Understanding Organic Processes in Ionic Liquids: Achievements So Far and Challenges Remaining

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Abstract: The use of ionic liquids as alternatives to traditional molecular solvents is a rapidly expanding field. Their many advantages, including negligible vapor pressures, tunable miscibilities and the ease of product isolation, mean that they have been considered (and shown to be effective) as solvents for a range of reactions. However, the outcomes of many of these organic processes differ on changing solvent to an ionic liquid. For these ionic liquid media to be truly considered as alternative solvents, these differences must be understood. This article seeks to extend this understanding by reviewing the variations in the outcome of organic processes along with the fundamental physical properties of ionic liquids that differ from molecular liquids. A case study on nucleophilic substitutions is used to demonstrate the usefulness of our approach.

Keywords: Ionic liquids, organic chemistry, physical properties, solvent effects.

1. INTRODUCTION

The drive towards environmentally sustainable, or so-called 'green chemistry', is providing one of the greatest challenges for the chemists of today [1]. For organic chemists, much effort has been made to reduce the use of volatile organic solvents. This has included the development of solvent-free technology [2] and the use of alternative solvents [3], including water [4] and supercritical fluids [5,6], particularly carbon dioxide [6]. In addition, ionic liquids, or room temperature molten salts, are becoming more prevalent as a group of nonvolatile solvents for chemical processing [7-9].

Ionic liquids are readily synthesized as they are usually based on either quaternized amines or phosphines (Fig. (**1**)), with the charge being balanced by one of a variety of anions such as chloroaluminates, halides, triflate, tetrafluoroborate, hexafluorophosphate and bis(triflimide) which can be readily exchanged [10-12]. Through modification of either the cation or the anion, the properties of the liquid, notably the melting point and liquid range [12-14], viscosity [12] and miscibility with other solvents [12,15], can be altered. Perhaps the most important property of ionic liquids is that, due to the electrostatic interactions between their component ions, they have vanishingly small vapour pressures [10,14], As such, ionic liquids are attractive as recyclable media which can be 'tuned' to have the appropriate properties and are often referred to as 'designer solvents' [7].

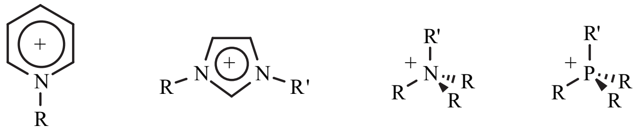

Fig. (1). Important types of cations found in ionic liquids.

A broad range of organic processes have been investigated in ionic liquid media and in biphasic mixtures containing ionic liquids. Much of the focus on ionic liquids as solvents has been on their use as solvents for industrially relevant processes, such as Friedels-Craft acylation [16], selective alkylation [17], Diels-Alder chemistry [18-24], transition metal catalyzed coupling and hydrogenation [25], and biotransformations [26]. The use of ionic liquids is particularly advantageous when the product can be removed from the mixture through distillation. However, differences in the rates and selectivities of the processes are often observed when compared to the corresponding reactions in molecular solvents. At the extreme, the outcome of reactions may not only vary from that observed in molecular solvents, but between different ionic liquids as well (Scheme **1**) [27]. While the latter effect may often be explained in terms of the reactivity of the components of the ionic liquid (demonstrated for the cation in Baylis-Hillman processes [28] and the anion in nucleophilic substitution processes [27,29] and dediazoniation [30]) it is important to recognize that there are limited reports detailing the origin of the changes in reaction outcome between molecular and ionic solvents. In contrast, the relationship between the character of a molecular solvent and the outcome of a reaction is generally well-understood [31]; undergraduates are taught these principles so they can choose appropriate solvents for a given reaction. In order for ionic liquids to be truly considered alternative solvents, the equivalent understanding for ionic liquids is required.

This review seeks to advance this understanding in two ways: First, by reviewing the variations in chemical reactivity with ionic solvent that have already been observed, and second, by reviewing the fundamental physical features of ionic liquids that distinguish them from molecular liquids. Our ability to apply the latter to understanding the former is limited by available experimental information, but we attempt to demonstrate the utility of the approach with a case study on nucleophilic reactions at the end of this review. We believe this approach allows efficient

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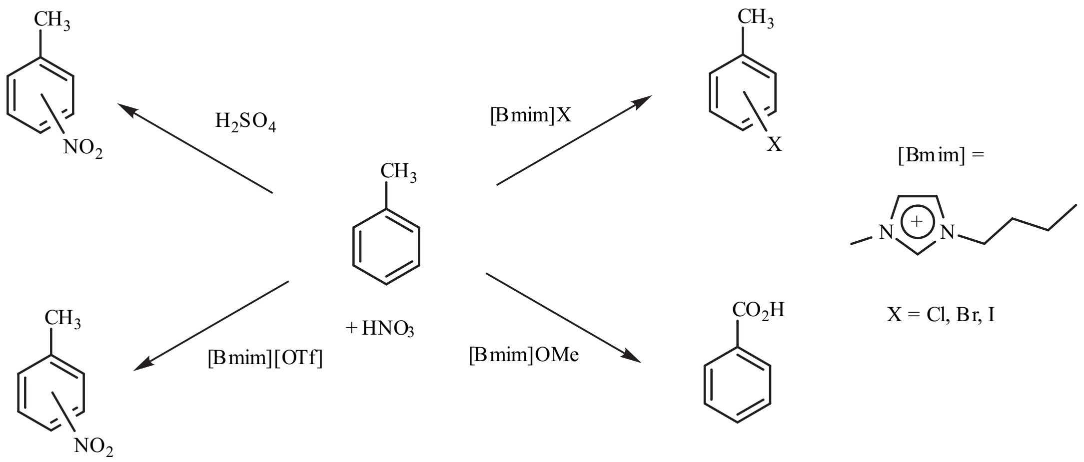

Scheme 1. The outcome of a reaction that is dependent on the ionic liquid used [27].

organization of the information that has been gained thus far, and illustrates the questions that must be answered before the outcome of organic processes in ionic liquids can be accurately predicted.

2. THE CHEMICAL ENVIRONMENT OF IONIC LIQUIDS

When considering the utility of a solvent for a given reaction, every chemist is obligated to ask a deceptively simple question: “What is its polarity?” In fact there is no fundamental physical definition of solvent polarity, and it can only be characterized empirically. Methods range from simple single-parameter approaches such as the dielectric constant of the medium, to multi-parameter fits based on a linear free energy relationship formalism [32,33]. We will briefly review some measurements of polarity that have been applied to ionic liquids before considering reactions in ionic liquids in detail.

Measurements of solvent polarity may be based either on the study of the outcome of a reaction, or on a physical property of the medium. Perhaps the simplest non-reactive approach is to measure the partitioning of a series of probe molecules between an ionic liquid phase and a reference phase of known polarity. Examples applied to ionic liquids include liquid-liquid partitioning in a biphasic system [15,34,35] or liquid-vapor partitioning, as when ionic liquids are used as stationary phases in gas chromatography [36,37]. In general, these studies have shown ionic liquids to have polarities comparable to moderately polar organic solvents such as acetonitrile. Some of these studies have been parameterized by semi-empirical linear free energy relationships [35,37].

Another physical approach is the study of the optical absorption and emission spectra of solvatochromic probe molecules in a given chemical environment [33,38]. Studies of the spectra of solvatochromic probes in ionic liquids have in general been consistent with the results of partitioning studies described above [39], though some anomalies have been noted [12]. Overall, however, the picture of ionic liquids as moderately polar organic solvents seems consistent.

We will consider organic processes in ionic liquids in **Section 3**, and discuss what their results imply about the solvent and its polarity in that context. However, one particularly thorough study of polarity using reaction dynamics bears special mention. Angelini *et al.* [40] observed the tautomerization of a nitroketone complex in a series of five imidazolium-based ionic liquids, and conducted a linear free energy analysis of the behavior of the equilibrium constant. The results indicate an overall polarity comparable to that of acetonitrile, and the details of the linear free energy relationship analysis seem consistent with the partitioning and spectroscopic studies above. Thus, by most metrics, ionic liquids appear to possess polarities comparable to moderately polar organic solvents.

The astute reader will note that we have not gone into detail as to which liquids were studied above, and how their structure affected the observed polarity. In fact, these studies spanned an enormous range of ionic liquid structures, but the observed polarities were remarkably consistent. While physical properties of ionic liquids seem to vary substantially, the chemical environment of ionic liquids appears to vary little between systems.

No discussion of the chemical environment of ionic liquids – or any solvent – would be complete without consideration of possible impurities. One of the great inconveniences of ionic liquids is that having limited vapour pressure, distillation is difficult [41] and so they must be purified by more laborious means [42]. It is often difficult to remove leftover ionic starting materials, such as halide ions or acids, and ionic liquids are notoriously hygroscopic. As well as potentially taking part in the reaction being studied [43]* and affecting the reactivity of reagents [45], these species can alter the physical properties of ionic liquids [46,47], and affect their stability [48]. Purification protocols have been discussed extensively elsewhere, and we note the issue here simply to make the reader aware of the difficulty.

3. ORGANIC CHEMISTRY IN IONIC LIQUIDS – OBSERVATIONS SO FAR

As described above, a wide range of organic chemistry has been examined in ionic liquids. It is not the aim of this review to discuss the extent of such chemistry in ionic

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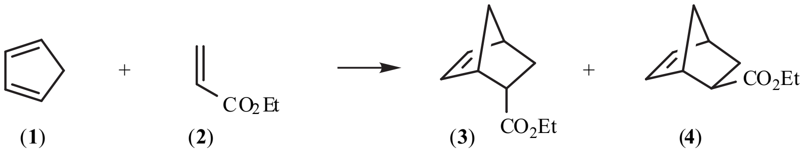
*It is worth noting that the largest effect here tends to be on organometallic processes [69].



diethyl ether	3	1
Bmim triflate	6	1

Scheme 2. A Diels-Alder reaction that proceeds with greater selectivity in ionic liquids than in molecular solvents such as diethyl ether [19,53].

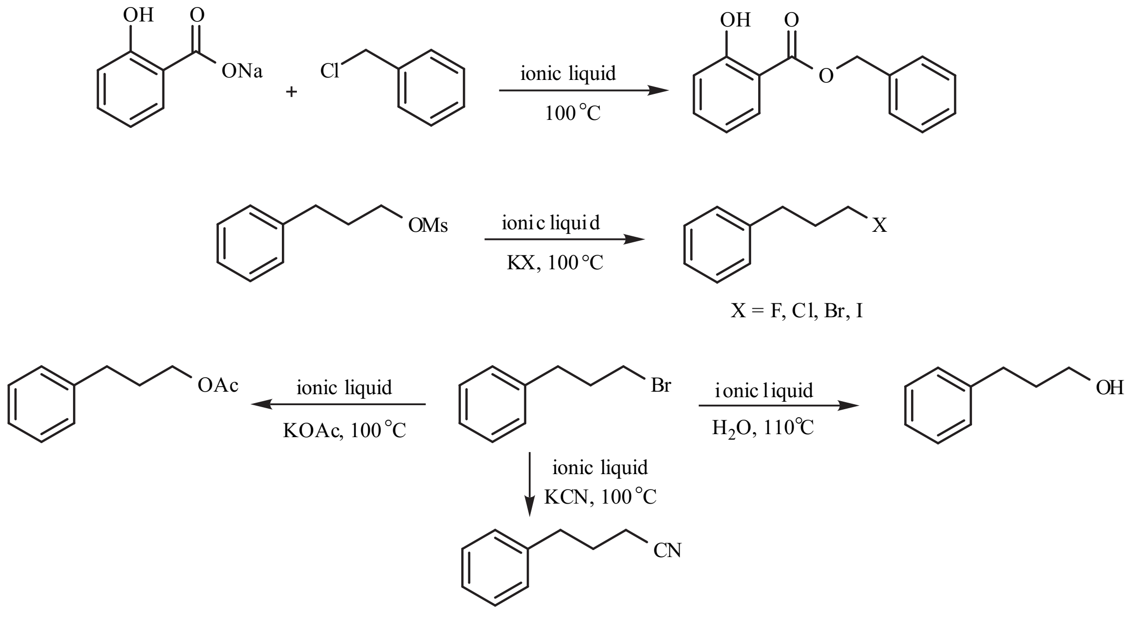
liquids, as this has been covered previously [8], rather to examine the changes in reactions on moving from molecular to ionic solvents. Also, the reactions in question will be limited to organic processes rather than organometallic reactions. Further, this review will not cover changes in processes in which the ionic liquid used has already been well characterized as having a particular nature. Phenomena such as the Lewis acidic effects of chloroaluminate based ionic liquids [49] and the nucleophilic properties of halide based ionic liquids [29] have been studied and reviewed extensively elsewhere and we will therefore focus on other aspects of these systems. Likewise, because our goal is to provide a broad overview of the field, phenomena linked to the reactivity of a specific functional group, such as the use of either a protonated imidazolium [50] or a sulfonic acid moiety [51,52] as a Brønsted acid, may be excluded unless they are representative of a larger class of reactions.

3.1. Diels-Alder Processes

The first series in which the change from molecular solvents to ionic liquids was well documented is the Diels-Alder reactions and there have been a significant number of reports on these processes in ionic liquids [18-24]. Significant rate increases have been observed though the major outcome is that, in each case, the *endo* : *exo* selectivity of the process is greater than observed in molecular solvents. As an example, the selectivity of the reaction between the diene (**1**) and the dienophile (**2**) to give the adducts (**3**) and (**4**) varies from 3:1 in diethyl ether [53] to 6:1 in 1-butyl-3-methylimidazolium ('Bmim') triflate (Scheme **2**) [19]. The related Aza-Diels Alder reaction has also been shown to proceed well in ionic liquids, even when they do not occur in molecular solvents, with notable *endo* selectivity [54].

There have been reports that seek to explain this selectivity, along with the observed rate enhancements, to hydrogen bond formation between the cation of the ionic liquid and the carbonyl oxygen of the dienophile [21,23]. Particularly, the effect of changing the hydrogen bond accepting capability of the anion of the ionic liquid has a dramatic effect on the stereoselectivity. The use of ionic liquids containing camphorsulfonate ions showed the largest stereoselectivity (*ca.* 10:1) and this was attributed to the decreased interaction between the anion and cation, as demonstrated by mass spectroscopic data [23].

However, these results also demonstrate some of the limitations currently in understanding and predicting reactions in ionic liquids. Firstly, the limited kinetic



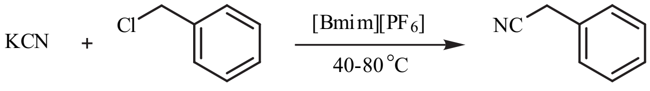
Scheme 3. A series of nucleophilic substitution processes in which the rate of reaction is faster in ionic liquids and ionic liquid / co-solvent mixtures [57,59,67]. In all cases, the ionic liquids were based on the Bmim cation.

analyses of these systems were based on biphasic mixtures and the selectivities determined from solutions in which the ionic liquid was significantly diluted by reagents. So, the exact nature of the medium in question is unclear. Further, these analyses do not account for other contributing properties, such as the internal pressure of the solvent†. The importance of these factors can be seen in that this explanation cannot account for the similar effects observed in phosphonium [20] and pyridinium [22] based ionic liquids, where hydrogen bonding is likely to be extremely limited. Subsequent studies suggest that there is not a strong correlation between hydrogen bonding and selectivity in Diels-Alder processes, even though the best selectivities were observed in the cases with the weakest hydrogen bonding interactions [24]. A reasonable correlation is observed between the selectivity and several measures of polarity, while other properties of the ionic liquid are shown to have little effect the selectivity of the process [24].

3.2. Nucleophilic Substitution

The other group of organic reactions that have been studied to a significant extent are nucleophilic substitution processes. It is this series that has seen the most kinetic and thermodynamic analysis. The most general result has been an increase in the rate of the reactions with the extent of any competing elimination reactions also being reduced. These studies have covered nucleophilic substitution processes involving a range of nucleophiles, including cyanide [56-58], carboxylates [57,59-62], the halides [57,63,64], azide [58,61], enolates [58], alkoxides [58,65], sulfur nucleophiles [61,66], water [67], pyrrole [68], and phosphoric and phosphinic acids [62], in both neat ionic liquids and as mixtures with a range of co-solvents (Scheme **3**). Perhaps surprisingly, in the cases where an increased rate of reaction with water was observed, the effect on the corresponding reactions with alcohols was not as great [67]. Further, in general Bmim tetrafluoroborate proved to be the ionic liquid of choice giving the largest yields in a given time. In addition, an increase in regioselectivity has been observed in the alkylation of indole [17] and 2-naphthol [17,69].

An early example provides a good indication as to some of the complexities of considering the origins of the observed rate acceleration. A study of the reaction of potassium cyanide with benzyl chloride (**5**) in Bmim hexafluorophosphate (Scheme **4**) was carried out in an effort to find a replacement for phase transfer catalysis in biphasic systems [56]. Importantly, the work involved a careful study of the rate and order of the reaction over a series of temperatures. The fact that at low temperature the reaction was zero order and this changed to first order at high temperatures was consistent with the rate at which the potassium cyanide dissolved into the ionic liquid being rate determining at low temperature. At higher temperatures, where the viscosity dropped dramatically [70], the change in rate was identified as the combination of a series of factors including the solubility of the potassium cyanide in the ionic liquid. It is worth noting that in both this report and a latter publication on the related reaction of the chloride (**5**) with a carboxylate [59] the possibility of the solvents 'activating' the anion is mentioned, though the origin of this activation is not discussed.



(**5**)

Scheme 4. The reaction of potassium cyanide with benzyl chloride (**5**) in an ionic liquid was carried out over a range of temperatures, with a difference in the observed order of the kinetics [56].

It should be noted that rate accelerations were reported for reactions of charged nucleophile known to proceed through an S_N2 mechanism [57,61,63,67], as well as those for which the mechanism is less well defined [56,59]. For the cases in which a bimolecular mechanism operates, the rate increase is attributed to an increase in the nucleophilicity of the reagents in ionic liquids and ionic liquid mixtures. The counterion to the nucleophile was shown to be important; it has been suggested that this is due to a reduction in the extent of ion pairing [57], though the concept of ion pairing in an ionic liquid is not a simple one. In fact a wide range of phenomena related to nucleophilic substitution in ionic liquids have been observed, including changes in both nucleophilicity of reagents and in the mechanism of reaction. We will reserve more detailed discussion of these phenomena until **Section 5**, where we will attempt to interpret the wealth of experimental data available on these systems using physical principles for molten salts laid out in **Section 4**.

3.3. Electrophilic Substitution

A range of electrophilic processes have also been investigated in ionic liquids, particularly motivated by the industrial relevance of the products. Friedel-Crafts alkylations of aromatic systems have been found to proceed more rapidly under milder conditions in hydrophobic ionic liquids than in traditional organic solvents [71]. This was attributed to the ionic liquid stabilizing the polar cationic intermediate.

Recently there has been a key report detailing the change in regioselectivity and substrate selectivity in triflic acid catalyzed adamantylation of aromatic compounds (Scheme **5**) [72]. On going from a molecular solvent to the ionic liquid Bmim triflate, the rate of reaction of toluene (**6**) with the chloride (**7**) decreases but there is a significant increase in the ratio of the *para* product (**8**) to the *meta* product (**9**) and a reduction in the amount of the reduction by-product (**10**). In competition experiments, the ratio of the rate of reaction of toluene (**7**) to benzene (**11**), increased by a factor of *ca*. 60, as determined by the ratio of the *para* adducts (**12**) and (**13**). This selectivity was rationalized by suggesting that the transition state for the reaction was comparatively later in the ionic liquid, corresponding to the greater stability of the adamantyl cation in the ionic liquid.

Electrophilic nitrations of aromatic systems have also been investigated in these systems. Generally, increases in rates were observed when the reactions were carried out in ionic liquids and ionic liquid/molecular solvent mixtures

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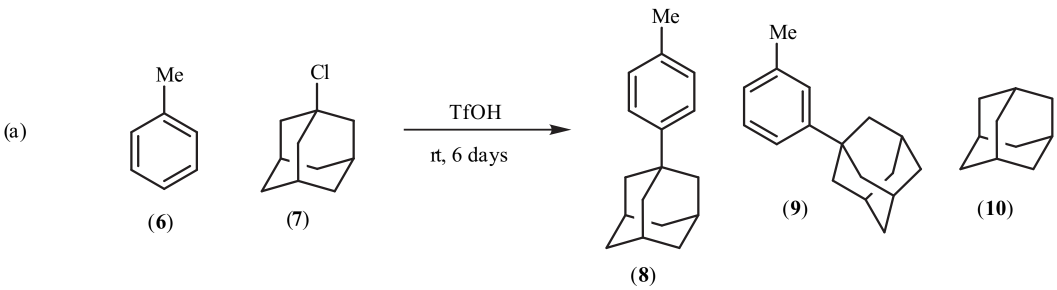
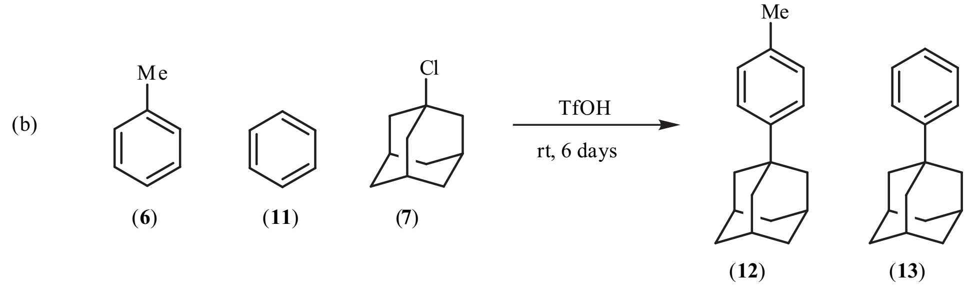
† The effect observed is similar to that when a salt is added to an organic solution [88].

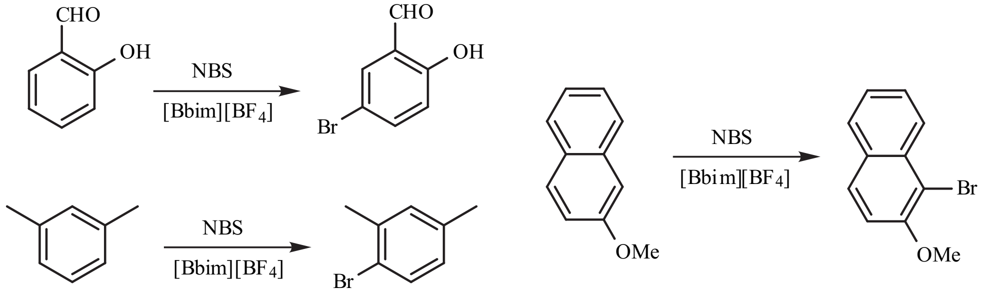


	(**8**)	(**9**)	(**10**)
$ClCH_2CH_2Cl$	25%	36%	39%
[Bmim][OTf]	77%	2%	-



	(**12**)		(**13**)
$ClCH_2CH_2Cl$	1	:	4.3
[Bmim][OTf]	14.7	:	1

Scheme 5. Regioselectivity (a) and substrate selectivity (b) in the adamantylation of aromatic compounds [72].



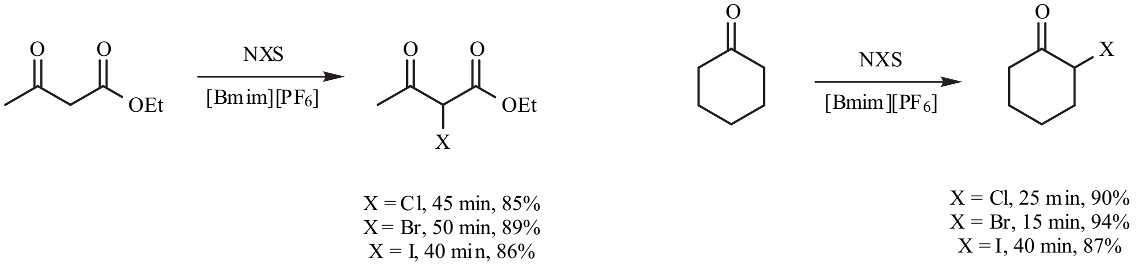
Scheme 6. Examples of monobrominations of aromatic compounds carried out in Bbim tetrafluoroborate [78].

rather than in neat molecular solvents though the distribution of isomers is typically comparable with that observed in molecular solvents [27,73-76][‡]. However, as mentioned above (Scheme **1**), there is the complication for this system in that components of the ionic liquid may take part in the reaction; the reaction is thus complicated by the presence of a competing electrophile [27,73][§] and by the possibility that the cation of the ionic liquid might be nitrated [73,74]. A stabilization of the charged intermediate [74] and increased dissociation of the nitrating agent [76] have been put forward as possible explanations for the observed rate increases. The latter was rationalized by noting that the reaction proceeds more effectively in solvents in which the hydrogen bond accepting ability of the anion is decreased.

In addition to electrophilic nitration, there has been a report of electrophilic monobromination of aromatic compounds using *N*-bromosuccinnimide (Scheme **6**) [78]. This reaction proceeds much more efficiently in 1,3-dibutylimidazolium ('Bbim') tetrafluoroborate than in traditional molecular solvents. The chemical shift of the carbonyl group of the succinimide was shown to increase on going from molecular solvents to the ionic liquid. This indicates an increase in the polarity of the nitrogen-bromine bond, indicating an electrophilic mechanism and explaining the observed order of reactivity. A similar argument has been used to account for the increased rate of halogenation of β-dicarbonyl compounds and cyclic ketones by *N*-halosuccinimides (Scheme **7**) [79].

[‡] It should be noted that there is a report of high *para* selectivity in the nitration of phenols in ethylammonium nitrate, however this reaction was promoted by ultrasonication [116].

[§] The competing electrophile is thought to be produced through reaction of the nitrating agent with the anionic component of the ionic liquid.



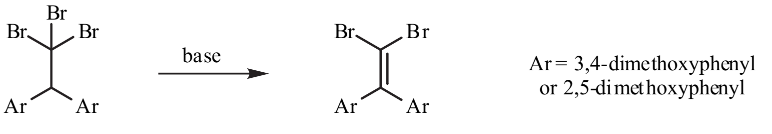
Scheme 7. Halogenations of β-dicarbonyl compounds and cyclic ketones by *N*-halosuccinimide [79].

3.4. Free-Radical Polymerisation

Another area in which solvent induced rate accelerations have been noted is free-radical polymerization [80-82]. These cover a range of monomers, including methyl methacrylate and styrene, and the observations include an increase in the rate of polymerization and in the molecular weight of the polymer produced when compared to molecular solvents. Pulsed laser polymerization studies have been used to determine the rate constants for propagation in the case of methyl methacrylate in Bmim hexafluorophosphate [82]. This was shown to increase with increasing ionic liquid concentration and several explanations for this increase have been proposed, including solvent polarity and complex formation, though the extent to which each contributes to the actual effect remains unclear. Further, the increase in the rate of propagation is not large enough to account for the overall increase in the rate of polymerization suggesting that there is also an effect on the termination process. It is worth noting that, in addition to accelerating the rate of polymerization, ionic liquids have been found to be excellent plasticizing agents [81].

3.5. Dehydrobromination, Debromination and Halogenation

Base promoted elimination of the sterically hindered bromides (**14**) (Scheme **8**) has been shown to proceed differently in ionic liquids when compared to molecular solvents [83]. Detailed kinetic analysis showed that an $E1_{cb}$ mechanism operates in methanol, but an E2 mechanism operates in ionic liquids. In addition, polarity alone cannot account for the observed increase in rate of reaction with electrostatic interactions of the cation with the bromine in the starting material (**14**) suggested as the contributing to the change in mechanism, as is potential change in basicity of the amines in ionic liquids.

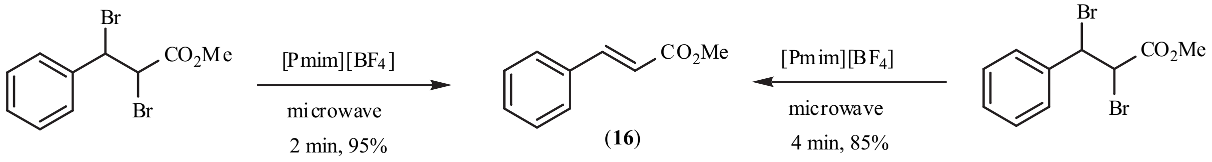


(**14**)

Scheme 8. The dehydrobromination of the bromides (**14**) on going from methanol to ionic liquids [83].

Debromination of vicinal dibromides, such as the cinnamate derivative (**15**), has also been investigated in 1-propyl-3-methylimidazolium ('Pmim') tetrafluoroborate (Scheme **9**) [84]. This reaction proceeds very rapidly under microwave irradiation, to give the corresponding unsaturated products, such as methyl cinnamate (**16**). Importantly, the stereochemistry of the product is *trans*, irrespective of the configuration of the dibromide. This stereochemical outcome, along with the fact that the equivalent reaction does not proceed in the corresponding bromide, led to the proposal of an ionic mechanism involving participation of the ionic liquid anion (Fig. (**2**)).

A reaction that is likely mechanistically related to the above is the halogenation of a series of alcohols (and protected alcohols) using the corresponding *tert*-butyl halide under either thermal or microwave heating, which does not proceed in conventional solvents (Scheme **10**) [85]. This may not immediately seem related to the above, but experimental evidence shows that the tertiary halide eliminates hydrogen halide under the reaction conditions, the latter being responsible for the halogenation of the alcohols and the deprotection and then halogenation of the protected alcohols.



(*erythro*)-(**15**) (*threo*)-(**15**)

Scheme 9. Debromination of vicinal dibromides proceeds rapidly under microwave irradiation in a tetrafluoroborate based ionic liquid. The stereochemistry of the product is independent of the configuration of the starting material [84].

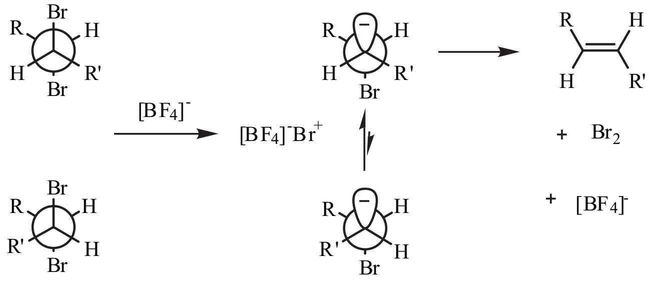
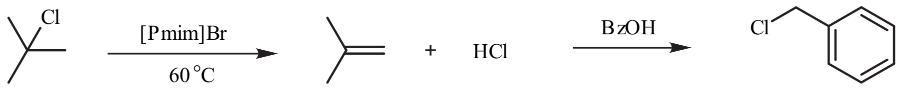


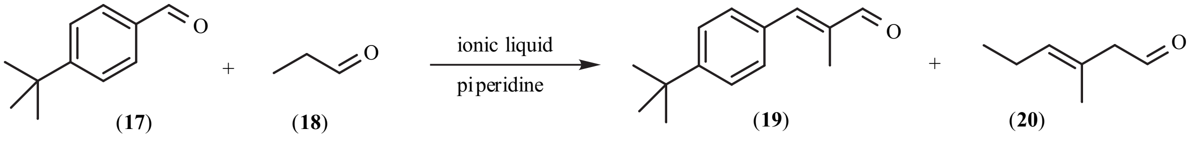
Fig. (2). Proposed process for the stereoselective debromination of vicinal dibromides. The anionic intermediates are stabilised through interaction with the imidazolium cation and the less sterically hindered case leads to the observed product [84].

3.6. Reactions of Carbonyl Groups (including Heterocycle Synthesis)

The rate of reaction of cross-aldol condensations has been observed to increase on changing to ionic liquid media [86,87]. A particular change in reaction outcome in an ionic liquid medium is the increased reaction yield in the synthesis of the aldehyde (**19**), a precursor to the fragrance Lillial® *via* a cross-aldol condensation (Scheme **11**) [87]. In molecular solvents, the yield is compromised by the self-condensation of the starting material (**18**). This reaction is suppressed in a range of ionic liquids based on the imidazolium, pyridinium, tetraalkylammonium and tetraalkylphosphonium cations. The extent of this suppression is dependent on the ionic liquid anion but not on the cation. The origin of this suppression is thought to be that the iminium adduct of the benzaldehyde (**17**) is insoluble in the ionic liquids and its precipitation ensures that no piperidine is available to catalyze the formation of the self-aldol product (**20**).



Scheme 10. An example of the halogenation of alcohols carried out in ionic liquids. The equivalent reaction with the corresponding bromide or iodide required ultrasonication [85].



Scheme 11. The aldol condensation producing the fragrance precursor 3-(4-tertbutylphenyl)-2-methyl-propenal (**19**). In ionic liquids the extent of formation of the byproduct 2-methyl-2-pentenal (**20**) is greatly reduced [87].

Related to above result is the efficient synthesis of the oxime of cyclohexanone (**21**) using aqueous hydroxylamine in Bmim tetrafluoroborate (Scheme **12**) [88]. This reaction is driven to completion by the insolubility of the oxime (**22**), which precipitates from the reaction mixture. Subsequent Beckmann rearrangement to give e-caprolactam (**23**) does not proceed well in the tetrafluoroborate salt[≠], but does occur efficiently in the hexafluorophosphate salt [89]. This was explained by the fact that the ionic liquid medium increases the stability of the transition state in which the nitrogen-oxygen bond is partially ionized.

Condensations to form heterocycles have also been dramatically affected. The synthesis of a range of 2-aryl benzimidazoles, benzoxazoles and benzthiazoles (**24**) proceeded well in ionic liquids, without the need for an additional catalyst as required in molecular solvents (Scheme **13a**) [90]. The rates of reaction were correlated with the basicity of the anion; decreasing the anion basicity increases the degree to which the cation might interact with the carbonyl group of the starting material and accelerate the reaction. This was also suggested after the efficient synthesis of 1,5-benzodiazepine derivatives in Bbim bromide [91]. Further, the formation of arylquinazolines (**27**) from 2-aminobenzamides (**25**) and benzoyl chlorides (**26**) (Scheme **13b**) was found to proceed more efficiently in imidazolium based ionic liquids than in molecular solvents at comparable temperatures [92]. Once again, the acceleration was attributed to the Lewis acid effect of the cation, as evidenced by a change in carbonyl stretching frequency in the IR spectrum of the starting material (**25**) on going from molecular solvent to ionic liquid. Along with these, Bischler-Napieralski cyclizations [93], syntheses of imidazo[1,2-a]pyridines [94], the synthesis of 2,3,5-trichloropyridine from trichloroacetaldehyde and acrylonitrile [95], synthesis of 2-arylimidazo[1,2-a]pyrimidines [96], 1,4-dihydropyridines [97] and trisubstituted imidazoles [98] also proceeded more effectively in ionic liquids, though no rationale was given in these cases[£].

While not strictly a reaction of a carbonyl group, Mannich-type processes are clearly related to this system. In particular, the synthesis of a number of β-amino esters has been investigated and found to proceed especially efficiently in some ionic liquids, but not others (Scheme **14**) [99]. It is worth noting that the authors were particularly careful in this case, ruling out the possibility of adventitious acidic impurities catalyzing the process. A Lewis acid effect of the cation, presumably mediated by differing anions, is proposed to account for this though no evidence akin to that described above is presented; though stoichiometric amounts

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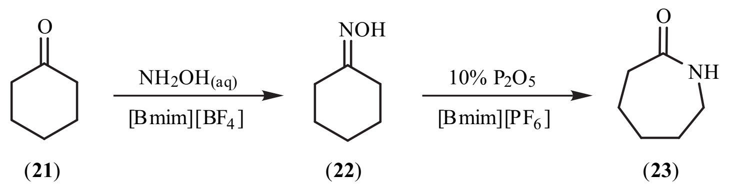
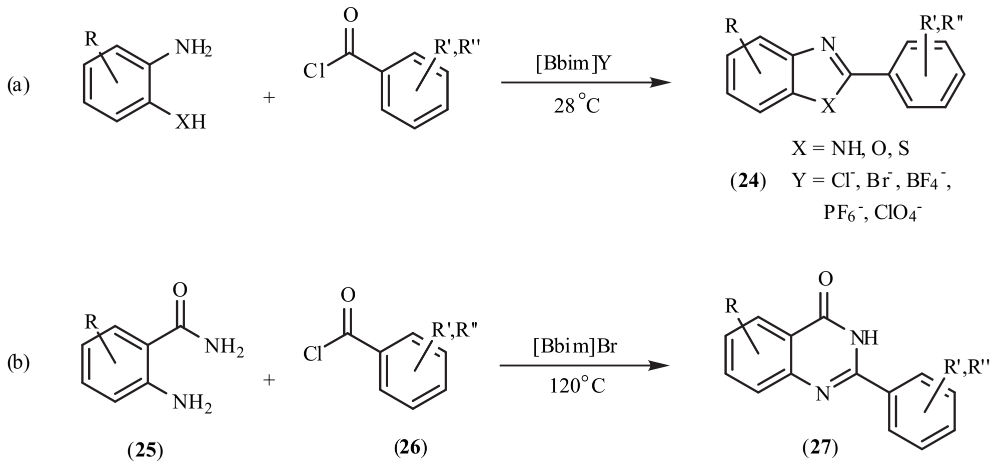
[≠] This was rationalised by the fact that the tetrafluoroborate salt is water miscible and the hydrolysis of the oxime becomes important. Presumably the solubility of the oxime also limits the effectiveness of the Beckmann rearrangement.

[£] In several of these cases the reactions were also carried out under ultrasonication.

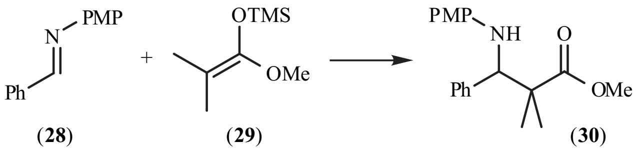


Scheme 12. The preparation of the oxime of cyclohexanone (**21**) is driven by the insolubility of the product (**22**) in the ionic liquid medium [88]. Subsequent Beckmann rearrangement proceeds efficiently in related ionic liquids in which the starting material is soluble [89].



Scheme 13. Synthesis of a range of (a) 2-aryl benzimidazoles, benzoxazoles and benzthiazoles (**24**) [90] and (b) arylquinazolines (**27**) [92] facilitated by the use of an ionic liquid as the solvent.

of the ionic liquid in toluene do promote the reaction. An earlier study on asymmetric Mannich reactions also reported an increased rate of reaction, though only Bmim tetrafluoroborate was used as a solvent and no account was given of the observed changes [100].



[Bmim][BF_4], 24 h, 11%
[Bmim][PF_6], 24 h, <5%
[Bmim]OTf, 1 h, 100%
[Emim]OTf, 1 h, 96%
1 eq. [Emim]OTf in toluene, 12 h, 96%

Scheme 14. Various ionic liquids and their affects on a Mannich-type process of the imine (**28**) and the alkene (**29**) to give the β-amino ester (**30**); all reactions were carried out at room temperature [99].

3.7. Other Organic Processes Affected by Ionic Liquids

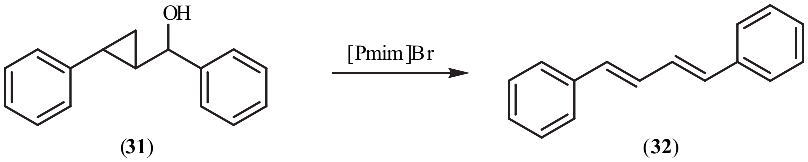
An increase in the rate of rearrangement of cyclopropyl carbinyl compounds has been observed in the presence of Pmim bromide (Scheme **15**); no reaction is observed in the absence of the ionic liquid [101]. Coordination of the imidazolium cation to the hydroxyl group is proposed to facilitate the cyclopropyl cleavage (Scheme **16**)[Δ].

There have also been isolated reports of either rate accelerations or changes in the reaction outcome of other organic processes. These have included chiral epoxidations [102], reduction of aldehydes using trialkylborons [103], 1,3-dipolar cycloadditions [104], Baylis-Hillman reactions [28,105], Knoevenagel condensations [106], α-tosylation of enolizable ketones [107], Rosenmund-von Braun reactions [108], acetylation [109] and benzoylation [110] of nucleosides, aza-Markovnikov addition to alkenes [111], three component syntheses to give 3-alkyl-5-arylmethylidene-1,3-thiazolidine-2,4-diones [112], conjugate addition of thiols to electron deficient alkenes [113], aromatic aminations [114], conversion of the acetates of Baylis-Hillman adducts to give trisubstituted alkenes [115], selective benzoylation of nucleosides with benzoyl cyanide [116], the synthesis of aromatic nitriles from aromatic aldehydes [117], the synthesis of *N*-substituted phthalimides [118], alkylation of thiazolidinediones [119], stereoselective conjugate additions [120], synthesis of 1,2-orthoesters of carbohydrates [121], Morita-Baylis-Hillman reactions [122], Huisgen cycloaddition to form 1,2,3-triazoles [123] and esterification of tertiary alcohols [124]. However, in each of these cases, no explanation for the different outcomes in ionic liquids was discussed.

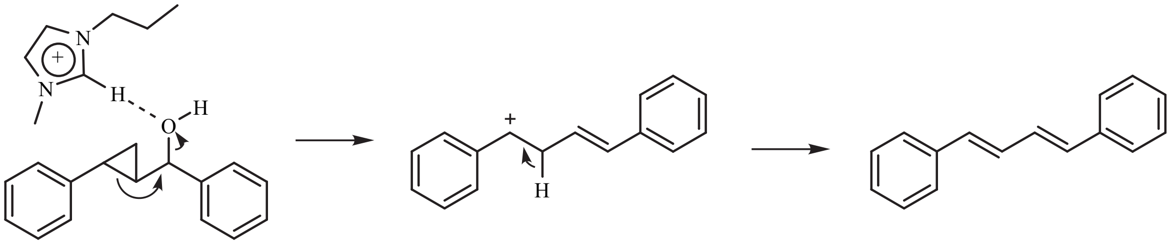
3.8. Fundamental Organic Processes Investigated in Ionic Liquids

In addition to the studies described above, that seek to explain the unusual reaction outcomes observed, a few studies have examined other more fundamental organic reactions to understand processes in ionic liquids.

[Δ] The reaction is further promoted by ultrasonication.



Scheme 15. Aryl substituted cyclopropyl carbinols, such as the diphenyl (**31**), undergo rearrangement to give all *trans*-butadienes, such as the diene (**32**), in the presence of Pmim bromide [101].



Scheme 16. The increased rate cyclopropyl carbinyl rearrangement is proposed to be due to coordination of the cation to the hydroxyl group [101].

An important set of studies have been on the reaction of trihalides with unsaturated systems [125], after these species were indicated as important in the addition of bromine to alkenes and alkynes [126]. A rate increase was observed on changing from molecular to ionic liquids, for both the tribromide and the dichloroiodide ions. The rates of these reactions were monitored in a range of ionic liquids with differing viscosities and hydrogen bonding capability. In the case of the tribromide processes, the rates of reaction were not greatly affected by either property and the enhanced rate of reaction relative to molecular solvents was attributed to a stabilization of the transition state[€]. For the chloroiodination process, while viscosity was found not to be a factor, the rates of reaction varied notably with the extent of hydrogen bonding to the cation. The difference between the two cases is attributed to the different hydrogen bond accepting capabilities of the two leaving groups (bromide and chloride, respectively) which in turn alters the charge distribution in the transition state. These examples demonstrate clearly the need for caution when comparing the effects of ionic liquids on 'similar' reactions.

The effect of ionic liquids on the stability of delocalized anions has also been investigated, through the observation of the cleavage of radical anions [128]. There was a marked difference in the effect on the rate of cleavage of the 9-chloroanthracene radical anion, which was accelerated, and that of the 4-chlorobenzophenone radical anion, which was decelerated. In the former, the negative charge is delocalized over the entire molecule while it is significantly localized on the oxygen in the latter. Gas phase calculations suggest that ion pairing is important in the latter case, between the cation of the ionic liquid and the carbonyl oxygen of the radical anion. Such associations had also been indicated by previous work on the oxidation of aromatic molecules in ionic liquids, particularly the decrease in the rate of electron transfer, as is consistent with greater solvent reorganization than in molecular solvents [129].

The above examples each demonstrate the range of properties that can influence the outcomes of reactions in ionic liquids and in ionic liquid mixtures. These include viscosity, various polarity parameters, internal pressure of solvation, the extent of ion association (including particular interactions such as hydrogen bonding) and solute-solvent interactions. Perhaps as important as having values for these properties is to understand why these vary between different ionic liquids and ionic liquid / co-solvent mixtures. Finally, and perhaps most challenging, is to demonstrate how these parameters relate to organic processes ('what they really mean') such that they might be used to predict the effect on reactions of changing to these new media. In the light of this, it is important to consider what is already known about the microscopic physics of ionic liquids.

4. THE PHYSICS OF AN IONIC LIQUID

The observations reviewed above demonstrate the utility of ionic liquids as media for organic reactions, and illustrate how the different physical properties of ionic liquids affect their role as solvents. But these observations are often interpreted in an *ad hoc* manner, without consideration of how the microscopic structure of a molten salt differs from that of a molecular liquid. Fundamentally, much of our current understanding of solvation phenomena is based, either explicitly or implicitly, on the assumption that the solvent is composed of neutral, dipolar (or nonpolar) molecules. In these systems, certain simple physical ideas apply: (i) that the solvent is a homogeneous environment, (ii) that solute-solvent interactions are described by a combination of specific chemical interactions and the alignment of the electrostatic dipole moments of the solvent molecules, and (iii) that solute-solvent forces are of roughly the same magnitude as solvent-solvent interactions. None of these assumptions hold true in ionic liquids. In this section,

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[€] Initial studies of bromination in the viscous Bmim bromide [127], suggested that the rate increase could be attributed to the viscosity of the solvent, favoring these reactions as they involve early transition states. This was subsequently [126] shown to be a special case, with the rate determining step involving nucleophilic attack of the bromide ion rather than the tribromide ion.

we will review the physics of molten salt systems, and discuss what is known about how those physical properties affect solvation and chemical reactivity. Key to the analysis will be understanding the structure of the liquid and the importance of different electrostatic interactions.

4.1. Microscopic Structure of an Ionic Liquid

With the exception of inhomogeneous media such as micellar dispersions, most discussions of molecular liquids assume the solvent is homogeneous. Even where co-solvents are employed, their effect on reaction dynamics is most often explained either by alteration of specific solute-solvent interactions or by a change in the dielectric constant for the medium. In contrast, ionic liquids are highly structured materials, and any consideration of their role as a solvent must begin by understanding that structure. Early work [130] on the structure of high-temperature molten salts such as alkali halides established that rather than being a disordered state analogous to molecular liquids, molten salts are best described as an ordered lattice containing a large number of voids and defects. The reason for this ordering is simply the dominant role of Coulomb interactions: The free energy of the liquid is minimized by maintaining a uniformly neutral distribution of electrostatic charge, which requires ions and counterions to assume a regular structure. More recent experiments on ionic liquids [131] confirm that these ideas apply in room-temperature ionic liquids as well.

The clearest expression of this ordering is the analysis of Stillinger [132], who showed that an ion in a molten salt is best described as surrounded by a spherical layer of counterions, which itself is surrounded by a layer of ions of like charge, and so on, creating a series of layers of alternating charge. Disorder in the medium ultimately leads to the decay of this correlation, typically after multiple layers of solvent. This is illustrated schematically in Fig. (**3**), which shows the radial distribution functions for ions in a melt for a simple molten salt. The figure is based on molecular dynamics simulation data for a salt consisting of positively and negatively charged spherical ions of radius 1 [133], which interact with each other through Coulomb forces and a short-ranged repulsive term representing dispersive interactions. The results clearly indicate the existence of shells of counterions about a given ion, from which like-charged ions are excluded, and subsequent layers of alternating charge density. This periodicity contrasts sharply with the prediction of Debye-Hückel Theory in molecular liquids, which dictates that an ion is surrounded by a monotonically decreasing charge density representing an "atmosphere" of counterions. The concept of an "ion pair," often invoked in molecular liquids, is thus inappropriate for ionic liquids, as the ion is associated with many counterions and can never exist in isolation.

While one expects a charged solute to intercalate into the charge ordering described above, the behaviour of a neutral solute species is less obvious. For a neutral solute, the electrostatic energy of solvent-solvent (ion-ion) interactions will always be substantially larger than solute-solvent (dipole-ion) interactions. This implies that the solute will do little to disrupt charge-ordering in the liquid, and simulations on small molecules suggest that this is indeed the case [134]. For very small molecules, such as carbon dioxide, one may view the solute as residing in an "existing" cavity in the medium – that is, a cavity comparable in size to the defects that characterize disorder in the neat liquid. The solubility of larger species such as enzymes, which can retain their activity in ionic liquids [135] suggests this "existing cavity" model cannot be the

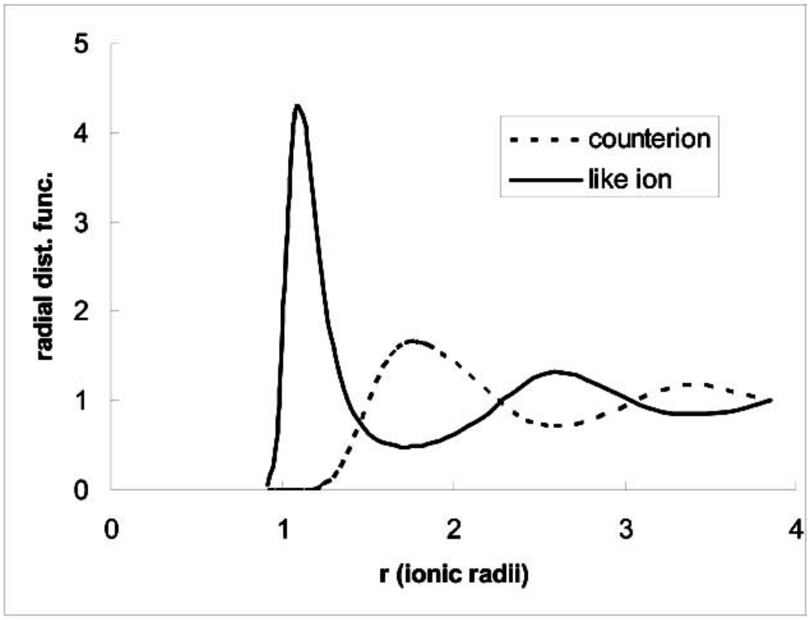


Fig. (3). Ion and counterion radial distribution functions from simulation data [133], as described in text.

whole story. This point is further driven home by the observation that the physical properties of ionic liquid solutions can change dramatically in the presence of neutral solutes [46]. The solubility of these species, and their capacity to disrupt the ionic lattice, are likely driven by entropic effects that favor its disruption, though the details of this process are not currently understood. In **Section 5**, we note a number of examples in which entropic effects apparently arising from the rearrangement of the solvent affect reaction dynamics, and this issue is thus very important in understanding reactions in ionic liquids.

4.2. Solute-Solvent Interactions

The discussion of liquid structure outlined above leads naturally to questions about the details of solute-solvent interactions. In general, solute-solvent interactions from specific chemical interactions such as hydrogen-bonding seem similar in ionic liquids and molecular liquids. For example, Dzubya and Bartsch [136] have shown that derivatization of the ionic liquid can increase its hydrogen-bonding character in very much the same way as one would expect for a molecular liquid. Other phenomena, such as Lewis acidity [137] are also readily explained using conventional ideas about solvent behaviour. The only potentially unique form of specific solute-solvent interaction that has been proposed is due to Hanke *et al.* [138], who use molecular dynamics simulations to show that the quadrupole moment of aromatic species leads to stronger solute-solvent interactions than are present in a comparable aliphatic species. They attribute this effect to ion-quadrupole interactions, which manifest in distinct ordering of the cation and anion of the ionic liquid around the neutral solute. We discuss how this effect could be responsible for certain experimental observations in **Section 4**.

But while specific interactions in ionic liquids are for the most part analogous to those in molecular liquids, their manifestation is subject to a peculiar twist. Experiments [139] and theoretical analysis [140] have shown that specific ion-counterion interactions can compete with ion-solute interactions. Thus, the hydrogen-bond donor character of a solvent can be effectively reduced by replacing a nonhydrogen-bonding counterion with a hydrogen-bond accepting species. This offers a convenient way to tune solvent properties, and we discuss how this phenomenon affects reaction dynamics in **Section 4**.

Non-specific electrostatic interactions in ionic liquids, however, require a careful re-thinking of solvation. When establishing the utility of a solvent for a given application, one of the first things a chemist does is to compare the electrostatic dipole moment of the solute molecule to that of the solvent molecules, operating under the assumption that "like dissolves like". Yet this concept is problematic in an ionic liquid, as the electrostatic dipole moment of an ion is not a good physical quantity. The fundamental definition of the electrostatic dipole moment is based on a Taylor series expansion of the electric potential of a distribution of charges [141], and is given by Equation **1**:

$$\underline{p} = \sum_{i=1}^{N} q_i \underline{r}_i \tag{1}$$

where $\underline{p}$ is the dipole moment, q_i is the charge on the i^{th} atomic center, and $\underline{r}_i$ is the position of the atom. It is easy to show [142] that for a charged system (*i.e.* the sum of the charges is not zero), the dipole moment $\underline{p}$ becomes dependent on the coordinate scheme chosen and therefore does not offer physical insight. The reason for this ambiguity is that the electrostatic potential of an ion is not appropriately described by a gradient, as assumed by the dipole treatment, but rather by a maximum (or minimum for negative ions).

A better description is the center of charge formalism [142], which seeks to describe the ion as a single charge localized at a point chosen to best describe the true electrostatic potential of the ion. This description has been used by Kobrak and Sandalow [143] to interpret dynamic properties of ionic liquids, such as viscosity and conductivity, and it may be useful in understanding solute-solvent interactions. Their preliminary results indicate that dynamic properties of an ionic liquid, such as viscosity, can be understood by comparing the locations of an ion's center of charge and center of mass, though as yet they provide little direct insight into reaction dynamics.

Electrostatic interactions are also complicated by the inherently conductive nature of the ionic liquid. The polarization of a molecular liquid by a polar solute can often be described using a dielectric continuum model, and the dielectric constant of a liquid is often used as a measure of its polarity. But ionic liquids are macroscopically conductive media, and while it is possible to separate the conductive and dielectric responses of a medium, it is not clear that this approach offers any insight on solute-solvent interactions. Recent experiments making use of dielectric reflectance spectroscopy [144] indicate dielectric constants in the range of 10-15 for a series of imidazolium-based ionic liquids. This is substantially lower than the dielectric constants for moderately polar liquids (*e.g.* 37 for acetonitrile [145]), which by most measures of polarity (discussed in **Section 2**) are found to possess comparable polarities.

There are likely several reasons for this discrepancy. First, the response of a conductive medium to an applied electric field is fundamentally different than that for a dielectric medium. A dielectric medium polarizes to create an electric field that interacts with the applied field, but its response is governed by the need to retain charge neutrality. In contrast, a conductor rearranges its charge density to counter the applied field at the surface of the conductor (*i.e.* at the surface of the cavity surrounding the solute) [141]. Znamenskiy and Kobrak [140] have studied this phenomenon in simulation, and have shown that while the "chunkiness" of the solvent ions prohibits perfect screening, the solute dipole is effectively screened within the first two solvation shells of a polar solute on thermodynamic timescales. This is somewhat surprising in light of the discussion of the magnitudes of solute-solvent interactions described above, but it is not clear that any major rearrangement of solvent ions is necessary to achieve this screening. Kim and co-workers [146] have shown that the density of the solvent can change about a neutral solute (a process known as electrostriction), but the significance of this effect and its relationship to the chemical structure of the ionic liquid are not known at this time.

A related issue is the relative size of the solute and the solvent ions. In general, ions in an ionic liquid are larger than the molecules typical of molecular solvents, and their regular distribution implies a characteristic lengthscale for their response. One expects, therefore, that the response of the ionic liquid to a macroscopic electric field may be substantially different than its response to a solute molecule that may only be 5-10 Å across.

Despite these ambiguities, we note that Halder *et al.* [147] have shown that certain spectroscopic results can be explained using a dielectric continuum theory in an ionic liquid. However, the method involves empirical fitting of a dielectric constant, and is based on a model using a complex-valued dielectric constant to account for ion-pairing in electrolyte solutions of molecular liquids. The physical basis for the model is therefore unclear, and must be investigated more deeply before an unambiguous dielectric constant may be ascribed to the system.

4.3. Rates of Reaction

Reaction kinetics are generally understood by consideration of two factors: The rate of diffusion of reactive species and the time and energy required to move from a reactive complex to the "transition state." We will consider the influence of an ionic solvent on each of these processes. While relatively few detailed studies of kinetics in ionic liquids have been performed, we will attempt to highlight the observed differences between reactions in molecular and ionic solvents.

In diffusion-limited reactions, solvent viscosity is the most important determinant of reaction rate. Even the intramolecular rearrangements characterizing unimolecular reactions are affected by the presence of the solvent. Ionic liquids typically possess high viscosities (~30 cP or greater [148]), much higher than is typical for molecular liquids (~1 cP for water). Experiments on bimolecular reactions in ionic liquids [149] show that the activation energy for reaction is equivalent to the activation energy for viscous flow of the ionic liquids, as observed for the same reactions in molecular liquids. But these experiments do not explore one of the more intriguing aspects of ionic liquids: Charged and neutral solutes have different rates of diffusion in ionic liquids. Kinetic analysis of electrochemical transport [150] and pulse radiolysis experiments [151] indicate that charged species diffuse substantially more slowly than comparably-sized neutral species in molecular media. The difference is explained by the "lattice with voids" model, which would interpret diffusion of neutral species as occurring through existing voids, while diffusion of charged species requires collective rearrangement of the solvent ions. This effect does not lead to any macroscopically observable consequence for uni- and bi-molecular reactions, but could have a dramatic effect for reactions involving competing rates in which one reaction involves charged species and one involves neutral species. We are not aware of any demonstrations of this principle at this time, but note it here as speculation.

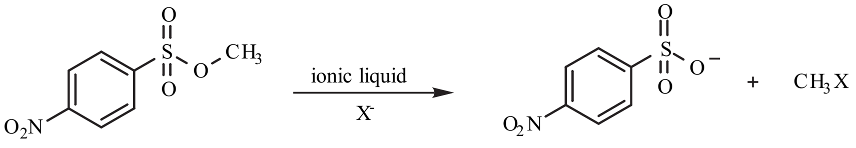
The solvent can also control the rate of formation of a complex through a "desolvation" process, in which solute-solvent interactions must be interrupted before a reactive complex can form. This is particularly relevant to catalysis, where the solvent can occupy a reactive site in competition with the reactant. A photochemical study by Swiderski and co-workers [152] indicates rapid exchange of bound and unbound solvent ions to a neutral metallo-organic complex. The observed kinetics indicate a more rapid exchange for the ionic liquid than for low-polarity molecular solvents studied concurrently, and that the results do not correlate with ligand basicity in a simple way. It may be that the charge-ordering of the ionic liquid plays a significant role, as the presence of counterions may stabilize the transition state of a binding or dissociation process. This is another area where further data would be valuable to the field.

In addition to diffusion, certain reactions require electrostatic polarization of the medium before they can proceed. Charge transfer reactions represent the classic example of such reactions [153], but any reaction involving a polar transition state is affected by the same principle. The timescale for such polarization can be determined from photophysical studies, the most common example being time-resolved fluorescence experiments. In these experiments, the chromophore is excited by a short light pulse, and the time-dependence of the fluorescence signal is monitored. The excitation process involves a change in the electrostatic dipole moment of the chromophore, and the observed Stokes shift in the fluorescence spectrum is dominated by the response of the solvent. Thus, the time-resolved fluorescence signal indicates the timescale of response of the solvent. An enormous number of such studies have been conducted in ionic liquids [154], and in virtually every case, the dynamics of the liquid are observed to range from picosecond timescales (or shorter) to multiple nanoseconds. This contrasts with the case in molecular liquids, where in the vast majority of cases the solvent response is complete on picosecond timescales. To some extent, this slow response is consistent with the high viscosity of ionic liquids. Nevertheless, it bears mention as a factor that may greatly slow reactions involving polar transition states.

5. A CASE STUDY ON NUCLEOPHILIC SUBSTITUTION

Perhaps the most extensively studied class of reaction in ionic liquids is nucleophilic substitution, which has been the subject of many kinetic and thermodynamic investigations in ionic liquids. We will attempt to interpret the existing literature on nucleophilic substitution using the physical principles described above. Our goal is not simply to understand this phenomenon, but to illustrate the kind of analysis that must be done to extend our understanding of ionic liquids and apply it to new areas.

A number of studies have been performed to gauge the effect of ionic liquids on the nature of the nucleophile [45,155]. In their landmark studies, Lancaster *et al.* [156-158] have concentrated on the reaction of methyl *p*-nitrobenzenesulfonate (**33**) with halide ions as described in Scheme **17**. They compare their results to studies of a similar reactive system in dichloromethane, which was studied both in dilute and concentrated solutions. In the dilute limit, the nucleophile is not coordinated with its counterion, while in concentrated solutions the reactive species is actually the ion pair. In the ionic liquid, Lancaster



(**33**)

Scheme 17. The reaction of halide ions with methyl *p*-nitrobenzenesulfonate (**33**) used to investigate the nucleophilicity of halide ions in ionic liquids ($X^- = Cl^-, Br^-, I^-$) [156-158].

et al. [157] found that while the system's enthalpic behaviour resembled that of the ion pair limit, its entropic behaviour resembled that of the "naked" ion. The reason for this apparent discrepancy is the structure of the ionic liquid discussed above. In both the ionic liquid and the ion pair limit, it is likely necessary to remove a coordinated cation from the nucleophile to permit formation of the activated complex. One might expect this displacement to be entropically favorable, but this contribution is likely cancelled out by subsequent coordination of the activated complex with another (less strongly enthalpically bound) cation. It is interesting to note that when Chiappe *et al.* studied azide as the nucleophile in an ionic liquid, they interpreted their results as indicating only weak azide-solvent association [159]. However, the authors did not examine this effect in detail.

The effect of the cation of the ionic liquid on halide nucleophilicity is dramatic [157], with the order of nucleophilicity inverting on going from the Bmim cation through *N*-methyl-1-butyl-3-methylimidazolium (Bm_2im) cation to the *N*-butyl-*N*-methylpyrrolidinim (Bmpy) cation. As the series in liquids based on the Bmpy cation is consistent with known gas-phase nucleophilicities (chloride > bromide [160]) it is the Bmim cation that is affecting the halide reactivities. It is clear from the study that the nucleophilicity of the iodide ion is essentially unchanged on switching cations, while the chloride varies most significantly. This is likely due to the changing hydrogen bond donor ability of the cations, which would affect the formation of the activated complex described above. Given the prevalence of imidazolium cations in ionic liquid chemistry, it is important to recognize that these interactions are not taken into account in the classical model of anion nucleophilicity in which ion solvation and ion association are considered to be absent [161].

Nucleophilic reactions also demonstrate the importance of competition in ion-counterion and ion-solute interactions. The effect of the anion of the ionic liquids on the nucleophilicity of halide ions in a series of ionic liquids was investigated [158], and it was observed that where anions with good hydrogen-bond acceptor capacity are incorporated into imidazolium based ionic liquids, the coordination of the halide nucleophile to the cation is weakened and the halide becomes more nucleophilic.

This work was extended by Landini *et al.* [45] who studied the nucleophilicity of the halides, azide, nitrophenolate and isothiocyanate. While the authors worked with a different substrate (either hexyl- or octylmethanesulfonate rather than the methyl derivative) and a different ionic liquid (based on 1-hexyl-3-methylimidazolium cations rather than Bmim), the general outcomes were the same for all ions studied. The order of halide nucleophilicity correlates well with that described above. Their results also demonstrate the effect of competition between solvent cation-solvent anion and cation-nucleophile interactions on nucleophilicity; nucleophilicity is reduced for systems where cation-solvent anion interactions are weaker and therefore cation-nucleophile coordination is favored. This latter point is dramatically demonstrated with the increased reactivity of the nucleophiles in a tetraalkylammonium based ionic liquid, in which hydrogen-bonding capabilities of the cation are dramatically reduced. This work also quantifies the effect of water concentration on reaction rate, with a linear decrease in rate observed with increasing water concentration. This indicates a decrease in effective nucleophilicity due to coordination of water with the nucleophile.

The effects of ionic liquids have also been extended to neutral nucleophiles [162] with the halide ion in Scheme **17** replaced by either mono-, di- or tri-*n*-butylamine¢. While the halide ions show reduced reactivity in ionic liquids when compared to molecular solvents, these neutral nucleophiles are more reactive in ionic media. The order of reactivity is di-*n*-butylamine > *n*-butylamine > tri-*n*-butylamine and the greatest enhancement is for the tri-*n*-butylamine. The origin of this effect for the primary and secondary amine is the hydrogen-bonding interaction of the amine with the anions of the ionic liquid, which stabilise the incipient cation (Fig. (**4**)). However, this cannot account for the increase in nucleophilicity observed for the tertiary amine. Calculation of Eyring parameters indicates that the difference in activation parameters between ionic liquids and molecular solvents is entropic. The authors interpret this as indicating that the reduction in entropy inherent in bringing together the reactive species is compensated by an increase in disorder in the solvent in the ionic liquid. This disorder may have something to do with the redistribution of charge in the transition state, which is somewhere between the neutral reagents and the ion pair formed on product formation, though this inference is uncertain at this time.

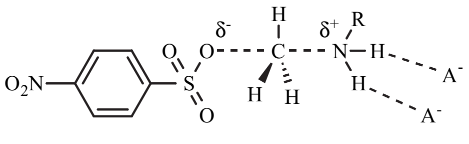
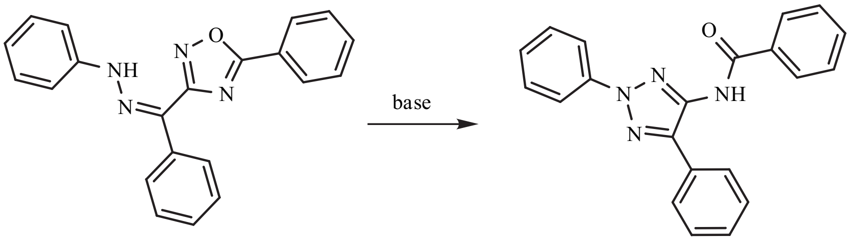


Fig. (4). The interaction of the amine with anions of an ionic liquid increases the nucleophilicity of the amine [162].

It is of interest to compare these studies with a recent paper in which an unusual base-assisted intramolecular substitution process was investigated (Scheme **18**) [163].

¢It is worth noting that care was taken to carry these reactions out in ionic liquids in which the amines would not deprotonate the cation.



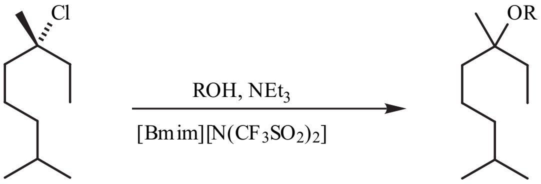
(**34**) (**35**)

Scheme 18. The rearrangement of a phenylhydrazone (**34**) to the triazole (**35**) which proceeds well in Bmim based ionic liquids [163].

Significant kinetic data were obtained and the rate of reaction was shown to be greater in ionic liquids. However, analysis is complicated as the order of the process differs, not just between ionic liquids and molecular solvents, but also between different molecular solvents. These difficulties limit interpretation but the authors do point out that the solvent effects cannot be correlated with reported measures of polarity. In addition, lack of solvation of the components of the reaction (particularly the hydrazone (**34**) and the amine) and conformational control of the starting material through 'some kind of clathrate formation' are cited [163]. While we are not aware of any clathrate-like phenomena in ionic liquids, it may be that the restrictions on molecular configuration arise from the unusual solute-solvent interactions reported for ionic liquids, as discussed above. Coordination of a cation with the aromatic system of the starting material (**34**) could both constrain the molecules motion and stabilize the anionic intermediate formed after abstraction of the proton, potentially retarding the reaction.

The possible change in mechanism of nucleophilic substitution on going from a molecular solvent to an ionic liquid has been investigated [159]. These studies have shown that the while these solvents are polar, processes which proceed without the formation of a charged intermediate are preferred. Thus ionic liquids have been referred to as behaving as "ionizing but not dissociating solvents" [159]. This could be a result of the different rates of diffusion for ionic and molecular species in ionic liquids, which would dramatically slow the formation of a reactive complex between charged reagents. Alternatively, there may be entropic issues favoring the formation of a transition state between two neutral species, as reported in Crowhurst *et al.*'s study discussed above.

In a related issue, studies investigating the reaction of the chiral tertiary chloride (**36**) in ionic liquid / alcohol mixtures (Scheme **19**) [164] have focused on the interactions of intimate ion pairs in first order substitution processes. Perhaps surprisingly, on increasing the proportion of the ionic liquid, there is an initial increase in the rate of reaction, followed by a decrease. This is not straightforward to explain but might be considered as arising from changes in the composition of the solvent shell for the reactants and/or transition state. Importantly, the extent of inversion of the process (which correlates with the degree of ion pairing between the carbocation and chloride anion) decreases as the proportion of ionic liquid increases, presumably due to competition between the solvent cation and the carbocation for coordination with the chloride anion.

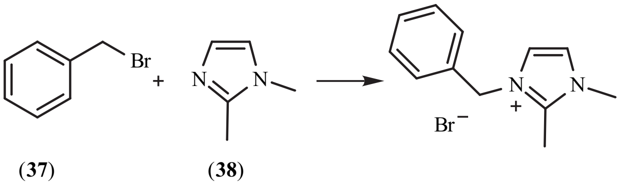


(**35**) (**36**)

ee = 70% R = CH_3, ee = 61-14%

Scheme 19. The reaction of the linalool derivative (**35**) in ionic liquid / alcohol mixtures to give the ether (**36**) [164].

Before finishing the section on nucleophilic substitution, it is worth considering some studies of a Menschutkin reaction in both ionic liquids and organic solvents (Scheme **20**) [165]. These are noteworthy not because there is a significant change in the rate of reaction on changing to an ionic liquid, rather that the authors investigate the relationship of the observed rates with certain solvent parameters, including polarity and hydrogen bonding capacity. While there is good correlation with a given parameter within a group of solvents, there is limited correlation between groups. This suggests that certain features of ionic liquids are not properly accounted for in even the most detailed existing descriptions of polarity, and new metrics may be necessary to account for the behaviour of ionic liquids as solvents.



(**37**) (**38**)

Scheme 20. The Menschutkin reaction of 1,2-dimethylimidazole (**38**) with benzyl bromide (**37**) carried out in a range of solvents including ionic liquids based on imidazolium, pyridinium and tetraalkylammonium cations, along with a range of molecular solvents [165].

6. CONCLUSIONS

Ionic liquids represent a new frontier for chemistry, and no review can map its breadth or present the full range of challenges to the field. Nevertheless, it is clear from even this limited presentation that ionic liquids are fundamentally different from molecular liquids. If ionic liquids are to become realistic, 'green' alternatives to existing molecular solvents for organic processes, these differences must be understood, as it is only in this way that reaction outcomes might be sensibly predicted. However, as has been demonstrated, this understanding requires not just the extension of existing chemical concepts but the development of novel descriptions of reaction media. Changes in the thermodynamics and kinetics of reactions on moving from molecular to ionic media, often resulting in notably different outcomes of organic reactions, range from the subtle to the bizarre, and require new concepts for their interpretation. Phenomena such as competition in ion-counterion and ion-solute interactions, the unusual solute-solvent interactions observed for aromatic systems, and the subtle interplay between the enthalpic demand for charge-ordering and the entropic penalty for obtaining it are crucially important in ionic liquids. Yet these phenomena have no clear analogs in molecular media. It is evident that the full exploitation of ionic liquids as solvents for organic reactions will require not just careful experimentation, but also the re-invention of the chemical intuition that is so fundamental to the practice of chemistry.

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