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Review Article

Ionic liquids: A green solvent for organic synthesis

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ABSTRACT

Industrial Chemistry in the new millennium is widely adopting the concept of "Green Chemistry" to meet the fundamental scientific challenges of protecting the health as well as environment, while maintaining the commercial viability. Use of Ionic liquids (IL) fit nicely into this bill with remarkably cutting the required reaction time and improving the yields and purity of the desired products. Other three more rapidly emerging areas of Green chemistry are Microwave Irradiation (MI), Phase transfer catalysis (PTC) & Sonochemistry (SC). Green chemistry is defined as the designing of chemical compounds and methods that minimizes or destroyed the use and generation of hazardous substances. The awareness of the said liquid is mainly due to their properties such as non flammability, lack of measurable vapor pressure, and good ability to dissolve organic, organometallic, and even some inorganic compounds. In this regards we report the applications of one of the Green Chemistry technique (Ionic liquid) with respect to Pharmaceuticals.

1. Introduction

Due to insignificant vapour pressure ionic liquids are considered as green solvents, environmentally safe to human life. Ionic liquids which are formed by non-renewable energy sources are poorly biodegradable in the environment.[1,2] Those liquids completely composedof ions and having melting point below 100^0c are called as Ionic liquids (ILs). In 1914 scientist called Paul Walden, was reported the first ILs (ethylammonium nitrate) he never realized that ILs would become a major scientific area after almost one century. From past two decades ILs has received wide attention as innovative fluids. Room-temperature ILs (RTILs), task-specific ILs (TSILs), polyconic liquids (PILs), and supported IL membranes (SILMs) are the types of ionic liquids which includes composites of ILs supported on metal organic frameworks (MOFs). In particular, their use as "Biphasic Catalysts", or "Immobilized Catalysts".[1] Traditional organic solvents including small vapor pressure at room temperature as well as high thermal stability, are the advantages of ILs which makes them nearly ideal solvents in extraction techniques. While designing and synthesizing new chemical products not only their cost and efficiency but also their toxicity to human health and environment should be considered. For commercial purpose ILs are not widely used recently. ILs was disposed mostly on waste water discharges and leaching of landfills which lead to better concern about pollute aquatic and terrestrial ecosystems.[2]

2. Importance of Ionic Liquids in Organic Synthesis

ILs has distinctive physical and chemical properties which are more and more influence chemists to explore their

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use as media for organic synthesis. In Organic synthesis ILs could have verity of applications in various fields like pharmaceuticals, fine chemicals, biotechnology, medical sciences, nanotechnology, bioremediation, and environmental and nuclear sciences. Absence of flammability, lack of measurable vapor pressure, and good ability to dissolve organic, organometallic, and even some inorganic compounds are the strange properties of ILs were the reasons of interest. Many commonly used ionic liquids contain the hexafluorophosphate (PF_6) anion, but those are unstable in water. To address the hydrolytic instability Merck has developed a range of new hydrophobic anions of ILs with these anions as replacements for the (PF_6) anion. The new anions is tris (perfluoroalkyl) trifluorophosphates also known as FAP anions such as $[(C_2F_5)_3PF_3]$. With 1-hexyl-3-methylimidazolium, 1-butyl-1-methylpyrolidinium they form room temperature ILs.

Fig. 1: 1-hexyl-3-methylimidazolium1butyl 1-methylpyrolidinium

FAP ionic liquids were developed for the use for battery applications in organic synthesis. It has been use as solvents in presence of Platinum as catalyst for the oxidation of benzyl alcohol to benzaldehyde and benzoic acid, as well as for the oxidation of cinnamyl alcohol to cinnamaldehyde and cinnamic acid using same catalyst. Poly (p-phenylene) is an important conducting polymer for the manufacture of blue polymer light-emitting diodes, till date the water and oxygen-free conditions are mandatory for making of polymer electrochemically has been a challenge. Hence the solvents like 18 M sulfuric acid as well as liquid sulfur dioxide were realistic for its electro synthesis. Under mild conditions electro polymerisation of benzene can be done by 1-hexyl-3-methylimidazolium tris(pentafluroethyl) triflurophosphate. Other ionic liquid, 1-butyl-1-methylpyrrolidinium bis (trifluoromethylsulfonyl) imide, is also suitable for a process as a solvent. Both ionic liquids are Lewis neutral, colorless, odorless, nonhazardous, and not aggressive. From pine tree Alpha pinene can be obtained which are readily available as chiral auxiliary. "High enantioselectivity is provided by large number of reagents derived from this molecule in various organic transformations. The two reactions are the addition of diethyl zinc to aldehydes and the 1, 4-conjugate addition of diethyl zinc to α, ß-unsaturated ketones. Asymmetric organic synthesis this is first synthesis of such chiral ILs from pinene and the first application of chiral ILs.

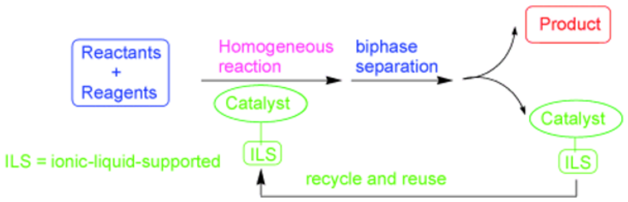

Fig. 2: Lonic liquids in organic synthesis

2.1. *Synthesis of ionic liquids*

$[EtNH_3][NO_3]$ (m.p. 12° C) is the first room temperature ionic liquid was discovered in the year 1914, but importance of the same was not develop until the finding of binary ionic liquids made from mixtures of aluminum(III) chloride and N-alkylpyridinium or 1,3-dialkylimidazolium chloride.

[emim] +Cl− + $AlCl_3$ [emim] +$[AlCl_4]$ (1)

[emim] +$[AlCl_4]$ − + $AlCl_3$ [emim] +$[Al2C_{l7}]$ (2)

[emim] +$[Al2Cl_7]$ − + $AlCl_3$ [emim] +$[Al3Cl_{10}]$ (3)

Mainly Ionic liquids variety in two categories, that is, simple salts (made of a single anion and cation) and binary ionic liquids (salts where equilibrium is involved). e.g, $[EtNH_3][NO_3]$ is a simple salt and the mixtures of aluminum (III) chloride and 1,3-dialkylimidazolium chlorides is a binary ionic liquid the properties of mixture depends upon their melting point and the mole fractions of aluminum (III) chloride and 1,3- dialkylimidazolium chloride present. The synthesis of ionic liquids can be described in two steps:

1. First is the the formation of the desired cation which can be synthesized either by the protonation of the amine by an acid or through quaternization reactions of amine with a haloalkane and heating the mixture.
2. Second one is by Anion Exchange reactions can be carried out by treatment of halide salts with Lewis's acids to form Lewis's acid-based ionic liquids or by anion metathesis.

Table 1: Examples of ionic liquids prepared by anion metathesi.[3]

Salt	Anion Source
[Cation]$[PF_6]$	HPF_6
[Cation] $[BF_4]$	HBF_4, NH_4, BF_4, $NaBF_4$
[Cation] $[CF_3SO_2)N]$	$Li[CF_3SO_2)_2N]$
[Cation] $[CF_3SO_3]$	$CF_3SO_3CH_3$,$NH_3NH_4[CF_3SO_3]$

3. Physical and Chemical Properties of Ionic Liquids

3.1. Viscosity

Basically those materials having greater *vander waals* interactions and hydrogen bonding have higher viscosities, however it has been experimentally proved that the size of the IL components has little effect on viscosity, The structure of anion has a large effect on the viscosity. This is an interesting observation that needs to be further substantiated by theoretical modeling. ILs is affected by specific structural features. e.g. the substituted imidazolium ILs, stacking of the aromatic rings leads to higher viscosity. Increasing the cation size by increasing the ring number in lactam-based PILs increases the viscosity by enhancing the cation-anion interaction. Analysis of the temperature dependence of viscosity for PILs with different glass transitions, suggests that PILs in general are among fragile material and the PILs with higher fragility have lower viscosity.

3.2. Conductivity

The ionic conductivity depends on the available charge carriers and their mobility (which depends on viscosity), varies with the molecular weight, and size of the ion. The ion mobility resulting from aggregation limits the conductivity of PILs. Therefore, less ionic interaction and more delocalized charge lead to higher conductivity; therefore, high ionic conductivity values will be expected for the stronger Bronsted acids and bases. The higher ionic conductivity of the 1-methyl-2-methyl imidazolium-based PILs compared with the 1-benzyl-2 methyl imidazolium based PILs and the higher conductivity value for methyl formate over butyl ammonium formate is because of the increase in the size of the cation. The ionic conductivity of heterocyclic PILs increases with less symmetrical cation structure and smaller molecular weight. There is no obvious trend which can be found for the anions used in the system: as an example, nitrate has the highest ionic conductivity in ethyl ammonium-based PILs in comparison with formate, acetate, but rate and lactate anions, but in the series of ethanol ammonium-based PILs, nitrate has the lowest ionic conductivity compared with the same anions.[4]

3.3. Density

The separation form of ILs in extraction process is determined by density of ILs. The density is the most often measured and reported physical property of ILs for its importance in related applications. ILs are generally denser than organic solvents, with typical density values ranging from 0.9 to 1.7 g cm-3. Many of the reported density values are at a single temperature, usually at 20 or 25° C. The density of ILs versus pressure and temperature has also been modeled. Significant amounts of data on the density of ILs are available in the literatures and reports of temperature parameters are most valuable. In general, temperature and pressure, relative molecular mass, the interaction between molecules and molecular structure are the factors on which density of matter depends. Anions and cations greatly affect the density of ILs.

Density formula provided by Fisher Company for dialkylimidazolium IL at different temperatures: ρ = a + b (T- 60).

3.4. Melting point

The lower end of liquidus range can be defined by melting point of ILs solvents. The properties which make ILs very attractive as solvent are low vapour pressure and very wide liquid range. Melting point of ILs is difficult to measure because many or most ILs are prone to supercooling. Instead of melting point ILs glass transition temperatures are usually reported as many ILs can form glasses. As ILs undergo considerable super cooling the melting point of many ILs are very uncertain.

3.5. Polarity

Solvents polarity is one of the important factor which significantly influences ILs application in extraction, more knowledge regarding the polarity of ILs can give a positive impacton the further application of ILs. We cannot lump together the polarities of ILs and molecular solvents because of abundant peculiar features of ILs are compared with ordinary molecular solvents. Definition of solvent polarity is not well-known, but we often consider polarity as an indicator of the combined strength of non-specific solute–solvent interactions and specific solute-solvent interactions. To a certain extend sepical solute-solvent interaction can be understood based on previous study on the polarity in ILs. The nonspecific solute-solvent interactions, such as electrostatic interaction, seem to be more complex and unpredictable.[5]

3.6. Toxicity of Ionic liquids

Using a wide range of targets, from proteins to animals' toxicity of ILs has been studied. An enzyme related to nerve signaling. Acteylcholinesteranse is frequently used as a model, for proteins. Certain reports have been published on other proteins as well. This article focused on living organisms, specifically on cells, which are the smallest units of living organisms, and higher organisms. A commonly used indicator of toxicity is EC_{50} is defined as the concentration of ionic liquids at which the growth of microorganisms and cells is halved compared to that without the ionic liquid.

3.7. Effect of ionic liquids on microorganisms

The most required characteristics of ionic liquids are antimicrobial and antifungal activities in life sciences and medicines. In Pharmacological applications, the antimicrobial and antifungal activities of ILs could be beneficial and a important for the development. However, such properties also have impact in unicellular organisms which play an important role in the balance of the ecosystems. In the ILs toxicity research or testing research most commonly used bacteria and fungi are *Pseudomonas putida (P. putida)*, *Escherichia oli (E. coli)*, *Staphylococcus aureus (S. aureus)* and *Aeromonashydrophila (A. hydrophila)*, and the yeast *Candida albicans (C. albicans)* and *Aspergillusniger (A. niger)* respectively.

3.8. Effect of ionic liquids on plants

The length of alkyl chains in the substituent, the type of anion and cation–anion interactions type and nature of the cation are important was found in several studies. It is important to ensure that any plant and environment in which the research is conducted should not be affected by the tested compound. The correlation between the toxicology of the tested ILs and the time of exposure of plants to them is also a factor to be considered in the many studies analyzed. There is still a poor understanding of the underlying processes that harm plants, besides the existing toxicology studies.

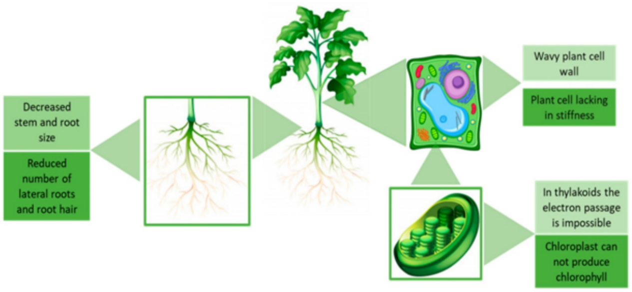

Fig. 3:

The length of the cation alkyl chain influences the toxicity of ILs, has been shown by toxicology studies, since it increases their lipophilic properties and, facilitating the interaction with the cell membrane, making it less rigid and wavier.

3.9. Effect of ionic liquids on animals

There is a need to discover the effects of Ionic Liquids contamination in marine and global ecosystems as they can enter the environment through waste water discharges and leaching of land fields. The effects of Ionic Liquids on living organisms and their risk of perseverance in the environment thus led researchers to explore the risk they could present to support habitats before and unsystematic use. The first choice is given to aquatic system by studying impact of ILs on organism like fish, algae for toxicological track.[2]

3.10. Applications of ionic liquids

An Alternative to detergents for cleaning up oil spillages is innovative and for [C4mim] Cl as a non-aqueous electrolyte for the recovery of spent uranium is also featured. A salient example is the Eastman Chemical Company synthetic plant for the production of 2,5-dihydrofuran which ran very successfully for 8 years. This process employed an IL as a co-catalyst for the isomerization of 3,4-epoxy-1-butene which gave the target product. The effective role, assumed by the IL used, was to produce a stable, selective and miscible co-catalyst system that was cheap (and so avoided the previous need to use of high boiling solvents which, themselves, created a number of unwanted side reactions).

3.11. ILs in their role as important solvents

Although theoretically able to deliver a whole range of both physical and chemical properties the concept of ILs as being "designed" solvents has not really materialized as yet. The wealth of data on solubility and miscibility characteristics, and indeed thermodynamic properties, necessary to tailor make ILs to return given target properties are still being assembled. The process of finding alternative solvents in the form of IL has, at least to date, rather been a trial-and-error procedure. It is the trends that are now becoming evident and these are used to inform choices. Examples can be found of ILs of differing types in respect of their coordinating ability and their inherent miscibility (which increases with temperature) with water. Complex bi- and indeed multi-phasic systems can be conceived owing to the range of properties exhibited.

3.12. ILs in their role as extractants and separators of chemicals from aqueous and organic media

Because of their properties, ILs has important applications as solvents in the industrial arena. ILs can be utilized effectively for the purposes of increasing the volatility difference between components that one wishes to separate by fractional distillation. This is particularly true for water-containing mixtures (e.g., alcohol – water) in view of the affinity which many ILs have for water. ILs can, for example, remarkably increase the volatility of the component with the lower boiling point, thus eliminating azeotropic behavior. As an example, we can cite the case where [C4mim] [BF4] is employed for the separation of ethanol–water Ionic liquids.[6]

Ionic Liquids are able to control many of the side effects of the conventional organic solvents or other catalysts during catalytic reactions and have productively been used in various catalytic areas affording high catalytic activity.[7–10]

4. Source of Funding

None.

5. Conflict of Interest

None.

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