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1. Introduction

Molten salts which are ionic (i.e. a mixture of cation and anion) in nature and have a melting point below 100 °C are termed as Ionic liquids (ILs). [1] Preferably salts which are liquid at room temperature are called room temperature ionic liquids (RTILs). ILs have received great attention in the last couple of decades due to their unique properties such as low vapour pressure, high thermal stability, recyclability, non-flammability, and control over the product distribution. [2,3] Due to the control over fugative emission; ILs can be a replacement for volatile organic compounds (VOCs) which are commonly used as solvents in organic processes. Since the first ionic liquid was reported, [4] there has been a large number of articles been published with different types of cations and anions. One can easily design $10^{18}$ possible structures of ILs by varying cations and anions. This makes them “designer” molecules. [5-9] These designed combinations have already been found useful in different fields of chemistry, such as organic chemistry, [10-14] electrochemistry, [15-19] analytical chemistry, [20-24] and biochemistry. [15,25]

There are five major classes of cations in ILs e.g. ammonium, pyridinium, imidazolium, phosphonium and sulfonium (Figure 1).

Along with these, there are a large number of commonly used anions such as halides (chloride, bromide, iodide), bis(trifluoromethanesulfonimide) (NTf$_2$), tetrafluoroborate (BF$_4$), hexafluorophosphate (PF$_6$), octyl sulfate (OctOSO$_3$), acetate (OAc) and dicynamide (N(CN)$_2$) to name a few. Change in the anionic component can drastically affect physical properties of an ionic liquid such as hydrophilicity, viscosity and melting point.
2. Applications of ionic liquids in organic synthesis

Ionic liquids have been widely exploited in numerous organic reactions due to the versatility in the physical properties such as ease of product separation, [26,27] enhancement in rate of reaction, [28-30] catalyst immobilization, [31-33] and recyclability. [34-36] Modifications in cations and/or anions have facilitated their use in organic reactions while playing a role of reagent, solvent or catalyst. This can be reflected in a huge number of publications. Hence we are discussing, in our opinion only interesting representative examples here in this chapter.

In this chapter the aim is to demonstrate the versatility of ionic liquids in organic synthesis. We are also going to discuss the environmental fate of ionic liquids by addressing the importance of toxicity, eco(toxicity), biodegradation and green chemistry metrics. By exploring these parameters one can design and synthesise safer and greener catalyst/solvent.
2.1. Heck reaction

The palladium catalysed C-C bond forming reaction between aryl halide or vinyl halide (or triflate) and activated alkene in presence of base is known as the Heck reaction. [37] This reaction is named after Prof. Richard F. Heck, for which he was awarded Nobel Prize in Chemistry 2010, “for palladium-catalyzed cross couplings in organic synthesis” jointly with Prof. Ei-ichi Negishi and Prof. Akira Suzuki. This reaction is also known as Mizoroki-Heck reaction, as Tsutomu Mizoroki was the first to report this reaction. [38] A large variety of organic and inorganic bases can be used in this reaction. Phosphine ligands have been used to stabilize the catalytic system in molecular solvents. Although the reaction conditions are mild, the major drawback is that it is difficult to recycle the palladium catalyst in traditional solvents. Kaufmann and co-workers (1996) were first to demonstrate the use of tetraalkylammonium salts as an effective solvent in Heck reaction. [39] Since then a large number of publications have shown that different class of ILs can be used as solvent, catalyst or as a ligand in the Heck reaction. [40] L. Wang and co-workers have reported the Heck reaction of aryl halide and styrene (Scheme 1) in an ethanolamine-functionalized quaternary ammonium bromide which act as base, ligand and solvent. [41]

![Diagram of Heck reaction](image-url)

**Figure 2.** The functions of DHEABTBAB IL in the Heck reaction
The task specific ionic liquid i.e. 4-Di(hydroxyethyl)aminobutyl tributylammonium bromide (DHEABTBAB) (Figure 2) and palladium acetate served as an excellent catalytic system for the cross-coupling of a variety of olefins and aryl halides to give good to excellent results. The Heck reactions of styrene and iodobenzene/bromobenzene have shown excellent conversions and yield (>99%), whereas reaction of styrene and chlorobenzene have given only 66% yield. The reactions of activated and deactivated bromobenzenes and styrene/acrylates generated good to excellent yields (82 to 99%). This catalytic system was also successfully recycled and reused up to 6 times without significant loss of activity. Transmission electron microscopy (TEM) image of Pd-nanoparticles formed in (DHEABTBAB) showed even distribution due to ethanolamine moiety of the IL, which can either coordinate to the palladium or point away from the surface of the nanoparticle.

Scheme 1.

In an attempt to eliminate the use of phosphine ligands, Xaio and co-workers demonstrated the *in situ* formation of a \(N\)-heterocyclic carbene complex with palladium when 1,3-dialkylimidazolium ILs were used as a solvent under basic conditions to generate carbene ligand. [42] They had successfully isolated the palladium carbene complex, by deprotonation of imidazolium-based ionic liquids in presence of base to form the catalytic precursor. Such participation of \(N\)-heterocyclic carbene as a ligand was predicted by Seddon. [43]
Scheme 2. Stepwise formation of N-heterocyclic carbene complex of palladium

[BMIM] based ionic liquid and palladium acetate in presence of base such as sodium acetate first formed dimeric carbene complex, which eventually gave monomeric carbene complexes (Scheme 2). Existence of all four isomers of monomeric carbene complex was confirmed by $^1$H-NMR. The Heck reaction of aryl halides with acrylates/styrene in ionic liquid under the reaction conditions have performed better than the isolated trans isomer of N-heterocyclic carbene complex in ionic liquid. This might be due to the presence of other active palladium species formed in situ. Shrinivasan and co-workers have further supported such formation of Pd-carbene complex in [BMIM] based IL and accelerated the reaction under ultrasonic irradiation even at room temperature. [44]

Attempts and further efforts into increasing the recyclability of palladium catalyst and to reduce the use of solvent resulted in exploration of solid supported ionic liquids for use in the Heck reaction. [45,46] B. Han and co-workers have reported copolymerized ionic liquid supported palladium nanoparticles as an effective catalyst for the Heck reaction under solvent-free conditions. [47] The 1-aminoethyl-3-vinylimidazolium bromide i.e. [VAIM][Br] ionic liquid was grafted on cross-linked polymer polydivinylbenzene (PDVB). The palladium nanoparticles were anchored onto the polymer via the amino group in the ionic liquid (Scheme 3). Formation of the catalyst was confirmed by a number of analytical techniques such as X-ray photoelectron spectroscopy, transmission electron microscopy, Fourier transform infrared spectroscopy, etc.
The Heck reactions of a variety of iodobenzenes and acrylates have shown excellent conversions (above 93%) irrespective to the substitution on benzene ring. Triethylamine served as a good base under the reaction conditions. Due to the insoluble nature of cross-linked polymer and strong co-ordination between amino group and palladium nanoparticles, the catalyst was recovered very easily by filtration and washed with ethanol. The PDVB-IL-Pd catalyst was very active even after the 4th recycle and was confirmed by TEM image. The excellent stability of the catalyst was due to its insoluble nature in both reactants and product, and high thermal stability i.e. up to above 220 °C.

2.2. Sonogashira reaction

The palladium catalysed C-C coupling reaction of aryl halide and terminal acetylene is known as the Sonogashira reaction. Copper iodides have also been used as a co-catalyst in this reaction. [48] A stoichiometric amount of base is always used as acid (HX) scavenger. This is a widely used and efficient way to prepare substituted or unsubstituted acetylenes. Although Sonogashira coupling reactions works well under mild conditions, the drawback of this reaction is that copper catalysts used can promote side reactions, such as Glaster-type homocoupling of acetylenes. [49-53]

Ryu and co-workers have reported a palladium(II) catalysed efficient Sonogashira coupling in ionic liquid, without any copper co-catalyst. [54] The reactions with an aryl halides and alkyl/aryl acetylenes were carried out in [BMIM][PF$_6$] as a solvent and diisopropylamine or piperidine as a base. A number of palladium catalyst were screened in the Sonogashira reaction, where bis(triphenylphosphine)palladium(II) dichloride showed high catalytic activity in absence of copper co-catalyst. The Sonogashira reactions of aryl halides and alkyl/aryl acetylenes gave respective dialkyl/diaryl acetylenes in good yields (87-97%).
The group has successfully demonstrated the application of this reaction in a microflow reactor with IMM micromixer. Iodobenzene, phenylacetylene and base dibutylamine (syringe A) was added via one inlet to IMM’s micromixer and Pd catalyst and [BMIM][PF$_6$] (syringe B) at the other inlet by using syringe pump (Scheme 4). After reacting in micromixer for 10 min., the product was easily isolated by Hexane/Water extraction, where Pd catalyst in ionic liquid was recycled and reused with slight loss of activity.

In an effort to develop an air stable copper free Sonogashira reaction, Wu, Liu and co-workers have reported palladium complex functionalized ionic liquid as a catalyst in Sonogashira reaction in [BMIM][PF$_6$] under aerobic and copper free conditions. [55]
The functionalized ionic liquid i.e. di-(1-butyl-2-diphenylphosphino-3-methylimidazolium)-dichloridopalladium(II) hexafluorophosphate showed efficient catalytic activity and recyclability in coupling reactions (Scheme 5). A clear trend i.e. I>Br>Cl was observed in aryl halide and phenylacetylene couplings. Iodobenzene have shown excellent reactivity with variety of terminal acetylenes (90-99%) in Sonogashira coupling. The phosphine-ligated palladium complex functionalized ionic liquid was easily recycled and reused. Recyclability experiments displayed a gradual loss of activity of the catalyst in [BMIM][PF$_6$] after 6 recycles (100% to 68% yields), whereas rapid loss of activity in CH$_3$CN after 4 recycles (98% to 48% yields).

2.3. Suzuki coupling

The Suzuki reaction is a palladium catalysed coupling between aryl/vinyl boronic acid and aryl/vinyl halide in presence of base. This reaction is named after Prof. Akira Suzuki (Nobel Prize in Chemistry, 2010) and also referred to as Suzuki-Miyaura coupling. [56-58] It is one of the important C-C bond forming reaction in the synthesis of styrene and substituted biaryl compounds.

Wei and co-workers have developed a highly efficient silica supported ionic liquid with palladium incorporated anion catalyst for the Suzuki-Miyaura cross-coupling in water under reflux conditions. [59] The catalyst was prepared by an anion exchange reaction between silica-immobilized diimidazolium ionic liquid brushes with the sodium salt of Pd-EDTA (Scheme 6). This catalyst has shown great stability in air and excellent reactivity without any phosphine ligands. The Suzuki coupling of a large variety of aryl bromide and aryl iodides with phenylboric acid in water and PdEDTA-Ionic liquid brush as a catalyst gave very high yields ranging from 89% to 100%. This catalyst did not show loss of activity even after 10 recycles. Another advantage of SiO$_2$-BisIL-sOct[PdEDTA] catalyst was that it also act as a phase transfer catalyst in the reaction of water insoluble aryl halides.

Lombardo and co-workers have reported the triethylammonium ion-tagged diphenylphosphine palladium(II) complex for Suzuki-Miyaura reaction in pyrrolidinium ionic liquids under mild reaction conditions. [60] In an effort towards increasing the recyclability of palladium catalyst, triethylammonium ionic liquid supported diphenylphosphine ligand have been prepared. 1-Butyl-1-methyl-pyrrolidinium bis(trifluoromethanesulfonimide) ([bmpy][NTf$_2$]) prove to be the best solvent along with water in presence of potassium phosphate as a base in the coupling of o-bromotoluene and phenylboronic acid. A Suzuki reaction of a number of electron donating and electron withdrawing groups on aryl halides and aryl boronic acids showed good to excellent results. 2-methylphenylboronic acid has given 99% yields when coupled with 1-naphthylbromide and also with 4-bromobiphenyl. The coupling of p-anisylboronic acid and 4-bromobiphenyl gave 84% yield with triethylammonium ion-tagged diphenylphosphine palladium(II) complex.
Scheme 6. Suzuki reaction with SiO$_2$-BisILsOct[PdEDTA] catalyst

Scheme 7. Suzuki cross-coupling between 5,11-dibromotetracene with arylboronic acids

Miozzo and co-workers have demonstrated an excellent use of such ionic liquid ligated palladium complex in the challenging Suzuki cross-coupling between 5,11-dibromotetracene
with arylboronic acids under mild conditions (Scheme 7). [61] These couplings have given very high yields with phenyl and substituted phenylboronic acid (93-97%) even with 2-naphthylboronic acid (95% yield).

2.4. Stille coupling

The palladium catalyzed C-C bond formation reaction between organotin reagents and sp²-hybridised organohalides are typically classed as Stille coupling reactions. [62,63] It is an important method of alkylation/arylation of vinyl/aryl halide. Organotin reagents used in this reaction are stable and easily stored in air. But the major drawbacks of Stille reaction are the toxicity of organotin reagents and recyclability of palladium catalyst.

To increase the recyclability of palladium catalyst and solvent, Handy and Zhang have reported the use of ionic liquid as an effective media for Stille coupling. [64] Stille coupling reactions were compared between NMP and [BMIM][BF₄] as a solvent with bis(benzonitrile)palladium(II) chloride as a catalyst and in the presence of triphenylarsine and Copper(I) iodide. These reactions demonstrated the compatibility of ionic liquid in Stille reactions.

![Scheme 8. Stille coupling of 4-iodotoluene and tributylphenyltin in [BMIM][BF₄].](image)

Aryl coupling of a variety of aryl iodides and bromides and tributylphenyltin afforded the respective products with good yields (Scheme 8). The coupling of 4-iodotoluene and tributylphenyltin showed the highest conversion with 95% yield, whereas p-bromoanisole and tributylphenyltin gave only 15% yield towards the desired product. Ionic liquid and the catalyst bis(benzonitrile)palladium(II) chloride were recycled without loss of activity even after 5th cycle.

Due to the toxicity of organotin reagents and contamination of product by tin, organotin reagents have been boycotted by the pharmaceutical industry. Legoupy and co-workers reported an ionic liquid supported organotin reagent which can recycled and minimise contamination of product by organotin compound, without the use of solvent and additives. [65] Ionic liquids supported dibutylphenyltin was successfully synthesized and used as a reagent in palladium catalyzed Stille cross-coupling reactions involving brominated substrates under solvent-free conditions.
Scheme 9. Recyclable organotin reagent for Stille coupling

An effective use of different ionic liquid supported vinyl, allyl, aryl and heteroaryl organo-tin reagents with aryl bromides have seen use in Stille cross-coupling reaction. Such ionic liquid incorporated organotin reagent was recycled and reused 5 times with good yields and without loss of reactivity by using Grignard reaction (Scheme 9). It also helped to minimise tin contamination to less than 3 ppm.

2.5. Diels-Alder reaction

The cycloaddition reaction between the conjugated diene and dienophile/substituted alkene is known as Diels-Alder reaction. [66] Prof. Otto Paul Hermann Diels and Prof. Kurt Alder was awarded Nobel Prize in Chemistry in 1950 for "for their discovery and development of the diene synthesis". Diels-Alder reaction is an important tool in synthesis of huge and complex cyclic molecules such as cholesterol, reserpine, etc. Heterocyclic compounds can also be prepared with this reaction by using heteroatom (most of the times N and O) either as the diene or dienophile component. Diels-Alder reaction has immense importance due to the 100% atom economy in product formation. The reaction can be performed either by heating or by using Lewis/Brønsted acid catalysts such as ZnCl₂, HBF₄, Sc(OTf)₃ etc. in organic solvents.

Scheme 10. Aza-Diels-Alder reaction of Danishefsky’s diene with imines
Pégot and Vo-Thanh have reported aza-Diels-Alder reaction of Danishefsky's diene with imines in ionic liquids, at room temperature without any acid catalyst and organic solvents. [67] The reaction of N-benzylidenebenzylamine and Danishefsky's diene in [BMIM][OTf] showed high i.e. 94% conversion (91% yield) in 1 hour at room temperature (Scheme 10). Only half an equivalent amount of ionic liquid as used with respect to N-benzylidenebenzylamine. In the study of an effect of counter anion of [BMIM] cation, triflate (OTf) and bis(trifluoromethanesulfonimide) (NTf₂) has shown high yields i.e. 91% and 94% respectively in comparison with tetrafluoroborate (BF₄) and hexafluorophosphate (PF₆) i.e. 62% and 53% respectively. Reactions using pyridinium and ammonium cations with triflate anion gave good yields (91% and 89% respectively). These studies have shown that ionic liquids can be used as both polar solvent and as a catalyst in Aza-Diels-Alder reaction.

Zhou and co-workers reported C₂-symmetric ionic liquid-tagged bis(oxazoline) copper catalyst for Diels-Alder reaction in ionic liquid. [68] Bis(oxazoline)-copper(II) complexes have already been used as a Lewis acid catalyst in enantioselective Diels-Alder reactions. [69] In order to increase recyclability of the catalyst, the imidazolium-tagged bis(oxazoline) ligand copper catalyst was synthesized. (Scheme 11) The ionic liquid part of the ligand increased the insolubility of the copper catalyst in typical reaction solvents like diethyl ether, which makes workup procedure very simple. The product was separated from catalyst just by washing with diethyl ether.

Scheme 11. Screening of the ligands in an asymmetric Diels-Alder reaction
The ionic liquid-tagged bis(oxazoline) copper catalyst did not show any conversion in the Diels-Alder reaction of N-acryloyloxazolidinone and cyclohexa-1,3-diene in DCM as a solvent. When the same reaction was carried out in [BMIM][NTf₂] has given required product with 98% conversion and 97% ee. N-Acryloyloxazolidinone was found to be more active than N-acryloylpyrrolidinone with cyclopentadine/cyclohexadiene in presence of C₅-symmetric ionic liquid-tagged (S,S)-t-Bu-box copper catalyst in [BMIM][NTf₂]. This efficient catalytic system (catalyst + IL) was recycled 20 times without loss of activity or enantioselectivity. This excellent recyclability was due to the ionic character of the ligand. The toxicity testing of the ligands synthesized were carried out on luminescent bacteria. The traditional t-Bu-box ligand has shown higher LC₅₀ values (45 μg/mL) than most active ligand (11 μg/mL).

2.6. Acetalisation reactions

The acid catalysed nucleophilic addition of an alcohol to aldehyde or ketone to form respective acetal or ketal is termed as an acetalisation reaction. This is one of the important reactions in organic synthesis. As the carbonyl functionality is very reactive, it is important to protect against the attack of nucleophiles, acidic, basic or reducing agents. [70] There are several methods to protect aldehydes/ketones. Acetalisation i.e. formation of acetal has its own advantages, as it is stable to all nucleophilic and basic reagents. This reaction can be catalysed by traditional liquid acids such as HCl, H₂SO₄, etc. and also by solid acids i.e. Lewis/Bronsted acid catalysts such as ZnCl₂, FeCl₃, Zeolites, p-TSA, etc. [70-72] A water molecule is formed as a by-product in this reaction, which is important from a Green Chemistry perspective. The major drawback of this reaction is involvement of harmful liquid acids, which also involves handling hazards.

Forbes, Davis and co-workers reported Bronsted acidic ionic liquids with covalently bonded sulfonic acid functionality containing imidazolium and phosphonium cations. [73] These ILs has shown dual use as both catalyst and solvent in Fisher esterification and pinacol/benzopinacol rearrangement. Fang and co-workers further exploited such covalently bonded sulfonic acid functionality in ionic liquid and its dual use in acetalisation reaction. [74]

The Bronsted acidic ionic liquid N,N,N-trimethyl-N-propanesulfonic acid ammonium hydrogen sulfate ([TMPSA][HSO₄]) has been prepared economically and used as a catalyst and as a solvent in acetalisation reactions. A number of aldehydes and ketones were reacted with 1,2-diols and methanol to form acetal/ketal in [TMPSA][HSO₄] (Scheme 12). All reactions showed 100% selectivity with excellent conversions within 5-60 minutes. Most of the reactions gave quantitative yields, except the protection of acetophenone with methanol with 65% conversion. This Bronsted acidic ionic liquid was recycled 9 times without loss of catalytic activity and selectivity.

Du and Tian have also demonstrated the use of simple protonated 1-methylimidazolium ionic liquids as a Bronsted acid catalyst in the protection of aldehydes and ketones. [75] The IL catalyst was inexpensively prepared by protonation of 1-methylimidazole. The protection of various aldehydes and ketones with triethyl orthoformate in presence of 1-methylimidazolium tetrafluoroborate displayed very high conversions (84% - 93% yields) at room tem-
perature (Scheme 13). The catalyst was easily recycled just by filtration and reused without any loss of activity.

![Scheme 12](image)

**Scheme 12.** Protection of aldehydes/ketones with alcohols in presence of [TMPSA][HSO₄]

![Scheme 13](image)

**Scheme 13.** Protection of aldehydes/ketones with triethyl orthoformate and IL catalyst

3. **Environmental fate of ionic liquids**

Due to the wide range of applications and versatility, ionic liquids are continually being used extensively in industry, [2] which has triggered an issue of waste management. Also, many of these are totally synthetic novel compounds. Hence it is important to study the environmental impact of such ionic liquids before releasing into the natural environment. Due to their low vapour pressure, ILs can reduce the possibility of air pollution. But bearing an
ionic nature; ILs have a notably high solubility in water [7,76,77] (except NTf$_2^-$ & PF$_6^-$) which is a viable and common means by which these ILs get released in nature. In order to check the biocompatibility of ILs, toxicity, eco-toxicity and biodegradation studies have to be carried out. ILs are usually referred to as “Green” alternatives to Volatile Organic Compounds (VOCs). Instead of the “Green” label, ILs can be categorized in the pattern of ‘Traffic Signal Lights’ as discussed at the BATIL (Biodegradation And Toxicity of Ionic Liquids) meeting in DECHEMA, Frankfurt, 2009 (Fig. 1.3). [78] As we start classifying ILs in three colours (Red, Yellow and Green), we can find that most ILs are in the Red and Yellow regions, although this information was solely based on toxicity data. For an IL to be classified more accurately by a ‘Traffic Signal Lights’ pattern, detailed information about the toxicity, biodegradation and ease of synthesis etc. are required. Similar classification can be applied to commonly used organic solvents (Figure 3). [79]

Figure 3. Recommendation for data representation of toxicity of ionic liquids and commonly used organic solvents [78,79]

3.1. Toxicity and eco(toxicity) of ionic liquids

As mentioned before, many ionic liquids are non-natural (synthetic) molecules. While a single toxicological test yields useful, albeit limited data, over the last decade, a large number of publications have demonstrated a wide variety of ‘biological test systems’ for toxicity testing of ionic liquids (Figure 4). [80,81] This includes fungi, bacteria, algae, enzymes, rat cell line, fish, etc. Only by assessing the toxicity of IL across a broad range of organisms can a ‘true’ understanding of how environmentally friendly the compound is?
Stock and co-workers reported the effect of ionic liquids on acetylcholinesterase. [82] Enzymes are a crucial part of the human nervous system. Acetylcholinesterase is known to catalyse the hydrolysis of the neurotransmitter acetylcholine, to acetate and choline. Inhibition of acetylcholinesterase results in muscular paralysis and other medically significant nervous problems. Organophosphates are a major class of acetylcholinesterase inhibitors. A range of commonly used imidazolium, pyridinium and phosphonium ionic liquids were tested in this assay. Imidazolium and pyridinium ionic liquids showed high toxicity to acetylcholinesterase at very low concentrations, whereas phosphonium ionic liquids were non-toxic within the test limits. This testing showed that toxicity of these ionic liquids lies in the cationic part and alkyl side chain and not in the anionic part.

Another important finding of this assay was that increasing the length of alkyl side chains increase the toxicity. This can be explained as long alkyl chain increases lipophilic nature of the ionic liquids, which can then easily incorporate within the biological membrane of nerve cell synapses. [83] Similar trends between the toxicity and length of alkyl chain on luminescence inhibition of *Vibrio fischeri* and *promyelocytic leukemia rat cell line* IPC-81 were reported by Ranke and co-workers. [84] Leukemia rat cell line IPC-81 was also used to observe the cytotoxic effect of commercially available anions. [85] No significant anion effect was found under the test system.

Bernot and co-workers demonstrated that acute toxicity of certain 1-butyl-3-methyl imidazolium ionic liquids on *Daphnia Magna* were mainly due to the cationic part. [86] *Daphnia Magna* has been extensively used for ecotoxicological evaluation of chemicals in invertebrates. Ionic liquids were found to influence the reproduction of *Daphnia Magna*. 1-Butyl-3-methyl-
midazolium bromide was found to be most toxic in the test system (LC$_{50}$: 8.03 mg/L). This study demonstrated that the toxicity of ionic liquids was influenced by the cation component, which was confirmed by high LC$_{50}$ values for sodium salts of similar anions. Yu and co-workers reported the toxicity study of 1-alkyl-3-methylimidazolium bromide ionic liquids towards the antioxidant defence system of Daphnia Magna. [87] Increasing the length of alkyl side chain was found again to increase toxicity. Toxicity of ionic liquids in this case was due to oxidative stress in Daphnia Magna, which was evaluated by measuring the activity of antioxidant defence enzymes, levels of the antioxidant glutathione and malondialdehyde i.e. peroxidation by-product of lipid. [C$_{12}$MIM][Br] showed very high toxicity with an LC$_{50}$ of 0.05 mg/L under 48h incubation time. Samori and co-workers reported the toxicity effect of oxygenated alkyl side chain imidazolium ionic liquids in Daphnia Magna and Vibrio Fischeri. [88] A direct comparison between the toxicity of 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF$_4$]) and 1-methoxyethyl-3-methylimidazolium tetrafluoroborate and dicyanamide ([MOEIM][BF$_4$] and [MOEIM][N(CN)$_2$]) proved that incorporation of oxygen functionality helps to lower the toxicity of the ionic liquids (Figure 5). The 50% effective concentration (EC$_{50}$) for [BMIM][BF$_4$] towards the inhibition of Daphnia Magna and V. Fischeri was lower (5.18 and 300 mg/L, respectively) than for [MOEIM][BF$_4$] (209-222 and 3196 mg/L, respectively) and [MOEIM][N(CN)$_2$] (209 and 2406 mg/L, respectively).

![Figure 5. Schematic of 1-methoxyethyl-3-methylimidazolium ILs towards Daphnia Magna](image)

Gathergood and co-workers further demonstrated that imidazolium based ionic liquids with an oxygen functionality i.e. ester and ether side chains, have reduced antimicrobial activity to a great extent. [89] Four Gram negative bacteria (Pseudomonas aeruginosa, Escherichia coli, Klebsiella sp., Salmonella sp.) and three Gram positive bacteria (Staphylococcus aureus, Enterococcus sp., Bacillus subtilis) were screened in the assay. A range of long ether and poly ether ester side chain imidazolium ionic liquids showed a huge reduction in the toxicity in this test system, compared with similar number of atoms in long alkyl side chains.

In order to check the toxicity effect of ionic liquids in humans, a cytotoxicity assay with human cell lines was designed. HeLa is one of the most extensively used cell lines in medicinal research. HeLa is a human tumor cell line, which is a prototype of epithelium. Due to the first contact of an organism with toxic materials, HeLa cell line has great importance. Stepnowski and co-workers reported the cytotoxic effect of imidazolium ionic liquids in Hela
cell line. [90] The EC\textsubscript{50} values of a range of 1-alkyl-3-methylimidazolium ionic liquids were evaluated on human epithelium HeLa cells. Ionic liquids with a decyl side chain with tetrafluoroborate as the anion component demonstrated high toxicity (EC\textsubscript{50} = 0.07 mM). This was supportive of the results with other test systems. The cytotoxicity of ionic liquids were compared with the known 50% effective concentrations (EC\textsubscript{50} values) of traditional organic solvents such as dichloromethane (71.43 mM), phenol (42.68 mM), xylene (52.43 mM) and ethanol (1501.43 mM). These studies revealed that the tested ionic liquids had significant toxicity against human cell line HeLa, compared with organic solvents. Lu and co-workers utilised this assay for testing the cytotoxicity of a large range of ionic liquids containing imidazolium, pyridinium, choline, triethylammonium and phosphonium cations with halide, NTf\textsubscript{2}\textsuperscript{−} and BF\textsubscript{4}\textsuperscript{−} anions. [91] In general, choline and alkyl-triethylammonium ionic liquids were found to be less toxic than their imidazolium and pyridinium salt counterparts.

In an effort to evaluate the eco(toxicity) of ionic liquids, Yun and co-workers reported an assay of freshwater microalgae *Selenastrum capricornutum*. [92] The bromide salts of commonly used 1-butyl-3-methylimidazolium, 1-butyl-3-methylpyridinium, 1-butyl-1-methylpyrrolidinium, tetrabutylammonium, and tetrabutylphosphonium ILs were tested against the *S. capricornutum* and compared with traditional water miscible organic solvents such as dimethylformamide, 2-propanol and methanol. Increase in the toxicity of imidazolium and pyridinium cations were observed with an increase in incubation time, whereas the opposite trend was found in the case of tetrabutylammonium, and tetrabutylphosphonium ILs. The growth inhibition of *S. capricornutum* was higher in ionic liquids than organic solvents. A similar test system was applied to investigate the toxicological effect of anions. [93] Toxicity of various anions incorporated with 1-butyl-3-methylimidazolium cation were compared with their respective sodium and potassium salts. The anions were found to inhibit the growth of freshwater algae *S. capricornutum*. The clear trend in algae toxicity was observed as hexafluoroantimonate (SbF\textsubscript{6}\textsuperscript{−}) > hexafluorophosphate (PF\textsubscript{6}\textsuperscript{−}) > tetrafluoroborate (BF\textsubscript{4}\textsuperscript{−}) > triflate (CF\textsubscript{3}SO\textsubscript{3}\textsuperscript{−}) > octyl sulphate (OctOSO\textsubscript{3}\textsuperscript{−}) > halide (Br\textsuperscript{−}, Cl\textsuperscript{−}). Toxicity studies (in fish, aquatic plants/invertebrates) on anionic surfactants have shown that toxicity is dependent on a number of factors such as alkyl chain length, solubility and stability in water. [94] As the length of alkyl chain increases, toxicity increases until certain limits. Further increase in chain length can decrease the hydrophilic nature of these materials, reducing bioavailability of compound which results in a general decrease in the toxicity. [95]

### 3.2. Biodegradation of ionic liquids

Ionic liquids are well known for being stable to heating and in a variety of reaction conditions. Although this is an important property in their applications, it can raise issues regarding degradation and bioaccumulation when released in nature. Accumulated data on the anti-microbial toxicity of novel ionic liquids can be used as a preliminary guideline before performing the biodegradation tests. The biological test system has its limitations, such as when reported toxicity data is only available for certain individual organisms, whereas biodegradation assays usually have a large sample group of organisms. Also, breakdown products/intermediates of ionic liquids can be toxic, which can be resistant to
further degradation, which leads to the issue of bioaccumulation. Hence it is important to perform biodegradation studies of ionic liquids. [96] Boethling and co-workers in their review article “Designing Small Molecules for Biodegradability”, gave useful and general guidelines for the design and synthesis of environmental friendly chemicals. [97] According to their observations, compounds containing unsubstituted alkyl chains, benzene rings, oxygen functionalities such as esters, aldehydes, and carboxylic acids (potential sites for enzymatic hydrolysis) greatly increase biodegradation. Whereas compounds containing halogens, branched chains, heterocycles, functional groups such as nitro, nitroso and arylamines motifs, adversely affect the biodegradation. There are several biodegradation study methods approved by the Organisation for Economic Cooperation and Development (OECD) (See Table 1).

| Test No. | Name | Analytical method |
|---------|------|-------------------|
| OECD 301 A | DOC Die-Away | Dissolved organic carbon |
| OECD 301 B | CO₂ evolution | CO₂ evolution |
| OECD 301 C | MITI (Ministry of International Trade and Industry, Japan) | Oxygen consumption |
| OECD 301 D | Closed bottle | Dissolved oxygen |
| OECD 301 E | Modified OECD screening | Dissolved organic carbon |
| OECD 301 F | Manometric respirometry | Oxygen consumption |
| ISO 14593 | CO₂ headspace test | CO₂ evolution |
| OECD 309 | OECD 309 | ¹⁴C labelling |
| ASTM 5988 | ASTM 5988 | CO₂ production / Biochemical oxygen demand |

Table 1. Biodegradation methods in use

Data collected from all of the tests mentioned in Table 1 can be catagorised according to OECD guidelines as - (a) Ultimate biodegradation: Denotes complete degradation/utilisation of a test compound to produce carbon dioxide (CO₂), water, biomass and inorganic substances. Such biodegradation can achieved due to the mineralisation by microorganisms. This is
one of the significant characteristics, before classed as a ‘biocompatible’ compound. (b) Readily biodegradable: These are positive results showing rapid ultimate degradation of the test compound under aerobic conditions in stringent screening tests. Both mineralisation and elimination/alteration (abiotic process such as hydrolysis, oxidation and photolysis) of the test substance can be observed. (c) Primary biodegradation: An elimination or alteration of the test sample by microorganisms, in order to lose its specific properties. [98]

Gathergood and Scammells reported the synthesis of ester and amide functionalised side chain imidazolium ionic liquids [99] according to the guidelines outlined by Dr. Boethling. [100] All of the novel alkyl ester and amide side chain methylimidazolium ionic liquids were subjected to biodegradation studies. A biodegradation study of bromide salts of these ionic liquids along with commonly used [BMIM][BF₄] and [BMIM][PF₆] ILs was carried out under the ‘Closed Bottle Test’ (OECD 301D) [101] although none of the tested ionic liquids passed the minimum 60% biodegradation threshold in order to be classified as ‘readily biodegradable’. However, [BMIM][BF₄] and [BMIM][PF₆] did not show biodegradation in the test system. Ester functionalised side chain ionic liquids demonstrated improved biodegradation. Increasing the length of the ester side chain increased the biodegradation, for example a methyl ester derivative showed 17% biodegradation, whereas biodegradation of an octyl ester derivative was 32% after 28 days. Another important observation was that amide side chain ionic liquids showed very negligible biodegradation. The effect of different anion on the rate of biodegradation was tested under the same test system. A range of 1-butyl-3-methylimidazolium and ester functionalised 3-methyl-1-(propoxycarbonylmethyl)-imidazolium ionic liquids were prepared with different anions such as Br, BF₄, PF₆, NTf₂, N(CN)₂ and OctOSO₃. BMIM⁺ based ionic liquids showed poor biodegradation, except with an octyl sulphate as anion. The biodegradation of 3-methyl-1-(propoxycarbonylmethyl)-imidazolium ionic liquid was increased from 19% with bromide anion to 49% with octyl sulphate anion after 28 days. Gathergood and co-workers further demonstrated that incorporation of ether and polyether linkages along with ester functionality in the side chain can increase biodegradation to a great extent. [89] The biodegradation of a large range of ether and polyether ester side chain methylimidazolium ionic liquids were studied using the CO₂ Headspace test. Octyl sulphate salts of 1-methylimidazolium ionic liquids with propoxyethoxy and butoxyethoxy esters were found to be readily biodegradable (> 60% biodegradation in 28 days).

Docherty and co-workers reported biodegradation studies of imidazolium and pyridinium based ionic liquids by OECD dissolved organic carbon Die-Away test. The test was carried out with the activated sludge microorganisms from wastewater treatment plant. [102] Denaturing gradient gel electrophoresis (DGGE) was also used to investigate the microbial community profile. The results showed that the tested pyridinium based ionic liquids has better biodegradability than the corresponding imidazolium salts. Octyl-3-methyl-pyridinium bromide was found to be readily biodegradable with complete degradation within 15-25 days of incubation, whereas hexyl-3-methyl-pyridinium bromide was degraded within 40-50 days. Such complete biodegradation was further supported by the work of Stolte and co-workers in their investigation of the primary biodegradation of a variety of
ionic liquids by the modified OECD 301 D test. [103] A range of 1-alkyl-3-methylimidazolium, 1-alkylpyridinium and 4-(dimethylamino)pyridinium halide salts were screened under the test system. The biodegradation products were identified by HPLC-MS analysis. 1-Octyl-3-methylimidazolium chloride gave a result of 100% primary biodegradation within 31 days. The stepwise degradation by two possible metabolic pathways was predicted based on HPLC-MS analysis. This predicted breakdown pathway was due to enzymatic oxidation of the terminal carbon.

Scammells and co-workers also reported biodegradation of ester functionalised pyridinium ionic liquids using the CO$_2$ Headspace test (ISO 14593). [104] Pyridinium ionic liquids with alkyl and ester side chains, along with ester derivatives of nicotinic acid with alkyl side chain were tested under aerobic conditions. The halide salts of pyridinium ionic liquids with alkyl side chain (C$_4$, C$_{10}$ and C$_{16}$) showed poor biodegradation, whereas it was improved up to a max. of 45% after 28 days by the use of octyl sulfate anion. Switching from alkyl chain to ester side chain in pyridinium ILs increased the biodegradation dramatically. Such substitution made them readily biodegradable, independent of the chosen anionic component. Bromide, hexafluorophosphate and octyl sulfate showed a high level of biodegradability (85% to 90%), whereas NTf$_2^-$ gave 64% biodegradation after 28 days. Ionic liquids derived from the nicotinic acid ester derivative i.e. ester group at 3-position of the pyridine ring were found to be readily biodegradable even with methyl or butyl side chain. Amide side chain derivatives showed low biodegradability, even with using octyl sulfate as the anion (30% biodegradation after 28 days). Scammells and co-workers further studied the effect of the incorporation of ester, ether and hydroxyl side chain in phosphonium based ionic liquids. [105] All phosphonium ionic liquids showed poor biodegradation independent of ester, ether and hydroxyl side chains and anions in CO$_2$ Headspace test. Only heptyl ester side chain ionic liquid with octyl sulfate anion showed highest 30% biodegradation after 28 days.

Most of the ionic liquids prepared are not ‘readily biodegradable’; however, several structural modifications have shown a positive improvement in the biodegradability of ionic liquids. [96,106] Striving towards compounds with ‘Ultimate biodegradation’ is preferred over ‘readily biodegradable’ examples and is a major research area. Hence it is important to study the biodegradation pathways of ionic liquids along with kinetics and metabolite studies to assist the ‘benign by design’ approach.

### 3.3. Guidelines for designing ‘Green’ ionic liquid catalysts/solvents

From the literature, the following observations were made and are summarised in Figure 6:

- Linear alkyl chains in general can increase biodegradation compared to branched hydrocarbon chains.
- Oxygen containing functionalities, such as ester and hydroxyl groups in the side chain of imidazolium cation, not only reduces microbial toxicity but also increases rate of biodegradation. This is, however, not effective in phosphonium based ionic liquids.
- Ether substitution reduces bactericidal toxicity.
• Ester substitutions at 1 and 3 position of pyridinium cation can improve biodegradation.

4. Green chemistry metrics

To achieve ‘Green’ synthesis of any chemical, the ‘12 Principles of Green Chemistry’ given by Anastas and Warner serves as the most useful set of guidelines and gives us the important message that ‘Prevention is better than cure’. [107] These principles suggest not only to consider toxicity and biodegradation, but also to measure the ‘greenness’ of the chemical process. To evaluate the ‘greenness’ of any process, a number of factors associated with the chemical process has to studied. Green Chemistry metrics can help to measure the efficiency and ‘greenness’ of the chemical process. There are several well established methods to determine the sustainability of a chemical process under areas such as the economical, technical and social effects of such processes. Economical methods mainly consist of profit related analysis, whereas technical methods analyses quality, productivity and related issues. Social methods concern the society and environmental aspect of the chemical process. [108] Porteous has shown that it is easy to correlate Green Chemistry metrics with the “12 Principles of Green chemistry”. [109] There are several metrics available to measure efficiency, use of energy and resources, toxicity, biodegradation, safety and life cycle impact of the chemical process, which are closely related to the 12 Principles.

The Environmental (E) factor is one of the most widely used and efficient methods to measure the amount of waste generated in the process. [110] This is also known as Sheldon’s E-factor.

$$E\text{factor} = \frac{\text{Total mass of waste (kg)}}{\text{Mass of product (kg)}}$$

E-factor calculations is one of the important methods to calculate the waste associated with the process, which includes all unwanted side products, reagents, solvents and energy. Wa-
Mass Intensity = \frac{\text{Mass all materials used (excluding water)}}{\text{Mass of product}}

Mass Intensity measures the amount of reagents, solvents and workup reagents used in the process. Hence it takes an account of product yields and stoichiometry of the reagents. In order to measure the synthetic efficiency of the process, the “Atom Economy” concept was found to be useful. Atom economy in chemical reactions is one of the 12 Principles of Green Chemistry, which gives indications as to the overall efficiency of a chemical reaction.

Atom Economy = \frac{\text{Molecular weight of desired product}}{\text{Molecular weight of all products/ reactants}} \times 100\%

Although this is an important concept, which suggests to minimise the waste. It does not consider the actual mass, yield, solvents and other reagents used in the process. Reaction mass efficiency (RME) has overcome these drawbacks. Reaction mass efficiency considers actual mass of reactants and product. This is one of the commonly used metrics to evaluate the efficiency of the chemical process.

Reaction Mass Efficiency = \frac{\text{Mass of product}}{\text{Mass of all reactants}} \times 100\%

Apart from these, real time analysis is also important to analyse the chemical process. Real time analysis is again one of the “12 Principles of Green Chemistry”, which enables the chemist to identify the formation of waste along the process. A number of analytical techniques such as HPLC, GC, NMR, FT-IR, and sensors etc. were already found to be useful in real time analysis. It’s also important to determine the robustness of the process, which will allow preparing chemicals on a large scale. The measurement of toxicity and biodegradation are also important metrics to evaluate ‘greenness’ of the chemical products.

5. Case study

In order to design and synthesise ‘Green’ ionic liquid catalysts, guidelines prepared from toxicity and biodegradation studies can be helpful. Novel ionic liquids have been extensively prepared and used in organic synthetic applications, but only few research groups have published complementary toxicity and biodegradation data to support its environmental impact.

Connon and co-workers reported an application of pyridinium salts as an effective catalyst in acetalisation reactions. Ester group substitution at either the 3 or both 3 and 5 positions of the pyridinium ring displayed excellent catalytic activity with very low
catalyst loading in the acetalisation of benzaldehyde with methanol. The remarkable feature of the catalyst was that it is not acidic in nature, but can act as a Brønsted acid in the presence of protic media. The highest catalytic activity pyridinium salts, 3,5-bis(ethoxycarbonyl)-1-(phenylmethyl) bromide, showed excellent catalytic activity in the protection of a variety of aldehydes with methanol. The catalyst was also found to be useful in diol and dithiol protections (Scheme 14). Catalytic activity of the catalyst was predicted based on anticipated nucleophilic attack of the alcohol to the pyridinium to generate the Brønsted acidic active species.

Scheme 14. Acetalisation of benzaldehyde with methanol catalysed by pyridinium IL

On the basis of previous findings, Gathergood, Connon and co-workers reported the design, synthesis and application of imidazolium ionic liquid catalysts in acetalisation reactions. [113] A range of ester and amide side chain imidazolium ionic liquids was
prepared. The catalytic activity of all of these imidazolium salts was evaluated in the acetalisation of benzaldehyde in methanol (Scheme 15). The absence of catalyst resulted in no formation of the corresponding acetal after 24 hours. All of the imidazolium bromide salts showed poor catalytic activity independent of ester or amide side chain (9 to 13% conversions). When switched to the NTf$_2$ anion, reaction conversions in amide side chain ionic liquids were increased marginally. Whereas ester side chain ionic liquids with NTf$_2$ anion gave 51% conversion. A tetrafluoroborate salt of a methyl ester side chain imidazolium ionic liquid gave high (85%) conversion towards required product. Hexafluorophosphate and octyl sulfate anions performed poorly in this reaction. The anion exchange from bromide to tetrafluoroborate had greatly influenced the acetalisation reaction of benzaldehyde with methanol, which gave 85% conversion.

![Scheme 15. Acetalisation of benzaldehyde using imidazolium IL as a catalyst. Biodegradation data for IL/Catalyst (ISO 14593) included.](image)

The ionic liquid did not appear to have an acidic nature, but in the presence of a protic medium was proposed to generate a Brønsted acid species to catalyse the acetalisation reaction. (Figure 7) The most active catalyst with tetrafluoroborate anion was further exploited in the acetalisation reactions of a variety of aldehydes with methanol at room temperature. These reactions showed good to excellent conversions with 5-10% catalyst loading. When saturated aldehyde such as 3-phenylpropanal reacted with deuterated methanol in presence of 1 mol% catalyst, the reaction gave quantitative conversion in only 1 minute. Diol and dithiol protection of benzaldehyde showed very good results. The BF$_4$ catalyst promoted protection of benzaldehyde with 1,2-ethanediithiol gave 92% conversion, whereas 1,3-propanedithiol and 1,3-propanediol gave 65% and 86% conversion respectively. Recyclability of the most active BF$_4$ anion catalyst was performed on the 1,3-dithiolane
protection of benzaldehyde. The catalyst was recycled and reused 15 times without significant loss of activity.

Biodegradation studies of pyridinium-based ILs have shown that esters substitution at either the 1 or 3-position have a beneficial effect on degradation of the heterocyclic core, independent of the anion. [104] Also biodegradation studies in the literature have shown that only the side chain of the imidazolium ionic liquids undergo degradation, whereas imidazole core was found to persist in most of the OECD tests. [103]

Biodegradation studies of ester and amide side chain ionic liquids along with substituted imidazolium salts was also carried out by using the “CO\textsubscript{2} Headspace” test (ISO 14593) (Scheme 14, 15). [113, 117] All imidazolium ionic liquids prepared failed to pass the minimum 60% biodegradation threshold value in order to be classified as ‘readily biodegradable’. Ester functionalised ionic liquids displayed higher biodegradation levels than amide functionalised ionic liquids in 28 days. The first generation imidazolium ionic liquid catalysts showed 10% to 14% biodegradation for methyl ester side chain ionic liquids, whereas maximum 3% biodegradation was observed in amide side chain ionic liquids after 28 days.

The toxicity of all ionic liquids was tested in an environmental and medicinally significant microbial assay including 12 fungal and 8 bacterial strains. [113,118] In vitro antifungal activities of the compounds were evaluated on a panel of four ATCC strains (Candida albicans ATCC 44859, Candida albicans ATCC 90028, Candida parapsilosis ATCC 22019, Candida kruze ATCC 6258) and eight clinical isolates of yeasts (Candida kruze E28, Candida tropicalis 156, Candida glabrata 20/I, Candida lusitaniae 2446/I, Trichosporon asahii 1188) and filamentous fungi (Aspergillus fumigatus 231, Absidia corymbifera 272, Trichophyton mentagrophytes 445). Whereas In vitro antibacterial activities of the compounds were evaluated on a panel of three ATCC strains (Staphylococcus aureus ATCC 6538, Escherichia coli ATCC 8739, Pseudomonas aeruginosa ATCC 9027) and five clinical isolates (Staphylococcus aureus MRSA HK5996/08, Staphylococcus epidermidis HK6966/08, Enterococcus sp. HK14365/08, Klebsiella pneumoniae HK11750/08, Klebsiella pneumoniae ESBL HK14368/08). All ester and amide side chain ionic liquids shown in Scheme 15 were non-toxic up to the 2000 μM concentration. This is less toxic than values reported for antimicrobial QAC (IC\textsubscript{95} >10 μM). [80,81]

In order to evaluate the ‘greenness’ of the synthesis of ionic liquid catalysts, Gathergood and Connon have also applied some important Green Chemistry metrics (Section 4), such as -
• Sheldon E-factor
• GSK Reaction Mass Efficiency,
• Andraos Reaction Mass Efficiency
• Atom economy
• 1 / stoichiom. factor (excess reagents)

These metrics assisted improvements in the synthetic process, by reducing amount of solvents in the work-up and purification procedure, reduce number of steps to make required compounds. For example, as the synthesis of tetrafluoroborate ionic liquids involves preparation of halide salts followed by anion exchange metathesis. In an effort to reduce the number of steps and amount of reagents and solvents in the synthesis, alkyl imidazoles were directly reacted to Meerwein’s salt i.e. trimethyloxonium tetrafluoroborate to give tetrafluoroborate ionic liquids in excellent yield. (For full analysis see ref. 117) Hence Green Chemistry metrics assessment is important to achieve green synthesis.

6. Conclusion

In this chapter we have demonstrated that ionic liquids have great potential and versatility in organic synthesis, with the dualistic ability to act as a solvent and as a catalyst. Ionic liquids were found to be possible replacements over traditional volatile organic solvents. Such ionic liquid solvents were found to be useful in transition metal catalysed reactions. They not only enabled catalyst immobilisation, but also increased recyclability of expensive transition metal catalysts. Ease of product separation and their stability against a variety of reagents has proved their important characteristics. We have seen that modification in the cationic part of the ionic liquids, according to the requirements of the aforementioned reactions, enabled them to act as organocatalysts or ligands for transition metal catalysts. These ionic liquid catalysts have shown comparative catalytic activity against known organocatalysts but such materials had a distinct advantage in that the ionic liquids could be recycled, with no discernible loss of activity. In order to increase recyclability, ionic liquid catalysts/ligands were grafted onto a solid/polymer support. These modifications helped to separate ionic liquid catalysts from the reaction mixture.

We have also illustrated the efforts attempted by the scientific community to evaluate the ‘greenness’ of ionic liquids, by using toxicity and biodegradation methods. The majority of ionic liquids are non-natural molecules, hence it’s important to check their biocompatibility. Toxicity studies can serve as a “first post” primary evaluation of biodegradation. A variety of test systems including fungi, bacteria, algae, enzymes, rat cell line, human cell line and fish etc. were implemented to check the toxicity of ionic liquids. Most of these test systems have shown that toxicity of the ionic liquids comes from the cationic component. Important observations from such test systems also included that (a) long alkyl chains increase the toxicity with increase in the length of hydrocarbons and (b) incorporation of oxygen functionalities (ether, ester, and hydroxyl etc.) reduces the toxicity.
A number of Organisation for Economic Cooperation and Development (OECD) tests were found to be useful in the estimation of biodegradation. These tests mainly involve calculation of CO$_2$ evolution and oxygen consumed. These tests showed that most of the 1,3-dialkyl imidazolium ionic liquids are non-biodegradable, in most of the test systems. Although the alkyl side chain can undergo degradation, the imidazole core can still persist during biodegradation studies. Introduction of oxygen functionality such as ether / ester, either in the side chain of the imidazolium cation or at the C1 or C3 position of the pyridinium cation, were found to increase the rate of biodegradation.

In the case study, we have demonstrated the schematic approach towards the design and synthesis of ionic liquid catalysts for acetalisation reactions and evaluation of the biocompatibility of such catalysts, by using toxicity and biodegradation methods. According to the guidelines laid by the toxicity and biodegradation testing, ionic liquid catalysts were designed and prepared. Such ester and amide side chain imidazolium catalysts were found to be useful in acetalisation and thiaacetalisation reactions. These catalysts have shown low toxicity against a variety of fungal and bacterial strains, but poor biodegradability in the “CO$_2$ Headspace Test”. Further modifications in the cationic part are underway with the goal of increasing biodegradation and catalytic activity. Although biodegradation was not improved by such modifications, the catalytic activity was modified and increased to a great extent. Green Chemistry metrics had given useful information about the ‘greenness’ of the synthetic route. Which allowed to modify the process by reducing the number of steps, amount of solvents, etc. This case study was a clear example of the importance, in the design of organocatalysts, of what the potential environmental impact of such compounds might be, and why it is important to understand that a truly “green” catalyst needs to possess a balance of both activity and eco-friendliness.

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