interactions are. This would typically be the case for immiscible liquids (where γ^∞ is usually greater than 10); e.g., butylbenzene dissolved in water has $\gamma^\infty > 500\,000$.¹⁸⁹ If $\gamma^\infty < 1$ (negative deviation from Raoult’s law), it indicates that the solvent–solute interactions are *more* favorable than the solvent–solvent interactions, and the smaller the value, the more favorable these interactions are. This situation is typical for cases where very strong specific interactions are present, such as hydrogen bonding; e.g., dimethyl sulfoxide (DMSO) dissolved in water has $\gamma^\infty = 0.09$.¹⁹⁰ Obviously, $\gamma^\infty = 1$ represents an ideal solution where solute–solvent interactions are indistinguishable from solute–solvent interactions; e.g., heptane dissolved in hexane has $\gamma^\infty = 1.05$.¹⁹¹

For organic solutes dissolved in ionic liquids, most measurements have been based on gas–liquid chromatography, taking advantage of the low volatility of ionic liquids for easy separations and analysis. The ionic liquid is generally used as a stationary phase in a coated column and the solute retention time used to determine the activity coefficient. The other popular technique is to use the “dilutor” process and extrapolate vapor–liquid equilibrium data to infinite dilution. Consequently, only molecular solutes have been investigated. While this in no way compromises these data, it must be recognized when drawing conclusions that this is a restricted data set, particularly given the importance of solvent–solute Coulombic interactions when they are possible, as described above.

5.3.1. Activity Coefficients and Solute–Ionic Liquid Interactions

5.3.1.1. General Solute Trends. In one of the first published studies on γ^∞ of organic solutes in ionic liquids, and the first in a long series on thermodynamic properties of mixtures containing ionic liquids, Heintz et al.¹⁹² reported several general trends. Although their original study was limited to $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, these trends apply to a wide range of ionic liquids. The γ^∞ values of 19 alkanes, alkenes, and alkylbenzenes, and other solutes added by later authors,^{193,194} increase as the linear hydrocarbon’s alkyl chain length increases (less favorable interactions) with branching, causing a reduction in γ^∞ . Alkenes have lower γ^∞ values than alkanes (more favorable interactions), and alkylbenzenes have substantially lower γ^∞ values than both; no branching effect was observed with alkylbenzenes. The temperature dependence of γ^∞ allows the calculation of the excess enthalpies at infinite dilution, $H_1^{\text{E},\infty}$. $H_1^{\text{E},\infty}$ is positive for linear alkanes (and increases with increasing chain length), less positive for alkenes, and negative for very short chain alkylbenzenes. These data suggest that, in terms of solute–solvent interactions in ionic liquids, the number of polarizable electrons in the solute has a large effect upon the dominant favorable interactions in these alkane/alkene/alkylbenzene solutions, which are primarily ion–induced dipole interactions.

Heintz later confirmed similar trends (though not values) for both hydrocarbons and more polar solutes in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ and $[\text{C}_2\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$.¹⁹⁵ As previously, the ionic liquid–hydrocarbon interactions become less favorable as the hydrocarbon’s alkyl chain length increases, with cyclization, branching, or unsaturation having the opposite effect. The same effect was found for changes to the alkyl groups in *n*-alcohols. However, more dipolar aprotic species (acetonitrile, acetone) had much more favorable solute–solvent interactions than less polar esters or ethers. Reported trends of $H_1^{\text{E},\infty}$ were similar to those reported before, with acetonitrile and acetone having large negative $H_1^{\text{E},\infty}$ values, indicating the greater strength of the ion–dipole interactions between these solutes and the ionic liquids compared to the ion–induced dipole interactions of the alkanes/alkenes/alkylbenzenes.

Results for a series of functionalized solutes (alcohols, acetone, acetonitrile, ethyl acetate, alkyl ethers, chloromethanes) in $[\text{C}_4\text{C}_1^4\text{pyr}][\text{BF}_4]$ also showed polar solutes having more favorable interactions with the ionic liquids.¹⁹⁶ Deenadayalu et al.¹⁹⁷ reported some discrepancies with Heintz’s measurements in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$, although the general trends were as expected. This does highlight the inherent difficulty in comparing chromatography results obtained by different groups. Vasiltsova et al.¹⁹⁸ extended this study to aliphatic and aromatic esters and amines in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$. Interestingly, the authors did not find noticeable specific interactions between benzylamine and the ionic liquid, indicating that the $-\text{NH}_2$

protons are not hydrogen bonding strongly to the $[\text{NTf}_2]^-$ anion nor is the imidazolium cation hydrogen bonding to the lone pair on the amine. High-boiling, highly functionalized solutes [methoxybenzene, (hydroxymethyl)benzene, 1,2-ethanediol, and 1,4-butanediol] dissolved in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ also showed somewhat higher activity coefficients than their less functionalized counterparts.¹⁹⁹ By contrast, the same group also explored solutions of *n*-alcohols and benzene in $[\text{C}_4\text{C}_1\text{im}][\text{C}_8\text{SO}_3]$ and $[\text{C}_8\text{C}_1\text{im}][\text{BF}_4]$ to reveal extensive hydrogen-bonding interactions between methanol and the $[\text{C}_8\text{SO}_3]^-$ anion.²⁰⁰

Secondary and tertiary alcohols were discovered to interact more favorably with the ionic liquid than the corresponding primary alcohol containing the same number of carbons.²⁰¹ This is likely to be due once again to hydrogen bonds donated by the hydroxyl proton to the anion of the ionic liquid, as one would expect on the basis of their Kamlet–Taft values (see above). By increasing the alcohol chain length {methanol, 1-butanol, and 1-hexanol dissolved in $[\text{C}_6\text{C}_1\text{im}][\text{NTf}_2]$ }, a small increase in γ^∞ was found to occur.²⁰² This suggests that for this ionic liquid the overall effect arises as a combination of changing hydrogen bonding and interactions between the alkyl chain of the alcohol and that of the imidazolium cation. While there was little difference in γ^∞ values for CH_2Cl_2 and CHCl_3 dissolved in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ and $[\text{C}_2\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$,¹⁹⁶ $H_i^{\text{E},\infty}$ for CHCl_3 was substantially more negative. The authors attributed this to the high polarizability of the chlorine atom and the “special” strength of ion–induced dipole interactions. However, it seems to us that strong hydrogen bonding between CHCl_3 and the anion of the ionic liquid is more likely to be responsible.

γ^∞ values for alcohols, ketones, and aromatics dissolved in two significantly different ionic liquids, $[\text{C}_4\text{C}_1\text{pyr}][\text{BF}_4]$ and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, yielded several interesting trends.²⁰³ In addition to the observation that anion effects were stronger than cation effects, the authors noted some interesting trends with regard to isomers. They found that branched alcohols interacted more favorably with the ionic liquids than straight-chain alcohols of the same carbon number. Additionally, for the xylenes, they found that *m*-xylene interacted the least favorably with the ionic liquid. It does appear that temperature plays a very strong role in the selectivity of the various xylenes, with the order and ratios of activity coefficients varying as the temperature is increased from 316 to 335 K. This temperature-dependent selectivity could be an important design parameter for separation processes, with xylene separation being an important industrial process. γ^∞ values for 20 solutes dissolved in 3 $[\text{NTf}_2]^-$ ionic liquids plus $[\text{C}_2\text{C}_1\text{im}][\text{C}_2\text{SO}_4]$ revealed substantial deviations from Raoult’s law for aliphatic hydrocarbons as opposed to aromatics, and this was proposed as a potential means of separating solutes from an ionic liquid via distillation.²⁰⁴ Selectivity increases of up to 168% were reported for the use of ionic liquids as entrainers relative to the standard 1-methylpyrrolidine for aqueous separations of hydrocarbons. This study also revealed very strong interactions between $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ and various ketones, again an indication of the importance of hydrogen bonding in these systems.

Anthony et al.²⁰⁵ measured a variety of thermodynamic properties for the dissolution of water in three ionic liquids: $[\text{C}_8\text{C}_1\text{im}][\text{BF}_4]$, $[\text{C}_8\text{C}_1\text{im}][\text{PF}_6]$, and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$. The reported measurements included both Henry’s law coefficients and γ^∞ values with a comparison of the ionic liquid/water systems to organic solvents/water. They found that the γ^∞ value for water in $[\text{C}_8\text{C}_1\text{im}][\text{BF}_4]$ was substantially lower than that in $[\text{C}_8\text{C}_1\text{im}][\text{PF}_6]$, which was slightly higher than that in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$. Not only did this demonstrate a strong anion component to these interactions, but the relative

comparisons to organic solvents were quite interesting. While $[\text{C}_8\text{C}_1\text{im}][\text{BF}_4]$ seemed to interact with water similarly to methanol, $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_8\text{C}_1\text{im}][\text{PF}_6]$ more closely resembled 2-propanol or acetone. However, all of these ionic liquids are immiscible with water, despite the γ^∞ values {1.76, 6.51, and 5.36 for $[\text{C}_8\text{C}_1\text{im}][\text{BF}_4]$, $[\text{C}_8\text{C}_1\text{im}][\text{PF}_6]$, and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, respectively, at 25 °C} being similar to those of molecules that are miscible with water. This clearly indicates that, despite very favorable interactions between water and ionic liquids with “hydrophobic” anions {such as $[\text{PF}_6]^-$ }, other factors, most likely entropic ones, dominate the solution thermodynamics.

An early review of the thermodynamic properties of solutes in ionic liquids has been provided by Heintz,²⁰⁶ and a treatise on the use of γ^∞ values for selection of ionic liquids as entrainers has been provided by Chiappe.²⁰⁷

5.3.1.2. Effect of Changing the Anion. Anion effects on γ^∞ differ fundamentally from cation effects, mainly due to the different interactions involved. As a simple example, the interactions of hydrocarbon solutes with $[\text{NTf}_2]^-$ ionic liquids¹⁹⁵ are distinctly less favorable than those involving the $[\text{BF}_4]^-$ anion.¹⁹² This difference was originally attributed to the $[\text{BF}_4]^-$ anion’s smaller size, but more recent studies suggest that the intermolecular interactions are much more dependent on the polarizability of the anion than initially thought. In a diverse look at anion effects, Dobryakov et al.²⁰⁸ measured γ^∞ values for eight alcohols in three ionic liquids with varying properties: $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, $[\text{C}_4\text{C}_1\text{im}][\text{C}_1\text{SO}_3]$, and $[\text{C}_6\text{C}_1\text{im}][\text{NTf}_2]$. They found that favorable hydrogen-bonding interactions increased from $[\text{PF}_6]^-$ to $[\text{NTf}_2]^-$ to $[\text{C}_1\text{SO}_3]^-$, as one would expect. The differences between the two hydrophobic anions $[\text{PF}_6]^-$ and $[\text{NTf}_2]^-$ were relatively small, but the hydrophilic $[\text{C}_1\text{SO}_3]^-$ anion showed a marked lowering of γ^∞ values. This provides strong evidence that specific hydrogen-bonding interactions are much more powerful than any size-based effects.

Letcher et al.²⁰⁹ determined γ^∞ values for organic solutes in the ionic liquid $[\text{C}_6\text{C}_1\text{im}][\text{PF}_6]$. Interestingly, they found that benzene interacts more favorably with this ionic liquid than does methanol. This suggests that hydrogen bonding to the $[\text{PF}_6]^-$ anion is less important than the “cation-delocalized electron” interactions, due largely to the weakly interacting nature of the anion (large, symmetric, less polarizable, poor hydrogen bond acceptor). A follow-up study explored many of the same solutes (plus He) in the ionic liquid $[\text{C}_6\text{C}_1\text{im}][\text{BF}_4]$.²¹⁰ For alkanes, alkenes, alkynes, and benzene, the γ^∞ values were only 2–5% lower when $[\text{BF}_4]^-$ was the anion as compared to $[\text{PF}_6]^-$, indicating essentially similar solute–solvent interactions. However, the γ^∞ value for methanol was more than 60% lower in $[\text{C}_6\text{C}_1\text{im}][\text{BF}_4]$ (0.75 vs 1.94 at 298.15 K), which has a much greater ability to act as a hydrogen bond acceptor. This large difference in values suggests that hydrogen bonding from the solute to the anion represents the largest solute–solvent interaction between alcohols and this ionic liquid. As part of that same series of studies, three very dissimilar ionic liquids, $[\text{C}_8\text{C}_1\text{im}]\text{Cl}$,²¹¹ $[\text{C}_6\text{C}_1\text{im}][\text{BF}_4]$,²¹² and $[\text{C}_4\text{C}_1\text{im}][(\text{C}_1\text{OC}_2\text{OC}_2\text{O})\text{SO}_3]$,²¹³ were reported to have very similar γ^∞ values. Also, values for $[\text{C}_6\text{C}_1\text{im}][\text{NTf}_2]$ ²¹⁴ were found to be very similar to those for $[\text{C}_6\text{C}_1\text{im}][\text{PF}_6]$,²¹⁰ including the result that benzene interacts more favorably with the ionic liquid than does methanol. This shows that hydrogen bonding to the $[\text{NTf}_2]^-$ anion or $[\text{PF}_6]^-$ anion is considerably weaker than for more hydrophilic ionic liquids.

For mixtures involving the ionic liquid $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$, the γ^∞ values decrease with increasing temperature for alkanes and alkenes and increase with increasing temperature for polar solutes and water,²¹⁴ further supporting the dominance of hydrogen-bonding

interactions in the latter systems as hydrogen bonds weaken with increasing temperature. These results were borne out later for polar solutes dissolved in $[C_4C_1im][OTf]$. Here γ^∞ values increased along the series ethyl acetate > tetrahydrofuran > 1,4-dioxane > acetone > acetonitrile.²¹⁵ This trend clearly indicates that aprotic solutes are capable of favorably interacting with the ionic liquid. It is unclear whether this is predominantly through hydrogen bond donation by the cation to the solute or simply ion–dipole interactions. However, the much lower values obtained for alcohols demonstrate that solute–anion hydrogen bonding was more significant than either solute–cation or ion–dipole interactions. The similarity in value obtained for $CHCl_3$ and CH_2Cl_2 (a trade-off of much polarity for a little hydrogen bonding) clearly demonstrates the complexity of balancing these interactions. A related study on $[C_2C_1im][BF_4]$ revealed γ^∞ values that were uniformly higher than for the same solutes dissolved in $[C_4C_1im][OTf]$.²¹⁶ The trends were, however, identical with γ^∞ values increasing along the series ethyl acetate > tetrahydrofuran > 1,4-dioxane > acetone > acetonitrile. Therefore, there would seem to be a relatively strong anion-related effect. This indicates that hydrogen bonding from the solute to the anion is very important to the activity coefficients. Measurements conducted using $[C_3C_1C_2im][BF_4]$ were also performed.²¹⁷ In this instance γ^∞ values were again uniformly higher than for the same solutes dissolved in $[C_4C_1im][OTf]$ and slightly higher than for $[C_2C_1im][BF_4]$. The trends were again identical with γ^∞ values increasing along the series ethyl acetate > tetrahydrofuran > 1,4-dioxane > acetone > acetonitrile {as was the case for $[C_2C_1im][BF_4]$ }. In this case the cation of the ionic liquid is capped by a methyl group at the C^2 position of the imidazolium ring, greatly reducing its potential to donate hydrogen bonds. Since the trend in solvation remains unchanged, this strongly suggests that favorable molecular solute–solvent interaction in ionic liquids can generally be classified as solute–anion hydrogen bonding being stronger than ion–dipole interactions being stronger than cation–solute hydrogen bonding. This trend is general for the classes of ionic liquids that do not contain specific protic functionality. Measurements in $[C_6C_1im][OTf]$ yielded values that were substantially higher (1–2 orders of magnitude) than for the polar solutes studied previously,²¹⁸ while results obtained in $[C_4C_1im][OTf]$ demonstrated that this ionic liquid behaved with polarity between those of $[C_4C_1im][NTf_2]$ and $[C_4C_1im][BF_4]$.²¹⁹

Measurements for hydrocarbons and methanol dissolved in the ionic liquid $[C_4C_1im][C_8SO_3]^{220}$ yielded some interesting trends in γ^∞ values. Even with the long alkyl chain on the anion, hydrogen-bonding interactions between methanol and the anion of the ionic liquid were found to be more favorable than interactions between the π electrons on benzene and the ionic liquid, and both of these were found to be much more favorable than van der Waals interactions between the hydrocarbons and the ionic liquid. However, the octyl chain did reduce the selectivity of the ionic liquid–solute interactions, reducing its potential as an entrainer for separations. Similar results were reported for $[C_4C_1im][C_8SO_3]^{221}$ where γ^∞ values are significantly lower than in the more common $[BF_4]^-$ or $[NTf_2]^-$ -based ionic liquids, particularly for alkanes. Meanwhile, solutes dissolved in $[C_2C_1im][OTf]$ exhibit significantly higher γ^∞ values at the low-polarity end (alkanes), but γ^∞ is 2 orders of magnitude lower for methanol. Therefore, while hydrogen bond donation by solutes to either anion appears to be strong and dominant, the interaction of the octyl chain with alkanes was significantly more favorable than for the tosylate anion. This is interesting, as it shows that a wide range of interactions are possible with nonpolar solutes (from favorable to very unfavorable) even

among solvents that display strong hydrogen-bonding interactions, giving rise to some degree of amphiphilicity.

$[C_2C_1im][CF_3CO_2]$ is an extremely hydrophilic ionic liquid. As such, the activity coefficients for alkanes²²² were found to be extremely high {roughly twice that of $[C_2C_1im][BF_4]$ } and for polar solutes (especially water) extremely low {roughly half that of $[C_2C_1im][BF_4]$ }. This presents an interesting option for separations as this polar solvent should behave very differently with solvents of varying functionality, particularly for aliphatic/aromatic separations and solutes with differences in hydrogen-bonding interactions.

Measurements for various organic solutes (benzene, 1-butanol, 2-pentanone, 1-nitropropane, and dioxane) dissolved in $[SCN]^-$ and $[NO_2]^-$ -based ionic liquids revealed, as expected, that strong interactions between the polar groups on the solute and the ionic liquid anions dominated all other effects.¹⁷¹ Domanska et al.²²³ studied γ^∞ values for organic solutes and water dissolved in the very hydrophilic (and even nucleophilic) ionic liquid $[C_2C_1im][SCN]$. Due to the extreme nature of the anion employed, the interactions with nonpolar solutes (such as alkanes) were markedly more unfavorable than for other ionic liquids, while interactions with polar solutes (alcohols) and water were extremely favorable. Arising from these effects, the separation efficiencies for both aromatic/aliphatic systems and alcohol systems were very high, yielding a promising solvent for conducting such separations. However, it bears noting that $[SCN]^-$ is potentially highly reactive in the presence of electrophiles.

Deenadayalu et al.²²⁴ measured γ^∞ values for organic solutes dissolved in the unusual ionic liquid $[C_8C_1im][(C_1OC_2-OC_2)OSO_3]$. While the values for solutes of low functionality were in line with those of other ionic liquids, the γ^∞ values for methanol and benzene were very low, with that of methanol being much lower than unity. This suggests that this anion has very favorable ion–dipole interactions (stronger than usual) and that this anion is extremely adept at accepting hydrogen bonds from methanol. This anion would be of interest for dissolving solutes that have a highly acidic component.

5.3.1.3. Effect of Changing the *n*-Alkyl Group on an Imidazolium Cation. The relatively weak anion–solute interactions available in $[NTf_2]^-$ ionic liquids helped to reveal the effect of changing the alkyl group of some imidazolium ionic liquids.²²⁵ Although the trends were the same, γ^∞ values for organic solutes in $[C_6C_1im][NTf_2]$ were universally lower than those measured for ionic liquids with shorter alkyl chains, even when more polar solutes (acetone, acetonitrile) were involved. Hence, the weak cation–solute interactions become more favorable with increasing cation alkyl chain length. These data also agree well with those obtained previously by Letcher using the same technique (gas–liquid chromatography).²¹³ Similarly, measurements made in $[C_8C_1im][BF_4]$ for linear alkanes were lower than in $[C_4C_1im][BF_4]$,²²⁶ indicating an increased lipophilicity for the ionic liquid with the longer alkyl chain that can mitigate other unfavorable solvent–solute interactions to some degree.

Foco et al.²²⁷ conducted a single study containing γ^∞ values for several classes of organic solutes (alkanes, alcohols, ketones, ethers, aromatic hydrocarbons, halogenated compounds) in $[C_nC_1im][BF_4]$ ($n = 2, 4, 6$, or 8). This provides a convenient means for examining the effect of lengthening the alkyl chain length on a substituted imidazolium cation. For most classes of solutes, the value of γ^∞ decreases as the alkyl chain length increases. However, alcohols are an exception to this trend. The γ^∞ value of each alcohol dissolved in the ionic liquids

increased when changing from the ethyl to the butyl side chain on the imidazolium ring. After that, the γ^∞ values decreased with increasing chain length. Therefore, there is a maximum value obtained at $n = 4$, corresponding to $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ having the least favorable interactions with alcohol solutes. This is likely to be due to the $[\text{C}_2\text{C}_1\text{im}]^+$ cation having particularly favorable interactions with the polar hydroxyl group on the alcohols. This effect is obscured somewhat by the increase in chain length to $n = 4$, before the normal behavior reasserts itself. The behavior for chlorinated solutes is similar, though less pronounced, ruling out a strong hydrogen-bonding component to this effect. The results of Inoue et al.²²⁸ for n -alkanes in $[\text{C}_4\text{C}_1^4\text{pyr}][\text{BF}_4]$ help to confirm this hypothesis for a less acidic cation. γ^∞ values for polar solutes dissolved in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ ¹⁹⁴ also support the notion that ionic liquids can act with dual nature in chromatography columns—as nonpolar stationary phases for nonpolar solutes and as polar stationary phases for more polar solutes. This amphiphilic behavior is an interesting indication of the balance between side chain interactions with nonpolar solutes and ion–dipole interactions with more polar solutes.

Mutelet and Jaubert determined γ^∞ values for organic solutes in an ionic liquid with a very long side chain, $[\text{C}_{16}\text{C}_1\text{im}][\text{BF}_4]$.²²⁹ In this extreme example, all experimentally determined γ^∞ values (for 31 organic solutes) were between 0.5 and 2.7, indicating that ion–dipole interactions and hydrogen-bonding interactions are being muted by van der Waals interactions. Interestingly, despite the long side chain, the alkanes still had the least favorable interactions, universally increasing with increasing chain length. Alcohols (methanol, ethanol) were still very favorable in their interactions, though less so than with other $[\text{BF}_4]^-$ -based ionic liquids. Aromatics and especially functionalized small organics (chloroform, dichloromethane, 1,4-dioxane, acetonitrile) now exhibited the most favorable interactions with the ionic liquid. These results suggest that lengthening the alkyl chain length of the cation can decrease the attraction between polar solutes and the ionic liquid while making interactions with nonpolar solutes more favorable. However, for imidazolium ionic liquids made with the $[\text{BF}_4]^-$ anion, it does not appear that interactions with alkanes will ever be more favorable than with solutes capable of hydrogen bonding.

5.3.1.4. Effect of Changing the Cation Type. γ^∞ values for solutes dissolved in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ were only slightly lower than in $[\text{C}_2\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$,¹⁹⁵ indicating that there was no large cation effect stemming from substitution of the acidic C^2 proton, with the important exception that the value for acetonitrile was *higher* in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$. Acetonitrile is a strong hydrogen bond acceptor; therefore, it would be expected to interact strongly with the C^2 proton. Hence, some other consequence of the presence/absence of the C^2 proton on the ionic liquid cation must be operating to oppose the direct hydrogen-bonding effect. The fact that similar trends were not observed for the n -alcohols again indicates that the importance of hydrogen bond donation from the solute to the ionic liquid anion is greater than that of the hydrogen bond donation by the imidazolium ring to the solute. This also agrees with the observation of water solubility being controlled by the anion much more so than the cation. Substitution of the C^2 proton to produce $[\text{C}_3\text{C}_1\text{C}_1^2\text{im}][\text{BF}_4]$ appears to vastly increase γ^∞ values for low-polarity solutes,²³⁰ an indication of much less favorable solvent–solute interactions. This cation effect was further illustrated by comparison with γ^∞ values for organic solutes in $[\text{C}_3(\text{C}_1)_3\text{N}][\text{NTf}_2]$.²³¹ Interactions with the tetraalkylammonium ionic liquid were

found to be significantly less favorable than those found with any $[\text{NTf}_2]^-$ ionic liquid with imidazolium or pyrrolidinium cations.

The phosphonium ionic liquid $[(\text{C}_6)_3\text{C}_{12}\text{P}][(\text{C}_2\text{F}_5)_3\text{PF}_3]$ revealed γ^∞ values that were all less than unity, indicating very strong favorable interactions with the hydrocarbon solutes.²³² The authors attribute this to the long C_{12} alkyl chain and cation interactions with the delocalized π -electron systems. Also, these ionic liquids had substantially more favorable interactions with hydrocarbons (both aliphatic and aromatic) than with alcohols, indicating that hydrogen-bonding interactions are less important for this particular ionic liquid. Bannerjee and Khanna measured γ^∞ values for solutes in three ionic liquids based on the $[\text{C}_{14}(\text{C}_6)_3\text{P}]^+$ cation.²³³ The anions were Cl^- , $[\text{BF}_4]^-$, and $[\text{NTf}_2]^-$. They found strong solute–solvent interactions (all γ^∞ values were less than unity) similar to those found in previous studies involving tetraalkylphosphonium ionic liquids.²³² These values are generally 1 order of magnitude lower than for the corresponding imidazolium-based ionic liquids, indicating substantially more favorable interactions of a very strong nature. The generally longer alkyl chains used for the tetraalkylphosphonium cations that give rise to ionic liquids, coupled with the relatively obscured charge of the cation, could explain this more lipophilic nature. The only unfavorable interactions observed involved alcohols dissolved in the $[\text{BF}_4]^-$ -based ionic liquids. Since these interactions were far less favorable than those for the less hydrophilic Cl^- and $[\text{NTf}_2]^-$ anions, it is likely that specific interactions, such as hydrogen bonding, are unfavorable in these systems. Measurements based on $[(\text{C}_4)_3\text{C}_1\text{P}][\text{C}_1\text{OSO}_3]$,²³⁴ a relatively more symmetric cation (compared to other phosphonium-based cations studied by the same group), yielded interactions with alkanes that were substantially less favorable. The geometry of these cations does appear to be relevant, as the less delocalized charge combines with the bulk and symmetry of the alkyl chains to exclude these solutes from the interior of the cation. Interactions with more polar solutes (ion–dipole) were less affected by the cation change than by the anion. Indeed, despite the use of a hydrophilic anion, the ionic liquid displayed behavior very similar to that of $[\text{C}_6\text{C}_1\text{im}][\text{PF}_6]$ —a hydrophobic ionic liquid. For the very hydrophobic ionic liquid $[\text{C}_{14}(\text{C}_6)_3\text{P}]^+[\text{NTf}_2]^-$ the most favorable interactions were with alkynes and benzene.²³⁵ The γ^∞ values for four-carbon to six-carbon alkanes and alkenes were very similar to that of methanol. Therefore, in this extreme example, the hydrogen-bonding effects are still present, though extremely muted, and favorable van der Waals interactions are becoming more prevalent. It would seem that generic ion–dipole interactions (between the ionic liquid and the π -electrons of the solutes) are dominant in these systems. Finally, measurements on $[\text{C}_{14}(\text{C}_6)_3\text{P}]^+[(2,4,4\text{-trimethylpentyl})\text{phosphinate}]$ yielded quite extreme results.²³⁶ The very lipophilic nature of this ionic liquid leads to all solutes, including straight-chain alkanes, having γ^∞ values below unity.

The contrast between phosphonium-based and ammonium-based cations is startling. Such a seemingly simple change yields qualitatively different behaviors; both cations yield hydrophobic ionic liquids, but tetraalkylammonium cations generate unfavorable interactions with all substrates while tetraalkylphosphonium cations yield ionic liquids displaying extraordinarily strong favorable interactions with all substrates—from alkanes to alcohols. The relatively charge diffuse nature of the larger phosphorus atom perhaps leads to some sort of charge-shielding effect, while the alkyl groups are relatively free to engage in van der Waals interactions with alkane

substrates. By contrast, the ammonium cations appear to behave similarly to point charges, as almost inorganic ions in nature, leading to very unfavorable interactions with all organic substrates.

Mutelet et al.²³⁷ reported γ^∞ values for organic solutes dissolved in the analogous ionic liquids $[\text{C}_3\text{C}_n\text{im}]\text{Br}$ and $[(\text{C}=\text{C}_2)\text{C}_n\text{im}]\text{Br}$ ($n = 3, 8, 10$, or 12). Very strong hydrogen-bonding interactions were inferred for alcohols dissolved in this latter ionic liquid. The resulting γ^∞ values were successfully correlated using an LSER to characterize the solute–solvent interactions. Measurements were also made in two more unusual bromides, $[1-[(\text{meth})\text{acryloyloxy}]\text{hexyl}]-3\text{-methylimidazolium}]\text{Br}$ and $[1-[(\text{acryloyloxy})\text{propyl}]-3\text{-methylimidazolium}]\text{Br}$, with cations that contain very polar side groups.²³⁸ These ionic liquids yielded very unfavorable interactions with nonpolar alkanes and very favorable interactions with polar compounds such as alcohols, even compared to other ionic liquids (γ^∞ values as low as 0.15 for methanol). This indicates that polar substituents on the cation can interact favorably with both acidic and basic sites on a solute (such as the hydroxyl in an alcohol) to yield very favorable solutions and thus great potential for reactions and separations.

Both the chain length and cation type (imidazolium vs pyrrolidinium) were examined in the same study of several classes of organic solutes and water dissolved in a range of $[\text{NTf}_2]^-$ ionic liquids.²³⁹ No noticeable effect of cation type on the γ^∞ values of alkanes dissolved in ionic liquids was observed. However, there was a noticeable decrease in γ^∞ as the alkyl chain length on $[\text{C}_n\text{C}_1\text{im}][\text{NTf}_2]$ ($n = 2, 4, 6$, or 8) increased, indicating that interactions become more preferable as the chain length increases. This suggests that favorable interactions between the alkane and the alkyl chain on the imidazolium cation are important. Similar trends for ethanol (despite the polarity change) indicate that cation hydrogen bond donation to the solute follows the same trend with respect to alkyl chain length. As expected, the γ^∞ values for water in these ionic liquids demonstrated the opposite trend; γ^∞ increased with increasing alkyl chain length as the interactions became less favorable. The authors also measured γ^∞ values for solutes in a 50:50 mixture of $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ and $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ and observed a close to ideal mixing effect.

5.3.2. Modeling of γ^∞ Values. In an early attempt to model activity coefficients in ionic liquids, Diedenhofen et al.²⁴⁰ compared the prediction of γ^∞ values for 38 organic compounds in several ionic liquids $\{[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2], [\text{C}_1\text{C}_1\text{im}][\text{NTf}_2]$ and $[\text{C}_4\text{C}_1\text{pyr}][\text{BF}_4]\}$ at 2 different temperatures (314 and 344 K) using the COSMO-RS model (conductor-like screening model for real solvents).²⁴¹ The data used were taken from several literature sources. The general trends that they reported were limited to an analysis of the model's predictive capabilities, and these results are discussed in more detail below.

Kato and Gmehling measured and correlated γ^∞ values for various organic solutes and water in several imidazolium and pyridinium ionic liquids.²⁴² The interactions between ionic liquids and these solutes were generally found to become less favorable as the alkyl chain length on the ionic liquid was increased. Also, the anion choice had a significant effect on the γ^∞ values for cyclohexane and benzene, with interactions becoming more favorable along the series $[\text{C}_1\text{SO}_4]^-$, $[(\text{C}_1\text{OC}_2)\text{OSO}_3]^-$, $[(\text{C}_1)_2\text{PO}_4]^-$, Cl^- , $[\text{BF}_4]^-$, $[\text{NTf}_2]^-$, and $[\text{PF}_6]^-$. This strongly indicates the importance of delocalization of electrons on the anion for determining solute–solvent interactions in the absence of significant hydrogen bonding (ion–induced dipole interactions).

Eike and Brennecke performed a large study on the prediction of γ^∞ values for 38 organic solutes in 3 ionic liquids, $[\text{C}_4\text{C}_1^3\text{pyr}][\text{BF}_4]$, $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$, and $[\text{C}_2\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$.²⁴³ They revealed that QSPR techniques are quite accurate for the correlation of γ^∞ values for a wide range of solute/ionic liquid combinations. They also had some limited success at predicting γ^∞ values for “unknown” organic solutes. The power of this technique, however, comes from the physical understanding of solute–solvent interactions that can be gleaned from the correlation parameters. Their key finding was that the γ^∞ values were most strongly dependent on the hydrophilicity parameter $\log K_{\text{OW}}$, which is strongly dependent on anion selection. Later QSPR analysis for γ^∞ values of 38 solutes in 3 ionic liquids confirmed this result.²⁴⁴

Verevkin et al. modeled solutions of aldehydes and ketones dissolved in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ using several standard activity coefficient models.²⁴⁵ In these systems, containing functionalities with interesting potential specific interactions, the nonrandom two-liquid (NRTL) model could accurately capture vapor–liquid equilibrium data in these binary systems by extrapolating from pure substance parameters. Similar conclusions were drawn for mixtures of $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ with n -alcohols and benzene.²⁴⁶ Despite the differences in specific interactions available in these two systems (e.g., hydrogen bonding), the authors found the NRTL equation superior for modeling the activity coefficients to the UNIQUAC (universal quasichemical) or Margules equation.

Regular solution theory has also been used to model ionic liquid solutions by estimating both solubility parameters and Hansen parameters for the three ionic liquids $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, $[\text{C}_8\text{C}_1\text{im}]\text{Cl}$, and $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ from other physical property measurements.²⁴⁷ The modeling was fairly successful, and the authors also found that increasing the alkyl chain length of n -alcohols decreased the favorable ionic liquid–alcohol interactions considerably, further strengthening the premise that these systems are dominated by hydrogen bonding from the alcohol solute to the anion of the ionic liquid. The poor suitability of regular solution theory for solutions containing polar solvents would seem to limit the application of this particular model.

UNIFAC (universal functional activity coefficient) is a group contribution model that has proved highly successful at correlating γ^∞ values for a wide range of solutes in several $[\text{NTf}_2]$ -based ionic liquids.²⁴⁸ These results compare favorably with COSMO-RS-based predictions and offer a possible route for predicting interactions with new solutes within a class of ionic liquids.

5.3.3. Summary. Activity coefficients at infinite dilution are an excellent means of isolating solvent–solute interactions. They add to the overall statement that most of the common ionic liquids behave similarly to short-chain alcohols, in accordance with spectroscopic quantification of their solvent potential. However, the wide availability of different cation and anion functionalities has led to a varied set of results for solutes in ionic liquids.

In general, interactions with small alcohols (such as methanol) and water are quite favorable; even water-immiscible ionic liquids yield activity coefficients of less than unity at infinite dilution. Those of functionalized organics can be either side of unity, depending on the nature of the ionic liquid employed and the functional group(s) of the solute. Unfunctionalized alkanes nearly always yield the least favorable interactions, though the activity coefficients can vary by up to 4 orders of magnitude across the range of ionic liquids reported in the literature. Functionalization to alkenes and then alkynes and finally aromatics has universally led to a lowering of activity coefficient and thus ever more favorable solvent–solute interactions.

When they can occur, hydrogen-bonding interactions are almost always dominant in these systems. Hydrogen bond donation from the solute to the anion is usually stronger than donation from the cation to the solute, though this may be related to the range of ions and organic functionalities used for study to date.

The most important use of these activity coefficients is to study the potential of ionic liquids as solvents for a variety of applications, from chemical reactions to entrainers for separation processes. In all, the power of these simple measurements has been greatly increased by successful attempts to correlate and predict these values using thermodynamic models. In this way, a suitable ionic liquid for many applications can be discovered and selected beforehand.

6. IONIC LIQUID EFFECTS ON STOICHIOMETRIC CHEMICAL REACTIONS

One way in which ionic liquids can affect chemical processes is to change the concentrations of solutes in equilibrium. The position of a chemical equilibrium is determined by the Gibbs free energy change of the reaction according to

$$\Delta G = -RT \ln K \quad (6)$$

When both the starting materials and the products of the reaction are present in solution, ΔG is sensitive to the energies of the interactions between these solutes and the solvent. Since these vary with the nature of the solvent, the equilibrium constant and hence the relative concentrations of the starting materials and products will change upon the solvent being changed. In spite of this, quantitative studies of chemical equilibria in ionic liquids remain rare.

The quantitative investigation of the influence of ionic liquids upon chemical kinetics has received much greater attention than equilibrium effects. Transition-state theory can be applied to those reactions in solution in which all of the species involved in the reaction, including starting materials, intermediates, and activated complexes, are in equilibrium with their environment, and through its application an understanding of solvent–solute interactions can be derived. This assumes that any reorganization of the solvent around the reacting species is fast in comparison to the reaction itself. The rates of these reactions are then dependent on the activation energy according to

$$k = Ae^{-\Delta G^\ddagger/RT} \quad (7)$$

The rates of these reactions are often labeled as “activation-controlled” or “static” reactions. When the solvent reorganization is slower than the reaction itself, simple transition-state theory cannot be applied and the reactions show different solvent dependencies, such as upon viscosities and densities. The rates of these reactions are often labeled as “dynamically controlled”. Anyone working with reaction rates in ionic liquids must be aware that their high viscosities and microscopic heterogeneity can result in such behaviors.^{185,186}

6.1. Energy Transfer

Energy transfer is perhaps the simplest reaction that can occur. It involves the transfer of energy from a species in an excited electronic state to another species. Dissolved oxygen is a perennial problem in the study of solutes in electronically excited states, which it can very effectively quench. The ability to purge ionic liquids of oxygen by the application of a vacuum makes them potentially very attractive solvents for the study of this chemistry. Early studies of the transient absorption spectrum of xanthone and pyrene in $[C_4C_1im][PF_6]$ confirmed this,²⁴⁹ showing the lifetime of the triplet excited state in $[C_4C_1im][PF_6]$ ($\tau = 4.5 \mu s$) to be considerably longer than in either

acetonitrile ($1.8 \mu s$) or 2-propanol ($0.37 \mu s$). The measured λ_{max} (622 nm) was between that found in acetonitrile (630 nm) and that found in 2-propanol (610 nm). However, the rate constant for the energy transfer between xanthone and naphthalene was as much as 2 orders of magnitude slower than that of the same reaction in molecular solvents. This was attributed to the reaction being dynamically controlled and the much slower diffusion of the reacting species in $[C_4C_1im][PF_6]$ associated with its high viscosity.

6.2. Electron Transfer Reactions

Electron transfer reactions have received considerable attention in ionic liquids. These fast reactions are usually diffusion controlled when they are bimolecular and are consequently expected to be slower in viscous ionic liquids than in more free flowing molecular solvents.²⁵⁰ However, experiments in ionic liquids have revealed a more complex situation than this. In molecular solvents the diffusion-limited rate coefficient is related to the bulk viscosity of the pure solvent; thus

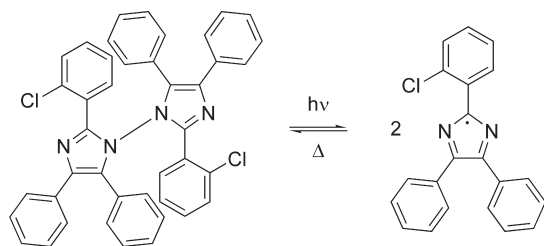
$$k_{diff} = 8000RT/3\eta \quad (8)$$

For a number of studies in ionic liquids this was indeed shown to be the case. The photoelectron transfer between the ruthenium tris-(4,4'-bipyridyl) dication, $[Ru(bpy)_3]^{2+}$, and methylviologen, MV^{2+} , has been investigated in a number of ionic liquids and shown to occur at an approximately diffusion controlled rate.^{251,252} The decay of $Br_2^{\bullet-}$ ions in $[(C_4)_3C_1N][NTf_2]$ via the bimolecular reaction $Br_2^{\bullet-} + Br_2^{\bullet-}$ was also found to be close to the diffusion-controlled limit predicted by its viscosity.²⁵³ Takahashi et al. subsequently²⁵⁴ found the same for the decay of $I_2^{\bullet-}$ radical anions in a series of $[NTf_2]^-$ ionic liquids. They noted the implication of this was that there was very little Coulombic repulsion of the radical ions for each other and interpreted this to be a consequence of the charge screening provided by the ionic liquid ions.

However, in a number of other studies the rates of electron transfer reactions have been considerably greater, by up to an order of magnitude or more, than would be predicted from the ionic liquids' viscosities. This covers a wide range of reacting species: benzophenone with naphthalene,²⁵⁵ alkylpyridinyl radicals with duroquinone,²⁵⁶ 9,10-dicyanoanthracene with 20 different aromatic single-electron donors,²⁵⁷ and pyrene²⁵⁸ or coumarin dyes²⁵⁹ with *N,N*-dimethylaniline. These results have been attributed to the microscopic viscosity experienced by these solute molecules being considerably lower than that expected from bulk viscosity measurements. Neta noted that the disparity between the observed and predicted rates increased with increasing length of the alkyl chains in $[(C_n)_3C_1N][NTf_2]$ ($n = 4$ or 8) and $[C_6(C_4)_3N][NTf_2]$.²⁵⁶ He attributed this to the presence of voids in the ionic liquid structure, as have others since.^{258,259} However, it is not clear what form such voids would take, and we have yet to see convincing evidence for large volumes of free space in ionic liquid structures.¹⁸⁶

Falvey went beyond the void model to suggest that the reactions between 9,10-dicyanoanthracene and aromatic single-electron donors occurred solely in the alkyl chain region of his ionic liquids.²⁵⁷ A study of the recombination of photolytically generated lophyl radicals in the ionic liquids $[C_4C_1im][NTf_2]$, $[C_4C_1im][BF_4]$, and $[C_6C_1im][PF_6]$ has shown that the situation may be complex.²⁶⁰ Again the rates of the reactions were greater in the ionic liquids than bulk viscosity would suggest. The authors suggested an overall reaction scheme with two possible recombination routes (Scheme 4)—rapid “in-cage” recombination and a long lifetime diffusive recombination of separated radicals. The authors note that this would lead to conflicting effects of increased viscosity. While the

Scheme 4



more viscous ionic liquid would lead to the photogenerated radicals being kept together in the solvent cage longer and so give more of the rapid recombination, it would also lead to slower diffusion-controlled recombination of the radicals once they had escaped the solvent cage. Hence, it was not possible to derive a simple relationship between the overall rate of recombination and the ionic liquids' viscosities. The authors did, however, note a distinct effect of changing the anion from $[\text{NTf}_2]^-$ to $[\text{BF}_4]^-$ for the $[\text{C}_4\text{C}_1\text{im}]^+$ ionic liquids. They considered that this might arise from direct interactions between the ionic liquid ions and the activated complex for the reaction. However, it should be noted that these types of solvent effects on the rates of reactions are not usually large when there is no significant charge rearrangement in the activation process.¹¹⁵ Their closer analysis of the activation parameters for the reactions in these two ionic liquids revealed a qualitative difference in the activation entropy for the reactions, with the expected negative value ($\Delta S^\ddagger = -107 \text{ J mol}^{-1} \text{ K}^{-1}$) in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, but a positive value ($\Delta S^\ddagger = 18 \text{ J mol}^{-1} \text{ K}^{-1}$) in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$. They concluded that this must arise due to solvent reorganization in the transition process. This would imply that the observed anion effect does not arise from the direct interaction of the anions with either the starting materials or the activated complex, but from the strength of the interaction between the ionic liquids' cations and anions, with the weaker of these, $[\text{C}_4\text{C}_1\text{im}]^+ - [\text{NTf}_2]^-$, allowing at least some solvent reorganization in the activation process and hence compensating for the large negative entropy change associated with the bimolecular recombination.

It can be seen from the above that the relationships between solute kinetic behaviors and the ionic liquid viscosities of ionic and molecular starting materials for these reactions are quite different, and we now propose a hypothesis to explain these apparently contradictory results. For the ionic solutes the rates of the reactions described above do appear to be classically diffusion controlled, whereas for neutral solutes the rates of the reactions are considerably faster than expected. In a study of N,N,N',N' -tetramethyl-*p*-phenylenediamine, TMPD, and its mono- and dication in acetonitrile and a variety of ionic liquids, $[\text{C}_n\text{C}_1\text{im}][\text{NTf}_2]$ ($n = 4$ or 10), $[\text{C}_4\text{pyr}][\text{NTf}_2]$, or $[\text{C}_{14}(\text{C}_6)_3\text{P}][\text{NTf}_2]$, the diffusion rates were found to vary in the order $\text{TMPD} > \text{TMPD}^{2+} > \text{TMPD}^{2+}$.²⁶¹ In acetonitrile the ratios of these compounds were 1, 0.89, and 0.51, whereas in the ionic liquids they were on average 1, 0.53, and 0.33. Clearly there is greater difference in the diffusion rates of molecules and ions in ionic liquids than is seen in acetonitrile.

We propose that when a salt is dissolved in an ionic liquid, its ions interact directly with the charge-bearing part of the ionic liquid's ions and break the solvent–solvent ion interactions, replacing them with solvent–solute ion interactions. Hence, the frictional forces and range of motion experienced by these solute ions are similar in nature to those experienced by the ions of the pure ionic liquid that give rise to its bulk viscosity. Consequently, bulk viscosity measurements would

be expected, and are observed, to give a reasonable guide to the diffusion of solute ions in ionic liquids and “normal” diffusion-controlled behavior. However, molecular solutes such as those used above are not expected to have such strong interactions with the ions of the ionic liquids, unless they have the ability to form hydrogen bonds with them.²⁶² In the absence of these interactions, the solute–solute Coulombic attraction of the ionic liquid ions is not (fully) disrupted by these neutral starting materials. This has several potential consequences. The first is that it leaves neutral solutes with a restricted volume in which to move. With a reduced volume to occupy, the encounter rate of the solute will be higher than expected for the concentration when considering the whole volume of the ionic liquid solution. The importance of this effect will depend upon the relative strengths of the solvent–solvent ionic interactions as well as the potential solvent–solute interactions and would be expected to be sensitive to the types of cations and anions composing the ionic liquid. In addition to this, the properties of this available volume will be dictated more by the nature of the nonpolar parts of the ionic liquid, the alkyl chains of the cations in the cases above. Hence, the frictional forces experienced by molecules moving through this reduced volume would be expected to be very different from those that give rise to the bulk viscosities of the ionic liquids, particularly lacking the ion–ion interactions. Consequently, bulk viscosity measurements do not give a guide to the diffusion of these solute molecules in ionic liquids. This effect would be expected to be sensitive to the length of the alkyl chains. Finally, if the solvent–solvent ionic interactions are disrupted during the activation process for the reaction, then this will contribute to a more favorable activation entropy for the reaction. This is somewhat similar to the model used to interpret of the rates of the $\text{S}_\text{N}2$ reaction of tributylamine with methyl *p*-nitrobenzenesulfonate in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ ²⁶³ and would be expected to be sensitive to the types of ions composing the ionic liquid. All of these sensitivities are observed in the reactions described above.

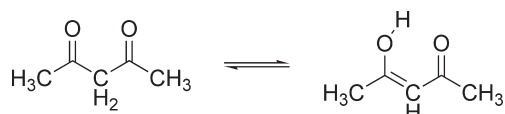
When pyridinium ionic liquids have been used as solvents for electron transfer reactions, a further effect has been observed. When pulsed radiolysis is used on a neat ionic liquid, it is usual for the solvated electron formed to not react rapidly with the ionic liquid's cations.²⁶⁴ However, when pyridinium ionic liquids are used, solvated electrons react with the cation to give pyridinyl radicals.²⁶⁵ These can, in turn, transfer an electron to solute acceptors to give a solvent-mediated electron transfer mechanism.²⁶⁶

6.3. Acid–Base Reactions

The well-known intramolecular proton transfer called “keto–enol tautomerism” was one of the first chemical phenomena found to be solvent dependent.²⁶⁷ The equilibrium of pentane-2,4-dione is one of the most widely studied of these proton transfers (Scheme 5). ¹H NMR has been used to investigate these proton transfers in the ionic liquids $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{PF}_6], [\text{BF}_4], [\text{OTf}], \text{or } [\text{NTf}_2]\}$.²⁶⁸ The percentage of the enol present at fixed overall concentrations of solute was used to compare the ionic liquids to molecular solvents. In molecular solvents this was found to correlate with the dielectric constant. However, the results in the ionic liquids would lead to predictions of between 40 and 55 for their dielectric constants, which are considerably higher than those found by physical measurements (see above). It is likely that this equilibrium is also very sensitive to hydrogen-bonding effects, which were not captured in this analysis.

The tautomeric equilibrium of 2-nitrocyclohexanone has also been studied in several molecular solvents and the ionic liquids $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, $[\text{C}_n\text{C}_1\text{im}][\text{NTf}_2]$ ($n = 2, 4, \text{or } 6$), and

Scheme 5



$[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$.²⁶⁹ The equilibrium constants for the ionic liquids were of the same order as those for polar aprotic solvents, such as acetonitrile. By this measure, the most polar of the ionic liquids was found to be $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$. The relationship found between ΔG° for this reaction and the Hildebrand parameter, δ_{H} , was used to predict the δ_{H} parameters for the ionic liquids, which were found to be in the range 23.6–26.9 (J cm^{−3})^{1/2}.

The discovery that acidic compositions of the chloroaluminate-(III) ionic liquids produce superacidic protons, with Hammett acidities as strong as −18, together with the potential of ionic liquids to act as catalysts/solvents (see below) has stimulated a considerable amount of interest in their acidity and in solutions of acids in ionic liquids.²⁷⁰

The relative Lewis acidities of a series of chlorometallate ionic liquids, $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{MCl}_x$ [$X(\text{MCl}_x) = 0.67$; $\text{MCl}_x = \text{AlCl}_3, \text{FeCl}_3, \text{ZnCl}_2$, or CuCl], and $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ have been measured using the infrared spectra of CH_3CN dissolved in the ionic liquids.²⁷¹ The spectrum in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ was found to be essentially unchanged in comparison to that in neat CH_3CN , suggesting that this ionic liquid can be considered to be Lewis neutral. However, the spectra in the other ionic liquids revealed a new peak that indicated that the ionic liquids were Lewis acidic in the order $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{AlCl}_3$ (2338 cm^{−1}) > $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{ZnCl}_2$ (2318 cm^{−1}) > $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{FeCl}_3$ (2310 cm^{−1}) > $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{CuCl}$ (2292 cm^{−1}). The effect of changing the composition of $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{AlCl}_3$ on the IR spectrum of CH_3CN was also investigated and shown to range from 2338 cm^{−1} for $X(\text{AlCl}_3) = 0.67$ to 2333 cm^{−1} for $X(\text{AlCl}_3) = 0.55$; for compositions with $X(\text{AlCl}_3) \leq 0.50$, this peak was not observed, indicating a lack of Lewis acidity. In this study similar conclusions were drawn using the IR spectrum of pyridine, which additionally showed an indication of Brønsted acidity in $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{AlCl}_3$ arising from adventitious water. When the halogenometallate complexes contained both bromide and chloride, the IR spectra of CH_3CN indicated the same ordering of acidity, $[\text{C}_4\text{pyr}]\text{Br}-\text{AlCl}_3 > [\text{C}_4\text{pyr}]\text{Br}-\text{FeCl}_3 > [\text{C}_4\text{pyr}]\text{Br}-\text{CuCl}_2$, but with no evidence for Lewis acidity of this copper(II) system.²⁷² When the mixed halide systems $[\text{C}_4\text{C}_1\text{im}]\text{X}-\text{AlCl}_3$ [$X(\text{AlCl}_3) = 0.67$; $X = \text{Cl}, \text{Br}$, or I] were compared, the Lewis acidity increased in the order $\text{Cl}^- < \text{Br}^- < \text{I}^-$, as one would expect.²⁷³

The Hammett acidity function gives a method for the measurement of the acidity of nonaqueous Brønsted acid systems.²⁷⁴ This has led a number of groups to measure the Hammett acidities of ionic liquids. Ideally, the measurements of absorptions of both protonated and unprotonated forms of a basic dye in the solution of interest are used to calculate the equilibrium constant between. In this scale, the more negative the value of H_0 , the stronger the acid. Neat sulfuric acid has a value of −12, and any system more acidic than this is generally considered to be a superacid. When the acid is dissolved in a solvent, the value of H_0 becomes more negative with concentration. Also the value of H_0 for the same acid at a fixed concentration in different solvents will vary.¹¹⁵ It is generally difficult to measure the acidity of the pure ionic liquids at room temperature, so measurements have been

Table 3. Hammett Acidities of Ionic Liquids^a

ionic liquid	measurement conditions	H_0
$[(\text{HSO}_3)_4\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ ²⁷⁵	CH_2Cl_2 solution (10 mM)	0.01
$[(\text{HSO}_3)_3\text{C}_3\text{C}_1\text{im}][\text{HSO}_4]$ ²⁷⁶	CH_2Cl_2 solution (5 mM)	−0.01
$[(\text{HSO}_3)_4\text{C}_4\text{pyr}][\text{HSO}_4]$ ²⁷⁷	CH_2Cl_2 solution (10 mM)	1.21
$[(\text{HSO}_3)_3\text{C}_3\text{pyr}][\text{pTSA}]$ ²⁷⁷	CH_2Cl_2 solution (10 mM)	3.98
$[(\text{HSO}_3)_4\text{C}_4\text{pyr}][\text{HSO}_4]$ ²⁷⁸	H_2O solution (32 mM)	1.42
$[(\text{HSO}_3)_4\text{C}_4\text{pyr}][\text{HSO}_4]$ ²⁷⁹	neat ionic liquid, 110 °C	−2.1
$[(\text{HSO}_3)_4\text{C}_4\text{pyr}][\text{pTSA}]$ ²⁷⁸	H_2O solution (32 mM)	1.6
$[(\text{HSO}_3)_4\text{C}_4\text{pyr}][\text{pTSA}]$ ²⁷⁹	neat ionic liquid, 110 °C	−1.2
$[(\text{HSO}_3)_4\text{C}_4\text{pyr}][\text{OTf}]$ ²⁷⁷	CH_2Cl_2 solution (10 mM)	1.06
$[(\text{HSO}_3)_4\text{C}_4\text{pyr}][\text{H}_2\text{PO}_4]$ ²⁷⁹	neat ionic liquid, 110 °C	−3.3
$[(\text{HSO}_3)_3\text{C}_3\text{pyr}][\text{pTSA}]$ ²⁷⁸	H_2O solution (32 mM)	1.59
$[(\text{HSO}_3)_3\text{C}_3\text{C}_2\text{bim}][\text{BF}_4]$ ²⁸⁰	CH_2Cl_2 solution (5 mM)	0.19
$[(\text{HSO}_3)_3\text{C}_3\text{C}_2\text{bim}][\text{HSO}_4]$ ²⁸⁰	CH_2Cl_2 solution (5 mM)	0.05
$[(\text{HSO}_3)_3\text{C}_4(\text{C}_1)_3\text{N}][\text{HSO}_4]$ ²⁸¹	H_2O solution (32 mM)	1.4
$[(\text{HSO}_3)_3\text{C}_4(\text{C}_2)_3\text{N}][\text{HSO}_4]$ ²⁸¹	H_2O solution (32 mM)	1.4
$[(\text{HSO}_3)_3\text{C}_4(\text{C}_1)_3\text{N}][\text{pTSA}]$ ²⁸¹	H_2O solution (32 mM)	1.58
$[\text{C}_1\text{Him}][\text{pTSA}]$ ²⁷⁶	CH_2Cl_2 solution (5 mM)	2.45
$[\text{C}_1\text{Him}][\text{OTf}]$ ²⁸²	$\text{CH}_2\text{ClCH}_2\text{Cl}$ solution (4.38 mM)	2.76
$[\text{C}_4\text{Him}][\text{OTf}]$ ²⁸²		1.38
$[\text{HC}_1^2\text{pyr}][\text{OTf}]$ ²⁸²	$\text{CH}_2\text{ClCH}_2\text{Cl}$ solution (2.89 mM)	2.19
$[\text{HC}_1^2\text{pyr}][\text{OTf}]$ ²⁸³		1.53
$[\text{HC}_1^2\text{pyr}][\text{CH}_3\text{SO}_3]$ ²⁸³	$\text{CH}_2\text{ClCH}_2\text{Cl}$ solution (4.38 mM)	3.13
$[\text{Hpyrrone}][\text{CF}_3\text{CO}_2]$ ²⁸⁴		3.48
$[\text{cplm}][\text{H}_2\text{PO}_4]$ ²⁸⁴	CH_2Cl_2 solution (5 mM)	2.08
$[\text{cplm}][\text{CF}_3\text{CO}_2]$ ²⁸⁴	CH_2Cl_2 solution (5 mM)	3.35
$[\text{cplm}][\text{ClCH}_2\text{CO}_2]$ ²⁸⁴	CH_2Cl_2 solution (80 mM)	5.04
$[\text{cplm}][\text{PhCO}_2]$ ²⁸⁴	CH_2Cl_2 solution (80 mM)	6.07
	CH_2Cl_2 solution (80 mM)	
$[\text{C}_4\text{C}_1\text{im}][\text{HSO}_4]$ ²⁷⁵	CH_2Cl_2 solution (80 mM)	0.73
$[\text{C}_4\text{C}_1\text{im}][\text{HSO}_4]$ ²⁷⁶	CH_2Cl_2 solution (80 mM)	0.08
$[\text{C}_4\text{C}_1\text{im}][\text{H}_2\text{PO}_4]$ ²⁷⁵		2.55
$[\text{C}_4\text{C}_1\text{im}][\text{H}_2\text{PO}_4]$ ²⁷⁶	CH_2Cl_2 solution (10 mM)	1.75
$[\text{C}_5\text{C}_1\text{im}][\text{HSO}_4]$ ²⁷⁶	CH_2Cl_2 solution (5 mM)	1.09
$[\text{C}_5\text{C}_1\text{im}][\text{H}_2\text{PO}_4]$ ²⁷⁶	CH_2Cl_2 solution (10 mM)	1.92
$[\text{C}_4\text{C}_2\text{bim}][\text{HSO}_4]$ ²⁸⁰	CH_2Cl_2 solution (5 mM)	1.26
$[\text{C}_5\text{C}_2\text{bim}][\text{HSO}_4]$ ²⁸⁰	CH_2Cl_2 solution (5 mM)	1.5
$[\text{C}_4\text{C}_2\text{bim}][\text{H}_2\text{PO}_4]$ ²⁸⁰	CH_2Cl_2 solution (5 mM)	1.83
$[\text{C}_5\text{C}_2\text{bim}][\text{H}_2\text{PO}_4]$ ²⁸⁰	CH_2Cl_2 solution (5 mM)	2.28
	CH_2Cl_2 solution (5 mM)	
	CH_2Cl_2 solution (5 mM)	

^a $[\text{C}_n\text{C}_m\text{bim}]^+ = \text{dialkylbenzimidazolium}$, $[\text{Hpyrrone}]^+ = 2\text{-pyrrolidonium}$, $[\text{cplm}] = \text{caprolactamium}$, and $[\text{pTSA}] = p\text{-toluenesulfonate}$.

made either at higher temperature or in a dilute solution in a molecular solvent, either CH_2Cl_2 or water.

The overwhelming message from the results in Table 3 is, perhaps unsurprisingly, that they depend upon the conditions of the measurement. This makes it difficult to compare the results across different reports by different groups. Ionic liquids with anions that are known to react with water to produce acid, e.g., $[\text{BF}_4]^-$ and $[\text{PF}_6]^-$, have been excluded, yet several discrepancies remain in the table. However, some general conclusions can be drawn.

None of these ionic liquids are in the superacid range. When the Brønsted acidity arises from the anion of the ionic liquid, as in the

$[\text{HSO}_4]^-$ and $[\text{H}_2\text{PO}_4]^-$ ionic liquids, the cation appears to generally have little effect upon the overall acidity of the ionic liquid. However, when the cation bears the proton, the anion does appear to influence the overall acidity of the ionic liquid. Using a Brønsted acidic anion appears to maximize the acidity of the ionic liquid for any given cation. This suggests that even when a Brønsted acid, the anion is the strongest base in the pure ionic liquid.

The gas-phase ion pair $[(\text{HSO}_3)_3\text{C}_3\text{C}_1\text{im}][\text{HSO}_4]^-$ has been investigated with density functional theory (DFT).²⁸⁵ In spite of the limitations of being restricted to a single ion pair, this study did give some useful insights. The first was that there is a low activation energy for the proton transfer between the $-\text{SO}_3\text{H}$ group and the $[\text{HSO}_4]^-$. It was also noted that hydrogen-bonding interactions between the protons of the imidazolium ring could act to stabilize the deprotonated $-\text{SO}_3^-$ group, but these bonds broke when the group was protonated.

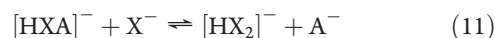
The acidities of solutions of the strong Brønsted acid $\text{H}[\text{NTf}_2]$ or $\text{H}[\text{OTf}]$ dissolved in a range of ionic liquids, $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{BF}_4]^-$, $[\text{PF}_6]^-$, $[\text{SbF}_6]^-$, $[\text{NTf}_2]^-$, or $[\text{OTf}]^-\}$, $[\text{C}_4\text{Him}][\text{NTf}_2]$, or $[(\text{C}_2)_3\text{NH}][\text{NTf}_2]$, have also been investigated using the Hammett method.²⁸⁶ In these studies, no major differences were observed for these acid solutions for ionic liquids with a common anion, even when the cation itself is protic as in $[\text{C}_4\text{Him}]^+$. However, large differences in the acidities were found when the anion was changed, such that $[\text{PF}_6]^- > [\text{BF}_4]^- \gg [\text{NTf}_2]^- > [\text{OTf}]^-$. This suggested solvent leveling by the ionic liquid, with the anion playing the role of base. Except in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$, the acidities of the $\text{H}[\text{NTf}_2]$ solutions were consistently higher than those of the $\text{H}[\text{OTf}]$ solutions, but these differences were not as great as those between the ionic liquids with different anions.

The acidities of solutions of weak carboxylic acids in $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$ and $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$ have also been investigated using sodium 4-nitrophenolate $\{\text{Na}[\text{ArO}]\}$ as an indicator.²⁸⁷ The acidities of these solutions vary such that $\text{H}_2\text{O} > [\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2] > [\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$. For the range of acids used there was a linear correlation of the acidities of the resultant solutions between water and $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$, but not with $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$, in which a different order of acidities was found. Given the observed insensitivity of other acidity measurements of solutions of acids in ionic liquids to the nature of the cation,²⁸⁶ this is an unexpected result. The authors interpret their results in terms of an equilibrium between the dissolved sodium 4-nitrophenolate and molecular acid (HA) on one hand and 4-nitrophenol (ArOH) and the sodium salt of the conjugate base of the acid (NaArO) on the other (eq 9). However, this probably does not well represent the species actually present in the solution (see below).

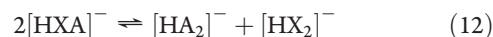


It is now possible to make some general comments about the speciation of protons in ionic liquids. First, it should be noted that protons are small and highly mobile species and acidic solutions should be regarded as highly dynamic. Also, protons are never found in a naked state in a condensed phase and will always seek out the best available base. The data above suggest, and by analogy with the formation of $[\text{HCl}_2]^-$ in $[\text{C}_1\text{C}_1\text{im}]\text{Cl}$ ²⁸⁸ and in chloride-rich compositions of chloroaluminate ionic liquids,²⁸⁹ that in neutral ionic liquids the simplest possible Brønsted acidic species when the acid is dilute is $[\text{HY}_2]^-$ (where $\text{Y}^- = \text{any anion}$). The anion Y^- may arise from the conjugate base of the acid added or from the ionic liquid. Thus, the addition of an acid to an ionic liquid in dilute solution is perhaps best viewed as

yielding two species in equilibrium:



where X^- is the ionic liquid anion. The concentrations of each species depend upon the relative basicities and concentrations of the ions X^- and A^- . It is also possible that the following equilibrium may need to be considered:



At higher concentrations ions of the type $[(\text{HA})_x\text{X}]^-$ can also be formed, as is found in $[\text{Hpyr}][(\text{HF})_{21}\text{F}]$.²⁹⁰

While solvent leveling by the ionic liquids' anions described above is to have been expected,²⁸⁶ the ordering found $\{[\text{PF}_6]^- > [\text{BF}_4]^- \gg [\text{NTf}_2]^- > [\text{OTf}]^-\}$ is not. Whether based upon calculated gas-phase acidities²⁹¹ or measured Kamlet–Taft β values,¹⁴¹ the expected order would be $\{[\text{PF}_6]^- > [\text{NTf}_2]^- > [\text{BF}_4]^- > [\text{OTf}]^-\}$. It is not immediately clear as to how this difference arises. However, the chemical similarities within and differences between the two sets of ions, $[\text{PF}_6]^-$ and $[\text{BF}_4]^-$, and $[\text{NTf}_2]^-$ and $[\text{OTf}]^-$, are well recognized. One possible reason for the unexpected acidities is that $[\text{PF}_6]^-$ and $[\text{BF}_4]^-$ are more reactive than $[\text{NTf}_2]^-$ and $[\text{OTf}]^-$ and that this results in the formation of new species that may contribute to the acidity of the solution (e.g., HF , BF_3 , or PF_5). Another possibility is that there may be subtle differences in the nature of the solution species, $[\text{HX}_2]^-$. These ions can take either a symmetrical form, $[\text{Cl}-\text{H}-\text{Cl}]^-$ as found in $[(\text{C}_2)_4\text{N}][\text{HCl}_2]$, or an unsymmetrical form, $[\text{Cl}-\text{H}\cdots\text{Cl}]^-$ as found in $[(\text{C}_1)_4\text{N}][\text{HCl}_2]$.²⁹² Computational studies on $[\text{HCl}_2]^-$ in solution in $[\text{C}_1\text{C}_1\text{im}]\text{Cl}$ indicate that this species is more stable (i.e., less acidic) when it is in the symmetrical form.²⁸⁸ Hence, if $[\text{NTf}_2]^-$ and $[\text{OTf}]^-$ are capable of forming the symmetric form of $[\text{HX}_2]^-$ and $[\text{PF}_6]^-$ and $[\text{BF}_4]^-$ are not, this could, at least in part, explain the results. However, at this stage this remains a conjecture.

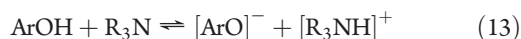
Less attention has been given to the effects of ionic liquids on the strengths of dissolved bases. This is in great part due to known sensitivity of imidazolium ionic liquids to even mild bases, which can lead to the formation of the deprotonated N-heterocyclic carbenes (NHCs) and seriously affect these types of reactions. Not only are these NHCs reactive species,²⁹³ they can also act as catalysts.^{294,295} Hence, NHCs can be significant contributors to the chemistry observed even when present in low concentrations, so relatively weak bases that can only partially deprotonate the imidazolium cation may be sufficient to produce these effects. Attempts have been made to prevent the formation of these carbenes by substituting the imidazolium ring at the 2-position, usually with a methyl group. However, it has been noted that these methyl protons are also sufficiently acidic to potentially lead to undesired side reactions.²⁹⁶ Other substitutions of the imidazolium have also been used,²⁹⁷ but it is usually simpler to avoid imidazolium cations when studying base solutes. However, even in the absence of this particular problem with imidazolium ionic liquids, the more general problem of the well-established instability of ammonium salts in the presence of bases/nucleophiles can further restrict the use of bases.^{6,83,298} Alkylphosphonium ionic liquids are more stable to bases than their ammonium analogues,³⁹ but even they are not immune to reaction with bases.

A study of the equilibrium constants of the reactions of *p*-nitrophenol (ArOH) with butylamine (BuNH_3), piperidine (pip), and triethylamine (Et_3N) (eq 13) was conducted in

Table 4. Predicted Effect of Using Polar Solvents for Nucleophilic Substitution Reactions¹¹⁵

reaction type	initial reactants	activated complex	change during activation	effect of polar solvent on rate
(a) S _N 2	Y [−] + R—X	Y ^{δ−} ...R...X ^{δ−}	dispersal of charge	decrease
(b) S _N 2	Y + R—X	Y ^{δ+} ...R...X ^{δ−}	separation of unlike charges	large increase
(c) S _N 2	Y + [R—X] ⁺	Y ^{δ−} ...R...X ^{δ+}	dispersal of charge	decrease
(d) S _N 2	Y [−] + [R—X] ⁺	Y ^{δ+} ...R...X ^{δ+}	destruction of charge	large decrease
(e) S _N 1	R—X	R ^{δ+} ...X ^{δ−}	separation of unlike charges	large increase
(f) S _N 1	[R—X] ⁺	R ^{δ+} ...X ^{δ+}	dispersal of charge	decrease

[C₄C₁im][BF₄].²⁹⁹ The base strength of the amines was found to be greater than in the molecular solvents studied. This was attributed to the ionic liquids stabilizing the product ions more than the neutral starting materials. The order of the basicity was BuNH₃ < Et₃N < pip in the ionic liquids and benzene, but Et₃N < BuNH₃ < pip in water. The reaction of *p*-nitrophenol with piperidine was further investigated in [C₄C₁im][PF₆], [C₄C₁im][NTf₂], and [C₄C₁C₁²im][NTf₂] and found to depend upon both the anion and cation of the ionic liquid, with *K* increasing in the order [C₄C₁C₁²im][NTf₂] < [C₄C₁im][PF₆] < [C₄C₁im][NTf₂] < [C₄C₁im][BF₄]. This study was later extended to include a wider range of amines and the ionic liquid [C₄C₁pyrr][NTf₂].³⁰⁰ Here the authors attempted an analysis based upon separating the “cation effect” and the associated Kamlet–Taft parameter α from the “anion effect” and the associated Kamlet–Taft parameter β . They noted a correlation with β , but not with α . However, α and β are not truly independent, solely cation and anion associated features, and one would not necessarily expect this kind of simple direct causation analysis to succeed. Our own reanalysis of their data using the LSER model shows that there are insufficient data points to yield statistically robust correlations, but that both α and β make positive (i.e., a higher value leads to increased basicity) contributions to the observed changes when only ionic liquids are considered and that π^* is important when the molecular solvent (benzene) that was used is included in the analysis.



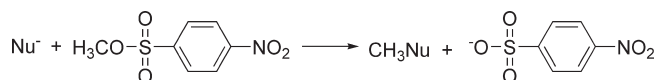
6.4. Substitutions

Nucleophilic substitutions are mechanistically extremely well understood and have a long history of being used to study the effects of solvents on solute reactivity, particularly through the pioneering work of Hughes and Ingold.^{115,301} Their rules for predicting the effect of changing the solvent on the rates of reactions were largely based upon studies of nucleophilic substitutions and can be summarized as follows:

- Increasing the polarity of the solvent increases the rates of reactions in which the charge density of the activated complex is greater than that of the reactants.
- Increasing the polarity of the solvent decreases the rate of reactions in which the charge density of the activated complex is lower than that of the reactants.
- Changing the polarity of the solvent has no effect on the rates of reactions in which the charge density of the activated complex is the same as that of the reactants.

Consequently, nucleophilic substitutions have been used to investigate the polarity of ionic liquids. Although these reactions are usually referred to by the molecularity of the rate-determining step (S_N1 or S_N2), this belies the variety of reactions that are available for study, particularly with respect to changes in charge

Scheme 6



distribution during the activation process. These types are listed in Table 4, together with the expected effect of using a polar solvent upon the rate of the reaction. As can be seen from the table, the potential impact of using these polar solvents changes dramatically with the type of reaction.

When considering competing mechanisms, the Hughes–Ingold rules can also be applied to predict which reactions might be preferred by changing the solvent. When changing to a more polar solvent, it is expected that selectivity to the product of those reactions that have activated complexes with greater charge density should be greater than that of the same reaction in nonpolar solvents. Therefore, it might be expected that greater selectivity to substitution and less competing elimination will be observed in ionic liquids. Also, a greater preference for S_N1 might be observed in ionic liquids.

6.4.1. Type a S_N2 Y[−] + R—X Reaction. The reactions of charged nucleophiles with neutral substrates are often conducted using phase transfer catalysis, often with undesirable chlorinated solvents. In an attempt to eliminate the need for these solvents, the reaction of potassium cyanide (3 mol dm^{−3}) with benzyl chloride (1 mol dm^{−3}) was conducted in [C₄C₁im][PF₆].³⁰² The potassium cyanide was not completely soluble at the concentrations used for the reaction, and at 40 °C the reaction kinetics were dominated by its dissolution. At higher temperatures classic pseudo-first-order kinetics were seen, indicating that this is indeed an S_N2 process in the ionic liquid. The ionic liquids could be recycled by extracting the phenylacetone nitrile product with supercritical CO₂ and then washing the KCl byproduct from the hydrophobic ionic liquid with water.

In a series of papers, Welton et al. investigated the reactions of a range of anionic nucleophiles {Cl[−], Br[−], I[−], [CH₃CO₂][−], [CF₃CO₂][−], [CN][−], and [SCN][−], Scheme 6} with methyl *p*-nitrobenzenesulfonate (Me-*p*-NBS) in detail in both ionic liquids {[C₄C₁im][NTf₂], [C₄C₁pyrr][NTf₂], or [C₄C₁pyrr][OTf]} and molecular solvents [dichloromethane (DCM), DMSO, or MeOH].³⁰³ This substrate was chosen because both the starting material and product have UV–vis absorptions that could be used to follow the progress of the reaction. The anions were used as salts with the cation common to that of the ionic liquids in which the reaction was being conducted.

These reactions were found to proceed smoothly in the ionic liquids with the same S_N2 mechanism as seen in the molecular solvents. If the Hughes–Ingold rules are applied to these reactions, then the ionic liquids can be said to be polar solvents, with polarities of

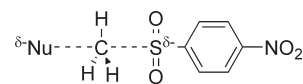
Table 5. LSER Correlations for $\ln k_2$ Obtained for Some Anionic Nucleophiles in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$, $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$, $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$, DMSO, DCM, and MeOH³⁰³

nucleophile	R^2	LSER
Cl^- ($\beta = 1.00$)	0.99	$\ln k_2 = 0.21 - 7.56\alpha$
Br^- ($\beta = 0.67$)	0.97	$\ln k_2 = -0.87 - 5.38\alpha$
I^- ($\beta = 0.30$)	0.95	$\ln k_2 = -2.57 - 3.05\alpha + 1.16\beta$
$[\text{CH}_3\text{CO}_2]^-$ ($\beta = 1.49$)	1.00	$\ln k_2 = -2.37 - 7.60\alpha + 2.65\beta + 1.83\pi^*$
$[\text{CF}_3\text{CO}_2]^-$ (no β available)	0.97	$\ln k_2 = -9.18 - 4.94\alpha + 5.76\pi^*$
SCN^- ($\beta = 0.33$)	0.89	$\ln k_2 = -3.87 - 2.46\alpha$
CN^- ($\beta = 1.37$)	0.99	$\ln k_2 = -3.16 - 5.07\alpha + 5.78\pi^*$

the order of those of the polar aprotic solvents and short-chain alcohols. However, no simple correlation was found with the dielectric constant, even for the molecular solvents investigated, and closer inspection revealed the importance of specific solvent–solute interactions in determining the reaction rates. The range of the solvent dependency of the reaction varied dramatically between the different nucleophiles; for $[\text{CH}_3\text{CO}_2]^-$ k_2 values varied greatly between the different solvents, whereas for $[\text{SCN}]^-$ k_2 values showed very little change. The solvents providing the fastest reaction also changed with the different nucleophiles. Similarly, the trend of the relative nucleophilicities of the nucleophiles was different in different solvents.

To understand these complex results, a Kamlet–Taft LSER approach was taken. Acceptable correlations, using data sets from both ionic liquids and molecular solvents, were achieved for all of the nucleophiles, clearly demonstrating that in this reaction there is no special ionic liquid effect and that all significant interactions between the ionic liquids and these solutes are adequately described by an appropriate combination of their Kamlet–Taft parameters. α appeared in all of the LSERs generated and always had a negative value. Two of the nucleophiles, I^- and $[\text{Ac}]^-$, had best fit LSERs with β in the correlations, but with a much lower contribution that was attributed to the antagonistic hydrogen-bonding effects described above. π^* appeared in the best fit LSERs for three of the nucleophiles, $[\text{CN}]^-$, $[\text{CH}_3\text{CO}_2]^-$, and $[\text{CF}_3\text{CO}_2]^-$.

The negative α values can be attributed to slowing of the reaction by the solvent hydrogen bonding to the nucleophile, stabilizing it with respect to the activated complex, which is a less strong hydrogen bond acceptor than the nucleophile itself. Since the hydrogen bond donor property of the ionic liquids is largely a result of the cation structure, this is generally seen as a strong cation effect for the ionic liquids. It can be seen that the stronger the hydrogen bond acceptor character of the nucleophile (represented by the nucleophile β values listed in Table 5), the larger this effect. This is particularly emphasized when anions of similar structure are compared {i.e., $\text{Cl}^- > \text{Br}^- > \text{I}^-$, $[\text{CH}_3\text{CO}_2]^- > [\text{CF}_3\text{CO}_2]^-$, and $[\text{CN}]^- > [\text{SCN}]^-$ }. The effect of changing the α value of the solvent on the reaction broadly splits into three groups: $\text{Cl}^- \approx [\text{CH}_3\text{CO}_2]^- > [\text{CN}]^- \approx [\text{CF}_3\text{CO}_2]^- \approx \text{Br}^- > \text{I}^- \approx [\text{SCN}]^-$. This again fits with the qualitative order that would be predicted from the β values of the anionic nucleophiles alone, with the exception of $[\text{CN}]^-$. This is an excellent demonstration of the intimacy of the solvent–solute relationship. While a solvent may have the potential to behave as a hydrogen bond donor to a solute species, this potential is only realized when the solute is a good hydrogen bond acceptor. The apparent anomaly of the $[\text{CN}]^-$ result was explained by invoking a hard/soft classification of the interactions, with the ionic liquids being considered to be hard hydrogen bond donors. Subsequent studies in $[\text{ClO}_4]^-$ and $[\text{PF}_6]^-$ ionic liquids showed similar effects and also demonstrated the influence that dissolved water can have on the rates of these reactions.³⁰⁴

**Figure 8.** Activated complex for the reaction of Me-*p*-NBS and anionic nucleophiles.

When studying the activation parameters for these reactions in ionic liquids, it was noted that ΔS^\ddagger for the reaction was more similar to that of the reaction of free solvated ions in molecular solvents, but ΔH^\ddagger was more similar to that of the ion-paired nucleophiles in molecular solvents. It was concluded that this apparent anomaly is a direct result of the nature of ionic association in ionic liquids. In an ionic liquid, there are no molecules available to separate ions and the ions of the solute will be repelled by the ions of the ionic liquid bearing the same charge (cation–cation or anion–anion) and attracted by anions of opposite charge. Hence, in an ionic liquid, a solute ion will always be closely associated with ions of opposite charge. Studies of the compound $[\text{C}_1\text{C}_1\text{im}]\text{Cl}$ by neutron diffraction showed that the anion is coordinated by six cations within 6.5 Å.¹⁷⁷ This is the same thing as neither a free ion nor an ion pair. This was used to propose a mechanism for the reaction which required the removal of a cation from the nucleophile to liberate an active site for reaction before the activation process itself occurred, which also involved a reduction hydrogen bonding. However, a subsequent simulation study has shown that the Me-*p*-NBS prefers to occupy a position similar to that of the cation in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$.³⁰⁵ The chloride ion occupies the anion position in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, with strong hydrogen bonds to the $[\text{C}_4\text{C}_1\text{im}]^+$. This suggests that while the two reactants must come together for the reaction to occur, there is no significant overall breaking of hydrogen bonds in this step, and its energetic demand is not likely to have a major effect on the rates of these reactions. Consequently, the negative α effect for this reaction can be attributed to the weakening hydrogen bonds between the solvent and the chlorine atom as its charge density decreases as the activated complex is formed (Figure 8). The simulations also show that hydrogen bonds are also formed to the nucleofuge, which is developing charge during the activation process, but this is obviously not sufficient to compensate for the loss of hydrogen bonding to the Cl^- .

The nucleofugacity of the leaving group is an important contributor to the rate of $\text{S}_\text{N}2$ reactions that can also be subject to solvent effects. The reactions of NaN_3 with a range of primary, secondary, and tertiary halides and tosylates have been investigated in the ionic liquids $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$, and $[\text{C}_6\text{pyr}][\text{NTf}_2]$.³⁰⁶ While the substrates were fully soluble in the ionic liquids, there was always some solid NaN_3 , which had been added in 3-fold excess, present in the reaction flask. The reactions proceeded cleanly without

the formation of elimination products, in agreement with predictions based upon the Hughes–Ingold approach. Since N_3^- is such a potent nucleophile, the changes in the reactivity could be attributed to effects on the leaving group; this was confirmed by the order of the reactivities of the substrates in the ionic liquids being $[\text{OTf}]^- > \text{Br}^- > \text{I}^- \gg \text{Cl}^-$. For the tosylates the rates in different ionic liquids increased in the order $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2] < [\text{C}_6\text{pyr}][\text{NTf}_2] < [\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$. For the halides $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ gave the fastest reactions, which was attributed to the ability of this ionic liquid to form hydrogen bonds to the leaving group.

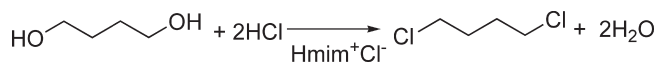
β -Phenylethyl bromides, mesylates, and triflates are susceptible to elimination reactions to form styrene. A study of the nucleophilic substitutions of these compounds with a range of nucleophiles (CN^- , N_3^- , NO_2^- , or BnNH_2) in $[\text{C}_{14}(\text{C}_6)_3\text{P}][\text{NTf}_2]$ showed no elimination products in most of the reactions.³⁰⁷ The one exception to this was the reaction of 2-phenylbromoethane with NaNO_2 at temperatures exceeding 85 °C, but this could be prevented at lower temperatures. This again confirms the usefulness of the Hughes–Ingold rules for mechanistic prediction in ionic liquids.

Nucleophilic fluorinations are an important class of reactions that yield many useful products. The use of ^{18}F , which has a half-life of 110 min, in positron emission tomography imaging agents means that there is a constant demand for ever more efficient and rapid ways of introducing fluorine into molecules. Consequently, the possible applicability of ionic liquids to these reactions has been investigated by several groups.

Chi et al. used 1:1 (v/v) mixtures of ionic liquids and CH_3CN as solvents for nucleophilic fluorinations of alkyl methanesulfonates.³⁰⁸ They found that the addition of ionic liquid led to increased reactivity of KF, presumably because of increased solubility, and greater selectivity to the substitution products alone, again in agreement with Hughes–Ingold rule based predictions. In the $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]/\text{CH}_3\text{CN}$ system the choice of salt that was used to introduce the fluoride greatly affected the reaction, with LiF, NaF, and CaF_2 giving no reaction, RbF and CsF giving the fastest reactions, and slightly slower reaction being given by KF. The same reactions in CH_3CN alone gave little or no product. To circumvent some of the product isolation problems that they had encountered, they developed a polymer-supported ionic liquid methodology for these reactions.³⁰⁹ Subsequently, they prepared some $[(\text{HO})(\text{CH}_2)_2\text{C}_3\text{im}]\text{X}$ $\{\text{X} = [\text{OTf}]$ or $[\text{C}_1\text{SO}_3]; n = 1, 3$ (isopropyl), 4, or 6 $\}$ ionic liquids which proved to be more effective in these reactions than the $[\text{C}_4\text{C}_1\text{im}]^+$ ionic liquids, even when *tert*-butyl alcohol had been added.³¹⁰

Attempts to use $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ itself as a solvent for the fluorination of a range of bromides using CsF led to reasonable conversions, but were accompanied by contamination of the product with elimination byproduct.³¹¹ Also the ionic liquid was found to be susceptible to decomposition via nucleophilic attack by the F^- on the cation of the ionic liquid at temperatures similar to those used by Chi et al.³⁰⁸ Later it was discovered that the addition of $[\text{C}_4\text{C}_1\text{im}]\text{Br}$ to a solution of trichlorotoluene in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ led to faster reaction to the monofluorinated product (with ~5% difluorination) than when the same reaction was conducted in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ alone. It was proposed that this occurred via the formation of a brominated intermediate that went on to give the fluorinated product. It was also found that the addition of $\text{K}[\text{PF}_6]$ to the reaction mixture in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ increased the rate of reaction compared to that of the reaction in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ alone. A similar increase was found when $\text{K}[\text{PF}_6]$ was added to the reaction mixture in sulfolane.

Scheme 7



6.4.1.1. “Nucleophilic HCl”. The conversion of alcohols to alkyl halides is used to prepare several industrially important intermediates. Unfortunately, this often requires the use of powerful and environmentally damaging and/or toxic chlorinating agents, such as COCl_2 , SOCl_2 , PCl_3 , etc. BASF has developed an ionic liquid based process in which HCl is the chlorinating agent in a chloride ionic liquid.³¹² When used in the chlorination of 1,4-butanediol, the ionic liquid method provides a route to the dichloride without the formation of partially chlorinated or ether byproduct (Scheme 7). As well as being a chlorination, this reaction is a dehydration, and it is noticeable that the traditional chlorinating agents for this reaction are also dehydrating agents. It is noted in the patent that the water level in the ionic liquid must be below 25 mol %. Indeed an earlier study that used 37% aqueous HCl in $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ in a 1:1 molar ratio showed no reaction, whereas 95% aqueous H_2SO_4 in $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ was an effective chlorinating mixture.³¹³ Although no detailed mechanistic study of this reaction has been conducted, the dominant acidic species in such an ionic liquid is the $[\text{HCl}_2]^-$ ion;²⁸⁹ consequently, this is likely to be a type $\text{Y}^- + \text{R}-\text{X} \text{ S}_{\text{N}}2$ reaction and not a type $\text{b Y} + \text{R}-\text{X}$ reaction that might have been expected. Hence, it is possible that it is the combination of a more reactive form of HCl and an ionic liquid that drives the reaction through dehydration, leading to the success of this process.

When a 1:1 mixture of *p*-toluenesulfonic acid (pTSA) and $[\text{C}_n\text{C}_1\text{im}]\text{X}$ ($n = 4$ or 8; $\text{X} = \text{Br}$ or I) was used as a halogenating mixture, good conversions of diols to dihalides were achieved.³¹⁴ Kinetic investigations confirmed that these reactions proceeded via fast initial protonation of the alcohol followed by substitution. It has also been found that $[\text{C}_4\text{C}_1\text{im}][\text{HSO}_4]$ is sufficiently acidic to act as the proton source for this reaction when used as the solvent with either NaBr or NaI as the halide source.³¹⁵

The products of the reactions above were prepared free from the ether byproducts that are common in these reactions. This can be explained by the ability of HX to cleave ethers in ionic liquids to give an alcohol and a halogenoalkane as products.³¹⁶ For HBr in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{BF}_4], [\text{PF}_6], [\text{NTf}_2], \text{ or } [\text{OTf}]\}$ the rates, as described by the greatest yields in the shortest reaction time, were in the order $[\text{BF}_4]^- > [\text{OTf}]^- > [\text{PF}_6]^- > [\text{NTf}_2]^-$; again the most hydrophilic ions give the fastest reactions.^{316d} However, very little reaction was found in $[\text{C}_4\text{C}_1\text{im}][\text{CH}_3\text{CO}_2]$. Other acids could be used if the Br^- ion was supplied as part of a $[\text{C}_4\text{C}_1\text{im}]\text{Br}/[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ mixture to achieve similar reactivities.

6.4.2. Type b $\text{S}_{\text{N}}2 \text{ Y} + \text{R}-\text{X}$ Reaction. The rate constants of the reaction of 1,2-dimethylimidazole with benzyl bromide in the 12 ionic liquids $[\text{C}_n\text{C}_1\text{im}]\text{X}$ and $[\text{C}_n\text{C}_1\text{C}_1^2\text{im}]\text{X}$ $\{n = 4$ or 8; $\text{X} = [\text{NTf}_2], [\text{PF}_6], \text{ or } [\text{BF}_4]\}$, $[\text{C}_4\text{C}_1\text{pyr}][\text{NTf}_2]$, and $[\text{C}_6(\text{C}_4)_3\text{N}][\text{NTf}_2]$ have been measured.³¹⁷ The reactions of neutral nucleophiles with neutral substrates are predicted to be accelerated in ionic liquids on the basis of a Hughes–Ingold analysis. Overall, the rates were found to be similar to those found in polar aprotic molecular solvents and were found to vary with the ionic liquid anion in the order $[\text{NTf}_2]^- < [\text{PF}_6]^- < [\text{BF}_4]^-$, with a far lesser effect from the cation. The authors correlated the results with the Kamlet–Taft parameters α and π^* (eq 14) to obtain an LSER. The noted anion dependence suggests that a better fit might have been obtained if β had been included in this analysis. Again the

negative α coefficient suggests that a hydrogen bond interaction between the solvents and the nucleophile reduces its reactivity.

$$\log k = -4.95 - 1.22\alpha + 2.61\pi^* \quad (14)$$

The rates of the reactions of benzyl chlorides with 1-methylimidazole have been shown to be consistently faster in ionic liquids $\{[C_4C_1im][PF_6], [C_4C_1im][NTf_2], [C_4C_1C_1^2im][NTf_2], \text{ or } [C_4C_1pyrr][NTf_2]\}$ than molecular solvents (MeCN, DMF), although the precise ordering changed with differently substituted benzyl chlorides.³¹⁸ An LSER for benzyl chloride itself revealed positive α and π^* effects and negative β and δ [$\delta = (CED)^{1/2}$] effects (eq 15). For benzyl bromide the solvent effect was only slight, and for benzyl iodide the reactions in the molecular solvents were faster than in the ionic liquids, but no LSER analysis was attempted. This suggests that stabilization of the activated complex for the reaction via interactions between the ionic liquid and the emerging nucleofuge weakens as the halide increases in size and decreases in charge density.

$$\log k_2 = -1.24 + 0.44\alpha - 2.62\beta + 0.64\pi^* - 0.10\delta \quad (15)$$

The reaction of water with 2-(3-bromopropyl)naphthalene in $[C_4C_1im][BF_4]$ proceeds smoothly to give a 65% yield of the alcohol in 65 h at 110 °C.⁹³ In spite of the fact that the reaction fails to proceed at all in 1,4-dioxane, addition of this leads to a substantial increase in the rate of the reaction (95% in 20 h), as does adding acetone or acetonitrile. Comparison of the ionic liquids $[C_4C_1im]X$, $\{X = [PF_6], [SbF_6], [OTf], \text{ or } [BF_4]\}$ in the ionic liquid/1,4-dioxane system showed that the more basic anions led to greater yields in shorter times. However, when $[C_4C_1im][CH_3CO_2]$ was the solvent, the acetate ester was the sole product formed.

The effective C-alkylation of pyrrole with alkyl halides has also been demonstrated in mixtures of $[C_4C_1im][SbF_6]$ and acetonitrile.³¹⁹ While the reaction could be conducted in $[C_4C_1im][SbF_6]$ alone, almost no alkylation was observed in acetonitrile alone. Some overalkylation to the disubstituted product was observed and the reactions were accelerated by the addition of K_2CO_3 .

The reactions of *n*-butylamine, di-*n*-butylamine, and tri-*n*-butylamine with Me-*p*-NBS have been studied in $[C_4C_1pyrr][NTf_2]$, $[C_4C_1pyrr][OTf]$, and $[C_4C_1im][OTf]$ and their reactivities compared to the same reactions in the molecular solvents dichloromethane and acetonitrile.²⁶³ It was shown that all of the amines were more nucleophilic in the ionic liquids than in the molecular solvents used, as one would expect from the Hughes–Ingold rules.

Analysis of Kamlet–Taft LSERs for these reactions (see Table 6) reveals that all of the reactions are accelerated by solvents with large π^* coefficients, as expected. Very different hydrogen-bonding dependencies are seen for BuNH₂ (Figure 9) and Bu₂NH in comparison to Bu₃N, which has an LSER more like that for the reaction of 1,2-dimethylimidazole with benzyl bromide (see above).³¹⁷ This can be interpreted as arising from the presence, or absence, of N–H protons on the nucleophile. In the absence of these protons, the primary interaction between the nucleophile and the solvents is via the lone pair of electrons of the nucleophile and the hydrogen bond donor site of the solvent, which slows the reaction. In the presence of the N–H protons, the effect of this interaction is overridden by the now preferred interaction between these protons and the hydrogen bond acceptor site of the solvent, the anion in the case of the ionic

Table 6. LSER Correlations for $\ln k_2$ Obtained for Butylamines with Me-*p*-NBS in $[C_4C_1pyrr][N(Tf)_2]$, $[C_4C_1pyrr][OTf]$, $[C_4C_1im][OTf]$, DCM, and MeCN

R ₃ N	LSER	R ²
BuNH ₂	$\ln k_2 = -8.77 + 4.57\beta + 6.32\pi^*$	0.93
Bu ₂ NH	$\ln k_2 = -8.57 + 2.23\beta + 7.30\pi^*$	0.92
Bu ₃ N	$\ln k_2 = 0.87 - 2.56\alpha + 12.80\pi^*$	0.70

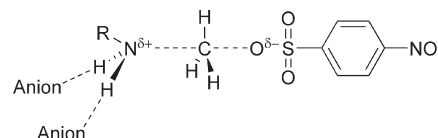


Figure 9. Ionic liquid anions hydrogen bonding with the emerging ammonium ion in the activated complex for the reaction of ⁿBuNH₂ with Me-*p*-NBS.

liquids. During the activation process this interaction increases in strength, as the positive charge develops, increasing the rate of reaction in good hydrogen-bond-accepting solvents.

It is interesting to note that the R^2 value for the LSER for the Bu₃N reactions is significantly poorer than for the other amines. This arose from the unexpectedly high k_2 for the reaction of ⁿBu₃N in $[C_4C_1pyrr][OTf]$, which was explained by investigation of the Eyring activation parameters for these reactions. It was concluded that the neutral starting materials interacted with the ionic liquid ions only weakly and failed to disrupt the Coulombic attraction of these ions, leaving a restricted volume in which to move. The developing charges on the activated complex allowed it to interact with the ionic liquid ions. In so doing, it disrupted the interionic interactions and caused some breakdown of the local structure of the ionic liquid. This has a dramatic effect on the ΔS^\ddagger for the reaction. This was a clear demonstration of an effect arising from the microscopic heterogeneity of the ionic liquid and can be thought of as a solvatophobic rate effect.

Croft et al.³²⁰ used Hammett plots together with an analysis of the activation parameters of the reaction of seven substituted benzyl bromides with pyridine in either CH₃CN or $[C_4C_1im][NTf_2]$ to find a detailed explanation for the acceleration of these reactions in the ionic liquid. The Hammett plots showed that there was greater charge development in the activated complexes for these reactions in $[C_4C_1im][NTf_2]$ than in CH₃CN. This might lead one to expect that this would lead to greater interaction between the ionic liquid and the activated complex and that a more favorable ΔH^\ddagger would be observed. In fact, the reverse was seen, and ΔH^\ddagger was always greater in the ionic liquid. $T\Delta S^\ddagger$ at room temperature in the two solvents was always greater in the ionic liquid and $T\Delta\Delta S^\ddagger$ at room temperature marginally greater than $\Delta\Delta H^\ddagger$. This could be explained in a number of ways: greater bond breaking and greater disorder within the activated complexes in the ionic liquid, greater disruption of the cybotactic region around the reacting species during the activation process in the ionic liquid, or disruption to the long-range organization of the ionic liquid during the activation process. The authors recognized the need for further work to fully differentiate between these explanations, but favored the explanation of solvent reorganization in the cybotactic region.

The LSER of the nitroso group transfer from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide to pyrrolidine showed a quite

different dependency (recalculated here, eq 16), having a positive coefficient for α .³²¹ This suggests that any inhibition of the nucleophile through hydrogen bonding is outweighed by stabilization of the developing nucleofuge in the activated complex.

$$\ln k_2 = -7.7 + 2.5\alpha + 4.2\pi^* \quad (16)$$

In an interesting application of the increased nucleophilicity of amines in ionic liquids, the amine-functionalized $[(\text{H}_2\text{N})^2\text{-C}_2\text{C}_1\text{im}][\text{PF}_6]$ has been used as a scavenger for excess electrophile in a toluene/ $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ biphasic system.³²² Here the neutral electrophile (e.g., PhCH_2Cl) reacts with the amino group of the $[(\text{H}_2\text{N})^2\text{-C}_2\text{C}_1\text{im}]^+$ ion to give ionic products (e.g., $[(\text{PhCH}_2\text{NH}_2)^2\text{-C}_2\text{C}_1\text{im}]^{2+} + \text{Cl}^-$) which are then trapped in the ionic liquid layer. This was found to be a more effective approach than others based upon solid-supported scavengers.

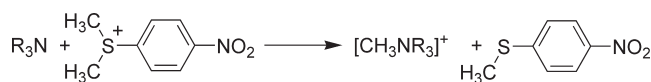
The ligand substitution reactions of $[\text{Rh}(\text{CO})(\text{PPh}_3)_2(\text{NO}_3)]$ with substituted pyridines have been investigated in $[\text{C}_6\text{pyr}][\text{NTf}_2]$ and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and compared to those in dichloromethane.³²³ It was found that conversions to the product $[\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{py}][\text{NO}_3]$ were poor in CH_2Cl_2 for all but the most basic substituted pyridines used, whereas in the ionic liquids complete conversions were achieved in all cases studied. This was attributed to the ability of the ionic liquids to preferentially stabilize the product ions over the molecular starting materials, while the reverse is true in dichloromethane.

Many catalytic cycles contain a step in which a coordinated solvent molecule is displaced by an incoming reagent. Consequently, the ease of solvent displacement is a concern when selecting the best solvent for catalytic reactions. Ionic liquids have a reputation for being “noncoordinating” solvents. The photoinduced decarbonylation of $[(\text{C}_6\text{H}_6)\text{Cr}(\text{CO})_3]$ leads to the rapid formation of $[(\text{C}_6\text{H}_6)\text{Cr}(\text{CO})_2(\text{solvent})]$. The rates of solvent displacements from these complexes, which in an ionic liquid are most likely to be $[(\text{C}_6\text{H}_6)\text{Cr}(\text{CO})_2\text{X}]$ $\{\text{X} = (\text{PF}_6) \text{ or } (\text{NTf}_2)\}$, have been investigated in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$.³²⁴ In $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ rapid displacement of $[\text{PF}_6]^-$ by water was observed, even in ionic liquids that had been through a drying procedure. When CH_3CN was included in the reaction mixture, $[(\text{C}_6\text{H}_6)\text{-Cr}(\text{CO})_2(\text{CH}_3\text{CN})]$ was formed with a bimolecular rate constant that was 2 orders of magnitude greater than that of the reaction of $[(\text{C}_6\text{H}_6)\text{Cr}(\text{CO})_2(\text{C}_2\text{H}_4\text{Cl}_2)]$ with CH_3CN in dichloroethane, showing the ease of this displacement in the ionic liquid. However, in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ no reaction occurred with CH_3CN , indicating that $[\text{NTf}_2]^-$ is a considerably more coordinating ligand.

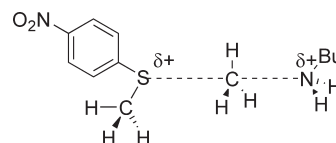
6.4.3. Type c $\text{S}_{\text{N}}2 \text{ Y} + [\text{R}-\text{X}]^+$ Reaction. Only one substantial study of a nucleophilic substitution of a neutral nucleophile with a charged electrophile is available in the literature. The reactivities of *n*-butylamine, di-*n*-butylamine, and tri-*n*-butylamine with dimethyl(4-nitrophenyl)sulfonium salts $\{[p\text{-NO}_2\text{PhS}(\text{CH}_3)_2]^+ \text{X}, \text{Scheme 8}\}$ have been investigated using UV-vis spectroscopy in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ and $[\text{C}_4\text{C}_1\text{pyrr}]\text{X}$ $\{\text{X} = [\text{NTf}_2]^- \text{ or } [\text{OTf}]^-\}$ and a range of molecular solvents (toluene, dichloromethane, tetrahydrofuran, acetonitrile, methanol).³²⁵

Attempts to correlate the rates of these reactions with dielectric constants of the liquids proved unsuccessful, and a Kamlet-Taft LSER approach (Table 7) was taken to understand the effects of the solvents on these reactions. The strongest effect for all of the amines is an overwhelmingly negative β effect. This arises from interactions between the solvent's hydrogen-bond-accepting site and acidic protons on $[p\text{-NO}_2\text{PhS}(\text{CH}_3)_2]^+$ which reduce the electrophilicity of the reacting carbon center. This is ameliorated to some extent by

Scheme 8

Table 7. Results of LSER Fits for Reactions of Butylamines with $[p\text{-NO}_2\text{PhS}(\text{CH}_3)_2]^+$

R_3N	LSER	R^2
BuNH_2	$\ln k_2 = -2.38 - 3.59\alpha - 4.16\beta + 2.10\pi^*$	0.96
Bu_2NH	$\ln k_2 = -2.66 - 2.79\alpha - 5.01\beta + 2.89\pi^*$	0.99
Bu_3N	$\ln k_2 = -5.62 - 6.46\beta + 4.26\pi^*$	0.87

Figure 10. Activated complex for the reaction of $[p\text{-NO}_2\text{PhS}(\text{CH}_3)_2]^+$ with butylamine.

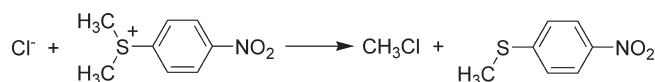
favorable interactions with the N-H protons of BuNH_2 and Bu_2NH . A less intense negative solvent α effect was observed for BuNH_2 and Bu_2NH , which was not observed for Bu_3N , probably being masked by the very large β effect for this amine. Finally, a positive dependence on π^* was observed for all of the reactions. These were effects again rationalized by consideration of the different strengths of solute-solvent interactions for the starting materials and activated complex of the reaction (see Figure 10).

6.4.4. Type d $\text{S}_{\text{N}}2 \text{ Y}^- + [\text{R}-\text{X}]^+$ Reaction. The Hughes-Ingold rules predict that the rates of the reactions of charged nucleophiles with charged electrophiles will be slower in ionic liquids than in molecular solvents. A study of the reactions of QCl salts (Q = quaternary ammonium or imidazolium cation) with $[p\text{-NO}_2\text{PhS}(\text{CH}_3)_2]^+$ has confirmed this, but also showed a change in mechanism between the ionic liquids and molecular solvents.³²⁶ In the molecular solvents (THF, acetone, 1-butanol, propylene carbonate, CH_2Cl_2 , CH_3CN , or DMSO) the reactions were shown to proceed through a mechanism that first forms a $[p\text{-NO}_2\text{PhS}(\text{CH}_3)_2]^+ \text{Cl}^-$ ion pair which then goes on to react with a further $\text{Q}^+ \text{Cl}^-$ ion pair to yield the products, whereas in the ionic liquids $\{[\text{C}_4\text{C}_1\text{im}]\text{X}, [\text{C}_4\text{C}_1\text{pyrr}]\text{X}, [\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]; \text{X} = [\text{NTf}_2]^- \text{ or } [\text{OTf}]^-\}$ there was no evidence for kinetically significant ion pairs and the reaction was that expected between the $[p\text{-NO}_2\text{PhS}(\text{CH}_3)_2]^+$ ion and Cl^- (Scheme 9).

The ion-pairing effects in molecular solvents prevented direct comparison of the rates of the reactions in these solvents and the ionic liquids with an LSER.³²⁶ The LSER for the ionic liquids alone showed a strong negative α correlation, showing that hydrogen bonding to the Cl^- ion slows the reaction.

Where the charged electrophile has been a transition-metal complex, this change of behavior has not been seen, in that no ion-pairing effects have been seen in the molecular solvents.^{327,328} However, in these reactions significant quantities of unreactive salts are added to maintain a high ionic strength throughout the reactions in molecular solvents. This appears to be sufficient to prevent the formation of kinetically active ion pairs. The reaction of $[\text{SCN}]^-$ ions with $[\text{Pt}(\text{terpyridine})\text{Cl}]^+$ in a series of $[\text{C}_2\text{C}_1\text{im}]\text{X}$

Scheme 9



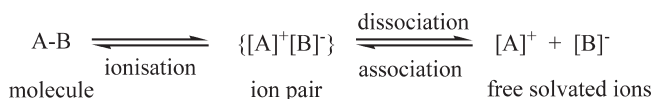
{X = [NTf₂], [N(CN)₂], [OTf], or [C₂OSO₃]} ionic liquids and CH₃OH showed that the rates of the reactions in the ionic liquids were considerably slower than that of the reaction in methanol and varied with the anion. This was interpreted as the anion interacting with the [Pt(terpyridine)Cl]⁺ to slow the rate of the reaction.

A study of the reactions of [SCN][−] ions with a similar complex, [Pt(di(2-picolyl)amine)Cl]⁺, in [C₄C₁im][NTf₂], [(C₁OC₂)C₁im][NTf₂], and [C₄C₁pyrr]X {X = [NTf₂] or [OTf]}, CH₃OH, DMSO, and H₂O revealed LSERs with a large positive π^* effect and a lesser positive α effect.²⁶³ This observation was used to suggest that hydrogen bonding to the emerging, hard Cl[−] nucleofuge was having a greater positive effect than any negative effect caused by hydrogen bonding to the soft [SCN][−] nucleophile.

6.4.5. Type e S_N1 R—X Reaction. Unimolecular substitution reactions in ionic liquids have been far less studied than bimolecular substitutions. The hydrolysis reactions of a number of organic triflates in [C₄C₁im][NTf₂] have been shown to lead to byproducts that were the result of rearranged carbocations.³²⁹ A more detailed examination of the hydrolysis of 1-adamantyl mesylate was found to yield a mixture of 1-adamantanol and diadamantyl ether, suggesting that the 1-adamantanol reacts with the adamantyl carbocation intermediate. On the basis of the activation parameters for the reaction, the authors proposed that the reaction to the 1-adamantanol followed an S_N1 mechanism, although a dependency of the reaction rate on the concentration of water in the ionic liquid was noted. The rate constants for the ionic liquid reactions were between those found for protic molecular solvents (CF₃CH₂OH, CH₃OH, or CD₃CO₂D) and DMSO-*d*₆. The authors concluded that carbocation intermediates did form in these reactions, but that the rates of ionization were not extraordinary and that they depended upon the nature of the leaving group. This suggests that specific interactions between the ionic liquid and the solute species are more important in determining the ability of an ionic liquid to promote ionization (Scheme 10) than the ionic nature of the solvent itself.

A study of the rates of the methanolysis of (*R*)-3-chloro-3,7-dimethyloctane to (*S*)-3-methoxy-3,7-dimethyloctane in [C₄C₁im][NTf₂]/MeOH mixtures showed that the ionic liquid did not significantly affect the rate of formation of the carbocation intermediate.³³⁰ However, analysis of the stereochemical outcome showed that there was greater racemization in the ionic liquid, suggesting that both faces of the carbocation were available for the nucleophile to attack. This in turn suggests that the intermediate is more ion paired in the methanol and more dissociated and symmetrically solvated in the ionic liquid. Analysis of the activation parameters for this reaction showed that addition of a small amount of ionic liquid to the reaction mixture led to stabilization of the activated complex and a decrease in the activation enthalpy.³³¹ However, at higher concentrations of ionic liquid an increased ordering of the system becomes a significant contributor to the overall activation energy as the charged activated complex forms from the neutral substrate. In contrast to the stereochemical outcomes, the activation parameters suggest a significant degree of ion pairing in the activated complex. As noted in previous studies of S_N2 reactions,²⁶³ again this apparent contradiction arises because, while the association of ions in ionic liquids shares some features

Scheme 10



with ion pairing in molecular solvents, there are also significant differences.

The related S_N1 ionizations of 2-chloro-2-methylpropane in [C₂C₁im][PF₆] and water have been modeled using molecular dynamics simulation.³³² It is interesting to see that in water the reaction proceeded through a contact ion pair to dissociated ions. In the ionic liquid there was no evidence for contact ion pairing; rather the intermediate was a solvent-separated ion pair with, on average, one ionic liquid cation and one ionic liquid anion separating the solute ions. This arrangement has been shown to have the solute ions fully screened from each other.³³³ These observations, together with the fact that the calculated activation energy for the reaction in water was much lower than for the reaction in [C₂C₁im][PF₆], suggest that the ionic liquid is not an unusually ionizing solvent.

6.4.6. Type f S_N1 [R—X]⁺ Reaction. Arenediazonium {ArN₂}X salts are highly reactive intermediates that often undergo substitution via an S_N1 pathway. Dissolving [ArN₂]X in [C_{*n*}C₁im]X {*n* = 2 or 4; X = [PF₆] or [BF₄]} and heating led to fluorodediazonization, forming ArF.³³⁴ Other ionic liquids, [C₂C₁im]X {X = [CF₃CO₂], [OTf], or [OTs]} gave ArX as the product. The authors suggested that this was the result of rapid metathesis of the solute and solvent anions, leading to trapping of the ionic liquid anion nucleophile.

While this might have been expected for these ionic liquids, arenediazonium ions have been shown to react with the supposedly non-nucleophilic [NTf₂][−] anion.^{335,336} Chiappe et al. found that when [PhN₂][BF₄] was dissolved in [C₄C₁im]Br, PhBr was formed. However, when [PhN₂][BF₄] was dissolved in [C₄C₁im]Br/[C₄C₁im][NTf₂] (1:2, 1:1, or 3:1), only products of the reaction with [NTf₂][−] were observed, yet when the same reaction was conducted in water with a 1:1 [C₄C₁im]Br/[C₄C₁im][NTf₂] mixture, the products were bromobenzene and phenol. This suggests that there is a radical change in the relative nucleophilicities of Br[−] and [NTf₂][−] on going from the aqueous to the ionic liquid system. On the basis of mass spectra of the [C₄C₁im]Br/[C₄C₁im][NTf₂] mixture, the authors proposed that this arises from the nucleophilicity of the bromide ion being sufficiently suppressed by its strong interaction with the [C₄C₁im]⁺ cation of the ionic liquids for it to become less nucleophilic than [NTf₂][−]. Interestingly, it was only for Br[−] that no halogenation was observed; in [C₄C₁im]Cl/[C₄C₁im][NTf₂] 20% chlorination was observed, and in [C₂C₁im]I/[C₂C₁im][NTf₂] iodobenzene was the only product.

6.4.7. Ionizing vs Dissociating Solvents. The formation of free solvated ions from a hypothetical molecular species can be represented as occurring in two steps: ionization and dissociation (Scheme 10).¹¹⁵ Early in the development of ionic liquids as solvents for synthesis, it was widely supposed that they would be especially highly ionizing solvents and that they would promote the formation of charged species. The survey of nucleophilic substitutions above suggests that while it is generally true that they are ionizing solvents, this behavior is in no way extreme and arises as a result of the specific solvent—solute interactions that are occurring in solution, rather than as a result of their ionic nature. However, these results do suggest that once ions have

been formed they dissociate more completely in ionic liquids than they do in molecular solvents. This could arise if the recombination (association) of dissociated ions was prevented by their mutual Coulombic attraction being highly screened by the ionic liquid ions. The potential extent of such screening has been shown by a recent molecular dynamics study to be not only essentially complete outside the first shell, but also large even when there is no ionic liquid between the solute ions.³³³

6.4.8. Nucleophilic Aromatic Substitutions. Nucleophilic aromatic substitutions, S_NAr , are an important class of reactions for the formation of a wide range of compounds, from pharmaceuticals to dyes. These reactions often require extreme reaction conditions and lead to mixtures of products that can be difficult to separate. Given the ability of ionic liquids to enhance the nucleophilicity of amines, the possibility that they might be useful solvents for these reactions has been investigated.³³⁷

The substitution reactions of some 2-substituted 5-nitrothiophenes with the secondary amines pyrrolidine, piperidine, and morpholine in $[C_4C_1im][PF_6]$, $[C_4C_1im][BF_4]$, and $[C_4C_1C_1^2im][BF_4]$ have been the subject of a detailed kinetics investigation (Scheme 11).³³⁸ This revealed that the reactions were faster in all of the ionic liquids than the same reactions in either methanol or benzene. This was attributed to a combination of stabilization of the activated complex by generalized polarity effects coupled with less inhibition of the reactivity of the amine by hydrogen bond donation from the solvent. It was also noted that the ionic liquid with the more basic anion, $[C_4C_1im][BF_4]$, gave faster reactions than that with the less basic anion, $[C_4C_1im][PF_6]$. It was also shown that the dependency of k_{obs} on the concentration of amine was different in $[C_4C_1C_1^2im][BF_4]$ than in the other solvents for the pyrrolidino debromination of 2-bromo-5-nitrothiophene. This was attributed to the low hydrogen bond donor ability of this solvent, leading to a second amine molecule being involved in the activated complex to assist the leaving of the nucleofuge. Analysis of the activation parameters showed that there was an important contribution to the activation energies in the ionic liquids from solvent reorganization.

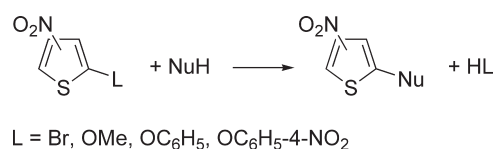
The “designer solvent” approach to ionic liquids was demonstrated for the reaction of *p*-anisidine with *p*-fluorobenzene.³³⁹ Previous results of studies of nucleophilic aliphatic substitutions and solvent–solute interactions in ionic liquids from the same group were used to predict and then to prepare the “best” ionic liquids for this reaction. These ionic liquids were then used as solvents for the reactions. This gave a conversion for this reaction in $[C_4C_1pyrr][C_1SO_3]$ of 77% under the same conditions under which a conversion of 0.4% was achieved in $[C_4C_1pyrr][NTf_2]$.

The reaction of azide salts with 2-bromo-5-nitrothiophene in $[C_4C_1im]X$ $\{X = [BF_4], [PF_6], \text{ or } [NTf_2]\}$, $[C_4C_1C_1^2im][NTf_2]$, or $[C_4C_1pyrr][NTf_2]$ was found to give higher yields than in methanol.³⁴⁰ Not surprisingly for this nucleophile, no strong anion effect was found upon changing the ionic liquid. The direct solvation of the anion by the more hydrogen bond donating cations was found to outweigh any solvent assistance to the leaving group and so led to a reduction in the rates of the reactions.

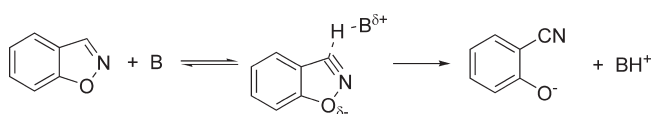
6.5. Elimination

In spite of the evidence presented above that ionic liquids favor nucleophilic substitution over base-induced elimination, it is possible to heavily favor elimination by selecting an appropriate substrate. 1,1,1-Tribromo-2,2-bis(dimethoxyphenyl)ethanes have just such a

Scheme 11



Scheme 12

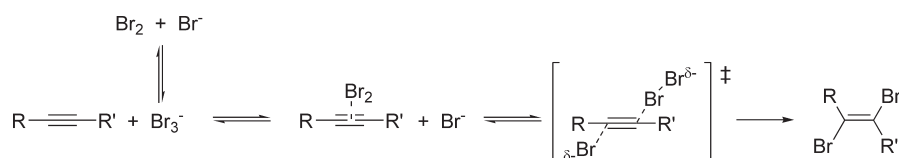


strong preference for elimination, and hence, their reactions with a range of amines in $[C_4C_1im][BF_4]$, $[C_4C_1im][PF_6]$, and $[C_4C_1C_1^2im][BF_4]$ have been investigated in some detail.³⁴¹ Remarkably, no elimination was observed for any of the primary or tertiary amines that were investigated, and only secondary cyclic amines were found to promote the reaction. This is in spite of the authors selecting primary amines with aqueous basicities (pK_{BH^+}) similar to that of the secondary amine employed. Consequently, the importance of amine geometry, flexibility, and steric hindrance in determining the outcomes of these reactions was emphasized. This, together with additional kinetics data, led the authors to propose a shift in mechanism from $E1cB$ in methanol to $E2$ in the ionic liquids, i.e., from more charge separation during the reaction to less. As above, this suggests that the ionic liquids are not specially ionizing solvents under these conditions.

The Kemp elimination of benzisoxazole to the *o*-cyanophenoxide anion by proton abstraction has been studied using a similar range of amines in $[C_4C_1im][BF_4]$ (Scheme 12).³⁴² For this reaction a wider range of amines were capable of acting as a base than had been observed with 1,1,1-tribromo-2,2-bis(dimethoxyphenyl)ethanes, but the reactivity range for benzisoxazole did vary in the order primary < tertiary < secondary for the amines, which is consistent with the results for that substrate and with basicity measurements of 4-nitrophenol/amine in ionic liquids.^{299,300} Again, the importance of amine geometry, flexibility, and steric hindrance in determining the rates of these reactions was emphasized, which was used to infer an $E2$ mechanism for the reaction (as seen in molecular solvents). The reactions with pyrrolidine and piperidine were further investigated in $[C_4C_1im][PF_6]$, $[C_4C_1im][NTf_2]$, $[C_4C_1C_1^2im][NTf_2]$, and $[C_4C_1pyrr][NTf_2]$. The rates of the reactions varied in the order $[C_4C_1im][NTf_2] < [C_4C_1C_1^2im][NTf_2] < [C_4C_1pyrr][NTf_2]$, probably because the $[C_4C_1im]^+$ cation strongly hydrogen bonds to the amines, effectively decreasing their basicities. The trend for changing the anion, $[C_4C_1im][NTf_2] < [C_4C_1im][PF_6] < [C_4C_1im][BF_4]$, was less clear. A subsequent study could not derive a satisfactory LSER for the reaction of 5-nitrobenzisoxazole with morpholine in ionic liquids.³⁴³ Analysis of the activation parameters shows that the changing activation entropy, which is not well modeled by the Kamlet–Taft parameters, gives a significant contribution to the activation energies for these reactions. Hence, it is likely that these differences arise from a complex set of contributions, including solvent reorganization as well as simple solvent–solute interactions.

In their study of reactions that proceed through carbocation intermediates, Creary et al. have observed the formation of base-induced elimination products.³²⁹ For instance, Cumyl

Scheme 13



trifluoroacetates yielded the appropriately substituted α -methylstyrene in dry $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$, but significant amounts of cumyl alcohols were formed when water was present. Kinetic investigations confirmed a carbocation-forming E1 mechanism for these reactions. Further confirmation of carbocation intermediates could be obtained through the formation of products that derive from rearranged carbocations, for instance, in the reactions of α -keto triflates.

Dyson and Daguene³⁴⁴ investigated the decomposition of the chloride-templated metallocage $[(\text{Ni}(\text{atu})_2)_4\text{Ni}_2\text{Cl}][\text{BF}_4]_3$ (Hatu = aminodithiorea). This decomposition leads to the release of chloride ions into solution, and in molecular solvents it had previously been noted that the equilibrium was strongly influenced by the solvation of the chloride ion.³⁴⁵ This equilibrium was studied in the ionic liquids $[\text{cat}][\text{NTf}_2]$ {where $[\text{cat}] = [\text{C}_4\text{C}_1\text{im}], [\text{C}_4\text{C}_1\text{C}_1^2\text{im}], [\text{C}_4\text{C}_1\text{pyrr}], [\text{C}_4\text{pyr}],$ or $[\text{C}_5(\text{C}_2)_3\text{N}]$ }. Although significant differences in the enthalpy of the reaction were seen, ranging from 4.32 kJ mol^{-1} for $[\text{C}_4\text{pyr}][\text{NTf}_2]$ to 16.8 kJ mol^{-1} for $[\text{C}_5(\text{C}_2)_3\text{N}][\text{NTf}_2]$, no simple relationship between this value and any available solvent polarity scale could be found. However, when $[(\text{HO})^2\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ was used, the decomposition proceeded to completion, suggesting the importance of hydrogen bond donation from the ionic liquid to the chloride ion, and the trend of increasing chloride ion solvation, $[\text{C}_5(\text{C}_2)_3\text{N}]^+ < [\text{C}_4\text{C}_1\text{pyrr}]^+ < [\text{C}_4\text{C}_1\text{im}]^+ \leq [\text{C}_4\text{C}_1\text{C}_1^2\text{im}]^+ < [\text{C}_4\text{pyr}]^+ \ll [(\text{HO})^2\text{C}_2\text{C}_1\text{im}]^+$, was proposed. The study of the entropic effects in the ionic liquids suggested that not only do they arise from rearrangements of the first solvation sphere around the solutes, but that correlated motion of the ions of the bulk ionic liquids is also involved.

6.6. Additions

The reaction of 4,4-bis(dimethylamino)benzophenone (Michler's ketone, MK) and tetracyanoethene (TCNE) has very interesting solvent-dependent behavior. In nonprotic molecular solvents an electron donor–acceptor complex, MK–TCNE, is formed, but in protic solvents an addition reaction occurs to give a zwitterionic compound.³⁴⁶ In the rigorously dried ionic liquids $[\text{C}_n\text{C}_1\text{im}][\text{NTf}_2]$ ($n = 2, 4,$ or 6), $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, and $[\text{C}_4\text{pyr}][\text{NTf}_2]$, the MK–TCNE complex was observed in the first instance.³⁴⁷ The ν_{max} in the visible spectrum of these solutions, together with those in aprotic molecular solvents, could be correlated with an LSER including contributions from α , β , and π^* ($R^2 = 0.859$, eq 17). This was noticeably different from the results for only the molecular solvents, for which a better correlation could be achieved using β and π^* alone.³³⁶ The MK–TCNE species was unstable in the ionic liquids on the time scale of a few hours, yielding the radical ions $[\text{MK}^\bullet]^+$ and $[\text{TCNE}^\bullet]^-$. In molecular solvents this is only seen in highly ionizing solvents, such as 1,1,1,3,3,3-hexafluoropropanol. Even in trifluoroethanol these ions are only seen in a mixture with the zwitterions. This strongly suggests that the ionic liquids are acting as highly ionizing solvents in this case. In $[\text{C}_4\text{C}_1\text{im}][\text{N}(\text{CN})_2]$ an unknown product was formed that appeared to be the same as that formed in other very high β solvents,

such as DMSO. When the ionic liquids were wet or contaminated with other nucleophilic impurities, the zwitterion was formed.

$$\nu_{\text{max}} \times 10^{-3} = 16.605 + 1.043\alpha + 3.018\beta - 2.351\pi^* \quad (17)$$

6.6.1. Electrophilic Addition. Electrophilic addition across a double or triple carbon–carbon bond is the characteristic reaction of alkenes and alkynes. In an attempt to find replacements for the commonly used halogenated organic solvents for these reactions, the bromination of alkenes was investigated in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ { $\text{X} = \text{Br}, [\text{PF}_6],$ or $[\text{BF}_4]$ }.³⁴⁸ In $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, the reactions gave mixtures of *syn* and *anti* products and the likely electrophile was identified as Br_2 itself, as in molecular solvents. When the rates of ICl and IBr additions were compared to those in CH_2Cl_2 , they were found to be appreciably faster. Applying the Hughes–Ingold rules to these reactions in ionic liquids suggests a mechanism with an ionic intermediate. In $[\text{C}_4\text{C}_1\text{im}]\text{Br}$ with Br_2 , the actual brominating agent was found to be Br_3^- and the brominations were *anti*-stereospecific. When Cl_2 was used as a chlorinating agent in $[\text{C}_4\text{C}_1\text{im}]\text{Br}$, 1,2-bromochlorides were produced, which was again taken as an indication of the presence of a trihalide electrophile, BrCl_2^- in this case. The regioselectivities of these reactions were found to vary with the particular trihalide halogenating agent and the structure of the alkene or alkyne. Using the same prepared trihalide salt as a solute in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ had no effect on the regioselectivity of most of the reactions investigated, indicating that there was no change of intermediate in the different ionic liquids. This intermediate was identified as being similar to that previously proposed to explain the kinetics of the bromination of alkynes in ionic liquids,³⁴⁹ in which early attachment by a halide nucleophile occurs on a 1:1 unsaturated alkene–halogen, or alkyne–halogen, π -complex (Scheme 13).

It might, at first glance, appear odd that these reactions do not pass through an ionic bromonium-type intermediate in the ionic liquids. However, that mechanism begins with Br_2 as the brominating agent, as in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$. However, in $[\text{C}_4\text{C}_1\text{im}]\text{Br}$ it is likely that Br_3^- and Br^- are the only bromine-containing species present in kinetically significant concentrations. Consequently, the absence of Br_2 means that any reaction mechanism that requires its presence will be unavailable.

A kinetic study of bromination of alkenes and alkynes in the ionic liquids $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$, $[\text{C}_4\text{C}_1\text{im}]\text{X}$ { $\text{X} = \text{Br}, [\text{NTf}_2],$ or $[\text{PF}_6]$ }, $[\text{C}_6\text{C}_1\text{im}][\text{NTf}_2]$, $[\text{C}_2\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$, and $[\text{C}_4\text{pyr}][\text{NTf}_2]$, using $[\text{C}_4\text{C}_1\text{im}][\text{Br}_3]$ as the brominating agent, showed little variation and no systematic trend in the rates of these reactions in the ionic liquids, all of which were faster than the same reactions in 1,2-dichloroethane.³⁵⁰ However, when $[(\text{C}_4)_4\text{N}][\text{ICl}_2]$ was used as the halogenating agent, definite effects of changing the ionic liquid were seen. While it was recognized that there were many effects on the changing rates of these reactions in the ionic liquids, the hydrogen bond donor

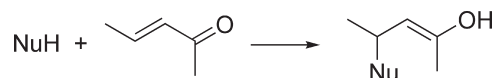
ability of the ionic liquid cations was indicated to be an important and readily identifiable one, probably due to the stabilization of the emerging Cl^- ion during the activation process. Finally, another hydrogen-bonding effect was noted. These ICl_2^- reactions lead in the first place to the mixed iodo-chloro addition product and a Cl^- ion. This Cl^- ion can act as a nucleophile toward the initial addition product to give the dichloride. Ionic liquids with strong hydrogen bond donor cations were found to suppress the nucleophilicity of the Cl^- ion and hence prevent this reaction. Tetraalkylphosphonium trihalides have also been used as halogenation agents.³⁵¹

6.6.2. Nucleophilic Addition. In addition to the solvatochromism of the longest wavelength absorption of merocyanine probes, the changing absorbances of this band can be used to estimate the equilibrium constant for the spiropyran–merocyanine equilibrium (Scheme 3). This is again well correlated with Reichardt's $E_T(30)$ scale in molecular solvents.³⁵² Also, by irradiating the sample, the reaction can be shifted to the right, after which the kinetics of the thermal re-equilibration, which can be thought of as a nucleophilic addition, can be measured. The relationship of these values to the nature of the ionic liquid has been shown to be more complex than that of the solvatochromism. An initial study of 2,3-dihydro-1',3',3'-trimethyl-6-nitrospiro[1-benzopyran-2,2'-1H-indole] (see Scheme 3, $R = \text{CH}_3$) in a range of $[\text{NTf}_2]^-$ ionic liquids showed that there were no longer simple linear relationships with the $E_T(30)$ scale, but both of these values are affected by the nature of the cation of the ionic liquids, with stronger hydrogen-bond-donating ions leading to slower re-equilibrium and a higher equilibrium concentration of the merocyanine form.¹³⁹ In subsequent investigations by the same group, the lack of a linear correlation between the equilibrium constants and the $E_T(30)$ scale was again noted for reactions in ionic liquids.³⁵³ Analysis of the activation parameters for these reactions showed that the changes in the activation entropies for the reactions in the phosphonium ionic liquids studied were significant in determining the observed solvent dependencies. This suggests that solvent reorganization is occurring on the same time scale as the reaction in this case. Entropic effects are poorly described by polarity scales based on solvatochromism, which probably explains the lack of linear correlation between these results and the $E_T(30)$ scale. Similar results have been reported for a range of imidazolium ionic liquids by Deng et al.¹³⁸

6.6.3. 1,4-Conjugate Additions. 1,4-Conjugate additions are conceptually simple reactions in which a nucleophile adds to a so-called Michael acceptor, which is activated by the presence of an electron-withdrawing group (EWG; Scheme 14). However, they usually require the use of catalysts and unfavored solvents, such as DMSO, to achieve the reaction. The first reported conjugate addition in an ionic liquid used $[\text{C}_4\text{N}]\text{Br}$ as the solvent for the reaction of β -oxosulfides of benzothiazole with various Michael acceptors.³⁵⁴ This allowed the stereoselective synthesis of spirocyclopropanes with a weaker base, sodium bicarbonate, than usually required.

Conjugate additions of a range of amine and thiol nucleophiles to various Michael acceptors in ethylammonium acetate have recently been reported.³⁵⁵ The interaction of the cation with the EWG of the Michael acceptor was proposed to explain the enhanced reactivities observed. However, it should also be noted that the ionic liquid increased the rates of the reactions of the thiols and the primary and secondary amines used, but not of the imidazoles, suggesting that activation of the nucleophile is also an important contributor. Thus, the cation effect and the anion effect on these reactions are acting synergistically.

Scheme 14



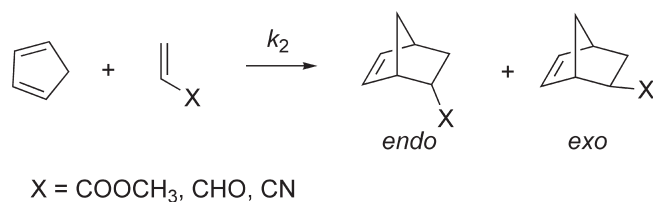
At the same time, conjugate additions of malonodinitrile, and other reagents, to chalcone were shown to proceed well in pure ionic liquids, without the addition of any catalyst.³⁵⁶ The authors explored several different possible explanations for this behavior and concluded that the most likely reason was the different dissociation constants of C–H acids in ionic liquids relative to molecular solvents. However, they subsequently demonstrated that residual methylimidazole, remaining in the ionic liquid from its preparation, can act as a base catalyst for these reactions.³⁵⁷ The proline ionic liquid $[\text{C}_2\text{C}_1\text{im}][\text{Pro}]$ has also been used for conjugate additions of cyclohexanone to chalcones.³⁵⁸ The use of this chiral ionic liquid led to both an increased reactivity compared to that found in the ionic liquids $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ and significantly improved enantioselectivity. L-Proline has been used as a catalyst for Michael addition of ketones to nitrostyrene,³⁵⁹ so it is possible that unreacted L-proline from the synthesis of the ionic liquid is acting as the catalyst for the reaction. Another conjugate addition in which impurities in the ionic liquid were important, this time giving a detrimental effect, was in the metal $\{\text{Ni}(\text{acac})_2 \cdot 2\text{H}_2\text{O}, \text{FeCl}_3 \cdot 6\text{H}_2\text{O}, \text{or Yb}(\text{OTf})_3\}$ catalyzed addition of acetylacetone to methyl vinyl ketone in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$.³⁶⁰ It was found that Cl^- ions in the ionic liquids led to the formation of stable metal halide complexes that did not catalyze the reaction. In the same paper it was noted that water in the ionic liquids did not have any detrimental effect on the reaction.

Another route to enantioselective conjugate additions was realized by the use of (*R,R*)-*trans*-1,2-diaminocyclohexane as a chiral auxiliary in ionic liquids.³⁶¹ For the asymmetric addition of ethyl cyclohexanone-2-carboxylate to methyl vinyl ketone, enantiomeric excesses of up to 91% were achieved. It was speculated that the role of the ionic liquid might be to favor enamine formation, the first step of the reaction. Interestingly, the addition of a variety of metal complexes only had detrimental effects on the reaction, presumably because this led to the diamine preferentially acting as a ligand for the metal center rather than a catalyst for the reaction.

The ionic liquids $[(\text{C}_8)_3\text{C}_1\text{P}][\text{C}_1\text{CO}_3]$ and $[(\text{C}_8)_3\text{C}_1\text{P}][\text{HCO}_3]$ were prepared for use as a combined solvent–catalyst for 1,4-conjugate additions.³⁶² However, they were such potent catalysts for the reaction of cyclohexanone and nitroethane that they were used in a ratio of IL to cyclohexanone of 0.004, with the reactant being the solvent. The Brønsted acidic ionic liquid $[(\text{HO}_3\text{S})^4\text{C}_4\text{pyr}][p\text{-CH}_3\text{PhSO}_3]$ has also been used as a catalyst in acetonitrile (10 mol %) for the reaction of indole and a range of 1,4-unsaturated ketones.³⁶³

6.6.4. Diels–Alder Reactions. Diels–Alder cycloaddition reactions were among the first to be studied in ionic liquids.³⁶⁴ This initial study explored the possibility of using the ionic liquid $[\text{C}_2\text{NH}_3][\text{NO}_3]$ as a substitute for water, which has become a popular solvent for these reactions. The reactions of cyclopentadiene with methyl acrylate and methyl vinyl ketone in this IL showed a strong preference for the *endo* product (see Scheme 15) and an acceleration of the reactions in comparison to those in nonpolar organic solvents, although the increased rate and selectivities were not as great as those seen in water.

Scheme 15



Nevertheless, the ionic liquid has the advantage that moisture-sensitive reagents can be used.

The Diels–Alder reaction of cyclopentadiene with methyl acrylate is well-known to have strong solvent dependencies for both its selectivity and its rate.¹¹⁵ It has even been used as the basis for a solvent polarity scale, $\Omega_{25^\circ\text{C}} \{\log(\text{endo}/\text{exo})\}$.³⁶⁵ The influence of hydrogen bonding on the *endo/exo* ratio and rate of this reaction in ionic liquids was rapidly recognized.¹⁸³ Hydrogen bond donation from the cation of the ionic liquid to the dienophile increased the *endo* selectivity of the reaction, while more hydrogen bond accepting anions decreased the *endo* selectivity of the reaction. This led to the use of a range of protic ionic liquids as solvents for reactions of cyclopentadiene with either methyl acrylate or dimethyl maleate.³⁶⁶ The *endo/exo* ratios of these reactions were particularly high when [C₁Him][NTf₂] was used as the solvent. A semiempirical computational model was used to further confirm the hypothesis that hydrogen bonding of protic imidazolium cations to the dienophile gives rise to the effects observed in the ionic liquids. Subsequent kinetic investigations of the rates of the reactions of cyclopentadiene with alkyl (methyl, ethyl, or butyl) acrylates in a range of imidazolium ionic liquids {[C₂C₁im][BF₄], [C₄C₁im]I, [C₄C₁im][BF₄], [C₄C₁im][PF₆], or [C₈C₁im][PF₆]} again confirmed the influence of hydrogen bonding on the rate of the reaction, but also showed that the rate slowed significantly with the increased viscosity of the ionic liquid.³⁶⁷ This had the effect that when the non-hydrogen-bonding solvent CH₂Cl₂ (55 mol %) was added to [C₄C₁im][BF₄] (45 mol %) and the mixture used as a solvent for the reaction, the rate of the reaction increased by 20%.

The effect of the viscosity on the intramolecular Diels–Alder reaction of (*E*)-1-phenyl-4-[2-[(3-methyl-2-butenyl)oxy]benzylidene]-5-pyrazolone has also been investigated in a variety of pyridinium tetrafluoroborate and bis(trifluorosulfonyl)imide ionic liquids.³⁶⁸ Two similar, but separate, trends were found in the correlation of the $\ln k_1$ with the viscosity of the ionic liquids for each of the two sets. The authors attributed this difference in the behaviors of the two sets of ionic liquids to microscopic frictional effects in which the microviscosity is different from the macroscopically observed value.

Dyson et al.³⁶⁹ conducted an extensive study of the selectivities and rates of the reaction of cyclopentadiene with methyl acrylate in 30 different [NTf₂][−] ionic liquids. They analyzed the results for the *endo/exo* selectivity by reference to the IR spectra of the ionic liquids and using the polarity scales derived from measurements of the NMR spectra of a series of probe molecules to derive a predictive equation for the selectivity of this reaction. Their kinetic data suggested that the selectivity was kinetically controlled, with the rate of formation of the *exo* product being unaffected by the presence of the ionic liquid, whereas higher overall selectivities were accompanied by more rapid formation of the *endo* product. This arose from a lowering of the relative energy of the transition states leading to the *endo* products, while the transition states yielding the *exo* products are not

significantly influenced by the choice of cation, at least in the cases studied. They concluded that hydrogen bonding, while important, cannot alone satisfactorily account for the observed selectivities and that any property of the ionic liquid that favored interaction of its cation with the activated complex leading to the *endo* product favored greater *endo* selectivity and vice versa. Important cation properties identified included hydrogen-bond-donating ability, steric bulk, with long substituents on the cation leading to lower selectivities, presumably due to unfavorable steric interaction between the TS[‡] and the cation, chemical hardness, with strong electrostatic association between the ionic liquid ions leading to less interaction between the ionic liquid and the TS[‡], the presence of a low-energy lowest unoccupied molecular orbital on the cation, and the fact that polarizable cations can lower the energy of the *endo* TS[‡] more than that of the *exo* TS[‡]. In a subsequent study they also showed that the application of pressure further affects the rates of the Diels–Alder reaction.³⁷⁰

In an attempt to derive LSERs that could be used to design ionic liquids to be solvents for a wide range of Diels–Alder reactions, Bini et al.³⁷¹ investigated the selectivities and rates of the reactions between cyclopentadiene and three dienophiles (acrolein, methyl acrylate, and acrylonitrile) in ionic liquids and molecular solvents. They succeeded in deriving an LSER for both properties of all three reactions. That these LSERs could be achieved including both molecular and ionic liquids shows that there are no qualitative differences in the ways in which these solvents affect the reactions. However, no two were precisely the same. For instance, when investigating both the selectivities and rates of these reactions, it was found that the solvent hydrogen bond donation ability was important in the reactions of acrolein and methyl acrylate, which both have strong hydrogen bond acceptor sites, but not of acrylonitrile, which does not. This demonstrates that the solvent effects that are seen in these Diels–Alder reactions are a function of *both* the solvent and the solute and that the properties of both should be considered when making predictions. Also, the *R*² values for the correlations of the LSERs derived from the kinetic data were much poorer than those found for the selectivities of the same reactions, suggesting that the combination of factors leading to the changes in the rates of the reactions are more complex than those leading to changes in selectivity and are more sensitive to effects not covered in the analysis, such as subtle fluctuations in the reaction conditions. This also partly arises from the selectivities being the result of the ratio of the reaction rates for the *endo* and *exo* products whereas the overall rate of the reaction is the sum of the rates for the two products. The consequence of this is that some effects are canceled out in the selectivities of the reactions. For instance, viscosity is present in the correlation for $\ln k_2$ for acrolein, whereas it is absent in the explanation for its selectivities. This experimental study was partnered with a theoretical investigation.³⁷² This focused on the two limiting cases with the highest *endo/exo* selectivities, acrolein and methyl acrylate in [C₄Him][NTf₂], compared to the lowest selectivity case, acrylonitrile in [C₄C₁C₁im][NTf₂]. Again both the abilities of the dienophile and the ability of the cation to enter into hydrogen bonding were found to be the important determinants of the strengths of the interactions between these compounds and hence the selectivities of the reactions.

Contrary to statements found in standard texts that the solvent effects on Diels–Alder reactions are well understood and relatively straightforward, perhaps the most overwhelming conclusion to be drawn from the studies presented above is that multiple factors influence differently both the rates and product selectivities of the Diels–Alder reactions and that these factors

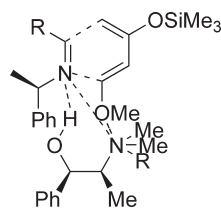


Figure 11. Proposed interactions between the chiral cation of an ionic liquid and the reagents in the activated complex of a diastereoselective aza-Diels–Alder reaction.³⁷⁴

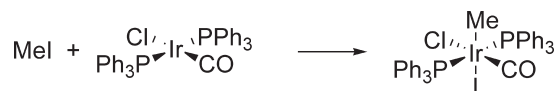
differ depending upon the reagents.^{370,371} Conclusions drawn on the basis of experiments taking a multiparameter approach are more reliable than those with a single variable, particularly when that variable may be acting as a proxy for others that have not been measured. It is possible to make rationalizations of observed reactions using quantitative measurements and comparison with multiple physicochemical parameters, but these are poor predictors for the effects of solvents on even closely related reactions. A case in point is the intramolecular Diels–Alder reaction of (*E*)-hexa-3,5-dienyl acrylate, which shows no strong rate effect from the hydrogen bond donor property of the ionic liquid.³⁷³

The interactions between the cation and both the diene and dienophile have been exploited in the asymmetric aza-Diels–Alder reaction of Danishefsky's diene with chiral imines.³⁷⁴ When ionic liquids prepared with cations derived from *N*-methylephedrine were used as the solvent for these reactions, moderate diastereoselectivities could be achieved. It was necessary to have a cation that could interact with both reagents to achieve the alignment in the activated complex that leads to the preferred diastereomer (Figure 11).

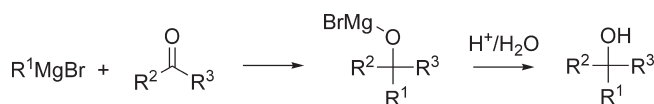
The organocatalyst (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one has been used as the catalyst for the Diels–Alder reaction between cyclohexadiene and acrolein in the ionic liquids [C₄C₁im][PF₆], [C₄C₁im][SbF₆], [C₄C₁im][BF₄], and [C₄C₁im][OTf].³⁷⁵ Both the *endo/exo* selectivity and the enantioselectivity of the *endo* adduct were reported. The *endo/exo* ratio was 17:1 for all of the ionic liquids used (cf. 14:1 in CH₃CN), but while the ee of the *endo* adduct was approximately 90% in the hydrophobic ionic liquids (cf. 94% in CH₃CN), it was zero in the two hydrophilic ionic liquids. Also the yield for the reaction in these two ionic liquids was only 5% or 7%, compared to 70–76% in the hydrophobic ionic liquids (cf. 82% in CH₃CN). Clearly, water plays an important role in these reactions. When water was deliberately added to the [C₄C₁im][OTf] ionic liquid up to 10%, no effect on either outcome of the reaction was seen. However, when this was increased to 20%, both the yield and the enantioselectivity of the *endo* adduct increased. It was concluded that water is needed for the hydrolysis of the iminium ion formed during the catalytic cycle and that the stronger interactions between the [OTf][−] and [BF₄][−] ions and water prevented this from occurring. Similar behavior, although with a positive outcome for giving the required product, has been seen in perruthenate-catalyzed reactions in ionic liquids.⁹⁴

6.6.5. Oxidative Addition. The oxidative addition reaction is encountered almost universally in mechanistic interpretations of synthetically important, metal-mediated processes. The oxidative addition of methyl iodide to Vaska's complex {[P(Ph₃)₂(CO)ClIr]; Scheme 16} has been studied in [C₄C₁im][OTf], [C₄C₁im][NTf₂], and [C₆pyr][NTf₂].³⁷⁶ In molecular solvents this reaction is generally agreed to proceed by an initial rate-limiting formation of the pentacoordinate [(PPh₃)₂(CO)Cl(CH₃)Ir]⁺.

Scheme 16



Scheme 17



Consequently, it was thought that it might be accelerated in the ionic liquids. We found the observed rate constants under *pseudo*-first-order conditions with a large excess of CH₃I to vary in the order toluene \approx [C₆pyr][NTf₂] < [C₄C₁im][OTf] \approx [C₄C₁im][NTf₂] < DMF. When the concentration of CH₃I was changed, complex changes in the observed rates were seen in the ionic liquids. This was interpreted as arising from the involvement of another ligand species, possibly Cl[−] or free-base impurities left from the ionic liquids' syntheses.

6.6.6. Metal Alkyl and Aryl Addition Reactions. Organo-metallic compounds are often used in stoichiometric quantities as activated reagents to facilitate the addition of one group to a compound. Probably the most well-known of these is the Grignard reaction, which is the addition of an alkyl- or arylmagnesium halide (most often bromide) to an aldehyde or ketone to form a secondary or tertiary alcohol, respectively (Scheme 17). Grignard reagents are strong bases and as such are unsuitable for use with unprotected imidazolium salts. The commercially available Grignard reagent PhMgBr in THF was found to give clear solutions in [C₁₄(C₆)₃P]X {X = Cl, Br, or [NTf₂]} which were stable for over one month.³⁷⁷ Reaction with acetone or benzaldehyde gave the expected alcohol products after hydrolysis. Unfortunately, attempts to form the PhMgBr directly in the ionic liquids were unsuccessful.

When iodoethane was reacted with magnesium metal in [C₄pyr][BF₄], it led to the formation of the Grignard reagent.³⁷⁸ However, when it was reacted with benzaldehyde, the product was a mixture of 1-iodo-1-phenylpropane and 1,2-diphenylpropanol. The former can be imagined to arise from a nucleophilic attack of iodide on the expected Grignard product 1-phenyl-1-propanol, which was confirmed by its addition to the reaction mixture, leading to the iodide. For the latter a ketyl radical intermediate was proposed. Addition of pyridine or triethylamine led to the formation of 1-phenyl-1-propanol. When expanding the scope of the reaction, the authors found that ketones were unreactive, which is an order of reactivity different from that found in molecular solvents, which they proposed resulted from the Grignard reagent having a polymeric structure in the ionic liquid. It is interesting to note that not only was the reaction unsuccessful when bromoethane was used, but when Br[−] was present in the ionic liquid, this prevented the reaction of iodoethane. While the lack of success of the reaction of bromoethane could arise from a failure of the initial oxidative addition of the bromoalkane to the magnesium metal, the suppression of the reaction by free bromide suggests that interference with the Schlenk equilibrium may be occurring.

The first of these organometallic additions to be demonstrated in ionic liquids was the addition of the allyl group of tetraallylstannane to the C=O group of benzaldehyde in good yields in

$[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{PF}_6] \text{ or } [\text{BF}_4]\}$.³⁷⁹ No specific investigations into the possibility of forming NHC-derived products were made, but it was noted that in some cases there was greater loss of benzaldehyde than tetraallylstannane. Allyldiisopropoxyborane has been shown to produce the same products in similar yields in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = \text{Br} \text{ or } [\text{BF}_4]\}$, $[\text{C}_3\text{C}_1\text{im}][\text{BF}_4]$, and $[\text{C}_2\text{NH}_3][\text{NO}_3]$.³⁸⁰

The need to preform the allyl metal reagent was circumvented by using allyl bromide as the reagent together with indium metal in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{NTf}_2], [\text{PF}_6], \text{ or } [\text{BF}_4]\}$.³⁸¹ The yields in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ were particularly poor, suggesting that the HF that would have been generated in these reactions, which were conducted open to the air, may have been assisting the activation of the metal surface. Unidentified impurities were noted in the product mixtures that could indicate the effects of NHC formation in these systems. Tin and zinc have been used in a similar way in $[\text{C}_n\text{C}_1\text{im}][\text{BF}_4]$ ($n = 2 \text{ or } 4$).³⁸²

Attempts to extend these methodologies beyond the allyl group have met with limited success. The reaction of benzaldehyde with α -bromoesters (the Reformatsky reaction) in ionic liquids have given only moderate yields, except for the most highly activated reagents.³⁸³ Reactions using diethylzinc led to the formation of zinc–NHC complexes in $[\text{C}_4\text{C}_1\text{im}]\text{Br}$ and $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ with Br^- contamination, and reasonable yields of addition products could only be achieved in very pure $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$.³⁸⁴ The same reaction in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ gave reduction of the aldehyde starting material to its alcohol. Clearly, a great deal more work is required for these reactions to become synthetically useful.

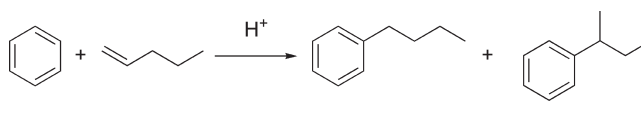
6.7. Acid-Catalyzed Reactions

Acid catalysis is one of the most important technologies used in the chemical industry, and it is applied throughout its value chain. However, it presents a number of environmental problems associated with the strong acids used and the waste that they generate. HF, for instance, is volatile, corrosive, and highly toxic; AlCl_3 is also toxic and corrosive and produces large amounts of HCl on contact with water. All strong acids produce large amounts of waste, causing significant treatment problems. This has led several groups to explore the possibility of using ionic liquids as more environmentally sustainable alternatives.

6.7.1. Electrophilic Aromatic Substitutions. Clean electrophilic substitution reactions remain one of the most important targets of the synthetic chemical industry. Conventional methods for these usually require strong acids, such as HF or AlCl_3 , as catalysts. Friedel–Crafts alkylations of benzene using haloalkanes were among the earliest reactions to be investigated in chloroaluminate ionic liquids.³⁸⁵ It was clearly demonstrated that acidic $[X(\text{AlCl}_3) > 0.5]$ ionic liquids were required to act as a combination of solvent and catalyst for the reaction and that the reaction proceeded via the dissociated carbonium ions. This was followed by interest in arene alkylation with alkenes, which are more desirable starting materials for industrial-scale reactions. These reactions are rarely completely selective to a single product. Since the alkylated product is more reactive than the parent arene, overalkylation is a common problem. This can be minimized by the use of a large excess of the arene. It is less easy to control the position along the alkyl chain at which it attaches to the arene ring. This arises because the carbocations formed during the reaction rearrange to more substituted forms, which are more stable, leading to a number of isomeric products for all but the simplest alkenes.

For the alkylation of anthracene with 2-chloropropane, both the overall yield and the selectivity to 2-isopropylanthracene reached a

Scheme 18



maximum when the composition of the $[\text{C}_2\text{C}_1\text{im}]\text{Cl}–\text{AlCl}_3$ ionic liquid reached $X(\text{AlCl}_3) = 0.67$. In compositions of $X(\text{AlCl}_3) \leq 0.5$ no reaction occurred,³⁸⁶ nor was any reaction observed in $[\text{C}_2\text{C}_1\text{im}]\text{Cl}–\text{ZnCl}_2$ $[X(\text{ZnCl}_2) = 0.67]$ and only the slightest amount in $[\text{C}_2\text{C}_1\text{im}]\text{Cl}–\text{FeCl}_2$ $[X(\text{FeCl}_3) = 0.67]$. It was also shown that the greatest yield and selectivity were found for reactions at 30 °C and under these conditions for 4 h, suggesting that there is a balance to be drawn between conditions that lead to insufficient reaction and those that lead to overreaction.

For the alkylation of benzene with 1-dodecene in $[\text{C}_4\text{C}_1\text{im}]\text{Cl}–\text{AlCl}_3$ with a fixed acidity $[X(\text{AlCl}_3) = 0.67]$, the primary factor influencing the conversion of the 1-dodecene was the temperature of the reaction, with quantitative conversions being achieved above 50 °C.³⁸⁷ Attempts to repeat reactions in a batch reactor were severely hampered by the exposure of the ionic liquid to moisture and its consequent deactivation. This was somewhat ameliorated by the use of a continuous-flow reactor. It has been demonstrated that the addition of HCl to a $[\text{C}_2\text{C}_1\text{im}]\text{Cl}–\text{AlCl}_3$ $[X(\text{AlCl}_3) = 0.67]$ ionic liquid leads to an increased selectivity to the 2-substituted isomer when the reaction is carried out to completion and under conditions that avoid polyalkylation (i.e., large excess of benzene).³⁸⁸ Similar results have been found when using either 1- or 2-methylnaphthalene as the arene.³⁸⁹ This clearly suggests that the reaction is proceeding via a free carbocation, which is rearranging to the more stable highly substituted form, for example, Scheme 18. It is well established that, unless specially treated, chloroaluminate ionic liquids will contain protons derived from hydrolysis with adventitious water.¹ Indeed, these reactions require the presence of some protons to generate the necessary carbocation for the reaction. Consequently, small amounts of adventitious water lead to the reaction being possible, whereas larger amounts lead to the deactivation of the ionic liquid. This makes it very difficult to compare results obtained from ionic liquids that have been handled differently because of the varying degree of contact between the ionic liquids and water.

Detailed kinetic investigations of the reaction of cumene (isopropylbenzene) with propene in $[\text{C}_2\text{C}_1\text{im}]\text{Cl}–\text{AlCl}_3$ $[X(\text{AlCl}_3) = 0.67]$ confirmed that the various products (di-, tri-, and tetra-isopropylbenzene) result from a series of successive alkylation reactions.³⁹⁰ These also showed that it was necessary to take into account the solubilities of the products to be able to explain the observed selectivity for the reaction and to fit the kinetic model to the data. To do this, and because of the difficulties faced in their experimental determination, the authors used the COSMO-RS model³⁹¹ to predict the relative solubilities of the products. This showed that the more alkylated products were less soluble in the reactive ionic liquid phase, leading to an improved selectivity for the monoalkylated product.

It is well established that varying the composition $[X(\text{AlCl}_3)]$ leads to chloroaluminate ionic liquids of different acidities.¹ This was demonstrated to affect the yield and selectivity in the alkylation of diphenyl oxide with 1-dodecene.³⁹² Ionic liquid with $X(\text{AlCl}_3) \leq 0.55$ did not show any catalytic activity in the alkylation, those with $X(\text{AlCl}_3) > 0.60$ gave increasing amounts of byproduct (e.g.,

polyalkylated products), and ionic liquids with $X(\text{AlCl}_3) = 0.6$ gave the maximum yield of monoalkylated product. This study also showed that the IR spectrum of acetonitrile ($2200\text{--}2400\text{ cm}^{-1}$) could be related to the Lewis acidity (i.e., composition) of the IL and hence to its catalytic activity. This technique was further developed to compare the Lewis acidity of a series of ionic liquids with mixed halogenoaluminate anions,²⁷³ which increased in the order $[\text{C}_{12}\text{C}_1\text{im}][\text{Al}_2\text{Cl}_6\text{Br}] < [\text{C}_8\text{C}_1\text{im}][\text{Al}_2\text{Cl}_6\text{Br}] \approx [\text{C}_4\text{C}_1\text{im}][\text{Al}_2\text{Cl}_7] < [\text{C}_4\text{C}_1\text{im}][\text{Al}_2\text{Cl}_6\text{Br}] < [\text{C}_4\text{C}_1\text{im}][\text{Al}_2\text{Cl}_6\text{I}]$. Clearly both the cation and the anion affect this value. The order for the $[\text{Al}_2\text{Cl}_6\text{Br}]^-$ salts shows the impact of decreasing chain length on the increased Lewis acidity, while the order for the $[\text{C}_4\text{C}_1\text{im}]^+$ salts is as one would expect from the acidities of the parent aluminum halides. When these results were compared to the results for the alkylation of benzene with 1-dodecene, it was found that the Lewis acidity alone could explain neither the conversion nor the selectivity of the reactions, and the authors also employed arguments based upon greater stabilization of the carbenium ions by more polarizable ionic liquids. It was also noted that the ionic liquids with more Lewis acidic anions were less hydrolytically stable and the reaction with trace amounts of water led to less Lewis acidic ionic liquids, which negatively impacted the results of the reactions.

The extreme moisture sensitivity of the halogenoaluminates has led several workers to attempt to use other Lewis acidic metal halides as solvents/catalysts for these reactions.^{272,393,394} Halogenoferrate-based ionic liquids were found to be both much less reactive and less selective catalysts/solvents for alkylations of substituted naphthalenes than the equivalent halogenoaluminate ionic liquids; halogenocuprate and halogenozincate ionic liquids were found to be inactive in these alkylations. The IR spectrum of acetonitrile in the ionic liquids proved to be a useful tool to demonstrate that these results arise from the relative Lewis acidities of the ionic liquids. The authors at least partly attributed this to the fact that the less Lewis acidic ionic liquids were less hydrolytically unstable, which in turn meant that no HCl was produced in the ionic liquid to catalyze the reaction. Furthermore,³⁹⁵ a study of the alkylation of benzene with 1-hexene in $[(\text{C}_1)_3\text{NH}]\text{Cl}-\text{FeCl}_3$ showed that the catalytic performance of the ionic liquid was greatly improved when HCl was added; indeed this modified ionic liquid was found to have greater selectivity to the desired monoalkylated product than a $[(\text{C}_1)_3\text{NH}]\text{Cl}-\text{AlCl}_3$ ionic liquid.

In a completely different approach, the ionic liquids $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ and $[\text{C}_n\text{C}_1\text{im}][\text{HSO}_4]$ and $[\text{C}_n\text{C}_1\text{im}][\text{B}(\text{HSO}_4)_4]$ ($n = 4$ or 8) were used as additives to H_2SO_4 to catalyze benzene alkylation with 1-decene.³⁹⁶ $[\text{C}_8\text{C}_1\text{im}][\text{HSO}_4]$ and $[\text{C}_n\text{C}_1\text{im}][\text{B}(\text{HSO}_4)_4]$ ($n = 4$ or 8) led to improved yields of the monoalkylated product in comparison to 100% H_2SO_4 . The addition of $[\text{B}(\text{HSO}_4)_4]^-$ to the sulfuric acid is unlikely to have had a great effect upon the overall acidity of the catalytic solution, whereas $[\text{HSO}_4]^-$ should have led to a reduction in its acidity. Hence, the increased solubility of the reactants in the catalytic solution is likely to be the cause of this improved performance.

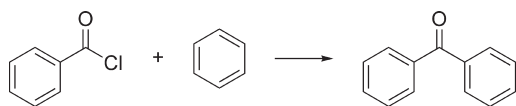
The alkylation of phenol with *tert*-butyl alcohol has been investigated both in ionic liquids and in their acid solutions.³⁹⁷ The distribution of products for this reaction is dependent upon the acidity of the reaction system. Weakly acidic media lead to *tert*-butyl phenyl ether, moderately acidic media lead to both 2- and 4-*tert*-butylphenol, and highly acidic media lead to 2,4-di-*tert*-butylphenol. When commercial samples of $[\text{C}_n\text{C}_1\text{im}][\text{BF}_4]$ ($n = 6$ or 8) were used as the solvent for the reaction with no added acid, conversions after 4 h were moderate (ca. 40%) with *tert*-butyl phenyl ether as the only product. When $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ was used,

the conversion increased to 90%, with the major product (75%) being 2,4-di-*tert*-butylphenol. This result arises from the fact that the $[\text{PF}_6]^-$ ion is hydrolytically unstable and that HF is formed in its reaction with water.^{52a} This HF is clearly acting as a catalyst for this reaction in the $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ ionic liquid. This is not necessarily to say that there is no HF formed in the $[\text{C}_n\text{C}_1\text{im}][\text{BF}_4]$ ($n = 6$ or 8) ionic liquids, which are also hydrolytically unstable.^{52b} However, in these ionic liquids it is likely that any HF that is formed would be somewhat neutralized by the more basic $[\text{BF}_4]^-$ ions. It is interesting to note that when H_3PO_4 is added to the ionic liquids (1:1, v/v), both the conversion of the phenol (70%) and the selectivity to 2,4-di-*tert*-butylphenol (59%) in the $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ ionic liquid were reduced, whereas in the $[\text{C}_n\text{C}_1\text{im}][\text{BF}_4]$ ($n = 6$ or 8) ionic liquids the conversion of the phenol (ca. 75%) was greatly increased and the major product was 2,4-di-*tert*-butylphenol (ca. 65%). These results were compared to those for H_3PO_4 itself, which gave conversion of the phenol of 45% and selectivity to 2,4-di-*tert*-butylphenol of 30%, with the major product being 4-*tert*-butylphenol (49%). This collection of results tells us again that an oversimplified analysis based on acidity arguments alone is not sufficient to explain the observed behaviors and it is necessary to consider other parameters, particularly the solubility of the reactants and intermediate products in the catalyst solutions.

The advent of $-\text{SO}_3\text{H}$ -functionalized ionic liquids has given another possibility to supply the Brønsted catalyst for these reactions as a component of the ionic liquid itself.⁴⁷ This has been used to effect the alkylation of 4-methylphenol with *tert*-butyl alcohol.²⁷⁸ The ionic liquids $[(\text{HSO}_3)^n\text{C}_n\text{pyr}][\text{OTf}]$ ($n = 3$ or 4) were found to be active in the alkylation, but greater conversion and selectivity to 2-*tert*-butyl-4-methylphenol was achieved by combining Brønsted acidic cations and anions in the $[(\text{HSO}_3)^4\text{C}_4\text{pyr}][\text{HSO}_4]$ ionic liquid. In fact, this latter ionic liquid outperformed H_2SO_4 in both conversion and selectivity. Hammett acidity measurements confirmed that this was indeed the most acidic of the three ionic liquids used, and consequently, it was concluded that this was the key performance parameter upon which to select the ionic liquid for this reaction. However, none of the ionic liquids were as acidic as 100% H_2SO_4 itself. Hence, it is possible, once again, that the increased solubility of the reactants in the catalyst/solvent also contributes to the improved performance of the ionic liquids and not just their acidity. Similar results were found for the alkylation of 2-methylphenol.³⁹⁸

Lewis acid catalysts have also been added to ionic liquids to promote these reactions. Scandium triflate was dissolved in a variety of dialkylimidazolium-based ionic liquids to provide a solution for these alkylations.³⁹⁹ When the ionic liquids contained $[\text{SbF}_6]^-$ or $[\text{PF}_6]^-$ ions, the catalyst was active, whereas when $[\text{BF}_4]^-$ or $[\text{OTf}]^-$ was used, it was not. It was noted that in the former ionic liquids the catalyst formed suspensions, while in the latter a true solution was formed. It was proposed that the more basic $[\text{BF}_4]^-$ and $[\text{OTf}]^-$ ions solvate the scandium sufficiently well, not only to dissolve it, but in so doing to also reduce its Lewis acidity enough to prevent it from acting as a catalyst in these reactions. However, in a study of the benzylation of arenes with PhCH_2OH or PhCH_2Cl in either $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ or $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ using $\text{Sc}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$, or triflic acid as the catalysts, no such total loss of reactivity in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ was observed.⁴⁰⁰ The reasons for these contradictory data are not immediately evident. One possibility is that Cl^- impurities left over from the synthesis of the ionic liquids are coordinating the scandium center in the former study, but not in the latter.

Scheme 19



Triflic acid itself has also been used as the promoter for the adamantylation of toluene by 1-adamantyl halides (Cl or Br) or 1-adamantyl alcohol in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$.⁴⁰¹ In the ionic liquid excellent yields of, almost exclusively, *p*-tolyladamantane could be achieved, while in the comparable solvent 1,2-dichloroethane *m*-tolyladamantane was the major product (ca. 40%), with *p*-tolyladamantane and adamantane being produced in roughly equal amounts. These data were rationalized by proposing that a more complete formation of the adamantyl cation occurred in the ionic liquid and that the transition state for the reaction was later in the reaction coordinate and with more benzenium ion character.

Arene acylation is also an industrially important reaction. It is in many ways a simpler reaction than alkylation. The reduced reactivity of the product means that overacylation is not a concern. The reaction requires the use of an activated acylating agent, usually an acid chloride or acid anhydride. A Lewis acid, commonly AlCl_3 , is required to generate the reactive acylium ion, which then attacks the arene, leading to the substitution of a proton on the arene. However, this reaction is not without its problems. The AlCl_3 is required in large excess to achieve useful conversions, and it forms an adduct with the carbonyl oxygen of the product. To liberate the product from this adduct, water is added to hydrolyze the AlCl_3 , consuming it and preventing its reuse. Early investigations of this reaction in chloroaluminate ionic liquids showed that they were effective catalysts/solvents, but that these problems also remained.^{1,389} Consequently, most of the focus for research in this area has been to find alternative systems that can overcome this need to destroy the catalyst to isolate the reaction products.

It has been shown that $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{FeCl}_3$ [$X(\text{FeCl}_3) = 0.67$] is a more effective catalyst/solvent for the reaction of benzene with benzoyl chloride (Scheme 19) than $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{AlCl}_3$ [$X(\text{AlCl}_3) = 0.67$], giving higher yields of benzophenone in shorter times.⁴⁰² The same study showed that $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{ZnCl}_2$ [$X(\text{ZnCl}_2) = 0.67$] was almost ineffective as a catalyst/solvent for the same reaction. The authors note that there is no correlation with the acidity of the ionic liquids, which are in the order $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{AlCl}_3 > [\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{ZnCl}_2 > [\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{FeCl}_3$.²⁷¹ The benzophenone product was isolated from the $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{FeCl}_3$ ionic liquid by simple extraction with cyclohexane, and the ionic liquid was reused. However, on the fourth run the yield collapsed from 85–95% to less than 30%. This was attributed to the accumulated loss of FeCl_3 into the product stream as a benzophenone– FeCl_3 adduct. Detailed spectroscopic measurements confirm the formation of a similar acetophenone– FeCl_3 adduct in $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{FeCl}_3$ ionic liquids.⁴⁰³ This study also confirmed that the acetylium ion $\{[\text{CH}_3\text{CO}]^+\}$ is the key intermediate in the reaction in this ionic liquid, as for the related chloroaluminate ionic liquids.

$[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{InCl}_3$ [$X(\text{InCl}_3) = 0.67$] has been used in an attempt to circumvent the problem of loss of catalyst into the product stream.⁴⁰⁴ Since these ionic liquids are not readily hydrolyzed, an aqueous workup is possible for the reactions of benzoic anhydride with various arenes in the ionic liquids, which are then recovered and reused. However, subsequent detailed evaluation of the benzoylation of anisole in $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{InCl}_3$

showed that even in this system the product was contaminated with an average 0.36 ppm indium after each reaction, which would require further separations in any commercial process and lead to the eventual deactivation of the catalyst/solvent.⁴⁰⁵

Several groups have investigated the use of catalysts dissolved in ionic liquids in an attempt to solve the problem of catalyst loss in Friedel–Crafts acylations. Metal triflate salts dissolved in a variety of ionic liquids have shown promise as catalysts for the benzoylation of arenes with benzoyl chloride.^{406,407} Activities, as expressed through conversion at fixed reaction time, varied with both the particular metal salt used and the nature of the ionic liquid. As one might expect of an acid-catalyzed process, ionic liquids with more basic anions {e.g., $[\text{BF}_4]^-$ or $[\text{OTf}]^-$ } provided lower conversions than those with less basic anions {e.g., $[\text{PF}_6]^-$ or $[\text{NTf}_2]^-$ }. The cation was also shown to impact the observed conversions, possibly due to solubility effects. However, in all cases where recycling of the catalyst solutions was attempted, diminishing conversions were seen. When Bi_2O_3 was used as the catalyst in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$, the formation of $[\text{C}_2\text{C}_1\text{im}][\text{BiCl}_4]$ during the reactions was clearly demonstrated. This occurs by the HCl byproduct of the acylation reacting with the bismuth complex to give the unreactive $[\text{BiCl}_4]^-$.⁴¹¹ An analogous mechanism is likely to be occurring in the other systems.

Since acylation with acid anhydrides does not lead to the formation of HCl , the formation of inactive metal chloride complexes cannot be a mechanism for catalyst deactivation. However, detailed kinetic studies have demonstrated that catalyst deactivation also occurs in these reactions.⁴⁰⁸ This elegant study showed that the catalysis was by a Brønsted acid, generated from a series of ligand exchange reactions, which was subsequently deactivated by complexation with the product. The use of a biphasic ionic liquid/ scCO_2 (sc = supercritical) system extended the active lifetime of the catalyst solution $\{\text{In}(\text{OTf})_3$ in $[\text{C}_4\text{C}_1\text{pyr}][\text{NTf}_2]\}$, probably by more effective separation of the product from the catalyst.⁴⁰⁹ However, deactivation was not totally prevented. An attempt at using zeolite catalysts in ionic liquids for this reaction also led to catalysis by a Brønsted acid liberated from the zeolite by ion exchange with the ionic liquid and subsequent deactivation of the catalyst solution.⁴¹⁰

An in situ generated 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) titanium(IV) complex in $[\text{C}_2\text{pyr}][\text{BF}_4]$ or $[\text{C}_2\text{pyr}][\text{CF}_3\text{CO}_2]$ ionic liquids has been used for the reaction of ethyl glyoxylate with aromatic amines.⁴¹¹ Good yields and enantioselectivities were achieved for this reaction, which only diminished a little after successive runs of the reaction. These results suggest that the metal complex is indeed the catalyst for the reaction and that its deactivation is lessened by the presence of this ligand environment.

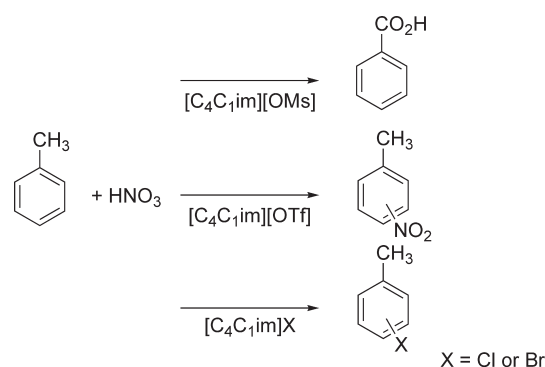
The electrophilic nitration of aromatics is also industrially important. The earliest studies in ionic liquids used acidic compositions of $[\text{C}_2\text{C}_1\text{im}]\text{Cl}-\text{AlCl}_3$ with KNO_3 .⁴¹² It was proposed that the nitrating agent was in situ generated $[\text{NO}_2]^+$. However, this reaction was accompanied by the product isolation difficulties that arise with the use of chloroaluminate ionic liquids. $[\text{NO}_2]^+$ can be delivered directly as the salt $[\text{NO}_2][\text{BF}_4]$. When it was used in $[\text{C}_2\text{C}_1\text{im}]\text{Cl}$ for the nitration of toluene, NO_2Cl was formed, which evaporated from the reaction mixture when the apparatus was not sealed.⁴¹³ Rapid (compared to nitration) ion metathesis was also seen in $[\text{C}_2\text{C}_1\text{im}]\text{Cl}-\text{AlCl}_3$, $[\text{C}_2\text{C}_1\text{im}][\text{PF}_6]$, and $[\text{C}_2\text{C}_1\text{im}][\text{OTf}]$. Of course, the metathesis of $[\text{NO}_2][\text{BF}_4]$ with $[\text{C}_2\text{C}_1\text{im}][\text{BF}_4]$ is a nil reaction. No useful yields of nitrotoluenes could be achieved in any of these ionic liquids. This was at least partly due to the formation of nitrated imidazolium cations in the ionic liquids.

Silver, copper, iron, or ammonium nitrates combined with either acetic anhydride or trifluoroacetic acid anhydride have also been shown to act as arene nitration agents.^{413–415} It was proposed that the *ortho/para* selectivity suggested that the nitration occurred via the in situ formation of acyl nitrates. The formation of nitrated imidazolium cations was seen again, and it was recommended that nonimidazolium ionic liquids, such as $[\text{C}_4\text{C}_1\text{pyrr}]^+$ or $[(^1\text{C}_3)_2\text{-C}_2\text{NH}]^+$ salts, are preferred.^{413,415} HNO_3 /acetic anhydride has been used to investigate the effect of the ionic liquid anion on the nitration of phenols.⁴¹⁶ Although little difference was seen in the reactivities of activated substrates, greater differences were seen for less reactive substrates (e.g., halobenzenes) in $[\text{C}_4\text{C}_1\text{pyrr}][\text{OTf}]$ or $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$, for which significantly greater yields at a fixed time were achieved in $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$ than in $[\text{C}_4\text{C}_1\text{pyrr}][\text{OTf}]$. No reaction was observed under the same conditions in CH_2Cl_2 . The results in the former ionic liquid were similar for these deactivated arenes when $[\text{NO}_2][\text{BF}_4]$ was used as the nitrating agent (with no added Ac_2O). These results were used together as evidence of nitration by $[\text{NO}_2]^+$ itself, although its reactivity is moderated through solvation by the ionic liquid anion. Similar results were seen in reactions in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, and $[\text{C}_4\text{C}_1\text{C}_1\text{im}][\text{BF}_4]$ that agree with this interpretation, although these authors speculated that the differences arose from solubility differences of Ac_2O in the ionic liquids.⁴¹⁷

Since the only reaction byproduct is water, the use of aqueous nitric acid for nitration has the potential to lead to an environmentally benign synthesis of nitroaromatic compounds. However, strong acids, such as concentrated H_2SO_4 , are required in commercial processes to give acceptable reactivities. These in turn lead to acid wastes that need to be disposed of, reducing the environmental efficiency of the processes. Consequently, a number of authors have attempted these reactions in ionic liquids. When HNO_3 alone was used as the nitrating agent, truly dramatic ionic liquid anion effects were seen (Scheme 20).⁴¹⁸ In ionic liquids with triflate or hydrogen sulfate anions, the expected nitrated arenes were produced. However, when halide ionic liquids were used, halogenated arenes were produced, the acid acting to oxidize the halide to the hypohalous acid halogenating agent. The same was seen when HCl was the acid used in $[\text{C}_4\text{C}_1\text{im}][\text{NO}_3]$. Finally, in methanesulfonate ionic liquids the nitric acid acted as an oxidizing agent for toluene to yield benzoic acid. Using methanesulfonic acid dissolved in $[\text{C}_4\text{C}_1\text{im}][\text{NO}_3]$ yielded the same result. These results show that the origin of various ions in the reaction mixture has no impact on the reactivity of that mixture. This suggests that complete dissociation of the dissolved acid occurs and the product mixture has a statistical distribution of ions.

$[(\text{HO}_3\text{S})^n\text{C}_n\text{C}_1\text{im}][\text{OTf}]$ ($n = 3$ or 4) have been used to supply catalysts for nitrations with 62% nitric acid.⁴¹⁹ At 5% loadings (arene:nitric acid = 2:1), these ionic liquids provided good conversions for activated and moderately deactivated arenes, but not for the strongly deactivated nitrobenzene. The biphasic system gave easy separation of the product and recycling of the aqueous layer, which contained both the ionic liquid and unreacted nitric acid. Unfortunately, conversions rapidly decreased with successive cycles. However, this may simply be due to the decreasing concentration of nitric acid in the solution. The, by then well-known, propensity of imidazolium-based ionic liquids to be nitrated led Liu et al. to prepare a range of $[(\text{HO}_3\text{S})^n\text{C}_n(\text{C}_m)_3\text{N}][\text{HSO}_4]$ ($n = 3$ or 4 ; $m = 1, 2$, or 4) ionic liquids for use in these reactions.⁴²⁰ The Hammett acidities of the ionic liquids in CH_2Cl_2 were compared and their solubilities in several nonpolar molecular solvents measured. Significant differences in reactivities were seen for moderately deactivated arenes,

Scheme 20

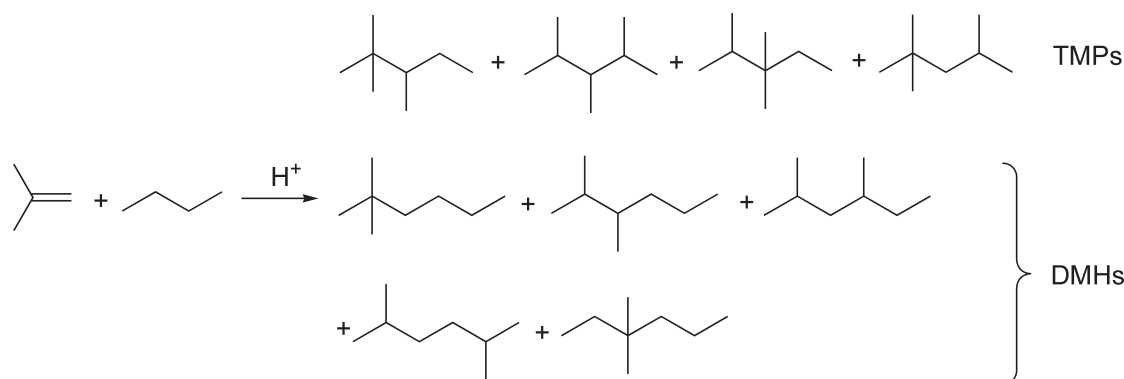


but all of the ionic liquids gave increased yields and *para*-selectivities compared to those seen for the same reaction in their absence. The order of the yields was consistent with the miscibility of the ionic liquid with the arene, rather than the acidity of the ionic liquid. The authors proposed that this was because the ionic liquids were behaving as phase transfer catalysts and allowing the arene to come into contact with the charged $[\text{NO}_2]^+$ nitrating agent.

6.7.2. Isobutane Alkylation. The acid-catalyzed alkylation of isobutane with 2-butene is conducted by the petrochemical industry on a massive scale.⁴²¹ Although at first sight simple, this reaction has a mechanism that passes through a succession of carbocations that readily rearrange to give a mixture of octanes (Scheme 21), some C_8 olefins, and heavier alkanes ($>\text{C}_8$, typically 15–20%) and cracking products of these alkanes (C_5 – C_7 alkanes, typically ca. 20%). The products of the reaction are added to automobile fuels to increase their octane rating. The performance of the mixed alkylate product depends upon its precise composition. Better performance is given by mixtures with a higher overall proportion of octanes and within that a greater trimethylpentane (TMP) to dimethylhexane (DMH) ratio. The conventional acids used for this process are HF and more recently H_2SO_4 .

In acidic compositions the ionic liquids $[\text{C}_n\text{C}_1\text{im}]\text{X}-\text{AlCl}_3$ ($n = 4, 6$, or 8 ; $\text{X} = \text{Cl}, \text{Br}$, or I) are highly effective catalysts/solvents for this reaction.⁴²² The highest olefin conversions were found for the $[\text{C}_8\text{C}_1\text{im}]\text{Br}-\text{AlCl}_3$ ionic liquid. Comparison of the best ionic liquid with H_2SO_4 showed that higher olefin conversions were achieved with the ionic liquid, which also maintained its performance for longer. It was particularly notable that the formation of heavy products, which are commonly catalyst deactivators, was less in the ionic liquids, largely due to the biphasic character of the ionic liquid system. However, the TMP:HMP ratio was less in the ionic liquid than in H_2SO_4 . The catalytic performance of the ionic liquid systems varied with both the cation and the anion of the ionic liquids. This was found to arise from a combination of solubility (increasing the cation alkyl chain length increases the hydrocarbon solubility in the ionic liquid) and acidity effects. It was also found that the TMP:DMH ratio was greater for the $[\text{C}_n\text{C}_1\text{im}]\text{Br}-\text{AlCl}_3$ ionic liquids, with variation in the cation having little effect, suggesting that acidity affects this result, but that reactant solubilities do not. However, the overall selectivity to octanes was lower for these ionic liquids, with a greater proportion of light cracking products being formed. Variation of the composition of the $[\text{C}_8\text{C}_1\text{im}]\text{Br}-\text{AlCl}_3$ ionic liquid showed that as the ionic liquid was made more acidic the amount of both cracking products and oligomerization products (olefins and heavy products) increased

Scheme 21



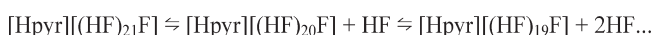
alongside the increased conversions. It was shown that the moisture sensitivity of these ionic liquids led to gradual deactivation of the catalyst/solvent. It has also been shown that the deliberate addition of HCl to a $[(C_2)_3NH]Cl-AlCl_3$ [$X(AlCl_3) = 0.67$] ionic liquid led to lower selectivity to octanes, with a concomitant increase in the proportion of cracking products.⁴²³ This arises because of the well-established superacidity of these systems.¹ Hence, as with many of the electrophilic aromatic substitutions described above, extreme care is required in controlling the conditions of these reactions. Some H^+ , often from contact with adventitious water, is required for the reaction to occur at all; too much leads to poor selectivity to the required products, and consequently, prolonged exposure to water leads to deactivation of the catalyst/solvent.

The addition of benzene (1%, w/w) to $[(C_2)_3NH]Cl-AlCl_3$ [$X(AlCl_3) = 0.67$] was found to decrease the formation of byproduct, increasing the selectivity to octanes and the TMP:DMH ratio, even though some alkylbenzenes were formed.⁴²⁴ This was attributed to the benzene moderating the ionic liquid's acidity, as indicated by the IR spectrum of CH_3CN . It was reasoned that the addition of benzene to the ionic liquid was expected to have a limited impact upon the number of acidic species in the solution and that the effect might be through its coordination to the chloroaluminate species. However, it was also noted that arenium cations, which might be the source of the Brønsted acid in these reactions, are formed under these conditions and that these cations could prevent the formation of cracking products.

The addition of metal halide salts to $[(C_2)_3NH]Cl-AlCl_3$ [$X(AlCl_3) = 0.67$] was found to have only a marginal impact on products for $SnCl_4$, $ZnCl_2$, or $NiCl_2$, but led to significantly improved overall selectivity to octanes and TMP:DMH ratio when $CuCl$ was used.⁴²³ In subsequent studies, this was attributed to the formation of a mixed-metal $[AlCl_4CuCl]^-$ anion, which was proposed to moderate the acidity of the ionic liquid.⁴²⁵ PetroChina has introduced a commercial alkylation process using these "composite ionic liquids" to tune the acidity of the ionic liquid for process optimization.⁴²⁶ In 2006 this process was retrofitted into an existing 65 000 t/year sulfuric acid alkylation unit in China.⁴²⁷ The process operates at ambient temperature and moderate pressure, with increased yields, greater process unit capacity (40% greater), and less reactor corrosion than the H_2SO_4 process. These properties together give a more economic process.

HF/amine (up to 22:1 molar ratio) mixtures have also been used for isobutane alkylation.²⁹⁰ These mixtures have formed the basis for UOP's commercial Alkad process.⁴²⁸ These compositions give

Scheme 22



equilibrium mixtures (e.g., for pyridine, Scheme 22) that are both far less volatile and less corrosive than pure anhydrous HF. The volatility of the mixtures (which is proportional to the concentration of free HF) increased with increasing HF:amine ratio, although no simple relationship between the volatility at any given composition of different amine mixtures and the basicity (pK_a) of the amine was found. It was also reported that the alkylate quality varied with the composition of the mixture, although no details are available in the public literature of the precise composition of the commercial system. However, since the more commonly used 9:1 HF/pyridine composition was said to be ineffective in this reaction, it can be speculated that the free HF that is present in the more acidic compositions is required for the reaction to occur. In this case, the catalysis is best described as being by a solution of HF in the ionic liquid $[Hpyr][(HF)_x F]$ (Scheme 22).

Protic ionic liquids have also been used as catalysts/solvents for isobutane alkylation.⁴²⁹ Whether the acidic site was on the cation {e.g., $[(HO_3S)^+C_4C_1im][NTf_2]$ } or the anion {e.g., $[C_4C_1im][HSO_4]$ }, lower conversions and selectivities, both selectivity to C_8 products and TMP:DMH ratio, were found in these ionic liquids than were found for sulfuric acid itself (97.3% conversion, 61.7% C_8 selectivity, and 6.1 TMP:DMH ratio). $[(HO_3S)^+C_4C_1im][HSO_4]$ gave a better TMP:DMH ratio, but again poorer selectivity to C_8 products and lower overall conversion. Adding H_2SO_4 (75 wt %) to this ionic liquid gave improved selectivities (62.3% C_8 selectivity and 6.4 TMP:DMH ratio) and hence a better product at only a slight cost in terms of conversion (95.6%) compared to using sulfuric acid alone.

6.7.3. Esterification. Esters are widely used compounds in a wide range of consumer products, from pharmaceuticals to fabrics. Consequently, esterifications are important industrial processes, and they have also attracted much fundamental academic interest. The simple direct stoichiometric condensation reaction of an acid with an alcohol should be a highly environmentally efficient process, with water as its only byproduct (Scheme 23). However, due to the usually unfavorable position of the esterification equilibrium, reactive acid derivatives or coupling agents are often required to achieve high yields. Since ionic liquids often mix well with carboxylic acids and short-chain alcohols but are only poorly miscible with simple esters, most of the reactions discussed below begin as monophasic solutions,

Scheme 23



but end as biphasic mixtures. These separations of the esters from the ionic liquid containing aqueous layer in biphasic systems can be used to drive the reaction to completion without requiring energetically costly water removal. Hence, ionic liquids have been used on a number of occasions in an attempt to conduct esterifications with unactivated starting materials.

The first reported Fischer esterification in ionic liquids used acidic chloroaluminate ionic liquids.⁴³⁰ However, the moisture sensitivity of these ionic liquids means that they could never become practical catalysts/solvents for these reactions. The Fischer esterification of ethanol and acetic acid was also one of the first reactions to be conducted in acid-functionalized ionic liquids.⁴⁷ $[(\text{HO}_3\text{S})^3\text{C}_3\text{-(Ph)}_3\text{P}][\text{pTSA}]$ was liquid at the temperature of the reaction, but solid at room temperature, giving a very simple method for its isolation and recycle at the end of the reaction. It was found that yields of the ethyl acetate product were actually improved by the presence of some water. Similar effects are known for solid polymeric sulfonic acids. Optimum conditions for the reaction were found to be 1:1:7 reactants/ionic liquid/water.⁴³¹ It is likely that the water is required for proton transfer from the $-\text{SO}_3\text{H}$ group to the acetic acid to occur efficiently.

Protic ionic liquids with a labile proton on the nitrogen of an ammonium ion can also act as Brønsted acids in esterifications.^{432,433} When methanesulfonic acid was added to the $[\text{C}_4\text{Hpyrr}][\text{C}_1\text{SO}_3]$ ionic liquid, its ester was found in the product mixture, which was not seen when the reaction was conducted with the neat ionic liquid. This clearly indicates that the catalysis was by the protic ionic liquid and that there are negligible amounts of free methanesulfonic acid in the pure ionic liquid itself.

Brønsted acidity can also be imparted to the ionic liquid via the anion. The ionic liquids $[\text{C}_n\text{C}_1\text{im}][\text{HSO}_4]$ ($n=4$ or 6), $[\text{C}_4\text{C}_1\text{im}][\text{H}_2\text{PO}_4]$, $[(\text{HO})^2\text{C}_2\text{OC}_2\text{C}_1\text{im}][\text{HSO}_4]$, and $[(\text{HO}_3\text{S})^n\text{C}_n\text{C}_1\text{im}][\text{PF}_6]$ ($n=1$ or 2) have been compared as catalysts/solvents for the Fischer esterification of a range of acids and alcohols.⁴³⁴ The ionic liquids had the advantage over concentrated H_2SO_4 that the reactions were more selective to the desired esters. Comparison of the various imidazolium ionic liquids showed a distinct anion effect on the rate of the esterification, with the more acidic $[\text{HSO}_4]^-$ anion giving more effective catalysis than $[\text{H}_2\text{PO}_4]^-$. For these ionic liquids the effect of the cation was much less marked and probably associated with changes in the solubilities of the reactants and products. Similar results were observed with some ethylammonium-based ionic liquids.⁴³⁵ However, the sulfonic acid-bearing $[(\text{HO}_3\text{S})^n\text{C}_n\text{C}_1\text{im}][\text{PF}_6]$ ($n=1$ or 2) ionic liquids were more effective catalysts than the $[\text{HSO}_4]^-$ ionic liquids. Subsequently, it was demonstrated that the rates of esterifications in $[\text{HSO}_4]^-$ ionic liquids could be greatly improved when 5% H_2SO_4 was added to the ionic liquid.⁴³⁶ It was noted that when this reaction system was recycled, there was no loss of activity, suggesting that the H_2SO_4 was not extracted during the workup.

Of course, it is possible to prepare ionic liquids with both a sulfonic acid-bearing cation and a Brønsted acidic anion.⁴³⁷ The ionic liquids $[(\text{HO}_3\text{S})^3\text{C}_3\text{pyrr}]\text{X}$ $\{\text{X} = [\text{BF}_4]^-$, $[\text{H}_2\text{PO}_4]^-$, $[\text{HSO}_4]^-$, or $[\text{pTSA}]^-\}$ have been compared in the esterification of benzoic acid with simple alcohols. The yield of esters in $[(\text{HO}_3\text{S})^3\text{C}_3\text{pyrr}][\text{HSO}_4]$ was considerably higher than that in the $[\text{BF}_4]^-$ or $[\text{pTSA}]^-$ salts. $[(\text{HO}_3\text{S})^3\text{C}_3\text{pyrr}][\text{HSO}_4]$ was the least miscible of the ionic liquids

with the products, which led to the greatest shift of the esterification reaction equilibrium to the product side. It was later confirmed by Hammett acidity measurements that the difference in the rates of the reactions arose from the different acidities of the ionic liquids.²⁷⁹ This has been reconfirmed in studies of other esterifications with closely related ionic liquids,^{438,439} including the esterification of acetonitrile.⁴⁴⁰

Two recent studies sought to directly compare the catalysis of the Fischer esterification by ionic liquids with different types of potential proton sources. In one, the catalytic activity of the ionic liquids $[(\text{HO}_3\text{S})^4\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{pTSA}]$, $[\text{OTf}]$, $[\text{CF}_3\text{CO}_2]$, $[\text{HSO}_4]$, or $[\text{H}_2\text{PO}_4]\}$, $[(\text{HO}_3\text{S})^4\text{C}_4\text{pyrr}][\text{OTf}]$, $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, and $[\text{HC}_4\text{-im}][\text{HSO}_4]$ in the esterification of butyric acid and methanol was studied.⁴⁴¹ High yields were only found for the $-\text{SO}_3\text{H}$ -bearing ionic liquids, with no significant difference between the pyridinium and imidazolium ionic liquids with a common cation. For the $[(\text{HO}_3\text{S})^4\text{C}_4\text{C}_1\text{im}]\text{X}$ ionic liquids the yields varied with the anion such that $[\text{H}_2\text{PO}_4]^- < [\text{CF}_3\text{CO}_2]^- \ll [\text{pTSA}]^- < [\text{HSO}_4]^- < [\text{OTf}]^-$. In the second study the ionic liquids $[\text{C}_4\text{Him}][\text{BF}_4]$, $[\text{C}_4\text{Him}][\text{OTf}]$, $[(\text{C}_2)_3\text{NH}][\text{HSO}_4]$, $[(\text{HO}_3\text{S})^4\text{C}_4\text{C}_1\text{im}][\text{pTSA}]$, and $[(\text{HO}_3\text{S})^4\text{C}_4\text{C}_1\text{im}][\text{HSO}_4]$ were compared.⁴⁴² This found that for ethanol with acetic acid the conversion of the acid varied such that $[\text{C}_4\text{Him}][\text{BF}_4] < [\text{C}_4\text{Him}][\text{OTf}] \ll [(\text{C}_2)_3\text{NH}][\text{HSO}_4] < [(\text{HO}_3\text{S})^4\text{C}_4\text{C}_1\text{im}][\text{pTSA}] < [(\text{HO}_3\text{S})^4\text{C}_4\text{C}_1\text{im}][\text{HSO}_4]$, in line with the expected acidity of the ionic liquids. In this study, it was also noted that when the reactants were water miscible, ionic liquids with more hydrophilic anions gave better conversions, but when they were water immiscible, the reverse was true.

Esterification catalyzed by a solution of acid in an ionic liquid has also been investigated. The effects of $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, and $[\text{C}_2\text{C}_1\text{im}][\text{PF}_6]$ on the equilibria of pTSA-catalyzed Fischer esterifications of ethanol and acetic acid showed distinct differences for the different ionic liquids.⁴⁴³ In the absence of ionic liquid the equilibrium alcohol conversion reached was 63% in 6 h. In the hydrophilic $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ only 38% conversion was achieved, whereas in the hydrophobic $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_2\text{C}_1\text{im}][\text{PF}_6]$ 73% and 83% conversions, respectively, were seen in 24 h under otherwise identical conditions. This, almost certainly, arises from the product water separating from the $[\text{PF}_6]^-$ ionic liquids, displacing the reaction equilibrium toward the products. A detailed kinetic study compared the rates of the pTSA-catalyzed reaction of benzyl alcohol and methoxyacetic acid in ionic liquids $\{[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$, $[\text{C}_4\text{C}_1\text{-im}][\text{OTf}]$, $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$, or $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]\}$ and molecular solvents (toluene, CH_3CN , or THF) using the LSER method.⁴⁴⁴ An LSER that included both the ionic liquids and molecular solvents was found (eq 18), indicating that there was no change in mechanism in moving from molecular solvents to ionic liquids. It also overwhelmingly demonstrated that the only factor that was important was the basicity of the solvent. This was interpreted as arising from the solvent reducing the acidity of the proton in solution and hence its ability to catalyze the reaction. These two studies together demonstrate that for both optimal equilibrium conversions and rates the basicity of the ionic liquids should be minimized when they are being used as solvents for esterifications.

$$\ln k_2 = -7.25\beta - 3.59 \quad (18)$$

Binary metal isopropoxide complexes $\{\text{Zr(IV)}$, Fe(III) , Ga(III) , and $\text{Sn(IV)}\}$ have also been used as catalysts for the direct esterification of 4-phenylbutyric acid with benzyl alcohol.⁴⁴⁵ When $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ or $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ was used with $\text{Zr(O}^i\text{Pr)}_4$, no reaction was seen, whereas the catalyst was

active in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ and $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$. This suggests that HF, generated from the reaction of water with the $[\text{PF}_6]^-$ and $[\text{BF}_4]^-$ ions, is suppressing the catalyst's activity. However, with all of the catalysts the use of large amounts of ionic liquid led to decreased reactivity, probably because of direct interactions between the ionic liquid ions and the catalysts.

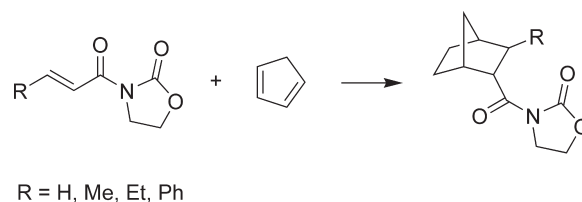
Esterifications can also be effected by biotransformations in ionic liquids.⁸ Due to their tolerance of organic solvents, the use of lipases in nonaqueous solvents has been widely explored for some time. Hence, they were considered to offer a good chance of showing good activities in ionic liquids. However, early studies of direct enzyme-catalyzed esterifications in ionic liquids have been unpromising.^{446–449}

Chemical catalysis of transesterifications has been far less widely investigated than direct esterification. Early studies showed that transesterifications of β -ketoesters with sulfamic acid as the catalyst were more selective in $[\text{C}_n\text{C}_1\text{im}]\text{Cl}$ ($n = 3$ or 5) than the same reactions in CH_2Cl_2 or hexane.⁴⁵⁰ Similar results have been found when $[\text{HSO}_4]^-$ ionic liquids have been used as catalysts for these transesterifications.⁴⁵¹ However, in neither case was any explanation for how the ionic liquid prevents attack by the alcohol at the β -carbon of the ketoester offered. More recently, the internal transesterification of 2-hydroxypropyl *p*-nitrophenyl phosphate in a number of ionic liquids showed a distinct increase in the rate of the reaction in ionic liquids when compared to water.⁴⁵² For the ionic liquids $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{CH}_3\text{CO}_2], [\text{OTf}], [\text{InCl}_4], \text{or } [\text{BF}_4]\}$ the rate of the reaction increased dramatically with the change of anion in the order $[\text{CH}_3\text{CO}_2]^- < [\text{OTf}]^- < [\text{InCl}_4]^- < [\text{BF}_4]^-$. However, no simple rationalization for this observation could be found. For the transesterification of cottonseed oil with methanol in a range of ionic liquids with sulfonic acid-containing cations, the changing reactivities were attributed primarily to the Brønsted acidities of the ionic liquids.⁴⁵³

The ring-opening polymerizations of lactones can be considered to be transesterifications. ϵ -Caprolactam has been polymerized by a range of rare-earth-metal triflate complexes in ionic liquids.⁴⁵⁴ When the ionic liquid was $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, the reactions were slower, and only afforded oligomers with $M_n \leq 600$, than when the ionic liquids were $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ or $[\text{C}_4\text{C}_1\text{im}][\text{SbF}_6]$, in which M_n values of up to 4400 could be achieved. When $\text{Sc}(\text{OTf})_3$ or $\text{Eu}(\text{OTf})_3$ was used as the catalyst in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, no reaction was observed.

6.7.4. Diels–Alder Reactions. A number of ionic liquids with Lewis acidic anions have been used as a combination of solvent and catalyst for Diels–Alder reactions. Lee noted that using $[\text{C}_2\text{C}_1\text{im}]\text{Cl}–\text{AlCl}_3$ ionic liquids with an excess of AlCl_3 (51 mol %) as the solvent/catalyst led to dramatically increased *endo/exo* selectivities for the reaction of cyclopentadiene and methyl acrylate, when compared to those with an excess of $[\text{C}_2\text{C}_1\text{im}]\text{Cl}$.⁴⁵⁵ The increased reactivity and selectivity arise due to the presence of $[\text{Al}_2\text{Cl}_7]^-$ in the acidic compositions of the ionic liquid. This was then subsequently used to invert the selectivity of the reaction of cyclopentadiene and methyl *trans*-crotonate from a slight *exo* preference to an *endo* preference.⁴⁵⁶ In an attempt to get away from the extreme moisture sensitivity and corrosiveness of these chloroaluminate ionic liquids, the use of $[(\text{HO})^2\text{C}_2\text{NH}_3]\text{Cl}–\text{MCl}_2$ $\{\text{M} = \text{Zn or Sn}\}$ with an excess (67 mol %) of the metal halide has been explored.⁴⁵⁷ Although the sensitivity of these reactions to the precise reaction conditions can affect the results, making direct comparisons difficult, the *endo/exo* ratio achieved with the $[(\text{HO})^2\text{C}_2\text{NH}_3]\text{Cl}–\text{ZnCl}_2$

Scheme 24



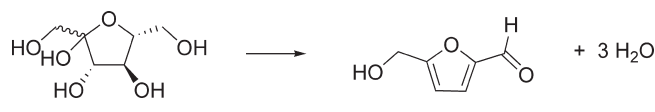
ionic liquid was noticeably higher (24:1) than had been achieved in the previously reported chloroaluminate ionic liquid (19:1). Given that chloroaluminate species are generally regarded as more potent Lewis acids than chlorozincate species, this difference may be the result of the composition of the $[(\text{HO})^2\text{C}_2\text{NH}_3]\text{Cl}–\text{ZnCl}_2$ ionic liquid giving rise to a higher concentration of active Lewis acid catalyst.

The reaction of myrcene with acrolein yields two regioisomers, “*p*”-myrac aldehyde and “*m*”-myrac aldehyde. In acidic $[\text{C}_4\text{C}_1\text{im}]\text{Cl}–\text{ZnCl}_2$ these reactions are considerably faster and marginally more selective to the “*para*” isomer than when conducted in a solution of ZnCl_2 in CH_2Cl_2 .⁴⁵⁸ This was attributed to the increased concentration of the active Lewis acid catalyst, which activates the dienophile via interaction with the carbonyl oxygen. The reaction with myrcene was repeated with methyl acrylate, methyl methacrylate, and mesityl oxide, and the relative reactivities of these compounds $\{\text{acrolein} > \text{methyl acrylate} > \text{methyl methacrylate} > \text{mesityl oxide}\}$ were used to confirm this explanation.

Chiral C_2 -symmetric bis(oxazoline)–copper $\{\text{BOX}–\text{Cu}\}$ complexes have been used as catalysts for Diels–Alder reactions in ionic liquids. When the IndaBOX–Cu-catalyzed reaction of cyclopentadiene with 3-acryloyloxazolidin-2-one (Scheme 24) was conducted in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{BF}_4], [\text{OTf}], [\text{PF}_6], \text{or } [\text{SbF}_6]\}$, it was faster and more selective when the less basic anions were used.⁴⁵⁹ It was proposed that this was the result of the elevated water levels in the hydrophilic ionic liquids, which were not predried before the reactions. Recycling experiments with the product extracted by diethyl ether demonstrated a steady drop in selectivity, although the reactivity remained high. This suggests that the ligand was being extracted from the solution, but that the copper remained in some other form. The use of imidazolium-tagged BOX–Cu complexes prevents this problem.⁴⁶⁰ Here it was found that marked improvements in both rates and selectivities could be demonstrated in ionic liquids with $[\text{NTf}_2]^-$ anions, when compared to using the same catalyst in dichloromethane. It was also found that the time taken for the catalytically active species to form was far shorter in the ionic liquids. However, it was also found that ionic liquids with bromide anions were substantially less effective solvents for these reactions. In these experiments considerable care was taken to exclude moisture, and its presence cannot be the explanation for the difference. It is more likely to be that the Br^- coordinates the copper directly, preventing the formation of the BOX–Cu complex.

The same reaction of cyclopentadiene with 3-acryloyloxazolidin-2-one (Scheme 24) has been studied using platinum diphosphine complexes in $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$.⁴⁶¹ As with the copper-based Lewis acid catalysts above, the rates of the reactions were appreciably greater in the ionic liquid than in dichloromethane. Although good selectivities could be obtained in the dichloromethane solutions, these required that the reaction be performed at -20°C , whereas in the ionic liquid excellent selectivities were achieved at room temperature. Here the effect of the ionic liquid was attributed to

Scheme 25



its stabilization of the catalytically active species, which formed unreactive complexes in dichloromethane.

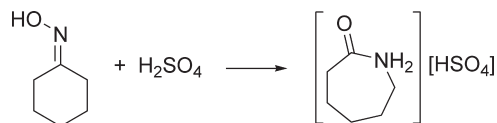
In an attempt to gain insight into the effects of Lewis acids in ionic liquids, the reactions of acrolein, methyl acrylate, and acrylonitrile with cyclopentadiene have been studied in some detail (Scheme 15).⁴⁶² In $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ the activity of the catalysts followed the trend $\text{ZnI}_2 < \text{AlCl}_3 < \text{InCl}_3 < \text{Sc}(\text{OTf})_3$. The fact that the effect of the Lewis acids was much less on the reactions of acrylonitrile was used as evidence that the catalysts interacted directly with the polar groups of the dienophiles. It was necessary to keep the catalyst concentrations below concentrations at which the polymerization of the starting materials began to compete with the cycloaddition. When the ionic liquids $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{MCl}_3$ ($\text{M} = \text{Al}$ or In) were used for the reactions of acrolein, reactivities were similar to and selectivities were less than those achieved using solutions of the respective metal halide in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$. Other studies in which several Lewis acids have been compared have used the ionic liquid $[\text{C}_6\text{C}_1\text{im}][\text{BF}_4]$.⁴⁶³ For the reaction of cyclopentadiene with methyl vinyl ketone the reactivities followed the trend $\text{Li}[\text{OTf}] \approx \text{Li}[\text{NTf}_2] < \text{BF}_3 \approx \text{ZnI}_2 \approx \text{AlCl}_3 < \text{HOTf} < \text{HNtF}_2 < \text{Y}(\text{OTf})_3 < \text{Sc}(\text{OTf})_3 \approx \text{Sc}(\text{NTf}_2)_3 < \text{Ce}(\text{OTf})_4 \cdot 5\text{H}_2\text{O}$. It is interesting to note that both of the pairs $\text{Li}[\text{OTf}]/\text{Li}[\text{NTf}_2]$ and $\text{Sc}(\text{OTf})_3/\text{Sc}(\text{NTf}_2)_3$ showed no significant change in reactivity or selectivity with the change of anion. It was suggested that the low reactivities of the lithium, zinc, and aluminum catalysts were due to partial deactivation by water in the ionic liquid.

Kumar and Pawar⁴⁶⁴ combined the use of the dissolved catalyst $[\text{Et}_3\text{NSi}(\text{toluene})][\text{B}(\text{C}_6\text{F}_5)_4]$ with an acidic chloroaluminate ionic liquid. The rates of reaction of the combined system were greater than those of either component alone for the same catalyst dissolved in a $[\text{BF}_4]^-$, $[\text{PF}_6]^-$, or $[\text{SbF}_6]^-$ -based ionic liquid or of a pure $[\text{C}_4\text{pyr}]\text{Cl}-\text{AlCl}_3$ ionic liquid. This use of the ionic liquid as an active catalyst support allowed for a reduction in the amount of catalyst used.

6.7.5. Dehydration. Renewed interest in the chemistry of biomass-derived compounds has led to attempts to dehydrate alcohols and particularly sugars in ionic liquids. 5-(Hydroxymethyl)furfural (HMF) can be prepared by the dehydration of fructose (Scheme 25) by heating with solid $[\text{Hpyr}]\text{X}$, $\{\text{X} = \text{Cl}, [\text{pTSA}], \text{or } [\text{CF}_3\text{CO}_2]\}$ or $[(\text{C}_2)_4\text{N}]\text{Br}$ in 65–75% yields without the need for added acids.⁴⁶⁵ Only very poor yields were obtained in this way from glucose. However, dehydration of the glucose derivative sorbitol and other polyols could be achieved under these conditions.⁴⁶⁶ This led Lansalot-Matras and Moreau to attempt the reaction in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ using Amberlyst-15 as a solid acid catalyst.⁴⁶⁷ The best results were achieved when DMSO was added as a cosolvent due to the poor solubility of fructose in these ionic liquids. The ionic liquids 3-allyl-1-(4-sulfobutyl)imidazolium triflate, $[(\text{HO}_3\text{S})^4\text{C}_4(\text{C}=\text{C}_2)\text{im}][\text{OTf}]$, and 3-allyl-1-(4-sulfuryl chloride butyl)imidazolium triflate, $[(\text{ClO}_2\text{S})^4\text{C}_4(\text{C}=\text{C}_2)\text{im}][\text{OTf}]$, have both been used as catalysts for this reaction, with the latter Lewis acidic form being more active than the Brønsted acidic version.⁴⁶⁸

When $[\text{C}_1\text{Him}]\text{Cl}$ was used as the solvent at 90 °C, no cosolvent nor added acid was required to achieve reasonable yields and rates.⁴⁶⁹ It was also found that selectivity to the

Scheme 26

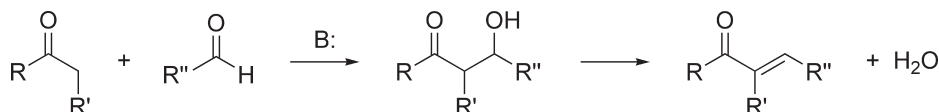


5-(hydroxymethyl)furfural was excellent, with no decomposition products (e.g., levulinic acid) seen. If sucrose was used as the starting material, it was rapidly cleaved by water into fructose, which reacted to form HMF and glucose, which did not react under these conditions. Subsequently, it was found that $[\text{C}_2\text{C}_1\text{im}]\text{Cl}$ could also act as a catalyst/solvent for the dehydration of fructose, showing that a protic ionic liquid is not required for dehydration to occur.⁴⁷⁰ Dehydration of benzyl alcohols has also been achieved under acid-free conditions in the ionic liquids $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = \text{Cl}, \text{Br}, [\text{BF}_4], \text{or } [\text{PF}_6]\}$ or $[\text{C}_6\text{C}_1\text{im}]\text{Br}$ using microwave heating.⁴⁷¹ It is particularly interesting to note that the rates as demonstrated by yields at fixed time varied in the order $[\text{PF}_6]^- < [\text{BF}_4]^- < \text{Cl}^- < \text{Br}^-$, i.e., with increasing hydrophilicity of the anion, but greater yield could be attained in less time in $[\text{C}_6\text{C}_1\text{im}]\text{Br}$, with the more hydrophobic cation, than in $[\text{C}_4\text{C}_1\text{im}]\text{Br}$.

The rate of the dehydration of fructose in $[\text{C}_2\text{C}_1\text{im}]\text{Cl}$ could be improved by the addition of several different metal chloride salts (CrCl_2 , CrCl_3 , FeCl_2 , FeCl_3 , CuCl , CuCl_2 , VCl_3 , MoCl_3 , PdCl_2 , PtCl_2 , PtCl_4 , RuCl_3 , or RhCl_3).⁴⁷² In contrast to this, the dehydration of glucose could only be achieved with CrCl_2 , for which good selectivity to 5-(hydroxymethyl)furfural was found. It was thought that this was because the solute metal complex $\{[\text{CrCl}_3]^- \}$ was coordinating to the glucose and facilitating its mutarotation into a more reactive form. SnCl_4 has also been reported to dehydrate glucose to HMF in $[\text{C}_2\text{C}_1\text{im}][\text{BF}_4]$.⁴⁷² For a range of $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{BF}_4], [\text{PF}_6], [\text{NTf}_2], [\text{OTf}], \text{or } [\text{saccharin}]\}$ ionic liquids, it was found that more coordinating anions lead to lower HMF yields, presumably by forming an unreactive tin complex. The only exception to this trend was the very poor reactivity found in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, but in this case the glucose was observed to be insoluble. Having settled on the $[\text{BF}_4]^-$ anion, the authors found that the yields of HMF increased in the order $[\text{C}_4\text{pyr}][\text{BF}_4] < [\text{C}_4\text{C}_1\text{im}][\text{BF}_4] < [\text{C}_2\text{C}_1\text{im}][\text{BF}_4]$, which also gave a higher yield than DMSO. ¹H NMR evidence was presented for the formation of a similar chelate complex between the tin and the glucose, which enabled the reaction to proceed. Although the formation of HMF from glucose has only been reported with the use of a metal catalyst, a partial dehydration has been reported in some $[\text{NTf}_2]^-$ ionic liquids at 200 °C.⁴⁷³

6.7.6. Beckmann Rearrangement. ϵ -Caprolactam is a monomer for the production of nylon-6. As such it is produced industrially on a huge scale by several producers. The first step in its synthesis is from cyclohexanone with hydroxylammonium sulfate, which melts with decomposition at 120 °C, to give the intermediate cyclohexanone oxime, which is then treated with concentrated sulfuric acid or oleum to yield ϵ -caprolactam. It has recently been pointed out that in the second step of this process the product ϵ -caprolactam reacts with the H_2SO_4 to give the salt ϵ -caprolactamium hydrogen sulfate (Scheme 26), which melts at 60 °C.⁴⁷⁴ This ionic liquid then acts as a solvent for the reaction. The synthesis of ϵ -caprolactam can therefore be considered to be a well-established large-scale industrial ionic liquid process. The lower than expected vapor pressures of solutions of SO_3 in this ionic liquid suggest that $[\text{HS}_2\text{O}_7]^-$ is formed in solution.

Scheme 27



The industrial production of ϵ -caprolactam also yields ammonium sulfate as a byproduct. Even though ammonium sulfate can be used as a fertilizer, attempts have been made to find an ionic liquid process that avoids this.^{475,476} It has been found that the ionic liquid ϵ -caprolactamium tetrafluoroborate can act as a catalyst/solvent for the reaction without the need to add acid, with product separation being achieved using molecular solvents.⁴⁷⁷

The Beckman rearrangement of a number of ketoximes into amides, catalyzed by Lewis acids (AlCl_3 , TiCl_4 , SnCl_4 , or BF_3) have been conducted in 17 different ionic liquids.⁴⁷⁸ AlCl_3 and TiCl_4 were found in all cases to be more effective catalysts than SnCl_4 and BF_3 . Generally, changing the ionic liquid had a greater effect on the reactions of these latter two catalysts than on the more reactive AlCl_3 and TiCl_4 . A small decrease in reactivity with increasing alkyl chain lengths of the cation was observed, and the rate of the reactions increased with C^2 substitution of the imidazolium ring. The impact of the anion of the ionic liquid on the rates of the reactions is less clear. It appears to be a combination of the basicity (possibly also hard/soft character) of the anion, hence its ability to interact with Lewis acids, and the degree of hydration of the ionic liquid, but no definitive conclusion can be drawn.

6.7.7. Ring Closing of Isonitrosoacetanilides. The ring closing of isonitrosoacetanilides to give isatin 3-oximes can be catalyzed by Lewis or Brønsted acids in ionic liquids.⁴⁷⁹ No reaction was observed in neutral $[\text{C}_4\text{C}_1\text{im}]\text{Cl}-\text{InCl}_3$, with acidic compositions being required to achieve modest reactivities. More useful yields were obtained with Brønsted acids in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$. The yields obtained with different dissolved acids increased in the order pTSA (31%) < $\text{CF}_3\text{CO}_2\text{H}$ (61%) < $\text{CH}_3\text{SO}_3\text{H}$ (88%) < HBF_4 (96%). However, HBF_4 in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ only yielded 25% of the product. The authors attributed this difference in the behavior of the two ionic liquids to the cationic charged intermediate being more stabilized by the “low coordinating” anions.

6.7.8. Mannich Reaction. The Mannich reaction is a method for preparing β -amino acids from an aldehyde, ketone, and monoalkylamine. It is usually catalyzed by either Brønsted or Lewis acids. The reaction in the ionic liquids $[\text{C}_4\text{C}_1\text{im}][\text{pTSA}]$, $[\text{C}_4\text{C}_1\text{im}][\text{CF}_3\text{CO}_2]$, $[\text{C}_4\text{C}_1\text{im}][\text{H}_2\text{PO}_4]$, and $[\text{C}_4\text{C}_1\text{im}][\text{HSO}_4]$ displayed an interesting reversal of activities in comparison to the reactions described above where reactivities in these ionic liquids, or closely related ones, were compared.⁴⁸⁰ No reaction at all was seen in $[\text{C}_4\text{C}_1\text{im}][\text{HSO}_4]$, and the greatest yields were observed in $[\text{C}_4\text{C}_1\text{im}][\text{pTSA}]$. This was rationalized by noting that although acid was required to catalyze the reaction, if the acid were too strong, it would react directly with the amine, preventing the formation of the Mannich base.

6.7.9. Glycosylation. The synthesis of carbohydrate derivatives remains an extremely demanding area of research. Many syntheses require protection/deprotection protocols and sophisticated coupling reagents to achieve a single anomeric product. The use of Lewis acids as promoters for alcohol glycosylation with trichloroacetinidates in ionic liquids has shown an inversion of stereochemical outcome depending on the ionic liquid used.⁴⁸¹ A detailed NMR experiment showed that the triflate ion of $[\text{C}_2\text{C}_1\text{im}][\text{OTf}]$ formed a transient α -glycosyl triflate intermediate,

which guides the subsequent attack of the glycosyl acceptor from the β -face. No such intermediate was formed in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, which behaved similarly to noncoordinating molecular solvents and provided products of the opposite configuration.

6.7.10. Summary. Ionic liquids have shown themselves to have great potential, both as acids themselves and as solvents for other acids. They can influence the reactions of solute species in many ways: as tunable acid systems, by being better solvents for starting materials and/or intermediates than aqueous acid systems, by giving effective separation of products, etc. Often more than one of these effects is operating in any one system, and oversimplified interpretations of results based on just one of these can fail to give adequate explanations for the observed behaviors. Ionic liquids can also give rise to problems, such as hydrolytic instability and the formation of acid wastes. Good understandings of these various effects and careful selection of the ionic liquid can lead to highly effective catalysts/solvents.

6.8. Base/Nucleophile-Catalyzed Reactions

Catalysis by bases in ionic liquids has received less attention than acid catalysis. This is in great part due to the known sensitivity of ionic liquids to even mild bases, which can seriously affect these types of reactions.⁴⁸² The formation of NHCs from imidazolium ionic liquids is a particular problem. For example, the disparity between the high benzaldehyde conversions (as determined by GC) and low product yields in the base-catalyzed Baylis–Hillman reaction of methyl acrylate and benzaldehyde catalyzed by 3-hydroxyquinuclidine or 1,4-diazabicyclo[2.2.2]octane (DABCO) in the presence of $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ can be explained by a reaction of the benzaldehyde with $[\text{C}_4\text{C}_1\text{im}]^+$, via the deprotonated NHC.⁴⁸³ Consequently, any interpretations of the results for base-catalyzed reactions in imidazolium ionic liquids must be viewed as potentially compromised unless a specific investigation into the involvement of NHCs, whether for good or ill, has also been reported and will not be reviewed here.

6.8.1. Aldol Reaction. The aldol addition is one in which a carbon of one aldehyde or ketone adds to the carbonyl carbon of another to yield a β -hydroxycarbonyl compound (Scheme 27), which may then dehydrate to an α,β -unsaturated carbonyl compound, at which point the reaction becomes known as the aldol condensation (Scheme 27). Not only is the aldol reaction significant in its own right, it also occurs as a step in mechanistic interpretations of other widely used reactions. It can be acid catalyzed, but is most often catalyzed by bases, traditionally metal hydroxides or alkoxides. The presence of these bases leads to the possibility of the formation of NHCs and the products of their reactions with the aldehyde starting materials, as described above.⁴⁸³

The reaction of *p*-(trifluoromethyl)benzaldehyde, which is a highly activated aldehyde for these reactions, with acetone in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ with no added catalyst showed no evidence of reaction.⁴⁸⁴ When NaOH was added to $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ as an ethanolic solution, the reaction of benzaldehyde with acetophenone (the Claisen–Schmidt variation of the aldol reaction) was found to proceed with good conversions.⁴⁸⁵ However, even when the ethanol had been removed by vacuum, ethyl benzoate

was formed as a byproduct and depletion of the base was noted. This was attributed to the formation of NHCs and hence to the formation of ethoxide ions. When a similar reaction system of aqueous NaOH and the ionic liquids $[C_nC_1im]X$ ($n = 2, 4, 6$, or 8 ; $X = [PF_6]$ or $[BF_4]$) and $[C_4C_1C_1^2im]X$ ($X = [PF_6]$ or $[BF_4]$) were used for the self-aldol reaction of propanal, no such problems were noted.⁴⁸⁶ Although conversions for these reactions were determined by GC and byproduct may have been missed, it is also possible that the presence of the water is preventing the formation of the NHCs. The increased solubility of the major product 2-methylpent-2-enal in the ionic liquid containing system in comparison to water alone led to its further reaction to higher boiling aldehydes and oligomers and poorer selectivities than in the purely aqueous system. Perhaps more surprisingly, in the ionic liquid containing systems some of the aldol addition product, 3-hydroxy-2-methylpentanal, was observed, whereas this was absent when they were not used. Conversely, the authors found that the selectivity to the condensation product was 20% higher for the $[C_4C_1im][BF_4]$ -containing systems than the purely aqueous system when the reaction was that between propanal and 2-methylpentanal.

The use of $[(HO)^2C_2C_2NH_2]X$ ($X = [HCO_2]$, $[CH_3CO_2]$, or $[C_2CO_2]$), $[(HO)^2C_2(C_2)_2NH]X$ ($X = [HCO_2]$, $[CH_3CO_2]$, or $[C_2CO_2]$), or $[(HO)^2C_2(C_2)_3N]X$ ($X = [CH_3CO_2]$ or $[C_2CO_2]$) as catalysts/solvents for the aldol condensations of citral/acetone, benzaldehyde/acetone, or benzaldehyde/heptanal, with no added catalyst, has been reported.⁴⁸⁷ These ionic liquids have anions that have the potential to act as moderate bases and cations that can act as moderate acids, but it is also possible that the free amine present could be active in the reaction (see below). A dependence of the rates and selectivities of the reactions on both the cations and the anions of the ionic liquids was indeed noted, but insufficient detail was given to allow any kind of mechanistic interpretation of these potentially very interesting results.

Most studies of aldol reactions in ionic liquids have used secondary amine "organocatalysts". Here the amine reacts with the carbonyl to give a nucleophilic enamine intermediate. If the amine is chiral, these reactions are enantioselective. This addition was first demonstrated in $[C_4C_1im][PF_6]$ for a range of substituted benzaldehydes with acetone using a 30 mol % loading of proline.⁴⁸⁴ Yields and enantioselectivities were similar to those that had been obtained in DMSO. The involvement of NHCs was discounted by a control reaction in which the acetone was not included, which showed no reaction of *p*-nitrobenzaldehyde. A subsequent study showed that the catalyst loading could be reduced to 5% for cross-aldol reactions of aliphatic aldehydes and that the addition of DMF helped to prevent overreaction to oligomers.⁴⁸⁸ An interesting observation showed that when the reaction of benzaldehyde with acetone was conducted using solutions of proline in ionic liquids as a thin film on solid supports, dehydration to the condensation product was seen, whereas the same reaction in the bulk ionic liquids only gave the addition product.⁴⁸⁹ It is not clear why this was the case, unless the silica gel support was also acting as a desiccant.

The use of an ionic liquid with a *D*-camphorsulfonate anion led to faster reactions between *p*-nitrobenzaldehyde and acetone with *L*-proline in the molecular solvents acetone, toluene, THF, dichloromethane, acetonitrile, and diethyl ether than the same reaction without the addition of the ionic liquid.⁴⁹⁰ In acetone, when the concentration of the ionic liquid was similar to that of the proline, the effect on the enantioselectivity was small, but large excesses of the ionic liquid led to significantly poorer

enantioselectivities. Although negative, this clearly shows that chiral ionic liquids can have a significant impact on the enantioselectivity of reactions. A variety of other closely related catalysts have also been used for aldol reactions in ionic liquids.⁴⁹¹

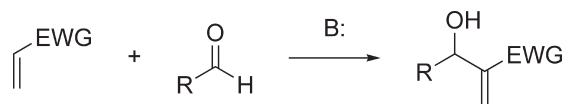
When piperidine was used as the amine for the aldol condensation of *p*-*tert*-butylbenzaldehyde with propanal in a range of ionic liquids, $[cat][NTf_2]$ ($[cat] = [C_4C_1im]$, $[C_4C_1C_1^2im]$, $[C_4C_1pyrr]$, $[C_{14}(C_6)_3P]$, $[C_6(C_2)_3N]$, or $[(C_8)_3C_1N]$), $[C_4C_1im][BF_4]$, and $[C_2C_1im]X$ ($X = [FAP]$ or $[C_2SO_4]$), it was found that changing the cation had very little effect upon the reaction, but a distinct effect of changing the anion was observed.⁴⁹² For the water-immiscible ionic liquids with the $[FAP]^-$ and $[NTf_2]^-$ ions good conversions and selectivities to the desired 3-(*p*-*tert*-butylphenyl)-2-propenal were observed. However, in the water-miscible ionic liquids with the more basic anions $[BF_4]^-$ and $[C_2SO_4]^-$, conversions were lower and greater formation of the 2-methyl-2-pentenal byproduct was seen. It was proposed that this difference arose from the proportion of the piperidine that was in the enamine form, with free piperidine remaining in the $[BF_4]^-$ and $[C_2SO_4]^-$ ionic liquids that can catalyze the conventional base-catalyzed reaction and therefore lead to lower selectivities. In contrast to these results, when argininium *p*-toluenesulfonate or lysinium *p*-toluenesulfonate was used as the catalyst in $[C_4C_1im]X$ ($X = [N(CN)_2]$ or $[OTf]$) or $[C_4C_1pyrr]X$ ($X = [OTf]$ or $[NTf_2]$), higher yields were found in the more basic $[C_4C_1pyrr][OTf]$.⁴⁹³

Several papers have reported the use of ionic liquids with proline or closely related base substituents on the side chain of the cation, often for use as a catalyst in other solvents.⁴⁹⁴ Two proline-substituted cations have been prepared, one an imidazolium and the other a simple ammonium, to use as catalysts for the aldol addition of *p*-nitrobenzaldehyde and acetone in the ionic liquids $[C_4C_1im]X$ ($X = [NTf_2]$ or $[OTf]$) or $[C_4C_1pyrr]X$ ($X = [NTf_2]$ or $[OTf]$).⁴⁹⁵ Both better yields and better enantioselectivities were achieved with the ionic liquids than under the same conditions in DMSO. The enantioselectivities were also appreciably better than those that had been obtained when free proline had been used as the catalyst in the same ionic liquid. Only marginal changes in yields were obtained with the different catalysts and ionic liquids.

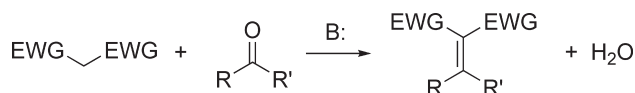
As an amino acid, the proline can also be incorporated into the ionic liquid as one of its ions. When the $[(HO)^2C_2(C_1)_3N]^-$ $[(C_4H_8)CO_2]$ ionic liquid was used as a combined solvent/catalyst for the aldol addition of *p*-nitrobenzaldehyde and acetone, moderate yields were obtained, with considerable yields of the product of a second aldol reaction.⁴⁹⁶ This overreaction could be suppressed by the addition of water as a cosolvent to achieve better selectivities to the desired product. This also facilitated the separation of the catalyst and the product.

Other ionic liquids have been prepared in which the cation is capable of acting as a catalyst for the aldol reaction. The 1,1,3,3-tetramethylguanidinium cation $\{[(C_1)_4gu]^+\}$ has been used with a number of different anions $\{[CH_3CO_2]^-$, $[C_4CO_2]^-$, $[(HO)^1-C_2CO_2]^-$, or $[CF_3CO_2]^- \}$ to produce ionic liquids that can act as a catalyst/solvent for the aldol reaction.⁴⁹⁷ The results showed a clear effect of the anion on the rates of the additions of *p*-nitrobenzaldehyde and cyclopentanone or 2-butanone, with the more basic ions leading to higher yields in shorter times. UV-vis spectroscopy confirmed that a common enamine intermediate (see below) was formed and suggested that the different rates of the reactions were, at least in part, due to the concentration of this species. Similar results previously obtained for the closely related Henry (nitroaldol) reaction in these ionic liquids yield the same explanation.⁴⁹⁸

Scheme 28



Scheme 29



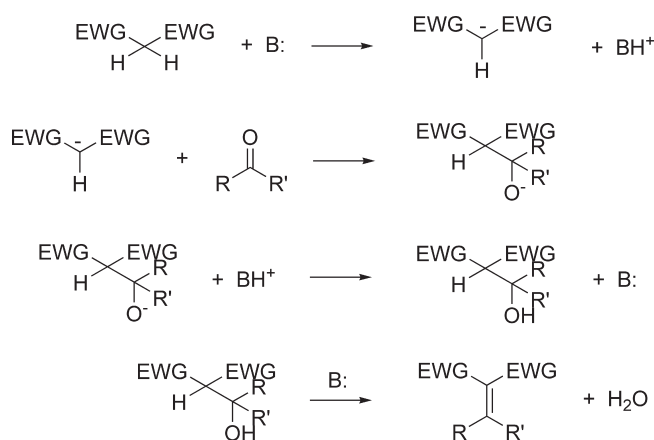
6.8.2. Morita–Baylis–Hillman Reaction. Closely related to the aldol reaction, the Morita–Baylis–Hillman (MBH) reaction (Scheme 28) of an aldehyde with an activated alkene was the first base-catalyzed reaction to be reported in ionic liquids.⁴⁹⁹ Although promising rate enhancements were observed, yields were generally disappointing. These results were later explained by Aggarwal et al. to be the consequence of the formation of NHCs and their subsequent reaction with the aldehyde starting material.⁴⁸³ Subsequent studies into the effects of Lewis acids or hydrogen bond donors on the MBH reaction of methyl acrylate and benzaldehyde in $[\text{C}_4\text{C}_1\text{im}]^+$ ionic liquids again showed excellent rates, but not quantitative yields, even to the extent that yields in the presence of the Lewis acids were lower than for the same reactions in their absence.⁵⁰⁰ To circumvent these NHC-related problems, DABCO-catalyzed MBH reactions have been investigated in the presence of $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{PF}_6]$.⁵⁰¹ Direct comparisons of the isolated yields of these reactions with those obtained for $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ showed that they were indeed always higher for $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{PF}_6]$. It has also been claimed that 1,3-bis[(2-naphthalen-2-yloxy)propyl]imidazolium bromide prevents the formation of carbene-derived byproduct.⁵⁰² Successes were also achieved by using phosphonium⁵⁰³ and pyridinium⁵⁰⁴ ionic liquids. Again in these systems the addition of Lewis acids has a detrimental effect on the yields of the reactions.

Ionic liquids have been prepared specifically for use as catalysts for MBH reactions in which a quinuclidine moiety is attached to one of the side chains of a butylimidazolium cation.⁵⁰⁵ The authors found that using methanol in conjunction with the ionic liquid prevented the formation of carbene-derived byproduct, and substantially higher yields of the desired products were achieved. This led the same group to prepare an ionic liquid in which one side chain of the cation bore the quinuclidine moiety and the other a hydroxyl group to use as an MBH catalyst.⁵⁰⁶ The ionic liquid butylethylphenylselenium tetrafluoroborate has been used as a catalyst for this reaction, which will also circumvent this problem.⁵⁰⁷

There have been attempts to use chiral ionic liquids as solvents for chiral induction in MBH reactions, but the enantioselectivities achieved were well below anything that might be synthetically useful.⁵⁰⁸

6.8.3. Knoevenagel Reaction. The Knoevenagel condensation, the nucleophilic addition of an active methylene compound to a carbonyl group followed by a dehydration (Scheme 29), is another derivative of the aldol reaction and was also one of the earliest base-catalyzed reactions to be attempted in an ionic liquid $\{[\text{C}_6\text{C}_1\text{im}][\text{PF}_6]\}$.⁵⁰⁹ The possibility of NHC involvement was noted from the start, although the problems related to reaction of the NHCs with the aldehyde starting materials were not reported until later.⁴⁸³ The loss of both the OH^- catalysts and benzaldehyde starting material in its reaction with malonitrile in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ can be attributed to this.⁴⁸⁵ However, it has also been claimed that postreaction analysis of

Scheme 30



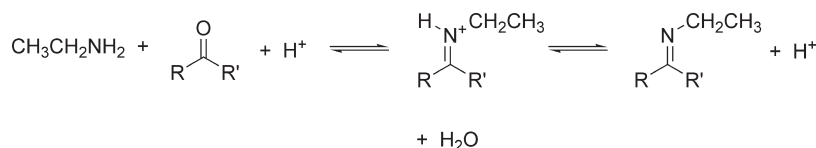
the glycine-catalyzed reaction of 2,6-dichlorobenzaldehyde and malonitrile in $[\text{C}_6\text{C}_1\text{im}][\text{PF}_6]$ shows no evidence for an NHC-derived byproduct, even after 10 runs.⁵¹⁰ It is possible that glycine is simply not sufficiently basic to cause the deprotonation of the imidazolium cation and/or that its acid part prevents this reaction. As with the MBH reaction, using a hydroxyl-substituted cation may also prevent this problem.⁵¹¹ The 1-(aminoethyl)-3-methylimidazolium hexafluorophosphate ionic liquid has been used as the catalyst for the condensation of aromatic aldehydes with malonitrile or cyanoacetate with amine functional groups on their cations in water.⁵¹² It would appear here that the water, which is in large excess, prevents the formation of NHC-derived products.

A number of studies have appeared in which ionic liquids have been used with no added base catalyst for the Knoevenagel condensation. As one would expect Hünig's base-functionalized ammonium cations provided $[\text{NTf}_2]^-$ ionic liquids that acted as a combination of both catalyst and solvent.⁵¹³ It was found that longer chains separating the base from the ammonium part of the cation led to more effective catalysis due to a decreased repulsion of the two cations present after protonation of Hünig's base.

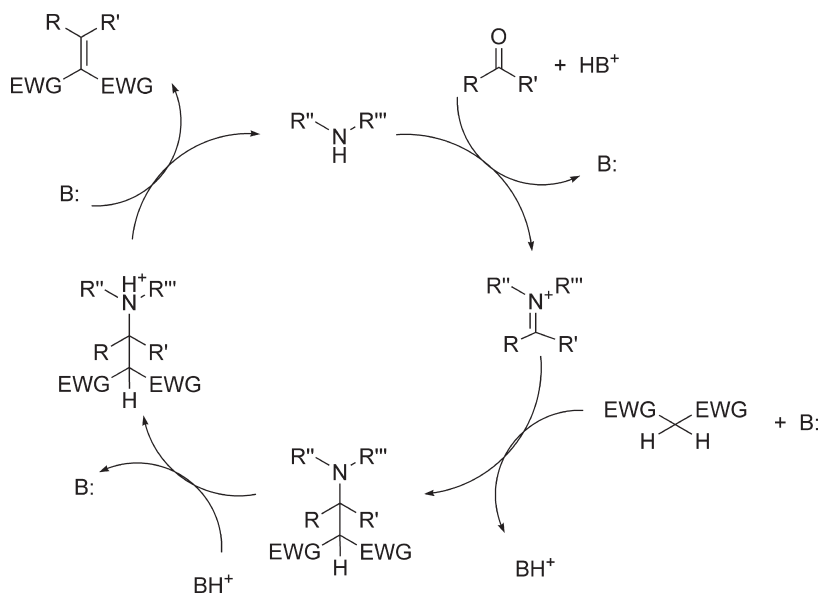
Successful Knoevenagel condensations have been reported in conventional ionic liquids. Reactions of malonitrile or ethyl cyanoacetate with benzaldehyde and substituted benzaldehydes in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ have been reported to give Knoevenagel condensation products in good yields.⁵¹⁴ At the same time, condensations of malonitrile or ethyl cyanoacetate with benzaldehyde and substituted benzaldehydes were reported to reach quantitative yields in 1–4 h in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$;⁵¹⁵ higher temperatures were required for reactions in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ (50 °C) to reach completion in times similar to those in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ (room temperature). However, elsewhere no reaction was observed for benzaldehyde with diethyl malonate in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ at 50 °C in 2 days⁵¹⁶ nor for *p*-nitrobenzaldehyde with malonitrile in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ or $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ in 6 h at room temperature.⁵¹⁷ Clearly there are some contradictions here that have yet to be resolved.

The salt ethylenediammonium diacetate was found to act as a catalyst for the reaction of benzaldehyde with ethyl cyanoacetate in molecular solvents and ionic liquids, with rates, as measured by the time required to achieve high yields, varying in the order $\text{PhCH}_3 \ll \text{CH}_3\text{OH} < \text{CH}_2\text{Cl}_2 \approx \text{CH}_3\text{CN} \ll [\text{C}_4\text{C}_1\text{im}][\text{PF}_6] \approx [\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$.⁵¹⁸ Ammonium acetate has also been used as a catalyst for this and other Knoevenagel condensations in $[\text{C}_4\text{pyr}][\text{NO}_3]$.⁵¹⁹ Just 4 drops of the related $[(\text{HO})^2\text{C}_2\text{NH}_3][\text{CH}_3\text{CO}_2]$ ionic liquid was found to catalyze reactions of malonitrile or ethyl cyanoacetate with

Scheme 31



Scheme 32



benzaldehyde and substituted benzaldehydes, with no additional solvent.⁵²⁰ $[(\text{C}_1\text{OC}_3)\text{NH}_3][\text{CH}_3\text{CO}_2]$ has been used similarly for the reactions of a number of aldehydes with a number of active methylene compounds.⁵²¹ A cyclic trimethylguanadinium lactate ionic liquid has been used as a catalyst/solvent for the reactions of benzaldehyde or a range of substituted benzaldehydes with malonitrile, ethyl cyanoacetate, or diethyl malonate, with reaction times and yields reflecting the relative reactivities of the reactants.⁵²² Ethylammonium nitrate has also been found to lead to high yields for the reaction of *p*-nitrobenzaldehyde with malonitrile in 3 h at room temperature⁵¹⁷ and to act as a catalyst/solvent for other Knoevenagel condensations more effectively than $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, water, or ethanol.⁵²³ Finally, for this group of ionic liquids, $[\text{C}_1\text{Him}][\text{CF}_3\text{CO}_2]$ has been used as the catalyst/solvent for the reaction of substituted benzaldehydes with 2,2-dimethyl-1,3-dioxane-4,6-dione, with reactions reaching 94% yields in 30 min, as opposed to 54% $\{[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]\}$, 76% $\{[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]\}$, or 77% $\{[\text{C}_6\text{C}_1\text{im}][\text{BF}_4]\}$.⁵²⁴

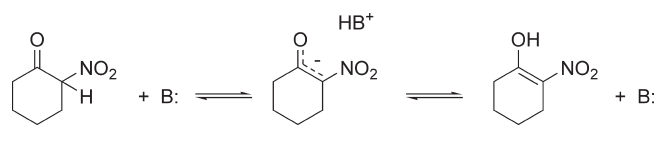
This collection of results indicates that the protic ionic liquids with basic anions are acting as effective catalysts/solvents for Knoevenagel condensations and together allow for some speculation about how this is achieved. The mechanism for the base-catalyzed Knoevenagel condensation has the activated methylene compound being deprotonated to give a carbanion intermediate (Scheme 30). The basic anions of the more effective ionic liquids above may be able to act as the base in the formation of the carbanion.⁵²¹ This could be further enhanced by the carbanion being stabilized by ionic liquids in comparison to molecular solvents. This is similar to the catalysis of Michael reactions by 1-methylimidazole in ionic liquids.³⁵⁷ The basic

anions of the ionic liquid could also facilitate the dehydration step (see above).

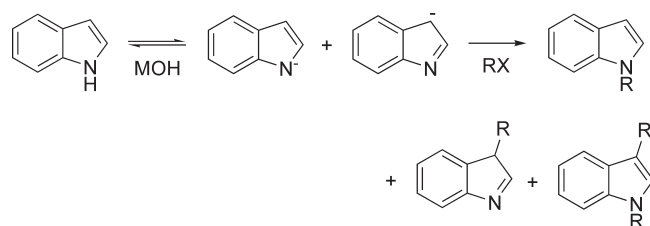
However, there is another potential mechanism for these reactions. The basicities of these anions are sufficient such that there will be a significant concentration of the free amine present when the cation carries a N–H proton.⁷² This has been demonstrated by the formation of ethylamine-derived products in nucleophilic aromatic substitution reactions in $[\text{C}_2\text{NH}_3][\text{NO}_3]$ or $[\text{C}_2\text{NH}_3][\text{CH}_3\text{CO}_2]$.⁵²⁵ These free bases could also act as base catalysts for the reaction. However, the same study showed that substituted benzaldehydes gave imines in $[\text{C}_2\text{NH}_3][\text{NO}_3]$, presumably via an iminium intermediate (Scheme 31). This gives rise to the second possible explanation of the results above. The free base, or perhaps the ammonium ion directly, reacts with the aldehyde to form an iminium ion, leading to nucleophilic catalysis of the reaction (Scheme 32).⁵²⁶ This has implications beyond the Knoevenagel reaction to any reaction for which this type of catalysis is possible when conducted in protic ionic liquids⁴⁸⁷ and as demonstrated in other aldol reactions.⁴⁹⁷

6.8.4. Keto–Enol Tautomerization. The keto–enol tautomerization of 2-nitrocyclohexanone can be base catalyzed (Scheme 33). The equilibrium constant for the uncatalyzed reaction has been used to predict Hildebrand parameters, δ_{H} for ionic liquids.²⁶⁹ The kinetics of the reaction catalyzed by excess pyridine in $[\text{C}_n\text{C}_1\text{im}][\text{NTf}_2]$ and $[\text{C}_n\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$ ($n = 2, 4, \text{ or } 6$), $[\text{C}_4\text{pyr}][\text{NTf}_2]$, and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ have been compared to those in a range of both pure molecular solvents and solvent mixtures.⁵²⁷ The second-order rate constant correlated well with ϵ_r for the molecular solvents, but it was not possible to include the ionic

Scheme 33



Scheme 34



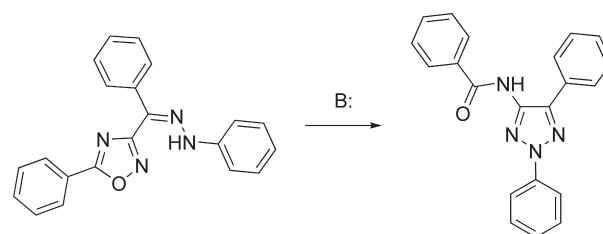
liquids in this analysis. However, a Kamlet–Taft type of analysis did provide a good LSER ($R^2 = 0.991$, eq 19), with the increased rates of reactions found in the ionic liquids being largely due to their ability to stabilize a more enolate-like transition state for the reaction than found in molecular solvents.

$$\ln k_2 = -11.3 + 1.86\pi^* + 4.73\alpha + 8.18F(\epsilon) + 0.021\delta^2 \quad (19)$$

6.8.5. Nucleophilic Substitutions. Indole is an ambident nucleophile that can be alkylated at either the nitrogen or the C³ position of its pyrrole ring or both (Scheme 34), with a distinct solvent effect on this regioselectivity.⁵²⁸ The reactions of indole with various halogenoalkanes in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ with KOH as the catalyst gave N-alkylindoles in almost quantitative yields, with only iodomethane and bromobenzene giving some dialkylation, as is typical for polar aprotic solvents.⁵²⁹ This methodology has been extended to other nitrogen heterocycles.⁵³⁰ Similar results were found for the reactions of 1-bromo-3-phenylpropane with indole catalyzed by potassium carbonate in acetonitrile/ $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{PF}_6], [\text{BF}_4], [\text{NTf}_2], \text{or } [\text{OTf}]\}$ mixtures, although with some formation of 1-(3-phenylpropyl)-1H-indole as a byproduct.⁵³¹ The selectivity to the desired 1-(3-phenylpropyl)-1H-indole varied with the anion in the order $[\text{PF}_6]^- \approx [\text{BF}_4]^- > [\text{NTf}_2]^- \approx [\text{OTf}]^-$, with the reactions in the latter ionic liquids also being slower. Pyrrole itself has been found to almost exclusively undergo C-alkylation under similar conditions in $[\text{C}_4\text{C}_1\text{im}][\text{SbF}_6]$, with some dialkylation.³¹⁹ In a study using a wider range of ionic liquids, it was shown that the selectivities found in alkylations with the halogenobutanes fell in the order found for polar protic solvents for $[\text{C}_4\text{C}_1\text{im}]\text{Br}$, but in the order found in polar aprotic solvents in $[\text{C}_7\text{pyr}]\text{Br}$ and $[\text{C}_1\text{C}_1\text{im}][\text{OTs}]$.⁵³²

Base-promoted alkylation of 2-hydroxypyridine in the ionic liquids $[\text{C}_n\text{C}_1\text{im}][\text{OTs}]$ ($n = 1$ or 4), $[\text{C}_4\text{C}_1\text{im}]\text{Br}$, and $[\text{C}_n\text{pyr}]\text{Br}$ ($n = 4$ or 7) with a range of bases $\{\text{MX}; \text{M} = \text{K}, \text{Na}, \text{Li}, \text{or Ag}; \text{X} = \text{H}, \text{C}_4\text{H}_9, \text{OH}, \text{or } \text{OCH}_3\}$ has been found to favor N-alkylation over O-alkylation in comparison to molecular solvents.⁵³³ The selectivities and rates of these reactions in the $[\text{C}_n\text{pyr}]\text{Br}$ ($n = 4$ or 7) ionic liquids were found to be greater than for the imidazolium ionic liquids. It was suggested that this was because hydrogen bonding between the imidazolium cations and the anionic nucleophile was suppressing its reactivity.

Scheme 35



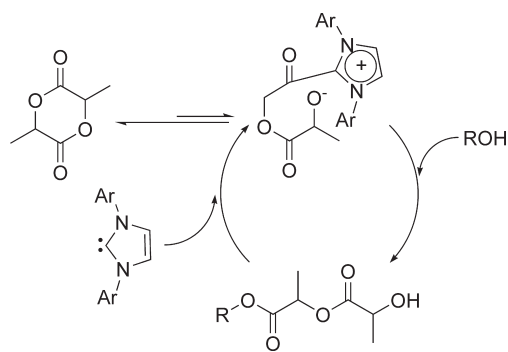
Base ($\text{CsOH} \cdot \text{H}_2\text{O}$) catalyzed N-alkylations of primary amines in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{PF}_6] \text{ or } [\text{NTf}_2]\}$, $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{PF}_6]$, or $[\text{C}_6\text{pyr}][\text{NTf}_2]$ have been shown to have excellent selectivity to secondary amines, with a markedly reduced overalkylation to tertiary amines.⁵³⁴ The results rivaled those possible in the best available alternative solvent, DMF. It is likely that this arises from the ability of the ionic liquids, and indeed DMF, to activate the primary amines more strongly than the secondary amines through hydrogen bonding. Dialkylation was only found for the activated halides allyl bromide and benzyl bromide. For the uncatalyzed reactions of $\text{C}_8\text{H}_{17}\text{X}$ the order of reactivity in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ was $[\text{OTs}]^- > \text{I}^- \approx \text{Br}^- \gg \text{Cl}^-$, with the addition of CsOH (i.e., the activation of the amine) reducing the differences.

The base-catalyzed rearrangement of the (Z)-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into the relevant 4-(benzoylamino)-2,5-diphenyl-1,2,3-triazole (Scheme 35) has been studied in both ionic liquids, $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{BF}_4], [\text{PF}_6], \text{or } [\text{NTf}_2]\}$, $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$, or $[\text{C}_4\text{C}_1\text{pyr}][\text{NTf}_2]$, and molecular solvents (benzene, 1,4-dioxane, ethyl acetate, MeOH, or MeCN).⁵³⁵ In the ionic liquids, the reaction was found to be first order in both reactant and base, but in the molecular solvents, more complex rate laws were found, which depended upon the solvent. This prevents a quantitative analysis of the bimolecular rate constants for the reactions in different solvents. The authors attributed the kinetic behaviors in the ionic liquids to their heterogeneous structures. However, the authors did report the *pseudo*-first-order rate constants for the reactions at a fixed concentration of base for the reactions with piperidine ($k_{\text{A,R}}$), which we have analyzed using the Kamlet–Taft approach and derived an acceptable LSER (eq 20, $R^2 = 0.85$). The positive β and π^* effects are in line with the LSERs found for other nucleophilic substitutions of amines (see above).

$$\ln k_{\text{A,R}} = -30.9 + 16.5\beta + 20.4\pi^* \quad (20)$$

6.8.6. Esterification/Acetylation of Alcohols. Base-catalyzed esterification has not received as much attention in ionic liquids as its acid-catalyzed counterparts. The transesterification of soybean oil with alcohols to give biodiesel and glycerol with ionic liquids has been achieved with both basic (K_2CO_3 , Cs_2CO_3 , or K_3PO_4) and H_2SO_4 catalysts.⁵³⁶ With ethanol the transesterification in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{NTf}_2], [\text{BF}_4], \text{or } [\text{PF}_6]\}$, $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$, or $[\text{C}_2\text{C}_1\text{im}][\text{C}_2\text{SO}_4]$ proceeded to almost quantitative yields with no obvious effect of changing either the cation or anion, although both the $[\text{BF}_4]^-$ and $[\text{PF}_6]^-$ ionic liquids decomposed under the reaction conditions via hydrolysis with adventitious water. However, the reactivities in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ were appreciably lower. A ^{13}C NMR spectrum of $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ with Cs_2CO_3 saw an almost complete collapse of the signal due to the C² carbon of the imidazolium ring, but with no new signal for the NHC appearing. Upon addition of ethanol this signal reappeared, suggesting that

Scheme 36



alcohols can suppress the action of bases on imidazolium rings. Unfortunately, after two or three repeated runs drastic reductions in yields were observed, presumably due to decomposition of the ionic liquids. This could be avoided by using H_2SO_4 as the catalyst, but the reactions themselves required considerably more time ($\times 5$) to reach completion than the base-catalyzed reactions.

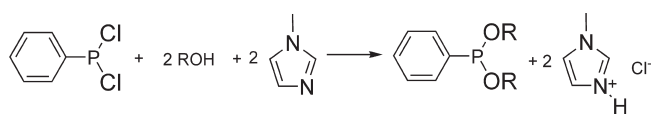
The methanolysis of ethylene carbonate to give dimethyl carbonate and ethylene glycol at 140°C and 200 psig can be catalyzed by the addition of a small amount of ionic liquid $\{[\text{C}_n\text{C}_1\text{im}]\text{Cl} (n = 2, 4, \text{ or } 6) \text{ or } [\text{C}_2\text{C}_1\text{im}]\text{X} (\text{X} = [\text{BF}_4] \text{ or } [\text{PF}_6])\}$.⁵³⁷ A slight effect of higher conversions with shorter alkyl chains on the cation was observed, but changing the anion had a more dramatic effect, with the more nucleophilic Cl^- ionic liquids giving the highest conversions.

The difficulties associated with esterifications failing to reach completion often lead to the use of activated starting materials, such as anhydrides, and acylation reactions to make esters. The focus of ionic liquids research in this area has been on the use of the ionic liquids as combined catalysts/solvents for these reactions. This was first demonstrated when it was shown that $[\text{C}_n\text{C}_1\text{im}][\text{N}(\text{CN})_2]$ ($n = 2$ or 4) ionic liquids were effective in this role for the reaction of acetic anhydride with a number of alcohols, including sugars.⁵³⁸ Shortly after this $[\text{C}_4\text{C}_1\text{im}]\text{Br}$ was found to behave similarly, particularly when assisted by the application of ultrasound.⁵³⁹ $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ has also been reported to lead to the acylation of alcohols with acetic anhydride,⁵⁴⁰ although the addition of catalytic amounts of substituted benzenesulfonate salts to $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ has been found to improve the rates of acetylations of benzyl alcohol and cyclohexanol.⁵⁴¹

The discovery by Rogers et al.⁵⁴² that some ionic liquids can make excellent solvents for cellulose and other carbohydrate polymers has stimulated a great deal of interest in the chemistry of these compounds in ionic liquids. Consequently, the acylation of these compounds,⁵⁴³ even directly of wood,⁵⁴⁴ has been explored using various chloride or dicyanamide ionic liquids, with a view to the exploitation of biomass.

So far we have discussed NHCs as if they can only be a problem in ionic liquids. However, a particularly interesting way of using them has arisen. Hedrick et al. have used ionic liquids as the source of the NHC as well as one of the solvents in a biphasic ring-opening polymerization of lactide and lactones.⁵⁴⁵ $[\text{C}_2\text{C}_1\text{im}][\text{BF}_4]$ with THF provided an excellent medium for the reaction (Scheme 36), which was initiated by the addition of a small amount of potassium *tert*-butoxide that deprotonates the imidazolium ring to generate the NHC. The now neutral NHC transfers to the THF layer, where the reaction occurs. The reaction is terminated by addition of a protic ammonium salt, which regenerates the imidazolium cation by proton transfer.

Scheme 37



6.8.7. Acid Scavenging. The most well-known industrial application of ionic liquids is the BASF SE BASIL process for the synthesis of alkoxyphenylphosphanes (Scheme 37).⁵⁴⁶ Formerly, a tertiary amine acid scavenger was used, but this gave a thick slurry that led to difficult separations and consequently poor yield (ca. 50%). Using 1-methylimidazole as the base gave $[\text{C}_1\text{Him}]\text{Cl}$ (mp 75°C) as the byproduct, which separated spontaneously as a second liquid phase under the reaction conditions. This not only solved the separation problem, but also led to no requirement for an added solvent.

As well as acting as the acid scavenger, BASF SE found that 1-methylimidazole also acts as a nucleophilic catalyst.⁵⁴⁷ This led to a completely new reactor design for this all-liquid process, which gave an increased productivity for the process by a factor of 8×10^4 to $690\,000\text{ kg m}^{-3}\text{ h}^{-1}$. At the end of 2004 BASF SE started a dedicated BASIL plant using this jet stream reactor technology. Of course, the technology is not limited to the original application and can be used for many different proton abstractions. A recent ecoefficiency analysis from BASF has shown that the BASIL technology is by far more environmentally sustainable than the process using tertiary amines.⁵⁴⁸ The BASIL process was awarded the European Chemical News Innovation for Growth Award in 2004.

6.8.8. Summary. The study of base catalysis in ionic liquids is still in its infancy. The formation of NHCs in the common imidazolium ionic liquids has proven to complicate many studies, particularly because their effects are not always seen under sometimes very similar conditions. There is good evidence that when ionic liquids are used in the presence of alcohols, either NHCs are not formed or their effects are suppressed. Systematic study of base catalysis is also severely hampered by the lack of current understanding of base strengths in ionic liquids. However, the studies above do indicate that this could be an area in which ionic liquids will be a useful addition to the range of solvents available.

7. TRANSITION-METAL-CATALYZED REACTIONS

Transition-metal-catalyzed reactions have been extensively studied in ionic liquids. Much of this has been descriptive in nature, and these studies have been the subject of several excellent recent reviews.¹² We recommend these reviews to the reader and do not attempt to reproduce them here. Some studies have focused on the ways in which the ionic liquids themselves affect the outcomes of catalytic reactions, and it is these studies that we concentrate on here. Changing the solvent can affect a catalytic reaction in many ways; e.g., the solvents may interact with the reactants as seen above and/or interact directly with the catalyst. In biphasic systems they can also affect the partitioning of solutes between the two phases. These interacting effects can lead to complex dependencies on changes of solvent that are difficult to interpret. In the discussion below, we report only those studies from which reasonably robust inferences can be drawn.

7.1. Ionic Liquids as Catalyst Immobilizers

If the product of a catalytic reaction in an ionic liquid is itself a liquid or if separation of the product can only be achieved by

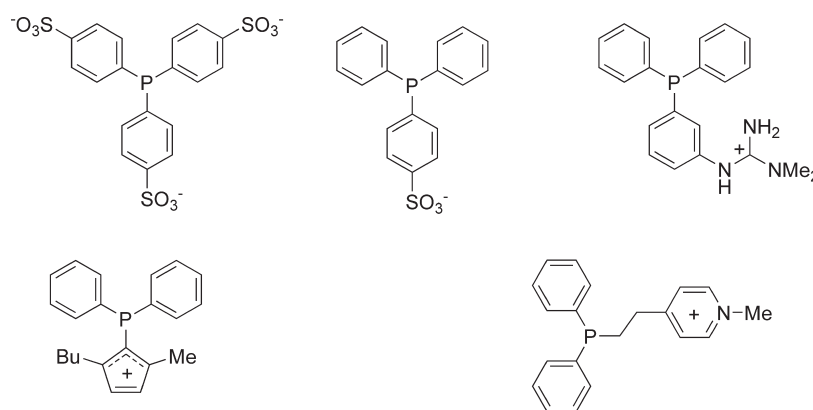


Figure 12. Some ionic liquid soluble phosphines.

extraction into another solvent, partitioning of solutes, including the catalyst, is a key process consideration. It is particularly important that the catalyst and the product are well separated, which usually means that it is preferable to have the product soluble in the extracting solvent and the catalyst not, so that it remains in the ionic liquid phase. This prevents the need for subsequent purification steps to remove the catalyst from the product. In many situations, such as when the starting materials only have limited solubility in the ionic liquid, it is preferable to have the extracting solvent present during the reaction itself. Hence, ionic liquids are often used in liquid–liquid biphasic systems.⁵⁴⁹

There are many examples in the literature that show that the most reliable way to have a catalyst that is not easily extracted from an ionic liquid is to prepare it in a salt form, usually by using a suitably derivatized ligand. Some of these ligands are even commercially available. The seminal Chauvin paper was the first to use this technique by preparing a hydroformylation catalyst from $[\text{Rh}(\text{CO})_2(\text{acac})]$ and either monosulfonated (TPPMS) or trisulfonated (TPPTS) triphenylphosphine ligands (Figure 12).⁵⁵⁰ Other ligands that have been used in this way include guanidinium-substituted,⁵⁵¹ imidazolium-substituted,⁵⁵² and pyridinium-substituted⁵⁵³ arylphosphines and 1,1'-bis(diphenylphosphino)cobaltocenium hexafluorophosphate.⁵⁵⁴

When the product and/or reactants are gases, a different set of concerns arise. The nonvolatile nature of most ionic liquids under standard operating conditions is a considerable potential process advantage that prevents the loss of the solvent for the reaction in the gas stream. However, set against this, the ionic liquids that are currently in widespread use are poor solvents for reactive gases such as O_2 , CO , and H_2 , which when combined with their high viscosities leads to mass transfer limits on reactivity. In an attempt to avoid these problems, the SILP concept has been developed.⁵⁵⁵

7.2. Hydrogenations

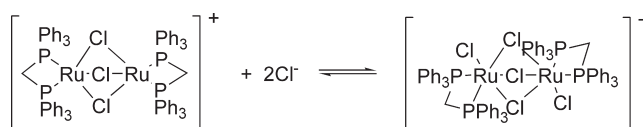
At first sight, the low solubility of H_2 in ionic liquids, which is similar to that in water,⁵⁵⁶ makes these unattractive solvents for these reactions. However, in biphasic reactions, the solubility of H_2 in the substrate-containing organic phase to some degree lessens this limitation, as do the high diffusion rates of this small molecule. Hence, there is an extensive literature on the use of ionic liquids as solvents for catalytic hydrogenations, most of which concentrates on catalyst immobilization in biphasic systems.^{12,549} The nature of the catalyst is the dominant factor in controlling catalytic processes, and knowing its identity is vital in being able to understand these reactions. In most of these investigations the homogeneous nature

of the catalyst has been assumed. However, as early as 2003 the possibility that the catalyst for hydrogenation reactions could be colloidal metal or nanoparticles was noted.⁵⁵⁷ The simplest test for this, the addition of mercury to the reaction to give a mercury–metal amalgam that does not catalyze the reaction, is unfortunately seldomly performed.

It is well-known that many catalysts are water sensitive and can be deactivated by low concentrations of water in ionic liquids.^{12,549} However, the role of water is not always negative. Dyson et al. found when attempting to use the water-soluble $[\text{Ru}_3(\text{CO})_{11}(\text{TPPTS})]^{3-}$ clusters for the hydrogenation of various alkenes in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ that the highly active aqueous catalyst showed little activity in the ionic liquid.⁵⁵⁸ The authors attributed this to a lower solubility of the complex in the ionic liquid compared to water. However, they later found that the hydrogenation activity of $[\text{Ru}_4(\eta^6\text{-C}_6\text{H}_6)_4(\text{OH})_4]^{4+}$ toward benzene is also nearly 10 times greater in water than in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$.⁵⁵⁹ They now proposed that this was due to the active role that water takes in hydrolyzing the catalytic tetramer to a dimer as part of the reaction cycle, which is inhibited by the low availability of water in the ionic liquid (see above). This interpretation is further supported by the finding of Rossi et al. that hydrated Ru nanoparticles were over 50 times more active than the anhydrous version as hydrogenation catalysts in ionic liquids.⁵⁶⁰ These authors also discovered a strong anion effect, with turnover frequencies (TOFs) increasing from 147 to 943 h^{-1} along the series $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$, $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$. They attributed this to mass transport limitations in the biphasic reaction system, but it is noteworthy that this is also the order of increasing water activity, and given the apparent need for water to activate the catalyst precursor, this explanation would seem more likely.

A similar inhibitory effect was found when the water-soluble catalyst $[\text{Ru}(p\text{-cymene})(\text{dppm})\text{Cl}][\text{OTf}]$ {dppm = 1,1-bis(diphenylphosphino)methane} was used in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ rather than water.⁵⁶¹ This was attributed to the lack of chloride dissociation from the catalyst, which is a vital part of the catalytic cycle. Catalytic activity could be restored by the addition of water (50%, v/v) to the ionic liquid or by prior substitution of the chloride by acetonitrile. A similar loss of activity was found for $[\text{Ru}(p\text{-cymene})(\text{dppm})\text{Cl}][\text{BF}_4]$ in a $[\text{C}_4\text{C}_1\text{im}]\text{X}$ {X = $[\text{CF}_3\text{CO}_2]$, $[\text{C}_1\text{SO}_4]$, $[\text{OTf}]$, $[\text{BF}_4]$, $[\text{NTf}_2]$, or $[\text{SnCl}_3]$ } ionic liquid.⁵⁶² However, when $[\text{Ru}(p\text{-cymene})(\text{dppm})\text{Cl}]\text{Cl}$ was used as the catalyst precursor, some catalytic activity was found in $[\text{C}_4\text{C}_1\text{im}][\text{CH}_3\text{SO}_4]$ and greater activity in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$, with very little in the remaining ionic liquids. Indeed, it was found that the addition of $[\text{C}_4\text{C}_1\text{pyrr}]\text{Cl}$ to the reaction mixture in $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$ also gave a catalytically active solution.

Scheme 38



This ruled out the possibility of a catalytic cycle that required chloride dissociation in the rate-limiting step, and the authors proposed that a different mechanism was operating in these ionic liquids compared to water. After careful kinetic investigations they proposed that it was the dissociation of the neutral *p*-cymene ligand that was occurring in the formation of the active catalyst, which was likely to be dimeric and in the presence of excess Cl^- ions was in equilibrium with more heavily chlorinated species (Scheme 38). This is one of very few examples in the literature of a clearly demonstrated mechanistic change upon using ionic liquids.

Differences in the solubilities of reactants and products in the ionic liquid can also have a pronounced effect on the catalytic activity. For example, Dupont et al.⁵⁶³ found that the Pd nanoparticle catalyzed partial hydrogenation of 1,4-butadiene to butene was far more selective in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ compared to $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$. The much higher solubility of alkenes in the $[\text{PF}_6]^-$ ionic liquid likely led to the reported 3-fold higher production of the over-hydrogenated product butane. Curiously, in this system, the addition of water had no effect, despite the likely reduction in alkene solubility that would result. The same authors reported higher activity for the partial hydrogenation using Ru nanoparticles prepared by controlled decomposition of $[\text{Ru}(\text{cod})(\text{cot})]$ (cod = 1,5-cyclooctadiene, cot = 1,3,5-cyclooctatriene) in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ over $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$;⁵⁶⁴ however, results with other substrates were somewhat mixed, and high conversions rendered interpretation of relative ionic liquid effects difficult.

Similarly, a number of ionic liquids were screened by Dyson et al.⁵⁶⁵ for the hydrogenation of styrene using the ionic cluster $[\text{H}_3\text{Os}_4(\text{CO})_{12}]^-$. While no clear solvation effect appears in these results, the more viscous ionic liquids, based on the $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}]^+$ cation, yielded lower TOFs, while the most active system used $[\text{C}_8\text{C}_1\text{pyrr}][\text{BF}_4]$, which was the only solvent found to completely dissolve the substrate.

The importance of enantioselective catalysis to pharmaceutical synthesis has led to many attempts to use ionic liquids for these reactions.^{12,549} Feng et al. screened a variety of ionic liquids for a Rh-catalyzed enantioselective hydrogenation of enamides.⁵⁶⁶ The results show that adding alcohols or water to the ionic liquid increases both the reaction rate and enantiomeric excess (ee) over those found in the ionic liquid alone. However, there is no clear trend among the ionic liquid anions with regard to hydrophobicity or basicity, with $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ outperforming $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ substantially, while little difference was seen between wet $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ and wet $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$. The longer chain $[\text{C}_8\text{C}_1\text{im}]^+$ cations also yielded superior reaction media. Selectivity differences were more marginal, with $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]/\text{iPOH}$ or $[\text{C}_8\text{C}_1\text{im}][\text{BF}_4]/\text{iPOH}$ mixtures generally providing the same ee as pure MeOH, though $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ did show a substantial drop in selectivity. The results across a series of catalyst complexes were even more confused, leading the authors to draw no conclusions based on solvent effects alone. It would appear that the primary effect of adding the water or alcohol is to prevent the decomposition of the catalyst into a nonchiral colloidal form. Furthermore, specific interactions between the protic (alcohol or water) cosolvent and the basic enamide substrate were competing

with alcohol/anion hydrogen bonding, with the result that more basic anions yielded higher activity and (marginally) higher selectivity. It remains unclear how much of an effect the changing catalyst had on this competition.

Hydrogen solubility may also be responsible for these differences. Jessop et al. compared the hydrogenation of tiglic acid (which gives higher ee's at lower H_2 concentrations) with that of atropic acid (which gives higher ee's at higher H_2 concentrations) using $\text{Ru}(\text{O}_2\text{CMe})_2(\text{R-tolBINAP})$ in several ILs.⁵⁶⁷ At various H_2 pressures the ionic liquids were found to be generally inferior to MeOH for the hydrogenation of atropic acid, with the differences in the ee becoming smaller as the H_2 pressure was increased. For the tiglic acid system, the ionic liquids were generally superior at lower H_2 pressures, with the differences again disappearing at higher pressures. This indicates that while the H_2 solubilities are lower in the ionic liquids than in MeOH, the changing solubility with changing pressure is less substantial. This result was also obtained for acid substrates by DuPont, which found no difference between alcohol and ionic liquid solvents over a pressure of 100 bar.⁵⁶⁸ The effect of changing the ionic liquid on these systems is less clear, however, with the $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{NTf}_2]^-$ ionic liquids yielding higher ee's for tiglic acid hydrogenation than $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, despite the lower solubility of H_2 in the latter solvent.⁵⁶⁶ The same solvent ordering was found for the atropic acid reactions, perhaps indicating that solvent effects on the catalytic reaction itself were at least as important as H_2 solubility, with more basic solvents strongly hydrogen bonding to the carboxylic acid substrates and lowering the ee, regardless of the preference of the substrate for a higher or lower H_2 concentration.

Yinghuai et al. used several different ionic liquids for the asymmetric hydrogenation of ketones.⁵⁶⁹ Their results indicate that more hydrophobic (or less basic) anions yielded higher ee's. However, the authors used a rhodacarborane catalyst, and the most active ionic liquid employed a very special decaborate anion, so specific catalyst stabilization may be responsible. Li et al. deployed TPPTS-based Ru complexes in a variety of ionic liquids.⁵⁷⁰ Their results are quite complicated; while ionic liquids with $[\text{pTSA}]^-$ anions were slightly more active than $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ barely gave any conversion at all. The highest ee was obtained using $[\text{C}_4\text{C}_1\text{im}]^+$ as the cation instead of $[\text{C}_2\text{C}_1\text{im}]^+$, $[\text{C}_8\text{C}_1\text{im}]^+$, or $[\text{C}_{12}\text{C}_1\text{im}]^+$, indicating that perhaps substrate interactions with the hydrophobic part of the ionic liquid (the cation side chain) have an effect on the ee, possibly through diffusion control. It is interesting that for this system the more hydrophilic (more basic anion) ionic liquids were generally superior, in contrast to the results obtained by Yinghuai.⁵⁶⁹

Lin et al. used 2-propanol/ionic liquid mixtures and a $\text{Ru}(\text{BINAP})(\text{DPEN})\text{Cl}_2$ catalyst for the asymmetric hydrogenation of ketones.⁵⁷¹ They found that $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ performed poorly when compared to $[\text{C}_3\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$. They proposed two possible explanations for this discrepancy. The first was that the relatively more nucleophilic $[\text{PF}_6]^-$ and $[\text{BF}_4]^-$ ions could be reducing the catalyst's efficiency. However, while $[\text{BF}_4]^-$ has been shown to be considerably more coordinating, $[\text{PF}_6]^-$ and $[\text{NTf}_2]^-$ have much more similar coordinating abilities.¹⁴¹ Their second explanation was that the KOH cocatalyst could be deprotonating the C^2 position of the imidazolium ring, leading to the formation of NHCs, which could then poison the catalyst. Their finding that the use of $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{BF}_4]$ gives results similar to those of $[\text{C}_3\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$ supports this latter argument. Indeed, it is possible that the poisoning of homogeneous catalyst complexes by NHCs is responsible for many irregular catalytic findings in ionic liquids.

In the enantioselective reduction of diketones using an ionic Ru–BINAP derivative, water outperformed a series of ionic liquids in terms of ee.⁵⁷² The most striking differences between the various ionic liquids studied involved a significant cation effect; both $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ and $[\text{C}_4\text{pyr}][\text{NTf}_2]$ gave good ee's (78% and 85%, respectively), though not quite as high as that of water (95%), while on switching to phosphonium ionic liquids the ee dropped to 2–3%. The anion effect was more marginal as changing the anion from $[\text{PF}_6]^-$ to $[\text{NTf}_2]^-$ to $[\text{BF}_4]^-$ for $[\text{C}_4\text{C}_1\text{im}]\text{X}$ raised the ee from 75% to 78% to 86%, respectively. The slightly more basic anions seem to favor the selectivity, while more acidic cations disfavor the reaction. This could be an ionic liquid specific effect as the ionic catalyst prefers minimal hydrogen bond donation from the solvent, either by removing it from the cation or by suppressing it with the anion (see above). When 10% water was added to $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, the ee dropped from 86% to 13%, which would support this observation. However, this does leave the origin of the higher ee in water itself unexplained. The authors attribute these effects to residual Cl^- in the ionic liquid poisoning the catalyst. Residual Cl^- from the ionic liquid precursor synthesis has certainly been shown to reduce catalytic activity for Ru-catalyzed hydrogenations, but it is unclear how this explains the effect of water addition to $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$.⁵⁷³ This may be a peculiar effect of water with this hydrophobic ionic liquid, as MeOH/ionic liquid mixtures did not show much deviation from normal mixing behavior in other studies using Ru–BINAP derivatives,^{574,575} although $[\text{BF}_4]^-$ ionic liquids were found to give higher ee's than $[\text{PF}_6]^-$ equivalents in these studies also. Interestingly, the $[\text{PF}_6]^-$ ionic liquids gave rates superior to those of either $[\text{BF}_4]^-$ ionic liquids or MeOH,⁵⁷⁵ suggesting that coordination of the anion to the metal center could be responsible for both these trends. Additionally, the ee difference was greater for esters with electronegative substituents, which suggests that the anion effects could also arise from solvation of the substrate rather than the catalyst. Strong solvent–solute interactions between ionic liquids and carbonyls have been shown to elevate boiling points and also affect the selectivity of heterogeneously catalyzed hydrogenations, where the catalyst solvation is not an issue.⁵⁷⁶ This would serve to further support the predominance of these effects for many types of catalytic reactions. However, the anion coordination effect on catalysts has been proposed for other asymmetric hydrogenation reactions, including for the reduction of imines wherein the ee improved from 30% to 78% upon changing from the more coordinating $[\text{BF}_4]^-$ anion to the very noncoordinating $[\text{BARF}]^-$.⁵⁷⁷ It is, of course, possible, even likely, that both catalyst coordination and substrate solvation are occurring in these systems.

Ionic liquids can sometimes provide more thermostable environments for catalysts, enabling an increase in reaction rate without a decrease in enantioselectivity. For example, in the hydrogenation of trimethylindolenine several ionic liquids were found to be inferior to toluene for ee at 50 °C (56–76% compared to 90%), but superior results were obtained at higher temperatures (ee increased to 86%).⁵⁷⁸ This effect was attributed to a drop in viscosity, which could inhibit gas-to-liquid mass transport, at higher temperatures. Hardacre^{12b} concluded that the high viscosity of the ionic liquids may have led to poor transport of O_2 into the liquid and therefore enhanced the robustness of this air-sensitive catalyst. It is intriguing that the high viscosity of ionic liquids—so often a drawback—might enhance catalyst stability. O_2 is also known to be very poorly

soluble in ionic liquids,^{56b} and this may further increase the lifetime of air-sensitive catalysts. Effects of the low solubilities of permanent gases have been seen in the reduction in the rates and increased selectivities of heterogeneous hydrogenations with Pd/C.⁵⁷⁹

Supported ionic liquids also offer the opportunity to fine-tune the catalyst loading or acid concentration. For example, the Rh-catalyzed hydrogenation of 1,3-cyclohexadiene showed greater activity when $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]/\text{HBF}_4$ was used instead of $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]/\text{H}_3\text{PO}_4$.⁵⁸⁰ The relative basicities of the ionic liquid anions allow for fine-tuning of H^+ activity in this system. The functionalized ionic liquid $[(\text{HO}_3\text{S})^+\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ was sufficiently acidic to not require the addition of another acid.

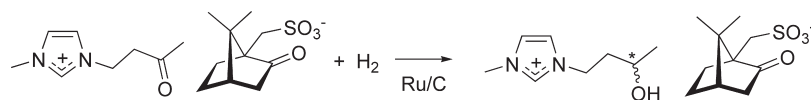
For the Pd-catalyzed hydrogenation of citral using various silica-supported ionic liquids, the choice of ionic liquid greatly affected both the rate and selectivity, with the main product reversing when different ionic liquids were used.⁵⁸¹ The highest activity was reported in $[\text{C}_4\text{pyr}][\text{BF}_4]$ (151 h^{-1} , compared to 35 h^{-1} in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$), but curiously, the primary product was different for the reaction in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ (citronellal) compared to $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ (dihydrocitronellal), though the activity was slightly higher. The authors attribute this selectivity difference to the higher H_2 solubility in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, which is reasonable, but this conflicts with the higher activity (60 h^{-1}) observed in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$. The hydrogenation of cinnamaldehyde using supported Pd nanoparticles in various Si-supported ionic liquids^{582,583} showed a limited effect of anion selection, beyond a poor result when using $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$, which is possibly related to Pd–NHC formation.⁵⁸⁴ This supposition is supported by the findings of Hou et al., who reported that the yield of the Pd nanoparticle catalyzed hydrogenation of cyclohexene decreased from 96% to 5% when $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{PF}_6]$ was replaced by $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$.⁵⁸⁵

Selectivity of the asymmetric hydrogenation of benzylacetone by $\text{RuCl}_2(\text{TPPTS})_2[(S,S)\text{-DPENDS}]$ in $[\text{C}_n\text{C}_1\text{im}][\text{pTSA}]$ ionic liquids was found to be dependent on the alkyl chain length of the cation, with ee decreasing from 71.8% for $[\text{C}_2\text{C}_1\text{im}]$ to 59.9% for $[\text{C}_{12}\text{C}_1\text{im}]$.⁵⁸⁶ The authors also reported that the addition of water improved the chemoselectivity, which indicates that the dependence on the alkyl chain length may also be linked to the water content, with the more hydrophobic ionic liquids performing more poorly. The same result was obtained for the *R,R*-based ligand where the ee dropped from 80.3% for $[\text{C}_2\text{C}_1\text{im}][\text{pTSA}]$ to 7.7% for $[\text{C}_{16}\text{C}_1\text{im}][\text{pTSA}]$.⁵⁸⁷

The Rh-catalyzed hydrogenation of chalcone in a large variety of ionic liquids revealed a large acceleration in those containing alkyl sulfate anions.⁵⁸⁸ Conversions were generally much higher in ionic liquids with more hydrophilic anions (such as the alkyl sulfates or $[\text{BF}_4]^-$), and a slight drop-off with an increase in the alkyl chain length of imidazolium cations was also observed, which is consistent with this being a water effect. However, since the reaction utilizes a base cocatalyst, and the selectivity in all ionic liquids is higher than in molecular solvents, it is likely that the more basic anions are accelerating the reaction. The authors also observed that the alkyl sulfate and $[\text{BF}_4]^-$ ionic liquids had lower viscosities, but this trend would not explain the disconnect between ionic liquids and molecular solvents.

The close association of the cations and anions of ionic liquids was demonstrated in the hydrogenation of the cation of $[N\text{-(3'-oxobutyl)-}N\text{-methylimidazolium}][(R)\text{-camphorsulfonate}]$ with a ruthenium on carbon catalyst (Scheme 39).⁵⁸⁹ The ionic liquid was highly viscous, and the reactions were conducted in the

Scheme 39



presence of ethanol. It is very interesting to note that the ee for the reaction at first increased with the concentration of the ionic liquid in the ethanol, but reached a maximum and then declined. This was interpreted as a consequence of an increasing concentration of ionic liquid ion pairs forming in solution, but that at higher concentrations higher order clusters were forming, which were less selective chiral transfer agents.

Ionic liquids have been shown to have striking effects on hydrogenations, even when used as additives. For the Ru-catalyzed asymmetric hydrogenation of β -keto esters both the rate and ee of the reaction in methanol were greatly affected by the addition of ionic liquids, with the ee dropping considerably in the presence of $[\text{C}_2\text{C}_1\text{im}][\text{NTf}_2]$ and increasing slightly when $[(\text{HO})^2\text{C}_2(\text{C}_1)_3\text{N}][\text{NTf}_2]$ was added.⁵⁹⁰ This stabilization effect also led to enhanced recyclability of the catalyst system. This stabilization of the catalyst was also seen in the Ru–BINAP-catalyzed hydrogenation of β -keto esters in $[(\text{C}_2)_3\text{C}_n\text{N}][\text{NTf}_2]$ ionic liquids.⁵⁹¹ In this study, the length of the alkyl chain did not affect the ee of the reaction on the first run, but the use of longer alkyl chains led to dramatically improved performance on subsequent runs.

While the formation of metal colloids from organometallic metal complexes can be seen as a problem for catalysis in ionic liquids, metal nanoparticle catalysts have been extensively investigated as catalysts in ionic liquids. The Rh nanoparticle catalyzed hydrogenation of styrene was examined in a variety of ionic liquids.^{592,593} The selectivity (ethylbenzene/ethylcyclohexane) was found to vary widely with both the cation and anion. For $[\text{C}_4\text{C}_1\text{im}]\text{X}$ the selectivity was found to vary with X in the order $[\text{N}(\text{CN})_2]$ (100%) > $[\text{NTf}_2]$ (70%) > $[\text{PF}_6]$ (40%) > $[\text{BF}_4]$ (8%), while for $[\text{cat}][\text{NTf}_2]$ the relative ordering was $[\text{C}_4\text{C}_1^4\text{pyr}]$ (85%) > $[\text{C}_4\text{C}_1\text{pyrr}]$ (70%) = $[\text{C}_4\text{C}_1\text{im}]$ (70%) > $[(\text{OH})^2\text{C}_2\text{C}_{12}(\text{C}_1)_2\text{N}]$ (40%). Although H_2 solubility data are not available for all of these ionic liquids, it appears that overhydrogenation is most prevalent in the ionic liquids with the highest H_2 solubility. Incorporation of a hydroxyl functionality into the side chain of a variety of ionic liquid cations was found to enhance the catalytic rate of the same reaction catalyzed by Rh nanoparticles with selectivities approaching 100% in all cases.⁵⁹⁴ This particular result could be due to the likely increased diffusivity of H_2 in these ionic liquids, as the selectivity for acetylene hydrogenation was lower for Pd nanoparticles in the same solvents compared to $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ due to overhydrogenation.⁵⁹⁵ In addition, for the Ru nanoparticle catalyzed hydrogenation of toluene in $[\text{C}_4\text{C}_1\text{im}]\text{X}$ and $[\text{C}_{10}\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{NTf}_2] \text{ and } [\text{BF}_4]\}$, there was a significant drop in activity when $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ was employed.⁵⁹⁶ The $[\text{BF}_4]^-$ ionic liquids performed poorly in all of these nanoparticle studies, and it is possible that breakdown of the $[\text{BF}_4]^-$ anion, or the poisoning of the catalyst surface by this anion, is the root cause for all of these findings.

In a heterogeneously catalyzed reaction mass transport is often an issue. This was highlighted in a study by Wasserschied wherein the activity of a ruthenium on carbon catalyst suspended in a single-phase ionic liquid system was twice as high as for a biphasic ionic liquid/organic solvent system, but the selectivity for the biphasic system was near 80% compared to 40–50% for the single-phase approach.⁵⁹⁷ Removing diffusion limits can eliminate some ionic liquid effects, as for the hydrogenation of citral

using Pd nanoparticles in a thin layer of ionic liquid coated on Si.⁵⁹⁸ In these studies, the activity in various ionic liquids was nearly the same, with a slight drop for $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ compared to $[\text{C}_4\text{C}_1\text{im}][\text{N}(\text{CN})_2]$. The same authors did report a small cation effect on the selectivity of this reaction using Ru nanoparticles in $[\text{C}_n\text{C}_1\text{im}][\text{NTf}_2]$ ($n = 4$ or 6) ionic liquids.⁵⁹⁹

Gholami et al. performed an LSER analysis of the solvent effects on the synchronous hydrogenation of cyclohexene and acetone by Pt/ Al_2O_3 in mixtures of the ionic liquid (2-hydroxyethyl) ammonium formate with ethanol and 2-propanol at various mole fractions.⁶⁰⁰ The authors found that the rates of both hydrogenation reactions increased with increasing π^* value, and the selectivity favors cyclohexene hydrogenation at higher π^* .

7.3. Oxidations

As well as being included in the general reviews of catalysis in ionic liquids,¹² a more specific review of oxidations in ionic liquids is available.⁶⁰¹ Ionic liquids have a number of advantages as solvents for oxidations, particularly when either Br^- anions or pyridinium cations are employed, as these are capable of oxygen transfer. More generally, ionic liquids have been found to stabilize the free radicals necessary for many oxidation mechanisms.⁶⁰² Also, a wide variety of ionic or peroxide oxidants can be used in ionic liquids, and many exhibit increased stability. Many ionic liquids are stable under oxidizing conditions and therefore constitute ideal solvents for this class of reactions.⁶⁰³ However, it should be noted that oxidation of imidazolium cations has been observed,⁹⁴ and unless this possibility has been explicitly considered, the formation of these oxidation products cannot be excluded. One of the main attractions of ionic liquids as solvents for this class of reactions is the selectivities that they can give; e.g., they have been found to promote oxidations of alcohols to aldehydes, but suppress the overoxidation of these aldehydes to acids.^{94,95} Ionic liquids can also be specially tailored to support ionic liquid modified oxidants; e.g., periodinanes have been supported by ionic liquids for the oxidation of alcohols in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$.⁶⁰⁴ Peracids⁶⁰⁵ and iodoacids⁶⁰⁶ have also been supported for use in ionic liquids.

Both Ley⁶⁰⁷ and Welton⁹⁴ performed early oxidation of alcohols in ionic liquids catalyzed by tetra-*N*-propylammonium perruthenate (TPAP) with the oxidant *N*-methylmorpholine *N*-oxide (NMO). While the reaction proceeded in all cases to high conversion with catalyst recycling, loss of catalytic activity was generally observed after 2–3 recycles. This was particularly evident when $[(\text{C}_4)_4\text{N}]\text{Br}$ was used as the ionic liquid (and oxidation promoter).⁶⁰⁷ Since the systems were biphasic, this could be an indication of phase transfer activity, which ionic liquids are known to promote.³⁰² Oxidations with molecular oxygen as the oxidant could be carried out using this catalyst system, but it was found that an organic cosolvent and vigorous agitation were necessary to maintain the reaction. This is a direct consequence of the extremely low solubility of O_2 in ionic liquids⁶⁰⁸ coupled with their generally poor mass transport properties.⁶⁰⁹

As with other forms of catalysis, oxidations can be affected by the presence of impurities in ionic liquids. For example, Zhang et al. reported that while benzyl alcohol is oxidized to benzaldehyde with

NaOCl in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ at room temperature (even without TEMPO), the reaction proceeded to much higher conversion and selectivity using a cyclic guanidinium ionic liquid, $[\text{C}_6(\text{C}_1)_3\text{cy-gu}][\text{PF}_6]$.⁶¹⁰ While it is possible that the guanidinium ion is able to stabilize free radicals much more easily than imidazolium salts, it seems more likely that residual guanidine from the synthesis of the ionic liquid is promoting the reaction. The base 4-(dimethylamino)pyridine (DMAP) has been clearly demonstrated to be a promoter for the Cu(II)-catalyzed oxidation of alcohols using TEMPO in $[\text{C}_4\text{C}_1\text{pyrr}][\text{PF}_6]$.⁶¹¹ A mechanism was proposed by which the base deprotonates the alcohol to promote its oxidation. Hence, residual base in ionic liquids is likely to be active in oxidation reactions.

The effect of varying the ionic liquid solvent on alcohol oxidations has received some attention. The nature of the anion does seem to play a major role in some oxidation catalyses in ionic liquids. Wolfson noted that Cl^- promoted oxidation of aliphatic alcohols using a Ru(II) catalyst more than OH^- , indicating that this is not a simple matter of basicity.⁶¹² The destructive nature of OH^- at high concentrations could also have been responsible for some catalyst degradation. This conclusion is supported by Seddon,⁹⁵ who found that the oxidation of benzyl alcohol with O_2 catalyzed by $\text{Pd}(\text{OAc})_2$ proceeded in a variety of imidazolium chlorides and $[\text{BF}_4]^-$ salts, but not in $[\text{C}_4\text{C}_1\text{im}]\text{Br}$, despite the oxidation-promoting properties of Br^- .⁶¹³ In each of these cases, the removal of byproducts improved the yield. $[(\text{C}_4)_4\text{N}]\text{Br}$ was used as a solvent for the PdCl_2 -catalyzed oxidation of indan-1-ol;⁶¹⁴ however, side reactions limited this reaction to low selectivity. It is noteworthy that this reaction did not proceed if $[(\text{C}_4)_4\text{N}]\text{Cl}$ was used as a solvent; clearly the Br^- ion is playing a key role as a catalyst promoter. It is unclear why the contradiction exists between these results. The role of Br^- as a promoter in ionic liquids has been established in other systems as well, such as for the oxidation of primary and secondary aliphatic or benzylic alcohols in $[\text{C}_2\text{C}_1\text{im}][\text{BF}_4]$ using an arylidene diacetate bound to an imidazolium ion. In this case, catalysis took place with or without a metal catalyst, indicating catalysis by bromide impurities remaining in the ionic liquid.⁶¹⁵ Li et al.⁶¹⁶ examined the oxidation of 2,3,6-trimethylphenol with molecular oxygen using hydrated CuCl_2 in a wide variety of ionic liquids. The best results were obtained when using $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ (82%), with the highly coordinating $[\text{HSO}_3]^-$, $[\text{NO}_3]^-$, Cl^- , and Br^- all yielding selectivities of less than 35%. The ionic liquids had drastic effects, even when used as a cosolvent in 1-hexanol.⁶¹⁷ Under the conditions of these reactions, these latter anions will lead to the formation of different new complex ions, and it is probably these ions that lead to the different selectivities. It is particularly notable that $[\text{NO}_3]^-$, Cl^- , and Br^- , all of which are likely to form $[\text{CuX}_4]^{2-}$ ions, also required longer reaction times to achieve complete reaction. This effect will be entirely independent of the observed cation effect, which the authors suggest may have arisen from 2,3,6-trimethylphenol solubilities.

In contrast, methyltrioxorhenium/ H_2O_2 oxidation of aromatic aldehydes and ketones was found to exhibit little discernible anion effect between $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$.⁶¹⁸ In a series of detailed studies Abu-Omar examined the kinetics and thermodynamics of methyltrioxorhenium/ H_2O_2 oxidations in a variety of ionic liquids and found that the reaction rate was independent of the ionic liquid type when dry, but instead depended linearly on the concentration of water in the ionic liquid.⁶¹⁹ This observation that an impurity (water) can be solely responsible for effects on a reaction rate, when coupled with the observation that the concentration of that impurity in various ionic liquids is likely to vary with some other parameter, such as anion type in the case of water,²⁶ can lead to an apparent solvent effect (anion basicity) that is actually a proxy for the true cause of the observed results

(water concentration). The same authors found little solvent effect between various dry ionic liquids or CH_3CN for olefin epoxidation using the same catalyst;⁶²⁰ however, the addition of an equal volume of water increased the reaction rate 10-fold. This water effect could be particularly important when aqueous H_2O_2 is used as the oxidant.

In an attempt to facilitate its use as an environmentally benign oxidant, H_2O_2 has been used for several catalytic oxidations in ionic liquids.⁶²¹ Aqueous (30%) H_2O_2 was used with $[\text{C}_4\text{C}_1\text{im}]_4[\text{W}_{10}\text{O}_{23}]$ in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ to oxidize both aliphatic and benzylic alcohols.⁶²² The authors reported that only secondary alcohols were oxidized under these reaction conditions and achieved the selective transformation of 1-phenyl-1,2-diethanol into α -hydroxyacetophenone. This selectivity was not apparent when $[\text{C}_4\text{C}_1\text{im}]_3[\text{PO}_4(\text{W}(\text{O})(\text{O}_2)_2)_4]$ was used as the catalyst with H_2O_2 .⁶²³ All selectivity and most activity were lost when either Na_2WO_4 or Na_2MoO_4 was instead used as the catalyst; it can be conjectured that low catalyst solubility could be a problem for these sodium salts.

Water slightly enhanced both the rate and selectivity of OsO_4 -based catalyst systems for the asymmetric dihydroxylation of olefins in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$,⁶²⁴ either alone or when $t\text{-BuOH}$ was used as a third solvent component. Interestingly, switching to a more hydrophobic cation, $[\text{C}_8\text{C}_1\text{im}]^+$, decreased the efficiency, as did using a more hydrophilic anion, such as $[\text{BF}_4]^-$.⁶²⁵ It should be noted that although the concentration of water is often higher in these hydrophilic ionic liquids, they have been demonstrated to interact sufficiently strongly with water to be dehydrating agents for solutes when dry (see above).⁹⁷ Hence, these results are not contradictory.

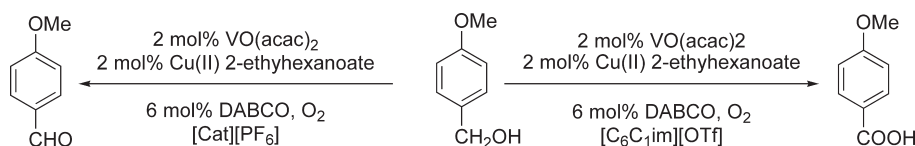
The Mo(VI)/ H_2O_2 -catalyzed oxybromination of phenylacetylene proceeded faster in ionic liquids than in the organic solvent CH_2Cl_2 .⁶²⁶ There was also a difference in selectivity among CH_2Cl_2 , $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, and $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$. This is consistent with results using vanadium(V),⁶²⁷ where the oxybromination selectivity increased with the hydrophobicity of the anion, from 58% in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ to >99% in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$. The authors attributed this result to the structure of the anion affecting the hydration of key intermediate species.

With aqueous H_2O_2 oxidations observed anion effects may also arise from changes in phase behavior. This was proposed to be the cause of differences in the rates of the oxidation of thiols to sulfones by acetic acid– H_2O_2 in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ and $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$.⁶²⁸ The much slower rate of the reaction when $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ was used was explained by the formation of a biphasic aqueous ionic liquid/tetradecane system with $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ rather than the triphasic $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ /tetradecane/water system. The authors concluded that this exclusion of water from the ionic liquid phase led to the large difference in reactivity.

Many aqueous H_2O_2 oxidations reported in the literature are in conjunction with water-sensitive ionic liquids. The decomposition of wet ionic liquids to release byproducts, such as HF, which can catalyze side reactions has been pointed out for olefin epoxidations,⁶²⁹ where $[\text{BF}_4]^-$ or $[\text{PF}_6]^-$ ionic liquids underperformed compared to more hydrolytically stable ionic liquids. Problems in catalysis associated with this were first noted by Dupont,⁶³⁰ and its effect on catalytic oxidations has been reviewed by Muzart.⁶⁰¹

The Baeyer–Villiger oxidation of cyclohexanone with aqueous H_2O_2 can be performed in biphasic water/ionic liquid systems using a range of ionic liquids of various hydrophilicities.⁶³¹ The catalyst in this study was $[\text{Pt}(\text{dppb})(\mu\text{-OH})_2][\text{BF}_4]_2$ [dppb = 1,4-bis(diphenylphosphino)butane]. Interestingly, the hydrophilic $[\text{C}_4\text{C}_1\text{im}]\text{X}$ {X = $[\text{BF}_4]$ or $[\text{OTf}]$ } produced lower yields (ca. 5% in 5 h) than the hydrophobic organic solvents investigated (CH_2Cl_2 or CHCl_3), but this could be increased to an 8% yield in 1 h in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and

Scheme 40



24% in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$, which is greater than those in the organic solvents. Very minor fluctuations in performance were observed by varying the alkyl chain length of $[\text{C}_n\text{C}_1\text{im}][\text{NTf}_2]$ ($n = 2, 4, \text{ or } 6$), with $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ proving to be the best ionic liquid. Since neither the longer chain lengths on the cation nor the more hydrophobic anion in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ proved more effective, it seems unlikely that these results are attributable to simple phase behavior in the biphasic systems. Either specific anion–substrate or specific anion–catalyst interactions might provide a more likely explanation. In this case, matching the anion of the ionic liquid anion to the catalyst did not provide superior performance, as it had for $\text{Co}(\text{PF}_6)_2$ -catalyzed oxidations in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$.⁶³²

Similarly, the selection of ionic liquid had little effect on the PdCl_2 -catalyzed oxidation of styrene with aqueous H_2O_2 in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ or $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$.⁶³³ Several reaction parameters were optimized, with a significant effect on the reaction rate and selectivity if the amount of H_2O_2 or temperature was changed. The authors also noted that adding an inert gas created a noticeable effect on the selectivity, by suppressing the competing oxidation via dissolved O_2 . The lack of a noticeable ionic liquid effect on this reaction could indicate that the solvation of the substrate (styrene) or the relatively simple catalyst was minimal. This same catalytic system can, however, be improved upon when carboxylic acid functionalities are introduced into the alkyl side chains of the imidazolium cations.⁶³⁴

Molecular oxygen is also recognized to be a green oxidant. The nonflammability of many ionic liquids makes them very attractive solvents for reactions of O_2 . The active role played by some ionic liquids was confirmed for the CuCl_2 -catalyzed oxidation of 2,3,6-trimethylphenol with O_2 , which was performed in 1-butanol with and without $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$. The authors established the in situ formation of the active species $[\text{C}_4\text{C}_1\text{im}]_4[\text{Cu}_4(\mu^4\text{-O})\text{Cl}_{10}]$,⁶³⁵ presumably via $[\text{C}_4\text{C}_1\text{im}][\text{CuCl}_4]$, while substitute ionic liquids or copper salts proved less effective.⁶³⁶ The fact that a 1:1 molar ratio of CuCl_2 to $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ was particularly effective led Muzart⁶⁰¹ to conclude that the ionic liquid is once again acting as a phase transfer catalyst, highlighting the many routes by which ionic liquids can promote chemical reactions.

Ragauskas reported the vanadium/copper(II)-catalyzed aerobic oxidation of activated primary alcohols to aldehydes and carboxylic acids, with 2-ethylhexanoate added as a cocatalyst (Scheme 40) in four ionic liquids.⁶³⁷ In most cases the aldehyde was the preferred product, with the aldehyde/acid selectivity decreasing in the order $[\text{C}_4\text{C}_1\text{pyr}][\text{PF}_6]$ (89%), $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ (74%), and $[\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]$ (66%) for the reaction of 4-methoxybenzyl alcohol. However, in $[\text{C}_6\text{C}_1\text{im}][\text{OTf}]$ the selectivity was reversed (aldehyde/acid selectivity 13%). The $[\text{C}_6\text{C}_1\text{im}][\text{OTf}]$ would be expected to be the more dehydrating ionic liquid if dry, but would have the greatest concentration of water if in equilibrium with moisture in the air. This latter explanation fits closest with the results.

There has been much focus on preparing transition-metal catalysts in forms that prevent their extraction from ionic liquids in biphasic systems.^{12,549} For the $\text{Cu}(\text{I})/\text{TEMPO}$ -mediated oxidation of benzyl alcohol⁶³⁸ in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, this was achieved by preparing a $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ -derivatized bipyridine ligand.⁶³⁹ However,

substantial differences in catalytic activity were observed when the product was removed by distillation (only 2% loss of activity over five cycles) or Et_2O extraction (19% loss). This is likely due to extraction of TEMPO from the ionic liquid by Et_2O , which has been observed in other systems.⁶⁴⁰ It has been shown that the loss of TEMPO via extraction can also be avoided by derivatizing it with an ionic liquid functionality, such as a $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ ester.⁶⁴¹ In this case, TEMPO was retained in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and the oxidation of various alcohols was accomplished with NaOCl as the oxidant and KBr used as a promoter. This system provided recyclability superior to that of unmodified TEMPO and similar activity.

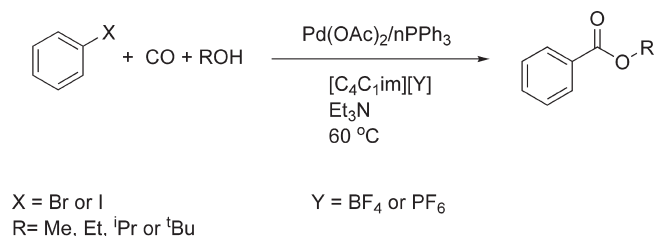
Han et al. examined the effect of scCO_2 on the PdCl_2 -catalyzed oxidation of 1-hexene by molecular oxygen (60–180 bar) in a $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]/\text{MeOH}$ mixture.⁶⁴² Supercritical fluids are often used as extraction solvents for IL processes,⁶⁴³ but their effect on reaction rates and selectivities is less well-known. In this study, the authors reported that the CO_2 pressure had a negligible effect on the reaction rate, but the selectivity toward 2-hexanone was increased from 64% to 92% when 125 bar of CO_2 was added to the ionic liquid. The authors attributed this change in selectivity to increased O_2 diffusivity in the presence of CO_2 , but the reason for the minimal effect on the (already high) conversion, or the role of CO_2 as a cosolvent, was not determined. Seddon reported an increase in the conversion of the oxidation of ethylbenzene using molecular O_2 in $[\text{C}_6\text{C}_1\text{im}][\text{BF}_4]$ when perfluorohexane was added as a cosolvent.⁹⁵ Since both perfluorohexane and CO_2 will increase the concentration of O_2 in the IL phase, it is unclear why the CO_2 system did not demonstrate a similar increase in activity, though the biphasic nature of each system could lead to large differences in phase transfer behavior.

Biphasic systems can often obscure solvent effects, with phase transfer being the dominant feature. For the metal-catalyzed H_2O_2 hydroxylation of benzene, in which the oxidant was always in a separate phase from the substrate and catalyst, no great effect was observed when a variety of metal salts were employed in $[\text{C}_1\text{C}_8\text{im}][\text{PF}_6]$, with minimum conversion and selectivity being for cobalt bis-(dodecanesulfonate), 35% and 85%, respectively, and the maximum being for iron tris(dodecanesulfonate), conversion 54% and selectivity 90%.⁶⁴⁴ Just as great an effect was seen for iron tris(dodecanesulfonate) catalyst on changing the ionic liquid, the conversions and selectivities being for $[\text{C}_8\text{C}_1\text{im}][\text{PF}_6]$ 39% and 85%, for $[\text{C}_{10}\text{C}_1\text{im}][\text{BF}_4]$ 40% and 87%, for $[\text{C}_8\text{C}_1\text{im}][\text{BF}_4]$ 44% and 90%, for $[\text{C}_{10}\text{C}_1\text{im}][\text{PF}_6]$ 51% and 89%, and for $[\text{C}_8\text{C}_1\text{im}][\text{PF}_6]$ 54% and 89%. It appears that both the cation and the anion are influencing these outcomes, probably through mass transfer effects. Similarly, the increased rates of the RuCl_3 -catalyzed oxidation of 1,2-dimethylcyclohexane when either $t\text{BuOOH}$ is substituted for H_2O_2 or CH_2Cl_2 is added as cosolvent are probably due to the reduction of mass transfer limitations.⁶⁴⁵ This is in contrast to the use of single-phase ionic liquid–organic mixtures for the oxidation of hydrocarbons using a soluble oxidant where any effect of the choice of organic solvent is less noticeable.⁶⁴⁶

7.4. Carbonylations and Hydroformylations

For the acid-catalyzed carbonylation of toluene in acidic $[\text{C}_n\text{C}_1\text{im}]\text{Cl}-\text{AlCl}_3-\text{HCl}$ $[X(\text{AlCl}_3) = 0.67; n = 2, 4, 6, 8, 10, \text{ or } 12]$

Scheme 41



benzyl] ionic liquids, the rate of carbonylation was found to depend on the length of the alkyl group on the imidazolium cation, though the absorption of CO into the ionic liquid appears to be independent of this parameter.⁶⁴⁷ This result is similar to findings for AlCl_3 dissolved in $[\text{NTf}_2]^-$ ionic liquids for carbonylation where a strong dependence on the cation was determined and linked to the trade-off between CO and substrate solubility in the ionic liquid, with pyrrolidinium ionic liquids outperforming imidazolium ionic liquids.⁶⁴⁸

Pd-catalyzed carbonylations of halogenoarenes have also been explored in ionic liquids, although side reactions often compete with the desired reaction. For example, $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ was found to be an excellent solvent for the carbonylative three-component coupling reaction of iodoarenes with terminal alkynes, while $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ proved unsuitable due to competitive Sonogashira coupling.⁶⁴⁹ The authors attributed this to the lower viscosity $[\text{NTf}_2]^-$ promoting Pd–NHC complex formation, which is always a possibility for many catalytic applications using imidazolium ionic liquids.⁵⁸⁴ Pd–NHC complexes have been specifically utilized to enhance carbonylations,⁶⁵⁰ but better reactivities are achieved when PPh_3 is added.⁶⁵¹ $[\text{Pd}(\text{OAc})_2]/4\text{PPh}_3$ and $\text{Pd}(\text{PPh}_3)_2$ have been used as the source of the catalyst for alkoxycarbonylation (Scheme 41) ionic liquids,⁶⁵² with some rate enhancement reported for the ionic liquids over organic solvents. The authors attributed this enhancement to ionic liquid stabilization of the polar transition state for the reaction. However, the effect of changing the ionic liquid type was rather mixed. Initially, deposition of palladium metal and deactivation of the catalyst solutions, which prevented efficient recycling, were observed. This was avoided by using 20 equiv of PPh_3 , with respect to the Pd, resulting in solutions that could be recycled.

Using a water-soluble Pd–TPPTS complex, the carbonylation of aryl iodides in several ionic liquids has been accomplished.⁶⁵³ In this study, the hydrophilic ionic liquids $\{[\text{C}_4\text{C}_1\text{im}][\text{pTSA}], [\text{C}_4\text{C}_1\text{im}][\text{BF}_4]\}$ outperformed the more hydrophobic $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, with the hydrophilic ionic liquids providing activities similar to those of water-miscible solvents such as 1,4-dioxane and THF. The authors attributed this to higher solubility of the complex in the more hydrophilic solvents. The solubility concern with various catalytic complexes is an often overlooked reaction hindrance when using ligands of this type, as salts are often assumed to be fully soluble in all ionic liquids, which was not true in this case.

The CuCl-catalyzed oxidative carbonylation of methanol to form dimethyl carbonate has been carried out in a wide variety of ionic liquids, $[\text{C}_n\text{pyr}]\text{X}$ $\{\text{X} = [\text{PF}_6], [\text{BF}_4], \text{or Cl}\}$, $[\text{cat}][\text{BF}_4]$ $\{[\text{cat}] = [\text{C}_8\text{pyr}], [\text{C}_2\text{C}_1\text{im}], [\text{C}_8\text{C}_1\text{im}], \text{or } [\text{C}_4\text{C}_1\text{C}_1^2\text{im}]\}$, $[\text{cat}][\text{PF}_6]$ $\{[\text{cat}] = [\text{C}_8\text{C}_1\text{im}] \text{ or } [\text{C}_4\text{C}_1\text{C}_1^2\text{im}]\}$, or $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$.⁶⁵⁴ For the $[\text{cat}][\text{BF}_4]$ ionic liquids the observed conversions were in the order $[\text{C}_n\text{pyr}]^+ > [\text{C}_4\text{C}_1\text{C}_1^2\text{im}]^+ > [\text{C}_8\text{C}_1\text{im}]^+ > [\text{C}_2\text{C}_1\text{im}]^+$, suggesting that the hydrogen bond donor property of the ionic liquid is reducing the reactivity of the system. For the $[\text{C}_4\text{pyr}]\text{X}$ ionic liquids the order was $[\text{BF}_4] > \text{Cl} \gg [\text{PF}_6]$. This trend is more difficult to interpret. Under the reaction conditions in the chloride ionic liquids the CuCl

is expected to form $[\text{CuCl}_2]^-$ ions. Both $[\text{PF}_6]^-$ and $[\text{BF}_4]^-$ are far less coordinating ions and would not be expected to form similar complexes. However, if it were just a matter of Cu coordination, one would expect the order to be $[\text{PF}_6]^- > [\text{BF}_4]^- > \text{Cl}^-$. However, the authors used FTIR spectroscopy to confirm that the $[\text{PF}_6]^-$ anion was interacting strongly with CuCl and deactivating the catalyst. This suggests to us that there has been sufficient hydrolytic decomposition of the $[\text{PF}_6]^-$ anion to give fluoride-containing copper complexes.

$[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{\text{X} = [\text{PF}_6], [\text{BF}_4], \text{or Cl}\}$ and $[\text{C}_{16}\text{C}_1\text{im}]\text{Cl}$ ionic liquids have been used to synthesize symmetric urea derivatives from amines and CO_2 .⁶⁵⁵ No reaction was seen at all in the latter ionic liquid. For cyclohexylamine the isolated yields were in the order $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ (98%) $> [\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ (84.5%) $> [\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ (56.6%). Since no dehydrating agent was added to the reaction mixture, the ionic liquid may be serving this role in a way similar to that previously observed for oxidations,^{94,95} with the more hydrophilic anions being more efficient dehydrating agents for the reaction. This ability to act as a dehydrating agent is not seen in traditional organic solvents and provides a clear advantage for ionic liquids. It was also reported that supported ionic liquids could accomplish this reaction (and duplicate the dehydrating effect), though in that paper the ionic liquid anion was not varied from $[\text{BF}_4]^-$.⁶⁵⁶ The SILP approach may improve the reaction by providing a greater surface area for gas absorption while maintaining the dehydrating properties of the hydrophilic ionic liquids. While this helpful dehydrating behavior is enhanced by using *hydrophilic* anions, it is also, although to a lesser extent, improved by using a more *hydrophobic* cation.⁶⁵⁷ It is worth noting that when the same group substituted a Pd/CO + O_2 system for the Rh/ CO_2 system described above, the ionic liquid effect on the yield was confused by decomposition, there was no selectivity effect between ionic liquids, and catalyst solubility proved to be a vital variable⁶⁵⁸ and the anion effect was completely reversed when acid-functionalized cations were employed.⁶⁵⁹ This anion effect can be taken to an extreme through the use of ionic liquids with the catalytically active methyl selenite anion, $[\text{SeO}_2(\text{OCH}_3)]^-$.⁶⁶⁰ In general, it is noteworthy that the effect of the anion on the reaction can be due to interactions within the catalytic cycle, with the catalyst, with the substrates, or through phase behavior and transport rate changes. The nature of the ionic liquid can play a determining role in any or all of these interactions and have a large effect on the overall catalytic efficiency of the system.

The anion effects on the alkoxycarbonylation of 4-iodotoluene by Pd(II) was explored using a wide range of $[\text{C}_{14}(\text{C}_6)_3\text{P}]\text{ILs}$.⁶⁶¹ The yield increased in the order $[\text{pTSA}]^-$ (0%), $[\text{SO}_4]^{2-}$ (28%), $[\text{PO}_4]^{3-}$ (33%), $[\text{BF}_4]^-$ (55%), Cl^- (60%), $[\text{N}(\text{CN})_2]^-$ (65%), $[\text{O}_2\text{C}_{10}\text{H}_{19}]^-$ (70%), $[\text{PF}_6]^-$ (73%), $[\text{NTf}_2]^-$ (75%), and Br^- (93%). Anionic complexes, such as $[\text{LPdX}]^-$ or $[\text{L}_2\text{PdX}]^-$, are the assumed reactive catalysts in these reactions. However, the results do not yield to a simple interpretation based upon the relative coordinating abilities of the different anions. The authors speculated that there may be a different mechanism in the bromide ionic liquid, but with little evidence to support this.

Hydroformylation of alkenes has been extensively studied in ionic liquids,^{12,549} and the effects of the reactant gas solubility, catalyst solubility, and substrate/product solubility as well as an in-depth discussion of the possible interactions between ionic liquids and catalyst complexes were recently covered in an extensive review on hydroformylations in ionic liquids.⁶⁶² Cole-Hamilton et al. reported that the choice of Rh/ligand catalyst had the biggest effect on the reaction efficiency, mostly due to solubility concerns.⁶⁶³ In terms of ionic liquid effects, longer chain alkyl groups on the $[\text{C}_n\text{C}_1\text{im}]^+$ cation

increased the reaction rate considerably, with conversions after 20 h increasing from 46.7% for $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ to 86.5% for $[\text{C}_8\text{C}_1\text{im}][\text{NTf}_2]$ or $[\text{C}_{10}\text{C}_1\text{im}][\text{PF}_6]$. For the $[\text{C}_4\text{C}_1\text{im}]^+$ ionic liquids the anion effect was quite strong, with the 46.7% conversion for $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ dropping to 6.4% in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$. This could be due to some hydrolytic decomposition of the $[\text{PF}_6]^-$ or simply a matter of the greatly lower viscosity of $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$, which should vastly increase gas/liquid transport for this reaction. Another possibility is that the solubility of the catalyst complex is being affected by the choice of the ionic liquid. For the water-soluble Rh–BISBIS complex {BISBIS = sodium salt of sulfonated 2,2'-bis[(diphenylphosphino)methyl]-1,1'-biphenyl} ligand, the reaction selectivity (for both aldehyde and linear:branched ratio) was greatly affected by the choice of the ionic liquid. The catalyst solubility in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ was limited, and these solvents yielded aldehyde selectivities of 20% and 16%, respectively, and linear:branched ratios of 1.5 and 8.2.⁶⁶⁴ Meanwhile, the catalyst was highly soluble in various $[\text{C}_n\text{C}_1\text{im}][\text{OTf}]$ ionic liquids, and the selectivities jumped to 82–85% and the linear:branched ratios to 34–43. A similar anion effect was observed by the same authors when Rh–TPPTS was employed as the catalyst.⁶⁶⁵ In this case a clear cation effect on the reaction rate, but not on the selectivity, was also observed, with longer alkyl chains on the cation reducing the reaction rate.

Several $[\text{NTf}_2]^-$ ionic liquids were compared to toluene for the hydroformylation of vinyl acetate.⁶⁶⁶ The ILs outperformed toluene in both rate and selectivity, with the linear:branched ratio surpassing 1:99 in the case of $[\text{C}_8(\text{C}_1)_3\text{N}][\text{NTf}_2]$. The authors attribute the rate and selectivity enhancements to the IL affecting the CO insertion equilibrium step of the catalytic cycle via ionic stabilization of the $18e^-$ complex.

Hydroformylation of alkenes using CO_2 has also been reported in biphasic ionic liquid/organic solvent systems.⁶⁶⁷ The conversion of 1-hexene was reported to increase as the organic solvent was changed from cyclohexane to diethyl ether to tetrahydrofuran to toluene, in line with increased cosolvent miscibility with the IL $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$. Thus, diffusion across the phase interface (and substrate solubility) is likely controlling the reaction efficiency, though the miscible toluene/ $[\text{C}_8\text{C}_1\text{im}]\text{Cl}$ mixture featured a drop in selectivity.

7.5. Dimerizations

The dimerization of propene to hexenes with nickel(II) catalysts in acidic chloroaluminate(III) ionic liquids was one of the earliest uses of ionic liquids⁶⁶⁸ and was described in the original review.¹ This work was further developed and led eventually to the Institut Français du Pétrole's Difasol process.^{549,669} Other ionic liquids have also been used as solvents for the biphasic oligomerization of ethane, with some success. For example, the Ni-catalyzed oligomerization has been performed in a wide variety of $[\text{C}_n\text{C}_1\text{im}][\text{PF}_6]$ ($n = 4, 6, 8, \text{ or } 10$) ionic liquids and organic solvents, with the effectiveness of the catalytic system being found to decrease as the alkyl chain length increased,⁶⁷⁰ which has been attributed to the higher solubility of the oligomerization products increasing the concentration of catalyst-poisoning internal higher olefins.^{12b} Also, the presence of impurities (most notably Cl^- and water) had a marked effect on product selectivity. However, the oligomerization showed higher reactivity and selectivity in all of the ionic liquids than in conventional solvents (ionic liquids > CH_2Cl_2 > n -pentane > toluene > acetone > THF = 1,4-butanediol), and the reaction rate (TOF) correlated well with the olefin solubility and solvatochromic polarity data.⁶⁷⁰ Similarly, the dimerization of 1,3-butadiene by PdCl_2 proceeded faster in several $[\text{C}_4\text{C}_1\text{im}]^+$ ionic liquids than in THF,⁶⁷¹ although there was no clear effect of changing the anion. The issue with halide impurities can be avoided by using

Brønsted acidic ionic liquids formed by direct protonation,^{672,673} which can raise the reaction rate, though whether this is a solubility phenomenon or catalyst activation is unclear. There was also a strong anion effect in these systems, as observed through the higher activity in $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ compared to $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$, though this is likely due to anion complexation with the catalyst as the same effect was observed when the catalyst anion was changed to $[\text{OTf}]$.⁶⁷² Similar anion effects were observed for the Fe-catalyzed dimerization of 1,3-butadiene,⁶⁷⁴ where the more strongly coordinating $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ greatly outperformed $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, and also for the selectivity of the hydrodimerization of 1,3-butadiene by Pd(II), which favored $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ over $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$.⁶⁷⁵ In this instance, the selectivity difference was attributed to water miscibility, which is consistent with the findings for the cyclooligomerization of arylethynes by Ru–porphyrins that showed a strong preference for $[\text{C}_8\text{C}_1\text{im}][\text{PF}_6]$ over $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$, which the authors attributed to the water content of the ionic liquid.⁶⁷⁶

7.6. Palladium-Catalyzed Coupling Reactions

Palladium-catalyzed coupling reactions are among the most extensively studied catalytic processes in ionic liquids.^{12,584} Herrmann reported that many 1,3-dialkylimidazolium ionic liquids formed Pd–NHC species that led to a large drop in the yield of Heck reactions when compared to tetraalkylammonium cation systems.⁶⁷⁷ This negative effect has also been observed for the Sonogashira coupling in ionic liquids,⁶⁷⁸ which proceeded to much higher yields when a tetraalkylphosphonium cation replaced $[\text{C}_4\text{C}_1\text{im}]^+$. The necessary presence of a strong base to promote these reactions can lead to other unwanted side reactions with the ionic liquid such as NHC formation for 1,3-dialkylimidazolium ionic liquids, on many tetraalkylammonium species being susceptible to the Hoffman elimination. The use of the anion as the base promoter provides an excellent opportunity to reduce the complexity of these systems,⁶⁷⁹ but the presence of a large amount of basic anions (such as $[\text{OAc}]^-$) can lead to changes in selectivity.⁶⁸⁰

Anion effects have been noted as a key parameter in determining the efficiency of ionic liquids as reaction media for the Heck reaction. It has been noted that halide ions (frequent synthetic impurities) can promote the reaction and improve catalyst stability,^{12b} with $\text{I}^- > \text{Br}^- > \text{Cl}^-$.⁶⁸¹ The Heck coupling of electron-rich olefins with aryl halides using Pd(OAc)₂ proceeded to very high selectivity in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$,⁶⁸² but switching to $[\text{C}_4\text{C}_1\text{im}]\text{Br}$ increased the reaction rate, which has been attributed to the incorporation of Br^- into the catalytic Pd complex.^{12b} This result does not appear to translate to molecular solvents, where the addition of $[\text{BF}_4]^-$ ionic liquids to DMSO and DMF was found to improve the selectivity of the Heck reaction, while the addition of Br^- ionic liquids did not.⁶⁸³

The regioselective Heck coupling of aryl bromides with allylic alcohols has been performed in a range of ionic liquids with Pd complexes by Hardacre.^{684,685} Although the activity in ionic liquids was higher than in organic solvents, a detailed kinetic analysis of the reaction revealed that there was an induction period when *trans*-bis(2,3-dihydro-3-methylbenzothiazol-2-ylidene)diiodopalladium(II) was used as the catalyst, leading the authors to conclude that Pd nanoparticles were forming during the reaction and that they were the active catalysts. The harsh conditions required by many Heck couplings can lead to some side reactions occurring, and in this case the relatively poor results when $[\text{BF}_4]^-$ ⁶⁸³ or Br^- ^{684,685} was used as the anion rather than the much less basic $[\text{NTf}_2]^-$ support the possible

formation of nanoparticles. It is worth noting^{12b} that the $[\text{NTf}_2]^-$ ionic liquids have much lower viscosities, and if the reaction is occurring at a nanoparticle/liquid interface, then diffusion considerations may be dominant.

Ionic liquids can also have an effect on the regioselectivity of Heck reactions. While linear selectivity was observed for Br^- -based ionic liquids,^{685–687} branched products predominated in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$.⁶⁸⁵ Molecular solvents have been reported to yield a mixture of regioisomers.^{12b}

Asymmetric Heck couplings of alkynes and imines have also been carried out using ionic liquids as solvents.⁶⁸⁸ The ee's were reported to be slightly higher in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ (94%) than $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ (86%). However, the choice of cation proved crucial, as the ee dropped to 27% when $[\text{C}_8\text{C}_1\text{im}][\text{PF}_6]$ was the solvent, showing that longer alkyl chains markedly decrease selectivity, perhaps through interaction with the hydrophobic substrates. However, this does not appear to be a simple hydrophilicity effect, as the ee was nearly identical when $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{BF}_4]$ (78%), $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{NTf}_2]$ (79%), or $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}][\text{PF}_6]$ (76%) was the solvent, so specific interactions with the cation are likely responsible. The anion had a more marked effect on yield, as once again the more basic $[\text{BF}_4]^-$ ionic liquid caused a significant reduction.

A cation effect has been noted in palladium-catalyzed allylic alkylations in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$.⁶⁸⁹ In these reactions the base for the reaction is generated during the catalysis via $[\text{MeOCO}_2]^-$. However, Xiao and Ross noted that hydrogen bonding from $[\text{C}_4\text{C}_1\text{im}]^+$ prevented this by suppressing the nucleophilicity of the base by hydrogen bonding to it.

Suzuki–Miyaura cross-coupling reactions of halogenoarenes with arylboronic acids have also been investigated in ionic liquids. There has been some discussion of the role of Pd–NHC carbene complexes. Welton et al.⁶⁹⁰ investigated these reactions in a range of ionic liquids in the presence of PPh_3 . They found that under carefully controlled conditions catalytically active solutions could be prepared that were sufficiently stable to allow recycling in $[\text{C}_n\text{C}_1\text{im}]^+$ ($n = 2, 4$, or 6) ionic liquids, but not when $[\text{C}_4\text{C}_1\text{C}_1^2\text{im}]^+$ or $[\text{C}_4\text{C}_1\text{pyrr}]^+$ ionic liquids were used. Subsequent investigation of the reaction conditions and analysis of the catalytically active solutions revealed the presence of a mixed phosphine–imidazolydene palladium complex (Figure 13 A). They found similar results when amine ligands were used in place of the PPh_3 .⁶⁹¹ More recently, Dyson studied the cation effects for this reaction in detail,⁶⁹² using ether-functionalized cations to prepare ionic liquids. In these experiments catalytically active, recyclable solutions could be formed for ionic liquids that are not capable of forming NHCs, e.g., $[(\text{C}_1\text{OC}_2)\text{C}_1^2\text{pyr}][\text{NTf}_2]$. Furthermore, when $[(\text{C}_1\text{OC}_2)\text{C}_1\text{imy}]_2\text{PdCl}_2$ (Figure 13 B) was used as the catalyst source, the reaction yields were very low, and the authors concluded that Pd–NHC complex formation in these ionic liquids terminated the catalytic cycle.

Although at first sight these studies may appear to contradict each other, the details of the experiments are quite different. In the Welton studies, strongly coordinating PPh_3 or amine coligands are added to the solutions and a meticulous initiation procedure to form the $[(\text{C}_4\text{C}_1\text{imy})(\text{PPh}_3)_2\text{PdX}]^+$ complex is conducted.^{690,691} The ether functionalities of Dyson's ionic liquids would be expected to be less well coordinating to palladium than these functionalities.⁶⁹² Combining these results shows that ether-functionalized ionic liquids are capable of providing palladium complexes of sufficient stability to be able to form catalytically active and recyclable solutions. When the $[(\text{C}_1\text{OC}_2)\text{C}_1\text{imy}]_2\text{PdCl}_2$ complexes are added to these ionic liquids, they are so stable as to be poor catalysts for these reactions. However, when appropriate coordinating ligands are added into the system, the

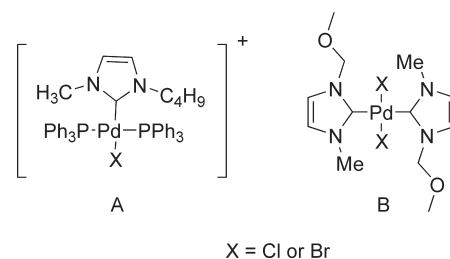


Figure 13. Phosphine–imidazolydene palladium complex $[(\text{C}_4\text{C}_1\text{imy})(\text{PPh}_3)_2\text{PdX}]^+$.

mono-NHC complexes $[(\text{C}_4\text{C}_1\text{imy})(\text{PPh}_3)_2\text{PdX}]^+$ are formed and the solutions are again both catalytically active and recyclable.

7.7. Olefin Metathesis

The Ru-catalyzed metathesis of methyl oleate was studied in detail in a variety of $[\text{C}_4\text{C}_1\text{im}]\text{X}$ $\{[\text{NTf}_2], [\text{PF}_6], \text{or } [\text{BF}_4]\}$ ILs. The choice of anion showed a clear effect on the reaction rate, with the activity decreasing slightly in the anion order $[\text{BF}_4]^- > [\text{NTf}_2]^- \approx [\text{PF}_6]^-$ for the first-generation Grubbs catalyst and $[\text{NTf}_2]^- \approx [\text{BF}_4]^- > [\text{PF}_6]^-$ for the second-generation catalyst.⁶⁹³ Ligand selection had a much more marked effect on the rate. Interestingly, this reaction has been demonstrated to show a clear solvent polarity trend in molecular solvents which is not present in these ionic liquids.⁶⁹⁴

7.8. Summary

The effects of ionic liquids on transition-metal-catalyzed reactions are much less well understood than those on stoichiometric or acid-catalyzed reactions. This is true of solvent effects in general. Much of the difficulty in this area is in its complexity. First, the selection of catalyst is a usually the dominating factor in determining the outcome of a transition-metal-catalyzed reaction, and even small changes to a ligand can lead to large changes in catalyst performance. Consequently, unless a reaction is studied using identical catalysts, it is not possible to even confirm whether solvent effects are occurring. Also, impurities in the system may also have a dominating effect on the catalysis, further confounding analysis. Even when solvent effects have been identified, the large number of possible sources of these effects, e.g., interaction with the catalyst, interaction with reactants, and solubilities of reactants and catalysts, makes it difficult to identify a sole cause, if one exists. All of these causes have been observed in ionic liquids.

8. OVERVIEW

In the past decade there have been extraordinary advances in the understanding of how ionic liquids can affect chemical synthesis. This astounding class of solvents has challenged both our experimental and our intellectual abilities. Detailed descriptions of how ionic liquids interact with solute species to change their reactivities have begun to emerge, yet much remains to be discovered. What could be better?

ASSOCIATED CONTENT

Supporting Information

List of abbreviations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Tom Welton was educated at the University of Sussex, graduating with both a Bachelor's degree and a D.Phil. degree in chemistry. He has worked at Imperial College since 1993, first as the Lloyd's of London Tercentenary Fellow and now as Professor of Sustainable Chemistry and Head of Department. He is interested in using solvents to improve chemical processes. He has worked with ionic liquids throughout his research career, but he also works with other solvents, such as siloxanes, PEGs, and solvents from renewable resources, all with a view to the development of sustainable solvent technologies. His research covers a broad range of the chemical sciences, and he has been the author of papers in all three of the traditional branches of the subject (inorganic, organic, and physical).

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