Room Temperature Ionic Liquids: a "Green" Alternative to Conventional Organic Solvents?

Angelamaria Maia*

CNR-Istituto di Scienze e Tecnologie Molecolari (ISTM), Via C.Golgi 19, I-20133 Milano, Italy

Abstract: Ionic liquids (ILs) are attracting increasing interest as a potential ecosustainable alternative to traditional volatile organic solvents (VOCs), generally used in large amounts. About the "greenness" of ILs a certain controversy still exists because their toxicity and biodegradability need to be fully assessed. Moreover, the real advantages of using this novel class of solvents should be more deeply studied in comparison with traditional media. This article presents some of the most recent findings in this field by reviewing selected examples of applications of ILs in organic synthesis and catalysis. In addition, anionic reactivity data for some organic reactions will be discussed and compared with those previously found for the same reactions in molecular solvents. Finally, updated results concerning toxicity, ecotoxicity and biodegradation of the most common ILs will be reported.

Keywords: Anion reactivity, biodegradability, ionic liquids, organic synthesis, toxicity, volatile organic solvents.

1. INTRODUCTION

Ionic liquids (ILs) have been one of the most rapidly growing areas of chemistry research in recent years [1]. These salts, which are liquids at around (and often below) room temperature, are typically composed of a bulk unsymmetrical organic cation and a charge–diffuse inorganic or organic anion (Fig. **1**). Among the many room temperature ionic liquids that have been synthetized, common systems are based on aromatic ammonium salts, such as imidazolium or pyridinium cations. The anions are simple inorganic species (BF_4^-, PF_6^-, Hal^-….) or more complex species like $[(CF_3SO_2)_2N^-]$ bis(trifluoromethanesulfonyl)imide (Tf_2N^-). In particular, imidazolium salts are popular in synthetic applications due to their easy preparation, in good to quantitative yields, from relatively cheap and easily available intermediates (Fig. **1**). Modification of either of the ionic components is found to alter the physicochemical properties (melting point, viscosity, polarity,…) allowing them to be tuned to a given process and then utilized as task-specific or "designer" solvents. They have widely been utilized in synthesis, catalysis, polymerization, industrial cleaning, liquid/liquid extraction and separation, as well documented by the growing number of reviews and books published in recent years [1]. In addition, ILs revealed multipurpose materials, rather than just solvents, finding useful applications in sensors, solar and fuel cells, batteries, thermal fluids, lubricants and so on [1]. Compared to molecular solvents, ILs possess many attractive properties that include extremely low volatility, low flammability, excellent thermal stability, easy preparation and recycling. Most importantly, their unique ability to solvate a number of inorganic, organic and polymeric materials makes them particularly appealing as potential "green" alternatives to conventional more volatile organic media (VOCs). However, in order that ILs can offer an environmentally benign alternative to molecular solvents, their toxicity and biodegradability must be carefully investigated. Moreover, additional studies should be performed in traditional media to assess whether a real advantage is obtained by using this class of novel solvents.

This mini-review intends to present some of the most recent results obtained up-to now in this field. The first part is centred on selected examples of IL applications as solvents in organic synthesis and catalysis. In the second part, the anion reactivity in ILs for some organic reactions has been compared with that observed for the same reactions in molecular solvents. Finally, up-to date studies concerning toxicity, ecotoxicity and biodegradation of the most commonly used ILs will be reported.
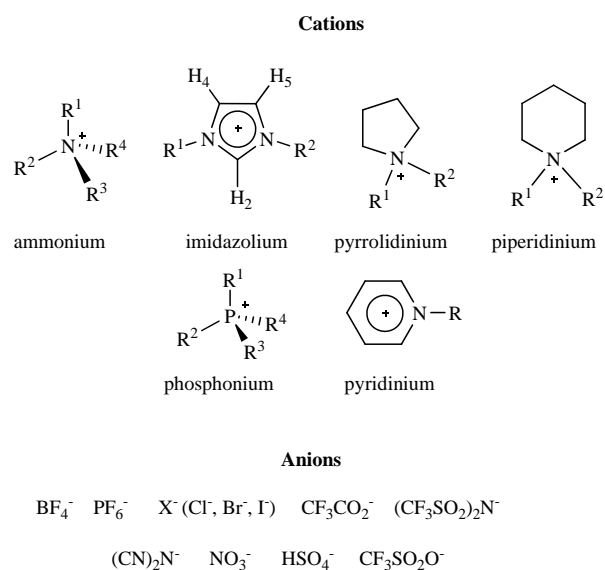
Cations

Anions

BF_4^- PF_6^- X^- (Cl^-, Br^-, I^-) $CF_3CO_2^-$ $(CF_3SO_2)_2N^-$

$(CN)_2N^-$ NO_3^- HSO_4^- $CF_3SO_2O^-$

Fig. (1). Some cations and anions frequently used in room temperature ionic liquid preparation.

2. SELECTED RECENT APPLICATIONS OF IONIC LIQUIDS IN ORGANIC SYNTHESIS AND CATALYSIS

The application of ILs as reaction media for organic synthesis is well documented [1]. To cite only a few recent examples, ILs have been utilized by Baj *et al*., as the solvent and catalyst, in the Bayer-Villiger (BV) oxidation of cyclic ketones to the corresponding lactones with bis(trimethylsilyl)peroxide (BTSP) [2]. When dichloromethane, classical solvent for these reactions, was substituted by 1-butyl-3-methylimidazolium salts [bmim][X] (X= Tf$_2$N, HSO$_4$, BF$_4$, TfO) higher or similar yields were obtained. In particular, with 1-butyl-3-methylimidazolium trifluoromethanesulfonate [bmim][TfO] as the solvent, the ketones are oxidized very efficiently (yields 72-91%) under mild conditions (25-40 °C) and within a short time, without any additional catalyst. The authors suggested an involvement of the anion TfO$^-$ in the reaction mechanism as confirmed by the fact that the reaction does not proceed without catalyst in the other ILs (Scheme **1**). Interestingly, the process is very selective for ketones possessing double bonds and no protection is needed [2]. In line with these results, Michael additions of malonodinitrile, and several other methylene active compounds, to chalcone were found to proceed successfully in pure ILs, mainly imidazolium salts; also in this case no additional catalyst was necessary [3].

*Address correspondence to this author at the CNR-Istituto di Scienze e Tecnologie Molecolari (ISTM), Via C.Golgi 19, I-20133 Milano, Italy; Tel +39-025-031-4162; Fax: +39-025-031-4159; E-mail: angelamaria.maia@istm.cnr.it
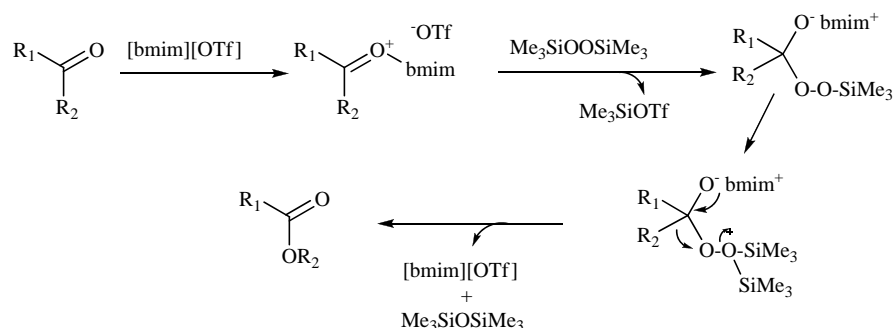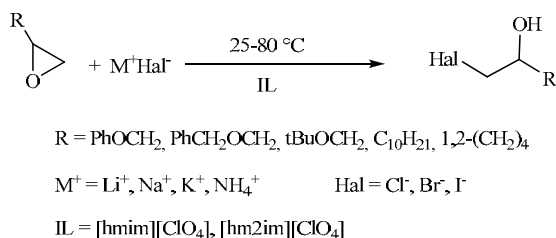
Scheme 1. Proposed mechanism of the BV oxidation of ketones by BTSP in the presence of [bmim][TfO] as the solvent and catalyst [2].

EWG = CN, COOMe, COMe
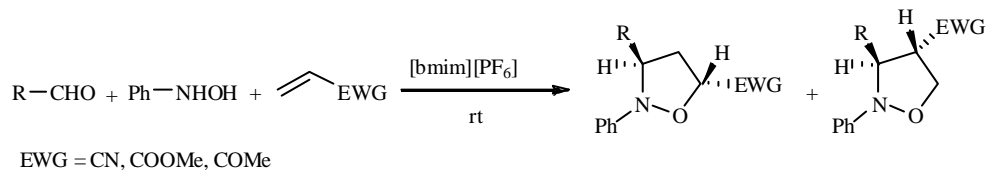
Scheme 2. One-pot preparation of isoxazolidines in imidazolium-based ILs [4].

An efficient protocol for the one-pot preparation of isoxazolidines has recently been performed by Yadav *et al.* [4]. 1-Butyl-3-methylimidazolium-based ILs significally accelerate the intermolecular 1,3-dipolar cycloaddition of nitrones, derived *in situ* from aldehydes and phenylhydroxylamine, with electrodeficient olefins (Scheme **2**). Isoxazolidines are obtained in high yields, with high regio- and diastereoselectivity. In addition, ILs can be easily recovered and reused in three to four subsequent runs without loss of activity, so making the process economic and environmentally benign [4].

We have reported a very simple and green procedure for the ring-opening of typical 1,2-epoxides to vic-halodrins by alkali metal and ammonium halides in 1-hexyl-3-methylimidazolium perchlorate [hmim][ClO$_4$] and 1-hexyl-2,3-dimethylimidazolium perchlorate [hm$_2$im][ClO$_4$] (Scheme **3**) [5].

R = PhOCH$_2$, PhCH$_2$OCH$_2$, tBuOCH$_2$, C$_{10}$H$_{21}$, 1,2-(CH$_2$)$_4$

M$^+$ = Li$^+$, Na$^+$, K$^+$, NH$_4^+$ Hal = Cl$^-$, Br$^-$, I$^-$

IL = [hmim][ClO$_4$], [hm2im][ClO$_4$]

Scheme 3. Ring-opening of 1,2 epoxides by alkali metal and ammonium halides in non-nucleophilic ILs [5].

In these systems the MHal salts are likely present as contact ion pairs externally solvated by the IL, in line with the low dielectric constant ($\varepsilon \leq 13$) inferred. When epoxides were treated with 2 equiv of metal halides, in [hmim][ClO$_4$] and [hm$_2$im][ClO$_4$] at 25-80 °C, they were converted into the corresponding β-halodrins in high to excellent yields (70-99%) depending on the metal salt.The data have evidenced metal ion electrophilic catalysis (Li$^+$>Na$^+$>>K$^+$).They have been rationalized on the basis of a transition state in which the cation M$^+$stabilizes the negative charge developing on the oxygen atom of the oxirane ring while favoring the nucleophilic attack at the adjacent carbon by the ion-paired anion Hal$^-$ (Scheme **4**).

Our results evidence in particular that Na$^+$ and NH$_4^+$ halides can be used as valid and ecosafe alternative to the more toxic and pollutive Li$^+$ salts in view of scaling-up processes. The reactions are
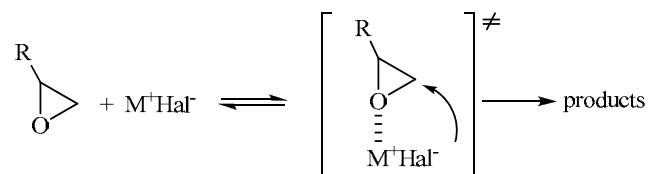

Scheme 4. Proposed transition state for the ring-opening of 1,2 epoxides [5].

highly regioselective affording the opening products in yields much higher than those reached in traditional dipolar media (MeCN) and comparable to those obtained in the very reactive MgHal$_2$/Et$_2$O system. Interestingly, the IL can be easily recovered and reused several times [5].

Recently, the Beckmann rearrangement of a representative series of oximes has been successfully carried out by us in imidazolium-based ILs in the presence of catalytic amounts of 2,4,6-trichloro[1,3,5]triazine (TCT), at 60 or 130°C (Scheme **5**) [6]. All reactions are fully regioselective affording only one of the two possible *N*-substituted amides in very good to quantitative yields. The results obtained with the cyclohexanone oxime are of particular interest due to the well known importance of ε-caprolactam. The conversion of the cyclohexanone oxime to ε-caprolactam proceeds quantitatively within two hours at 60°C in the presence of 20 mol% of TCT (82% with 2 mol% of catalyst after 14h). It is worth noting that cyanuric chloride revealed a cheap and effective catalyst and no Lewis or Brönsted acids as additional cocatalysts were necessary. Our data seem to indicate, once again, that not only the most acidic H-2 [7] (Fig. **1**), but all the hydrogens of the imidazolium cation are involved in the reaction (slightly slower reactions by using the methylated IL in which the hydrogen in the position C-2 is substituted by a methyl group). Comparison with common organic solvents has shown that in acetonitrile the amide formation proceeds in 3 h instead of 2 h under similar conditions. Also in this case IL was easily recovered and reused several times [6].

ILs are also found to play a leading role on the electron transfer reactions. These reactions are very common in nature, due to their importance in significant processes such as photosynthesis, respiration, nitrogen fixation. Song *et al.* have reported that imidazolium-based ILs exhibit a dramatic acceleration effect on the electron transfer from metal complexes [*e.g.* (C5Me5)$_2$ Fe(II) and (C5Me5)$_2$ Co(II)] to the oxygen molecule; this effect has been ascribed to the stabilization of the oxygen radical anions (1/4 O$_2^-$) by coordination
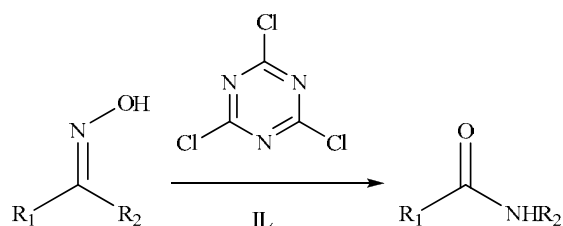
Scheme 5. TCT-catalyzed Beckmann rearrangement of oximes in ILs [6].

with the acidic H-2 of the IL [7] in the oxidation process (Fig. **2**) [8]. These findings have been confirmed in a recent paper concerning the reaction of thioanisole with singlet oxygen ($^1O_2$) in pyrrolidinium- and imidazolium-based ILs [9]. In these solvents, thioanisole shows a strongly enhanced reactivity with respect to molecular aprotic solvents (benzene, MeCN) probably due to a stabilization of the persulfoxide intermediate in the ionic medium. In addition, product isotope effects suggest a different mechanism, changing from imidazolium to pyrrolidinium solvents [9].
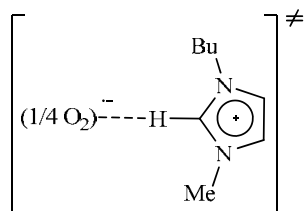

Fig. (2). Proposed intermediate for the aerobic oxidation in imidazolium-based IL [8].

ILs also revealed suitable solvents for photochemical reactions. In a recent study we have checked the stability of imidazolium-based ILs in the presence of the photogenerated *N,N*-dimethylaminophenyl cation, an highly reactive electrophile [10]. In arylation reactions, phenyl cation showed the same reactivity previously observed in medium polar solvents, such as CH_3CN, MeOH. However, it is worth noting that ESI-MS experiments, carried out at the end of the reaction, have revealed a partial functionalization of IL by an unprecedented insertion of the phenyl cation into the cation of the imidazolium salt. In addition, the non-negligible H-donor ability of the IL cation was once again confirmed [6-10].

Biocatalysis in imidazolium- or pyridinium-based ILs was reported for the first time by Erberlinger *et al.* in 2000 [11]. These unconventional media seem to affect enzymes in the same way that common organic solvents: some are tolerated well, but others much less, depending on the nature of the enzyme. Activities are generally comparable with or higher than those observed in organic media. Moreover, enhanced thermal and operational stabilities as well as regio- and enantioselectivities have been observed. In addition, it is worth noting the great potentiality of ILs as reaction media for biotransformations of highly polar substrates such as amino acids, nucleotides, and polysaccharides which cannot be performed in water due to the equilibrium limitations [12,13]. Recently, "task-specific" ionic liquids, obtained by chemical modification of their components (mainly the cationic part), have been successfully utilized in enzyme immobilization, a key technique for the preparation of robust biocatalysts [14].

ILs were also found novel solvents for biomass processing. For efficient energy conversion it is necessary to dissolve and depolymerize cellulose, the major component of such biomass, under mild reaction conditions. Cellulose is stabilized by multiple inter- and intramolecular H-bonding, resulting in highly ordered crystalline regions, and hence its solubilization is almost impossible with water or conventional media. At present, all the systems utilized for cellulose solubilization suffer drawbacks such as volatility or generation

of poisonous gas. In addition, multistep pretreatments and prolonged stirring are needed. Very recently, a series of alkylphosphate type [C2mim(MeO)(R)PO$_2$] ILs (Fig. **3**) has been prepared by a one-pot procedure. These high polarity ILs with strong H-bonding basicity β, relatively low viscosity and good thermal stability, successfully solubilize cellulose at high concentrations and, most importantly, at room temperature [15].
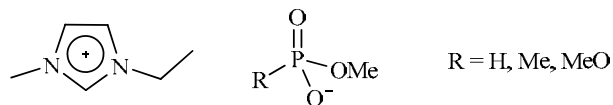

Fig. (3). Alkylphosphate type [C2mim(MeO)(R)PO$_2$] ionic liquids [15].

At present, the asymmetric catalysis in ILs is attracting increasing attention. Among the most recent examples, Nakano *et al.* have developed a highly efficient catalytic asymmetric Diels-Alder (DA) reaction of cyclopentadiene with acryloyl-1,3-oxazolidin-2-one using chiral Palladium-phosphinooxazolidine (POZ) catalysts (Fig. **4**) in seven different ILs (Scheme **6**). The best results, much better than those in a molecular solvent (CH_2Cl_2), were obtained using [bmim][BF$_4$] as IL (89% yield and 96% ee). In addition, the catalyst was easily reused eight times without any significant decrease in chemical yields or enantioselectivity [16a].
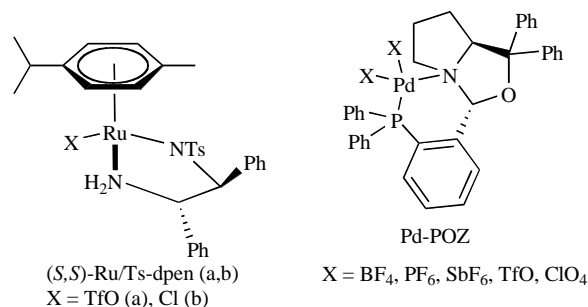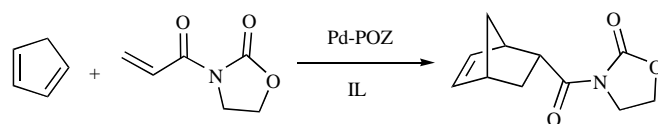

(*S,S*)-Ru/Ts-dpen (a,b)   Pd-POZ
X = TfO (a), Cl (b)   X = BF$_4$, PF$_6$, SbF$_6$, TfO, ClO$_4$

Fig. (4). (I)Ru/Ts-dpen catalysts.Ts-dpen=N-(p-toluenesulfonyl)-1,2-diphenylethylene-diamine. (II) Pd-phosphinooxazoline (Pd-POZ) complexes.

Scheme 6. Pd-POZ catalyzed asymmetric Diels-Alder reaction in IL [16a].

More recently, quinoline substrates were efficiently hydrogenated to give the corresponding 1,2,3,4-tetrahydroquinolines with excellent enantioselectivities (up to 99% ee) in neat [bmim][PF$_6$] without the need for additives (Scheme **7**) [16b]. The catalyst Ru/Ts-dpen (Fig. **4**), which was highly stable in IL and maintained the same activity even after exposure to air for 30 days, could be easily recycled. The enhancement of the catalyst stability by the IL was attributed to the solvation effect of [bmim][PF$_6$] on the cationic Ru catalyst and to the very low solubility of the oxygen in the IL [16b].
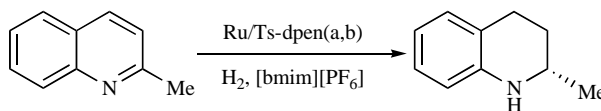
Scheme 7. Asymmetric hydrogenation of 2-methylquinoline catalyzed by Ru/Ts-dpen catalysts [16b].

The first example of an asymmetric synthesis in which only the reaction medium contains chiral information was reported by Leitner and co-workers [16c]. They have prepared the methyltrioctylammonium dimalatoborate in which the anion is chiral (Fig. **5**).
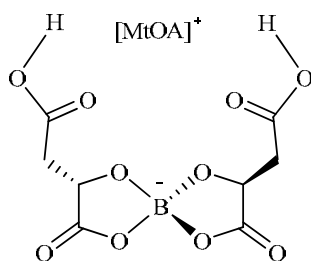
Fig. (5). Methyl trioctylammonium dimalatoborate (only one of the two possible diastereoisomers) [16c].

When this chiral IL was used as solvent, in aza-Baylis-Hillman reactions, high enantioselectivities (up to 84%) were obtained. In this case IL offers the possibility of establishing a bifunctional interaction between its chiral anion, containing a H-bond donor, and the zwitterionic intermediate of the reaction. These results are comparable with the values obtained with the best catalysts for the asymmetric aza-Baylis-Hillman reaction in conventional media (94% *ee* in THF, at -30 °C; 83% *ee* in CH$_2$Cl$_2$ at 40 °C) [16c].

ILs could also play an important role in the area of carbon dioxide fixation. Recently, the synthesis of disubstituted ureas from amines and CO$_2$ has been carried out by using the basic IL 1-butyl-3-methylimidazolium hydroxide [bmim][OH] as the catalyst [17]. Aliphatic amines, cyclohexylamine, and benzylamine have been selectively converted to the corresponding ureas in moderate yields (up to 58%) under solvent free conditions, without using any dehydrating agent. In addition, IL could be easily reused. (Scheme **8**) [17].
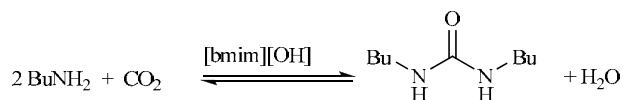
Scheme 8. Synthesis of *N,N'*-dibutylurea from *n*-butylamine and CO$_2$ [17].

3. REACTIVITY IN IONIC LIQUIDS AND MOLECULAR SOLVENTS

Despite the explosion of interest in developing the use of ILs as a potential "environmentally friendly" alternative to VOC solvents, there is a shortage of reliable quantitative information on reaction rates and rate constants in these novel media. The main reason is probably because some well-established rules and correlations for assessing the properties of molecular liquids cannot be easily transferred to ILs.

The simple qualitative theory of Hughes-Ingold [18], based upon an entirely electrostatic model of solvation, revealed not sufficient, as H-bonding interactions were often the main solvent-solute effects in these systems. The environment, in fact, is completely different. In ILs, as evidenced by theoretical and experimental studies [1], the strong ion-ion interactions lead to highly ordered three-dimensional supermolecular polymeric networks of anions and cations linked by H-bonds and/or Coulombic interactions. Interestingly, the long-range structural order found in solid phase is maintained in liquid phase and, to some extent, even in gas phase [1f]. ILs can be regarded as nano-structures with ionic networks permeated by non-polar regions, interacting with both dissolved polar species and with unpolar compounds. They can solvate not only long-lived dissolved species (reagents and products) but also transient species (transition states and intermediates) so determining selectivity and reactivity. Hence, the study of how the physicochemical properties of ILs can affect solute species and their reactivities is of great importance and topicality for predicting the optimum "designing" of IL solvents and decide when they provide substantial advantages over traditional media. The medium is well

known to play a leading role in determining the rate and outcome of a chemical process, particularly when anionic species are involved.

To date, only a few studies have quantitatively evaluated the effect of this novel class of solvents on the anion reactivity and made a comparison with traditional molecular solvents [19-23]. Nucleophilic substitution is the most extensively studied class of reactions in ILs. The pioneering papers by Lancaster, Welton *et al.* [19] have evidenced, for the first time, that the Hugues-Ingold approach describes well the effect of using an IL instead of a molecular solvent, but gives no insight into how changing the ions of the IL can exert an influence. The IL, in fact, is capable of acting both as a H-bond donor (cation) and /or as a H-bond acceptor (anion), so determining a different reactivity of the charged nucleophile, depending on the IL-solute interactions. The authors have measured the halide (Cl$^-$, Br$^-$, I$^-$) nucleophilicity in the S$_N$2 reaction with methyl *p*-nitrobenzenesulfonate to give methyl halide and *p*-nitrobenzenesulfonate anion in ILs with different cations [bmim]$^+$, [bm$_2$im]$^+$, [bmpy]$^+$ and anions [BF$_4$]$^-$, [PF$_6$]$^-$, [SbF$_6$]$^-$, [TfO]$^-$, and [Tf$_2$N]$^-$ (Scheme **9**).

$$X^- = Cl^-, Br^-, I^-$$
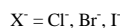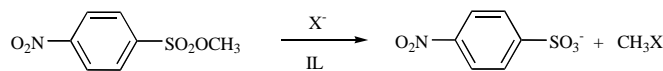
Scheme 9. Nucleophilic substitution reaction of methyl *p*-nitrobenzenesulfonate by halides in ILs [19].

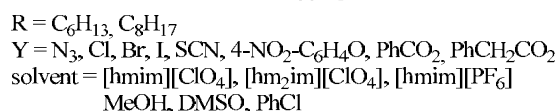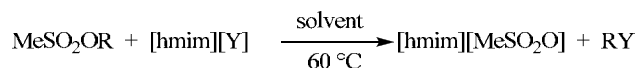The nucleophilicity order obtained is mainly determined by the IL cation-Hal$^-$ interaction, inverting on going from [bmim]$^+$ through [bm$_2$im]$^+$ to [bmpy]$^+$ (where the well known gas-phase nucleophilicities Cl$^-$> Br$^-$>I$^-$ are found) [19b]. On the other hand, changing the anion, when cation is [bmim]$^+$, also affected the nucleophilicity scale, *e.g.* in [bmim][BF$_4$] the order of nucleophilicity was Cl$^-$ > Br$^-$ >I$^-$ while in [bmim][Tf$_2$N] the order was I$^-$ > Br$^-$ > Cl$^-$ [19c]. The results as a whole are explained on the basis of empirical measures of solvent polarity, such as the Kamlet-Taft parameters, that describe H-bond acidity (α), H-bond basicity (β) and dipolarity/polarizability effects (π^*) of the IL, evidencing once again the importance of competition between ion-counterion and ion-solute interaction [19c-e]. To get more informations about the reaction mechanism, the authors have also compared the activation parameters with those previously found for the same reaction in dichloromethane, where the nucleophile (Cl$^-$) was either the free ion or an ion pair [19c]. They found that, while the $\Delta H^{\neq}$ values are comparable with those of the $\Delta H^{\neq}$ $_{ion\ pair}$ in dichloromethane, the T$\Delta S^{\neq}$ term presents a much higher barrier to reaction in IL, resembling that of the naked anion Cl$^-$. As expected, the reaction in IL is less favoured (higher $\Delta G^{\neq}$ values). These results suggest that the same process is occurring in the rate-limiting step of both dichloromethane and IL. In the latter, in particular, the nucleophile Cl$^-$ is coordinated by a number of IL cations to give ion-pair like behavior [19c].

The nature of both cation and anion of the IL was found to dramatically affect the reaction of alkyl halides and tosylates with NaN$_3$ and KCN under solid-liquid (IL) phase-transfer conditions (SL-PTC) [20]. Reactivity has been interpreted by considering a gradual shift of the mechanism from concerted S$_N$2 to stepwise S$_N$1 in the case of primary and tertiary substrates, respectively [20].

A kinetic study of the Menschutkin reaction of 1,2–dimethylimidazole with benzyl bromide to give 3-benzyl-1, 2-dimethylimidazolium bromide was performed by Neta *et al.* in 12 ionic liquids [21]. The results showed that the rate constants in the ILs are comparable with those in dipolar aprotic molecular solvents (acetonitrile, propylene carbonate) but much higher than those in weakly polar organic solvents and in alcohols. They mainly depend on the IL anion whereas the variations with the solvent cations are minimal. Harper *et al.* showed that the rate of the Menschtukin

reaction, between a series of benzyl bromides and pyridine, increases on going from CH_3CN to [bmim][Tf$_2$N] [22]. They attributed the rate acceleration in the IL to the change in the entropy of the system on reaching the transition state, which offsets a small increase in the entropy of activation. The reaction rate is independent of the nature of both aromatic substrate and the leaving group, being probably governed by the reorganization of the IL [22].

More recently, we have carried out a systematic study on the nucleophilicity of a representative series of anions by imidazolium salts in the S_N2 reaction of the methanesulfonic group, in *n*-hexyl- and *n*-octylmethanesulfonate, in non-nucleophilic ILs (1-hexyl-3-methylimidazolium perchlorate [hmim][ClO$_4$] and hexafluorophosphate [hmim][PF$_6$], 1-octyl-2,3-dimethylimidazolium perchlorate [om$_2$im][ClO$_4$]) and in common molecular solvents (MeOH, DMSO, PhCl) (Scheme **10**) [23].

$$MeSO_2OR + [hmim][Y] \xrightarrow[60\ °C]{solvent} [hmim][MeSO_2O] + RY$$

$R = C_6H_{13},\ C_8H_{17}$
$Y = N_3,\ Cl,\ Br,\ I,\ SCN,\ 4\text{-}NO_2\text{-}C_6H_4O,\ PhCO_2,\ PhCH_2CO_2$
$solvent = [hmim][ClO_4],\ [hm_2im][ClO_4],\ [hmim][PF_6]$
$\qquad\qquad MeOH,\ DMSO,\ PhCl$

Scheme 10. Nucleophilic substitution reactions in *n*-alkylmethanesulfonates by anions Y$^-$ in ILs and molecular solvents [23].

The results (Table **1**) show that the nucleophilicity order obtained in [hmim][ClO$_4$] (N$_3^-$>Cl$^-$>Br$^-$>I$^-$>SCN$^-$) parallels the well-known scales of these anions, in dipolar non-HDB solvents and in gas phase [24]. However, in the IL the values span a relatively narrow range, in particular for halides. These reactivity data are determined by the interaction of the anion with the ion-paired imidazolium cation as well as on the specific solvation by water present in the IL. When the substrate is reacted, in dry chlorobenzene, with the series of 1-octyl-2,3 dimethyl derivatives [om$_2$im] [Y$^-$], in which the H-2 is substituted by a methyl group, the nucleophilicity of all the anions increases, from 1.3 to 2.4 times (Table **1**).

These values are close to those obtained, for the same reaction, with the corresponding tetraoctylammonium salts that, due to their topology, are less prone to hydrogen-bond formation [23]. The enhancements found likely reflect the increasing interaction (H-bonding) of Y$^-$ with the ion-paired IL cation on increasing the charge density (charge *vs* ionic radius) of the anion, in particular for halides.

In addition, ILs are known to retain a significant amount of water after a standard work-up. This residual water can lead to unwanted by-products, change the product distribution and, most importantly, remarkably affect the reaction rate, especially when hydrophilic anions are involved [23]. We have explored the reactivity

of Cl$^-$ and PhCOO$^-$ in a wide hydration range (about 60 -19000 ppm H$_2$O) and found that the progressive water reduction in the IL produced a dramatic increase of the second-order rate constant k (M^{-1} s^{-1}) [23]. Interestingly, by plotting log$k$ *vs* log(ppmH$_2$O) an excellent linear correlation (R^2 = 0.999) is found so allowing to obtain the k value under hypothetical anhydrous conditions. Changing from 19000 to 0 ppm H$_2$O the gain of Cl$^-$ nucleophilicity is extrapolated to be 287 times for [hmim][Cl] and up to about 360 times for the dimethyl derivative [om$_2$im] [Cl], where no H-bond formation is expected [23]. Comparison with molecular solvents (Table **1**) has evidenced that when the IL is largely dehydrated the [hmim][Cl] reactivity approaches those of the "free ion" in DMSO and of the "loose ion pair" in low polarity media (PhCl). Our data, as a whole, have quantitatively proved that, for hydrophilic anions (Cl$^-$ and PhCOO$^-$), water plays the main role in determining the anion reactivity whereas the interaction with the imidazolium cation has, in this case, a lower effect [23].

4. COMPARISON WITH MOLECULAR SOLVENTS

When ILs are chosen as alternative to molecular solvents it is necessary at first to control the behavior (chemical stability) of the components ions, both cation and anion, under the reaction conditions to prevent "undesired" transformations. To name only a few examples, the hexafluorophosphate anion, in presence of moisture, can hydrolyze giving phosphate and HF, the hydrolysis being more pronounced in reactions involving metals which behave as catalysts [25]. Basic conditions favour the deprotonation, at the C-2 position of relatively high acidity (pKa = 21-23), of imidazolium cations generating *N*-heterocyclic carbenes [26]. In imidazolium-based ILs containing [Tf$_2$N], such as [bmim][Tf$_2$N], this "non nucleophilic" anion competes with the "nucleophilic" Br$^-$ in heterolytic dediazoniation reactions (99% of product Tf$_2$NPh) [27]. It confirms that nucleophilicity scales of common anions depend on the nature of IL and may be remarkably different from those in molecular media [19,23].

There are about 600 conventional solvents used in industry, whereas at least one million (10^6) simple ILs, 10^{12} binary combinations of these and 10^{18} ternary systems are potentially possible. In general, the cations of ILs control their physical properties (melting points, viscosity, density) and the anions are responsible for the chemical properties and reactivity. This means that, unlike molecular solvents, the ILs can be fine-tuned to optimize the chemistry, the chemical engineering, and the cost of the process.

4.1. Recycling

Despite the well documented advantages, ILs still remain almost 5-20 times more expensive than common molecular solvents, on a laboratory scale, unless there is the possibility of recycling them several times. Recycling is an important issue that addresses

Table 1. Second-order Rate Constants k (M^{-1}s^{-1}) for the Substitution Reaction of the Methanesulfonic Group by Anions Y$^-$ in [hmim][ClO$_4$] and Molecular Solvents, at 60 °C

Y	MeOH	$k\times10^4$ (M^{-1}s^{-1}) [hmim][ClO$_4$]^a	DMSO	PhCl^{b,c}
N$_3$	6.0	56.3	135.0	358
Cl	0.9	7.1(71)^d	36.0	75(280)^e
Br	2.2	5.3	23.0	71(196)^e
I	5.8	4.2	5.3	32(59)^e
SCN	1.7	1.3	2.7	7.2
4-NO$_2$C$_6$H$_4$O	–	5.4	–	41.5(73)^e
PhCO$_2$	–	5.3	–	32
PhCH$_2$CO$_2$	–	5.6	–	7.4

^{a} About 2000 ppm of water. ^{b} 30 ppm of water. ^{c} From [hmim][Y]. ^{d} Extrapolated value at 30 ppm of water. ^{e} From [om$_2$im][Y].

the economics of ILs use, particularly for large-scale applications.

Among the numerous examples, Afonso *et al.* reported that the recovering and reuse of the [bmim][PF$_6$] is feasible for almost 15 cycles in the azide substitution of 2-bromo-acetofenone in a [bmim][PF$_6$]-water two-phase system under liquid-liquid PTC conditions (r.t., 1.5 h, isolated yield > 94%) [28]. Efficient IL recycling was previously obtained by the same authors in the Baylis-Hillman reaction performed for a series of aldehydes in [bmim][PF$_6$] [29]. Since this IL is known to react with electrophilic aldehydes under basic conditions, Chu *et al.* prepared the 1-butyl-2,3 dimethylimidazolium-based IL [bm$_2$im][PF$_6$] in which its C-2 carbon is methylated. This new modified IL proved to be inert under the reaction conditions. Consequently, the Baylis –Hillman reaction proceeded smoothly with better yields (up to 99%) and [bm$_2$im][PF$_6$] could be recovered and reused at least four times [30] (Scheme 11).
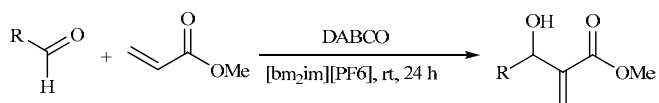

Scheme 11. DABCO-catalyzed Baylis-Hillmann reaction of aldehydes in ILs [30]

More recently, our group reported the recycle of [hmim][ClO$_4$] in the Beckmann rearrangement of ketoximes, catalyzed by cyanuric chloride. For example, the benzophenone oxime rearranged to the corresponding amide in similar yields and purity of the first run over three cycles (87%, 91%, 90%, respectively) [6].

4.2. Ionic Liquid Purity

Negligible volatility and non-flammability are two unique properties that distinguish ILs from traditional media. Although Seddon *et al.* demonstrated that several ILs could be vaporized (high temperature and low pressure) and recondensed without significant decomposition [31], the vapour pressure of all ILs is negligible near ambient temperature. As a consequence, conventionally used operations for the purification of organic compounds, in particular distillation, are not feasible for this new class of solvents [32]. On the other hand, an analytic purity of an IL is necessary for reliable data; variation in purity, in fact, is another major factor in reported discrepancies in physicochemical and thermodynamic property data [32]. The most important source of impurities in ILs originates from their preparation (Scheme 12).
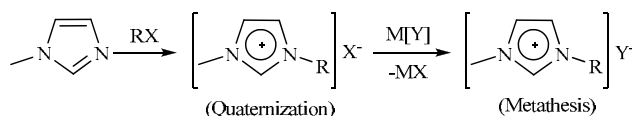
Scheme 12. Typical imidazolium-based ionic liquid synthesis.

When are IL syntheses green? In a recent paper Deetlefs and Seddon [33] assessed the greenness of some typical laboratory IL preparations using strengths weaknesses opportunities threats (SWOT) analysis, including their adherence to the twelve principles [34] of green chemistry, % atom economies and E-factors. For determining if a given process is "truly green" the E-factor concept, where all compounds that are not product are classified as waste, is of particular utility.

$$\text{E-factor} = \frac{\text{amount of waste produced in the process/kg}}{\text{amount of the desired product(s) produced in the process/kg}}$$

The nature of this equation dictates that the greenest chemical reactions have E-factor values close to zero. The E-factors for the preparations of imidazolium-based ILs fall between good and ex-

cellent, provided excess 1-haloalkane is kept to a minimum, no harmful organic solvent is used during the preparation, and any solvent is recycled [34]. Additionally, it is worth noting that the greenness factors associated with laboratory-scale IL preparations (< 2 kg) are quite different than those for industrial-scale syntheses. For example, in industrial scale processes, excess of 1-haloalkane is typically recycled, whereas in the laboratory it is usually discarded. Another example is that, on an industrial scale, the use of conductive heating (superheated stem) is preferred to microwave irradiation, the latter more convenient for laboratory-scale preparations. Microwave-promoted reactions, in fact, are faster than the same preparations performed using conductive heating, much smaller 1-haloalkane excess (about 1 mol %) compared to conventional preparations (up to 400 mol%) is required and the syntheses can be carried out solvent-free. As a consequence, the reactions are 100% atom efficient and have excellent (low) E-factors [34].

4.3. Toxicity of IL

The knowledge about the hazard potential of ILs to human beings and environment (cyto- and ecotoxicity) is still very basic and limited to only a few available ILs [35]. For this purpose Ranke *et al.* performed a systematic study on 100 ILs with different head groups, side chains and anions [36]. They found a general dependency between the IL cation lipophilicity and cytotoxicity, by using an HPLC derived lipophilicity parameter. Their investigations support the general hypothesis that the cytotoxicity effects of IL can be attributed to lipophilic interactions with cell membranes and cellular proteins, leading to disruption of membrane or protein function. The authors demonstrated that in general EC_{50} (μM) values of the ILs examined cover five orders of magnitude but significant cytotoxicity ($EC_{50} < 100$ μM) was only found for 4 compounds. Interestingly, a common IL such as [bmim][BF$_4$] shows neither a significant nor a negligible cytotoxicity (EC_{50} ~ 1000 μM) if compared with the reference 1-ethyl-3-methylimidazolium ethylsulfate (EC_{50} ~10 000 μM). The latter is, in turn, still some orders of magnitude more cytotoxic than ordinary polar organic solvents, *e.g.* methanol (1 600 000 μM), ethanol (700 000 μM), propanol (100 000 μM) [36].

In order to confirm the effects found in the cytotoxicity studies, the same research group examined the influence of anion species on the toxicity of 1-alkyl-3-methylimidazolium ILs in an (eco)toxicological test battery [37]. To take the complexity of an ecosystem into account, the test battery included enzymes, mammalian cells, bacteria, algae, aquatic and terrestrial plants, invertebrates. The results confirmed higher toxicity with increasing side alkyl chain length: [omim][BF$_4$] toxicity 1 or 2 orders of magnitude higher than [bmim][BF$_4$]. For Tf$_2$N$^-$ a clear (eco)toxicological hazard potential is evident, whereas for the other anions the effect is not as distinct as the demonstrated side chain length effect. Finally, when comparing the results of [bmim][BF$_4$] and [omim][BF$_4$] with acetone and CH$_3$CN the toxicities of both ILs were found to be 2 to 7 orders of magnitude higher [37].

In a recent paper, Pretti *et al.* studied the acute toxicity (EC_{50}) of three commonly used ILs ([bmim][Tf$_2$N], [bpy][Tf$_2$N], [bmpyrr][Tf$_2$N]) and 15 other less known salts for three fresh water organisms [38]. Their results are in line with the previous literature data. ILs show a different degree of acute toxicity to aquatic organisms and the cation plays a leading role. Generally ILs having structures more similar to those of surfactants (long-chain ammonium salts) showed higher toxicities, whereas very low toxicities characterized sulfonium- and morpholinium-based ILs [38].

4.4. Biodegradability

Although toxicity determinations of ILs have been widely reported in the literature, biodegradation data are comparatively scarce and more recent. Biodegradable ILs have been prepared, by

Boethling *et al.*, starting from the same principles used to improve biodegradation of the structurally closed surfactants [39, 40]. Gathergood and Scammel were the first to introduce functional groups which would be susceptible to enzymatic hydrolysis (esters/amides) into the IL imidazolium cation side chain (Scheme **13**) [41, 42]. Whereas imidazolium–based ILs with ester side chains are generally liquids at room temperature, the amide derivatives have higher melting points.

$X = BF_4$, PF_6, Tf_2N, $(CN)_2N$
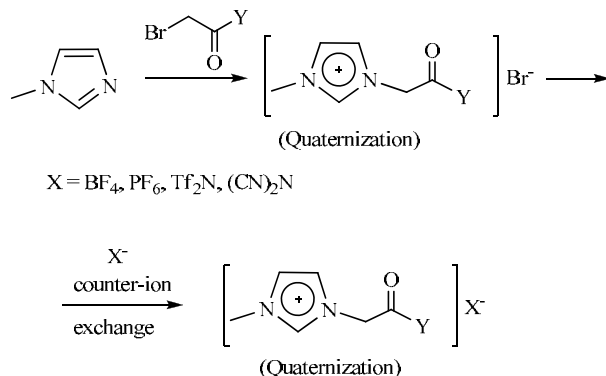
Scheme 13. Functionalization of imidazolium-based ILs [41, 42].

The authors found that incorporation of an ester group, into the IL side chain, significantly improved the biodegradation, whereas amide analogous proved resistant to biodegradation. The presence of the ester in the side chain, in fact, provides a site for possible enzymatic cleavage to give the parent imidazolium fragment and the corresponding primary alcohol that may be readily metabolised *via* fatty acid β-oxidation [41, 42].

It is worth noting, however, that the design of biodegradable ILs has to balance the favourable biodegradability with the required stability and the practical applicability. When biodegradable imidazolium-based ILs have been utilized as reaction media, for Diels-Alder and hydrogenation reactions, superior product selectivities have been observed compared with conventional organic solvents (THF, MeOH, Ethylacetate) and even commercial ILs [43, 44].

5. CONCLUSIONS

The data here reported show that ILs behave as a valid alternative to traditional organic solvents in a number of common reactions. They are found to enhance rates and isolated yields of products, often influencing the selectivity of the process. Kinetic measurements have also evidenced that anionic reactivity in these high polarity media is mainly determined by the structure of IL (different IL-solute interaction) and may be remarkably different from that in traditional media. In addition to the favourable physical and chemical properties, the negligible vapour pressure and low flammability of ILs make them interesting as potentially "green" alternative to VOCs. These added benefits, however, are not sufficient to label ionic liquids as "green" if the effect on the human beings and environment are not carefully examined. Cyto- and ecotoxicity evaluations have evidenced that only some ILs are not "environmentally benign" solvents, the structure of the cationic part playing a leading role. On the other hand, recent biodegradation studies have shown that the introduction of an hydrolyzable ester functionality into the alkyl side chain of the cation reduces toxicity and improves ecosustainability. Recovering and reuse of the solvent could be a useful tool to cut down not only toxicity but also the cost of many ILs, particularly for large scale applications. It is desirable that, in the near future, ecological considerations are just as important as synthetic parameters in designing the structures of the next generation of ILs. The ILs, so tailored by an appropriate choice of cation and anion, could represent a real "green" alternative to traditional organic solvents.

REFERENCES

[1] For general books and reviews on ionic liquids, see: (a) *Ionic Liquids III A: Fundamentals, Progress, Challenges and Opportunities-Properties and Structure*; Rogers, R. D.; Seddon, K. R., Eds; American Chemical Society: Washington DC, **2005**. (b) *Ionic Liquids III B: Fundamentals, Progress, Challenges and Opportunities-Transformations and Processes*; Rogers, R. D.; Seddon, K. R., Eds; American Chemical Society: Washington DC, **2005**. (c) *Ionic Liquids in Synthesis (2nd ed.)*; Wasserscheid, P. ; Welton, T., Eds; Wiley-VCH: Weinheim, Germany, **2008**. (d) Plechkova, N. V.; Seddon, K.R. Applications of ionic liquids in the chemical industry. *Chem. Soc. Rev.,* **2008**, *37*, 123-150. (e) Kerton, F. M. in *Alternative Solvents for Green Chemistry* RSC Green Chemistry Series, The Royal Society of Chemistry: Cambridge, UK, **2009**. (f) Dupont, J.; de Souza, R.F.; Suarez, P.A.Z. Ionic liquid (molten salt) phase organometallic catalysis. *Chem. Rev.* **2002**, *102*, 3667-3692.

[2] Baj, S.; Chrobok, A.; Slupska, R. The Baeyer-Villiger oxidation of ketones with bis(trimethylsilyl) peroxide in the presence of ionic liquids as the solvent and catalyst. *Green Chem.*, **2009**, *11*, 279-282.

[3] Meciarova, M.; Toma, S. Michael additions of methylene active compounds to chalcone in ionic liquids without any catalyst: the peculiar properties of ionic liquids. *Chem. Eur. J.*, **2007**, *13*, 1268-1272.

[4] Yadav, J.S.; Reddy, B.V.S.; Sreedhar, P.; Murthy, Ch.V.S.R.; Manesh, G.; Kondaji, G.; Nagaiah, K. Three component coupling reactions in ionic liquids: One-pot synthesis of isoxazolidines. *J. Mol. Catal. A: Chem.*, **2007**, *270*, 160-163.

[5] Betti, C.; Landini, D.; Maia, A. Metal ion electrophilic catalysis' in ring-opening reactions of 1,2-epoxides by metal halides in ionic liquids. *Synlett*, **2006**, 1335-1338.

[6] Betti, C.; Landini, D.; Maia, A.; Pasi, M. Beckmann rearrangement of oximes catalyzed by cyanuric chloride in ionic liquids. *Synlett*, **2008**, 908-910.

[7] Kim, Y.-J.; Streitwieser, A. Basicity of a stable carbene, 1,3-di-*tert*-butylimidazol-2-ylidene, in THF. *J. Am. Chem. Soc.*, **2002**, *124*, 5757-5761.

[8] Choi, D.S,; Kim, D.H.; Shin, U.S.; Deshmukh, R.R.; Lee, S., Song, C.E. The dramatic acceleration effect of imidazolium ionic liquids on electron transfer reactions. *Chem. Commun.*, **2007**, 3467-3469.

[9] Baciocchi, E.; Chiappe, C.; Del Giacco, T.; Fasciani, C.; Lanzalunga, O.; Lapi, A.; Melai, B. Reaction of singlet oxygen with thioanisole in ionic liquids: a solvent induced mechanistic dichotomy. *Org. Lett.*, **2009**, *11*, 1413-1416.

[10] Dichiarante, V.; Betti, C.; Fagnoni, M.; Maia, A.; Landini, D.; Albini, A. Characterizing ionic liquids as reaction media through a chemical probe. *Chem. Eur. J.*, **2007**, *13*, 1834-1841.

[11] Erbeldinger, M.; Mesiano, A.J.; Russel, A.J. Enzymatic catalysis of formation of Z-aspartame in ionic liquid-an alternative to enzymatic catalysis in organic solvents. *Biotechnol. Prog.,* **2000**, *16*, 1129-1131.

[12] Van Rantwijk, F.; Lau, R.M.; Sheldon, R.A. Biocatalytic transformations in ionic liquids. *Trends Biotechnol.*, **2003**, *21*, 131-138.

[13] Van Rantwijk, F.; Sheldon, R.A. Biocatalysis in ionic liquids. *Chem. Rev.,* **2007**, *107*, 2757-2785.

[14] Nakashima, K.; Kamiya, N.; Koda, D.; Maruyama, T.; Goto, M. Enzyme encapsulation in microparticles composed of polymerized ionic liquids for highly active and reusable biocatalysts. *Org. Biomol. Chem.,* **2009**, *7*, 2353-2358.

[15] (a) Fukaya, Y.; Hayashi, K.; Wada, M.; Ohno, H. Cellulose dissolution with polar ionic liquids under mild conditions: required factors for anions. *Green Chem.* **2008**, *10*, 44-46. (b) Ohno, H.; Fukaya, Y. Task specific ionic liquids for cellulose technology. *Chem. Lett.*, **2009**, *38*, 1-7.

[16] (a) Takahashi, K.; Nakano, H.; Fujita, R. Reuse of chiral cationic Pd-phosphinooxazolidine catalysts in ionic liquids: highly efficient catalytic asymmetric Diels-Alder reactions. *Chem. Commun.*, **2007**, 263-265. (b) Zhou, H.; Li, Z.; Wang, Z.; Wang, T.; Xu, L.; He, Y.; Fan, Q.-H.; Pan, J.; Gu, L.; Chan, A. S. C. Hydrogenation of quinolines using a recyclable phosphine-free chiral cationic ruthenium catalyst: enhancement of catalyst stability and selectivity in an ionic liquid. *Angew. Chem. Int. Ed.,* **2008**, *47*, 8464-8467. (c) Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C.W.; Klankermayer, J.; Leitner, W. Highly enantioselective Aza-Baylis-Hillman reaction in a chiral reaction medium. *Angew. Chem. Int. Ed.*, **2006**, *45*, 3689-3692 and references cited therein.

[17] Jiang, T.; Ma, X.; Zhou, Y.; Liang, S.; Zhang, J.; Han, B. Solvent-free synthesis of substituted ureas from CO_2 and amines with a functional ionic liquid as the catalyst. *Green Chem.,* **2008**, *10*, 465-469.

[18] (a) Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Itaca/NY and London, **1969**. (b) Hughes, E. D.; Ingold, C.K. Mechanism of substitution at a saturated carbon atom. Part IV A discussion of constitutional and solvent effects on the mechanism. Kinetics, velocity, and orientation of substitution. *J. Chem. Soc.*, **1935**, 244-255; The mechanism and kinetics of elimination reactions. *Trans. Faraday Soc.* **1941**, *37*, 657-685. (c) Cooper, K.A.; Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J.; Woolf, L.I. Mechanism of elimination reactions. Part VII. Solvent effects on rates and product-proportions in uni- and bi-molecular substitution and elimination reactions of alkyl halides and sulphonium salts in hydroxylic solvents. *J. Chem. Soc.*, **1948**, 2043-2049.

[19] (a) Lancaster, N.L.; Welton, T.; Young, G.B. A study of halide nucleophilicity in ionic liquids. *J. Chem. Soc. Perkin Trans. 2*, **2001**, 2267-2270. (b) Lan-

caster, N.L.; Salter, P.A.; Welton, T.; Young, G.B. Nucleophilicity in ionic liquids. 2. Cation effects on halide nucleophilicity in a series of bis(trifluoromethylsulfonyl)imide ionic liquids. *J. Org. Chem.*, **2002**, *67*, 8855-8861. (c) Lancaster, N.L.; Welton, T. Nucleophilicity in ionic liquids. 3. Anion effects on halide nucleophilicity in a series of 1-butyl-3-methylimidazolium ionic liquids. *J. Org. Chem.,* **2004**, *69*, 5986-5992. (d) Lancaster, N.L. Organic reactivity in ionic liquids: some mechanistic insights into nucleophilic substitution reactions. *J. Chem. Res.,* **2005**, 413-417 and references cited therein. (e) Crowhurst, L.; Falcone, R.; Lancaster, N.L.; Llopis-Mestre, V.; Welton, T. Using Kamlet-Taft solvent descriptors to explain the reactivity of anionic nucleophiles in ionic liquids. *J. Org. Chem.,* **2006**, *71*, 8847-8853.

[20]   Chiappe, C.; Pieraccini, D.; Saullo, P. Nucleophilic displacement reactions in ionic liquids: substrate and solvent effect in the reaction of NaN$_3$ and KCN with alkyl halides and tosylates. *J. Org. Chem.*, **2003**, *68*, 6710-6715.

[21]   Skrzypczak, A.; Neta, P. Rate constants for reaction of 1,2-dimethylimidazole with benzyl bromide in ionic liquids and organic solvents. *Int. J. Chem. Kinet.*, **2004**, *36*, 253-258.

[22]   (a) Yau, H.M.; Howe, A.G.; Hook, J.M.; Croft, A.K.; Harper, J.B. Solvent reorganisation as the driving force for rate changes of Menschutkin reactions in an ionic liquid. *Org. Biomol. Chem.*, **2009**, *7*, 3572-3575. (b) Harper, J.B.; Kobrak, M.N. Understanding organic processes in ionic liquids: achievements so far and challenges remaining. *Mini-Rev. Org. Chem.*, **2006**, *3*, 1-17.

[23]   (a) Landini, D.; Maia, A. Anion nucleophilicity in ionic liquids: a comparison with traditional molecular solvents of different polarity. *Tetrahedron Lett.,* **2005**, *46*, 3961-3963. (b) Betti, C.; Landini, D.; Maia, A. Reactivity of anionic nucleophiles in ionic liquids and molecular solvents. *Tetrahedron*, **2008**, *64*, 1689-1695.

[24]   (a) Landini, D.; Maia, A.; Montanari, F. Phase-Transfer catalysis. Nucleophilicity of anions in aqueous organic two-phase reactions catalyzed by onium salts. A comparison with homogeneous organic systems. *J. Am. Chem. Soc.* **1978**, *100*, 2796-2801 and references cited therein. (b) Maia, A. Anion activation by quaternary onium salts and polyether ligands in homogeneous and heterogeneous systems. *Pure Appl. Chem.* **1995**, *67*, 697-702. (c) Reichardt, C. In: *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, **2003**; pp. 237-273 and references cited therein.

[25]   Dupont, J.; Spencer, J. On the noninnocent nature of 1,3-dialkylimidazolium ionic liquids. *Angew. Chem. Int. Ed.,* **2004**, *43*, 5296-5297.

[26]   Chowdhury, S.; Mohan, R.S.; Scott, J.L. Reactivity of ionic liquids. *Tetrahedron,* **2007**, *63*, 2363-2389.

[27]   Bini, R.; Chiappe, C.; Marmugi, E.; Pieraccini, D. The "non-nucleophilic" anion [Tf$_2$N]$^-$ competes with the nucleophilic Br$^-$: an unexpected trapping in the dediazoniation reaction in ionic liquids. *Chem. Commun.,* **2006**, 897-899.

[28]   Afonso, C.A.M.; Branco, L.C.; Candeias, N.R.; Gois, P.M.P.; Lourenço, N.M.T.; Mateus, N.M.M.; Rosa, J.N. Efficient catalyst reuse by simple dissolution in non-conventional media. *Chem. Commun.,* **2007**, 2669-2679 and references cited therein.

[29]   Rosa, J.N.; Afonso, C.A.M.; Santos, A.G. Ionic liquids as a recyclable reaction medium for the Baylis-Hillman reaction. *Tetrahedron*, **2001**, *57*, 4189-4193.

[30]   Hsu, J.; Yen, Y.; Chu, Y. Baylis-Hillman reaction in [bdmim][PF$_6$]ionic liquid. *Tetrahedron Lett.,* **2004**, *45*, 4673-4676.

[31]   Earle, M. J.; Esperança, J.M.S.S.; Gilea, M.A.; Canongia Lopes, J.N.; Rebelo, L.P.N.; Magce, J.W.; Seddon, K.R.; Widegren, J.A. The distillation and volatility of ionic liquids. *Nature*, **2006**, *439*, 831-833.

[32]   Stark, A.; Behrend, P.; Braun, O.; Müller, A.; Ranke, J.; Ondruschka, B.; Jastorff, B. Purity specification methods for ionic liquids. *Green Chem.,* **2008**, *10*, 1152-1161.

[33]   Deetlefs, M.; Seddon, K.R. Assessing the greenness of some typical laboratory ionic liquid preparations. *Green Chem.,* **2010**, *12*, 17-30.

[34]   Tang, S.; Bourne, R.; Smith, R.; Poliakoff, M. The 24 principles of green engineering and green chemistry: "improvements productively". *Green Chem.,* **2008**, *10*, 268-269.

[35]   Ranke, J.; Stolte, S.; Störmann, R.; Arning, J.; Jastorff, B. Design of sustainable chemical products-the example of ionic liquids. *Chem. Rev.,* **2007**, *107*, 2183-2206.

[36]   Stolte, S.; Arning, J.; Bottin-Weber, U.; Müller, A.; Pitner, W.; Weltz-Biermann, U.; Jastorff, B.; Ranke, J. Effects of different head groups and functionalised side chains on the cytotoxicity of ionic liquids. *Green Chem.,* **2007**, *9*, 760-767.

[37]   Matzke, M.; Stolte, S.; Thiele, K.; Juffernholz, T.; Arning, J.; Ranke, J.; Welz-Biermann, U.; Jastorff, B. The influence of anion species on the toxicity of 1-alkyl-3-methylimidazolium ionic liquids observed in an (eco)toxicological test battery. *Green Chem.,* **2007**, *9*, 1198-1207.

[38]   Pretti, C.; Chiappe, C.; Baldetti, I.; Brunini, S.; Monni, G.; Intorre, L. Acute toxicity of ionic liquids for three freshwater organisms: Pseudokirchneriella subcapitata, Daphnia magna and Danio rerio. *Ecotoxicol. Environ. Saf.,* **2009**, *72*, 1170-1176.

[39]   Boethling, R.S. *Cationic Surfactants*, in *Surfactant Science Series*, Marcel Dekker, New York, **1994**, vol. *53*, pp. 95-135.

[40]   Boethling, R.S.; Sommer, E.; DiFiore, D. Designing small molecules for biodegradability. *Chem. Rev*., **2007**, *107*, 2207-2227.

[41]   Gathergood, N.; Scammells, P.J. Design and preparation of room-temperature ionic liquids containing biodegradable side chains. *Aust. J. Chem.*, **2002**, *55*, 557-560.

[42]   Coleman, D.; Gathergood, N. Biodegradation studies of ionic liquids. *Chem. Soc. Rev.,* **2010**, *39*, 600-637.

[43]   Bouquillon, S.; Courant, T.; Dean, D.; Gathergood, N.; Morrissey, S.; Pegot, B.; Scammells, P.J.; Singer, R.D. Biodegradable ionic liquids: selected synthetic applications. *Aust. J. Chem.,* **2007**, *60*, 843-847.

[44]   Morrissey, S.; Pegot, B.; Coleman, D.; Garcia, M.T.; Ferguson, D.; Quilty, B.; Gathergood, N. Biodegradable, non-bactericidal oxygen-functionalised imidazolium esters: A step towards "greener" ionic liquids. *Green Chem.,* **2009**, *11*, 475-483.