Ali Mohammad · Inamuddin *Editors*

Green Solvents II

Properties and Applications of Ionic Liquids

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Preface

The fast-growing process of urbanization, industrialization, and unethical agriculture that has been implemented until recently has neither taken in consideration nor foreseen its effect on the environment, flora and fauna, and peoples' health and safety. Thus, over the last decade, green chemistry research has been focusing on finding and using safer and more environment-friendly solvents.

Indeed, every process in chemistry, physics, biology, biotechnology, and other interdisciplinary fields of science and technology makes use of *solvents, reagents, and energy* that not only are highly toxic but also produce a great amount of undesirable waste, damaging irreparably our environment.

However, according to one of the green chemistry principles, the use of solvents should either be avoided or limited as much as possible, and although sometimes this is not possible, we ought to try to use greener alternatives to toxic solvents.

Green Solvents Volume I and II has been compiled to broadly explore the developments in the field of green solvents.

Written by 87 leading experts from various disciplines, these remarkable volumes cover the most comprehensive, in-depth, and state-of-the-art research and reviews about green solvents in the field of science, biomedicine, biotechnology, biochemistry, chemical engineering, applied chemistry, metallurgical engineering, environmental engineering, petrochemicals engineering, etc. With more than 3,000 references, 325 figures, 95 tables, and 25 equations, *Green Solvents Volume I and II* will prove to be a highly useful source for any scientists working in the fields of organic synthesis, extraction and purification of bioactive compounds and metals, industrial applications of green solvents, bio-catalysis, acylation, alkylation and glycosylation reactions, oxidation of alcohols, carbon nanotube functionalization, hydrogen sulfide removal, pharmaceutical industry, green polymers, nanofluid coolants, high-performance liquid chromatography, and thin layer chromatography. Based on thematic topics, the book edition contains the following 17 chapters:

Chapter 1 introduces the history of ionic liquids as green solvents and discusses the synthesis of ionic liquids and their effects and properties, such as density, melting point, water-cosolvent miscibility, viscosity, polarity, acid/base character, and coordinating ability etc.

Chapter 2 reviews the progress in the applications of ionic liquids as a green solvent, dual green solvent, and catalyst for alkylation and acylation.

Chapter 3 demonstrates the development of environmentally benign *O*- and *C*-glycosylation methods using glycosyl phosphates, glycosyl fluorides, methyl glycosides, and 1-hydroxy sugars in several ionic liquids.

Chapter 4 examines the development of ionic liquid crystals (ILCs) based on organic cations (and anions), metal-based ILCs and polymeric ILCs, and their important applications.

Chapter 5 explores fundamental and applied studies on the extraction and separation of metals using ionic liquids with the aim of highlighting their novel application.

Chapter 6 discusses the progress, advantages, challenges, and opportunities associated with the removal of hydrogen sulfide using ionic liquid solvents.

Chapter 7 presents a comprehensive description of the versatility of ionic liquids as environmentally friendly green solvents for various biochemical transformations.

Chapter 8 focuses on the properties of ionic liquids/supercritical carbon dioxide biphasic systems for enzymatic applications.

Chapter 9 reviews state-of-the-art research on ionic liquid (IL) lubricants and introduces the tribological properties and functionalization of IL lubricants. The prospects of ILs as future lubricants are discussed.

Chapter 10 outlines the recent studies on the stability of enzymes and their reactivity toward a wide range of catalytic reactions in ionic liquids. A careful approach has been taken to establish the relationship between stability/activity of enzymes versus chaotropic/kosmotropic nature of cations and anions of ionic liquids.

Chapter 11 examines the methods of preparation and characterization, stability, transport mechanisms, and fields of application of supported ionic liquid membranes.

Chapter 12 illustrates the applicability of ionic liquids in multicomponent reactions and confirms the usefulness of ionic liquids as substituents of traditional organic solvents in certain synthetic transformations.

Chapter 13 discusses the design and analysis of the microscopic features of binary solvent systems formed by room temperature ionic liquids (RTILs) with molecular solvents. For this purpose, protic ionic liquids (PILs), ethylammonium nitrate (EAN), and 1-n-butyl-3-methylimidazolium (bmim)-based ILs and the molecular solvents such as acetonitrile, dimethyl sulfoxide, *N,N*-dimethylformamide, and protic (different alcohols) are selected. The study focuses on the identification of solvent mixtures of relevant solvating properties to propose them as "new solvents."

Chapter 14 describes the methods of oxidation of alcohols using different types of oxidizing agents and/or systems using ionic liquids as green solvents.

Chapter 15 reviews recent scientific accomplishments and addresses future perspectives about the functionalization of CNTs with Ils.

Chapter 16 outlines the possible utilization of room-temperature ionic liquids (RTILs), instead of volatile organic compounds (VOCs), in the electrochemical procedures of organic synthesis of alpha- and beta-lactams. The activation of carbon dioxide and its utilization as a renewable carbon source is also highlighted.

Chapter 17 introduces the latest developments in the area of organic ILs as green solvents in organic synthesis.

Ali Mohammad and Inamuddin
Editors

Editor's Biography

Ali Mohammad is Professor of Chemistry in the Department of Applied Chemistry, Faculty of Engineering and Technology, Aligarh Muslim University, Aligarh, India. His scientific interests include physico-analytical aspects of solid-state reactions, micellar thin layer chromatography, surfactants analysis, and green chromatography. He is the author or coauthor of 230 scientific publications including research articles, reviews, and book chapters. He has also served as editor of Journal, Chemical and Environmental Research being published from India since 1992 and as the Associate Editor for Analytical Chemistry section of Journal of Indian Chemical Society. He has been the member of editorial boards of Acta Chromatographica, Acta Universitatis Cibiniensis Seria F. Chemia, Air Pollution, and Annals of Agrarian Science. He has attended as well as chaired sessions in various international and nation conferences. Dr. Mohammad obtained his M.Phil (1975), Ph.D. (1978), and D.Sc. (1996) degrees from Aligarh Muslim University, Aligarh, India. He has supervised 51 students for Ph.D./M.Phil and M.Tech. degrees. Recently, he has been nominated as visiting professor at King Saud University, Kingdom of Saudi Arabia.

Inamuddin is currently working as Assistant Professor in the Department of Applied Chemistry, Aligarh Muslim University (AMU), India. He received his Master of Science degree in Organic Chemistry from Chaudhary Charan Singh (CCS) University, Meerut, India, in 2002. He received his Master of Philosophy and Doctor of Philosophy degrees in Applied Chemistry from AMU in 2004 and 2007, respectively. He has extensive research experience in multidisciplinary fields of Analytical Chemistry, Material Chemistry, and Electrochemistry and, more specifically, Renewable Energy and Environment. He has worked on different projects funded by University Grant Commission (UGC), Government of India, and Council of Scientific and Industrial Research (CSIR), Government of India. He has received Fast Track Young Scientist Award of Department of Science and Technology, India, to work in the area of bending actuators and artificial muscles. He has published 28 research articles and four book chapters of international repute. He is editing one more book entitled *Ion-Exchange Technology: Theory, Materials and Applications* to be published by Springer, United Kingdom. Recently, he edited a book entitled

Advanced Organic–Inorganic Composites: Materials, Devices and Allied Applications published by Nova Science Publishers, Inc. He is presently working as editor in chief of *The Journal of Chemical and Environmental Research* published from The Muslim Association for the Advancement of Science, India. He has worked as a Postdoctoral Fellow leading a research team at Creative Research Initiative Center for Bio-Artificial Muscle, Hanyang University, South Korea, in the field of renewable energy, especially biofuel cells. He has also worked as Postdoctoral Fellow at Center of Research Excellence in Renewable Energy, King Fahd University of Petroleum and Minerals, Saudi Arabia, in the field of polymer electrolyte membrane fuel cells and computer fluid dynamics of polymer electrolyte membrane fuel cells. He is a life member of the Journal of the Indian Chemical Society.

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Chapter 1
Ionic Liquids as Green Solvents: Progress and Prospects

Shadpour Mallakpour and Mohammad Dinari

Abstract Volatile organic solvents (VOS) creating increasing air pollution are common reaction media for many chemical processes. VOS cannot be easily separated from the desired reaction products and difficult to recycle. In view of awareness of the deteriorating environment, researches are directed on developing alternative environmental friendly solvent systems to replace traditional volatile organics. Within this context, the interest of ionic liquids (ILs) as "green" solvents resides in their extremely low vapor pressure and high thermal stability, which offers advantages such as ease of containment, product recovery, and recycling ability. In addition, ILs show considerable variation in their stability to moisture and their miscibility with molecular liquids. Properties such as density, melting point, water and cosolvent miscibility, viscosity, polarity, acid/base character, and coordinating ability can be tailored by the appropriate selection of the cation and/or anion component. ILs have been implemented as solvent systems in chemical reactions, separations, extractions, electroanalytical applications and chemical sensing, among many others. Also, they have high ionic character that enhances the reaction rates to a great extent in many reactions. These features allow ILs to be used as potential alternative solvents to VOS in a wide variety of industrial chemical processes. Furthermore, the use of ILs as industrial solvents can result in economical, social, and ecological impact due to their effect on the human health and environment.

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1.1 Introduction

Solvents are high on the list of damaging chemicals for two simple reasons: (a) they are used in large quantity and (b) they are usually volatile liquids. Volatile organic solvents, which have caused concerns on increasing air pollution and worker's health, are common reaction media for commercial production of different chemicals. It is an enormous challenge to reduce the amount of volatile organic compounds (VOCs) used in chemical and industrial processes. Governmental policies for the control of emissions of different substances which are released into the environment will become more restrictive as pollution increases worldwide. Therefore, the development of more efficient and environmentally friendly processes will be obligatory in the coming years [1–6]. These developments must be designed on the basis of two main characteristics: energy saving to avoid excessive emission of carbon dioxide (CO_2) and reduction of emissions related to harmful VOCs. Research on chemical manufacturing has focused on the investigation of different approaches for diminishing the emission of VOCs including solvent-free processes and the use of water, supercritical CO_2, and, more recently, ionic liquids (ILs) as the reaction media [7–10]. Among solvents, ILs have been rather sanguinely viewed as environmentally friendly or "green" solvents. Because of multiplicity of their uses, attention in ILs suddenly increased. ILs are organic salts that are liquid at ambient temperatures, preferably at room temperature. The reason why ILs are liquid at room temperature is still not fully understood. From recent X-ray crystal structure studies, we know that some of these tend to crystallize into disordered solids, and, depending upon the rate of cooling, crystal polymorphism can be observed. On the basis of these observations, it has been speculated that the gain in energy upon formation of the crystal is not as large as in traditional inorganic salts and is not enough to compensate for the loss in entropy that accompanies the formation of the crystal at room temperature. Experiments show that several of these systems have a tendency toward glassy behavior, and, depending upon the length of alkyl substituents in the cations, their properties range from those of normal liquids to glassy or even liquid crystals [11]. There are many synonyms including ionic fluid, molten salt, liquid organic salt, fused salt, or neoteric solvent [12–15] that used for ILs, which can complicate a literature search. "Molten salts" is the most common and most broadly applied term for ionic compounds in the liquid state. It appears that the difference between ILs and molten salts is just a matter of degree; however, the practical differences are sufficient to justify a separately identified niche for the salts that are liquid around room temperature.

Some useful properties of ILs are as following: they are relatively nonvolatile, which means they do not produce atmospheric VOCs and can be used in low-pressure environments. They possess good thermal stability and do not decompose over a large temperature range, thereby making it feasible to carry out reactions requiring high temperature conveniently in ILs. They can be considered both a polar and a noncoordinating solvents and show a high degree of potential for enantioselective reactions as a significant impact on the reactivities and selectivities. Chiral ILs have been used to control the stereoselectivity. ILs are complex and versatile solvents capable to interact via hydrogen bonding, π–π, n–π, dispersive, dipolar, electrostatic, and hydrophobic interactions and serve as a good medium to solubilize gases such as H_2, CO, O_2, and CO_2. Many reactions are now being performed using ILs and supercritical CO_2. They can be immiscible with nonpolar organic solvents and/or water. ILs have high ionic character that enhances the reaction rates to a great extent in many reactions including microwave-assisted organic synthesis as well as polymerization reactions. The solubility of ILs depends upon the nature of the cations and counter anions. They have physicochemical properties that can be controlled by judicious selection of the cation and/or anion. Many of them can be stored without decomposition for a long period of time [16–27].

There are several important review articles on the synthesis, properties, and applications of room temperature ILs (RTILs), including solvents for synthesis and catalysis [28], ILs – new solutions for transition metal catalysis [29], a short history of ILs [30], IL (molten salt) phase organometallic catalysis [12], RTILs as replacements for conventional solvents [31], biocatalysis in ILs – advantages beyond green technology [32], ILs and chirality: opportunities and challenges [33], biocatalytic transformations in ILs [34], application of ILs as solvents for polymerization processes [35], chromatographic and spectroscopic methods for the determination of solvent properties of RTILs [36], development of ILs as green reaction media and catalysts [37], ILs for the convenient synthesis of functional nanoparticles and other inorganic nanostructures [38], ILs in catalysis [39], non-haloaluminate RTILs in electrochemistry [40], task-specific ILs (TSILs) [41], application of ILs in analytical 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transfer radical polymerization and ring-opening metathesis polymerization in ILs [121], the design of polymeric ILs for the preparation of functional materials [122], assessing the greenness of some typical laboratory IL preparations [123], biodegradation studies of ILs [124], extraction of organic compounds with RTILs [125], ILs in analytical chemistry [126], ILs and catalysis [127], ILs for CO_2 capture [128], methods for stabilizing and activating enzymes in ILs [129], microwave-assisted synthesis using ILs [130], recent advances of enzymatic reactions in ILs [131], recent applications of ILs in separation technology [132], task-specific ILs [133], the Heck reaction in ILs [134], the roles of ILs in sorptive microextraction techniques [135] and toward advanced ILs, and polar, enzyme-friendly solvents for biocatalysis [136].

1.2 History of Ionic Liquids (ILs)

Although Osteryoung, Wilkes, Hussey, and Seddon are pioneers in the field of ILs, the first report on room-temperature molten salt was published by Welton in 1914 [28]. He reported the physical properties of ethylammonium nitrate ($[C_2H_5NH_3]NO_3$), which is formed by the reaction of ethylamine with concentrated nitric acid and has a melting point of 12°C. Later on, by mixing and warming 1-ethylpyridinium chloride with aluminum chloride ($AlCl_3$), Hurley and Weir prepared another molten salt [137]. With quaternization of the heterocycle and forming mixtures with $AlCl_3$, Osteryoung revolutionized this field and reported new salts in 1978. Consequently, the effect of changing the cation was investigated by Hussey and Wilkes, and the dialkylimidazolium-based ILs were discovered [111]. The ILs based on $AlCl_3$ can be considered as the first generation of ILs, but the advancement in their use was restricted due to hygroscopic nature. Thus, they were not found suitable for open-air applications. However, the second generation of ILs as named air and water stable ILs were synthesized and attracted auxiliary attention in the use of ILs in different fields. Wilkes and Zaworotko [138] reported the synthesis of water- and air-stable dialkylimidazolium ILs. They revealed that upon anion exchange with more hydrolytically stable anions such as BF_4^-, PF_6^-, NO_3^-, SO_4^{-2} or acetate, the resulting ILs could be prepared and safely stored outside of an inert atmosphere as they are water insensitive. As regards the synthesis and applications of air-stable ILs, $[BMIm][BF_4]$ and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ($[BMIm][PF_6]$) were the first. After that, the magnitude of air- and water-stable ILs has started to increase quickly [139]. Then ILs based on more hydrophobic anions such as tri-fluoromethanesulfonate ($CF_3SO_3^-$), bis-(trifluoromethanesulfonyl)imide $[Tf_2N]^-$, and tris-(trifluoromethanesulfonyl)methide $[(CF_3SO_2)_3C^-]$ were reported [140]. This development led to the birth of the modern day ILs. Rogers focuses on the synthesis and characterization of environmentally friendly ILs as green solvents and found that cellulose could be dissolved in 1-butyl-3-methyl imidazole chloride ([BMIm]Cl), which opened a new way for the development of a class of cellulose solvent systems. Many papers dealing with the applications of ILs as solvents for synthesis and catalysis have been published by Welton. He focused his study on interaction of ILs with solute species and tried to replace environmentally damaging solvents with more benign alternatives [28]. Preparation and characterization of ILs for use in the biphasic catalysis were reported by Wasserscheid and Welton [141]. Jessop et al. indicated that functional groups can be incorporated in IL and make them to behave not only as a reaction medium but also as a reagent or catalyst in some reactions or processes. This group of ILs was named as "task-specific ILs." Addition of pressurized carbon dioxide into an organic mixture transforms it into an IL, generating a safer solvent in situ. Releasing of the pressure reverses the phenomenon, and the IL is retransformed into the original mixture, thus removing completely the solvent and eliminating tedious purification and extraction steps [142].

1.3 Structure of Ionic Liquids (ILs)

Similar to all salts, ILs are made up of separate cationic and anionic species, but unlike common salts, ILs have a low tendency to crystallize due to their bulky and asymmetrical cation structure. The nearly infinite combinations of suitable cations and anions lead to the possibility of tailoring the IL properties, with the anion responsible for such qualities as air and water stability and the cation responsible for melting temperature and organic solubility. They are also known as "designer solvents" since they give the opportunity to tune their specific properties for a particular need. The researchers can design a specific IL by choosing negatively charged small anions like $[Tf_2N]^-$, PF_6^-, or PF_4^- and positively charged large cations of alkylimidazolium, alkylpyridinium, alkylpyrrolidinium, alkylphosphonium, or alkylmorpholinium. These specific ILs may be utilized to dissolve a particular chemical or to extract a certain material from a solution. The fine-tuning of the structure provides tailor-designed properties to satisfy the specific application requirements. Although these particular cations and anions and their various combinations have already been studied extensively for their potential applications in numerous chemical and physical processes, every year more and more cations and anions forming liquid salts at room temperature are reported [54, 143–145]. Plechkova and Seddon estimated that there may be in excess of 10^6 possible ILs if all currently known IL cations and anions were to be paired and as many as 10^{18} if all ternary systems were to be investigated [90]. Their structures play a key role in several interesting and useful ways because their unique properties that departs from those of conventional solvents. Their coulombic nature imposes a degree of order on the short-range scale, and their amphiphilic combination of polar and nonpolar components leads to different types of correlations on longer scales [146].

The structure of cation–cation and anion–anion peaks and valleys in the pair distribution is diametrically out of phase with the cation–anion pair distribution [147]. The overall properties of ILs result from the composite properties of the cations and anions and include those that are superacidic, basic, hydrophilic, water miscible, water immiscible, and hydrophobic. The structures of most normally used cations and some possible anion are represented in Fig. 1.1.

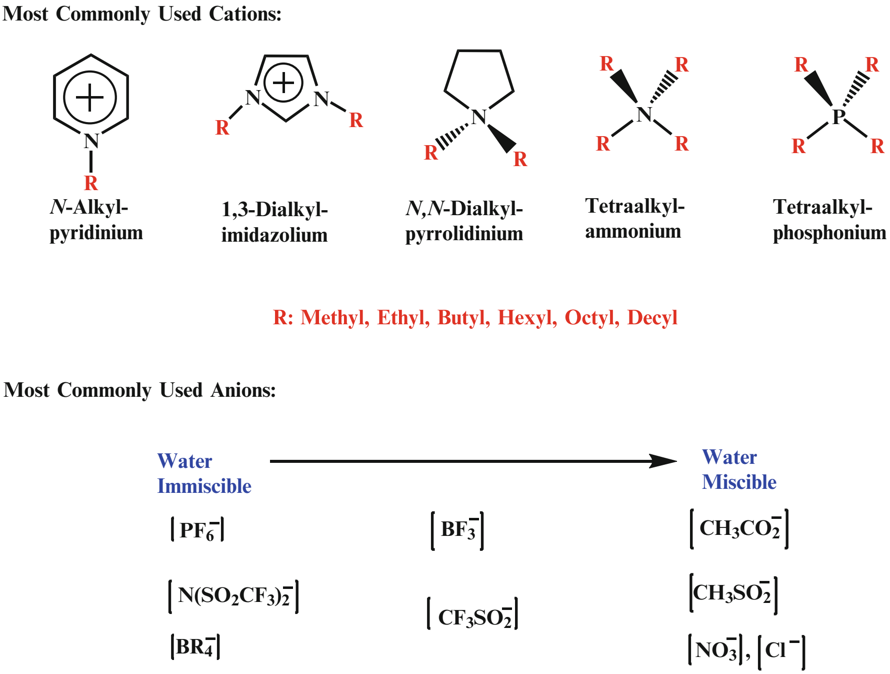

Fig. 1.1 Most commonly used cation structures and possible anion types

1.3.1 *Cations*

The cation of IL is usually a bulk organic structure with low symmetry which gives salts having low melting points even though dibutyl, dioctyl, dinonyl, and didecylimidazolium hexafluorophosphates are liquid at room temperature [148]. The majority of ILs are based on imidazolium, pyridinium, ammonium, phosphonium, sulfonium, thiazolium, pyrazolium, and oxazolium cations. The research mainly focuses on RTILs composed of asymmetric *N*,*N*-dialkylimidazolium cations associated with a variety of anions. The melting points of the most ILs are indecisive. For that reason, by examining the properties of a series of imidazolium-cation-based ILs, it has been concluded that as the size and asymmetry of the cation increases, the melting point decreases. Further, an increase in the branching on the alkyl chain increases the melting point.

ILs with specific functional groups on the cation have been prepared by different groups. For example, ILs bearing a fluorous tail have been synthesized to facilitate the emulsification of perfluorocarbons in ILs. These ILs perform as surfactants and appear to self-aggregate within imidazolium ILs [149]. A free amine group or a urea or thiourea has been inserted to capture H_2S or CO_2 or heavy metals, respectively [150]. Moreover, ether and alcohol functional groups have been attached to imidazolium cations to promote the solubility of inorganic salts. The presence of these extra potential complexing groups makes these ILs suitable for specific applications [11, 151, 152].

1.3.2 Anions

Since the nature of anion has a great effect on the properties of IL, there are major differences between ILs with different anions. The introduction of different anions results in an increasing number of alternative ILs with various properties [153]. The physical and chemical properties of the ILs can be determined by different ion pairs. IL with 1-*n*-butyl-3-methylimidazolium cation and PF_6^- anion is immiscible with water, whereas IL with same cation and BF_4^- anion is water soluble. This example represents the "designer solvent" property of ILs. By changing the anion, the hydrophobicity, viscosity, density, and solvation of the IL system may be changed [67].

On the basis of the anion, ILs may be divided into four groups: (a) systems based on $AlCl_3$ and organic salts such as [BMIm]Cl; (b) systems based on anions like PF_6^-, BF_4^-, and SbF_6^-; (c) systems based on anions such as $[CF_3SO_3]^-$, $[(CF_3SO_2)_2N]^-$, $[Tf_2N]^-$, and similar; and (d) systems based on anions such as alkylsulfates and alkylsulfonates [19, 154, 155]. The first group represents the ILs of "first generation," whose Lewis acidity can be varied by the relative amounts of organic salt/$AlCl_3$. With a molar excess of $AlCl_3$, these ILs are Lewis acidic; with an excess of organic salt, they are Lewis basic; and Lewis neutral liquids contain equimolar amounts of organic salt and $AlCl_3$. These ILs are, however, extremely hygroscopic, and handling is possible only under a dry atmosphere. The systems mentioned in (b) are nearly neutral and air stable, although they have the drawback of reacting exothermically with strong Lewis acids, such as $AlCl_3$, and with water [141]. ILs based on anions mentioned in (c) are much more stable toward such reactions and are generally characterized by low melting points, low viscosities, and high conductivities. Structural studies of organic $[Tf_2N]^-$ salts have shown only weak coulombic interactions between $[Tf_2N]^-$ and weak Lewis acids, attributable to delocalization of the negative charge within the S–N–S core [156, 157].

Probably, the metal enhances the contribution of the resonance structure bearing the negative charge on the nitrogen atom. Lately, the synthesis of numerous ILs based on the bis(methanesulfonyl)amide ($[Ms_2N]^-$) anion has provided new insights into the effect of anion fluorination on the properties of ILs. The substitution of $[Tf_2N]^-$ anion with $[Ms_2N]^-$ induces a significant increase in hydrogen bonding, which determines a significant rise in the glass transition temperature with concurrent increase in viscosity, which in turn produces a drop in conductivity [158].

ILs bearing perfluorinated anions are expensive (in particular, those having $[Tf_2N]^-$ as counter anion), and the presence of fluorine makes the disposal of spent ILs more complicated. For these reasons, research on new ILs bearing inert low-coordinating and nonfluorinated anions represents a field of intense investigation in the chemistry of ILs. Among the possible alternatives recently proposed are the ILs having as carboranes and orthoborates counter anions [4]. ILs based on anions mentioned in (d) may conquer at least some of the above-mentioned problems. These anions are relatively cheap, do not contain fluorine atoms, and often the corresponding ILs can be easily prepared under ambient conditions by reaction of organic bases with dialkyl sulfates or alkyl sulfonate esters. Moreover, these new ILs are characterized by a wide electrochemical window and air stability [153].

1.4 Synthesis of Ionic Liquids (ILs)

The growing attention in ILs, especially in the light of their current common commercial applicability, has resulted in further progresses in their synthesis and purification. Above all, this has required a shift toward improving the standard of synthetic procedures to ensure consistency in the quality of the materials. Furthermore, in order to improve the chances of large-scale commercial applications, the efficiency of synthetic procedures, IL toxicity, and biodegradation have all become important topics [141]. Notably, the inherent synthetic flexibility afforded by pairing different cations with any of a growing number of anions provides the possibility for “fine-tuning” certain IL solvent properties to the particular task at hand.

There are three basic methods to synthesize ILs: metathesis reactions, acid–base neutralization, and direct combination. Many alkylammonium halides are commercially available which can be organized simply by the metathesis reaction of the appropriate halogenoalkane and amine. Pyridinium and imidazolium halides are also synthesized by metathesis reaction. On the other hand, monoalkylammonium nitrate salts are best prepared by the neutralization of aqueous solutions of the amine with nitric acid. After neutralization reactions, ILs are processed under vacuum to remove the excess water [28]. Tetraalkylammonium sulfonates are also prepared by mixing sufonic acid and tetraalkylammonium hydroxide [159]. In order to obtain pure IL, products are dissolved in an organic solvent such as acetonitrile and treated with activated carbon, and the organic solvent is removed under vacuum. The final method for the synthesis of ILs is the direct combination of halide salt with a metal halide. Halogenoaluminate and chlorocuprate ILs are prepared by this method. The synthesis methods of ILs have been given in numerous articles [89, 138, 160, 161].

The protonation of suitable starting materials (generally amines and phosphines) still represents the simplest method for the formation of such materials, but unfortunately, it is restricted to the small range of useful salts. The possibility of decomposition via deprotonation has adversely affected the use of such salts. Probably, the most widely used salt of this type is pyridinium hydrochloride as evident from literature reviewed by Pagni [162].

The majority of ILs are formed from cations that have not been obtained by protonation of a nucleophile. A summary of the applications and properties of ILs may be found in a number of review articles [12, 19, 41, 163]. The synthesis of ILs can generally be divided into two steps: the formation of the desired cation, and anion exchange to form the desired product. In some cases, only the first step is required, as with the formation of $[C_2H_5NH_3]NO_3$. In many cases, the desired cation is commercially available at reasonable cost, most commonly as a halide salt, thus requiring only the anion exchange reaction. The steps involved in the synthesis of ILs are described below.

1.4.1 Quaternization Reactions

The formation of the cations may be carried out either via protonation with a free acid or by quaternization of an amine, phosphine, or sulfide, most commonly using a haloalkane or dialkylsulfates. The protonation reaction, as used in the formation of salts such as $[C_2H_5NH_3]NO_3$, involves the addition of nitric acid to a cooled aqueous solution of ethylamine [164]. The excess amine is removed along with the water by heating to 60°C in vacuum. The same general process may be employed for the preparation of all salts of this type, but when amines of higher molecular weight are employed, there is clearly a risk of contamination by residual amine. A similar method has been reported for the formation of low-melting, liquid crystalline, long-alkyl-chain-substituted 1-alkylimidazolium chloride, nitrate, and tetrafluoroborate salts [165]. At this point, a slight excess of acid could be employed as the products are generally crystalline at room temperature.

The quaternization of amines and phosphines with haloalkanes has been known for many years. In general, the reaction may be carried out using chloroalkanes, bromoalkanes, and iodoalkanes, with the milder reaction conditions in the order $Cl \rightarrow Br \rightarrow I$, as is expected for nucleophilic substitution reactions. Fluoride salts cannot be formed in this manner.

In theory, the quaternization reactions are extremely simple: the amine (or phosphine) is mixed with the desired alkylating agent, and the mixture is then stirred and heated. The following section refers to the quaternization of 1-alkylimidazoles, as these are the most common starting materials. The common methods are similar, but for other amines such as pyridine, isoquinoline, 1,8-diazabicyclo[5.4.0]-7-undecene, 1-methylpyrrolidine, and trialkylamines, as well as for phosphines, it is not popular [140, 166–168]. The reaction temperature and time varied according to the nature of the alkylating agent employed, chloroalkanes being the least reactive and iodoalkanes the most. The reactivity of the haloalkanes generally decreases with increasing alkyl chain length. Several different protocols have been reported, but most researchers use a simple round-bottomed flask/reflux condenser experimental setup for the quaternization reaction. If possible, the reaction should be carried out under dinitrogen or some other inert gas in order to exclude water and oxygen during the quaternization reactions [141].

1.4.2 Anion-Exchange Reactions

The anion-exchange reactions of ILs can be alienated into two distinct categories: direct reaction of halide salts with Lewis acids and the formation of ILs via anion metathesis.

1.4.2.1 Lewis-Acid-Based Ionic Liquids (ILs)

The formation of ILs by the reaction of halide salts with Lewis acids (most notably $AlCl_3$) dominated in the infancy of this area of chemistry. The great breakthrough came in 1951 with the report by Hurley and Weir on the formation of a salt that was liquid at room temperature based on the combination of 1-butylpyridinium with $AlCl_3$ in the relative molar proportions 1:2 [169]. The technology of room-temperature chloroaluminate melts based on 1-alkylpyridinium and 1-alkyl-3-methylimidazolium $[RMIm]^+$ cations has been developed in recent years [170]. In general, the reaction of a quaternary halide salt Q^+X^- with a Lewis acid MX_n results in the formation of more than one anion species, depending on the relative proportions of Q^+X^- and MX_n. The chloroaluminates are not the only ILs prepared in this manner. Other Lewis acids employed include $AlEtCl_2$, BCl_3, CuCl, $SnCl_2$, and $FeCl_3$. In most cases, the preparative methods employed for all of these salts are similar to those indicated for $AlCl_3$-based ILs [141].

The most common method for the formation of such liquids is simple mixing of the Lewis acid and the halide salt, with the IL forming on contact of the two materials. The reaction is generally quite exothermic, which means that care should be taken when adding one reagent to the other. Although the salts are relatively thermally stable, the buildup of excess local heat can result in decomposition and discoloration of the IL. This may be prohibited either by cooling the mixing vessel or by adding one component to the other in small portions to allow the heat to dissipate. Considering the water-sensitive nature of most of the starting materials, the reaction be carried out in a drybox and the ILs should preferably be stored in a drybox until use [141].

1.4.2.2 Anion Metathesis

The first report on the development of air- and water-stable ILs was reported by Wilkes and Zaworotko [138] which was based on 1,3-dialkylmethylimidazolium cations. The preparation involved a metathesis reaction between 1-ethyl-3 methylimidazolium iodate [EMIm]I and a range of silver salts ($Ag[NO_3]$, $Ag[NO_2]$, $Ag[BF_4]$, $Ag[CH_3CO_2]$, and $Ag_2[SO_4]$) in methanol or aqueous methanol solution. The very low solubility of silver iodide in these solvents allowed its separation simply by filtration, and removal of the reaction solvent allowed isolation of the ILs in high yield and purity. This method remains the most efficient for the synthesis of water-miscible ILs, but is obviously limited by the relatively high cost of silver salts, not to mention the large quantities of solid by-product produced [141]. The first report on a water-insoluble IL appeared 2 years later, with the preparation of $[EMIm][PF_6]$ from the reaction of [EMIm]Cl and HPF_6 in aqueous solution [171]. Though the protocols reported in the above two papers were sound, subsequent authors suggested refinements in the methods employed. Most of the $[EMIm]^+$-based salts are solid at room temperature, facilitating purification via recrystallization. In many applications, however, a product is required that is liquid at room temperature. Therefore, it is useful to employ cations with 1-alkyl substituents of chain length 4 or greater, which results in a considerable lowering in melting point. The main goal of all anion exchange reactions is the formation of the desired IL uncontaminated with unwanted cations or anions, a task that is easier for water immiscible ILs.

It should be noted, however, that low-melting salts based on symmetrical onioum cations have been prepared using anion-exchange reactions for many years. For instance, the preparation of tetrahexylammonium benzoate (a liquid at 25°C) from tetrahexylammonium iodide, silver oxide, and benzoic acid was reported in 1967. The same authors also commented on an alternative approach involving the use of an ion-exchange resin for the conversion of the iodide salt to hydroxide, but concluded that this approach was less desirable. Low-melting salts based on cations such as tetrabutylphosphonium [172] and trimethylsulfonium [173] have also been produced using very similar synthetic methods.

As the preparation of water-immiscible ILs is considerably more straightforward than the preparation of their water-soluble analogues, these methods will be considered first. The water solubility of the ILs is highly dependent on the nature of both the anion and cation present and, in general, will decrease with increasing organic character of the cation. The most common approach for the preparation of water-immiscible ILs is first to prepare an aqueous solution of a halide salt of the desired cation. The cation exchange is then carried out using either the free acid of the appropriate anion or a metal or ammonium salt. Where available, the free acid is probably to be favored, as it leaves only HCl, HBr, or HI as the by-product which can be easily removed from the final product by washing with water. It is recommended that these reactions are carried out with cooling of the halide salt in an ice bath, as the addition of a strong acid to an aqueous solution is often exothermic [141]. In cases where the free acid is inconvenient to use, however, alkali metal or ammonium salts may be substituted without major problems. It may also be preferable to avoid using the free acid in systems where the presence of traces of acid may cause problems. A number of authors have outlined broadly similar methods for the preparation of $[PF_6]^-$ and $[Tf_2N]^-$ salts that may be adapted for most purposes [170, 174]. When free acids are used, the washing should be continued until the aqueous residues are neutral, as traces of acid can cause decomposition of the IL. The most common approach is to perform the exchange in aqueous solution using either the free acid of the appropriate anion, the ammonium salt, or an alkali metal salt. When using this approach, it is significant that the desired IL can be isolated without excess contamination from unwanted halide-containing by-products. A reasonable compromise has been suggested by Welton et al. for the preparation of $[BMIm][BF_4]$ [175]. In this method, which could in principle be adapted to many other water-miscible systems, the IL is formed by metathesis between [BMIm]Cl and HBF_4 in aqueous solution. The product is extracted into CH_2Cl_2, and the organic phase is then washed with successive small portions of deionized water until the pH of washings reach to neutral value. Although the water wash can result in a lowering of the yield, the aqueous wash solutions may ultimately be collected together, the water removed, and the crude salt added to the next batch of IL prepared. In this manner, the amount of product loss is minimized, and the purity of the IL prepared appears to be reasonable for most applications.

Alternatively, the metathesis reaction may be carried out entirely in an organic solvent such as CH_2Cl_2, as described by Cammarata et al. [176], or acetone, as described by Fuller et al. [177]. In both of these systems, the starting materials are not fully soluble in the reaction solvent, so the reaction is carried out in a suspension. In the case of the CH_2Cl_2 process, the reaction was carried out by stirring the 1-alkyl-3-methylimidazolium halide salt with the desired metal salt at room temperature for 24 h. Although the halide by-products have limited solubility in CH_2Cl_2, they are reasonably soluble in the IL/CH_2Cl_2 mixture. Thus, when this method is employed, it is important that the CH_2Cl_2 extracts are washed with water to minimize the halide content of the final product. This approach clearly results in a lowering of the yield of the final product. Therefore, care must be taken that the volume of water used to carry out the washing is low. Lowering the temperature of the water to near 0°C can also reduce the amount of IL loss. The final product can be purified by stirring with activated charcoal followed by passing through an alumina column, as described in the previous paragraph. This process was reported to give final yields in the region of 70–80% and was used to prepare ILs containing a wide variety of anions ($[PF_6]^-$, $[SbF_6]^-$, $[BF_4]^-$, $[ClO_4]^-$, $[CF_3SO_3]^-$, $[NO_3]^-$, and $[CF_3CO_2]^-$). In the case of the acetone route, [EMIm]Cl was stirred with $[NH_4][BF_4]$ or $[NH_4][CF_3SO_3]$ at room temperature for 72 h. In this case, all starting materials were only slightly soluble in the reaction solvent. The insoluble $[NH_4]Cl$ by-product was removed by filtration. No water wash was carried out, but trace organic impurities were removed by stirring the acetone solution with neutral alumina for 2 h after removal of the metal halide salts by filtration. The salts were finally dried by heating at 120°C for several hours, after which they were analyzed for purity by electrochemical methods, giving quoted purities of at least 99.95% [177].

1.5 Properties of Ionic Liquids (ILs)

ILs with many interesting properties are currently enjoying popularity among chemists. Overall, generalizing and reporting their properties is not easy because some of the properties such as electrochemical window, long-term thermal stability, polarity, and volatility have been the subject of debate. This happens due to better understanding and adequate characterization of ILs with improved quantification of their impurities which are well known to affect the thermophysical properties of them [127]. Water solubility of an IL can be tuned by changing the R group on the cation component. In addition, by the choice of the anion, chemical and physical properties can be changed significantly. The generic properties of ILs have been described in literature [146] and can be easily found in a database.

1.5.1 Melting Point

The key criterion for the evaluation of an IL is its melting point. Although ILs have been defined to have melting points below 100°C and most of them are liquid at room temperature, data must be considered with caution. The melting point of many ILs may be uncertain because they undergo considerable supercooling, the temperature of the phase change which can differ considerably depending on whether the sample is heated or cooled, and also because of the potential presence of impurities [127]. There is a significant relationship between the structure and chemical composition of an IL and its melting point. This physical property can be adjusted through variations on the cation and/or anion, and both cations and anions contribute to the low meting points of ILs. The increase in anion size leads to a decrease in melting point. For instance, the melting points of 1-ethyl-3-methylimidazolium-type ILs with different anions, such as $[BF_4]^-$ and $[Tf_2N]^-$, are 15°C and −3°C, respectively [178]. Comparison of the melting points of different chlorine salts illustrates the influence of the cation clearly. High melting points are characteristic for alkali metal chloride, whereas chloride with suitable organic cation melts at temperatures below 150°C. In the literature, the following features are discussed for the cations of low-melting salt: low symmetry, weak intermolecular interaction such as avoidance of hydrogen bonding, and a good distribution of charge in the cation. For IL prepared by reaction of halide $[\text{cation}]^+X^-$ with a Lewis acid MX_λ, the molar ratio of two reactants influences the melting point [29]. Further, an increase in the branching on the alkyl chain increases the melting point.

1.5.2 Volatility

In addition to the favorable physical and chemical properties of ILs, an important property of ILs that stimulates interest in using them in the context of so-called green chemistry is their essentially zero vapor pressure even at elevated temperatures. ILs are indeed nonvolatile in that sense that at near ambient temperatures their vapor pressure is negligible. For typical ILs, normal boiling temperatures (T_b), which correlate with their vapor pressure at one atmosphere, cannot be experimentally determined as ILs decomposes at a lower temperature. It has nevertheless been reported that ILs can be distilled at 200–300°C but under significantly reduced pressure and at very low distillation rate ($<0.01\ \text{g}\,\text{h}^{-1}$). Vapor pressure of ILs remains, however, negligible at near ambient conditions; thus, for all practical purposes, they may be considered as nonvolatile solvents [35]. On the whole, the negligible volatility of these ILs denotes that air pollution by gaseous release is not a concern. ILs are considered as nonvolatile and, consequently, nonflammable at ambient and higher temperatures. However, the potential release of IL vapors (or decomposition products) must be considered when ILs are used at elevated temperatures.

1.5.3 Thermal Stability

Thermogravimetric analysis indicates high thermal stability for many ILs, generally >350°C. For example, ILs $[EMIm][BF_4]$, $[BMIm][BF_4]$, and 1,2-dimethyl-3-propylimidazolium bis(trifluorosulfonyl)imide are stable up to temperatures of 445°C, 423°C, and 457°C, respectively [127]. Such high temperatures are only tolerated by most liquids for a short time. For example, after 10 h, even at temperatures as low as 200°C, [RMIm][PF_6] and 1-decyl-3-methylimidazolium triflate show an appreciable mass loss [179]. The ILs with low thermal stability are [EMIm][X], where X=[Tf_2N]$^-$, [M_SN]$^-$, and Br^- [68]. Phosphonium ILs with [Tf_2N]$^-$ or [$N(CN)_2$]$^-$ anions decompose completely to volatile products in a single step. The degradation products indicate that Hofmann elimination process and/or dealkylation reactions occurred. Conversely, ILs based on nitrogen cations do not decompose completely [127]. The start of thermal decomposition is furthermore similar for the different cations but appears to decrease as the anion hydrophilicity increases. It has been suggested that the stability dependency on the anion is in the order [PF_6]$^-$>[Tf_2N]$^-$ [BF_4]$^-$>halides. An increase in cation size, at least from 1-butyl to 1-octyl, does not offer large effect [19].

1.5.4 Viscosity

The viscosity of many ILs is relatively high compared to conventional solvents, one to three orders of magnitude higher. The viscosity is determined by van der Waals forces, hydrogen bonding, and electrostatic forces. The ability of fluorinated anions such as BF^{-4} and PF^{-6} to the formation of hydrogen bonding results in the formation of viscous ILs [178]. The presence of $AlCl_4^-$ and $Al_2Cl_7^-$ in acidic mixture leads to formation of weaker hydrogen bond and much lower viscosity. The transition from triflate ion to n-$C_4F_9SO_3$ and from the triflouroacetate ion to the n-$C_3F_7COO^-$ ion shows an obvious increase in viscosity. In fact, stronger van der Waals forces lead to increase in the energy required for molecular motion. The case of n-$C_4F_9SO_3$ and n-$C_3F_7COO^-$ ions results in a higher viscosity of IL. Comparison of the viscosity of the [BMIm]CF_3SO_3 with [BMIm][Tf_2N] reveals a lower viscosity despite stronger van der Waals interaction. In this case, the almost complete suppression of hydrogen bond is responsible for expected increase viscosity [29]. For a variety of ILs, viscosity has been reported in the range 10–500 mPa s^{-1} at room temperature. The viscosity of ILs can affect transport properties such as diffusion and plays a major role in stirring, mixing, and pumping operations.

1.5.5 Density

ILs are generally denser than either organic solvents or water, with typical density values ranging from 1 to 1.6 g cm^{-3}. Their densities were found to decrease with increase in the length of the alkyl chain in the cation. For example, for ILs composed of substituted imidazolium cations and $CF_3SO_3^-$ anion, the density decreases from 1.39 g cm^{-3} for [EMIm] 1 to 1.33 g cm^{-3} for [E_2Im], to 1.29 g cm^{-3} for [BMIm], and to 1.27 g cm^{-3} for [BEIm] 1.22. Density of an IL depends on the type of cation and anion. The density of comparable ILs decreased as the bulkiness of the organic cation increase. The order of increasing density for ILs composed of a single cation is $[CH_3SO_3]^- \approx [BF_4]^- < [CF_3CO_2]^- < [CF_3SO_3]^- < [C_3F_7CO_2]^- < [(CF_3SO_2)_2N]^-$ [178]. The molar mass of the anion significantly affects the overall density of ILs. The $[Ms_2N]^-$ species have lower densities than the $[Tf_2N]^-$ salts, in agreement with the fact that the molecular volume of the anion is similar but the mass of the fluorine is greater. In the case of orthoborates, with the exception of bis(salicylato)borate, the densities of the ILs having the [BMIm] cation decrease with increase in anion volume. This order is also followed in ILs, those having $[Tf_2N]^-$, $[TfO]^-$, or $[BF_4]^-$ as anion. This behavior has been attributed to the fact that packing becomes more compact as the alternating positive and negative species are more even in size [19]. Density measurement of IL with triflate or trifluoroacetete ions confirms the more general trend. Furthermore, a certain density range is established by the choice of anion, within which a fine adjustment is possible by careful choice of cation [29].

1.5.6 Polarity

To classify the solvents, the polarity is one of the most important properties for characterizing the solvent effect in chemical reactions. In IUPAC document, polarity is defined as "the sum of all possible, nonspecific interactions between the solute ions and molecules and solvent molecules, excluding such interactions leading to definite chemical alterations of the ions or molecules of the solute" [67]. The subject of IL polarity has been addressed by a variety of methodologies. As an example, the property of solvents to stabilize a charge is usually determined from the absorption maximum of a solvatochromic dye. By this measurement, the polarity, archetypical $[BMIm][BF_4]$, is in the range of the lower alcohols. A solvatochromic test for the coordination strength (nucleophilicity) of the anion, in contrast, indicates that the often used $[PF_6]$ and $[Tf_2N]$ anions are much less nucleophilic than the lower alcohols [32]. Although solvatochromic dyes can be used to determine empirical polarity parameters, these parameters are probably not truly independent on the probe molecule used. The difficulty in the case of ILs is to find a suitable soluble probe which measures the polarity parameters as independently as possible from other influences of the solvent [127]. Measurement of keto-enol equilibria is another approach to solvent polarity, which is dependent on the polarity of the medium. Based on this methodology, the polarity of $[BMIm][BF_4]$, $[BMIm][PF_6]$, or $[BMIm][NTf_2]$ was higher than methanol or acetonitrile. Microwave dielectric spectroscopy measurements can also be used for the remaining measurement of dielectric constants of a number of ILs. By this measurement, the polarities of $[BMIm][BF_4]$ and $[BMIm][PF_6]$ are in the range of a medium-chain alcohol, such as 1-hexanol or 1-octanol, with marked contributions from the anion as well the cation [32].

1.5.7 Conductivity and Electrochemical Window

An attractive aspect of ILs is their conductivity by virtue of which they are very useful solvents and electrolytes in electrochemical reactions. Based on the fact that ILs are composed solely of ions, it would be expected that ILs have high conductivities. However, the conductivity of any solution depends not only on the number of charge carriers but also on the viscosity, density, ion size, anionic charge delocalization, aggregations, and ionic mobility. The large size of ions of ILs reduces the ion mobility which, in turn, leads to lower conductivities. Furthermore, ion pair formation and/or ion aggregation leads to reduced conductivity. The conductivity of ILs is inversely linked to their viscosity. Hence, ILs of higher viscosity exhibit lower conductivity [178]. In general, higher conductivities are found for imidazolium-based ILs in comparison with the ammonium-based ILs. Strong ion-pair associations have been invoked in the case of $[Tf_2N]^-$-based ILs, to understand their lower conductivity in comparison with $[BF_4]^-$-based ILs. ILs exhibit broad range of conductivities spanning from 0.1 to 20 mS cm^{-1} [127]. ILs by their electrochemical window play a key role in electrodeposition of metals and semiconductors. By definition, the electrochemical window is the electrochemical potential range over which the electrolyte is neither reduced nor oxidized at an electrode. Because of its low electrochemical window, the electrodeposition of elements and compounds in water is restricted. On the contrary, ILs have significantly larger electrochemical windows, found in the range 4.5–5 V, which is similar to or slightly larger than that found in conventional organic solvents, but larger than that of aqueous electrolytes. In general, the wide electrochemical windows of ILs have opened the door for electrodeposit ion of metals and semiconductors at room temperature which were formerly obtained only from high temperature molten salts. For example, Al, Mg, Si, Ge, and rare earth elements can be obtained from RTILs. The thermal stability of ILs allows to electrodeposit Ta, Nb, V, Se, and presumably many other ones at elevated temperature [19, 178, 180].

1.5.8 Toxicity

The main reason for believing ILs to be nontoxic results from their nonvolatile properties, which makes them potential green substitutes for conventional volatile organic solvents. Unfortunately, this green image is misplaced and has recently aroused the awareness of chemists, especially those working in the area of green chemistry. It is easy to found that some of cations and anions for preparing IL are hazardous, so it is wrong to assume that the risk hazards of these precursors will fade away following their conversion into ILs. On the other hand, incorporating different functional groups makes it complicated to investigate the toxicity of ILs because of the potential virulence of the incorporated functionalities. Though ILs may help in reducing the risk of air pollution, their release to aquatic environments could cause severe water contamination because of their potential toxicity and inaccessible biodegradability. Because of the relative stability features of ILs, their accumulation in the environment becomes feasible, if they are applied in operational use. Thus, the fundamentals of IL biodegradability turn out to be an important issue for the reduction of ignition and landfill-waste risks. Therefore, various efforts to produce biodegradable and biorenewable ILs that can be obtained through modification of natural sources have been undertaken [67, 127].

1.5.9 Air and Moisture Stability

Many of ILs are both air and moisture stable. Conversely, most imidazolium and ammonium salts are hydrophilic, and if they are used in open vessels, hydration will certainly take place. The hydrophobicity of an IL increases with increasing length of the alkyl chain. Despite their widespread usage, ILs containing PF_6^- and BF_4^- have been reported to decompose in the presence of water, giving off HF. Wasserscheid et al. [181] pointed out that ILs containing halogen anions generally show poor stability in water and also produce toxic and corrosive species such as HF or HCl. Therefore, they suggest the use of halogen-free and relatively hydrolysis-stable anions such as octylsulfate compounds. The interaction between water and ILs and their degree of hydroscopic character are strongly dependent on anions. The amount of absorbed water is highest in the BF_4^- and lowest in PF_6^- [182]. However, $[Tf_2N]^-$ is much more stable in the presence of water as well as having the advantage of an increased hydrophobic character. ILs immiscible with water tend to absorb water from the atmosphere. The infrared studies demonstrated that the water molecules absorbed from the air are mostly present in the free state and bonded via H-bonding with the PF_6^- and BF_4^- anions. The presence of water may have dramatic effect on the reactivity of ILs. Since water is present in all ILs, they are usually utilized after a moderate drying process. The newly synthesized ILs are more stable than the old halogenoaluminate systems. Certain ILs incorporating 1-3-dialkylimidazolium cations are generally more resistant than traditional solvents under harsh process conditions, such as those occurring in oxidation, photolysis, and radiation processes [167].

1.5.10 Cost and Biodegradability

Cost and biodegradability have also been major concerns, and new families of ILs derived from renewable feedstock or from “low-cost” starting materials have been described. These “Bio-ILs” are entirely composed of biomaterials [183]. An example to be cited is the development of the “deep eutectic mixtures” liquid systems based on choline chloride [184] for which the qualification of “ILs” is still the subject of controversies. Choline can be used as alternative cation in combination with suitable anion to generate ILs. The biodegradable properties of these ILs have been reported [185].

Very recently, it was shown that the introduction of an ester group into long alkyl chains leads to reduce toxicity and improve ecotoxicity of ILs. Further, incorporation of ether groups into the side chain improves the biodegradability of imidazolium-based ILs, while the introduction of the biodegradable octylsulfate anion has a further beneficial effect. Recent work on pyridinium-based ILs demonstrated how the heteroaromatic cationic core can be modified to produce biodegradable ILs. As with the imidazolium examples, the inclusion of an ester group in the cation side chain led to improved biodegradability. High levels of biodegradability have also been reported in cases where environmentally benign anions such as saccharinate and acesulfamate are included. Several ammonium ILs based on choline have been introduced which are biodegradable and can be readily prepared [124].

1.6 Solvent Properties and Solvent Effects

Solvents are commonly characterized by macroscopic physical constants such as vapor pressure, surface tension, boiling point, density, relative permittivity ε_r (dielectric constants), cohesive pressure, and refractive index. Many chemical reactions are carried out in homogenous media using conventional solvents. However, it is difficult to find solvents in which covalent organic compounds and ionic inorganic reagents as well as catalysts are adequately soluble to achieve a homogeneous reaction mixture. Furthermore, upon the completion of reaction, chemical products have to be removed from the solvent. There are some methods to recover a product from a solvent. For example, water-soluble compounds may be extracted in water and the distillation may be used for chemicals with high vapor pressures [67]. Alternatively, for chemicals with low vapor pressures, distillation must be performed at low pressures. In addition to this, there are some chemicals that can decompose as a result of heating, such as pharmaceutical compounds. Additionally, isolation of the product(s) requires a fairly lengthy work-up procedure. ILs seem to be potentially good solvents for many chemical reactions in cases where distillation is not practical, or water insoluble or thermally sensitive products are the components of a chemical reaction. They are immiscible with most of the organic solvents, thus they provide a nonaqueous, polar alternative for two-phase systems [67]. Moreover, ILs which are not miscible with water can be used as immiscible polar phases with water. Although all other conventional solvents evaporate to the atmosphere, ILs do not evaporate and their nonvolatility gives an opportunity to utilize them in high vacuum systems. The negligible volatility is the basic property which characterizes them as green solvents. Considering as potential solvents, ILs can easily replace other conventional organic solvents which are used in large quantities in chemical processing industries to eliminate major environmental problems. Many studies have been directed to the characterization of ILs and their "bulk" physicochemical properties [56].

The dielectric constant is an important parameter of solvent that reflects its molecular symmetry. It is worth to emphasize that the favorable methods for determining dielectric constants fail in case of ILs because of their high electrical conductivities. However, it could be measured for a series of imidazolium-based ILs using microwave dielectric spectroscopy. ILs can be classified as moderately polar solvents. Dielectric constant (ε) values are found in the range of 8.8–15.2, decreasing with increasing the length of the alkyl chain on the imidazolium cation. However, the variation is small compared to the wide range variation in (ε) values of molecular solvents (2–180) [85, 186]. The dielectric constants were found to depend mainly on the nature of the ILs anions. However, the abundant different interactions acting together in ILs make them very complex so that it is not surprising that a single physical parameter such as the dielectric constant is incapable of adequately modeling the solvent–solute interactions. This parameter has often failed in correlating solvent effects qualitatively and quantitatively. An example is given by the solvent effect study on nucleophilic reactions in ILs compared to molecular solvents where Hugues–Ingold viewpoint using dielectric constant as a measure of solvent polarity proved to be insufficient to explain the IL system [187]. For a rational design and a better choice of ILs, better understanding of their properties is required.

1.6.1 Solute–Ionic Liquids (ILs) Interactions

The solvent properties of ILs are mainly determined by the ability of the salt to act as a hydrogen bond donor and/or acceptor and the degree of localization of the charges on the anions [28]. Charge distribution on the anions, H-bonding ability, polarity, and dispersive interactions are the main factors that influence the physical properties of ILs. For example, imidazolium-based ILs are highly ordered hydrogen-bonded solvents and they have strong effects on chemical reactions and processes [67].

Many studies have focused on the cation–anion interactions (solvent–solvent interactions) rather than ions–solute interactions (solvent–solute interactions or solvent solvation). In conventional medium, solvent–solute interactions are generally predominant, while in ILs, interactions inside the solvent are more important. The Diels–Alder reaction is an interesting example because it is a key step in many syntheses. In the case of the reaction of cyclopentadiene and methyl acrylate, the ability of the IL to act as H-bond donor (cation effect) appeared to be a key criterion to explain the enhancement of reaction rate and endoselectivity [188]. This effect has to be moderated by the H-bond acceptor ability of the IL (anion effect). ILs with strong H-bond interaction between the cation and the anion (contact pair ions) are poor solvents for Diels–Alder due to competition between the anion and the H-bond acceptor dienophile for H-bonding with the cation. It is not surprising that low yields have been reported for dialkylimidazolium bromide and trifluoroacetate ILs. This H-bonding with the substrate can be influenced by p-stacking of the imidazolium cations and H-bonding interactions between the cation and the anion of the IL [127].

Another good example of model reaction to examine the IL effect is the nucleophilic substitution reactions [127]. In molecular solvents, the Hughes–Ingold qualitative model describes the solvent effect considering the pure electrostatic interactions between ions or dipolar molecules in initial and transition states (solvent polarity). This model does not take into account the H-bond interactions and proved to be limited to describe ILs effect. Kamlet–Taft linear solvation energy relationship has also been utilized to describe ILs effect on nucleophilic reactions. The characteristic values of α, β, and π^* have been collected for ILs [189]. The solvent's hydrogen donor ability (α value) appears as the dominant effect in reducing the nucleophilicity of the nucleophile and slowing the reaction rate [190]. Hard and soft natures of the nucleophile also proved to be important, the [BMIm] cation of the ILs acting as a hard "solvent" in interacting more strongly with hard anions (e.g., $[Cl]^-$) than soft ones (e.g., $[CN]^-$). Compared to molecular solvents, the nucleophilicity of halide anions (e.g., $[Br]^-$) in the S_N2 reactions of methyl-*p*-nitrobenzenesulfonate was reduced in ILs (the reaction is 15 times slower in *N*-butyl-3-methylpyridinium ([BMP])[Tf_2N] than in dichloromethane, and it is roughly two times slower in [BMIm][Tf_2N] than in [BMP][Tf_2N]). This can be ascribed to the existence of strong H-bond between the nucleophile (the anion, particularly the chloride) and the [BMIm] cation. This difference arises largely from the α value [127].

Another systematic study on nucleophilicity of a series of anions on the substitution reaction of methanesulfonic group was conducted in different ILs and compared with that obtained in organic solvents (PhCl, DMSO, and MeOH). The results emphasize the predominant role of water for hydrophilic anions ($[Cl]^-$ and $[PhCO_2]^-$). In this case, the interaction of the anion with the imidazolium has a lower effect. These results confirm that water molecules create H-bond with the imidazolium cation replacing the cation–anion interactions present in the ILs [191]. Higher reactivity is also observed in C(2)-protected imidazolium-based ILs. The case of charged electrophiles within the framework of S_N2 reactions is also of fundamental interest since many catalytic centers carry positive charges. The reaction of chloride ion with an ionic electrophile (sulfonium associated with $[Tf_2N]^-$ or $[TfO]^-$) was studied in several molecular solvents and ILs. The nucleophilic substitution reaction does not take place in either strong dissociating molecular water solvents or in methanol. In nondissociating solvent, the reaction is supposed to occur via a solvated ion pairs. The behavior of this reaction in ILs is different from that in molecular solvents; the kinetic experiments in ILs are in favor of reaction via dissociated ions. The results show that ILs can be considered as superdissociating solvents, this effect arising from the fact that ILs are at the same time liquid and ionic. The reaction mechanism would proceed through a true S_N2 reaction of free solvated ions rather than with α ion-pair mechanism seen in molecular solvents [192]. Based on these model reactions, we can assume that the interactions between ILs and different species are of diverse nature and complex which significantly modify their reactivity. The interactions of ILs with selected solutes will be discussed below.

1.6.1.1 Interaction of Ionic Liquids (ILs) with Water

The hydrophilic/hydrophobic behavior is significant for the solvation properties of ILs as it is essential to dissolve reactants, but it is also relevant for the recovery of products by solvent extraction. In addition, the water content of ILs can affect the rates and selectivity of reactions. One potential problem with ILs is the possible pathway into the environment through wastewater. The effect of water in modifying IL properties has been a central focus of recent interest [127]. This factor has been illustrated by the examination of water solvation at low and high concentrations. IR [176] and dielectric constant [193] studies have revealed that water is molecularly dispersed in 1-alkyl-3-methyl imidazolium-based ILs ($[H_2O < 2\ M]$) at low concentrations. When the water concentration is increased, water molecules aggregate and form a well-defined water hydrogen-bonds network [193]. It is found that the local organization between ions precludes any specific interactions between water and the proton of the imidazolium cation. Water would be doubly hydrogen-bonded with two anions, in symmetric 2:1 [Anion–H–O–H–Anion] structures. PCl_3 and $POCl_3$ show unexpectedly high hydrolytic stability in wet ILs. For example, in the $[Tf_2N]^-$-based ILs, PCl_3 was soluble at concentrations up to 0.20 M, and in $[BMP][Tf_2N]$, it was found to be hydrolytically stable for weeks, even when stirred in air. The ability of even wet ILs to stabilize hydrolytically unstable solutes may be understood by considering the interaction of water with IL. The nucleophilicity of water and therefore its hydrolysis tendency can be reduced due to its interaction with IL anions. In hydrophilic ILs, the higher water content results in higher rate of hydrolysis [194]. Interestingly, ILs have been used to improve the solubility of hydrophobic compounds in water. For example, the solubility of acetophenone in aqueous solution can be increased by a factor of 10 by addition of $[BMIm][BF_4]$, which can be important for application in biocatalysis. This phenomenon can be explained by the ability of ILs to form small aggregates which are solvent dependent [195].

1.6.1.2 Interaction of Ionic Liquids (ILs) with Acid and Base

The importance of ILs as solvents to perform acid–base reactions has been recently realized. A straightforward way to create and modulate the acidity is to add a Brønsted acid into the IL. Therefore a new level of acidity can be found either by varying the acid concentration in the IL or by changing the nature of the IL [161]. A lot of acid-catalyzed reactions have been reported in ILs, but only few studies have been devoted to the quantification of the acidity level of the proton in these media. However, as the acidity of protons is mainly determined by their solvation state, the properties of protons will depend strongly on the nature of the IL and the nature and concentration of the acid. Relative estimation of the proton acidity level has been reported using the determination of the Hammett acidity functions, by UV–vis spectroscopy [160]. For the same content of added strong acid, the anion of ILs plays a fundamental role; the acidity levels are in the order: $[PF_6]^- > [BF_4]^- > [Tf_2N]^- > [TfO]^-$, thus implying that the solvating power (or basicity) of the anions follows the reverse order. The presence of basic impurities in the ILs can also have a dramatic effect. Even if absolute acidities cannot be determined with this method, global acidity must be higher than that observed in water [161].

1.6.1.3 Interaction of Ionic Liquids (ILs) with Aromatic Hydrocarbon

Aromatic hydrocarbons show unusual high solubility in ILs as compared to aliphatic compounds. This extent of solubility decreases with an increase in the molecular weight of the hydrocarbon, but the differences of solubilities of *o*-, *m*-, and *p*-xylenes are not significant [161]. Previous studies show that imidazolium-based ILs can form liquid clathrates in the presence of aromatic hydrocarbons [160]. Dialkylimidazolium cations are able to form specific and oriented interactions with arenes. For instance, in the salt crystal $[BMIm][PF_6]$, 0.5 benzene, a three-dimensional network has been observed with H-bonds between anion and cation. This results in the formation of channels containing the benzene molecules. Short interactions between methyl hydrogen of the cation and aromatic hydrogen are present [196]. Interactions between *p*-aromatic systems and inorganic cations (Li^+, Na^+, K^+, or Ag^+) or organic cations (ammonium) are already well known as the “p-cation interaction,” important in biochemistry, and experimentally evidenced [197]. A detailed study conducted with the aid of NMR and molecular simulation shows difference in interaction of toluene with the ILs due to the substitution of the C(2) of the imidazolium cation. In the case of the [BMIm] cation, toluene is located closer to the methyl group at the end of the butyl chain, whereas in the case of [BMMiI] cation, toluene was closer to C(2)-Me of the imidazolium. The H-bonding association between $[BMI]^+$ and $[Tf_2N]^-$ is too strong to be cleaved by toluene. In the case of C(2)-Me cation, the less strongly bonded IL network renders possible the penetration and interaction of toluene [197].

1.6.1.4 Interaction with Chiral Substrates

Some chiral ILs have been designed and synthesized. They have already been applied in different fields such as asymmetric synthesis, stereoselective polymerization, chiral chromatography, liquid crystals, chiral resolution, and NMR shift reagents [20, 106, 107]. Chiral solvents have been reported in asymmetric syntheses. In the Baylis–Hillman reaction of benzaldehyde and methyl acrylate in the presence of bases, chiral ILs demonstrate their ability in the transfer of chirality, even if the enantiomeric excesses (ee) are still moderate. The presence of an alcoholic functional group on the *N*-alkyl-*N* methylephedrinium is primordial and acts as a fixing point of the chiral IL on the reactants. It is assumed that the OH is connected with a carbonyl group of the substrate (from either benzaldehyde or methyl acrylate) via H-bonding [127, 198]. However, with *N*-methylephedrine, very low ee are obtained which also indicate that the ammonium group plays a crucial role in the chirality induction. Even if not directly demonstrated, it seems that the key of effective asymmetric induction is the existence of both strong intermolecular interactions, like electrostatic attraction and hydrogen bonding, between ionic solvents and intermediates or transition states of the diastereoselective reaction step. The need of H-bonding in the transfer of chirality has also been confirmed in the case of borate-based chiral IL bearing maleic acid functions. In this latter case, by incorporating the acidic center into the chiral anion of the solvent, the IL offers the possibility of establishing a bifunctional interaction, which allows monofunctional achiral nucleophiles to be used as catalysts [199–201].

1.7 Conclusions

VOCs are often difficult to separate from the desired reaction products, problematic to recycle, and challenging to dispose of without encountering extra costs and/or adversely affecting the environment. Therefore, the interest of ILs as "green" solvents resides in their extremely low vapor pressure and high thermal stability, which offer advantages such as ease of containment, product recovery, and recycling ability. Due to their attractive properties, ILs are being used for a wide variety of applications. Current research indicates that replacing an organic solvent with an IL can bring about remarkable improvements in well-known chemical processes. ILs are being used extensively as solvent systems for chemical and polymerization reactions in addition to their use as biocatalysis. ILs have also been increasingly used in separation science, gas chromatography, liquid chromatography, and capillary electrophoresis. ILs have also found uses in liquid–liquid extraction, immunoassays, lubricants, and embalming/tissue preservation. Additionally, the change of the cation and/or anion component of the IL provides a way to adjust all properties, allowing the potential to fine-tune an IL for specific tasks. These features allow ILs to be used as potential alternative solvents to VOCs in a wide variety of industrial chemical applications.

It is hoped that successful commercialization of technologies utilizing these neoteric solvents will be a key driver for their continued development and integration into the chemical industry. Large-scale industrial manufacture of the ILs themselves is clearly a necessary precursor for this process. We also believe that due to the extensive variety in ILs formation and applications, they will play an important role in future environmentally friendly science and technology.

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Chapter 2
Ionic Liquids as Green Solvents for Alkylation and Acylation

Zhongkui Zhao and Yitao Dai

Abstract Many clean solvents like water, ionic liquids, supercritical fluid, polyglycol, fluorine-containing solvents, and so on are employed to replace the conventional organic solvents. Among these, ionic liquids have attracted considerable attention as the clean designable solvents. Ionic liquids received global attention not only in the academic fields but also in the industrial circles. So far, the normal ionic liquids as the clean solvents, and the functional ionic liquids as the special clean solvents (e.g., chiral solvents), the catalysts, and the supports for reagents as well, have been applied extensively in many organic reactions, such as the alkylation, acylation, esterification, rearrangement, hydroformylation, coupling reactions, Diels–Alder reactions, asymmetric synthesis, and so on. This chapter mainly reviews the progress in the applications of the ionic liquids as the green solvent, dual green solvent, and catalyst for the alkylation and acylation; it is our expectation that this review would provide useful guidance for the related researchers.

2.1 Introduction

There is a need for a large amount of the solvent for the chemical reactions, in which the solvents are not only used to disperse the reactants but also to intensify the heat transfer, in order to prevent the side reactions resulted from the overheating in the hot spot. Moreover, the presence of the solvents has a potential for changing the reaction routes, promoting the reactions, and reducing the side reactions,

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which enable the feasibility of carrying out reactions under the mild reaction conditions with high conversion, selectivity, and yield. On the other hand, the solvents play a significant role on the product isolation for the synthesis of organic compounds, especially the solid fine chemicals. The popularly used solvents include petroleum ether, alcohols, ketones, esters, alkyl halides, and alkylated aromatic compounds, which basically meet the needs of several kinds of chemical industrial production processes according to the varieties and large quantities. The excess utilizations of volatile organic solvents have already brought great harm to the environment and human being. Therefore, the emphasis is on the environment protection by reducing the use of traditional organic solvents or developing alternative methods. Thus, the research and exploration of the clean solvents as the alternative to the traditional organic solvents is of great importance considering either the environmental protection or the demand of the development of chemistry. At present, some of the clean solvents are under investigations, such as water, ionic liquids, supercritical fluid, polyglycol, the fluorine-containing solvents, and so on. Among these, the ionic liquids received considerable attention as the clean designable solvents. The variety of the cations and anions constituting the ionic liquids demonstrates the extensive research space. In comparison to the conventional organic molecular solvents, the ionic liquids have exhibited certain advantages: (1) hardly detectable vapor pressure (insignificant volatility of ionic liquid would not pollute the air, and the products can be isolated by simple distillation from reaction media); (2) excellent solubility (the ionic liquids can dissolve a variety of substrates, and for the gas reagents, the ionic liquids show better solubility than the traditional organic solvents); (3) facile tunability (i.e., adjusting the cations and anions making up the ionic liquids with varying the polarity, hydrophility, density, solubility, and viscosity, and as well as functionalizing the ionic liquids to make them equipped with the special properties such as acidity, basicity, and chirality); (4) indissolubility toward large numbers of organic solvents, for which the ionic liquids can be utilized for the biphasic reactions; and (5) inherent property as the ionic solvents with which the ionic liquids are expected to present strong solvent effect in the reactions.

Then what are the ionic liquids? In people's usual opinions, the salts that consist of organic cations and inorganic or organic anions, in the form of liquid at or around the ambient temperature, are called usually the room-temperature ionic liquid (RTIL), the ambient-temperature ionic liquid (ATIL), or the room-temperature molten salts (RTMS), the room-temperature fused salts (RTFS), and can be called the ionic liquid (IL) for abbreviation. The feature of ionic liquids being liquid at the room temperature is attributed to the asymmetric structures of the ionic liquids with big difference in volume of anions and cations leading to little electrostatic attraction.

The earliest appearing ionic liquid is $[EtNH_3][NO_3]$ (*m.p.* 12°C), which was reported by Walden [1] in 1914, but because of its unstability in the air, its appearance did not attract much attention. However, in the 1960s, the Academy of American Air Force had done the systematic research on the ionic liquids based on alkyl-substituted pyridinium cations, with halides or trihalogenoaluminates anions. With the efforts of Chum [2] in 1975, the chloroaluminate ionic liquid of *N*-alkyl-pyridinium cation was synthesized. Later on, Wilkes et al. [3] prepared the stable dialkylimidazolium chloroaluminate melts, which was then applied extensively in the electrochemistry as the reaction medium or catalyst, and at that time, the ionic liquids could be gradually well known throughout the world. The chloroaluminate ionic liquids are regarded as the first generation of ionic liquids. In 1992, Wilkes's group [4] obtained the air- and moisture-stable dialkylimidazolium ionic liquids with "neutral" weekly coordinating anions such as $[BF_4]^-$ and $[PF_6]^-$, which was symbolized as the second-generation ionic liquids. The water-tolerant merit of these ionic liquids favors their suitability as the reaction medium for the homogeneous transition metal catalytic reactions. With the deep research in ionic liquids, toward the specific task, the functionalized ionic liquids were constructed. These kinds of ionic liquids were called as task-specific ionic liquids or functionalized ionic liquids, which are considered as the third-generation ionic liquids. In 2002, Wasserscheid et al. [5] had synthesized three types of chiral cations to build the ionic liquids by use of the common chiral materials. Bao et al. [6] reported the novel method for preparation of the stable chiral imidazole cation from natural amino acid in 2003. It is obvious that the introduction of chirality has brought significant new energy to the ionic liquids, and therefore, the research of this kind of ionic liquids attracted great attention. The chiral ionic liquids belong to one kind of the functionalized ionic liquids. The third-generation ionic liquids are famous for the title *Design Solvent* referred to the functionalized ionic liquids which could be designed to meet the special demand; thus, more and more attention is attached on the functionalization of the ionic liquids. The functionalized ionic liquid as one of the most promising ionic liquids can be employed as the reaction medium (generally providing chiral environment, increasing dissolubility, etc.) or the catalyst (or ligand for catalyst) as well as special media for changing the reaction mechanism and increase the conversion or selectivity.

The ionic liquids have already exhibited their significant role in various fields such as the organic synthesis, separation, analysis, electrochemistry, and materials, especially for the green chemical synthesis as the clean and efficient reaction medium. It is feasible to obtain the catalysts or solvents with good properties via the molecular design.

Especially, the eco-friendly ionic liquids have obtained extensive attention in organic synthesis with the merits provided as above. The ionic liquids as the unusual green solvents are applied extensively in various organic synthesis reactions, such as Friedel-Crafts reactions, oxidation reactions, reduction reactions, addition reactions, C–C formation reactions, nucleophilic substitution reactions, esterifications, rearrangements, hydroformylations, and nitration reactions [7–14]. Besides, the ionic liquids also have applications in the extraction separation, the electrochemistry, and preparation of nanostructured materials, the production of clean fuel, environmental science, and biocatalysis. This chapter would present in detail the application of the ionic liquids as the unusual green solvents (also as dual green solvent and catalyst) for the alkylation and acylation.

2.2 Alkylation

In organic chemistry, the reactions involved with the introduction of the alkyl groups are called as "alkylation," among which Friedel-Crafts alkylation reactions usually refer to the electrophilic substitution reactions that happen at the carbon atoms on the aromatic rings, and this type of reaction has played an important role on the applications for industrial production of medicine products and fine chemicals. The alkyl halides, alkenes, alcohols, and ethers are commonly employed as the alkylating agents for the alkylation in which the traditional solvents like benzene, chlorobenzene, petroleum ether, etc., are used as reaction media. The catalysts extensively used in this industrial process are $AlCl_3$, HF, and sulfuric acid. However, the utilizations of the above solvents and catalysts not only do the erosive attacks to the equipments but also have hazardous effects on the environment, and as well as after the reaction, it is difficult to recycle catalyst which is usually hydrolyzed or diluted. Therefore, the eco-friendly ionic liquids with acid sites as dual green solvent and catalyst for Friedel-Crafts alkylation exhibit great advantages in contrast to the traditional acid catalysts, such as mild reaction conditions, high conversions and selectivities of the products, the simplification of the product isolation, the facile operation for experiments, and potential for the easy recovery and reuse of the catalytic systems. Besides, the ionic liquids have showed great potentials for the alkylation of nonaromatic compounds, for example, the *C*-alkylation mainly related to the alkylation of C_4-isoparaffins with C_4-olefins, the *N*-alkylation, the *O*-alkylation, and *S*-alkylation. On the other hand, there still exist some problems to be resolved in the application of ionic liquids for alkylation, such as the high cost, large quantity for use, difficulties in the purification of ionic liquids, the lack of data concerning the effects on the environment, and the toxicity of ionic liquids. These problems often appear in the utilizations of ionic liquids for other types of reactions, and, hence, further studies are required to overcome the above problems. Nowadays, significant progress in the applications of ionic liquids as unconventional green medium or as dual green and catalyst for the various alkylation reactions has been made.

2.2.1 Ionic Liquids as Green Solvents

Recently, much attention has been focused on the utilization of ionic liquids as reaction media for a wide variety of organic reactions, for example, Friedel-Crafts alkylation, Diels–Alder reaction [15], esterification [16], Trost-Tsuji coupling [17–20], and others [21–23]. Because of their favorable properties [24], such as negligible vapor pressure, incombustibility, high ionic conductivity, and moreover, they are noncoordinating but strong solvating nature. Ionic liquids have generated a lot of interest in their use. They have a significant effect on the activity and selectivity of the reactions in which they substitute the molecular solvents, and for most of the reactions, they can simplify the product isolation and help the catalyst-solvent system to be recycled and reused for several times without any significantly decreasing activity of the catalysts. In recent years, there are many reports with regard to the ionic liquids as green solvents, especially for the alkylation reactions.

The Friedel-Crafts alkylation of aromatic compounds is of great importance in laboratory synthesis and industrial production. For example, the industrial processes for ethylbenzene, cumene and linear alkylbenzenes, etc., are on the base of this kind of reaction. It is well known that the drawbacks of the traditional acid catalysts such as $AlCl_3$, H_2SO_4, and HF do great harm to the equipment and the environment, and these catalysts cannot be reused after the usual aqueous work-up; besides, most of the reactions are carried out in the harmful and volatile organic solvents which can cause the environmental pollution; all of these problems need the replacement of the solvents or the acid catalysts. In this context, room-temperature ionic liquids have been increasingly employed as green solvents.

Song's group [25] has developed a novel and recyclable catalytic system for Friedel-Crafts alkylation of aromatic compounds with alkenes. The $Sc(OTf)_3$ was immobilized in the ionic liquids, to obtain quantitatively the desired alkylated products in the reaction of the alkylation of benzene with hex-1-ene, in which the ionic liquids containing 20 mol% $Sc(OTf)_3$ such as [EMIM][SbF_6] ([EMIM] is denoted as 1-ethyl-3-methylimidazolium cation), [BMIM][PF_6] ([BMIM] is denoted as 1-butyl-3-methylimidazoluim cation), [BMIM][SbF_6] were used. Besides, they also examined Friedel-Crafts alkylation with other substrates with the use of [BMIM][SbF_6]. The results showed that the conversions based on the alkene were all more than 99% with the yields ranging from 84% to 93%, and for the reuse of the catalytic system, there is a simple decantation of the organic layer after the reaction. They demonstrated a quantitative yield of cyclohexylbenzene in the second and third reactions of benzene with cyclohexene with the use of the recovered ionic liquid containing $Sc(OTf)_3$. The novel reusable catalytic system $Sc(OTf)_3$-ionic liquid provides a simple, benign, waste-free process for the alkylation of the aromatic compounds with alkenes.

Besides, Shen et al. [26] have performed comparative studies on alkylation of phenol with *tert*-butyl alcohol (TBA) with liquid acids such as H_3PO_4 or solid acids, for example, HZSM-5, H-β, dodecatungstophosphoric acid (HPW), and HPW/MCM-41, in the ionic liquids [BMIM]PF_6, [OMIM]BF_4 ([OMIM] = *1*-octyl-*3*-methylimidazolium cation), and [HMIM]BF_4 ([HMIM] = *1*-hexyl-*3*-methylimidazolium cation). The results suggested that ionic liquids improve the catalytic activity of H_3PO_4, with the conversion of phenol increasing from 44.5% to the maximum value of 77.3% in the alkylation of phenol with TBA by H_3PO_4 in different ionic liquids. This improvement effect in conversion may be attributed to the higher solubility of *2,4*-DTBP (*2,4*-di-tert-butylphenol) in ionic liquids. Moreover, the selectivity to *2,4*-DTBP was increased from 29.7% to 64.9%. For the HPW/MCM-41-catalyzed alkylation reactions, the improvement in effects of ionic liquids was also observed.

In the Xiao's laboratory [27], the pyridinium-based ionic liquids as the suitable media were used for the Friedel-Crafts alkylation of benzene, which was carried out at a better rate but at relatively lower temperature with high product conversion. They found that the [EtPy][CF_3COO] (*1*-ethyl-pyridinium trifluoroacetate)-$FeCl_3$ was an environmental friendly, recyclable, and reusable solvent-catalyst system to replace the traditional aluminum catalysis system. During the process, the alkylation

Table 2.1 The ionic liquids [EtPy][CF_3COO]–$FeCl_3$/$AlCl_3$ as catalytic system for the Friedel-Crafts alkylation

		$FeCl_3$–[EtPy][CF_3COO]		$AlCl_3$–[EtPy][CF_3COO]	
Entry	Substrates	Con.[a] (%)	Sel.[b] (%)	Con.[a] (%)	Sel. (%)
1	Benzene + *1*-bromopropane	71 (90)	77 (89)	72 (91)	78 (93)
2	Benzene + *1*-chlorobutane	77 (94)	83 (94)	77 (96)	81 (93)
3	Benzene + benzyl chloride	33 (56)	–	35 (59)	–

[a] Reactions were performed at 50°C, Con. stands for as conversion

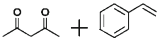
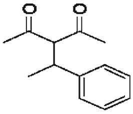
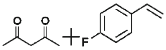
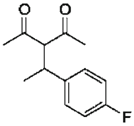
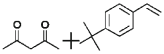
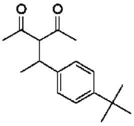
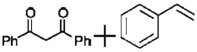
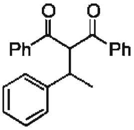
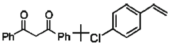
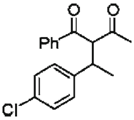
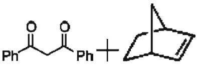
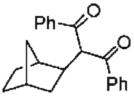
[b] Sel. is denoted as selectivity

of benzene with *1*-bromopropane accurately occurred in the ionic liquids in the absence of a catalyst, which could make the system truly green, but the low conversions showed the need for a catalyst. Some results are presented in Table 2.1; it is from where it is clear that the $FeCl_3$-IL system demonstrated the same catalytic activity as the $AlCl_3$-IL system, which indicated that $FeCl_3$-IL system can substitute the $AlCl_3$-IL system because of the latter environmentally hazardous property.

It is well known that the ring-close cyclization by *C*-alkylation of phenyl ethers or *O*-alkylation of alkyl phenols is the typical synthetic processes for the preparation of chromanes. Due to the more difficulty in preparation of the alkyl phenol substrates, much interest has been generated in the C–C bond formation process, in which the general method is via Friedel-Crafts approach, usually with a strong Lewis acid as the catalyst. However, Dong's group [28] has developed a novel synthetic method using ionic liquids as the reaction media in the absence of any catalysts for the ring-closure cyclization by nucleophilic *C*-alkylation in high yields. Results showed that the ionic liquids exhibited a significant improvement effect on the reactions. The cyclization of the compound *2*-(*3*-methanesulfonyloxypropoxy)naphthalene in the presence of [BMIM][PF_6] accelerated the reaction significantly. The reaction can be completed at 150°C within 24 h obtaining cyclic product *2,3*-dihydro-*1H*-naphthol*[2,1-b]*pyran in 85% yield, while in organic solvents such as DMF, at 150°C, the reaction hardly occurred even after 48 h. Besides, when cyclization of various substrates in [BMIM][PF_6] was tested, the results showed that nucleophilic cyclization of indo- and bromo-substrates proceeded selectively to afford cyclic product in 79% and 75% yield, respectively, and at the same time, chloro- and fluoro-substrates were hardly converted to the cyclic product even after 48 h.

Although Friedel-Crafts alkylation plays an important role in the industrial processes, the significance of *C*-alkylation (not F-C reaction) cannot be neglected. Kryshtal's group [29] has used the ionic liquid [BMIM][PF_6] as the recyclable reaction medium in the base-promoted alkylation of malonic and acetoacetic esters with alkyl, benzyl, and prenyl halides, which solved the problems encountered in the traditional alkylation procedures due to the use of flammable organic solvents and phase-transfer catalysts where the difficulties in their regeneration as well as the isolation of reaction products raised. The results showed that 53–80% yield was obtained in the K_2CO_3-promoted alkylation of diethylmalonate with alkyl, benzyl, and prenyl halides (the ratio $\leq$ 1.5) in [BMIM][PF_6] at 85–130°C for 5–20 h. Further,

Table 2.2 Hydroalkylation of β-dicarbonyl compounds with alkenes

Substrates	Catalysts	Ionic liquids	Products	Yields (%)
	Amberlyst-15	[BMIM][PF_6]		79 [32]
	Amberlyst-15	[BMIM][PF_6]		81 [32]
	Amberlyst-15	[BMIM][PF_6]		87 [32]
	$SnBr_4$	[BMIM]OTf		60 [33]
	$SnBr_4$	[BMIM]OTf		61 [33]
	$SnBr_4$	[BMIM]OTf		31 [33]

the results indicated that the yields of the alkylation of malonic and acetoacetic esters in the ionic liquid as well as in the commonly used catalytic conditions were similar. However, the ionic liquid systems have the advantages of the simplification in the product isolation and solvents reuse over the latter. Moreover, Su et al. [30] have used ionic liquid [BuPy]BF_4, *N*-butylpyridinium tetrafluoroborate, for the alkylation of isopropylidene malonate (*2,2*-dimethyl-*4,6*-dioxo-*1,3*-dioxane, Meldrum's acid), which itself has high acidity and rigid cyclic structure. The yields (based on isopropylidene malonate) of the dialkylation of isopropylidene malonate with various alkyl halides using triethylamine as a base ranged from 75% to 90%. In addition, Chan's research group [31] found the ionic liquid [BuPy]BF_4 to be the excellent solvent for the alkylation of aldehydes with diethylzinc. In the presence of ionic liquid, the reaction proceeded smoothly, and the 90% of yield for the alkylation reaction of *2,6*-$Cl_2C_6H_5CHO$ with diethylzinc was obtained at room temperature for 2 h.

To the best of our knowledge, there are few reports focused on the hydroalkylation of β-dicarbonyl compounds in the ionic liquids [32, 33]; some of the obtained results are tabulated in Table 2.2. It is obvious that the use of the ionic liquids [BMIM][PF_6] and [BMIM]OTf as the green solvents promotes the hydroalkylation to proceed smoothly in excellent yields. In addition, it is worthy to be mentioned that under the neat conditions with no solvents, a high yield (88%) was obtained in the $Cu(OTf)_2$-catalyzed alkylation of dibenzoylmethane with styrene, which is another promising green alternative to the hazardous solvents.

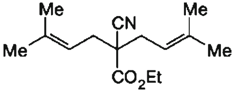
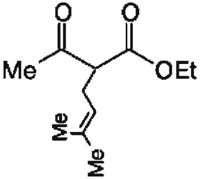
Zlotin's group [34] has developed a method for the synthesis of carboxylic acid derivatives which is based on the alkylation of *di*-alkyl malonates, cyanoacetates, and acetoacetates with acyclic prenyl halides in ionic liquids [BMIM][PF_6] and [BMIM][BF_4] in the presence of K_2CO_3 or $LiOH{\cdot}H_2O$ as the base for deprotonation. The good results are shown in Table 2.3. According to Table 2.3, it is clear that the reaction involving $LiOH{\cdot}H_2O$ could proceed under milder conditions than that using K_2CO_3, and besides the higher product yields in comparison with that obtained in molecular organic solvents, the easy of the product isolation and the potential for recovery of the ionic solvents constitute the advantages of the reactions conducted in ionic liquids.

Another interesting *C*-alkylation is about the palladium-catalyzed Tsuji-Trost coupling reaction. Concerning this C–C bond forming reaction, Xiao's group [20] has studied the ligand effects on palladium-catalyzed allylic alkylation in the ionic liquid [BMIM][BF_4]. They discovered that in the molecular solvent THF, the reaction is sluggish and the effects of the ligand get weakened with the presumable reasons that there are two different forms of the allylpalladium intermediate in the above two kinds of solvents. However, using ionic liquids [BMIM][BF_4] as solvent, the ligand effect was intensified and the satisfactory results were obtained. Moreover, this research group [19] further studied the effect of hydrogen bond for the allylic alkylation in the [BMIM][BF_4] ionic liquid. They found that the hydrogen bonding between the H proton of [BMIM][BF_4] and OAc^- or $MeOCO_2^-$ ions which made the anions not to act as the effective bases to remove the proton of the nucleophile leads to the sluggish neutral allylic alkylation reactions in dialkylimidazolium ionic liquids. However, this problem could be easily solved just by using a relatively strong base generated in situ or added externally. It is interesting that they found that the hydrogen bonding in the imidazolium ionic liquids could be advantageous to suppress the unwanted isomerization of allylic acetates. Leclercq et al. [18] have prepared a series of halide-free highly-pure imidazolium triflate ionic liquids, which were applied to the palladium-catalyzed allylic alkylation of *(rac)-(E)-1,3*-diphenyl-*3*-acetoxyprop-*1*-ene with dimethylmalonate. The good results were obtained, and the conversions reached to the extent of 75%. This convenient method developed a new and effective strategy to avoid a metathesis process, as well as the contamination by halides.

In *C*-alkylation of other compounds containing nitrogen atoms, Chi's group [35] has done a lot of work. They have described a novel approach for pyrrole *C*-alkylation in which [BMIM][SbF_6] and CH_3CN as a mixture was employed for the synthesis of 2-(3-phenylpropyl)pyrrole from pyrrole and *1*-bromo-*3*-phenylpropane with the results that 81% yield was achieved at 115°C for 44 h with 5% yield of dialkylated compound. It is obvious that the ionic liquid demonstrated an important driving force in the regioselective alkylation of pyrrole. Moreover, it is worthy to be noted that in this reaction, no Lewis acid/base catalysts were needed.

Not only in Friedel-Crafts alkylation or *C*-alkylation but also in the *N*-alkylation, ionic liquids have obtained much attention for obvious advantages including

Table 2.3 Alkylation of *di*-alkyl malonates, cyanoacetates, and acetoacetates with acyclic prenyl halides in ionic liquids

Substrates	Ionic liquids	Time (h)	Temp.[a] (°C)	Products	Yields (%)
Diethyl malonate + *1*-bromo-*3*-methylbutane	[BMIM][PF_6]	15	110	$(CH_3)_2CHCH_2CH_2CH(CO_2Et)_2$	70
Ethyl cyanoacetate + *1*-bromo-*3*-methylbut-*2*-ene	[BMIM][BF_4]	5	20		80
Ethyl acetoacetate + *1*-chloro-*3*-methylbut-*2*-ene	[BMIM][PF_6]	6	90		66

[a] Reaction temperature

regioselectivity and potential for the green media and recycling. Earle et al. [36] have studied the regioselectivity alkylation at the heteroatom of indole with [BMIM][PF_6] as a green recyclable alternative to dipolar aprotic solvents. The results of the reaction of indole with simple alkyl halides at room temperature in [BMIM][PF_6] with solid KOH as base obviously showed that the reaction proceeded smoothly in more than 90% yield, obtaining almost exclusive *N*-alkylated products in all cases. Moreover, Dae et al. [37] have developed a highly effective method of *N*-alkylation of indole and pyrrole under mild conditions using [BMIM][BF_4] as the sustainable reaction medium with acetonitrile as the cosolvent in the presence of potassium carbonate as a base. The obtained yield of *1*-(*3*-phenylpropyl)-*1H*-indole reached 82% with 3% of carbamate in the K_2CO_3-promoted *N*-alkylation of indole with *1*-bromo-*3*-phenylpropane in [BMIM][BF_4] at 110°C. They further studied the reactivity in a series of reactions of different simple alkyl halides and sulfonates with indole and pyrrole in the ionic liquid [BMIM][BF_4]. The results showed good yields to suggest that the approach using the ionic liquid as alternative to the traditional organic solvents such as dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) is feasible and reasonable, in addition to the avoidance of a strong base.

Chen's group [38] has used [BMIM]BF_4, [BMIM]PF_6, and [BuPy]BF_4 ([BuPy] = butylpyridinium) in the *N*-alkylation of heterocyclic compounds with alkyl halides in the presence of potassium hydroxide as a base. This convenient, efficient, and environmentally benign method affords the *N*-alkylated products exclusively. The results suggested that when the alkylating agents are primary alky iodide or bromide and activated chloride, the alkylation of phthalimide in ionic liquids could be carried out smoothly in high yield, although a lower yield was obtained in the case of a secondary alkyl halide, for example, in *N*-ethylation of phthalimide with ethyl bromide in [BMIM]BF_4, [BMIM]PF_6, and [BuPy]BF_4. In the *N*-alkylation of phthalimide with *i*-PrBr in [BMIM]BF_4, the yield was 78%. Moreover, the ionic liquids can be recycled and reused for at least three times without considerable decrease in yield. These *N*-alkylation reactions demonstrated that the development of a potential, simple, and efficient procedure was developed, in contrast to the traditional method in which more difficult longer operation and a strong base such as potassium *tert*-butoxide required [39, 40].

Furthermore, Chiappe and Pieraccini [41] have proved the feasibility of the direct *mono-N*-alkylation of primary amines with simple alkyl halides or tosylates in ionic liquids such as [BMIM][PF_6], [BMIM][NTf_2], [HexPy][Tf_2N] (hexylpyridinium bis(trifluoromethylsulfonyl)imide), and [BDMIM][PF_6] (*1*-*n*-butyl-*2,3*-dimethylimidazolium hexafluorophosphate) with CsOH as the base [42]. And the results showed that in [BMIM][PF_6], the primary bromide, iodide, and tosylate could easily react with benzylamine or *2*-phenylethylamine to produce expected secondary amine with high selectivity ranging from 82% to 100%, for example, sec-C_8H_{17}OTs reacted with benzylamine to give exclusively the *mono-N*-alkylated product with complete conversion at about 45°C in 24 h in the presence of CsOH using [BMIM][PF_6] as the solvent, while the primary alkyl chloride did not react. Furthermore, active halides such as allyl bromide and benzyl bromide would react with benzylamine at a relatively high rate to form exclusively the tertiary amine. They found that the addition of CsOH could only decrease the reaction times to reduce the importance of the leaving group and the chemoselectivity is not affected by the hydrogen bond acidity of the ionic liquid alone. Besides, they have studied further the effect of the ionic liquids as the solvent on the selectivities of *N*-alkylation of anilines [43]. Several ionic liquids such as [BMIM][PF_6], [BMIM][Tf_2N], [EMIM][Tf_2N], [BMIM][OTf], [EMIM][OTs], and [EMIM][$EtSO_4$] were tested as the solvents for the *N*-methylation and *N*-ethylation of aniline. They found that the ionic liquids not only promoted *N*-alkylation but also reduced the formation of multialkylation products, and the results showed that [BMIM][PF_6] was the preferable solvent among the above ionic liquids with the high conversion and easier isolation of product from the solvent. They carried out the subsequent reactions of different substituted anilines with several alkylating agents in [BMIM][PF_6]. The results revealed that in the alkylation of activated alkyl halides with activated anilines, the tertiary amines were the predominantly produced while deactivated anilines led to the exclusive products of secondary amines to which the selectivity could reach 100% in some cases. And they suggested that the chemoselectivity in ionic liquids mainly resulted from the precipitation of the *mono-N*-alkylanilinium salts.

Also, the effects of the ionic liquids as solvents on the *N*-alkylation of other compounds containing nitrogen atoms have been further investigated in detail by many chemists. For example, Frizzo et al. [44] recently have focused on the synthesis of *N*-alkyl trifluoromethyl pyrazoles in [BMIM][BF_4] with KOH as a base. The good yields (65–98%) from simple alkyl halides to excellent yields (80–96%) from functionalized alkylating agent in the alkylation of *3,5*-dimethy- and *5*-trifluoromethyl-*3*-methyl-*1H*-pyrazoles have obviously proved the efficiency of [BMIM][BF_4] as the solvent. Not only higher yields but also short reaction times were demonstrated in these reactions with the ionic liquid solvent in contrast to the results obtained in molecular solvents. More interestingly, Saidi et al. [45] have used $[Cp^*IrI_2]_2$ as an efficient catalyst in the absence of a base for the alkylation of amines with alcohols in ionic liquids with the borrowing hydrogen strategy; it is noteworthy that for the formation of more hindered tertiary amines, the reactions conducted in ionic liquid have performed considerably excellent conversions, for example, 100% conversion was obtained in 3 h in the case of the reaction of dimethylamine with *p*-methoxybenzyl alcohol to produce *1*-(*4*-methoxyphenyl)-*N*,*N*-dimethylmethanamine. Besides, a convenient approach for the alkylation of sterically hindered secondary amine *N*-heterocycle *3*-azabicyclo[*3.2.2*] nonane (*3*-ABN) under mild conditions using the room-temperature ionic liquids *1*-butyl-*3*-methylimidazolium hexafluorophosphate [BMIM][PF_6] and *1*-butyl-*1*-methylpyrrolidinum bis(trifluoromethylsulfonylimide) [P14][Tf_2N] in combination with KOH was presented by T. Rüther's group [46]. For example, 70–77% yields were achieved in [BMIM][PF_6] for the alkylation of *3*-ABN with *1*-iodoethane after 48 h at 60°C and 24 h at 80°C, respectively. They also tested the [BMIM][PF_6] as the solvent for the alkylations of *3*-ABN with different alkyl halides and obtained good results as well. Their report presented an efficient method with improved yields (70% to >90%) without considerable formation of quaternary amine as by-product. Being released from the reaction medium to form a separated layer, the tertiary amine products can be simply isolated in good yields by decantation.

In despite of few reports mainly concerning the *O*-alkylation in the ionic liquids, it is still obvious that the ionic liquids have exhibited powerful effects on the *O*-alkylation. Earle's group [36] has found that predominant *O*-alkylated products were observed in the alkylation of *2*-naphthol with simple alkyl halides at room temperature in [BMIM][PF_6], for example, the selectivity to *1*-bromonaphthalen-*2*-ol reached more than 99% with the 98% yield of mixed products containing *N*-alkylated and *O*-alkylated compounds in the alkylation of *2*-naphthol with BuBr in [BMIM][PF_6]. Moreover, a new phosgene-free approach for the synthesis of symmetrical organic carbonates through enhanced alkylation of K_2CO_3 or Cs_2CO_3 (suitable for the reactions due to their high solubility in ionic liquids) with various alkyl halides and sulfonates in [BMIM][PF_6] as the solvent was presented by Chi et al. [47]. In the alkylation of K_2CO_3 with 1-bromo-3-phenylpropane which was completed within 30 h at 110°C, an excellent yield of 89% of *di*-(*3*-phenylpropyl) carbonate was obtained, along with the yield of 86% when K_2CO_3 was replaced by Cs_2CO_3. In addition, they also examined this novel method with several different electrophilic moieties. This group exhibited a very potential and efficient method for synthesis of symmetrical organic carbonates not only with excellent yields but also avoiding hazardous chemicals such as phosgene and carbon monoxide.

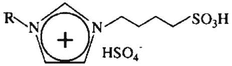
From above, it is evident that ionic liquids used as unconventional green solvents may promote alkylation reactions and allow the recycling of homogeneous catalysts. Ionic liquids have exhibited wide prospects on their applications in alkylation.

2.2.2 Ionic Liquids as Dual Green Solvents and Catalysts

It is well known that the acidic room-temperature ionic liquids like chloride aluminates have potential for acting as efficient combinations of catalyst and solvent in the Friedel-Crafts (F-C) alkylations. To the best of our knowledge, there are many reports investigating the F-C alkylations with ionic liquids as dual catalyst and green reaction medium. Table 2.4 shows some progresses of the different ionic liquids used as dual catalyst and solvent for the various F-C alkylations.

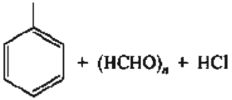
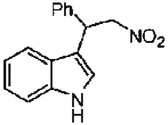
According to Table 2.4, the acidic ionic liquids performed excellent catalytic properties in Friedel-Crafts alkylations with high conversions and selectivities. In our research group, the application of ionic liquids to the alkylation of methylnaphthalene with long-chain mixed alkenes, which is believed to be a typical Friedel-Crafts reaction, due to the long-chain alkylmethylnaphthalenes being the core intermediates for alkylnaphthalene sulfonate anionic surfactants has been thoroughly studied [70–74]. It is known that alkylnaphthalene sulfonates are one of the most important anionic surfactants for all kinds of industrial purposes, and by using them as a chemical oil-displacing agent for enhanced oil recovery, researchers could obtain satisfactory results and the ultralow interfacial tension between oil and water could be achieved [75]. Moreover, because of their eminent surface activity, these kinds of surfactants may be used in many fields such as cleaning, dying and printing, emulsifying, ore milling, and nanotechnology. Zhao's group investigated Friedel-Crafts alkylations

Table 2.4 Friedel-Crafts alkylations using ionic liquids

Entry	Substrates	Ionic liquids	Desired products	Results		
				Con.[a]/%	Yields/%	Sel.[b]/%
1	Benzene + *1*-octadecene	[BMIM]Cl/[$FeCl_3$] [48]	Monoalkylbenzene	100	–	98
2	Benzene + *1*-dodecene	[BMIM]Al_2Cl_6Br [49]	*2*-Dodecylbenzene	91.8	–	38
		[EMIM]Cl/[$AlCl_3$][c] [50]		100	–	40.5
		[BMIM][$AlCl_4$] [51]		99.9	–	35.2
3	Toluene + *1,3*-pentadiene	[BuPy]BF_4-$AlCl_3$ [52]	Pentenyltoluene	65	6	–
4	Diphenyl oxide + *1*-dodecene	[BMIM]Cl/$AlCl_3$ [53]	Monododecyl diphenyl oxides	–	90	–
5	Diisobutene + Phenol	[BMIM]Cl[d]-$InCl_3$ [54]	*4*-(*tert*-Octyl)phenol	–	83	–
	2-Methylhept-1-ene		*4*-(*2*-Methyl-l-heptyl)phenol	–	81	–
	Isobutene		*2,4*-(*Di*-*tert*-butyl)phenol	–	78	–
6	Benzene + *1*-hexene	Et_3NHCl-$FeCl_3$[c] [55]	Monoalkylbenzen	100	–	100
7	Phenol with *tert*-butyl alcohol	[BMIM]PF_6 [56]	*2,4*-*Di*-*tert*-butylpheol	90	–	75
		 [R = $(CH_2)_5CH_3$] [57]		80.4	–	60.2
		[2-MPyH][e]OTf [58]		94	–	83
8	*m*-Cresol with *tert*-butanol	[$(C_2H_5)_3$-*N*-$(CH_2)_4$-SO_3H][HSO_4] [59]	*2*-*tert*-butyl-*5*-methyl phenol	80.9	78.1	96.5
9	*p*-Cresol with *tert*-butanol	*N*-(*4*-sulfonic acid)butyl triethylammonium hydrogen sulfate [60]	*2*-*tert*-butyl-*p*-cresol	80.7	–	90
		1-(*4*-sulfonic acid)butyl-pyridinium hydrogen sulfate [61]		79	–	92
10	Catechol + *tert*-butanol	[$(CH_3)_3$-*N*-$(CH_2)_4$-SO_3H][HSO_4] [62]	*4*-*tert*-butylcatechol	41.5	–	97.1
11	Naphthalene + ethylbromide	[BMIM]Cl-$AlCl_3$ [63]	*Mono-/di-/tri-* ethylnaphthalenes	98	–	–
12	Naphthalene + *iso*-propylchloride	[BDBN][f]Cl-$AlCl_3$ [64]	*Mono-/di-/tri-* isopropylnaphthalenes	90	–	–

(continued)

Table 2.4 (continued)

Entry	Substrates	Ionic liquids	Desired products	Results Con.[a]/%	Yields/%	Sel.[b]/%
13	Benzene + dichloromethane	Et$_3$NHCl-AlCl$_3$ [65]	Diphenylmethane	83.8	–	86.3
14		[C$_{12}$mim]Br [65]	*mono*-Chloromethylated product	70	–	100
15	Anthracene + 2-chloropropane	[EMIM]Cl-AlCl$_3$ [66]	2-Isopropylanthracene	–	74.5	82.9
16	Indole + *trans*-β-nitrostyrene	[C$_4$H$_8$NH$_2$][H(CF$_2$)$_4$O(CF$_2$)$_2$SO$_3$] [67]		–	92	–
17	Indole + benaldehyde	*N,N,N,N*-tetramethylguanidinium trifluoroacetate [68]	3-((*1H*-Indol-3-yl)(phenyl) methyl)-*1H*-indole	–	93	–
18	Indole + styrene oxide	[BMIM]OTf [69]	2-(3-Indolyl)-2-(4-phenyl) ethanol	–	85	–
	Pyrrole + styrene oxide		2-(2-Pyrrolyl)-2-(4-phenyl) ethanol	–	80	–

[a] Con. is denoted as conversion

[b] Sel. is denoted as selectivity

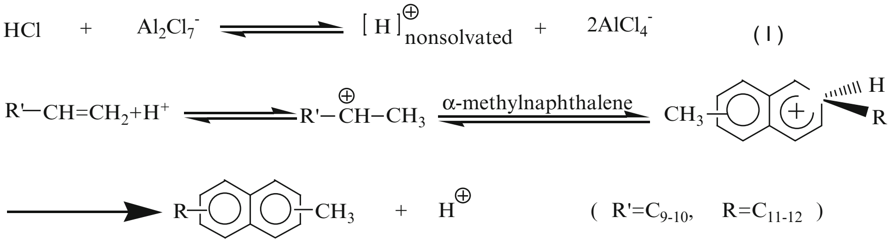
[c] Modified with HCl

[d] [C$_4$mim]Cl refers to *1*-butyl-*3*-methylimidazolium chloride

[e] [2-MPyH] refers to 2-methylpyridinium trifluoromethanesulfonate

[f] [BDBN] refers to 5-butyl-*1,5*-diazabicyclo*[4,3,0]*-non-5-enium

of 2-methylnaphthalene with long-chain alkenes (mixed C_{11-12} olefins) in the ethyl-containing amine chloroaluminate ionic liquids modified with HCl as environmentally friendly catalysts to yield the significant intermediates, alkylmethylnaphthalene with a green protocol. In this reaction, they studied the influences of the type and dosage of catalysts, molar ratio of 2-methylnaphthalene to alkenes and solvent to 2-methylnaphthalene, reaction temperature, and time on the reactions. Conversion of alkenes more than 90% and about 100% of selectivity for monoalkyl methylnaphthalene were obtained under the optimal reaction conditions (molar ratio of 4:1 for aromatic hydrocarbon to alkenes, and molar ratio of 2:1 for cyclohexane to 2-methylnaphthalene in the presence of 7% of catalyst at 333 K for 0 min) [70]. The products and unreacted reactants do not dissolve in ionic liquids and, therefore, can be isolated easily by decantation. The possible catalysis processes are given in Scheme 2.1. Besides, they found that the catalysis activity of ionic liquids investigated was in the order of $EtNH_3Cl–AlCl_3$ ($n=0.71$) < $Et_2NH_2Cl–AlCl_3$ ($n=0.71$) < $Et_3NHCl–AlCl_3$ ($n=0.71$) (n is the mole fraction of $AlCl_3$), and n value was a key factor for deciding catalysis activity. And the results observed in the reaction demonstrated that the use of alkyl-containing amine chloroaluminate ionic liquids modified by HCl in the Friedel-Crafts alkylation reaction of aromatic hydrocarbon could be considered as eco-friendly alternative to the existing homogeneous catalysts. It could be a practical catalyst for long-chain alkylation of 2-methylnaphthalene with alkenes. In addition, our group also compared the $Et_xNH_{4-x}Cl–AlCl_3$ ($x=1–3$) ionic liquids with HY, USY zeolite, and the other ethylamine-containing ionic liquids as the catalysts in the alkylation of α-methylnaphthalene with long-chain mixed alkenes (C_{11-12}) and found that $Et_xNH_{4-x}Cl–AlCl_3$ catalyzes the reaction with high conversion of long-chain olefins and excellent selectivity toward monoalkylated methylnaphthalene [71]. More interestingly, we found another ionic liquid, $BuPyBr–AlCl_3$, with outstanding catalytic properties which was used as the efficient catalyst and solvent in the alkylation of α-methylnaphthalene with long-chain alkenes obtaining higher than 90% conversion of alkenes and 100% selectivity for the desired products under the optimum reaction conditions [72]. Furthermore, we discovered that 7% of Cu^{2+}-modified ionic liquid exhibited more excellent catalysis performance for alkylations of α-methylnaphthalene with long-chain olefins than that of unmodified $BuPyBr–AlCl_3$ ionic liquid, although the change was not remarkable [74].



Scheme 2.1 The possible catalysis process of the Friedel-Crafts alkylations of 2-methylnaphthalene

For the *C*-alkylations, the main interest was on the alkylation of C_4-isoparaffins which is useful as a high octane and eco-friendly blending component for gasoline [76, 77]. Although at present the two industrial catalysts are H_2SO_4 and HF, both are highly toxic, corrosive, and hazardous to the environment. Thus, the green and environmental friendly ionic liquids with efficient catalytic activities are the alternative to the above two traditional catalysts. As a result, several research groups have investigated the activities of ionic liquids as the catalysts for the alkylation of isobutane with butene. For example, Bui et al. [78] have reported the alkylation of isobutane with *2*-butene using the ionic liquid, *1*-*n*-octyl-*3*-methylimidazolium bromide aluminum chloride ([OMIM]Br–$AlCl_3$), and found a promising approach to tune the acidity of ionic liquids, i.e., via protonic additives such as water, cation exchange resins (Dowex, Amberlyst), and the IL [(HO_3SBu)MIM]HSO_4. The results showed that the optimum content of water was 90 ppm when the desired trimethylpentane (TMP) yields raised from 20 wt.% (no water) to 50 wt.% along with the increase of the research octane number (RON) from 90.5% to 94%; besides, the yields of TMPs reached 52.7%, 57.8%, and 63.9% corresponding to RON of 94.8%, 95.2%, and 96.2% for the addition of [(HO_3SBu)MIM]HSO_4, Dowex, and Amberlyst, respectively, which is comparable or higher than that with H_2SO_4 as the catalyst. In addition, the products were separated easily by decantation, and therefore, the catalyst could be reused in all cases. Furthermore, Liu's group [79] has prepared a composite ionic liquid $[(C_2H_5)_3NH]Cl–AlCl_3/CuCl$ to catalyze the identical reaction obtained the TMP of >85 wt.% and the RON of 98–101. According to their results, when the value of N (= mole of CuCl/mole of $[(C_2H_5)_3NH]Cl–AlCl_3$) equals 0.5, the IL $[(C_2H_5)_3NH]Cl–AlCl_3/CuCl$ displayed the best performance in terms of activity and selectivity for the reaction; moreover, a new anion species $[AlCl_4CuCl]^-$ came to appear, which plays a significantly important role in reducing the side reactions of alkylation to improve the amount of TMPs. In addition, Liu's group [80] and Chen's group [81] have studied the effects of additives on the activity of ionic liquid catalysts for alkylation of isobutane and butane. In their reports, HCl, CuCl, and benzene have been employed as the additives to chloroaluminate ionic liquids. Zhi-Chang Liu et al. [80] found that the introduction of HCl could maintain the high activity of ionic liquids to obtain 97% of the conversion of butene but decrease the selectivity of C_8 in alkylate from 56.2 to 50.4 wt.%. In contrast, the addition of CuCl demonstrated excellent performance with the selectivity of C_8 increasing to 74.8 wt.% and the ratio of trimethylpentane (TMP) to dimethylhexane (DMH) in isooctane rising to 6.5. Chen et al. have also analyzed the $AlCl_3$ molar fraction on the catalytic performance of chloroaluminate ionic liquids and the effects of the addition of aromatic compounds for the alkylation of isobutane and *2*-butene. The data showed that at the ratio of $AlCl_3$ to $Et_3NHCl > 1.0$, high catalytic activity was exhibited with more than 95% of the conversion of 2-butene, about 50% of the selectivities to isooctane (C_8), and the ratio of TMP to DMH ranging from 2.2 to 2.8. They postulated that the π-complexation of Lewis acid sites of chloroaluminate ionic liquids and π-cloud of the aromatic ring were formed after the introduction of benzene to chloroaluminate ionic liquids and the π-complexation is probably beneficial for the alkylation because of its preventability of the side reactions with about

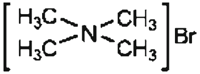
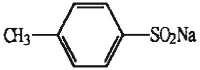
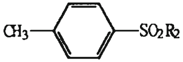
98% of the conversion of *2*-butene and 76.2 wt.% of the selectivities to isooctane (C_8) and the ratio of TMP to DMH reaching 8.8. It is obvious that Chen's group [81] has increased the concentration of acid sites of the ionic liquids by changing the molar fraction of $AlCl_3$ in the ionic liquids and improved the properties of the Lewis acid sites by adding the aromatic compounds to the ionic liquids. With their efforts in these two aspects, the obtained acidity of the ionic liquids significant improvement which could be clearly observed from the alkylation results and related infrared spectra. Besides, for the reaction of isobutane with *2*-butene, a detailed study emphasizing the role of both cations and anions on the catalytic activity of the ionic liquids was conducted by Kyesang's group [82], and they found that a larger alkyl group on the cation of ionic liquid [C_8mim] showed relatively higher activity than a smaller one [C_6 or C_4mim] with the same anion due to the former's higher solubility of reactants. In addition, Subramaniam's group obtained exciting results that showed more than 95% conversion, better C_8-alkylates selectivity (>70%), and TMP/DMH >7 for *1*-butene/isobutane alkylation using binary mixtures of certain acidic imidazolium ionic liquids and sulfuric or trifluoromethanesulfonic acid in comparison with the pure acids [83]. Olah et al. [84] have employed the ionic liquid amine-poly(hydrogen fluoride) complexes (prepared by combining pyridine or its analogues with anhydrous HF) as the catalyst and reaction medium for the alkylation of isobutane with isobutylene and *2*-butene. They found that the novel green catalytic systems exhibited excellent yields of high-octane alkylates (up to RON = 94). The catalytic systems have been popularly used as Olah's reagent [85–87].

Moreover, toward *N*-, *O*-, and *S*-alkylations, the ionic liquids have also demonstrated good catalytic activity and potential application for recycling and reuse by playing the dual role of solvent and promoter. There have certain advantages compared to the traditional catalytic systems, including high regioselectivities, higher yields, being more environmentally benign, and generality. Part of the results is shown in Table 2.5. If some of the readers are interested in the *N*-, *O*-, or *S*-alkylation, they can refer to the related references [88–94].

2.2.3 Ionic Liquids Immobilized on Solid Supports

The utilization of ionic liquids has brought many advantages such as the simple isolation process of products from the reaction mixture, the potential for recycling and reuse and avoidance of the hazardous organic solvents over the traditional molecular solvents. However, when ionic liquids are employed in their liquid form in continuous reaction systems, great inconveniences are encountered. The immobilization of ionic liquids on some solid supports can resolve these problems. Currently, many research groups [95–102] are involved in the investigation of ionic liquids immobilization on solid supports. The immobilized ionic liquids have some advantages that the acidity can be easily tuned, the recovery of the catalyst can be simpler, and they can be applied for the gas-phase reactions. They introduced the term "Novel Lewis-Acid Catalysts" (NLACs) to refer to the acid catalysts in which covalent bonds between silanol groups

Table 2.5 The *N*-, *O*-, and *S*-alkylation using various ionic liquids as the reaction medium

Entry	Substrates	Ionic liquids	Products	Yields/%
1	Aniline + BuBr	[BMIM]I [88]	*N*-butylaniline	99
2	Morpholine + BuBr	[BMIM][PF_6] [88]	*N*-butylmorpholine	99
3	*1*-Amino-*9,10*-anthraquinone + $(MeO)_3P$	[BPIM][Br][a] [89]	*1*-(Methylamino)-*9,10*-anthraquinone	95
4	*2*-Amino-*9,10*-anthraquinone + $(MeO)_3P$	[BBIM][Br][b] [89]	*2,2*-(Dimethylamino)-*9,10*-anthraquinone	98
5	NH_3Br + dimethyl carbonate	[EMIM]Br [90]		96.5
6	Pyrrole + $C_6H_5CH_2Cl$	[BMIM]PF_6 [91]	*N*-benzylpyrrole	99
7	*2*-Mercaptobenzothia(xa)zole + benzyl chloride	[BMIM]PF_6 [93]	The *S*-alkylated products	96
		[BMIM]BF_4 [93]		97
8	 + *n*-Hexyl chloride	[BMIM]BF_4 [94]	 (R_2 = *n*-hexyl)	67

[a] [BPIM][Br](BP = *n*-Bu, *n*-Pr)
[b] [BBIM][Br](BB = *n*-Bu, *n*-Bu)

Table 2.6 The immobilized ionic liquids as the catalysts for alkylation

Catalysts	Reactions	Results	
		Con.[a]/%	Sel.[b]/%
T350/Al-IL[c] [96]	Benzene + dodecene	99.9[d]	99.8[e]
	Naphthalene + dodecene	66.9[d]	71.7[e]
	Phenol + dodecene	56.6[d]	–
[EMIM]Cl/AlCl$_3$–SiO$_2$	Cumene + propylene [98]	90[f]	50 (*p*–)
	Toluene + propylene [97]	–	>95[g]
Si[pmim]Cl[h]-MCM-41	Isobutene + raffinate II [99]	97	–
	Benzene + C$_{12}$ olefin [95]	100[i]	85.6[c]

[a] Con. is denoted as conversion

[b] Sel. is denoted as selectivity

[c] Al-IL refers to the IL consisting of [BMIM]Cl and AlCl$_3$, and T-350 is a kind of silica support

[d] Conversion based on dodecene

[e] Selectivity to the monoalkylated product

[f] Conversion based on cumune

[g] Selectivity to the monoalkylated product in the gas-phase alkylation for more than 210 h time-on-stream

[h] Si[pmim]Cl refers to *1*-(*3*-trethoxysilyl)-propyl-*3*-methylimidazolium chloride

[i] Conversion based on C$_{12}$ olefin

of the solid supports and the anion or cation of the ionic liquids exist. They classified the NLACs according to the method of their preparation such as incipient wetness method, grafting method, and sol-gel method [95]. The immobilized ionic liquids have been used as the acid catalysts for the different alkylation reactions, for example, the alkylation of benzene, toluene, naphthalene, and phenol with dodecene [96]; the continuous gas-phase isopropylation of toluene and cumene [97]; the slurry-phase Friedel-Crafts alkylations of cumene [98]; and the liquid-phase alkylation of raffinate II with *iso*-butene [99]. Some results are tabulated in Table 2.6, from which it is obvious that the immobilized ionic liquids T350/Al-IL and Si[PMIM]Cl-MCM-41 have exhibited excellent performance in the alkylation of benzene by dodecene. Moreover, in these studies, the so-called supported ionic liquid phase (SILP) has been introduced. This new concept is related to the short diffusion distances in the supported ionic liquid films breaking through the mass transfer limitations existing in the traditional ionic liquid-liquid catalysis because of the high viscosity of ionic liquids; thus, a more effective utilization of the catalytic ionic liquids can be realized by the use of SILP catalysts. It is noteworthy that the SILP catalysts can be easily employed in the fixed bed reactors for industrial process without any complex modifications.

2.3 Acylation

The acylation refers to the process of the introduction of acyl groups to the *C*, *N*, and *O* atoms, which is extensively applied to the fields of fine chemical industry and the medicine synthesis as the important organic unit reactions for synthesis. Besides, the acylation is employed as the efficient protocol for the protection of the OH, NH_2, and SH groups and for the kinetic resolution of racemates as the one major routes to form pure organic compounds. The conventional acylation needs $AlCl_3$ in a stoichiometric amount as the catalyst (reaction reagent) with the heavy environment pollution. The ionic liquids as the eco-friendly solvents and catalysts have attracted great attentions in the acylation. The following content would be divided into three parts (green solvent, dual green solvent and catalyst, immobilized ionic liquids) to review the research progress in the application of ionic liquids for the acylation.

2.3.1 Ionic Liquids as Green Solvents

The ionic liquids, as the green solvents, have been extensively applied to the *C*-, *O*-, *N*-, and *S*-acylations. It is obvious that the use of ionic liquids as replacement to the conventional organic solvents has been eco-friendly to the environment. Besides, the ionic liquids as the unusual reaction medium could promote the reaction and increase the conversion and selectivity as well. Moreover, the immobilization of homogeneous catalysts in the ionic liquids to form composite catalytic systems could make the catalysts to be more easily separation and reuse.

The acetylation of typical aromatic compounds such as benzene, toluene, and bromobenzene catalyzed by $AlCl_3$ and $FeCl_3$ in the presence of pyridine-based ionic liquids $[EtPy]^+BF_4^-$ and $[EtPy]^+CF_3COO^-$ was carried out by Y. Xiao's group [103]. The excellent outcome could be obtained using either $AlCl_3$ or $FeCl_3$ as the catalyst in the presence of $[EtPy]^+CF_3COO^-$. The comparable conversion and selectivity could be achieved at 50°C under the mild reaction conditions by using the cheap and stable $FeCl_3$ with abundant resources as the catalyst, employing $[EtPy]^+CF_3COO^-$ as the green solvent in contrast with the $AlCl_3$ catalyst. And when the reactants were benzene, toluene, and bromobenzene, 97%, 96%, and 93% of conversion to acetic anhydride with 97%, 80%, and 93% of selectivities to the major products, respectively, were obtained. It exhibits the simple separation of product and potential of solvent's recycling in the presence of the ionic liquids as the green solvents [103]. Diarylketones are the important fine chemical intermediates, which could be prepared by the acylation of aromatic hydrocarbon with benzoyl chloride and benzoic anhydride. Gmouh's group [104] has investigated various ionic liquids applied to the benzoylation reactions with different reactants catalyzed by Bi(III). The results showed that the ionic liquids as the green solvents promoted obviously the reactions and the design for anions and cations of the ionic liquids had a significant effect on the reactions. And 98% conversion could be achieved in the acylation of toluene with benzoyl chloride using $[BMIM][NTf_2]$ as the clean reaction medium, but the utilization of this ionic liquid led to the difficulty in the separation from the organic phase, while in the presence of $[EMIM][NTf_2]$, the reaction system became biphasic around the room temperature (one phase is the ionic liquid containing the catalyst $Bi(OTf)_3$ and the other is the organic phase). The catalyst/solvent system $Bi(OTf)_3/EMIMNTf_2$ maintains the excellent catalytic activity for acylation, allowing a promising future of industrial application [104]. Earle et al. have examined the benzoylation reactions of substituted benzene catalyzed by metal bis{(trifluoromethyl)sulfonyl}amide complexes in the ionic liquids and noted that the ionic liquids could promote the benzoylation reactions with high reaction rate and short time, and even for the aromatic hydrocarbon with electron-withdrawing group, good results could also be obtained. Besides, the catalysts were able to be recycled because of the facile separation of the ionic liquids containing the catalysts from the organic phase [105]. Moreover, the acylation of anisole with benzoyl chloride with $Cu(OTf)_2$, $Zn(OTf)_2$, and $Sc(OTf)_3$ as the catalysts in the presence of [BIMI]BF4 and normal organic molecular solvents was carried out by J. Ross et al. for comparative purpose. The ionic liquids exhibited obvious acceleration for the reactions in contrast to the normal molecular solvents. Under the same conditions with $Cu(OTf)_2$ as the catalyst, the mole ratio of anisole/benzoyl chloride being 5:1 at 80°C for 1 h, the conversions of benzoyl chloride (*o-/p*-acylates) observed were 100% (4/96), 64% (7/93), and 73% (7/93), correspondingly using $[BIMI]BF_4$, CH_3CN, and CH_2ClCH_2Cl as the reaction medium. According to the results, the ionic liquid evidently promoted the benzoylation reactions catalyzed by $Cu(OTf)_2$ and was beneficial to the formation of *p*-acylates; besides, the ionic liquid has no vapor pressure, no toxicity, and excellent solubility of $Cu(OTf)_2$, and the catalysts in the ionic liquids could be easily recycled for the simple separation from the organic phase [106]. Zayed's research group has also studied the application of the green ionic liquid/supercritical carbon dioxide as the biphasic reaction medium, the employment of the proper ionic liquids (i.e., not only possessing the excellent solubility of the catalysts but also not losing in the extractions of the supercritical carbon dioxide) with the Lewis catalysts $M(OTf)_3$ immobilized, and the supercritical carbon dioxide as the tool for the extraction of the products is expected to realize the clean, highly effective, and continuous industrial process of the Friedel-Crafts acylation [107]. Furthermore, the ionic liquids as the green solvents for the acylation of derivants of *m*-dihydroxybenzene have gained great success as well [108]. From the beginning of the discovery of ferrocene, the derivant of ferrocene was applied widely especially in the fields of the asymmetric catalysis, material chemistry, and biochemistry. The acylation of ferrocene has been emphasized with great importance for the easiness of the reactions between carbonyl and many reagents. And the ionic liquids have also applied in the acylation of ferrocene as well. As early as 1999, Stark reported the acylation of ferrocene with $R(CO)_2O$ and RCOCl (R = Me, Pr, n-Bu, t-Bu, Ph) to synthesize a series of acylated ferrocene in the presence of ionic liquid $[EMIM]I\text{-}(AlCl_3)_X$ [109]. Li et al. have studied the Ytterbium triflate–catalyzed acylation of ferrocene with various anhydrides and acyl chlorides in the presence of $[BPy]BF_4$ to obtain the high yields of monoacetylated products under the mild conditions, and they found that after the recycling of the solvent/catalyst system, no significant decrease in the activity was observed [110]. Within 1.5 min, 100% gas chromatography (GC) conversion was achieved in the acylation of ferrocene with acetic anhydride catalyzed by $Sc(OTf)_3$ with the help of microwave in the presence of the ionic liquid [BMIM][Tf_2N], which was conducted by Berardi et al. [111]. In addition, the ionic liquids as the green solvents could also be applied to other *C*-acylation and could show excellent acceleration for many reactions with the simple product isolation and recyclable catalysts [112–114]. It is absolute that the application of the eco-friendly ionic liquids is promising. And because of the space limitation, the more related information would not be offered.

The ionic liquids as the green solvents have been extensively used for the O-acylation to realize the kinetic resolution of racemic compounds. The kinetic resolution of racemates is considered as one of the important methods to manufacture optically pure compounds. In the report of Habulin's group, the enzymatic kinetic resolution of (*R,S*)-*1*-phenylethanol over *Candida antarctica* lipase B (CALB) by using vinyl acetate as the acyl donor in the acylation reaction was chosen as model reaction. It was found that, while 6.6% (w/w) of Novozym 435 was dispersed in [BMIM][PF_6] at 40°C, using an equimolar vinyl acetate/(*R,S*)-*1*-phenylethanol after 3 h of bioconversion, the highest possible conversion (50%) was reached with enantiomeric excess for substrate higher than 99%. The results demonstrated that the ionic liquids showed evident advantages as the unusual green solvents for the kinetic resolution catalyzed by the bio-enzyme [115]. Besides, the utilization of ionic liquids for the efficient enantioselective acylation of (*R,S*)-*1*-trimethylsilylethanol {(*R,S*)-*1*-TMSE} with vinyl acetate catalyzed by immobilized lipase from *Candida antarctica* B (i.e., Novozym 435) to yield (*S*)-*1*-TMSE with the high value for industrial application has obtained great success. In comparison with the conventional organic solvents, the lipase's initial rate and enantioselectivity of the acylation were increased considerably in the ionic liquids. After a reaction time of 6 h, the ee of the remaining (*S*)-*1*-TMSE reached 97.1% at the substrate conversion of 50.7% [116]. There are several reports concerning the research on the lipase-catalyzed *O*-acylation for the kinetic resolution of racemates with the ionic liquids as the green and highly efficient reaction medium [117–119].

The *O*-acylation reactions of monohydroxy-alcohol, dihydroxy-alcohol, and polyhydroxy-alcohol to synthesize the corresponding esters have widely used ionic liquids as the green solvents. Xi et al. have reported the ruthenium (III) chloride–catalyzed acylation of a variety of alcohols and phenols with acetic anhydride in the presence of the ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]), with the considerably high yields of the *O*-acylated products under the mild conditions. Besides, they tested the recyclable property of the solvent/catalyst system with the acylation of benzyl alcohol with acetic anhydride as the model reaction, and as a result, they found that the catalytic system could be recycled for 10 times with no significant change of the benzyl acetate's yield. It is evident that the employment of ionic liquids as the reaction medium could not only replace the normal organic solvents such as acetonitrile but also resolve the problems for the recycling and reuse of the homogeneous catalyst ruthenium (III) chloride [120]. *1*-Butyl-*3*-methylimidazolium tetrafluoroborate [BMIM]BF_4 as the eco-friendly reaction medium could also be applied to the *O*-acylation reaction of dehydroabietic acid chloride with *2*-hydroxyethyl acrylate to yield dehydroabietic acid (*2*-acryloloxy) ethyl ester. This new method showed the advantages of mild reaction conditions, short reaction times, good yields, and recyclable solvent [121].

The ionic liquids as the green solvents for the *O*-acylation of *2*-octanol with succinic anhydride brought good results for the reactions [122]. Water-tolerant ionic liquid [BMIM][PF_6] as the clean reaction medium was applied to the acylation of *1,2*-ethanediol with ethyl acetate, which was catalyzed by the Novozym 435 lipase. It showed the evident synergistic effect with bio-enzyme to promote the reaction effectively, and the researchers found that the introduction of trace of water to the water-tolerant ionic liquids would be beneficial for the increase of the conversion of *1,2*-ethanediol and selectivity to ethane-*1,2*-diol monoacetate [123]. Besides, the *O*-acylation of polyhydroxy-alcohol has also taken advantage of the ionic liquids as the green reaction medium. Liu's group has found that the ionic liquids promoted obviously the acylation of ribavirin with divinyladipate catalyzed by the lipase acrylic resin from *Candida antarctica* [124]. A series of ionic liquids as the unusual green solvents were applied to the immobilized *Candida antarctica lipase B*–catalyzed regioselective acylation of *1*-β-*D*-arabinofuranosylcytosine by vinyl propionate. The results indicated that designing the anions and cations of the ionic liquids had a significant effect on the initial rate and the conversion of substrate. Moreover, it was found that the mixing ionic liquids with proper molecular solvents could enhance the acceleration. In fact, 94.0 mM h^{-1} of initial rate, 98.5% of substrate conversion, and 99% of regioselectivity to desired product were achieved under the mild conditions by the use of 10% (v/v) [BMIM]PF_4-tetrahydrofuran as the reaction medium. Interestingly, the stability of the bio-enzyme was increased in the presence of the ionic liquids [125].

The functionalized natural polyhydroxy compounds such as phenolic and flavonoid glucosides (salicin, helicon, esculin, and naringin), nucleoside, starch, zein protein, cellulose, chitin, etc., are utilized widely in the fields of medicine, food additives, and fine chemical industry. However, the poor solubility of these materials in the normal organic solvents leads to the low conversion for the functionalization of those natural polyhydroxy compounds. Based on the special behaviors of ionic liquids, especially the functionalized ionic liquids, the above natural compounds can be well dissolved. As a result, the reactions for the functionalization of these can be effectually improved. Katsoura et al. found that the immobilized lipase B–catalyzed acylation is promoted in the ionic liquids, and the conversions, regioselectivity, and the reaction rate all strongly depended on the nature of the used ionic liquid [126]. The acylation of biomass polymer starch and zein with acetic anhydride as the acylating agent in the ionic liquids to synthesize acetylated starch and zein in high yields was performed by A. Biswas's group [127]. Chen et al. have studied the effects of the conventional organic solvents like *tert*-butanol, etc., and the various ionic liquids ([EMIM]BF_4, [BMIM]BF_4, [OMIM]BF_4, [BMIM]PF_6, and [BMIM]Cl) on the lipase-catalyzed acylation of konjac glucomannan with vinyl acetate as the acyl donor. Compared to the normal organic solvents, the ionic liquids as the green solvents were found to significantly enhance the stability and activity of the bio-enzyme. The results of experiments also demonstrated that the anions and cations of the ionic liquids played a considerably important role on the reactions and [BMIM][PF_6] exhibited the best performance as the reaction medium [128]. It is also discovered that the application of ionic liquids to nucleoside chemistry could obtain great success as the alternative to the traditional organic solvents [129]. The researches concerning the ionic liquids as the unusual green solvents for the *O*-acylation of polyhydroxy compounds have obtained extensive attentions, with more and more related reports being appeared, the reader with interest please consult the corresponding references [130–135].

Beside the *C*- and *O*-acylations, the ionic liquids as the green solvents have been widely used for the *N*- and *S*-acylations as the alternative to the normal organic solvents. R. Irimescu et al. have investigated the lipase-catalyzed enantioselective acylation of *1*-phenylethylamine and *2*-phenyl-*1*-propylamine in the ionic liquids and under solvent-free conditions, respectively, which were performed by the amines with carboxylic acids. The results of the experiments indicated that for the acylation of *1*-phenylethylamine and *2*-phenyl-*1*-propylamine with various acylating agents, the ionic liquids as the reaction medium could increase the conversions of amine, enantiomeric excess of unreacted amine, and enantiomeric excess of acylated amine, and when [BMIM][PF_6] was employed as the green solvent and dodecanoic acid as acylation agent, 48.9% conversion of 1-phenylethylamine, 95.9% of ee to unreacted amine, and more than 99% of ee to acylated amine can be obtained at 55°C in 19 h so as to realize the highly effective kinetic resolution of the racemate *1*-phenylethylamine [136]. Toral's group has compared the results of the *N*-acylation reaction for the kinetic resolution (*R,S*)-*1*-phenylethylamine with the immobilized *Candida antarctica lipase B* as the catalyst in the reaction medium of [BIMI]NO_3 and normal organic solvents, respectively, and found that higher stereoselectivity was obtained when ionic liquids were employed as the solvents [137]. There are large numbers of the reports with regard to the ionic liquids as the green solvents for the kinetic resolution of (*R,S*)-*1*-phenylethylamine [138, 139]. In addition, the ionic liquids could also be used for the *N*-acylation of chiral oxazolidin-*2*-ones to produce *N*-acyloxazolidin-*2*-ones with good yield [140]. In contrast to *C*-, *O*-, and *N*-acylations, the application of the ionic liquids to the *S*-acylation is limited. Xi et al. reported that good results were obtained with the isolation yield of acylate reaching >90% in the acetylation of thiophenol, *t*-butyl mercaptan, *p*-chlorothiothiophenol, and *p*-methylthiothiophenol using $RuCl_3$ as the catalyst in the ionic liquids [120].

2.3.2 Ionic Liquids in Dual Role as Green Solvents and Catalysts

Besides only as green reaction media, ionic liquids as dual green solvents and catalysts are also widely used in acylation reactions, especially *C*-acylation. Benzophenone and its derivatives are important fine chemicals or intermediates in dyes, pharmaceuticals, and other chemical industries. Li et al. have studied the Friedel-Crafts acylation reactions using ionic liquids like BMIMCl-$FeCl_3$, BMIMCl-$AlCl_3$, and BMIMCl-$ZnCl_2$ as dual catalyst-solvent to synthesize benzophenone and its derivatives. They found that BMIMCl-$FeCl_3$ showed much higher catalytic activity than that observed for the other two ionic liquids, and in conventional organic solvents. Using this highly efficient and clean process, more than 97% yield could be obtained within a short time, employing the ionic liquids as the dual solvents and catalysts; meanwhile, the isolation of products could be simply operated, and the ionic liquids were able to be recycled and reused [141].

5-Acetylsalicylamide is an important intermediate exploited to synthesize medicaments for curing heart and irritability diseases. Chen's group via using Lewis acidic ionic liquids, 1-butyl-3-methylimidazolium chloroaluminate ([BMIM]Cl-nAlCl$_3$), and *N*-butylpyridinium chloroaluminate ([BPy]Cl-nAlCl$_3$) as the dual solvent and catalyst investigated the acylation of salicylamide with acetyl chloride to *5*-acetylsalicylamide. The results of the experiments demonstrated that the Lewis acidic ionic liquids, substituting for the conventional carcinogenic nitrobenzene solvent and anhydrous AlCl$_3$ catalyst, showed excellent catalytic activity in the acylation of salicylamide to 5-acetylsalicylamide. When [BPy]-*2*AlCl$_3$ was used as the catalyst and solvent, the maximum yield of *5*-acetylsalicylamide was 89.2% [142].

Diarylketones are also the important fine chemical intermediates, which could be prepared by the acylation of aromatic hydrocarbon with benzoyl chloride and benzoic anhydride. The ionic liquids have also been used to catalyze the synthesis of diarylketone. Earle et al. [105] have reported the benzoylation of benzene, derivants of benzene (toluene, anisole, isobutyl benzene, phenyl chloride and fluoride) to synthesize the diarylketone by use of chloroindate (III) ionic liquids as the green dual catalysts and solvents. As a result, good yields (75–96%) were obtained under proper conditions with the ionic liquids as the clean reaction medium and recyclable catalysts.

Acylated indoles are important building block for pharmaceutical synthesis. The chloroaluminate ionic liquids have been applied as the eco-friendly catalysts and reaction mediums to the acylation of indoles and substituted indoles. Yeung et al. have investigated the acylation of poor electron indole ring with acidic ionic liquid, *1*-ethyl-*3*-ethylimidazolium chloroaluminate with 0.67–0.75 mole fraction of aluminum chloride as the catalyst, which provides a practical and convenient protocol for clean and efficient synthesis of multiple-point pharmacophores of indoles substituted at different positions with versatile functionalities (e.g., Br, CN, NO$_2$, CO$_2$H) with high yield [143]. Subsequently, they studied the green synthesis of 3-glyoxylic acid derivatives of electron-deficient, substituted *4-/6*-azaindoles by using *1*-ethyl-*3*-ethylimidazolium chloroaluminate (the mole fraction of AlCl$_3$ is 0.75) as the green reaction medium and highly efficient catalyst [144].

The ionic liquids as the eco-friendly catalysts and clean reaction medium have also been used for the acylation of polynuclear aromatics. Chen [145–147] and Yuan [148] have investigated the Friedel-Crafts acylation reactions of anthracene with oxalyl chloride by use of the chloroaluminate ionic liquids as the catalysts. In these reactions, the ionic liquids exhibited excellent performance as the efficient clean catalysts and reaction media. Almost 100% selectivity with 90% yield of *1,2*-aceanthrylenedione was obtained at 40–45°C for 6 h. The catalytic system can be recovered and recycled.

Besides, the *C*-acylation of nonaromatic compounds has also been examined using the ionic liquids as the efficient green solvents and catalyst [149, 150]. It is worthy to mention that the ionic liquids play dual roles as catalyst and green solvent for acylation to replace the traditional hazardous $AlCl_3$ catalyst. Using ionic liquids as catalysts and solvents, the eco-friendly reaction processes with mild reaction conditions, high efficiency, and good selectivity can be realized. However, due to their sensitivity to the moisture, the application of the Lewis acid ionic liquids has been limited. Therefore, the search of stable ionic liquids to the moisture and air is urgently needed.

2.3.3 Immobilized Ionic Liquids

In the alkylation section, it was stated that the immobilized ionic liquids can combine the advantage of green media with solid support materials, which may enable the wide application of precious ionic liquids by the reduction of usage and also realize the sustainability of the chemical reaction process. The supported ionic liquids (SILs) catalysts commonly employ the supports such as the macroporous polymer, metal oxide (SiO_2, Al_2O_3, etc.), zeolite, clay, and active carbon, and after the immobilization of the ionic liquids, the ionic liquids still maintain their special solvent effect. Presently, the immobilized ionic liquids have been applied extensively to the alkylation, acylation, hydroformylation, oxidation, esterification, hydrolyzation, hydrogenation, and other unit reactions; this part of the chapter only discusses the application of immobilized ionic liquids to the acylation.

Valkenberg et al. have studied the acetylation of benzene, toluene, *m*-xylene, mesitylene, and anisole by use of supported ionic liquids as the catalysts. The reactions were carried out in two different forms, the batch mode and the continuous reactions, respectively. The results showed that the inactivation of catalysts was serious. The HCl formed in the process could accelerate the reactions, but it is not removed from the mixture fast enough, thus reacted with the products arones to form *1*-(*1*-chlorovinyl)-*2,4*-dimethyl-benzene, and release the water at the same time, leading to the decreasing of selectivity toward the main products and the permanent inactivation of catalysts resulting from the water. On the other hand, the serious leaching of active constituent in the liquid-phase reactions also induced the inactivation of catalysts. And they planned to adopt the gas-phase reaction to avoid the leaching problems. The results showed that the catalytic activity was slightly lower than that in liquid phase and the selectivity reached more than 90%. But the catalysts would be inactive soon as well which may be caused by the adsorption of the large molecules onto the catalysts. They suggested that the optimization of the conditions could increase the yields of products [151].

In addition, immobilized ionic liquids have been employed for the *O*-acylation and *N*-acylation. Hara et al. have investigated the reactions that supported ionic liquids in lipase-catalyzed asymmetric acylation of *1*-phenylethanol with vinyl acetate in the reaction temperature range of 25–60°C and found that the immobilized [EMIM][NTf_2] can stabilize the lipase against inactivation and maintain good enantioselectivity [152]. Furthermore, Paun's group via grafting *1,3*-dimethyl-*3*-(*3*-triethoxysilylpropyl)-imidazolium tetrafluoroborate or bis{(trifluoromethyl) sulfonyl} imide on to the silica supports succeeded in preparing the immobilized ionic liquids, by use of which as the catalysts the research group tested the acylation of three different sulfonamines: benzenesulfonamine, *p*-nitrobenzenesulfonamine, and *p*-methoxybenzene-sulfonamine with acetic acid, acetic anhydride, and maleic anhydride. They proposed that the prepared immobilized ionic liquids catalysts demonstrated good activity and stability for the acylation of sulfonamines and the corresponding *N*-acylsulfonamines could be cleanly synthesized under the mild conditions [153]. Besides, Coman et al. have prepared successfully, mesoporous MCM-41 immobilized ionic liquids and ionic liquids-metal triflate catalysts via grafting method, and they used these catalysts to promote acylation of amines and sulfonamides with carboxylic acids. The results showed that the synthesized materials were efficient catalysts for the acylation of amines under green and mild conditions and with a very high atom economy by directly using acetic, propionic, and butyric acids as acylating agents instead of acid anhydride. These catalysts also exhibit good catalytic properties for the synthesis of *N*-acylsulfonamides from sterically and electronically diverse aromatic substrates, but in that case, the acylation can take place only when the acetic anhydride is used as acylating agent [154].

For the application of the immobilized ionic liquids to the acylation (although the advantages are obvious, such as the simplification of the product isolation), the realization of the continuous reactions, the leaching of the ionic liquids, and the inactivation of the catalysts because of carbon distribution are still the problems urgently needed to be resolved. Therefore, the interaction of the ionic liquids with supports, the recovery of the supported catalysts, and so on need the in-depth and intensive research.

2.4 Remarks

Ionic liquids used as the green solvents could avoid the utilization of volatile hazardous organic solvents, simplify the product isolation in the homogeneous catalytic reaction systems, and provide the access to the recovery and reuse of the catalytic systems as well; besides, it can avoid the pollution. Furthermore, the ionic liquids could act as the catalysts, ligands, or supports of reagents through the functionalization of the ionic liquids.

At present, the ionic liquids have been extensively employed for the alkylation, acylation, cyclization, condensation, addition, oxidation, reduction, esterification, hydrogenation, and inorganic porous materials, nanoparticles synthesis, and so on. This chapter only demonstrated the applications of ionic liquids for the two unit reactions: alkylation and acylation. According to the reports concerning the ionic liquids, it is clear that a great progress has been made, and the future of the ionic liquids is suggested to be considerably promising. However, many issues on ionic liquids, like the high cost in synthesis, difficulties in purification, the lack of the physical and chemical or thermodynamic data, the deficiencies in the characterization methods, and incomprehension of the promoting mechanism, remain to be resolved. In addition, although the ionic liquids from the beginning are labeled as the eco-friendly, green solvents, the greening of ionic liquid itself is still a problem kept to be solved. At the same time, the research workers should be addressed to develop the novel synthesis methods, techniques, and separation approaches to yield the ionic liquids with the features of green, high efficiency, energy saving, and low cost. Thus, it can lay the foundation of the large-scale applications of the ionic liquids. In a word, although the above issues need to be addressed, it is no doubt that the ionic liquids will play a significant role in the alkylation, acylation, and other unit reactions in terms of clean solvent or green solvent/catalyst.

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Chapter 3
Ionic Liquids as Green Solvents for Glycosylation Reactions

Kaname Sasaki, Daisuke Takahashi, and Kazunobu Toshima

Abstract This chapter deals with how we took advantages of unique properties of ionic liquids in glycosylation reactions, such as their tunability, basicity of anion moieties, and nonvolatility. Thus, we developed environmentally benign *O*- and *C*-glycosylation methods using glycosyl phosphates, glycosyl fluorides, methyl glycosides, and 1-hydroxy sugars in several ionic liquids.

3.1 Introduction

Ionic liquids are among the most promising alternatives to molecular organic solvents due to their unique properties and, in particular, are considered to be green solvents due to their nonvolatile and nonflammable nature [1–5]. Furthermore, the structures of ionic liquids can generally be modified, and thus, functionalized ionic liquids have attracted considerable attention [6, 7]. Carbohydrates are sustainable natural resources that can be converted to useful products via the fundamental and important glycosylation reaction. We have developed a simple, easy, and environmentally benign glycosylation method, namely, *green glycosylation*, using ionic

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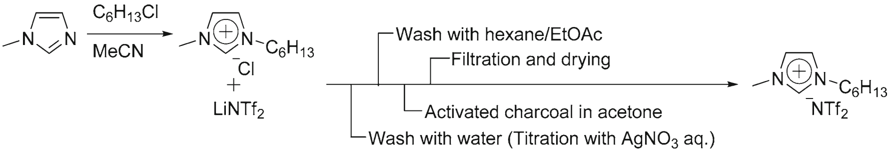
liquids [8]. Glycosylations in ionic liquids have been reported by Yadav et al. [9], Poletti et al. [10–12], and Pakulski [13]. In this chapter, we discuss advantageous features of ionic liquids as used in glycosylation reactions.

3.2 Preparation of Acid-Ionic Liquids

Our initial investigation of glycosylations in an ionic liquid suffered from a lack of reproducibility. We ultimately realized that chloride anions, which are the most likely expected impurity, are detrimental to the glycosylation reaction [14]. In order to prepare a chloride-free ionic liquid, we adopted the procedure shown in Scheme 3.1, with 1-hexyl-3-methylimidazolium trifluoromethanesulfonimidide ($C_6mim[NTf_2]$) as an example.



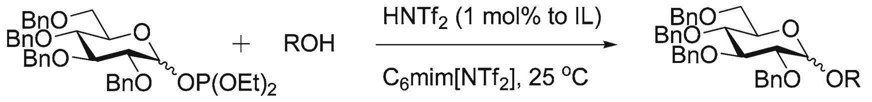
Scheme 3.1 Procedure for preparation of chloride-free ionic liquids

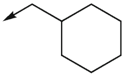
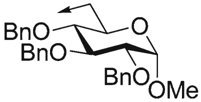
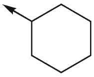
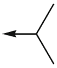
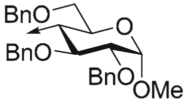
Instead of using the generally and widely employed ethyl or butyl groups, we selected the longer hexyl chain as the second substituent on the imidazolium because of its greater hydrophobicity, which made it more suitable for a water-wash at a later step. *N*-Methylimidazole was alkylated with hexyl chloride to give the imidazolium chloride followed by anion exchange in water. The reaction gave a biphasic system after the anion metathesis. The organic layer was separated and washed with water. Titration of the water washings with Ag^+ ensured complete removal of chloride ions. The chloride-free mixture was then washed with organic solvent to ensure removal of any nonionic impurities such as *N*-methylimidazole and hexanol produced in the previous step. Decolorization of the mixture with activated charcoal was followed by drying under high vacuum with heat. Lastly, a protic acid possessing the anion moiety of the ionic liquid as a conjugated base was added to prepare the "acid-ionic liquid" (acid-IL).

3.3 Reusability of Acid-Ionic Liquids

Nonvolatility and immiscibility with a wide range of organic solvents are among the main virtues of ionic liquids. We have demonstrated the usefulness of these virtues in glycosylations. In this section, we discuss glycosylation reactions with a glucosyl phosphite [15–23] and the reusability of the acid-ionic liquid [14]. The acid-ionic liquid $C_6mim[NTf_2]$ with $HNTf_2$ worked well as an activator and as a reaction medium in the glycosylations of several acceptors including aliphatic alcohols and

Table 3.1 Glycosylations of perbenzylated glucosyl phosphite in $C_6mim[NTf_2]$ with $HNTf_2$



R =		$\leftarrow C_8H_{17}$	
	91% (α:β = 18:82)	99% (α:β = 17:83)	84% (α:β = 23:77)
			
	88% (α:β = 20:80)	99% (α:β = 25:75)	63% (α:β = 57:43)

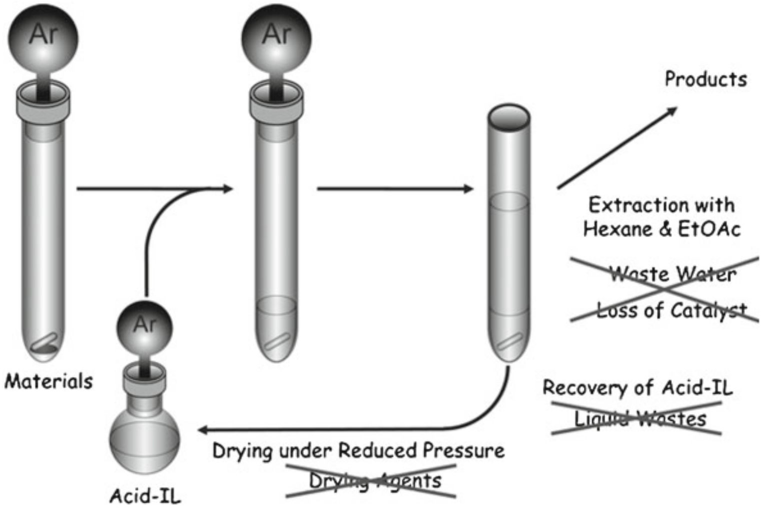


Fig. 3.1 General procedure for glycosylations in acid-ionic liquids

for reactions based on carbohydrates with perbenzylated glucosyl phosphite, as shown in Table 3.1. This glycosylation proceeded in good yield with β-stereoselectivity, except in the case of highly hindered 4-OH on glucose as an acceptor.

The general procedure for the glycosylation is illustrated in Fig. 3.1. No predrying agents are required to dry the reaction media because the acid-ionic liquids can be dried under high vacuum in advance. The ionic liquid was added to the mixture of glycosyl donor and acceptor under a dry argon atmosphere. After completion of the reaction, the products were extracted with a mixture of 5:1 hexane-ethyl acetate without either neutralization or quenching with water, and the combined extracts were purified to obtain the glycosides.

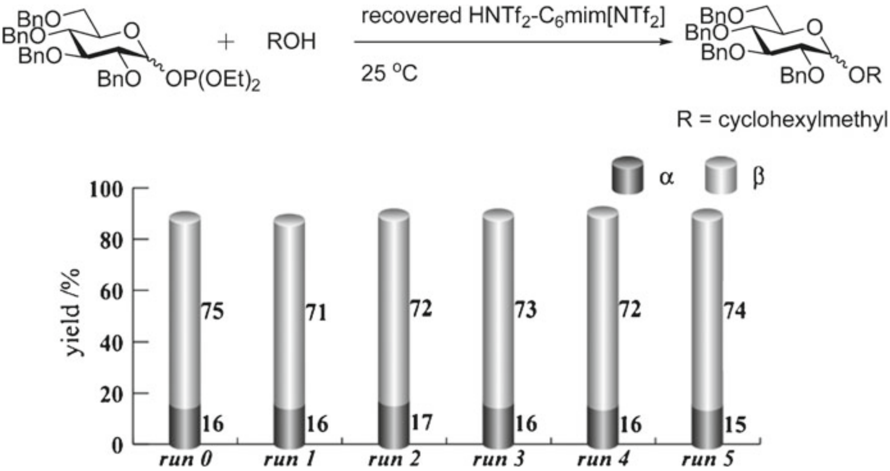
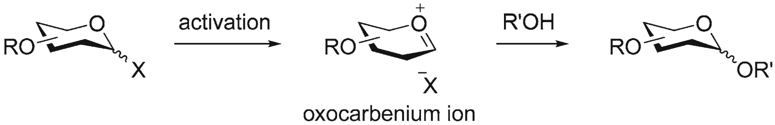


Fig. 3.2 Reusability of an acid-ionic liquid for glycosylation reactions

The used acid-ionic liquid was recovered and its reusability investigated. It was dried following the same procedure employed when first prepared and then used for the glycosylation of cyclohexylmethanol with the glucosyl phosphite (Fig. 3.2). The recovered acid-ionic liquid could be reused at least five times without any loss in efficiency or need for addition of any further protic acid.

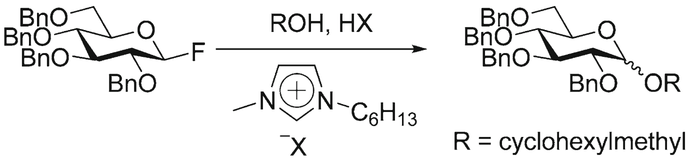
3.4 Tunability and Basicity of Ionic Liquids

In the course of our research, we realized that the stereoselectivity of the glycosylation reaction was dependent on the nature of selected ionic liquids. In this section, we discuss the glycosylation with glucosyl fluoride [24] and the tunability of ionic liquids including a correlation between the basicity of their anion moiety and the stereoselectivity of the glycosylation [25]. Generally, the mechanism of most glycosylation reactions is thought to involve a glycosyl oxocarbenium ion (Scheme 3.2), and we are of the opinion that the anions from the reaction media interact with this oxocarbenium ion to affect the stereochemical outcome. The work reported from Mukaiyama laboratory clearly demonstrated the possibility that the conjugated bases of the activator strongly affected the anomeric selectivity in the glycosylations with glucosyl fluoride in a molecular organic solvent [26].



Scheme 3.2 General mechanism of the glycosylation reaction

Table 3.2 Glycosylations of glucosyl fluoride in various acid-ionic liquids



X	yield /%	α:β ratio	δ of imidazolium 2-H
NTf_2	86	2.13: 1	8.43
ClO_4	83	1:2.33	8.78
OTf	89	1:3.17	8.90

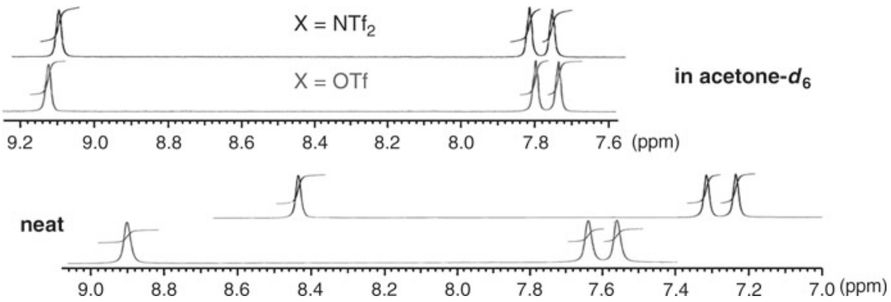


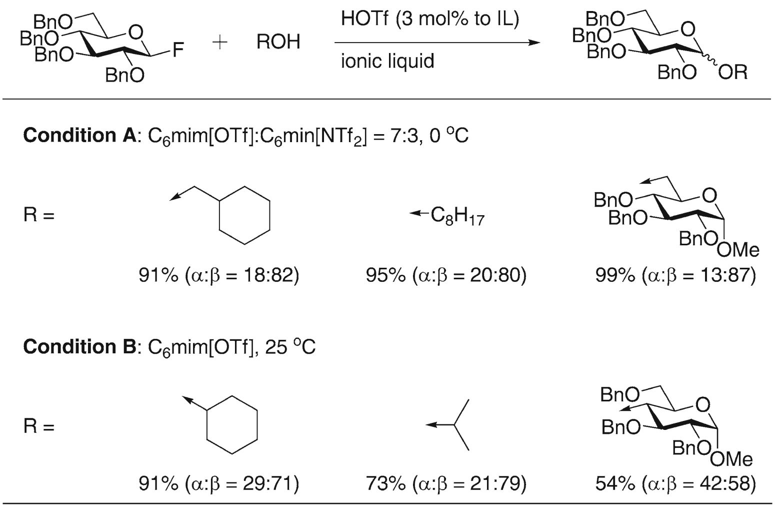
Fig. 3.3 ^{1}H-NMR spectra of C_6minXs in acetone-d_6 and neat

Indeed, the stereoselectivity in glycosylation reactions with glucosyl fluoride was strongly affected by the anion moiety of the ionic liquid employed, as shown in Table 3.2.

We speculated that the stereoselectivity in these reactions varied with the basicity of the anion moiety of the ionic liquids. The ^{1}H-NMR spectra of C_6mim[OTf] and C_6mim[NTf_2] in dilute acetone-d_6 were almost identical, while the spectra of the neat compounds were quite different. The expanded spectra of the protons on the imidazolium ring in the two compounds are shown in Fig. 3.3. The protons of C_6mim[OTf], which gave the higher β-stereoselectivity, appeared at a much lower field than those of C_6mim[NTf_2].

We referred to Avent et al.'s work [27] to interpret these spectra. We assumed that both of the ionic liquids were solvated to free ions in acetone, while the cation and the anion interacted somehow under solventless conditions, with the chemical shifts indicating the relative basicity of these anions. In fact, as can be seen in Table 3.2, the β-stereoselectivity of the glycosylation reactions with glucosyl fluoride was

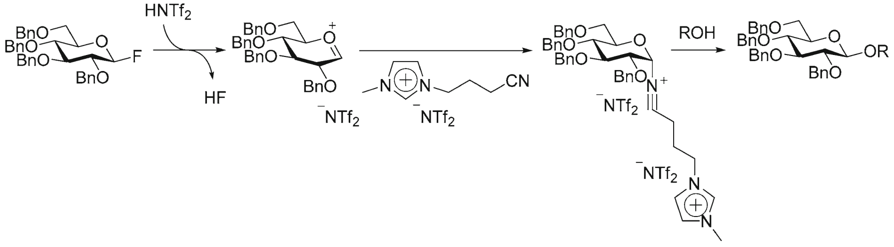
Table 3.3 Glycosylation of perbenzylated glucosyl fluoride in an acid-ionic liquid



correlative to the chemical shift of the imidazolium H-2 or, in other words, the basicity of the anion moiety. Actually, a similar study from the Poletti laboratory revealed that the triflate anion from an ionic liquid could afford a glycosyl triflate at low reaction temperature, indicating that anions from ionic liquids possess a coordinating ability to the oxocarbenium ion [10, 11].

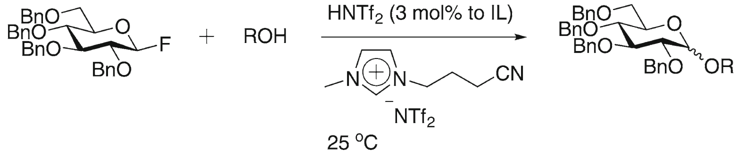
When we attempted to achieve higher stereoselectivity by lowering the temperature, we met with a dilemma; we wanted to keep the reaction temperature low to stabilize the α-triflate so as to obtain the higher β-stereoselectivity, but ionic liquids based on the triflate anion are solids at lower temperatures (melting point ~15°C for C_6mim[OTf]). The solution to this problem was to use a mixture of C_6mim[OTf], which induces β-stereoselectivity, and C_6mim[NTf_2], which has the lower melting point. In fact, a 7:3 mixture of C_6mim[OTf] and C_6mim[NTf_2] worked well for the glycosylation of several alcohols and particularly primary substrates at 0°C (Condition A in Table 3.3). Less reactive secondary alcohols required 25°C to obtain a better yield (Condition B).

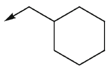
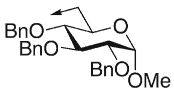
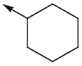
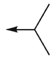
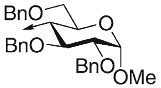
We next turned our attention to modification of the cation moiety in order to impart a coordinating ability to the reaction media. We designed and prepared 1-(3-cyanopropyl)-3-methylimidazolium trifluoromethanesulfonimidide as a reaction media and used it for glycosylation reactions with glucosyl fluoride. In organic solvents, α-nitrilium ions generated from glycosyl cations and nitrile groups have been known as β-directing intermediates since the 1980s [28]. We demonstrated the same kind of β-directing coordination of a cyano group on the side chain of the imidazolium cation onto the glycosyl oxocarbenium ion in reactions run in ionic liquids (Scheme 3.3). This β-directing effect could be generalized to glycosylations of several alcohols, as shown in Table 3.4.



Scheme 3.3 Plausible mechanism of β-stereoselective glycosylation in an ionic liquid possessing a cyano substituent on its cation moiety

Table 3.4 Glycosylations of glucosyl fluoride in an acid-ionic liquid possessing a cyano group on the side chain

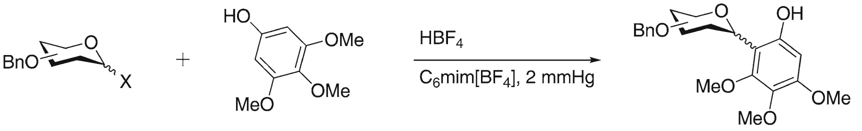


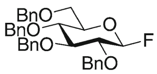
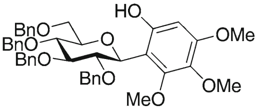
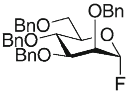
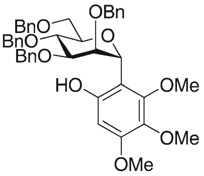
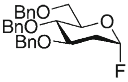
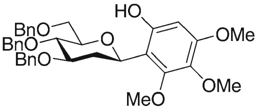
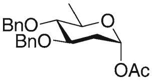
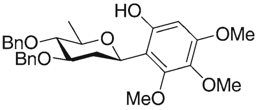
R =	 85% (α:β = 23:77)	$-C_8H_{17}$ 73% (α:β = 27:73)	 76% (α:β = 30:70)
	 99% (α:β = 27:73)	 76% (α:β = 30:70)	 31% (α:β = 35:65)

3.5 Nonvolatility of Ionic Liquids

One of the biggest advantages of ionic liquids over conventional organic solvents is their nonvolatility. When we attempted *C*-glucosylation of 3,4,5-trimethoxyphenol with glucosyl fluoride in C_6mim[BF_4] with HBF_4, the desired *C*-glucoside was generated only in 40% yield, accompanied by significant amounts of the hydrolyzed glycosyl donor under ambient pressure. To ensure that the reaction conditions remained anhydrous, we then carried out the same reaction under reduced pressure and managed to eliminate the hydrolysis side reaction and improve the chemical yield to 60%. This example revealed that the nonvolatility of ionic liquids can be used to remove water from the reaction mixture in water-sensitive reactions.

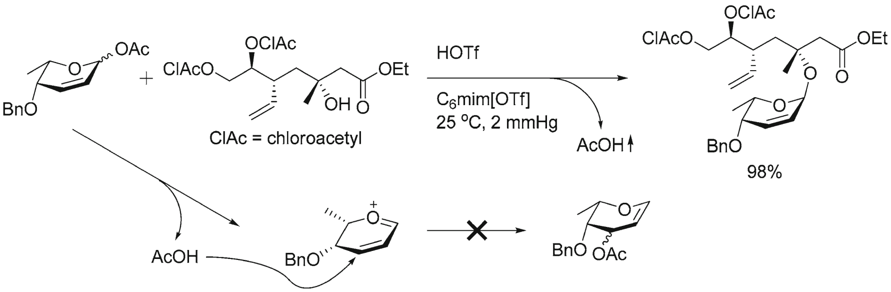
Table 3.5 *C*-Glycosylations with 3,4,5-trimethoxyphenol



Donor	HBF$_4$ /mol% to IL	Temp. /°C	Product
	1.0	60	 60% (40% under 760 mmHg)
	0.5	60	 82%
	0.5	25	 93%
	1.0	25	 98%

This *C*-glycosylation reaction developed in our laboratory turned out to be applicable to several glycosyl donors, as shown in Table 3.5 [29].

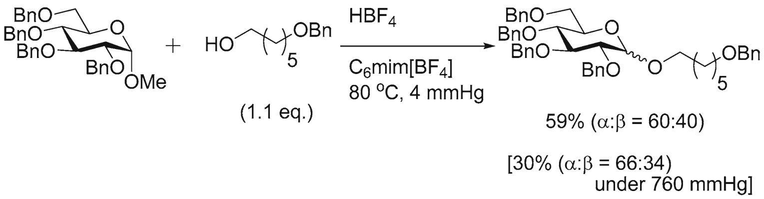
Reducing the reaction pressure was also effective for removing by-products during the course of the reaction. We have developed a methodology for introducing highly deoxygenated sugars into hindered alcohols using hex-2-enopyranosyl donors in organic solvents [30]. When we attempted a glycosylation of a less reactive β-oxo-*tert*-alcohol with hex-2-enosyl acetate, however, the leaving acetate created a problem due to retro-Ferrier-type rearrangement, and the reaction did not provide any desired products. We, therefore, employed an acid-ionic liquid instead of organic solvents and carried out the reaction under reduced pressure to remove the by-product, acetic acid. These conditions inhibited the undesired reaction path and gave the desired glycoside in excellent yield (Scheme 3.4) [31].



Scheme 3.4 Glycosylation of a β-oxo-*tert*-alcohol with a hex-2-enosyl acetate

Based on our previous findings, we have recently developed effective glycosylations with methyl glycosides [32, 33] and 1-hydroxy sugars [34–40] as glycosyl donors [41]. These glycosyl donors are supposed to give methanol or water as a by-product, which obviously does harm as a competitive glycosyl acceptor. We anticipated that these side reactions are avoidable by reducing the reaction pressure.

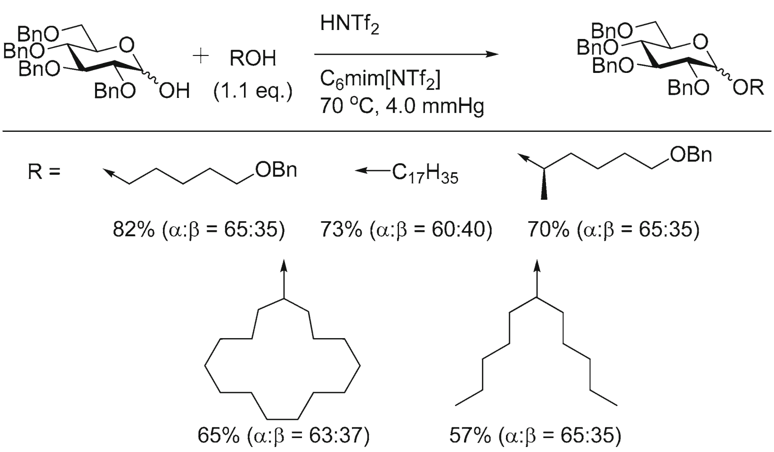
Methyl glucoside could be activated in C_6mim[BF_4]/HBF_4 at 80°C under 4 mmHg and coupled with monobenzylated hexanediol in 59% yield, which was better than that under 760 mmHg (30% yield) (Scheme 3.5).



Scheme 3.5 Glycosylations of methyl glucoside using an acid-IL under reduced pressure

2,3,4,6-Tetrabenzylglucose afforded the same glycoside in even better yield (82%) in C_6mim[NTf_2]/$HNTf_2$ at 70°C under 4 mmHg. We also examined the scope and limitations of these reaction conditions with alcohols including less reactive secondary substrates, as shown in Table 3.6. It was found that the glycosylation of inactive 1-hydroxy sugars with nearly stoichiometric amounts of various alcohols in an acid-IL under reduced pressure conditions proceeded effectively to give the corresponding glycosides in good to high yields.

Table 3.6 Glycosylations of 1-hydroxy sugars in an acid-IL under reduced pressure



3.6 Conclusions

The properties of ionic liquids in respect of their application to glycosylation reactions were reviewed. The immiscibility of ionic liquids with organic solvents/water was utilized in preparing chloride-free acid-ILs. The tunability of ionic liquids and the basicity of their anion moieties were found to be advantageous (compared to organic solvents) for inducing β-stereoselectivity. Furthermore, the nonvolatility of ionic liquids enabled the removal of undesired by-products from various reaction mixtures, which enhanced the efficiency of the glycosylation reactions. We believe that the knowledge obtained through these experiments will help us to apply this class of “green” solvents in many other organic synthetic reactions.

Acknowledgment The authors want to thank all the coworkers who have worked on this project presented here, Dr. Hideyuki Nagai, Ms. Chigusa Yamada, Mr. Yoshitaka Kuroiwa, Mr. Satoshi Tomono, and Ms. Maiko Sekine in Keio University, Japan.

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Chapter 4
Ionic Liquid Crystals

Valerio Causin and Giacomo Saielli

Abstract Ionic liquid crystals (ILCs) are emerging as interesting materials since they are expected to combine together the technological properties of ionic liquids (ILs) and liquid crystals (LCs). In this chapter, we will present a survey of the literature of the last 5 years, from 2005 to mid-2010 concerning ILCs. The chapter is divided into four sections: ILCs based on organic cations (and anions), metal-based ILCs and polymeric ILCs, and applications of ILCs.

4.1 Introduction

Ionic liquid crystals (ILC) are a new class of materials that can be viewed either as ionic liquids (IL) which, on cooling, exhibit one or more mesophases (or liquid-crystal phases) or as liquid crystals (LC) made of ions. These two complementary perspectives, in fact, can also be linked to a microscopic or macroscopic level of description, respectively: at a molecular level, ILCs are hardly distinguishable from ILs (actually above the clearing point, they are ILs) since the long-range orientational and/or translational order of the mesophases is a macroscopic property while the local structure of isotropic, nematic and smectic phases is dominated by short-range molecular interactions. In contrast, at the macroscopic level, ILCs are in all respects LCs, since the behavior of the material depends on the structure of the phase. Thus, ILCs are nowadays attracting some interest because they are expected to combine together the many interesting technological applications of ILs and LCs, the former being largely discussed in the other chapters of this

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A. Mohammad and Inamuddin (eds.), *Green Solvents II: Properties and Applications of Ionic Liquids*, DOI 10.1007/978-94-007-2891-2_4,

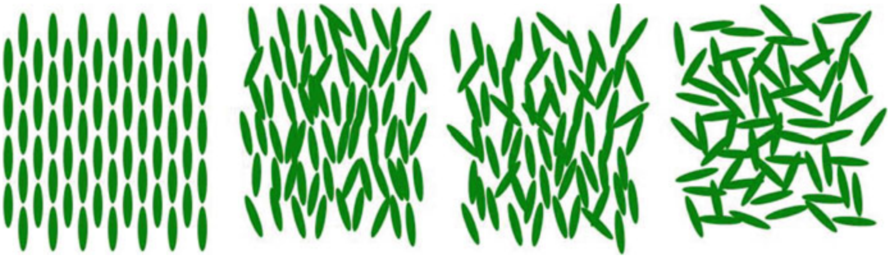


Fig. 4.1 Schematic representation of (from *left* to *right*) the crystal (K), smectic (Sm), nematic (N) and isotropic (I) phases

book while the latter ones can be found in recent reviews [1]. However, based on Murphy's law, we have to be prepared to find out that they will also combine together the negative features of the two class of compounds, particularly high viscosity. ILs are generally more viscous than dipolar liquids because of strong electrostatic interactions; LCs are generally more viscous than isotropic liquids because of long-range order; thus, ILCs are expected to be quite viscous fluids. Nevertheless, the field is still in its infancy, and thus, there is plenty of room for improvements.

Since this book is devoted to ILs, there is no need to introduce them here; however, a short summary concerning the structure and properties of LCs might be useful for the reader.

Liquid crystal phases, or mesophases, are characterized by a partial order, intermediate between the full orientational and translational disorder of the isotropic liquid phase and the full orientational and translational order of the crystalline phase. Thermotropic liquid-crystal phases are obtained for a given compound (or possibly a mixture) as a function of temperature, while the so-called lyotropic liquid-crystal phases are obtained as a function of the concentration of a given solute in a solvent. Typical examples of the latter systems are the various types of aggregates formed by amphiphilic molecules either in water or in organic solvents. In this chapter we will be interested only in thermotropic systems. An interesting review on lyotropic ionic liquid crystals can be found in Ref. [2].

Schematically, the two most common types of mesophases can be depicted as in Fig. 4.1, together with the well-known isotropic and crystal phases.

The isotropic phase, usually indicated as I, is characterized by the absence of any long-range order, either orientational or translational. Orientation and position of the molecules are distributed at random. Although locally ordered structures are present in real liquids, the phase is macroscopically isotropic; thus, no preferential directions can be identified. On the other side, the well-known crystal phase, K, is characterized by a full order, both translational and orientational, with a unit cell which is replicated over the three directions.

Starting from the isotropic phase and increasing the degree of order, we may encounter the nematic phase, N. This is characterized by a long-range orientational order: molecules are, on average, oriented along a common direction. The unit vector defining that direction is called the director, **n**. No translational order is present in the nematic phase; thus, as far as the center of mass of the molecules is concerned, there are no differences between a nematic and an isotropic liquid phase. In contrast, a smectic phase, Sm, has a partial long-range translational order, in addition to the orientational order also present in the nematic phase: in fact molecules are arranged in layers and the molecules are oriented, on average, perpendicularly to the plane defined by the layers. In the least ordered smectic phase, SmA, molecules are disordered within the layer and there is no correlation between adjacent layers. SmC phase is similar, except that the director **n** forms an angle with respect to the layer normal axis. This is because molecules are tilted with respect to the normal of the plane defined by the layers. In the SmB phase, molecules are again aligned with the layer normal axis, but, in addition, they have a short-range translational order within the plane with molecules arranged in hexagonal fashion. Several other types of smectic phases having a higher degree of order exist. Other types of mesophases are formed by disklike molecules, such as cubic and columnar. We refer the reader to the specialized literature existing on the subject. Moreover, since this book is devoted to ionic liquids we will be mainly concerned with low-order mesophases.

It is well known that ILs can form thermotropic mesophases. However, the most common type of organic ionic molecules, where a polar head is linked to a relatively long chain, usually form smectic-type mesophases. The microphase segregation is thought to be the origin of this marked preference for smectic-type liquid crystals by ionic compounds, in contrast to nonionic systems which often form nematic phases. However, microphase segregation is found also in the isotropic liquid phase of some ILs or in water/organic solvent mixtures; thus, in principle, ionic nematic phases should be observed. A theory of the stability of ionic mesophases has been presented recently [3]. Though the range of stability of ionic smectics was predominant, ionic nematics were also predicted. In fact a limited number of these latter phases have been reported recently and will be discussed in the following sections.

For a large number of systems, the mesogenic unit is based on quaternized nitrogen salts, often imidazolium derivatives. The salts of these cations have low melting points, and, hence, they are a good starting point to obtain room temperature ILCs. Phosphonium salts can also form mesophases. A relatively minor number of systems are found where the mesogenic unit is given by the anion. Finally, several metallomesogens are known.

The last comprehensive review about ILCs, by Binnemans, dates back to 2005 [4]. Rapid progresses in these last 5 years lead us to believe that a critical assessment of the state-of-art in the field of ILCs would be beneficial for the scientific community. Thus, in this chapter, we report on the advancements in ILCs science, reviewing the literature published during 2005–2010 and highlighting the technological applications that have been recently proposed.

4.2 Ionic Liquid Crystals Based on Organic Cations and Anions

In Table 4.1, we report a summary of the various types of mesophases based on organic systems that have been reported in the literature between 2005 and 2010. They are discussed in the next paragraphs and are grouped depending on the chemical structure of the mesogenic core.

Table 4.1 Type of ionic mesophases based on organic cations and their respective references

Type of mesophase	References
Nematic	[5–7]
Smectic	[5–38]
Columnar/cubic	[8, 17, 31, 39–52]

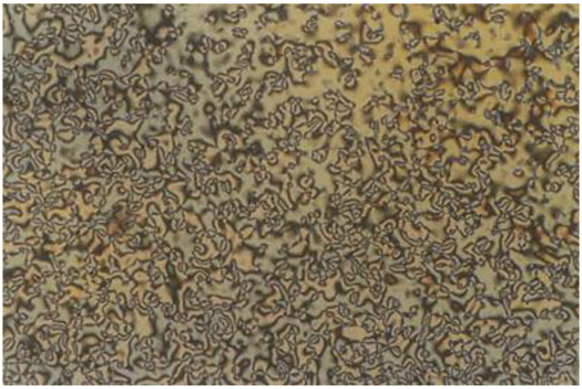
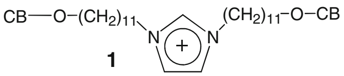


Fig. 4.2 Schlieren texture of the nematic phase of 1 (Tf_2N^- salt) (Reproduced from Ref. [6] with kind permission of © The American Chemical Society)

4.2.1 *Imidazolium-Based Ionic Liquid Crystals*

One of the few examples of ionic nematic (monotropic phase) was reported by Cardinaels and coworkers [6]. The Tf_2N^- imidazolium salt **1**, symmetrically substituted with two mesogenic cores of alkoxycyanobiphenyl, showed a nematic phase between 47°C and 31°C. Typical schlieren textures are shown in Fig. 4.2.

However, smectic phases are, by far, the most abundant kind of mesophases reported for ionic systems. Analogous compounds with only one cyanobiphenyl group or one or two pendant cholesterol units, **2**, **3**, and **4**, with Br^-, Tf_2N^-, and $Eu(tta)_4^-$ (tta^- = 2-thenoyltrifluoroacetonate) only showed SmA or chiral SmA.



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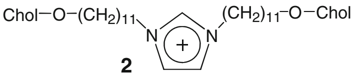

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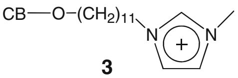

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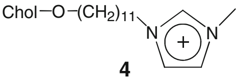

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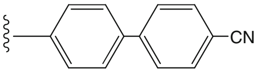
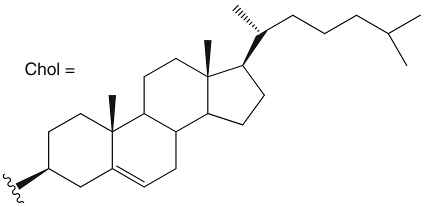


Chol =



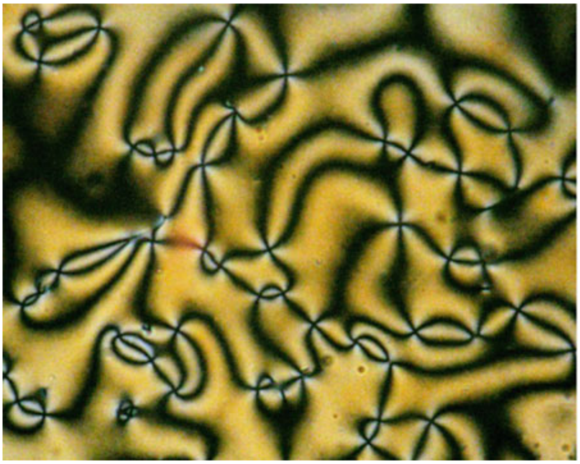
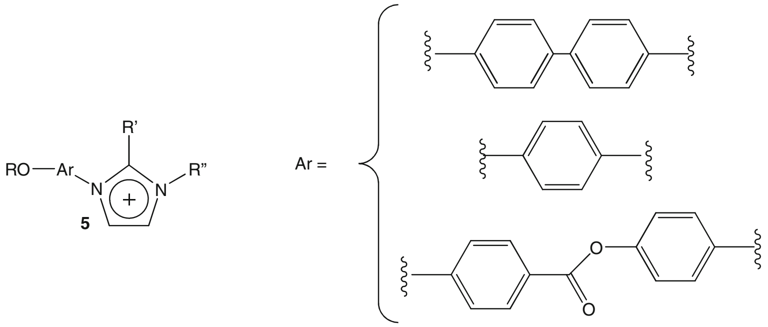


Fig. 4.3 Schlieren textures of SmC phase of the symmetric nonyl derivative 1 (bromide salt) at 90°C with only four-brush defects (Reproduced from Ref. [31] with kind permission of © Elsevier)

It was found that the most stable mesophases were obtained with Tf_2N^- salts, and the cholesterol group is a more stronger mesogenic promoter than the cyanobiphenyl group. Similar bromide salts of cyanobiphenyl dimeric systems **1** were synthesized by Pal and Kumar [31] using microwave irradiation, either symmetric with a nonyl chain, or asymmetric with alkyl chains of 9 and 4, and 9 and 6 carbon atoms, respectively. An SmC phase was observed on cooling for all three examples investigated (Fig. 4.3). Analogous bromide salts of imidazolium-based dimers, but bearing two alkoxytriphenylene moieties rather than a CB substituent, formed a columnar mesophase [31]. Notably, the imidazolium compound substituted with a calamitic and discotic core did not show any mesomorphism.

Kower and Swager also attached rigid anisotropic cores, such as biphenyl and phenylbenzoate, to several substituted imidazolium salts, **5**, of I^-, ClO_4^-, BF_4^-, PF_6^-, $C_{12}H_{25}SO_3^-$ [26]. In all cases, a stable SmA phase was observed with a variable degree of interdigitation of the alkyl chains.



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A different mesogenic core, 4-(4-nitrophenylazo)phenyloxy, was attached to the imidazolium core by Zhang et al. [24].

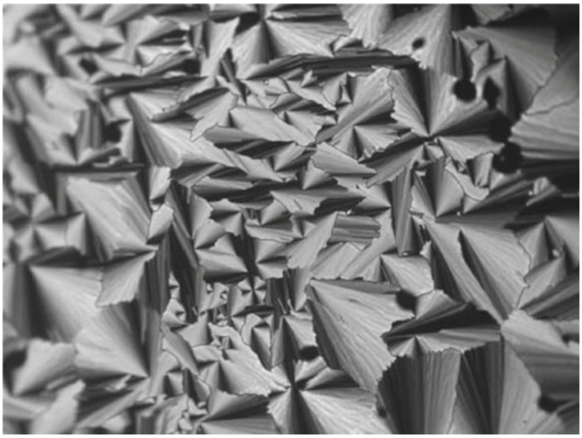
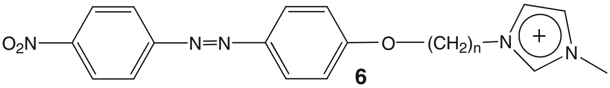


Fig. 4.4 Fan textures of the SmA phase of [C_{10},C_6(2-OH)-im]Br at room temperature (Reproduced from Ref. [32] with kind permission of © The Royal Society of Chemistry)



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Bromide and tetrafluoroborates salts of compound **6** with alkyl chain of 3, 6, and 10 carbon atoms were prepared. While the short chain salts were nonmesomorphic, focal-conic fan textures typical of an SmA phase were observed for n = 6 and n = 10 homologues. The longer chain also resulted in a wider range of thermal stability of the smectic phase. For example, for the BF_4^- salt of **6** the SmA range was from 115°C to 149°C for n = 3 and from 104°C to 165°C for n = 10. In all cases, a strong supercooling of the SmA phase up to room temperature was observed.

The SmA phase was observed with *N*-substituted-*N*-methylimidazolium (*N*-substituted-mim) with *p*-alkoxybenzyl groups [10, 33] (with Br^-, BF_4^-, PF_6^-, SCN^-, $CF_3SO_3^-$, Tf_2N^-) and with *p*-alkoxyphenyl groups [15] (with I^-, BF_4^-, PF_6^-, $CF_3SO_3^-$). Mesomorphism was reduced, in favor of the isotropic liquid, by increasing the chain length from 8 to 14, and with the bulky and low-coordinating Tf_2N^- anion. The interplay between the chain length of *N*-alkyl-mim and alkylsulfonates was investigated in Ref. [19]. An SmA phase observed only for the case of octyl chains for both cation and anion was stable from 78.9°C to 114°C. The effect of water of crystallization on the stability of the SmA phase of C_{12}mim and C_{14}mim bromides was investigated in Ref. [22]. It was found that the H_2O molecule increases the transition temperatures of both the K-SmA and the SmA-I transitions. Metastable smectic phases were observed for [C_{18}mim][Cl] and [C_{16}mim][Cl] which only served as a nucleation for the stable crystal phases [36].

Disubstituted imidazolium salts also show smectic phases, e.g., [$C_{12}C_{12}$Im][BF_4] and [$C_{12}C_{12}$Im][ClO_4] [11]. A significantly larger temperature range of stability of the SmA phase was observed by Chiou et al. [32] for disubstituted imidazolium salts bearing a hydroxyl group on one arm (Figs. 4.4 and 4.5).

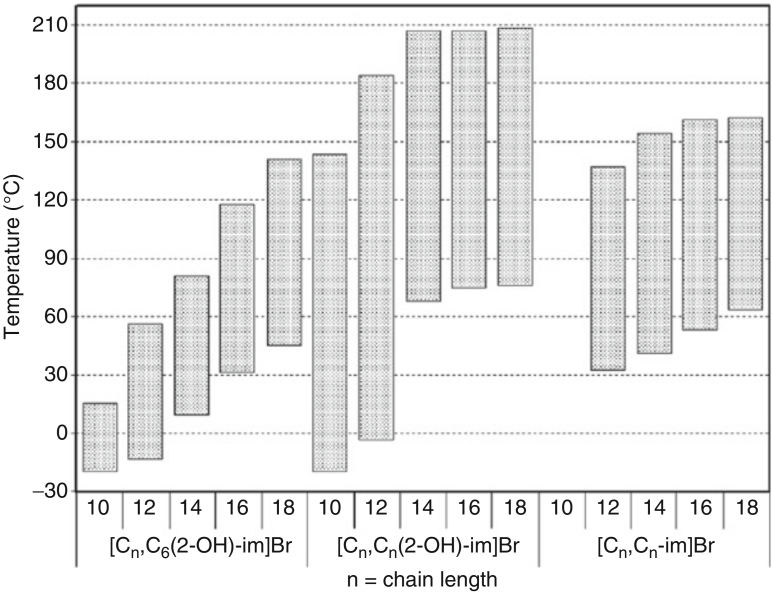
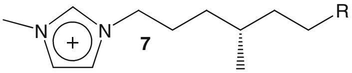


Fig. 4.5 Phase transition behavior of $[C_n,C_6(2\text{-}OH)\text{-}im]Br$, $[C_n,C_n(2\text{-}OH)\text{-}im]Br$ and [Cn,Cn-im] Br upon heating (Reproduced from Ref. [32] with kind permission of © The Royal Society of Chemistry)

Chiral ILCs based on citronellyl-derived mim salts **7** of I^-, Br^-, BF_4^-, PF_6^-, SCN^-, and OAc^-, with R ranging from hexyl to dodecyl, were found to have a wide range of stability of SmA phases, from about 0°C up to about 170°C [13].



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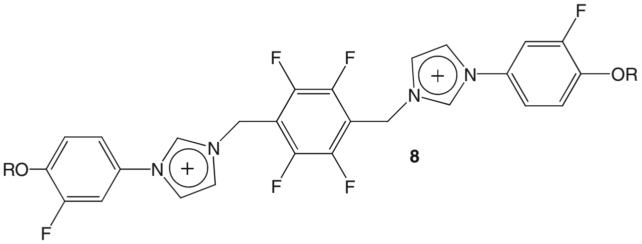
Interestingly, the mesophase dependence on the counteranion was found to correlate with the chemical shift of the acidic H2 proton revealing the importance of the ion-pair contacts in the formation of the mesophase.

The SmA phase was also observed for dicationic imidazolium-based ILCs **8** with chloride and Tf_2N^- as counteranions [14].



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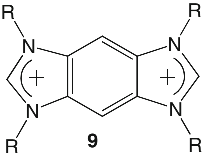
The effect of the presence of fluoro substituents either on the central phenyl ring or in the two side phenyl rings was examined, and it was found to affect significantly the thermal range of stability of the smectic phase.

Bis- and trisimidazolium salts of I^-, BF_4^-, and Tf_2N^-, bearing a hydrophobic hexadecyl chain and a bridging mesitylene moiety were described in Ref. [25]. Some of the compounds showed an SmA phase stable over a large temperature range, from room temperature to ca. 150°C. The systems also exhibited a significant supercooling.

Dicationic salts were also reported by Bielawski and coworkers: Br^-, BF_4^-, $MeSO_4^-$, and PF_6^- salts of benzobis(imidazolium) **9** and 5,5′-bibenz(imidazolium) **10** showed a smectic or cubic mesophase, persisting from 27.5 up to 216.2°C. The stability was generally found to increase with the increase in the *N*-alkyl chain length. An interesting feature of these systems was a high fluorescence yield [37].



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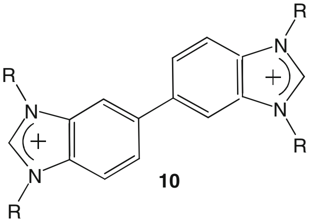

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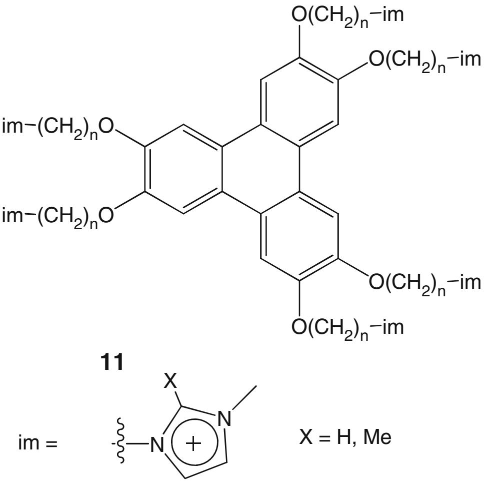
Mesophases were observed by combining pyridinylmethylimidazolium salts (acting as H-bond acceptors) with several alkoxybenzoic acids (acting as H-bond donors) [8]. Depending on the number of alkoxy substituents, SmC, rectangular columnar or cubic phases were observed for mono-, di-, and trisubstituted benzoic acids, respectively.



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Self-assembly was also exploited to make fluorescent columnar mesophases by ionic interaction of a central dianionic anthracene-2,6-disulfonate core with flexible 1-methyl-3-(3,4,5-trialkoxybenzyl)imidazolium units. *N*-Methylimidazolium and 2-methyl-*N*-methylimidazolium moieties **11** appended to a triphenylene core via alkoxy chains of 8, 10, 12, and 14 carbon atoms were prepared with BF_4^-, PF_6^-, and Tf_2N^- counteranions [40]. Cubic and/or columnar mesophases were observed in the range from about room temperature up to ca. 200°C for the long chain homologues while the octyl derivatives were only ionic liquids or displayed a limited range of thermal stability of the mesophase. Mixtures with simple imidazolium ILs improved the range of stability of the mesophases [35].

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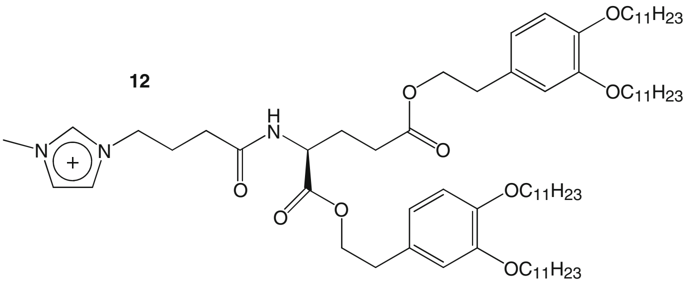

Columnar and cubic mesophases were also observed for imidazolium salts of bromide and Tf_2N^- (only Col_h in the latter case) substituted with a L-glutamic acid **12** although ionic conductivities were larger for the Col_h phase of the bistriflimide salt [44]. Counteranion effects (BF_4^-, PF_6^-, $CF_3SO_3^-$, Tf_2N^-) on the ionic conductivities in columnar ionic mesophases were measured for trialkoxybenzyl-*N*-methylimidazolium and analogous 2-methyl-*N*-methylimidazolium salts **13**, the optical textures of **13** is shown in Fig. 4.6 [46].

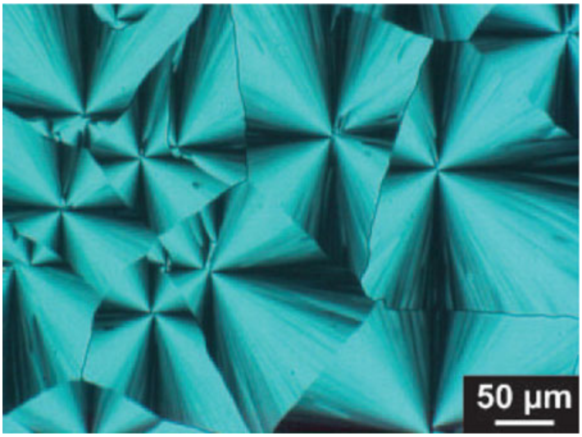

Fig. 4.6 Polarized optical micrographs of 13 (X = H, n = 17) in the Col_h phase at 57°C (Reproduced from Ref. [46] with kind permission of © The Chemical Society of Japan)

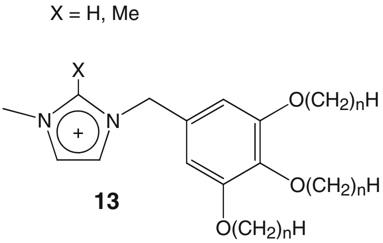

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Table 4.2 Thermal range of stability of the SmA phase of some pyrrolidinium ILCs, after Ref. [53]

Compound	SmA range/°C
$[C_{18}mpyr][Br]$	221–229
$[C_{19}mpyr][Br]$	216–233
$[C_{20}mpyr][Br]$	214–233
$[C_{18}mpyr][SCN]$	86–164
$[C_{19}mpyr]_2[UO_2Br_4]$	185–227
$[C_{20}mpyr]_2[UO_2Br_4]$	186–267

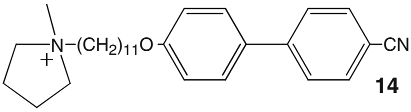
The same cation, but with an antracene-2,6-disulfonate, was investigated in Ref. [39] and, again, a hexagonal columnar mesophase was observed for the octyl, dodecyl and hexadecyl derivatives, with an increasing thermal range of stability with increasing chain length. In fact, the C16 compound had a Col_h phase from room temperature up to the decomposition temperature (240°C). In contrast, when the antracene-2,6-disulfonate anion was coupled with ammonium cations, mesophases were not observed [39].

4.2.2 *Pyrrolidinium-Based Ionic Liquid Crystals*

Some examples of pyrrolidinium-based ILCs have been reported in recent years, in all cases forming smectic phases, from low ordered SmA phases of de Vries type to highly ordered smectic phases of T type. These will be discussed in the following paragraphs.

Cardinaels and coworkers have prepared several *N*-alkyl-*N*-methylpyrrolidinium, $[C_n mpyr]$, compounds using Br^-, Tf_2N^-, BF_4^-, PF_6^-, SCN^-, $Eu(tta)_4^-$, and tetrabromouranyl ($UO_2Br_4^{2-}$) counteranions [53]. A rich polymorphism was observed, ranging from SmA phase to the highly ordered, and quite uncommon, smectic T phase. The absence of charge delocalization of the pyrrolidinium core seemed to be of crucial importance for the stabilization of the tetragonal lattice of the T phase. Of the many systems investigated, only few having long alkyl chains, showed the appearance of the SmA phase at relatively high temperatures, as shown in Table 4.2.

In a subsequent study [20], the authors attached pendant calamitic mesogenic cores to the pyrrolidinium cation, **14**, **15,** and **16**. In some cases, a low-ordered SmA phase of de Vries type was observed; in this phase, the molecules are tilted but without any correlation in the tilt direction.



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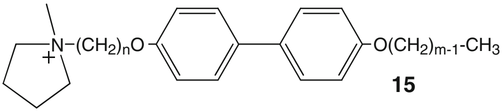

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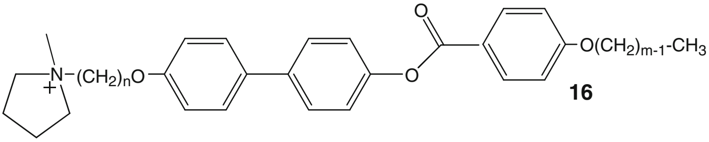

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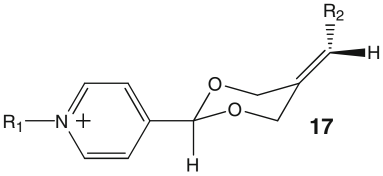
[C_{10}mpyr][Br] and [C_{12}mpyr][Br] were also investigated in Ref. [12]. The authors reported a detailed X-ray analysis of the crystal structure at room temperature.

4.2.3 Pyridinium and Bipyridinium-Based Ionic Liquid Crystals



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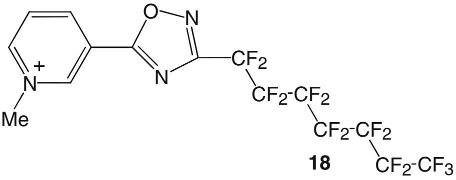
Chiral pyridinium salts having a 1,3-dioxane ring in their central core, with Br^-, I^-, BF_4^-, PF_6^-, Tf_2N^-, TfO^-, and CF_3COO^- were reported by Baudoux et al. [5]. Many compounds exhibited smectic phases while few showed chiral ionic nematic phases, N*, when optically pure, or ionic nematic phases when racemic. An example is the iodide salt **17** with R_1 = decyl and R_2 = *p*-BuOPh.

SmA phases were reported for the iodide salts of perfluoroalkylated-1,2,4-oxadiazolylpyridines **18** and **19**, between ca. 100°C and 150°C [30]. These compounds also showed luminescence and thermochromism, suggesting their useful application in optoelectronics.



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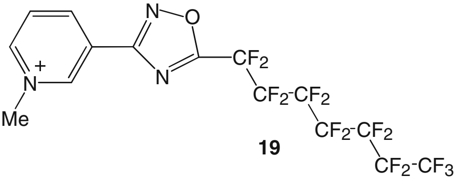

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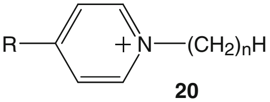
Similarly to the imidazolium **7** salts, citronellyl-based salts of pyridinium with I$^-$, Br$^-$, BF$_4^-$, PF$_6^-$, SCN$^-$, and OAc$^-$ as counteranions showed a stable SmA phase [13].

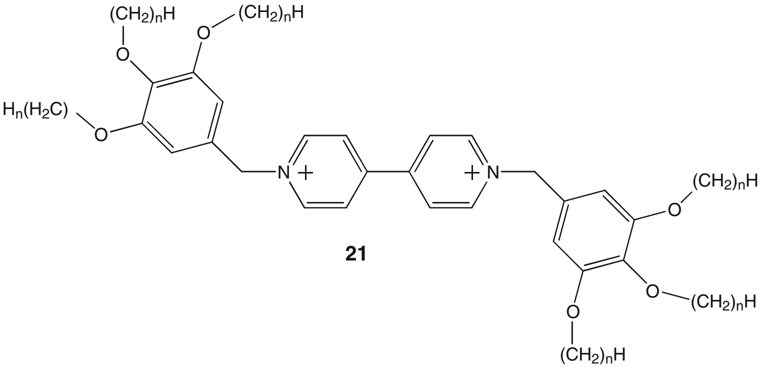


20

N-Alkylpyridinium salts **20** with alkyl chains from 14 to 22 carbon atoms and *p* substituents such as methyl, phenyl, and styryl groups (stilbazolium salts) with Cl$^-$, Br$^-$, I$^-$, BPh$_4^-$, and C$_7$H$_8$SO$_3^-$ counteranions were prepared by Ster et al. [27]. The stability of the SmA phase increased with the size of the anion, but no mesophase was observed with heptyl sulfonate.

Bipyridinium salts (also known as viologens) of Tf$_2$N$^-$ were reported by Bhowmik and coworkers [54, 55]. These systems showed an SmA phase in the range from room temperature to ca. 130–140°C. More recently, the effect of methylation of the bipyridinium core was studied by causin and Saielli: the augmented steric hindrance of the central core resulted in the destabilization of the smectic phase [56]. In contrast, unsymmetric viologens with relatively long alkyl chains exhibited an increased range of smectic phase, particularly in the true room temperature region, even though the type of smectic phase observed was more ordered than an SmA [9].

Viologen-based discotic ILCs were prepared by Kato and coworkers by alkylating bipyridine with trialkoxybenzyl substituents, **21** [47]. Columnar phases, either Col$_r$ or Col$_h$, were observed, the latter one found with shorter alkyl chains (octyl) and the former ones with longer alkyl chains (dodecyl and hexadecyl) having PF$_6^-$ as counteranion.



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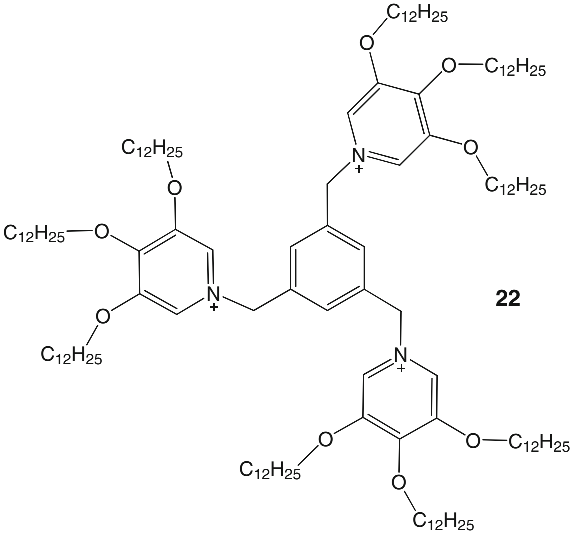
The same authors also investigated discotic ILCs formed with threefold symmetric pyridinium salts tethering tridodecyloxyphenyl substituents, **22**, with Br^-, BF_4^-, and PF_6^-. A Col_r phase for the larger PF_6^- anion, a Col_h phase for the smaller BF_4^-, and sequence of Col_h and Cub phases for the even smaller Br^- anions were observed [41].



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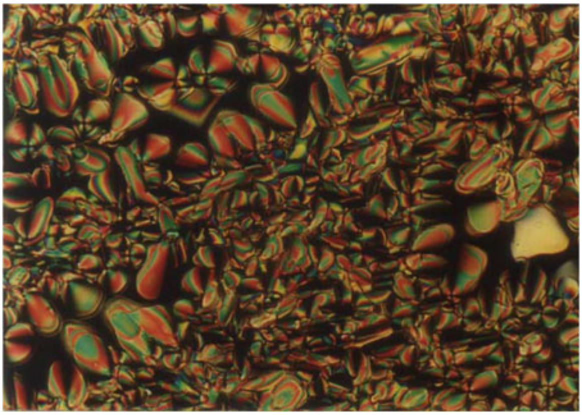
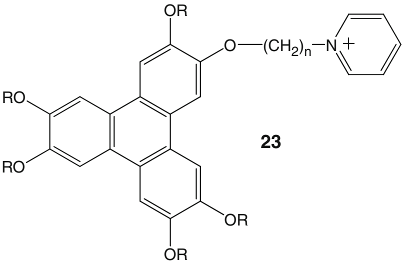
More recently the investigation has been extended to redox-active ionic liquid crystals based on cyclobis(paraquat-*p*-phenylene)s complexed with anionic surfactants [57, 58].

Finally, bromide salts of pyridinium tethered with hexaalkoxytriphenylene unit, **23**, were prepared by Kumar and Pal [50] and showed columnar mesophases (Fig. 4.7) over a wide temperature range.

Fig. 4.7 Optical micrograph of 23 (n = 5, R = C_4H_9) in the columnar mesophase at 78°C (Reproduced from Ref. [50] with kind permission of © Elsevier)





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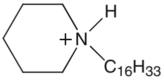
4.2.4 *Morpholinium-, Piperazinium-, and Piperidinium-Based Ionic Liquid Crystals*



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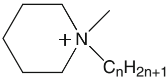

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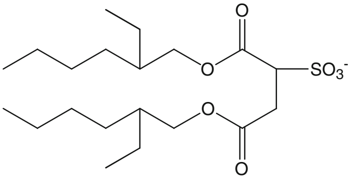
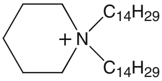


DOSS



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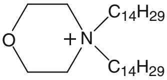

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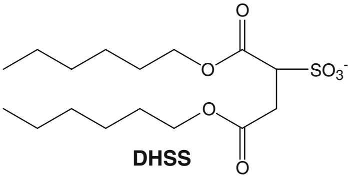
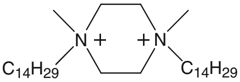


DHSS



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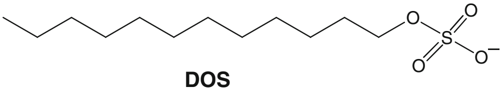
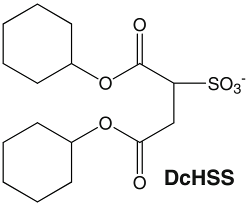


DOS

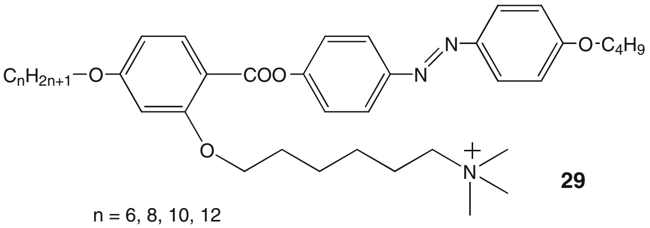


DcHSS

N-hexadecylpiperidinium **24** [16], *N*-alkyl-*N*-methylpiperidinium **25** [16, 17], *N*,*N*-ditetradecylpiperidinium **26**, *N*,*N*-ditetradecylmorpholinium **27**, and *N*,*N′*-dimethyl-*N*,*N′*-ditetradecylpiperazinium **28** [17] ionic liquid crystals have also been reported. Counteranions were Br^-, for **25** with alkyl chain from octyl to octadecyl and BF_4^- with alkyl chains from decyl to hexadecyl (in both cases only even number of carbon atoms). For compound **24**, anions were $CH_3SO_3^-$, *p*$TolSO_3^-$, PF_6^-, and Tf_2N^- while compounds **26**, **27**, and **28** were also tested with DOS, DOSS, DcHSS, and DHSS. Only a limited number of low-ordered smectic phases were observed for morpholinium and piperazinium salts while for piperidinium salts' crystal phases, highly ordered smectic phases or columnar phases were found.

4.2.5 Ammonium-Based Ionic Liquid Crystals

Ammonium salts may exhibit ionic mesophases despite missing a rigid moiety similar to the mesogenic core of dipolar liquid crystals, which may be found in the other quaternary nitrogen salts. In fact, an interesting example of an ionic nematic phase was reported recently for a mesogen bearing a terminal ammonium bromide group, **29**, on a lateral alkyl chain [7].



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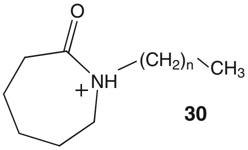
The ionic nematic phases have a range of stability from 23°C to 36°C and from 25°C to 68°C for n = 6 and n = 8, respectively, while with the longer alkyl chains an SmA phase was observed. In all cases the system undergoes a transition to a glass state at low temperature without crystallization.

Other ammonium salts have been synthesized and characterized: columnar phases are formed by ammonium salts of tris(2-aminoethyl)amine and di- or tri-alkoxybenzoic acids with alkyl chain from pentyl to octadecyl [43]. Interestingly, by varying the amine/benzoic acid molar ratio, a smectic phase could also be found [45]. Systems with fluorinated alkyl chains were also investigated [42]. A bilayer smectic phase, SmA_2, was reported for didodecyldimethylammonium-benzene-hexacarboxylate [35] while a bicontinuous cubic phase was observed for 1,3,5-tri-alkoxybenzyltrimethylammonium tetrafluoroborate [49].

Finally, SmA phases with a relatively small range of thermal stability (ca. 10–20°C centered around 100°C) were reported for hydrated salts of *N*-alkylcaprolactam **30** and *p*$TolSO_3^-$ and $CH_3SO_3^-$ [29].



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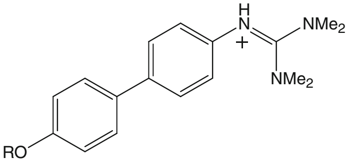
4.2.6 Guanidinium-Based Ionic Liquid Crystals

Laschat and coworkers have investigated the mesomorphic behavior of guanidinium salts [38, 52]. When calamitic mesogenic groups were attached to the guanidinium head, such as **31**, SmA phases were observed: chloride salts showed a smectic phase from above room temperature up to more than 200°C, depending on the chain length [38]. The dependence of the mesomorphism on the counteranion was also investigated by exchanging chloride with Br^-, I^-, BF_4^-, PF_6^-, and SCN^-. In contrast, when triphenylene moieties were considered, as in **32**, chloride salts showed columnar mesophases [52].



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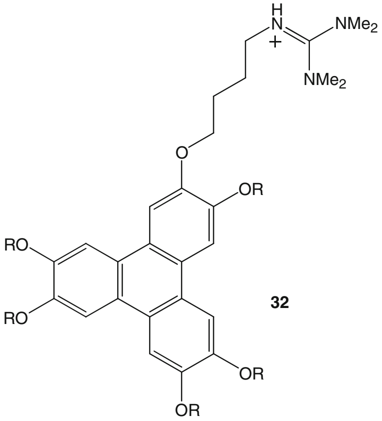

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4.2.7 Phosphonium-Based Ionic Liquid Crystals

There are few examples in the recent literature on phosphonium based ILCs. Ma et al. have investigated the structure of a series of phosphonium salts, including zwitterionic systems and mixtures with water and alcohols [21, 23].

The stability of the smectic phases is greatly enhanced by the presence of water or alcohols in equimolar amount which have been found to weaken the cation–anion interaction, thus destabilizing the crystal phase. A similar behavior is observed when one of the alkyl chains of the phosphonium cation contains hydroxyl groups. For the same reason, mesophases are not observed with trialkylmethylphosphonium with small anions due to the strong electrostatic interaction.

4.2.8 Anions

ILCs where the mesomorphic properties of the phases are dictated by the structure of an organic anion are rare. A sulfonate group attached to a cholesteryl unit was synthesized and exhibited a smectic phase [34]. An SmA phase was also observed in pyridinium salts of the [closo-1CB_9H_{10}] anion [18]. Metal alkanoates will be discussed in the next section.

4.3 Ionic Liquid Crystals Based on Metal Ions

The promising properties and applications of ionic liquid crystals are driving an ever increasing amount of research, focused at developing and optimizing mesomorphic systems. In addition to the traditional approach focused at identifying design principles based only on the shape and the symmetry of the mesogenic molecules, another trend centered on the quest for supramolecular strategies yielding classes of mesogenic molecular system has emerged. Such research lines exploit self-assembly of species, through inter- or intramolecular interactions of different nature (hydrogen bonds, ionic interactions, dipole interactions). Self-assembly driven by coordination chemistry offers a wide array of possibilities for the chemist wishing to obtain metallomesogenic species. A number of reviews describing the advances in such a field have appeared [4, 59–63]. Some recent examples of metal-containing ionic liquid crystals will be discussed in the following paragraphs.

Oftentimes the synthetic approach chosen is that of combining organic mesogens with a metal ion. Klimusheva and coworkers worked very actively in the field of metal alkanoates. Such group of molecules have the general formula $(C_nH_{2n+1}COO^-)_kM^{k+}$, where M is a metal and k = 1–3. Every molecule consists of alkyl chains with a carboxyl anion at one end, which are connected with a mono-, di-, or ter-valence metal cation. This class of compounds has a propension for mesomorphism, being able to yield lyotropic and thermotropic liquid crystals and ionic smectic glasses. Smectic glasses have a layered, nanoporous structure that makes them suitable for novel solid materials embedding nanoparticles and nanoclusters.

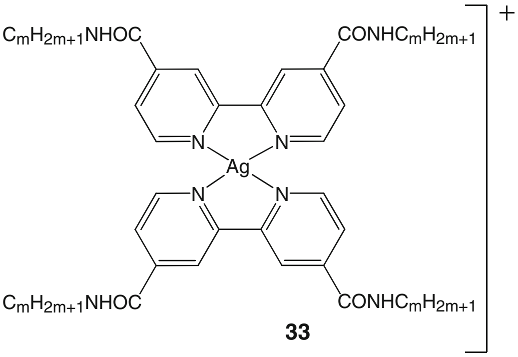
On the basis of small angle X-ray scattering, it was shown that the metal alkanoate matrix in the mesophase consists of bilayers. In thermotropic ionic liquid crystals, an alternation exists of hydrophobic alkyl chains and conductive layers which contain metal cations and anionic carboxylic groups. In lyotropic ionic liquid crystals, there are metal cations, carboxylic groups, and water between the hydrophobic alkyl chains' layers. As a result, metal alkanoates form an SmA structure [64].

These materials are extremely attractive for their optical and electrical properties. They have a high intrinsic ionic conductivity, which varies exponentially with temperature and is also anisotropic due to their bi-layer spatial structure [64]. For example, the lyotropic metal alkanoate potassium caproate showed a higher electrical conductivity in the smectic phase than in isotropic solutions. Since they are much less solvated within the layered structure of the smectic phase than in dilute solution, potassium cations have a larger mobility in the mesophase of the metal alkanoate.

Thermotropic cobalt decanoate showed interesting electric properties since the conductivity along the cation–anion layers was larger by four orders of magnitude than that in the perpendicular direction. The activation energy of electrical conductivity along the cation–anion layers is in fact four times smaller than the activation energy across the layers because in the latter case, the long alkyl chains prevent the transport of cobalt cations, due to the configuration of alkyl chains which are partly overlapped.

A pure lyotropic metal alkanoate matrix is usually transparent in the visible range of the spectrum, but its amphiphilic nature favors the dissolution of various light-absorbing species both organic and nonorganic, such as polymethine dyes and electrochromic and photochromic impurities (viologens). On the other hand, thermotropic metal alkanoates and smectic glasses are often colored and absorb light in the visible spectral range. Colored metal alkanoates are particularly promising for applications that exploit their optical properties. For example, mesomorphic glasses based on cobalt alkanoates or lanthanum capronate with ionic and neutral organic dyes, as well as cadmium alkanoates containing semiconductor nanoclusters, showed high values of optical nonlinearity, fast times of recording and relaxation of holographic gratings, therefore being very well suited for the development of high-speed telecommunication devices [65]. Remarkable nonlinear optical properties were exhibited also by a lyotropic ionic liquid crystal of potassium caproate and by ionic smectic glasses of La-capronate containing a photosensitive polymethine dye of the anion type [66]. Moreover, mesomorphic metal alkanoates have the ability to quickly remove heat when exposed to laser radiation [65, 66]. Analogous materials based on a silver amino complex with alkylamines or with primary amines with a rigid part in the amine ligand (anilines and benzylamines) and alkyl or alkoxy terminal chains, were reported by Espinet and colleagues. They displayed a thermotropic lamellar mesophase very similar to that of the metal alkanoates just described [67].

Pucci and coworkers recently described a series of multifunctional metallomesogens, based on mainly nitrogen and oxygen ligands with a variety of metal centers, some of them innovative such as the rarely encountered Pt(II), Zn(II) and Ga(III) [68]. The main result of such a work is that the nature of the metal center is a fundamental factor for the design of new metallomesogens [68]. By changing the central metal atom and wisely choosing the ligands, it is possible to accurately control the shape of the resulting complex. For example, it is possible to work with the square planar geometry of [Pd(II)], or with the tetrahedral [Zn(II)] or the pentacoordinate [Ga(III)]. The size and shape of the ligands are chosen in order to calibrate the shape of the complex and thus to promote the formation of liquid crystalline phases. The role of the ligands is also that of conferring to the material novel and functional properties such as luminescence and bioactivity [68]. Other tunable features are the number of flexible chains at the periphery, and the nature of counterions in ionic complexes.



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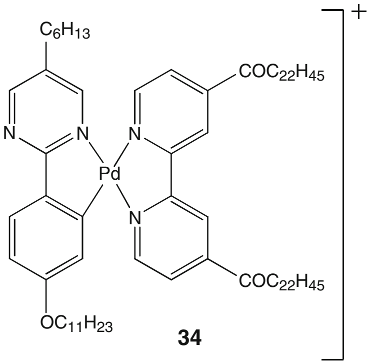
As an example, it was reported that the TfO^- salt of the tetracoordinated silver(I) complex with 2,2′-bipyridine-4,4′-disubstituted ligands **33** yielded a novel ionic liquid crystal displaying columnar mesomorphism [69]. The coordination and the ionic bonds drive the supramolecular assembly because the ligand is nonmesogenic or smectic, but when coordinated to the metal, it gives columnar mesomorphism [69]. The flexibility of such approach can be further exploited for the design of mesogens with innovative shapes. Pucci and coworkers prepared ortho-palladated complexes with a molecular shape which can be considered at the crossover point between calamitics and discotics [70].



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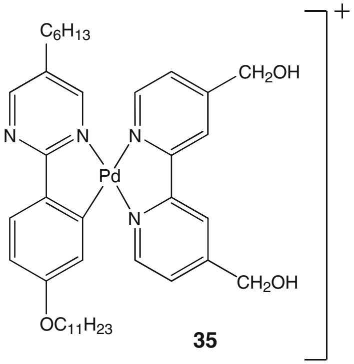

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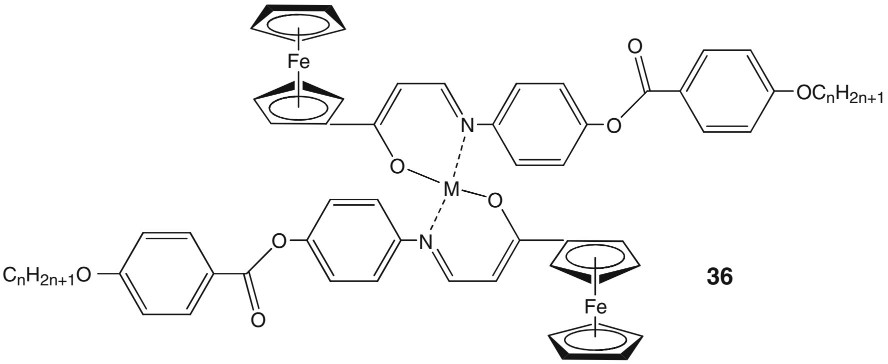
This was achieved by combining palladium with a nematic rodlike phenylpyrimidine ligand and with a laterally substituted nonmesogenic 4,4′-disubstituted-2,2′-bipyridine bidentate chelating ligand, **34** and **35**. Such complexes allowed a very easy modulation of molecular shape, and they were extremely versatile, because their polymorphism was very sensitive to slight changes in the structure of the complex building blocks (for example to substituents in the bipyridine fragment) [70]. Obviously, this flexibility in design is very attractive because it allows to carefully design the shape of the molecule that yields the optimal mesomorphic behavior, which is ideal for the intended application. It is interesting to note that, differently from purely organic mesogens, the mesomorphic properties of these systems are not much dependent on the nature of the counteranion [70].

A further possibility offered by metallomesogen systems is that of building molecular structures with multiple metal centers. This allows to confer to the liquid-crystalline material various functional properties, such as color, luminescence, metamagnetism, or electric conductivity (Ref. [71] and references therein). Kadkin, Choi, and coworkers used ferrocene as a building block for obtaining heteropolynuclear mesogenic structures as **36**; they reported ferrocene-containing complexes with a chelate functionality that could coordinate a metal [71].



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In complexes like these, the metal centers are close to each other, and thus, this geometry is the optimal one for exploiting the potential of heteronuclear metallomesogens. The nature of the metal coordinated to the chelate β-aminovinylketone group is key for determining the liquid-crystalline behavior. For instance, the synthesized heteronuclear complexes of copper(II), showed a soft crystal phase, analogously to the free ligands, whereas when palladium(II) was used as a metal center, a monotropic smectic C mesophase appeared [71]. Although still in their infancy, these compounds, which have the potential for electronic exchange interactions between the metal centers, can possibly have interesting magnetic, optical, and redox properties.

The design of lanthanide-containing liquid crystals is rather difficult because their high coordination numbers are quite incompatible with the structural anisotropy that is necessary to exhibit liquid-crystalline behavior. However, a large amount of research has been devoted to complexes containing these metals, due to their applicative potential in luminescent materials. Lanthanides emit in a much narrower spectral range (10 nm) than the known organic materials (100 nm), and allow to vary the emission color from blue to near IR. They may theoretically reach 100% quantum efficiency [72]. Lapaev and coworkers showed that mesogenic complexes of europium (III) exhibit a high photostability and an intense luminescence due to interligand and intramolecular electron transfers, strictly related to the peculiar shape and morphology of these materials [72, 73].

Bidentate ligands can be useful in preparing lanthanide-based metallomesogens because they allow the lanthanide ion to easily obtain a high coordination number. Rao and coworkers, for example, worked systematically on the investigation of complexes of 3d and 4f metals with a series of mesogenic and nonmesogenic organic Schiff bases in zwitterionic form [74, 75]. Ironically, it was easier to obtain liquid-crystalline phases, of the nematic or smectic phase, with the nonmesogenic ligand [74] rather than with the mesogenic ligand, [75] which yielded mesophases just when coordinated with La or Pr.

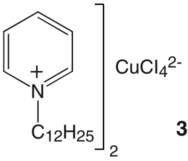
Columnar phases could also be obtained by reacting disk-shaped molecules such as crown ethers with lanthanide salts. Bünzli and coworkers reported, for example, the preparation of thermotropic hexagonal columnar phases from nonmesogenic crown ethers and several different ions of the lanthanide family [76]. An additional property of these compounds is a metal-centered emission, in the case of the liquid-crystalline phases containing Eu and Tb, making them attractive for the design of luminescent liquid-crystalline materials [76].

Even though in most of the cases the metallic center is part of the cationic moiety of the ionic liquid-crystalline compound, the opposite approach must not be ruled out. Anion-driven mesogenicity is a favorable option in some cases [18]. Goossens et al. [53] recently prepared mesogenic compounds based on pyrrolidinium salts, **14**, **15**, and **16**, with two organometallic complexes as counteranions: tetrakis(2-thenoyltrifluoroacetonato)europate(III) and tetrabromouranyl. The uranyl compound has two crystallographically independent alkylated pyrrolidinium cations around a $[UO_2Br_4]^{2-}$. Varying the functionalization of the pyrrolidinium species, an extremely rich polymorphism was observed for such compounds [53] with the appearance of SmA and a SmE phase, of a hexagonal columnar phase Col_h and of several crystalline phases. Obviously the inclusion of U or La nuclei in the mesogenic species improved the multifunctionality of the materials, which acquired novel photophysical properties: uranium-containing complexes luminesced by dissolving them in an ionic liquid matrix, whereas the europium-containing compound showed intense red photoluminescence with high color purity [53].

Getsis et al. [77] investigated ionic liquid crystals containing imidazolium-based cations and hexabromodysprosiate(III), $[DyBr_6]^{3-}$. Smectic liquid-crystalline mesophases were stable in a wide temperature range from −20°C up to 115°C [77]. An interesting cooperative effect on the luminescence behavior was noted. Excitation with a wavelength of $\lambda_{ex} = 366$ nm lead to the characteristic blue-whitish luminescence from the imidazolium cation itself [77]. Upon irradiation with a shorter wavelength $\lambda_{ex} = 254$ nm, the sample was orange due to the onset of emission from Dy(III) [77]. These complexes were also notable for their magnetic properties, especially their superparamagnetism that allows to exploit an external magnetic field for orienting the mesophases [77].

An original use of lanthanide metals in the field of ionic liquid crystals was proposed by Bünzli and coworkers [78, 79]. They doped ionic liquid crystals with europium ions, and exploited their photophysical properties. They showed that emission characteristics, lifetime of the excited state, and intensity of the hypersensitive transition were ideal indicators of the changes occurring during the crystalline to liquid-crystalline transitions [78, 79].

Although most of the times it is of interest to obtain stable mesophases, it may be useful also to exploit their controlled degradation or transformation. Taubert and coworkers reported a very interesting application of metallomesogens [80, 81]. They prepared mixtures of bis(dodecylpyridinium) tetrachlorocuprate **37** and of 6-*o*-palmitoyl ascorbic acid **38** with different relative proportions.



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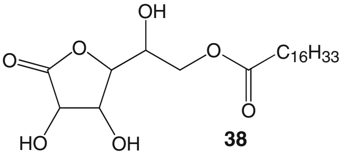

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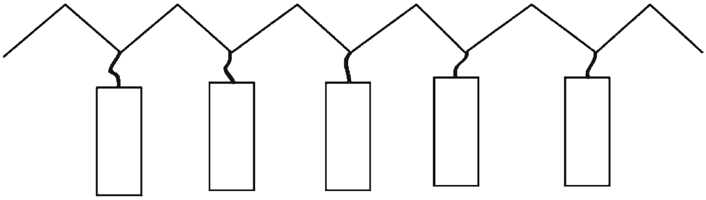
They determined the phase diagram of such mesogenic mixture. Bis(dodecylpyridinium) tetrachlorocuprate yields columnar mesophases, whereas its mixtures with 6-*o*-palmitoyl ascorbic acid gives smectic phases. This system is interesting because it is stable at ambient conditions, but at moderate temperatures, it undergoes thermally induced formation of CuCl. So, the ionic liquid-crystalline phase can be dissolved in tetrahydrofuran (THF), it can be cast onto a surface, and then it can be heated to 50–80°C, yielding a macroporous CuCl network, which can be retrieved and used as a heterogeneous catalyst [80, 81]. It can be envisaged that, applying a similar approach with ionic liquid-crystalline phases with other symmetries, other morphologies could be obtained for the final inorganic compounds.

4.4 Polymeric Ionic Liquid Crystals

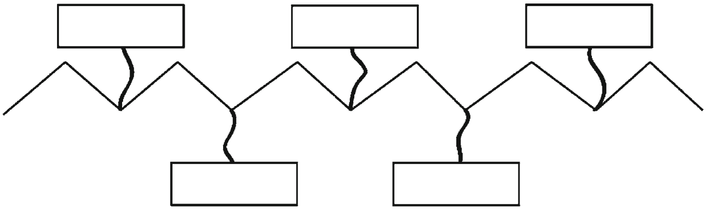
If low molecular weight ILC are a yet not well-studied class of compounds, high molecular weight ILC are even less investigated. Polymeric liquid crystals are attractive because they conjugate the characteristics of low molecular weight liquid crystals with the physical-mechanical properties of polymers. To confer a liquid-crystalline behavior to polymers, mesogen moieties are usually included into a macromolecule. Two main approaches have been applied for achieving such objectives (Fig. 4.8) [82]:

1. In main-chain polymer liquid crystals (MCPLC), the rigid mesogenic units are inserted into the chain, along with some more flexible spacers that allow the attainment of the liquid-crystalline degree of order.
2. In side-chain polymer liquid crystals (SCPLC), the mesogenic units are attached, by grafting or by polymerization of appropriate monomers, to the main chain,

Main-chain type polymeric liquid crystal



Side-chain type polymeric liquid crystal with end-on attachment



Side-chain type polymeric liquid crystal with side-on attachment

Fig. 4.8 Basic types of liquid crystalline polymers

usually through a spacer. Flexible chains are desired to allow the mesogens to attain the desired degree of order, and adequate spacers are necessary to decouple the interactions between the main chain and the mesogen side groups. SCPLC can be of the end-on type, in which the mesogens are pendant groups with respect to the main chain, or of the side-on type, in which the mesogens are oriented parallel to the main chain and act as a jacket that enhances the rigidity of the whole polymer, which becomes similar to a giant calamitic structure.

4.4.1 Main-Chain Ionic Liquid-Crystalline Polymers

When the mesogen moiety is included into the main chain of the polymer, the obtained macromolecule contains inherently rigid units, which usually result in remarkable mechanical properties and thermal stability. Fibers made by these polymers compete with the best ceramic fibers and are far superior to metal fibers [83]. They therefore are ideal candidates as reinforcements for polymer-based composites. However, these materials often have a poor miscibility and adhesion to other polymeric substrates, limiting the range of their applications. This problem basically arises from weak intermolecular interactions either within the liquid-crystalline polymer itself or with the matrix of the composite. Strong ionic interactions between polymer molecules can significantly enhance mechanical properties and may improve the compatibility between different polymers in polymer blends.

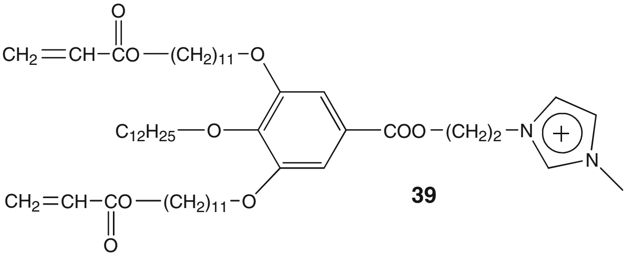
The first investigations on ionic liquid crystals of main-chain liquid-crystalline ionomers stemmed from the polymerization of monomers based on bipyridinium by Bhowmik group [84–87]. Zhang and Weiss [88, 89] used interfacial polymerization methods for the preparation of LC polyester ionomers with flexible spacers, whereas Hara and coworkers [83] incorporated an ionic monomer, sodium 5-sodiosulfoisophthalic acid, into an all-aromatic LC polyester. More recently, Zhang's group focused on introducing sulfonate groups into nonionic-MCPLC chains to obtain better mesogenic and ionic properties [90–92]. They selected sulfonate groups as ionic units which can be easily copolymerized with mesogenic monomeric units, thus being able to calibrate the ionic properties of the final polymer, while preserving the LC mesophase. This approach allowed to investigate the link between ionic aggregation and the liquid-crystalline behavior, and to study how the ionic interactions modify liquid crystallinity. The polymers containing a small quantity of ionic groups displayed only one mesophase, but when the concentration of sulfonic acid groups was increased, a smectic–nematic phase transition appeared [90, 92]. Liquid-crystalline polymers usually contain an alternation of flexible and rigid moieties: self-assembly and microphase separation into specific microstructures occurs because of the geometric and chemical dissimilarity of the two moieties. Addition of ionic groups brings about the formation of aggregates that may lead to microphase-separated morphologies as well. Competition between the formation of ionic cluster phases and the LC phase depends on the chemical structure. For polymers with a few sulfonated benzene groups, such groups are preferentially accumulated around the rigid mesophase moieties, whereas for polymers with an increased number of sulfonic groups, the ionic groups are more evenly distributed in both the soft matrix and the liquid-crystalline microphase [90, 92]. The disturbance to the regular mesogen/soft matrix phase structure leads to the appearance of a smectic–nematic transition [90, 92].

The same authors increased the complexity of their systems by introducing in a polyester chain both ionic and chiral chain segments. The series containing both the isosorbide chiral units and the ionic moieties yielded chiral smectic C (SmC*) and chiral smectic B (SmB*) liquid-crystalline phases, exhibiting broken focal-conic texture and schlieren texture. Not surprisingly, the analogous polymer without the chiral units exhibited only the nonchiral SmC mesophase. On the other hand, in this case, the effect of ionic units on the phase behavior was negligible [91].

The work described above focused on the introduction of ionic groups into a polymer that, in the neutral state, already exhibited a liquid-crystalline behavior.

Another approach is that of polymerizing low molecular mass mesogens. For example, Bhowmik and coworkers polymerized viologen-based monomers and obtained liquid-crystalline ionomers which yielded smectic phases [84–87].

Kato and coworkers reported the preparation of one-dimensional conductive films containing ion channels formed by self-organization of polymerizable columnar liquid crystals [93]. Such films were obtained by photopolymerization of aligned columnar liquid crystals of a fan-shaped imidazolium tetrafluoroborate salt, having acrylate groups at the periphery, as in **39** and **40**.



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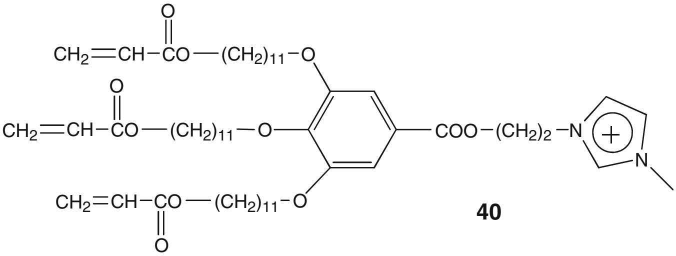

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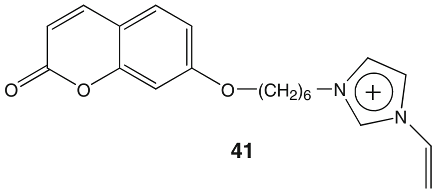
Polymerization was useful as a fixation medium of such oriented columns. In the columnar structure, the ionic portion self-assembled into the inner part of the column. The orientation of the columns could be controlled by following different preparation methods or by changing the substrates. The ionic conductivities parallel to the columnar axis were higher than those perpendicular to the columnar axis because of the insulating effect of the lipophilic part of the system. The orientation of the columns with respect to the film surface also had a significant role in shaping the macroscopic properties because the film with the columns oriented vertically to the surface showed an anisotropy of ionic conductivities higher than that of the film with the columns aligned parallel to the surface.

However, the strategy of producing MCPLC does not always give the expected results, i.e., polymerization of mesogenic monomers does not necessarily bring about a mesogenic polymer. As an example, Jazkewitsch and Ritter polymerized bromide salts of vinylimidazolium ionic liquids containing mesogenic coumarin, **41**, and biphenyl units, **42**, respectively [94]. The monomers self-assembled into liquid-crystalline phases. The polymers thereby obtained by a free-radical mechanism, though, were amorphous and did not show any mesophase [94].



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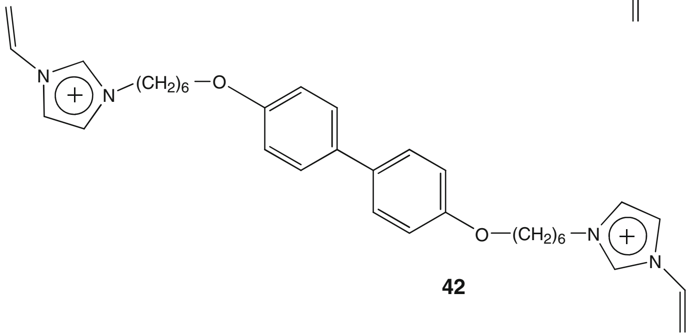

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4.4.2 Side-Chain Ionic Liquid-Crystalline Polymers

Thermotropic side-chain ionic liquid-crystalline polymers are particularly attractive when the aim is that of merging the liquid-crystalline characteristics of the low molecular weight mesogen side groups with the mechanical properties of the polymeric main chain. It is not surprising, then, that they attracted most of the research efforts in the polymeric ionic liquid crystals field.

A supramolecular approach is usually employed in the preparation of such materials. Commonly used base polymers are ionomers containing sulfonate groups, such as poly(styrenesulfonate). Azo-containing molecules are frequently employed for the side-chain mesogen [95].

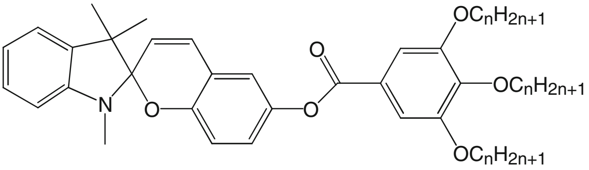
Ionically complexed liquid-crystalline polymers are more robust than their hydrogen-bonded counterparts. Ionic bonds are generally stronger and require higher temperatures to be broken, leading to highly viscous melts, difficult to process. Ion-containing systems are moreover very sensitive to the presence of even small amounts of water, but on the other hand, they are less prone to plasticization by side chains[95].

Zhang and Bazuin reported the preparation of a series of ionically bonded side-chain polymer complexes, synthesized by 1:1 complexation of poly(styrenesulfonate) and quaternary ammonium-functionalized azo-containing surfactomesogens with hexyl and decyl spacers. Care was taken to work in extremely dry conditions to accomplish such syntheses. In most cases, the very strong ionic interactions lead to a crystalline structure, but in some instances, lamellar mesophases appeared. A very extensive annealing process was in many cases necessary to induce the formation of the mesophases because the chains were very less mobile, due to the relatively high molecular weight of the polystyrene backbone and especially to the strong ionic interactions that greatly retarded the kinetics of chain reorganization toward equilibrium [95]. As a further confirmation of the relevant effect of the presence of ionic moieties on the mobility of macromolecular chains, the values of the glass transition temperature of the samples were found to depend not only on the spacer length but also on the dipole moments of the mesogenic cores [95]. Ionic complexes modify the shape of the polymer chains, inducing variations in the free volume within the samples and thus changing the glass transition temperature, T_g [91]. The formation of ionic complexes is a further interesting feature. The introduction in the system of polar tails produced a smectic A phase with a peculiar XRD trace, with an extinction or at least a reduction of the intensity of the first-order diffraction peak. A possible rationalization of such datum offered by the authors is that dipole–dipole interactions between the polar mesogenic cores and the ion pairs can result in both moieties sharing the same subplanes, thus reducing the effective lamellar periodicity by about half.

As discussed before, azo-containing mesogens are frequently employed as side groups for SCLCP because of their potential important applications, in particular, based on the photoisomerization reaction of azobenzene which induces significant motion of the matrix. Yoshimi and Ujiie reported a study in which they compared two analogous polymers, one containing charged nitrogen cations and the other one neutral, both containing an ethylazobenzene mesogen in the side chains [96]. They observed that the sample with a polyion backbone formed a smectic A phase with a focal conic fan texture and a perpendicular structure. On the other hand, the material based on the neutral backbone formed a nematic phase with a schlieren texture. Once again, the presence of charges in the polymer severely influenced the polymorphism of the compounds. The authors showed the potential of these LC systems in the fields of photomemory, optical storage, and light drive display, especially because these amphiphilic polymers yield excellent azodense LC thin films [96].

Similar materials, in which an azobenzene dye was ionically grafted as side chains in a poly(1-butyl-vinylpyridinium) [97, 98] or polyacrylic acid [99], were at the center of very application-oriented studies for the design of photosensitive polymeric liquid crystals. These systems formed lamellar structures with very remarkable optical properties related to the possibility of inducing a photoinduced anisotropy [97–99]. This photoinduced orientation results in macroscopic anisotropy, thus severely influencing the dichroism and birefringence in polymer films. The dichroism represents the absorbance variations along the directions parallel and perpendicular to the pump polarization, while the birefringence represents the phase modulation effect of the photo-oriented polymer film. Moreover, the samples based on poly(1-butyl-vinylpyridinium) displayed a very large nonlinear refractive index, making it a very promising candidate for the manufacture of nonlinear optical devices [97].

Kato and coworkers combined a very peculiar mesogen, fan-shaped spiropyran derivatives, **43**, to a poly(styrenesulfonate) main chain, **44** [100, 101].



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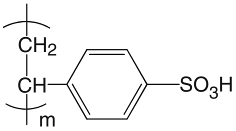

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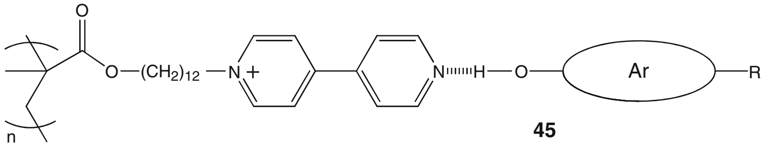
Spiropyrans are an important class of materials that show interesting properties such as photochromism and acidichromism. Similar to azo compounds, photoirradiation or the addition of acidic molecules to spiropyrans lead to drastic changes in physical and chemical properties due to spiro-merocyanine isomerization. Hexagonal columnar LC complexes of a spiropyran derivative with 4-methylbenzenesulfonic acid were formed due to the acid-induced spiro-merocyanine isomerization [100]. The columnar LC mixture aligned uniaxially on a substrate can serve as one-dimensional ion conductors. When poly(styrenesulfonate) was employed as a complexing agent for spiropyran, no mesophase was observed.

All the examples cited so far involve the formation of side chains by ionic complexation. Sallenave and Bazuin studied the selectivity of hydrogen-bond complexation in the presence of both ionic moieties and highly polar groups and also investigated the effect of these potentially interacting functions on the thermotropic behavior of SCLCP complexes [28]. A scheme of the compounds studied by these authors is **45**:



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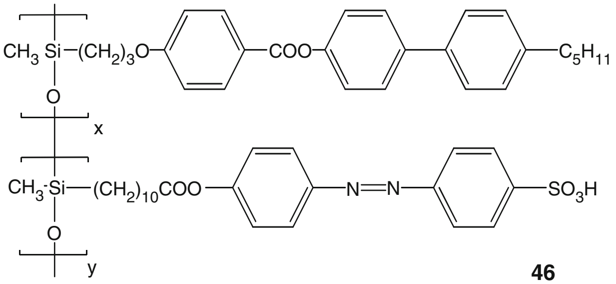
As the base polymer, they used a weakly mesomorphic polyamphiphile, poly(ω-pyridylpyridinium dodecylmethacrylate) bromide (P12PP), where the side chains were terminated by a hydrogen-bond acceptor in close proximity to an ion pair, and they combined it with equimolar quantities of a series of phenol-functionalized mesogenic complexants. Some of the complexants had highly polar or chiral tails. Two types of aromatic cores, biphenyl and azobenzene, were employed. They obtained crystalline compounds at room temperature which underwent glass transition and a crystalline-smectic phase transformation at higher temperature. The nature of the tail linked to the aromatic core of the hydrogen-bonded mesogen influenced the thermal properties and the type of smectic phase that formed [28]. Polar tails, for example, due to the increased intensity of electrostatic interactions, reduced the mobility of the chains, thereby hampering the recrystallization of the compound after melting [28].

Zhang and coworkers chose a base polymer alternative to poly(styrenesulfonate) and prepared SCLCP with a polysiloxane backbone [102]. Differently from the previous cases, side groups were linked to the main chain by covalent bonding.

They incorporated (4-allyoxybenzoyloxy-40-amylbenzoyloxy biphenyl) as mesogenic units and (4-undecylenicoxy-40-phenylazobenzene sulfonic acid) as ionic units by graft copolymerization as in **46**. The mesogenic monomer moiety had a nematic thermotropic behavior, which was transferred to the polymers. The introduction of ion charges in the macromolecular chains reduced the clearing point, but did not affect the nature of the mesophase attained by the material [102].



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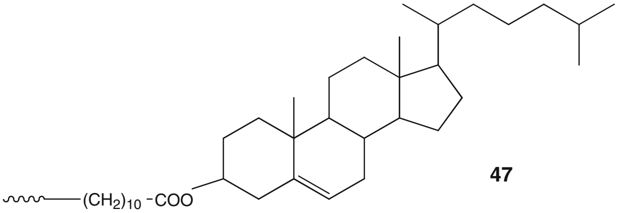
The same authors prepared a series of liquid-crystalline polysiloxanes copolymerizing the nonionic mesogenic monomer cholest-5-en-3-ol(3β)-10-undecenoate **47** and the ionic mesogenic monomer potassium 2-allyloxy-5-cholesteryloxycarbonyl-benzenesulfonate **48**.



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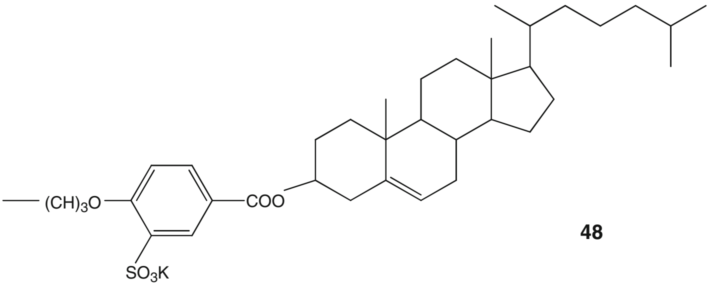

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In this case, the polymers containing less amounts of sulfonate groups showed a cholesteric mesophase, while if the content of ionic groups was increased, also a smectic phase appeared besides the cholesteric one [103]. This is because at higher ionic component, the ionic hard phases aggregate in domains due to their electrostatic interactions, thus forcing the siloxane chains to fold and form a lamellar structure [103]. These two examples emerging out from the work of the same group show that the sensitivity of the polymorphism from the molecular structure is more dependent on the nature of the side groups, rather than the backbone of the chain.

4.4.3 Dendrimers

Since their discovery in the late 1970s, dendrimers have drawn the attention of the research community, becoming a rapidly expanding branch of current science [104]. The attractiveness of such class of compounds is mainly due to the possibility of controlling their molecular architecture by modulating the generation number, the multiplicity of branching, and the connectivity of the core. With a size comparable to that of proteins, dendrimers have been proposed for a variety of applications, among which as mimics of enzymes, as drug- or gene delivery devices, for catalysis and also as building blocks for functional assemblies in nanoscience, nanotechnology, and supramolecular chemistry [105]. Dendrimers and dendritic molecules can also give rise to liquid-crystalline phases, which result from the microsegregation of incompatible structural units and from the overall molecular shape, which is, among other things, largely influenced by the topology of the branching points [105]. Dendrimers with a liquid-crystalline behavior can be synthesized by two general approaches: (a) the formation of macrostructures with a regular structural growth by successive introduction of the mesogenic units within the branches in each dendrimer generation or (b) the functionalization of a preexisting dendrimer by the covalent linkage of the mesogenic units to its peripheral functional groups (amino, carboxylate, silane, etc.) [106]. According to this latter method, it is possible to obtain geometries containing rodlike or disklike mesogenic units at the periphery of the original dendrimer, thus forming a LC shell around the central dendritic nucleus [106]. The formation of a mesophase arises from the microsegregation and the competitive drive for self-assembly of the three different molecular regions within the dendrimer (central dendrimeric core, mesogenic units, and terminal flexible chains). Lamellar phases are formed when the molecular shape approximates that of rods, whereas columnar mesophases are observed when the dendrimers have a disklike shape and are stacked into columns. Most of the literature on this subject deals with neutral molecules. The introduction of charged moieties into a dendritic structure is expected to magnify the strength of the interactions between the different regions of the molecules and, thus, offers stronger segregation effects [107, 108]. Tschierske and coworkers showed such effect by preparing dendrimers by assembling first- to fifth-generation amino-terminated propylene imine dendrimers with facial amphiphilic carboxylic acids [105]. These carboxylic acids contain three distinct incompatible segments, a rigid rodlike terphenyl core, two terminal alkyl chains, and a polar lateral carboxylate group. The COOH groups were either directly connected to the terphenyl core or via oligo(oxyethylene) chains of different lengths. The length of the spacer, the dendrimer generation, the quantity of carboxylic acid in the molecule and the temperature were

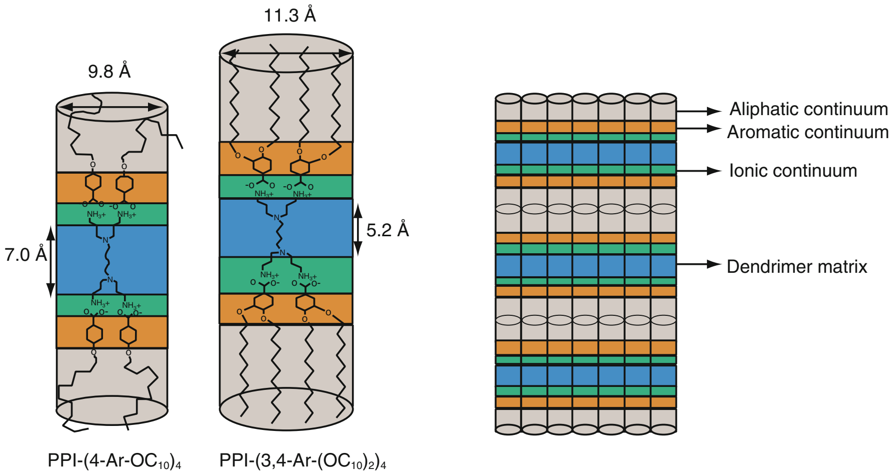

Fig. 4.9 Molecular model for the ionic dendrimers with a lamellar mesomorphism and schematic representation of the molecular organization of the SmA mesophase (Reproduced from Ref. [106] with kind permission of © The American Chemical Society)

the most significant factors that influenced the shape of the molecule, and thereby the observed liquid-crystal phase. A smectic A mesophase, two different square columnar phases, a hexagonal organization of columns, and two additional columnar phases with unknown structures were obtained by varying such features. The introduction of ionic species into the dendrimer molecules, therefore, brought about the insurgence of novel interactions, yielding a rich polymorphic behavior, with the formation of unconventional and yet unresolved mesophases [105].

Serrano and coworkers were very active in the synthesis of ionic dendrimer molecules. Their work focused on the introduction of ionic moieties in dendrimers [106, 109, 110]. They prepared a number of thermotropic dendrimers by assembling carboxylic acids with amino-terminated dendrimers of the poly(propylene imine) PPI or of the poly(amidoamine) (PAMAM) type [109, 110]. This very easy and straightforward synthesis procedure allows the preparation of a great variety of ionic dendrimer systems. It is interesting to note that the liquid-crystalline behavior is not achieved by introducing anisotropic mesogenic units, but just by converting the dendrimer surface from hydrophilic (-NH_2) to hydrophobic (alkyl chains). Moreover, the incorporation of an alkanoic acid onto the periphery of PPI dendrimers via a covalent amide bond affords non mesomorphic materials [111]. Ionic interactions are thus the driving force that leads to the formation of thermotropic mesophases. In the case of this class of compounds, the generation of the dendrimer and the number of alkyl chains on its surface are the key features that determine the type of LC phase which is formed. Generally, increasing the generation of the dendrimer, the molecules approach a disklike shape, and therefore, the mesophase changes from smectic to columnar. Approximating the dendrimer molecule to a cylinder (Fig. 4.9), the height of the molecular cylinder does not change much as a

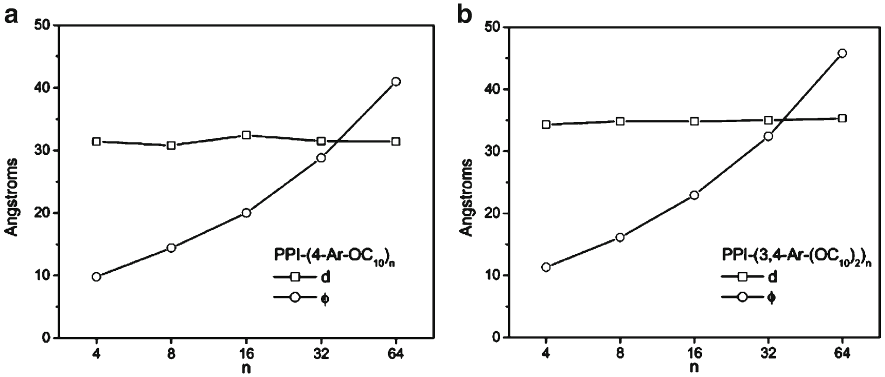

Fig. 4.10 Graphical representation of the evolution of the cylinder diameter (ϕ) and height (d) with the generation number for dendrimers (a) PPI-(4-Ar-OC$_{10}$)$_n$ and (b) PPI-(3,4-Ar-(OC$_{10}$)$_2$)$_n$ (Reproduced from Ref. [106] with kind permission of © The American Chemical Society)

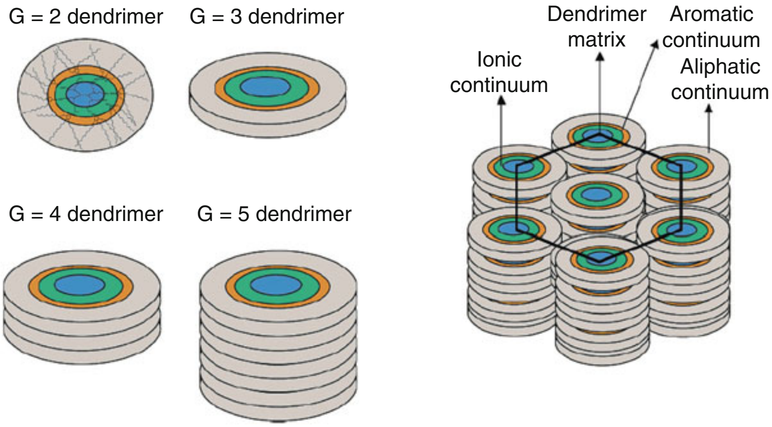

Fig. 4.11 Molecular model for the ionic dendrimers with a hexagonal columnar mesomorphism and schematic representation of the molecular organization in the mesophase (Reproduced from Ref. [106] with kind permission of © The American Chemical Society)

function of the dendrimer generations, whereas the cylinder diameter increases from one generation to the next one (Fig. 4.10), up to a point where the diameter of the cylinder is larger than its height, achieving a disklike shape (Fig. 4.11) [106]. The shape of the molecule is also strictly dependent on the quantity of alkyl chains on the surface of the dendrimer because the increase of the number of chains that have to be accommodated around the central dendrimer nucleus may force it to adopt a more elongated conformation [106, 109].

The effect of introduction of ionic pairs in the molecule could be investigated by comparing the covalent analogues. The covalent dendrimers showed hexagonal columnar mesophases, whereas when ionic pairs were included in the structure, the smectic mesophase was favored [106]. The reason of these starkly different behaviors is due to the difference in intermolecular forces which can appear when the dendrimer is covered with the amide functional groups or with the alkyl chains [106]. Moreover, ionic pairs modify the stability of the crystalline structure, with a consequent variation in the clearing points.

Serrano and coworkers also extended their approach with the aim of obtaining ionic photosensitive nematic materials by synthesizing ionic liquid-crystal dendrimers and hyperbranched polymers complexed with an azobenzene moiety [110]. PPI and PAMAM dendrimers were covered with a layer of an aromatic-based carboxylic acid: 5-(4-cyanophenylazophenyloxy)pentanoic acid. It did not show mesogenic properties, but all the obtained ionic complexes displayed a nematic mesophase, differently from the previous work from the same group, where most of the ionic homodendrimers formed by spontaneous assembly of long-chain carboxylic acids or (mono, di, or tri) alkoxybenzoic acids onto the surface of amino-terminated PPI or PAMAM showed lamellar mesomorphism. The appearance of the nematic phase could be associated with the presence of the azo group of the carboxylic acid, which also conferred to the final material stable birefringence and other optical properties, making it very attractive for different optical applications. Antharjanam and Prasad also reported the preparation of dendrimer-based materials with promising optical properties. They peripherally modified PAMAM and PPI dendrimers, which already had intrinsic luminescence properties, by different acids, generating materials that gave smectic and columnar phases [112]. These ionic complexes showed a blue emission upon excitation at 370 nm, which was greatly enhanced by increasing the generation of the base dendrimer. The luminescence appeared either in solution or thin-film form and was retained in the thin solid film for a long period of time, proving to be a very stable material.

By this approach, it was therefore possible to retain the intrinsic emission properties of PAMAM and PPI dendrimers and manufacturing liquid crystals luminescent in the visible region, without introducing conventional fluorophores [112]. Incorporation of rigid fluorophores in a mesophase quite often alters the phase transition temperatures of liquid-crystal materials to higher values, so these results are interesting because they provide the possibility of preparing luminescent liquid crystals close to room temperature.

In an analogous approach to those discussed above, Klok, Mezzenga, and coworkers prepared bioinspired complexes by ionic complexation of hyperbranched polypeptides and surfactants [113] that lead to columnar hexagonal or lamellar mesophases, as a function of surfactant alkyl chain length [113].

4.5 Applications of Ionic Liquid Crystals

Many applications have been reported for ionic liquid crystals. Among these, most important applications related to their intrinsic or induced luminescent properties [22, 53, 64, 71–79, 112, 114–116]. To this purpose, metallomesogens containing lanthanides are particularly useful [53, 72–79]. The interest in coordination compounds of lanthanides is due to the wide range of application of such materials. They are used as luminescent probes and markers in chemistry, biology, and biomedicine; in optoelectronics, these complexes are used in optical communication devices as luminophores for fluorescent light sources, laser materials, ultraviolet dosimeters, and emitters in organic light-emitting diodes and color displays ([72] and references therein).

The nonlinear optical properties of ionic liquid crystals, especially of polymer liquid crystals with azobenzene groups in the side chain and metallomesogens, are promising for their large nonlinear refraction and long-term optical stability. These open a wide array of possible applications in optical storage, optical limiting and optical switching devices, photomemory, and light drive display [64–66, 70, 97, 117, 118]. The liquid-crystalline morphology and the photoinduced trans to cis transformation of the azo group confer to these materials a large value of nonlinear refractive index, and a remarkable and stable photoinduced molecular reorientation, making them suitable for nonlinear photonic devices, holographic recording, and polarization reconstruction. The large value of photoinduced birefringence indicates a good potential for application of nonlinear photonic devices and optical storage [96–98, 119].

Exploiting the anisotropy intrinsic in mesophases, coupled to the presence of ionic charges, one dimensional conductor can be manufactured [64, 100] while the remarkable optical and electrical properties associated to ionic liquid crystals make them very promising materials for the manufacture of solar cells [120, 121]. One of the most innovative and interesting applications of ionic liquid crystals is the possibility offered by these materials to assist the manufacture of nanostructured objects. Guari and coworkers exploited the nanosized lamellar arrangement of a methylimidazolium ionic liquid crystal in the smectic phase as a stabilizing and structuring agent and as a solvent in the *in situ* synthesis and organization into a two-dimensional array of magnetically active cyano-bridged coordination polymer nanoparticles [122]. This may prove to be a very powerful tool for scientists wishing to achieve a control at the nanometric level of their materials.

In the case just described, the space between the layers of the smectic structure acted as a “confined reactor” for the synthesis of nanoparticles. Another approach for the preparation of nanostructured materials assisted by ionic liquid crystals can be that of preparing a liquid-crystalline compound, which is afterward degraded, yielding the desired product and at the same time retaining a morphology similar to that of the precursor. An example was reported by Taubert and colleagues who employed the reactivity of a metallomesogen to obtain CuCl nanoparticles [80, 81]. This aim was achieved by preparing a stable smectic precursor, composed of mixtures of bis(dodecylpyridinium) tetrachlorocuprate and of 6-o-palmitoyl ascorbic acid. Heating this precursor, the copper complex undergoes a degradation with formation of an ordered network of CuCl nanoparticles [80, 81]. Douce and coworkers deposited metal nanoparticles by electrochemical reduction of a silver or gold salt of an imidazolium anion. The mesophase templates particles with a controlled and very ordered shape and size [123].

Some applications in the biomedical field have been also envisaged for ionic liquid crystals. Transition metal complexes have potential antitumor activity, so metallomesogens could in principle be useful in the therapy for cancer [68].

Other miscellaneous applications of ionic liquid crystals have been reported as lubricants, [124] for the preparation of membranes, [125] and as additives for food bars [126].

4.6 Conclusions

In this chapter we have revised the recent literature, since 2005, concerning ionic liquid crystals and their applications. The field is quickly growing in importance, as suggested by the relevant number of publications appeared on high impact journals. For rodlike mesogens, the smectic phase seems largely predominant. Nevertheless, the few examples of ionic nematic phases discussed indicate that the efforts in the future should be directed to the design of systems exhibiting nematic phases. The expected low viscosity of these latter materials will be beneficial for applications in the various fields that have been highlighted in the latter section of this chapter.

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Chapter 5
Application of Ionic Liquids in Extraction and Separation of Metals

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Abstract Ionic liquids as green solvents have shown important application in extraction and separation of metals. In this chapter, the new application perspective and the important fundamental and applied studies of the extraction and separation of metals in ionic liquids which include metal oxide processing, mineral processing, electrodeposition of metals (especially reactive metals such as Al, Mg, and Ti), and extraction of metal ions are presented.

5.1 Introduction

Metals are important resources and have a wide range of applications. Metals are often extracted from ores. Once the ore is mined, the metals must be extracted, usually by chemical or electrolytic reduction. Pyrometallurgy uses high temperatures to convert ore into raw metals, while hydrometallurgy employs aqueous chemistry for the same purpose. The methods used depend on the metal and their contaminants. Most metals are obtained by hydrometallurgical processes such as aqueous acids or alkalis are predominantly used to dissolve the metal oxides, sulfides, or silicates. Electrowinning and solvent extraction are frequently used to recover and concentrate the metals. A limited number of high-temperature molten salts have also been used for the recovery of refractory metals, such as titanium and aluminum, from their ores [1]. Metal industry has a rapid development and has achieved remarkable results in recent years [2]. Ionic liquids are considered to be the most promising candidates due to their low toxicity and lower environmental impact in recent years. The application of ionic liquids as solvent to metallurgical ore beneficiation may offer potential as environmentally sensitive media and alternatives to hydrometallurgical processes.

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Ionic liquids (ILs) which are liquids at ambient temperature [3], also called ambient-temperature molten salts and room-temperature ionic liquids, are completely composed of organic cations and inorganic/organic anions. Due to the ionic nature of ILs, they present several physical and chemical advantages over conventional and molecular organic solvents, namely, negligible flammability and vapor pressure, high solvation ability, high chemical stability, and high selectivity, which make them of fundamental interest to all chemists, since both the thermodynamics and kinetics of reactions carried out in ionic liquids are different to those in conventional molecular solvents, then the chemistry is different and unpredictable at our current state of knowledge, and they have been widely and successfully used in synthesis and preparation of materials, catalysts, electrodeposition of metals, and fuel cell [4–6].

Main characteristics of ILs [4–6] are (1) negligible or very low vapor pressure and nonflammability; (2) high electrochemical stability, ion conductivity, and wide electrochemical window; (3) air and water stability, lower melting points, wide liquids, and thermal stability range; (4) a wide range of inorganic and organic compounds solubility; and (5) “designer” solvents.

The properties of ionic liquids can be adjusted to suit the requirements of a particular process by changing the cations and anions. For example, the density, melting point, and the viscosity of ionic liquids can be easily varied by simply changing the structure of the ions. The miscibility of water in these ionic liquids can be beneficial to solvent extraction or product separations.

Preliminary studies have shown that ionic liquids have potential as solvents and electrolytes for metal recovery, and the feasibility of these solvents has been demonstrated for the extraction of gold and silver from a mineral matrix [7], the recovery of uranium and plutonium from spent nuclear fuel [8], and the electrodeposition and electrowinning of metals (especially, for active metals such as Li, Na, Al, Mg, and Ti) from ionic liquids [9–11]. Ionic liquids as green solvents and electrolytes have shown important and potential application in extraction and separation of metals. In this chapter, the new applications and the important fundamental and applied studies on the extraction and separation of metal in ionic liquids including metal oxides and minerals or ores processing, electrodeposition of metals (mainly for active metals), and extraction and separation of metal ions are described.

5.2 Processing Metal Oxides and Ores with Ionic Liquids

5.2.1 Metal Oxides Processing

The processing of metal oxides is essential for metal extraction, waste recycling, and catalyst preparation [12]. One of the major difficulties with metal oxides is that metal oxides are insoluble in most molecular solvents and generally strong aqueous mineral acids are used for their dissolution. Separation has usually been achieved using solvent extraction with specific chelating agents for given metals, especially high-temperature molten salts are also used extensively for the recovery of refractory metals, such as titanium and aluminums, from their ores [1, 12, 13]. However, there are many disadvantages of these processes such as high energy consumptions, serious corrosion, large acid consumption, recycle of acid waste, and environmental pollution. Therefore, there has been a worldwide interest in seeking for new and green solvents for processing metal oxides under ambient atmosphere and low temperature with low consumption of energy, acid, and oxygen as well as free from pollutants release. Ionic liquids, which have abilities to dissolve a wide range of inorganic and organic compounds, provide a potential way to process metal oxides greenly at low temperature. Dai et al. [14] determined the solubility of UO_3 in imidazolium-based chloroaluminate melts as 24.58 mmol at 65°C. The dissolution of V_2O_5 in ionic liquid 1-ethyl-3-methylimidazolium (Emim) chloroaluminate was studied by Bell and coworkers [15]. The oxide was found to be not only highly soluble in the basic melt, 0.15 g in 1 g, but also soluble in the neutral melt. The authors reported that V_2O_5 reacts with the acidic chloroaluminate melt, forming a volatile $VOCl_3$ compound.

High solubility of inorganic salts such as LiCl and AgCl, aromatic acids, amino acids, and metal oxides CuO choline in chloride eutectics $[HOC_2H_4\ N(CH_3)_3]Cl$ (ChCl)/urea mixtures was reported by Abbott and coworkers in 2003 [16]. One year later, they reported the solubility of ZnO, CuO, and Fe_3O_4 in three deep eutectic solvents (DES) formed between ChCl and carboxylic acids at 50°C [17]. They found that Fe_3O_4 is most soluble in the oxalic acid/ChCl mixture, whereas its solubility is 20 times lesser in the phenylpropionic acid mixture, but CuO shows the opposite behavior. It was suggested that solvents can be designed to preferentially extract one metal oxide with respect to another. The majority of the more ionic transition metal oxides were found to be soluble in a DES, although the more covalent metal oxides such as aluminates and silicates are insoluble in all DES studied to date, which suggests that metal ions could be extracted from an aluminosilicate matrix without dissolving the matrix. Metals such as copper can be recovered electrochemically from the DES with high current efficiencies using bulk electrolysis, which could have potential applications to mineral extraction or metal oxide processing.

The ionic liquid ChCl with urea was applied to the processing of electric arc furnace (EAF) dust by Abbott and coworkers [18]. It was found that the solubility of ZnO, Cu_2O, and PbO_2 was good, zinc and lead can be selectively removed and subsequently electrowon from the liquid, whereas the insoluble iron and aluminosilicates can be recycled through the electric arc furnace. The process developed for treating EAF dust involves extraction of lead and zinc from matrix, isolation of lead, and recovery of zinc. The pilot plant built for 5-kg dust extraction batches is given in Fig. 5.1 [19].

The solubility of 17 common metal oxides in three ionic liquids based on choline chloride with urea, malonic acid, and ethylene glycol has been determined and compared with aqueous solutions of HCl and NaCl [20]. Details are presented in Table 5.1. The order of solubility was HCl > malonic acid > urea > NaCl > ethylene glycol. Higher solubility was observed with the more ionic oxides such as ZnO in

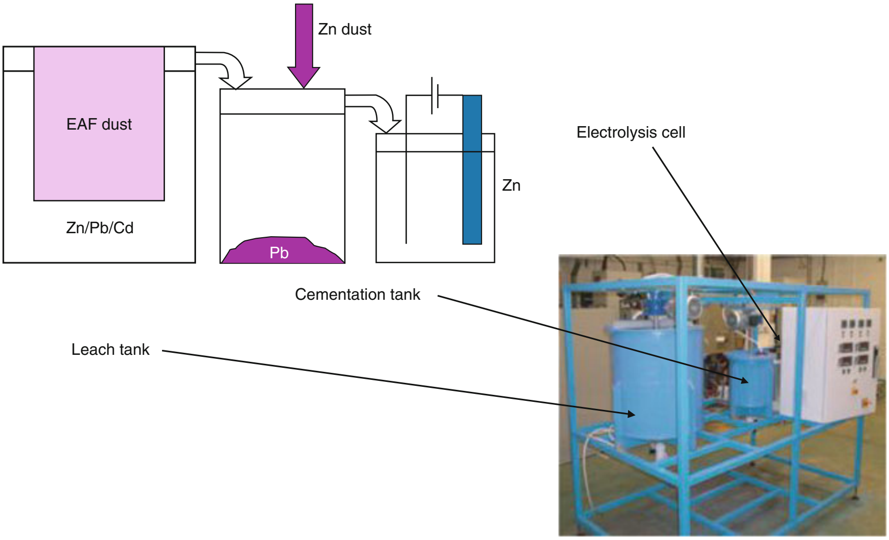

Fig. 5.1 Schematic diagram of the cell for extracting lead and zinc from electric arc furnace (EAF) dust together with a photograph of the pilot plant built for 5-kg dust extraction batches (Reproduced from Ref. [19], with kind permission of © The Royal Society of Chemistry)

Table 5.1 Solubility of metal oxides in eutectic mixtures of ChCl with malonic acid (1:1), urea (1:2), and ethylene glycol (1:2), compared to the solubility in aqueous 0.181 mol dm^{-3} NaCl and 3.14 mol dm^{-3} HCl after 2 days; solubility/ppm were measured at 50°C except for last column, which was obtained at 70°C

MO	ChCl with malonic acid (1:1)	ChCl with urea (1:2)	ChCl with ethylene glycol (1:2)	NaCl	HCl	Urea
TiO_2	4	0.5	0.8	0.8	36	
V_2O_3	365	148	142	3,616	4,686	
V_2O_5	5,809	4,593	131	479	10,995	
Cr_2O_3	4	3	2	13	17	
CrO_3	6,415	10,840	7	12,069	2,658	
MnO	6,816	0	12	0	28,124	
Mn_2O_3	5,380	0	7.5	0	25,962	
MnO_2	114	0.6	0.6	0	4,445	
FeO	5,010	0.3	2	2.8	27,053	
Fe_2O_3	376	0	0.7	11.7	10,523	3.7
Fe_3O_4	2,314	6.7	15	4.5	22,403	
CoO	3,626	13.6	16	22	166,260	
Co_3O_4	5,992	30	18.6	4	142,865	
NiO	151	5	9	3.3	6,109	21
Cu_2O	18,337	219	394	0.1	53,942	22,888
CuO	14,008	4.8	4.6	0.1	52,047	234
ZnO	16,217	1,894	469	5.9	63,896	90,019

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Table 5.2 Solubility of metal oxides (g/L) in $[Bmim]HSO_4$ and $[Bmim]HCO_3$ ionic liquids

Metal oxides	$[Bmim]HSO_4$	$[Bmim]HCO_3$
Al_2O_3	11.6	14.8
TiO_2	6.85	25.2
PbO_2	9.65	16.18
MnO_2	2.19	21.37
ZnO	1.378	24.13
Fe_2O_3	2.516	16.22

an analogous manner to that expected for aqueous acidic solutions, whereas more covalent oxides such as TiO_2 exhibit negligible solubility.

The task-specific ionic liquid protonated betaine bis(trifluoromethylsulfonyl) imide($[Hbet]Tf_2N$) was applied for selective solubilization of metal oxides and metal salts by Abbott and coworkers [21]. They found that the metal oxides such as Sc_2O_3, Y_2O_3, La_2O_3, Pr_6O_{11}, Nd_2O_3, Sm_2O_3, Eu_2O_3, Gd_2O_3, Tb_4O_7, Dy_2O_3, Ho_2O_3, Er_2O_3, Tm_2O_3, Yb_2O_3, Lu_2O_3, UO_3, PbO, ZnO, CdO, HgO, CuO, Ag_2O, NiO, PdO, and MnO were soluble in the ionic liquid $[Hbet][Tf_2N]$, whereas iron and cobalt oxides, as well as aluminum oxide and silicon oxide were insoluble or very poorly soluble. Very recently, they have reported solubility trend of metal oxides in various task-specific ionic liquids, such as $[Hbet]Tf_2N$, $[C_4Hbet]Tf_2N$, $[C_6Hbet]Tf_2$, [HbetmPyr] Tf_2N, $[HbetmPip]Tf_2N$, $[HbetmMor]Tf_2N$, $[EtHbetmMor]Tf_2N$, $[HbetPy]Tf_2N$, and $[HbetmIm]Tf_2N$ [22]. It was shown that the oxides, such as Sc_2O_3, Y_2O_3, La_2O_3, Pr_6O_{11}, Nd_2O_3, Sm_2O_3, Eu_2O_3, Gd_2O_3, Tb_4O_7, Dy_2O_3, Ho_2O_3, Er_2O_3, Tm_2O_3, Yb_2O_3, Lu_2O_3, UO_3, PbO, ZnO, CdO, HgO, CuO, Ag_2O, NiO, and PdO, as well as the hydroxides such as $Pb(OH)_2$, $Zn(OH)_2$, $Cd(OH)_2$, $Cu(OH)_2$, $Ni(OH)_2$, $Fe(OH)_2$, $Fe(OH)_3$, $Co(OH)_2$, $Cr(OH)_3$, $Mn(OH)_2$, LiOH, NaOH, KOH, RbOH, CsOH, $Mg(OH)_2$, $Ca(OH)_2$, $Sr(OH)_2$, and $Ba(OH)_2$, were soluble in ionic liquids. However, the oxides such as Co_3O_4, CoO, Co_2O_3, Cr_2O_3, FeO, and Fe_2O_3 were found to be insoluble in the ionic liquids. Ma et al. [23] reported that alumina (Al_2O_3) can be made soluble in the 1-ethyl-3-methyl-imidazolium hydrogen sulfate ($[Emim]HSO_4$) ionic liquid, and the solubility was 3.81 g/L at 20°C which suggests that alumina could be reduced to aluminum at a platinum electrode. Recently, we found that most oxides such as Al_2O_3, TiO_2, PbO_2, ZnO, Fe_2O_3, and MnO_2 were soluble in the 1-butyl-3-methylimidazolium hydrogen sulfate ($[Bmim]HSO_4$) and 1-butyl-3-methylimidazolium bicarbonate ($[Bmim]HCO_3$) ionic liquids; results are given in Table 5.2.

5.2.2 *Mineral Processing*

Efficient separation of metals from their ores followed by metals recovery from concentrate is most important process in metal production. In recent decades, increasing importance has been attached to processing of sulfide ores, such as chalcopyrite, as more attentions have been paid to the green and sustainable development of

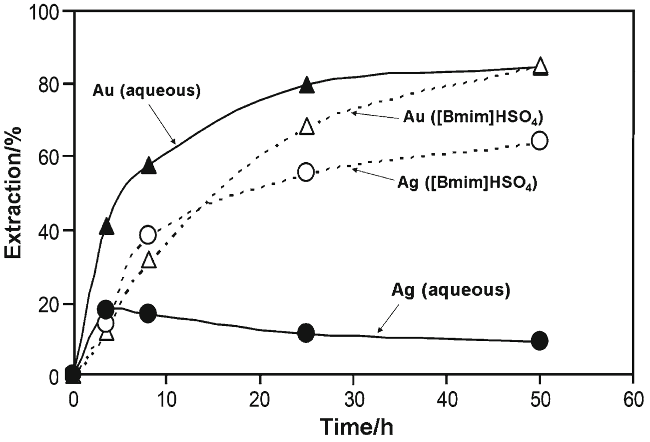


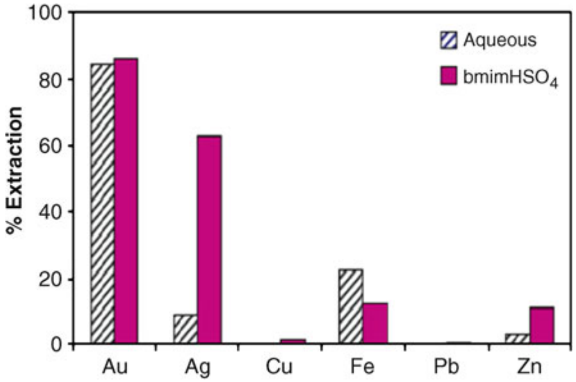
Fig. 5.2 Comparative leaching of gold and silver from ore using aqueous H_2SO_4 or [Bmim]HSO_4 in presence of $Fe_2(SO_4)_3$ and thiourea (Reproduced from Ref. [7], with kind permission of © The Royal Society of Chemistry)

metallurgical industry [7, 11, 24, 25]. Some leaching processes, including chloride leaching, bioleaching, and pressure sulfate leaching, have been developed to recover copper from chalcopyrite concentrates. However, due to the highly toxic nature of cyanide and environmental consequences, the process is very controversial and provokes examination of new leaching agents. Therefore, there has been a worldwide interest in searching of new and green processes for the production of copper under ambient atmosphere and low temperature with low consumption of energy and acid. Ionic liquids were examined as solvents (either as a neat liquid or as aqueous mixtures) for the leaching of gold, silver, copper, and base metals from sulfidic ores [7, 24, 25].

The possibility of application of ionic liquids in processing of copper sulfide ores and base metal sulfides supported by preliminary findings in the use of ionic liquids in the electrorefining of chalcopyrite ($CuFeS_2$) was also indicated by Mccluscey et al. [11]. 1-Butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) ionic liquid with ferric tetrafluoroborate ($Fe(BF_4)_3$) was used as the leaching agent for chalcopyrite leaching, and an extraction of 90% of available copper was achieved at 100°C after 8 h leaching.

Whitehead et al. [7] have reported the recovery of gold and silver from ore in [Bmim]HSO_4 ionic liquid with added urea using iron(III) sulfate as oxidant. Figure 5.2 shows the comparative leaching of gold and silver from ore using aqueous H_2SO_4 or [Bmim]HSO_4 in presence of $Fe_2(SO_4)_3$ and thiourea [7]. The extraction of gold was achieved to be >85% from synthetic oxide ore as well as natural sulfide ore at 20–50°C using ionic liquid as a solvent. Gold extraction was close to results achieved for aqueous system (H_2SO_4/thiourea/$Fe_2(SO_4)_3$), whereas recovery of silver from the natural sulfide ore was significantly higher (≥60%) for the neat ILs compared to aqueous acid solution (<10%). Moreover, high selectivity for the extraction of gold and silver and minimal selectivity of other metals (Cu, Zn, Pb, and Fe) have been reported.

Fig. 5.3 Extraction of metals from Perseverance gold ore in dilute aqueous acid compared with that observed in ionic liquid (20°C, 50 h leaching) (Reproduced from Ref. [24], with kind permission of © Elsevier)



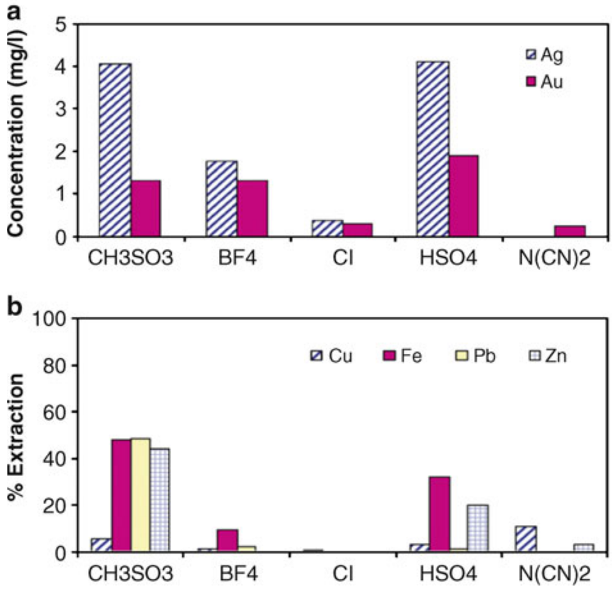


Fig. 5.4 Extraction of gold and silver (**a**) and base metals (**b**) from Perseverance ore using thiourea in ionic liquids with the [Bmim$^+$] cation and different anions (50°C, 48 h leaching) (Reproduced from Ref. [24], with kind permission of © Elsevier)

The [Bmim]HSO$_4$ ionic liquid was used as a solvent medium to leach the gold, silver, copper, and base metals from sulfide ores using thiourea (mainly) in the presence of iron(III) as oxidant by Whitehead et al. [24]. Figure 5.3 shows the comparison of metals extraction from Perseverance gold ore in dilute aqueous acid and that in ionic liquid [24]. Gold and silver recovery was >85% and >60% in this ionic liquid with iron(III)/thiourea at 20–50°C, respectively. Extension of *n*-alkyl chain length in imidazolium cation resulted in decreasing extraction efficiency of gold and silver that might have resulted from the increasing viscosity of ILs. Figure 5.4 shows the leaching results obtained with 1-butyl-3-methylimidazolium ILs containing different types of anions. Ionic liquid [Bmim]HSO_4 was the most effective medium for this purpose [24].

Recently, the leaching of chalcopyrite with [Bmim]HSO_4 and its aqueous solution was studied systematically by our group [26]. A high copper extraction of 95% was achieved by using pure [Bmim]HSO_4 at temperature 90°C, oxygen partial pressure of 81 kPa, stirring speed of 800 rpm, concentrates of 74/65 μm fraction, pulp density of 100 g/L, and leaching time of 24 h. Compared to leaching of chalcopyrite in traditional H_2SO_4–$Fe_2(SO_4)_3$ system, the copper extraction was increased by three to four times. It was found that the order of extraction efficiency of leaching chalcopyrite with ionic liquids is [Bmim]HSO_4 > [Omim]HSO_4 > [Hmim]HSO_4.

As mentioned above, it is clear that most of the metal oxides can be selectively solubilized in ionic liquids, providing a new method to produce the specific metal ion in ionic liquids for further extraction and separation. Especially, it may be used as a potential "green" leaching agent for low-grade ore and refractory oxide ore. Ionic liquids have good selectivity for gold and silver leaching from ores. It is indicated that ILs may be used as a green solvent to develop the efficient processing technology for the recovery of gold and silver from ores, which may replace traditional use of cyanides in the commercial hydrometallurgical leaching of these metals from ores. Although many efforts have been made in this filed, there are still certain challenging issues. Firstly, the low solubility of metal salts is a serious drawback for possible applications of ionic liquids that require high concentrations of dissolved metal salts, for example, the electrodeposition of metals or solvents for the synthesis of nanoparticles [27]. Secondly, availability of quantitative solubility data of metal salts in ionic liquids is lacking. Finally, since it has been reported recently that the coordination environments of the solvates in ionic liquids might be quite unique [28, 29], the dissolution mechanism of metal oxides and the formation or existence of metal ions in ionic liquids are key issues that need to be further investigated.

5.3 Electrodeposition of Metals Using Ionic Liquids

Electrodeposition is a commonly used method to obtain metals and alloys from their aqueous or nonaqueous solutions or molten salts, which is the fundamental process of electrowinning, electrorefining, and electroplating. It has been an essential technology for the advanced electronics industry, besides its conventional industrial uses in electrorefining, decoration, corrosion protection, and other functional surface finishing. However, the metals that can be deposited from aqueous media by the electrochemical potential window of water are limited. Thus, such nonaqueous media as aprotic organic electrolytes and high-temperature molten salts have been investigated as the alternative electrolytes for the electrodeposition of active metals. Room-temperature ionic liquids are the promising electrolytes for the electrodeposition of various metals because they have the merits of both organic electrolytes and high-temperature molten salts. Preliminary studies have shown that ionic liquids have potential as solvents for metal recovery [3–6]. It was found that almost all of the metals that can be deposited from aqueous solutions can also be obtained from ionic liquids, principally most of the active metal such as Li, Na, Al, Mg, and Ti that could not be deposited from aqueous solutions [27–183].

Since 1980s, a large number of studies on the electrodeposition of metals have been reported. Historically, the water-sensitive chloroaluminate first-generation ILs are the most intensively studied. However, in future, the focus will rather be on air- and water-stable ionic liquids due to their variety and the less strict conditions under which they can be handled. Several review articles, books, and book chapters on the electrodeposition of metals and alloys from ILs have already been published [27–183]. Ionic liquids can be classified as water/air sensitive (first-generation ionic liquids based on AlX_3 ($X = Cl$, Br)) and water/air stable (discrete anions based and eutectic solvents/ionic liquids such as $ZnCl_2$, urea, ethylene glycol, and choline chloride). A selection of published examples of the electrodeposition of metals and alloys from ionic liquids is listed in Table 5.3; the original work for each metal can be found in Refs. [23, 29–183]. In this section, we mainly focus on the electrodeposition of active metals such as Al, Mg, and Ti in ionic liquids.

The production value of active metals (such as aluminum, magnesium, etc.) accounts for half that of the nonferrous metal, only lower than that of the steel. It is well known that the active metals cannot be recovered by electrodeposition directly from aqueous solutions due to the liberation of hydrogen molecule during electrolysis, the narrow electrochemical windows, and the chemical reaction with water. The common method applied to obtain active metals is by electrolysis of molten salts of active metals. High-temperature molten salts have been extensively used for the electrowinning of metals such as Li, Na, Ti, and Al at temperatures of up to 1,000°C [5–7]. They have wide potential windows, high conductivities, and high solubilities for metal salts; in fact, they have most of the advantages of aqueous solutions and overcome most of the limitations of aqueous solutions, but clearly, they have many disadvantages such as high temperature, high energy consumption, serious equipment corrosion, and high environmental pollution. Therefore, the development of new effective, low-temperature, and environmentally benign technologies for active metals processing to reduce energy consumption and to lower investment costs and the greenhouse gas emissions is an industrial demand and challenge for the twenty-first century [1].

The "green solvent" ionic liquids may offer potential as environmentally sensitive media and alternatives to active metals production processes. Ionic liquids have attracted extensive attention since they have extraordinary physical properties, superior to those of water or organic solvents. They are usually nonvolatile, nonflammable, less toxic, good solvents for both organics and inorganics, and can be used over a wide temperature range. Moreover, ionic liquids have quite large electrochemical windows, up to 6 V, and hence, they give access to elements which cannot be electrodeposited from aqueous or organic solutions. A fundamental advantage of using ionic liquid electrolytes in electroplating is that, since these are nonaqueous solutions, there is negligible hydrogen evolution during electroplating and the

Table 5.3 Electrodeposition of various metals and alloys in ionic liquids

		Electrodeposition of metal and alloy	
The type of ionic liquids (ILs)		Metal and alloy	System (define as A + B, where A is ionic liquid, and B is the solute, M(I or II) are the metal ions obtained from anodic dissolution of pure metal)
First-generation haloaluminate-based ILs	$AlCl_3$	Al	[BP]Cl/$AlCl_3$, [Emim]Cl/$AlCl_3$, [Bmim]Cl/$AlCl_3$, [TMHA]Cl/$AlCl_3$ [33, 34]
		Fe	[BP]Cl/$AlCl_3$ + $FeCl_2$, [Emim]Cl/$AlCl_3$ + $FeCl_2$ [35–38]
		Co	[BP]Cl/$AlCl_3$ + $CoCl_2$, [Emim]Cl/$AlCl_3$ + $CoCl_2$ [38, 39]
		Ni	[Emim]Cl/$AlCl_3$ + $NiCl_2$ [38]
		Cu	[Emim]Cl/$AlCl_3$ + $CuCl_2$ or CuCl or Cu(II), [Bmim]Cl/$AlCl_3$ + $CuCl_2$ or CuCl or Cu(II), [BP]Cl/$AlCl_3$ + $CuCl_2$ or CuCl or Cu(II), [MP]Cl/$AlCl_3$ + $CuCl_2$ or CuCl or Cu(II) [38, 40, 41]
		Zn	[Emim]Cl/$AlCl_3$ + $ZnCl_2$ or Zn(II), [Bmim]Cl/$AlCl_3$ + $ZnCl_2$ or Zn(II) [42]
		Ga	[Emim]Cl/$AlCl_3$ + $GaCl_3$ or Ga(III) [43, 44]
		Pd	[Emim]Cl/$AlCl_3$ + $PdCl_2$ [45]
		Au	[Emim]Cl/$AlCl_3$ + $AuCl_3$ [46, 47]
		Ag	[Emim]Cl/$AlCl_3$ + AgCl, [Bmim]Cl/$AlCl_3$ + AgCl [38, 48, 49]
		Cd	[Emim]Cl/$AlCl_3$ + AgCl [50]
		In	[DMPIm]Cl/$AlCl_3$ + $InCl_3$ [51]
		Sn	[Emim]Cl/$AlCl_3$ + $SnCl_4$ [52]
		Sb	[BP]Cl/$AlCl_3$ + $SbCl_3$ [53]
		Te	[Emim]Cl/$AlCl_3$ + $TeCl_4$ [54]
		Ti	[Emim]Cl/$AlCl_3$ + $TiCl_2$ [55]
		Cr	[BP]Cl/$AlCl_3$ + $CrCl_2$ [56]
		Hg	[Emim]Cl/$AlCl_3$ + $HgCl_2$ [57]
		Na	[Emim]Cl/$AlCl_3$ + NaCl, [TMHA]Cl/$AlCl_3$ + NaCl + $SOCl_2$ [58]
		Li	[Emim]Cl/$AlCl_3$ + LiCl [59]
		Tl	[Emim]Cl/$AlCl_3$ + $TlCl_3$ [60]
		La	[Emim]Cl/$AlCl_3$ + $LaCl_3$ [61]
		Pt	[Bu_3MeN]Cl/$AlCl_3$ + $(Bu_3MeN)_2PtCl_6$ or $(TEA)_2PtCl_2$ [62]
		GaAs	[Emim]Cl/$GaCl_3$ + $AsCl_3$ [63]
		Pb	[Emim]Cl/$AlCl_3$ + $PbCl_2$ [64]
		Bi	[BP]Cl/$AlCl_3$ + $BiCl_3$ [65]
		Al–Ag	[Emim]Cl/$AlCl_3$ + AgCl [66, 67]
		Al–Fe	[Emim]Cl/$AlCl_3$ + $FeCl_2$ [68]
		Al–Mg	[Emim]Cl/$AlCl_3$ + $MgCl_2$ [69]
		InSb	[Emim]Cl/$InCl_3$ + $SbCl_3$ [29]
		AlSb	[Bmim]Cl/$AlCl_3$ + $SbCl_3$ [29]
		CaSr	[Emim]Cl/$AlCl_3$ + $CaCl_2$ + $SrCl_2$ [29]

(continued)

Table 5.3 (continued)

		Electrodeposition of metal and alloy	
The type of ionic liquids (ILs)		Metal and alloy	System (define as A + B, where A is ionic liquid, and B is the solute, M(I or II) are the metal ions obtained from anodic dissolution of pure metal)
		Al–Mn	[Emim]Cl/AlCl$_3$+MnCl$_2$ [69]
		Al–Ni	[BP]Cl/AlCl$_3$+NiCl$_2$, [Emim]Cl/AlCl$_3$+NiCl$_2$ [38, 70, 71]
		Al–Cu	[BP]Cl/AlCl$_3$+CuCl$_2$ or CuCl, [Emim]Cl/AlCl$_3$+CuCl$_2$ or CuCl [72]
		Al–Co	[BP]Cl/AlCl$_3$+CoCl$_2$, [Emim]Cl/AlCl$_3$+CoCl$_2$ [73]
		Al–Ti	[Emim]Cl/AlCl$_3$+TiCl$_2$, [Bmim]Cl/AlCl$_3$+TiCl$_4$ [74]
		Al–Nb	[BP]Cl/AlCl$_3$+NbCl$_5$ or Nb$_3$Cl$_8$ [75, 76]
		Al–La	[Emim]Cl/AlCl$_3$+LaCl$_3$+SOCl$_2$ [77, 78]
		Al–Mo	[Emim]Cl/AlCl$_3$+(Mo$_6$Cl$_8$)Cl$_4$ [79]
		Al–Zr	[Bmim]Cl/AlCl$_3$+ZrCl$_4$ [80]
		Al–Pt	[Bu$_3$MeN]Cl/AlCl$_3$+(Bu$_3$MeN)$_2$PtCl$_6$ or (TEA)$_2$PtCl$_2$ [81]
		Al–Mo–Mn	[Emim]Cl/AlCl$_3$+(Mo$_6$Cl$_8$)Cl$_4$+MnCl$_2$ [82]
		Al–Cr–Ni	[Emim]Cl/AlCl$_3$+NiCl$_2$+CrCl$_2$ [83]
Discrete anions–based ILs	NTf$_2$	Li	[Emim]TSAC+LiTf$_2$N [86], [Me(CH$_3$OCH$_2$)Pip]Tf$_2$N + LiTf$_2$N [86], [Me(CH$_3$OC$_2$H$_4$)Pip]Tf$_2$N+LiTf$_2$N [86],[Me(CH$_3$(C$_2$H$_4$O)$_2$)Pip]Tf$_2$N+LiTf$_2$N [86], [TMHA]Tf$_2$N+LiTf$_2$N [87], [Me$_3$PrN] Tf$_2$N+LiTf$_2$N [88], [Et$_4$N]TSAC+LiTf$_2$N [88], [Me$_3$(CH$_2$CN)N]Tf$_2$N+LiTf$_2$N [89], [C$_n$H$_{2n+1}$Me$_2$(CH$_2$CN)N]Tf$_2$N+LiTf$_2$N [90], [BMPyrr]Tf$_2$N+LiTf$_2$N [90], [BMPyrr]Tf$_2$N+LiTf$_2$N(ethylene carbonate) [90], [MPPyrr]Tf$_2$N+LiTf$_2$N [91], [MPPyrr]Tf$_2$N+LiTf$_2$N(Pyrr+MeBuSO$_3$) [92], [BMPip]Tf$_2$N+LiTf$_2$N [93] [MPPip]Tf$_2$N+LiTf$_2$N [94]
		CsHg	[Bu$_3$MeN]Tf$_2$N+Cs(I) [95], [Bu$_3$MeN]Tf$_2$N+BOBCalixC$_6$·2Cs(I) [96]
		SrHg	[Bu$_3$MeN]Tf$_2$N+DCH18C6·Sr(II) [96]
		Mg	[MPPip]Tf$_2$N+MgTf$_2$N [97]
		Ti	[Bmim]Tf$_2$N+TiCl$_4$ [98]
		Ta	[BMPyrr]Tf$_2$N+TaF$_6$ [99, 100]
		Fe	[BMPyrr]Tf$_2$N+Fe(Tf$_2$N)$_2$ [101]
		Co	[BMPyrr]Tf$_2$N+Co(Tf$_2$N)$_2$ [102]
		Mn	[Bu$_3$MeN]Tf$_2$N+Mn(II) [103], [BMPyrr]Tf$_2$N+Mn(II) [104]
		Cu	[HexMe$_3$N]Tf$_2$N+Cu(Tf$_2$N)$_2$ [105], [BMPyrr]Tf$_2$N+Cu(I) [106]
		Se	[BMPyrr]Tf$_2$N+SeCl$_4$ [106]

(continued)

Table 5.3 (continued)

The type of ionic liquids (ILs)		Electrodeposition of metal and alloy Metal and alloy	System (define as A + B, where A is ionic liquid, and B is the solute, M(I or II) are the metal ions obtained from anodic dissolution of pure metal)
		Zn	$[Me_3PrN]Tf_2N + Zn(Tf_2N)_2$ [107], $[Bu_3MeN]Tf_2N + Zn(Tf_2N)_2$ [108]
		Zn–Mn	$[Bu_3MeN]Tf_2N + Mn(II), Zn(II)$ [108]
		Al	$[BMPyrr]Tf_2N + AlCl_3$ [108]
		Au	$[Bmim]Tf_2N + NaAlO_4$ [109]
		In	$[BMPyrr]Tf_2N + InAlCl_3$ [29]
		Si	$[Emim]Tf_2N + (Emim)_2SiF_6$, $[BMPyrr]Tf_2N + SiCl_4$ [110–112]
		Sn–Cu	$[HexMe_3N]Tf_2N + Sn(Tf_2N)_2$ [113]
Discrete anions–based ILs	PF_6^-	LiHg	$[Bmim]PF_6 + LiPF_6$ [114]
		NaHg	$[Bmim]PF_6 + NaPF_6$ [114]
		KHg	$[Bmim]PF_6 + KPF_6$ [114]
		Ge	$[Bmim]PF_6 + GeCl_4$, $[Bmim]PF_6 + GeBr_4$, $[Bmim]PF_6 + GeI_4$ [115–121]
	BF_4^-	Mg	$[Bmim]BF_4 + MgTf_2$ [122]
		Pd–In	$[Emim]BF_4 + PbCl_2 + InCl_2$ [123]
		Pd–Ag	$[Emim]BF_4 + PdCl_2 + AgCl$ [124]
		Pd–Au	$[Emim]BF_4 + PdCl_2 + Au(I)$ [125]
		Pd	$[Emim]BF_4 + PdCl_2$ [123–125]
		Cu	$[Emim]BF_4 + Cu(II)$ [126]
		Ag	$[Emim]BF_4 + AgCl$ [124], $[Emim]BF_4 + AgBF_4$ [49]
		Au	$[Emim]BF_4 + Au(I)$ [125]
		Zn	$[Emim]BF_4 + ZnCl_2$ [126, 127]
		Cd	$[Emim]BF_4 + CdCl_2$ [50]
		In	$[Emim]BF_4 + InCl_2$ [123, 128, 129]
		Sn–In	$[Emim]BF_4 + SnCl_2 + InCl_2$ [129]
		Sn	$[Emim]BF_4 + SnCl_2$ [129, 130]
		Sb	$[Emim]BF_4 + SbCl_3$ [128, 131]
		In–Sb	$[Emim]BF_4 + PbCl_3 + InCl_3$ [128]
Eutectics	$ZnCl_2$	Fe	$[Emim]Cl/ZnCl_2 + FeCl_2$ [132]
		Co	$[BP]Cl/ZnCl_2 + CoCl_2$ [133], $[Emim]Cl/ZnCl_2 + CoCl_2$ [134]
		Cu	$[Emim]Cl/ZnCl_2 + CuCl$ [135]
		Zn	$[(HOC_2H_4)Me_3N]Cl/ZnCl_2$ [136], $[Emim]Cl/ZnCl_2$ [137], $[Emim]Br/ZnBr_2$ [138]
		Cd	$[Emim]Cl/ZnCl_2 + CdCl_2$ [139]
Eutectics	$ZnCl_2$	Te	$[Emim]Cl/ZnCl_2 + TeCl_4$ [140]
		Zn–Mg	$[Emim]Br/ZnBr_2 + MgBr_2$ [29]
		Zn–Fe	$[Emim]Cl/ZnCl_2 + FeCl_2$ [29]

(continued)

Table 5.3 (continued)

The type of ionic liquids (ILs)		Electrodeposition of metal and alloy Metal and alloy	System (define as A + B, where A is ionic liquid, and B is the solute, M(I or II) are the metal ions obtained from anodic dissolution of pure metal)
		Zn–Co	[BP]Cl/$ZnCl_2+CoCl_2$ [141, 142], [Emim]Cl/$ZnCl_2+CoFeCl_2$ [133, 134], $[(HOC_2H_4)Me_3N]Cl/ZnCl_2+CoCl_2$ [136]
		Zn–Ni	[Emim]Cl/$ZnCl_2+NiCl_2$ [143]
		Zn–Pd	[Emim]Cl/$ZnCl_2+PdCl_2$ [144]
		Zn–Pt	[Emim]Cl/$ZnCl_2$ [145, 146], [Emim]Cl/$ZnCl_2+PtCl_2$ [146]
		Zn–Cu	[Emim]Cl/$ZnCl_2+CuCl$ [147]
		Zn–Ag	[Emim]Cl/$ZnCl_2$ [148]
		Zn–Cd	[Emim]Cl/$ZnCl_2+CdCl_2$ [139]
		Zn–Te	[Emim]Cl/$ZnCl_2+TeCl_4$ [140]
		Zn–Co–Dy	[Emim]Cl/$ZnCl_2+CoCl_2+DyCl_3$ [149]
		Zn–Sn	$[(HOC_2H_4)Me_3N]Cl/ZnCl_2+SnCl_2$ [136]
	Urea	Fe	Urea/NaBr + $FeCl_2$ [150], Urea/acetamide/NaBr/KBr + $FeCl_2$ [151]
		Co	Urea/acetamide/NaBr + $CoCl_2$ [152]
		Ni	Urea/$[(HOC_2H_4)Me_3N]Cl+NiO$ [153]
		Cu	Urea/$[(HOC_2H_4)Me_3N]Cl+CuO$ [153], Urea/$[(HOC_2H_4)Me_3N]Cl+Cu_2O$ [154], Urea/$[(HOC_2H_4)Me_3N]Cl+CuCl_2$ [155]
		Ag	Urea/$[(HOC_2H_4)Me_3N]Cl+Ag_2O$ [153]
		Zn	Urea/$[(HOC_2H_4)Me_3N]Cl+ZnCl_2$ [153], Urea/$[(HOC_2H_4)Me_3N]Cl+ZnO$ [156]
		Cd	Urea/$[(HOC_2H_4)Me_3N]Cl+CdCl_2$ [156]
		Ga	Urea/$[(HOC_2H_4)Me_3N]Cl+GaCl_3$ [155]
		In	Urea/$[(HOC_2H_4)Me_3N]Cl+InCl_3$ [155]
		Pb	Urea/$[(HOC_2H_4)Me_3N]Cl+PbO_2$ [153]
		Se	Urea/$[(HOC_2H_4)Me_3N]Cl+SeCl_4$ [155]
		Fe–Nd	Urea/acetamide/NaBr/KBr + $FeCl_2+NdCl_3$ [151]
		Fe–Sm	Urea/NaBr + $FeCl_2+SmCl_3$ [150]
		Co–Sm	Urea/acetamide/NaBr + $CoCl_2+SmCl_3$ [152]
		Cu–In	Urea/$[(HOC_2H_4)Me_3N]Cl+CuCl_2+InCl_3$ [155]
		Cu–In–Se	Urea/$[(HOC_2H_4)Me_3N]Cl+CuCl_2+InCl_3+SeCl_4$ [155]
		Cu–In–Ga–Se	Urea/$[(HOC_2H_4)Me_3N]Cl+CuCl_2+InCl_3+SeCl_4+GaCl_4$ [155]
		Zn–Pb	Urea/$[(HOC_2H_4)Me_3N]Cl+ZnO+PbO_2$ [153]
		Zn–S	Urea/$[(HOC_2H_4)Me_3N]Cl+ZnCl_2$, Na_2S [156]
		Cd–S	Urea/$[(HOC_2H_4)Me_3N]Cl+CdCl_2+Na_2S$ [156]

(continued)

Table 5.3 (continued)

		Electrodeposition of metal and alloy	
The type of ionic liquids (ILs)		Metal and alloy	System (define as A + B, where A is ionic liquid, and B is the solute, M(I or II) are the metal ions obtained from anodic dissolution of pure metal)
		Cd–Se	Urea/[(HOC$_2$H$_4$)Me$_3$N]Cl + CdCl$_2$ + Na$_2$SeSO$_3$ [156]
	CrCl$_2$·6H$_2$O	Cr	[(HOC$_2$H$_4$)Me$_3$N]Cl + CrCl$_2$·6H$_2$O [84]
	Ethylene Glycol	Zn–Sn	Urea/[(HOC$_2$H$_4$)Me$_3$N]Cl + ethylene glycol + ZnCl$_2$ [156]
		Cu	[(HOC$_2$H$_4$)Me$_3$N]Cl + ethylene glycol + CuCl$_2$·2H$_2$O [154]
		Zn	[(HOC$_2$H$_4$)Me$_3$N]Cl + ethylene glycol + ZnCl$_2$ [85]
		Sn	[(HOC$_2$H$_4$)Me$_3$N]Cl + ethylene glycol + SnCl$_2$ [85]

BP: 1-*n*-butylpyridinium, Emim: 1-ethyl-3-methylimidazolium, Bmim: 1-*n*-butyl-3-methylimidazolium, TMHA: trimethylammonium, MP: 1-metylpyridinium, DMPIm: 1-Propyl-2,3-dimethylimidazolium, TEA: tetraethylammonium, TSAC: (CF$_3$SO$_2$) (CF$_3$CO)N, Et$_4$N: tetraethylammonium, BMPyrr: 1-*n*-butyl-1-methylpiperidinium, MPPyrr: 1-methyl-1-*n*-propylpyrrolidinium, MPPip: 1-methyl-1-*n*-propylpiperidinium, BMPip: 1-*n*-propyl-1-methylpiperidinium, Bu$_3$MeN: *n*-butyl-trimethylammonium, HexMe$_3$N: *n*-hexyltrimethylammonium, Me$_3$PrN: trimethyl-*n*-propylammonium, Bu$_3$MeN: *n*-butyl-trimethylammonium, Tf$_2$N: (CF$_3$SO$_2$)$_2$N

coatings possess the much superior mechanical properties of the pure metal. This may allow thinner deposits to be used, thus reducing overall material and power consumption still further.

5.3.1 Electrodeposition of Aluminum

Aluminum is an indispensable metal to modern manufacturing. Its low density and corrosion resistance make it the preferred metal for many manufactured products, from spacecraft components to beverage cans. As is known, the main commercial production of aluminum is carried out by electrolysis of molten cryolite (Na$_3$AlF$_6$) in which aluminum oxide is dissolved at an elevated temperature of about 1,200 K.

The first electrodeposition of aluminum from an ionic liquid was reported in 1994 by Carlin et al. [157]. Two years later, Zhao et al. [158] studied the aluminum deposition processes on tungsten electrodes in trimethylphenylammonium chloride/aluminum chloride with mole ratio 1:2. It was shown that the deposition of aluminum was instantaneous as a result of three-dimensional nucleation with hemispherical diffusion-controlled growth, underpotential deposition of aluminum, corresponding to several monolayers. Liao et al. investigated the constant current electrodeposition of bulk aluminum on copper substrates was in 1-methyl-3-ethylimidazolium chloride/aluminum chloride ([Emim]Cl/AlCl$_3$) with mole ratio

Table 5.4 Parameters of electrowinning and electrorefining in ionic liquids and in industrial processes

Parameter	Electrowinning in ionic liquids	Conventional industrial electrowinning	Electrorefining in ionic liquids	Industrial electrorefining
Cell voltage	1.5–3.5	4.2–5.0	1.0	5.0–6.0
Energy consumption, kWh/kg	3.0–4.0	13.2–18.7	2.5–3.0	15–18
Current density, A/m^2	200–700	–	300	–
Electrode distance, mm	5–20	100	–	–
Temperature, °C	25–150	850–1,000	25–100	850–1,000
CO emission, kg/t-Al	0	340	–	–
CF_4 emission, kg/t-Al	0	1.5–2.5	–	–

1:2 [159]. It was found that the quality of the electrodeposit was greatly enhanced by the addition of benzene as a cosolvent, and electrodeposits produced exhibited a grain size of the order of 5–15 μm.

Reddy et al. [160, 161] studied the reduction of aluminum in a mixture of 1-butyl-3-methylimidazolium chloride and aluminum chloride ionic liquid in the range of 100–140°C. It was shown that high-purity (>99.9%) aluminum was deposited at the copper cathode and chlorine gas was evolved at the graphite anode, when the current density was 200–400 A/m^2 and 0.1–0.2-mm-thick dense aluminum deposition was obtained. Again, they studied the electrowinning of aluminum with molar ratio from 1:1 to 1:2 at temperature range 90–140°C and with cell voltage from 2.50 to 3.40 V [162, 163]. The optimum electrowinning parameters under laboratory conditions were determined to be 110°C, 3.50 V, and electrolyte molar ratio of 1:1.7. Table 5.4 gives the parameters of electrowinning and electrorefining in ionic liquid and in industrial process. Large-scale aluminum electrowinning experiments in ionic liquid electrolyte were carried out in a batch recirculation type of 5 L electrowinning cell along with ceramic piston pump for electrolyte recirculation [164]. The schematic setup and cell are shown in Fig. 5.5.

Jiang et al. studied the electrodeposition and surface morphology of aluminum on tungsten (W) and aluminum (Al) electrodes from 1:2 M ratio of [Emim]Cl/$AlCl_3$ ionic liquids [165, 166]. They found that the deposition process of aluminum on W substrates was controlled by instantaneous nucleation with diffusion-controlled growth. It was shown that the electrodeposits obtained on both W and Al electrodes between −0.10 and −0.40 V (vs. AI(III)/Al) are dense, continuous, and well adherent. Dense aluminum deposits were also obtained on Al substrates using constant current deposition between 10 and 70 mA/cm^2. The current efficiency was found to be dependent on the current density varying from 85% to 100%. Liu et al. showed in similar work that the 20-μm-thick dense smooth aluminum deposition was obtained with current density 200 A/m^2 for 2 h electrolysis [167].

Endres et al. [168, 169] reported that nano- and microcrystalline aluminum can be electrodeposited in 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)

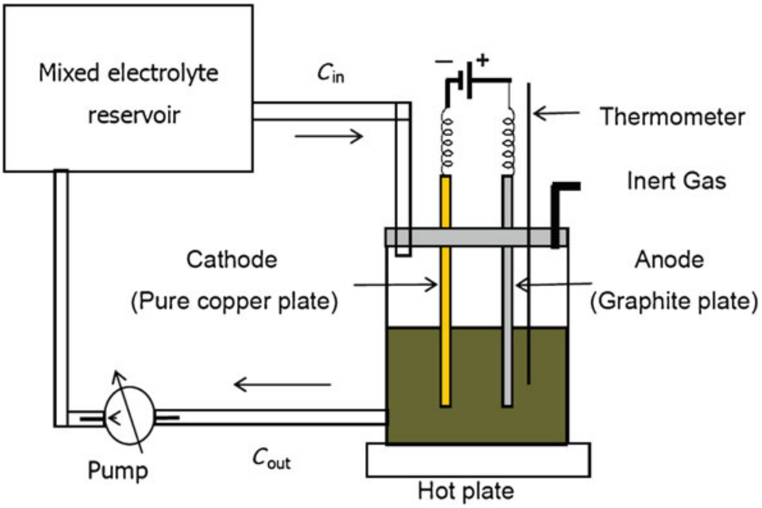


Fig. 5.5 Experimental setup of batch recirculating electrodeposition (Reproduced from Ref. [164], with kind permission of © The Electrochemical Society)

amide ([BMP]Tf_2N), 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide ([Emim]Tf_2N), and trihexyl-tetradecyl phosphonium bis(trifluoromethylsulfonyl) amide ([$P_{14,6,6,6}$]Tf_2N). It was found that the ionic liquids [BMP] Tf_2N and [Emim] Tf_2N form biphasic mixtures in an $AlCl_3$ concentration range 1.6–2.5 mol/L and 2.5–5 mol/L, respectively. Moreover, the electrodeposition of aluminum at room temperature occurs only from the upper phase at $AlCl_3$ concentrations ≥1.6 mol/L and ≥5 mol/L in the ionic liquids [BMP]Tf_2N and [Emim] Tf_2N, respectively.

The electrodeposition of Al on Au(111) and polycrystalline Au substrates in 1-butyl-1-methyl-pyrrolidinium bis(trifluoromethylsulfonyl)amide([$Py_{1,4}$]Tf_2N), and [Emim]Tf_2N, was reported by Moustafa et al. [170]. It was shown that the electrodeposition process is completely reversible, and a cathodic peak at an electrode potential of about 0.55 V versus Al/Al(III) is correlated to the aluminum UPD process. The 100-nm-thick dense aluminum deposition was obtained at −2.0 V versus Al/Al(III). Dreisinger et al. [171, 172] studied the aluminum electrodeposition in $AlCl_3$–trihexyl(tetradecyl) phosphonium chloride ([$P_{14,6,6,6}$]Cl/$AlCl_3$) system at an $AlCl_3$ concentration of 0.67 mol fraction (x_{AlCl3}) at a constant potential over a range of potentials (0.3–0.75 V). It was shown that the energy consumption in this system is 1.06–1.32 kWh/kg Al which is lower than Reddy's result.

Recently, aluminum was successfully electrodeposited on Al electrodes from 1: 2 M ratio of triethylamine hydrochloride to aluminum chloride by the constant potential electrolysis by Gao et al. [173]. They found that the deposition process of aluminum on Al substrates was controlled by instantaneous nucleation with diffusion-controlled growth and the electrodeposits obtained on Al electrodes were dense, continuous, and well adherent, and the current efficiency was 73% at −2.4 V (vs. Pt) for 20 min electrolysis at room temperature. The purity of aluminum electrodeposits on Al electrodes was above 96% (w).

Aluminum was deposited on mild steel in [Bmim]Cl/$AlCl_3$ ionic liquid with 1:2 M ratio of [Bmim]Cl to $AlC1_3$ under different conditions [174, 175]. Figure 5.6 shows the aluminum deposit on the different metal substrates with different electrolysis time. It was shown that a thicker aluminum deposition layer could be obtained at higher current, but the tree crystal phenomena would become more serious if the current is too large. A better aluminum deposition layer with a thickness of 70 μm could be obtained at 100°C and current density about 110.09 A/m^2, and the aluminum purity of the deposition was over 99.9%. The effect of additives of C_7H_8 and NH_4Cl on the electrodeposition of aluminum was studied. Figure 5.7 gives the SEM of electrodeposited Al layer surface by electrowinning at 373.15 K. It was found that the cell voltage becomes smaller when NH_4Cl is added in ionic liquid, but it becomes bigger for C_7H_8, the crystal size of the deposition layers (Fig. 5.7) becomes smaller on addition of NH_4Cl or C_7H_8. The color of the layer becomes brighter on adding NH_4Cl, but it becomes blacker with added C_7H_8.

The published works mentioned above show the opportunity to save significant amounts of energy by substituting room-temperature ionic liquids as the electrolyte to produce primary aluminum and electrorefine aluminum scrap, which demonstrated the feasibility of low-temperature electrolysis in the range of 25–110°C. Energy consumption for the electrolysis using ionic liquids was in the range of 9.5–10.5 kWh/kg, which is 30–37% lower than energy consumed by the current technology. The technology introduced above has the potential to displace the Hall–Héroult process and save significant energy for the aluminum industry. The technology of aluminum electrorefining in ionic liquids has been strongly supported as an industrial technologies project by the partners of University of Alabama, Albany Research Center, Century Aluminum Company, Secat, Inc., and University of Kentucky.

5.3.2 Electrodeposition of Magnesium

Magnesium is the third most commonly used structural metal, following iron and aluminum. Magnesium and its alloys offer a high potential for use as lightweight structural materials in automotive and aircraft applications. As magnesium is a very reactive metal ($E = -2.37$ V vs. NHE), it can be only obtained from aprotic electrolytes. Magnesium is commonly produced by electrowinning from a molten mixture with alkali chloride at 700–800°C. The energy consumption is 10–13 kWh/kg Mg. It is worth noting that the electrodeposition of magnesium in organic electrolytes or in ionic liquids is feasible but not straightforward (Fig. 5.8).

Electrodeposition and dissolution of magnesium film were studied from the ionic liquid of $[Bmim]BF_4$ with 1 M $Mg(CF_3SO_3)_2$ at room temperature by Nuli et al. [176, 177]. It was shown that magnesium can be electrodeposited on Ag substrate and the deposits were dense. They also studied the electrochemical magnesium deposition and dissolution on metal substrates in organic electrolyte

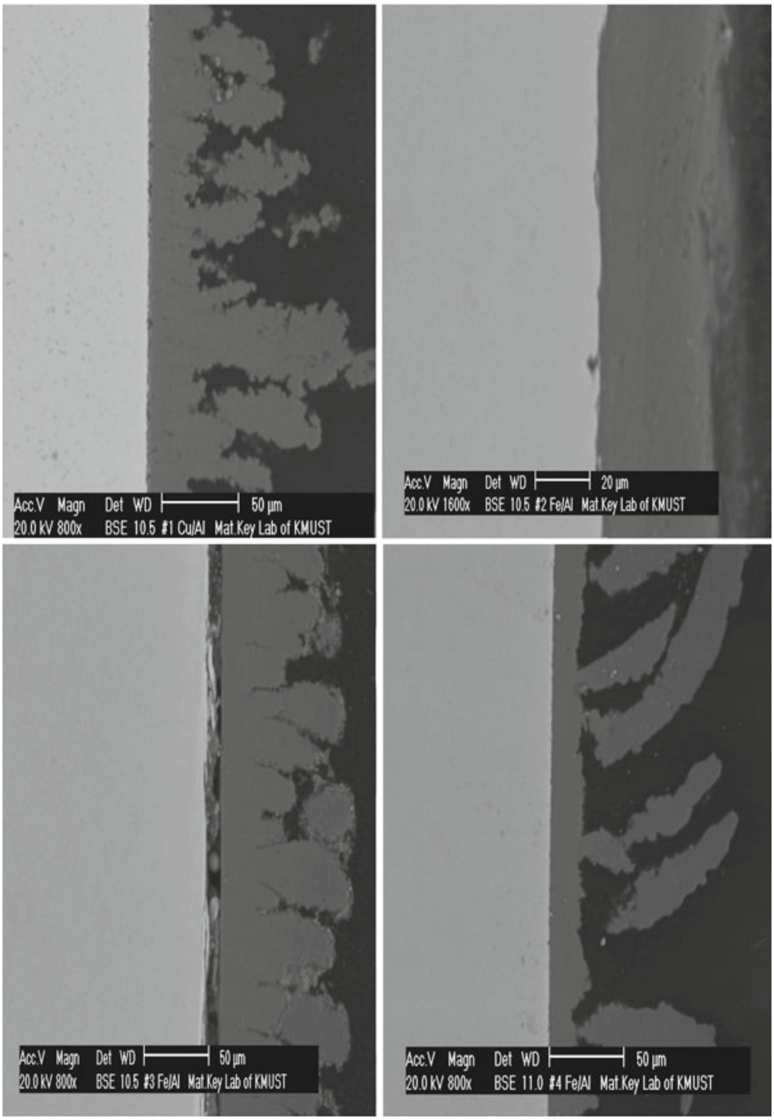


Fig. 5.6 The aluminum deposit on the different metal substrates with different electrolysis time: (**a**) electrodeposition on Cu substrate for 4 h, (**b**) electrodeposition on mild steel substrate for 4 h, (**c**) electrodeposition on mild steel substrate for 6 h, and (**d**) electrodeposition on stainless steel substrate for 6 h

0.25 M $Mg(AlCl_2EtBu)_2$/tetrahydrofuran and ionic liquid 0.3 M $Mg(CF_3SO_3)_2$/[Bmim]BF_4. It was shown that the deposited magnesium can react with silver substrate to form silver–magnesium alloy [178].

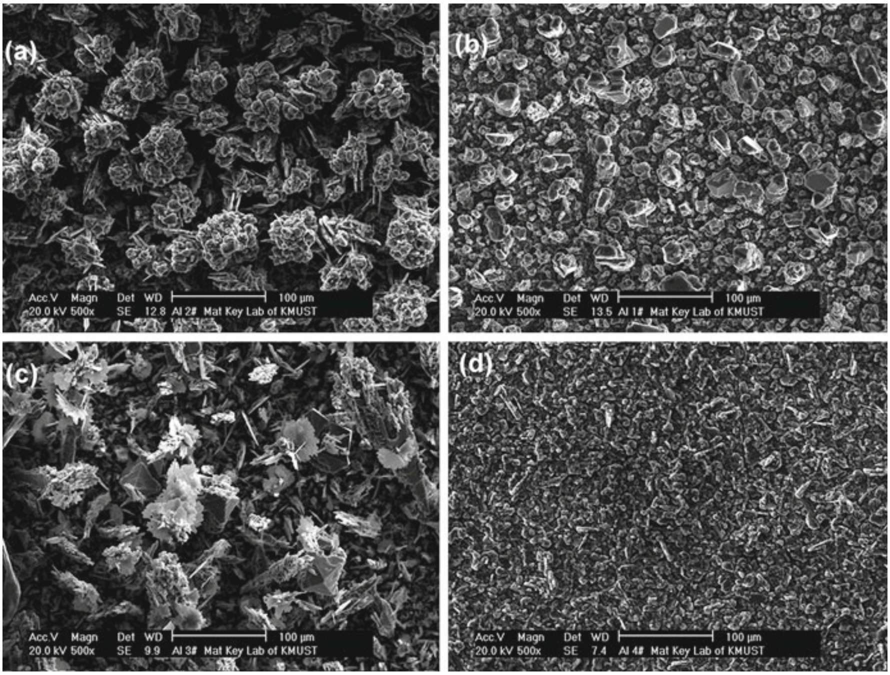
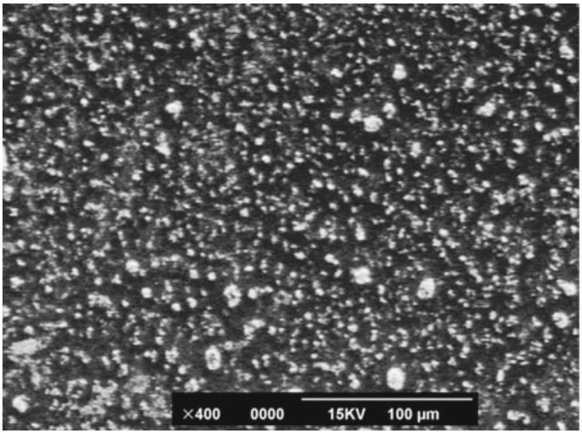


Fig. 5.7 SEM of electrodeposited Al layer surface by electrowinning at 373.15 K for 6 h with different additives and currents: (**a**) $[Bmim]Cl/AlCl_3$ (100%), $i=130$ A/m^2; (**b**) $[Bmim]Cl/AlCl_3+C_7H_8$ (0.942 mol/L), $i=130$ A/m^2; (**c**) $[Bmim]Cl/AlCl_3$ (100%), $i=45.45$ A/m^2; (**d**) $BMIC\text{-}AlCl_3+NH_4Cl$ (0.04 mol/L), $i=45.45$ A/m^2

Fig. 5.8 SEM of electrodeposited Mg on the Ag substrates (Reproduced from Ref. [177], with kind permission of © Elsevier)



The electrochemical deposition of magnesium was investigated in the ionic liquids $[Emim]BF_4$, 1-butyl-1-methylpyrrolidinium triflate ([BMP]TfO) and 1-butyl-1-methylpyrrolidinium bis (trifluoromethylsulfonyl)amide ($[BMP]Tf_2N$) by Cheek et al. [179]. It was found that the electroreduction of Grignard reagent in the ionic liquid [BMP]Tf_2N might lead to the formation of thin Mg films which, under air, are susceptible to oxidation to magnesium oxide and hydroxide. Furthermore, the reduction of $Mg(ClO_4)_2$ in [BMP]TfO is followed by an anodic process showing typical stripping peak behavior. However, the current efficiency for magnesium deposition is not very high. The electrodeposition of magnesium in ionic liquids should, thermodynamically, be possible. Nevertheless, more effort is required to find a suitable ionic liquid and suitable magnesium precursors for a technically relevant process.

5.3.3 Electrodeposition of Titanium

Titanium owes its great importance due to its excellent mechanical and corrosion performance. Titanium is produced by reduction of $TiCl_4$ with magnesium (Kroll method) or sodium (Hunter method). As the cost of Hunter method is higher than Kroll method, Kroll method is considered the most efficient method for titanium electrodeposition.

The electrochemistry of titanium (IV) has been examined in acidic 1-ethyl-3-methylimidazolium chloride/$AlCl_3$ ([Emim]Cl/$AlCl_3$) in 1990 by Carlin et al. [180]. It was shown that titanium is reduced to Ti(III) and Ti(II) in two one-electron steps, both of which exhibit slow electron-transfer kinetics. Ten years later, Mukhopadhyay et al. studied the deposition of Ti nanowires at room temperature from 0.24 M $TiCl_4$ in the ionic liquid 1-butyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)amide [181]. They found that up to six wires grow at constant potential over a period of about 20 min; wires exhibit a narrow width distribution of 10 ± 2 nm and have a length of more than 100 nm. The chemical and electrochemical behavior of titanium was examined in the Lewis acidic [Emim]Cl/$AlCl_3$ molten salt at 353.2 K. The electrodeposition of Al–Ti alloys at Cu rotating disk and wire electrodes was investigated by Tsuda et al. [55]. It was found that Al-Ti alloys which contain up to 19% (atomic fraction) titanium, could be electrodeposited from saturated solutions of Ti(II) in the 33.3–66.7 (mass fraction) melt at low current densities, but the titanium content of these alloys decreased with the increase in the reduction current density.

Mukhopadhyay et al. [98] studied the titanium electrodeposition on a Au(111) substrate in the l-methyl-3-butyl-imidazolium bis(trifluoromethylsulfone) imide ([Bmim]BTA) ionic liquids with 0.24 M $TiCl_4$ at room temperature. It was found that $TiCl_4$ is converted to $TiCl_2$ in a first step, which is subsequently reduced to metallic Ti. Two-dimensional (2D) clusters form preferentially on the terraces in underpotential deposition range. At a potential of −1.8 V, a dense layer of three-dimensional (3D) clusters of titanium of 1–2 nm thickness is formed. The electrochemical reduction of tetravalent titanium species in hydrophobic 1-*n*-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide ([BMP]TFSI) room-temperature ionic liquid was studied by Kayayana et al. [182]. It was found that the stepwise reduction from Ti(IV) to Ti(III) and probably Ti(II) in [BMP]TFSI containing $TiBr_4$ without [BMP]Br. The potentiostatic cathodic reduction gave some deposits at 180°C. The reduction of Ti(IV) species at −2.3 V led to the deposition of some Ti compounds containing

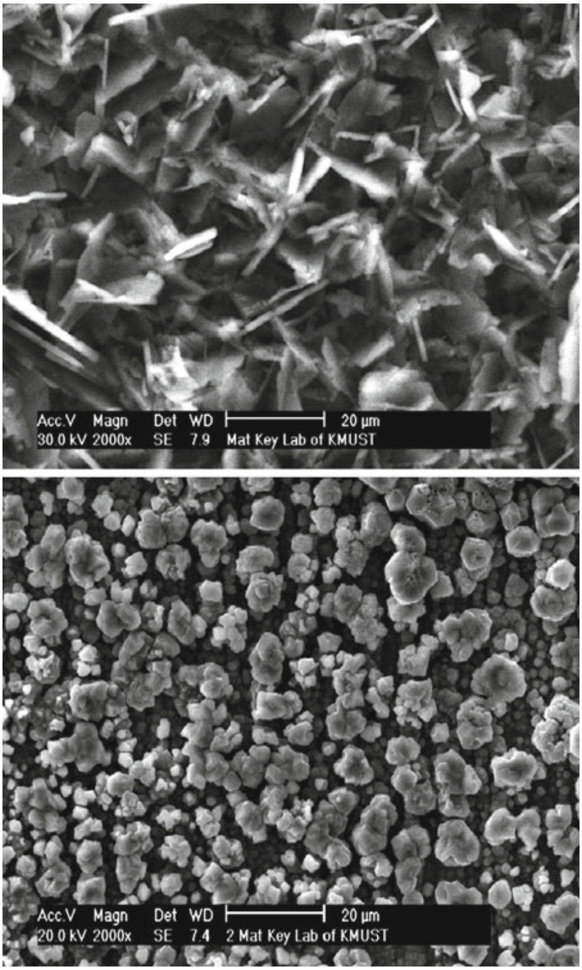


Fig. 5.9 SEM of electrodeposited Ti–Al alloy on the Ti (*top*) and Cu (*bottom*) substrates

TFSI anions. The electrodeposit containing Ti without TFSI anions was obtained by the potentiostatic cathodic reduction below −3.0 V. Andriyko et al. studied the electrochemical behavior of titanium tetrachloride solutions in 1-butyl-2,3-dimethylimidazolium azide ([BMMIm]N_3) at 65°C [183]. It was found that Ti (IV) formed a hexaazidotitanate complex which can only be irreversibly reducted to Ti(III) species.

Recently, The reduction of $TiCl_4$ has been studied in Lewis acid ionic liquids [Bmim]Cl/$AlCl_3$ in our laboratory. It was found that the aluminum–titanium alloy of 14 µm thickness as given in Fig. 5.9 can be deposited on the titanium or aluminum substrate. Thermodynamically, Ti deposition should be possible in thick layers in ionic liquids, but the right ionic liquid and especially the right titanium precursors still have to be found. An idea might be to make $Ti(Tf_2N)_4$ or similar compounds for titanium electrodeposition.

From the above, it is clear that almost all of the metals can be electrodeposited from ionic liquids. However, there are still some key issues that need further study. The deposited layers of metal from ionic liquids are too thin to use for the commercial industrial production. The efficiency for Mg and Ti deposition was not very high, and most metals were deposited from the aluminum chloride–based ionic liquids as mention above. It is known that these ionic liquids can absorb significant amount of water from the air which can react with the ionic liquids based on PF_6 or $AlCl_3$ to produce HF or HCl. Therefore, efforts may be directed to find more suitable ionic liquid and suitable precursors for a technically relevant process. Again, the mechanism of the electrodeposition of metals from ionic liquids still needs to be clarified.

5.4 Ionic Liquids in Solvent Extraction of Metal Ions

Solvent extraction is a process that allows the separation of two or more components due to their unequal solubilities in two immiscible liquid phases. It is an important method in hydrometallurgy for separation of metal ions from their solution. The unique properties, such as good stability, nonvolatility, a wide liquid range, low flammability, and adjustable miscibility and polarity, the hydrophilic and hydrophobic depending on the structures of cations and anions, make ILs attractive as alternative media in liquid–liquid extraction of metal ions from aqueous solutions.

Dai et al. [184] observed large distribution coefficient values for extraction of $Sr(NO_3)_2$ from aqueous solutions by using dicyclo-hexyl-18-crown-6 (DCH18C6) as extractant and imidazolium hexaflurophosphates and bis[(trifluoromethane)-sulfonyl]amides as solvent. Rogers et al. [11] reported the extraction of sodium, cesium, and strontium nitrates from aqueous solution into 18-crown-6 (18C6), DCH18C6, and 4,4′(5′)-di-(tert-butylcyclohexanol)-18-crown-6 (Dtb18C6) in $[C_n\text{mim}]PF_6$ (n = 4, 6, 8). The best extraction was with Dtb18C6, and the selectivity pattern was $Sr^{2+} > Cs^+ > Na^+$. Chun et al. [185] observed the low extraction efficiency of competitive alkali metal salts from aqueous phase in $[C_n\text{mim}]PF_6$ (n = 4–9), the high extraction efficiency was when extractant, DCH18C6, was added, and the selectivity trend was $K^+ > Rb^+ > Sr^{2+}\ Cs^+ > Na^+ >= Li^+$.

Since the partitioning of metal ions from aqueous solutions into ionic liquids is inefficient as a result of the tendency of the metal cations to remain hydrated in the aqueous phase, additional extractants, such as crown ethers [185], calixarenes [186], dithizone [187], and others [188–214], were used. These species significantly enhance the partitioning of metal ions by forming complexes. Most of the research work has been concentrated on the extraction and separation of radioactive metals [187, 188, 191, 192, 196–213], alkali metals [185, 186, 193, 194], heavy metals [184, 192–196], and rare earth metals [197–215] and Aluminum [216, 217]. The work reported in this field has been reviewed by Zhao et al. [190] and Chen et al. [211]. The progress made in IL extractions of metal ions (alkali, alkaline earth, heavy metals, radioactive elements, and rare earth) in recent years has been encapsulated in Table 5.5.

Table 5.5 Extractions of metal ions in ionic liquids

Substances	Metal ions	Extractant/ligand/ metal chelator	Extractant/ligand/ metal chelator	References
Alkali metals	Li^+, Na^+, K^+, Rb^+, Cs^+	$[C_n mim]PF_6$ (n = 4–9)	DC18C6	185, 193
	Na^+, Cs^+	$[C_n mim]PF_6$ (n = 4, 6, 8)	18C6, DC18C6, Dtb18C6	194
	Cs^+	$[C_n mim]Tf_2N$ (n = 2, 3, 4, 6, 8)	BOBCalixC6	186
	Na^+, K^+, Cs^+	$[C_n mim]Tf_2N$ (n = 2, 4, 6, 8)	DC18C6, *N*-alkylaza-18-crown-6 ethers	184
Alkaline earth metals	Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}	$[C_n mim]PF_6$ (n = 4–9)	DC18C6	193
	Sr^{2+}	$[C_n mim]PF_6$ (n = 4, 6, 8)	18C6, DC18C6, Dtb18C6	194
	Sr^{2+}	$[R_1R_2MeIM]PF_6$ $[R_1R_2MeIM]Tf_2N$	DC18C6	184
	Sr^{2+}	$[C_n mim]Tf_2N$ (n = 2, 4, 6, 8)	DC18C6, *N*-alkyl aza-18-crown-6 ethers	195
	Sr^{2+} and Cs^+	$[Bu_3MeN]TFSI$	DCH18C6, BOBCalixC6	196
Heavy and radioactive metals	Pb^{2+}	$[C_n mim]PF_6$ (n = 4–9)	DC18C6	192
	Cu^{2+}, Ag^+, Pb^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}	$[C_4mim]PF_6$	Dithizone	187
	Cd^{2+},Co^{2+}, Ni^{2+}, Fe^{3+}, Hg^{2+}	$[C_4mim]PF_6$, $[C_6mim]PF_6$	PAN, TAN	197
	Ag^+	$[C_n mim]PF_6$ (n = 4, 6, 8)	Calix[4]arene-bearing pyridine	198
	Cu^{2+}, Cr^{6+}, Zn^{2+}	$[C_n mim]BF_4$ (n = 1, 3, 6, 8, 10) $[C_n mim]PF_6$ (n = 6, 10)	–	199
	Hg^{2+}, Cd^{2+}	TSILs	–	191, 192
	Nd^{3+}, La^{3+}, Er^{3+}, Ce^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Ho^{3+}	$[C_4mim]PF_6$	CMPO	200
	Th^{4+}, U^{2+}, Pu^{4+}	$[C_4mim]PF_6$, $[C_4mim]NO_3$	Dtb18C6, CMPO, TBP	188, 201
	Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}	$[C_8mim]BF_4$, $[3MOPYR]BF_4$, $[4MOPYR]BF_4$	–	203
	Cu^{2+}, Tl^+, Hg^{2+}	$[4MOPYR]Tf_2N$, [4MOPYR]TfO, [4MOPYR]NfO	–	

(continued)

Table 5.5 (continued)

Substances	Metal ions	Extractant/ligand/ metal chelator	Extractant/ligand/ metal chelator	References
	Mg^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Tl^{+}, Pb^{2+}, Sn^{4+}, Ag^{+}, Pd^{2+}	$[4MPYRCN]Tf_2N$, $[MPIPCN]Tf_2N$	–	
	Mg^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Tl^{+}, Pb^{2+}, Sn^{4+}, Ba^{2+}	$[MPYRROS_2]Tf_2N$, $[MPIPS_2]Tf_2N$	–	
	Ni^{2+}, Cu^{2+}, Co^{2+}	Di-tert-butyl ester		
Rare earth metals	Sc^{3+}, La^{3+}, Y^{3+}, Yb^{3+}	$[C_8mim]PF_6$	Cyanex925	204
	Y^{3+}, Sc^{3+}, Ho^{3+}, Er^{3+}, Yb^{3+}	$[C_8mim]PF_6$	Cyanex923	205
	Yb^{3+}	$[C_nmim]PF_6$ (n = 4, 6, 8)	Cyanex923	206
	Y^{3+}, Er^{3+}, Tm^{3+}, Yb^{3+}	$[C_8mim]PF_6$	Cyanex923, EDTA	207
	Ce^{4+}, Th^{4+}, Ce^{3+}	$[C_nmim]PF_6$ (n = 4, 6, 8)	DEHEHP P503	208
	Th^{4+}, La^{3+}, Ce^{3+}, Nd^{3+}, Gd^{3+}, Er^{3+}	$[C_8mim]PF_6$	N1923	209
	Sc^{3+}	$[A336]NO_3$, $[C_8mim]PF_6$	TBP, Cyanex923	210
	Y^{3+}	$[BAAZM]PF_6$, $[C_8mim]PF_6$	–	211
	Y^{3+} Tb^{3+},Yb^{3+}, Ho^{3+}, Er^{3+} Sc^{3+}	$[C_8mim]PF_6$	Cyanex923	212
	Y^{3+} Sc^{3+}, Ho^{3+}, Er^{3+}, Yb^{3+}	$[C_8mim]PF_6$ $[C_nmim]PF_6$/ Tf_2N (n = 4, 6, 8)	Cyanex923/EDTA	213
	Ce^{4+}, Th^{4+}, Ce^{3+},La^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+}, Er^{3+}, Tm^{3+}, Yb^{3+}	$[C_8mim]PF_6$	DEHEHP	214
	Ce^{4+}, Th^{4+}, Ce^{3+}, Gd^{3+}, Yb^{3+}	$[C_8mim]PF_6$	–	215
Others	Al^{3+}	$[C_4mim]Tf_2N$, $[C_6mim]PF_6$, $[C_8mim]PF_6$	n/a	216, 217

C_nMIM 1-alkyl-3-methylimidazolium, DC18C6 dicyclohexano-18-crown-6, 18C6 18-crown-6, Dtb18C6 4,4′-(5′)-di-(*tert*-butylcyclohexanol)-18-crown-6, BOBCalixC6 calix[4]arene-bis(*tert*-octylbenzo-crown-6), Tf_2N bis[(trifluoromethyl) sulfonyl]amide, R_1R_2MeIM 1-R_1-2-R_2-3-methylimidazolium (R_1 = Bu, Et, or Pr; R2 = H or Me), PAN 1-(2-pyridylazo)-2-naphthol, TAN 1-(2-thiazolylazo)-2-naphthol, CMPO octyl(phenyl)-*N*,*N*-diisobutylcarbamoy lmethyl phosphine oxide, TBP tri-*n*-butylphosphate, BOBCalixC6 calix[4]arene(*tert*-octylbenzo-crown-6), Bu_3MeNTFSI tri-1-butyl-methylammonium bis-((trifluoromethyl)sulfonyl) imide

To improve the solubility of metal ion, the commonly used method is including a metal ion–ligating functional group in structure of one of the ions named task-specific ionic liquids, which play dual role as hydrophobic solvent and as extractant. Visser et al. [191, 192] presented new thiourea, urea, and thioether derivatives of ILs designed to extract heavy metal ions (e.g., Hg^{2+} and Cd^{2+}), and the same methods have been used to the extraction and separation of rare earth metals by Chen et al. [210, 211].

Research efforts described above indicate that the application of ILs as an alternative solvent to replace traditional organic solvents in liquid–liquid extraction of metal ions is very promising and may also offer potential for the development of efficient processing of nuclear materials.

5.5 Conclusions

Ionic liquids are salts with melting temperatures below the boiling point of pure water (~100°C). These are nonvolatile, nonflammable, and thermally and chemically stable, and most of them exhibit good conductivity. Because of attractive potential applications and their inherently excellent characteristics, ionic liquids are usually called as green solvents or designer solvents. Ionic liquids as a new type of “green” media have shown important and potential application in the extraction and separation of metals. It has been shown that ionic liquid processes can be carried out at or near room temperature and can significantly lower the energy consumption, operation costs, and pollutant emissions. In recent years, many efforts have been made to achieve efficient extraction and separation of metals in ionic liquids. In summary, ionic liquids are unique and promising solvents for extractions because of their nonvolatility, adjustable hydrophobicity and polarity, and dissolution ability.

However, there are still some problems to be solved, since most information of ionic liquids are not well known up to now and most of works are only performed in laboratory. The relationships between the properties and the structure of ionic liquids are not well understood. Variations in cations and anions can produce a large number (10^{18}) of ionic liquids, and properties of ionic liquids depend on the structure of ions.

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Chapter 6
Potential for Hydrogen Sulfide Removal Using Ionic Liquid Solvents

Jason E. Bara

Abstract The removal of hydrogen sulfide (H_2S) via absorptive processes is an important consideration in the oil and gas and electric power industries. The use of ionic liquid (IL)-based solvents in this application is emerging as a new research area. Published data indicate that ILs are capable of absorbing H_2S from gas streams, as well as selectively separating H_2S from carbon dioxide (CO_2). As the solubility of H_2S in ILs is highly dependent on the partial pressure of H_2S, most ILs should be classified as "physical" solvents and would be best used under conditions where H_2S is present at high concentrations and/or high partial pressures. Preliminary results also show that the solubility differences between H_2S and other gases can be advantageously employed in membranes, as an alternative to using absorptive processes. Furthermore, ILs can be combined with amines to create "hybrid" solvents that utilize chemical reactions as well as physical solubility to increase the capacity of the solvent for H_2S, especially at low concentrations and/or low partial pressures. Hybrid IL-amine solvents can be attained either through formation of "task-specific" ILs with covalently attached amines or through directly mixing ILs with common (e.g., monoethanolamine) and/or specialty amines. This chapter discusses the progress in this field to date as well as the advantages, challenges, and opportunities associated with each approach.

6.1 Introduction

Hydrogen sulfide (H_2S) is a highly toxic and potentially lethal gas, and when combined with water, it forms a weak yet corrosive acid [1, 2]. H_2S is often present in natural gas (methane (CH_4) and ethane (C_2H_6)) wells. Natural gas containing H_2S is

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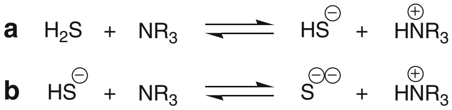


Fig. 6.1 Chemical reactions between H_2S and amines

often referred to as “sour” gas. The nearly complete removal of H_2S from natural gas is required in order to safely transport and utilize this vital fuel source. Pipeline quality or “sweet” gas may contain no more than four parts per million by volume (ppmv) of H_2S [1, 2]. Many refinery gas streams as well as synthesis gas or “syngas” (mixtures of carbon monoxide (CO) and hydrogen (H_2)) must also be treated to remove H_2S, which is a poison to many catalysts used in water-gas shift (WGS) reactions and methanol (MeOH) production [2].

A number of solvent-based processes have been developed to remove H_2S from gas streams [1, 2]. Separation of H_2S is achieved through preferential chemical reaction (chemical solvents), differential physical solubility (physical solvents), or a combination of both mechanisms (hybrid solvents) [1, 2]. Choice of process type is primarily related to the partial pressure of H_2S in the stream [1, 2]. Chemical solvents have very high absorption capacities for H_2S at low partial pressures, but become less effective as the reactive agent approaches saturation [1, 2]. For physical solvents, the solubility of H_2S typically increases in a linear fashion with increasing H_2S partial pressure (i.e., Henry’s Law behavior) [1, 2].

Aqueous amine solutions are the most common chemical solvents for H_2S removal, wherein the weakly acidic H_2S is neutralized by the alkaline amine solution. H_2S reacts rapidly and directly with 1°, 2°, or 3° amines to form the bisulfide (HS^-) anion and a protonated ammonium cation (Fig. 6.1a) [1, 2]. The bisulfide anion can then react with another amine to form the sulfide (S^{2-}) anion and another equivalent of the protonated ammonium cation (Fig. 6.1b).

Common amines used for removing H_2S from sour natural gas include monoethanolamine (MEA), diglycolamine (DGA), and diethanolamine (DEA) (Fig. 6.2) [1, 2].

While aqueous amine solvents are effective for removing H_2S from gas streams, their use is highly energy intensive due to the heat requirements to release H_2S from the solvent (i.e., the reverse reactions in Fig. 6.1). Aqueous amine solvents are most commonly used in “absorber-stripper” (also known as “contactor-regenerator”) processes, and thorough details on their operation can be found in other works [1, 2].

Often, carbon dioxide (CO_2) is present alongside H_2S in natural gas and other process streams and must also be removed to meet product gas specifications [1, 2]. In addition to CO_2, contaminants commonly appearing with H_2S may include carbonyl sulfide (COS), carbon disulfide (CS_2), and mercaptans (RSH), and elemental sulfur, typically present at levels well below 1% [1]. Natural gas containing both H_2S and CO_2 is known as “acid” gas [1]. Natural gas with a residual CO_2 content of <2% CO_2 is considered to be “sweet” or pipeline quality [1]. Liquefied natural gas (LNG) production requires both H_2S and CO_2 to be removed to <4 and <50 ppm, respectively [1]. In either case, selective separation of H_2S from CO_2 is often desirable as

Fig. 6.2 Commonly used 1° and 2° amines for H_2S removal

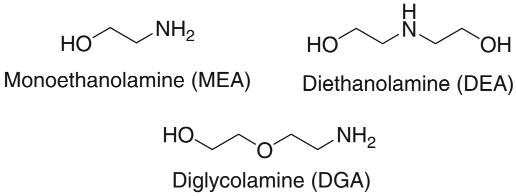
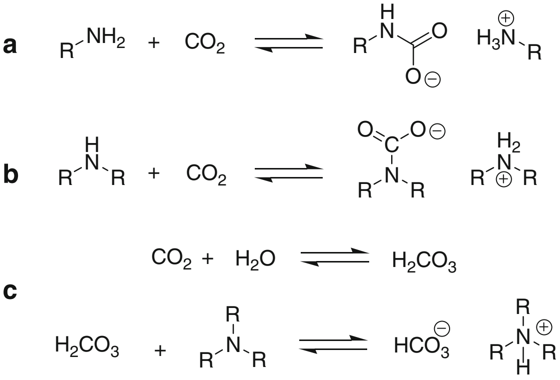


Fig. 6.3 Chemical reactions between CO_2 and amines



H_2S can be transformed to elemental sulfur through the Claus process, while CO_2 (as of this publication) may simply be vented to the environment [1, 2].

The integrated gasification combined cycle (IGCC) process can be used to produce syngas [3]. Syngas is a feedstock for Fischer-Tropsch process to create liquid hydrocarbon fuels [3]. Syngas can also be used in WGS reactions to create additional H_2 for electric power generation with the aim of zero emissions [3]. In either case, the production of syngas from coal generates both H_2S and CO_2 [3], which must not only be removed from the syngas but be separated from each other, as an essentially pure stream of CO_2 is required for the purposes of compression and carbon sequestration [3]. This approach is known as precombustion CO_2 capture [4]. Solvents for H_2S removal processes are often selected based on their ability to selectively separate H_2S from CO_2 [1, 2]. In chemical solvents, selectivity for H_2S can be achieved through preferential reactions favoring rapid reaction of H_2S with amines but disfavoring its reaction with CO_2 through steric hindrance or slow kinetics [1, 2].

While CO_2 reacts rapidly with 1° and 2° amines to form a carbamate (Fig. 6.3a, b), it cannot form a carbamate with 3° amine or bulky 2° amines. Instead, CO_2 reacts with water to form carbonic acid, which can be neutralized by a 3° amine (Fig. 6.3c). The latter mechanism is much slower and, with proper process design, provides the opportunity to selectively separate H_2S from CO_2.

3° Amines, such as *N*-methyldiethanolamine (MDEA), or sterically hindered 2° amines, such as diisopropanolamine (DIPA) (Fig. 6.4), and others are employed when selective separation of H_2S from CO_2 is desired [1, 2].

Physical (organic) solvents are also employed for the bulk removal of H_2S and/or CO_2 from gas streams [1, 2]. In a physical solvent, acid gases dissolve without

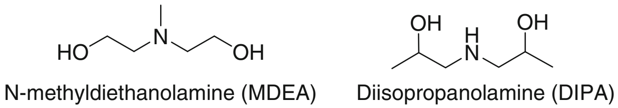


Fig. 6.4 Commonly used amines for selective H_2S removal

chemical reaction, and thus, the acid gas loading of the solvent is proportional to the partial pressure of the acid gas in the feed gas stream [1, 2]. Compared to amine solvents, physical solvents offer an advantage of being regenerable at lower temperatures and/or via "flashing" under a moderate vacuum [1, 2]. Typically, a chilled organic solvent is used to separate the acid gas(es) from the feed gas. Well-known examples of physical solvents include methanol (MeOH), dimethylethers of poly(ethylene glycol), and morpholine derivatives used respectively in commercial processes such as Rectisol®, Selexol®, and Morphysorb® [1, 5].

Hybrid processes utilize a physical solvent and an amine to combine the benefits of both chemical and physical solvent processes [1, 2]. Typically, hybrid processes are employed at high acid gas partial pressures [1, 2]. However, it is possible to implement a hybrid process for low-pressure applications when the hybrid process is competitive with aqueous amine processes. A well-known hybrid process is Sulfinol®, which combines the organic solvent sulfolane with MDEA or DIPA and varying amounts of water to achieve selective removal of H_2S from CO_2 [1]. Potential disadvantages of hybrid processes relative to aqueous amine processes include increased overall solvent costs and the loss of valuable product gas (i.e., hydrocarbons) due to the likelihood for increased absorption in the physical solvent [1, 2].

6.2 Ionic Liquids as Physical Solvents for H_2S Removal

With respect to CO_2 separations, almost all ionic liquids (ILs) are appropriately classified as physical solvents [6]. While interactions between CO_2 and the IL anion have been observed, there is no appreciable chemical reaction between CO_2 and the IL, as the solubility of CO_2 in ILs has been shown to be highly dependent on the partial pressure of CO_2 (i.e., Henry's Law behavior) [6]. IL capacities for CO_2 are on par with the low range of values observed in conventional organic solvents [6]. ILs might be best suited to perform bulk removal when the CO_2 content of the gas is high and the feed stream is at high pressure. Figure 6.5 provides approximate guidelines for the use of various solvent-based processes for CO_2 removal when only CO_2 is present [7], and any areas labeled "physical solvent" would also apply to ILs. In Fig. 6.5, K_2CO_3 refers to processes using aqueous solutions of potassium carbonate. K_2CO_3 is considered to be activated when amines (such as piperazine) are added to the solution to promote CO_2 absorption.

While much research has been conducted to examine the use of IL solvents to remove CO_2 from gas streams for target applications including natural gas

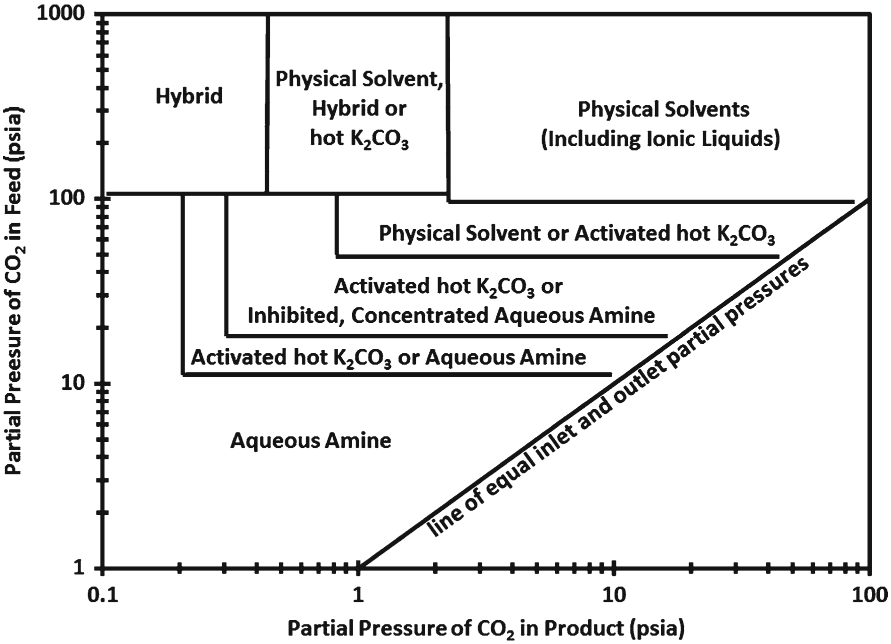


Fig. 6.5 Process selection chart for the removal of CO_2 from gas streams (Reproduced from Ref. [7] with kind permission of © PennWell Corporation (1997))

sweetening and postcombustion carbon capture [6], only a few reports have been devoted to the application of ILs for H_2S removal [8–13]. While the existing data set for H_2S solubility in ILs is relatively quite small to that for CO_2 [6], there is a strong indication that ILs must strictly be considered as physical solvents for H_2S removal [11]. The published work on this topic has reported the solubility of H_2S in terms of a Henry's Law constant, or mole fraction, as a function of temperature and/or pressure. Jalili and coworkers have studied the solubility of H_2S in imidazolium-based ILs including 1-butyl-3-methylimidazolium ([bmim]) cations with hexafluorophosphate ($[PF_6^-]$), tetrafluoroborate ($[BF_4^-]$) and bis(trifluoromethane)sulfonimide ($[Tf_2N^-]$) anions [8], 1-hexyl-3-methylimidazolium ([hmim]) cations paired with the same anions [9], and a 1-(2-hydroxyethyl)-3-methylimidazolium ([hemim]) cation with a $[BF_4^-]$ anion [10]. These studies determined H_2S solubility over pressure ranges from approximately 1–10 atm and at temperatures ranging from 30°C to 70°C [8–10]. Mole fractions of H_2S in the IL of greater than 0.500 could be achieved at the high end of this pressure range and at the lowest temperature [8–10]. H_2S was found to become increasingly soluble with increasing pressure while solubility decreased with increasing temperature [8–10]. The presence of the hydroxyl group in $[hemim][BF_4]$ was found to reduce H_2S solubility relative to the ILs with alkyl functional groups [10]. These trends are consistent with the behaviors observed for CO_2 in similar ILs over comparable temperature and pressure ranges [6, 14].

Table 6.1 Solubility of H_2S and CO_2 and ideal solubility selectivity for H_2S/CO_2 in selected common organic solvents, water, and ILs at 25°C and low pressure (Data reproduced from Refs. [6, 15], with kind permission of © The American Chemical Society (2009) and of © Elsevier (2005)) (S data in cm^3 (STP)/cm^3 solvent/atm)

Solvent	MW (g/mol)	SH_2S	SCO_2	H_2S/CO_2
DMF	73.09	38	4.1	9.3
DMSO	78.13	32	2.9	11
$CHCl_3$	119.38	31	3.6	8.6
THF	72.11	31	6.2	5.0
Acetone	58.08	22	6.6	3.3
CH_3CN	41.05	21	7.1	3.0
MeOH	32.04	16	3.6	4.4
PC	102.09	13	3.9	3.3
n-Hexane	86.16	7.3	2.1	3.5
Water	18.02	2.3	0.76	3.0
Ionic liquids	>175	4–8	1.5–2.2	2–4

Because of the much larger molecular weights of ILs relative to common organic solvents, the use of mole fraction data to compare the solubility of H_2S in ILs relative to the solubility of H_2S in common organic (physical) solvents does not provide a sufficiently robust analysis [6, 15]. A more appropriate comparison of H_2S solubility in organic solvents to ILs must take into account solubility of H_2S per volume of the solvent [6, 15]. Equation 6.1 provides the most commonly used expression for volume-based solubility (S).

$$S\,[=]\,\frac{cm^3\ gas\,(STP)}{cm^3\ liquid \cdot atm} \tag{6.1}$$

Volume-based solubilities are crucial data used in engineering and economic models in the design of industrial gas treating processes [1]. The amount of solvent required or solvent flow rate (e.g., L/min, etc.) is often the first consideration for projecting process capital and operating expenses, as the size of the process will be directly proportional to the flow rate of solvent [1]. Thus, one consideration of determining whether ILs can be competitive with organic solvents for H_2S removal is the relative solubility of H_2S as it will directly impact the process scale and economics.

Using density and molecular weight data for ILs, the Henry's Law constants for gas solubilities in ILs can be transformed to fit the form of the expression in (6.1). Examination of Table 6.1 shows that H_2S and CO_2 [6] are less soluble in ILs than in most common organic solvents [15].

Using the solubility data presented by Jalili [8–10], and the data available in the literature for CO_2 in ILs [6], the ideal (i.e., single gas) selectivities for H_2S/CO_2 separation that can be achieved in ILs have been calculated to be in the range of 2–4 (Table 6.1). Thus, it can be anticipated that for the majority of ILs where physical solubility is the dominant mechanism by which separation of gases occurs, H_2S will be 2×–4× more soluble than CO_2 under identical temperature and pressure conditions. These ideal selectivity values for H_2S/CO_2 solubility selectivity in ILs are at par with those found in some organic solvents [15] but certainly are in line with the lower end of the range found in Table 6.1.

Pomelli and coworkers have examined the mechanisms through which H_2S dissolves in ILs by screening the interactions of H_2S with different cation–anion pairs [12]. Cations were selected from imidazolium, pyridinium, pyrrolidinium, and ammonium species with anions chosen from chloride ([Cl^-]), [BF_4^-], [PF_6^-], [Tf_2N^-], and triflate ([OTf^-]) [12]. Their work revealed that the acidic H_2S undergoes interactions with the basic anions, while both H_2S and ILs remain stable in the presence of each other with no irreversible chemical reactions occurring [12]. The authors also highlight that IL solvents containing high mole fractions of H_2S experience only about 20% of the volumetric expansion that occurs in organic solvents such as MeOH or THF with high mole fractions of H_2S in the liquid phase [12]. However, as shown in Table 6.1, these organic solvents can absorb several times more H_2S per unit volume than ILs, and this is likely a reason why ILs do not undergo similar expansions.

Jou and Mather examined the solubility of H_2S in [bmim][PF_6] [11], as a function of temperature and pressure, and their results were consistent with those of Jalili et al. [8]. Mather has studied the solubility of acid gases in aqueous amine solvents for several decades, generating an extensive publication record [16–19]. Mather's paper concludes with a clear statement as to the capabilities of ILs for H_2S removal relative to aqueous amine solvents: "The dependence of the solubility of hydrogen sulfide in [bmim][PF_6] on pressure is typical of that of 'physical' solvents. This is also the case of carbon dioxide as shown by Perez-Salado Kamps et al. Hence, it is unlikely that ionic liquids can supplant alkanolamines for the removal of hydrogen sulfide and carbon dioxide from gas streams. They would be useful only for bulk removal of the acid gases, when the partial pressure of the acid gases is high. They are unable to reduce the concentration of the acid gases to the low levels required in gas processing" [11].

A report from the United States Department of Energy (DOE) National Energy Technology Laboratory (NETL) analyzed the use of a commercially available ammonium-based IL (TEGO IL K5), manufactured by Evonik, as a physical solvent for the removal of CO_2 and H_2S from dry fuel gas streams (i.e., syngas) produced via the IGCC process, toward the aim of precombustion CO_2 capture [3]. TEGO IL K5 features long oligo(ethylene glycol) chains bound to the ammonium center, and although TEGO IL K5 is properly classified as an IL due to its charges and the vast bulk of the molecule structure associated with the neutral, pendant organic groups bound to the cation. TEGO IL K5 has many similarities to the solvent used in the Selexol® process [1, 3]. The authors have stated that in the IGCC process, it is desirable to treat the fuel gas streams at higher temperatures than typical of current processes so as to maximize process efficiency and minimize the impact of precombustion CO_2 capture [3]. Commercial aqueous amine *and* physical solvent processes respectively require the gas stream to be cooled to 40°C and to −40°C or lower [3]. Minimization of the cooling requirement through "warm" treating (~200°C) is an optimal temperature range which enables not only the removal of CO_2 and H_2S but other contaminants such as sulfur, ammonia, chlorides, and heavy metals (Hg, Cd, etc.) whose emissions are regulated [3]. Because of its negligible volatility and thermal stability, TEGO IL K5 was identified as a solvent potentially capable of accomplishing warm gas cleanup [3]. The results of this work were consistent with those of Jalili and Mather [8–11], with the solubility of H_2S found to increase with increasing pressure and decrease with increasing temperature. It was found that H_2S could be more readily removed from the gas stream than CO_2, due to a higher solubility in the IL and higher rate of mass transfer, potentially enabling some reductions in process costs as a shorter absorption column could be used to separate H_2S from CO_2 [3].

Since ILs are physical solvents for acid gases and cannot serve as a direct replacement for amine-based processes in applications requiring H_2S removal, the use of most ILs can only be considered where physical solvents are employed in industrial processes. Figure 6.6a illustrates the conditions under which ILs might best be employed to remove H_2S from gas streams (where no CO_2 is present). Figure 6.6b presents conditions where ILs might be used to remove both H_2S and CO_2 simultaneously. Figure 6.6c provides guidelines for process selection when the separation of H_2S from CO_2 is required. In all cases, it becomes obvious that ILs are most applicable when the partial pressure of the acid gas is high. Physical solvents, including ILs, cannot be utilized to effectively remove H_2S (or CO_2) from streams where the partial pressure of the acid gas in the feed is low or when the process requires virtually complete removal of the acid gas from the product. For reference in the charts, “DEA” refers to aqueous diethanolamine (Fig. 6.2), ADIP refers to aqueous mixtures of MDEA and DIPA (Fig. 6.4), and “Stretford” represents the Stretford process, a liquid phase oxidation of H_2S to elemental sulfur.

In addition to their use as physical solvents for H_2S removal, the approach of ILs as the selective component of membranes has also received consideration [6, 20]. Membranes can provide an alternative mechanism to physical solvent processes with potentially lower energy requirements and capital costs for the removal of acid gases from gas streams [21]. As ILs do not evaporate, they can be incorporated into a porous substrate (either a polymer or inorganic material) to provide selective separation in the form of supported ionic liquid membrane (SILM) [6, 21]. Park and coworkers found that a SILM containing [bmim][BF_4] on a poly(vinylidene difluoride) (PVDF) support was capable of separating H_2S from CH_4 at pressures up to 5 bar with ideal selectivities for H_2S/CH_4 of ~150–250 based on single gas measurements [22]. While this is certainly a positive initial result, further research is needed to determine the viability of the SILM approach due to the complex nature, high pressures, and highly variable compositions of sour natural gas wells [1].

6.3 Hybrid Solvents Comprising Ionic Liquids and Amines

While Fig. 6.6a–c indicates the potential process conditions where ILs might find applicability as physical solvents for H_2S removal, these ranges represent only a fraction of the conditions that must be addressed by industrial gas treating processes [1–4]. In view of the unique physical and thermodynamic properties of ILs and the

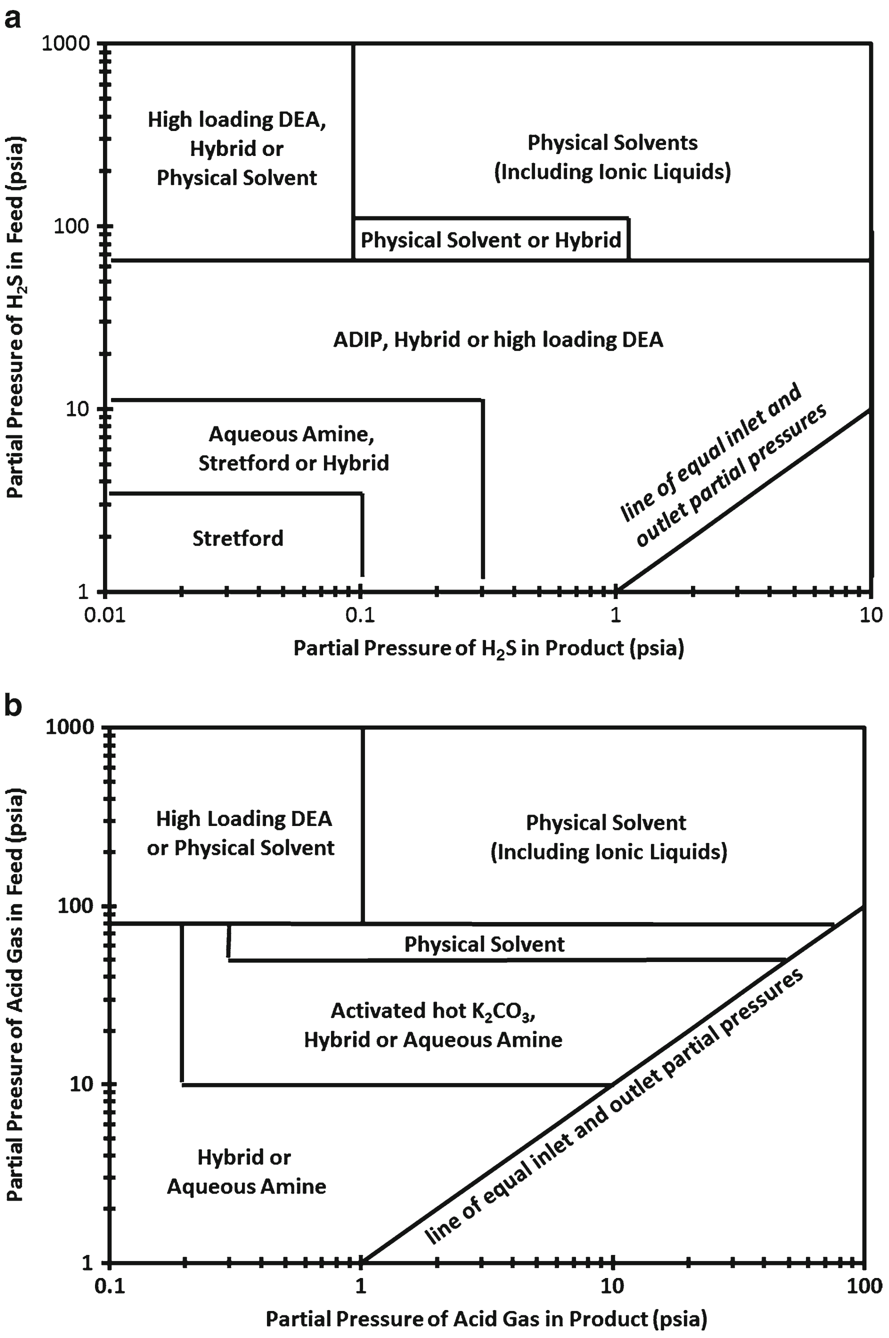


Fig. 6.6 (**a**) Process selection chart for the removal of H_2S from gas streams when no CO_2 is present (Reproduced from Ref. [7] with kind permission of © PennWell Corporation (1997)). (**b**) Process selection chart for the simultaneous removal of H_2S and CO_2 from gas streams [7]. (**c**) Process selection chart for the selective removal of H_2S from gas streams with both H_2S and CO_2 present [7]

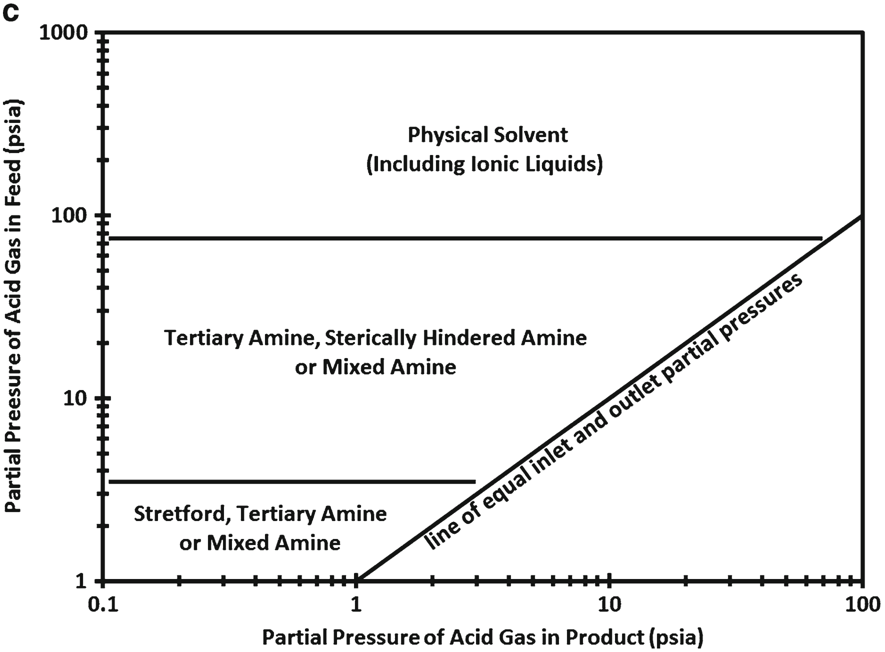


Fig. 6.6 (continued)

potential advantages that those properties may impart upon a process, it is desirable to maximize the applicability of IL-based solvents through chemical modification of the IL itself or to develop hybrid solvents that enable the use of IL-based solvents in lower pressure applications [23].

IL-based solvents might be used to remove H_2S at lower partial pressures through a 1:1 chemical complexation with amines, as shown in Fig. 6.1. Amine-functionalized “task-specific” ionic liquids (TSILs) where the reactive group is attached to the cation and/or anion have received significant attention for their capability to reversibly capture CO_2 [24]. TSILs can be designed to contain 1°, 2°, or 3° amines so as to provide some selectivity to separate H_2S from CO_2 [25]. Amine-containing anions are readily available from natural and synthetic amino acids [26]. Figure 6.7 illustrates just a few of the many possible amine-functionalized TSILs that might be used to complex H_2S through a reversible chemical reaction analogous to that shown in Fig. 6.1.

The concept of a TSIL as a nonvolatile, nonaqueous chemical solvent to capture H_2S is interesting, as much higher loadings could be achieved than with analogous IL physical solvents, with a mole fraction of H_2S of 0.500 in the IL likely readily achievable at less than 1 atm. However, TSILs are difficult and extremely costly to manufacture, with multiple reaction and work-up stages needed [24]. Additionally, ILs of this type are known to be highly viscous and become even more intractable upon complexation with CO_2, as the capture of one molecule of CO_2 bridges two TSIL amine groups, creating bulky multi-ion complexes [27]. In the case of H_2S

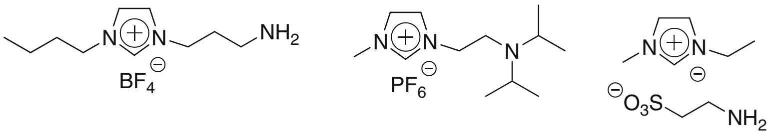


Fig. 6.7 TSILs with amine groups tethered to the cation or anion

capture by a TSIL, the detrimental effect on viscosity might not be as severe as only one equivalent of the TSIL is required per mole of H_2S, creating a much less bulky complex. An approach that might be used to lower viscosity could be to dissolve the amine-functionalized TSILs in a common IL (e.g., [bmim][PF_6]) to form what Davis called a "mixed ionic liquid eurytrope" or "MILIEU" [28]. While this approach would lower the capacity of the solvent for chemical reaction with H_2S, it might alleviate the issues associated with the high viscosity of the TSIL, such as poor mass transfer.

However, significant economic incentives must exist to utilize TSILs as replacements for conventional amines, as many amines are commercially available as commodity chemicals. An alternative approach for researching solvents to capture H_2S is to blend ILs with amines including those shown in Figs. 6.2 and 6.4 [6, 23, 29]. By directly adding amines to an IL, there is no need to synthesize TSILs in order to increase the acid gas capacity of the solvent. Furthermore, higher amine concentrations in the solvent can be achieved in this manner [23]. As amines typically have viscosities lower than most ILs, this approach could be used to reduce overall solvent viscosity, while TSILs often result in increased viscosity relative to structurally similar ILs without amines. In a report by Camper and coworkers, commodity amines (e.g., MEA or DEA) were added to [hmim][Tf_2N] and [hemim][Tf_2N] to reversibly capture CO_2 [29]. About approximately ten times improvement in mass transfer rate for CO_2 capture in IL amine blends was achieved relative to the TSIL approach, owing to much lower solution viscosity [29]. This same approach might be taken to capture H_2S, with selective H_2S/CO_2 removal achievable through tuning the solvent mixture via amine selection [1, 2]. However, as with TSILs for H_2S removal, this is an area that has yet to be explored.

6.4 Conclusions and Outlook

The majority of ILs must be considered as physical solvents for H_2S removal, as the capacity of ILs for H_2S is much lower than aqueous amines at low pressures, and is comparable, but on the low end, of common organic solvents at moderate and high pressures. The use of ILs for H_2S removal will likely be best suited to situations where the partial pressure of H_2S is high and when the intrinsic properties of the IL can provide a cost-effective solution. SILMs may provide an alternative mechanism to physical solvents for H_2S removal, but much more development in this area will be required before a proper judgment can be made as to the viability of this approach.

Hybrid solvents comprising ILs and amines (whether covalently attached or as mixtures) represent a promising approach by which the applicability of IL-based solvents may be extended to lower pressure applications and compete with established aqueous amine technologies.

As the field of H_2S removal using IL-based technologies continues to develop, researchers must emphasize safety not only in their laboratory procedures but also in their reports and publications. H_2S is corrosive, flammable, toxic, and potentially lethal – it must be transported, handled, and disposed of responsibly by persons with proper training, experience, and protective equipment.

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Chapter 7
Biocatalytic Reactions in Ionic Liquid Media

A.P. de los Ríos, F.J. Hernández-Fernández, L.J. Lozano, and C. Godínez

Abstract Ionic liquids hold potential as green solvents because of their lack of vapour pressure, and are opening up a burgeoning new field of nonaqueous enzymology. Remarkable results with respect to yield, enantioselectivity or enzyme stability have been observed using ionic liquids as reaction media, as compared to those observed in conventional organic solvents. In this work, a detailed and comprehensive revision of the versatility of ionic liquids as environmentally friendly green solvents for various biochemical transformations is presented.

7.1 Introduction

The use of enzymes in organic solvents rather than in aqueous media greatly enhances their technological applications due to the advantages they offer, such as the possibility of carrying out processes involving hydrolytic enzymes which are thermodynamically unfavourable in water (e.g. transesterification reaction) and their ability to increase the solubility of organic substrates [1]. Biocatalysis in organic solvents, however, often suffer from the disadvantages of reduced activity, selectivity or stability of the enzyme, as compared to aqueous media. Furthermore, organic solvents are usually volatile liquids that may evaporate into the atmosphere with a detrimental impact on the environment and human health.

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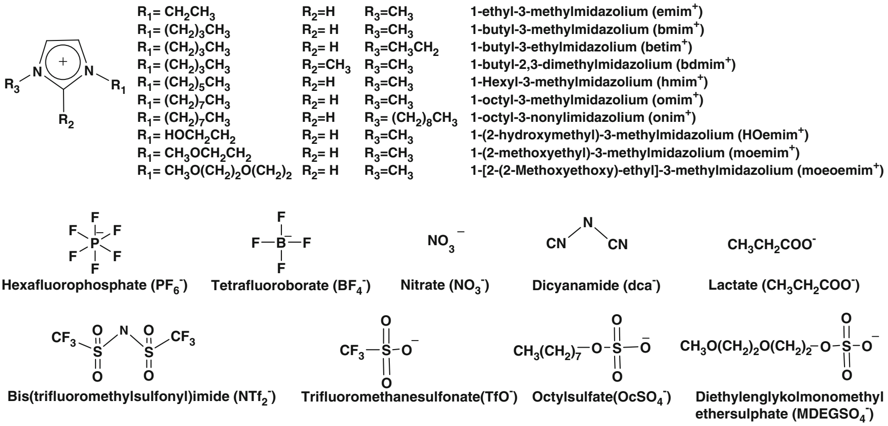


$R_1 = CH_2CH_3$	R_2=H	$R_3=CH_3$	1-ethyl-3-methylmidazolium (emim$^+$)
$R_1 = (CH_2)_3CH_3$	R_2= H	$R_3=CH_3$	1-butyl-3-methylmidazolium (bmim$^+$)
$R_1 = (CH_2)_3CH_3$	R_2= H	$R_3=CH_3CH_2$	1-butyl-3-ethylmidazolium (betim$^+$)
$R_1 = (CH_2)_3CH_3$	$R_2=CH_3$	$R_3=CH_3$	1-butyl-2,3-dimethylmidazolium (bdmim$^+$)
$R_1 = (CH_2)_5CH_3$	R_2=H	$R_3=CH_3$	1-Hexyl-3-methylmidazolium (hmim$^+$)
$R_1 = (CH_2)_7CH_3$	R_2= H	$R_3=CH_3$	1-octyl-3-methylmidazolium (omim$^+$)
$R_1 = (CH_2)_7CH_3$	R_2=H	$R_3 = (CH_2)_8CH_3$	1-octyl-3-nonylimidazolium (onim$^+$)
$R_1 = HOCH_2CH_2$	R_2= H	$R_3=CH_3$	1-(2-hydroxymethyl)-3-methylmidazolium (HOemim$^+$)
$R_1 = CH_3OCH_2CH_2$	R_2= H	$R_3=CH_3$	1-(2-methoxyethyl)-3-methylmidazolium (moemim$^+$)
$R_1 = CH_3O(CH_2)_2O(CH_2)_2$	R_2= H	$R_3=CH_3$	1-[2-(2-Methoxyethoxy)-ethyl]-3-methylmidazolium (moeoemim$^+$)

Fig. 7.1 Common ions involved in ionic liquids

In recent years, ionic liquids (ILs) have emerged as clean alternatives to classical organic solvents for a wide variety of nonaqueous biocatalytic processes [2–7]. The use of these solvents in biocatalytic transformations has solved some of the problems encountered in their applications in aqueous and organic solvents. Although, in many cases, ionic liquids have simply been used to replace organic solvents, they have often led to improved process performance and increase in enzyme activity, stability and selectivity. Interest in these compounds, often heralded as the green, high-tech media of the future, is still increasing rapidly [8]. Ionic liquids are organic salts, which are liquids at ambient temperatures. Unlike traditional solvents, which can be described as molecular liquids, ionic liquids are composed of ions (Fig. 7.1). Their unique properties such as nonvolatility, nonflammability and excellent chemical and thermal stability have made them an environmentally attractive alternative to conventional organic solvents. Ionic liquids have low melting points (<100°C) and remain as liquids within a broad temperature window (<300°C). Furthermore, all the physico-chemical properties of ILs including their hydrophobicity, density, viscosity, melting point, polarity and solvent miscibility can be finely tuned by selecting appropriate combinations of cations and anions [5], and the optimal IL might be designed for each specific biocatalytic system. Indeed, this feature is a key factor for realising successful reactions since the suitable selection of cation and anion composition might increase the substrates solubility, improve the enzyme selectivity or enhance the enzyme activity or/and stability.

Here, we will review the various issues related to biocatalytic reactions in ionic liquids. Biocatalyst tested in ionic liquids will be discussed firstly, and then the effect of ionic liquids on the activity, selectivity as well as on the stability of biocatalyst in ionic liquids will be surveyed. Finally, various applications of ionic liquids as reaction medium for biocatalytic transformations will be reviewed.

7.2 Biocatalyst Tested in Ionic Liquids

7.2.1 Lipases

Different types of lipases have been demonstrated to show catalytic activity in ILs. The use of *Candida antarctica* lipase B (CaLB) in ionic liquids is particularly interesting due to the higher stability and reactant specificity showed by this type of lipases in organic solvents compared with other lipases [9]. In fact, numerous examples of CaLB-catalysed esterification reactions in ILs reported increased synthetic activity, enantioselectivity and stability of the biocatalyst in these media. The first example of ester biosynthesis catalysed by CaLB in ionic liquid media ($[bmim^+][PF_6^-]$ and $[bmim^+][BF_4^-]$) was reported by Sheldon's group [10]. They found reaction rates comparable with or better than those observed in *t*-BuOH, a conventional organic reaction media, using an immobilised derivative of CaLB (Novozym® 435). Lozano et al. [11] reported other successful use of CaLB in the biosynthesis of ester in ionic liquids based on dialkylimidazolium or quaternary ammonium cations associated with perfluorinated or bis(trifluoromethyl)sulphonyl amide anions. All the assayed ionic liquids proved adequate media for lipase-catalysed transesterification, the synthetic activity being clearly enhanced with respect to that obtained with organic solvents. Other interesting example of using CaLB in ILs was reported by de los Ríos et al. [12]. They studied the synthesis of butyl butyrate by transesterification from vinyl butyrate and 1-butanol catalysed by CaLB in a wide range of imidazolium-based ILs. These authors reported higher enzymatic activities and selectivities in all the water-immiscible ionic liquids assayed ($[bmim^+][PF_6^-]$, $[bdmim^+][PF_6^-]$, $[hmim^+][PF_6^-]$, $[omim^+][PF_6^-]$, $[emim^+][NTf_2^-]$, $[bmim^+][NTf_2^-]$, $[hmim^+][NTf_2^-]$ and $[omim^+][NTf_2]$) than that obtained in *n*-hexane, as a reference organic solvent.

Even though CaLB is the lipase most widely used in ionic liquids, other lipases such as *Pseudomonas cepacia* lipase (PcL) and *Candida rugosa* lipase (CrL) have been often used as biocatalyst for ester synthesis in ionic liquid [13, 14]. Nara et al. [14] studied the ability of *Pc*L to catalyse the transesterification of 2-hydroxymethyl-1,4-benzodioxane using vinyl acetate as acyl donor in organic and ionic liquid reaction media. They reported that lipase *Pc*L initially exhibited a relatively high extent of transesterification in $[bmim][PF_6]$ in comparison to dichloromethane. CrL was also successfully used in ILs as reported by Kim et al. [7]. These authors studied the enzymatic selective acylations of carbohydrates with vinyl acetate in both organic solvents (THF and chloroform) and in ionic liquids ($[bmim^+][PF_6^-]$ and $[moemim^+][PF_6^-]$) as reaction media. They observed that the reactions in ionic liquids were more rapid, highly selectively and provide higher yields than those appeared in organic solvents.

The application of ionic liquids in lipase biocatalysis has not remained entirely restricted to *Ca*LB, *Pc*L or *Cr*L. Other lipases have been used in ionic liquids for ester synthesis such as *Candida antarctica* lipase A (*Ca*LA) [15, 16], *Thermomyces lanuginosus* lipase [17] (*TL*L), *Rhizomucor miehei* lipase (*Rm*L), *Pseudomonas fluorescens* lipase (*Pf*L) [18], *Pig pancreas* lipase (*Pp*L) [17] and *Alcaligenes* sp. lipase (*As*L) [16].

7.2.2 Esterases and Proteases

The behaviour of other esterases has been also investigated in ILs; however, they have been found to be much less tolerant to these anhydrous media than lipases. In this context, the esterases from *Bacillus stearothermophilus* (*Bst*E) and *Bacillus subtilis* (*Bs*E) were used as reaction media for the transesterification of *rac*-1-phenylethanol in [bmim$^+$][BF$_4^-$], [bmim$^+$][PF$_6^-$] and [bmim$^+$][NTf$_2^-$]. An immobilised derivative of these enzymes onto Celite showed comparable transesterification activities in ionic liquids and conventional organic solvents (*n*-hexane, methyl tert-butyl eter-MTBE- and vinyl acetate) [6]. A *feruloyl esterase* from Aspergillus niger (*AnFae*A) was also used to catalyse the esterification of glycerol with sinapic acid in [OHemim$^+$][PF$_6^-$] and [m*oeo*emim$^+$][PF$_6^-$]. About 15% water content and 150-fold molar excess of glycerol over sinapic acid was necessary to reach about 75% conversion yield [19].

The cutinase from *Fusarium solani pisii* immobilised on zeolite NaY also showed activity in [bmim$^+$][BF$_4^-$], [bmim$^+$][PF$_6^-$] and [omim$^+$][PF$_6^-$] at $a_W = 0.7$ as reported by García et al. [20]. They found that the catalytic activities of cutinase in the transesterification of 2-phenyl-1-propanol with vinyl butyrate in [bmim$^+$][PF$_6^-$] was similar to that in *n*-hexane.

Catalytic activities of proteases like α-chymotrypsin [21, 22] and subtilisin Carlsberg [23] have been also studied in ILs. Laszlo and Compton [24] examined the transesterification reaction of *N*-acetyl-L-phenylalanine ethyl ester with 1-propanol catalysed by α-chymotrypsin in ionic liquids ([bmim$^+$][PF$_6^-$] and [omim$^+$][PF$_6^-$]) and organic solvents (isooctane, acetonitrile and *n*-hexane). They found that the transesterification rates using α-chymotrypsin freezedried with K_2HPO_4 in ionic liquids, at 1% water content, were comparable with that obtained in organic solvents. The protease subtilisin in free form did not show any significant transesterification activity in ILs [25]. However, modified subtilisin was able to catalyse the transesterification of *N*-acetyl-L-phenylalanine ethyl ester in [emim$^+$][NTf$_2^-$], [bmim$^+$][PF$_6^-$] and [bmim$^+$][BF$_4^-$] [23, 25].

7.2.3 Glycosidases

Glycosidases have been used as biocatalysts for carbohydrate synthesis in vitro [26, 27]. In this context, β-galactosidase from *B. circulans* catalysed the tranglycosylation of lactose with *N*-acetylglucosamine in [mmim$^+$][MeSO$_4^-$]-water (25:75, v/v), with an increase in product yield from 30% in aqueous buffer to 58% in [mmim$^+$][MeSO$_4^-$]-water (25:75, v/v) [26]. Similarly, using another glycosidase-β-glycosylhydrolase CelB from Pyroccocus furiosus in 45 vol% [mmim$^+$][MeSO$_4^-$] increased the yield of galactosyl transfer from lactose to glycerol by 10% [27].

7.2.4 Oxidoreductases

A wide range of oxidoreductases have been tested in ionic liquid media including peroxidases, chloroperoxidases, laccases and dehydrogenases [28–34].

Horseradish peroxidase (HPO) has been reported to be threefold more stable at 80°C in 5–10% $[\text{bmim}^+][\text{BF}_4^-]$ as compared to phosphate buffer [28]. Okrasa et al. [29] reported the asymmetric oxidation of phenyl methyl- and 2-naphthyl methyl sulphides to sulphoxides catalysed by peroxidase from Coprinus cinereus in $[\text{bmim}^+][\text{PF}_6^-]$ with 10% water [29]. Although the enantioselectivity (63–92% ee) and yields (<32%) were similar to those in water, the reaction workup was easier because ionic liquids and the extraction solvent did not form emulsions.

Chloroperoxidase from Caldariomyces fumago was successfully used as catalyst in the enantioselective oxidation of 1,2-dihydronaphthalene to the corresponding epoxide in 10–30 vol% $[\text{mmim}^+][\text{MeSO}_4^-]$ and $[\text{bmim}^+][\text{MeSO}_4^-]$. The activity was comparable to acetone/water and *t*-butanol/water mixtures, but lower and less enantioselective than in pure citrate buffer [30]. Laccase C from Trametes species gave up to 30-fold higher conversion in 25% ionic liquid $[\text{bmPyr}^+][\text{BF}_4^-]$ as compared to in 20% *t*-butanol [31]. Shipovskov et al. [32] reported that the addition of 10–20% $[\text{bmim}^+][\text{Br}^-]$or 50–60% $[\text{bmim}^+][\text{dca}^-]$ increased the laccase-catalysed oxidation of catechol to benzoquinone [32]. Horse liver alcohol dehydrogenase (ADH) was reported to be slightly more active in 15% (w/v) $[\text{bmim}^+][\text{Cl}^-]$ than in buffer alone, but activity decreased with higher amounts of ionic liquid [33]. Fujita et al. [34] reported the oxidation of cellobiose to cellobiolactone catalysed by cellobiose dehydrogenase (CDH) in 65% choline phosphate [34].

7.3 Effect of the Ionic Liquid Composition on the Activity and Stability of Enzymes

From literature, it seems that enzymes basically follow the same catalytic mechanism in ILs as in water and in organic solvents. An enzyme in an ionic liquid, as in an organic solvent, functions with a microaqueous phase surrounding the enzyme molecules. Therefore, an ionic liquid may play the same role as an organic solvent [35–38] in affecting the enzyme performance by (1) stripping off the essential water associated with the enzyme; (2) penetrating into the microaqueous phase to interact with the enzyme by changing the protein dynamics, the protein conformation, and/or the enzyme's active site; and (3) interacting with the substrates and products by either direct reactions with them or by altering their partitioning between the aqueous and nonaqueous phases [39].

Among the ionic liquids used for enzyme-catalysed reactions, those containing dialkylimidazolium cations are showed to be one of the most interesting. In spite of this, it is known that some of these ionic liquids have strong impact on the activity and stability of lipases [40–43]. Ríos et al. [12] studied the effect of dialkylimidazolium-based ionic liquid on activity, selectivity and stability of CaLB for the synthesis of butyl butyrate by transesterification from vinyl butyrate and 1-butanol. These authors tested 19 different water-immiscible and water-miscible ionic liquids consisting of dialkylimidazolium cations combined with a wide range of anions, including hexafluorophosphate, bis(trifluoromethylsulphonyl)imide, tetrafluoroborate, dicyanamide, nitrate, acetate, octylsulphate and ethylenglycolmonomethylethersulphate as reaction media at 2% (v/v) water content and 30°C. Specifically, the water-immiscible ILs tested were: (1) [bmim$^+$][PF$_6^-$], (2) [bdmim$^+$][PF$_6^-$], (3) [hmim$^+$][PF$_6^-$], (4) [omim$^+$][PF$_6^-$],(5) [emim$^+$][NTf$_2^-$], (6) [bmim$^+$][NTf$_2^-$], (7) [hmim$^+$][NTf$_2^-$] and (8) [omim$^+$][NTf$_2$] and the water-miscible ILs were: (1) [emim$^+$][BF$_4^-$], (2) [bmim$^+$][BF$_4^-$], (3) [bdmim$^+$][BF$_4^-$], (4) [hmim$^+$][BF$_4^-$], (5) [emim$^+$][dca$^-$], (6) [bmim$^+$][dca$^-$], (7) [omim$^+$][dca$^-$], (8) [bmim$^+$][NO$_3^-$], (9) [bmim$^+$][CH$_3$COO$^-$], (10) [bmim$^+$][OcSO$_4^-$] and (11) [bmim$^+$][MDEGSO$_4^-$]. In all the water-immiscible ionic liquids assayed, the enzymatic activity was higher than that obtained in *n*-hexane. On the contrary, in all the water-miscible ionic liquids assayed, the enzymatic activity was lower than that obtained in *n*-hexane.

Regarding anion composition of water-immiscible ionic liquids, de los Ríos et al. [12] observed that *Ca*LB activity was greater in ionic liquids containing the anion [PF$_6^-$] than that in [NTf$_2^-$], which was explained because of the higher tendency of the most nucleophilic anion ([NTf$_2^-$]) to change the enzyme's conformation by interacting with the positively charged sites in the enzyme structure. However, contrary to what might be expected from this tendency, the reaction rate in [bmim$^+$][NTf$_2^-$] was greater than in [bmim$^+$][PF$_6^-$]. This could be due to the high viscosity of [bmim$^+$][PF$_6^-$] (207 cP) compared with [bmim$^+$][NTf$_2^-$] (52 cP), which would involve more diffusional limitations. Several other authors have also reported that lipases are more active in [bmim$^+$][NTf$_2^-$] than in [bmim$^+$][PF$_6^-$] [6, 17].

In the case of most of the water-miscible ILs [12], the negative effect observed on the lipase activity at low water content can be attributed to the direct interaction of the anion with the enzyme molecules, which would lead to protein denaturation [14, 22]. CaLB was inactive in [bmim$^+$][NO$_3^-$], which was attributed to the high nucleophilicity of the anion [NO$_3^-$], which may coordinate very strongly to positively charged sites in the enzyme structure changing the enzyme's conformation. The negative effect of strongly coordinating anions was reported by van Rantwijk et al. [44] in the synthesis of butyl butyrate from ethyl butanoate and 1-butanol catalysed by *Ca*LB. They observed a deactivation of CaLB in water-miscible ILs, [bmim$^+$][NO$_3^-$], [bmim$^+$][CH$_3$CH$_2$COO$^-$] and [bmim$^+$][dca$^-$], due to the dissolution of CaLB in these ILs. Therefore, the hydrophobic ionic liquids are better media for the biotransformations investigated than hydrophilic ionic liquids. Similar behaviour was observed for other enzymes such as lipase from *Pseudomonas sp*. (*Ps*L) [14, 45–49], CrL [35] and subtilisin [24]. It has been observed that, with few exceptions [47, 48], enzyme activity and solubility in ionic liquids are mutually exclusive [42, 49]. Ionic liquids which dissolve enzymes could form strong hydrogen bonds that may dissociate the hydrogen bonds that maintain the structural integrity of the α-helices and β-sheets, causing the protein to unfold wholly or partially [42].

Structural studies of enzymes in two water-immiscible ionic liquids (1-ethyl-3-methylimidizolium bis(trifluoromethylsulphonyl)imide and butyltrimethylammonium bis(trifluoromethylsulphonyl)imide) have also been carried out [50]. From these studies, it was concluded that an aqueous solution of free-enzyme molecules added to the water-immiscible IL could be considered as being included in a strong ionic matrix but not dissolved in the medium, providing a suitable microenvironment able to keep the protein conformation active. This fact was associated with the observed evolution of α-helix to β-sheet secondary structures of the enzyme, resulting in a more compact enzyme conformation able to exhibit catalytic activity.

On the other hand, strongly coordinating ionic liquids, such as $[\mathrm{bmim}^+][\mathrm{dca}^-]$ are potentially useful solvents due to its high solvent capability [3, 51, 52]. For that reason, enzymes derivatives compatible with this kind of ionic liquids have been developed. In this context, CaLB, adsorbed and cross-linked on a polypropylene carrier, maintained its transesterification activity in the ionic liquids $[\mathrm{bmim}^+][\mathrm{NO_3}^-]$ and $[\mathrm{bmim}^+][\mathrm{dca}^-]$, which deactivate the free enzyme [3].

Regarding the cation composition of ionic liquids [12], the synthetic activity has been reported to gradually enhance by increasing the length of the alkyl group on the cation which results in an increase in hydrophobicity of the ionic liquid media. The increase in hydrophobicity of the medium could allow the preservation of the essential water layer around the protein molecule, thus reducing direct protein–ion interactions. Furthermore, ion size could matter because sterically demanding ions would require many hydrogen bonds to be broken to create a few new ones, which could contribute to maintaining the active conformation of the enzyme [53]. An increase in the enzyme activity with the alkyl chain length of the cation was also observed by several authors [15, 54, 55].

Differences in the selectivity of the biosynthetic reactions in ILs have been attributed to their specific abilities to reduce water activity (a_{W}) in the enzyme microenvironment. Thus, an increase in the hydrophobicity of ILs generally involves an increase in free water molecules (water molecules dispersed in the ionic liquid), which can act as nucleophile acceptors in transesterification reaction, thus leading to a loss in selectivity [12]. Other key criterion for selecting an enzyme-solvent system is the stability of the catalyst within the reaction medium. It has been reported that the stability of enzymes is often better in ionic liquids than in organic media [50, 56]. Different types of enzyme stabilities such as storage and operational stabilities in ionic liquids have been investigated. Storage stability has been measured by enzyme incubation in an ionic liquid at a certain temperature, monitoring the residual activity in the same medium or in other medium. Values of operational stability of enzyme in ionic liquids under the operational reaction conditions for a certain period of reaction time have also been reported.

The storage stability of CaLB in $[\mathrm{bmim}^+][\mathrm{PF_6}^-]$, $[\mathrm{hmim}^+][\mathrm{PF_6}^-]$, $[\mathrm{omim}^+][\mathrm{PF_6}^-]$, $[\mathrm{hmim}^+][\mathrm{NTf_2}^-]$, $[\mathrm{hmim}^+][\mathrm{BF_4}^-]$ and $[\mathrm{bmim}^+][\mathrm{dca}^-]$ was studied by de los Ríos et al. [12]. They found the most important effect on *Ca*LB stability by changing the nature of IL anions. For the ionic liquids containing the cation $[\mathrm{bmim}^+]$, the increase in half-life time was in the order: $[\mathrm{bmim}^+][\mathrm{dca}^-] < [\mathrm{bmim}^+][\mathrm{PF_6}^-]$, and for those containing the cation $[\mathrm{hmim}^+]$, the order was: $[\mathrm{hmim}^+][\mathrm{BF_4}^-] < [\mathrm{hmim}^+][\mathrm{NTf_2}^-] < [\mathrm{hmim}^+]$

[PF_6^-]. This observation was explained by the fact that the most nucleophilic anion may interact more strongly with the enzyme, causing changes in the active enzyme structure. The same tendency was observed by Kaar et al. [57] with Novozym® 435, which was more stable in [$bmim^+$][PF_6^-] than in [$bmim^+$][NO_3^-] and by Persson and Bornscheuer [6] using an esterase from *B. stearothermophilus*, which showed greater stability in [$bmim^+$][PF_6^-] than in [$bmim^+$][BF_4^-], being considerably higher in these ionic liquids than in conventional organic solvents such as *n*-hexane and MTBE. It was also found that the stability of *Ca*LB was increased with the increase in the alkyl chain length attached to the cation, that is with the increase in IL's hydrophobicity. These results are in accordance with those obtained by Lozano et al. [58], who found that this enzyme was very sensitive to deactivation when hydrophobicity decreased.

The storage stability of other lipases has been also analysed. For instance, the storage stability of *Ps*L in hydrophobic ILs for a period of 20 days at room temperature, measured with the variation of the transesterification activity of this enzyme during transesterification of ethyl 3-phenylpropanoate with different alcohols, resulted in an increased yield of 62–98% in [$bmim^+$][NTf_2^-] and 45–98% in [$bmim^+$][PF_6^-], respectively, depending on the nature of alcohol used in the transesterification reaction. In these ionic liquids, the operational stability was also measured and found that the *Ps*L-IL mixture was recycled five times without any decrease in the transesterification activity [13].

Other hydrolases have been studied in ionic liquid media such as *Penicillin G acilase (PGA)* [2]. Stability studies on this enzyme have been carried out in organic solvents as well as in ionic liquids. The enzyme deactivation was practically instantaneous in toluene and dichloromethane, and only measurable stability was in 2-propanol. The stability of PGA in ILs was notably improved with respect to 2-propanol. A half-life time of 23 h was obtained in 1-ethyl-3-methylimidazolium bis{(trifluoromethyl)sulphonyl}imide ([$emim^+$][TfN_2^-]) which was about 2000-fold higher than that in 2-propanol.

The storage stability of proteases in ionic liquid media has also been studied [37, 59, 60]. Erbeldinger et al. [59] reported that the activity loss of thermolysin during preincubation proceeded much slower in [$bmim^+$][PF_6^-] than in ethyl acetate. The storage stability of R-chymotrypsin in the ionic liquid [$emim^+$][TfN_2^-] was compared with that in water, 3 M sorbitol and 1-propanol. The enzyme's lifetime in [$emim^+$][TfN_2^-] at 30°C was 2, 6 and 96 times higher than that observed in 3 M sorbitol water and 1-propanol, respectively [37, 60].

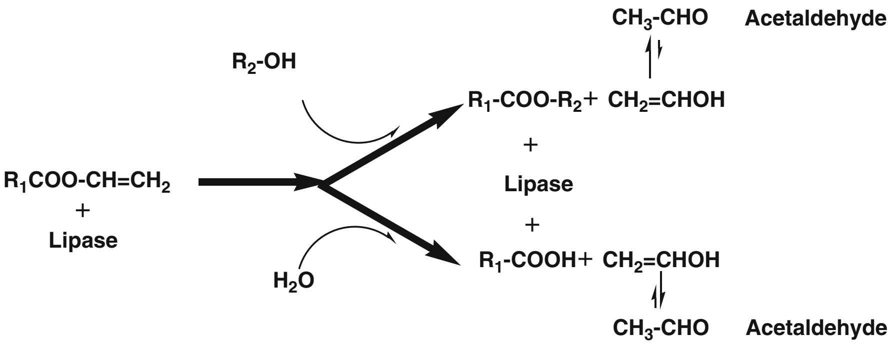
Although, most studies of biocatalysis in ionic liquids have been focussed on the use of isolated enzymes. However, whole cells have also been used as biocatalyst and their stability in ionic liquid media has been analysed. In this context, the stability of *Rhodococcus* R312 in a biphasic [$bmim^+$][PF_6^-]-water system was studied using a nitrile hydrolysis as test reaction from where it was noticed that the microorganism maintained its activity in a better was in an ionic liquid than in a biphasic toluene-water system [61]. It has been also reported that baker's yeast [62] as well as *Rhodococcus* R312 and *E. coli* [63] maintain their activity in ionic liquids containing no or a very small separate aqueous phase.

7.4 Biotransformation in Ionic Liquids

7.4.1 Synthesis of Flavour Esters

The work from Sheldon's group [10] was the first to present the use of ionic liquids in the enzymatic synthesis of esters. Since then, there have been many reports on biosynthesis of esters in ionic liquids. De los Ríos et al. [64, 65] synthesised a wide range of aliphatic organic esters, commonly used in the perfumery, flavour and pharmaceutical industries, by transesterification from vinyl esters and alcohols catalysed by free *Ca*LB in different 1,3-dialkylimidazolium-based ILs (Fig. 7.2). They analysed the effects of the alkyl chain lengths of the acyl donor and the alcohol. The optimum (C6 for acyl donor and C4 for alcohol) chain lengths were found because the activity decreased with further increase in alkyl chain length. The authors attributed the enzyme behaviour to a substrate modulation mainly due to the different affinity of the lipase towards the different substrates and steric hindrance and denaturalisation by small alcohol molecules.

Aromatic esters have been synthetised in ionic liquids. In this context, the lipase-catalysed acylation of 2-hydroxymethyl-1,4-benzodioxane with vinyl acetate was carried out in two ionic liquids, $[\mathrm{bmim}^+][\mathrm{PF}_6^-]$ and $[\mathrm{bmim}^+][\mathrm{BF}_4^-]$ [14]. They found better or comparable conversion in these unconventional media than in conventional organic solvents. Another interesting example of aromatic ester biosynthesis in ILs was reported by Vidyaa and Chadhaa [13]. These authors carried out the transesterification of ethyl 3-phenylpropanoate with 11 alcohols catalysed by *Ps*L in $[\mathrm{bmim}^+][\mathrm{PF}_6^-]$, $[\mathrm{bmim}^+][\mathrm{BF}_4^-]$ and $[\mathrm{bmim}^+][\mathrm{NTf}_2^-]$ as reaction media.



R_1= CH_3-, CH_3CH_2-, $CH_3(CH_2)_2$-, $CH_3(CH_2)_8$-, $CH_3(CH_2)_{10}$-, CH_2CH-, $CH_2C(CH_3)$-
R_2= CH_3-, $CH_3(CH_2)_3$-, $CH_3(CH_2)_5$-, $CH_3(CH_2)_7$-

Fig. 7.2 Stoichiometric scheme of kinetically controlled synthesis of esters by transesterification from vinyl esters and alcohols catalysed by CALB

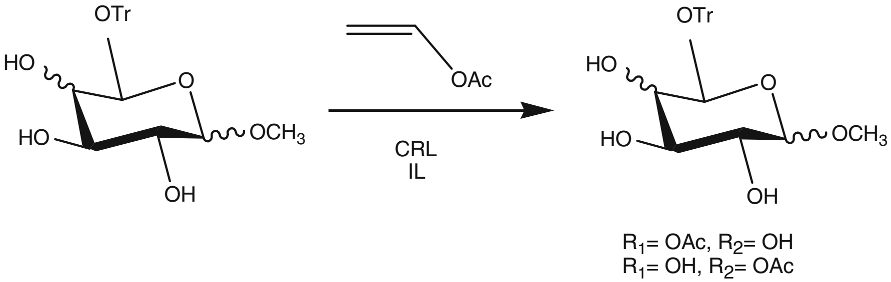


Fig. 7.3 CRL-catalysed acylation of glycosides [7]

7.4.2 Biotransformations of Polysaccharides and Nucleotides

Ionic liquids are particularly useful as the media for enzymatic transformations of polar substrates, such as polysaccharides and nucleotides, that are difficult to dissolve in conventional organic solvents. Park and Kazlauskas [46] carried out the acetylation of glucose catalysed by *Ca*LB in ionic liquids and found that the reaction was more regioselective in these media than in organic solvents because glucose was up to 100 times more soluble in the ionic liquids. Other example is the selective acylations of monoprotected glycosides catalysed by *Cr*L in both organic solvents (THF and chloroform) and ionic liquids ([bmim$^+$][PF$_6^-$] and [moemim$^+$][PF$_6^-$]) (Fig. 7.3) [7]. It was found that these reactions proceeded more rapidly and selectively providing higher yields in ionic liquids than those in organic solvents. The selective lipase-catalysed synthesis of glucose fatty acid esters in two-phase systems consisting of an ionic liquid ([bmim$^+$][PF$_6^-$] or [bmim$^+$][BF$_4^-$]) and *t*-butanol as organic solvent was also investigated [66]. After thorough optimization of several reaction conditions, conversions up to 60% could be achieved using fatty acid vinyl ester as acyl donors in [bmim$^+$][PF$_6^-$] in the presence of 40% *t*-BuOH with CaLB at 60°C.

Different ways of enhancing the solubility of polysaccharides in ionic liquids have been reported. Recently, ultrasound irradiation has been used to increase enzyme activity in lipase-catalysed esterifications of glucose with vinyl laurate or lauric acid in ILs [67]. It was found that ultrasound irradiation significantly enhances the enzyme activity probably due to an increase in the dissolution and mass transfer rates of substrates, without any loss in enzyme stability.

Reactions with nucleotides have also been carried out in ionic liquids. In this context, the transesterification of *N*-acetyl-L-phenylalanine ethyl ester with *n*-propanol catalysed by subtilisin (previously precipitated and rinsed with *n*-propanol) was succesfully carried out in [bmim$^+$][PF$_6^-$] and [bmim$^+$][BF$_4^-$] (Fig. 7.4) [23].

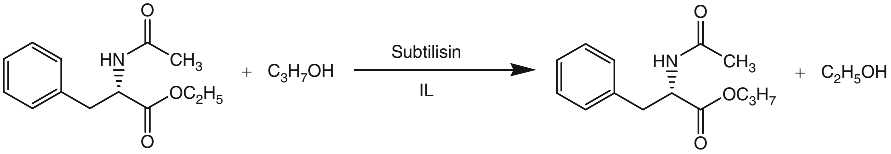


Fig. 7.4 Subtilisin-catalysed transesterification of *N*-acetyl-L-phenylalanine ethyl ester with *n*-propanol [25]

7.4.3 Synthesis of Biodiesel

The production of biodiesel in ionic liquids through immobilised *Candida antarctica* lipase–catalysed methanolysis of soybean oil has been investigated [54]. For this purpose, 23 ionic liquids were tested, the highest fatty acid methyl esters (FAMEs) production after 12 h at 50°C was in [emim$^+$][TfO$^-$]. With this ionic liquid, the production yield was 80%, which was eight times higher compared to the conventional solvent-free system and around 15% higher than that obtained using *tert*-butanol as an additive. Recently, fungus whole-cell biocatalysts, specifically lipase-producing filamentous fungi immobilised on biomass support particles, have been successfully used for the biosynthesis of biodiesel by methanolysis of soybean oil in [emim$^+$][BF$_4^-$] and [bmim$^+$][BF$_4^-$]. In these systems, the ionic liquids would work as a reservoir of methanol to suppress the enzyme deactivation [68].

7.4.4 Synthesis of Polyesters

Ionic liquids have also been used as reaction media in lipase-catalysed polyester synthesis, replacing the traditional chemical polymerization at >200°C. Nara et al. [69] reported the lipase-catalysed aliphatic polyester synthesis in [bmim$^+$][PF$_6^-$] (Fig. 7.5). They found that *Ps*L-C exhibited a high catalytic activity in polycondensation of diethyl octane-1,8-dicarboxylate and 1,4-butanediol at room temperature and at 60°C. The ring-opening polymerization of five lactones catalysed by *Ca*LB in ionic liquids has been also studied (Fig. 7.6) [70]. These reactions yielded poly(hydroxyalkanoates) of moderate molecular weights up to $M\text{n} = 13{,}000$. Using the ionic liquid [betim$^+$][NTf$_2^-$] and with a low weight ratio of enzyme to lactone (1:100), the following were obtained: (1) polymers from β-propiolactone, δ-valerolactone, and ε-caprolactone with degrees of polymerization as high as 170, 25, and 85, respectively; (2) oligomers from β-butyrolactone and γ-butyrolactone with degrees of polymerization of 5; and (3) a copolymer of β-propiolactone and β-butyrolactone with a degree of polymerization of 180.

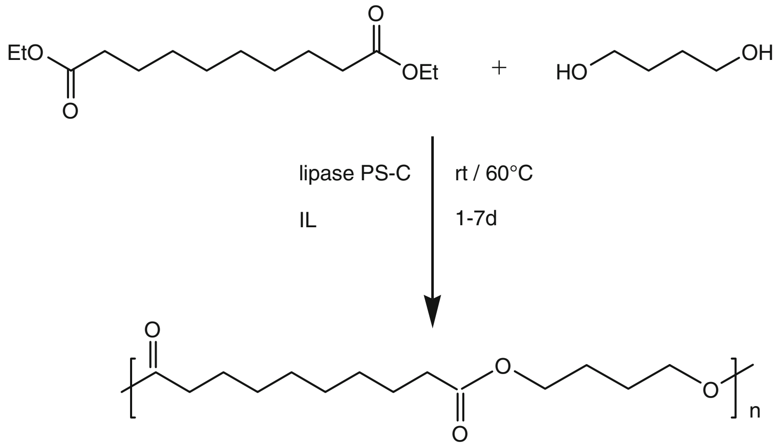


Fig. 7.5 *Pseudomonas cepacia* **lipase** supported on ceramic particles PS-C catalysed polyester synthesis using diethyl octane-1,8-dicarboxylate and 1,4-butanediol in [bmim]PF6 at room temperature or at 60°C [69]

7.4.5 Resolution of Racemates

The lipase-catalysed enantioselective acylation of allylic alcohols in an ionic liquid solvent was demonstrated by Itoh et al. [16] (Fig. 7.7). They found that the acylation rate was strongly dependent on the counter anion of the imidazolium salt, while the lipase-catalysed acylation proceeded with high enantioselectivity in all ionic liquid tested. Good results were obtained when the reaction was carried out in [bmim$^+$][PF$_6^-$] or [bmim$^+$][BF$_4^-$]. Other examples of kinetic resolution of allylic alcohols catalysed by lipases in ionic liquids were also reported by these authors [71, 72]. The transesterification of 5-phenyl-1-penten-3-ol under reduced pressure at 27 hPa and 40°C was carried out using methyl phenylthioacetate as acyl donor in [bmim$^+$][PF$_6^-$] and [bdmim$^+$][BF$_4^-$], for obtaining the corresponding acylated compound in optically pure form [71]. The acetylation of methyl mandelate catalysed by immobilised *Ps*L in [bdmim$^+$][BF$_4^-$] is another example reported by these authors about the successful application of ionic liquids as reaction media in racemic resolutions [72]. The kinetic resolution of *rac*-2-pentanol, a *sec*-alcohol catalysed by free *Ca*LB using vinyl propionate has been successfully carried out in [bmim$^+$][NTf$_2^-$] at 2% (v/v) water content [73]. The synthetic activity of lipase in [bmim$^+$][NTf$_2^-$] was up 2.5 times greater than in *n*-hexane, and showed high enantioselectivity (>99.99%).

Different groups have studied the kinetic resolution of rac-1-phenylethanol by transesterification with vinyl acetate using lipases in ionic liquids as the reaction media [6, 17, 46] (Fig. 7.8). Schöfer et al. [17] screened a set of nine lipases and two esterases for activity in ten different ionic liquids and compared the results with the reaction performed in methyl tert-butyl eter (MTBE) as the solvent. The lipases showed good activity and, in some cases, improved enantioselectivity in these new reaction media. For example, the enantiomeric excess with *Ps*L and *As*L in [bmim$^+$]

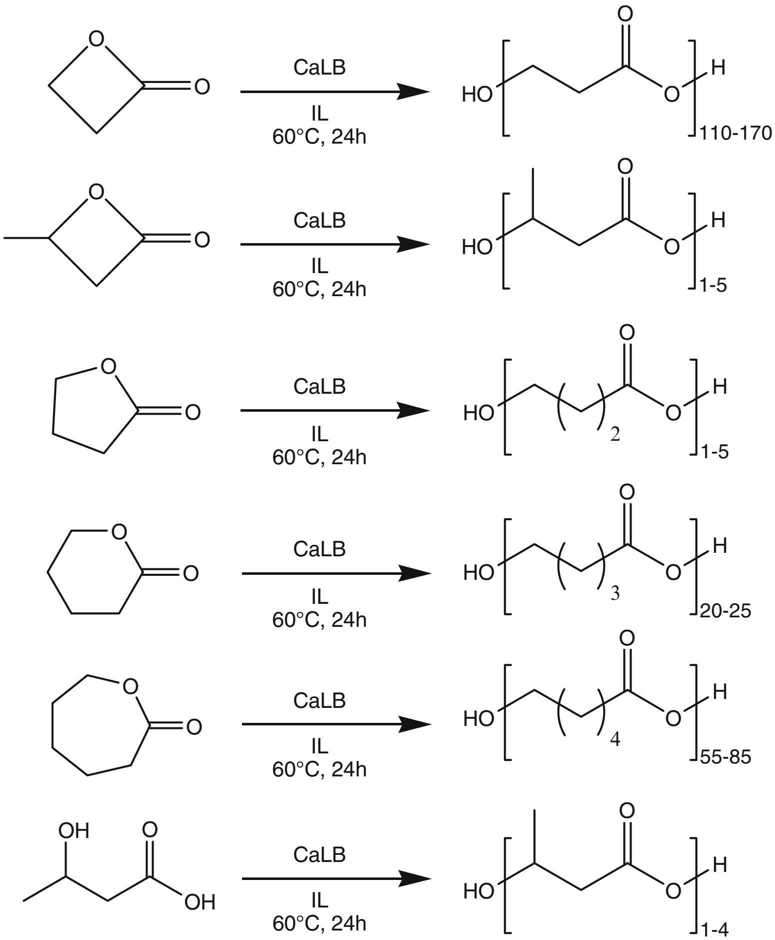


Fig. 7.6 Polymerization reactions carried out in [bmim$^+$][Tf$_2$N$^-$] [70]

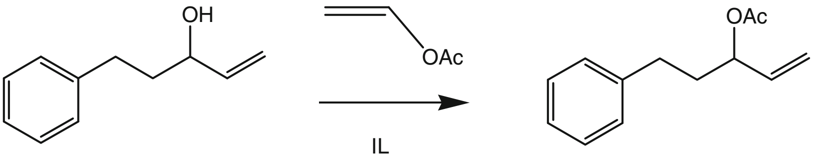


Fig. 7.7 Enantioselective acylation of allylic alcohols [16]

[NTf$_2^-$] were 98 and 15, respectively, while this parameter for these enzymes in MTBE was 84 and 0, respectively.

Different approaches have been developed to improve the activity of lipases in the kinetic resolution of 1-phenylethanol in ionic liquids. For example, Park and

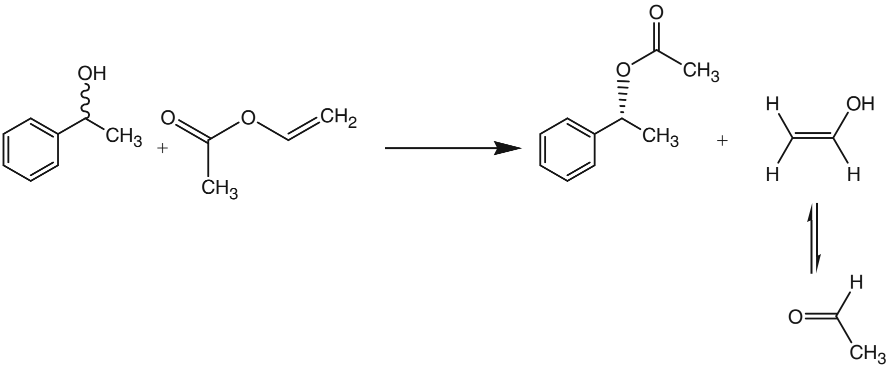


Fig. 7.8 Reaction scheme of kinetic resolution of racemic 1-phenylethanol [3]

Kazlauskas [46] introduce a wash with aqueous sodium carbonate in the preparation of ionic liquids. The acetylation of 1-phenylethanol catalysed by lipase from *Pc*L in these ionic liquids was as fast and as enantioselective as in nonpolar organic solvents such as toluene. Other authors used immobilised derivates of lipases to improve stability in ionic liquids. In this context, the transesterification of 1-phenylethanol catalysed by esterases from *Bacillus subtilis* and *Bacillus stearothermophilus* immobilised onto Celite was also successfully carried out in [bmim$^+$][NTf$_2^-$], [bmim$^+$][PF$_6^-$] and [bmim$^+$][BF$_4^-$] [6]. The kinetic resolution was performed with two lipases, *Ca*LB and *Ps*-D, in these ionic liquids [6]. Habulin and Knez [74] also investigated this kinetic resolution using an immobilised CaLB commercial preparation (Novozym® 435). They found that using Novozym® 435 as biocatalyst in [bmim$^+$][PF$_6^-$] at 313.15 K, the highest possible conversion (50%) was reached with enantiomeric excess for substrate higher than 99%. Sheldon's group [3] found that *Ca*LB, adsorbed and cross-linked on a polypropylene carrier, maintained its transesterification activity in the ionic liquids [bmim$^+$][NO$_3^-$] and [bmim$^+$][dca$^-$], which deactivate the free enzyme. This latter biocatalyst mediated the acylation of 1-phenylethanol and 1-phenylethylamine with high enantioselectivity, in conventional organic solvents as well as in [bmim$^+$][NO$_3^-$].

The first example of the use of a two-enzyme system in ionic liquids was reported by Kaftzik et al. [75], who investigated the deracemization of (±)-mandelic acid using a lipase-mandelate racemase two-enzyme system in ionic liquids (Fig. 7.9). They used a combination of the mandelate racemase–catalysed racemisation of (*R*)-mandelic acid and the lipase-catalysed kinetic resolution of (*S*)-mandelic acid to (*S*)-acetyl mandelic acid in a biphasic system consisting of [omim$^+$][PF$_6^-$] and water in a ratio of 1:10, a measurable racemase activity along with the formation of a measurable amount of (*S*)-acetyl mandelic acid was observed.

Ionic liquids have also been used as reaction media in biocatalytic esterification reactions. In this context, the enantioselective esterification of 2-substituted-propanoic acids with 1-butanol catalysed by *Cr*L in ionic liquids has been carried out by Ulbert et al. [76] (Fig. 7.10). It was demonstrated that application of [bmim$^+$][PF$_6^-$] and [onim$^+$][PF$_6^-$] ionic liquids was beneficial from not only enzyme activity

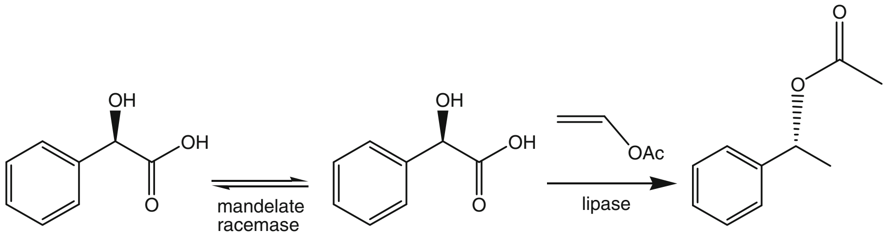


Fig. 7.9 Deracemization of (±)-mandelic acid via a lipase-mandelate racemase two-enzyme system: *Pseudomonas* sp. lipase–catalysed O-acylation of (±)-mandelic acid and by mandelate racemase catalysed racemisation of the remaining unreacted (*R*)-mandelic acid [75].

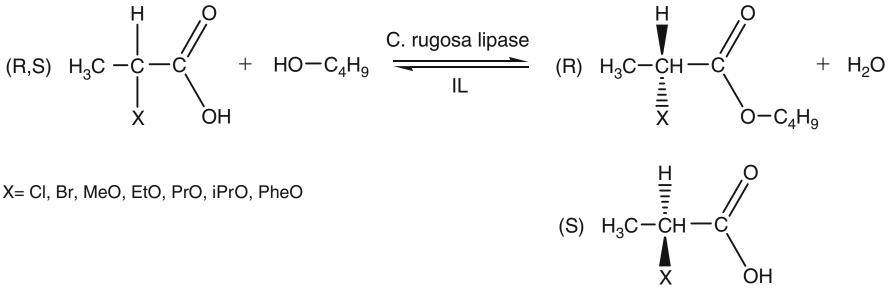


Fig. 7.10 Lipase-catalysed enantioselective esterification of 2-substituted-propanoic acids with 1-butanol [76]

point of view but also from enantioselectivity aspect. In the esterification of (*R*,*S*)-2-chloro-propanoic acid, 98 and 150% higher enantioselectivity could be achieved in ionic liquids [bmim$^+$][PF$_6^-$] and [onim$^+$][PF$_6^-$] respectively compared to that obtained in *n*-hexane. Yuan et al. [43] studied the enantioselective esterification of (±)-menthol with propionic anhydride using CrL in ionic liquids [bmim$^+$][PF$_6^-$] and [bmim$^+$][BF$_4^-$] and in organic solvents of different hydrophobicities. Comparable conversion yield and enantioselectivity were realised in [bmim$^+$][PF$_6^-$] and *n*-hexane during 24 h reaction time. The ionic liquid system showed an advantage of using less acid anhydride to achieve higher (±)-menthol conversion yield and better enantioselectivity. In addition, CrL exhibited higher stability and enantioselectivity during a long-term incubation in the ionic liquid than in *n*-hexane. Other interesting example was reported by Contesini and Oliveira [77], who tested four commercially available lipases and two native lipases from *Aspergillus niger* AC-54 and *Aspergillus terreus* AC-430 for the resolution of (R,S)-ibuprofen by esterification in systems containing the ionic liquids [bmim$^+$][PF$_6^-$] and [bmim$^+$][BF$_4^-$]. The lipases showed higher conversion in a two-phase system using [bmim$^+$][PF$_6^-$] and isooctane compared to that in pure isooctane. Fehér et al. [78] tested an immobilised derivative of *Ca*LB (Novozym® 435) in the enzymatic production of isoamyl acetate from acetic acid and isoamyl alcohol substrates, using as reaction medium a biphasic mixture of excess of isoamyl alcohol and [bmim$^+$][PF$_6^-$] ionic liquid. Under optimum

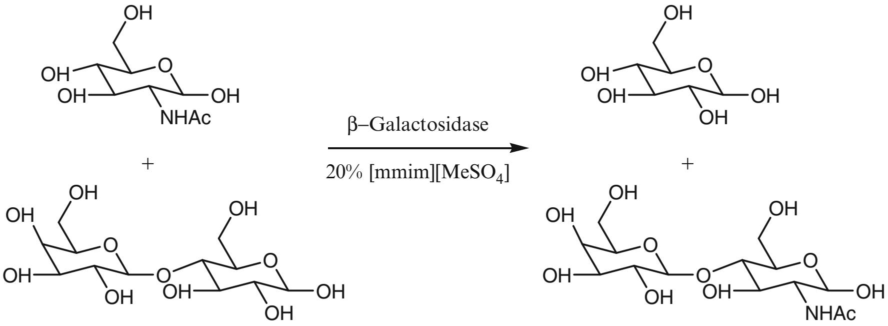


Fig. 7.11 Tranglycosylation of lactose with *N*-acetylglucosamine catalysed by β-galactosidase from *B. circulans* in [mmim$^+$][MeSO$_4^-$]-water (25:75, v/v) [26]

conditions, excellent yield and initial reaction rate were realised. The enzymatic esterification of glycerol with sinapic acid catalysed by a *feruloyl* esterase (*AnFae*A), free and immobilised as cross-linked enzyme aggregates, was the first example of use of this esterase in ILs [19]. Two hexafluorophosphate anion-containing ionic liquids ([OHemim$^+$][PF$_6^-$] and [m*oeo*emim][PF$_6^-$]) were used as reaction medium.

7.4.6 Synthesis of Carbohydrates

Carbohydrates have been synthetised in ionic liquid media using tranglycosylation reaction catalysed by glycolases [26, 27]. β-Galactosidase from *B. circulans* catalysed the tranglycosylation of lactose with *N*-acetylglucosamine in [mmim$^+$][MeSO$_4^-$]-water (25:75, v/v) [26] (Fig. 7.11), and β-glycosylhydrolase CelB from Pyroccocus furiosus catalysed the tranglycosylation of lactose with glycerol in [mmim$^+$][MeSO$_4^-$]-water (45:55, v/v) [27]. In both cases an increase of the reaction yield was observed.

7.5 Conclusions

The results reported so far have clearly shown the potential of using ionic liquids as solvents for biocatalysis. Many hydrolases, specially lipases, are eminently capable of performing nonhydrolytic reactions in ionic liquids showing comparable or higher activity than that observed in conventional organic solvents. Enhanced storage and operational stabilities and selectivity and regio- or enantioselectivities have been also reported in these media. Isolated enzymes as well as whole-cell preparations have been tested in ionic liquids. It is hoped that hydrophobic ionic liquids will prove promising and attractive replacements for molecular solvents in whole-cell biotransformations. Among the compounds synthetised in ionic liquid media, it is worthy to highlight the importance of aliphatic and aromatic esters commonly used in the perfumery, flavour and pharmaceutical industries, polymers and biodiesel. To sum up, the recent studies on biocatalysis in ionic liquids take a further step towards the efficient design of green chemical industrial processes. It is also expected that ionic liquid-based solvent systems will have enormous potential in different biocatalyst transformations.

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Chapter 8
Ionic Liquids/Supercritical Carbon Dioxide as Advantageous Biphasic Systems in Enzymatic Synthesis

A.P. de los Ríos, F.J. Hernández-Fernández, L.J. Lozano, and C. Godínez

Abstract Ionic liquids/supercritical carbon dioxide (ILs/scCO$_2$) biphasic systems have recently proved as interesting clean alternatives to classical organic solvents in enzymatic synthesis. The success of IL/scCO$_2$ biphasic systems is based on the fact that ILs provide an adequate microenvironment for the catalytic activity of the enzyme, while supercritical carbon dioxide acts as extracting phase, making possible the easy recovery of the products. This new methodology avoids the use of volatile organic solvents and hence is considered as a green technology. In this chapter, the properties of ionic liquids/supercritical carbon dioxide biphasic systems for enzymatic applications have been examined.

8.1 Introduction

The use of biocatalysis in organic solvents has greatly enhanced their technological applications during the last two decades due to certain advantages, such as the possibility of carrying out synthetic reactions by hydrolytic enzymes, increasing the solubility of organic substrates and facilitating enzyme and product recovery [1, 2]. However, volatile organic solvents (VOS) have a detrimental impact on the environment and human health. Because of this fact, it is necessary to develop green and clean reaction media before scaling-up biocatalytic processes of industrial interest [3]. Ionic liquids/supercritical carbon dioxide (ILs/scCO$_2$) biphasic systems have recently been considered as interesting clean alternatives to classical organic

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solvents [4]. Ionic liquids, which are salts with melting points close to room temperature, are emerging as potentially green solvents for chemical processes because they combine good and tunable solubility properties with negligible vapour pressures and high thermal and (electro-) chemical stabilities. They can be used as reaction media in enzymatic catalysis, where they enhance reaction rates, stability and selectivities. Moreover, the combination of ionic liquids and supercritical carbon dioxide is advantageous because products can be separated from ionic liquids by extraction with supercritical carbon dioxide without detectable ionic liquid contamination due to negligible solubility of ionic liquids in carbon dioxide.

In this report, the use of ionic liquids/supercritical carbon dioxide in biocatalytic reactions has been extensively reviewed. Properties of supercritical carbon dioxide, ionic liquids and ionic liquids/supercritical carbon dioxide biphasic systems have been analysed. Representative examples of the enzyme catalytic reactions in IL/$scCO_2$ biphasic systems have been included. Finally, the effect of the biphasic systems on activity, selectivity and stability of enzymes has been carefully analysed.

8.2 Supercritical Carbon Dioxide in Enzymatic Synthesis

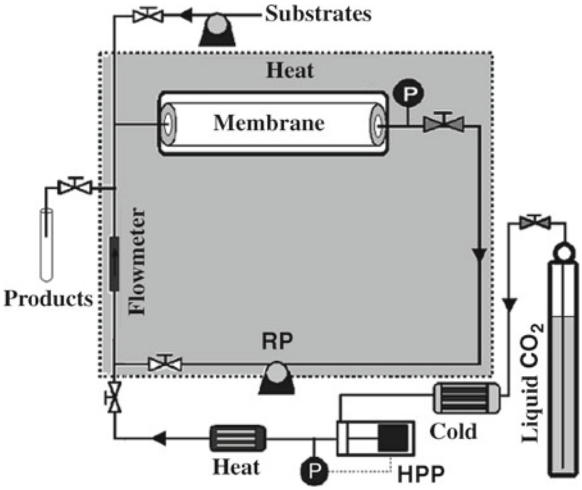
A supercritical fluid (SCF) is any substance above its critical temperature (T_C) and critical pressure (P_C). In general terms, SCFs have properties like density, viscosity and diffusivity between those of a gas and a liquid. One of the most important properties of those is that by changing the pressure and temperature of the fluid, its solvent power can be tuned. In Table 8.1, the critical properties of several supercritical fluids are presented [5].

Supercritical fluids have been used as solvents for a wide variety of applications such as essential oil extraction [6], metal extraction [7], polymer synthesis [8] and particle nucleation [9]. Most applications of supercritical fluids are in combination with carbon dioxide. Among SCFs, supercritical carbon dioxide ($scCO_2$) is especially advantageous because of its near ambient critical temperature (304.1 K) and its moderate critical pressure. Water, which is also a desirable solvent, has a higher critical

Table 8.1 Critical pressure, temperature and density of various solvents

Solvent	Critical temperature (K)	Critical pressure (MPa)	Critical density (g/cm^3)
Methane	190.4	4.60	0.162
Ethylene	282.4	5.04	0.215
Carbon dioxide	304.1	7.38	0.469
Ethane	305.3	4.87	0.203
Propylene	364.9	4.60	0.232
Propane	369.8	4.25	0.217
Acetone	508.1	4.70	0.278
Methanol	512.6	8.09	0.272
Ethanol	513.9	6.14	0.276
Water	647.096	22.064	647.096

Fig. 8.1 Experimental set-up of the recirculating enzymatic membrane reactor used for the synthesis of butyl propionate from vinyl propionate and 1-butanol catalysed by *Candida antarctica* lipase B in supercritical carbon dioxide and supercritical carbon dioxide/ionic liquid biphasic system [17]



temperature and pressure than CO_2, making it difficult to ensure a safety work under these conditions. Furthermore, supercritical carbon dioxide is relatively non-toxic, non-flammable, available in high purity at relatively low cost and is easily removed from the extract. As a supercritical fluid, its solvent power can be tuned by changing either the pressure or the temperature, and the reaction products can be separated by tuning their solubility as a function of operating conditions. When the pressure and temperature of $scCO_2$ are near to critical point, $scCO_2$ becomes a solvent of low polarity. At constant temperature, the solubility of a non-polar compound in the fluid is favoured at lower pressures, whereas at higher pressures, polar compounds become more soluble. The solubility of organic polar compounds could be improved by addition of a small amount of an organic solvent such as methanol or acetonitrile which acts as a modifier. It is also removable by post-reaction depressurization. For these reasons, $scCO_2$ is frequently designated a 'green designer' solvent [10].

The use of $scCO_2$ as a novel medium for enzymatic reactions has attracted considerable interest [11]. Most of the enzymes used in supercritical carbon dioxide are hydrolytic enzymes, especially lipases [12–15]. However, other types of enzymes like oxidoreductases [16] have also been used in supercritical carbon dioxide. One interesting example was reported by Hernández et al. [17], who studied the synthesis of butyl propionate from vinyl propionate and 1-butanol in supercritical carbon dioxide catalysed by *Candida antarctica* lipase B. The initial substrate concentration ranges were 75–200 mM for both substrates, vinyl propionate and 1-butanol. In these ranges, strong alcohol inhibition was observed. Alcohol inhibition is generally observed during lipase esterification and transesterification reactions. Indeed, some authors have demonstrated, in both conventional and non-conventional media (e.g. $scCO_2$), that the kinetic mechanism for these reactions was a Ping Pong Bi-Bi with competitive alcohol inhibition [18, 19]. The experimental set-up used by Hernandez et al. [17] consists of a recirculating enzymatic membrane reactor with the enzyme immobilized on the surface of the membrane (Fig. 8.1).

These authors considered that as the recirculation rate is high enough, the conversion per pass is low, so the system acts as an ordinary batch reactor, which could be represented by the following continuity equation, with time corrected through the ratio $\frac{S}{V_{total}}$:

$$\left(\frac{S}{V_{total}} \times dt\right) = \frac{dCa}{(-ra)} \tag{8.1}$$

where S is the membrane internal surface (cm^2), V_{total} the reactor internal volume (mL), t the reaction time (min), Ca the product concentration in the reactor (mol/L) and ra the reaction rate (mmol · min^{-1} · cm^{-2}).

The initial reaction rate, referring to the effective surface of the membrane, was obtained from the initial rate of change of the concentration as follows:

$$V_0 = \left(\frac{V_{total}}{S}\right) \times \left(\frac{dCa}{dt}\right)_0 \tag{8.2}$$

The corresponding kinetic equation for Ping Pong Bi-Bi mechanism with competitive alcohol inhibition was used to fit the experimental data, determining the kinetic parameters by the following expression:

$$V_0 = V_{\max} \cdot \frac{[PV] \cdot [Bu]}{[Bu] \cdot \left(K_{mPV} \cdot \left(\frac{[Bu]}{K_I} + 1\right)\right) + (K_{mBU} + [Bu]) \cdot [PV]} \tag{8.3}$$

where V_0 and $V_{\max}$ are the initial and the maximum reaction rates, respectively, [PV] and [Bu] the initial vinyl propionate and 1-butanol molar concentrations, K_{mPV} and K_{mBU} the Michaelis constants of vinyl propionate and 1-butanol, and K_I the inhibition constant of 1-butanol.

The results for the kinetic parameters involved: $V_{\max} = 0.851$ mmol · min^{-1} · cm^{-2}; $K_{mPV} = 0.9985$ M; $K_{mBU} = 0.0102$ M; $K_I = 0.776$ M, and the sum of the mean square error was 5.77×10^{-6}. The kinetic parameters obtained may be considered as apparent values because of the possibility of internal and/or external diffusional limitations.

Srivastava et al. [12] studied the esterification of myristic acid with ethanol with crude hog pancreas lipase. Conversions of up to 76% were obtained under solvent-free conditions while conversions of only up to 37% and 4% were obtained in scCO$_2$ and acetonitrile, respectively. However, for similar enzyme concentrations, 37% of the myristic acid was converted to ester in scCO$_2$, but only 4% was converted in acetonitrile and solvent-free conditions. The alcohol was also found inhibitory for the reaction in scCO$_2$.

Other lipases have also been tested in supercritical carbon dioxide for ester synthesis. In this context, the synthesis of terpinyl acetate from α-terpineol and acetic anhydride in supercritical carbon dioxide (scCO$_2$) was carried out using five different lipases as catalysts (*Candida rugosa* type VII, Amano PS, Amano AP-6, Amano G and Lipozyme RM IM) [20]. The highest yield of terpinyl acetate was obtained by using *Candida rugosa* type VII. Near cero yield of terpinyl acetate was obtained with Amano PS and Amano G. An esterification up to of 53.0% was obtained under optimized conditions in continuous operation using acetic anhydride as acyl donor and *Candida rugosa* lipase as enzyme at 10 MPa and 50°C for 1.5 h. However, the enzyme activity decreased up to 50% after 10.5 h repeated esterification in a batch.

Although very interesting biotranformations have been reported in supercritical carbon dioxide, this solvent has been found to affect enzyme activity adversely. CO_2 can react reversibly with free amino groups (lysine residues, specifically) on the surface of the protein to form carbamates, leading to low activity enzyme. [21]. Furthermore, carbon dioxide dissolves in water at molar concentrations at moderate pressures (<100 bar) and rapidly forms H_2CO_3. This can create some problems in biocatalytic reactions because many enzymes are denatured (unfolded and/or deactivated) at low pH. Enzymes can also be denatured by pressurization/depressurization cycles. For all of them, it is necessary to develop new enzyme stabilization strategies.

8.3 Ionic Liquids as Reaction Media in Enzymatic Synthesis

Ionic liquids have recently appeared as clean alternatives to classical organic solvents for a wide variety of biochemical processes due to their unique properties [22–26]. Ionic liquids are organic salts which are liquid close to room temperature. They normally consist of an organic cation (e.g. dialkylimidazolium, tetraalkylammomium) and a polyatomic inorganic cation (e.g. hexafluorophosphate, tetrafluoroborate, bis(trifluoromethylsulphonyl)imide) (Fig. 8.2).

From an environmental point of view, the most important properties of ionic liquids are their negligible vapour pressure and good chemical and thermal stabilities [25]. Additionally, the physico-chemical properties of ionic liquids, such as hydrophobicity, density, viscosity, melting point, polarity and solvent properties, may be tunable by appropriate modification of the cation and/or anion [27]. These features are important to design an optimal IL for each specific enzymatic reaction system. In fact, lipase-catalysed reactions in ILs have been seen to have several potential advantages over conventional organic reaction media, including increased synthetic activity, (enantio)selectivity and stability [26, 28–31]. An interesting example of the use of lipases in ILs was reported by de los Ríos et al. [30], who studied the effect of dialkylimidazolium-based ionic liquids on activity, selectivity and stability of CaLB for the synthesis of butyl butyrate by transesterification from vinyl butyrate and 1-butanol. For that, 19 different water-immiscible and water-miscible ionic liquids consisting of dialkylimidazolium cations combined with a wide range of anions, including hexafluorophosphate, bis(trifluoromethylsulphonyl)imide, tetrafluoroborate, dicyanamide, nitrate, acetate, octylsulphate and ethyleneglycolmonomethylethersulphate were tested as reaction media at 2% (v/v) water content

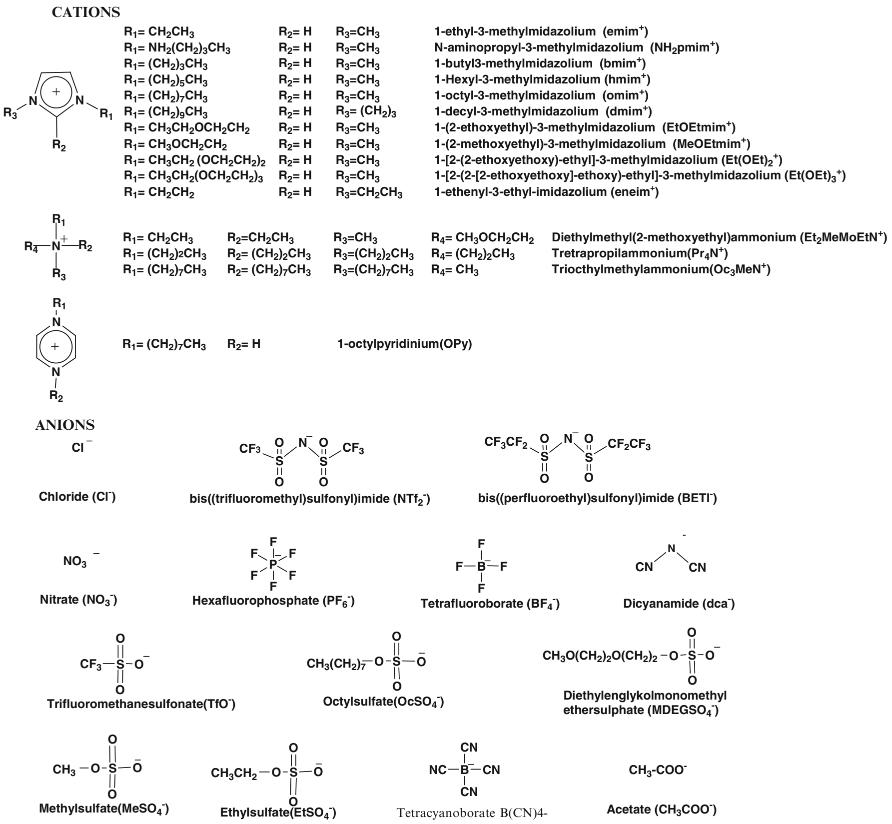


Fig. 8.2 Example of ions involved in ILs

and 30°C. In all the water-immiscible ionic liquids assayed, the enzymatic activity was higher than that obtained in *n*-hexane which was used as reference organic solvent. However, lower or non-enzymatic activity was found in all the water-miscible ionic liquids assayed. In the latter case, the negative effect observed on the lipase activity was attributed to the stronger interaction of the anion such as nitrate or acetate with the enzyme molecules, which would lead to protein denaturation. Therefore, the hydrophobic ionic liquids proved to be better media for the investigated biotransformations than the hydrophilic ones, increasing the enzyme activity with respect to organic solvents. It is also worthy to note that the synthetic activity of the enzyme was gradually enhanced by increasing the length of the alkyl group on the cation which involves an increase in hydrophobicity of the ionic liquid media. The increase in hydrophobicity of the medium allows the preservation of the essential water layer around the protein molecule, thus reducing direct protein–ion interactions. Furthermore, ion size could matter because sterically demanding ions would require many hydrogen bonds to be broken to create a few new ones, which could contribute to maintaining the active conformation of the enzyme [32]. The storage stability of native penicillin G acylase in ionic liquids (based on dialkylimidazolium cations associated with perfluorinated and bis{(trifluoromethyl)sulphonyl}imide anions) and in organic solvents (toluene, dichloromethane and 2-propanol) has been investigated by de los Ríos et al. [31]. The hydrolysis of penicillin G was used as activity test for this purpose. Native penicillin G acylase showed greater stability in IL media than in organic solvents. For example, a half-life time of 23 h was obtained in 1-ethyl-3-methylimidazolium bis{(trifluoromethyl)sulphonyl}imide, [emim$^+$][TfN$_2^-$], which was about 2,000-fold higher than that in 2-propanol.

To sum up, enzymes in ionic liquids could maintain their activity over a much longer period than in molecular organic solvents. This stabilization has been explained on the basis of the interaction of the ionic liquid ions as well as higher viscosity of ionic liquids with respect to conventional organic solvent, which could cause slower migration of protein domains from the active conformation into the inactive one. [33].

8.4 Supercritical Carbon Dioxide/Ionic Liquid Biphasic System in Enzymatic Synthesis

Once a biocatalytic reaction is carried out in ionic liquids, it is necessary to extract the reaction products from the ionic liquid. Distillation could be used as separation method since ionic liquids have an almost negligible vapour pressure. However, this method is not useful if the reaction products are heat labile. Furthermore, the enzyme could be denatured if it is not separated in a previous step. One potential alternative to overcome these inconveniences could be the use of an organic solvent immiscible with the ionic liquid phase as extracting phase. However, the use of organic solvents implies that the overall process is not totally green. Therefore, the most suitable option could be the use of supercritical carbon dioxide as extracting solvent. In fact, IL/scCO$_2$ biphasic systems have shown good behaviour to carry out integral green biocatalytic processes in non-aqueous media [17, 34]. The success of these biphasic systems is based on the fact that, while scCO$_2$ is highly soluble in the IL phase, the same IL shows non-appreciable solubility in the scCO$_2$ phase [35]. Moreover, scCO$_2$ has been demonstrated to have exceptional ability to extract a wide variety of hydrophobic compounds (aliphatic and aromatic) from ILs without any cross-contamination of the extract by the ILs [4, 36] due to the low solubility of ILs in the scCO$_2$ phase [35]. Other advantages of using scCO$_2$ include their high diffusivity and the resulting decrease in the viscosity of ILs, which improves the mass transfer [35]. In addition, IL/scCO$_2$ biphasic systems have clearly been demonstrated to have a stabilizing effect against enzyme deactivation even under extremely severe conditions [37].

Several authors have demonstrated the capability of enzymes to catalysing reaction in scCO$_2$/IL biphasic systems [34, 37, 38]. The synthesis of butyl propionate, which is a flavour agent, was successfully carried out in a recirculating bioreactor in scCO$_2$/IL biphasic systems at 50°C and 80 bars [38]. This reactor was made from stainless steel (internal volume = 178 mL) equipped with valves, pressure and flow

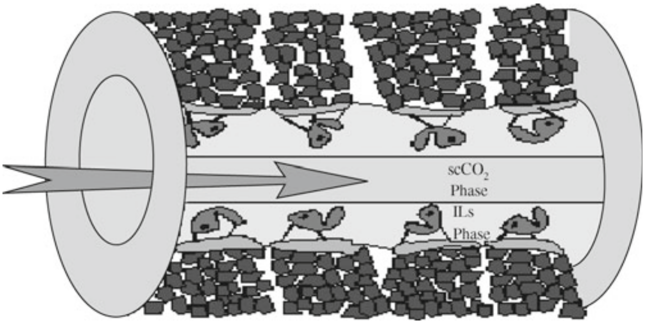


Fig. 8.3 Ceramic membrane with enzyme immobilized and ionic liquids absorbed on the surface

controls (see Fig. 8.1). The enzyme, *Candida antarctica* lipase B, was immobilized on the surface of α-alumina microporous membranes using a cross-linking agent and then coated with a thin layer of ionic liquid (Fig. 8.3). The active membrane was introduced into the reactor case and the reactor was filled by pumping liquid CO_2 with a high-pressure pump (HHP, Dosapro, Milton-Roy, USA) up to the desired pressure (80 bar) and the $scCO_2$ was recirculated by a magnetic pump (RP, Micropump Mod. 219, USA). Different active membranes based on ionic liquid containing 1-*n*-alkyl-3-imidazolium cations and hexafluorophosphate and bis {(trifluoromethyl)sulphonyl}imide anions were tested. The higher production of the alkyl ester was found in $[omim^+]$ $[PF_6^-]/scCO_2$ biphasic system [38].

The synthesis of butyl butyrate was also successfully carried out in $[bmim^+]$ $[NTf_2^-]/scCO_2$ biphasic systems using free *Candida antarctica* lipase B as catalyst [37]. The continuous biocatalytic process was carried out in an ISCO 220SX high-pressure extraction apparatus. The activity and selectivity exhibited by the enzyme at 40°C and 150 bars was 44 U/mg enz and 96%, respectively, being the half-life time of 284 cycles for 4 h each.

Reetz et al. [39] carried out the continuous kinetic resolution of chiral alcohols using $IL/scCO_2$ biphasic systems with high enantioselectivity. In this approach, the racemic alcohol and the acylating agent were transported into the reactor using $scCO_2$ as the mobile phase. The basis of the proposed approach is that one of the enantiomers is esterified selectively by the lipase in the ionic liquid and the mixture of products is continuously extracted with the $scCO_2$ stream. The ester and unreacted alcohol were then separated downstream by controlled density reduction via variation of temperature and/or pressure of CO_2. The authors found that vinyl laureate, which is a cheap acylation agent, renders an ester less soluble than the unreacted alcohol, which allows an efficient recovery of the former compound.

In order to optimize and/or improve the behaviour of bioprocesses in ionic liquids/supercritical carbon dioxide biphasic systems, a better understanding of the chemical reaction and mass-transfer phenomena in these biphasic systems is required. In this context, de los Ríos et al. [38] analysed the chemical reaction and the mass-transfer phenomena in the synthesis of butyl propionate from vinyl propionate and 1-butanol catalysed by CaLB immobilized on dynamic membranes at

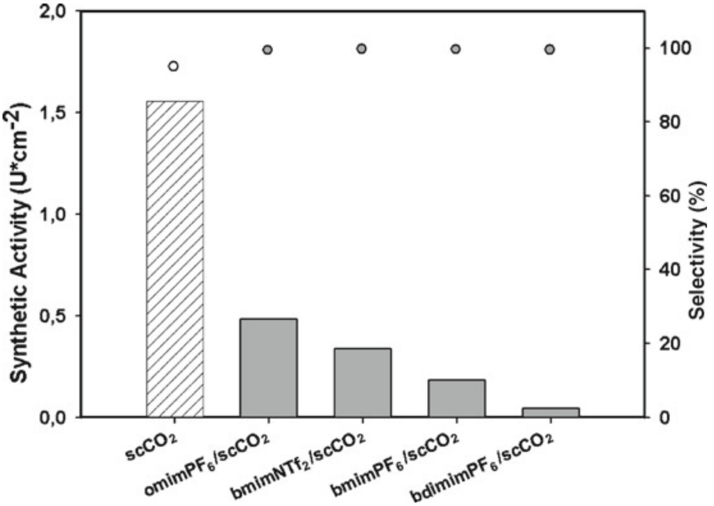


Fig. 8.4 Initial reaction rate (*bars*) and selectivity (*points*) exhibited by free *Candida antarctica* lipase B for butyl propionate synthesis in supercritical carbon dioxide and in four different ionic liquids/supercritical carbon dioxide systems. The reaction conditions were $T = 50°C$, vinyl propionate 150 mM and 1-butanol 100 Mm [38]

50°C and 80 bars. For that, four ionic liquids, namely [bmim$^+$][NTf$_2^-$], [bmim$^+$][PF$_6^-$], [bdimim$^+$][PF$_6^-$] and [omim$^+$][PF$_6^-$], were used. Figure 8.4 shows the synthetic activity and selectivity of immobilized *Candida antarctica* lipase B, CaLB, on ceramic membranes in $scCO_2$ medium as well as in four different IL/$scCO_2$ biphasic systems.

As evident from Fig. 8.4, an increase in the selectivity has been observed in IL/$scCO_2$ biphasic systems media (>99.5%) with respect to $scCO_2$ assayed alone (95%). These results could be explained by the use of water-immiscible ILs which have a specific ability to reduce water activity in the enzyme microenvironment. The synthetic activity of the immobilized lipase in IL/$scCO_2$ biphasic systems is lower than that in $scCO_2$ assayed alone. Similar results were found by Mori et al. [40] in IL/hexane biphasic systems. These authors reported that the enzymatic membranes prepared by simple adsorption of CaLB onto the surface were more reactive than membranes prepared with ILs. As can be observed in Fig. 8.4, the initial reaction rate in the assayed IL/$scCO_2$ biphasic systems increased in the following sequence: [bdimim$^+$][PF$_6^-$] < [bmim$^+$][PF$_6^-$] < [bmim$^+$][NTf$_2^-$] < [omim$^+$] [PF$_6^-$], which was practically in agreement with the activity sequence reported by these authors using free *Candida antarctica* lipase B in homogeneous ionic liquid systems ([bmim$^+$][PF$_6^-$] < [bdmim$^+$][PF$_6^-$] < [bmim$^+$][NTf$_2^-$] < [omim$^+$][PF$_6^-$]), with the exception of [bmim$^+$][PF$_6^-$] and [bdimim$^+$][PF$_6^-$]. These results were explained taking into account that biotransformation occurs within the ionic liquid phase, so substrates have to be transported from $scCO_2$ to the ionic liquid phase. The mechanism of substrate transport between the ionic liquid and the supercritical carbon dioxide could be by three consecutive steps: diffusion of the substrates through the diffusion layer from the bulk of the $scCO_2$ phase to the IL/$scCO_2$ interface (step 1), partitioning of the substrates between the $scCO_2$ and the IL phase (step 2) and diffusion into the IL phase towards the immobilized enzyme (step 3). In order to analyse step 2, the partition coefficients of the substrates and products of the transesterification reaction between the ILs and *n*-hexane were determined. *n*-Hexane was chosen as reference organic solvent because its solvent capability is comparable to that of $scCO_2$ in mild operating conditions. The sequence found in the partition coefficients of the substrates was $[bmim^+][NTf_2^-] > [omim^+] [PF_6^-] > [bmim^+][PF_6^-] > [bdimim^+][PF_6^-]$. Compounds with high IL/hexane partition coefficients were more strongly absorbed in ILs. This sequence explained the change in the initial reaction rate sequence between $[bdimim^+][PF_6^-]$ and $[bmim^+][PF_6^-]$ in the IL/$scCO_2$ biphasic in respect to the ionic liquid used as homogeneous medium since the higher K value for $[bmim^+][PF_6^-]$ indicates greater absorption of the substrates in this ionic liquid and therefore an easier contact between the substrates and the catalytic core of the enzyme. Furthermore, K values showed that the substrates of the reaction are more strongly absorbed in $[bmim^+][NTf_2^-]$ than in $[omim^+][PF_6^-]$. This fact explained the lower difference in the activity values between $[bmim^+][NTf_2^-]$ and $[omim^+][PF_6^-]$ in the biphasic systems compared with that observed in the homogeneous media. It is important to point out that in the recirculating reactor, the enzyme was attached to the membrane by cross-linking techniques. This provides an additional stabilization at least in the first reaction cycle. For that, the loss of activity due to the denaturation of the enzyme by supercritical conditions in absence of ionic liquid was lower than the loss of activity due to the mass-transfer resistance when ionic liquids/supercritical carbon dioxide was used. The observed low activity in IL/$scCO_2$ biphasic systems was attributed to limitations in the mass-transfer phenomena across the IL layer around the biocatalyst, rather than to an enzyme deactivation phenomenon. In fact, the efficiency of ILs to protect enzymes against extremely harsh $scCO_2$ conditions has been reported [37]. In this work, the synthetic activity of CaLB in the kinetic resolution of *rac*-1-phenylethanol was found to be higher when the enzyme was suspended in ILs ($[emim^+][Tf_2N^-]$ and $[bmim^+][Tf_2N^-]$) than when assayed in the absence of IL. One of the most important advantages of using ionic liquids is that the optimum ionic liquid for each specific application can be designed by changing the nature of the cation and/or the anion. By using this property of ionic liquids, we could design ionic liquids which absorb selectively the substrates in respect to the products, and therefore, the mass transfer and even the biocatalytic reaction process could be improved. This fact was corroborated by the work of Lozano et al. [41] who studied the synthesis of esters catalysed by CaLB in ionic liquid/supercritical carbon dioxide using the ionic liquids (3-cyanopropyl)-trimethyl- and butyltrimethyl ammonium associated with bis(trifluoromethane)sulphonylimide anion ($[C_3Cntma^+][NTf_2^-]$ and $[C_4tma^+][NTf_2^-]$, respectively). These authors found that the synthetic activity of CaLB in $[C_4tma][NTf_2]/scCO_2$ was higher than that in $[C_3CNtma][NTf_2]/scCO_2$. This behaviour was opposite than that observed in pure ILs. Analysing the solubility of the substrates and the products through the Hansen's solubility parameter (δ) and having in mind that in the IL/$scCO_2$ system the substrates must be transported from the supercritical to the IL phase, and vice versa in the case of products, the authors found that the activity was higher in the IL in which the solubility of the substrates was higher and the solubility of the products was lower.

To sum up, the appropriate selection of the IL will greatly improve the enzymatic activity, selectivity and the mass-transfer phenomena, permitting better design of IL/scCO$_2$ biphasic systems, while the use of supercritical carbon dioxide as a second phase will facilitate recovery of the products without any cross-contamination of the extract with the ILs.

8.5 Conclusions

The use of ILs/scCO$_2$ dioxide biphasic systems has been successfully applied to the biosynthesis of alkyl esters and the kinetic resolution of chiral alcohols. The success in the use of IL/scCO$_2$ dioxide biphasic systems in the enzymatic synthesis of esters is based on the fact that ILs provide an adequate microenvironment for the catalytic activity of the enzyme, avoiding the enzyme deactivation under harsh conditions, while the use of supercritical carbon dioxide makes possible the easy recovery of the products without any cross-contamination of the extract with ionic liquid. By tailoring the cation and anion composition of the ionic liquid, the activity and selectivity of the enzyme and the mass transfer between phases could be improved. Furthermore, this property of ionic liquids facilitates the design of suitable ionic liquids for each specific bioprocess problem which will open new fields of application of ILs/scCO$_2$ in biotechnology. From an environmental point of view, this new methodology avoids the use of volatile organic solvents, for that could be considered as the clean and green technology of the future.

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Chapter 9
Ionic Liquids as Lubricants

Meirong Cai, Yongmin Liang, Feng Zhou, and Weimin Liu

Abstract This chapter reviews state-of-the-art research on ionic liquids (ILs) as lubricants. The discovery of ILs as high-performance synthetic lubricants in 2001 immediately attracted considerable attention in the field of tribology. Such lubricants have better lubrication performance and antiwear capabilities than conventional lubrication oils. This chapter first introduces a brief summary of tribology and ILs. It then details the tribological research status of ILs, including their tribological properties and functionalization. Finally, trends in future ILs research are presented.

9.1 Introduction

Lubrication, a part of tribology created by the UK scientist H. Peter Jost in his famous "Jost Report" submitted to the government in 1966, refers to the science and technology of interacting surfaces in relative motion and their associated subjects and practice [1]. Tribology is regarded as an aspect of mechanical engineering and includes lubrication, friction, wear, erosion, and corrosion [2]. Friction and lubrication have attracted attention all over the world, especially in the industrial and

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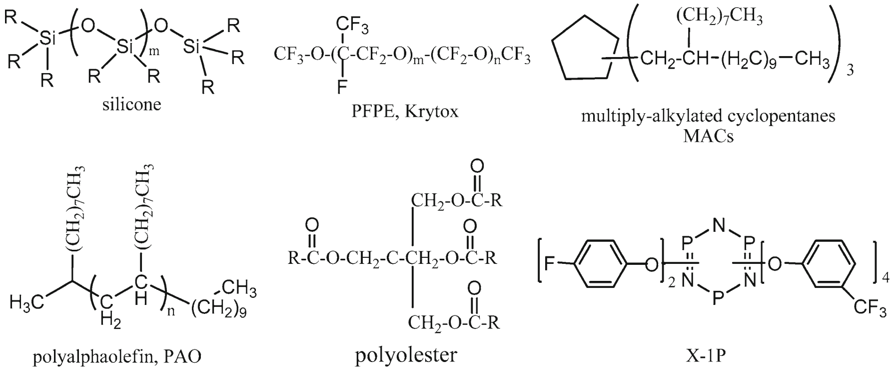


Fig. 9.1 Structures of common high-performance synthetic lubrication oils

educational sectors. Lubrication is key to ensuring the stable operation and longevity of machines. In fact, lubrication is currently a core technique that targets low carbon emissions and the creation of a sustainable society. Lubrication aims to reduce the friction on a surface with a bearing capacity and tangential shear strength. Lubricating films are usually used to reduce frictional resistance and material wear and tear.

Lubricants can be classified into three categories: liquid lubricants (such as water, mineral oils, and synthetic oils), solid lubricants (such as graphite and molybdenum sulfide), and greases. In practice, fluid lubrication is most commonly used. Compared to solid lubrication, fluid lubrication has a number of advantages, such as long-term endurance, low mechanical noise, promotion of thermal conductance, and very low friction in the elastohydrodynamic regime [2]. Dating back to over 3,500 years ago in old China and Egypt, people realized the need to reduce friction between moving objects. In ancient Egypt, for example, workers used friction reduction technology, such as water as a lubricant, when handling huge paving stones or constructing monuments. During these days, oils or greases from plants or animals were also normally used as lubricants. Advances in the petroleum industry in Scotland, Canada, and the United States brought about the use of mineral oil as a lubricant mostly because it was inexpensive and widely available [3, 4]. Mineral oils were able to satisfy the lubrication requirements of most mechanical equipment. Since then, petroleum-based lubricants have been long used successfully as natural lubrication oils. Synthetic lubricants were developed in the metaphase of the 1930s. Compared to mineral oil, synthetic oils have better properties, such as good thermal stability, high thermal decomposition temperature, high flash and ignition points, and good additive sensitivity. Synthetic lubricants are applied in a wide variety of industries. In order to improve the friction reduction and antiwear properties of a lubricant under harsh conditions, a growing number of chemists have become involved in the research and development of synthetic lubricants and lubrication additives. Some of the molecular structures of currently used synthetic lubricants include those shown in Fig. 9.1.

Ionic liquids (ILs) have unique properties, including high thermal stability, nonvolatility, nonflammability, high ionic conductivity, wide electrochemical window, miscibility with organic compounds, and structure scalability [5, 6]. These properties allow the use of ILs as good solvents or soft functional materials, and they are widely used in organic reactions, electrochemistry, polymer chemistry, analytical chemistry, and separation and purification technology. ILs are further used in energy production, the environment, life sciences, and aerospace technology, among others. Their characteristics are in sync with the demands for high-performance lubricants, making them ideal candidates for new lubricants under severe conditions, including ultrahigh vacuum and extreme temperatures, where conventional oils and greases or solid lubricants do not work very well. The discovery of ILs as high-performance synthetic lubricants was first reported in 2001 [7]. This chapter describes the concept of ILs, as well as their composition and characteristics, and introduces the tribological research status of ILs, including the tribological properties of common ILs, the functionalization of ILs, and the future research of ILs in tribology.

9.2 Overview of Ionic Liquids (ILs)

9.2.1 Definition and Types of Ionic Liquids (ILs)

ILs are composed of organic cations and weakly coordinating anions and have considerably low melting points (<100°C) [8]. Figure 9.2 shows the most-often studied structures of such cations and anions [2]. The most widely used cations are imidazolium, pyridinium, ammonium, and phosphonium, but new cations for application in ILs are constantly discovered as well. Common IL anions may be grouped into two major categories: one is composed of adjustable aluminum chloride anions, while the other is composed of fixed anions, such as hydrophilic Cl^-, Br^-, I^-, NO_3^-,

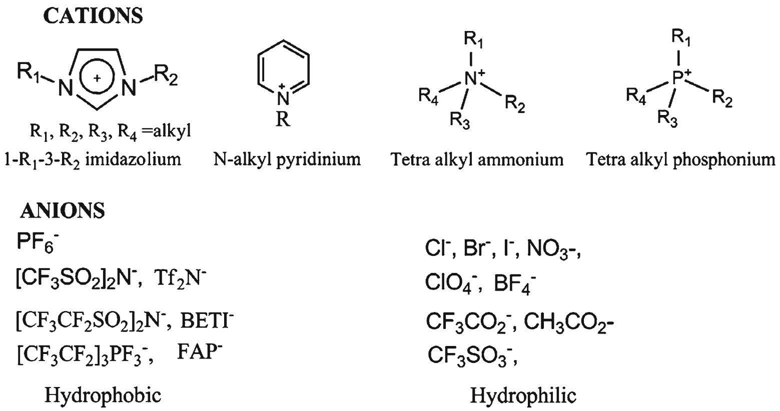


Fig. 9.2 Cations and anions that constitute ILs

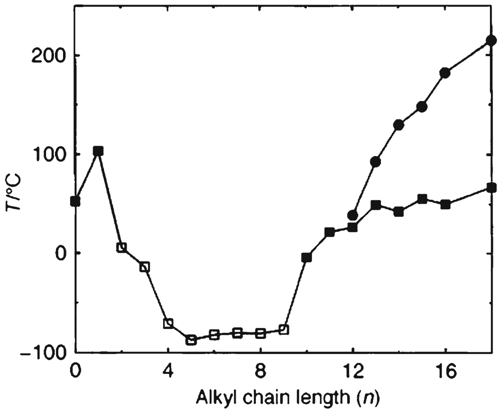


Fig. 9.3 Phase diagram for 1-alkyl-3-methylimidazolium tetrafluoroborate ILs and liquid crystals showing the melting (*closed square*), glass (*open square*), and clearing (*circle*) transitions as measured by differential scanning calorimetry (DSC) (Reproduced from Ref. [15] with kind permission of © The Royal Society of Chemistry)

CF_3COO^-, CH_3COO^-, and BF_4^-, and hydrophobic PF_6^-, $(CF_3SO_2)_2N^-$, $(C_2F_5SO_2)_2N^-$, and $(CF_3CF_2)_2PF_3^-$, among others. Various combinations of different cations and anions yield a wide variety of ILs, which can total as many as 10^{18} different kinds of ILs [9]. The combination of any two cations and anions is not necessarily liquid at room temperature because such a property is strongly dependent on the molecular structures of the starting materials. As such, tribological researchers must determine the appropriate anion–cation combination to obtain suitable ILs for use as lubricants. Understanding the structural properties of each component is essential for a systematic design [10–13]. Typical cations and anions tested as IL lubricants are summarized in a review by Torimoto et al. [14].

9.2.2 Relationship Between Molecular Structure and Properties of Ionic Liquids (ILs)

The melting point, viscosity, and thermo-oxidative stability are important parameters of ILs as lubricants, and these depend strongly on their molecular structures and the types and lengths of alkyl chains on the cations and anions. The size and shape of cations play an important role in determining the melting point of ILs.

Generally speaking, if the size of cation is larger, the corresponding melting point of ILs is smaller. The melting point of imidazolium-based ILs is lower than that of other ammonium salt ILs with the same carbon number. Figure 9.3 shows increasing the alkyl chain length of imidazolium ILs, starting from methyl, initially decreases the melting points of ILs due to reduced polarity. Little change is observed for carbon numbers (n) 4–8, after which the melting point increases significantly for n > 8, due to increased packing orders [15–17]. For ILs with the same cation structure, the melting points increase in the following sequence: $Tf_2N^- < BF_4^- < PF_6^- < Cl^- < Br^-$. For ILs with the same anion and alkyl chain on the cation, the viscosities decrease in the order of pyrrolidinium < pyridinium < imidazolium. When ILs have the same cation structure, the viscosity increases with different anion types, following the trend of $Tf_2N^- < FAP^- < BETI^- < BF_4^- < PF_6^- < Cl^- < Br^-$.

ILs’ viscosity increased when the chain length of the side chain increases, the side chain is composed of fluoride or an imidazole ring in position 2 methylation, or there is increased cation symmetry. Generally, when the cation is composed of the thermally stable imidazolium ion, the anion determines the thermal stability of the entire IL, increasing in the order $Tf_2N^- > BF_4^- > PF_6^- >$ halogen ions. Minami et al. [18] studied thermo-oxidative stability and volatility of ILs and found that ILs have greater thermal stability than conventional synthetic lubricants. It was also found that the stability of an ILs depends on the structures of both the anion and the cation. For example, the stability of 1, 3-dialkyl-imidazolium is more stable than quaternary ammonium.

In case of imidazolium-derived samples when kept at 200°C for 1,000 h, the viscosity and color of the samples changed with the passage of time. 1-Methyl-3-ethylimidazolium bis(trifluoromethylsulfonyl)imide (L-F102) transformed into a dark liquid, while 1-methyl-3-hexylimidazolium bis(trifluoromethylsulfonyl)imide (L-F106) and 1-methyl-3-dodecylimidazolium bis(trifluoromethylsulfonyl)imide (L-F112) formed a solid deposit. This tendency to form deposits indicates that the thermo-oxidative stability of the molecule decreases as the chain length increases.

The relationship between the molecular structure of ILs and their performance was summarized by Minami and is shown in Fig. 9.4. Hydrophobic anions improve the thermo-oxidative stability and tribological properties of the ILs. Increasing alkyl chain lengths on the imidazolium ring improves tribological properties, but it causes a decline in thermo-oxidative stability [19]. Thus, the relationship between the molecular structure and properties of ILs provides useful guidance for tribologically oriented molecular design.

9.3 Common Ionic Liquids (ILs) as Lubricants

Due to the continuous development of high-tech industries and the increasingly harsh conditions of friction, demand for lubricants of comprehensive performance is increasing. The mechanical, electronic, and computer industries have pursued studies with the aim to produce lubricants with high thermal stability, nonvolatility, nonflammability, and excellent low-temperature fluidity. In space machinery lubrication, for example, the current lubricant used does not meet the requirements of a low pour point, high viscosity index, high thermal oxidative stability, low volatility, and other performance requirements. High-performance liquid lubricants for space machinery are commonly composed of mainly perfluoropolyether (PFPE) and phosphazene (X-1P). However, PFPE features poor boundary lubrication, rapid high-temperature corrosion of some iron and titanium alloy class, easy degradation, and poor additive solubility. While X-1P has good performance at high temperatures, it is highly volatile and its liquidity requires further improvement [20].

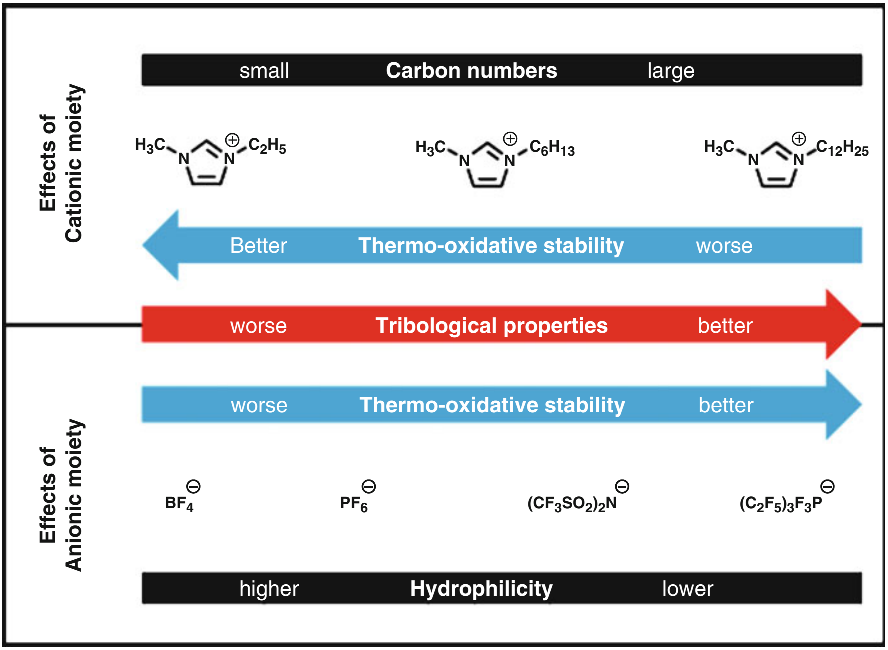


Fig. 9.4 The relationship between structure and lubricant properties of ILs (Reproduced from Ref. [19] with kind permission of © Molecules)

Therefore, the discovery of lubricants possessing very low vapor pressure and high thermal stability for use in space technology, microelectronics, and various other industries is of great significance. In this regard, ILs appear to be a promising alternative. ILs have attracted considerable attention in tribology because of their remarkable lubrication and antiwear capabilities [2]. This summary reviews the tribological properties of common ILs in lubrication engineering.

9.3.1 Ionic Liquids (ILs) as Lubrication Oils

9.3.1.1 Ionic Liquids (ILs) as Lubrication Oils for Fe Alloy/Steel or Steel/Steel Contacts

In 2001, Liu et al. [7] were the first to report ILs as promising high-performance lubricants with very good tribological properties. Table 9.1 shows the friction coefficients and wear volumes of steel/steel contacts lubricated by 1-ethyl-3-hexylimidazolium tetrafluoroborate (LB206), X-1P, and PFPE. Compared to common synthetic X-1P and PFPE lubricant, ILs have very low friction coefficients and wear volumes. The carrying capacity of ILs can reach 1,000 N, much higher than either X-1P (300 N) or PFPE (400 N). In another report, four-ball test results showed that

Table 9.1 Tribological properties of ILs L206, X-1P, and PFPE for steel/steel contacts (SRV tester, load 50 N, frequency 25 Hz, amplitude 1 mm, duration 30 min) (Reproduced from Ref. [7] with kind permission of © The Royal Society of Chemistry)

	Friction coefficient			Wear volume/×10^{-4} mm^3		
Load/N	L206	X-1P	PFPE	L206	X-1P	PFPE
200	0.060	0.070	0.120	0.05	0.07	0.60
300	0.055	0.065	0.110	0.22	2.21	1.90
400	0.050	–	0.105	0.39	–	5.03
500	0.045	–	–	0.45	–	–
600	0.045	–	–	0.53	–	–

– Lubrication failure

Table 9.2 Tribological properties of L206, X-1P, and PFPE for steel/steel contacts (100°C)

	Friction coefficient			Wear volume (×10^{-4} mm^3)		
Load(N)	L206	X-1P	PFPE	L206	X-1P	PFPE
100	0.085	0.100	0.130	1.41	1.60	1.42
200	0.085	0.085	0.125	2.68	4.01	2.81
300	0.085	0.080	0.110	3.11	6.59	6.50
400	0.085	–	–	3.72	–	–
600	0.080	–	–	4.79	–	–

– Lubrication failure

the friction coefficient of a steel ball lubricated by LB206 and 1-ethyl-3-octylimidazolium tetrafluoroborate (LB208) remained low with increasing loads, much lower than that of liquid paraffin (LP) containing 1% zinc dialkyldithiophosphate (ZDDP). Both ILs tested withstood loads of up to784 N, while lubrication failure occurred at 490 N in the case of LP plus 1% ZDDP [21]. ILs have a very low pour point (−50°C) and a high thermal decomposition temperature (400°C), making them usable in a wide temperature range. SRV-1 oscillation friction and wear test results show that LB206 has better tribological properties than the X-1P and PFPE at 100°C. The specific data are shown in Table 9.2.

Alkyl imidazolium hexafluorophosphate ILs were studied as lubricants for steel/steel contacts [22] and showed tribological performance in terms of friction-reducing abilities and load-carrying capacities superior to those of conventional lubricants made from LP containing 2 wt.% of ZDDP. XPS results indicated the formation of $FePO_4$ and FeF_2 as a result of the tribochemical reaction of the ILs, resulting in excellent friction reduction and antiwear performance. Lu et al. [23] synthesized and evaluated the performance of 1-ethyl-3-hexylimidazolium bis(trifluoromethylsulfonyl) imide (L-F206) as a lubricant for steel/steel contacts. L-F206 showed excellent tribological performance and superiority to alkyl imidazolium tetrafluoroborate ILs, X-1P, and PFPE in terms of its antiwear performance and load-carrying capacity [23].

A series of asymmetrical tetraalkylphosphonium ILs were synthesized and evaluated as a new kind of lubricant for steel/steel contacts under ambient conditions [24]. Tetraalkylphosphonium ILs showed better antiwear performance and load-carrying capacity than X-1P, PFPE, and even L-P206. The friction reduction and antiwear mechanisms of tetraalkylphosphonium were proposed to originate from the reaction of the active P elements in the tetraalkylphosphonium ILs with the fresh surface to form a reaction film on the specimen surface. This extreme-pressure film, which featured low shearing strength, was believed to lead to lower friction coefficients and good wear resistance.

Xia et al. [25] studied the friction and wear properties of modified and unmodified 1Cr18Ni9Ti stainless steel specimens sliding against SAE52100 steel under the ILs lubrication of 1-propyl-3-octylimidazolium hexafluorophosphate (L-P308) and PAO. Their results showed that the modified sample had better antiwear abilities than the unmodified one, but the friction coefficient of the treated sample was slightly higher than that of the untreated one. X-ray photoelectron spectroscopy (XPS) analysis showed that this was partly due to the formation of Fe_xN, so that the composition and hardness of the stainless steel surfaces changed after plasma nitriding. As such, tribochemical reactions between the steel and the lubricant occurred, and the surface protective film and the adsorbed boundary lubricant film contributed significantly to the reduction in friction and wear.

Minami et al. [26] evaluated the tribological properties of trifluorotris (pentafluoroethyl) phosphate[$(C_2F_5)_3PF_3^-$ and FAP]-derived ILs under boundary conditions. The anion in this case was more hydrophobic than that of bis (trifluoromethylsulfonyl)imide [$(CF_3SO_2)_2N^-$, TFSI]. For ILs with the same cations, FAP salts have generally much lower friction and better antiwear properties than the TFSI salts.

Phillips et al. [27] studied the surface chemistry of IL-lubricated steel/steel sliding contacts under temperature variation from room temperature to 300°C. This study was focused on understanding the high-temperature stability of the liquids in contact with metal under tribological stress [27]. Some Fe samples were oxidized to Fe_2O_3 and Fe_3O_4 via thermal evaporation prior to treatment with ILs. The metallic and oxidized Fe samples were then reacted with ILs at elevated temperatures. Results showed that the friction coefficient of different fluorinated ILs was below 0.1 in both the room temperature and 100°C tests. The friction coefficient ranged from 0.07 to 0.3 for temperatures up to 300°C. During the friction tests, ILs generated the new compound FeF_2, which led to the decomposition of the lubricant and thus causes the corrosion of the substrate surface. Common ILs are used as lubricants in tribological systems at room to moderate temperatures. Jiménez and Bermúdez [28] studied the tribological properties of 1-methyl-3-octylimidazolium tetrafluoroborate (LB108), 1-methyl-3-hexylimidazolium hexafluorophosphate (L-P106), and the quaternary ammonium chloride AMMOENG™101 under a wide range of temperature (25, 100, 200, and 300°C) and compared their results to those of a mineral base oil. Their results showed that imidazolium derivatives were the best lubricants at all temperatures. A series of long-chain 1,3-dialkyl imidazolium ILs were synthesized and evaluated as lubricants for steel/steel contacts both at room temperature and 150°C [29]. They investigated the relationship between the alkyl chain length and the tribological properties of ILs in detail. Their results indicated that ILs bearing long alkyl side chains have excellent friction-reducing and

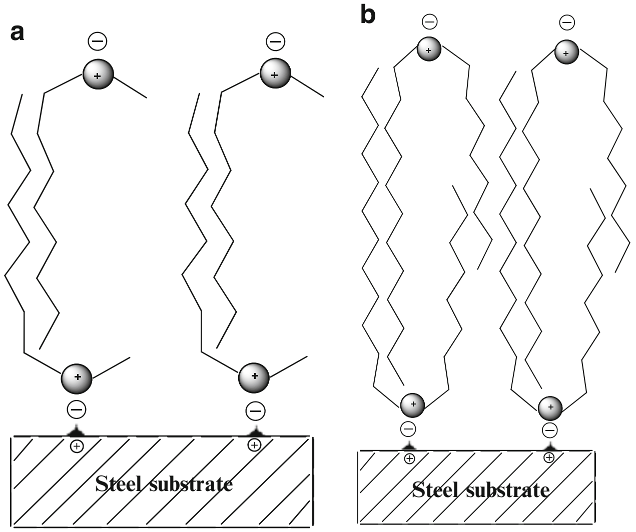


Fig. 9.5 Diagrams of ILs with (**a**) short alkyl chains and (**b**) long alkyl chains adsorbed onto steel substrate/liquid interfaces (Reproduced from Ref. [29] with kind permission of © Elsevier)

antiwear properties, especially at high temperatures and high loads. They proposed a possible model of how different ILs adsorb onto steel substrate-liquid interfaces (Fig. 9.5) and explained the possible reasons of this effect. Murakami et al. [30] investigated the tribological properties of Fe_7Mo_6-based alloy, Mo, Fe, and American Society for Testing Materials ASTM class no. 45 cast iron disk specimens against ASTM 52100 steel balls under the lubrication of two different kinds of hydrophobic ILs, *N*-methyl-*N*-propylpiperidinium bis(trifluoromethanesulfonyl)imide (PP13-TFSI) and *N*-*N*-*N*-trimethyl-*N*-propylammonium bis(trifluoromethanesulfonyl) imide (TMPA-TFSI). When PP13-TFSI or TMPA-TFSI was used as a lubricant for four kinds of contacts, the Fe_7Mo_6-based alloy specimens exhibited lower friction coefficients and lower wear rates than the Mo, Fe, or ASTM class no. 45 cast iron disk specimens. It was later found that the worn surfaces were composed of low friction materials, such as MoO_3 and $FeSO_4$.

Yu et al. [31] synthesized and evaluated α, ω-diimidazoliumalkylene hexafluorophosphate as a lubricant for steel/steel contacts and found that the tribological properties of ILs was superior to those of traditional space PFPE lubricants and L-P106. In particular, high-temperature diimidazolium-based ILs showed very good antiwear properties.

The tribological properties of tetraalkylphosphonium ILs were evaluated on the basis of the chemical structure of their salts [32]. The results showed that the structure of the alkyl group in the phosphonium ILs also had a slight effect on the tribological properties of the salts. Tetraalkylphosphonium ILs have better tribological properties than 1,3-alkylimidazolium ILs. The interaction of phosphate or thiophosphate anions and substrate surfaces yielded a phosphate boundary film that exhibited better tribological properties than those of a fluoride boundary film. In this chapter, Minami et al. [19] proposed a model of the boundary film and surface chemistry of these ILs.

9.3.1.2 Ionic Liquids (ILs) as Lubrication Oils of Light Alloys

Light alloys include alloys composed of Mg, Al, and Ti. These alloys have low density, high specific strength, excellent corrosion resistance, good heat resistance, and the ability to form corrosion-protective surface layers. Because of these characteristics, light alloys are slowly replacing traditional iron-based materials, especially in aerospace, chemical, and energy applications. However, effective lubricants for the industrial applications of light alloy have not been discovered, thereby presenting a problem that must be urgently resolved.

Aluminum alloys are extensively used for tribological applications because of their wide range of applications in sliding components, particularly in the automotive industry [33]. Although Al alloys meet many of the requirements for such applications, their poor resistance to seizures and difficulty to lubricate make them vulnerable to friction [34, 35].

ILs as lubricants exhibit generally good tribological properties, not only for steel/steel contacts but also for steel/aluminum, steel/copper, and steel/SiO_2, among others.

Jiménez and Bermúdez [36] studied 1-*N*-alkyl-3-methylimidazolium ILs as neat lubricants and lubricant additives in steel/aluminum contacts. At room temperature and at 100°C, all the ILs gave friction coefficients lower than 0.15, except for LB102 and L-P106. Results also showed that changing the tetrafluoroborate anion to triflate or tosylate reduces friction and wear, but the lowest coefficients are obtained by increasing the alkyl chain length (from $n = 2$ to 6 or 8). The tribological performance of the imidazolium ILs 1-hexyl-3-methyl (LB106) and 1-octyl-3-methyl (LB108) imidazolium tetrafluoroborate as lubricants for steel/aluminum contacts under a wide range of temperatures (−30°C, 100°C, and 200°C) was also investigated [37].

Liu et al. [38] synthesized asymmetrical tetraalkylphosphonium ILs and evaluated their performance as lubricants for steel/aluminum contacts. Their results showed that tetraalkylphosphonium ILs as lubricant for various contacts were superior to L-P206 in terms of antiwear performance and load-carrying capacity. A possible structure for these ILs is shown in Fig. 9.6, which shows that the ILs have a layered structure similar to that of graphite and molybdenum disulfide. It is this layered structure that confers good lubricity to graphite and molybdenum disulfide because layered structures generally have low shearing strengths (Fig. 9.6). Thus, the good lubricity of ILs is believed to result from their double bilayer structure.

ILs show higher thermal stability and better lubricating performance than synthetic ester propylene glycol dioleate (PGDO) and a mineral oil at all tested temperatures. The tribological characteristics of different aluminum alloys sliding against steel lubricated by ammonium- and imidazolium-based ILs were evaluated [39, 40]. Different aluminum alloy and ILs interactions gave different results.

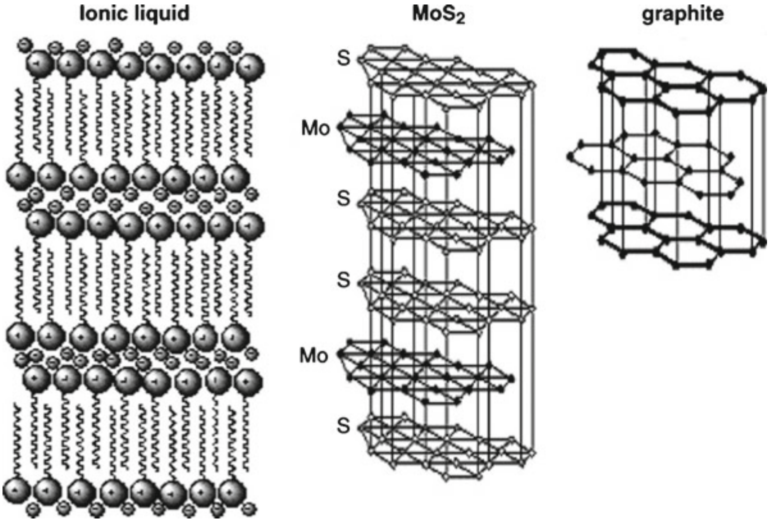


Fig. 9.6 Comparison of the structure of IL in its crystal form, MoS_2 and graphite (Reproduced from Ref. [38] with kind permission of © Elsevier)

Generally, however, it was found that ILs provide better lubrication for aluminum compared to conventional lubrication oils because the former has better friction reduction and antiwear properties compared to the latter.

Titanium is another important light alloy. Because of its low density, high specific strength, excellent corrosion resistance, good heat resistance, and other advantages, Ti has become the basis of many structural materials used in the aerospace, chemical, and energy industries. However, the low carrying capacity and poor tribological properties of the current crop of lubricants limit the scope of application of titanium alloys.

Jiménez and Bermúdez [41] studied ammonium and imidazolium ILs as lubricants for titanium/steel contacts at room temperature and 100°C and compared their results with those of mineral base oil. Their results showed that both types of ILs gave better antiwear abilities for titanium with increasing alkyl chain length. At room temperature, the best antiwear performance was found for the imidazolium chloride, although corrosion of the AISI 52100 steel ball was observed. At 100°C, L-P106 showed the lowest friction and wear. The pair then studied the tribological behavior and surface interactions of titanium sliding against AISI 52100 steel at 200 and 300°C in the presence of dialkylimidazolium ILs with long alkyl side chains and fluorine-containing anions [42]. Both at 200 and 300°C, LB108 presented higher thermal stability but gave higher friction coefficients and wear rates than L-P106. At 200°C, L-P106 showed a constant friction coefficient and produced mild wear on titanium without damaging the surface of the steel, but it fails to work at 300°C, probably because this temperature is close to its degradation temperature. When the steel ball was substituted with a ruby sphere under the same conditions at

300°C, L-P106 produced a low friction coefficient and mild wear at the ruby/Ti interface. These results showed that some reactive ILs could be used as high-temperature lubricants of corrosion-resistant materials, even at temperatures close to their thermal decomposition. The tribological behavior and surface interactions of Ti6Al4V sliding against AISI 52100 steel in the presence of imidazolium ILs with different alkyl chain lengths was studied [43]. The research results were mainly consistent with those of previously studied ILs (ILs reduced friction coefficients). Some minor differences were also found, one of them being that increasing the alkyl side chain length on the cation increased wear rates. This is attributed to the higher molecular polarity [44], surface tension, and thermal stability of the IL with the shortest alkyl chain, which allows the formation of a more stable adsorbed tribo-layer on the metal surface without severe tribocorrosion [43]. So far, ILs as lubricants for Mg alloys have not been reported. It is hoped that tribological researches can develop a series of IL lubricants with excellent friction reduction and antiwear properties for Mg alloys.

9.3.1.3 Ionic Liquids (ILs) as Lubrication Oils for Specific Contacts

Ye et al. [45] investigated the friction and wear behaviors of dysprosium (Dy)-sialon ceramics sliding against Si_3N_4 under the lubrication of PFPE, X-1P, and LB108 at room temperature and 150°C. LB108 was superior to X-1P and PFPE in terms of friction reduction and antiwear performance. Xia et al. electrodeposited nano-Si_3N_4 with nickel onto a copper substrate from a Ni bath, after which they electrodeposited a nanocrystalline (NC) and coarse-grained (CG) nickel coating onto AISI 1045 steel substrates. The friction and wear properties of the coatings were evaluated under lubrication by either imidazolium-based ILs or conventional oils using a ball-on-disk sliding tester. As the electrodeposition of Ni coatings increases the hardness of the copper matrix from 1.16 to 4.75 GPa, the antiwear properties of L-P206 ILs significantly improved 30-fold in comparison to the liquid paraffin, and its friction coefficient was only 0.033. In the steel matrix, the hardness of the NC nickel coating was much higher than that of the CG nickel (6.15 and 2.26 GPa, respectively). PFPE showed poor lubricity compared to both L-P206 and L-P408. These results showed that phosphate-containing surface protective films, together with hardened surfaces, contributed to the significantly improved tribological performance of the coatings [46, 47]. Monocationic and dicationic 2-substituted imidazolium ILs with bis(trifluoromethylsulfonyl)imide anions were synthesized and evaluated as lubricants for Si_3N_4/steel contacts at 250°C [48]. Figures 9.7 and 9.8 show that 2-substituted imidazolium ILs with inert methyl group have better friction reduction and antiwear properties compared to conventional unsubstituted ILs, probably due to the improved chemical inertness of the lubricants at the C2 position.

Xie et al. [49] investigated the tribological behaviors of different ILs as lubricants for tribo-pairs (low-temperature silicon oxide film/Si_3N_4 ball, polysilicon Si film/Si_3N_4 ball, and silicon nitride (Si_3N_4) film/Si_3N_4 ball) by varying the applied load and the sliding velocity. The ILs lubricants showed the best lubricating properties for the three tribo-pairs at the intermediate load of 150 g.

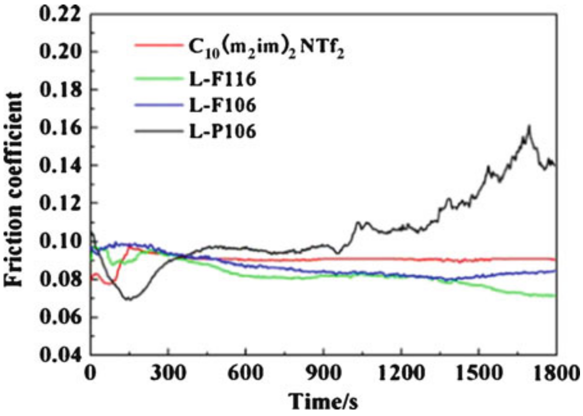


Fig. 9.7 Evolution of friction coefficients with time at 100 N (temperature 250°C, stroke 1 mm, frequency 20 Hz) (Reproduced from Ref. [48] with kind permission of © Springer)

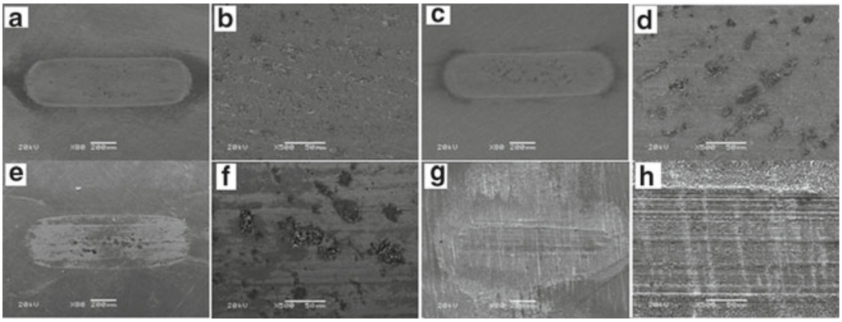


Fig. 9.8 SEM images of the worn surfaces lubricated by different ILs. (**a**) and (**b**) $C_{10}(m_2im)_2NTf_2$. (**c**) and (**d**) L-F116. (**e**) and (**f**) L-F106. (**g**) h L-P106 (magnification on the *left* is 80×, while that on the *right* is 500×; load 100 N; stroke 1 mm; frequency 20 Hz; temperature 250°C; duration 30 min) (Reproduced from Ref. [48] with kind permission of © Springer)

Sanes et al. investigated six kinds of room-temperature ILs as external lubricants in polystyrene (PS) and polyamide 6 (PA6)/steel contacts [50]. For PS/AISI 316L stainless steel contacts, ILs gave low friction and negligible wear rates compared to the dry PS/AISI 316L, which showed severe wear and no tribocorrosion reactions. For PS/AISI 52100 contacts, tribocorrosion processes accompanied by precipitation of FeF_2 particles and related friction increments were observed [50]. They further studied the influence of temperature on PA6/steel contacts in the presence of IL lubricants [51]. These lubricants showed excellent tribological performance under a wide range of temperature conditions (−35, 25, and 67°C). Low friction values were also obtained when ILs were used as external lubricants for AISI 52100 steel, except at high temperatures. The failure in this case may have been due to tribocorrosion reactions.

The interactions between selected ILs and modified silicon surfaces are modeled using semiempirical methods [52] and so the tribological properties of these ILs and their interactions with silicon surfaces using a rolling hydroxylated silicon surface.

Table 9.3 Vacuum friction results of lubricants

Lubricant	L106	L206	PFPE
Friction coefficient	0.070	0.067	0.142

Results showed that ILs formed a complex with this surface, and the enthalpies of complex formation were seen to correlate with the tribological properties of the ILs.

9.3.1.4 Ionic Liquids (ILs) as Lubrication Oils Under Vacuum

ILs are applicable even under vacuum. Table 9.3 shows that, under a vacuum, the friction coefficients and wear of LB106 and LB206 are lower than those of PFPE in steel/steel (SAE52100) contacts. This indicates that ILs could provide effective lubrication in space applications [21]. Wang et al. [22] studied hexafluorophosphate ILs as lubricants of steel/steel contacts under vacuum. They found that the friction coefficient of ILs were lower than those of PFPE and X-1P in vacuum, and these friction coefficients decreased with increasing alkyl chain lengths under relatively low loads. Suzuki et al. investigated the viscosity/temperature properties, thermal stability, and tribological properties of L-B106 and L-P106 under high vacuum (5.0×10^{-5} Pa) [53]. Their results showed that the two ILs having high viscosity index and thermal stability and low volatility, under high vacuum, have better friction reduction and antiwear properties and load-carrying capacity than the commonly used space lubricant perfluoropolyether (PFPE) and multiply alkylated cyclopentanes (MACs) [53].

The tribological behavior of an IL that could be used for four kinds of metal (Al, Cu, Fe, and Ti) was evaluated using a high-vacuum (5.0×10^{-5} Pa or less) pin-on-disk sliding tester equipped with a Q-mass spectrometer according to Sasaki et al. [54]. The results showed that the IL exhibited the expected lubricity for Fe and Cu sliding against SiC and decreased the friction coefficient. The highest and most unstable friction coefficient was observed for Ti. Increasing several partial gas pressures was observed during the sliding for all metals: for Fe and Cu almost no change was observed, but for Ti and Al, deterioration of the vacuum level was found. Thus, selection of a suitable combination of sliding materials and ILs appears to be an important factor in the design of a high-vacuum tribosystem. Currently, the tribological investigation of IL lubricants under vacuum remains very rare. It is hoped that tribological researchers can invest more human and financial resources in simulation studies of space environments to determine the performance of ILs lubricants in such an application.

9.3.2 Ionic Liquids (ILs) as Lubrication Additives

ILs can be used as additives in common lubrication oils. For example, ILs could be added to polyether, polyester, and even mineral oils, thus significantly enhancing the triboperformance of these base oils. Doing so would result in additives that perform better and cost less. Such additives must have a high performance-to-price ratio so that replacement of normal additives by ILs can be feasible and economical. Additives to which ILs have been added show increased tribological performance compared to neat additives because of the small fraction of ILs in the composition of the former.

9.3.2.1 Ionic Liquids (ILs) as Water Additives

Phillips et al. [55] first studied the tribological properties of ILs as additives for water in lubricating silicon nitride ceramics and found that the addition of ILs to water dramatically shortened the running-in periods for silicon nitride from thousands to only hundreds of cycles. They proposed a mechanism to explain this behavior. Initially, mechanical wear smoothen the ceramic surface, forming BFx and PFx films and creating an electric double layer of ILs, which increases the local viscosity near the surface and the load-carrying ability, and lowers friction and wear. Ge et al. [56] investigated the microstructure of lamellar liquid crystals composed of polyoxyethylene lauryl ether (Brij30), L-P106, and water using deuterium nuclear magnetic resonance (^{2}H NMR) and rheological techniques, describing the lubrication properties of the lamellar mesophase and the microstructure relationship in the process. Their results were as follows: Increasing the amount of Brij30 increases the structural strength of the lamellar phase, so its antiwear capacity is improved. Increasing the water content in the system impairs both the structure strength and the lubrication properties. Although the structure of the lamellar phase is disturbed by L-P104, its lubrication properties are still improved due to the excellent lubrication properties of the ILs. Xie et al. [57] investigated the tribological properties of three different films commonly used in microelectromechanical systems (MEMS) under the lubrication of IL/water mixtures with various concentrations in the running-in process. They observed that the period of the running-in process shortened with increasing IL/water concentration for all tribo-pairs. ILs may not be good alternatives as additives due to the hydrolysis of commonly used anions, such as BF_4^- or PF_6^-. While corrosion attacks on ceramic materials may not be serious, they may be severely detrimental to metals [2].

9.3.2.2 Ionic Liquids (ILs) as Mineral Oil Additives

The tribological properties of SAE52100 steel/ASTM 2011 aluminum contacts under the lubrication of paraffinic/naphthenic mineral with 1 wt.% imidazolium ILs additives were studied [36, 58]. All ILs additives selected for this study showed better lubrication and antiwear properties than neat ILs. This is attributed to the formation of effectively adsorbed lubricating layers in the absence of severe tribocorrosive processes caused by the reaction of neat ILs at the Al/steel interface. Qu et al. [59] synthesized and investigated a series of new protic alkylammonium ILs as neat lubricants or lubricant additives in reciprocating sliding tests of 52100 bearing steel on aluminum 6061-T6511 alloys. A mixture of mineral oil and 10 vol.% ILs demonstrated lower wear than either the base oil or neat ILs alone, and no wear reduction was observed when using only the ILs. The same group then evaluated the lubricating properties of ammonium ILs and imidazolium ILs as a neat lubricant and 15W40 engine oil additives in lubricating a Cr-plated engine piston ring against a cast iron flat [60]. They observed that neat ILs produced 17–55% friction reduction and 21–34% wear reduction compared to the fully formulated 15 W40 diesel engine oil. As well, 5 vol.% additives for mineral oil demonstrated up to 45% wear reduction. The results suggested the great potential of ILs for use as base lubricants or lubricant additives for diesel engine applications.

The friction properties LB106 and L-P106 were studied as 1 wt.% additives of a mineral hydrocracking oil for steel/steel contacts [61]. It was found that LB106 and L-P106 increased the viscosity of the base oil and decreased friction and wear. These are attributed to reactivity of the anion of the ILs with the steel surfaces, forming FeF_3, B_2O_3, and species, such as P_2O_5 or PO_4^{3-}.

9.3.2.3 Ionic Liquids (ILs) as Synthetic Oil and Lubrication Grease Additives

L-P106, LB102, LB106, and L-T102 were studied as 1 wt.% additives of PGDO in pin-on-disk tests for AISI 52100 steel/ASTM 2011 Al contacts at 25°C and 100°C [62]. All additives had better friction reduction and antiwear properties than base oil at 100°C. At room temperature, friction values for PGDO + 1 wt.% IL were either similar to or higher than that of the base oil, and only the more polar additives, L102 and L-T102, reduced wear rates. Recently, bisimidazolium ILs [$C_{10}(m_2im)_2(NTf_2)_2$, $C_{10}(m_2im)_2(PF_6)_2$, and $C_{10}(m_2im)_2(BF_4)_2$] with same cation and different anions were evaluated as additives in poly(ethylene glycol) for steel/steel contacts at room temperature [63]. Results showed that ILs with NTf_2^- and BF_4^- anions were capable to effectively reduce the friction and wear of sliding pairs compared to the cases without these additives (Fig. 9.9). When the concentration was 3 wt.%, the antiwear property of $C_{10}(m_2im)_2(NTf_2)_2$ was significantly improved with respect to the base oil. This was attributed to the formation of high-quality physical adsorption films and tribochemical products during friction and the good miscibility of ILs with the base oil. Xia et al. [64] studied the influences of methyl groups at the C2 position of the imidazolium ring on the tribological properties of ILs as additives in poly(ethylene glycol) for steel/steel contacts. Their results showed that L-F116 had better antiwear performance and load-carrying capacity than L-F106.

Fox and Priest [65] studied ILs as additives in grease and found surprisingly large increases in the weld load during the four-ball extreme pressure test. It was found that the alkyl substituent chain length on the imidazolium cation had no influence on the four-ball test wear scar diameter. However, in addition to Fox's study, ILs as lubrication grease additives were rarely studied. Five alkyl imidazolium ILs as friction reduction and antiwear additives in polyurea grease for steel/steel contacts were studied in detail [66]. The results showed that ILs as 1 wt.% additives can significantly improve the friction reduction and antiwear properties of polyurea grease compared to base grease containing 1 wt.% zinc dialkyldithiophosphate (T204), as well as better friction reduction and antiwear properties at high tempera-

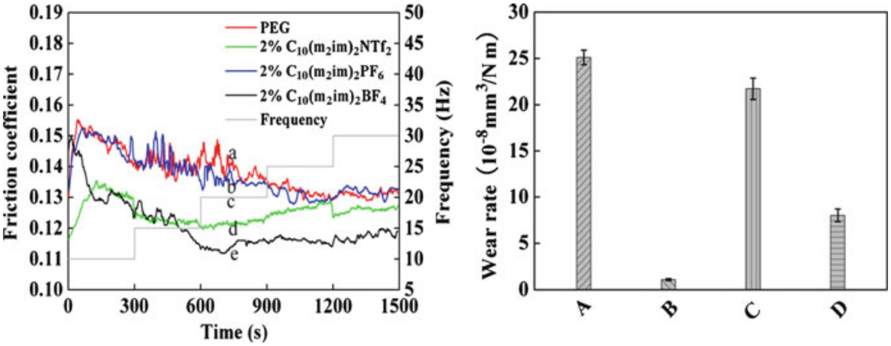


Fig. 9.9 Evolution of the friction coefficient and wear rates of disks lubricated by PEG with time during a frequency ramp test from 10 to 30 Hz for (**a**) PEG and (**b**) 2% $C_{10}(m_2im)_2(NTf_2)_2$, (**c**) 2% $C_{10}(m_2im)_2(PF_6)_2$ and (**d**) 2% $C_{10}(m_2im)2(BF_4)_2$ at room temperature (stroke 1 mm, load 100 N) (Reproduced from Ref. [63] with kind permission of © The American Chemical Society)

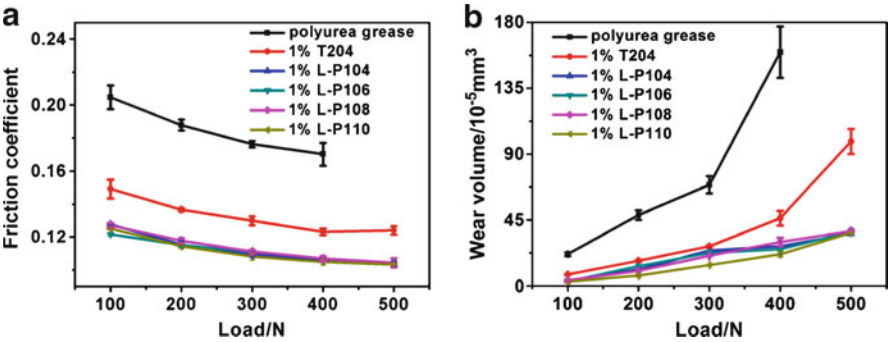


Fig. 9.10 (**a**) Friction coefficient and (**b**) wear volumes of steel disks lubricated by 1 wt.% T204, 1 wt.% L-P104, 1 wt.% L-P106, 1 wt.% L-P108, 1 wt.% L-P110, and 1 wt.% LB106 at 150°C (load 100–500 N, stroke 1 mm, frequency 25 Hz) (Reproduced from Ref. [66] with kind permission of © Springer)

ture than at room temperature (Fig. 9.10). These excellent tribological properties are attributed to the formation of a surface protective film composed of FeF_2, nitrides, compounds containing P–O bonds, and ordered adsorbed films and the good miscibility of ILs with the base grease.

9.3.2.4 Ionic Liquids (ILs) as Polymer Material Additives

In addition to ILs as additives in liquid lubricant, they can also be added in polymer materials. Bermúdez et al. [50, 51, 67, 68] performed several studies on the use of ILs as additives for polymer materials. They found that polymers to which ILs had been added produced better friction reduction and antiwear properties than blank polymer.

The tribological properties of ILs as internal lubricants in new polymer–IL dispersions were investigated [50]. It was observed that the dry mean friction coefficients and wear rates of PS + LB102 blends against AISI 52100 steel depended on the IL concentration and decreased when the LB102 contents dispersed in the PS matrix increased from 1 to 3 wt.%. L-P106 reduced friction and wear in PA6 + 3% L-P106 dispersions against AISI 316L compared to PA6 against AISI 316L.

Pin-on-disk tests for neat PA6 and for PA6 + 3 wt.% IL blend disks were carried out against AISI 52100 steel pins at varying temperatures (−35, 25, and 67°C) [51]. The results showed that PA6 + 3% IL produced low constant friction values under the entire range of temperatures, so the addition of IL reduced the influence of temperature on the tribological properties of PA6. This was attributed to the formation of stable adsorbed layers of highly polar IL molecules on the steel surface.

Bermúdez et al. [67] studied the tribological properties of PC + 0.5% ZnO + 1.5% IL composites and showed an 80% friction reduction and wear reduction of nearly two orders of magnitude with respect to PC + 0.5% ZnO. They then investigated ILs as an effective lubricant additive of epoxy resin under the pin-on-disk configuration and showed a friction reduction higher than 50% and a wear rate reduction of two orders of magnitude for epoxy resin (RE) + 1.5% IL with respect to the neat Re and Re + 0.5% ZnO [68]. The ability of ILs to act as lubricant additives of polymers under sliding conditions can thus be confirmed by the above report.

9.3.3 Additives of Ionic Liquid (IL) Lubricants

Chen et al. [69] studied the interactions of ILs lubricants with water and found that the addition of a small amount of water (5 wt.%) to the ILs could be beneficial to improve their antiwear behavior for some metal/metal contacts. In order to reduce the corrosive attack of the more reactive ILs, particularly those containing fluorine anions, several studies have attempted their modification by wear-reducing and corrosion inhibitor additives [33]. The tribological properties of benzotriazole (BTA) as a lubricant additive of ILs was studied [31, 70]. BTA can greatly improve the tribological behaviors of ILs with hexafluorophosphate anions as lubricants for steel/Cu–Sn alloy contacts mainly because of corrosion inhibition [70]. BTA and the surface of the Cu alloy have strong interaction (Fig. 9.11). XPS analysis showed that the surface of the Cu alloy formed a protective film containing [Cu($C_6H_5N_3$)] and Cu_2O, which can effectively protect the surface against tribology and corrosion.

Yu et al. [31] evaluated the tribological performance of diimidazoliumalkylene hexafluorophosphate (L-P6D6) IL–containing BTA for steel/steel contacts. They found that BTA can improve the antiwear abilities of L-P6D6 at high temperatures. This was attributed to the fact that BTA can inhibit the corrosive behavior of ILs during the friction process. The conventional lubricant additives (TCP and DBDS) have been found to improve the tribological properties of ILs to some extent [71]. The addition of these additives easily produces boundary films with antiwear properties through tribochemical reactions. The effect of tetraalkylammonium and

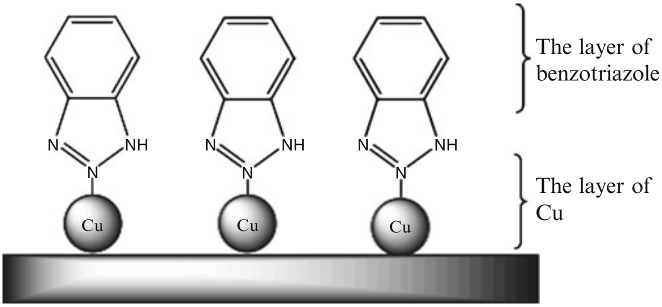


Fig. 9.11 Illustration of the adsorption of BTA on the surface of copper (Reproduced from Ref. [70] with kind permission of © Springer)

tetraalkylphosphonium salts of *N*-protected aspartic acid as additives in 1-alkyl-3-methylimidzolium bis(trifluoromethylsulfonyl)imide was studied by Minami et al. [72, 73]. The addition of these additives can prevent wear remarkably and also reduced friction considerably. As such, a model of a boundary film with a liquid clathrate structure was proposed. Addition of 1% tricresyl phosphate (TCP) to ILs rapidly established a tribofilm and reduced the wear volume by 64% compared to neat IL or neat TCP [65].

9.3.4 Thin Films

Future development of microelectromechanical systems (MEMS) will require significant decrease of gaps of component in relative motion. The proportion of its surface area and volume increased considerably. Friction and wear become a constraint to the development of miniaturized devices. These devices cannot be lubricated with lubricating oils, but lubricating film with nanometer thickness that can adapt MEMS friction lubrication requirements [74, 75]. ILs show potential application as lubricating films due to their excellent performance [76–82]. MEMS devices coated with a thin film of ILs showed significant improvement in wear life [76, 77]. Bhushan et al. have used atomic force microscopy (AFM) with a liquid cell to study friction and wear properties of surfaces lubricated with ILs. It was found that the friction and wear data obtained for these tests showed good correlation with the failure life span of lubricated MEMS motors. Palacio and Bushan [78] studied the formation of ultrathin wear-resistant 1-butyl-3-methylimidazolium hexafluorophosphate and 1-butyl-3-methylimidazolium octyl sulfate ILs films for MEMS/NEMS applications and compared their performance with a previously known lubricant, Z-TETRAOL (a hydroxyl functionalized PFPE), from the standpoints of adhesion, friction, and wear resistance. It was found that ILs had a friction coefficient comparable to Z-TETRAOL. Because of their low friction, wear resistance, and favorable charge dissipation properties, ILs showed strong potential as lubricants for MEMS/NEMS.

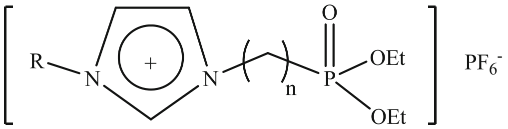
Patton et al. [79] synthesized a nanoparticle liquid (NPL) and deposited it on MEMS switch contacts as a nanotechnology-based lubricant. The NPLs used contained Au or Pt nanoparticles as the core and a mercaptoethanesulfonate IL as the corona. It was observed that the NPLs exhibited excellent electrical performance and durability compared to a SAM-based switch lubricant, indicating their potential for application as MEMS switch lubricants. Bai et al. [80, 81] investigated the effect of the anion on the tribological properties of 1-alkyl-3-methyl imidazolium ILs nanofilms on surface-modified silicon wafers. Among BF_4^-, PF_6^-, and adipate, the hexafluorerophosphate IL showed the best tribological properties. They then studied the effect of cations on the micro-/nanotribological properties of ultrathin IL films [82]. Three kinds of ILs films with the same anion but different cations were prepared on single-crystal silicon wafer by the dip-coating method. It was found that LB104 films on a hydroxyl-terminated surface showed better friction reduction and antiwear properties than I-P (tetraalkylphosphonium tetrafluoroborate) and I-N (*N*-butyl-pyridinium tetrafluoroborate) ILs.

9.4 Function of Ionic Liquids (ILs) as Lubricants

Ionic liquid (IL) is a special kind of molten salt compared with ordinary molten salt. ILs can be designed by the modulation of cationic type, or modification combined with the cationic center of the alkyl, or modified/modulation type and composition of the anion and so their chemical (polarity, pH, coordination ability, solubility) and physical (mobility, transmission capacity, the liquid range) properties. For some specific targets, ILs can also be designed to meet specific functional requirements of the ILs [83]. The research on the function of ILs has focused mainly on the introduction of carboxyl, hydroxyl, ester, sulfonate, phosphonate, and other functional groups to the alkyl imidazolium cation side chain. Each of these functional groups makes the ILs exhibit different physical and chemical properties, and these properties directly influence changes in the tribological properties of the ILs. Therefore, in order to design and develop better friction reduction and antiwear behaviors of new ILs lubricants, the functions of ILs and their tribological properties must be studied. This section reviews the synthesis and the tribological application of some ILs.

9.4.1 Function of Ionic Liquids (ILs) as Lubrication Oils

In order to make ILs a more effective lubricant for steel/aluminum friction pair especially at higher loads to reduce corrosion and wear Al matrix, a series of phosphate ester functional group–containing ILs was designed and synthesized. Mu et al. [84–86] synthesized a new series of imidazolium cation–based ILs with *O*,*O*-diethylphosphonyl groups on the alkyl side chain (Fig. 9.12), evaluated the tribological properties of the ILs, and discussed possible mechanisms of action.



1a: R= C_4H_9, n=2, [DPEBIM][PF_6] 1b: R= C_4H_9, n=3, [DPPBIM][PF_6]
2a: R= C_6H_{13}, n=2, [DPEHIM][PF_6] 2b: R= C_6H_{13}, n=3, [DPPHIM][PF_6]
3a: R= C_8H_{17}, n=2, [DPEOIM][PF_6] 3b: R= C_8H_{17}, n=3, [DPPOIM][PF_6]

Fig. 9.12 Molecular structure of new functional ILs

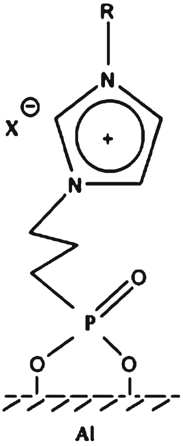


Fig. 9.13 Diagram of the chemical adsorption and interaction of ILs with an Al surface during sliding (Reproduced from Ref. [86] with kind permission of © Elsevier)

Their results showed that the synthesized ILs had better antiwear ability and load-carrying capacity for the aluminum-on-steel system than either LB206 or 1-propyl-3-octylimidazolium hexafluorophosphate (L-P308). This was attributed to the generation of physically adsorbing and chemically reacting films composed of five-member ring complex compounds, metal fluorides, nitrogen oxide, and $FePO_4$ on the rubbed Al surface. They supposed that ILs bearing functional groups react with fresh Al alloy surfaces under severe sliding conditions to form boundary films composed of five-member ring complex of Al–O–P–O–Al, which prevent the Al alloy from seizing and reduce the friction and wear of the Al-on-steel sliding system (Fig. 9.13).

In recent years, dicationic imidazolium ILs have attracted the attention of researchers. Jin et al. [87] synthesized a series of new polyethylene glycol–functionalized dicationic ILs with alkyl or polyfluoroalkyl substitutents (Fig. 9.14a, b) and studied their thermal decomposition behavior and the glass transition as well as tribological properties. They found that such ILs had very good thermal stability and the introduction of fluorine substituents can improve their antiwear properties [87].

Zeng et al. [88] prepared a new class of geminal dicationic ILs with a bridging moiety, such as a polyalkyl ether, polyfluoroalkyl, 1,4-bismethylenebenzene, or 1,4-bismethylene-2,3,5,6-tetrafluorobenzene link, between alkyl-substituted

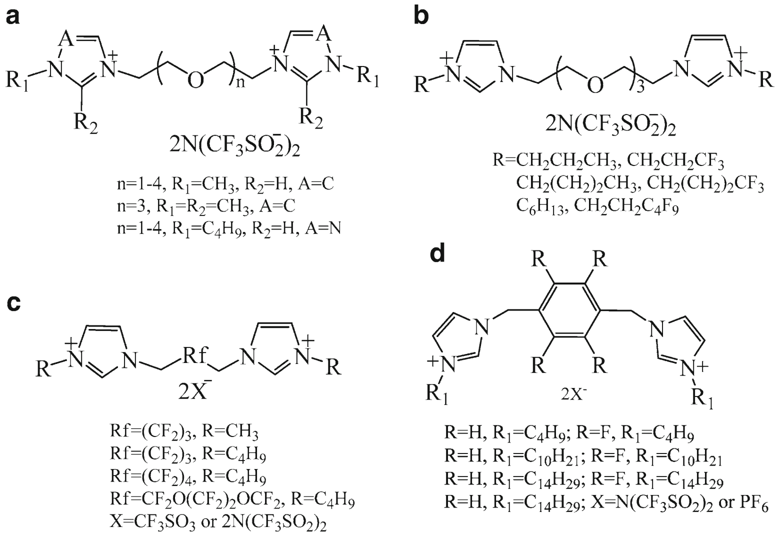


Fig. 9.14 Chemical structures of some dicationic ILs

imidazolium rings (Fig. 9.14c, d) and studied their melting point, thermal decomposition temperature, solubility, density, viscosity, conductivity, and other physical parameters. They found that the nature of dicationic ILs can be varied, depending on the connection chain. Polyfluoroalkyl bridged dicationic ILs exhibited the high densities and viscosities. Longer alkyl substituents on the imidazolium rings and the presence of fluorinated benzene as the linking chain can significantly reduce the polarity of these ILs and increase their solubility in toluene. These new dicationic ILs (except that with PF_6^- as an anion) displayed outstanding tribological properties in temperature ramp tests by performing very well at 300°C, thus meeting one criterion for high-temperature lubricants [88].

Li et al. [89, 90] synthesized a series of new fluoroalkoxycyclophosphazene and aryloxycyclophosphazene derivatives substituted with imidazolium ILs and studied their tribological properties on an Optimol SRV-IV oscillating friction and wear tester under ambient conditions. They found that these ILs exhibited better antiwear ability and load-carrying capacity in steel/steel contacts than X-1P.

ILs containing fluorine anions, BF_4^- and PF_6^-, which are very sensitive to moisture, may hydrolyze to generate hydrogen fluoride (HF) that could erode substrates and pollute the surrounding environment [2]. To solve this problem, imidazolium-based ILs containing triazole groups were synthesized. Figure 9.15 shows the corrosion/oxidation tests of small amounts of triazole-ILs, [C1C6im]BF_4, and [C1C6im]BF_4 containing 1% benzotriazole on different substrates. It was observed that the colorless [C1C6im]BF_4 turned deep brown under 100°C and black under 200°C after 10 h in air. This showed that complex reactions may include corrosion to the substrate and that oxidation and decomposition of [C1C6im]BF_4 occurred when [C1C6im]BF_4 came into contact with a Cu plate upon heating. Addition of benzotriazole could

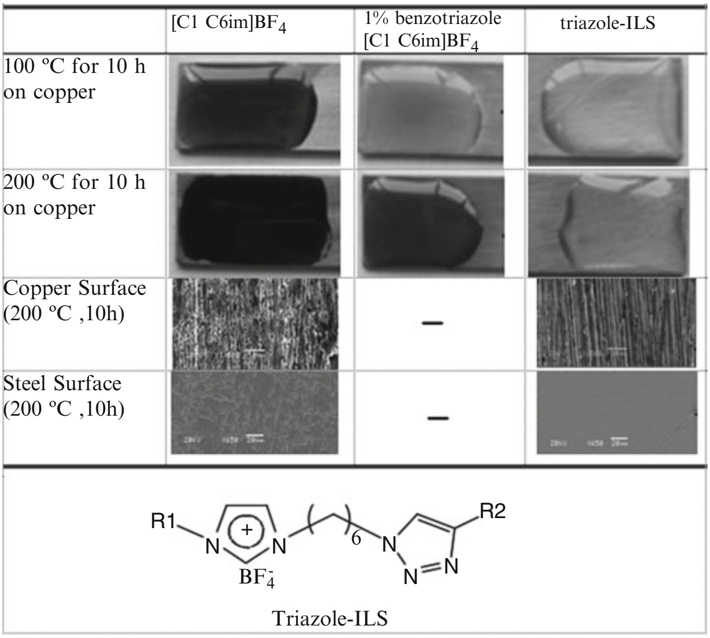


Fig. 9.15 Corrosion and oxidation test of ILs and the structure of triazole containing imidazolium IL (Reproduced from Ref. [2] with kind permission of © The Royal Society of Chemistry)

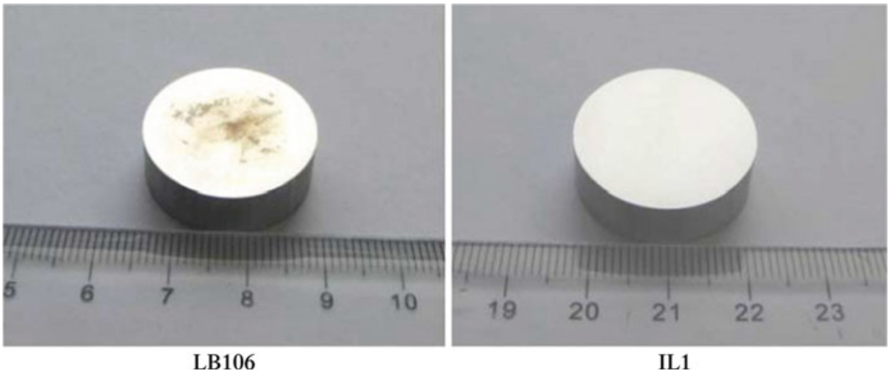
slightly reduce the corrosion of [C1C6im]BF_4 at 100°C, but the corrosion resistance was lost at 200°C, as evident by the obvious color change after 10 h. In contrast, the color of triazole-ILs remained clear and colorless even at 200°C for 10 h. This was attributed to the anticorrosion capability of the triazole groups.

The tribological properties of three novel anions ILs were studied. Phosphate ILs were synthesized and evaluated as lubricants for steel/steel sliding pairs [91, 92]. It was found that alkyl imidazole phosphate ILs exhibit excellent lubrication and anticorrosion properties (Fig. 9.16). This was attributed to their reaction with the friction surface to generate a $FePO_4$-alkyl imidazole protective film which can significantly reduce friction and wear.

Itoh et al. [93] evaluated the tribological properties of three types of alkyl sulfate ILs and showed that the increased hydrophobicity of these ILs was important to obtain steady friction coefficients.

9.4.2 Function of Ionic Liquids (ILs) as Additives or Thin Films

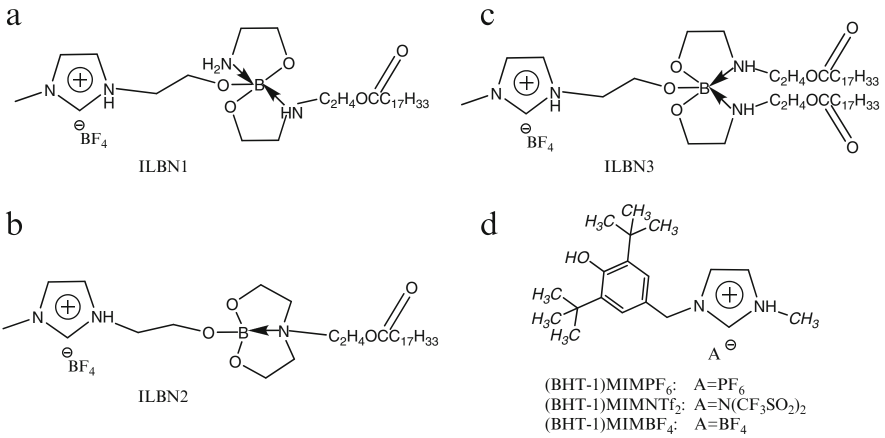
The tribological properties of four phosphazene-based ILs as boundary lubrication additives in water for Si_3N_4/Si_3N_4 ceramic interfaces were evaluated [94]. The most significant observation was that IL additives reduced the running-in period for Si_3N_4/



LB106 IL1

Fig. 9.16 Corrosion capability comparative test of IL1 and LB106 on steel SAE52100 (temperature50°C, time 1.5 h, and relative humidity 80%) (Reproduced from Ref. [91] with kind permission of © Springer)

Si_3N_4 ceramics. This behavior was similar to the results obtained by Phillips et al. [54]. Yu et al. [95] synthesized novel ILs materials based on 1-alkyl-4-[5-(alkylsulfanyl)-1,3,4-oxadiazol-2-yl] pyridinium tetrafluoroborate derivatives and investigated the tribological properties of ultrathin ILs films on silicon wafers by means of spin-coating. They observed that the films sliding against the AISI 52100 steel ball displayed good tribological properties under low loads and the wear life increased with increasing chain length. This was closely related to the interaction between ILs and the substrate surface. They then synthesized a new series of novel dicationic symmetrical and asymmetrical ILs consisting of tributylalkyl phosphonium and alkylimidazolium and studied their tribological properties in the form of spin-coated ultrathin films, using PFPE and normal ILs as comparisons. They found that the tribological performance of IL films was closely related to the chain length of the substituents, the functional groups, and the anions in the ILs [96]. The tribological properties of hydroxyl- and allyl-functionalized imidazolium ILs films sliding against AISI 52100 steel ball and Si_3N_4 ball were investigated on a dynamic-static friction coefficient measurement apparatus, using PFPE [97]. The results showed that hydroxyl- and allyl-functionalized imidazolium ILs films had better tribological properties than PFPE films with similar thickness (Zdol-2000). This was attributed to relatively strong H-bonds and/or physicochemical adsorptions of ILs on the hydroxyl-terminated surface of the vinyl-terminated substrate. The films on the hydrogen-terminated and methyl-terminated substrate showed poor tribological performance; this was ascribed to the weak interaction between the films and the substrates. The effect of more functional substituent groups on the tribological properties of IL films in micro-/nanoelectromechanical (M/NEMS) systems was studied by Mo et al. [98]. Methyl- and cyano-substituted ILs had lower adhesion and friction than the films made with –OH and –COOH functional ILs or uncoated silicon. Methyl-ILs had the poorest tribological properties in all cases. Miscibility with lubrication oils can be promoted by producing combinational molecules with



(BHT-1)MIMPF$_6$: A=PF$_6$
(BHT-1)MIMNTf$_2$: A=N(CF$_3$SO$_2$)$_2$
(BHT-1)MIMBF$_4$: A=BF$_4$

Fig. 9.17 Molecular structures and codes of the ILs

components of conventional oil. Three imidazolium-based ILs containing borate esters groups were synthesized, all of which showed good miscibility with poly-alpha-olefin (PAO) [99]. The tribological properties of borate ester–functionalized ILs as additives in poly-alpha-olefin (PAO) were measured for diamond-like carbon (DLC) coatings on plasma-nitrided AISI 1045 steel (Fig. 9.17a, c). It was seen that borate ester–based ILs showed much better friction reduction and antiwear properties for DLC coating/steel and DLC coating/DLC coating sliding pairs compared to zinc dialkyldithiophosphate (ZDDP). This was attributed to the adsorption of borate ester–based ILs to the worn surface of the pair because of triboplasma and the penetration of B atoms into the defects and sublayer of the worn surface during sliding. Formation of a tribofilm composed of B, N, and F elements resulted in excellent friction reduction and antiwear performance.

Not only can molecular design improve the miscibility with other oils, it can also confer ILs with special functions, such as antioxidation and the ability to adapt to a broader temperature range. We synthesized three imidazolium-based ILs containing sterically hindered phenol groups with antioxidant functions and evaluated the tribological behaviors of these ILs as additives for PEG application in steel/steel contacts on an Optimol SRV-IV oscillating reciprocating friction and wear tester, as well as on MRS-1J four-ball testers [100]. The rotary bomb oxidation test (RBOT) test, thermal analysis, and Cu strip test results revealed that synthesized ILs possessed excellent antioxidation capability.

It was observed that these ILs could effectively reduce the friction and wear of sliding pairs compared to PEG films without the additives. Specifically, 1-(3,5-Ditert-butyl-4-hydroxybenzyl)-3-methyl-imidazolium hexafluorophosphate (BHT-1) MIMPF$_6$ exhibited better antiwear properties at an optimum concentration of 1 wt.%. At this level, its antiwear property was significantly improved 100-fold with respect to the PEG base oil (Figs. 9.17d, 9.18).

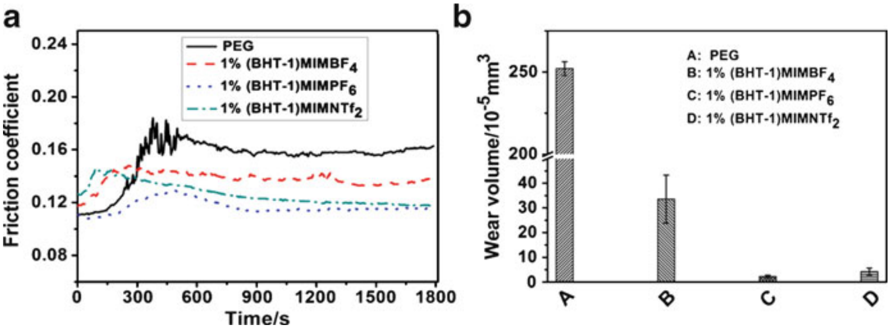


Fig. 9.18 (**a**) Friction coefficient and (**b**) wear volumes of steel disks lubricated by PEG and different IL additives at room temperature. (SRV tester, load 100 N, stroke 1 mm, frequency 25 Hz, duration 30 min) (Reproduced from Ref. [100] with kind permission of © the American Chemical Society)

9.5 Lubrication Mechanism

ILs possess unique characteristics, including nonvolatility, nonflammability, and thermo-oxidative stability, and these characteristics make them ideal candidates for lubrication under severe conditions, where conventional oils and greases or solid lubricants fail. Some studies on the ILs lubrication theory exist, but how ILs behave during the process of friction production remains unclear. It is, generally, believed that ILs molecules on the friction surface undergo physical and chemical reactions and chemical adsorption to play a role in the formation of a lubricant film. Kajdas [101] developed the anion adsorption model, which will be very helpful to interpret the underlying mechanism. Minami [19] proposed a model where the rubbing surface is treated as a reaction zone. Lubricating oil that is applied between rubbing surfaces is exposed to extreme pressures of up to several gigapascals, so certain high-pressure reactions may take place under these conditions. Low-energy electrons are emitted from contact convex points on the metal surface caused by mechanical stress to crystalline solids, leaving a positive charge formed on the surface of a tiny convex volume that strengthens the adsorption mode. Clearly, the anions in ILs can easily adsorb onto the positively charged sites of a worn metallic surface and the counter cations assemble successively by the electroneutrality principle [2]. It can be speculated here that under the collective impact of high pressure, exoelectron emission, and frictional heat on the specimen surface, complicated tribochemical reactions can occur on the surfaces lubricated by ILs and a surface protective film composed of FeB and B_2O_3 (in case of BF_4^-) and FeS (in case of Tf_2N^-) and $FePO_4$ (in the case of $PF6^-$) can be generated on the lubricated metal surface. This can prevent a fresh metal surface from developing serious wear.

9.6 Conclusions and Outlook

ILs have attracted considerable attention in the field of tribology because of their remarkable lubrication and antiwear capabilities compared to lubrication oils. In recent years, ILs have been applied and yielded excellent performance compared to traditional lubricants, but they have a number of problems, such as corrosion, oxidation instability, and very poor miscibility with base oil. These factors limit their industrial applications as lubricants [2]. Fortunately, these problems are not very difficult to address, as ILs have structures that may easily be modified. Conferring ILs with special functions, such as antioxidation and anticorrosion properties and enhanced capability for specific substrates, may be easily performed by synthetic chemists. It is hoped that future work on ILs will produce multifunctional lubricants with oxidation and corrosion resistance that may be applied in the industrial scale [2, 100].

We can also improve ILs and base oil compatibility through molecular design by creating combination molecules with components of conventional oils [56, 99], such as PFPE-ILs, X-1P-ILs, PAO-ILs, MACs-ILs, silicone-ILs, and polyether-ILs. These may or may not further improve the lubrication properties of ILs, but they can definitely improve the tribological properties of base oils and avoid severe tribocorrosion. The use of reactive ILs as lubricant additives rather than as neat lubricants, particularly in the case of fluorine-containing ILs [33] is possible. The tribological performance of ILs as additives in grease needs to be studied. Researches on the lubrication mechanism of ILs have made some progress, but tribological workers have to do more work to disclose the exact lubrication mechanism, which will guide for designing new ILs lubricant for specific applications.

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Chapter 10
Stability and Activity of Enzymes in Ionic Liquids

Nusrat J. M. Sanghamitra and Takafumi Ueno

Abstract This chapter discusses the potential usefulness of ionic liquids with respect to biocatalysis by illustrating the stability and activity of enzymes in ionic liquids in the presence or absence of water. Ionic liquids are a class of coulombic fluids composed of organic cations like alkyl-substituted imidazolium, pyrrolidinium, and tetraalkylammonium ions and anions such as halides, tetrafluoroborates, hexafluorophosphates, tosylates, etc. The possibility of tunable solvent properties by alternation of cations and anions has made ionic liquids attractive to study biocatalysis which warrants an understanding of enzyme stability and activity in ionic liquids. This chapter systematically outlines the recent studies on the stability of enzymes and their reactivity toward a wide range of catalytic reactions. A careful approach has been taken toward analysis of relationship between stability/activity of enzymes versus chaotropic/kosmotropic nature of cations and anions of ionic liquids.

10.1 Introduction

> If ionic liquids are to impact the field of green chemistry then we need to know much more about them, experimentally and theoretically than we do now
>
> Prof. Kenneth R. Seddon, Queens University, Belfast, Green Chemistry 2002

"Ionic liquids are starting to leave academic labs and find their way into a wide variety of industrial applications." The quote in the cover story of Chem and Engg News April 2006 [1] carefully outlines one of the noteworthy objectives of chemistry,

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A. Mohammad and Inamuddin (eds.), *Green Solvents II: Properties and Applications of Ionic Liquids*, DOI 10.1007/978-94-007-2891-2_10,

i.e., “sustainability,” and thereby rightly emphasizes the need of the hour to study, explore, and understand the issue of “stability and activity of enzymes in ionic liquid.” In this chapter, we discuss the viability of ionic liquids as a benign/hostile transient home to the enzymes by illustrating their kinetic and thermodynamic stability leading to the enzyme activity/passivity.

10.1.1 Ionic Liquid in Reference to Its Origin

The history of ionic liquids dates back to more than 100 years where its root is seeded on “high-temperature molten salts” [2]. But industrial chemists or in general synthetic organic chemists witnessed a *renaissance* of molten salt chemistry with the development of a class of coulombic fluid, i.e., ionic liquids (ILs), as a promising “neoteric solvent.” Prof. Jerry Atwood first pointed out the early ionic liquid, i.e., the heptachloroaluminate salt, having the sigma complex of Friedel–Crafts reaction as a cation [2]. IL can be defined as “a salt with a melting temperature below the boiling point of water” [2]. IL stands out over all other solvents owing to its property of large “liquidus” range, i.e., it spans over a large range of temperature between its freezing point and boiling point, its nonvolatile nature, and high thermal stability [2, 3]. Over the last two decades, ILs have emerged as a potentially green alternative to environmentally unfriendly and toxic organic solvents for variety of reactions and often with remarkably better results [4]. Generally, ILs are composed of organic cations like alkyl-substituted imidazolium, pyrrolidinium, and tetraalkylammonium ions in combination with variety of anions such as halides, tetrafluoroborates, hexafluorophosphates, tosylates, nitrates, acetates, and hydroxides, to name a few. The success story of ILs remarkably stands out in clean technology. ILs have conferred a new dimension to the field of catalysis in general, but in particular, they have attracted a great deal of attention in biocatalysis to study the catalytic reactions promoted by enzymes in ILs [5, 6]. Especially, ILs have gained popularity in biocatalysis because of its tailor-made nature, i.e., alteration in properties by carefully changing the cationic and anionic part of the ionic liquid and thus optimizing the solvent properties for the requirement [3]. Since catalytic activity of the enzymes is closely related to their stability, the focus of this chapter is to explore the catalytic reactions promoted by various enzymes carried out in ionic liquid, to carefully examine the kinetics of enzymatic reactions, the enantioselectivity, to assess the stability of enzymes in such a reaction medium, and to analyze the stability versus activity issue in a proactive manner.

10.1.2 Ionic Liquid as a Solvent

As mentioned above, ILs are known to have versatile and distinct solvent properties such as high thermal stability over a range of 300°C, good chemical resistance toward degradation, wide electrochemical window, high electrical conductivity, and almost no vapor pressure which makes them "green solvents" due to the reduction in environmental levels of volatile organic content [3]. Furthermore, ILs possess wide tunability in ameliorating other important solvent properties like solvent polarity, miscibility, and hydrophobicity/hydrophilicity by carefully modifying the cation/anion and thus have emerged as "designer solvents" [2, 7]. But due to the diversity in structure and functionality, the most important facet of ILs as solvent is their solvation characteristics, which is important to understand. In comparison to conventional solvents, ILs come in the category of the most complex solvents due to the plethora of possible solute–solvent interactions. Utilizing a linear free energy approach, Anderson et al. [8] have classified ILs based on the hydrogen bond basicity, polarizability, dispersion forces, interaction via nonbonding electrons, and hydrogen bond acidity. The authors have shown that hydrogen bond basicity is the most remarkable feature of ILs which also plays an important role in classifying the usefulness of a particular IL as an organic solvent, and hydrogen bond acidity is controlled by anionic portion of ILs [8]. Among the most commonly used ILs, [BMIM][Cl] which is capable of dissolution of cellulose has high hydrogen bond basicity in comparison to [BMIM][BF_4] and [BMIM][PF_6] which do not dissolve cellulose suggesting the key role of the anion [9]. As observed from the strong retention ability of ILs toward probe molecules, ILs seem to have significant capability of producing stronger interaction by π–π and n–π interactions which is controlled by the cationic counterpart. But a more practical and useful parameter to assess the solvation characteristics with regard to enzyme stability and activity is the effect of the solvent as a water "structure maker" or water "structure breaker" which is popularly known as Hofmeister effect. Based on the phenomenological study of Hofmeister on the effect of salts on hen egg white proteins [10], ions have been classified as "kosmotropes" which promote the ordered structure formation of water and "chaotropes" which destroy the ordered structure of water molecules in the solution [11]. H. Zhao has been able to review a range of ILs and empirically ranked them based on the available thermodynamic parameters [12]. According to Zhao's analysis, smaller organic cations like $[MMIM]^+$, $[EMIM]^+$, $[MePy]^+$, $[MePy]^+$, $[EtPy]^+$, and $[Me_4N]^+$ could be classified as chaotropes, while larger anions like $[BMIM]^+$, $[Pr_4N]^+$, and $[Bu_4N]^+$ come in the kosmotrope category with few borderline ions such as $[BuPy]^+$ and $[Et_4N]^+$ [12]. The size of the alkyl group on the organic cation largely governs the nature of the ILs like its hydrophobicity and miscibility with water. Whereas anion classification of ILs as kosmotrope or chaotrope is relatively easier due to the readily available values of several important parameters such as ionic mobility and structural entropy–related relaxation parameters of IL anions. For example, acetate anion is considered to be a stronger kosmotrope than $[CF_3COO]^-$ based on viscosity B coefficients and $[BF_4]^-$ has a stronger water–anion interaction. Based on Walden products or ionic mobility data, $[SCN]^-$, $[PF_6]^-$, $[BF_4]^-$, $[I]^-$, and $[Br]^-$ are categorized as chaotropes having high ionic mobility, while acetates, haloacetate, alkyl sulfate, tosylates, and F^- are kosmotropes with $[Cl]^-$ and $[MeSO_4]^-$ lying in borderline anions [12]. Thus, given the complexity in the nature of interactions between the ions in ILs and limited thermodynamic data available, although it is not very straightforward to categorize ILs on the basis of Hofmeister series per se, but with regard to biocatalysis, it provides a valuable guide to relate stability and activity of enzymes observed in aqueous solutions. A detailed analysis of dependence of enzyme stability or activity and Hofmeister effect will be given as few case studies later in this chapter.

10.1.3 Enzymes in Ionic Liquids

Enzymes have been studied in ionic liquids mostly in the context of biocatalysis. In biocatalysis, ILs have been used either as a neat solvent or as a cosolvent with water or as a biphasic reaction medium. Most studies involve the use of different imidazolium salts like [BMIM][BF_4], [BMIM][PF_6], [BMIM][Tf_2N], and [MMIM][$MeSO_4$] as pure solvent and biphasic systems depending on the miscibility with water [3, 4]. The first trial reaction in the field of biocatalysis was carried out by Magnuson et al., a study of activity of alkaline phosphatase using ethylammonium nitrate in salt/water mixture where an increased activity of alkaline phosphatase was observed with the use of low concentrations of ethylammonium nitrate [13]. However, exactly a decade back, the first ever report came describing the use of pure IL as a neat reaction medium for Z-aspartame synthesis by thermolysin [14] and transesterification reaction by the biocatalysis "workhorse" enzyme lipases [15]. Following this work, during the last 10 years, there is a considerable increase in the number of studies carried out on enzymes in ILs discerning the activity and stability of various enzymes especially esterases, proteases, glycosidases, oxynitrilases, and oxidoreductases in pure as well as in aqueous mixture of ILs. Table 10.1 can be conferred with for a brief account on the enzymes studied in various formulations, their reactivity and stability in various ILs [16].

Thermolysin-mediated Z-aspartame synthesis had a 40% turnover rate in [BMIM][PF_6] in comparison to ethyl acetate [14]. Lipase from *Candida antarctica* (CaLB)–catalyzed transesterification reaction was more effective in [Tf_2N] containing ILs having 2% water in comparison to n-hexane: $[NCPrMe_3N]^+ > [NCPnMe_3N]^+ > [BuMe_3N]^+ > [HxMe_3N]^+ > [HOPrMe_3N]^+ \sim$ n-hexane [17]. Similarly, lipase A from *Candida antarctica* (CaLA) was ten times more active in [BMPY][BF_4] and [BMIM][Tf_2N] than in di-isopropylether (DIPE), but its activity was comparable in *tert*-butyl alcohol, dioxane, and toluene [15, 18–20]. Lipase from *Candida rugosa* (CrL), a less tolerant enzyme to nonaqueous media, is dissolved in hydrated ILs and performed better in ILs containing $[BMIM]^+$ and $[HMIM]^+$ cations and $[BF_4]^-$, $[PF_6]^-$, and $[HpSO_4]^-$ anions than in isooctane [21]. α-Chymotrypsin-mediated transesterification reaction of *N*-acetyl-L-amino acid esters occurred in [EMIM][Tf_2N] at higher rate than that in isooctane and acetonitrile, whereas reaction rates were of similar magnitude in [BMIM][PF_6] and [OMIM][PF_6] [22]. Although lipases are active in most of the ILs, there are a few exceptions. CaLB and CrL were found to be inactive in water miscible ILs containing $[MeSO_4]^-$, $[NO_3]^-$, and $[CH_3COO]^-$ anions. Hemin and microperoxidase [23–25] showed very high activity in alkylmethylimidazolim ILs with $[PF_6]^-$ and $[Tf_2N]^-$ anions whereas cytochrome c showed comparable activity toward oxidation of 2-methoxyphenol [25].

Table 10.1 Summarized examples of stability and activity of proteins/enzymes in ILs (Reproduced from Ref. [16], with kind permission of © Elsevier)

Enzymes	Conditions	Activity/stability order
Chloroperoxidase	Conversion (30%)	$[MMIM][MeSO_4] > [BMIM][MeSO_4]$
Lysozyme	Melting temperature (1 M)	Cation effect (Cl^- as common anion): $[EMIM]^+ > [BMIM]^+ > [HMIM]^+$ $[OH\text{-}EMIM]^+ > [OH\text{-}PMIM]^+ > [OH\text{-}HMIM]^+$
Lipase	Initial rate (20–25%)	Cation effect ($[BF_4]^-$ as common anion) $[EMIM]^+ > [PMIM]^+ > [BMIM]^+$
	Initial rate (10–20%)	Anion effect ($[BMIM]^+$ as common cation) $[BF_4]^- > [Cl]^- > [Br]^- > [NO_3]^- > [HSO_4]^-$
	Conversion (33%)	$[EtOMG][PF_6] > [EtOMG][BF_4]$
D-amino acid oxidase	Initial rate (20%)	$[MMIM][MMPO_4] > [BMIM][BF_4] > [BMIM][OctSO_4]$
	Stability (40%)	$[MMIM][MMPO_4] > [BMIM][BF_4] > [BMIM][OctSO_4]$
Protease P6	Stability (0.7 M)	$[EMIM][CH_3COO] \sim [EMIM][CF_3COO] > [EMIM][Br] > [EMIM][TOS] > [BMIM][CF_3COO]$
	Activity (0.5 M)	$[EMIM][CF_3COO] > [BMIM][CF_3COO]$
3α-Hydrosteroid hydrogenase	Activity (10%)	$[BMIM][lactate] > [EMIM][CF_3SO_3] > [BMIM][BF_4] > [BMIM][CF_3SO_3]$
Cytochrome c	Stability (20 wt%)	$[Choline][H_2PO_4] > [Choline][dbp] > [BMIM][CH_3COO] > [BMIM][lactate] > [BMIM][MeSO_4]$
RNase A	T_m (0–2 M)	Cation effect ($[Cl]^-$ and $[Br]^-$ common anion): $[K]^+ > [Na]^+ > [Me_4N]^+ > [Li]^+ > [Et_4N]^+ > [EMIM]^+ > [Pr_4N]^+ > [HMIM]^+$ Anion effect ($[EMIM]^+$ as common cation) $[SO_4]^{2-} > [HPO_4]^{2-} > [Cl]^- > [EtSO_4]^- > [BF_4]^- \sim [Br]^- > [MeSO_4]^- > [CF_3COO]^- > [SCN]^- > [N(CN)_2]^- > [Tf_2N]^-$
Alcohol dehydrogenase	Conversion (20%)	$[EMIM][CH_3COO] > [BMIM][CH_3COO] > [EMIM][MeSO_4]$
	Initial rate (20%)	$[BMIM][PF_6] > [BMIM][BF_4] > [EMIM][TOS]$
	Half-life (10%)	$[BMIM][EtSO_4] > [BMIM][PF_6] > [EMIM][TOS] > [BMIM][BF_4]$
Glucose dehydrogenase	Half-life (10%)	$[BMIM][EtSO_4] > [BMIM][BF_4] > [BMIM][PF_6] > [EMIM][TOS]$
Tyrosinase	Half-life (2%)	$[BMIM][BF_4] > [BMIM][PF_6] > [BMIM][MeSO_4]$
	Activity (2%)	$[BMIM][PF_6] > [BMIM][BF_4] > [BMIM][MeSO_4]$

ILs have been used for immobilization of enzymes. Horseradish peroxidase (HRP) activity is evaluated in a $[BMIM][BF_4]$ sol–gel matrix [26]. Higher activity in $[BMIM][PF_6]$ is also observed when lipase from an unspecified *Pseudomonas* (PsL) is immobilized on methacryloxypropyl-modified mesoporous silica [27]. Similarly, IL-coated enzyme was found to completely retain the activity and easily reusable [28].

The activity and stability of many enzymes have been studied in water-ILs mixtures. Alkaline phosphatase is the very first enzyme of which the activity was studied in [EtNH$_3$][NO$_3$]. The detail of catalytic activity of various enzymes under different conditions will be discussed in a later Sect. 10.6 of this chapter. However, few instances can be depicted here. Horseradish peroxidase shows a thermal destabilization as well as a 30% loss in activity in 25% [BMIM][Cl] in aqueous buffer whereas papain from *P. latex* (PPl) loses 65% of its original activity in aqueous buffer containing 15% [BMIM][Cl] [29, 30]. Similar effect, i.e., 30% loss in activity, was also observed for Amano protease in 20% [EMIM][CF$_3$COO], [BuPy][Cl], and [BuPy][CF$_3$COO]. The loss of activity in this case was explained in connection with the hydrogen bonding ability of the organic ions with the enzyme [31]. Similarly, β-galactosidase from *P. furiosus* showed reversible deactivation in 10% [BMIM][BF$_4$], whereas the same enzyme from *E. coli* retained 36% of its activity in 50% [BMIM][BF$_4$]. β-Galactosidase from *Bacillus circulans* behaved in a similar way in [BMIM][OctSO$_4$] as in [BMIM][BF$_4$] with 35% and 10% of activity in 25% and 50% of IL, respectively [32]. In contrast, oxynitrilase from almonds was activated by ~10% of [BMIM][BF$_4$], but when concentrations were increased to ~50%, loss in activity was accounted to be 50%. It is interesting to note that rehydration of the enzyme after incubation in [BMIM][BF$_4$] recovers to ~85% of native state activity whereas in organic solvents like acetonitrile and tetrahydrofuran, the enzyme is deactivated irreversibly to about 70% [33]. Unlike the enzymes discussed above, chloroperoxidase from *Caldariomyces fumago* seems to be quite tolerant of the ILs as observed from the remarkably high activity in 50% [MMIM][Me$_2$PO$_4$] which is higher than the enzyme activity in water [34].

10.2 Enzyme Stability in Ionic Liquids

The discussion in the above Sect. 10.3 gives a clear indication that with a few exceptions in most ILs, enzymes remain active and perform better or comparable to conventional organic solvents. Enzyme activity is closely related to the structure and conformational change at the microenvironment of the enzyme active site. As discussed before (Sect. 10.2) microenvironments of the enzyme active site is affected by ILs, which has complicated solvation characteristics due to different interactions of large organic cations and anionic counterparts of ILs with the enzyme. So it is important to understand the stability of enzymes in ILs.

10.2.1 Stability of Lipases

Lipases are the most extensively studied enzyme in ILs. Sheldon et al. studied the thermal stability of CaLB in [BMIM][PF$_6$] at 80°C by measuring its activity at different time points. CaLB in both free form (SP 525) and immobilized formulation

(Novozyme 435) are stable in [BMIM][PF_6] as evident from the higher activity after incubation for 20 h [3]. With increased incubation time of 100 h, there was no reduction in activity whereas in butyl alcohol, the activity of CaLB decreased linearly with time [3]. A similar study with CaLB stability in various ILs containing 2% water at 50°C was studied by monitoring the transesterification reaction between vinyl butyrate and 1-butanol. The activity measurement showed an increased half-life ($t_{1/2}$) of the enzyme in ILs in comparison to traditional organic solvents like butanol and hexane which might be due to the shielding effect of strong ionic matrix of IL on the enzyme microenvironment. Further, the $t_{1/2}$ was remarkably increased (~three orders of magnitude) when the enzyme was incubated in ILs with substrates. The increase in $t_{1/2}$ was attributed to the protective effect of substrates on the active structure of the enzyme [35]. However, when lipases are used as cross-linked enzyme crystals [36–38] and cross-linked enzyme aggregates [39, 40], no such stabilizing effect was observed. Operational and thermal stabilities of CaLB were studied by monitoring the kinetic resolution of 1-phenylethanol by CaLB. In this study, CaLB showed higher stability in [BMIM][PF_6], [EdMIM][Tf_2N], and [EMIM][Tf_2N] than organic solvents like toluene, isooctane, and 3-pentanone at 80°C. Operational stability of CaLB was also quite high as observed from almost unchanged residual activity after multiple (five times) use of the enzyme in the ILs [41].

De Diego et al. [42] discussed the stability of CaLB in ILs by analyzing the circular dichroism (CD) and fluorescence spectra of CaLB after incubation in ILs at higher temperature. Characteristic shape and intensity of far UV (190–240 nm) CD spectrum is informative about the secondary structure of a protein [43–46]. CD spectrum of native CaLB in water has a characteristic positive band at 203 nm and a negative band at 208 nm [42]. Under denaturing condition, i.e., in the presence of 8 M urea at 50°C, unfolding of CaLB is indicated by the loss of secondary structure elements (like α helix, β sheets) and increased formation of random coils in the far UV CD spectra of CaLB. In n-hexane, the situation was similar to that of the denaturing condition pointed out above. The calculated secondary structure components from the far UV CD spectra at different time points showed a reduction in α helix with an increased percentage of β sheet content upon incubation with both n-hexane and ILs in comparison to the native condition in water (Fig. 10.1a) [41]. Though β sheet formation was observed in both n-hexane and ILs, but interestingly in the ILs ([EMIM][Tf_2N] and [BTMA][Tf_2N]), percentage of β sheet was higher than in n-hexane but random coil formation was lower (Fig. 10.1a). Thus, the secondary structure components were retained even after 4 days of incubation of protein in the ILs. This indicates the change in the microenvironment of the protein due to the loss of water molecules which could be due to the protective nature of the ILs toward preservation of the native-like conformation of the enzyme by formation of a strong ionic supramolecular net around CaLB molecules. This is further reflected in the near UV CD spectrum (Fig. 10.1b) which is indicative of tertiary structure of the enzyme. It is known that stronger interaction between the aromatic residues (Phe, Trp, Tyr) is manifested by an increase in the intensity of near UV CD band [43]. The more intense CD signal in ILs than in water and n-hexane demonstrates a more

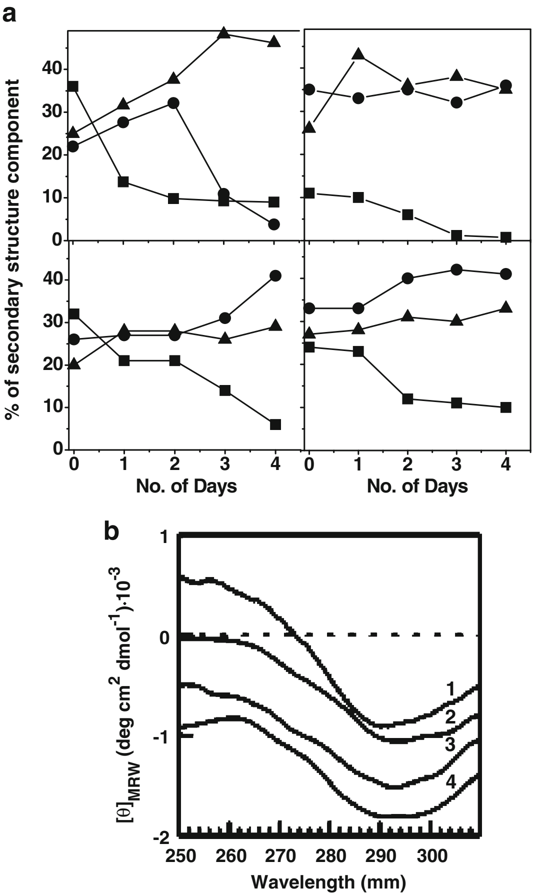


Fig. 10.1 (**a**) Variation in the secondary structure components calculated from far UV CD spectra of CALB in water (A), n-hexane (B), [EMIM][Tf$_2$N] (*C*), and [BTMA][Tf$_2$N] (*D*) (*square* α helix, *circle* β sheet, *triangle* random coil); (**b**) Alteration in near-UV CD spectra of CaLB in water (*1*), n-hexane (*2*), [EMIM][Tf$_2$N] (*3*), and [BTMA][Tf$_2$N] (*4*) after 24 h incubation at 50°C (Reproduced from Ref. [42], with kind permission of © The American Chemical Society)

compact structure of CaLB in ILs (Fig. 10.1b). CaLB has five Trp, nine Tyr, and ten Phe residues (Fig. 10.2a). Since CD band at 290 nm is characteristic of Trp residues, it is indicative of the alteration in the microenvironment of Trp residues in the folded and unfolded states of configuration of the enzyme. This was further evidenced by the intrinsic fluorescence spectra of CaLB in the presence of ILs.

CaLB emits at 322 nm in water which is red-shifted to 347 and 337 nm in n-hexane and ILs, respectively [42]. In n-hexane or water, emission maxima were progressively red-shifted toward 350 nm which is the emission maxima for Trp residues in water. This is indicative of the opening up of the conformation of the enzyme exposing the Trp residues to bulk solvent. The slight red shift of emission maxima in ILs could be due to the difference in the positioning of the Trp residues in the 3D structure (Fig. 10.2b). As seen in Fig. 10.2b, three Trp residues are located in α helices (red labeled) and two are located in the β sheets (blue color). The slightly high β sheet content of CaLB in ILs could account for the red shift in Trp fluorescence due to structural transition from α helix to β sheet. The interesting observation was the

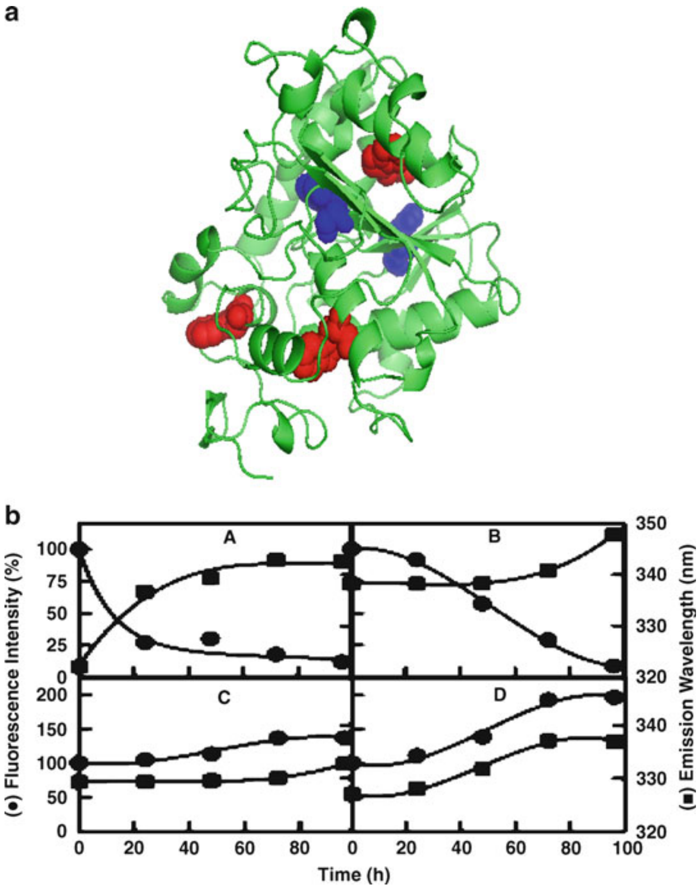


Fig. 10.2 (**a**) Crystal structure of CaLB (1TCC.pdb); (**b**) Change in tryptophan fluorescence intensity (*filled circle*) and fluorescence emission maxima (*filled square*) of CaLB with time in water (*A*), n-hexane (*B*), [EMIM][Tf_2N] (*C*), and [BTMA][Tf_2N] (*D*) at 50°C (Reproduced from Ref. [42], with kind permission of © The American Chemical Society)

substantial increase in the fluorescence intensity in the ILs (Fig. 10.2a) in contrast to the considerable reduction in intensity parameter in water and n-hexane after 4 days of incubation at 50°C. The increased fluorescence intensity is indicative of reduced exposure of Trp residues, i.e., an ordered and more compact structure of the enzyme in ILs. This illustrates the higher stability of the enzyme in ILs.

Protein secondary structure of CaLB in ILs was also studied by FTIR spectra. The IR bands at 1,650 and 1,658 cm^{-1} were due to α helix and at 1,620 and 1,640 cm^{-1} were because of β sheet content of the protein [47]. Protein secondary structure was undisrupted in [MTEOEIM][CH_3COO] and [MTEOTEAm][CH_3COO], but in [EMIM][CH_3COO] and [BMIM][HCOO], secondary structure was significantly changed as indicated by the altered band positions and intensities. IR spectra of

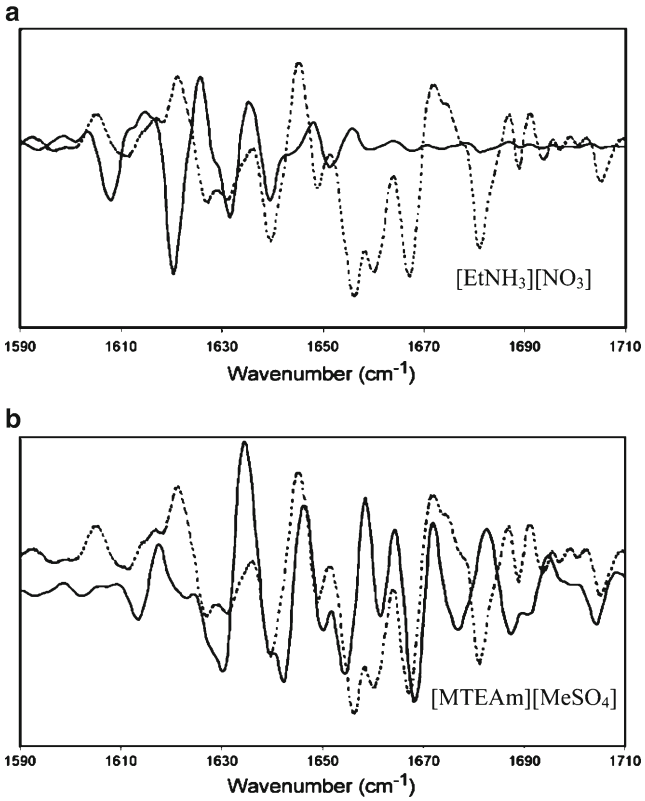


Fig. 10.3 Second derivative FTIR spectra of CaLB in (**a**) [EAm][NO_3] and (**b**) [TEAM][$MeSO_4$]. In both the cases, second derivative IR spectra of CaLB in aqueous solution is given by the *dotted line*, and *solid line* is the spectra in IL (Reproduced from Ref. [47], with kind permission of © The Royal Society of Chemistry)

CaLB in [$EtNH_3$][NO_3], [BMIM][lactate], and [BMIM][NO_3] were substantially changed. In [$EtNH_3$][NO_3], all the bands above 1,650 cm^{-1} disappeared (Fig. 10.3a), indicating the loss of bands due to α helix and β sheets. Similar changes occurred with [BMIM][lactate] and [BMIM][NO_3], but in [MTEAm][$MeSO_4$], IR spectrum in the 1,640–1,670 cm^{-1} region was the same as was in water and thus indicates the preserved secondary structure of the enzyme (Fig. 10.3b) [10].

Thus, with reference to lipase, it seems that loss of water molecules from the microenvironment of the enzyme structure may not be the key for destabilization or deactivation of the enzyme since lipase is fairly stable under anhydrous condition. However, H-bonding nature of the component ions of ILs might be important for maintaining the integrity of the native conformation of the enzyme. At the same time, too strong H-bond could be detrimental due to the disruption of key H-bonds responsible for maintaining native structure which leads to the collapse of the protein framework or unfolding of the protein.

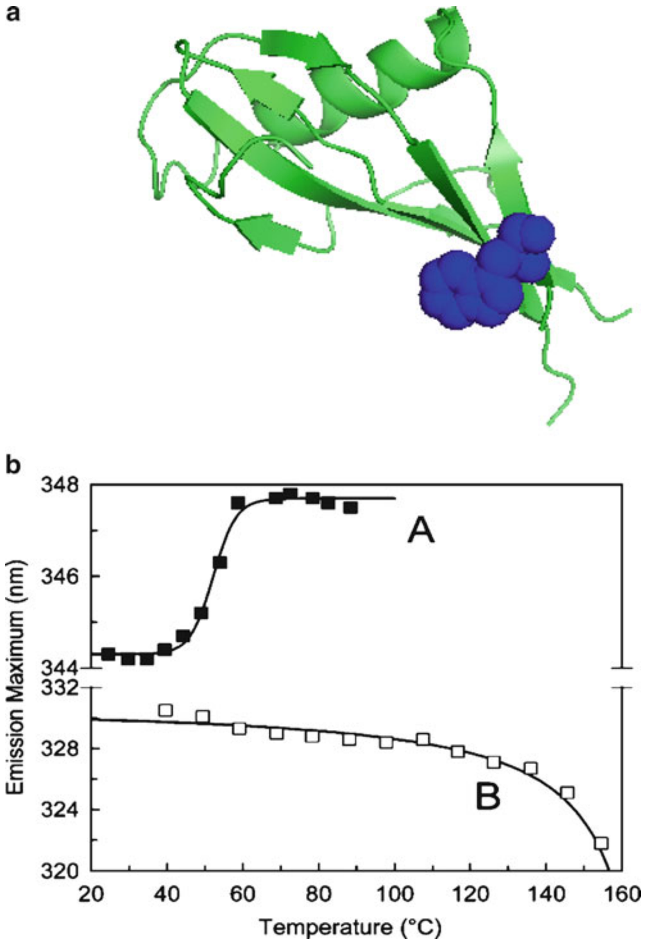


Fig. 10.4 (**a**) Crystallographic structure of monellin (PDB id 4mon); (**b**) Thermal stability of monellin in ILs: change in emission maxima of monellin in water (*filled square*) and in [BMPY][Tf_2N] (*empty square*) (Reproduced from Ref. [48], with kind permission of © The Royal Society of Chemistry)

10.2.2 Stability of Monellin

Monellin is a sweet protein which could be used as artificial noncarbohydrate sweetener. But it denatures at high temperature and becomes unsuitable for food processing. It is a small protein of ~11 kDa containing a single tryptophan residue, a 17 residue α-helix, and an antiparallel β sheet formed by five β strands (Fig. 10.4a). Thus, it is interesting both from application and structural point of view to study the thermal stability of monellin in ILs since ILs are known to have unconventional properties toward preservation of enzyme structure as observed above for lipases.

Baker et al. [48] studied the thermal stability of monellin in [BMPY][Tf_2N] by analyzing the fluorescence emission properties. Trp emission is very sensitive to the milieu around Trp residue. Emission from a well-shielded Trp residue from the bulk solvent undergoes blue shift from the free Trp emission at 350 nm. The temperature-dependent emission profile (Fig. 10.4b) gives a very clear indication of the alteration in the environment around Trp residue as the temperature increases, in water as well as ILs. In water, the emission shifts gradually from 344 nm toward free Trp emission value, i.e., 350 nm, indicating an opening up of the structure and unfolding of protein structure. However, in ILs, Trp in monellin emits at ~330 nm which is highly blue-shifted indicating significant alteration in the microenvironment of protein in IL to completely shield Trp residue. The emission maxima did not change much till 120°C, but when temperature was further increased, there was a gradual blue shift in Trp emission. The authors analyzed the unfolding curve and calculated the thermodynamic parameters from van't Hoff analysis and suggested an entropically driven thermodynamic stability of protein in IL [48]. Based on these results, the authors put forward that IL results in a close-packed structure of monellin giving minimal exposure of Trp residue to the surrounding solvent milieu and ultimately exhibiting higher thermal stability [48].

10.2.3 Stability of Cytochrome c

Cytochrome c (cyt c) is a well-characterized protein studied in ILs to insinuate their protein-stabilizing properties. Fujita et al. [7, 49, 50] studied the temperature-dependent structural changes of cyt c in a range of protein solubilizing ILs having [BMIM], [BMPY], and [choline] as cations and [H_2PO_4], [Bu_2PO_4], [lactate], [acetate], and [$MeSO_4$] as anions. Differential scanning calorimetric (DSC) thermograms of cyt c (Fig. 10.5a) showed absence of any denaturing peak in [BMPY][H_2PO_4] and [choline][H_2PO_4] in 20 wt% water, whereas in water as well as phosphate buffer, DSC traces contain a peak at ~80°C which is indicative of unfolding of cyt c [7]. Further evidence of unfolding event was given by ATR–FTIR spectra (Fig. 10.5b) in which onset of a new band at 1,626 cm^{-1} corresponding to the thermal event in DSC profile occurs at 80°C and 100°C for cyt c in buffer and [choline][H_2PO_4], respectively [49]. Whereas in [BMPY][H_2PO_4], the 1,626 cm^{-1} band is insignificant even at 130°C indicating an elevation of thermal stability of cyt c in these ILs. However, the authors found the unfolding of cyt c at ~60–70°C when water was increased from 20 to 80 wt% in ILs [49].

Fujita et al. [49] further tested the long-term structural integrity of cyt c by superoxide reduction activity assay after storing cyt c in ILs for 3 weeks. They observed a complete loss of activity of cyt c in [BMIM][$MeSO_4$] and [BMIM][lactate], whereas [choline][H_2PO_4] retained the activity of cyt c as good as the fresh buffer solution. The observed activity correlated well with the secondary structure information obtained from ATR–FTIR. No change in amide I bands was observed for cyt c in [choline][H_2PO_4] which is indicative of the intact native structure of cyt c even after

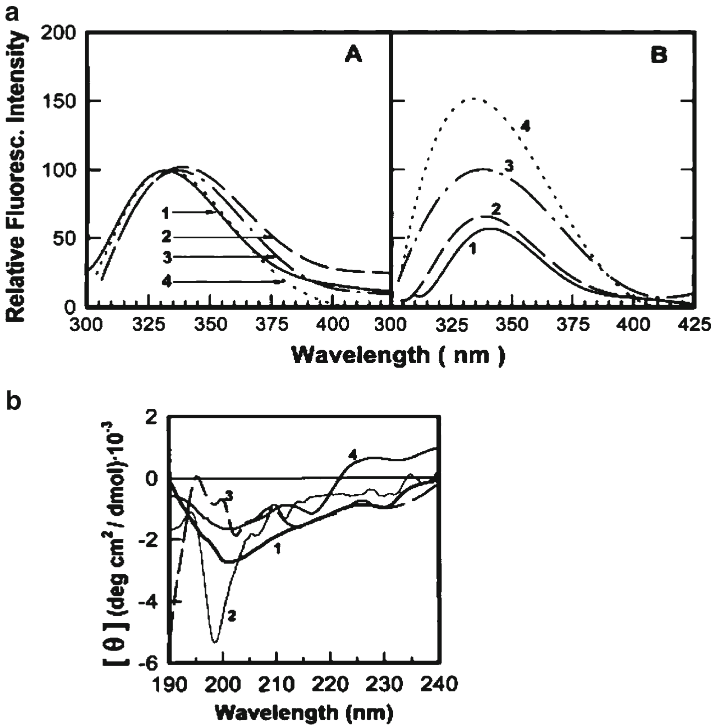


Fig. 10.5 Differential scanning calorimetry profile (**a**) and Amide I region in ATR–FTIR spectra (**b**) of cyt c in ILs (Reproduced from Ref. [7], with kind permission of © The Royal Society of Chemistry)

3 weeks of incubation in IL, whereas in [BMIM][lactate] considerable change in amide I bands pointing toward a loss of secondary structure was observed. They further pinpointed the iron coordination site in heme with the aid of resonance Raman (RR) spectroscopy [49]. As expected, the structural integrity of cyt c in [choline][H_2PO_4] was retained since RR spectrum was same as was in water showing intense bands at 1,372 (ν4), 1,502 (ν3), 1,586 (ν2), and 1,634 (ν10) cm^{-1}. This observation is indicative of a six coordinated iron center in low spin state in oxidized form of heme. However, in [BMIM][lactate] and [BMIM][H_2PO_4], the bands were at 1,355, 1,469, and 1,592 cm^{-1} exhibiting typical characteristics for five coordinated iron center in high spin state in a reduced heme. Hence, based on these results, the authors demonstrated that in [BMIM][lactate], cyt c undergoes changes in both secondary and tertiary structures whereas [choline][H_2PO_4] preserved completely the native structure of cyt c even under long-term storage condition [49]. However, in other ILs such as [BMIM][H_2PO_4] and [BMPY][H_2PO_4], though secondary structure remained unchanged, there was an alteration in tertiary structure as indicated by the change in RR spectra due to modified heme crevice. It is interesting to note that cyt c was stable in [choline][H_2PO_4] for a year which is not possible in aqueous buffer solution [49].

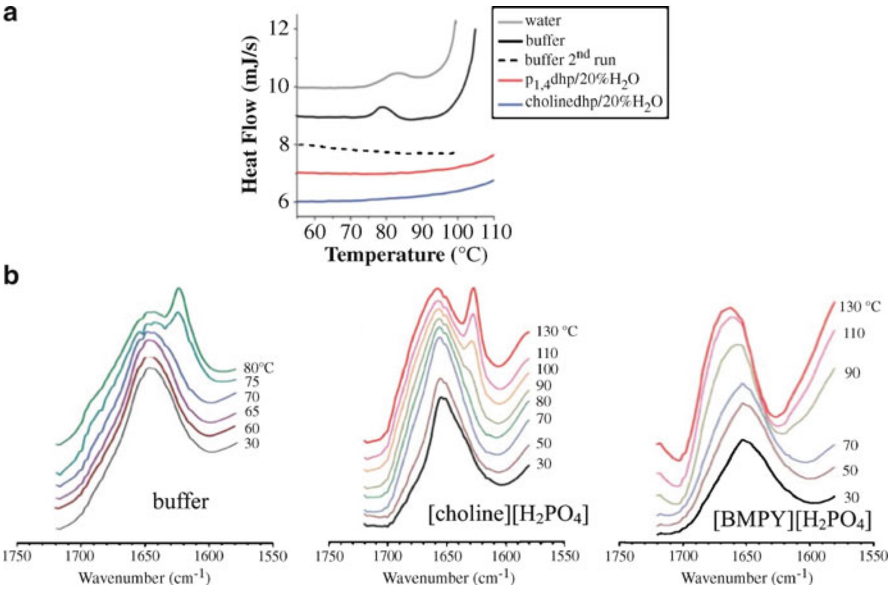


Fig. 10.6 Temperature-dependent (**a**) fluorescence emission profile and (**b**) Far-UV CD spectra of α-chymotrypsin in water (*1*), 3 M sorbitol (*2*), 1-propanol (*3*), and [EMIM][Tf_2N] (*4*) (Reproduced from Ref. [51], with kind permission of © John Wiley and Sons)

10.2.4 Stability of α-Chymotrypsin

Serine protease, α-chymotrypsin is an important enzyme to be studied with respect to stability in ILs owing to its wide application in ester and peptide synthesis. De Diego et al. [51] examined the thermal stability of α-chymotrypsin in [EMIM][Tf_2N] at various temperatures by CD and fluorescence spectroscopy. DSC analysis showed an increase in melting temperature (T_m) by 10°C with a threefold increase in the enthalpy of denaturation in comparison to water indicating an improvement in thermal stability of α-chymotrypsin in [EMIM][Tf_2N]. Further, fluorescence spectrum of α-chymotrypsin was changed significantly in [EMIM][Tf_2N] (Fig. 10.6a) where λ_{em} showed blue-shifting from 340 nm in water to 333 nm with an increase (1.5-fold) in fluorescence intensity (I_{em}) with time over 60 min.. However, the intensity continuously decreased with time in water as well as in sorbitol. Both the changes in λ_{em} and I_{em} are reflective of conformational changes around the Trp residue in the protein as described before. Hence, the blue shift in λ_{em} with increased I_{em} indicates a preserved native structure of α-chymotrypsin in [EMIM][Tf_2N]. This suggests that the IL retained the conserved water layer responsible for the native conformation of the protein by forming a strong ionic matrix around the enzyme. The native-like conformation of α-chymotrypsin was maintained even at 50°C in the IL studied, whereas in water and sorbitol, the enzyme was completely unfolded. CD measurements further help to confirm structural parameters corresponding to native or unfolded configuration of the enzyme. Far UV CD spectrum (Fig. 10.6b) showed different secondary structure in different medium. As evident from the crystallographic study, α-chymotrypsin has highly distorted antiparallel β sheets. Secondary structure parameters calculated from the measured CD spectrum (Fig. 10.6b) revealed that α-chymotrypsin has ~33% β sheets. In [EMIM][Tf_2N], an improvement (47%) in β sheets was observed which was ascribed to a more compact 3D structure and thus CD results were in agreement with the fluorescence data discussed above. Similarly, near UV CD measurements were also in accord with a more tightly packed structure evidenced by the increased intensity of CD bands in 250–300 nm regions. Sorbitol had a similar stabilizing effect but to a lesser extent than IL on the enzyme structure, whereas 1-propanol showed a denaturing effect [44, 46, 52].

10.2.5 Stability of Penicillin G Acylase

Penicillin G acylase (PGA) has pivotal role in industry for the synthesis of penicillin antibiotics. PGA catalyzes the hydrolysis of penicillin and other β-lactam antibiotics to produce 6-amino penicillinic acid [53, 54]. Stability of PGA was investigated by assaying the enzyme activity at different time points after incubation of PGA in various ILs [53]. In the absence of substrate, about 2,000-fold increase in $t_{1/2}$ was observed in a hydrophobic IL, [EMIM][Tf_2N] with respect to *iso*propanol. Whereas in the presence of substrate, PGA showed less stability in $[Tf_2N]^-$ containing ILs. The reverse trend was found for PGA in a water miscible IL [BMIM][PF_6], i.e., PGA showed ~9 times increase in $t_{1/2}$ in [BMIM][PF_6] in the presence of substrate even at an elevated temperature of 40°C [54]. These altered $t_{1/2}$ values in hydrophobic ILs in the presence of substrates were explained on the basis of cumulative outcome of specific interaction of substrates with the active site of enzyme and inhibitory effect of the hydrolytic products formed in the reaction medium. It can be speculated that in a more hydrophilic IL like [BMIM][PF_6], substrates shield the enzyme active site from direct interaction with the ionic matrix and thus imparts a stabilizing effect whereas in hydrophobic IL [EMIM][Tf_2N], the inhibitory effect of hydrolytic products predominates and destabilizes the enzyme.

The studies discussed above gives an idea of conformational stability of proteins in ILs as inferred from the $t_{1/2}$ measurement and melting temperature determination followed by various spectroscopic methods. However, stability of a protein/enzyme has contributions from both thermodynamic and kinetic parameters [55]. While thermal unfolding studies help to extract important thermodynamic parameters, stability of the proteins could also arise from the kinetic barrier to the conformational changes in the protein scaffold [55]. However, except for monellin [48], the thermodynamic stability in other cases has not been examined. Thus, in context of stability of proteins/enzymes in ILs, it is important and imperative to study and probe thermal unfolding as well as the thermodynamics and kinetics of the conformational change of the proteins in ILs.

10.3 Methods of Stabilizing Proteins/Enzymes in Ionic Liquids

The issue of enzyme/protein stabilization per se is an age old issue. Out of the large number of methods used in literature, one of the convenient attempts is to enhance the stability of the enzymes by immobilizing them on various support systems (Fig. 10.7) [56]. The phenomenal stabilizing effect of some ILs on particular proteins and enzymes increasing their $t_{1/2}$ and thermal stability parameters is encouraging enough to develop methods to overcome the problem of enzyme deactivation issues using ILs. From the discussions in previous sections, it is clear that the interaction of the ILs with the enzymes and proteins is a complex phenomenon. Hence, there is no universal rule to stipulate enzyme stability/activity in ILs. However, several methods have been developed for using ILs as immobilization support to address the enzyme deactivation issues. There are also other modification methods by glutaraldehyde cross-linking of enzymes, poly(ethylene)glycol (PEG) modification of enzymes, and/or ILs and emulsification of ILs [57]. Some of the illustrative methods are summarized in this section.

10.3.1 Stabilization by Ionic Liquid Coating

There are distinct methods to improve the enzyme stability either by simple coating of enzymes by ILs or by noncovalent adsorption or by covalent linking of the enzymes with the solid supports such as polymers, nanoparticles, carbon nanotubes, and encapsulation in hydrogels. One of the interesting and new features of ILs as an immobilization support for enzymes evolved out of its incompetence for retaining

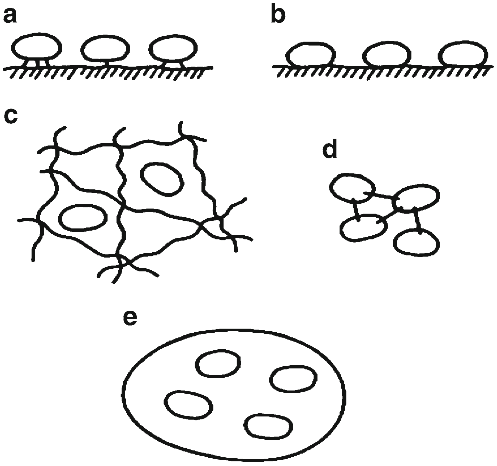


Fig. 10.7 Various immobilization strategies: (**a**) covalent attachment, (**b**) physiosorption, (**c**) entrapment in gel, (**d**) intermolecular cross-linking, and (**e**) encapsulation (Reproduced from Ref. [56], with kind permission of © The Academic Journals)

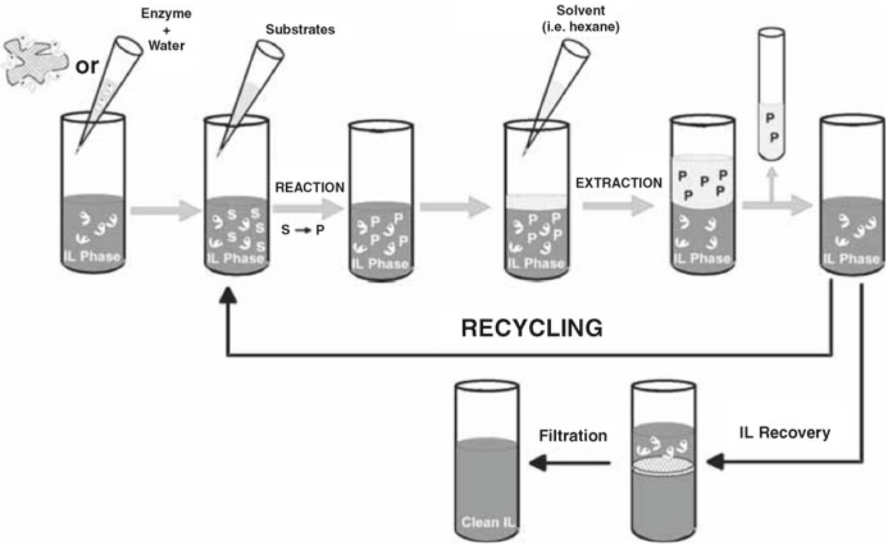


Fig. 10.8 Strategy of recycling and recovery of ILs for enzyme catalysis in ILs (Reproduced from Ref. [59], with kind permission of © Springer Verlag-Berlin)

enzyme activity when enzyme is dissolved in neat anhydrous ILs having high miscibility with water. But hydrophobic water-immiscible ILs could be used as anchor points to hold enzymes in the strong ionic matrix. Lee and Kim were the first to exploit this interesting feature of IL and prepared an ionic liquid–coated enzyme (ILCE) by simply mixing lipase from *Pseudomonas cepacia* (PcL) and [PMIM][PF_6] [58]. Such ILCE showed remarkably high enantioselectivity for transesterification reaction of several secondary alcohols in the presence of vinyl acetate in toluene, and there was no significant deterioration in activity even after multiple (five times) use. Horseradish peroxidase (HRP) is another example to be coated with both hydrophobic and hydrophilic ILs such as [BMIM][Tf_2N] and [BMIM][PF_6] toward enzymatic synthesis of polyaniline [23]. An attractive point of the ILCE-based immobilization method is easy recovery of enzyme/IL phase by liquid–liquid phase separation and effective reusability of the enzyme (Figs. 10.8, 10.9) [23, 59].

10.3.2 Stabilization by Anchoring with Carbon Nanotubes

The other immobilization methods include carbon nanotubes and nanoparticles. Poly(glycidyl methacrylate)-grafted multiwalled carbon nanotubes (MWNT) were covalently attached to *N*-butyl imidazolium bromide. An indium tin oxide (ITO) electrode coated with such MWNT-IL successfully immobilized tyrosinase and showed sensing response toward phenol at the range of 0.01–0.08 mM at ambient pH and temperature [60]. Similarly, glassy carbon (GC) electrode was coated with

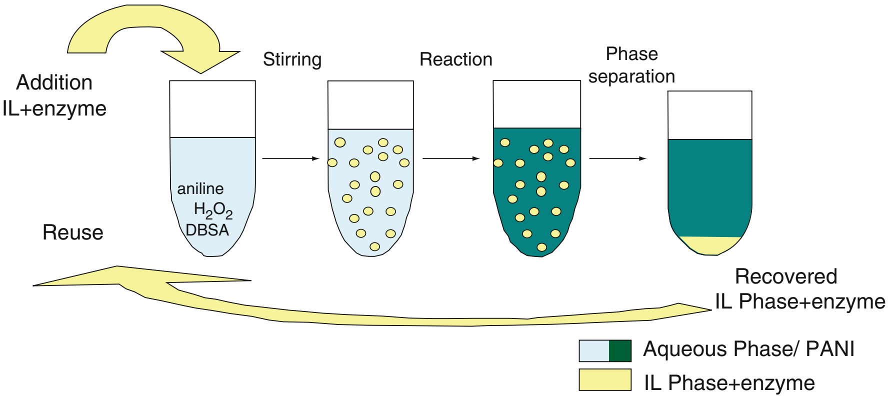


Fig. 10.9 Enzyme catalysis in ILs/water biphasic system (Reproduced from Ref. [23], with kind permission of © The American Chemical Society)

nanocomposites of single-walled carbon nanotubes (SWNT) and [BMIM][PF_6] or [BMIM][BF_4] (formed by simple grinding of SWNT and ILs) and used for immobilization of heme-containing proteins such as cyt c, HRP, and myoglobin (Mb) [61]. The structural integrity of the heme proteins/enzymes was maintained as observed from the unchanged Soret band in UV-visible spectroscopy and CD spectroscopy. Such an immobilization environment could also retain the electrocatalytic activity of the proteins/enzymes toward reduction of oxygen and hydrogen peroxide [61]. This is in contrast to the observed inactivity and denaturation in hydrophilic IL upon direct dissolution of proteins/enzymes in ILs such as [BMIM][BF_4] [24, 62]. Apart from the electrode-based immobilization methods, SWNT and MWNT are also used to physically adsorb enzymes and showed good activity in ILs. Lipase (CrL) could adsorb on MWNT and show eight times high conversion than the free enzyme with more than 99% ee toward transesterification reaction in [BMIM][PF_6] [63]. Likewise, noncovalently adsorbed proteinase-K on SWNT exhibited enhanced thermal stability and higher catalytic efficiency in hydrophobic ILs such as [BMIM][PF_6] [62].

10.3.3 Stabilization by Capping with Nanoparticles

Core-shell nanoparticles with silica shell and ferrite nanoparticles at the core can be covalently attached to ILs. Such IL conjugates/composites were able to load high amount (64%) of lipase (CrL) by ionic adsorption [64]. These nanoparticle-ILs-bound lipases showed ~118% more activity than native enzyme at room temperature. Even at 80°C and eight times repeated use, the enzyme retained 60% of its activity whereas free enzyme loses all its activity within six cycles [64]. The high loading and catalytic efficiency of the enzymes on nanostructured materials are ascribed to the high surface area of nanoparticles. In another study, cyt c entrapped in polymeric nanoparticles (fluoroalkyl end-capped acrylic acid oligomers having poly(oxyethylene) units) showed high dissolution in [EMIM][Tf_2N] and [BMIM][Tf_2N] and markedly high (~28 times) catalytic efficiency toward guaiacol oxidation with hydrogen peroxide in 50% aqueous [MP][BF_4] [65]. Enhanced activity is also observed when *Rhus vernificera* laccase (RvL) and lipase (CaLB) are immobilized on cellulose composites of [BMIM][Cl] [66].

10.3.4 Stabilization by Entrapment in Hydrogels

Entrapment in sol–gel matrix is an interesting method of stabilization of proteins/enzymes. HRP immobilized on a sol–gel matrix containing [BMIM][BF_4] showed higher stability and catalytic activity compared to the matrix without ILs [26]. Such a system having micromolar detection sensitivity has been constructed toward application as a biosensor for electrochemical sensing of hydrogen peroxide [26]. Heme proteins such as Mb, hemoglobin (Hb), cyt c, and HRP were also stabilized by encapsulation in agarose hydrogels, and the entrapped proteins/enzymes exhibited good electrocatalytic activity toward reduction of trichloroacetic acid and *ter*-butyl peroxide in hydrophobic IL [BMIM][PF_6] and 5% aqueous solution of hydrophilic IL [BMIM][BF_4]. The authors noted that anhydrous [BMIM][BF_4] deactivates the enzyme. However, the structural integrity of proteins/enzymes as interpreted by the authors from the redox potential determination is not very clear [24, 67, 68].

10.3.5 Stabilization by Enzyme Modification

Cross-linking the enzymes via glutaraldehyde is a well-known approach to enhance the enzyme stability. This approach is also used to design several enzyme formulations with or without polypropylene supports. Cross-linked enzyme crystals (CLEC) and cross-linked enzyme aggregates (CLEA) with lipase have been prepared and used successfully in enzyme denaturing ILs such as [BMIM][DCA],[BMIM][NO_3], [BMIM][lactate], and [BMIM][CH_3COO] with considerably high catalytic activities and stereoselectivity [69, 70]. Modification of enzymes by covalent or noncovalent linking with PEG is also a useful method of enzyme stabilization. PEG (Mw 4,000–35,000) modified lipases showed ~14-fold higher activity than unmodified enzyme for alcoholysis reaction in hydrophobic ILs [71, 72]. Similarly, cellulase modified with PEG (Mw 1,000) also showed higher enzyme activity in [BMIM][Cl] than free enzyme but PEG (Mw 1,000) modified α-chymotrypsin showed no significant enhancement in reactivity in [BMIM][PF_6] [73]. This disparity in results clearly demonstrates that there is no universal rule of stabilizing enzymes/proteins in ILs. It gives an undeniable indication that various factors such as overall charge distribution of the protein/enzyme surface, chaotropicity/kosmotropicity of the cations and anions of the ILs influences the enzyme stability and activity in ILs. In addition to modification of enzymes, ILs also have been modified and functionalized to improve substrate solubility and enzyme dissolution ability [74].

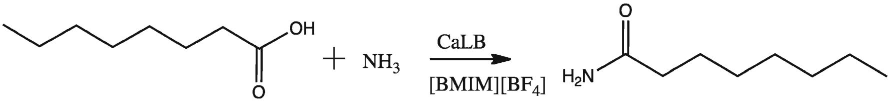
10.3.6 Stabilization by Emulsification of Ionic Liquids

ILs have also been emulsified by using surfactants. Lipases showed higher hydrolytic activity in water–IL [OMIM][Tf_2N] emulsions compared to that in water–isooctane emulsions. Effective activity of HRP is also observed in these IL emulsions [75]. Similarly, lignin peroxidase, alcohol dehydrogenase, and laccase were found to show higher catalytic activity in an emulsified medium containing [BMIM][PF_6] and triton X-100 in comparison to the medium having pure ILs [76, 77]. Lipases from *Chromobacterium viscosum* (CvL), *Thermomyces lanuginosa* (TlL), and CrL exhibited much higher conformational stability as well as activity in emulsions containing [BMIM][PF_6], Tween 20, or Triton X-100 [78].

10.4 Catalytic Activity of Enzymes in Ionic Liquids

10.4.1 Biotransformations by Lipases and Esterases

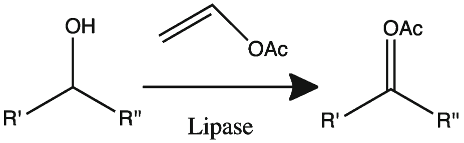
One of the extensively studied enzymes in ILs is lipase. Lipases are known to readily catalyze a wide range of reactions such as esterification, transesterification, ammoniolysis, and perhydrolysis (Scheme 10.1). Madeira Lau et al. [15] were the first to use neat ILs such as [BMIM][BF_4] and [BMIM][PF_6] as reaction medium for CaLB [15]. They observed that CaLB either in free form (SP525) or in immobilized form (Novozym 435) catalyzes reactions like transesterification and ammoniolysis with better or at least comparable reaction rates in comparison to conventional organic solvents. The transesterification reaction of ethyl butanoate with butanol yielded butyl ester as reaction product in more than 80% yield in both [BMIM][BF_4] and [BMIM][PF_6] with negligible effect of anions on the reaction rate [15]. Both the reaction rate and the product yield (~74%) were slightly lower in *ter*-butanol. On the other hand, ammoniolysis reaction of ethyl octanoate to octanamide was found to have significantly lower product yield in comparison to *tert*-butyl alcohol [15]. However, product yield was subsequently improved to 99% upon addition of ammonia to the reaction mixture albeit with a longer reaction time of 4 days in contrast to 24 h in *tert*-butyl alcohol.



Scheme 10.1 Example of lipase-catalyzed biotransformations (Reproduced from Ref. [15], with kind permission of © The American Chemical Society)

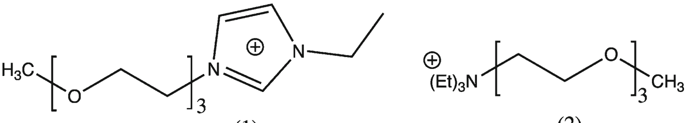
10.4.1.1 Esterification and Transesterification Reaction

Lipase (CrL)–catalyzed enantioselective esterification of ibuprofen takes place with approximately double E value (24) in [BMIM][PF_6] in comparison to 13 in isooctane [79]. Not only lipases are effective in ILs with improved or comparative performance like in conventional organic solvents but remarkably high enantioselectivity has also been observed when transesterification reaction was carried out in ILs. Lipase (CaLB and PcL)-catalyzed transesterification reaction on various substrates has been found to proceed with considerably high enantioselectivity of more than 99.5% in [EMIM][BF_4] and [BMIM][PF_6] (Scheme 10.2) [80]. Further, the kinetics of lipase-catalyzed transesterification reaction has been altered by using a promising IL containing phosphonium ion, i.e., [$MEBu_3P$][Tf_2N]. Remarkably high reaction rate of 1,000 mM/mg enzyme h^{-1} was obtained with [$MEBu_3P$][Tf_2N] in comparison to the rate ~300–400 mM/mg enzyme h^{-1} in other ILs and other common organic solvents except in DIPE [81].



Scheme 10.2 Transesterification reaction catalyzed by lipase (Reproduced from Ref. [80], with kind permission of © The American Chemical Society)

Though synthesis of long-chain fatty acid esters of carbohydrates is potentially useful, but the solubility of carbohydrates in ILs suitable for enzyme activity has been a limiting factor [10, 47, 70]. High solubility of carbohydrates without any compromise on enzyme activity has been obtained in ILs containing imidazolium ring grafted with glycol substituents (Scheme 10.3), i.e., [MTEOEIM][CH_3COO] and [MTEOTEAm][CH_3COO] which dissolve ~10% (wt) cellulose and ~80% (wt) D-glucose [47, 74]. Lipase (using both CaLB and Novozyme 435)-catalyzed transesterification reaction between D-glucose and vinyl laurate was successful with a high yield of 85% and high regioselectivity [47]. Synthesis of polyester catalyzed by CaLB is successfully carried out in ILs such as [BMIM][BF_4] and [BMIM][PF_6] at 60°C though with products having lower molecular weight than the conventional system [82–84].



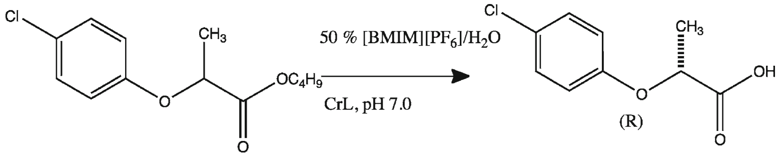
(1) (2)

Scheme 10.3 Structure of glycol-grafted ionic liquids (1) MTEOEIM and (2) MTEOTEAm (Reproduced from Ref. [47], with kind permission of © The Royal Society of Chemistry)

10.4.1.2 Enantioselective Hydrolysis Reaction

Hydrolysis of 2-(4-chlorophenoxy)propionic ester is nonselective in aqueous buffer (Scheme 10.4). When 50% aqueous mixture of [BMIM][PF_6] is used in the presence of lipase (CrL), the enantioselectivity increases remarkably with more than

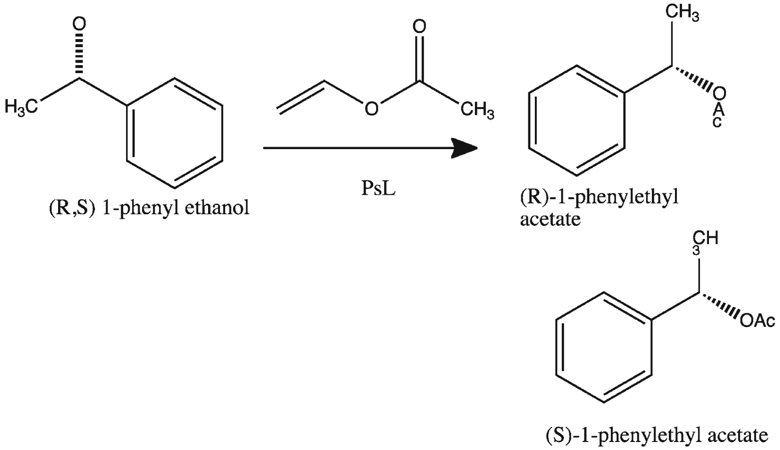
99% ee though with a compromise on reaction rate which was 30–40 times slower than in aqueous medium [85].



Scheme 10.4 Example of enantioselective hydrolysis reaction (Reproduced from Ref. [85], with kind permission of © Elsevier)

10.4.1.3 Enantioselective Acylation Reaction

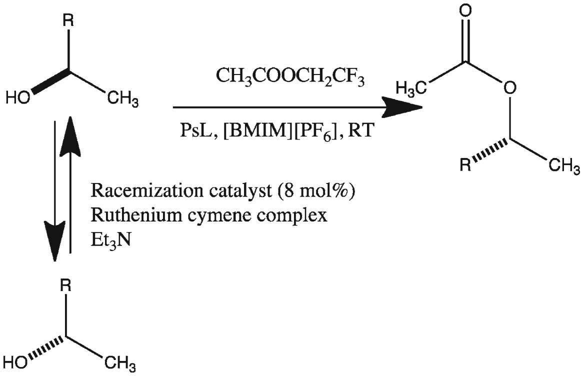
Lipase (PsL)-mediated acylation reaction of α-methyl benzyl alcohol by vinyl acetate (Scheme 10.5) gives high enantioselectivity (E value 200) in [BMIM][Tf_2N] than in methyl *ter*-butyl ether (MTBE) (E=4) at 55°C. At the boiling point of vinyl acetate, the E value was reduced to 150 from 200 [86, 87]. Similarly, lipase from *Pseudomonas fluorescens* (Lipase AK)-catalyzed enantioselective acylation of phosphate substituted primary alcohols in [BMIM][PF_6] with enantioselectivity comparable to DIPE, though no selectivity was obtained in [BMIM][BF_4] [87].



Scheme 10.5 Enantioselective acylation reaction of 1-phenyl ethanol (Reproduced from Ref. [86], with kind permission of © Springer Verlag-Berlin)

10.4.1.4 Kinetic Resolution of Alcohols

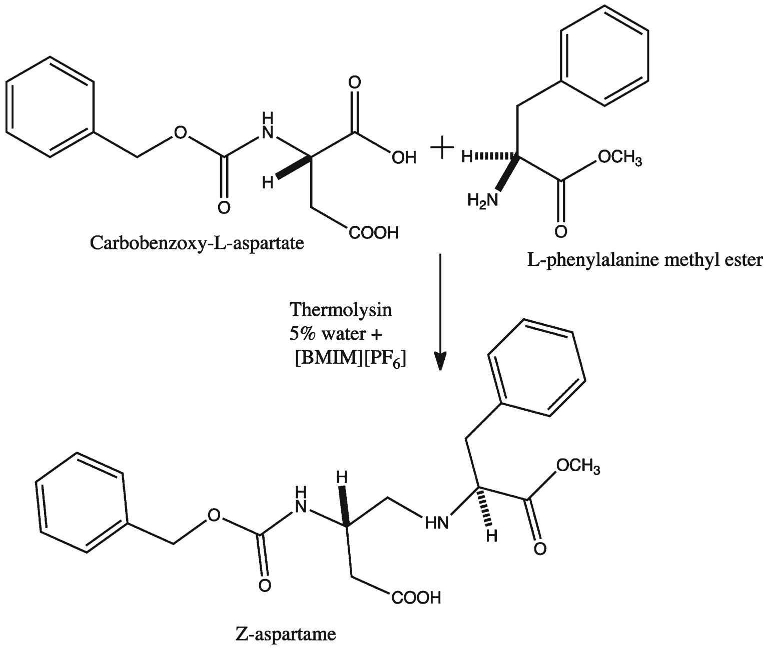
Dynamic kinetic resolution (DKR) is an important and useful method to generate enantiomerically pure compounds from racemic substrates [87]. In this case, an in situ racemization of slow reacting enantiomer of chiral alcohol has been successfully carried out by metal–enzyme catalyst where metal complex acts as a racemizing catalyst (Scheme 10.6) [88]. The racemization was found to be more efficient in [BMIM][PF_6] than in toluene. Lipase and subtilisin in combination with ruthenium cymene complex have been chosen as DKR catalysts for dynamic resolution. Lipase and subtilisin being opposite in their enantiopreference, racemic alcohols could be transformed to enantiomerically rich (R)- and (S)-esters, respectively. Similarly, a serene endoprotease Bl-alcalase from *Bacillus licheniforms* catalyzes enzymatic resolution of homophenylalanine ester. It shows a decrease in enantioselectivity with increasing concentration of IL in the reaction medium which correlates to the decrease in stability of the enzyme at that concentration of IL [89].



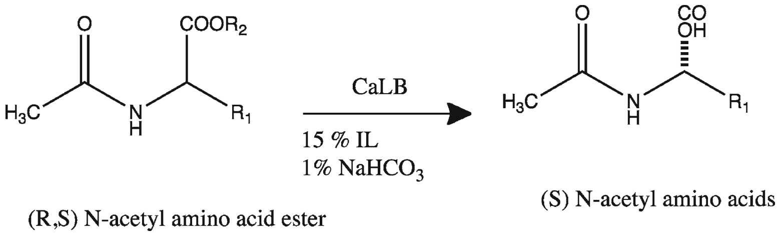
Scheme 10.6 Dynamic kinetic resolution of chiral alcohols (Reproduced from Ref. [88], with kind permission of © The Royal Society of Chemistry)

10.4.2 Reactions Catalyzed by Proteases

The first protease-catalyzed reaction in ILs was the Z-aspartame synthesis (Scheme 10.7) from carbobenzoxy-L-aspartate and L-phenylalanine methyl ester catalyzed by thermolysin in [BMIM][PF_6] [14]. Subtilisin is a serine protease responsible for the conversion of *N*-acyl amino acid ester to the corresponding amino acid derivatives. Zhao et al. [90] have used subtilisin in water with 15% [EtPy][CF_3COO] as cosolvent to hydrolytically convert a series of *N*-acyl amino acid esters often with higher enantioselectivity than with organic cosolvent like acetonitrile (Scheme 10.8, Table 10.2). They specifically achieved L-serine and L-4-chlorophenylalanine with an enantiomeric access (ee) of ~90% and ~35% product yield which was not possible with acetonitrile as a cosolvent [90]. Another example is hydrolysis of *N*-unprotected amino acid ester in the presence of a cysteine protease known as papain. Liu et al. [91] have shown an improved enantioselectivity in the hydrolytic reaction catalyzed by papain in 80% [BMIM][BF_4] in comparison to acetonitrile as a cosolvent. Whereas with subtilisin, the same reaction gave a very low enantiomeric access in [BMIM][BF_4]. But subtilisin-catalyzed hydrolysis of phenylalanine methyl ester gave high enantiomeric access of ~90% in 0.5 M of ILs containing chiral or ω-amino acid anions and [EMIM]$^+$ cation [92]. However, with increase in concentration of ILs to 1 M, the enantioselectivity remarkably suffered. Peptide amidases are another type of proteases which have been studied in ILs, for example, [BMIM][$MeSO_4$] has been used for the amidation reaction of dipeptide H-Ala-Phe-OH, where only 15% of product yield was reported after 12 h of reaction [93].



Scheme 10.7 Thermolysin-catalyzed synthesis of Z-aspartame (Reproduced from Ref. [14], with kind permission of © John Wiley and Sons)



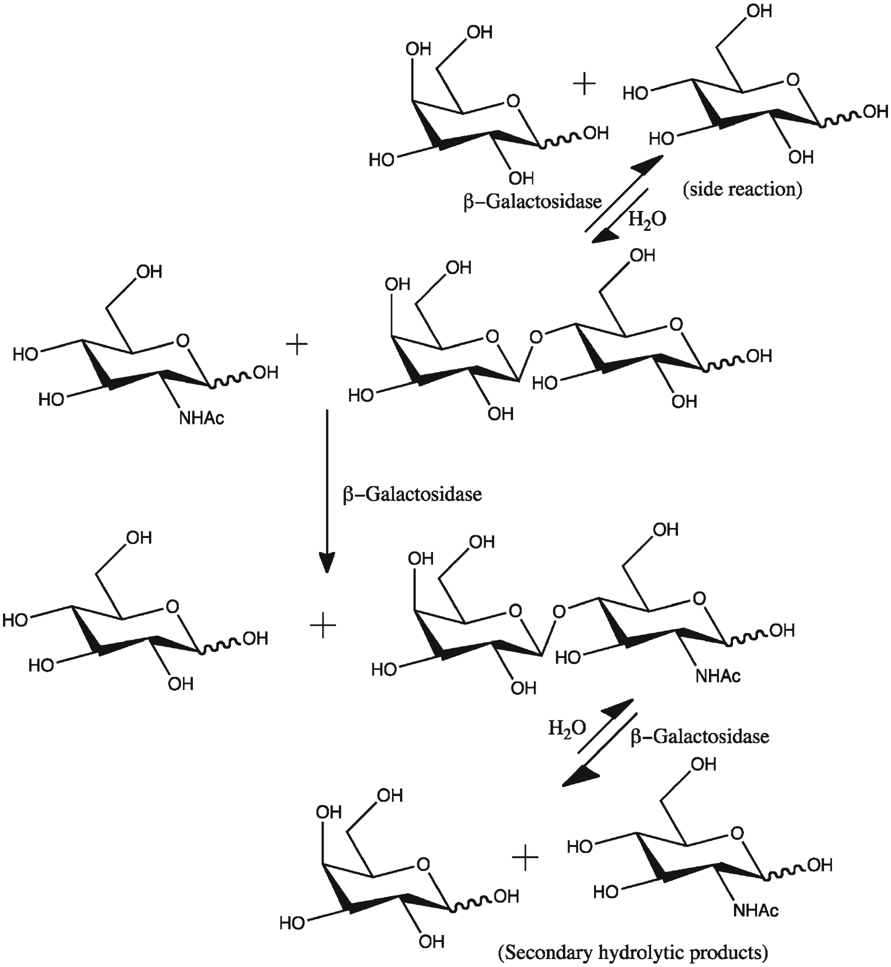
Scheme 10.8 Enantioselective hydrolysis of *N*-acetyl amino acid esters (Reproduced from Ref. [90], with kind permission of © Springer Verlag-Berlin)

Table 10.2 Enantioselective hydrolysis of *N*-acetyl amino acid esters (Reproduced from Ref. [90], with kind permission of © Springer Verlag-Berlin)

		Acetonitrile		[EtPy][CF$_3$COO]	
R$_1$	R$_2$	ee(%)	Yield (%)	ee(%)	Yield (%)
CH$_3$	C$_2$H5	63	31	86	33
CH$_2$OH	CH$_3$	NA	NA	90	35
CH$_3$CH(OH)	CH$_3$	92	15	97	36
CH$_3$S(CH$_2$)$_2$	CH$_3$	83	30	89	29
C$_6$H$_5$(CH$_2$)$_2$	C$_2$H$_5$	95	35	93	38
P–Cl–C$_6$H$_4$CH$_2$	C$_2$H$_5$	NA	NA	96	39
CH$_3$(CH$_2$)$_3$	CH$_3$	18	32	88	30

10.4.3 Carbohydrate Synthesis by Glycosidases

Due to the implication in the fundamental structure of glycoproteins and glycolipids, synthesis of oligosaccharides like *N*-acetyllactosamine has been important from pharmacological and immunological point of view [87]. Remarkable β-1,4 selectivity and synthesis of regioisomerically pure oligosaccharide have been achieved in the enzymatic catalysis by β-galactosidase [32]. But a limitation in product yield is the secondary hydrolysis product (Scheme 10.9) [32]. The β-galactosidase-catalyzed transgalactosylation reaction between lactose and *N*-acetylglucosamine in [MMIM][MeSO$_4$]–water mixture (1:4) (vol/vol) results in the formation of *N*-acetyllactosamine with improved selectivity and yield 58%

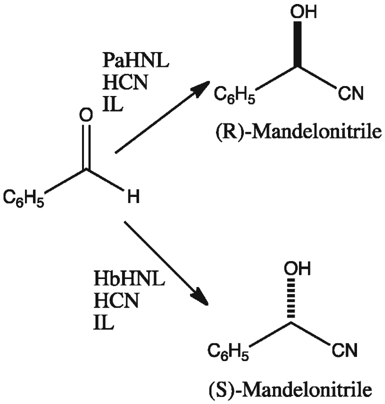


Scheme 10.9 β-Galactosidase-catalyzed transgalactosylation reaction (Reproduced from Ref. [32], with kind permission of © The American Chemical Society)

(Scheme 10.9). The same reaction in aqueous buffer gives only 30% product yield and substantially low selectivity over time due to secondary hydrolysis reaction which was found to be suppressed by IL [32]. The authors found no reduction in enzyme activity after three times of repeated use in [MMIM][$MeSO_4$], indicating good stability of the enzyme in such a medium. However, in this case, rate of hydrolysis of both lactose and *N*-acetyllactosamine was lower which is ascribed to the reduced water activity value. Similarly, β-galactosidase-catalyzed galactosylation reactions of various alcohols have been investigated in [MMIM][$MeSO_4$] [87, 93, 94].

10.4.4 Hydrocyanation Reaction by Lyases

The catalytic application of hydroxynitrile lyases (HNL) toward hydrocyanation reaction of aldehydes or ketones is no longer a laboratory curiosity rather has found potential interest as industrial biocatalyst [95–98]. Although (R)-selective *Prunus amygdalus* HNL (PaHNL) and (S)-selective *Hevea brasiliensis* HNL (HbHNL) have been found to be highly stereoselective, a competing nonenzymatic background reaction has undermining effect in the enantioselectivity [87]. The detrimental effect of the background reaction was suppressed by changing the reaction system from purely aqueous medium to biphasic organic aqueous mixture because of resultant low reactant concentration in the aqueous medium. Hence, in the light of the success of ILs especially in lipase-catalyzed reactions, Gaisberger et al. [99] carried out conversion of several aldehydes in ILs such as [EMIM][BF_4], [PMIM] [BF_4][BMIM][BF_4] catalyzed by both PaHNL and HbHNL (Scheme 10.10, Table 10.3). Surprisingly, when the reaction was carried out in neat ILs with trace amount of water (1%), only racemic mixture was obtained. However, ee was accelerated and more than 95% ee was obtained in a 50% aqueous mixture of the same ILs with PaHNL [99]. But since the reaction is done at low pH to suppress the nonenzymatic reaction and HbHNL is less stable at such low pH, it yielded a low ee value. The most remarkable achievement was with longer chain aldehydes as



Scheme 10.10 HNL-catalyzed cyanohydrin reaction (Reproduced from Ref. [99], with kind permission of © Elsevier)

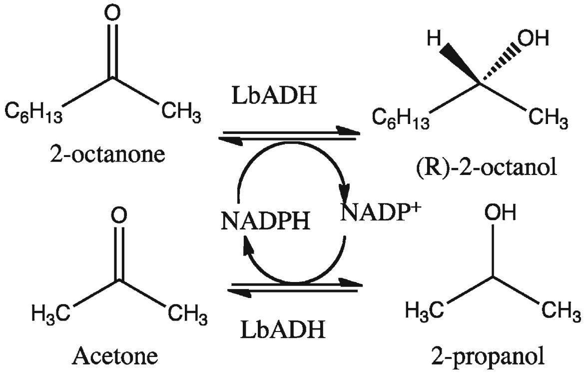
Table 10.3 HNL-catalyzed yield and ee of mandelonitrile (Reproduced from Ref. [99], with kind permission of © Elsevier)

Enzyme	Solvent	Yield (%)	ee (%)
HbHNL	[EMIM][BF_4]	98	80
HbHNL	[PMIM][BF_4]	86	74
HbHNL	[BMIM][BF_4]	98	24
PaHNL	[EMIM][BF_4]	98	93
PaHNL	[PMIM][BF_4]	95	96
PaHNL	[BMIM][BF_4]	97	97

substrates, where both product conversion and ee were found to be high in [PMIM][BF_4] than in the conventionally used organic solvent MTBE when reaction was catalyzed by PaHNL at pH 3.8.

10.4.5 Biocatalytic Redox Reactions by Oxidoreductases

Among the various oxidoreductases studied in ILs, alcohol dehydrogenase from *Lactobacillus brevis* (LbADH) drew attention because of the remarkably different partitioning behavior of 2-propanol and acetone in a biphasic reaction system of aqueous buffer and [BMIM] [Tf_2N] than in buffer-organic solvent methyl *ter*-butyl ether (MTBE) [100]. Partition coefficients (m) of 2-propanol and acetone are approximately equal in buffer-MTBE whereas in buffer-IL, 2-propanol has an m value of 0.4 indicating its higher preferential distribution in aqueous phase. But acetone (a known inhibitor of alcohol dehydrogenase) that resides in preferably in IL phase has m value 2.0 (five times higher than 2-propanol). This difference in partitioning behavior of substrate and product shifts the thermodynamics of cofactor regeneration favorably which is a rate-limiting step in the reduction reaction of ketone to alcohol catalyzed by alcohol dehydrogenase (Scheme 10.11) [100]. Thus, alcohol dehydrogenase from *Lactobacillus brevis* (LbADH) has been found to give higher reaction rates in the ILs in comparison to MTBE toward conversion of 2-octanone to (R)-2-octanol with an ee of more than 99%. LbADH also has substantially good

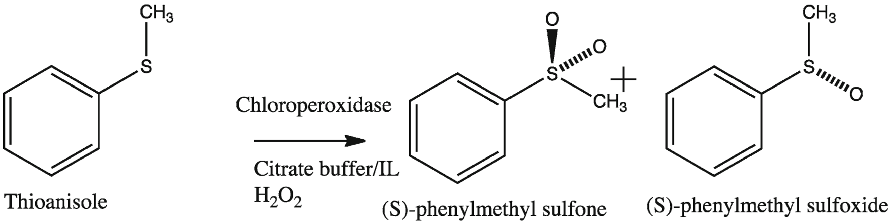


Scheme 10.11 Reduction of 2-octanone mediated by LbADH and substrate-coupled NADPH regeneration of 2-propanol (Reproduced from Ref. [100], with kind permission of © The Royal Society of Chemistry)

stability in the IL having a $t_{1/2}$ value of 50 h [100]. Alcohol dehydrogenase has also been studied in hydrophilic neat ILs in the context of detrimental effect of hydrogen bonding between the enzyme and the ions of ILs [101].

Most industrially driven biocatalytic redox reactions are studied using whole-cell biocatalysts [102–105]. One such example is asymmetric reduction of 4-chloroacetophenone to (R)-1-(4-chlorophenyl)ethanol in [BMIM][Tf_2N] with *Lactobacillus kefir* [104]. Without any destructive effect on the cell membranes, the chemical yield of the product chlorophenylethanol was found to be doubled (93%) in [BMIM][Tf_2N] with an ee of ~100% in comparison to 46% product yield in MTBE. In other ILs like [BMIM][Tf_2N] and [OMA][Tf_2N], though 30% degradation of the cell membrane was observed like organic solvents, the product yield was still better than MTBE. The advantage of the whole system studied in this case is an infinite cofactor turnover number since the reaction proceeds even in the absence of any additive redox equivalent like nicotinamide adenine dinucleotide phosphate (NADPH). Similarly, Baker's yeast–catalyzed reduction of a range of ketones to corresponding alcohol has also been studied in [BMIM][PF_6]. The performance was comparable to conventional aqueous–organic reaction medium [106]. Whole-cell catalysis by *E. coli* expressed cyclohexane monooxygenase has been studied toward regioselective oxidation of bicyclo[3.2.0]hept-2-en-6-one to lactone in [BMIM][PF_6] with no enhanced performance compared to the native aqueous reaction medium [87].

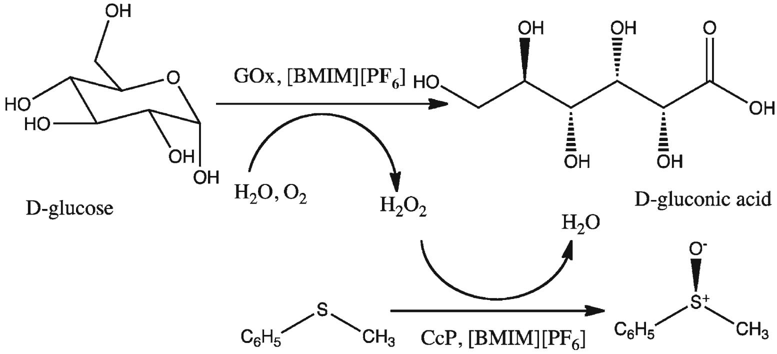
Comparatively, less-studied system is the peroxidase-catalyzed oxidations. One such example is the enantioselective oxidation of phenylmethylsulfide catalyzed by chloroperoxidase from *Caldariomyces fumago* in several buffer-IL mixtures at different pH values (Scheme 10.12) [107]. In this case, the chloroperoxidase-catalyzed sulfoxidation showed 70% product yield and above 99% ee, in ILs like [MMIM][Me_2PO_4] and cholinium acetate and cholinium citrate. But for the same sulfoxidation reaction catalyzed by chloroperoxidase, complete loss of enzyme activity was observed in morpholine containing ILs and [MMIM][$MeSO_4$] [107]. The authors have pointed out that the addition of IL to the reaction medium influences the pH level and enzyme activity. For example, addition of 30% (vol/vol) [MMIM][Me_2PO_4] increases the pH of a potassium phosphate buffer solution from 2.7 to 3.7. Enzyme activity of chloroperoxidase was significantly reduced at pH 2.7 which was recovered by increasing the pH to 3.7. (Note: The authors have chosen potassium



Scheme 10.12 Chloroperoxidase-mediated sulfoxidation reaction (Reproduced from Ref. [107], with kind permission of © Elsevier)

phosphate buffer which does not have good buffering capacity at such low pH. So it is not surprising that pH was altered with the addition of ILs. It should be checked with a suitable buffer system for low pH.)

Similarly, *Coprinus cinereus* (CcP) peroxidase–catalyzed conversion of thioanisole to sulfoxides has been studied in [BMIM][PF_6] in a biphasic reaction medium [108]. Ten percent water in IL was found to be optimum for reaction in this case giving a moderate product conversion of ~30%, with ~70% enantiomeric purity (Scheme 10.13) [108]. In situ generation of hydrogen peroxide by autoxidation of glucose in the presence of glucose oxidase in [BMIM][PF_6] could add an additional point in the unconventional properties of ILs as pointed out by Rantwijk and Sheldon [87].



Scheme 10.13 GOx-peroxidase-mediated enantioselective sulfoxidation of thioanisole (Reproduced from Ref. [108], with kind permission of © Elsevier)

The other noteworthy oxidoreductase system is the redox activity of polyethylene oxide modified cyt c in [EMIM][CF_3MeSO_2] by optical waveguide spectroelectrochemical analysis [109]. Cyt c was effectively dissolved in IL due to the polyethylene oxide side chains and found to be stable over a period of a month [109]. But the report also confirms that organic bulky ions in ILs do not offer any advantage rather are disadvantageous for electron transfer reactions of proteins having shielded cofactor inside the folded polypeptide domain since no cyclic voltammogram of polyethylene oxide coated cyt c was detected in IL.

10.4.6 Enzymatic Polymerization Reaction in Ionic Liquids

Enzymatic polymerization reaction has gained great interest since biodegradable polymer synthesis could be achieved without the use of toxic catalysts [110]. Due to the possibility of high performance of enzymes in ILs, a large number of polymer synthesis reactions have been carried out in ILs. First of such reactions was studied in [BMIM][BF_4] and [BMIM][PF_6] at 60°C using lipase from *C. antarctica* demonstrating the production of high molecular weight polymers by a ring-opening polymerization of ε-caprolactone [84]. Lipase from the same source has also been as a catalyst for the synthesis of poly(hydroxyalkanotes) with higher conversion in [BMIM][PF_6] and [BMIM][Tf_2N] than in water miscible ILs like [BMIM][DCA] [111]. The reduction in product formation has been attributed to the decrease in lipase activity in highly polar ILs [18, 88]. Phenolic polymerization in aqueous mixture of [BMIM][BF_4] and [BMPY][BF_4] catalyzed by soybean peroxidase has been studied by Eker et al. [112]. They have reported that size of the polymer could be controlled by using different concentrations of ILs as indicated by gel permeation chromatography and MALDI-TOF analysis. Similarly, [BMIM][PF_6] can also used as a faster and easier immobilization support system for HRP and biocatalytic synthesis of polyaniline [23]. Lipase-catalyzed ring-opening polymerization of L-lactide is reported in ILs at room temperature though with a low product conversion. But the molecular weight of the polymers synthesized was higher than that generated by conventional methods [113]. Although a range of biocatalytic polymer synthesis reactions has been established in ILs toward synthesis of higher molecular weight polymers, further extensive study is required to improve the product conversion.

10.5 Stability/Activity Vis-à-vis Solvent Property of Ionic Liquids: A Structure–Activity Relationship (SAR) Analysis

As evident from the above discussion, ILs have emerged as alternative solvent systems for biocatalysis which has already established with a range of different class of enzymes performing better or at least comparable to conventional organic solvents. The added advantages of easy work up procedure, possibility of recycling the solvent and multiple uses of enzymes were also noted. However, the complexity in the nature of ILs has resulted variation in enzyme performance in terms of reaction rate and enantioselectivity. A brief comparative analysis of enzyme activity versus nature of the component of ILs would be helpful for better understanding of the subject and careful selection of ILs for a desired reaction.

Enzyme stability and activity not only depend on the overall solvent properties but the individual ionic counterparts of an IL significantly alter the enzyme performance. So in the context of understanding the structure–activity relationship (SAR), it is imperative to discuss the well-known Hofmeister effect with respect to enzyme stability and activity. In the previous Sect. 10.2, chaotropicity and kosmotropicity of the components of ILs have been discussed briefly. Few interesting studies correlating Hofmeister effect and behavior of hen egg white lysozyme (HELW) have been reported. IL (ethyl ammonium nitrate [$EtNH_3$][NO_3]) assists in refolding of HELW although ethyl ammonium nitrate is a known denaturant having structure breaking hydration behavior since both $[EtNH_3]^+$ and $[NO_3]^-$ are chaotropes and have low B-coefficients. Hence, the renaturant effect could be attributed to favorable interactions between the ethyl group of ethyl ammonium nitrate and hydrophobic surfaces of the protein and/or stabilizing effect of electrostatic interaction between ions and charged residues of the protein. Enhanced activity and solvent-induced refolding were also observed in 1-alkyl and 1-(ω-hydroxyalkyl)-3-methylimidazolium chlorides [114]. Activity (A) and renaturation (R) of HEWL were higher in the hydroxy-substituted ILs than the unsubstituted ones when ILs of same alkyl groups were compared: $(A, R)\text{–}HEWL_{[HO\text{-}EMIM][Cl]} > (A, R)\text{–}HEWL_{[EMIM][Cl]}$, $(A, R)\text{–}HEWL_{[HO\text{-}HMIM][Cl]} > (A, R)\text{–}HEWL_{[HMIM][Cl]}$ which follows the Hofmeister series since hydroxy group–containing cations are less hydrophobic and thus less kosmotropic. Comparison of ILs having cations with increasing carbon chain length showed that activity and refolding ability of HEWL decreases with increasing hydrophobicity of cation, i.e., with increase in the carbon chain length of the cation alkyl group: $(A, R)\text{–}HEWL_{[EMIM][Cl]} > (A, R)\text{–}HEWL_{[PMIM][Cl]} > (A, R)\text{–}HEWL_{[BMIM][Cl]} > (A, R)\text{–}HEWL_{[HMIM][Cl]}$. However, thermal unfolding analysis shows decrease in melting temperature (T_m) of HEWL in the ILs than in comparison to aqueous buffer which further reduces with increased hydrophobicity of the group: $T_m\text{–}HEWL_{[EMIM][Cl]} > T_m\text{–}HEWL_{[PMIM][Cl]} > T_m\text{–}HEWL_{[BMIM][Cl]} > T_m\text{–}HEWL_{[HMIM][Cl]}$. Hence, renaturation effect of ILs in this case follows by suppression of aggregate formation but with a reduction in the thermal stability of the proteins. Thus, ILs could be categorized as cosolvents having little to moderate chaotropic nature and preferential binding tendency. A similar study was done with proteases illustrating the effect of both cations and anions on the protease activity and stability [31]. As observed in HEWL [114], the stability of the enzyme increased in the presence of ILs having chaotropic cations and kosmotropic anions. Stability of protease increases with increase in the chaotropicity of the cations and kosmotropicity of the anions as follows:

$$[EMIM]^+, [BuPy]^+ > [BMIM]^+ > [EtPy]^+$$

$$CH_3COO^- > CF_3COO^- > Cl^- > Br^- > BF_4^-$$

At the same time, activity of the enzyme was lost when very high concentrations of the ions were used. The optimum activity was observed when the ion concentration was within 0.3–0.8 M. But unlike stability and activity, enantioselectivity of protease seemed to markedly decrease with reduction in ee of protease with increasing kosmotropicity of both cations and anions of the ILs. δ Value, i.e., the difference in viscosity B values of anion and cation, is indicative of overall kosmotropicity of cations and anions of ILs. Enantioselectivity of the enzymes increases in ILs having high δ value [92, 115].

Several dehydrogenases like morphine dehydrogenase from *Pseudomonas putida* M10, alcohol dehydrogenase from *Thermoanaerobium brockii*, and glucose dehydrogenase from *Cryptococcus uniguttulatus* have been studied in the context of detrimental effect of hydrogen bonding between enzyme and the component ions of ILs [101]. Forty percent water in [BMIM][glycolate], [HMIM][glycolate], and [HMIM][Cl] denatured the enzymes, but higher activity was maintained even with 1% water in $[HMIM][PF_6]$. Infrared spectra in the amide II region suggested a stronger interaction between protein and [BMIM][glycolate] than with $[HMIM][PF_6]$ indicating a more influential effect of anions. Overall, higher activity of hydrogenases was observed in ILs having cations and anions of high and low hydrogen bonding capabilities, respectively. Thus, a combination of moderately hydrophilic cation with a hydrophobic anion such as [HMIM][PF_6] seemed to sustain the activity of all hydrogenases studied. Whereas an FTIR study indicated that cyt c preserved its secondary structure upon dissolution in ILs ([BMPYRR][H_2PO_4] and [choline][H_2PO_4]) having cations with no hydrogen bonding capability [49].

Stability and activity of cyt c were also investigated in various ILs with various kosmotropic and chaotropic ions by superoxide reduction assay [49]. It was observed that activity and thermodynamic stability of cyt c were reduced in the following order: [BMIM][$MeSO_4$] < [BMIM][lactate] < [BMIM][acetate] < [choline][Bu_2PO_4] < [BMPY][H_2PO_4] < [choline][H_2PO_4]. This trend agrees well with the kosmotropicity order of the anions present in the ILs indicated by the viscosity B coefficient of the anions [116]: $[MeSO_4]^-$ < $[lactate]^-$ < $[acetate]^-$ < $[Bu_2PO_4]^-$ < $[H_2PO_4]^-$ < $[H_2PO_4]^-$.

Hydrolysis of penicillin G by PGA was assayed in a range of ILs and $t_{1/2}$ value was estimated. From a comparison of $t_{1/2}$ values in ILs with same cation $[BMIM]^+$ and different anions, an increase in $t_{1/2}$ with increased hydrophobicity of the anions was observed.

$$t_{1/2}\text{ increases } \longrightarrow$$

$$[BMIM][Tf_2N] > [BMIM][PF_6] > [BMIM][BF_4]$$

$$\text{hydrophobicity increases } \longrightarrow$$

$$[BF_4]^- < [PF_6]^- < [Tf_2N]^-$$

Equilibrium distribution coefficient (log P or log D) is an important parameter to assess the solvent effect. Asymmetric reduction of 4-chloroacetophenone to (R)-1-(4-chlorophenyl)ethanol by *Lactobacillus kefir* showed an increase in product yield with increase in log D value of the ILs [104]. However, another study [117], which used ILs as coating of lipase (Novozyme 435) for esterification of methyl α-D-glucopyranoside with fatty acids, showed a remarkable increase in the product yield with increase in the polarity of the IL used for coating which is opposite in trend to that observed when ILs were used as solvent as discussed above. This altered effect of more polar IL coating on product yield was attributed to their better absorption ability on the polyacrylate beads used for immobilization of enzymes in this case [117].

In a different set of ILs having hydroxyl, ether oxygen, and long hydrocarbyl groups in the cationic counterpart, enzymatic glycerolysis of triglyceride to monoglyceride conversion catalyzed by lipases (Novozyme 435) was markedly influenced by the H-bonding ability of the functional groups present [118].

DSC studies of thermal denaturation studies of ribonuclease A (RNase A) showed a decrease in T_m values in ILs with various cations and anions as follows [11]:

$$[TMA]^+ > [TEA]^+ > [EMIM]^+ > [BMPYRR]^+ > [BMIM]^+ \sim [TPA]^+ > [HMIM]^+ \sim [TBA]^+$$

$$[SO_4]^{2-} > [HPO_4]^{2-} > Cl^- > [EtSO_4]^- > [BF_4]^- \sim Br^- > [MeSO_4]^- > [CF_3COO]^-$$
$$> [SCN]^- \sim [N(CN)_2]^- > [Tf_2N]^-$$

The trend in cations matches with a trend in the increase in viscosity B coefficients, indicating greater kosmotropicity of the cations which varies as follows:

$$[\mathrm{TMA}]^+ < [\mathrm{TEA}]^+ < [\mathrm{EMIM}]^+ < [\mathrm{BMIM}]^+ < [\mathrm{TPA}]^+ < [\mathrm{TBA}]^+$$

Viscosity B coefficients of $[\mathrm{TMA}]^+$, $[\mathrm{TEA}]^+$, $[\mathrm{TPA}]^+$, and $[\mathrm{TBA}]^+$ were experimentally determined as 0.123, 0.385, 0.916, and 1.275, respectively [116]. Although no experimental data for $[\mathrm{BMIM}]^+$, $[\mathrm{EMIM}]^+$, $[\mathrm{BMPY}]^+$, and $[\mathrm{HMIM}]^+$ are known, calculated values of viscosity B coefficients for $[\mathrm{BMIM}]^+$ and $[\mathrm{EMIM}]^+$ are 0.610 and 0.491, respectively, which follows the trend quite well [12]. However, such correlation with kosmotropicity/chaotropicity of anions was not straightforward and there were many discrepancies. This is in accord with the general notion that variations in anions have more complicated consequences on protein stability than cations [119].

The activity and stability of mushroom tyrosinase in $[\mathrm{BMIM}]^+$ containing ILs were analyzed in detail with respect to the influence of Hofmeister effect of the anions on the catalytic performance of the enzyme and active site structure as well as reaction mechanism [120]. Enzyme activity was in the opposite order to that of the Hofmeister series: $[\mathrm{BMIM}][\mathrm{PF}_6] > [\mathrm{BMIM}][\mathrm{BF}_4] > [\mathrm{BMIM}][\mathrm{MeSO}_4]$ which was attributed to the more influential kosmotropic effect of the cation [121].

Hofmeister effect and its impact on enzyme stability and activity in ILs has been surveyed by Z. Yang [16]. In almost all the cases, stability or $t_{1/2}$ of the enzymes followed Hofmeister effect directly, but activity of the enzymes or kinetics of the catalytic reaction often showed an opposite trend. Although Hofmeister effect provides an empirical guide to relate enzyme behavior in ILs with the properties of cationic and anionic counterparts, rationalizing enzyme activity and stability observed in ILs with regard to the Hofmeister effect per se is probably oversimplistic. Similarly, other singularly defined solvent parameters like polarity and logP values are also ill defined for ILs which cannot describe the enzyme behavior in ILs. Hence, it is argued that a theory incorporating the destabilizing interactions of ions resulting from the stronger interaction of the ions with the unfolded form of the enzyme than the native form, possible pH drifts rendered by the basic or acidic ions of the ILs, water activity parameter of ILs, anion nucleophilicity, and hydrogen bond acidity would be more appropriate to predict the compatibility between enzymes and ILs [29, 122].

10.6 Conclusions

IL has been used to solubilize and stabilize a diverse number of proteins and enzymes. Remarkable enhancement in activity and stability has been observed in neat ILs or composites in many cases. However, it is important to note some disparity in results reported especially in the case of resolution of phenylethanol by lipases [18, 19]. The contradictory results were ascribed to the purity of ILs used [87, 123, 124]. In particular, halides or HF contamination are known to decrease the activity of the enzyme [87]. With regard to enzyme compatibility of ILs, though hydrophilic ILs dissolve the enzymes, enzyme–IL interaction is strong enough to strip off the essential water molecules responsible for maintaining the enzyme native conformation. On the other hand, hydrophobic ILs are proven to be more enzyme compatible and suspended enzymes in such ILs showed higher activity and stability, may be due to preservation of the water layer by the ionic matrix. Hofmeister explanation provides an empirical guideline for optimum stability and activity of the proteins/enzymes in ILs. But there is no straightforward and universal principle to predict and select ILs which can stabilize and activate any enzyme. It is also important to note that though catalytic activity of various enzymatic reactions has been observed with high stereoselectivity in ILs, mechanism of improved enantioselectivity has not been elucidated. Similarly, in the context of enzyme stability except in the case of monellin, there is no other study with detail analysis of thermodynamic and/or kinetic stability parameters which is important to assess the activity of the enzymes. A potential roadblock in this regard could be the multiple interactions due to solvation of ILs which are complicated. Hence, more systematic structure–activity studies and information on physical properties and thermodynamic parameters of ILs would probably help to predict the behavior and performance of a certain enzyme in a particular IL and thereby rationally design an IL suitable for any enzyme perfectly. An ideal IL which can dissolve the enzyme as well as retain the native conformation and activity is yet to be synthesized.

Thus, a decade-long extensive evaluation of ILs in biocatalysis has revealed valuable information and knowledge on stability, activity, and stereoselectivity of many different enzymes/proteins. A large number of new methods have been developed to improve and enhance the stability and activity of proteins/enzymes in ILs. But in order to make our chemical industries still greener, further extensive studies are warranted to fully exploit the unprecedented potential of the neoteric solvent IL especially in combination with different ILs and/or other green solvents such as supercritical CO_2. In spite of the fact that there are few discrepancies and enzyme compatibility issues, the observed enhancement in enzyme activity and stability is still impressive. The real beauty of ILs is the possibility of designing a tailor-made solvent depending on the requirement and effective reusability/recycle of enzymes which would serve as the raison d' être for choosing the ILs over conventional organic solvents in nonaqueous enzymology.

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Chapter 11
Supported Ionic Liquid Membranes: Preparation, Stability and Applications

A.P. de los Ríos, F.J. Hernández-Fernández, L.J. Lozano, and C. Godínez

Abstract Supported ionic liquid membranes (SILMs) consist of a thin microporous support whose pores are filled with an ionic liquid. The liquid supported membranes have been extensively used for the selective separation of organic compounds and mixed gases during the last decade. The unique properties of ionic liquids such as negligible vapour pressure, greater viscosity and the possibility of minimization of solubility in the surrounding phases by adequate selection of the cation and anion could overcome the instability associated with supported liquid membranes based on organic solvents. Furthermore, it is possible to tailor ionic liquids for specific separation problems by changing the nature of the cation and/or the anion, which opened up new fields of application of supported ionic liquid membranes. In this chapter, an overview is given of methods of preparation and characterization, stability, transport mechanisms and fields of application of supported ionic liquid membranes.

11.1 Introduction

Supported liquid membranes (SLMs) based on organic solvents are usually unstable [1]. SLM usually is the progressive loss of the liquid embedded in the membrane into the surrounding phases due to liquid vaporization, dissolution into the adjacent liquid phases and/or shifting from the porous structure of the supported membrane under low-pressure gradients [2]. The use of ionic liquids as liquid phase could overcome these inconveniences due to their unique properties [3–5]. Ionic

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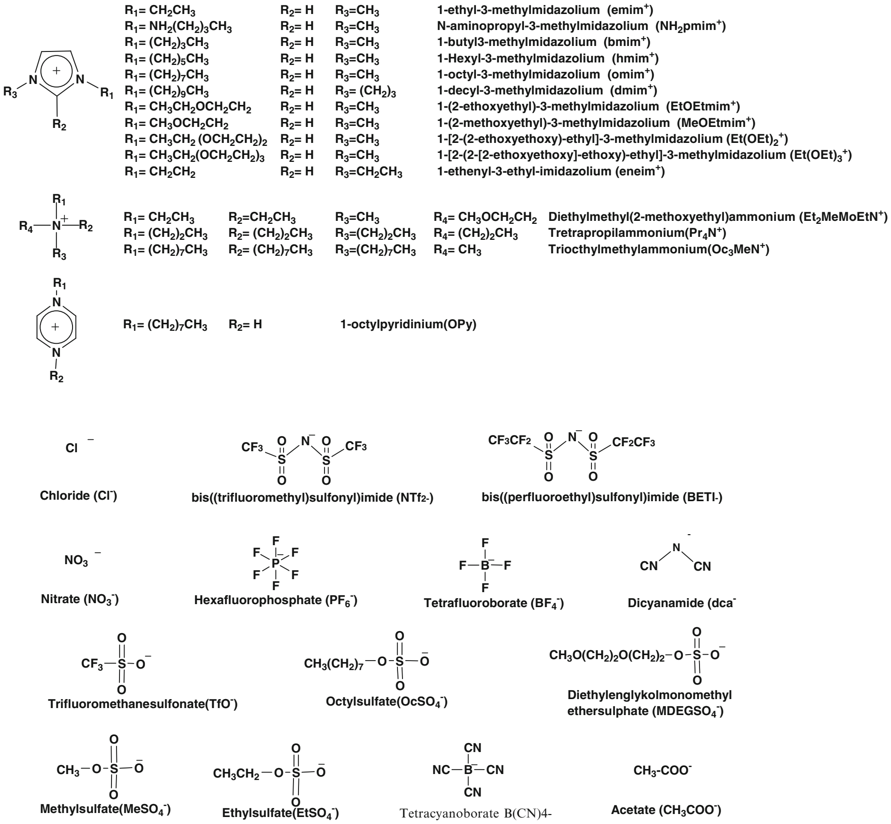

Fig. 11.1 Example of ions involved in ILs

liquids (ILs) are organic salts which are liquids at room temperature. They normally consist of an organic cation, such as dialkylimidazolium and tetraalkylammonium, and an inorganic anion, such as tetrafluoroborate, hexafluorophosphate and bistrifluoromethylsulphonylimide (Fig. 11.1) [6]. The use of ionic liquids as liquid membrane phase stabilizes SLMs due to their negligible vapour pressure, the possibility of minimizing their solubility in the surrounding phases by adequate selection of the cation and anion composition, and their high viscosity, which could reduce displacement of the liquids from the micropores under pressure [7]. Other interesting properties of ILs in the context of liquid membranes are their high chemical and thermal stability, reasonable ion conductivity [8] and good solvent power [9]. All these mentioned properties have led ILs to being considered 'green designer solvents' [10]. Indeed, ionic liquids have received growing attention during the last decade as clean alternatives to classic organic solvents in chemical and biochemical reactions [11–15].

In the last decade, supported liquid membranes based on ionic liquids (SILMs) have been successfully applied in separation and purification of organic compounds, involved in the synthesis of pharmaceutical and fine chemicals, (alcohol, esters, organic acids and amino acids) and mixed gases [16–25].

Here, a review on supported ionic liquid membrane technology including issues such as methods of preparation and characterization, stability, transport mechanisms and applications is presented.

11.2 Methods of Preparation and Characterization of Supported Ionic Liquid Membranes

Due to relatively high viscosity of the ionic liquids, the method of preparation of supported ionic liquid membranes can play an important role on the membrane performance. Three methods are commonly used for the preparation of supported ionic liquid membranes: direct immersion, pressure and vacuum methods [17, 21, 26]. In the former case, immobilization takes places by contacting the supporting membrane with the ionic liquid, allowing it to soak up the liquid [21]. In the pressure method, the immobilization is achieved by placing the membrane in an ultrafiltration unit, adding an amount of ionic liquid and applying nitrogen pressure to force the ionic liquid to flow into the pores of the membrane [17]. In the vacuum method, the supporting membrane is submerged in a volume of IL and vacuum is applied to release all air occluded in the pores of the membranes [26]. After all procedures, the excess ionic liquid should be removed from the membrane surface either by leaving to drip overnight or by blotting with paper tissue.

Scanning electron microscopy (SEM) combined with energy dispersive X-ray (EDX) analysis could be used to physico-chemical characterization of SILMs [26]. This technique allows the characterization of the membrane surface morphology and the examination of the global chemical composition of the membranes and the distribution of the ILs within pores. Figure 11.2 shows examples of SEM micrographs of a plain nylon membrane and supported liquid membranes based on [bmim^+][PF_6^-] prepared by using the pressure method [26].

SEM micrograph of the nylon membrane shows a highly porous material consisting of macropores of about 1 μm average size. The morphological study of SILM based on [bmim^+][PF_6^-] shows that, after impregnation by pressure method, the IL is homogeneously distributed in the pores of the membrane, except for the largest macropores that remained partially filled. These pictures also show the presence of a small amount of excess IL located on the external membrane surface.

The EDX spectrum of the nylon membrane (not shown) presents the characteristic peaks assigned to the C, O and N Kα lines, the last two as a single broad peak unresolved due to their proximity and small concentration. The presence of these chemical elements corresponds to the chemical formulation of polyamide [26]. The EDX study of supported ionic liquid membranes is based on the selection of characteristic elements of interest in each ionic liquid, for example F and P for [bmim^+]

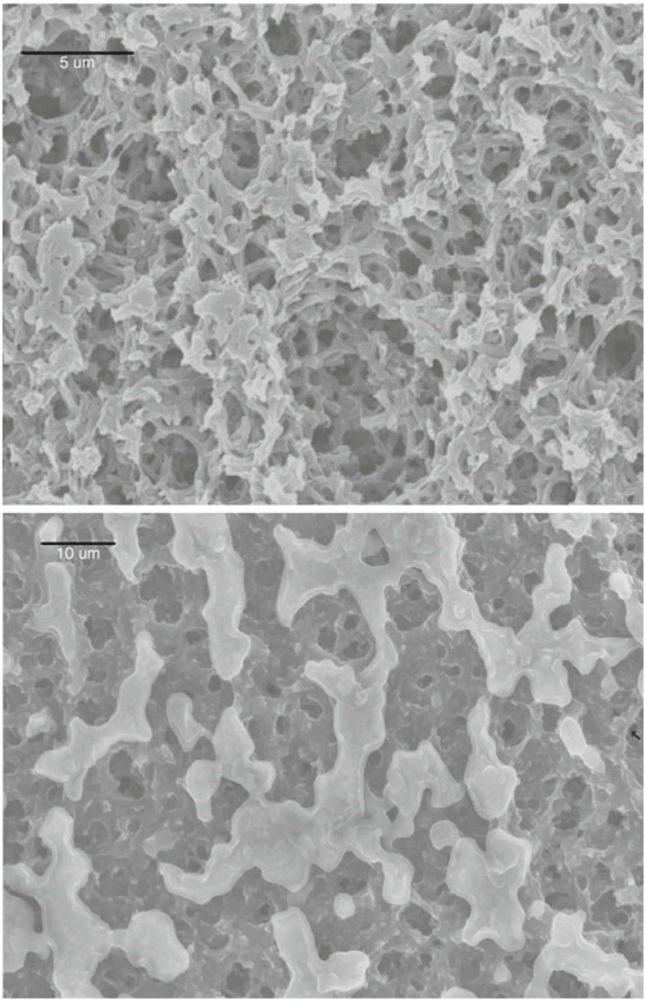

Fig. 11.2 Scanning electron micrographs of the (**a**) nylon membrane (3,040×) (scale bar = 5 μm) and (**b**) the nylon membrane impregnated with $[\text{bmim}^+][\text{PF}_6^-]$ by pressure (1,010×) (scale bar = 10 μm)

$[\text{PF}_6^-]$, F for $[\text{bmim}^+][\text{BF}_4^-]$ and F and S for $[\text{bmim}^+][\text{NTf}_2^-]$, as shown in Fig. 11.3. The relative peak heights of identical elements in the different compounds are grossly related with their respective concentrations [26].

It has been also demonstrated by SEM–EDX and weight studies that the amount of IL immobilized is independent of the type of ionic liquid used when the immobilization is carried out under pressure [26]. In contrast, following immobilization under vacuum, less ionic liquid is absorbed into the membranes when more viscous ILs are used. This behaviour could be explained by the fact that the high viscosity of these ILs makes their penetration difficult into the middle of the deeper pores of the membrane under vacuum. From these findings, it was concluded that

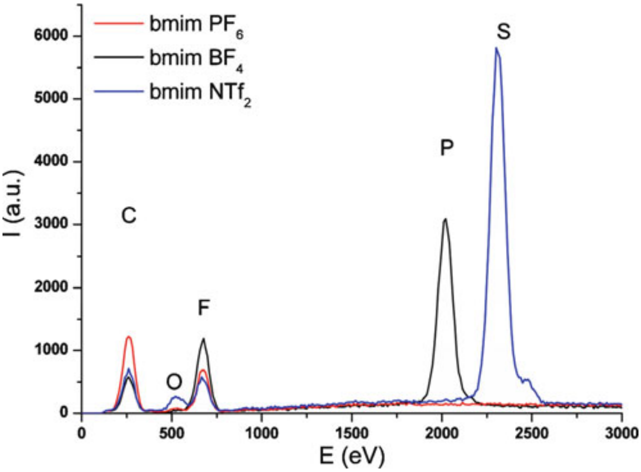

Fig. 11.3 EDX spectra of the nylon membrane impregnated with [bmim$^+$][PF$_6^-$], [bmim$^+$][BF$_4^-$] and [bmim$^+$][NTf$_2^-$]

immobilization under vacuum can be considered suitable for low-viscosity ionic liquids, with the added advantage of being an easier preparation method. However, for high-viscosity ionic liquids, immobilization of the ionic liquid should use pressure in order to ensure that all membrane pores are filled with liquid.

The nature of the supporting membrane also plays an important role in the performance of supporting ionic liquid membranes. In this context, de los Rios et al. [3] used two polymeric membranes, nylon and mitex, as supporting membranes. Nylon membrane was a hydrophilic polyamide membrane with a pore size of 0.45 µm and a thickness of 170 µm. Mitex membrane was a hydrophobic polytetrafluoroethylene membrane with a pore size of 10 µm and a thickness of 130 µm. It was observed that less ionic liquid was absorbed into the mitex membranes, which was explained by the different textural properties and the high hydrophobic character of these membranes, which probably restrict interaction with the hydrophilic ionic liquids used [27].

The use of nanofiltration membranes as supporting membranes have been also reported [28]. In this case, direct filtration of ionic liquids through the nanofiltration membrane was not possible at a gas pressure up to 7 bars. The ionic liquids with cations associated with straight or branched hydrocarbon chains were easily absorbed into the polymeric membrane allowing the nanoporous structure saturated with the ionic liquids.

11.3 Stability of Supported Ionic Liquid Membranes

One of the most important properties for the industrial application of SILMs is their stability. Therefore, stability studies of SILMs prepared by several methods at different operating conditions (e.g. surrounding phases, pressure and temperature) have been reported [3, 26, 29–33].

The immobilization method was also found to have influence on the membrane stability. A comparative study of the preparation of SILMs by two different methods, under pressure and vacuum were reported by Hernández-Fernández et al. [26]. They used the ionic liquids, [bmim$^+$][Cl$^-$], [bmim$^+$][BF$_4^-$], [bmim$^+$][PF$_6^-$] and [bmim$^+$][NTf$_2^-$] as liquid phase supported on a nylon membrane. Small losses of ionic liquid were observed after 7 days of operation when the ionic liquid was immobilized under pressure in a diffusion cell using n-hexane/n-hexane as surrounding phases. However, the losses of IL were higher when immobilization was carried out under vacuum, especially with the most viscous ionic liquids ([bmim$^+$][PF$_6^-$] and [bmim$^+$][Cl$^-$]). This behaviour was explained by the fact that the higher viscosity of ILs makes difficult their penetration into the middle of the deeper pores of the membrane, and therefore, the ionic liquid was mainly immobilized on the most external layer of the membrane, and consequently, the immobilized ionic liquid is more easily removed during operation.

The influence of the ionic liquid composition on the stability of the resulting SILM in organic environments has also been analysed. In this context, de los Rios et al. [3] analysed the stability of SILMs based on [bmim$^+$][PF$_6^-$], [bmim$^+$][BF$_4^-$] and [bmim$^+$][NTf$_2^-$] using nylon membranes as support in n-hexane/n-hexane. Stability tests were performed by keeping the respective impregnated membranes immersed for a week in a diffusion cell including two independent compartments and using n-hexane/n-hexane as the respective feed and receiving phases. Figure 11.4 shows the microstructure of the nylon membrane impregnated with [bmim$^+$][PF$_6^-$] after cell operation, which could be compared with the appearance of the SILM before cell operation (Fig. 11.2b).

It was concluded that most of the ionic liquid from the external surface of the membrane disappeared during cell operation. However, comparison of the SEM–EDX spectra taken from membranes before (Fig. 11.3) and after (Fig. 11.5) immersion in the n-hexane/n-hexane solution showed similarity. The EDX spectra taken from a sample of up to a few micrometres thick/depth demonstrate the contribution of ionic liquid within the membrane pores which is more important than the accumulated liquid found on the surface. Consequently, from the SEM study, it was deduced that only the ionic liquid deposited on the external membrane surface has been stripped off during operation. The amount of ionic liquid retained in the membrane pores, however, was apparently kept constant, and consequently, the membrane was stable against the possible solvent action of n-hexane.

From the SEM–EDX study, it was concluded that, in all three cases of ILs supported on nylon membranes, no substantial loss of ionic liquid occurred after a week of operation in an n-hexane/n-hexane diffusion cell. Only minimal loss of the ionic liquid accumulated on the external surface of SLMs was detected from the SEM pictures.

The stability of a SILM based on [bmim$^+$][BF$_4^-$] supported in a nylon membrane has been also analysed in other organic solvents, such as n-hexane/*tert*-butyl methyl ether and n-hexane/dimethyl sulphoxide [29]. The SEM–EDX study of the membranes after continuous operation showed that the stability of the supported liquid membrane increases with the decrease of the polarity of the solvent used.

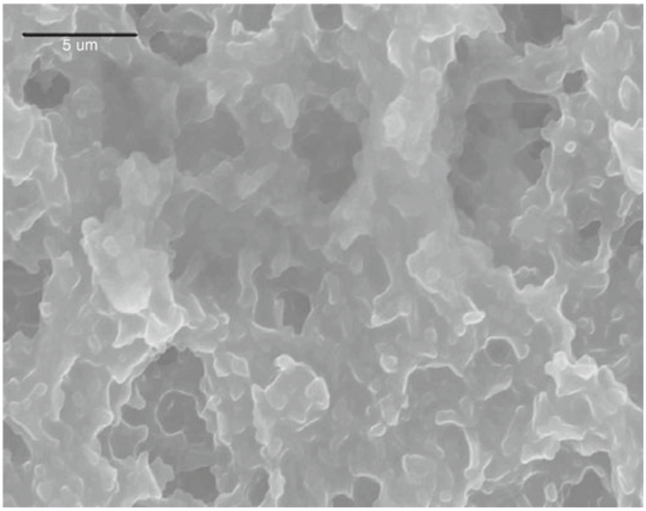

Fig. 11.4 Scanning electron micrograph of the nylon membrane impregnated with [bmim$^+$][PF$_6^-$] after 7 days' operation (3,040×) (scale bar = 5 µm) in n-hexane/n-hexane

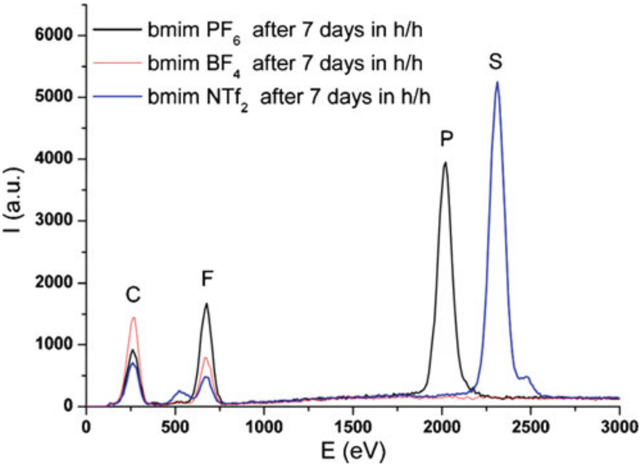

Fig. 11.5 EDX spectra of the nylon membranes impregnated with [bmim$^+$][PF$_6^-$], [bmim$^+$][BF$_4^-$] and [bmim$^+$][NTf$_2^-$] after 7 days' operation in n-hexane/n-hexane

The relationship established between polarity and stability allows the design of more stable SILMs for use in organic environments.

The stability of SILMs based on 1-n-alkyl-3-methylimidazolium hexafluorophosphate (n = 4, 8, 10) supported on polyvinylidene fluoride (PVDF) membrane towards contacting aqueous phase has been also analysed by several authors [4, 17, 30].

The resulting SILMs were stable under assayed conditions. These authors highlighted the importance of the consideration of two main possible effects on the performance and stability of SILMs in water mediums: (a) the loss of ionic liquids phase from the supporting membrane to the adjacent aqueous solutions by dissolution/emulsification and (b) the formation of water microenvironments inside the ionic liquids phase, which constitute new, non-selective environments for solute transport, leading to a deterioration of the SLM performance and selectivity.

Stability studies of SILM have been also carried with gases as contacting phases [23–25, 31, 32]. The stability of SILMs based on the ionic liquid $[\mathrm{Et(OEt)_2}^+][\mathrm{PF_6}^-]$ supported on Durapore hydrophobic PVDF was studied at 25°C with a pressure difference of 1.2 bars [31]. Experiments concerning stability showed that after eight cycles, the permeability of H_2 slightly decreased while the CO_2/H_2 ideal selectivity improved. Other interesting example was reported by Hanioka et al. [23], who examined the long-term stability of an SLM based on a functionalized ionic liquid ($[\mathrm{NH_2pmim}^+][\mathrm{NTf_2}^-]$) in the separation of the CO_2/CH_4 gas mixture at atmospherical pressure. These authors did not found observable change in permeability or selectivity after 260 days' operation. Scovazzo et al. [24] analysed the stability of SILMs used in the separation of gas pairs CO_2/CH_4 and CO_2/N_2 using continuous flow of the mixed gases. They achieved long-term stability in continuous operation, from 24 to 106 days, by using imidazolium ionic liquids supported on hydrophilic PVDF or hydrophilic polystyrene (PES) membranes, respectively, without performance degradation under CO_2 partial pressures of at least 2.07 bars.

Temperature stability is important for some applications of SILMs in gas separation, such as capture of CO_2 from coal gasification plants. Ilcovich et al. [25] analysed the stability of a SILM based on $[\mathrm{hmim}^+][\mathrm{NTf_2}^-]$ supported on a polysulphone organic membranes in the selective separation of CO_2 from He at high temperature. This membrane was found to be stable up to 125°C, the failure of the membranes above that temperature being attributable to support failure rather than any effect on the ionic liquid. Recently, Myers et al. [32] reported operation of $[\mathrm{hmim}^+][\mathrm{NTf_2}^-]$ supported on nylon membranes up to 300°C. It was found that permeability in this $[\mathrm{hmim}^+][\mathrm{NTf_2}^-]$ membrane increased with temperature while the selectivity decreased.

SILMs are usually prepared using microfiltration membranes. To avoid the pitfall of liquid instability associated with micron porous membranes, nanofiltration membranes were used which greatly reduce the instability problem, but potentially at the expense of increased gas transport resistance provided by the NF membranes [34]. Experimental stability tests demonstrated that the impregnated ionic liquids did not discharge from the nanofiltration (NF) membrane structure even under a high transmembrane pressure of 10 bars, which suggests that SILMs supported on NF membranes offer a good stability and are capable to sustain high gas phase pressure relevant to practical applications.

11.4 Mechanism of Transport Through Supported Ionic Liquid Membranes

The solution-diffusion model has been used to explain the transport mechanism of organic molecules through supported ionic liquid membranes [19, 22]. In this model, the driving force is due to the concentration gradient existing between the feed and receiving phases, so the flux of the organic species is assumed to be given by the Fick's first law. Based on the solution-diffusion model, the permeability of a specific compound can be expressed in terms of the partition coefficient of this compound between the liquid membrane phase (ionic liquid) and the feed/receiving phase, the diffusion coefficient and the thickness of the membrane as indicated by Eq. 11.1 [35]:

$$\bar{P} = \frac{K\bar{D}}{l} \tag{11.1}$$

This relationship between the permeability values of several compounds ($\bar{P}$) and the partition coefficient of these compounds between the ionic liquid phase immobilized on the membrane and the feed/receive phase (K) has been examined by several authors [16, 18]. The increase in the K values for the compounds was reflected in an increase in the $\bar{P}$ values. A mathematical correlation between these parameters has been established by de los Ríos et al. [22], given in Eq. 11.2:

$$\bar{P} = C\frac{K}{V_m^{0.6}} \tag{11.2}$$

where C is a constant term at a fixed temperature for each supported liquid membrane Eq. 11.3:

$$\mathrm{C} = 7.4 \cdot 10^{-8}\frac{\chi^{0.5}M^{0.5}T}{\eta l} \tag{11.3}$$

As can be seen from Eq. 11.2, the permeability can be expressed in terms of the partition coefficient (K) and the molar volume of the diffusant (V_m) for each supported liquid membrane.

The transport mechanism of gases through supported ionic liquid membranes has also been studied by several workers [24, 28, 36]. The basic governing principle in solution-diffusion-based mass transport process applicable to gas separation in ionic liquids is embodied in the Eq. 11.4:

$$\mathrm{Ji} = (\mathrm{Pi}\,\Delta p_i)/l \tag{11.4}$$

where Ji is the steady-state flux through the membrane of the gas i, Pi the permeability coefficient and Δp_i the pressure drop across the membrane.

11.5 Fields of Application of Supported Liquid Membranes

The use of supported ionic liquid membranes in different fields of application has received growing attention during last decade. One of the most studied applications of SILMs is the selective separation of organic compounds. The first example was reported by Branco et al. [18], who studied the selective transport of 1,4-dioxane, 1-propanol, 1-butanol, cyclohexanol, cyclohexanone, morpholine and methylmorpholine as a model seven-component mixture of representative organic compounds. For that, four ionic liquids based on the 1-n-alkyl-3 methylimidazolium combined with the anions hexafluorophosphate or tetrafluoroborate, immobilized on different organic polymeric membranes, were used. The use of the ionic liquid [bmim$^+$][PF$_6^-$] immobilized on a polyvinylipolyvinylidene fluoride membrane allowed an extremely highly selective transport of secondary amines over tertiary amines (up to a 55:1 ratio).

Other interesting examples were reported on the use of SILM for the selective separation of the substrates and products of transesterification reactions. The biosynthesis of organic esters commonly used in the perfumery and flavour industries can be carried out by transesterification from vinyl esters and alcohols catalysed by enzymes in non-conventional media (i.e. n-hexane [33] and ionic liquid [37]) at low water content. When the biochemical reaction reach the equilibrium, the reaction medium consists of a mixture of alcohol, vinyl ester, organic acid and alkyl ester (flavour ester). The possibility of using SILMs for the selective separation of these reaction mixtures has been extensively examined [19, 33, 38–40]. In these cases, substantial permeability differences between the target compounds were found on the basis of (1) their functional groups and (2) their alkyl chain lengths. It was noticed that selectivity values were mostly dependent on the type anion composition of the ionic liquid, increasing for a given cation ([bmim]) in the sequence: [OcSO$_4^-$] < [PF$_6^-$] < [NO$_3^-$] < [BF$_4^-$] < [dca$^-$] < [Cl$^-$] < [EtSO$_4^-$] < [MDEGSO$_4^-$] < [MeSO$_4^-$] [40]. These results were quite encouraging and suggested that these SLMs based on ILs could be used for the selective separation of the organic esters from the reaction mixture. SILMs can also be used for the separation of aromatic hydrocarbons from aliphatic hydrocarbons. In this context, the selective separation of benzene, toluene and *p*-xylene from n-heptane was achieved using SILMs based on [bmim$^+$][PF$_6^-$], [hmim$^+$][PF$_6^-$], [omim$^+$][PF$_6^-$] and [Et$_2$MeMoEtN$^+$][Tf$_2$N$^-$] supported on a polyvinylidene fluoride membrane [9]. It was found that aromatic hydrocarbons were successfully transported through the membrane based on these ionic liquids, and the maximum selectivity to n-heptane was when benzene used in the aromatic permeation and [bmim$^+$][PF$_6^-$] was taken in the liquid membrane phase.

Other interesting field of application of supported ionic liquid membranes is the separation of mixed gases. Since SILMs may have the potential for industrial applications, specifically, low-pressure systems such as the treatment of bio-methane from anaerobic digesters and CO$_2$ capture from flue gases, much effort and many resources have been extended on developing new SILMs [24, 41–43]. In this context, Scovazzo et al. [24] explored the selective separation of the gas pairs CO_2/CH_4 and CO_2/N_2 using continuous flow of the mixed gases using [emim][BF_4] [$emim^+$][TfO^-] and [$emim^+$][dca^-] supported on hydrophilic PVDF and [$emim^+$][Tf_2N^-], [$hmim^+$][Tf_2N^-] and [$emim^+$][$BETI^-$] supported in a hydrophilic PES membrane. The highest CO_2/CH_4 and CO_2/N_2 selectivities were 27 and 21.2 using the ionic liquids [$emim^+$][BF_4^-] and [$emim^+$][Tf_2N^-], respectively.

Supported ionic liquid membranes have also been successfully applied to the separation of various liquids or vapour mixtures by *pervaporation and vapour permeation* [44–46]. The major problem associated with solute recovery by these techniques is the restrictive compromise between selectivity and flux: High solute selectivity involves the use of conditions that lead to relatively low mass fluxes in the membrane. This problem would be overcome if the feed solvent could not permeate through the membrane, for example, using SLMs based on ILs. In this case, solute to solvent selectivity could be significantly increased and the process could be operated under conditions that provide high fluxes [44]. In this context, the use of SLMs based on the ionic liquid [Pr_4N^+][$B(CN)_4^-$] in a nanofiltration ceramic module allowed the removal of 1,3-propanediol from aqueous solution by pervaporation, increasing the selectivity of the process by more than two orders of magnitude while the permeability was only in one order of magnitude slower [44].

Other interesting field of application of supported ionic liquid membranes is the removal of metal ions from aqueous solutions. In this context, Alguacil et al. [47–49] evaluated the use of ionic liquids as carrier, diluted in an organic solvent, in SILM for the extraction of Cr(VI), Cr(III) and Fe(III) from aqueous solutions. The transport of chromium(VI) was carried out by using CYPHOS IL101 (phosphonium salt) as ionophore reaching recoveries in the 60% range [49]. The permeation of chromium (III) was successfully carried out using the ionic liquid trioctyl methylammonium chloride ($TOMA^+Cl^-$) as carrier and the transport of iron(III) was facilitated by the ionic liquid $(PJMTH^+)_2(SO_4)^{2-}$.

Supported ionic liquid membranes have also found application in *analytical chemistry*, specifically in the trace determination of toxic substances. Several examples of the application of ionic liquids as liquid membrane in hollow fibre–supported liquid-phase microextraction have been reported [50, 51]. This technique, combined with high-performance liquid chromatography was used for the determination of chlorophenols and sulphonamides in environmental water samples.

11.6 Conclusions

Supported ionic liquid membranes have emerged as a novel material for a wide range of separation processes including separation of organic molecules and mixed gases. Experimental studies with supported ionic liquid membranes have demonstrated their high operational and structural stability to make them useful for industrial applications. Furthermore, the use of ionic liquids instead of volatile organic solvents as liquid make SILM more environmentally benign materials. Nowadays, supported ionic liquid membrane technology is in continuous progress mainly due to the constant development of new ionic liquids.

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Chapter 12
Application of Ionic Liquids in Multicomponent Reactions

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and Somayeh Akbari-Dadamahaleh

Abstract This chapter reports the applicability of ionic liquids in the formation of different types of multicomponent reactions. Easy work-up, relatively short reaction times, good to high yields of the desired products, mild reaction conditions, low cost, availability, and reusability of the employed ionic liquids are the striking features of the reported methodologies.

12.1 Introduction

During the last few years, multicomponent reactions (MCRs) have proved to be remarkably successful in generating molecular complexity in a single synthetic operation. These processes consist of two or more synthetic steps, which are progressed without isolation of any intermediates, thus reducing time and saving both energy and raw materials. MCRs are powerful tools in the modern drug discovery process and allow fast, automated, and high-throughput generation of the libraries of organic compounds.

In recent years, use of ionic liquids in organic reactions is attracted the attention of organic chemists. This attention can be attributed to their important physicochemical properties, e.g., low melting point, negligible vapor pressure, low flammability, tunable polarity, miscibility with other organic or inorganic compounds, and their low solubility toward compounds of low polarity. Because of these unique properties, ionic liquids have found widespread applications in organic reactions, i.e., as solvent catalyst, co-catalyst, or catalyst activator for the reactions. This chapter attempts to present a summary of recent developments in the rapidly growing field of the application of ionic liquids in multicomponent reactions.

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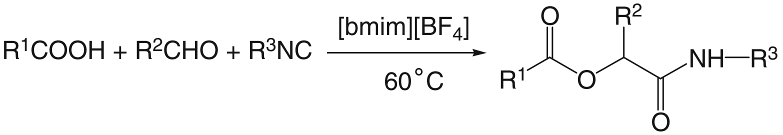


Fig. 12.1 The Passerini reaction promoted in [bmim][BF_4]

12.1.1 Ionic Liquids Based on 1-Butyl-3-methylimidazolium

12.1.1.1 1-Butyl-3-methylimidazolium

In view of the rapidly increasing importance of imidazolium-based ionic liquids as novel reaction media, use of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) as a recyclable solvent and promoter for greener organic synthesis is attracted the attention of many organic chemists.

The Passerini reaction, also called the 3-CC reaction, which consists of the reaction of a carboxylic acid, a carbonyl compound, and an isocyanide providing an α-(acyloxy)carboxamide in a single step, was carried out for the first time in [bmim][BF_4] (Fig. 12.1) [1].

This reaction was done with a variety of substituted aromatic and aliphatic carboxylic acids and aldehydes. Unlike the aromatic aldehydes that produced the corresponding products in high purity and good yields, reactions with aliphatic aldehydes produced several unidentified substances together with the desired α-(acyloxy)carboxamide products. In the case of ketones, cyclohexanone was successfully included into this 3-CC process and gave the corresponding products in reasonable yield, but attempts to use acetophenone as the carbonyl substrate failed. The inactivity of the acetophenone in this reaction may be due to the steric effect of the relatively bulky phenyl group.

Actually, a steric congestion effect was also manifested with other substrates. For example, with aromatic carboxylic acids or aldehydes substituted on the o-position of the aromatic ring, the reactions gave lower yields compared with those unsubstituted or substituted on *p*- or *m*-position. This method had the advantages of high efficiency, a green nature, simple operation, and ease of recovery and reuse of the reaction medium. The recovered [bmim][BF_4] could be successively recycled in subsequent reactions without obvious loss in its efficiency.

Three categories of agents against the human immunodeficiency virus (HIV) are nucleoside analogues, protease inhibitors, such as thiourea derivatives. Therefore, Le and his coworkers developed a simple, mild, and efficient method for the synthesis of thiourea derivatives via the reaction of phenyl isothiocyanate and amines in [bmim][BF_4] (Fig. 12.2) [2]. The method is also useful for the preparation of 1,3-disubstituted thioureas from the reaction of butylisocyanate with aniline and/or butyl amine. They have found that the ionic liquid which plays the dual role of solvent and promoter is recyclable and can be reused in subsequent runs without decrease of the yield.

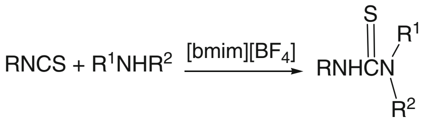


Fig. 12.2 Preparation of thiourea derivatives in [bmim][BF_4]

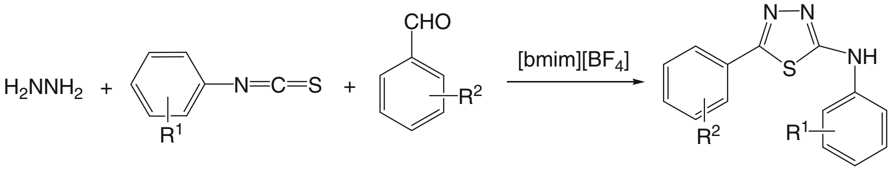


Fig. 12.3 Synthesis of 1,3,4-thiadiazoles promoted by [bmim][BF_4]

1,3,4-Thiadiazoles have attracted significant interest in medicinal chemistry and many fields of technology. Some of the technological applications involve dyes, lubricating compositions, optically active liquid crystals, and photographic materials. In medicinal field, one of the best-known drugs based on 1,3,4-thiadiazole is the acetazolamide (Acetazola), which is a carbonic anhydrase inhibitor launched in 1954.

In 2008, Rostamizadeh and his coworkers reported that one-pot condensation of hydrazine hydrate with phenylisothiocyanate and benzaldehydes in the presence of [bmim][BF_4] led to the formation of 1,3,4-thiadiazoles in excellent yields during relatively short reaction times (Fig. 12.3) [3]. A mechanism was proposed for these reactions (Fig. 12.4). From where it can be observed that after from formation of 4-phenylthiosemicarbazide, the ionic liquid amplifies the partial positive charge on carbon in carbonyl group, producing thiosemicarbazone intermediate (1). In the next step, the ionic liquid accelerates the cyclization to form a cyclic intermediate (2) followed by aromatization to final 1,3,4-thiadiazole product, affecting its activity and the rate enhancement role in this process. Here, the ionic liquid acted not only as a solvating medium but also as a promoter, and catalyst for the reaction, giving rise to advantage of both mild temperature conditions and the nonrequirement of a catalyst.

The easy work-up, the absence of a catalyst, and short reaction times when nonvolatile ionic liquid is used as the reaction medium make the method amenable for scale-up operations.

Tetrahydroquinoline derivatives are an important class of compounds in the field of pharmaceuticals due to their wide-spectrum biological activities including psychotropic, antiallergenic, anti-inflammatory, and estrogenic behaviors.

Particularly, isoquinolonic acids are useful precursors for the total synthesis of naturally occurring phenanthridine alkaloids such as corynoline, oxocorynoline, and epicorynoline as well as indenoisoquinolines possessing significant antitumor activity.

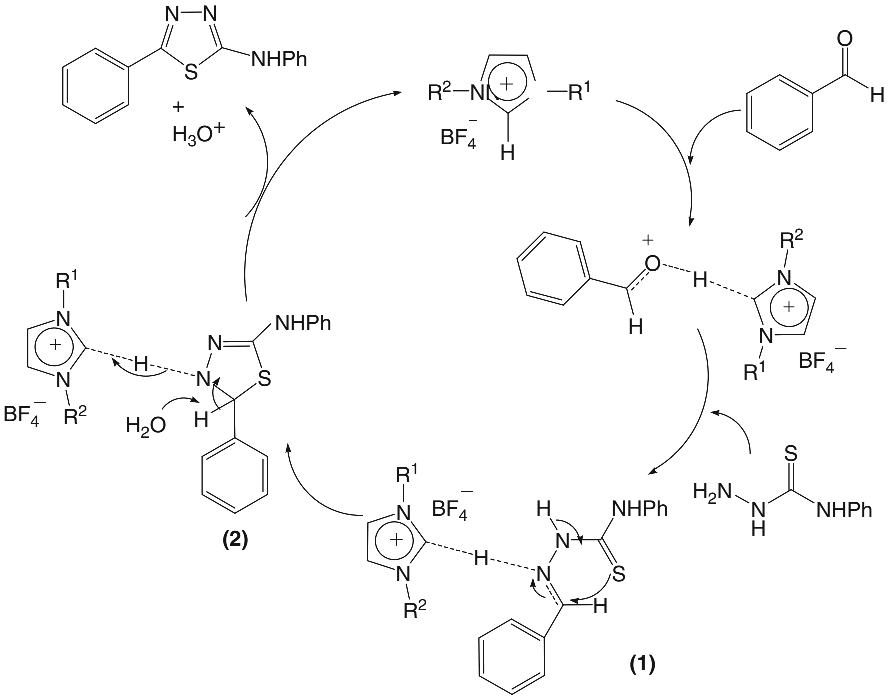


Fig. 12.4 Mechanism of the synthesis 1,3,4-thiadiazoles in [bmim][BF_4]

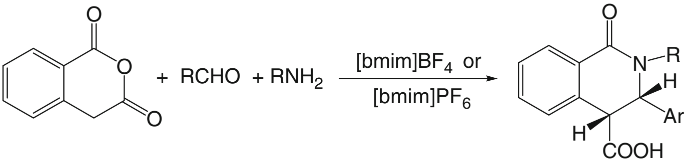


Fig. 12.5 Synthesis of *cis*-quinolonic acids in [bmim][BF_4]

In view of the emerging importance of the ionic liquids as novel reaction media, Yadav and his coworkers explored the use of ionic liquids as promoters for the synthesis of *cis*-quinolonic acids. The reactions of various aldehydes, amines, and homophthalic anhydride were studied in different ionic liquids (Fig. 12.5) [4]. Among these ionic liquids, [bmim][BF_4] was found to be superior in terms of yields, reaction rates, and reusability.

In all cases, the reactions proceeded efficiently at ambient temperature under mild conditions to afford the corresponding isoquinolonic acids in high yields. However, in the absence of ionic liquids, the reaction did not yield any product even after a long reaction time. This observation clearly indicated the efficiency of ionic liquids for this transformation.

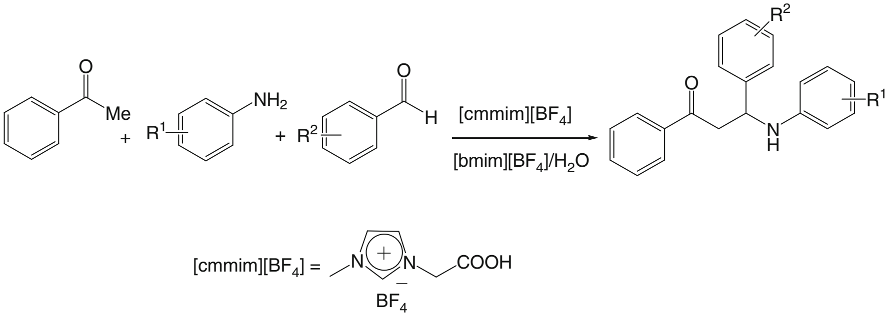


Fig. 12.6 Condensation of aldehydes, ketones, and amines in ionic liquids

Li and coworkers reported their primary results on the Mannich reaction catalyzed by a cation-functionalized acidic ionic liquid, 1-carboxymethyl-3-methylimidazolium tetrafluoroborate ($[cmmim][BF_4]$) in the mixture of water and 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim][BF_4]$) (Fig. 12.6) [5]. β-aminoketone derivatives were synthesized successfully in aqueous $[bmim][BF_4]$ with satisfactory to excellent yields, and the catalyst-containing aqueous media can be recycled at least six times with similar activity. In their procedure, the recovered catalyst-containing aqueous media could be reused directly (straightforwardly) without other manipulation such as distillation and dehydration.

Investigations showed that electron-donating substituents of aniline and aromatic aldehydes were disadvantageous to Mannich reaction; the yields of 4-methyl-aniline were lower than those of other aromatic amines. Moreover, no β-aminoketones were obtained on using 4-aminoanisole as an amine component.

Benzimidazoles possess important pharmacological activities such as antimicrobial, antifungal, antiparkinson, anticancer, and antibiotic. The one-pot regioselective synthesis of these compounds has been performed by taking a heteroaromatic amine and/or 1,2-phenylenediamine with 2-mercaptoacetic acid and an aromatic aldehyde in ionic liquids, namely, 1-butyl-3-methylimidazolium trifluoroborate ($[bmim][BF_4]$) and 1-methoxyethyl-3-methylimidazolium trifluoroacetate ([MOEMIM][TFA]). The reaction has been carried out under nitrogen atmosphere (Figs. 12.7, 12.8) [6]. Consideration of the yields of compounds revealed that [MOEMIM][TFA] is a better reaction media in comparison to $[bmim][BF_4]$.

This may be attributed due to the ability of [MOEMIM][TFA] to hydrogen bond with aromatic/heterocyclic/1,2-phenylenediamine. Studies for recyclability of the regenerated ionic liquids cleared that the yield of the products decreases in various cycles, yet ionic liquid can be reused with significant success. The absence of catalyst and recyclability of ionic liquid make this procedure cleaner and promising for scale-up.

Isatin is the privileged lead molecule for designing potential bioactive agents, and its derivatives have been shown to possess a broad spectrum of bioactivity as many of which were assessed anti-HIV, antiviral, antitumor, antifungal,

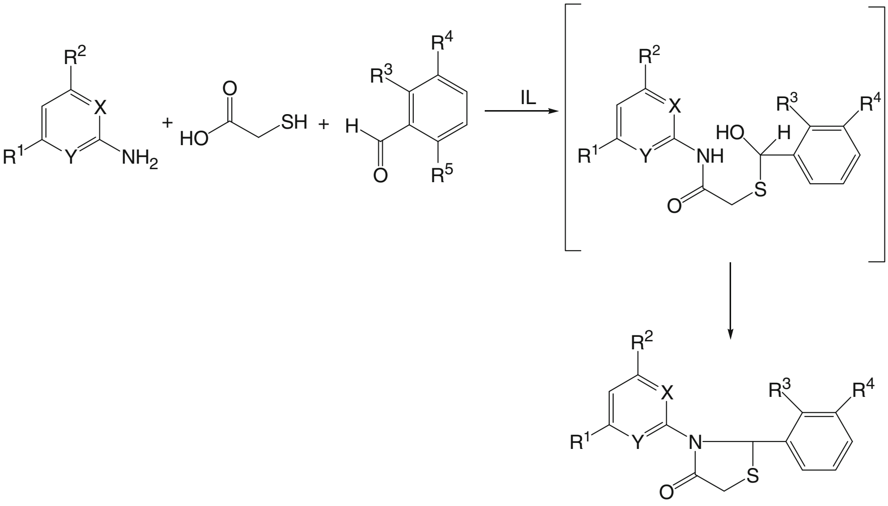


Fig. 12.7 Synthesis of benzimidazoles in [bmim][BF_4]

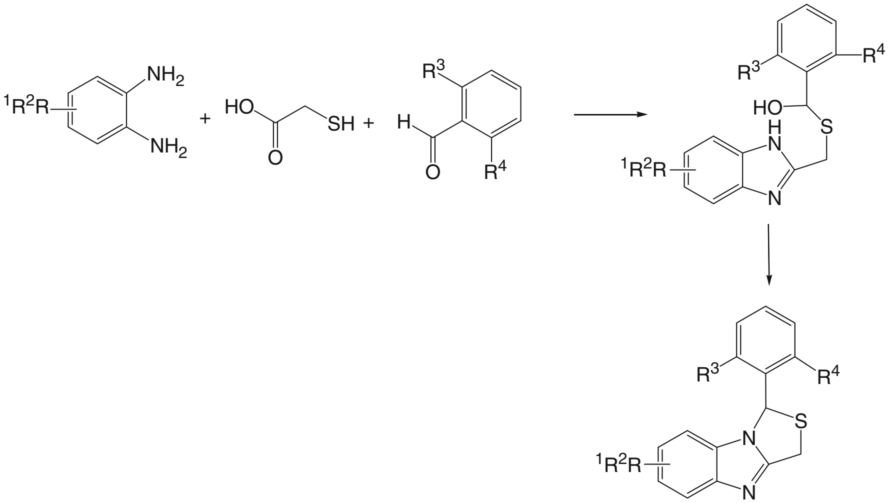


Fig. 12.8 Preparation of benimidazoles promoted by [MOEMIM][TFA]

antiangiogenic, anticonvulsants, anti-Parkinson's disease therapeutic, and effective SARS coronavirus 3CL protease inhibitor. Rad-moghadam and coworkers had demonstrated the application of three ionic liquids in the synthesis of 3- (indol-3-yl) -3-hydroxy indolin-2-ones (Fig. 12.9) and symmetrical as well as unsymmetrical 3,3-di(indol-3-yl)indolin-2-ones (Fig. 12.10) of biological interests at room temperature [7]. The reaction of an indole and an isatin derivative even 3:1 mole ratio

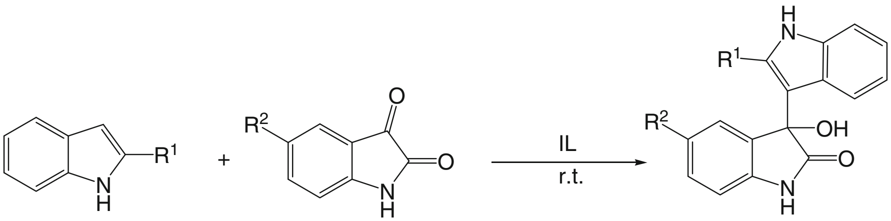


Fig. 12.9 Synthesis of 3- (indol-3-yl) -3-hydroxy indolin-2-ones in ionic liquids

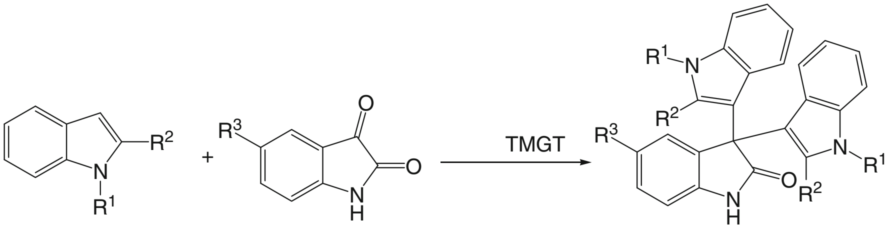


Fig. 12.10 Synthesis of symmetrical 3- (indol-3-yl) -3-hydroxy indolin-2-ones

under catalysis of *N,N,N,N*-tetramethylguanidinium triflate (TMGT$_f$) or [bmim] BF$_4$-LiCl ionic liquids gave solely the 1:1 adduct, 3- (indol-3-yl) -3-hydroxy indolin-2-ones, in fairly high yields at room temperature. It seems that in the case of [bmim]BF$_4$-LiCl, Li$^+$ played the same role as H$^+$ in TMGT$_f$. Similar reaction in *N,N,N,N*-tetramethylguanidinium trifluoroacetate (TMGT) favored to form solely symmetrical 3,3-di(indol-3-yl) indolin-2-ones. The probable mechanism of the reaction is shown in Fig. 12.11.

Experimental simplicity associated with the high yield of products, recyclability of ionic liquids, and short reaction times render the methods presented here highly competitive compared to existing procedures.

12.1.1.2 1-Butyl-3-methylimidazolium Hexafluorophosphate

1-(α-aloxyalkyl)benzotriazoles are of great importance for biochemistry and antitumor activity. Le and coworkers used three-component condensation of benzotriazole, aldehydes, and alcohols in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF$_6$]) in the presence of catalytic amounts of sulfuric acid for preparation of these type of compounds (Fig. 12.12) [8].

The ionic liquid can be recovered after extracting the product with ether. The recovered ionic liquid can be reused. The ionic liquid played the dual role of solvent and promoter. This method consists many obvious advantages compared to the conventional methods, including rate acceleration, environmentally more benign, and

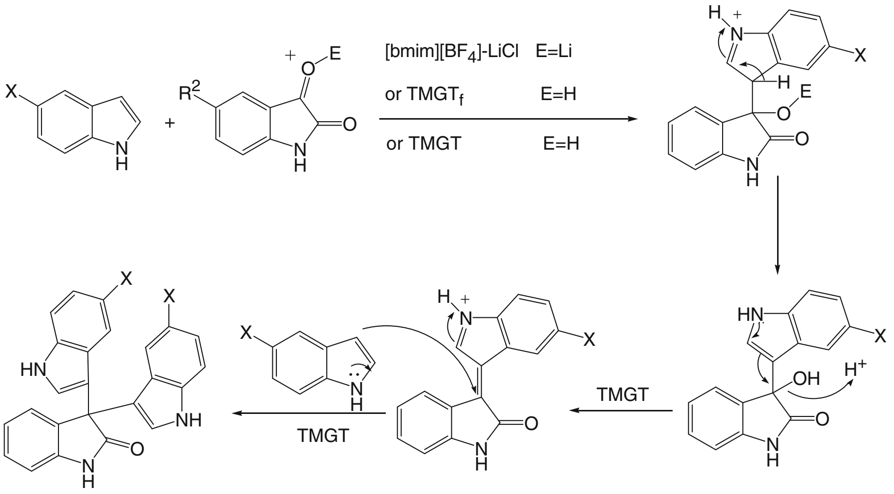


Fig. 12.11 Probable mechanism of the synthesis of 3- (indol-3-yl) -3-hydroxy indolin-2-ones

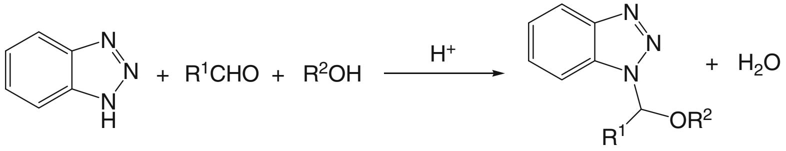


Fig. 12.12 Synthesis of 1-(α-aloxyalkyl)benzotriazoles in [bmim][PF$_6$]

the simplicity of isolation of the product, higher yield, and possibility of recycling of the ionic liquid.

Thiazolidinone and their derivatives are important heterocyclic compounds due to their broad biological activities such as anti-inflammatory, antiproliferative, anti-cyclooxygenases (COX-1 and COX-2), antihistaminic, and antibacterial activities. More importantly, some of the 2,3-diaryl-1,3-thiazolidin-4-ones were found to be highly effective against HIV-1 replication.

In 2009, Zhang et al. have investigated the preparation of thiazolidinones via the one-pot three-component condensations of aldehydes, amines, and 2-mercaptoacetic acid in ionic liquids (Fig. 12.13) [9].

They found that out of the two ILs studied, namely, [bmim][PF$_6$] and [bmim][BF$_4$], [bmim][PF$_6$] gave better results presumably due to its hydrophobic activation activity. It is postulated that water formed in situ from the condensation process is miscible with hydrophilic [bmim][BF$_4$] and thus detained, which prevents the reaction from completion. In contrast, the hydrophobic nature of [bmim][PF$_6$] would create a microenvironment to drive the equilibrium by extruding water out of the ionic liquid phase and thus results in a higher conversion.

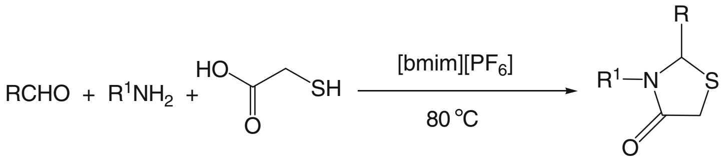


Fig. 12.13 Synthesis of thiazolidinone in [bmim][PF_6]

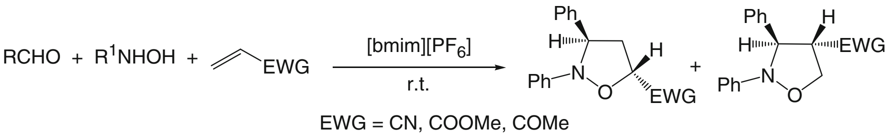


Fig. 12.14 1,3-Dipolar cycloaddition reaction

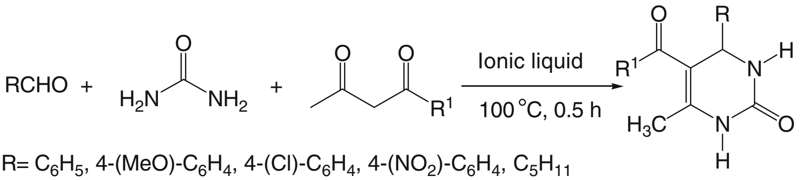
Ionic liquids exhibited enhanced reactivity by reducing reaction time and improving the yields significantly. The recovered [bmim][PF_6] could be successively recycled for at least five times without obvious loss in its efficiency.

Nitrones are effective 1,3-dipoles, and they can undergo readily cycloaddition with electron-deficient olefins to produce substituted isoxazolidines. Yadav and coworkers reported that these type of reactions are efficiently promoted in ionic liquid [bmim][PF_6] (Fig. 12.14) [10]. The method is highly regio- and diastereoselective, and products are obtained in excellent yields. They also showed that the same results can be obtained by using [bmim][BF_4] ionic liquid.

The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media contribute to the development of green strategy for the preparation of isoxazolidines. Furthermore, the use of [bmim][PF_6]solvent system for this transformation avoids the use of toxic or corrosive reagents and high temperature reaction conditions, and thus, it provides convenient procedure to carry out the reactions at ambient temperature.

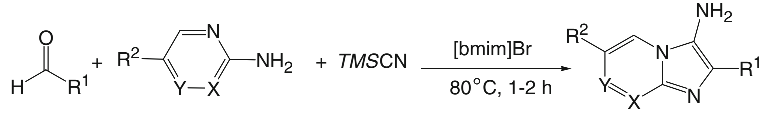
3,4-Dihydropyrimidine-2-(1*H*)-ones (DHPMs) and their derivatives have attracted considerable interest because of their therapeutic and pharmacological properties. They have emerged as integral backbones of several channel blockers, antihypertensive agents, β-1a antagonists, and neuropeptide **Y** (NPY) antagonists. Different types of methods are reported for the preparation of DHPMs, out of which the Biginelli's method is the most important.

The classical Biginelli synthesis is a one-pot condensation using β-dicarbonyl compounds with aldehydes (aromatic and aliphatic ones) and urea or thiourea in ethanol solution containing catalytic amounts of acid. Peng et al. for the first time reported a novel method for the synthesis of dihydropyrimidinones by three-component Biginelli condensations of aldehydes with 1,3-dicarbonyl compounds and urea using room temperature ionic liquids based on [bmim][BF_4] or [bmim][PF_6] as catalyst under solvent-free and neutral conditions (Fig. 12.15) [11].



R= C_6H_5, 4-(MeO)-C_6H_4, 4-(Cl)-C_6H_4, 4-(NO_2)-C_6H_4, C_5H_{11}
R^1= OEt, CH_3

Fig. 12.15 The Biginelli reaction catalyzed by [bmim][PF_6]



R= C_6H_5, 3-(NO_2)-C_6H_4, 4-(MeO)-C_6H_4, 4-(Cl)-C_6H_4, 4-(NO_2)-C_6H_4, 4-(Me)-C_6H_4, 2-pyridyl, 4-pyridyl
R^1= H, CH_3, Br
X= Y = CH
X = CH, Y= N
X = N, Y= CH

Fig. 12.16 Use of [bmim][Br] in the synthesis of imidazo[1,2-a]azines

The main advantages of this methodology are (1) relatively simple catalytic system, (2) shorter reaction times, (3) higher yields, (4) free of organic solvent, and (5) easy synthetic procedure. Comparison between the results obtained in [bmim][BF_4] and [bmim][PF_6] indicated that the BF_4^- and PF_6^- anions have some impact on the catalytic performance, and the PF_6^- anion is more favorable for such reactions.

12.1.1.3 1-*n*-Butyl-3-methylimidazolium Bromide

Imidazo[1,2-a]pyridines have emerged as versatile biologically active compounds spanning applications in anti-inflammatory and antibacterial agents, as inhibitors of gastric acids secretion, as calcium channel blockers, and in antiulcer-based therapies.

Shaabani et al. reported a facile method for the synthesis of imidazo[1,2-a]azines by a one-pot three-component condensation of an aldehyde, a 2-aminoazine, and trimethylsilylcyanide, as an isocyanide equivalent, in the presence of 1-*n*-butyl-3-methylimidazolium bromide ([bmim][Br]) as a promoter under classical heating conditions in high yields with rather short reaction times (Fig. 12.16) [12].

The efficiency and the yield of the reaction in [bmim][Br] was higher than those obtained in other solvents, such as MeOH, EtOH, CH_2Cl_2, and toluene and other ionic liquids like [bmim][PF_6] and [bmim][BF_4]. [bmim][Br] was separated from the reaction medium easily by washing with water and evaporating the solvent under vacuum and reused for subsequent reactions.

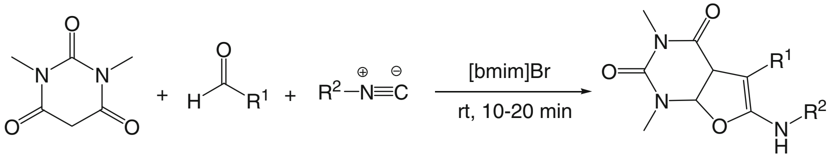


Fig. 12.17 Synthesis of furo[2,3-d]pyrimidine derivatives promoted by [bmim][Br]

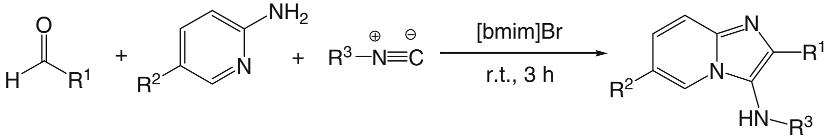


Fig. 12.18 [bmim][Br] promoted the synthesis of imidazo[1,2-a]pyridines

It is well known that pyrimidine systems as purine analogues exhibit a wide range of biological activities. Among them, the furo[2,3-d]pyrimidine derivatives act as sedatives, antihistamines, diuretics, muscle relaxants, and antiulcer agents.

Shaabani and co-workers reported the synthesis of furo[2,3-d]pyrimidine-2,4 (1H,3H)-diones via the three-component condensation of *N,N′*-dimethylbarbituric acid, aldehyde, and an alkyl or aryl isocyanide in 1-butyl-3-methylimidazolium bromide ([bmim][Br]) as the solvent and promoter at room temperature (Fig. 12.17) [13].

They have found that the presence of electron-withdrawing functional groups is necessary for the formation of the desired product.

On the contrary, with aromatic aldehydes carrying electron-releasing groups (such as 4-CH_3, or 4-OCH_3), products were obtained in poor yields. Several significant advantages, such as operational simplicity, mild reaction conditions, enhanced rates, improved yields, ease of isolation of products, recyclability, and the eco-friendly nature of the solvent, make this method a useful and attractive strategy for the synthesis of 2-aminofuran derivatives.

Imidazo[1,2-a]pyridines, an important class of pharmaceutical compounds, exhibit a wide spectrum of biological activities. Shaabani and coworkers developed the synthesis of 3-aminoimidazo [1,2-a] pyridines via the three-component condensation of an aldehyde 1,2-amino-5-methylpyridine or 2-amino-5-bromopyridine 2 and 3 isocyanide in 1-butyl-3-methylimidazolium bromide ([bmim][Br]) at room temperature (Fig. 12.18) [14].

Under the selected conditions, the ionic liquid [bmim][Br] can be easily separated by washing with water and evaporating the solvent under vacuum, and reuse it for subsequent reactions.

Biginelli-like reactions were performed by using a conjunction of silica sulfuric acid (SSA) as a solid acid and 1-butyl-3-methylimidazolium bromide [bmim][Br] as an ionic liquid. It is important to note that in the presence of only one of the two species, SSA or IL, the reaction proceeds in a different way, so that **(4)** were formed as the main products of the reaction (Fig. 12.19) [15].

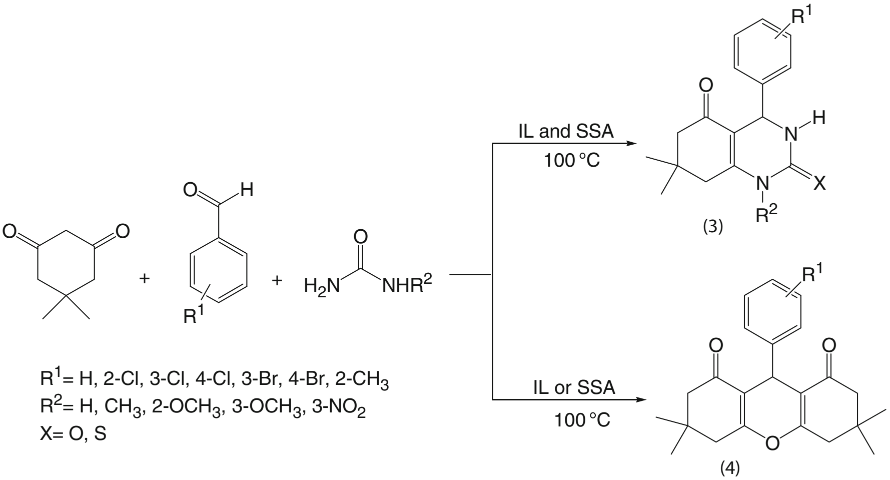


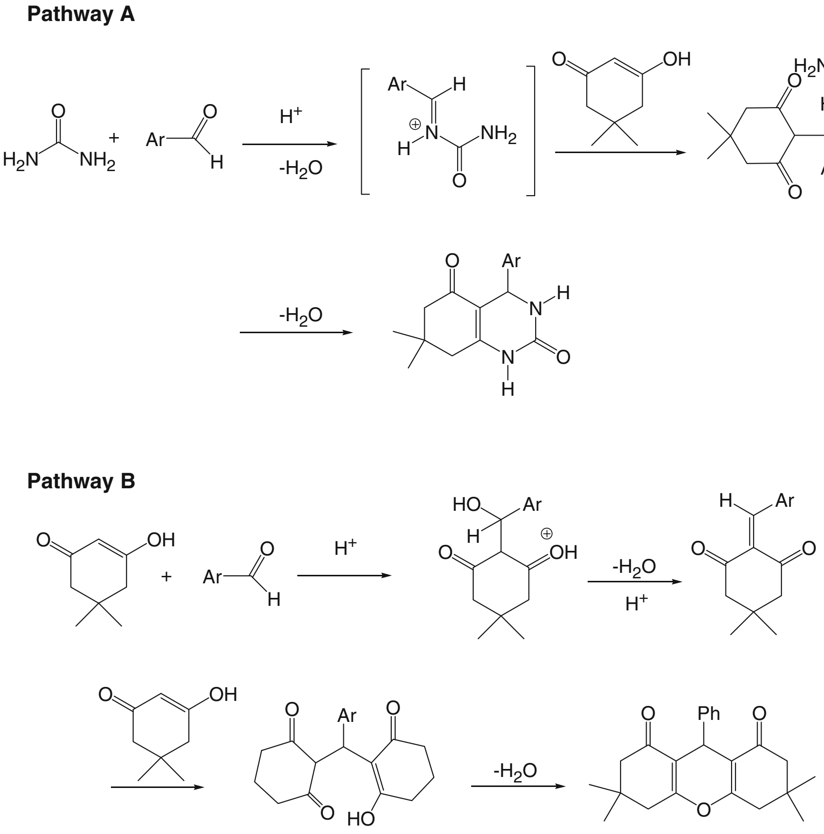
Fig. 12.19 Biginelli-like reactions in the presence of SSA and IL

The reason for this behavior is not clear, although an explanation may be presented, namely, that the *N*-acylium intermediate formation is accelerated and stabilized in the presence of SSA and IL (pathway A). However, the reaction proceeds via pathway B in the presence of only IL or only SSA (Fig. 12.20).

The IL effects can be explained with solvophobic interactions that generate an internal pressure, which promoted the association of the reactants in a solvent cavity during the activation process and showed an acceleration of the multicomponent reactions (MCRs) in comparison to conventional solvents. The reaction proceeded very efficiently with benzaldehyde and electron releasing and electron-withdrawing *ortho-*, *meta-*, and *para-*substituted benzaldehydes. IL was easily separated from the reaction medium by washing with water and distillation of the solvent under vacuum and it can be reused for subsequent reactions and recycled. IL showed no loss of efficiency with regard to reaction time and yield after four successive runs.

12.1.1.4 Butyl Methyl Imidazolium Hydroxide

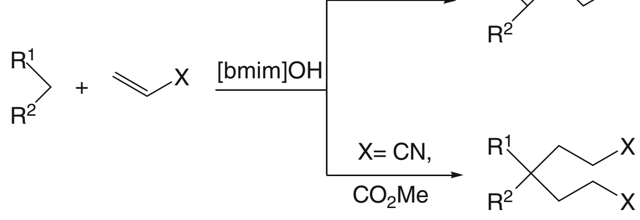
Ranu et al. reported the dramatic influence of a new tailor-made, task-specific, and stable ionic liquid, *butyl methyl imidazolium hydroxide* ([bmim][OH]), in Michael addition. They have discovered that a task-specific ionic liquid [bmim][OH] efficiently promoted the Michael addition of 1,3-dicarbonyl compounds, cyano esters, and nitro alkanes to a variety of conjugated ketones, carboxylic esters, and nitriles without requiring any other catalyst and solvent (Fig. 12.21) [16]. Very interestingly, all open-chain 1,3-dicarbonyl compounds such as acetylacetone, ethyl acetoacetate, diethyl malonate, and ethyl cyanoacetate reacted with methyl vinyl ketone and chalcone to give the usual monoaddition products, whereas the same reactions with methyl acrylate or acrylonitrile provided exclusively bis-addition products.



Pathway A

Pathway B

Fig. 12.20 Pathways of the Biginelli-like reaction in [bmim][Br]



R^1, R^2 = CH3, COMe, COPh, CO_2Me, CO_2Et, NO_2 etc.

Fig. 12.21 Michel addition promoted in [bmim][OH]

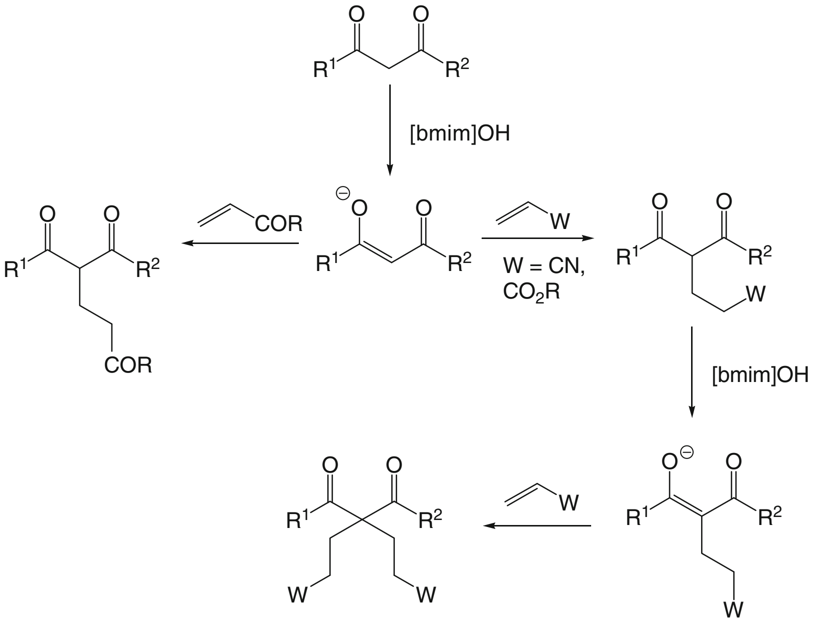


Fig. 12.22 Proposed mechanism for the Michel addition in [bmim][OH]

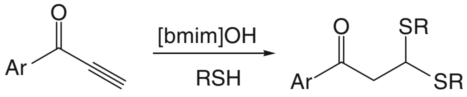


Fig. 12.23 Addition of thiols with terminal acetylenic ketones

In general, the great significance of this rather unusual bis-addition is the formation of two C–C bonds in one step. These adducts have great synthetic potential, as they contain several important functional groups. This ionic liquid, [bmim][OH], is very successful in catalyzing this process and making it feasible within a reasonable time period at room temperature to provide high yields of products. All the reactions are very clean and reasonably fast. The reaction conditions are mild (room temperature), accepting several functional groups present in the molecules.

The following mechanism was proposed for these transformations (Fig. 12.22).

Several thiols and dithiols underwent double conjugate addition with conjugated terminal acetylenic ketones in the presence of [bmim][OH], to produce the corresponding β-keto 1,3-dithane derivatives (Fig. 12.23). It should be noted that in the case of C-S Michel addition, [bmim][OH] was diluted with another neutral ionic liquid, [bmim][Br], to get the best results. These compounds are of much importance in organic synthesis.

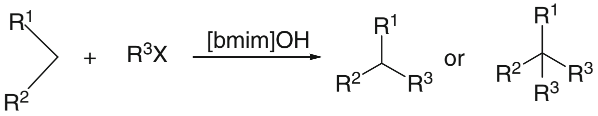


Fig. 12.24 Alkylation of 1,3-diketones compounds in [bmim][OH]

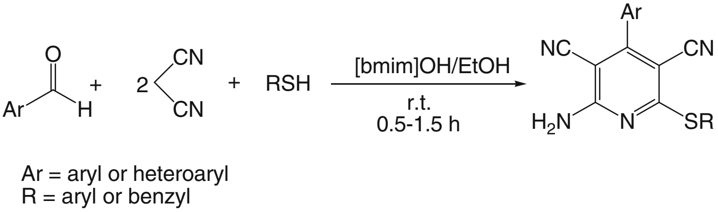


Fig. 12.25 Preparation of highly substituted pyridins in [bmim][OH]

Active methylene compounds such as 1,3-diketones, 1,3-keto carboxylic esters, malononitrile, and ethyl cyanoacetate were alkylated by alkyl halides catalyzed by the ionic liquid [bmim][OH] under microwave irradiation. The alkyl halides included allyl, benzyl, methyl, and butyl bromides/iodides. The open-chain 1,3-ketones produced the monoalkylated products, whereas the cyclic diketones provided the dialkylated products in one stroke. Malononitrile and ethyl cyanoacetate also furnished the dialkylated products (Fig. 12.24) [17].

The highly substituted pyridine derivatives are of intense attention because of their potential for biological activities, and thus, an efficient procedure for their synthesis is of high importance. The basic ionic liquid, [bmim][OH], efficiently promotes a one-pot, three-component condensation of aldehydes, malononitrile, and thiophenols to produce highly substituted pyridines in high yields at room temperature (Fig. 12.25) [18]. The present procedure using a basic ionic liquid, [bmim][OH], in place of conventional bases provides a selective, high-yielding one-pot synthesis of highly substituted pyridines through a three-component condensation process. Significantly, the formation of a side product, enaminonitrile, was virtually eliminated. The other advantage of this procedure is that it does not require the use of hazardous organic solvent. The residual ionic liquid was rinsed with ethyl acetate, dried under a vacuum, and recycled.

The first step of this process involves the Knoevenagel condensation of an aldehyde with malononitrile to form the corresponding Knoevenagel product (5). The second molecule of malononitrile then undergoes Michael addition to 5 followed by simultaneous thiolate addition to C≡N of the adduct and cyclization to dihydropyridine (6) which on aromatization and oxidation (air) under the reaction conditions leads to pyridine.

It may be speculated that the difference in basicity of [bmim][OH] used in this reaction compared to 1,4-diazabicyclo[2.2.2]octane (DABCO), and Et_3N may play a crucial role in suppressing the enaminonitrile formation. The use of other ionic

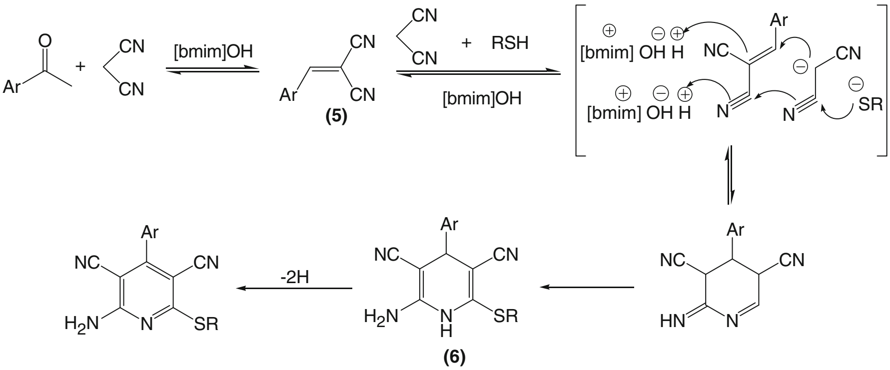


Fig. 12.26 Proposed mechanism for the synthesis of highly substituted pyridines in [bmim][OH]

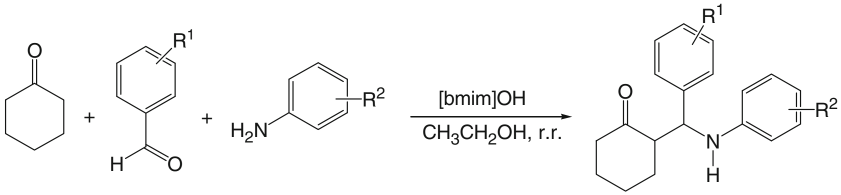


Fig. 12.27 Mannich-type reaction promoted by [bmim][OH]

liquids such as [bmim][Br] or [bmim][BF$_4$] failed to push the reaction to the pyridine stage, and the reaction was stopped at an intermediate step with the formation of compound 5 (Fig. 12.26).

A Mannich-type reaction including the one-pot three-component condensation of benzaldehydes, anilines, and ketones in [bmim][OH] was reported by Gong et al. (Fig. 12.27) [19]. It should be noted that benzaldehydes and anilines carrying either electron-donating or electron-withdrawing substituents all reacted well. Particularly, aryl aldehydes bearing an electron-withdrawing group are favorable for the transformation, while anilines with electron-donating groups are beneficial for these reactions.

The most attractive part of this work is that [bmim][OH] is easily recycled and can be reused without obvious loss of the catalytic activity. This approach could make a valuable contribution to the synthesis of β-amino carbonyl compounds.

The ionic liquid [bmim][OH] has also been used as an efficient catalyst for the synthesis of a variety of 4H-benzo[b]pyran derivatives by a one-pot three-component condensation of aldehydes, cyclohexa-1,3-diones, and malononitrile/ethyl cyanoacetate at room temperature (Fig. 12.28) [20].

The significant advantages offered by this methodology were (1) operational simplicity, (2) general applicability to all types of aldehydes, (3) mild reaction

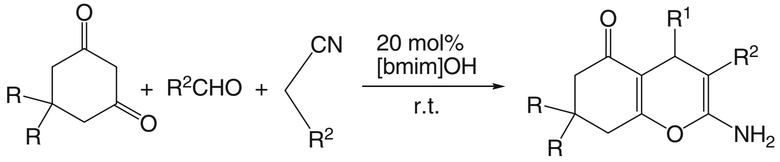


Fig. 12.28 Synthesis of 4H-benzo[b]pyran derivative in [bmim][OH]

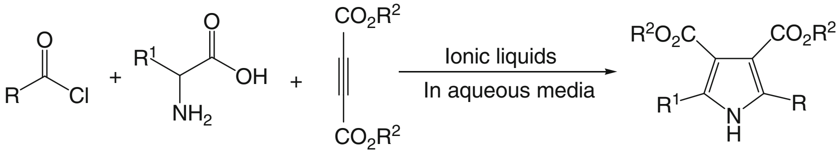


Fig. 12.29 Synthesis of pyrrols catalyzed by ILs

conditions, (4) excellent yields of products, and (5) green procedure avoiding hazardous organic solvents and providing reusability of ionic liquid catalyst.

An efficient three-component, one-pot synthesis of functionalized pyrroles, catalyzed by basic ILs in aqueous media, has been described (Fig. 12.29) [21].

Among the ionic liquids used, the basic functionalized ionic liquid, butyl methyl imidazolium hydroxide [bmim][OH], was the most effective catalyst. The [bmim] OH/H_2O catalyst system could be reused for at least five recycles without appreciable loss of efficiency. Reactions in aqueous media offer many advantages such as simple operation and high efficiency in many organic transformations that involve water-soluble substrates and reagents. These advantages become even more attractive if such reactions can be conducted using ILs in aqueous media. The presented protocol not only is simple and high yielding but also greatly decreases environmental pollution. The probable mechanism of the reaction is shown in (Fig. 12.30).

12.1.1.5 Other 1-Butyl-3-methylimidazolium-Based Ionic Liquids

Indole and its derivatives have versatile biological activities and found in various biologically active natural products. Chakraborti and coworkers reported the catalytic applications of various room-temperature ionic liquids (RTILs) during the reaction of aldehydes with indole under solvent-free conditions for the synthesis of bis(indolyl)methanes. The reaction of indole with benzaldehyde under neat conditions and at room temperature was considered for a model study (Fig. 12.31).

The catalytic efficiency of the RTILs derived from 1-butyl-3-methylimidazolium (bmim) cation is influenced by the structure of the imidazolium moiety and the counteranion following the order: [bmim][$MeSO_4$] > [bmim][HSO_4] ≈ [bmim]

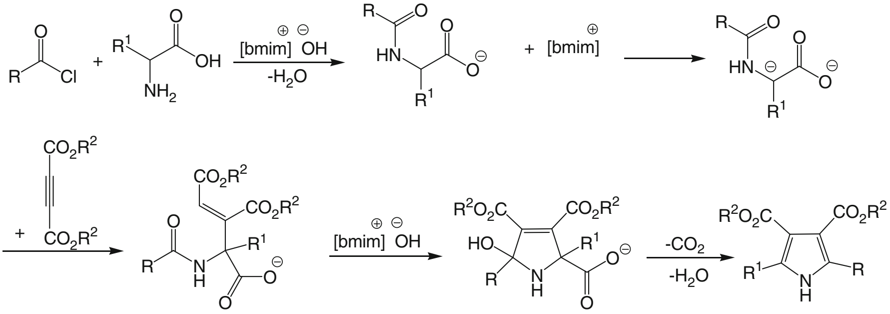


Fig. 12.30 Probable mechanism of the synthesis of pyrroles promoted by [bmim][OH]

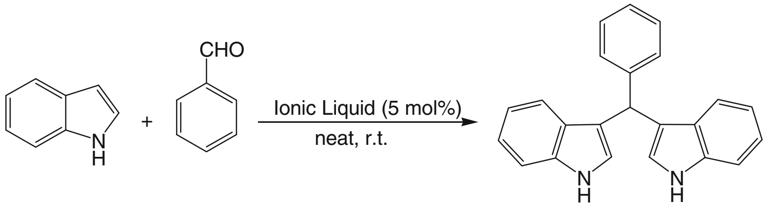


Fig. 12.31 Condensation of indole with benzaldehyde using ILs

$[MeSO_3] >> [bmim][BF_4] > [bmim][Br] > [bmim][NTf_2] \approx [bmim][PF_6] > [bmim][N(CN)_2] \approx [bmim][ClO_4] \approx [bmim][HCO_2] > [bmim][N_3] > [bmim][OAc]$. Substitution of the C-2 hydrogen in $[bmim][MeSO_4]$ decreased the catalytic efficiency. In case of 1-methyl-3-alkylimidazolium methyl sulfates, the best results were obtained with 3-butyl derivative and the catalytic property was retained with ethyl, *n*-propyl, and *n*-pentyl groups at N-3 although to a lesser extent with respect to 3-butyl analogue.

The reaction is compatible with a variety of functional groups such as halogen, alkoxy, nitrile, hydroxy, and tert-butylcarbamate (O-*t*-Boc). The $[bmim][MeSO_4]$ exhibits an ampiphilic "electrophile–nucleophile" dual activation role through the intermediate **7** in which the aldehyde carbonyl undergoes hydrogen bond formation (electrophilic activation) with the C-2 hydrogen atom of the bmim cation due to its acidic nature. The quaternary nitrogen atom of the bmim cation undergoes electrostatic interaction with the nitrogen lone pair of the indole and enforces the N–H hydrogen of the indole for hydrogen bond formation with the oxygen atom of the $MeSO_4$ anion (nucleophilic activation) through a six-membered chair-like cyclic structure. In a similar fashion, the intermediate indolyl methanol **8** undergoes complex formation with another molecule of indole and $[bmim][MeSO_4]$ forming **9** that leads to the formation of product and liberates the IL (Fig. 12.32). The decrease in the product yield on using C-2 methyl substituted $[bmim][MeSO_4]$ provides supports to the electrophilic activation of the aldehyde through hydrogen bond formation with C-2 hydrogen of $[bmim][MeSO_4]$.

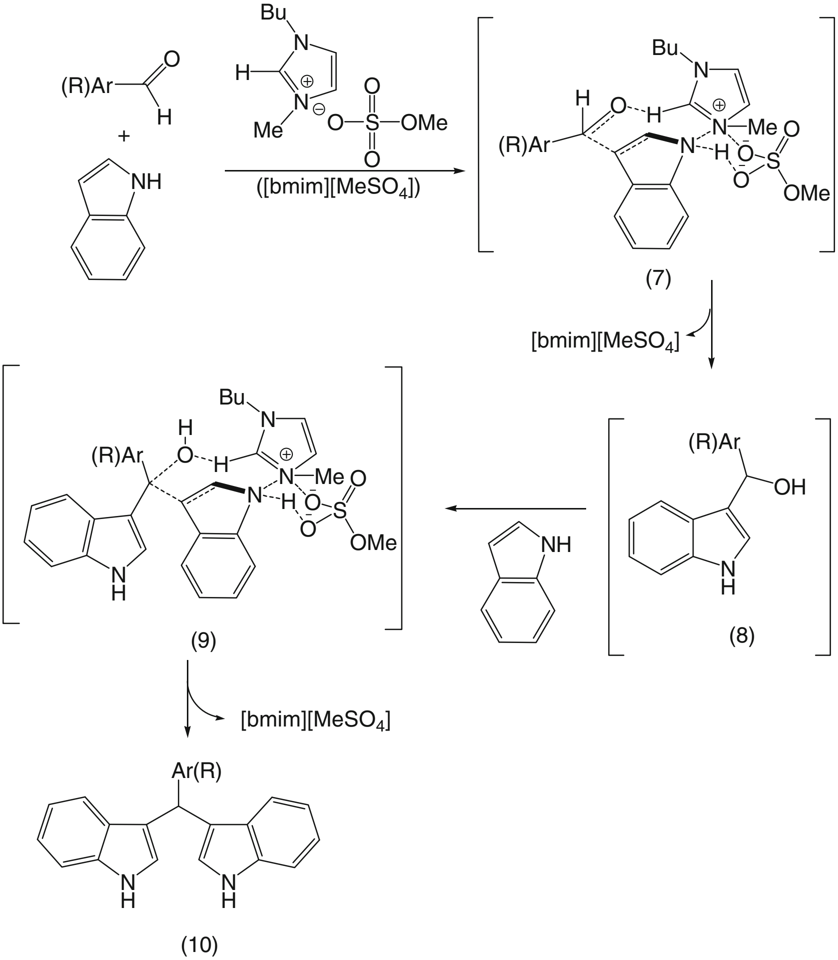
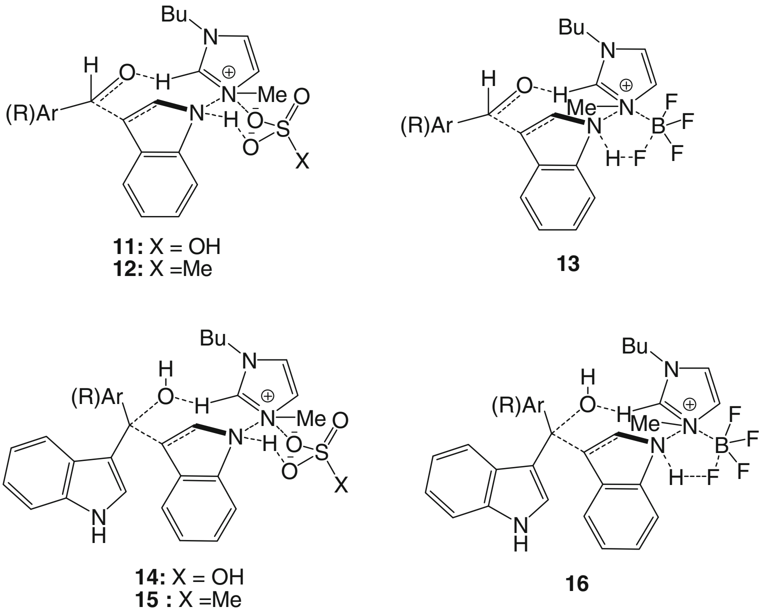


Fig. 12.32 Mechanism of the condensation of indole with aldehydes in the presence of [bmim][MeSO$_4$]

The lack of appreciable amount of hydrogen bond formation between the aldehyde carbonyl group and the C-2 hydrogen atom of the bmim cation in the hydroxylic solvents (EtOH and water) that are themselves hydrogen bond donors causes a drastic reduction in the product yield. Similarly, the reaction is retarded in MeCN, a hydrogen bond acceptor, due to disruption of the hydrogen-bonded structures **7/9**. These observations suggest that the catalytic efficiency of the IL is best exhibited under neat conditions where a conducive environment for the hydrogen bond formation between the aldehyde carbonyl oxygen and the C-2 hydrogen atom of the bmim cation is available. A similar acceleration effect of the imidazolium-based ILs has been observed during electron transfer reaction by coordination of the acidic C-2 hydrogen atom of imidazolium ILs with the oxygen radical anions.



11: X = OH
12: X =Me

13

14: X = OH
15 : X =Me

16

Fig. 12.33 Hydrogen bond formation between ILs and indole

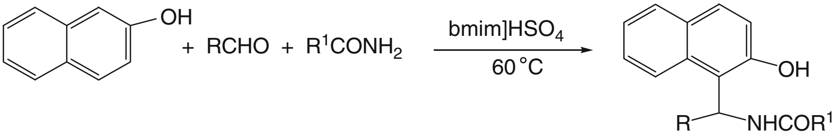


Fig. 12.34 [bmim][HSO$_4$] promoted synthesis of amidoalkyl naphthol derivative

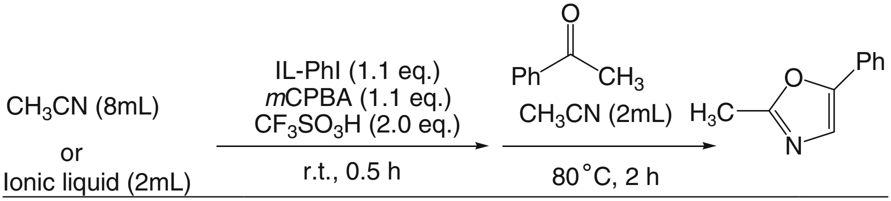
The influence of the anion in contributing to the catalytic potency toward the IL can be rationalized with this mechanistic proposal. The catalytic activity of ILs is determined by the feasibility of hydrogen bonding between indole and HSO_4^-, $MeSO_3^-$, and BF_4^- anions through six-/five-membered chair-/envelop-like cyclic structures **11–13** and **14–16** (Fig. 12.33) [22].

Compounds bearing 1,3-amino-oxygenated functional groups are ubiquitous to a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors such as ritonavir and lipinavir, and the hypotensive and bradycardiac effects of these compounds have been evaluated.

Sapkal and coworkers explored the use of ionic liquids as promoters and recyclable solvent systems for a one-pot three-component synthesis of amidoalkyl naphthol derivatives under mild conditions (Fig. 12.34) [23].

They reported for the first time a very simple and efficient methodology for the high-yielding synthesis of amidoalkyl naphthols by the straightforward one-pot

Table 12.1 Preparation of oxazoles using IL-supported PhI



Entry	Solvent	IL-PhI	Yield (%)
1	CH_3CN	A	0
2	CH_3CN	B	44
3	CH_3CN	C	0
4	CH_3CN	D	59
5	CH_3CN	E	<5
6	CH_3CN	F	23
7	CH_3CN	G	39
8	CH_3CN	H	34
9	CH_3CN	I	48
10	[emim]OTs	D	0
11	[bmim]PF_6	D	33
12	[bmpy]NTf_2	D	45

three-component condensation of aromatic/heteroaromatic/aliphatic aldehydes, 2-naphthol, and amides or urea at mild (60°C) condition in acidic ionic liquid.

The operational simplicity of the procedure, shorter reaction times, simple work-up procedure, cost-effective recovery, and reusability of ionic liquid make this method much attractive.

12.1.2 Other Imidazole-Based Ionic Liquids

12.1.2.1 Ionic Liquid–Supported Iodoarenes

Kawano and Togo introduced an ionic liquid group into iodoarenes, to form ionic liquid–supported iodoarenes, and used them for the promotion of the synthesis of oxazoles [24]. The results of the reactions of acetonitrile, *m*-chloroperbenzoic acid (*m*CPBA), trifluoromethanesulfonic acid (TfOH), and acetophenone are shown in Table 12.1, using various IL-supported iodoarenes (IL-supported PhIs). The reactivities of IL-supported iodoarenes (PhIs) **17–25** are shown in entries 1–9, and IL-supported PhI **20** showed the best reactivity. Instead of acetonitrile as solvent, room temperature ILs, such as [emim][OTs], [bmim][PF_6], and [bmpy][NTf_2], were used in the presence of IL-supported PhI **20** (entries 10–12). However, [emim][OTs] did not promote the oxazole formation at all, while [bmim]PF_6 and [bmpy][NTf_2] provided the oxazole in moderate to low yields. Thus, use of acetonitrile as solvent yielded the best reactivity as compared with these ILs.

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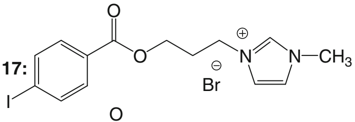

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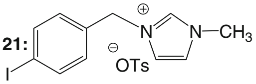

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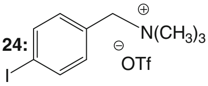

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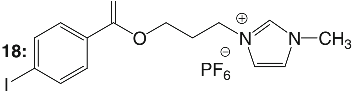

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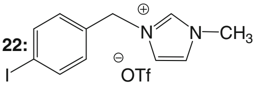

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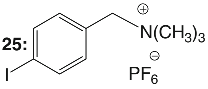

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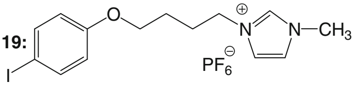

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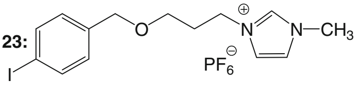

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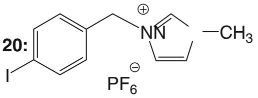
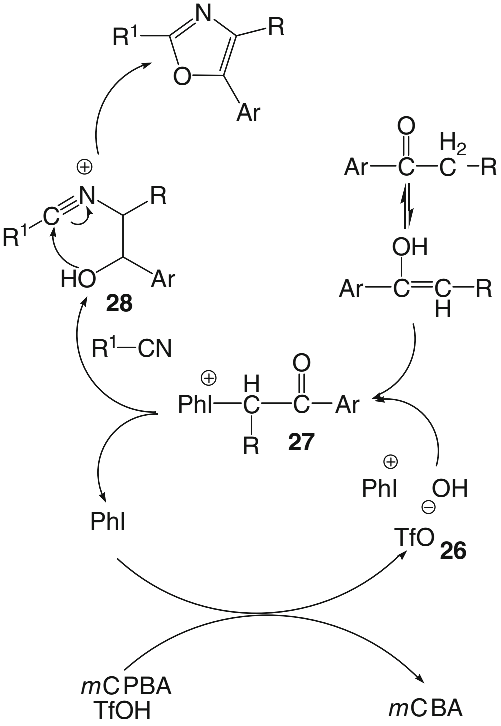


Fig. 12.35 Mechanism of the synthesis of oxazoles in liquid-supported iodoarenes



The proposed reaction pathway is shown in the Fig. 12.35.

Here, iodoarene worked as a catalyst. IL-supported PhI can be used in the same preparation of oxazoles from ketones and reused in the same reaction to obtain moderate yields of oxazoles.

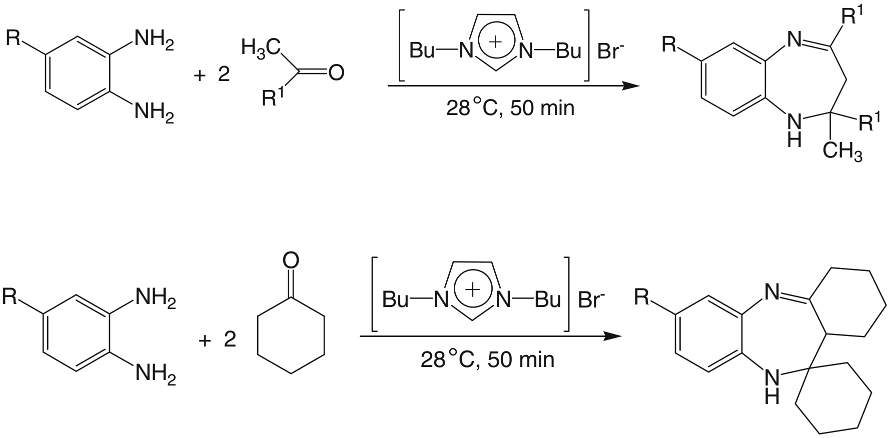


Fig. 12.36 Synthesis of 1,5-benzodiazepines in [bbim][Br]

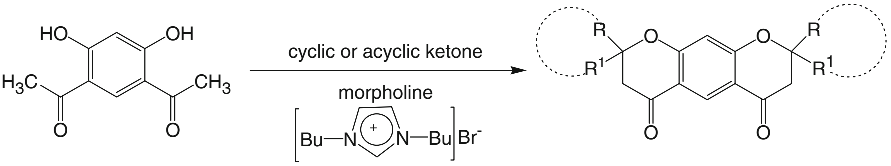


Fig. 12.37 Morpholine-catalyzed synthesis of 2-spiro-chroman-4(1*H*)-ones in [bbim][Br]

12.1.2.2 1,3-*n*-Dibutylimidazolium Bromide

Benzodiazepines are an important class of pharmacologically active compounds finding application as anticonvulsant, antianxiety, and hypnotic agents. Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers and as anti-inflammatory agents. Jarikote and coworkers have developed a new and efficient method for the regioselective synthesis of 1,5-benzodiazepines in excellent isolated yields in short reaction times using a room-temperature ionic liquid, namely, 1,3-*n*-dibutylimidazolium bromide [bbim][Br], as a reaction medium for the first time (Figs. 12.36, 12.37) [25].

Importantly, the IL not only acts as a solvating medium but also as a promoter for the reaction giving rise to twin advantages of ambient temperature conditions and the nonrequirement of a catalyst. The easy work-up procedures, the absence of a catalyst, and recyclability of the nonvolatile IL used as the reaction medium make the method amenable for scale-up operations.

Chromone derivatives, in particular 2-spiro-chroman-4(1*H*)-ones, are ubiquitous in nature and possess various biological activities which include antiarrhythmic, anti-HIV, antidiabetic, acetyl-CoA carboxylase (ACC) inhibitor, vanilloid receptor antagonist, growth hormone secretagogues, histamine receptor antagonist, and

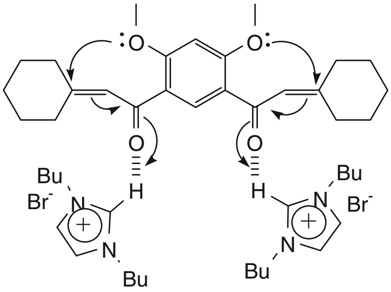


Fig. 12.38 Activation of the carbonyl carbons by [bbim][Br]

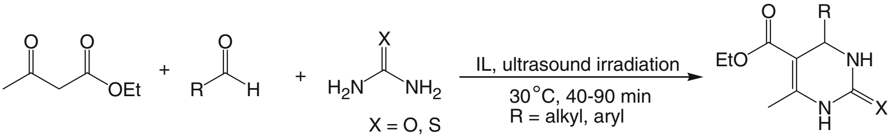


Fig. 12.39 The Biginelli reaction catalyzed by [Hbim][BF_4]

antiviral. Furthermore, these 2-spiro-chroman-4(1*H*)-ones serve as an important precursor for the synthesis of other medicinally important compounds such as rotenoids and xanthones. Recently, these structural scaffolds have been assigned as privileged structures for drug development. Muthukrishnan and coworkers described an extremely facile and environmental-friendly synthesis of bis-2-spirochromanones in one pot by carrying out Kabbe condensation in [bbim][Br] catalyzed by morpholine (Fig. 12.37) [26].

The role of the ionic liquid [bbim][Br] in the Kabbe condensation may be attributed to its inherent Brönsted/Lewis acidity and high solvating ability. Probably, the highly acidic 2H proton of [bbim]Br activates the carbonyl carbon of both alkanone and acetophenone, thus facilitates the enamine formation as well as the ready cyclization of unsaturated ketone intermediate **I** to the final product (Fig. 12.38).

12.1.2.3 1-*n*-Butylimidazolium Tetrafluoroborate

3,4-Dihydropyrimin-2-(1H)-ones (DHPMs) have been synthesized in excellent yields in short reaction times at ambient temperature in the absence of any added catalyst by the reaction of aromatic or aliphatic aldehydes with ethyl acetoacetate (EAA) and urea (or thiourea) at room temperature in 1-*n*-butylimidazolium tetrafluoroborate ([Hbim][BF_4]) under ultrasound irradiation (Fig. 12.39) [27].

The IL [Hbim][BF_4] has not only acted as a favorable medium with improved energetics of cavitation for the sonochemical MCR but also promoted the reaction with its inherent Brönsted acidity, thus obviating the necessity of using additional acid catalyst. The Brönsted acidity is conferred by the –NH proton of [Hbim][BF_4]

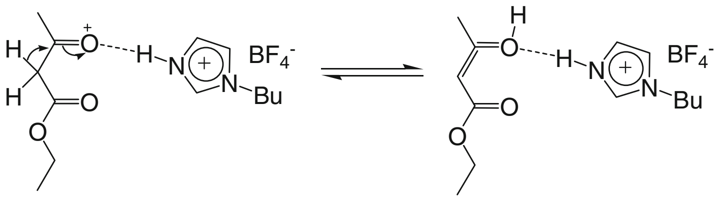


Fig. 12.40 Activation of carbonyl groups using [Hbim][BF_4]

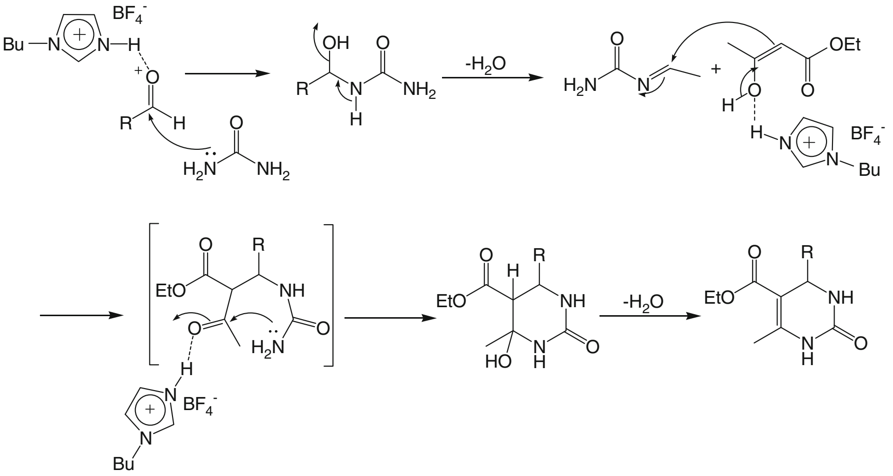


Fig. 12.41 Proposed mechanism for the promotion of the Biginelli reaction in the presence of [Hbim][BF_4]

(chemical shift of 14.59 ppm) capable of bonding with the carbonyl oxygen of the aldehydes as well as that of the β-keto ester (EAA) (Fig. 12.40).

Based on this evidence, a plausible mechanistic pathway has been postulated (Fig. 12.41).

12.1.2.4 1-Ethyl-3-methylimidazole Acetate

Synthesis of imidazole ring system and its derivatives occupy an important place in the realm of natural and synthetic organic chemistry because of their therapeutic and pharmacological properties. They have emerged as an integral part of many biological systems, namely, histidine, histamine, and biotin; an active backbone in existing drugs such as losartan, olmesartan, eprosartan, and trifenagrel; and agrochemical, fungicides, herbicides, and plant growth regulators; and large classes of imidazole derivatives are also used as ionic liquids. In addition to these important

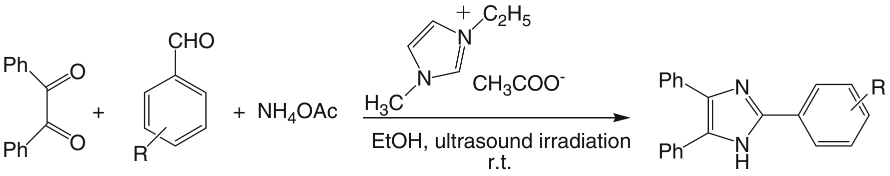


Fig. 12.42 Preparation of 2-aryl-4,5-diphenyl imidazoles in [emim][OAc] under ultrasonic irradiation

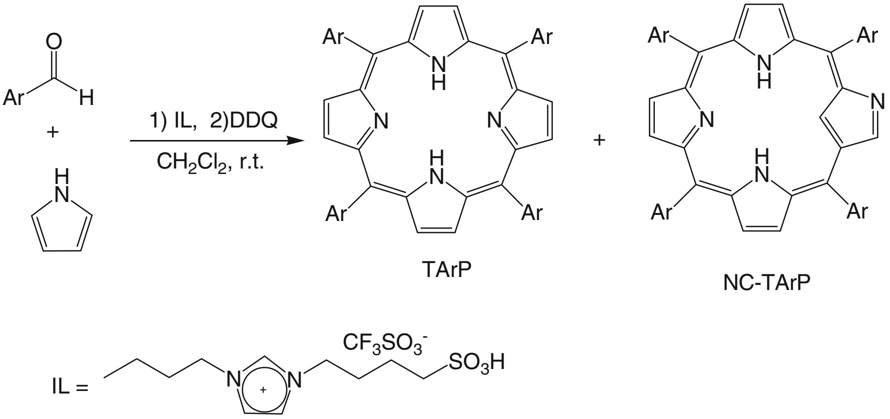


Fig. 12.43 Synthesis of porphyrin catalyzed by an acidic liquid

applications, imidazole derivatives are ideal scaffolds to make libraries of anti-inflammatory, antiallergic, and analgesic-drug-like compounds and to generate inhibitors of P38 MAP kinase.

The ionic liquid 1-ethyl-3-methylimidazole acetate ([emim][OAc]) was found to be a mild and effective catalyst for the efficient, one-pot, three-component synthesis of 2-aryl-4,5-diphenyl imidazoles at room temperature under ultrasonic irradiation (Fig. 12.42) [28].

This procedure has many obvious advantages compared to those reported in the literatures, including avoiding the use of harmful catalysts, reacting at room temperature, high yields, and simplicity of the methodology.

12.1.2.5 An Acidic Ionic Liquid

Kitaoka and coworkers provided a new methodology for porphyrin preparation with an acidic IL (Fig. 12.43) [29]. The acidic IL phase separated with dichloromethane becomes quite instrumental for reducing the amount of the halogenated solvents used in porphyrin preparation.

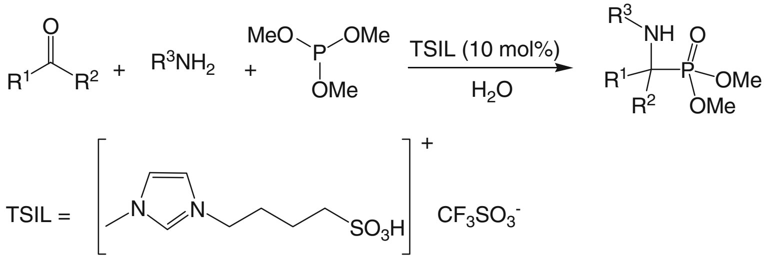


Fig. 12.44 TSIL promoted the synthesis of α-aminophosphonates in H_2O

More important than the superior productivity in the high reactant concentration is the reusability of the acidic IL to catalyze the formation of porphyrinogens without deterioration of the activity.

12.1.2.6 Task-Specific Ionic Liquids

α-Aminophosphonates can act as peptide mimetics, enzyme inhibitors, antibiotic and pharmacological agents, and as herbicides, fungicides, insecticides, and plant growth regulators. Akbari et al. have demonstrated that a readily available, highly efficient, task-specific ionic liquid (TSIL) can be used as a recyclable catalyst for the synthesis of α-aminophosphonates from aldehydes and ketones in water (Fig. 12.44) [30]. This is the first report of a functionalized ionic liquid–catalyzed synthesis of α-aminophosphonates.

The mechanism of this reaction is believed to involve formation of an activated imine by the ionic liquid so that addition of the phosphite is facilitated to give a phosphonium intermediate, which then undergoes reaction with the water generated during the formation of the imine to give the α-aminophosphonate and methanol (Fig. 12.45).

12.1.2.7 1-Methyl-3-heptyl-imidazolium Tetrafluoroborate

The structures of trisubstituted imidazoles are prevalent in natural products and pharmacologically active compounds, like the known P38 map kinase inhibitor and losartan. Besides, triarylimidazoles display various bioactive effects such as herbicidal, fungicidal, analgesic, anti-inflammatory, and antithrombotic activities as well. The three-component synthesis of 2,4,5-trisubstituted imidazoles, a typical acid-catalyzed reaction, could be conducted successfully with good to excellent yields in a neutral ionic liquid, 1-methyl-3-heptyl-imidazolium tetrafluoroborate ([Hemim][BF_4]), under solvent-free and microwave-assisted conditions (Fig. 12.46) [31].

The combined merits of microwave irradiation and ionic liquid make the three-component condensation with safe operation, low pollution, and rapid access to

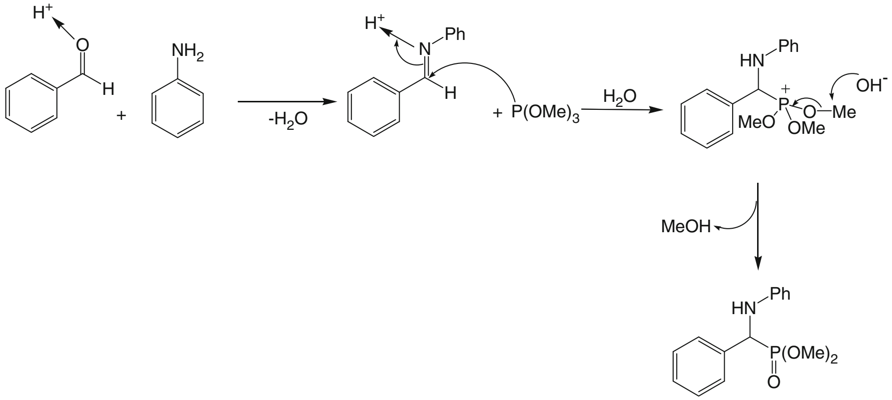


Fig. 12.45 Mechanism of the synthesis of α-aminophosphonates

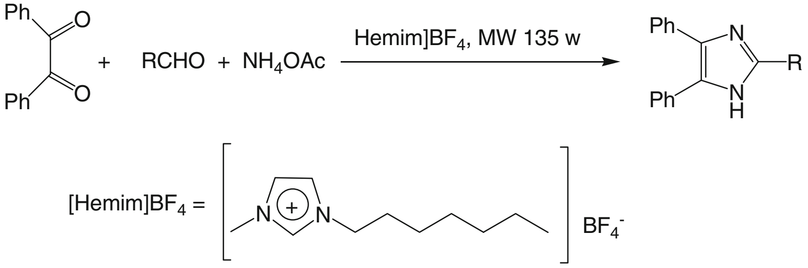


Fig. 12.46 Synthesis of 2,4,5-trisubstituted imidazoles in [Hemim][BF_4] under microwave irradiation

products and simple work-up. The polar nature of ionic liquid makes it ideal for use in solvent-free microwave irradiation. It was shown that [Hemim][BF_4] was so extremely suitable as the catalytically active medium that the yields of the products were not dramatically decreased even after four cycles.

12.1.2.8 1-[2-(Acetoacetyloxy)ethyl]-3-methylimidazolium Hexafluorophosphate-Bound Acetoacetate

A novel and efficient task-specific ionic liquid synthesis of Biginelli compounds has been developed. Ionic liquid phase–bound acetoacetate reacted with urea or thiourea and various aldehydes in the presence of a cheap catalyst to afford ionic liquid phases supported 3,4-dihydropyrimidine-2-(thi)ones. The desired 3,4-dihydropyrimidine-2-(thi)ones were easily cleaved from the ionic liquid phase by transesterification under mild conditions in good yields and high purity. The task-specific ionic liquid technology represents an attractive alternative to the classical solid- and

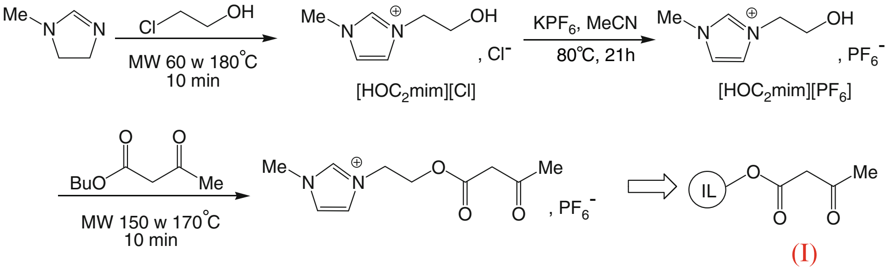


Fig. 12.47 Preparation of [HOC_2mim][PF_6]-bound acetoacetate

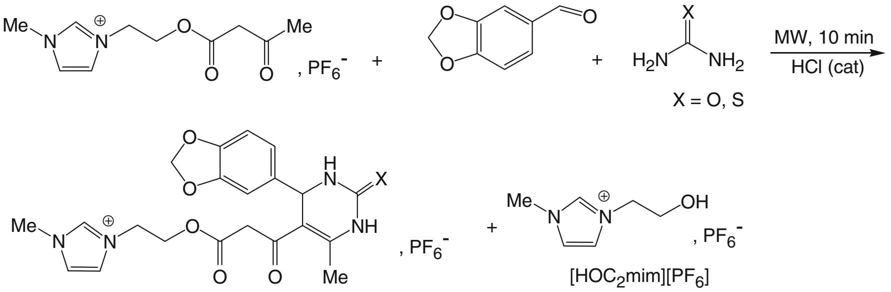


Fig. 12.48 The Biginelli reaction under microwave irradiation

solution-phase syntheses strategies and combines the advantage of performing homogeneous chemistry for multicomponent reactions. General route used for the synthesis of ionic liquid phase–bound acetoacetate **I** is as Fig. 12.47. A model Biginelli reaction under microwave irradiation (μω) is as Fig. 12.48 [32].

12.1.2.9 1-[2-(Acetoacetyloxy)ethyl]-3-methylimidazolium Tetrafluoroborate- or Hexafluorophosphate-Bound *β*-oxo Esters

1,4-Dihydropyridine (1,4-DHP) derivatives have been widely explored as a consequence of their pharmacological profile and as the most important calcium channel modulators. Nifedipine 2 represents the prototype 1,4-DHP structure found useful in both antianginal and antihypertensive treatment that has been approved for clinical use. The liquid phase–bound *β*-keto esters **31**(**a–c**) were prepared by transesterification of methyl or *tert*-butyl *β*-oxo carboxylates **30**(**a**, **b**) with the ionic liquid phases [HOC_2mim][PF_6] **29a** and [HOC_2mim][BF_4] **29b** under solvent-free microwave irradiations (Fig. 12.49) [33].

A new strategy for the synthesis of polyhydroquinolines from task-specific ionic liquids (TSIL) as a soluble support was developed. The preparation of the polyhydroquinolines by a three-component reaction was achieved by using ionic liquid

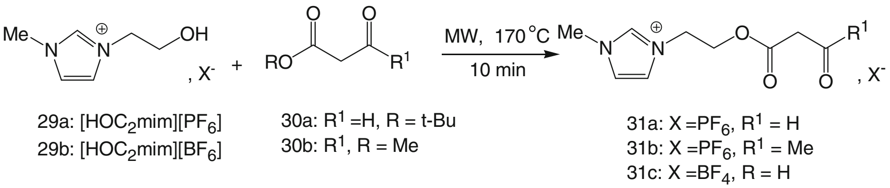


Fig. 12.49 Preparation of ionic liquid phase–bound *β*-oxo esters under microwave irradiations

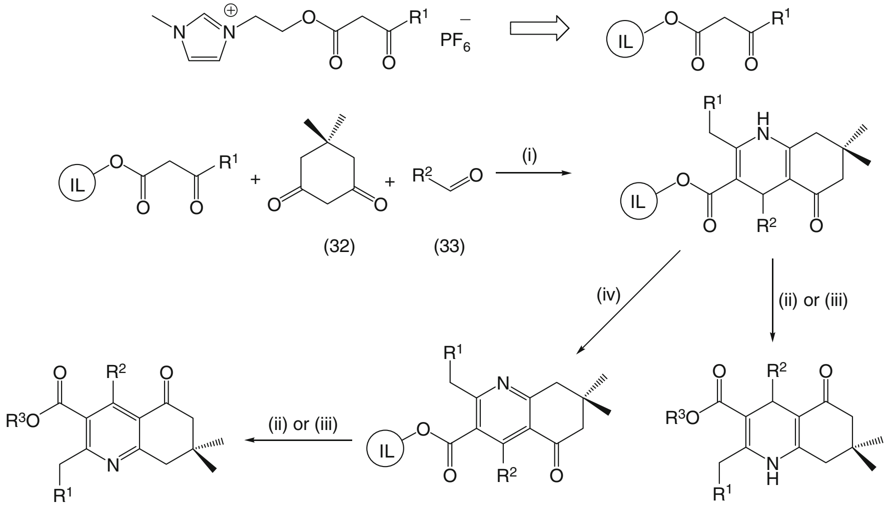


Fig. 12.50 Synthesis of 1,4-dihydropyridines using [HOC$_2$mim][PF$_6$]- and [HOC$_2$mim][BF$_4$]-bound *β*-oxo esters

phase–bound *β*-oxo esters. These starting functionalized esters were synthesized by a solvent less transesterification without catalyst under microwave irradiation. The structure of the intermediate in each step was verified by spectroscopic analysis, and after oxidation of the polyhydroquinolines grafted on the TSIL with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or after cleavage (transesterification, saponification/acidification), the target compounds were obtained in good yields and high purities.

The ILP-bound *β*-oxo esters **29**(**a**, **b**) with PF$_6$ anion are the preferred precursors because after microwave dielectric heating, the excess of *β*-oxo esters **28**(**a**, **b**) and eventually unreacted starting ILP **27a** were eliminated easily by washing with AcOEt. With the selected ILP-bound *β*-oxo esters **29**(**a**, **b**) with PF$_6$ anion, Legeay and coworkers have examined the polyhydroquinoline synthesis under neat conditions (Fig. 12.50).

Reagents and reaction conditions: (1) **32** 1 equiv, **33** 1.1 equiv, NH$_4$OAc 1.5 equiv, neat, 90°C, 20 min; (2) MeONa 1 equiv, MeOH, reflux, 18 h; (3) LiOH 1 equiv, THF/H$_2$O (2:1), reflux, 20 h, then 3 M HCl; (4) 2,3-dichloro-5,6-dicyano-1, 4-benzoquinone (DDQ) 1.1 equiv, CH$_2$Cl$_2$, reflux, 2 h.

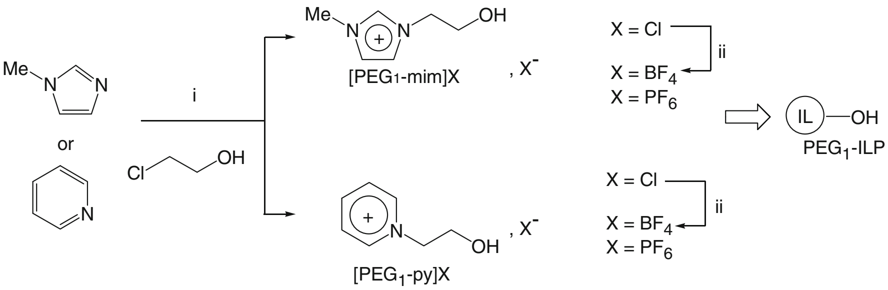


Fig. 12.51 Preparation of new task-specific ionic liquids

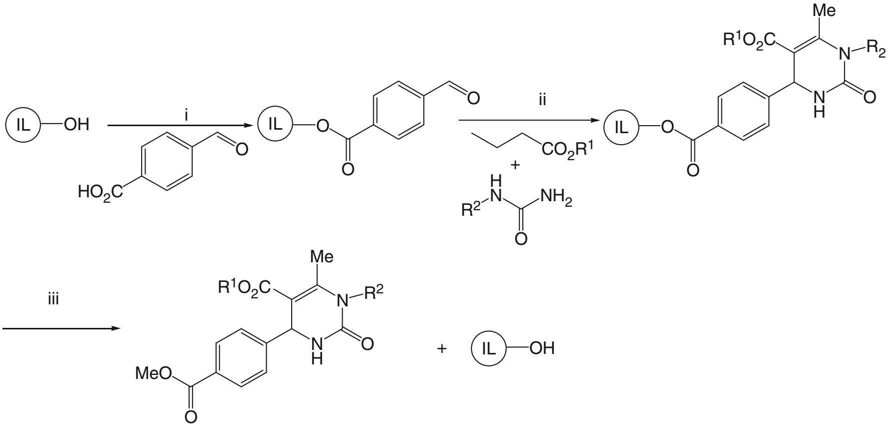


Fig. 12.52 Use of PEG_1-ILP in the synthesis of Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones

12.1.2.10 1-(2-Hydroxyethyl)-3-methylimidazolium Tetrafluoroborate or Hexafluorophosphate and *N*-(2-Hydroxyethyl)pyridinium Tetrafluoroborate or Hexafluorophosphate

In 2005, Legeay and his coworkers reported the preparation of two new types of task-specific ionic liquids, 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate or hexafluorophosphate and *N*-(2- hydroxyethyl)-pyridinium tetrafluoroborate 3c or hexafluorophosphate ([PEG_1-mim][X] and [PEG_1-py][X]), via an efficient method, which is shown in Fig. 12.51. [34].

They have demonstrated that the combination of IL phase–bound aldehyde and microwave dielectric heating allows a rapid and practical preparation of Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones, Hantzsch 1,4-dihydropyridines, pyridines by oxidation, and polyhydroquinolines using a one-pot three-component methodology (Fig. 12.52).

The specific advantages of the IoLiPOS methodology are the following: (1) the reactions under microwave irradiation are performed in homogeneous solution

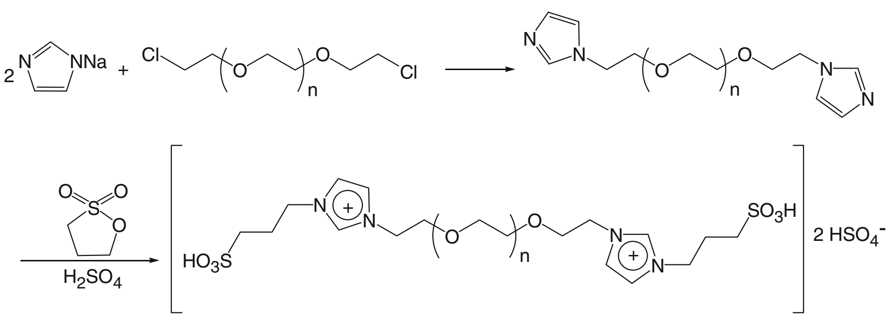


Fig. 12.53 Synthesis of PEG1000-DAIL

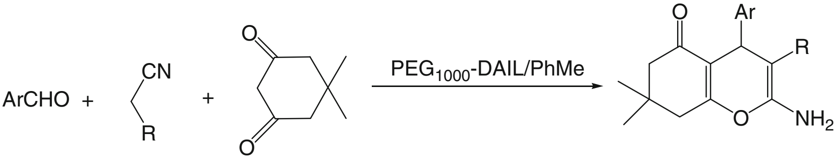


Fig. 12.54 Application of PEG1000-DAIL in the synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans

without solvent, (2) the loading capacity of the ILPs is higher because only a molar equivalent of the low-molecular-weight ionic liquid phase is used, (3) the stable intermediates in the sequence can be purified by simple washings with the appropriate solvent and the structure could be verified easily by routine spectroscopic methods at each step, and (4) the final cleavage is possible by transesterification, saponification/acidification, or ester aminolysis.

12.1.2.11 PEG-1000-Based Dicationic Acidic Ionic Liquid

Zhi and co-workers reported a new temperature-dependent biphasic system, including recoverable novel PEG-1000-based dicationic acidic ionic liquid (PEG1000-DAIL) (Fig. 12.53), and its application in the synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans by a three-component condensation in toluene (Fig. 12.54) [35].

PEG1000-DAIL could be efficiently recovered by simple decantation after reaction without any apparent loss of catalytic activity and little loss of weight even after ten times recycling. The PEG1000-DAIL/toluene system has several advantages: (1) PEG1000-DAIL is a strong Brönsted acid and shows superior catalytic activity, (2) PEG1000-DAIL can be separated by simple decantation without apparent loss of catalytic activity and little loss of weight, and (3) this catalytic system has a wide range of applications for different substrates and the products can be obtained conveniently and in excellent yield and purity. In fact, PEG1000-DAIL/toluene system is an excellent recyclable catalytic reaction media for these types of reactions.

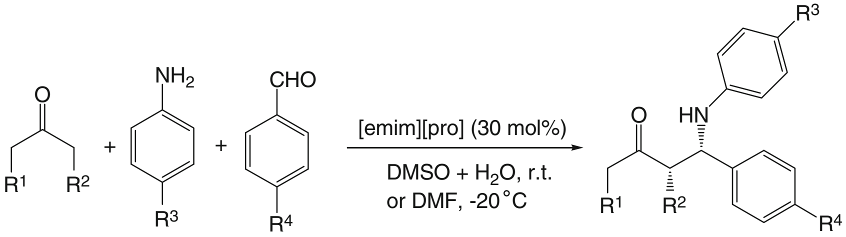


Fig. 12.55 Asymmetric Mannich reaction promoted by [emim][Pro]

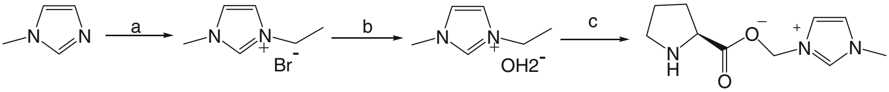


Fig. 12.56 Preparation of [emim][Pro]

12.1.2.12 1-Ethyl-3-methylimidazolium (*S*)-2-Pyrrolidinecarboxylic Acid Salt

Zheng and coworkers have reported the first use of chiral amino acid ionic liquid, 1-ethyl-3-methylimidazolium (*S*)-2-pyrrolidinecarboxylic acid salt [emim][Pro], as a catalyst for the one-pot three-component asymmetric Mannich reaction with excellent chemo-, regio-, and enantioselectivities either under mild conditions or at a low temperature (Fig. 12.55) [36].

The chiral amino acid ionic liquid, 1-ethyl-3-methylimidazolium (*S*)-2-pyrrolidinecarboxylic acid salt [emim][Pro] (**1**), is synthesized in 70% overall yield by the following procedure (Fig. 12.56).

This asymmetric Mannich reaction could also proceed by an enamine pathway because nucleophilic addition of the in situ–generated enamine would be faster to an imine than to an aldehyde. As shown in the Fig. 12.59, the reaction starts with enamine **34** activation of the cyclohexanone by the proline anion and an electrostatic interaction with the imidazolium moiety of the catalyst. In a second pre-equilibrium, the aldehyde and aniline produce an imine. Then enamine-activated **35** reacts with the imine to form **35** via transition state **A**. The last step is a dehydration reaction to afford the corresponding product. The catalyst is regenerated in the subsequent step.

The stereochemical results can be explained by the plausible transition state **A** (Fig. 12.57). Because additional water is added and the reaction is conducted in wet solvents, the transition state is stabilized by hydrogen bonding between the nitrogen atom of the imine and the nitrogen atom of the imidazolium moiety of the catalyst. A switch of the facial selectivity is disfavored because of steric repulsion between the Ar group of the imine and the imidazolium moiety of the catalyst.

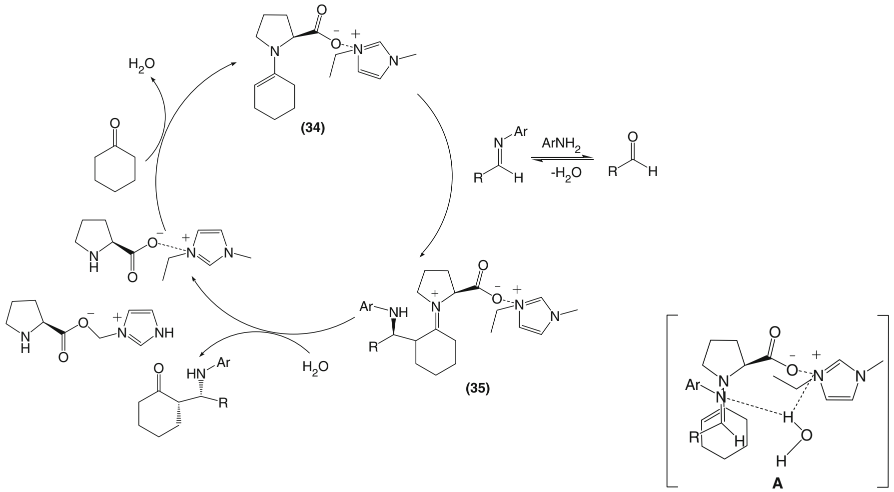


Fig. 12.57 Mechanism of the operation of [emim][Pro]

12.1.2.13 1-Methyl-3-pentylimidazolium Bromide

Dithiocarbamates have received considerable attention in recent times because of their occurrence in a variety of biologically active compounds. They also play pivotal roles in agriculture, and they act as linkers in solid-phase organic synthesis. In addition, functionalized carbamates are an important class of compounds and their medicinal and biological properties warrant study.

An easily accessible neutral ionic liquid, 1-methyl-3-pentylimidazolium bromide ([pmim][Br]) is prepared by Ranu et al. and used for the promotion of the one-pot three-component condensation of an amine, carbon disulfide, and an activated alkene/dichloromethane/epoxide to produce the corresponding dithiocarbamates in high yields at room temperature (Fig. 12.58) [37]. The reactions proceed at faster rate in ionic liquid relative to their rates in other reaction media. These reactions do not require any additional catalyst or solvent. The ionic liquid can be recovered and recycled for subsequent reactions.

They speculated that the imidazolium cation of [pmim][Br] activates CS_2 toward nucleophilic attack by amine to generate a dithiocarbamate anion, which can then undergo Michael-type addition to conjugated alkenes to afford the substituted dithiocarbamate (Fig. 12.59).

The significant advantages of this procedure include remarkably faster reactions relative to those in other procedures, higher yields, excellent regio- and stereoselectivity, and the reusability of the ionic liquids.

12.1.2.14 3-Methyl-1-sulfonic Acid Imidazolium Chloride

Recently, Zolfigol et al. reported that the ionic liquid, 3-methyl-1-sulfonic acid imidazolium chloride ([msim][Cl]), as a new Brönsted acidic ionic liquid, can be easily

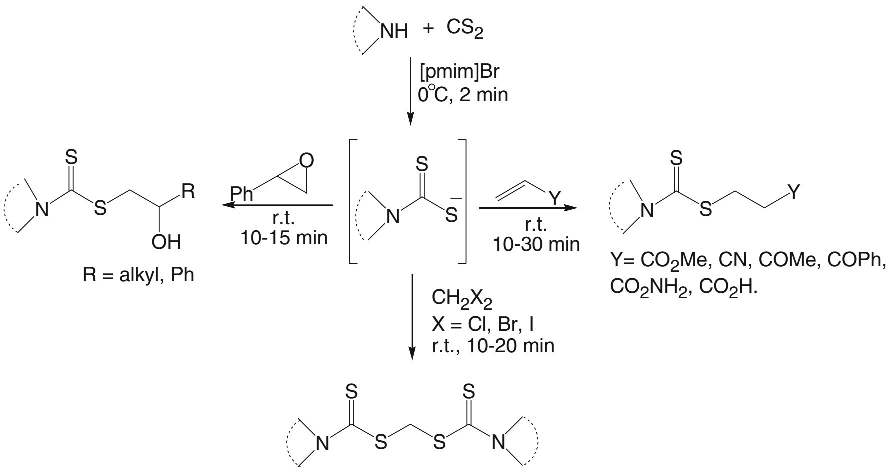


Fig. 12.58 Synthesis of dithiocarbamates in [pmim][Br]

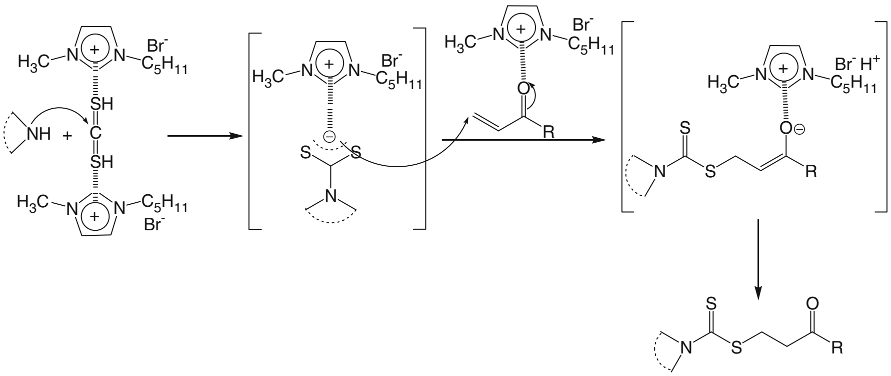


Fig. 12.59 Mechanism of the synthesis of dithiocarbamates in the presence of [pmim][Br]

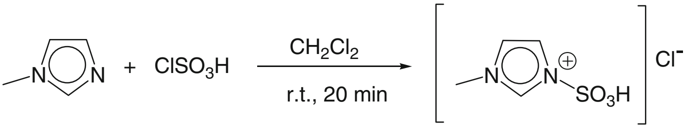


Fig. 12.60 Preparation of [msim][Cl]

prepared from the reaction of 1-methyl imidazole and chlorosulfonic acid at room temperature (Fig. 12.60) [38].

This reagent was capable to catalyze the preparation of bis(indolyl) methanes via the condensation of indoles with aldehydes as well as ketones in the absence of

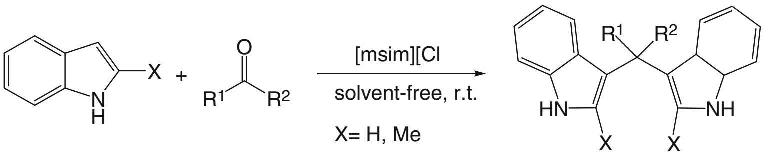


Fig. 12.61 Preparation of bis(indolyl) methanes promoted by [msim][Cl]

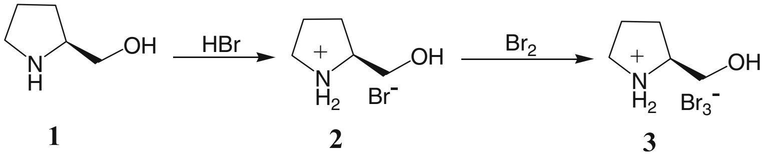


Fig. 12.62 Preparation of L-prolinol-based ionic liquids

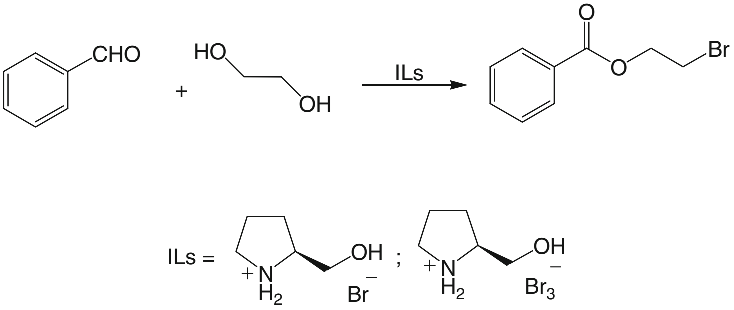


Fig. 12.63 Synthesis of bromoesters from aldehydes

solvent at room temperature (Fig. 12.61). All reactions were performed in relatively short reaction times in high yields.

12.1.3 Other Ionic Liquids

Bromoesters are valuable intermediates in organic synthesis. They could be employed as building blocks in organic, bioorganic, medicinal, and material chemistry. Two kinds of ionic liquids (2) and (3) in Fig. 12.62 have been directly synthesized from L-prolinol (1) by a simple and convenient method in excellent yields [39].

The application of these types of ionic liquids as reagents and solvents for the chemoselective, regioselective, and stereoselective syntheses of 1,2- or 1,3-bromoesters from aromatic aldehydes and 1,2- or 1,3-diols at room temperature has been studied (Fig. 12.63). Good to excellent yields and moderate enantiomeric excesses were obtained under these reaction conditions.

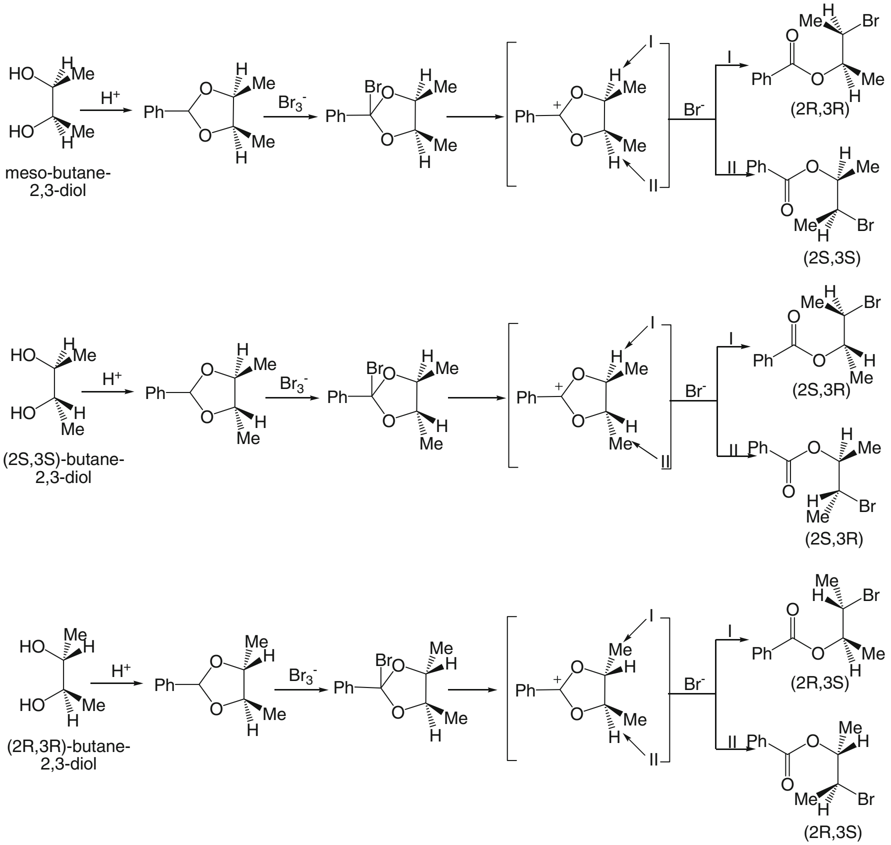


Fig. 12.64 Proposed mechanism for the preparation of 1,2- or 1,3-bromoesters

While there is still a need to use organic solvents for the product extraction, this process provides an opportunity to reduce solvent consumption and the selection of less hazardous reagents compared to the reaction system of traditional brominating reagents. The simplicity of the methodology, ease of the product isolation, mild conditions, and possibility of IL recycling could make this process available in the future on the industrial scales.

Plausible mechanism for stereoselective synthesis of 3-bromobutan-2-yl benzoate is as following (Fig. 12.64).

A novel acyclic SO_3H-functional Brönsted acidic halogen-free TSIL that bears a butane sulfonic acid group in an acyclic tri-methyl-ammonium cation has been synthesized (Fig. 12.65) [40] and used as the catalyst for one-pot three-component Mannich reaction (Fig. 12.66). The procedure was made up of two-step atom economic reaction. The zwitterionic-type precursor (trimethylammonium butane sulfonate) was prepared through a one-step direct sulfonation reaction of trimethylamine and 1,4-butanesulfone. The zwitterion acidification was accomplished by

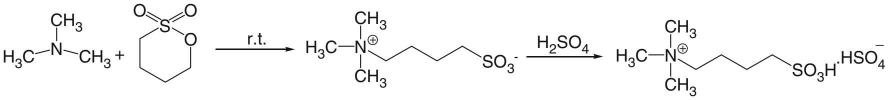


Fig. 12.65 Preparation of [TMBSA][HSO_4]

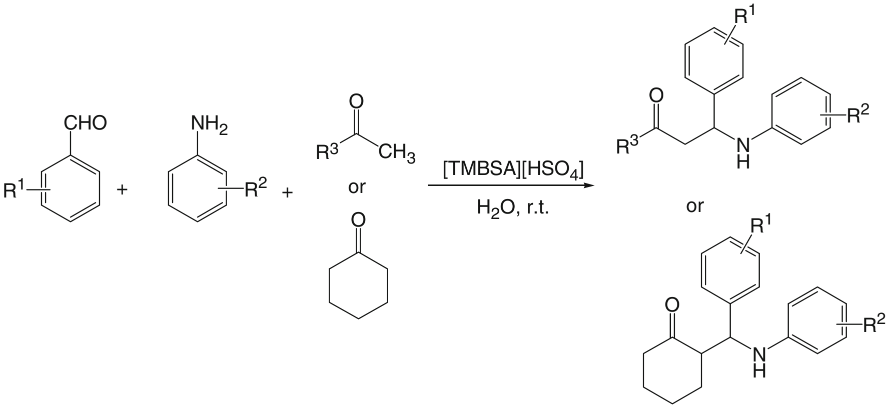


Fig. 12.66 Mannich reaction promoted by [TMBSA][HSO_4]

mixing of zwitterions with sulfuric acid (98%, aq.) to convert the pendant sulfonate group into trimethylbutansulfonic acid ammonium hydrogen sulfate.

The chemical yields for both the zwitterions formation and acidification steps were essentially quantitative since neither reaction produced by-products; the TSIL synthesis was 100% atom efficient.

Using this method, *β*-amino carbonyl compounds were obtained in good yields under the mild conditions. The products could simply be separated from the catalyst/water, and the catalyst could be reused at least seven times without noticeably decreasing the catalytic activity.

Compounds containing 1,3-amino-oxygenated functional groups are frequently found in biologically active natural products and potent drugs such as nucleoside antibiotics and HIV protease inhibitors. Furthermore, 1-amidoalkyl 2-naphthols can be converted to useful and important biological building blocks and to 1-amino methyl 2-naphthols by an amide hydrolysis reaction since compounds exhibit depressor and bradycardia effects in humans.

Hajipour and coworkers reported a new, convenient, mild, and efficient procedure for one-pot three-component synthesis of amidoalkyl naphthol derivatives from various aryl aldehydes, 2-naphthol, and different amides (acetamide, benzamide, and urea) in the presence of *N*-(4-sulfonic acid) butyl triethyl ammonium hydrogen sulfate ([TEBSA][HSO_4]) as an effective and recoverable catalyst under solvent-free conditions (Fig. 12.67) [41].

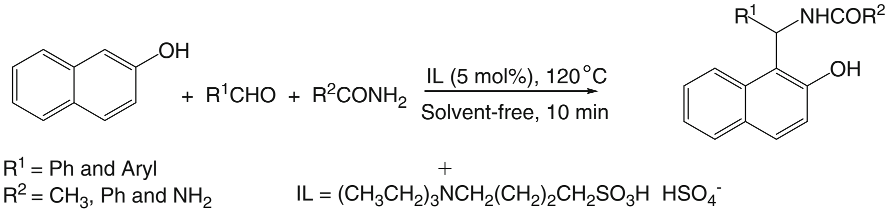


Fig. 12.67 Synthesis of amidoalkyl naphthol derivatives in the presence of [TEBSA][HSO_4]

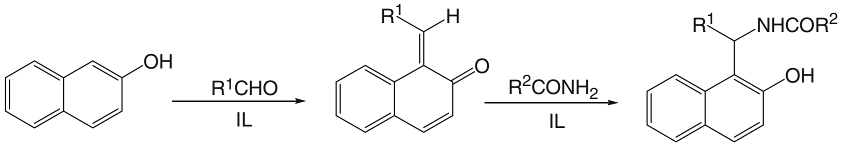


Fig. 12.68 Pathway of the preparation of amidoalkyl naphthol derivatives

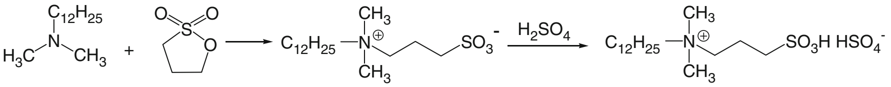


Fig. 12.69 Synthesis of [DDPA][HSO_4]

The reaction of 2-naphthol with aromatic aldehydes in the presence of acid catalyst is known to provide ortho-quinone methides (o-QMs). The o-QMs were reacted with amides or urea to produce 1-amidoalkyl-2-naphthol derivatives (Fig. 12.68).

The results showed that the catalyst can be employed four times, although the activity of the catalyst gradually decreased. This indicated that the Brönsted acidic ionic liquid ([TEBSA][HSO_4]) as a catalyst for the preparation of amidoalkyl naphthols was recyclable.

The advantages of this method, in which a relatively nontoxic (halogen-free) and reusable Brönsted acidic ionic liquid is employed as an effective catalyst, are high catalytic efficiency, short reaction times, high yields, a straightforward work-up, and environmental benignancy.

Dong et al. reported the preparation of a novel Brönsted acid-surfactant-combined halogen-free ionic liquid [DDPA][HSO_4] that bears a propane sulfonic acid group in an acyclic dimethyldodecylammonium cation (Fig. 12.69) [42] and its use in the heterogeneous catalysis procedure of one-pot three-component Mannich-type reaction in aqueous media.

They found that the catalytic procedure is simple, and the catalyst could be reused at least six times without noticeably decreasing the catalytic activity.

It should be noted that in the case of anilines, both the electron-donating and weak electron-withdrawing substituents were advantageous to Mannich reaction.

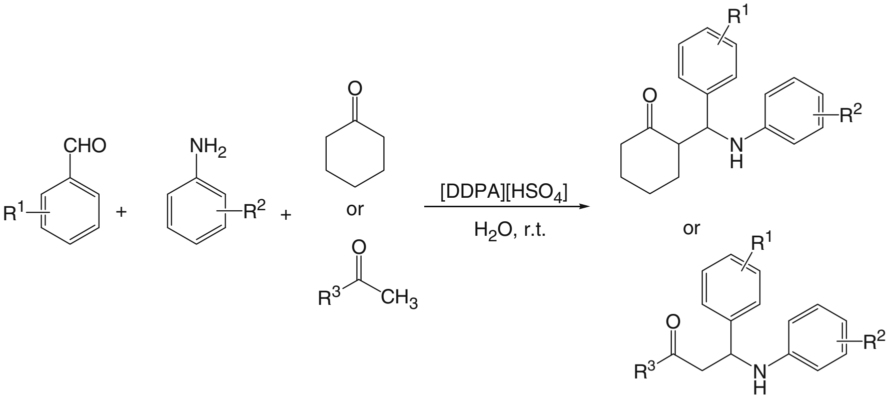


Fig. 12.70 Use of [DDPA][HSO_4] in multicomponent reactions

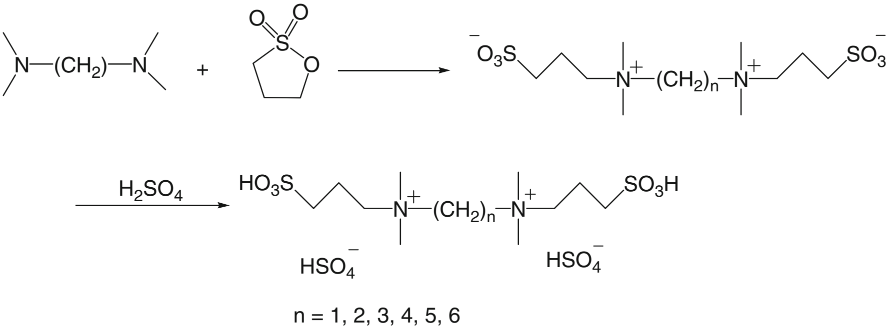


Fig. 12.71 Preparation of dicationic acidic ionic liquids

In addition, besides the aromatic ketones, aliphatic ketones could also be employed to give good yields (Fig. 12.70).

However, in the case of cyclohexanone as substrate anti/syn ratio of the product was nearly 1:1, this procedure could not afford the corresponding Mannich base with the same obvious antiselectivity as the literature reported.

Dong and coworkers have also reported the preparation of some dicationic acidic ionic liquids as halogen-free TSILs that bear dialkane sulfonic acid groups in acyclic diamine cations (Fig. 12.71) [43] and their application as catalysts in a one-pot three-component Biginelli-type reaction (Fig. 12.72).

The products could be separated simply from the catalyst–water system, and the catalysts could be reused at least six times without noticeably reducing catalytic activity. The methodology has the advantages of short reaction times, lack of organic solvent, recyclability of catalysts, and easy work-up for isolation of the products in good yields with high purity.

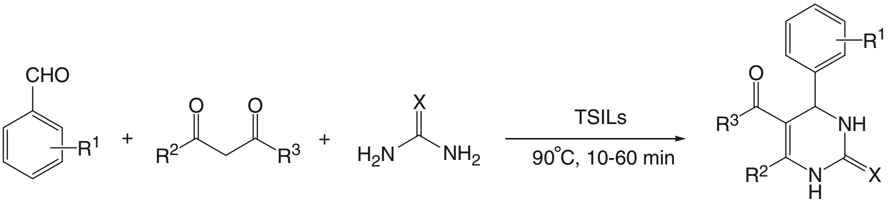


Fig. 12.72 Synthesis of 3,4-dihydropyrinidin-2-(1*H*)-ones and -thiones

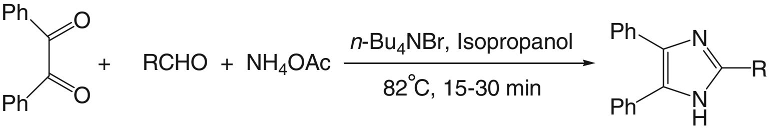


Fig. 12.73 Synthesis of 2,4,5-triaryl imidazoles in TBAB

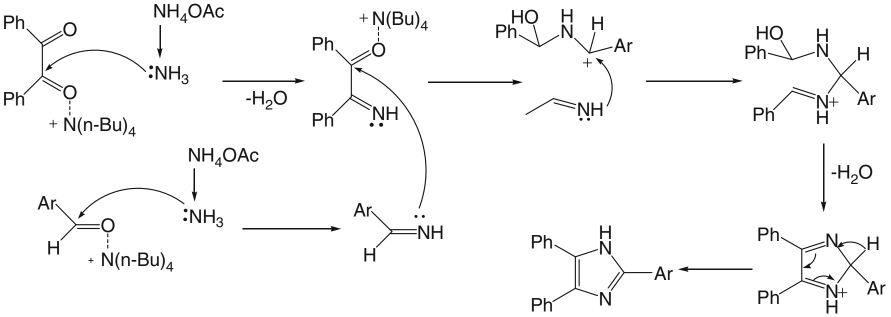


Fig. 12.74 Proposed mechanism for the preparation of 2,4,5-triaryl imidazoles in TBAB

A simple, efficient, and eco-friendly procedure has been developed using tetrabutylammonium bromide ((TBAB), 10 mol%) as a novel neutral ionic liquid catalyst for the synthesis of 2,4,5-triaryl imidazoles by a one-pot three-component condensation of benzil, aryl aldehydes, and ammonium acetate in refluxing isopropanol (Fig. 12.73) [44].

A mechanism for the catalytic activity of TBAB in the synthesis of trisubstituted imidazoles may be postulated (Fig. 12.74). The tetrabutylammonium ion probably induces polarization in carbonyl group of aldehydes as well as benzil. Then nucleophilic attack of the nitrogen of ammonia obtained from ammonium acetate, on activated carbonyl, results the formation of aryl aldimine and α-imino keone. Their subsequent reaction followed by intramolecular interaction leads to cyclization.

This methodology offers several advantages such as excellent yields, short reaction times, and environmentally benign mild reaction conditions; moreover, the

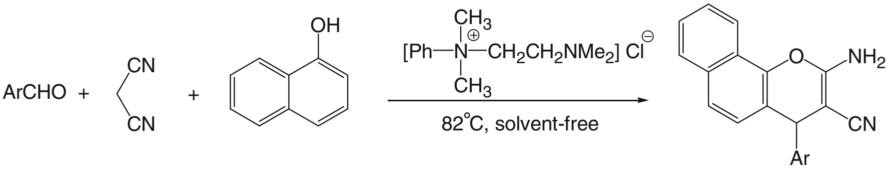


Fig. 12.75 Synthesis of 2-aminochromenes in *N,N*-dimethyl aminoethylbenzyldimethylammoniumchloride

catalyst in isopropanol solvent exhibited reusable activity. In addition, the pure products were obtained by simple filtration of the cooled reaction mixture. Furthermore, this procedure is readily amenable to parallel synthesis and generation of combinatorial 2,4,5-trisubstituted imidazole libraries.

2-Aminochromenes represent an important class of compounds being the main components of many naturally occurring products and have been of interest in recent years due to their useful biological and pharmacological aspects, such as anticoagulant, spasmolytic, diuretic, insecticidal, anticancer, and antianaphylactic activities. Some of these can also be employed as cosmetics and pigments and can be utilized as potential biodegradable agrochemicals.

A simple, clean, and environmentally benign three-component process to the synthesis of 2-amino-4*H*-chromenes using *N,N*-dimethyl aminoethylbenzyldimethylammoniumchloride, $[PhCH_2Me_2N^+CH_2CH_2NMe_2]Cl^-$, as an efficient catalyst under solvent-free condition was reported by Chen et al. (Fig. 12.75) [45].

Following this method, a wide range of aromatic aldehydes easily undergo condensations with α-naphthol and malononitrile under solvent-free condition to afford the desired products of good purity in excellent yields.

This procedure offers several advantages including mild reaction conditions, cleaner reaction, and satisfactory yields of products, as well as a simple experimental and isolation procedure, which makes it an attractive protocol for the synthesis of these compounds. Furthermore, the catalyst can be easily recovered and reused for at least five cycles without losing its activities.

The chiral ionic liquids L-prolinium sulfate (Pro_2SO_4), L-alaninium hexafluorophosphate ($AlaPF_6$), and L-threoninium nitrate ($ThrNO_3$), which are directly obtainable from a natural α-amino acid, have been used by Yadav et al. for the promotion of an unprecedented version of the Biginelli reaction for an efficient enantio- and diastereoselective synthesis of polyfunctionalized perhydropyrimidine scaffolds of pharmacological potential in a one-pot procedure (Fig. 12.76) [46].

This three-component domino cyclocondensation reaction is effected via ring transformation of an isolable intermediate in a one-pot procedure.

Tentative mechanism for the formation of 5-aminoperhydropyrimidines 7 is as shown in Fig. 12.77.

Tentative mechanism for the formation of 5-mercaptoperhydropyrimidines 10 is as Fig. 12.78.

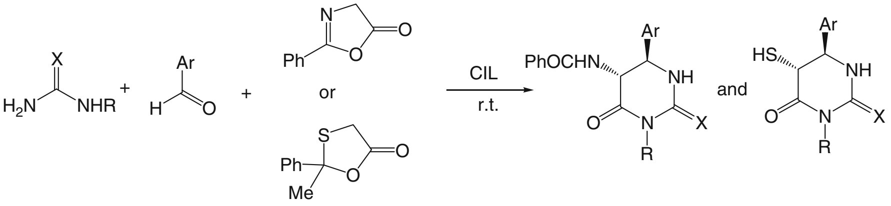


Fig. 12.76 Chiral ionic liquids catalyzed the preparation of 5-amino-mercaptoperhydropyrimidines

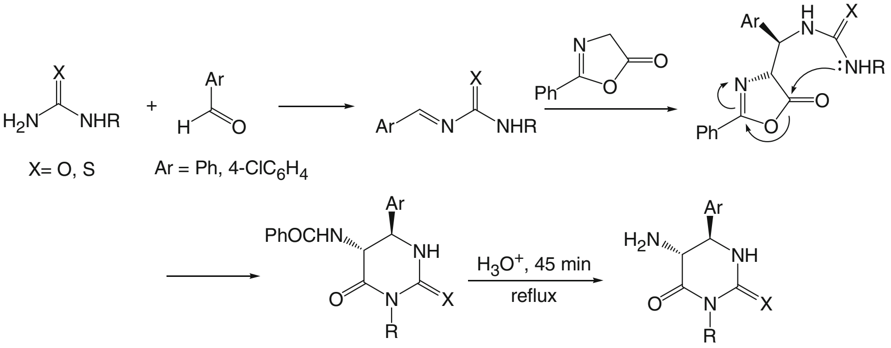


Fig. 12.77 Mechanism of the formation of 5-aminoperhydropyrimidines

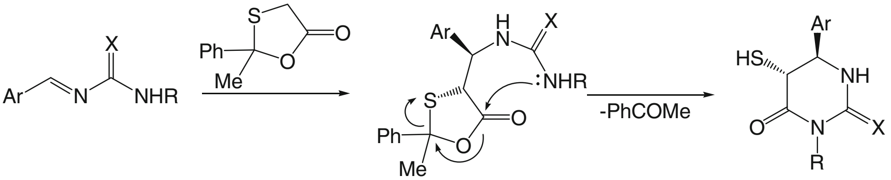


Fig. 12.78 Mechanism of the formation of 5-mercaptoperhydropyrimidines

12.2 Conclusions

It should be noted that a correct and updated citation and literature survey is very important for researchers to find relevant information, pioneer ideas, and progress of any subject. On the other hand, published data using ionic liquids indicate a wide synthetic potential of the desired reagents and a great interest of researchers in these compounds. A wide range of original procedures for synthesizing various classes of organic compounds, including multicomponent reactions have been developed on the basis of ionic liquids. We hope that the present chapter may be an important source of advance information on activating for the synthesis of new ionic liquids.

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Chapter 13

Ionic Liquids as Binary Mixtures with Selected Molecular Solvents, Reactivity Characterisation and Molecular-Microscopic Properties

Pedro M.E. Mancini, Maria V. Bravo, Graciela G. Fortunato, and Claudia G. Adam

Abstract This chapter presents the design and analysis of the microscopic features of binary solvent systems formed by ionic liquids, particularly room temperature ionic liquids with molecular solvents. Protic ionic liquids, ethylammonium nitrate and 1-*n*-butyl-3-methylmidazolium (bmim)-based ILs, were selected considering the differences in their hydrogen-bond donor acidity. The molecular solvents chosen were aprotic polar (acetonitrile, dimethylsulphoxide and *N*,*N*-dimethylformide) and protic (different alcohols). The empirical solvatochromic parameters E_T^N, π^*, α and β were employed in order to analyse the behaviour of each binary solvent system. The study focuses on the identification of solvent mixtures of relevant solvating properties to propose them as 'new solvents'. Kinetic study of aromatic nucleophilic substitution reactions carried out in this type of solvent systems is also presented. On the other hand, this is considered as a new approach on protic ionic liquids. Ethylammonium nitrate can act as both Brönsted acid and/or nucleophile. Two reactions (aromatic nucleophilic substitution and nucleophilic addition to aromatic aldehydes) were considered as model reactions.

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13.1 Introduction

The design and discovery of ionic liquids (ILs) displaying a melting point lower than 100°C, mainly room temperature ionic liquids (RTILs), have been the subject of considerable research efforts over the past decade. RTILs have attracted considerable attention because these are expected to be ideal solvents to provide novel reactions in green chemistry [1, 2]. The interest in this class of molecules arises from their use as liquid media for a variety of chemical transformations and as substitutes for organic molecular solvents.

The interest in ILs has been generated due to their unique properties and potential uses in areas as diverse as synthesis, biocatalysis, electrochemistry, etc. Thus, this class of molecules is increasingly employed in organic chemistry, material sciences and physical chemistry [3, 4]. ILs are salts – substances composed exclusively of cations and anions. This fact differentiates them from simple ionic solutions, in which ions are dissolved in a molecular medium. They are also different from inorganic molten salts because their melting points are lower than 100°C (most of them exist in liquid form at or near room temperature).

RTILs exhibit a variety of desirable properties, such as negligible vapour pressure, which makes them interesting for various applications. In particular, the option of fine-tuning chemical and physical properties by an appropriate choice of cations and anions has stimulated much of the current excitement with respect to these compounds and has led to the term ‘designer solvents’. An alternative, complementary strategy to tailor properties is not only to mix two (or more) ionic liquids but also to mix ionic liquids with molecular solvents.

The majority of ILs belong to the family of *N*,*N*-methyl-(alkyl)imidazolium, alkyl-pyridinium or ammonium cations associated with a variety of anions such as X^-, BF_4^-, BPh_4^-, PF_6^-, NO_3^-, $CF_3SO_3^-$ NCS^-, $N(CN)_2^-$, TfO^-, NTf_2^-, $AlCl_4^-$, etc. (Fig. 13.1). Recently, a few amidinium-based ILs have also been reported [5].

Several opportunities arising from all possible combinations of cations and anions allow tuning with good precision the characteristics of ILs such as melting point, viscosity, hygroscopicity, dielectric constant and microscopic molecular properties [6–12]. Due to the great variety of ionic liquids, imidazolium ILs constitute a large family of anion–cation couples which is considered as a model system. Specifically, imidazolium ILs formed by 1-alkyl-3-methylimidazolium cations with different types of anions exhibit nano-scale structural organisation in polar and non-polar regions for which the spatial distribution evolves with the alkyl chain length. This phenomenon results from the structural asymmetry of cations composed of a polar head group and a non-polar alkyl side chain. This asymmetry leads to a balance between domains in which the spatial organisation is due to the ionic interactions between charged species coexisting with non-polar domains constituted by the non-polar alkyl chain interacting through van der Waals forces. The existence of the microphase segregation in polar/non-polar domains provides new perspectives to elaborate high-performance materials or to consider new selective solvation abilities in imidazolium ILs with respect to non-polar solutes and/or associated species [13–22]. As regards their ionic

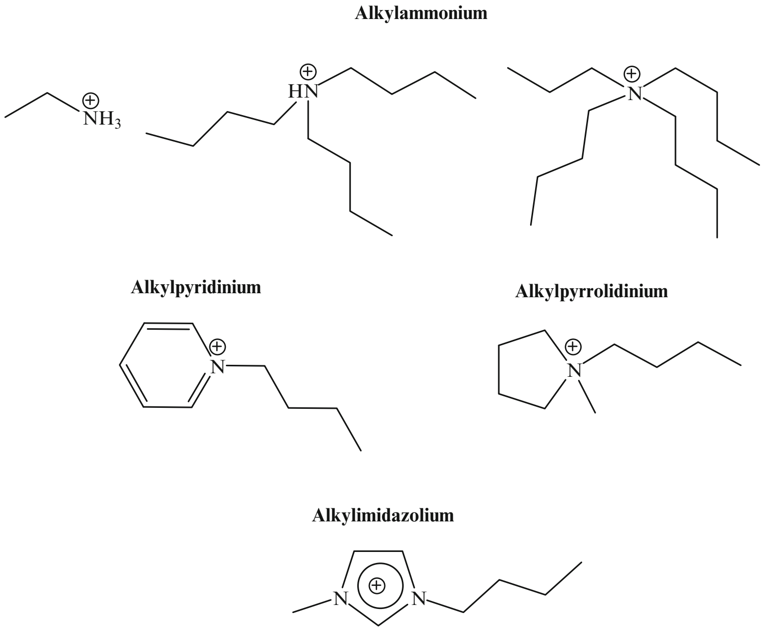

Fig. 13.1 Principal cations part of ionic liquids

nature, the structure of ILs incorporates different levels of complexity. First, in order to maintain local electroneutrality, the high-charge density parts of cations and anions must create a three-dimensional network where the nearest neighbours of a given ion are ions of opposite charge. Second, the low-charge density residues that are often present in the ions (generally as alkyl side chains) are segregated from the polar network, forming non-polar domains. This nano-segregation/structuration between polar and non-polar regions, first predicted by molecular dynamics simulation studies and later corroborated by diffraction techniques, implies the existence of differentiated and complex interactions not only in pure ionic liquids but also in their mixtures with molecular solutes or even with other ionic liquids.

Various physical and chemical properties useful to understand the solubility of RTILs have been studied, among which dielectric properties are crucially important. However, there are, at least, two problems in the study of dielectric properties. One problem concerns the experimental techniques and the other, the scientific aspects. Furthermore, there arises a basic question about how the permittivity derives, assuming that ILs are homogeneous. This is related to the interconnection polar to non-polar domains as predicted by computer simulation and evidenced by experiments. In addition, anomalous phase separation behaviour has been reported for binary systems of RTILs with some organic compounds.

The specific properties of the RTILs mostly result from having both a very low vapour pressure gaseous phase and a liquid phase of significant polarity, and the high thermal conductivity offering wide electrochemical windows is very important. ILs have a high solvation ability for a wide variety of polar, non-polar, organic and inorganic molecules as well as organometallic compounds. Moreover, the possibility of changing their properties allows the selective solvation of solutes and thus controls the mutual miscibility of particular organic compounds such as alcohols and water. As a consequence, the characterisation of the properties of different classes of ILs used as solvents for specific applications and for chemical reactions and catalysis has been intensively investigated. Nevertheless, many questions are still open and more fundamental studies remain to be done before achieving a better understanding of the physical properties of ILs at the molecular level. Experimental and rhetorical investigations have been devoted to determine the connection existing between the nano-structural organisation in ILs or in their mixtures with molecular solvents and their remarkable solvation and/or chemical properties. In order to select appropriate media, some useful properties such as polarity and ionising power, based on dipole moment, relative permittivity, donor number, solubility parameter and solvatochromic characteristics such as Z, E_T^N and Kamlet-Abboud-Taft parameters π^*, α and β have to be considered.

The aim of the present chapter is twofold. The first is to consider the molecular-microscopic features of binary mixtures between ILs and molecular solvents in order to modulate the most relevant microscopic properties so as to understand how a single mixture will interact with potential solutes and contribute to designing solvents based on microscopic properties. Ammonium- and imidazolium-based ILs have been selected because of the differences in their hydrogen-bonding donor (HBD) acidity. The second is to discuss the participation of ILs as reagents and/or catalysts in chemical transformations.

13.2 General Considerations on Binary Solvent Mixtures Containing Ionic Liquids and Molecular Solvents

Over the last few years, the development of solvents of desired properties with a particular use in mind has been challenging. To evaluate the behaviour of a liquid as solvent, it is necessary to understand the solvation interactions at molecular level. In this vein, it is of interest to quantify its most relevant molecular-microscopic solvent properties, which determine how it will interact with potential solutes. An appropriate method to study solute–solvent interactions is the use of solvatochromic indicators that reflect the specific and non-specific solute–solvent interactions on the UV-Vis spectral band shifts. In this sense, a number of empirical solvatochromic parameters have been proposed to quantify molecular-microscopic solvent properties. In most cases, only one indicator is used to build the respective scale. Among these, the $E_T(30)$ parameter proposed by Dimroth and Reichardt [23] to measure solvent dipolarity/polarisability which is also sensitive to the solvent's hydrogen-bond donor capability. On the other hand, the π^*, α and β (Kamlet, Abboud and Taft)

[24–26] multiparametric approach assigns different parameters to each particular solvent characteristic: dipolarity/polarisability, HBD acidity and hydrogen-bonding acceptor (HBA) basicity.

From the combinations of pure solvents in binary mixtures, the availability of media with diverse properties can be obtained. Attention has now been drawn to the use of RTILs as solvents for different applications. Moreover, some binary mixtures of molecular solvent with ILs have been investigated. Attention is given to the microenvironment of solutes in order to investigate the solvation capability of this type of binary mixtures. In this sense, the discussion about the notion of 'property of a mixed solvent' and whether such a property can be defined, not to say be measured, by means of chemical probes is proposed. In fact, the ideas behind this part of the presentation are related to the quantification of the microscopic properties measured by a set of empirical parameters for molecular solvent plus ionic liquid systems and to the discussion of the response patterns *property versus solvent composition* focusing on the changes in the ability to develop the most relevant interactions. The preferential solvation of the solute by one of the solvent component of the mixture is a major molecular-microscopic characteristic of binary solvent systems. A preferential solvation model was applied in the ionic liquid mixtures to study the effects of solvent mixtures on the solvation of the indicators. The observed deviations from the ideal behaviour of the probes were explained by considering the preferential solvation (specific solute–solvent interactions) or the solvent–solvent interactions. When an ionic liquid is mixed with other solvents, physical and chemical properties are tunable. Hence, ILs can be used as cosolvents in binary or ternary solvent mixtures to increase the efficiency of the processes and to change the physicochemical properties of the solvents [27, 28]. Various interactions in mixed solvents are much more complex than in neat solvents when the solute is preferentially surrounded by the mixture components or the complex formed by the interaction of both components. In this situation, the strong negative Gibbs energy of solvation is operated [29, 30]. To interpret the behaviour of solvents in chemical processes, an understanding of the solution–solute interactions is necessary.

With respect to ILs as cosolvents, the interest was centred on two types of ILs: alkylammonium and 1,3-dialkylimidazolium-based ionic liquids. For the first type, we selected ethylammonium nitrate, considering that it is a protic ionic liquid (PIL) and that it can act as a potential acid catalyst. With respect to the second type of ILs, we selected those based on 1-methyl-3-*n*-butylimidazolium cation, characterised by a slighter HBD acidity than that of the alkylammonium type (Figs. 13.2, 13.3). These ILs exhibit a wide spectrum of physicochemical properties. It was demonstrated that their water content, density, viscosity, surface tension, melting point and thermal stability are affected by the length of the alkyl chain and the nature of the anion. Several anions were incorporated in this class of ILs.

Recently, PILs have been extensively used in organic synthesis as catalysts and as self-assembly media. Drummond and Greaves published an extensive review on PILs, analysing the favourable features of these materials as protic solvents in several reactions. While the use of pure ILs as reaction media has been investigated in

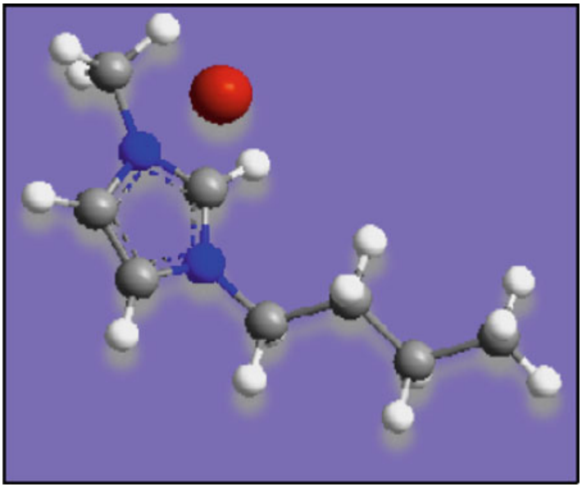

Fig. 13.2 [bmim][Br]

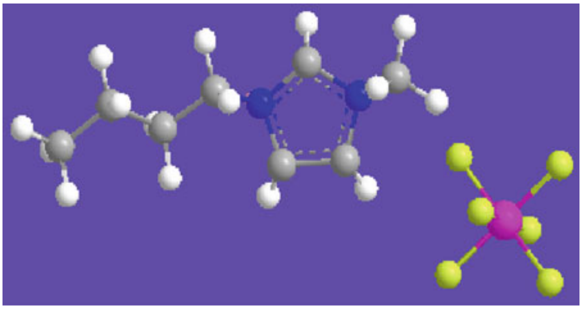

Fig. 13.3 [bmim][PF_6]

a variety of chemical processes, reactions carried out in their binary mixtures with molecular solvents have not been so widely studied. In this connection, it is convenient to discuss how a reaction medium is modified, at microscopic level, by adding small amounts of a PIL to a molecular solvent and evaluate if the presence of small amounts of a PIL could affect the course of a chemical reaction. Kinetic study of aromatic nucleophilic substitution (S_NAr) reactions carried out in mixed solvent systems containing some molecular solvents in combination of IL is reported. The selected nucleophiles were primary and secondary amines, and the corresponding substrate was 2,4-dinitrofluorobenzene, which can exhibit base catalysis. Moreover, it was possible to analyse if the protic IL could act as both Brönsted acid and nucleophile. In this last connection, addition reactions to the carbonyl group were carried out in the cited binary mixtures without the participation of an external nucleophile species.

13.3 Development

13.3.1 Designing Solvents Based on the Determination of Their Microscopic Properties: Molecular Solvent + Ionic Liquid Binary Mixtures

13.3.1.1 Protic Ionic Liquids

Using ethylammonium nitrate (EAN) as PIL ($E_T^N = 0.95$, $\pi^* = 1.12$, $\alpha = 1.10$, $\beta = 0.46$), following types of binary mixture models were selected for the analysis and quantification of the microscopic solvent properties: (a) [molecular aprotic solvent with HBA ability + PIL cosolvent], (b) [molecular aprotic solvent with both HBD and HBA ability + PIL cosolvent] and (c) [molecular protic solvent + PIL cosolvent] [31]. The molecular solvents included in this analysis were dimethylsulphoxide (DMSO) ($E_T^N = 0.44$, $\pi^* = 1.00$, $\alpha = 0.02$ and $\beta = 0.76$) as a polar aprotic HBA solvent, acetonitrile (AN) ($E_T^N = 0.46$, $\pi^* = 0.75$, $\alpha = 0.19$, $\beta = 0.40$) as polar aprotic HBA/HBD solvent and methanol ($E_T^N = 0.76$, $\pi^* = 0.60$, $\alpha = 0.98$, $\beta = 0.66$) as a protic solvent. EAN is a N–H-bond donor. In all cases, the pure component part of the mixtures was capable of forming associated species through hydrogen-bonding interactions. For the explored solvent mixtures, empirical parameters E_T^N, π^*, α and β were calculated from the wave numbers of the absorbance maxima of the corresponding chemical probes at 25°C.

In DMSO + EAN solvent system, the π^* and β values vary almost ideally with the changes in the cosolvent concentration. In the case of π^*, the plot shows an *S*-shaped curve. In contrast to this, E_T^N and α parameters are always higher than the values expected for the ideal behaviour. Moreover, some parameter values are higher than those of the pure solvents showing a synergistic effect on the property. This effect is particularly marked on acidity α. Of particular interest is the mixed solvent corresponding to $x_{EAN} = 0.6$ which exhibits high dipolarity/polarisability ($\pi^* = 1.07$), moderate HBA ($\beta = 0.61$) and high HBD ($\alpha = 1.16$), even higher than the one corresponding to EAN.

In the AN + EAN solvent system, the addition of small quantities of ionic liquids results in the abrupt increase in E_T^N values, which became constant on reaching to the value equivalent to pure EAN. In this case, the π^* values exhibit positive deviations from the ideal behaviour, while β values show synergistic effects on the property. The basicity of the pure components of the mixture has similar property values. In all explored mixtures, α values are higher than those of the pure solvents manifesting synergism on the acidity. In the mixture, $x_{EAN} = 0.05$, the π^* and β values are close to those of AN while the HBD value is higher than the one corresponding to EAN.

With methanol (MeOH) + EAN mixtures, the addition of EAN rapidly increases E_T^N and π^* values, producing a positive deviation from ideal behaviour. The β property exhibits small negative deviations from ideality, a fact which suggests that this property is dominated by the anion. The behaviour of α is similar to that observed for mixtures with AN, showing synergism on the property values. In this case, special interest should be given to EAN-poor mixtures since dipolarity/polarisability and acidity are maximised, whereas basicity is minimised.

In order to understand the changes of the microscopic properties of these selected mixtures, it is possible to consider the formation of intersolvent-associated species through specific molecular interactions. Moreover, in mixed solvents, different (in terms of type and strength) and often simultaneous solute–solvent interactions can be established.

For this class of solvent mixtures, it is possible to predict that they will show basically similar E_T^N response patterns. The parameter values abruptly increase with a small increase of PIL exhibiting positive deviations from ideal behaviour. A low synergistic effect would be observed on the property when the molecular solvent is polar aprotic HBA. The specific hydrogen-bonded interactions between the highly dipolar ground state of Reichardt's dye and EAN cation are responsible for the striking shifts in the transition energy of the indicator in mixtures of EAN and a similar type of organic solvent. On the other hand, the π^* parameter response pattern suggests preferential solvation of the indicator by the more dipolar/polarisable solvent, except for the mixtures rich in EAN. This behaviour could be related to the influence of the possible contamination of π^* parameter values because the probe is capable of accepting hydrogen bonds. In the mixtures of the PIL with polar aprotic molecular solvents with HBA character, the interactions are dominated by the non-specific type, while in the mixtures with HBA/HBD aprotic polar molecular solvents and with protic solvents, the specific interactions predominate. The property β clearly exhibits different response patterns for the explored systems. The EAN is moderately basic as expected since the anion is the conjugated base resulting from a strong acid. The behaviour of the mixtures with DMSO and MeOH shows the influence of the anion, whereas the synergism observed on β values by AN systems indicates the presence of complexes, which adds enhanced basicity to the mixtures. The behaviour of the α parameter for these types of binary mixtures is unexpected. The general tendency is that the solvent mixtures exhibiting a higher ability to donate a hydrogen atom than the pure solvent component of the mixtures show strong synergistic effect on the property. At first instance, it appears that the HBD ability of the cation increases in EAN diluted mixtures. On the one hand, this fact could be related to the abrupt increments observed in E_T^N values when small amounts of EAN are added to the molecular solvents due to a preferential interaction of the PIL with the ground state of the betaine dye. On the other hand, it could be related to the structural features of the mixtures. In this connection, previous studies on the characterisation of mixed solvents by means of empirical solvatochromic parameters report that binary mixtures of molecular solvents, in which the components are solvent-active to one another forming complexes or associated species through hydrogen-bonding interactions, can exhibit synergism on the microscopic properties.

This type of binary solvent mixtures containing a PIL could be deliberately used to improve their characteristics to affect reaction rates, mechanisms, selectivity, chemical equilibria, position and intensity of spectral absorption bands and liquid chromatographic separation. The most remarkable microscopic property of these binary systems in order to design solvents, with particular effects, is the α acidity.

Specific Conclusions

It was possible to demonstrate that the addition of a PIL to a molecular solvent results in an abrupt increase in the ability of donating hydrogen atom for the formation of a hydrogen bond. Moreover, the general tendency reflects synergistic effects on the microscopic property.

It is possible to prepare strong HBD molecular solvent + PIL binary solvent mixtures as a 'new solvent' with particular microscopic solvent features, and in a first instance, these observations could be extended to similar systems.

One advantage of this type of mixtures is that the IL need not be a liquid at room temperature, but be soluble in the selected molecular solvent.

13.3.1.2 1,3-Dialkylimidazolium Ionic Liquids

Considering ILs composed of 1-butyl-3-methylimidazolium as the cation and tetrafluoroborate and hexafluorophosphate as the anions ([bmim][BF_4]: $E_T^N = 0.67$, $\pi^* = 1.05$, $\alpha = 0.63$, $\beta = 0.38$; [bmim][PF_6]: $E_T^N = 0.67$, $\pi^* = 1.03$, $\alpha = 0.63$, $\beta = 0.21$), three kinds of binary mixture models were selected for the analysis and quantification of the microscopic solvent properties: (a) [molecular aprotic solvent with HBA ability + IL cosolvent], (b) [molecular aprotic solvent with both HBD and HBA ability + IL cosolvent] and (c) [molecular protic solvent + IL cosolvent] [32, 33]. The [bmim][BF_4] and [bmim][PF_6], the most currently used ILs are non-protic solvents having the same cation and a different anion. The anion mainly determines the water miscibility. With respect to their physical properties, [bmim][PF_6] exhibits lower melting point, higher viscosity, higher density and lower conductivity than [bmim][BF_4]. While the latter one displays a complete miscibility with water at 25°C, the first one shows a very low miscibility with water. The E_T^N, π^* and α values corresponding to [bmim][BF_4] and [bmim][PF_6] are similar, but the β value of [bmim][BF_4] is about twofold compared to the value of [bmim] [PF6]. The E_T^N values lie in the range associated with polar HBD solvents such as short chain alcohols. The π^* values are high in comparison with non-aqueous molecular solvents, and both the cation and the anion affect this parameter. The α values are largely determined by the nature of the cation. It is known that 1-methyl-3-alkylimidazolium cations can act as weak HBD because of the weak acidic C(2)-H atom at the heterocyclic ring, which is the most acidic of all imidazolium H atoms. Finally, the β values are dominated by the nature of the anion. The HBA basicity of the IL with [BF_4] as anion is parallel to the value of the acetonitrile. The higher proton acceptor ability of [BF_4] with respect to [PF_6] has been confirmed employing other solutes as solvatochromic probes.

In turn, the molecular solvents used are acetonitrile, *N*,*N*-dimethylformamide (DMF, $E_T^N = 0.40$, $\pi^* = 0.89$, $\alpha = 0$, $\beta = 0.71$) and methanol. This selection is made taking into account the structural characteristics, the miscibility with the IL and the microscopic properties. It is well known that AN is a polar aprotic HBA/HBD solvent and MeOH is a protic solvent and DMF is an HBA polar aprotic molecular solvent.

The E_T^N values for the binary mixtures of the above-cited molecular solvents and ILs under study are very similar. In all cases, the E_T^N values exhibit positive deviation from ideal behaviour. However, in the mixtures with AN, a slight synergetic effect appears at high IL mole fraction, and in mixtures with MeOH, this effect is clearly noticeable at all compositions. The prominence of the synergetic effect in mixtures with MeOH could be related to the fact that the E_T^N values of both pure solvent components of the mixture are nearly equal. Also, synergism on E_T^N values was reported for the [bmim][PF_6] + ethanol solvent mixtures.

On the other hand, the π^* values exhibit positive deviation from ideal behaviour and are more dominant when the difference between the molecular-microscopic properties of both pure liquids is larger. The π^* values of mixtures with both ILs are similar. For the mixtures with AN, the response pattern shows an *S* type curve, whereas in the mixtures with DMF, the behaviour is nearly ideal. Additionally, the results for MeOH + IL mixtures clearly reflect that the dipolarity/polarisability is dominated for the IL, showing the largest preferential solvation. These results could be related to the ion-indicator non-specific interactions which control the solvation pattern.

The plots of β values *versus* solvent composition reveal that in all cases the basicity values of the mixtures composed of molecular solvent plus [bmim][BF_4] are higher than those of the mixtures consisting of molecular solvent plus [bmim][PF_6]. The general trend shows a negative deviation of β values from ideal behaviour, excluding AN + [bmim][BF_4] mixtures. The latter solvent system exhibits a synergetic effect for this property. In this connection, it is important to notice that the basicity of [bmim][BF_4] matches that of AN. The response patterns exhibit that the influence of the IL is strong except at the lowest IL concentration, suggesting that the values of the property are dominated by the anion. These results could be related to the preferential solvation of the solutes by the ILs through the anions, with [BF_4] being a better solvating species compared to [PF_6]. There are some differences for the values corresponding to the basicity of MeOH + [bmim][BF_4] reported in the literature.

In turn, the α values exhibit positive deviation from ideal behaviour. Taking into account the type of molecular solvent analysed, two different response patters can be observed, independently of the IL that forms part of the binary mixture. For AN and DMF, the parameter values abruptly increase with small increase in the content of IL because this effect is controlled by the IL. On the other hand, the acidity decreases continuously when the IL is added to MeOH, exhibiting a positive deviation from ideal behaviour. The solvation pattern is controlled by the protic solvent. These results could be ascribed to two reasons. On the one hand, Reichardt's dye has a strong HBD phenolate oxygen which interacts with the cation of the IL, and the $E_T(30)$ values are key factors in the measurements of acidity α, the MeOH + [bmim][PF_6] mixtures showing a higher HBD ability than the MeOH + [bmim][BF_4] mixtures. Considering that these binary solvent mixtures differ only in the nature of the anion, these results could be connected with an anion effect on acidity. In consequence, the HBD ability of this type of mixtures is controlled by the HBA ability of the anion. The more basic the anion, the greater the effect, and this is particularly significant in protic solvents.

With this type of mixtures, it is possible to select individual binary mixtures with the aim of providing 'new solvents' with particular solvating properties. In order to compare the behaviour of [bmim][BF_4] in respect of [bmim][PF_6], the selected mixtures should be of similar concentrations with respect to both ILs.

In solvents of the type (x_{AN} 0.9/x_{IL}0.1), the basicity either remains constant or is slightly increased, the dipolarity/polarisability being moderately increased and the acidity markedly increased in relation to the AN. On the other hand, these solvents are comparable with respect to their HBD ability and dipolarity/polarisability, but differ in the HBA ability which is slightly higher in the first one.

Solvent (x_{AN} 0.5/$x_{[bmim][BF4]}$0.5) shows a slightly higher dipolarity/polarisability ($\pi^* = 1.01$) than solvent (x_{AN} 0.5/$x_{[bmim][PF6]}$ 0.5) ($\pi^* = 0.94$). However, it is the basicity that clearly characterises the solvation behaviour of each of these solvents, the former being nearly twice as basic as the other ($\beta = 0.45$ vs. $\beta = 0.24$). Solvents (x_{DMF}0.9/x_{IL} 0.1) have a similar behaviour. Finally, solvents (x_{MeOH}0.5/x_{IL}0.5) show dipolarity/polarisability and basicity values comparable to those of the pure ILs ($\pi^* = 1.03$ and 1.0, respectively, and $\beta = 0.46$ and 0.17, respectively), whereas the acidity values are greatly increased with respect to the values of both ILs ($\alpha = 0.86$ and 0.96, respectively).

With the aim of completing this study, we analysed the microscopic features of solvent systems resulting from the basis of binary mixtures formed by a protic molecular solvent (MeOH, ethanol (EtOH), propan-1-ol, propan-2-ol or 2-ethoxyethanol (EtOEtOH)) and a bmim-based ionic liquid cosolvent composed of different anions: [BF_4], [PF_6], chloride [Cl] and bromide [Br]. The selection of these molecular solvents was done mainly on the basis of their HBD capacity. At the same time, it was convenient to discuss the incidence of anion type on the solvation pattern.

In general, the above-discussed systems exhibit positive deviation from ideal behaviour. As previously shown for the mixtures of [bmim][BF_4]/[PF_6] with MeOH, the parameter exhibits a slight synergism in the binary systems composed of these ILs, the selected alcohols and this synergetic effect being clearly manifest in the whole range of ionic liquid compositions for ethanol + [bmim][BF_4] and 2-ethoxyethanol + [bmim][BF_4]/[PF_6]} binary solvent systems. For the mixtures comprised of [bmim][Cl]/[Br], the E_T^N values were higher compared to the values in pure alcohols and were more pronounced at low IL mole fractions. The synergism of E_T^N values was also reported for similar binary solvent systems. The solvation effect of betaine dye was more pronounced for HBD and EPA (electron pair acceptor) solvents than for EPD (electron pair donor) solvents. Therefore, the E_T^N scale is particularly sensitive to the HBD ability of the cation part of the IL. All ILs considered for this study contained the same cation, so it is reasonable to expect that the parameter values and the shapes of the response curves (parameter value vs. mixture concentration) would be similar. Nevertheless, the betaine dye can take part in hydrogen-bond formation with alcohols via its phenoxide oxygen and the hydroxylic proton, forming 1:1 intermolecular complexes. On the other hand, 1,3-dialkylimidazolium-based ionic liquids can act as acceptors to establish hydrogen bonding with alcohols, competing with betaine for the hydroxylic hydrogen . At the same time, they can act as donors to interact with the dye through hydrogen bonding. These interactions have a singular effect on the parameter values.

On the other hand, π* values show a marked increase by adding small amounts of the IL. Moreover, they exhibit positive deviations from ideal behaviour in all systems. For instance, in case of EtOH + [bmim][BF$_4$] mixture, at $x_{IL}=0.1$, a maximum deviation of 47% with respect to the ideal additive behaviour was observed. However, π* values were comparable despite the involvement of alcohol. The response patterns between [bmim][BF$_4$]/[PF$_6$] and [bmim][Cl]/[Br] were complementary, particularly in mixtures with propan-1-ol and propan-2-ol. The β basicity values of the mixtures with [bmim][Cl] were the highest, whereas for mixtures with [bmim][PF$_6$], the basicity values were small. For all binary mixtures, basicity follows the order [bmim][Cl] > [bmim][Br] > [bmim][BF$_4$] > [bmim][PF$_6$]. The systems ethanol/2-ethoxyethanol + [bmim][BF$_4$] and 2-ethoxyethanol + [bmim][PF$_6$] exhibit a negative deviation from ideal behaviour (maximum deviation of 27% at $x_{IL}=0.3$, 19% at x_{IL} = 0.5 and 38% at $x_{IL}=0.7$, respectively), as observed in MeOH. For the mixtures of [bmim][BF$_4$]/[PF$_6$] with the other alcohols, it was observed that while the ionic liquid concentration increases, the parameter value decreases. With regard to the systems with [bmim][Cl], the general trend shows that basicity increases as the ionic component is increased, reaching the highest magnitude for the system with ethanol. Its mixture with methanol exhibits a maximum positive deviation of 22% considering $x_{IL}=0.9$ as the pure solvent. The mixtures with [bmim][Br] do not follow a clear trend. For the systems with 2-ethoxyethanol, a clear opposite tendency is manifested between [bmim][Cl]/[Br] and [bmim][BF$_4$]/[PF$_6$].

The mixtures with [bmim][BF$_4$] in ethanol and in 2-ethoxyethanol manifest a positive deviation from ideal behaviour at low concentrations of the IL (maximum deviation of 11% at $x_{IL}=0.1$ and 15% at $x_{IL}=0.1$, respectively), exhibiting a gradual linear decrease at higher concentrations. The mixture, 2- ethoxyethanol + [bmim][PF$_6$] exhibits the same pattern, with a maximum deviation of 15% at $x_{IL}=0.1$. Additionally, a slight synergetic effect operates in these systems at low IL concentration. For the systems with [bmim][Cl] or [bmim][Br], the HBD ability experiments show a marked decrease, following approximately an additive behaviour. The mixtures of [bmim][Cl] with ethanol and methanol exhibit negative deviations at high concentrations of IL. Considering $x_{IL}=0.9$ as the pure solvent, the maximum deviations were 38% at $x_{IL}=0.7$ and 48% at $x_{IL}=0.5$, respectively. As a general tendency, the property follows the order [bmim][PF$_6$] = [bmim][BF$_4$] > [bmim][Br] > [bmim][Cl]. This trend is roughly opposite to that observed for the basicity.

With respect to the influence of the anion and cation interactions, at first glance, the hydrogen bond basicity is controlled by the anions. However, this is a general trend because the hydrogen-bond acceptor ability of the ionic liquid also depends on the nature of cation. Thus, the overall ability of the IL to form a hydrogen bond with a molecule of solute comes from an antagonistic relationship between its constituent ions. This fact may be described in terms of two competing equilibria.

Thus, before hydrogen bonding with a solute, the anion could form a hydrogen bond with the cation. As this last equilibrium becomes more preferential, the anion–solute interaction becomes less favoured. Thus, the prevalence of the ion-pair character in the ionic liquid will determine its interactions with other species, such as a probe or a molecular solvent.

The interactions between cations and anions in ILs are too complex. They involve not only Coulombic interactions but also van der Waals and other dipole–dipole derived interactions. For example, the aromatic p_π interactions above and below the ring plane of imidazolium cations can interact with the anion electron cloud, giving rise to significant dispersion forces. All possible interactions would be different if the ions are densely charged. The selected ionic liquids comprise the charge delocalised 1-butyl-3-methylimidazolium cation, the [Cl]/[Br] anions with a high degree of charge localisation and $[BF_4]$ and $[PF_6]$ as charge delocalised anions. In this direction, the ion pairs arising from [bmim][Cl] and [bmim][Br] would be more loosely bound than those from ILs with the fluorinated anions. In line with this trend, [bmim][Cl] and [bmim][Br] would exhibit more basicity than $[bmim][BF_4]$ and $[bmim][PF_6]$ because their anions are more easily available to interact with the probe. The basicity trend experimentally observed is in agreement with this interpretation. Additionally, the higher proton acceptor ability of $[BF_4]$ with respect to $[PF_6]$ was reported employing other solutes as solvatochromic probes. In an earlier independent study, proton acceptor abilities of a variety of anions ($[BF_4]$, [Cl] and [Br], among others) were reported using phenol and water as proton donors. The proton acceptor ability trend was $[Cl] > [Br] > [BF_4]$ [21].

Taking into account of IL-alcohol interactions, it is known that water and alcohols modify the ordered three-dimensional networks of cations and anions of ionic liquids. For example, in water at infinite dilution, ionic liquid components break away from their pure environment and settle in the water environment, probably as separated ions. As the concentration of the IL increases, its anions and cations begin to interact with each other, directly or mediated by water. At higher concentrations, IL ions cluster provides an arrangement very similar to that obtained in the pure state [22]. Water and small alcohols are strongly hydrogen-bonded with the anion rather than the cation. The degree and type of interaction will depend on both the IL and the alcohol.

In the solvent systems with $[bmim][BF_4]$ and $[bmim][PF_6]$, the basicity decreases as the IL concentration increases. This tendency is the consequence of a favoured interaction between anion and cation and/or between the IL and the corresponding alcohol. This last strong association can be connected with the negative deviation from ideality exhibited in some mixtures, in which a singular complex formed by the IL and the alcohol (a ‘mixed solvent’) surrounds the probe, solvating it preferentially. On the other hand, basicity increases with the increase in concentration of the IL in the systems comprised of [bmim][Cl] or [bmim][Br] (although the trend is clearer for the anion [Cl]). Since the ion pairs in these ILs are loosely bound, a better interaction with the probe exists. This last tendency could be ascribed to a preferential solvation by the ionic liquid and, as a consequence, to a lesser preponderance of the ‘mixed solvent’ in the solvation process.

$$I(S1)_2 + 2S2 \rightleftharpoons I(S2)_2 + 2S1$$

$$I(S1)_2 + S2 \rightleftharpoons I(S12)_2 + S1$$

Fig. 13.4 Solvation behaviour. Simple exchange models of two solvents

The acidity trend is consistent with the above analysis. Taking into account that these solvent systems differ only in the nature of the anion and that α values are mainly determined by the nature of the cation, the behaviour can be connected with an anion effect on the acidity. The positive deviation manifested in some solvents with [bmim][BF_4] and [bmim][PF_6] and the slight synergetic effect can be attributed to the strong intersolvent interactions mentioned above. The almost linear decrease of the property in several mixtures comprised of [bmim][Cl] and [bmim][Br] also demonstrates that the 'mixed solvent' is less favoured, although a slight negative deviation in some solvents with [bmim][Cl] can be noticed.

The application of preferential solvation models in mixed solvents is a useful tool to describe the behaviour of solvatochromic indicators and the structure of binary mixtures, providing valuable solute–solvent and solvent–solvent structural information. Thus, in order to evaluate the experimentally observed solvation pattern and obtain a deeper insight into the influence of anion and cation type on the solvation behaviour, the Buhvestov [34, 35] and Skwierczynsi [36] models can be applied. These models are based on a simple exchange of two solvents according to Fig. 13.4, where I stands for the corresponding indicator, S1 and S2 for the pure solvents and S12 for the mixed solvent. I(S1) represents the indicator solvated by the S1 component, I(S2) by the S2 component and I(S12) by the S12 mixed solvent. The equations of the above scheme reflect the total exchange of solvent 1 by solvent 2 in the solvation sphere of the indicator and the exchange by the mixed solvents, respectively. The constants in these processes are defined by the preferential salvation parameters ($f_{2/1}$ and $f_{12/1}$) that relate the ratio of the mole fractions of solvents S1 and S2 and the mixed solvent S12 (structure attributed to the formation of intersolvent complexes or associates by hydrogen-bond interactions) solvating the probe (x_1^s, x_2^s and x_{12}^s) to the ratio of the mole fractions of the two solvents in the bulk mixed solvent (x_1 and x_2, respectively). Constants $f_{2/1}$ and $f_{12/1}$ measure the tendency of the probe to be solvated with cosolvent S2 and 'mixed solvent' S12, with reference to solvent S1.The constant $f_{12/2}$ corresponding to the 12/2 exchange can be calculated from the relation $f_{12/1}/f_{2/1}$. Thus, the solvatochromic mixture property Y can be evaluated as an average of the properties in pure solvents S1, S2 and S12 (Y_1, Y_2 and Y_{12}, respectively), according to Eq. 13.1:

$$Y = \frac{Y_1(1-x_2)^2 + Y_2 f_{2/1}(x_2)^2 Y_{12/1}(1-x_2)x_2}{(1-x_2)^2 + f_{2/1}(x_2)^2 + f_{12/1}(1-x_2)x_2} + \Delta Y$$

Equation 13.1 Evaluation of the solvatochromic property Y

The correction term ΔY (Eq. 13.2) was originally introduced [34, 35] to take into account the enhancement of water structure caused by the alcohol molecules in alcohol–water mixtures at a low mole fraction of alcohol, yielding Eq. 13.2, where k is a proportionality constant:

$$Y = \frac{k f_{2/1}(x_2)^2\left[(1-x_2)^2 + f_{12/1}(1-x_2)x_2/2\right]}{\left[(1-x_2)^2 + f_{2/1}(x_2)^2 + f_{12/1}(1-x_2)x_2\right]^2} + \Delta Y$$

Equation 13.2 Introduction of the correction term in Eq. 13.1

As previously discussed, the solvation patterns are characterised by exhibiting a significant change as low amounts of IL are added to the molecular alcohols, particularly for the dipolarity/polarisability and basicity properties.

In order to take into account this ionic liquid effect on the solvatochromic property (Y) of the mixtures, the wave numbers of maximum absorptions of the solvatochromic indicators (*N*,*N*-diethyl-4-nitroaniline, 4-nitroaniline and Reichardt's betaine dye) at different compositions of S1 (alcohol) and S2 (IL) were fitted to the equations.

N,*N*-Diethyl-4-nitroaniline is sensitive to the dipolarity/polarisability of the solvent. Since it shows positive solvatochromism, a decrease in the property increases the wave number of maximum absorption. It is possible to show that the wave numbers of maximum absorptions of pure solvents (Y_1 and Y_2) increase in the order [bmim][Cl], [bmim][BF_4], [bmim][PF_6], MeOH, EtOEtOH and EtOH. The wave numbers of maximum absorptions of the mixed solvent S12 (Y_{12}) are close to Y_2 values, and in some mixtures, they are lower than Y_1 and Y_2 values. Mixed MeOH/EtOH + [bmim][Cl] display the strongest dipolarity/polarisability, exhibiting a minimum in the Y_{12} values. In general, the order of the preferential solvation parameters $f_{2/1}$, $f_{12/1}$ and $f_{12/2}$ suggests that, while in the mixtures with [bmim][BF_4] and [bmim][PF_6], the probe is preferentially solvated by the mixed solvent. However, in the mixtures with [bmim][Cl], it is preferentially solvated by the IL. Particularly in the MeOH and EtOH solvent systems, the dipolarity/polarisability property exhibits a significant increment in the presence of low concentration of the ionic liquid in the mixture. This effect is manifested in the form of decrease in the wave numbers of maximum absorptions and as negative values of k constants. 4-Nitroaniline is also a positive indicator and is sensitive to both solvent dipolarity/polarisability as well as to solvent hydrogen-bond basicity. The combination of these solvent properties determines the order of the wave numbers of the maximum absorption of this indicator. The wave numbers of maximum absorptions of the pure solvents (Y_1 and Y_2) increase in the order [bmim][PF_6], [bmim][BF_4], MeOH, EtOEtOH, EtOH and [bmim][Cl]. The wave numbers of maximum absorptions of the mixed solvent S12 (Y_{12}) are close to Y_2 values in most mixtures. The solvents with [bmim][PF6] exhibit the highest values of Y_{12}. For mixed MeOH + [bmim][PF6], Y_{12} is higher than the Y_1 and Y_2, manifesting a minimum in the β basicity. Compared to the previous probe, the k constants are less negative than in the previous probe, as the increase in the wave numbers is partially compensated by the variation in dipolarity/polarisability. On the other hand, mixed MeOH + [bmim][Cl] displays the lowest Y_{12} value, indicating a maximum in the HBA property. In the solvent systems with [bmim][PF_6] and [bmim][BF_4], the $f_{2/1}$ parameters are lower than unity, indicating that the indicator is preferentially solvated by the alcohol; $f_{12/1}$ and $f_{12/2}$ are higher than unity, suggesting that the mixed solvent is solvating preferentially. Thus, the preferential solvation order is: mixed solvent > IL > alcohol. For the solvent systems comprised of [bmim][Cl], the $f_{2/1}$, $f_{12/1}$ and $f_{12/2}$ values suggest that the preferential solvation order is: IL > mixed solvent > alcohol.

Reichardt's betaine dye exhibits negative solvatochromism and is sensitive to dipolarity/polarisability and HBD ability. The wave numbers of maximum absorptions of pure solvents (Y_1 and Y_2) increase in the order [bmim][Cl], EtOEtOH, EtOH, [bmim][BF_4] ~ [bmim][PF_6], MeOH. The wave numbers of maximum absorptions of the corresponding alcohol-IL S12 solvents (Y_{12}) increase approximately in the same order. In the mixtures exhibiting a slight synergism on the E_T^N parameter (and in α parameters, although to a minor extent), the Y_{12} values are somewhat higher than the Y_1 and Y_2 values, especially in MeOH + [bmim][BF_4]/[PF_6] solvent systems. The *k* constants are positive as expected and, in general, similar in absolute values to the positive indicators. The $f_{2/1}$ values, which measure the preferential solvation of the indicator by IL with reference to the alcohol, are higher than unity in all solvents. The [bmim][Cl] ionic liquid displays the highest values of this parameter. For the mixtures with [bmim][BF_4] and [bmim][PF_6], the high $f_{12/1}$ and $f_{12/2}$ values demonstrate that the indicator is preferentially solvated by the mixed solvent S12. On the other hand, for the solvent systems comprised of [bmim][Cl], the $f_{2/1}$, $f_{12/1}$ and $f_{12/2}$ values suggest that the preferential solvation order is: IL > mixed solvent > alcohol.

In order to provide 'new solvents' of this type of binary mixtures, it is interesting to take into account the following considerations on the general tendencies.

In solvent (x_{EtOH} 0.9/$x_{[bmim][BF4]}$ 0.1), the acidity is synergic with respect to the pure solvents, exhibiting the highest value of the property corresponding to the whole IL mixtures with ethanol. Simultaneously, this liquid manifests the maximum positive deviation from ideal behaviour on π* property. Solvents (x_{EtOH} 0.7/$x_{[bmim][BF4]}$ 0.3), (x_{EtOH} 0.7/$x_{[bmim][Cl]}$ 0.3) and (x_{EtOH} 0.7/$x_{[bmim][Br]}$ 0.3) are comparable with respect to their dipolarity/polarisability, exhibiting a large increase with reference to pure ethanol. On the other hand, solvent (x_{EtOH} 0.4/$x_{[bmim][PF6]}$ 0.6) exhibits almost analogous dipolarity/polarisability with respect to previous solvents, but it is characterised by an HBD acidity similar to liquid (x_{EtOH} 0.9/$x_{[bmim][BF4]}$ 0.1). For solvent (x_{EtOH} 0.1/$x_{[bmim][Cl]}$ 0.9), its HBA ability should be remarked.

Solvents ($x_{EtOEtOH}$ 0.9/$x_{[bmim][BF4]}$ 0.1), ($x_{EtOEtOH}$ 0.9/$x_{[bmim][PF6]}$ 0.1), ($x_{EtOEtOH}$ 0.9/$x_{[bmim][Cl]}$ 0.1) and ($x_{EtOEtOH}$ 0.9/$x_{[bmim][Br]}$ 0.1) are characterised by an HBD acidity higher than that of the pure alcohol. They exhibit similar dipolarity/polarisability and a significant HBA ability. Moreover, the last two solvents have higher HBA ability than 2-ethoxyethanol. Solvents ($x_{EtOEtOH}$ 0.3/$x_{[bmim][PF6]}$ 0.7) and ($x_{EtOEtOH}$ 0.3/$x_{[bmim][Cl]}$ 0.7) are HBD and HBA solvents, respectively. The former solvent exhibits the maximum negative deviation on basicity in all solvent systems.

The solvent mixtures that comprise propan-1-ol as molecular solvent have higher HBD than HBA ability, and their solvation behaviour is comparable to solvents containing EtOH. Regarding the mixtures containing propan-2-ol in the same compositions corresponding to the liquids with propan-1-ol, the solvation properties are analogous.

Finally, solvents (x_{MeOH} 0.5/$x_{\mathrm{[bmim][Cl]}}$ 0.5) and (x_{MeOH} 0.5/$x_{\mathrm{[bmim][Br]}}$ 0.5) are HBA solvents, particularly the first one. This liquid manifests the maximum positive deviation on basicity and the maximum negative deviation on acidity considering all solvent systems. In contrast, the liquids previously selected comprising [bmim][BF_4] and [bmim][PF_6], at the same compositions, are clearly HBD solvents. On the other hand, solvatochromic parameters have been demonstrated to be successful in correlating a wide range of chemical and physical properties involving solute–solvent interactions. Because of their empirical origins, their ability to make a priori predictions has been somewhat limited. For these reasons, the prediction of solvatochromic parameters in mixed solvents based on a minimum number of experiments provides a useful computational tool. In this sense, the Redlich–Kister equation was used to correlate solvatochromic parameters. The experimental data of E_T^N, π^*, β and α parameters of 15 binary mixtures of the type protic molecular solvent + ILs at various compositions have been fitted to the simplified combined nearly ideal binary solvent/Redlich–Kister (CNIBS/R-K) model [37]. The model proved to be statistically valuable, showing a strong correlation between predicted and experimentally measured values.

Specific Conclusions

In general, for the proposed 'new solvents', it can be observed that the dipolarity/polarisability and basicity are similar to those of AN and DMF. The acidity is quite different being highly increased, particularly in the case of AN. In relation to the protic solvent + imidazolium-based ILs binary solvent mixtures, the compositions of the mixtures are dependent on both the nature of the protic solvent as well as on the anion type of the ionic liquid. With ethanol and 2-ethoxyethanol as molecular solvents, the IL displays large solubility, particularly when the anions are [BF_4] or [Cl]. The ILs [bmim][PF_6] and [bmim][Br] exhibit the lowest solubility, so their mixtures were explored at the smallest range of compositions.

In general, E_T^N displays a similar response pattern in all solvent systems exhibiting positive deviation from ideal behaviour characterised in some mixtures by a synergetic effect. The mixtures composed of [bmim][BF_4] and [bmim][PF_6] exhibit higher E_T^N polarity. The feature of π^* dipolarity/polarisability also shows similar solvation patterns in spite of the presence of alcohol. Moreover, the values of the property match for all ILs as they are compared using the same range of compositions.

The influence of nature of anion is clearly manifested through specific solute–solvent and solvent–solvent interactions (basicity and acidity). The systems comprised of [Cl]/[Br]anions display the highest values of basicity, while the systems composed of $[BF_4]/[PF_6]$ exhibit the maximum values of acidity. This trend is connected with the degree and type of interactions between the anions and the 1-butyl-3-methylimidazolium cation. Thus, in $[bmim][BF_4]$ and $[bmim][PF_6]$, the ion-pair character is enhanced with respect to [bmim][Cl] and [bmim][Br], affecting their interactions with a solute or a molecular solvent. The α parameter, the same as the E_T^N polarity, also shows a synergetic behaviour in the systems ethanol/2-ethoxyethanol + $[bmim][BF_4]$, but the effect is less prominent.

Most of the solvent systems exhibit a non-ideal additive behaviour. This result can be ascribed to (a) the preferential solvation of the cybotactic region by some of the solvents present in the mixture, (b) the occurrence of strong solvent–solvent interactions that can generate complex intersolvent structures affecting solute–solvent interactions or (c) a combination of the two phenomena.

The preferential solvation model allowed us to explain the positive and negative deviations from ideal behaviour and the synergetic effect exhibited for the solvatochromic properties with the predominance of a species in the solvation sphere of the indicators. In the solvent systems comprised of $[BF_4]/[PF_6]$ anions, the probes are preferentially solvated by the mixed solvent, while in the systems with [Cl]/[Br] anions, the IL controls the solvation behaviour. These results are indicative of the involvement of ion-pair character of the IL. Additionally, it was possible to select binary mixtures with particular solvating properties varying not only in the solvent compositions but also the nature of the ionic or the molecular component of the mixture.

These results reflect the importance of the employment of these types of binary solvent systems can be, for instance, as reaction media. Additionally, the experimental data of E_T^N, π^*, β and α parameters of 15 binary mixtures of the type [protic molecular solvent + IL] at various compositions have been fitted to the CNIBS/R-K model. The model proved to be statistically valuable, showing a strong correlation between predicted and experimentally measured values.

13.4 Reactivity

13.4.1 General

For many years, chemists have been trying to unravel the role of the solvent in organic reactions. In this direction, ILs, which have similar properties to water, such as being highly ordered media and good HBD, have also been shown to have the potential to influence the outcome of different organic reactions. Therefore, ILs and their binary mixtures with molecular solvents have been used as media to understand solvent effects in a series of reactions. An example that frequently appears in the literature is the participation of ILs as solvent in Diels-Alder (D-A) cycloaddition reactions. In this direction, Jaeger and Tucker have investigated the reaction between cyclopentadiene and methylacrilate in EAN, and surprisingly, the reaction gave a mixture of *endo* and *exo* products in a radio 7:1. Since then, a number of examples of D-A reactions in ILs have been reported. More recently, our group has studied two types of thermal D-A reactions with normal electron demand, using ILs as reaction media. The reactions between 5- and 8-nitroquinolines and 5- and 8-nitroisoquinolines as dienophiles with different dienes were studied [38]. The cycloaddition reactions between 2- and 3-nitrofurans with isoprene, 1-trimethylsyliloxy-1,3-budiene and Danishefsky's diene were also examined. The presence of the IL with respect to the molecular solvent was found to improve the reaction yields, while the temperature and time of reactions significantly decreased [39].

During the last two decades, our group has studied solvent effects on the S_NAr process development in different molecular solvents (aprotic and protic, polar and non-polar) or in their binary mixtures, correlating the kinetic data of this reaction with empirical solvent parameters (E_T^N, π^*, α and β) through Linear Free Energy Relationship's – LFER's – simple and multiparametric equations. The principal S_NAr reactions studied comprise 1-halo-2,4-dinitrobenzene or 1-halo-2,6-dinitrobenzene as substrates and primary and secondary amines as nucleophiles. For the 1-fluoro-dinitrobenzenes derivatives, the reaction can exhibit base catalysis, which is normally solvent dependent. In general, solvent effects were related to reaction rates, mechanisms and catalysis. These studies were extented employing ILs as reaction media.

13.4.1.1 Solvent Effects of Binary Solvent Mixtures Molecular Solvent + Imidazolium-Based IL on Chemical Processes: S_NAr

In order to investigate this type of binary solvent systems as reaction media, a kinetic study on the S_NAr reaction between 1-fluoro-2,4-dinitrobenzene (FDNB) and the primary amine *n*-butylamine (BU) was performed [32, 33]. The selected mixtures were composed of AN and DMF as molecular solvent and [bmim][BF_4] and [bmim][PF_6] as imidazolium-based ILs. It is possible to assume that the reaction proceeds by the classical two-step mechanism as shown in Fig. 13.6. The application of the steady-state approximation affords Eq. 13.3 for the second-order reaction rate k_A.

$$k_A = \frac{k_1(k_2 + k_3^B[B])}{k_{-1} + k_2 k_3^B[B]}$$

Equation 13.3 Expression of the second-order reaction rate constant for an S_NAr reaction

When $k_{-1} << k_2 + k_3^{[B]}$, Eq. 13.3 is reduced to $k_A = k_1$, the formation of the intermediate is rate limiting, and the reaction is not base catalysed. If the previous condition is not obeyed, the decomposition of the intermediate is rate limiting, and base catalysis is observed, the kinetic form of the catalysis depending on the relative magnitudes of k_{-1} and $k_2 + k_3^{[B]}$.

The kinetic results show that no acceleration in rate is produced for an increasing amount of amine, so the reactions do not exhibit base catalysis and the formation of the intermediate is rate determining. This trend is reasonable considering that base catalysis, in general, is not operative in S_NAr reactions with primary amines as nucleophiles.

Considering the kinetic response of the reactive systems and analysing the changes in the second-order rate constant when the IL is added to the molecular solvent, the following comments can be made.

Undoubtedly, a synergetic effect on the reaction rate occurs in the case of AN + [bmim][BF$_4$]. In some binary mixtures, the k_A values are higher than those in pure AN and in the (x_{AN} 0.1/$x_{[bmim][BF4]}$ 0.9) mixture. It can be observed that k_A values experience a remarkable enhancement when small amounts of IL are added to the molecular solvent. Focusing the attention on the proposed 'new solvents' (x_{AN} 0.9/$x_{[bmim][BF4]}$ 0.1) and (x_{AN} 0.5/$x_{[bmim][BF4]}$ 0.5), the k_A values were found to increase (referred to the k_A AN value) 90% and 130%, respectively. This special kinetic synergism behaviour was manifested in S_NAr reactions between FDNB and secondary amines in some binary mixtures of molecular solvents, in which base catalysis is operative. In this latter case, it was concluded that this effect is concerned with a complex combination of factors related to the variation of the influence of base catalysis (which changes with solvent composition) and to specific solvent effect, particularly hydrogen-bond interactions. From the results observed with IL solvent mixtures, it can be remarked that the synergism is manifested in non-catalysed reactions.

The k_A values experience a slight enhancement in AN + [bmim][PF$_6$] mixtures. The reaction rate remains unchanged for the proposed 'new solvent' (x_{AN} 0.9/$x_{[bmim][PF6]}$ 0.1), while the second-order rate undergoes an increase of 30% for (x_{AN} 0.5/$x_{[bmim][PF6]}$ 0.5).

As the kinetic data obtained for the mixtures with AN corresponding to the 'new solvents' at the same concentration of IL are compared, the resulting ratios are $k_{A[bmim][BF4]}/k_{A[bmim][PF6]}$ 1.9 and 1.75, respectively, indicating that the system is almost more reactive in mixtures with [bmim][BF$_4$] than in mixtures with [bmim][PF$_6$].

For the reaction performed in DMF + [bmim][PF$_6$] mixtures, the k_A response patterns reveals a continuous decrease with the increase in the concentration of IL. Moreover, it was of interest to relate the kinetic data to the molecular-microscopic solvent properties in order to aid in the interpretation of the solvent effects in the reaction under study. In order to quantitatively interpret the influence of the solvent effects on the reaction, the reported kinetic data and the quantified molecular-microscopic solvent properties were correlated by means of the multiparametric approach developed by Kamlet-Abboud-Taft [26].

$$\log k_A = Y + s\pi^* + a\alpha + b\beta$$

Equation 13.4 Relationship between k_A and KAT parameters

where *s*, *a* and *b* measure the relative susceptibilities of the reactive system with respect to the solvent properties (dipolarity/polarisability, HBD and HBA ability), respectively. The correlations were good (the r values are between 0.94 and 0.95). The values of the *s*, *a* and *b* correlation coefficients reveal the following facts: (a) the incidences of the solvation effects ascribed to the dipolarity/polarisability and HBA character of the solvents are more important than those attributed to the HBD solvent ability and (b) the dipolarity/polarisability and HBA solvent character manifest positive influence on k_A values. In contrast, the incidence of solvation effects originated on the HBD capability is negative. The obtained data reveal that, in general, an accelerating effect on the reaction rates can be attributed to a combination of the dipolarity/polarisability and HBA ability of the solvent. Moreover, it can be pointed out that the observed kinetic synergetic effect on k_A values could be related to the solvent basicity.

The increase in the reaction rate due to the increase of dipolarity/polarisability is related to the major polarity of the zwitterionic intermediate. Consequently, the activated complex leading to the zwitterionic intermediate is favoured by increasing solvent dipolarity/polarisability. The increase in the reaction rate due to an increase in the solvent HBA ability indicates that the zwitterionic intermediate and the corresponding transition state have HBD character owing to the extra hydrogen on the primary amine. Finally, the reaction rate decreases with increasing HBD ability of the solvent due to the solubilisation of amine via hydrogen-bonding interactions [40–47].

Specific Conclusions

The multiparametric correlation treatment of the kinetic data with the molecular-microscopic solvent properties allowed determining the incidence of each type of solvent property on the kinetics of reaction. For polar aprotic molecular solvent + [bmim][BF_4] or [bmim][PF_6], the solvation effects are dominated by both the dipolarity/dipolarisability and the basicity of the media. Such solvent properties contribute to accelerate the chemical process.

The reactions carried out in AN + [bmim][BF_4] mixtures exhibited higher rates than the ones performed in AN + [bmim][PF_6] mixtures. Considering that the reactions are non-catalysed, these results can be related to a more efficient solvation of the transition state when the anion is [BF_4]. Moreover, the higher k_A values detected for the reaction performed in DMF + [bmim][PF_6] mixtures with respect to the mixtures with AN can also be related to the high HBA ability of the media.

The special kinetic synergetic effects observed in AN + [bmim][BF_4] can be principally attributed to the solvent basicity. Thus, the mixed solvents behave as ‘new solvents’ with particular solvating properties. Moreover, it can be noticed that this particular kinetic effect was not previously observed in non-catalysed S_NAr reactions performed in binary mixed organic solvent systems.

13.4.1.2 Protic Ionic Liquids: Nucleophilic and Acid Catalysis Behaviour

In view of the fact that the addition of small amounts of a PIL to a pure molecular solvent modifies the microscopic characteristics of a reaction medium, a kinetic study of the S_NAr reaction was developed in molecular solvent + PIL binary mixtures [48]. The aim was also to verify if a PIL can act as both Brönsted acid and nucleophile.

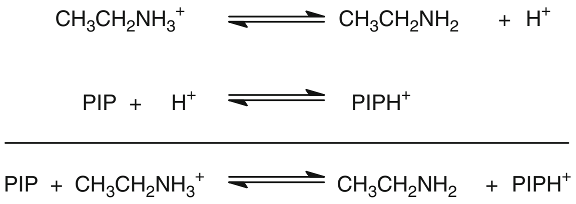

Fig. 13.5 Equilibrium reactions between EAN and PIP

Moreover, in order to complete this approach the nucleophilic addition reaction to aromatic aldehydes was performed in the presence of a PIL.

Kinetic Determinations of the S_NAr Reactions in AN + PIL Binary Solvent System

The kinetic study of the S_NAr reactions of FDNB with BU and piperidine (PIP) was performed in order to examine the influence of EAN on the reaction system. The reactions were carried out in AN and in the presence of low EAN concentration (6.25×10^{-4} up to 0.3 M).

The analysis of the spectra of the reaction with PIP reveals a decrease in the absorbance value of the substitution product corresponding to this amine ($\lambda_{max} = 382$ nm) at low EAN concentration (from 0 to 0.025 M). In contrast, the formation of a new species with λ_{max} at 350 nm was detected at EAN concentration $\geq$ 0.05 M. This result can be understood by taking into account the fact that EAN can act as a Brönsted acid and establishes an acid–base equilibrium with the amine, making it possible to predict nucleophile competition. For the reaction with BU, the above differences in the absorbance values with the increase of the EAN concentration cannot be observed because the wavelengths of absorption for both products are similar. In the light of these results, the corresponding reactions with both amines at preparative scale were carried out. The only substitution product *N*-(2,4-dinitrophenyl) ethyl amine was observed in both cases, and it was confirmed by ^1H NMR, ^{13}C NMR and mass spectroscopy.

Figure 13.5 presents the equilibrium between EAN and PIP. This equilibrium modifies the reactive system so the corresponding product yields will depend on the equilibrium constant magnitudes. The values corresponding to the equilibrium constants for PIP and ethylamine (EA) in AN were obtained from the literature [49, 50].

In order to confirm the non-participation of the nitrate ion in this equilibrium, ethylammonium acetate (EAAc) was used as IL and the same methodology as cited above was applied. In this experiment, only the *N*-(2,4-dinitrophenyl) ethyl amine was obtained as product.

For these S_NAr reactions, it was demonstrated that at low concentration of EAN, two processes are taking place simultaneously as a consequence of the competition

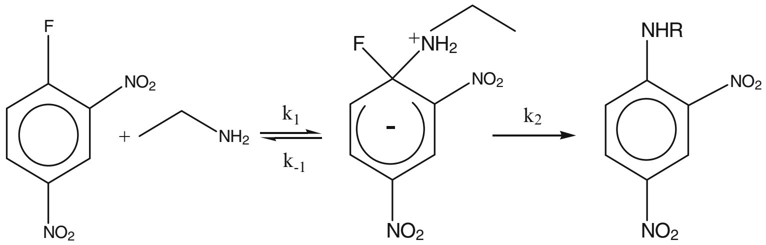

Fig. 13.6 Mechanism for the reaction between primary amines and 2,4-DNFB

of both nucleophiles, EA with PIP or BU, respectively. In the same sense, it can be inferred that for concentrations of EAN $\geq$ 0.05 M, the effective concentrations of PIP^{eff} and BU^{eff} are similar to the substrate concentration. At this point, the EA concentration is close to 0.02 M, making this amine the only effective nucleophile. Moreover, under the indicated conditions these reactions are not base catalysed. This assumption finds support from the abundant evidence of strong hydrogen-bonding interactions between amines and protic solvents. Several contributions have revealed that the strong solvation of the amine molecule by protic solvent is responsible for the observed decrease in rate [51].

Figure 13.6 shows the reaction mechanism in all solvents when primary amines are the nucleophile. In this type of S_NAr reactions, base catalysis is not operative, so the formation of the zwitterionic intermediate is rate limiting and the k_A second-order rate constant is simplified to $k_A = k_1$.

EAN in Addition Reactions of Carbonyl Compound with Nitrogen Nucleophile: Imine Formation

While the use of pure ILs as reaction media has been studied in a variety of chemical processes, reactions in which ILs take part as reagents have not been so widely investigated. Taking into account that EAN can act as a Brönsted acid catalyst and at the same time generate a nucleophilic species, it was interesting to explore this dual behaviour in nucleophilic addition reactions to carbonyl compounds. This latter type of reaction participates in an important number of chemical and biochemical processes that have been the subject of extensive study [52, 53]. Due to their diverse reactivity, imines are common substrates in a wide range of chemical transformations. However, the equilibrium in these reactions usually lies in favour of the free carbonyl compound and amine. Consequently, it is generally necessary to remove water and/or employ an excess amount of the reactants for satisfactory conversion to product. At weakly acidic pH, the addition of amines to carbonyl compounds can follow either a concerted or a stepwise mechanism. The predominant mechanism depends on the basicity of the amine and the mutual equilibrium affinity for adduct formation between the carbonyl compound and the amine. Recently, a

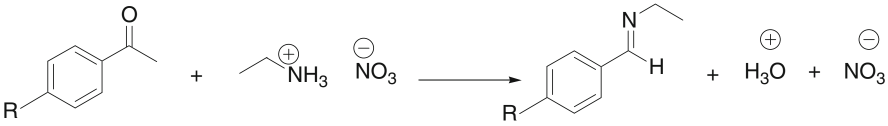

Fig. 13.7 Reactions between different aldehydes and EAN

series of solid-state reactions between gaseous amines and aldehydes to render imines has been reported [54].

In the light of the above facts, the behaviour of 4-(dimethyl)aminobenzaldehyde, 4-hydroxy benzaldehyde, benzaldehyde and 4-nitrobenzaldehyde was analysed in the presence of EAN. The aromatic aldehydes were selected in view of the electronic effects of the *p*- substituent, and benzaldehyde was chosen as reference. The reactions were carried out at preparative level, and the formation of the product was confirmed. The experimental results showed that the electronic nature of the substituent groups in the aromatic ring played a key role in the quantitative conversion to imine product. The experimental yields followed the order: 4-(dimethyl) aminobenzaldehyde > 4-hydroxybenzaldehyde > benzaldehyde ≈ 4-nitrobenzaldehyde (97%, 64%, 14% and 10%, respectively). It is interesting to note that the above reactivity trend for the selected aldehydes followed an opposite direction to the one expected if the reactions were carried out under usual conditions. The imine product formation is promoted by electron-donating groups which favour the acid–base equilibrium between EAN and the aldehydes.

In order to get a deeper insight into the reaction feature, the influence of adding small amounts of EAN ($0.05 \leq 0.3$ M) to a solution of 4-(dimethyl)aminobenzaldehyde in pure AN was analysed, following the methodology previously applied for the S_NAr reactions. From this analysis, it can be concluded that, as EAN concentration in the media is increased, a new species appears (λ_{max} near 400 nm) corresponding to the formation of the imine product. In the light of these results, a simplified reaction scheme is presented in Fig. 13.5.

Specific Conclusions

For the discussed S_NAr reactions, it was possible to confirm that EAN can take part in an acid–base equilibrium with amines even at very low concentration, generating a nucleophile species which can participate in the reaction. The substitution product *N*-(2,4-dintrophenyl)ethylamine was obtained, and therefore, the k_A second-order rate constant for ethylamine could be determined.

In the nucleophilic addition reactions of amines to substituted aromatic aldehydes where acid catalysis is required, the use of EAN seems to be convenient. The EAN can take part in an acid–base equilibrium with the aromatic aldehydes substituted by electron-withdrawing groups. The imine products from the selected aldehydes could be obtained, confirming the dual behaviour of EAN as Brönsted acid and potential nucleophile in these type of processes (Fig. 13.7).

13.5 Conclusions

In this chapter, we presented an approach related to the molecular-microscopic properties of binary mixtures composed of two types of ILs – alkylammonium and dialkylimidazolium-based ILs – with molecular solvents of different structures.

These mixtures were proposed as 'new solvents' suitable as media for chemical processes. In this direction, some of these solvents were employed as media to carry out different S_NAr reactions. The multiparameter correlations of the kinetic data with the molecular properties of the 'new solvents' allowed us to determine the incidence of the solvent properties on the reaction processes.

A special consideration related to EAN and its binary mixtures with molecular solvents allowed us to demonstrate that this protic IL can act both as Brönsted acid and nucleophile. The selected model reaction constitutes a suitable example of how the microscopic feature of a reactive system can be modified by adding aliquots of a protic IL to a molecular solvent. Moreover, the whole reactive system can be modulated with the aim not only to promote acid-catalysed reactions but also to generate nucleophilic species in situ. In this sense, the design of IL can be formulated according to the particular requirement of a reactive system.

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Chapter 14
Ionic Liquids as Green Solvents for the Oxidation of Alcohols

Farhad Shirini, Masoumeh Abedini, and Seyyed Vahid Atghia

Abstract Carbonyl compounds are of central importance to organic chemistry, biochemistry, and biology. Aldehydes and ketones are used as starting materials or reagents for the synthesis of other organic compounds, drugs, and polymeric products. Out of the several available methods for the synthesis of these compounds, oxidation of alcohols is the most important. In this chapter, we will discuss and summarize the methods of oxidation of alcohols using different types of oxidizing agents and/or systems using ionic liquids as green solvents. Mild reaction conditions, simple and easy work-up procedure, high or excellent yields, and stability and reusability of catalyst and ionic liquids are noteworthy advantages of these methods.

14.1 Introduction

Oxidation of alcohols to corresponding carbonyl compounds is one of the important reactions and fundamental transformations both at laboratory and industrial scales. Although numerous methods using a variety of reagents and conditions have been explored for this purpose, most of them suffer from drawbacks such as use of stoichiometric amounts of compounds with concomitant environmental problems, use of organic solvents with volatility, toxicity, and flammability problems, overoxidation, and nonrecoverability of the reagent. Therefore, the development of selective oxidation methods using safe, economic, and environmentally benign agents remains a

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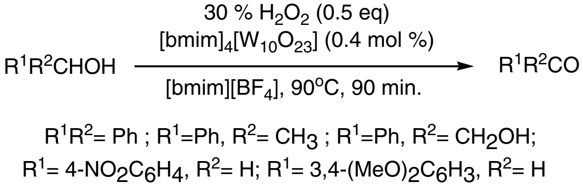
critical challenge in organic synthesis. The chemical and physical properties of ionic liquids have been extensively investigated. Because of their unique properties, they can solvate various organic, inorganic, and organometallic compounds and have been used as green solvents for liquid–liquid separations, extractions, recycling in homogeneous catalysis, and different types of organic reactions.

Herein, we report a summary of researches on the application of ionic liquids, as green, useful, and efficient solvents, in the oxidation of alcohols using different types of reagents.

14.1.1 Peroxides

Aqueous hydrogen peroxide, as a cheap and commercially available reagent, is an ideal oxidant because it can be safely stored and handled, contains effective oxygen, and produces water as the only by-product. Due to the low standard redox potential of hydrogen peroxide in neutral or weak acidic media, it has been usually used in the presence of inorganic acids or organocatalysts.

Catalytic oxidations of alcohols with hydrogen peroxide using different imidazolium wolframate catalysts and [bmim][BF_4] as solvent have been described by Chhikara et al. [1, 2]. Using imidazolium decatungstate $[bmim]_4[W_{10}O_{23}]$ as catalyst, secondary and benzylic alcohols could be oxidized to the corresponding carbonyl compounds affording very good yields, but primary aliphatic alcohols were not oxidized under the same reaction conditions. The recyclability of the catalyst was demonstrated for the oxidation of diphenylmethanol that due to its good solubility in the ionic liquid $[bmim]_4[W_{10}O_{23}]$ could be employed in five consecutive reactions (Scheme 14.1).

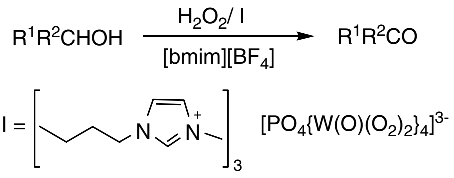


$$R^1R^2CHOH \xrightarrow[\text{[bmim][BF}_4\text{], 90°C, 90 min.}]{30\ \%\ H_2O_2\ (0.5\ eq)\ \ [bmim]_4[W_{10}O_{23}]\ (0.4\ mol\ \%)} R^1R^2CO$$

R^1R^2= Ph ; R^1=Ph, R^2= CH_3 ; R^1=Ph, R^2= CH_2OH; R^1= 4-$NO_2C_6H_4$, R^2= H; R^1= 3,4-$(MeO)_2C_6H_3$, R^2= H

Scheme 14.1 Oxidation of alcohols catalyzed by $[bmim]_4[W_{10}O_{23}]$

Investigations clarified that when $[bmim]_3[PO_4\{W(O)(O_2)_2\}_4]$ is used as catalyst, oxidation of primary alcohols under the same reaction conditions leads to the formation of aldehydes in good yields together with modest amounts of acids; also with increase in H_2O_2, acids could be obtained as the major products of the reaction (Scheme 14.2).

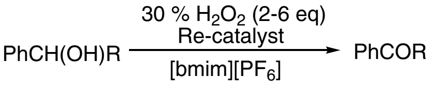


Scheme 14.2 Chemo-selective oxidation of primary alcohols with H_2O_2

Oxidation of secondary alcohols with H_2O_2 catalyzed by methyltrioxorhenium (MTO) as homogeneous catalyst and supported MTO (polyvinylpyridine/MTO and polystyrene/MTO) as heterogeneous catalysts was investigated by Crucianelli et al. [3].

Comparison of the results obtained in different solvents showed better results when the ionic liquid [bmim][PF_6] was used as solvent (Scheme 14.3).

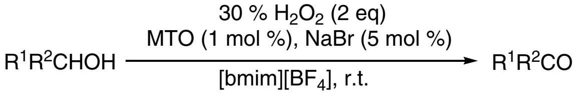
Scheme 14.3 MTO catalyzed oxidation of alcohols with H_2O_2



$$\text{PhCH(OH)R} \xrightarrow[\text{[bmim][PF}_6\text{]}]{\text{30 \% H}_2\text{O}_2\text{ (2-6 eq)}\ \text{Re-catalyst}} \text{PhCOR}$$

Also, oxidation of primary and secondary alcohols with hydrogen peroxide in the presence of catalytic amounts of MTO and NaBr in [bmim][BF_4] has been reported by Sain and coworkers [4]. The results obtained from ionic liquid as solvent were better than those obtained from some organic solvents (Scheme 14.4).

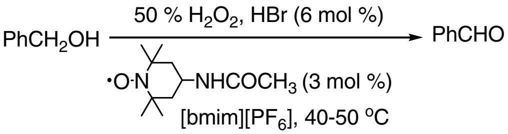
Scheme 14.4 Oxidation of alcohols in the presence of MTO and NaBr



$$\text{R}^1\text{R}^2\text{CHOH} \xrightarrow[\text{[bmim][BF}_4\text{], r.t.}]{\text{30 \% H}_2\text{O}_2\text{ (2 eq)}\ \text{MTO (1 mol \%), NaBr (5 mol \%)}} \text{R}^1\text{R}^2\text{CO}$$

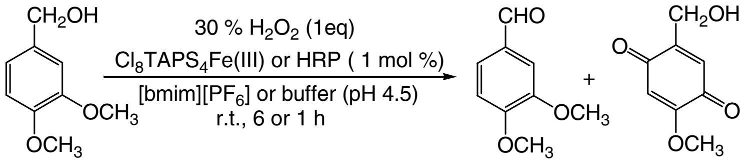
Ragauskas et al. reported the oxidation of benzylic alcohols to their corresponding carbonyl compounds in [bmim][PF_6] using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/HBr/H_2O_2 and acetamide-TEMPO/HBr/H_2O_2 catalytic systems [5]. TEMPO being expensive agent, its efficient recycling is very desirable. It cannot be reused in ionic liquid after ether extraction, due to its good solubility in ether. In contrast, the use of insoluble acetamide-TEMPO, as a stable reagent, rendered product isolation by extraction, and the catalyst recycling is also possible (Scheme 14.5).

Scheme 14.5 Oxidation of benzylic alcohols catalyzed by acetamide-TEMPO/HBr



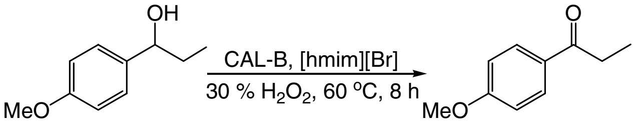
Using this method, benzylic alcohols with electron-deficient and electron-neutral groups were oxidized in good to excellent yields. However, electron-rich benzylic alcohols such as p-methoxybenzyl alcohol failed to afford the target products due to side reactions.

Biomimetic oxidation of 3,4-dimethoxybenzyl alcohol (veratryl alcohol), with H_2O_2 in the presence of catalytic amounts of iron(III) porphyrin complex (Cl_8TAPS_4FeCl) and/or horseradish peroxidase (HRP) in [bmim][PF_6], was studied by Kumar et al. (Scheme 14.6) [6]. Comparison of the obtained results showed better catalytic activity for iron complex.



Scheme 14.6 Biomimetic oxidation of veratryl alcohol

Sinha et al. [7] for the first time reported a highly efficient and recyclable combination of *Candida antarctica* lipase B (CAL-B) and neutral ionic liquid [hmim] [Br] for metal-free H_2O_2 activation in the chemoselective oxidation of aryl alcohols. Initial study was carried out using 4-methoxyphenyl propanol, as substrate, and H_2O_2 at 40°C in the presence of CAL-B/[hmim][Br], thereby providing aldehyde in 90% yield after 16 h. Increasing the reaction temperature to 60°C significantly brought down the reaction time from 16 to 8 h (Scheme 14.7).



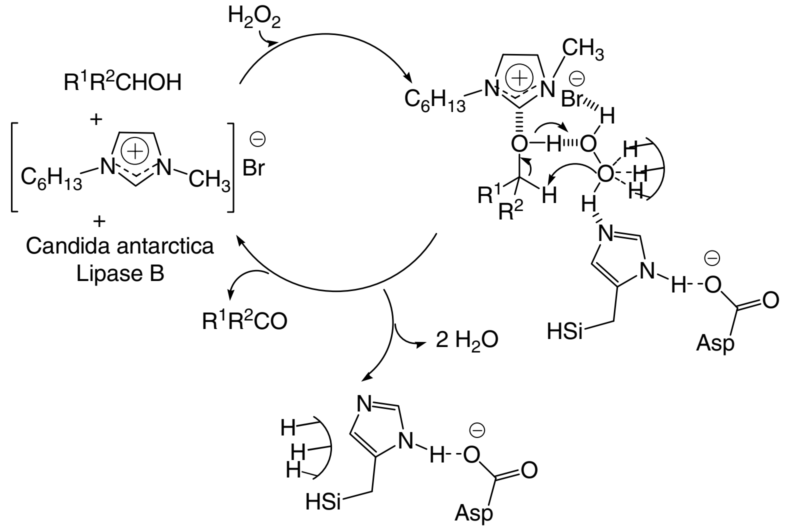
Scheme 14.7 Oxidation of 4-methoxyphenyl propanol using H_2O_2

Generalization of this method to other alcohols showed that primary and secondary benzylic alcohols were efficiently converted to their corresponding carbonyl compounds under the selected conditions. Because of the stability of aliphatic alcohols, this method can be used for the chemoselective oxidation of aryl alcohols in the presence of aliphatic ones.

It is important to note that the recovered catalysts retained high activity for ten cycles but yield decreased, which was compensated by adding a few milligrams of fresh lipase and IL. The proposed mechanism involves interaction of hydroxyl group of alcohol with the imidazolium cation of IL and polarization of C–O bond, followed by attack with H_2O_2 (Scheme 14.8).

Han et al. reported that the oxidation of alcohols with t-BuOOH in [bmim][BF_4] is efficiently catalyzed in the presence of a novel amino acid Schiff base copper ligand (I) (Scheme 14.9) [8]. This method is very useful for the selective oxidation of primary and secondary alcohols to their corresponding carboxylic acids and ketones, respectively. They also showed that the selective oxidation of secondary alcohols to ketones with t-BuOOH is promoted in [bmim][PF_6] using copper acetyl acetonate as catalyst (Scheme 14.10) [9]. These catalytic systems could be recycled and reused for five runs without any significant loss of catalytic activity, and the obtained products were in excellent yields.

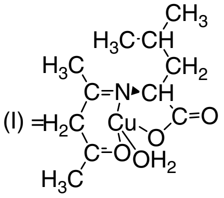
1,2-Allenic ketones are important materials due to their interesting utility as Michael acceptors, Diels–Alder dienophiles, and 1,3-dipoles in unusual [8+2] annulation and building blocks in furan. For the first time, oxidation of homopropargilic alcohols to 1,2-allenic ketones with t-BuOOH as oxidant and $RuCl_3$ as catalyst



Scheme 14.8 Mechanism of the oxidation of alcohols in the presence of CAL-B

$$R^1R^2CHOH \xrightarrow[\text{[bmim][BF}_4\text{], 1h, r.t.}]{t\text{-BuOOH, 1 mol \% Catalyst I}} R^1R^2CO$$

R^1 = alkyl, aryl; R^2 = alkyl, aryl, H

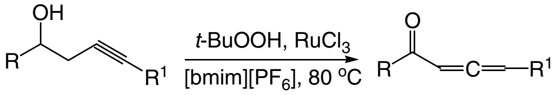


Scheme 14.9 Oxidation of alcohols with t-BuOOH

$$R^1R^2CHOH \xrightarrow[\text{[bmim][PF}_6\text{], r.t.}]{t\text{-BuOOH, Cu(acac)}_2} R^1R^2CO$$

Scheme 14.10 Chemoselective oxidation of secondary alcohols catalyzed by Cu(acac)$_2$

in ionic liquid was reported by Fan and coworkers (Scheme 14.11) [10]. Initially, [bmim][BF$_4$] and [bmim][PF$_6$] were used as solvents and compared to conventional solvents such as CH_3CN, THF, H_2O, and CH_2Cl_2. Although the yield of the product was lower than in CH_2Cl_2, [bmim][PF$_6$] was preferred as the oxidation medium due to the fact that ionic liquids have emerged as promising alternative green solvents for chemical synthesis because of their specific properties.



Scheme 14.11 RuCl$_3$ catalyzed oxidation of homopropargilic alcohols with t-BuOOH

It was observed that with aryl-substituted derivatives, the reactions underwent smoothly and the products were produced in moderate yields. In addition, results indicated that electronic effect did not play a significant role in affecting the oxidation, while the steric hindrance seemed to be important factor. The ionic liquid [bmim][PF_6] containing $RuCl_3$ is also recyclable and can be reused for a new cycle with adding certain amount of t-BuOOH.

Heel and coworkers studied the oxidation of primary and secondary benzylic alcohols in [bmim][BF_4] using urea hydrogen peroxide (UHP) in the presence of catalytic amount of $MgBr_2$ (Scheme 14.12) [11]. All reactions were performed under mild conditions in good to high yields.

$$R^1R^2CHOH \xrightarrow[\text{MgBr}_2\text{, [bmim][BF}_4]]{\text{Urea Hydrogen Peroxide (UHP)}} R^1R^2CO$$

Scheme 14.12 Oxidation of benzylic alcohols using UHP/$MgBr_2$ reagent system

14.1.2 *Iodine and Hypervalent Iodine Reagents*

Molecular iodine can be considered as one of the ideal oxidants due to its many desirable properties like low cost, safe to handle/use, and easy availability. Because of the intrinsic low reactivity of I_2 compared to the other highly reactive hypervalent iodine reagents, oxidation reactions with I_2 required the concomitant use of activating agents.

The mixture of I_2 and Li_2CO_3 was tested in the oxidation of alcohols by Lee et al. [12].The reactions were carried out in [bmim][BF_4] at 60°C for primary benzylic alcohols and at room temperature for secondary benzylic alcohols. Various primary and secondary benzylic alcohols underwent smooth oxidation to provide high yields of the corresponding aldehydes and ketones, and acid products were not detected for primary alcohols (Scheme 14.13).

Replacement of Li_2CO_3 by other bases gave inferior yields of desired products.

$$ArCH(OH)R \xrightarrow[\text{[bmim][BF}_4]]{I_2\text{ / }Li_2CO_3} ArCOR$$

Scheme 14.13 Li_2CO_3 catalyzed oxidation of alcohols with I_2

Hypervalent iodine reagents have attracted increasing interest as oxidants in organic synthesis due to their mild, selective, and environmentally benign oxidizing properties. Among the various hypervalent iodine reagents, o-iodoxybenzoic acid (IBX) is a versatile oxidizing agent because of its high efficiency in mild reaction conditions, nontoxicity, easy availability, and stability against moisture and air. In spite of the above mentioned features, its solubility only in highly polar and aprotic solvents such as DMSO prevented its application in oxidation reactions.

In 2003, Chen et al. studied the effect of different types of ionic liquids in the oxidation of alcohols and 1,2-diols with IBX. The DMSO is not protic solvent found that [bmim][Cl] is the better choice because it can readily dissolve IBX in the presence of small amounts of water at room temperature to form a homogeneous solution, but IBX in other ionic liquids can be dissolved on heating to 80°C (Scheme 14.14) [13].

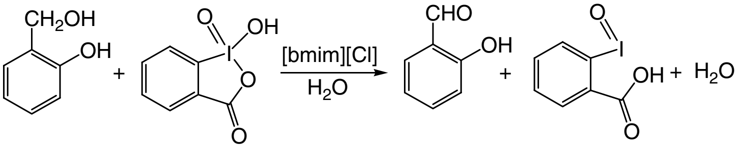
Under the selected conditions, aliphatic and benzylic alcohols could be oxidized to their corresponding aldehydes and ketones in good to excellent yields. 1,2-Diols were also cleanly oxidized to α-dicarbonyls or α-ketols using this method.

Scheme 14.14 Oxidation of alcohols and 1,2-diols with IBX in [bmim][Cl]

$$X \xrightarrow[\text{[bmim][Cl]/H}_2\text{O, r.t.}]{\text{IBX}} Y$$

if $X= R^1R^2CHOH$; $Y=R^1R^2CO$
if $X= R^1CH(OH)CH(OH)R^2$; $Y= R^1COCOR^2$

This reagent system is also used for the oxidation of salicylic alcohol by Montagnaro et al. (Scheme 14.15) [14]. The procedure is easy, and both the side-products iodobenzoic acid (IBA) and the ionic liquid are separated by ether extraction and treatment of the ethereal phase with water.



Scheme 14.15 Oxidation of salicylic alcohols to salicylaldehyde

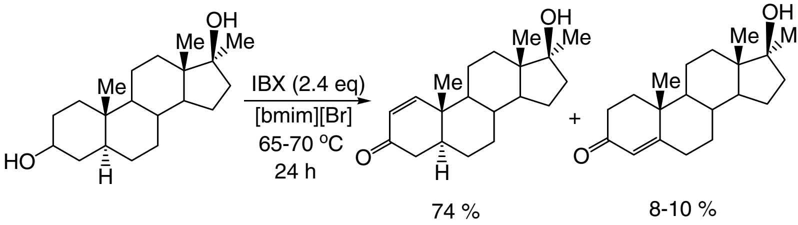
Also, oxidation of alcohols and *N*-protected amino alcohols with IBX in [bmim][Cl] without H_2O was reported by Perumal et al. [15]. In comparison with the previous method, these reactions, for example, oxidation of benzyl alcohol, require longer time for completion.

Yadav et al. reported the use of $[bmim][BF_4]$ as a solvent in the oxidation of different types of alcohols, including benzylic, aliphatic, and α,β-unsaturated ones and 1,2-diols, with IBX and Dess–Martin periodinane (DMP). The method is easy, and the products were isolated in high to excellent yields (Scheme 14.16) [16]. They also showed that $[bmim][BF_4]$ is recyclable and can be used for several times with consistent activity.

$$R^1R^2CHOH \xrightarrow[\text{[bmim][BF}_4\text{], r.t.}]{\text{IBX and / or DMP}} R^1R^2CO$$

Scheme 14.16 IBX and DMP as versatile reagents for the oxidation of alcohols

Chhikara and coworkers [17] have reported that ionic liquids are excellent reaction media for the oxidation and dehydrogenation of steroids with IBX. In a systematic study, they investigated the efficacy of the oxidation of cyclic secondary alcohols with IBX in [bmim][Br] (Scheme 14.17). They noticed that the nature of the products formed is influenced by several factors such as the relative ratio of IBX, quantity of IBX, and temperature of the reaction. For example, when 1.2 eq. of IBX was used, corresponding ketones were obtained at room temperature. When the initial temperature was kept at 70–80°C, considerable amounts of α,β-unsaturated ketones were obtained as by-products. By increasing the stoichiometric amounts of IBX, the α,β-unsaturated ketones were formed as the major product of the reaction. They also found that the ionic liquid [bmim][Br] could be recovered and reused in up to three recycles without affecting the yield of the product.



Scheme 14.17 Oxidation-dehydrogenation with IBX

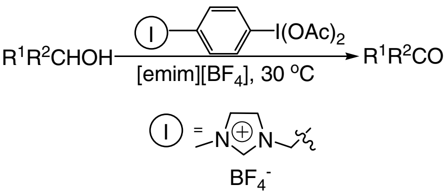
Xia et al. reported the oxidation of secondary alcohols with PhI(OAc)$_2$/Mn(salen) reagent system in a mixture of CH_2Cl_2 and [bmim][PF$_6$] (Scheme 14.18) [18]. Under the reaction conditions, ketones were produced in relatively good yields. Ionic liquid phase containing Mn(salen) catalyst could be recovered and employed in five consecutive reactions.

$$R^1R^2CHOH \xrightarrow[CH_2Cl_2,\ [bmim][BF_4],\ r.t.]{PhI(OAc)_2,\ Mn(Salen)complex} R^1R^2CO$$

Scheme 14.18 Mn(salen) complex catalyzed oxidation of alcohols with PhI(OAc)$_2$

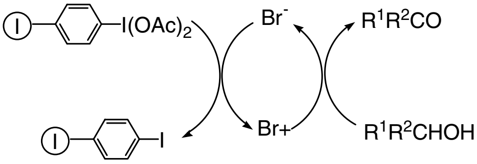
Selective oxidation of alcohols with ion-supported hypervalent iodine(III) reagent was investigated by Zhang et al. [19]. This reaction was carried out in [emim][BF$_4$] using 1-(4-diacetoxyiodobenzyl)-3-methylimidazolium tetrafluoroborate [dibmim][BF$_4$] as an oxidant in the presence of a low concentration of bromide ions under mild conditions. A variety of primary and secondary alcohols were oxidized to carbonyl compounds in moderate to excellent yields at room temperature, but secondary alcohols were oxidized over longer reaction times (Scheme 14.19).

Scheme 14.19 Oxidation of alcohols in [emim][BF$_4$]

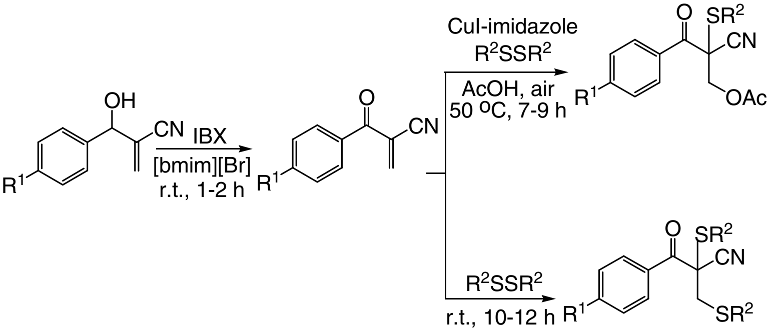


It has been suggested that the oxidation of alcohols is catalyzed by a small amount of bromide ion remaining in [emim][BF$_4$]. A possible mechanism is described that bromide ion present in [emim][BF_4] seems to be oxidized by [dibmim][BF_4] to form a highly active intermediate Br^+ ion, probably in the form of acetyl hypobromite or the bromate complex, which reacts with alcohols to produce the corresponding carbonyl compounds with regeneration of the bromide ion (Scheme 14.20).

Scheme 14.20 Mechanism of the oxidation of alcohols in [emim][BF_4]



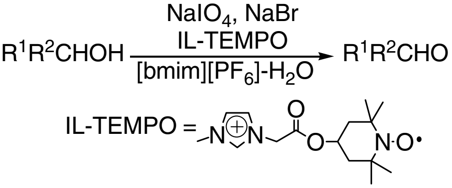
The first example of tandem oxidation and 1,2-acetoxysulfenylation/1,2-disulfenylation of Baylis–Hillman (BH) alcohols was reported by Yadav et al. [20]. The reaction involves oxidation of BH alcohols with IBX in [bmim][Br] to give β-ketomethylene compounds, followed by CuI-imidazole catalyzed 1,2-acetoxysulfenylation with an organodisulfide and AcOH to afford vicinal acetoxysulfides in excellent yields with complete regioselectivity (Scheme 14.21). This reaction was tested in six different ionic liquid imidazolium salts. Among these ILs, [bmim][Br] dissolved IBX at room temperature and gave the best result in the one-pot oxidative reaction. After isolation of final products, the IL could be recycled for four times with up to 70% recovery and reused without any loss of efficiency.



Scheme 14.21 Preparation of vicinal acetoxysulfides and/or vicinal disulfides

Periodides are the other kinds of the hypervalent iodine reagents. Sodium periodate ($NaIO_4$) is a stable and conventional inorganic nonmetal oxidant, and potassium periodate (KIO_4) is a mild and inexpensive oxidizing agent. Oxidation of various alcohols with these reagents in the presence of ionic liquids was studied. Oxidation of benzyl alcohol using $NaIO_4$ and IL-TEMPO as catalyst in [bmim][PF_6]–H_2O and/or CH_2Cl_2–H_2O was investigated by Wang et al. [21]. Compared to CH_2Cl_2–H_2O medium version, IL-TEMPO-catalyzed oxidation in water-IL showed similar activity and selectivity, but facility of the product separation and catalyst recovery were better in water-IL than CH_2Cl_2–H_2O (Scheme 14.22). Furthermore, the IL solution containing the catalyst could be reused up to six times without significant decrease of activity or selectivity.

Scheme 14.22 IL-TEMPO-catalyzed oxidation of alcohols with $NaIO_4$



A chemoselective oxidation of alcohols using potassium periodate (KIO_4) in the presence of a catalytic amount of tetramethylammonium bromide (Et_4NBr) as ionic liquid under microwave irradiation (MW) was reported by Hajipour et al. (Scheme 14.23) [22].

$$PhCH(OH)R \xrightarrow{KIO_4,\ Et_4NBr} PhCOR$$

Scheme 14.23 Oxidation of benzylic alcohols in Et_4NBr

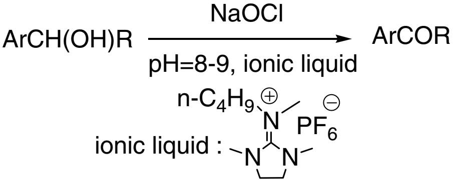
They tested different conditions for optimization of the reaction conditions. Results showed that oxidation with KIO_4/Et_4NBr without microwave irradiation (MW) or KIO_4/MW without Et_4NBr was unsuccessful since the yield was less than 15%.

Using this method, oxidation of benzylic alcohols with electron donor substituents takes place faster than benzylic alcohols with electron-withdrawing groups. Also, reaction of aliphatic alcohols occurred with lower yields and longer reaction times. Therefore, chemoselectivity with this system was observed. Ionic liquid is recyclable in this method and can be reused for four times without loss of activity.

14.1.3 Sodium Hypochlorite (NaOCl)

Sodium hypochlorite is an effective, inexpensive, and nontoxic oxidant. Zhang and coworkers [23] have prepared a hexaalkylguanidinum-based ionic liquid and applied it as both a phase transfer catalyst (PTC) and solvent in the biphasic oxidation of substituted benzyl alcohols using sodium hypochlorite as an oxidant (Scheme 14.24).

Scheme 14.24 Oxidation of benzylic alcohols in hexaalkylguanidinum-based ionic liquid



This ionic liquid was a good alternative to the traditional toxic solvents and catalysts in the selective oxidation of benzylic alcohols to carbonyl compounds. The obtained results show good selectivity (no acid was observed) and high yields. This ionic liquid could be recycled for five times with no appreciable decrease in yield.

A selective oxidation of alcohols at room temperature in ionic liquid was reported by Han and coworkers [24]. First, three different ionic liquids were tested as the solvents for this reaction. Among ([bmim][PF_6], [bmim][BF_4], [bmim][CF_3CO_2]) solvents, the reaction proceeded rapidly in BF_4-type ionic liquid, slowly in PF_6-type ionic liquid, and no reaction occurred in CF_3CO_2-type ionic liquid. Also, common organic solvents showed poor activity. Later, various types of oxidants such as t-BOOH, NaClO, and H_2O_2 were tested that only NaClO gave good results (Scheme 14.25). After optimization of the reaction conditions, oxidation of different alcohols was examined. Results showed that all primary aromatic alcohols gave excellent yields in short times, but oxidation of both secondary aromatic and aliphatic alcohols could not be completed. Most importantly, in this reaction, [bmim][BF_4] was used as both catalyst and solvent. The catalytic system could be recycled and reused for five runs without any significant loss of the catalytic activity.

$$R^1R^2CHOH \xrightarrow[\text{r.t., 15 min.}]{\text{NaClO, [bmim][BF}_4\text{]}} R^1R^2CO$$

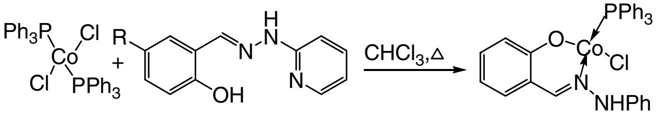
R^1= H, aryl, alkyl; R^2= alkyl, aryl

Scheme 14.25 [bmim][BF_4] catalyzed oxidation of alcohols with NaClO

Catalytic oxidation of alcohols by nickel (II) Schiff base complexes containing triphenylphosphine using NaOCl has been studied by Bhat et al. [25].

In this study, at first a series of nickel(II)-triphenylphosphine complexes with derivatives of *N*-(2-pyridyl)-N′-(salicylidene)hydrazine (NiL1–NiL5) were prepared and catalytic activity of complexes was studied in ethyl-methylimidazolium (emim) at room temperature. The results show that this method is very useful for the oxidation of aromatic, aliphatic, and allylic alcohols to their corresponding carbonyl compounds in a conversion range of 60–96%. The catalytic activity of complexes notably varies with the size of the substituents. It was observed that the activity decreases with increase in the bulkiness of the substituents. This may be due to steric hindrance causes by the substituent, which can affect the planarity of the ligand in the complexes. Further, ionic liquid ethyl-methylimidazolium (emim) was recycled up to 90% along with the catalyst. Both ionic liquid and catalyst could be reused at least for ten times.

In a similar approach, Bhat and coworkers [26] have developed a method to synthesize a series of cobalt triphenylphosphine complexes (CoL1–CoL5) containing *N*-(2-pyridyl)-*N*′-(salicylidene)hydrazine and its derivatives (Scheme 14.26). They



(CoL1: R= H, CoL2: R= Cl, CoL3: R= Br, CoL4: R= NO_2, CoL5: R= OCH_3)

Scheme 14.26 Preparation of new types of cobalt complexes used these type of reagents in the promotion of the oxidation of alcohols with NaOCl in [emim][Cl] (Scheme 14.27).

$$R^1R^2CHOH \xrightarrow[\text{[emim][Cl], r.t.}]{\text{NaOCl,Co(II)complex}} R^1R^2CO$$

Scheme 14.27 Co (II) complexes catalyzed oxidation of alcohols with NaOCl

Although all the synthesized cobalt (II) complexes were found to catalyze the oxidation of alcohols with NaOCl, the results show better efficiency for CoL1.

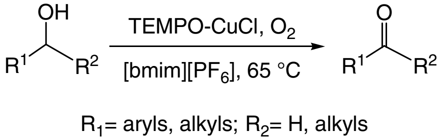
14.1.4 Aerobic Oxidation

Numerous oxidizing reagents (i.e., $KMnO_4$, MnO_2, CrO_3, SeO_2, Br_2, etc.) in stoichiometric amounts have been traditionally employed to accomplish oxidation of alcohols to corresponding aldehydes and ketones. But these oxidants have considerable drawbacks such as high cost and a large amount of waste by-products.

From an economic and environmental perspective, catalytic aerobic alcohol oxidation represents a promising protocol. The use of molecular oxygen as the primary oxidant has several benefits, including low cost, improved safety, abundance, and water as the sole by-product. In this way, many catalytic systems have been used for the aerobic oxidations in ionic liquids as green solvents. Different types of catalysts or catalytic systems useful for the oxidation of alcohols with O_2 as terminal oxidant in ionic liquids as solvent will be discussed below.

14.1.4.1 (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO)-Type Oxidants

In 2002, Ansari et al. reported the conversion of primary and secondary alcohols to corresponding aldehydes and ketones in the ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]). These conversions catalyzed by TEMPO/CuCl system in the presence of molecular oxygen as a terminal oxidant at 65°C (Scheme 14.28) [27].



Scheme 14.28 Aerobic oxidation of alcohols catalyzed by TEMPO/CuCl system

Various types of benzylic, allylic, and aliphatic alcohols, both primary and secondary, had been successfully converted to corresponding aldehydes and ketones using this method. The procedure was very simple, and it has to be noted that the reaction was performed directly under O_2 atmosphere because of good solubility of

O_2 in [bmim][PF_6]. In addition, the solvent can be recycled and reused eight times with only a slight decrease in isolated yields.

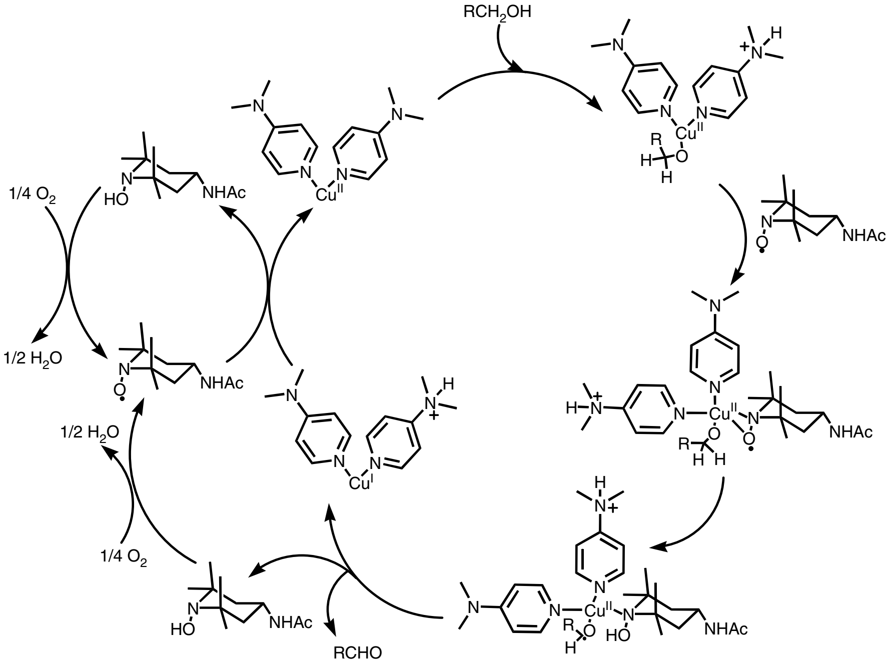
Jiang et al. used another Cu complex for the promotion of the oxidation of primary alcohols with O_2. They applied a three-component system including acetamido-TEMPO/$Cu(ClO_4)_2$/DMAP in the ionic liquid 1-butyl-4-methylpyridinium hexafluorophosphate ([bmpy][PF_6]) at room temperature (Scheme 14.29) [28].

Scheme 14.29 Aerobic oxidation of alcohols in [bmpy][PF_6]

$$RCH_2OH \xrightarrow[\substack{\text{5 mol\% acetamido-TEMPO} \\ [\text{bmpy}][PF_6],\ O_2,\ \text{rt.}}]{\text{5 mol\% } Cu(ClO_4)_2\text{, 10 mol\% DMAP}} RCHO$$

R= aryls, vinyls, alkyls

The possible mechanism of the reaction is shown in Scheme 14.30.

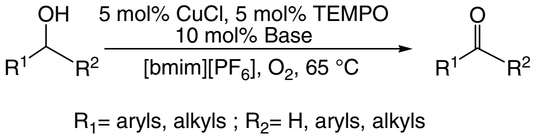


Scheme 14.30 Mechanism of the aerobic oxidation of in [bmpy][PF_6]

It should be mentioned that, due to the good solubility of acetamido-TEMPO and DMAP in [bmpy][PF_6], these reagents could be recycled and reused for five runs after full extraction of the products, without any significant loss of catalytic activity.

Another three-component catalytic system including CuCl, TEMPO, and a base was developed for the oxidation of alcohols with molecular oxygen in the ionic liquid [bmim][PF_6] by Lin et al. (Scheme 14.31) [29].

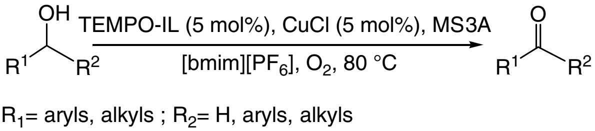
Scheme 14.31 CuCl/TEMPO/base-catalyzed oxidation of alcohols with O_2



Addition of base as a cocatalyst significantly promotes the catalytic activity. Among a range of bases (aqueous or alcoholic NaOH, pyridine, triethylamine, and *N*-methyl imidazole) examined, bases with high coordinating ability showed high promoting effect and probably play dual roles: as a base to deprotonate the alcohol and as a ligand to coordinate with copper(I) salt. Under the selected conditions, various types of benzylic, allylic, heterocyclic, and aliphatic alcohols undergo oxidation to produce corresponding aldehydes or ketones in [bmim][PF_6].

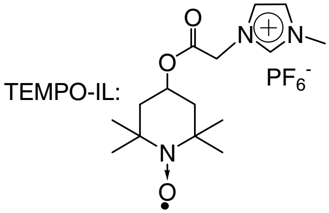
Molecular sieve 3A (MS3A) was also used by Lin et al. for the aerobic oxidation of alcohols in ionic liquid (Scheme 14.32) [30]. It seems that the molecular sieve 3A serves as a heterogeneous Brønsted base to enhance the reaction rate remarkably. With TEMPO-IL and the use of MS3A, the catalytic system could easily be recycled and reused three times without loss in its activity.

Scheme 14.32 Use of MS3A in the oxidation of alcohols



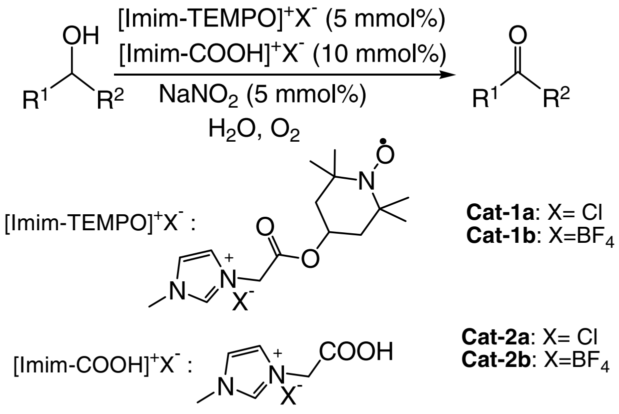
In this system, TEMPO is immobilized on ionic liquid to form TEMPO-IL (Scheme 14.33).

Scheme 14.33 TEMPO immobilized on ionic liquid

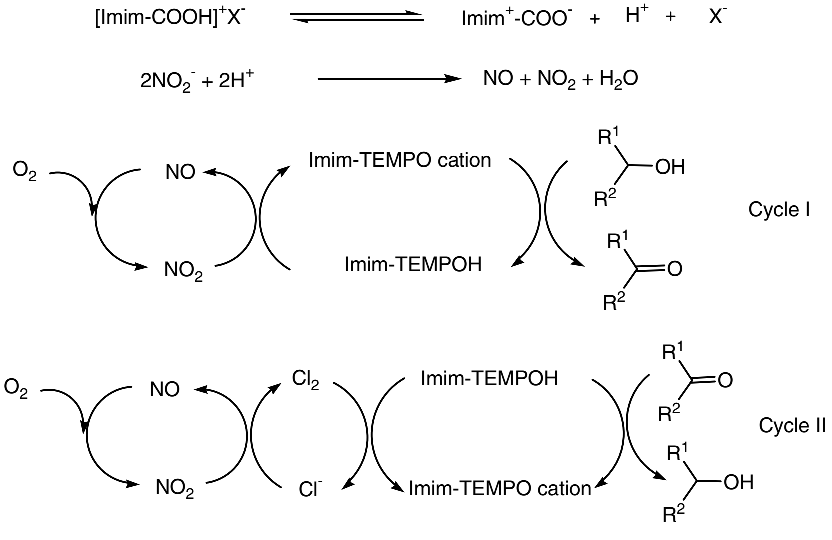


Miao and his coworkers developed an efficient and reusable catalytic system containing TEMPO functionalized imidazolium salt ([Imim-TEMPO]$^+X^-$, **Cat-1a** or **Cat-1b**), a carboxylic acid substituted imidazolium-based ionic liquid ([Imim-COOH]$^+X^-$, **Cat-2a** or **Cat-2b**), and $NaNO_2$ for the aerobic oxidation of alcohols with oxygen in water as solvent (Scheme 14.34) [31].

They proposed a tentative mechanism for their aerobic oxidation that presented in Scheme 14.35. The designed transition metal–free aerobic system was completed by a sequential bicycle (cycle I) or tricycle (cycle II) involving a two-electron transfer step. As shown in Scheme 14.36, NO_2^- could release NO and NO_2 under acidic conditions, and the oxidation of NO into NO_2 could proceed easily with molecular oxygen.



Scheme 14.34 Aerobic oxidation of alcohols in the presence of $NaNO_2$ and two functionalized imidazolium salts

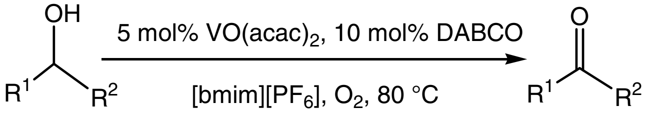


Scheme 14.35 Mechanism of the oxidation of alcohols in the presence of $NaNO_2$

Their process represents a greener pathway for the aerobic oxidation of alcohols to carbonyl compounds by using the present task-specific ionic liquids without the need of a transition metal.

14.1.4.2 Vanadium Complexes

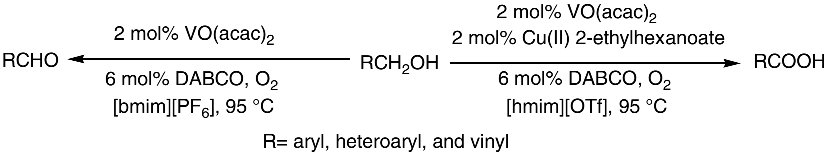
A selective aerobic oxidation of alcohols to the corresponding aldehydes or ketones was reported by Jiang et al. using a two-component system $VO(acac)_2$/DABCO in the ionic liquid $[bmim][PF_6]$ [32] (Scheme 14.36).



Scheme 14.36 Oxidation of alcohols promoted by $VO(acac)_2$/DABCO system

The catalytic system showed excellent selectivity toward oxidation of benzylic and allylic alcohols and was notably not deactivated by heteroatom-containing (S, N) compounds. Also, no overoxidized product was observed. This system could be recycled and reused for three runs without any significant loss of catalytic activity.

They also investigated the oxidation of primary alcohols to their corresponding aldehydes and acids under other conditions (Scheme 14.37) [33].



Scheme 14.37 Oxidation of primary alcohols to aldehydes and carboxylic acids

They showed that the oxidation of primary alcohols to their corresponding aldehydes can be completed by using lower amounts of $VO(acac)_2$ and DABCO at higher temperature (90°C). When Cu(II) 2-ethylhexanoate (2 mol%) was added to the reaction mixture and [hmim][OTf] was used as ionic liquid, carboxylic acids were formed as the only products of the oxidation reactions. These catalytic systems could also be recycled and reused for three runs without any significant loss of catalytic activity.

14.1.4.3 Palladium and Cobalt Complexes

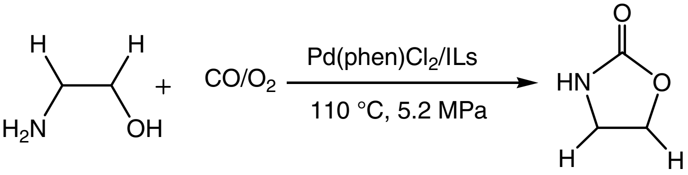
Industrially performed catalytic oxidation reactions often suffer from drawbacks such as poor conversion and selectivity due to overoxidation, corrosive reaction media, lack of solvent and catalyst recycling, and negative environmental impact due to evaporation of the solvents. In order to provide a methodology that addresses these problems, ionic liquids have been investigated as reaction media. For example, the aerobic oxidation of benzyl alcohol and alkylbenzene to benzaldehyde and benzoic acids was performed in 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ($[C_4dmim][BF_4]$) using palladium and cobalt complexes respectively [34, 35].

The study of the oxidation of toluene and ethylbenzene in the presence of $Co(acac)_2$ as catalyst showed that the introduction of oxygen (as opposed to dehydrogenation) is feasible using this concept. The oxidation of toluene is not yet fully investigated, and it gives slow conversions. However, the oxidation of ethylbenzene produces acetophenone in satisfying yields. Due to the possibility of recycling of the solvent and catalyst, the ionic liquid processes provide a greener scenario.

The aerobic oxidation of alkyl arenes and alcohols to the corresponding carbonyl compounds have been achieved using cobalt(II) phthalocyanine (CoPc) as catalyst and oxygen (0.1 atm) in the ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim][Br]). Excellent yields were obtained under mild and easily obtainable conditions [36].

To evaluate the effect of molecular solvents, the above mentioned reactions were carried out using methanol, water, acetonitrile, and xylene as solvents and the reactions were found to be very slow (10–40%) even after 12–24 h. It is important to note that in water, no reaction took place, even after 24 h. Acceleration of these oxidation reactions in [bmim][Br] can be demonstrated by its ability to act as both a phase transfer catalyst and a solvent. Most importantly, [bmim][Br] and CoPc could be recycled and reused in further reactions for six runs.

Li et al. investigated biphasic oxidative cyclocarbonylation of β-amino alcohols and 2-aminophenol to 2-oxazolidinones in the presence of the ionic liquid 1-butyl-3-methylimidazolium iodide ([bmim][I]) and Pd(phen)Cl_2 complex (Scheme 14.38) [37].



Scheme 14.38 Preparation of 2-oxazolidinones

It has been found that 1-butyl-3-methylimidazolium iodide salt can serve simultaneously as a specific stabilizer to protect the transition metal complex against deactivation, a promoter to increase the catalytic performance and a reaction medium to recycle the catalyst.

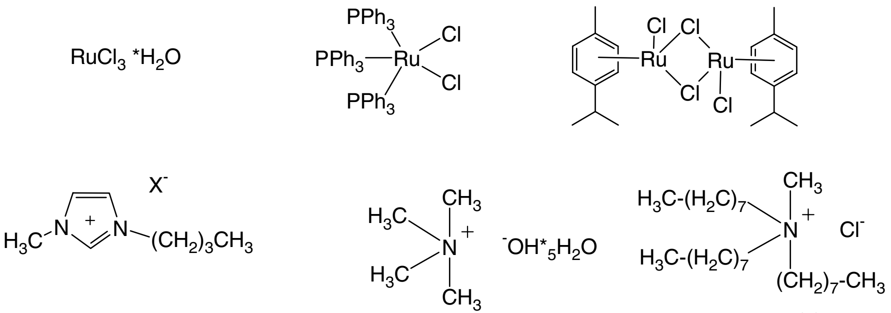
A methodology was introduced to separate polar reaction products from ionic liquids without the need for organic solvent extraction or distillation by Doorslaer et al. [38]. They investigated product isolation after an alcohol oxidation was performed in ionic liquids. Suitable ionic liquids were selected based on their mixing or demixing with a range of alcohols and the derived ketones. The aim was to obtain complete miscibility with the alcohol substrate at reaction temperature and a clear phase separation of the derived ketone product at room temperature. Six imidazolium-based ionic liquids displayed this desired behavior and were sufficiently stable to oxidation. These ionic liquids were then employed in the oxidation of nonactivated aliphatic alcohols with molecular oxygen in the presence of palladium(II) acetate. In the case of 1-butyl-3-methylimidazolium tetrafluoroborate, 2-octanon and 2-decanon obtained with 79% and 86% yields, respectively. After cooling to room temperature, the ionic liquid expels the immiscible ketone and the product phase can be isolated by decantation. In addition, the ionic liquid acts as an immobilization medium for the palladium catalyst, allowing efficient catalyst recycling.

14.1.4.4 Ruthenium Complexes

Tetra-*N*-propylammonium perruthenate (TPAP) has been known as a homogenous and versatile reagent for the catalytic oxidation of alcohols. One of the problems in the use of TPAP is its removal from the reaction mixture. Ley et al. disclosed a system that permits recycling and reuse of TPAP [39]. They used TPAP and alcohol in CH_2Cl_2 in the presence of 1-ethyl-3-methyl-1H-imidazolium hexafluorophosphate ([emim][PF_6]) and Et_4NBr accompanied with *N*-methylmorpholine *N*-oxide (NMO) as cooxidant. They demonstrated that both Et_4NBr and [emim][PF_6] may be used to enable the recovery and reuse of TPAP. Also, performing the reaction under moderate oxygen pressure (30–40 bar) in dichloromethane and Et_4NBr at room temperature resulted in rapid and clean oxidation of sec-phenethyl alcohol.

In continuation of this study, Farmer and Welton investigated the selective oxidation of alcohols to aldehydes and ketones by TPAP in conjunction with either *N*-methylmorpholine-N′-oxide or molecular oxygen as oxidants [40]. In the case of molecular oxygen (as oxidant), Cu(I) and a diamine ligand must also be added. Under the optimized conditions, benzylic alcohols were oxidized in good to excellent yields, whereas aliphatic alcohols required longer reaction time and gave poor yield. The reaction products were easily removed from the reaction mixture by extraction with diethyl ether.

A novel methodology, including the aerobic oxidation of alcohols to their corresponding carbonyl compounds in the presence of several ruthenium catalysts in various ammonium salts, as ionic liquids, was proposed by Wolfson et al. (Scheme 14.39) [41].



1-Butyl-3-methyl-imidazolium=bmim$^+$
X= PF_6, BF_4, Cl

Tetramethylammonium hydroxide pentahydrate

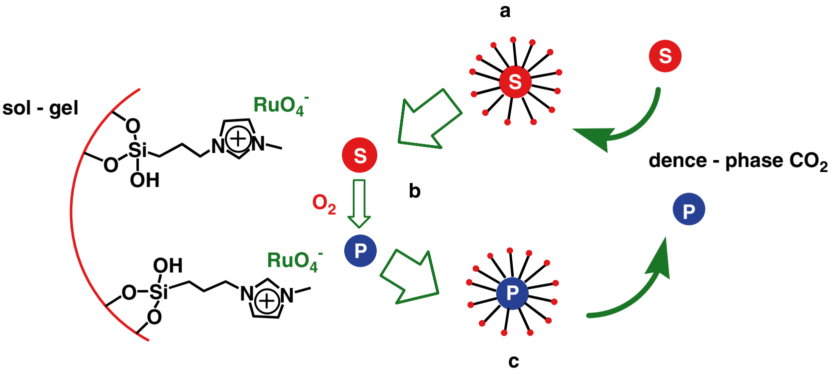
Aliquat$^{(R)}$ 336

Scheme 14.39 Ruthenium and ammonium salts used in the aerobic oxidation of alcohols

Investigations clarified that the oxidation rate depends on the cation and anion of the ionic liquid, and among a range of ionic liquids, tetramethylammonium hydroxide and Aliquat® 336 showed the best results in the presence of $Ru(PPh_3)_3Cl_2$.

These reagent systems are very effective for the oxidation of primary and secondary alcohols, without the formation of any by-products.

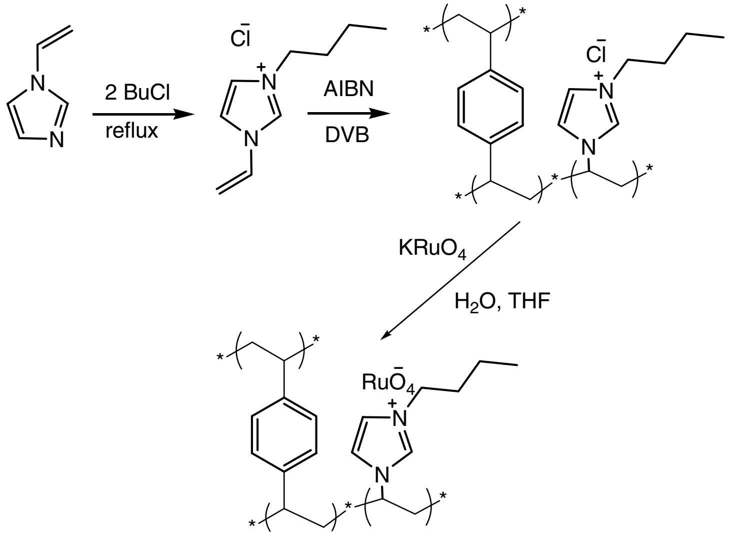
Study of the reusability of the catalyst shows a 10% decrease in the activity of the tetramethylammonium hydroxide/$RuCl_2(PPh_3)_3$ reagent system in the oxidation of 1-phenylethanol after three runs. Due to the higher activity of the supported ionic liquids (ILs) than the free ones, the preparation of heterogeneous catalysts by immobilization of functional ionic liquids attracted the attention of many scientists. Criminna et al. used this concept for the preparation of a silica-immobilized ionic liquid containing imidazolium cation and perruthenate anion [42]. This reagent shows high activity in the aerobic oxidation of alcohols in supercritical carbon dioxide ($scCO_2$) reaction media. The mechanism of the oxidation is represented in Scheme 14.40.



Scheme 14.40 Mechanism of the aerobic oxidation of alcohols in $scCO_2$

The alcohol substrate and O_2 at low partial pressure are dissolved in the homogeneous $scCO_2$ phase which, upon contact with the powdered sol–gel entrapped catalyst, spills the reactants into the pores where the oxidative dehydrogenation takes place. It then extracts the products. Furthermore, the RuO_4^- immobilization at an imidazolium-modified surface which acts as a potent solubilizing agent accelerates substrate/product dissolution and thus the reaction rate. As evident by the smooth oxidation of the less reactive primary aliphatic alcohol, 1-octanol, a versatile active catalyst is obtained that can be used for the fast conversion of different substrates. Moreover, $scCO_2$ assists in water removal (thus preventing aldehyde hydration and overoxidation) through its well-known ability of drying solid matrices.

Another example in which perruthenate immobilized on a polymer-supported ionic liquid is used for the promotion of the aerobic oxidation of alcohols is reported by Xie and his group [43]. The catalyst preparation represented in Scheme 14.41.



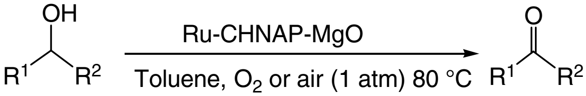
Scheme 14.41 Preparation of a perruthenate immobilized on a polymer-supported ionic liquid

They used this catalyst for the aerobic oxidation of benzyl alcohol to benzaldehyde in $scCO_2$ as solvent. This conversion is time dependent, and most of the alcohol was converted to aldehyde after 24 h. The pressure also influences the reaction. The increase in the pressure of CO_2 was found to accelerate the reaction rate as well as the yield. The catalyst could be reused directly after in situ extraction of the products using $scCO_2$, and it remains active after being reused for four times.

$RuCl_3$ as a simple complex is able to catalyze the aerobic oxidation of alcohols in different types of ionic liquids [44]. A new fluorinated ionic liquid, 1-n-butyl-3-methylimidazolium pentadecafluorooctanoate $[bmi.COO(CF_2)_6CF_3]$, was synthesized because of its ability to dissolve higher amounts of oxygen which demonstrates better performance than the other commonly employed ionic liquids.

The advantages of this oxidation system are numerous: (a) transition metal–catalyzed oxidation reactions could be performed at room temperature using ionic liquids; (b) $RuCl_3$ is completely soluble in ionic liquids tested, giving a homogeneous oxidation solution; (c) the ionic liquid media have a beneficial effect on the $RuCl_3$ catalyst performance from selectivity point of view; (d) molecular oxygen with an oxidizing agent produces water as the only by-product that is removed by molecular powder sieves; (e) this system could be reused; (f) rates of the oxidation reactions in these systems were comparable to previously published data; and (g) the new fluorinated ionic liquid has better performance than the other ionic liquids employed.

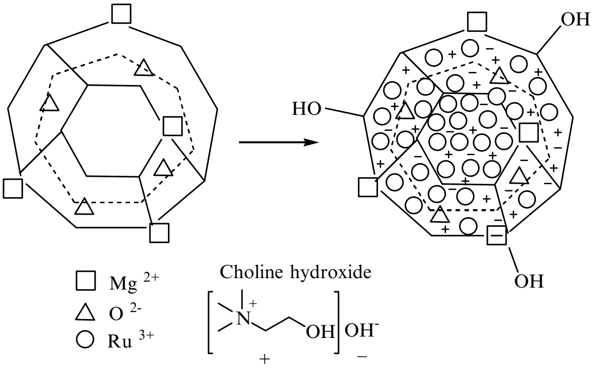
Kantam et al. investigated the selective oxidation of various alcohols into their corresponding aldehydes and ketones by ruthenium species stabilized on the nanocrystalline magnesium oxide (NAP-MgO) by the incorporation of choline hydroxide, a basic ionic liquid, in excellent yields [45]. Their procedure was simple, efficient, and environmentally benign, and the catalyst could be used for four cycles with almost consistent activity (Scheme 14.42).



Scheme 14.42 Aerobic oxidation of alcohols catalyzed by Ru-CHNAP-MgO

NAP-MgO is purely ionic and has a three-dimensional polyhedral structure. High surface concentrations of edge/corner and various exposed crystal planes lead to inherently high surface reactivity per unit area of this reagent. NAP-MgO has (a) Mg^{2+} sites, (b) O^{2-} sites, (c) lattice bound hydroxy groups, (d) isolated hydroxy groups, and (e) anionic and cationic vacancies. NAP-MgO is treated with choline hydroxide (CH) to make CHNAP-MgO, which then dispersed in an aqueous solution of $RuCl_3$ and stirred for 24 h at 25°C under a nitrogen atmosphere (Scheme 14.43). The catalyst was then filtered, washed with deionized water and acetone, and dried.

Scheme 14.43 Preparation of Ru-CHNAP-MgO

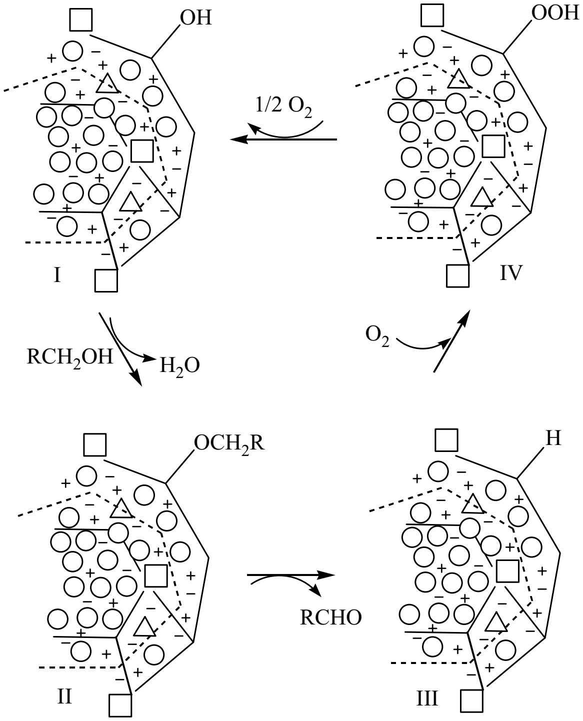


Ru^{3+} ions are distributed on the outer surface by a combination of strong electrostatic interaction and coordination between choline hydroxide of the surface functionalized CHNAP-MgO and Ru^{3+}.

The proposed mechanism for the oxidation reaction is presented in Scheme 14.44. The formation of Ru-alcoholate (species II) by the reaction of catalyst I with benzyl alcohol is considered to be the first step of the catalytic cycle, followed by β-hydride elimination to produce the corresponding carbonyl compound and probably a ruthenium hydride species. Subsequent reaction of complex III with O_2 may afford the complex Ru-hydroperoxide IV. The uptake of alcohol again completes the cycle with the formation of O_2 and H_2O.

14.1.4.5 12-Tungstophosphoric Acid, $H_3PW_{12}O_{40}$ (HPW)

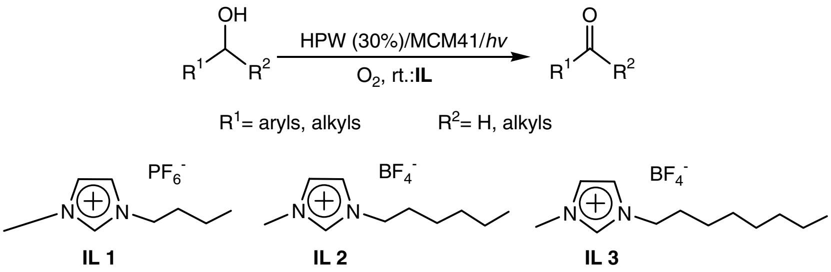
12-Tungstophosphoric acid $H_3PW_{12}O_{40}$ (HPW) was found to be the most acidic of the Keggin series [46]. Most reports on its catalytic properties were based on its acidic property. It was found that the catalytic activity of this reagent can be improved by supporting on a carrier of large surface [47, 48].



Scheme 14.44 Proposed mechanism for the oxidation of alcohols in the presence of Ru-CHNAP-MgO

Shen et al. used HPW/MCM-41 system for the photocatalytic selective aerobic oxidation of alcohols to aldehydes and ketones in ionic liquids [49]. Based on the property of this photocatalytic reaction, many variables such as the amount of HPW, irradiation energy and time, substrates, reaction media, etc., that may affect the reaction were considered.

The photocatalytic oxidation of alcohols was performed in the presence of different loading amounts of HPW on MCM-41 (15, 30, and 50 wt.%) in three different ionic liquids (Scheme 14.45).



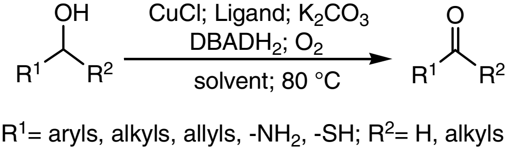
Scheme 14.45 Photocatalytic oxidation of alcohols in ionic liquids

The optimal loading amount of HPW in HPW/MCM-41 was 30%, and IL2 showed better results in the oxidation reaction. The catalytic performance of HPW(30%)/MCM-41 in ILs was also better than that in CH_3CN.

14.1.4.6 Copper Bisisoquinoline

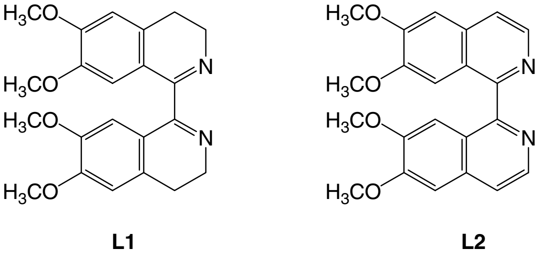
Because of the promotion of the oxidation of alcohols using copper chloride in the presence of nitrogen-containing ligands, Shen et al. decided to investigate the oxidation of alcohols in the presence of copper-bisisoquinoline-based catalysts under air conditions using ionic liquids as solvent [50]. Solvent effect has been studied using ionic liquids, [bmim][PF_6] (IL1), [hmim][BF_4] (IL2), and [omim][BF_4] (IL3) and traditional volatile organic solvents.

This method applied for the oxidation of a wide range of primary, secondary, allylic, and benzylic alcohols producing the corresponding carbonyl compounds with good conversions (Scheme 14.46).



Scheme 14.46 Use of CuCl-bisisoquinoline-K_2CO_3 in the aerobic oxidation of alcohols

Although the difference between L1 and L2 is due to the additional C=C bonds in the nitrogen rings of L2 (Scheme 14.47), the conversion of alcohols was higher in the catalytic system containing L2 than that of L1. This result is attributed to the better conjugated structure, which may stabilize the Cu-L complex system in L2 for better catalytic properties.

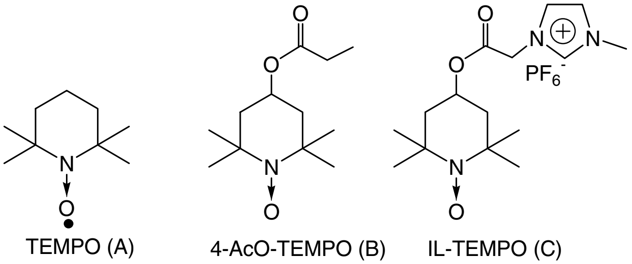


Scheme 14.47 Bisisoquinolines used for the preparation Cu-L complexes

In this system, the active catalyst appears to be heterogeneous and adsorbed on the insoluble K_2CO_3. Besides its role as a solid support, the carbonate also acts as a base, initiating the addition of alcohol or $DBADH_2$ (ditert-butylazodicarboxylate) or both to the copper complex, and as a water scavenger.

14.1.5 Other Oxidants for the Oxidation of Alcohols in Ionic Liquids

Use of TEMPO immobilized on ionic liquid was reported by Ruijun et al. [51]. They used three TEMPO catalysts (Scheme 14.48) for the oxidation of alcohols in the presence of two types of ionic liquids: H_2O and ([bmim][BF_4]-H_2O and [bmim][PF_6]-H_2O).

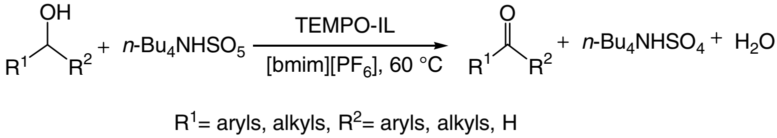


Scheme 14.48 TEMPO catalysts used for the oxidation of alcohols

In their systems, *N*-chlorosuccinimide (NCS) accompanied with NaBr performed as oxidant. After optimization of the reaction conditions, IL-TEMPO (C) catalyst showed better results in [bmim][PF_6]-H_2O, with high chemoselectivity in the oxidation of benzylic alcohols in the presence of aliphatic ones. Moreover, the [bmim][PF_6] containing IL-TEMPO could be easily recycled without decreasing the efficiency of the reaction in terms of yields and selectivity of the products.

In their oxidation mechanism, NCS and NaBr lead to the formation of hypobromous acid, which oxidizes the nitroxyl radical to the *N*-oxoammonium ion. For efficient oxidations, the presence of both nitroxyl radical and halide ion is required.

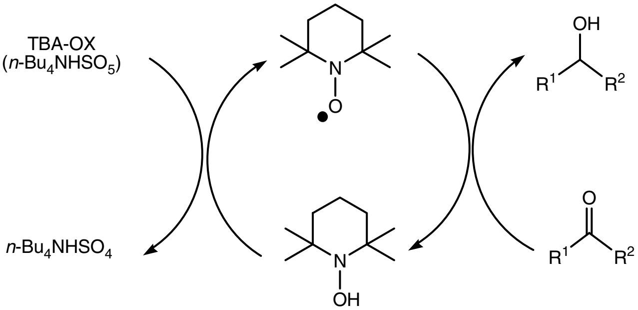
Similarly, Zhu and coworkers used IL-TEMPO (C) to improve the oxidizing ability of n-Bu_4NHSO_4 (TBA-OX) in [bmim][PF_6] (Scheme 14.49) [52].



Scheme 14.49 Oxidation of alcohols with n-Bu_4NHSO_5 in [bmim][PF_6]

First, the solubility property of TBA-OX in some traditional solvents and a variety of natural, acidic, and basic ionic liquids was investigated. From where it was noticed that TBA-OX was nearly insoluble in [bmim][PF_6] at low temperature, but it was miscible at high temperature. Furthermore, [bmim][PF_6] is immiscible with water. This observation could be beneficial since it can provide an easy route to remove the oxidant and its by-product (n-Bu_4NHSO_4) after completion of the reaction by simple washing of the reaction mixture with water.

In TBA-OX/TEMPO catalytic oxidation system, TEMPO is the active oxidant and TBA-OX is used to regenerate TEMPO or TEMPO-IL. A plausible mechanism of the reaction is depicted in Scheme 14.50.

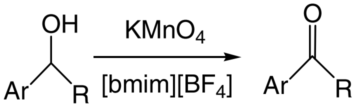


Scheme 14.50 Mechanism of the oxidation of alcohols with n-Bu_4NHSO_5 in [bmim][PF_6]

It is noteworthy to mention that the catalyst and solvent could easily be recycled and reused without loss of activity and the oxidant's by-product (n-Bu_4NHSO_4) can also be recycled.

In 2004, Kumar and coworkers reported that $KMnO_4$ in the ionic liquid [bmim][BF_4] can be used as an efficient reagent for the chemoselective oxidation of benzylic alcohols in the presence of aliphatic ones (Scheme 14.51) [53]. They also showed that the oxidation of benzyl alcohols using recycled $KMnO_4$ and [bmim][BF_4] gave benzaldehyde with excellent yields even after five runs.

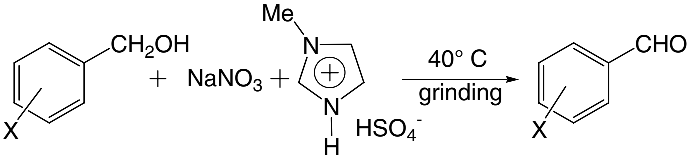
Chromium trioxide (CrO_3) is one of the most widely used reagents for the oxidation of organic compounds because it is cheap, readily available, and easy to handle. This reagent has been modified to improve its selectivity. The Jones (CrO_3-H_2SO_4-acetone), Collins (CrO_3-pyridine), and PCC (CrO_3-pyridine-HCl) reagents are well-known oxidants in homogeneous liquid systems.



Scheme 14.51 Chemoselective oxidation of alcohols using $KMnO_4$ in [bmim][BF_4]

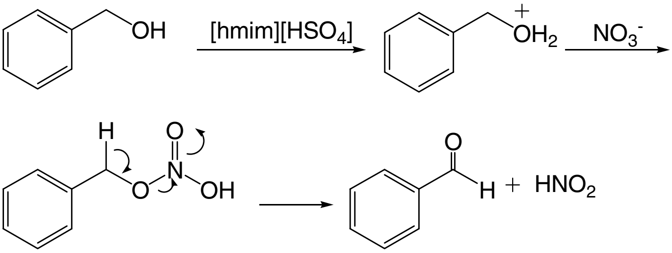
In 2005, Zheng et al. reported an efficient method for the conversion of primary and secondary benzylic alcohols to carbonyl compounds using CrO_3 in [bmim][BF_4] [54]. Because of the formation of lower amounts of the products at higher temperatures, this method can be used for the chemoselective oxidation of benzylic alcohols in the presence of aliphatic ones. Higher yields of the products, chemoselectivity, and easy work-up procedure are among the other advantages of this method.

Brønsted acidic ionic liquids have been successfully applied to a variety of reactions including esterification of carboxylic acids [55], protection of aldehydes and ketones [56], and cleavage of ethers [57]. 3-Methylimidazolium hydrogen sulfate ([hmim][HSO_4]) is a Brønsted acidic ionic liquid that applied for the oxidation of alcohols to carbonyl compounds in the presence of $NaNO_3$ as oxidant [58] (Scheme 14.52).



Scheme 14.52 [hmim][HSO_4] catalyzed oxidation of alcohols with $NaNO_3$

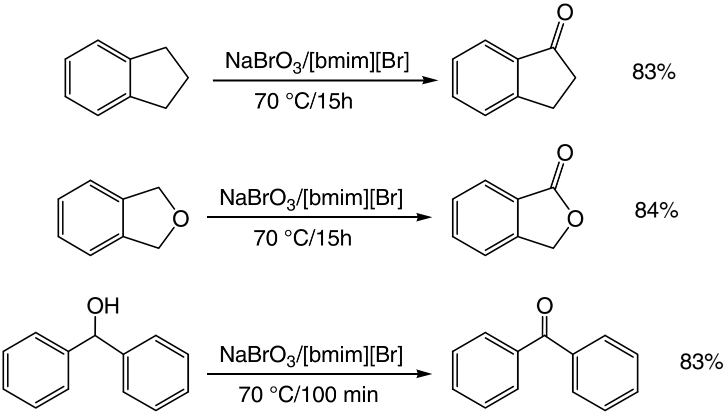
The role of [hmim][HSO_4] in this reaction is both as the acidic catalyst and also as the solvent. The oxidation of various benzylic alcohols gave high yields of carbonyl compounds in short reaction times, and the overoxidation products (carboxylic acids) were not observed. The possible mechanism for the oxidation of benzylic alcohols by sodium nitrate in the presence of [hmim][HSO_4] is shown in Scheme 14.53.



Scheme 14.53 Mechanism of the oxidation of alcohols with $NaNO_3$ in [hmim][HSO_4]

$NaBrO_3$ is another oxidant that is used for the selective oxidation of alkyl arenes and alcohols in ionic liquids by Shaabani et al. (Scheme 14.54) [59]. They used various ionic liquids, such as 1-butyl-3-methylimidazolium bromide ([bmim][Br]), 1-butyl-3-methylimidazolium chloride ([bmim][Cl]), and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) for the oxidation of fluorene to 9-fluorenone and benzoin to benzil as the model compounds. 1-Butyl-3-methylimidazolium bromide was the best suited ionic liquid for oxidation reactions at 70°C in terms of yields and easy work-up.

Most importantly, [bmim][Br] could be recycled and reused in further reactions without any significant loss of its activity. This method is compatible with different functional groups, and the oxidation reactions were carried out in neutral conditions. Use of imidazolium ionic liquids as solvents for organic transformations with

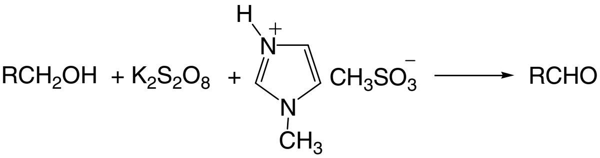


Scheme 14.54 Oxidation of alkyl arenes and alcohols in [bmim][Br]

tetravalent cerium salts as oxidizing agents was evaluated by Mehdi and coworkers [60]. Good solubility was found for ammonium hexanitratocerate(IV) (ceric ammonium nitrate, CAN) and cerium(IV) triflate in 1-alkyl-3-methylimidazolium triflate ionic liquid. Oxidation of benzyl alcohol to benzaldehyde in 1-ethyl-3-methylimidazolium triflate was studied by in situ FTIR spectroscopy and ^{13}C NMR spectroscopy on carbon-13-labeled benzyl alcohol. Careful control of the reaction conditions is necessary because ammonium hexanitratocerate(IV) dissolved in an ionic liquid can change benzyl alcohol not only into benzaldehyde but also into benzyl nitrate or benzoic acid. The selectivity of the reaction of cerium(IV) triflate with benzyl alcohol in dry ionic liquids depends upon the degree of the hydration of cerium(IV) triflate; anhydrous cerium(IV) triflate transforms benzyl alcohol into dibenzyl ether, and hydrated cerium(IV) triflate affords benzaldehyde as the main reaction product.

Reactions of ammonium hexanitratocerate(IV) with organic substrates other than benzyl alcohol have also been examined, and 1,4-hydroquinone was quantitatively transformed into 1,4-quinone. Anisole and naphthalene can be nitrated. For the cerium-mediated oxidation reactions in ionic liquids, high reaction temperature is beneficial because of the formation of smaller amounts of by-products.

Another efficient conversion of alcohols to aldehydes was achieved using potassium persulfate and 3-methylimidazolium methanesulfonate by Chaskar and his coworkers (Scheme 14.55) [61].

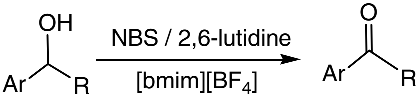


Scheme 14.55 Oxidation of alcohols with potassium persulfate in the presence of [Hmim][CH_3SO_3]

Oxidation of alcohols using potassium persulfate without 3-methylimidazolium methanesulfonate was unsuccessful. In this reaction, [Hmim][CH_3SO_3] plays a dual role as acidic catalyst and as solvent. Use of such a reaction medium should be appreciated because of its easy preparation, convenient separation, and eco-friendly nature. The ionic liquid can be reused after washing with diethyl ether to remove the unreacted starting materials and products.

Lee et al. developed an efficient methodology for the oxidation of various benzylic alcohols to the corresponding carbonyl compounds in the presence of *N*-bromosuccinimide (NBS) and 2,6-lutidine in [bmim][BF_4] (Scheme 14.56) [62].

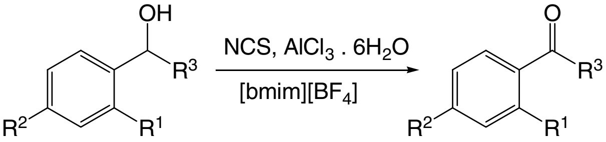
The competitive aromatic bromination has not been observed in all of the cases tested. It is also noteworthy that prolonged reaction times were required in cases of benzylic alcohols with electron-withdrawing groups on the aromatic rings. This result can be rationalized by the sluggish formation of hypobromite reaction intermediates in cases of the less reactive electron-deficient benzylic alcohols.



Scheme 14.56 Oxidation of benzylic alcohols in the presence of NBS and 2,6-lutidine in [bmim][BF_4]

Similar to NBS, *N*-chlorosuccinimide (NCS) was used for the oxidation of benzylic alcohols by Chang et al. [63]. They used aluminum chloride hexahydrate for the activation of NCS (Scheme 14.57).

Their protocol involved the reaction of benzylic alcohols with NCS in the presence of aluminum chloride hexahydrate in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), ionic liquid medium. At optimum reaction conditions, benzylic alcohols were efficiently converted into the corresponding aldehydes and ketones in excellent yields. Furthermore, recycling of ionic liquid with three runs of reactions gave comparable yields.

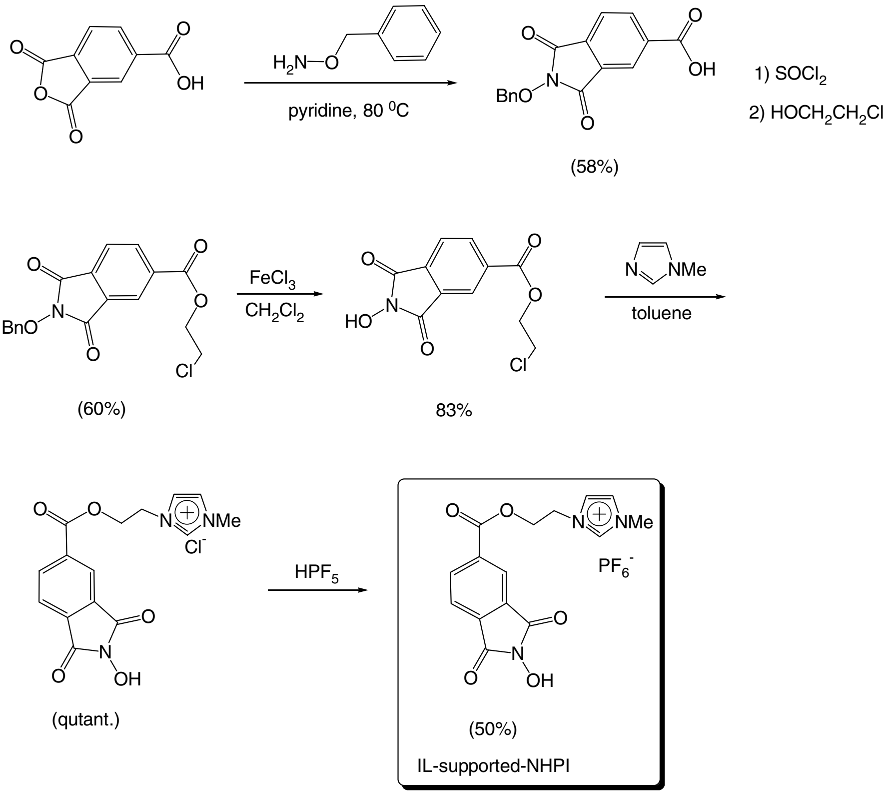


Scheme 14.57 Oxidation of benzylic alcohols with NCS in [bmim][BF_4]

14.1.6 Miscellaneous Reactions

N-hydroxy-phthalimide (NHPI) acts as a catalyst for transformation of alkanes to alcohols, ketones, carboxylic acids, and/or nitroalkanes under mild oxidation conditions [64]. Koguchi et al. [64] used NHPI–$Co(OAc)_2$–O_2 system for the oxidation of alcohols in ionic liquids. They found that NHPI is separated easily from ionic liquid with organic solvents, and hence, it was impossible to construct the reusable reaction system because of the disappearance of NHPI. Therefore, they designed the ionic liquid–supported NHPI complex which offers several benefits in comparison to homogeneous and/or heterogeneous catalysts, including easier product isolation, purification, and the possibility to reuse the system.

Ionic liquid (IL)-supported NHPI was prepared via the synthetic route shown in Scheme 14.58.

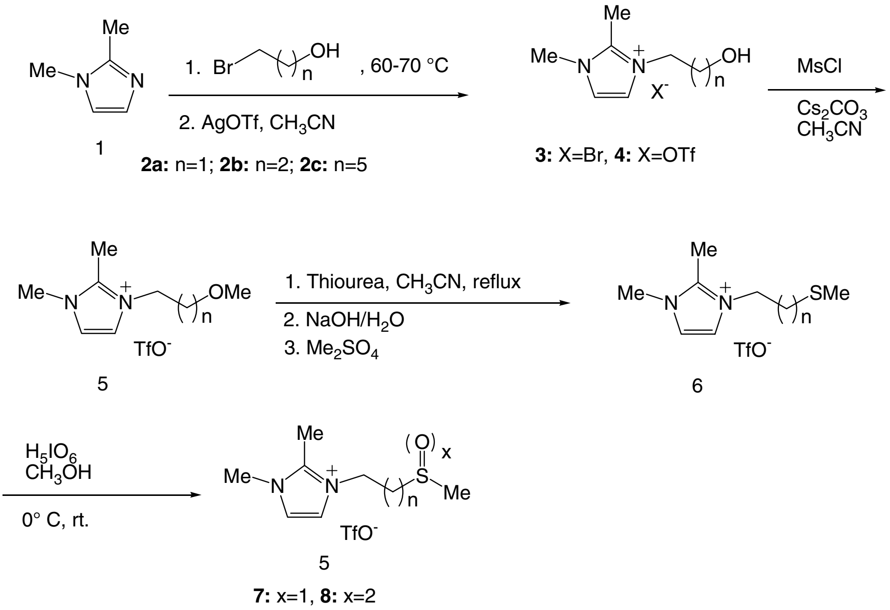


Scheme 14.58 Synthesis of IL-supported-NHPI

From the results obtained for the oxidation of 1-phenylethanol to acetophenone, they have found that the system using IL-NHPI (10 mol%)–$Co(OAc)_2$–O_2 in the ionic liquid [bmim][PF_6] was reusable. In the same system, various types of carbinols were transformed into the corresponding aldehydes and/or ketones in good yields.

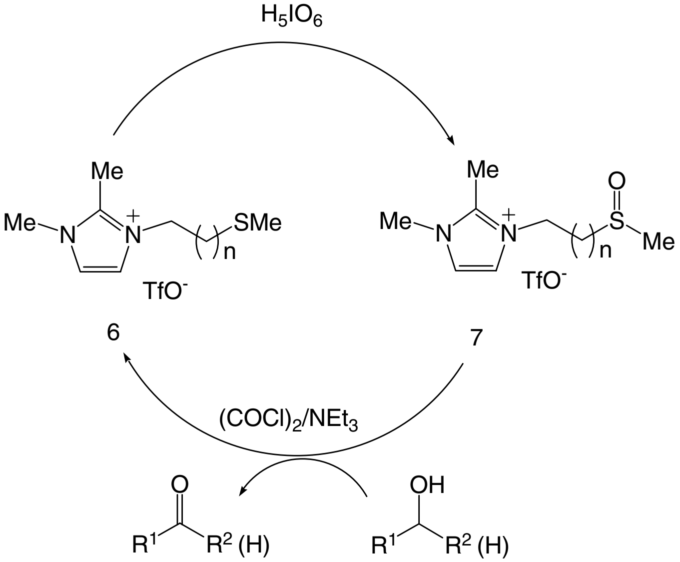
Recently, a new class of odorless and nonvolatile organosulfur compounds grafted to imidazolium ionic liquid scaffold has been synthesized and used effectively for the oxidation of primary allylic and benzylic alcohols into aldehydes and secondary alcohols to ketones under Swern oxidation conditions [65].

The preparation of the ionic liquid–supported sulfur compounds started from 1,2-dimethylimidazole **1** and bromoalkyl alcohols **2**. The consecutive reactions are presented in Scheme 14.59.



Scheme 14.59 Preparation of the ionic liquid–supported sulfur compounds

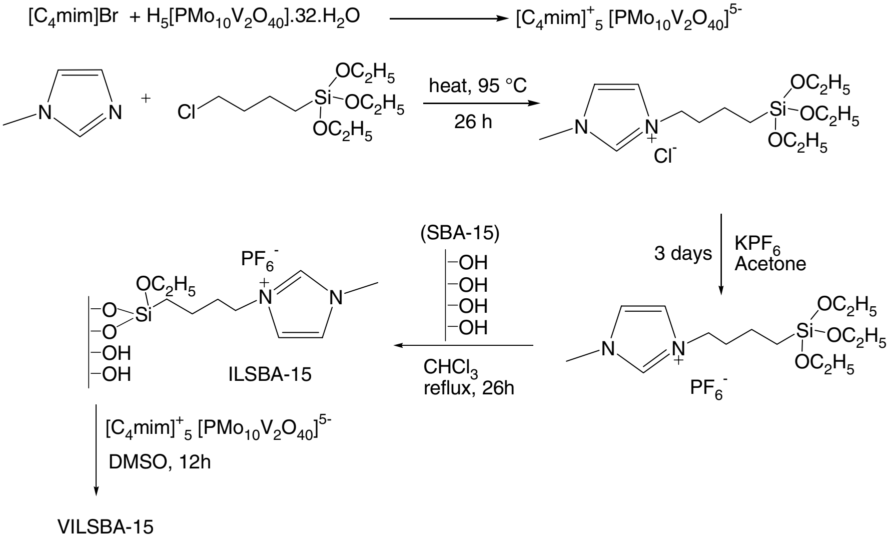
The ionic liquid–supported sulfoxide **7** as a recoverable and recyclable reagent for the Swern oxidation of various alcohols has also been proposed. The carbonyl product was easily separated from the ionic liquid anchored sulfide **6** by simple phase separation with diethyl ether after Swern oxidation. As shown in Scheme 14.60,



Scheme 14.60 Swern oxidation of alcohols catalyzed by the ionic liquid–supported sulfoxide

the produced sulfide **6** can be recovered easily from the reaction mixture and converted to **7** and thus reused for at least four cycles.

A novel and efficient protocol for the oxidation of a broad range of benzylic, allylic, and aliphatic alcohols under mild conditions with a high degree of chemoselectivity using imidazolium cation–exchanged $H_5[PMo_{10}V_2O_{40}]\cdot 32.5H_2O$ (V2) immobilized on to ionic liquid–modified SBA-15 by the SILP strategy (V2ILSBA) as a catalyst and air as an oxidant was developed by Bordoli et al. [66]. The schematic representation for the preparation of the catalyst is shown in Scheme 14.61.



Scheme 14.61 Preparation of V2ILSBA-15

The selective oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, without the overoxidation of aldehydes to carboxylic acids, was performed under mild reaction conditions using this reagent system, via the mechanism shown in Scheme 14.62 [67].

$$ArCH_2OH + PMo_{10}V^{V}_2O_{40}{}^{5-} \xrightarrow{-2H^+,\ -2e^-} ArCHO + H_2\ PMo_{10}V^{IV}_2O_{40}{}^{5-}$$

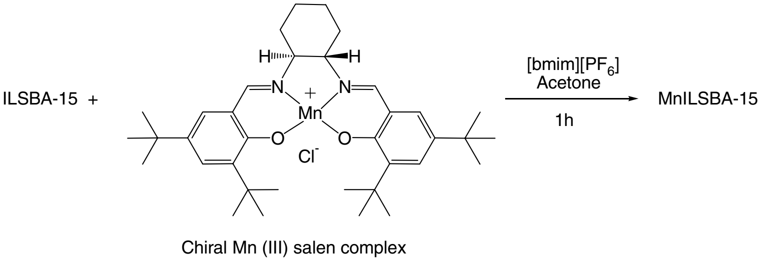
$$H_2\ PMo_{10}V^{IV}_2O_{40}{}^{5-} + 1/2\ O_2 \longrightarrow PMo_{10}V^{V}_2O_{40}{}^{5-} + H_2O$$

Scheme 14.62 Mechanism of the oxidation of alcohols in the presence of V2ILSBA-15

The high catalyst activity and ease of catalyst recovery for organic syntheses and the industrial oxidation of alcohols were demonstrated.

Optically active alcohols are extremely useful starting materials and intermediates in synthetic organic chemistry and pharmaceutical industry. Oxidative kinetic resolution of racemic alcohols is a feasible approach that gives optically active alcohols. Sahoo et al. prepared chiral Mn(III) salen complex that was immobilized over silica through a thin film of covalently anchored imidazolium ionic liquid [68]. Their results showed that the chiral Mn(III) salen complex could be successfully immobilized onto the modified mesoporous materials and that the long-range mesoporous ordering of parent supports was maintained after the immobilization.

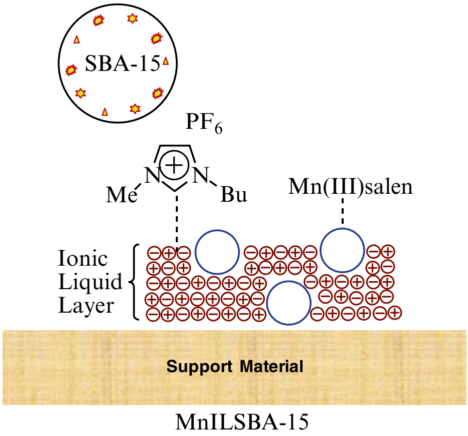
The supported ionic liquid catalyst over mesoporous silica, SBA-15 (See Scheme 14.56), was synthesized following the literature procedure [69, 70] (Scheme 14.63).



Scheme 14.63 Preparation of MnILSBA-15

As shown in the schematic Scheme (14.64), the ionic liquid was hooked onto the support by covalent bond and the Mn(III) salen complex appeared in the ionic liquid in which it is highly soluble.

Scheme 14.64 Schematic figure of MnILSBA-15



The immobilized catalyst provided good enantioselectivity and activity in the heterogeneous catalysis of the oxidative kinetic resolution of secondary alcohols and can be recovered and recycled for four times without obvious loss of enantioselectivity and activity. Oxidative kinetic resolutions of meso-diols, hydroxyl esters, and primary alcohols were also studied using this catalytic system.

14.2 Conclusions

In this chapter, we reviewed protocols for the oxidation of alcohols in the presence of different types of oxidizing agents, including peroxides, iodine, hypervalent iodine reagents, sodium hypochlorite (NaOCl), and O_2 or air (aerobic oxidation), in ionic liquids as catalysts or solvents. The important feature of these protocols is the use of ionic liquids which provide simple isolation of products, easy, high yields of the products, easy separation of the catalyst, and recyclability and reusability of the catalyst. As efficient and recyclable solvents or catalysts, ionic liquids also provide green conditions for these strategies.

Acknowledgment The authors thank their coworkers, named in the references, for their experimental and intellectual contributions.

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Chapter 15
Functionalization of Carbon Nanotubes with Ionic Liquids

Ying-Kui Yang, Xiao-Lin Xie, and Wei Cui

Abstract Ionic liquids (ILs) have attracted considerable attention as solvents, electrolytes, catalysts, and specific additives for the fabrication of various materials due to their combined characteristics of green chemistry, tunable solubility, and designable functionality. Recently, ILs have already catalyzed interdisciplinary exploration of both physicochemical properties and potential applications, especially in the functionalization of carbon nanotubes (CNTs). However, remarkable structure-dependent properties and realistic applications of CNTs have been hindered by processing and manipulation difficulties due to their intrinsic insolubility and easy of aggregation into bundles. Recent studies have proved that ILs can act as green solvents and dispersants to exfoliate and stabilize CNTs in solvents and various matrices, as compatibilizers and modifiers to improve the interface binding between multiple components, as well as additives to endow the final composites with new functionalities. In this chapter, a comprehensive review about the functionalization of CNTs with ILs is presented by summarizing recent scientific accomplishments and addressing future perspectives in this research area.

15.1 Introduction

Carbon nanotubes (CNTs) are considered to be all-carbon inorganic macromolecules which generally consist of one or more graphene sheets seamlessly wrapped into cylinder-shaped tubes, corresponding to single-walled carbon nanotubes

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(SWCNTs) or multiwalled carbon nanotubes (MWCNTs), respectively [1–3]. Their pseudo one-dimensional nanostructures endow them with high surface areas, large aspect ratios, and unusual physicochemical properties, such as excellent electrical and thermal conductivities and mechanical strength [4, 5]. CNTs have already shown great promise in many applications of molecular devices, (bio) sensors, catalyst supports, electrodes, and components in high-performance composites ever since their discovery [6–8]. Most of properties and applications are closely associated with isolated nanotubes; however, nanosized CNTs are intrinsically insoluble and have a strong tendency to aggregate into large bundles in solvents and matrices, due to attractive van der Waals forces and electrostatic interactions [9, 10]. Therefore, realistic applications of CNTs are being encumbered by the fact that bundle properties are inferior to those of individual nanotubes. At present, many improved strategies have been developed to enhance the dispersibility and stability of CNTs in solvents and matrices through covalent and noncovalent functionalization [11–13]. The former is generally carried out by attaching organic molecules or polymers to the surface of CNTs [14, 15]. Recently, we have found that functionalized MWCNTs with small molecules [16], linear polystyrene (PS) [17, 18], hyperbranched poly(urea-urethane) [19, 20], biodegradable poly(ε-caprolactone) (PCL) [21, 22], ionic polymers [23, 24], and photoresponsive polyurethane containing azobenzene [25] are well soluble in water or organic solvents. Also, MWCNTs after functionalization can be uniformly dispersed in polymer matrices [26, 27]. However, covalent functionalization of nanotubes involves more or less the structural damages (e.g., tube breakage, tip or sidewall opening). This process inevitably disrupts their electronic continuum and weakens their intrinsic electrical and thermal conductivities, thereby adversely impacting their properties [28, 29]. Instead, noncovalent methods can make CNTs effectively dispersed and exfoliated in solvents and matrices by polymers wrapping, addition of surfactants, π–π stacking with aromatic molecules, and specific solvents [30, 31]. The advantage is that both structures and properties of CNTs are not altered and destroyed during noncovalent functionalization, but isolated CNTs are stable only for limited time in some cases and even revert to bundles [32]. It is believed that both methodologies would play an equally important role in the developments and applications of CNTs depending upon the circumstances applied [33].

Ionic liquids (ILs) are generally defined as low-melting organic salts that are liquid below 100°C, while those with higher melting points are frequently referred to as molten salts [34]. ILs were first reported by Walden in 1914 [35]. Since then, ILs have attracted more and more attention due to their obvious advantages over conventional organic solvents and electrolytes, such as negligible vapor pressures, good chemical and thermal stabilities, wide electrochemical windows and liquid ranges, considerable electric conductivities, and tunable physicochemical properties by a judicious choice of cation–anion combination [36, 37]. As potential green and designable solvents, ILs have been very useful in organic reactions [38, 39], polymerization [40, 41], catalysis [42, 43], biotransformations [44], self-assembly media [45], electrochemistry [46, 47], supercritical fluid [48], and lubricants [49] and so on. In particular, various crystalline nanoparticles with specific function have been successfully synthesized in ILs due to their high polarities and self-organization abilities [50–52]. This chapter is not to focus on the above properties and applications of pure ILs since there are a number of excellent reviews [36–50] and books [53, 54] available.

Recently, the extraordinary potential of ILs in materials synthesis has triggered an increasing attention in the functionalization of CNTs [55, 56]. Fukushima and Aida et al. [57] first found that room-temperature ILs (RTILs) were excellent dispersants to exfoliate CNT bundles into smaller, even individual ones by mechanical milling, resulting in the formation of a thermally stable bucky gel. Tour et al. [58] first reported that SWCNTs were exfoliated and functionalized predominantly as individuals by grinding with aryl diazonium salts in the presence of ILs as green solvents. Later, Choi [59] and Liu et al. [60] independently found that IL-functionalized MWCNTs could show reversibly switchable solubility between water and organic solvents through simple anion exchange. In recent years, using ILs to functionalize CNTs has been gradually realized [55, 56]; however, a comprehensive review of this research area is absent from the literatures. This chapter aims to provide an overview on the use of ILs as green solvents, functional additives, and modifiers for CNTs. Four sections will be involved in this chapter. Section 15.2 describes recent developments about ILs as green reaction media to functionalize CNTs since they provide an environmentally benign alternative to organic solvents. Section 15.3 summarizes current knowledge concerning the fabrication and applications of bucky gels from ILs and CNTs. Section 15.4 focuses on the use of ILs as functional additives and modifiers in their composites with CNTs. The first three parts are mainly related to noncovalent functionalization of CNTs with ILs. In Section 15.5, IL-grafted CNTs through chemical bonding is considered. Some open problems, current controversies, and future prospects in this area will be also included.

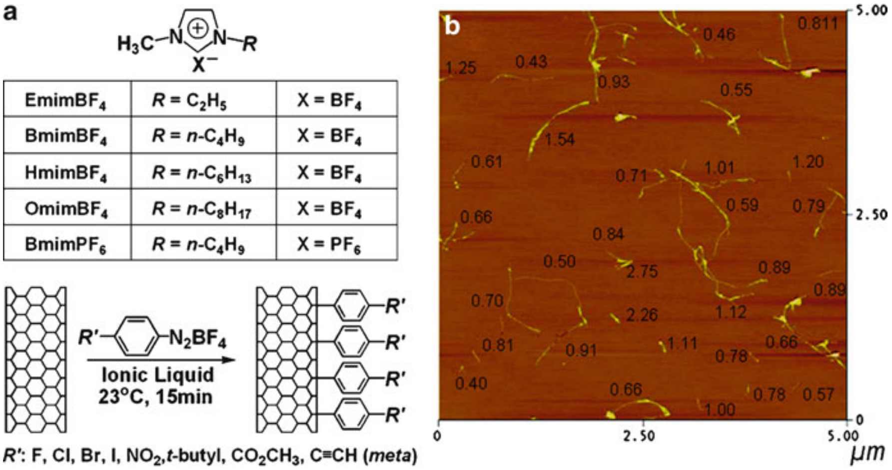
15.2 Ionic Liquids as Green Solvents to Functionalize Carbon Nanotubes

CNTs are indeed promising building blocks for high-performance composites. An obstacle to facilitate their practical applications is how to homogenously disperse and exfoliate them in solvents and matrices [9–13]. The common method is to separate CNTs from their bundles through liquid-phase exfoliation and stabilization before and after functionalization [61]; hence, both dispersion quality and functionalization effectiveness of nanotubes closely depend on the choice of solvents. It has been reported that CNTs, only after acid treatment, can be well dispersed and stable in water and organic solvents containing an amide functionality, such as *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMAC), and *N*-methylpyrrolidone (NMP) [62, 63]. However, current functionalization of CNTs has been mainly carried out in strong acids (e.g., nitric acid, sulfuric acid, or their mixture) and volatile organic solvents (VOS), causing some problems of environmental pollution, equipment corrosion, and health hazard [11, 13]. Therefore, it is a matter of developing environmental-friendly technologies to functionalize CNTs. It has been widely recognized that the green chemistry process can be achieved by solvent-free manufacturing or by the use of water, supercritical carbon dioxide (SC-CO_2), and ILs as reaction media. Pristine CNTs often tend to aggregate into clusters, ropes, and bundles, and they are insoluble in water and common organic solvents due to their intrinsic van der Walls forces of intertubes associated with high aspect ratio [64, 65]. Therefore, the solvent-free process is generally not available for the exfoliation of nanotube aggregates. Though CNTs functionalized by water-soluble molecules can be well dispersed and stable in solvents as reported from our laboratory [16], aqueous processes are still not common due to the severe limitations on the use of water-insoluble ones. During the last decade, the use of SC-CO_2 as green medium has attracted much interest instead of VOS in the synthesis and processing of materials, due to its nontoxicity, nonflammability, low viscosity, and tenability [66]. Functionalization of CNTs in SC-CO_2 has been studied intensively over several years [67]; however, there is a rigorous requirement for high pressures to reach critical conditions. Recently, ILs-assisted functionalization of CNTs has triggered an emerging field.

15.2.1 Chemical Functionalization of Carbon Nanotubes in Ionic Liquids

Fukushima and Aida et al. [57] and Tour et al. [58] were the first to recognize that ILs can serve not only just as excellent dispersants for exfoliating nanotube bundles but also as green reaction media for functionalizing them. It is found that SWCNTs bundles can be chemically functionalized by mechanically grinding with aryl diazonium salts in ILs for few minutes at room temperature [58]. The presence of ILs makes SWCNT ropes exfoliate into smaller ones even individuals, with subsequent aryl free radical addition, affording the functionalized SWCNTs collected from ILs by washing with acetone, DMF, and water. SWCNTs after functionalization remain predominantly as individuals (Fig. 15.1). Especially, ILs used herein can be characteristic of hydrophilicity as well as hydrophobicity, either imidazolium or pyridinium in their cation moieties. These parameters have no clear effect on the dispersion and degree of functionalization of SWCNTs. This method does not require adverse solvent conditions and constitutes an extremely rapid and mild green chemical protocol to exfoliate and functionalize SWCNTs. Afterward, Sessler et al. [68] performed the supramolecular functionalization of SWCNTs with sapphyrin by grinding them in an IL of 1-butyl-3-methylimidazolium hexafluorophosphate (BmimPF_6). The exfoliated nanotubes during processing permit sapphyrin molecules to come in contact with the newly exposed annotate surface, resulting in the formation of supramolecular nanotube-sapphyrin complexes. The resulting functionalized SWCNTs undergo photoexcited intramolecular electron transfer and can act as antennae for light harvesting.

Li and Niu et al. [69] employed the BmimPF_6-supported SWCNT electrode to execute electrografting poly(*N*-succinimidyl acrylate) (PNSA) onto their surfaces.



$EmimBF_4$	$R = C_2H_5$	$X = BF_4$
$BmimBF_4$	$R = n\text{-}C_4H_9$	$X = BF_4$
$HmimBF_4$	$R = n\text{-}C_6H_{13}$	$X = BF_4$
$OmimBF_4$	$R = n\text{-}C_8H_{17}$	$X = BF_4$
$BmimPF_6$	$R = n\text{-}C_4H_9$	$X = PF_6$

Fig. 15.1 (**a**) Schematic illustration for the functionalization of SWCNTs in various ILs by mechanically grinding them with diazonium salts at room temperature for minutes and (**b**) AFM analysis by height of SWCNTs functionalized with 4-chlorobenzenediazonium tetrafluoroborate in $OmimBF_4$. The vertical distances measured (shown as numbers, in nm, on the micrograph) are predominantly <1.4 nm, therefore indicating individual SWCNTs (Reproduced from Ref. [58] with kind permission of © the American Chemical Society)

In this work, SWCNTs were considerably untangled in $BmimPF_6$ so as to increase the effective area of electrode, and NSA monomer could be well dissolved in the supporting ILs. After electrochemical functionalization, PNSA-grafted SWCNTs could be separated from $BmimPF_6$ and purified by repeated centrifugation and ultrasonication with acetone. Herein, $BmimPF_6$ acts both as a supporting electrolyte as well as a green solvent to disperse and functionalize SWCNTs via electrochemical grafting. Ahmad et al. [70, 71] reported the electrochemical polymerization of methylpyrrole in a hydrophobic IL of [1-ethyl-3-methylimidazolium bis(perfluoroethylsulfonyl)imide] at room temperature in the presence of MWCNTs. The resultant poly(methylpyrrole)/MWCNT composite shows high cycle life, good electrochromism behavior, and enhanced flexibility and electrical properties due to the uniform dispersion of MWCNTs in the polymer matrix. This approach can be further applied to other organic conjugated polymers and, thus, opens an avenue for applications of host polymers in electronic devices. A mixture of $BMIPF_6$ and trifluoroacetic acid (CF_3COOH) was also chosen by Kvarnström et al. [72] as reaction media to disperse SWCNTs and electropolymerize aniline. This method combines *p*-type conducting polyaniline (PANI) with *n*-type SWCNTs and provides a possibility to fabricate PANI-SWCNT donor-acceptor dyads for applications in organic electronics.

Recently, we have developed a relatively green process for covalently functionalizing nanotubes. Versatile functional groups were covalently anchored onto MWCNTs by one-step free radical addition of water-soluble azo initiators in water, and their coverage densities were easily controlled by adjusting feed ratio of initiators to

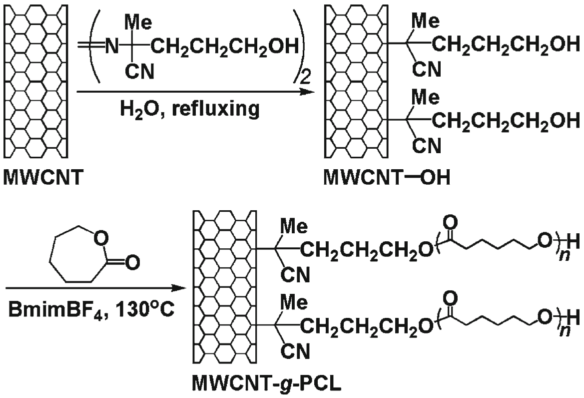


Fig. 15.2 Schematic representation for covalent attachment of hydroxyl groups to MWCNTs by free radical addition of 4,4′-azobis(4-cyanopentanol) in water and subsequent surface-initiated ring-opening polymerization of ε-caprolactone in room-temperature ionic liquids ($BmimBF_4$)

nanotubes or selecting the starting chemicals of multifunctional groups [16]. Among the functionalized nanotubes, MWCNTs containing terminal hydroxyl groups (MWCNT–OH) can be used as the supporting macroinitiators to trigger graft polymerization of ε-caprolactone in 1-butyl-3-methylimidazolium tetrafluoroborate ($BmimBF_4$) to generate PCL-grafted MWCNTs (MWCNT-*g*-PCL) [22], as shown in Fig. 15.2. Interestingly, the amount of the grafted PCL synthesized in $BmimBF_4$ is clearly higher than that obtained in 1,2-dichlorobenzene under comparable conditions. All functionalized MWCNTs have much better dispersibility and stability than pristine ones in polar solvents. It is worth mentioning that the use of ILs as solvent can not only improve the dispersibility and stability of nanotubes during polymerization but also enhance the functionalization effectiveness as a result of higher reaction rate and grafting amount of polymer compared to conventional organic solvents [41]. The proposed methodology using water and ILs as reaction media appears relatively facile and green, which may provide an entry to facilitate the chemical functionalization of nanotubes and accelerate their practical application.

15.2.2 Ionic Liquids–Assisted Dispersion of Carbon Nanotubes in Water

It is really difficult to directly disperse and stabilize CNTs in an aqueous solution due to high intermolecular cohesive forces of nanotubes themselves and poor compatibility with water. However, Han et al. [73] have recently found that both amino groups and imidazolium or pyridinium ions had a significant affinity with nanotubes and made them stably dispersed in water with the help of very small amounts of specific ILs, such as 1-aminoethyl-3-methylimidazolium bromide and 1-(2-aminoethyl) pyridinium bromide. This observation is related to the strong affinity of ILs that gains access to the surface of CNTs by physical adsorption. Subsequently, the strong polarity and charged moieties of the adsorbed ILs make the surface of CNTs hydrophilic, thereby enhancing their dispersibility and stability in water. Fontana et al. [74]

have obtained stable homogeneous suspensions of pristine SWCNTs in water by exfoliating them into aqueous solution of 1-hexadecyl-3-vinylimidazolium bromide (HvimBr) above its critical micelle concentration. The higher weight fraction of SWCNTs in suspensions can be reached by increasing the amount of HvimBr and sonication time. Under identical conditions, the suspension concentrations of SWCNTs in HvimBr solutions were found to improve by about 20% relative to commonly used surfactants like sodium dodecyl sulfate (SDS), sodium dodecyl benzene sulfonate (SDBS), and cetyl trimethyl ammonium bromide (CTAB) [75]. Yu et al. [76] found that the dispersing power of butyl-α,β-bis(alkylimidazolium bromide) $[C_n\text{-}C_4\text{-}C_n\text{im}]Br_2$ ($n = 12, 14, 16$) for MWCNTs was clearly stronger than that of 1-butyl-3-alkylimidazolium bromide in aqueous solutions. This is due to their special molecular structures of the former, including two imidazole ring head groups and two hydrophobic chains. It is found that $[C_n\text{-}C_4\text{-}C_n\text{im}]Br_2$ with a longer hydrocarbon chain can give a stronger dispersion ability for MWCNTs, and the resulting MWCNT suspension can be stable for 1 month at least. This present work here would provide an entry to design more suitable dispersants for CNTs.

15.2.3 Ionic Liquids–Assisted Fabrication of Cellulose/Carbon Nanotube Composites

Cellulose is generally difficult to process in solution or as a melt due to its large proportion of intra- and intermolecular hydrogen bonds; however, ILs are found to be a powerful and green solvent for it [77]. Lu et al. [78] reported the facile preparation of a cellulose/SWCNT complex by ultrasonically mixing SWCNTs with cellulose in 1-butyl-3-methylimidazolium bromide (BmimBr). The presence of BmimBr accelerates simultaneously the dispersion of SWCNTs and dissolution of cellulose. The resulting cellulose/SWCNT complex is easily redispersed in water to form a stably homogenous suspension that can be kept at room temperature for 1 year at least. Moreover, the scaffold fabricated from the cellulose/SWCNT complex shows good biocompatibility and promotes the growth of HeLa cells without effect on their proliferation. Recently, Linhardt et al. [79] have fabricated the core-sheath MWCNT-cellulose fibers using coaxial electrospinning from an IL solvent of 1-methyl-3-methylimidazolium acetate (MmimAc). Initially, MWCNTs were well dispersed in MmimAc to form a gel core solution, and this core solution was then electrospun surrounded by a sheath solution of cellulose dissolved in MmimAc with good spinnability. Electrospun fibers were finally collected in a coagulation bath of ethanol and water to remove MmimAc and dried to form cable structure with a conductive core and insulating sheath, as shown in Fig. 15.3. The resultant fiber mats exhibit excellent conductivity that is increased with increasing MWCNTs in the matrix because of improved core continuity. A similar IL of 1-butyl-3-methylimidazolium acetate (BmimAc) was also chosen by Ren et al. [80] to dissolve cellulose and disperse SWCNTs in turn. Their suspension was finally extracted by addition of water to completely remove BmimAc. The resulting cellulose/

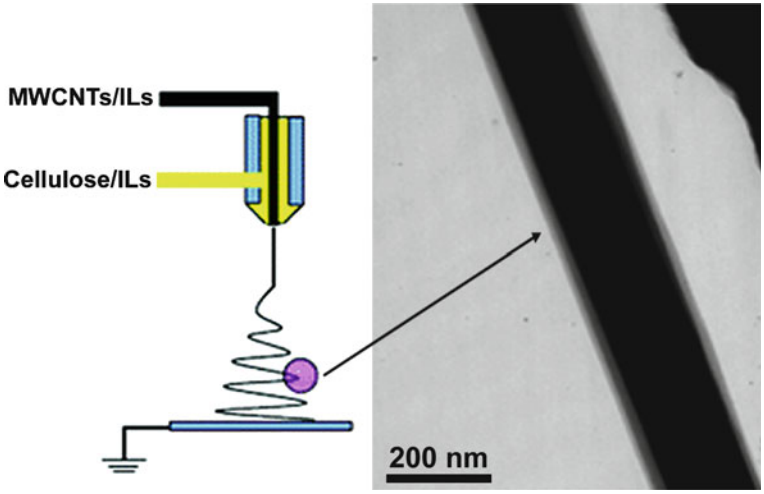


Fig. 15.3 TEM image of core sheath of MWCNT-cellulose nanofiber (MWCNTs/cellulose = 40/60 wt%) (Reproduced with permission from Ref. [79] with kind permission of © The American Chemical Society)

SWCNT composite was found to be homogenous, hydrophilic, conductive, and biocompatible and was further utilized for immobilization of leukemia K562 cells on a gold electrode to form an impedance cell sensor with a relatively low detection limit. By using ILs as intermediary solvents, the fabricated composite from cellulose and CNTs effectively combines the biocompatibility of the former and the conductivity of the latter. It is believed that these methods would have great potential from the creation of novel biocomposites to the use as scaffolds, biosensors, drug carriers, and biological transporters.

15.2.4 Dispersion Mechanism of Carbon Nanotubes in Ionic Liquids

It is indisputable that ILs can be widely applied to functionalize CNTs due to their excellent dispersing power. Recently, liquid-phase exfoliation of CNTs has been reviewed by Coleman [61]; however, the dispersion mechanism for CNTs in ILs is still controversial. A "cation–π" interaction between nanotubes and imidazolium ions was first proposed by Fukushima and Aida [55, 57] to account for the exfoliation of entangled SWCNTs into smaller bundles, even individuals. On the basis of combined results of differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectrum, and X-ray diffraction (XRD) analysis, Gilman et al. [81] provided the evidence for a "cation–π" interaction in the imidazolium-treated MWCNTs. Some researchers also cited this interpretation to support their cases [82].

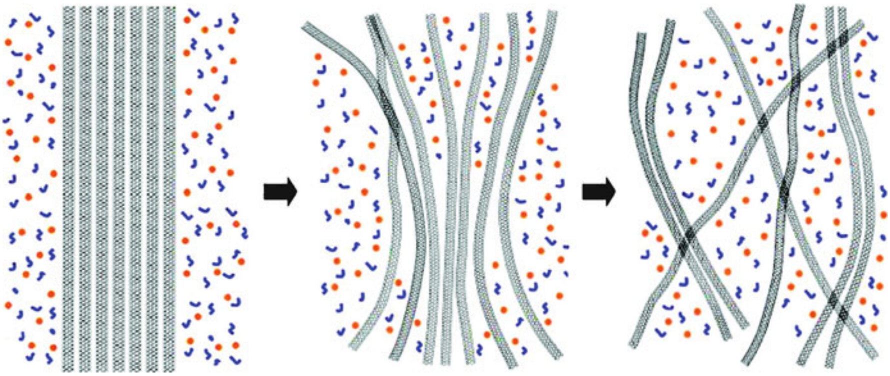


Fig. 15.4 Schematic representation for dispersion process of SWCNTs in ILs (Reproduced from Ref. [84] with permission of © The American Chemical Society)

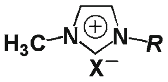
Recently, Shim and Kim [83] have used molecular dynamics (MD) simulations to study the solvation of SWCNTs and double-walled CNTs in 1-ethyl-3-methylimidazolium tetrafluoroborate ($EmimBF_4$). It is found that solvent cations and anions form smeared-out cylindrical shell structures outside of SWCNTs irrespective of their diameters, and imidazole rings of cations are mainly parallel to the surface of SWCNTs, indicating π stacking between the nanotubes and ions there. Li et al. [84] demonstrated the dispersion mechanism of SWCNTs in ILs on the basis of spectroscopic studies and molecular simulation. They considered that ILs interacted with SWCNTs through weak van der Waals forces rather than the previous so-called cation–π interaction. Instead, a "π–π" interaction-shielding model is proposed to account for the dispersion of SWCNTs in ILs. As shown in Fig. 15.4, upon mechanically grinding SWCNTs in ILs, the nanotubes bundles are exfoliated by shear force into smaller ones even individuals, and these detached nanotubes are immediately surrounded by ILs. The strong π–π interaction between SWCNTs is simultaneously shielded by ILs due to large dielectric constants of the latter, thereby preventing the exfoliated bundles from rebundling. Meanwhile, the high surface energy of the isolated nanotubes can be relatively balanced since they are encapsulated by ILs through van der Waals forces.

Moreover, considering that graphene and CNTs have similar conjugated structures and physicochemical features [85], these methods to exfoliate nanotubes in ILs should be applicable for graphene. Recently, Han et al. [86] have reported an approach to uniformly disperse graphene sheets in $BmimPF_6$ in the presence of poly(1-vinyl-3-butylimidazolium chloride) as stabilizer through noncovalent π–π interaction. The resultant composite solution shows higher conductivity than pure IL. Afterward, Zhang et al. [87] found that stable dispersions of reduced graphene oxide were easily achieved by chemical reduction of graphene oxide sheets in aqueous ILs in the absence of other surfactants and stabilizers. The rheological characterization further confirms that graphene sheets are well dispersed in ILs to form a gel network structure similar to the SWCNT/IL gel [57]. These findings imply that cation–π and/or π–π interactions may also exist between graphene nanosheets and imidazolium rings. It is believed that the new graphene/IL composites would have great potentials for the use of electrochemistry, catalysis, solar cells, and other functional devices due to their unique properties.

15.3 Fabrication and Applications of Bucky Gels from Ionic Liquids and Carbon Nanotubes

A free-standing "bucky paper" has been fabricated by filtration from an aqueous solution of acid-treated SWCNTs [88]. In 2003, Fukushima et al. [57] first reported that a variety of imidazolium ion-based RTILs (Fig. 15.5) were mixed with pristine SWCNTs under mechanical grinding to form thermally stable gels (so-called bucky gels), in which the heavily entangled nanotube bundles were exfoliated into finer bundles even individuals. Based on phase transition and rheological properties of gels, they deduced that the formed bucky gels resulted from physical cross-linking of SWCNTs were mediated by local molecular ordering of RTILs regardless of the entanglement of nanotubes. It is herein implied that imidazolium ions of RTILs interact with the π-electronic surface of SWCNTs through possible cation–π and/or π–π interactions. Similar bucky gels were prepared by grinding hydrophilic $\mathrm{BmimBF_4}$ with pristine SWCNTs and purified SWCNTs, respectively [89]. It is found that purified SWCNTs show better dispersion in $\mathrm{BmimBF_4}$, and the corresponding gel behaves more solid-like structure than the gel of $\mathrm{BmimBF_4}$ with pristine SWCNTs. This is due to the larger number of cross-linking points and denser physical network structure of the former. Bazhenov et al. [90] also produced a bucky gel of SWCNTs in hydrophobic $\mathrm{BmimPF_6}$ using similar method [57].

Bucky gels are easily obtained by mechanically grinding CNTs with ILs, and they combine the excellent electrical properties and high specific surface area of CNTs, as well as high ionic conductivity and wide potential window of ILs. Thus,



IL Code	*R* Group	X Anion
$\mathrm{EmimBF_4}$	C_2H_5	BF_4
$\mathrm{BmimBF_4}$	n-C_4H_9	BF_4
$\mathrm{HmimBF_4}$	n-C_6H_{13}	BF_4
$\mathrm{EmimTf_2N}$	C_2H_5	$(CF_3SO_2)_2N$
$\mathrm{BmimTf_2N}$	n-C_4H_9	$(CF_3SO_2)_2N$
$\mathrm{BmimPF_6}$	n-C_4H_9	PF_6
$\mathrm{ABmimPF_6}$	$CH_2{=}CHCO_2(CH_2)_4$	PF_6

Fig. 15.5 Schematic illustration of molecular structure of RTILs used

bucky gels would have great potentials in the field of electrochemistry. Zeng et al. [91] studied the voltammetric behavior of uric acid (UA) at a hydrophobic BmimPF$_6$-MWCNT gel-coated glassy carbon (GC) electrode (BmimPF$_6$-MWCNT/GC). They found that UA effectively accumulated at this electrode and caused a sensitive anodic peak, which could be used to determine UA in the human urine. By comparison, the BmimPF$_6$-MWCNT/GC electrode exhibits higher sensitivity and selectivity than a MWCNT-doped GC electrode. The BmimPF$_6$-SWCNT/GC electrode was fabricated by the same method [92, 93]. Such an electrode shows good selectivity, repeatability, and sensitive voltammetric response to xanthine and nitroaromatic compounds, say, *p*-nitroaniline, *p*-nitrophenol, *o*-nitrophenol, *m*-nitrophenol, *p*-nitrobenzoic acid, and nitrobenzene, thus finds application in the determination of these samples to some extent. The same group found [94] that the 1-octyl-3-methylimidazolium hexafluorophosphate (OmimPF$_6$)-SWCNT/GC electrode doped with gold nanoparticles (AuNPs) also showed good repeatability, sensitivity, and stability as well as accumulation function and promotion to electron transfer. It has application in detecting the chloramphenicol residue. Dong et al. [95] reported that the BmimPF$_6$-MWCNT/GC electrode had good biocompatibility with biomolecules like glucose oxidase (GOD). The resultant GOD/BmimPF$_6$-MWCNT/GC electrode exhibits excellently bioelectrochemical catalytic activity to glucose and the higher electron transfer rate than that of GOD adsorbed on MWCNTs. Recently, Lei et al. [96] have prepared a new gel by grinding SWCNTs with hematin porphyrin and BmimPF$_6$, in which porphyrin absorbed on SWCNTs leads to good dispersion of nanotubes in BmimPF$_6$. The presence of SWCNTs and BmimPF$_6$ can produce a synergic effect that accelerates electron transfer between redox probe or porphyrin and electrode, thereby endowing the hematin/BmimPF$_6$-MWCNT-modified GC electrode with excellent electrocatalytic activity toward the reduction of trichloroacetic acid. This biosensor exhibits rapid electrocatalytic response, wide linear range, low detection limit, and detection precision in neutral media. A gel of *n*-octylpyridinum hexafluorophosphate (OpmPF$_6$) and MWCNTs upon grinding was also applied to construct a highly sensitive, stable, and robust electrode [97]. This electrode is accessible to glucose determination and is also available to different probes such as ascorbic acid, ferricyanide, and hydrogen peroxide. To all appearances, the bucky-gel-modified electrodes can show better performance as electrochemical sensors in comparison with the CNT-modified electrodes in the absence of ILs. The discussed methods have taken advantage of nanotubes and ILs to provide a promising platform for electrochemistry applications.

In general, the modification of hydrophobic IL-CNT gels at the Au or GC electrodes needs to operate very carefully so as to obtain a stable modified layer [98, 99]. Dong et al. [99] employed a hydrophobic BmimPF$_6$-MWCNT gel to modify a graphite electrode instead of a GC electrode. As shown in Fig. 15.6, the BmimPF$_6$-MWCNT gel forms a more stable film on the hydrophobic graphite electrode surface compared to that on a GC electrode, due to the hydrophobic interaction and, especially, π–π stacking between MWCNTs and graphite. The BmimPF$_6$-MWCNT/graphite electrode shows higher conductivity, better biocompatibility, and larger surface area compared to the bare graphite electrode. Besides, laccase immobilized

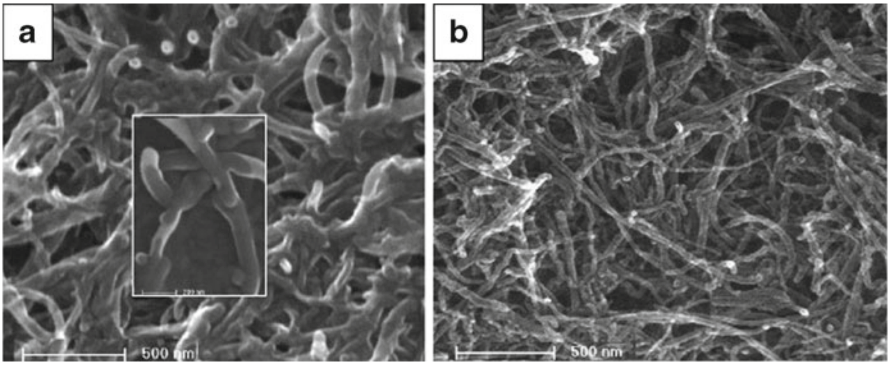


Fig. 15.6 Environmental scanning electron microscope (ESEM) images of (**a**) the BmimPF$_6$-MWCNT gel modified the graphite electrode surface (inset: high-magnification ESEM image) and (**b**) the BmimPF$_6$-MWCNT gel modified the GC electrode surface after immersing in water for 10 h (Reproduced from Ref. [99] with kind permission of © Elsevier)

on the BmimPF$_6$-MWCNT/graphite electrode exhibits higher thermal stability and enhanced biocatalytic activity than that of the free one. Furthermore, the detection of oxygen can be performed at the fabricated electrode when using 2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid)diammonium salt as a mediator. This special bucky gel provides an avenue for the development of multifunctional bioelectrochemical devices.

However, Yao et al. [100] fabricated a hydrophilic bucky gel from BmimBF$_4$ and acidic-treated MWCNTs by grinding them in an agate mortar. The resulting gel succeeds in keeping the bioactivity and facilitating direct electron transfer of heme proteins. Mao et al. [101] constructed a stable water-miscible IL/electrolyte interface by confining BmimBF$_4$-SWCNTs onto a GC electrode and found that this electrochemical interface was relatively stable in aqueous media and possessed a fast electron transfer property. Recently, organophosphorus hydrolase (OPH) immobilized on the MWCNT/IL electrodes was also fabricated by Lee et al. [102] using BmimPF$_6$, BmimBF$_4$, and BmimTf$_2$N as binders. Functionalization of MWCNTs with ILs not only leads to high dispersion of nanotubes and good compatibility with OPH but also accelerates electron transfer reaction at the interface. It is found that the electrochemical properties and sensor performances of three electrodes depend strongly on the types of ILs used due to the conformational changes of the microenvironment between OPH and electrodes. Among them, the BmimPF$_6$-MWCNTs/Au electrode displays the best sensitivity and a fast response time for detecting organophosphorus. This finding would give a deep understanding of the role of ILs on the modified electrodes for the use of biosensors. C$_{60}$ is another π-electron carbon material of fullerene family similar to CNTs, so it is expected to form similar composites with ILs. For example, Yang et al. [103] fabricated a BmimPF$_6$-C$_{60}$ composite upon grinding C$_{60}$ in BmimPF$_6$ and found that the BmimPF$_6$-C$_{60}$-modified GC electrode decreased the oxidation potential of dihydronicotinamide adenine dinucleotide (NADH). This makes it possible to be used in the detection of NADH.

In particular, Miyako et al. [104] developed a near-infrared (NIR) laser triggered thermoelectric convertor based on the SWCNT-RTIL gel composites. SWCNTs were first mixed with different RTILs, such as $BmimPF_6$, $OmimPF_6$, $BmimTf_2N$, and 1-*n*-hexyl-3-methylimidazolium hexafluorophosphate ($HmimPF_6$), leading to the formation of the SWCNT-RTIL gels. The gels should possess a high concentration of SWCNTs (20 mg/mL) in order to make them suitable for application onto the ceramic surface of a thermoelectric convertor, due to the practical requirement of strength, flexibility, and adhesiveness. Interestingly, the present convertors can generate sufficient electrical energy to power a light-emitting diode (LED) when the center of the SWCNT-RTIL gel module is irradiated by a continuous-wave laser. These bucky-gel-based NIR-driven thermoelectric convertors will have potential applications in robotics, aerospace engineering, and sensors.

15.4 Ionic Liquids as Additives and Modifiers in Carbon Nanotube Composites

During functionalization of CNTs with ILs as green solvents, ILs are generally required to remove from their reaction systems so as to obtain the neat functionalized CNTs. When ILs are used as functional additives and modifiers, however, they still retain in their CNT composites containing ternary components in most cases. As such, these materials combine the unusual properties of ILs and CNTs as well as other materials, thus have attracted more extensive investigations in recent years.

15.4.1 Ionic Liquids–Assisted Preparation of Polymer Carbon Nanotube Composites

Polymer-based nanocomposites possess the desirable combined properties that cannot be displayed by individual components. CNTs have been considered as ideal candidates for substituting or complementing conventional fillers in the fabrication of multifunctional nanocomposites. The critical challenge is to uniformly disperse and exfoliate CNTs into the polymer matrix to optimize the matrix/nanotube adhesion. Dispersion is a fundamental issue for filler-reinforced polymer composites [105]. Homogeneous dispersion of CNTs not only minimizes the stress concentration sites and obtains a more uniform stress distribution throughout the composite but also effectively transfers the excellent properties of CNTs to the host polymer [10, 106]. The latter strongly depends upon the interfacial bonding between them. However, realistic applications for polymer/CNT composites have been impeded due to poor dispersibility and compatibility of CNTs and weak matrix-nanotube interaction [9, 10]. There is a pressing need to maximize the final properties of composites utilizing optimal methodologies during processing.

ILs have played an important role in the dispersion and exfoliation of CNTs through cation–π and/or π–π interactions [55]. Such interactions can enhance their compatibility and interface adhesion by maximizing the CNT-matrix physical contact. It seems that ILs might be a judicious choice as functional additives of polymer/CNT composites to improve their performance. Gilman et al. [81] prepared a series of PS/MWCNT composites by melt blending of PS with unmodified and modified MWCNTs at 195°C for 5 min in a miniextruder. Before extrusion, 1,2-dimethyl-3-hexadecylimidazolium tetrafluoroborate ($DmHdimBF_4$) was melt mixed with MWCNTs at 185°C for 2 min since $DmHdimBF_4$ has a liquid-crystalline transition temperature as 175°C. The resulting imidazolium-modified MWCNTs after cooling were ground into powders and were added to PS matrix during extrusion. It is found that unmodified MWCNTs are hardly dispersed in PS; instead, large bundles dominate. However, well-dispersed, even individual nanotubes are easily observed in the PS/modified-MWCNT composites. This observation implies that $DmHdimBF_4$ may locate on the nanotube-PS interface by either an edge-on association of imidazolium rings with MWCNTs or a π-stacking interaction between the MWCNT surface and imidazolium. Therefore, it appears that imidazolium molecules can increase the affinity of MWCNTs for polymer and prevent them from aggregating, acting as compatibilizers and dispersants. Zhang et al. [107] employed 1-allyl-3-methylimidazolium chloride (AmimCl) as solvent for cellulose and dispersant for MWCNTs to prepare cellulose/MWCNT composite fibers that were spun from their solution by dry-jet wet spinning. Dynamic rheology measurements were performed to investigate linear viscoelastic properties of the AmimCl/MWCNT composites prepared by grinding. The observed gel-like rheology behavior was due to the formation of a nanotube network structure mediated by ILs. Such special network possibly results from both π–cation interactions and hydrogen bonding between acid-treated MWCNTs and AmimCl. After electrospinning, MWCNTs are homogenously dispersed and aligned in the cellulose fibers, resulting in the improved mechanical properties and thermal stability. Moreover, the cellulose materials can be regenerated by coagulation with water, and the residual AmimCl in the coagulation bath is further recovered after regeneration. Such a simple and effective method can be used to fabricate the potential precursors of the cellulose-based carbon fibers.

Someya et al. [108] demonstrated the fabrication of a SWCNT composite film by ILs induced exfoliation of SWCNTs into a fluorinated copolymer matrix. Initially, SWCNTs were mixed with 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl) imide ($BmimTf_2N$) by an automatic grinding system to give a bucky gel. The gel was then stirred with poly(vinylidene fluoride-*co*-hexafluoropropylene) (PVDF-HFP) in the presence of 4-methyl-2-pentanone followed by ultrasonication. A composite film was finally achieved by drop casting of the resulting swollen gel onto a glass plate and air drying. SWCNTs were uniformly dispersed into the fluorinated copolymer as the base matrix. Surprising, the content of SWCNTs can be increased up to 20 wt% without reducing the mechanical flexibility or softness of copolymer. In order to improve its tensibility and elasticity, the composite film was further coated by a silicone rubber of polydimethylsiloxane (PDMS) to get a so-called elastic conductor with a conductivity of 57 S/cm and a stretchability of 134%. Specially, they made this elastic

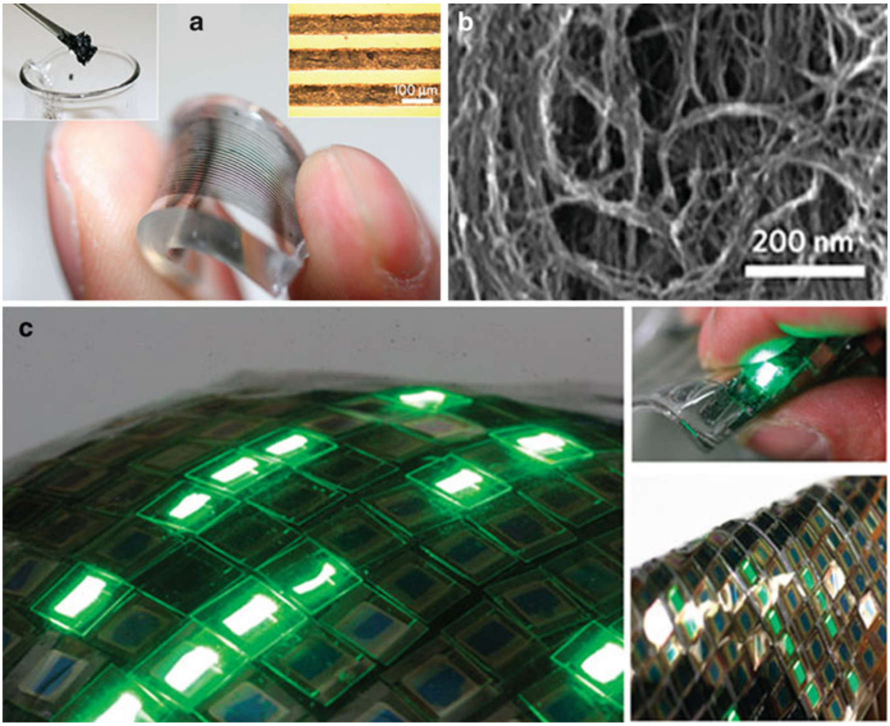


Fig. 15.7 (**a**) Printed elastic conductors on a PDMS sheet. The insets show SWCNTs dispersed in paste and a micrograph of printed elastic conductors; (**b**) typical SEM image of the elastic conductor, in which finer or exfoliated SWCNTs are uniformly dispersed in the rubber and formed well-developed conducting networks; and **(c)** a stretchable display that can be spread over arbitrary curved surfaces (Reproduced from Ref. [109] with kind permission of © Nature Publishing Group)

conductor integrated with printed organic transistors to fabricate a rubberlike active matrix with an effective area of 20 × 20 cm^2. It is found that the active matrix sheet can be uniaxially and biaxially stretched by 70% without mechanical or electrical damage. Afterward, the same group used a different weight ratio of SWCNTs to $BmimTf_2N$ and another fluorinated copolymer of vinylidene fluoride-*co*-tetrafluoroethylene-*co*-hexafluoropropylene to afford a SWCNT-rubber composite gel with a viscosity of 10 Pa.s [109]. The gel was then patterned on the PDMS rubber sheets using screen printing through shadow masks, followed by air drying to afford fine SWCNT-based elastic conductors with a linewidth of 100 μm (Fig. 15.7a). Note that SWCNTs are uniformly dispersed in the fluorinated copolymer matrix to form well-developed conducting networks (Fig. 15.7b), and the printed elastic conductors have a conductivity of 100 S/cm and can be stretched by ca. 100% without mechanical damage or delamination from the PDMS matrix. Furthermore, a rubberlike stretchable active-matrix organic LED display was constructed by integrating printed elastic conductors and organic transistors with organic light-emitting diodes. As shown in Fig. 15.7c, the display can be stretched by 30–50% and spread over a hemisphere without any mechanical or electrical damage. These elastic conductors are expected to have potential applications in high-performance and large-area electronic integrated circuits, especially on the arbitrary curved surfaces and movable parts, thereby significantly expand the areas for application of electronics [110, 111].

Aida, Asakaa, and Sugino et al. [112–116] developed fully plastic actuators that had a bimorph configuration with a polymer-supported internal IL electrolyte layer sandwiched by two polymer-supported bucky-gel electrode layers. The former consisted of PVDF-HFP and imidazolium-based ILs, while the latter was a gelatinous composite including PVDF-TFP, ILs, and SWCNTs. These bucky-gel actuators were easily fabricated through either layer-by-layer casting technique [112] or hot-pressing the electrolyte film sandwiched by two electrode films [113]. It is found that SWCNTs bundles are fine exfoliated into the bucky-gel electrode layers. More importantly, the bimorph actuators allow quick and long-lived operation in air at low applied voltages, comparable with any other low-voltage-driven solid-state actuators. Moreover, their actuated properties are related to the IL species and additives used [114, 115]. These methods are easy to process for the fabrication of actuators and provide an important step for constructing electromechanical plastic devices.

Wei et al. [117] reported the use of an IL gel to fabricate a memory device. In their work, SWCNTs and PS beads were ground in $BmimPF_6$ to form the composite gel, followed by sandwiching it between a bottom ITO glass and a top aluminum electrode to get the ITO/$BmimPF_6$-PS-SWCNT/Al device. Two other devices, referred to as ITO/$BmimPF_6$-PS/Al and ITO/$BmimPF_6$-SWCNT/Al, were also produced for comparison. It was found that the ITO/$BmimPF_6$-PS/Al and ITO/$BmimPF_6$-SWCNT/Al devices behave like an insulator and a conductor, respectively, whereas the ITO/$BmimPF_6$-PS-SWCNT/Al device showed a memory in terms of impedance switching and negative differential resistance (NDR). These results are possibly attributable to the hopping of electrons between metallic SWCNTs embedded in insulating PS and semiconducting SWCNTs in $BmimPF_6$. The impedance states for NDR are nonvolatile in nature and can be read and switched several times inside a nitrogen-filled glove box. Recently, Terasawa et al. [118] have employed SWCNTs, Li salts, ILs ($EmimBF_4$, $EmimTf_2N$), and PVDF-HFP to successfully fabricate a polymer-supported bucky-gel actuator with large capacitance. It was found that the actuators containing Li salt/ILs exhibited faster response and larger generated strain than those containing only ILs, due to the higher ionic conductivities and larger capacitance of the former. These methods would open a new and robust way for construction of actuators and electric devices.

15.4.2 Poly(Ionic Liquid) Carbon Nanotube Composites

In most cases, the ILs used were low molecular weight organic melt salts during processing of CNTs. A few researchers have reported the use of polymerizable ILs to directly fabricate polymer/CNT composites. Fukushima et al. [57] first succeeded in fabricating a polymeric bucky gel (bucky plastic) by in situ free radical polymerization of 1-(4-acryloyloxybutyl)-3-methylimidazolium hexafluorophosphate (ABmimPF_6) gel with SWCNTs under mechanical grinding using 2,2′-azobisisobutyronitrile (AIBN) as an initiator. The resulting poly(ABmimPF_6)/SWCNTs (3.8 wt%) bucky film is highly electroconductive with an electrical conductivity of 0.56 S/cm at room temperature and shows a nearly 400% increase in dynamic hardness in comparison with pure poly(ABmimPF_6). Later, they employed similar methods to prepare a series of bucky plastic films by free radical polymerization of imidazolium ion-based polymerizable ILs in the presence of SWCNTs [119]. SWCNTs can be uniformly dispersed in the polymer matrix to form finely cross-linked networks, which likely suppress slipping of entrapped polymer molecules via a strong interfacial interaction and also facilitate intertubular carrier transport. Hence, the composite films display excellent electroconductive properties (0.1–1.3 S/cm) even at a low loading of SWCNTs (3–10 wt%). Such soft materials could be applicable to electrodes, antistatic coating materials, and sensors [120].

Mecerreyes et al. [121] demonstrated the use of imidazolium-based poly(ionic liquid)s (PILs) to directly stabilize and disperse SWCNTs in water and organic solvents. They found that the water and organic suspensions of SWCNTs in acetone could be reversibly switched by in situ counter anion exchange between hydrophilic bromide (Br^-) and hydrophobic bispentafluoroethanesulfonimide (Pf_2N^-). Moreover, the PIL/SWCNT powder in water is easily recovered by addition of Pf_2N^- salt followed by filtration and drying and vice versa. The powder can be dissolved in solvents again to form an optically transparent black suspension. Recently, Kim et al. [122] have reported the preparation of PIL/SWCNT gels by in situ radical polymerization of a hydrophilic IL of 1-vinyl-3-ethylimidazolium bromide (VEimBr) in the presence of oxidized SWCNTs. The resulting poly(VEimBr)/SWCNT hydrogel was subjected to an anion-exchange reaction with lithium Tf_2N^- salt, in which hydrophilic anions exchanged with hydrophobic anions (Tf_2N^-), leading to an organogel of SWCNTs. This organogel can be easily dispersed in various organic solvents including acetone, DMF, tetrahydrofuran (THF), NMP, nitromethane, and methyl ethyl ketone. This method was extended by them to the preparation of solution-processable graphene sheets that were readily transferred between the aqueous and organic phases using PILs as the transferring vehicle [123]. The successful round trip of CNTs using PILs appears very simple and versatile and may be useful for further processing and manipulation of CNTs. Chen et al. [124] also found that poly(VEimBr) could uniformly coat the surface of MWCNTs after in situ radical polymerization of VEimBr. The resulting poly(VEimBr)/MWCNT gel is stably dispersed in water and exhibits superior electrocatalytic activity for reduction of O_2 and H_2O_2, as compared to pristine MWCNTs and the mixture of VEimBr monomer and nanotubes. Furthermore, the immobilized GOD on the poly(VEimBr)/MWCNT modified GC electrode can display excellent direct electrochemical response and biosensing performance for glucose. The proposed biosensor may offer a new strategy for investigating direct electron transfer of the redox proteins.

Recently, Dubios et al. [125] have developed another efficient strategy for making CNTs disentanglement in the polymer matrix. In their work, an imidazolium

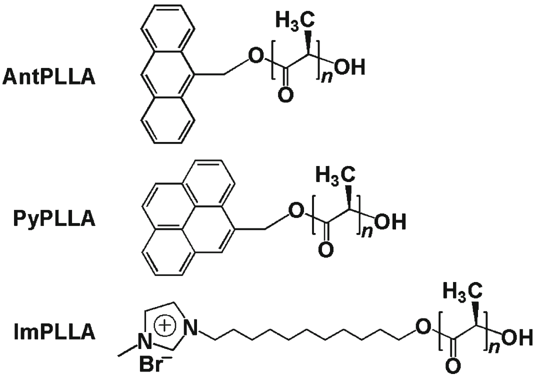


Fig. 15.8 Chemical structures of different groups end-functionalized poly(L-lactide)

end-functionalized poly(L-lactide) (ImPLLA) was synthesized by ring-opening polymerization of L-lactide in the presence of a hydroxylated IL as an initiator. For comparison, pyrene and anthracene end-functionalized PLLA, namely PyPLLA and AntPLLA, were also synthesized by the same method, using 1-pyrene- and 9-anthracenemethanol as initiators, respectively (Fig. 15.8). In order to evaluate the dispersing power of three PLLA samples toward MWCNTs in a given solvent, these samples were stirred overnight in chloroform at room temperature, followed by centrifugation for a moment to get different suspensions of PLLA and MWCNTs. It is observed that MWCNTs got sedimentated quickly from their suspensions with PyPLLA and AntPLLA, due to the weak interaction between the aromatic end groups and the surface of nanotubes. However, the MWCNTs dispersion with ImPLLA clearly showed a stable behavior over a period of about 2 months, which is attributable to the high binding ability of imidazolium moieties with the conjugated surface of MWCNTs. Similarly, a polyethylenimine-functionalized IL containing imidazolium cations was employed by Shan et al. [126] to construct a novel glucose biosensor based on MWCNT-AuNP-PFIL-GOD thin film at a GC electrode. This IL was used for the exfoliation of MWCNTs and protection of AuNPs to achieve a uniform MWCNT, AuNP, and GOD composite. The resulting composite film retains the bioactivity of GOD and exhibits a good electrochemical response to glucose, leading to an excellent possibility for glucose biosensing. Therefore, the use of imidazolium rings as modifiers for polymers appears as an efficient, rational, and reliable strategy for the dispersion of CNTs in solvents and polymer matrices through noncovalent interactions.

Hitherto, there have also been some reports on the use of polymers containing ionic moieties except for polymeric ILs to functionalize CNTs [127–130]. For instance, Yoshida et al. [128] found that a slightly concentrated solution (20 g/L) of an ionic electrolyte of poly(pyridinium-1,4-diyl-iminocarbonyl-1,4-phenylene-methylene chloride) was most appropriate for stable dispersion of SWCNTs in water to form a SWCNT-containing gel. This ionic polymer, capable to act both as a "dispersant" and as a "gelator," may contribute to the development of a novel hydrogel filled with CNTs for the biological, medical, and pharmaceutical applications.

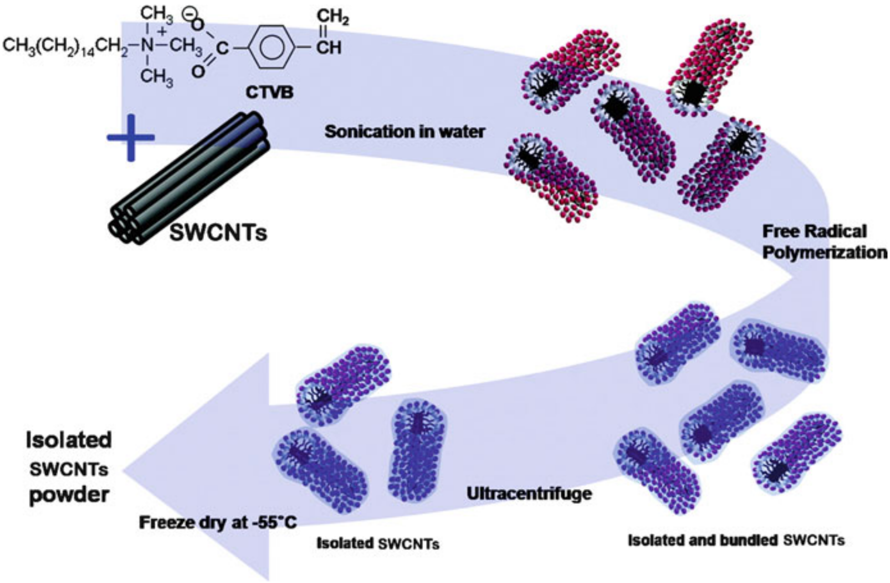


Fig. 15.9 Schematic view of the procedure to fabricate the polymer cationic surfactant/SWCNT composite (Reproduced from Ref. [130] with kind permission © The American Chemical Society)

It is particularly worth noting that Kim et al. [129, 130] developed an effective method to functionalize SWCNTs by directly polymerizing a cationic surfactant. As shown in Fig. 15.9, SWCNTs were first dispersed in water with the aid of cetyltrimethylammonium 4-vinylbenzoate (CTVB), followed by polymerizing CTVB molecules to cover the surface of SWCNTs, and then freeze-drying to obtain a powder of PCTVB-coated SWCNTs. The resulting PCTVB/SWCNT composite is highly dispersible in alcohols and water by simple vortex mixing or mild sonication and predominantly exists as individually isolated nanotubes. Moreover, this composite can be readily redispersed after their dispersions are completely dried, demonstrating excellent stability of the polymerized surfactant layer on the surface of SWCNTs. This method makes possible to prepare highly dispersible nanotubes in suspension and provides new opportunities for further solution processing in various practical applications.

15.4.3 Ionic Liquids–Assisted Preparation of Inorganic Carbon Nanotube Composites

Over the last decade, ILs have been actively utilized for the preparation of a variety of inorganic materials, including metal particles, metal oxides, metal salts, and nonmetal elements, due to their unique roles in the structural templates, coordination

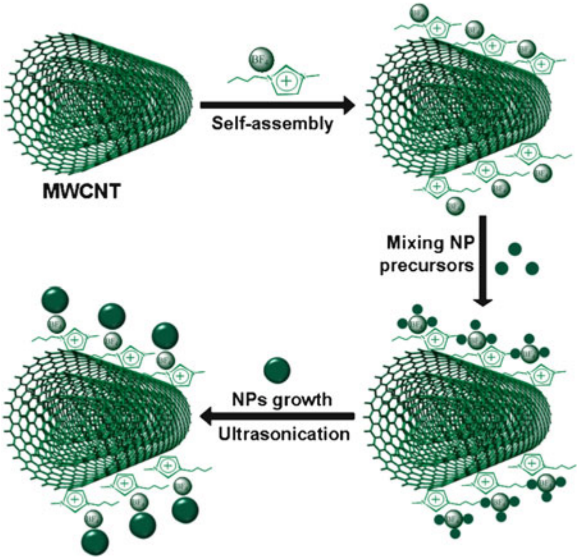


Fig. 15.10 Illustration for synthetic process of IL-assisted sonochemical method (ILASM) to fabricate the CNT-based nanohybrids functionalized with nanoparticles (NPs)

abilities and precursors to materials [131–133]. On the other hand, CNTs have proved to be excellent nanoparticle supports due to their unique geometry and properties [134]. Recently, usefulness of ILs to fabricate inorganic CNT composites has been gradually realized due to the unique properties and the additional benefits in the effective exfoliation and uniform dispersion of CNTs.

Mao et al. [135] fabricated the multifunctional $BmimPF_6$-MWCNT bucky gel through grinding them with cobalt porphyrin (CoP) and Prussian blue (PB) NPs. The resulting gel not only serves as a "reservoir" to homogeneously "culture" the tailor-made electrocatalysts but also enhances the electrocatalytic activities of the "cultured" dual electrocatalysts toward the reduction of O_2 into H_2O_2 by CoP and H_2O_2 into H_2O by PB NPs, respectively. The same group reported an electrochemical method for in situ deposition of Pt NPs onto MWCNTs to form a three-dimensional uniform Pt/MWCNT nanocomposite [136]. In this work, chloroplatinic acid (H_2PtCl_6) was dissolved into $BmimPF_6$ followed by grinding with MWCNTs in an agate mortar to form a homogeneous and electronic conductive gel matrix. The Pt/MWCNT nanocomposite was finally achieved by the electrochemical reduction of the H_2PtCl_6 precursor onto MWCNTs. Voltammetric study shows that the nanocomposite possesses excellent electrocatalytic activity toward the oxidation of methanol.

In particular, Hong et al. [137] developed a so-called IL-assisted sonochemical method (ILASM) to fabricate CNT-based nanohybrids functionalized with various NPs. As shown in Fig. 15.10, MWCNTs and $BmimBF_4$ were first mixed by mechanical grinding to produce $BmimBF_4$-wrapped MWCNTs ($BmimBF_4$-MWCNTs) due to the self-assembly of $BmimBF_4$ through cation–π and/or π–π stacking interactions. After that, the precursors of NPs were mixed with $BmimBF_4$-MWCNTs, resulting in the electrostatic interaction with BF_4 anions on the surface of MWCNTs. Finally, NPs were in situ grown and deposited onto the surface of $BmimBF_4$-MWCNTs during ultrasonic irradiation. The presence of $BmimBF_4$ not only acts as dispersants for MWCNTs but also provides active sites for the growth and decoration of NPs. Moreover, ILASM combines supramolecular chemistry between ILs and CNTs with sonochemistry, and it can readily control the size, amount, and distribution of various NPs (e.g., Pt, Pd, Au, Ag, SnOx, FeOx, ZnOx) by adjusting the sonication time and the concentration of NP precursors. Furthermore, they combined ILASM with the vacuum filtration method to fabricate a flexible and transparent, conducting AuNP/MWCNT film with improved optoelectronic properties [138]. It was found that AuNPs can be uniformly distributed onto the sidewalls of MWCNTs, and the resulting hybrid film gives more than twofold lower sheet resistance than the pristine MWCNT film. Also, Zeng et al. [139] reported an ultrasonic-electrodeposition method for the fabrication of highly dispersed PtM (M = Ru, Pd, and Au) NPs on the surface of IL-MWCNT composite film. Electrochemical observation indicates that PtM/IL-MWCNT-modified electrodes have large active surface and show high electrocatalytic activity for glucose oxidation in neutral solutions. These demonstrated strategies are facile, cost-effective, environmentally benign and versatile for developing the CNT-based inorganic materials with promising applications for smart devices, catalyst support, and fuel cells.

During fabrication of inorganic CNT composites, stable dispersion of NPs in water is important to realize their applications [140]. It has been found that functionalized ILs make the dispersed NPs much more stable in solution relative to the original ones [141]. Kocharova et al. [142, 143] found that IL-based surfactants were highly efficient for the functionalization of pristine SWCNTs to form stable aqueous suspensions. Recently, Cui and Zhang [144] found that two functional ILs of 1-carboxymethyl-3-methylimidazolium chloride (CMmimCl) and 1-aminoethyl-3-methylimidazolium bromide (AEmimBr), can be used to stabilize AuNPs and PtNPs in aqueous solution. All the IL-stabilized metal NPs could directly decorate on the pristine MWCNTs without additional additives. The resulting metal NP/MWCNT composites can be well dispersed in water, which might find future applications in catalysis, nanoscale electronics, and sensors. In contrast to the mentioned process by Cui and Zhang [144], AuNPs can be electrodeposited onto the surface of amine-terminated IL-SWCNT/GC electrode to create a glucose biosensor, due to the affinity of $-NH_2$ toward AuNPs [145]. Meanwhile, ILs assembled on SWCNTs and AuNPs can accelerate the electron transfer between GOD and electrode, leading to an excellent electrocatalytic activity to the reduction of glucose.

As described above, ILs for functionalization of CNTs are generally low molecular organic salts. Recently, Chen et al. [146] have employed PIL-functionalized MWCNTs to serve as the templates for fabrication of metal NP hybrids. In this method, the IL of 3-ethyl-1-vinylimidazolium tetrafluoroborate ($EVimBF_4$) was in situ polymerized to form a poly($EVimBF_4$) shell on the surface of MWCNTs (Fig. 15.11). This not only makes MWCNTs uniform dispersion in water but also serves as the medium to stabilize and grow metal NPs. It is noted that metal NPs (e.g., Pt, PtRu) are uniformly dispersed on the supported surface of poly($EVimBF_4$)/

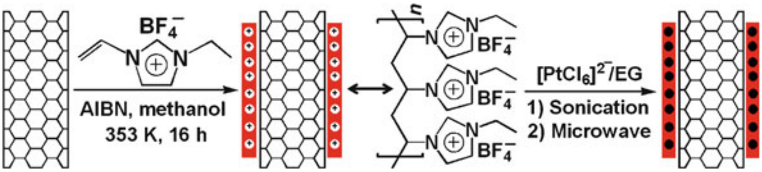


Fig. 15.11 Schematic diagram of the preparation of Pt/poly(EVimBF_4)/MWCNT hybrids (*EG* ethylene glycol, *AIBN* 2,2′-azobisisobutyronitrile)

MWCNTs with smaller sizes and better dispersion than those on MWCNTs without poly(EVimBF_4) modification, thereby showing better electrocatalytic properties toward methanol oxidation.

In contrast, recent experimental results [147, 148] and MD simulations [149, 150] have proved that ILs could be confined inside CNTs or between graphite walls and underwent a fully different phase transition, resulting in the formation of a high-melting-point crystal or solid. These phenomena are mostly due to the multiple stable hydrogen bonding networks when ILs enter into the narrow channel from the bulk phase. Recently, metal NPs intercalated into and encapsulated inside SWCNTs and double-walled CNTs have been successfully prepared by Kaneko et al. [151] using a plasma technique combined with the introduction of ILs under low gas pressures. It is found that the static plasma/IL interfaced field is advantageous to directly synthesize metal NPs in the nanospaces of CNTs. These results not only open an entry to understand the phase transition within the nanoscale confined spaces but also provide an opportunity to develop new types of CNT-based composites available for the construction of optoelectronic devices.

15.5 Covalent Grafting of Ionic Liquids onto Carbon Nanotubes

Immobilization of ILs on the solid supports has been well known for their combined advantages of ILs with those of heterogeneous supports [152–154]. The preference for the supported IL catalysts is primarily motivated by the advantages of convenient separation from the reaction mixtures and the ability to use fixed bed reactors. Immobilized ILs offer additional benefits that they can be used in gas-phase reactions due to low volatility and require a few amount of ionic phase compared to pure ILs and other biphasic catalysis system. On the other hand, physicochemical properties, especially hydrophilicity and hydrophobicity of ILs, are rationally tuned by changing cation and/or counter anions, thereby controlling the miscibility of ILs with organic solvents and water [155, 156]. The tunable properties of ILs would provide new opportunities for tailoring the final performance and engineering the surface of materials. Such attractive features have been receiving great attention in the covalent functionalization of CNTs with ILs in recent years.

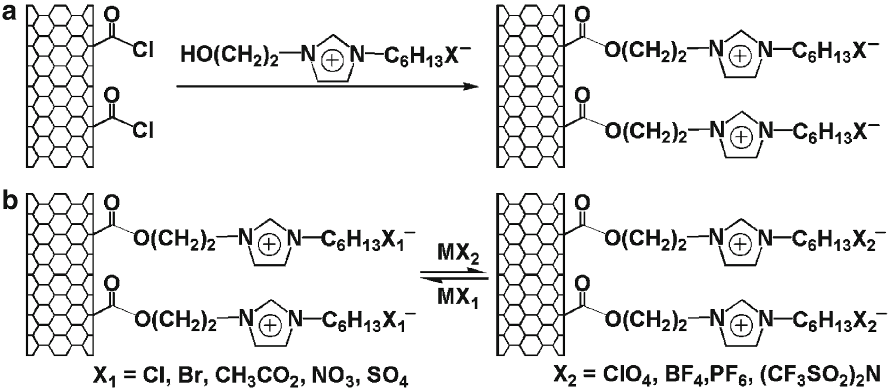


Fig. 15.12 (**a**) Schematic illustration of covalent functionalization of MWCNTs with hydroxyl-terminated ILs, X = Cl, Br, NO_3, SO_4, CH_3CO_2, BF_4, PF_6, ClO_4, and $(CF_3SO_2)_2N$, and (**b**) reversible solubility of IL-functionalized MWCNTs in aqueous and organic solvents by anion exchange

15.5.1 *Grafting of Ionic Liquids for Improving Surface Properties of Carbon Nanotubes*

Lee et al. [157] demonstrated for the first time the preparation of covalently functionalized MWCNTs with imidazolium-salt-based ILs. Briefly, pristine MWCNTs were chemically oxidized in a nitric acid solution under sonication to produce carboxylic acid-modified MWCNTs, followed by reacting with thionyl chloride and *n*-butyl bromide (BuBr) in turn to afford 1-butylimidazolium bromide salt-functionalized MWCNTs (MWCNT-imBr). The bromide anion of MWCNT-imBr was further exchanged with BF_4^-, PF_6^-, and NTf_2^- [*N*,*N*-bis((trifluoromethyl)sulfonyl) amide] by metathesis to give MWCNT-imBF_4, MWCNT-imPF_6, and MWCNT-imNTf_2, respectively. The relative solubility of the functionalized MWCNTs in water and organic solvents can be varied depending on the nature of counteranions, and the water-soluble MWCNT-imBr can be phase-transferred to the chloroform phase from the aqueous phase through anion exchange with NTf_2^-. Especially, all imidazolium-salt-functionalized MWCNTs show a preferential solubility in a hydrophobic IL, BmimNTf_2 (Bmim = 1-buthyl-3-methylimidazolium).

A sequential chemical processing of acidification-acylation-esterification was adopted by Liu et al. [60] to perform the functionalization of MWCNTs with 1-hydroxyethyl-3-hexylimidazolium chloride (HEHimCl), as shown in Fig. 15.12, resulting in the HEHimCl-functionalized MWCNTs (MWCNT-imCl). After that, other functionalized MWCNTs with different counteranions were obtained by the bromide anion exchange of MWCNT-imCl with an excess of other target anions. It was found that IL-modified MWCNTs by hydrophilic anions (Br^-, $CH_3CO_2^-$, NO_3^-, and SO_4^-) were water soluble, and MWCNTs substituted with lipophilic anions (BF_4^-, PF_6^-, ClO_4^-, and Tf_2N^-) were easily soluble in CH_2Cl_2. Of interest, the

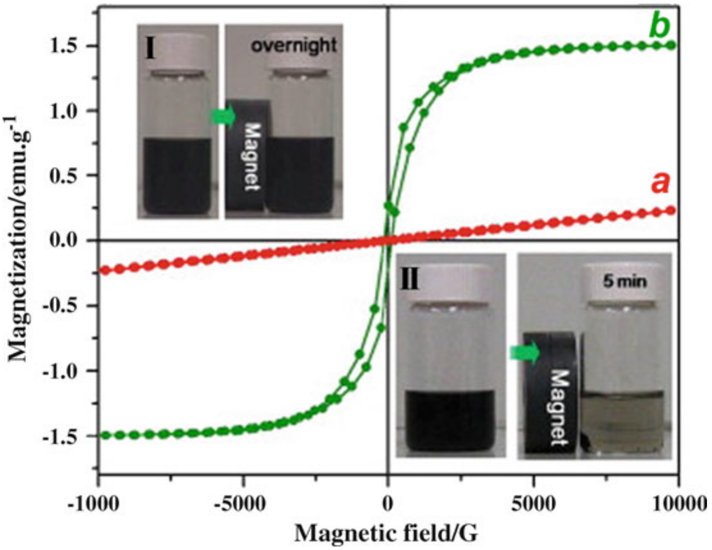


Fig. 15.13 Magnetic hysteresis of (**a**) pure $BAPimFeCl_4$ and (**b**) SWCNT-$imFeCl_4$. Magnetic responsive behavior of as-received SWCNTs (Inset I) and SWCNT-$imFeCl_4$ (Inset II) dispersed in *N*-methyl pyrrolidone (NMP) (Reproduced from Ref. [164] with kind permission of © Elsevier)

solubility of IL-modified nanotubes can be reversibly switched between water solubility and oil solubility by simple anion exchange. For instance, the hydrophobic MWCNT-$imPF_6$ in CH_2Cl_2 can transfer into the water phase upon mixing with an aqueous solution of NaCl, $NaNO_3$, NaAc, or Na_2SO_4. Besides, chemical modification of MWCNTs with ILs also facilitates the dispersion and solubility of MWCNTs in ILs, especially in structurally similar ILs. Covalent immobilization of ILs bearing different anions onto SWCNTs was also carried out by coupling of carboxylic-acid-functionalized SWCNTs with 1-propylamine-3-methylimidazolium bromide (PAmimBr) followed by a simple anion-exchange reaction [158]. To be specific, the properties derived from anions (Br^-, BF_4^-, PF_6^-, and polyoxometalates) can be delivered into the IL-modified SWCNTs, thereby modulating their tunable wettability and functionality. IL-functionalized CNTs have promised potential applications in electrochemical biosensors [159, 160], lubricants [161, 162], and nanofluids [163].

Interestingly, Chan-Park et al. [164] coupled acylated SWCNT with a magnetic NH_2–IL of [1-butyl-3-aminopropylimidazolium]$FeCl_4$ ($BAPimFeCl_4$) to afford a new magnetically responsive material (SWCNT-$imFeCl_4$). As shown in Fig. 15.13, SWCNT-$imFeCl_4$ is easily dispersed in NMP and can be quickly (less than 5 min) separated from its suspension using a magnet (Inset II). The dispersion/separation process is reversible and can be readily reproduced, thus leading to a convenient manipulation of CNTs under magnetic field. In contrast, the as-prepared SWCNTs are not responsive to the external magnetic field (Inset I), although they can be

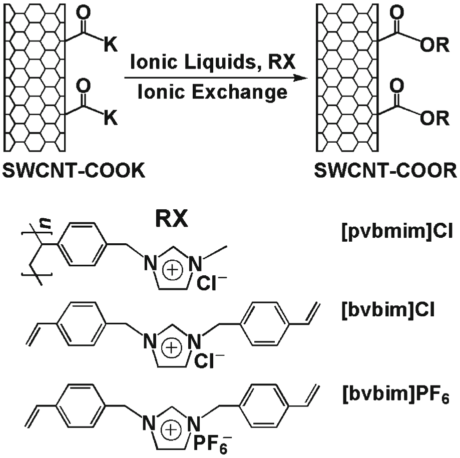


Fig. 15.14 Schematic illustration of fluorescent imidazolium salts modified SWCNTs

stably dispersed in NMP during ultrasonication. Besides, the magnetization of pure BAPimFeCl_4 displays a linear field dependency in the range of −10, 000 to 10, 000 G (Fig. 15.13a), corresponding to a typical paramagnetic behavior. The magnetic susceptibility (M_s) of BAPimFeCl_4 is found to be 2.4×10^{-5} cm^3/g; however, the M_s value for SWCNT-imFeCl_4 dramatically increases to 1.49 emu/g according to its hysteresis loop (Fig. 15.13b). Therefore, SWCNT-imFeCl_4 has a strong magnetic response due to the covalently attached magnetic IL shell on the surface of SWCNTs. This novel magnetic CNT-based material is anticipated to have potential applications in biomedical and bioengineering fields, especially for targeted drug delivery, controlled release, and protein separation.

Recently, Lu and Dyson et al. [165] have succeeded in attaching the fluorescent imidazolium salts to SWCNTs through metathesis of potassium ions (K^+) in the carboxylate salt of SWCNTs (SWCNT-COOK) with imidazolium cations (Fig. 15.14). The resulting composites form a typical core-shell nanostructure in which SWCNT acts as the hard core and imidazolium salts as the soft shell. It is found that the composites possess a high fluorescence quantum yield and retain one-dimensional electronic states of SWCNTs, which make them suitable for applications in photoresponsive materials, biomedical probes, and fluorescent nanosensors. Of interest, coupling of carboxylate SWCNTs with polyethylene glycol-substituted tertiary amine results in a meltable, amphiphilic nanotube derivative [166]. This special composite can undergo a reversible transition from waxy solid to tar-like liquid at 35°C, and can be highly dispersible in both aqueous and organic media to form stable sols. Afterward, Xiong et al. [167–169] also found that polysiloxane quaternary ammonium salt, poly(ethylene glycol) (PEG)-functionalized sulfonate salt, and PEG-substituted tertiary amines could interact with shortened carboxylate MWCNTs to yield the modified MWCNTs with an ionic-liquid-like behavior (referred to as CNT-based ionic liquids, CNT-ILs) at a given temperature. The entangled nanotube bundles are effectively exfoliated into much finer ones upon the formation of CNT-ILs. These results would offer a new process for the preparation of the CNT composites from “solid CNTs” and facilitate the applications of CNTs in nanocomposites, lubricants, nanofluids, and related fields.

15.5.2 Deposition of Nanoparticles onto Ionic-Liquid-Grafted Carbon Nanotubes

Note that covalently functionalized CNTs with ILs are well soluble and dispersed in water or organic solvents [60, 157–169]. These features are critically important and also highly advantageous to the fabrication of supported IL phase catalysts on the solid supports [152–154]. For example, rhodium (Rh)-based IL phase catalysts could be prepared using the functionalized MWCNTs as solid supports [170], in which MWCNTs were chemically treated in turn by oxidization in HNO_3, acylation in $SOCl_2$, amidation with amine-terminated imidazole, and quaternization with BuBr, followed by anion exchange with KPF_6, affording imidazolium-based ILs bearing PF_6^- modified MWCNTs. The resulting Rh/MWCNT-IL composite catalysts showed higher stability and catalytic activity for 1-hexene hydrogenation than other IL catalysts supported on oxide, silica, and activated carbon. Also, Lee et al. [171] successfully deposited PtNPs onto the imidazolium bromide IL-modified MWCNTs (MWCNT-imBr) through hydrogen reduction of Na_2PdCl_4 in an aqueous solution. The experimental conditions are relatively mild without the aid of surfactants due to excellent solubility, stability of MWCNT-imBr in water, and its coordination ability toward metal. Moreover, direct anion exchange of Br^- in Pd/MWCNT-imBr to hydrophobic NTf_2^- and SbF_6^- anions can be performed without changing the size and distribution of PdNPs around MWCNTs, resulting in the hydrophobic Pd/MWCNT-imNTf$_2$ and Pd/MWCNT-imSbF$_6$ hybrids, respectively. Among these, the Pd/MWCNT-imSbF$_6$ hybrid shows superior catalytic activity compared with the Pd/MWCNT-imBr and Pd/MWCNT-imNTf$_2$ composites. Meanwhile, the Pd/MWCNT-imSbF$_6$ can be effectively immobilized in BmimSbF$_6$ with extraordinary stability and easily recovered by simple phase separation, consequently creating a new recyclable IL-based catalytic system that allows up to 50 times recycling.

Similarly, AuNPs were electrodeposited onto the surface of PAmimBr-modified SWCNTs by in situ chemical reduction of $HAuCl_4$ [145, 172]. Control experiments prove that the presence of both ILs and Au significantly increases the electrocatalytic activity of SWCNTs toward oxygen reduction, relative to the GC electrode [172]. Furthermore, GOD was assembled on this AuNP/SWNT-IL composite through ionic interaction. This composite provides an excellent microenvironment and accelerates electron transfer between GOD and electrode because of the presence of IL and nanotube. The resultant GOD-modified electrode exhibits an excellent electrocatalytic activity to the reduction of glucose, indicating the potential to construct a novel glucose biosensor [145]. Hou et al. [173] also employed the HEHimCl-functionalized MWCNTs as a support to fabricate the Au/MWCNT-IL hybrid in which the IL layer acts as interlinkers.

15.6 Concluding Remarks

Impressive progress has been made in the functionalization of CNTs with ILs over the last decade. It has been clearly demonstrated that ILs are excellent functional modifiers for CNTs and provide an effective impetus toward expanding the scope of their applications. As green solvents and dispersants, ILs not only improve the dispersibility and stability of nanotubes in reaction media during functionalization but also enhance the functionalization effectiveness as a result of shorter reaction time and faster reaction rate compared to the functionalization performed in conventional organic solvents. In particular, covalent attachment of IL moieties to CNTs allows to chemically tailor surface properties and electronic structures of the latter, whereby new functions are created that cannot otherwise be implemented by pristine CNTs. The resulting IL-grafted CNTs can exhibit reversibly switchable solubility between water and organic solvents through anion exchange. This enables researchers to easily manipulate and process CNTs in solvents or even in solvent-free conditions (for ionic-liquid-like CNTs) and facilitates the practical applications of CNTs in functional devices, lubricants, nanofluids, and other related fields.

The integration of CNTs with ILs has allowed the fabrication of multifunctional materials, such as bucky gels, polymer/CNT nanocomposites, and inorganic materials containing metal NPs. CNT bundles can be quickly exfoliated into smaller ones, even individuals through mechanically grinding with ILs to form bucky gels, in which CNTs are well dispersed and stable in ILs, organic solvents, water, and polymer matrices as well. Bucky gels combine excellent electrical properties and high specific surface area of CNTs as well as high ionic conductivity and wide potential window of ILs and provide great potentials in the field of multifunctional electrochemical sensors and actuators. Especially, the unique geometry of CNTs makes them excellent solid supports for NPs; meanwhile, ILs can be capable of acting as stabilizers and surfactants during in situ deposition of NPs onto the surface of CNTs. The resulting metal NP/CNT inorganic composites mediated by ILs enable the use of the hybrid systems as heterogeneous phase catalysts, active transistors, immunosensors, functional electrodes, and other biosensors due to the combined advantages of CNTs, ILs, and metal NPs.

It is becoming increasingly clear that it is possible to construct the elastic polymer conductors by incorporating ILs into the polymer/CNT composites. The presence of ILs facilitates the homogeneous dispersion of CNTs in polymer and enhances the interface binding between CNTs and polymer, resulting in the excellent electrical, thermal, and mechanical properties for the composites. Such materials are promised to have potential applications in fully plastic actuators and large-area electronic integrated circuits, especially for constructing electromechanical devices on the arbitrary curved surfaces and movable parts. In particular, polymeric ionic liquids combine the advantages of conventional polymers (stability, processability, and durability) and polyelectrolytes (eletrochemistry) with the unusual properties of CNTs and may open up a new avenue for the development of high-performance polymer-based nanocomposites.

ILs, as optimal modifiers, have played an increasingly important role in the functionalization of CNTs through covalent or noncovalent methodologies. Large evidences have being accumulated indicating that ILs can act not only as green solvents and excellent dispersants to exfoliate and stabilize CNTs in solvents and various matrices, as compatibilizers to improve the interface binding between multiple components, but also as multifunctional additives to endow the final composites with new functions. However, there are several problems to be solved in the future. Firstly, possible "cation–π" and/or "π–π" interactions between ILs and CNTs have been proposed to account for the dispersion process from entanglement to disaggregation of nanotube bundles, but this mechanism has not inversely acceptable and is still open for debate. It needs to be carefully concluded through a deep combination of experimental data and theoretical simulation. Secondly, ILs have a relatively high viscosity and polarity as compared to common solvents, and there may encounter some new, unknown phenomena when using ILs as reaction media to covalently functionalize CNTs. Thirdly, using ILs to directly graft CNTs inevitably involves the structural damages (tube breakage, tip or sidewall opening), thereby adversely affects the final performance of CNTs. Meanwhile, isolated nanotubes through noncovalent functionalization are stable only for limited time in some cases and even revert to bundles. Using poly(ionic liquid)s to functionalize CNTs should be an optimal method in which pristine or purified CNTs are only physically wrapped by poly(ionic liquid) chains. Finally, the combined advantages of IL/CNT multifunctional composites are anticipated to have great potentials in practical applications. Notably absent, however, are contributions developing theoretical description and practical products to help better characterize these complex systems and facilitate their industrialization. Moreover, some of methods to functionalize CNTs with ILs would be applicable for the functionalization of graphene since they represent similar conjugated structural features and physicochemical properties.

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Chapter 16
Room Temperature Ionic Liquids (RTILs) Versus Volatile Organic Compounds (VOCs) in Organic Electrosynthesis: The Requirement of a Careful Comparison

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Abstract The possible utilization of room temperature ionic liquids (RTILs), instead of volatile organic compounds (VOCs), in the electrochemical procedures of organic synthesis has been discussed. The synthesis of $\beta-$lactams, the activation of carbon dioxide and its utilization as renewable carbon source and the carbon–carbon bond formation reactions via umpolung of aldehydes (benzoin condensation and Stetter reaction) and via Henry reaction have been selected as typical electrochemical methodologies. The results, related to procedures performed in RTILs, have been compared with those performed in VOCs. The double role of RTILs, as green solvents and parents of electrogenerated reactive intermediates or catalysts, has been emphasized.

16.1 Introduction

The present great demand for efficient and sustainable procedures to synthesize new complex molecular structures, with planned physical, chemical and biological properties, poses an exciting challenge to organic chemists [1, 2]. However, in the manufacture and application of chemical products, the setting-up of eco-friendly methodologies could involve very serious efforts. Actually, an efficient and serious green chemistry *utilizes (preferably renewable) raw material, eliminates*

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waste and avoids the use of toxic and/or hazardous reagents and solvents [3–7]. In addition, the effectiveness of a green procedure must be controlled evaluating, inter alia, the relevant values of the E factor [8] and of the atom economy [9, 10]. Significant goals are obtained by elimination of solvents (the best solvent is no solvent) or by substitution of volatile and toxic organic solvents (VOCs) with benign green solvents, as well as by utilization of alternative eco-friendly methodologies. Room temperature ionic liquids (RTILs) and the electrochemical methodology are indicated by many authors as green solvents and green methodology, respectively.

Accordingly, in the first part of the chapter, we wish to discuss (a) the reason, the problems and the limitations of electrochemistry as a possible eco-friendly methodology in organic synthesis; (b) the utilization of RTILs instead of VOC-supporting electrolyte systems in the electrochemical methodology; and (c) the possible double role of ionic liquids as pre-catalysts and green solvents.

In the second part, we want to report some significant procedures of electrosynthesis, carried out in RTILs as well as in VOC-supporting electrolyte systems, including a comparison between the results obtained according to the two different procedures. The synthesis of β-lactams, the utilization of CO_2 as renewable carbon source and the carbon–carbon bond formation via umpolung of aldehydes (benzoin condensation, Stetter reaction) and via Henry reaction have been selected as typical procedures.

16.2 Organic Electrosynthesis: Reasons and Limits of an Eco-friendly Methodology

The reactions of organic synthesis are related to many steps (bond breaking, bond formation, atom or group transfer) frequently triggered, or anyway associated, with electron transfer processes [11]. In principle, every step may be able to affect the efficiency of the overall reaction.

In a classical organic synthesis (e.g. in a procedure carried out in homogeneous liquid phase), the electron transfer may be regarded as a process in which an electron is transferred from the electron-donating species (the reducing agent) to the electron-accepting species (the oxidant agent). Accordingly, at the end of the procedure, the product related to the reduction of the electron-accepting species as well as the one related to the oxidation of the electron-donating species are both present in the crude of the reaction. Nevertheless, only one of these products is the effective goal in the synthetic design. In addition, when a single group present in polyfunctional molecules, it must be selectively modified, via an electron transfer.

Sometimes the electrochemical methodology is able to resolve these troubles. In a procedure of electrochemically induced organic synthesis (e.g. by electrolysis carried out in a divided cell, of a solvent-supporting electrolyte solution containing the dissolved electroactive substrate), the role of electron-donating and electron-accepting agents with respect to the substrate is performed by the metallic surfaces of the electrodes [12, 13]. Thus, the electrode serves essentially as an 'innocent' electron reservoir or sink [14]. The presence of both the by-products (sons of the reductive or oxidant agent) in the same solution can be avoided. In addition, as the electrode potential of the metallic surfaces can be prefixed, the driving force of the reaction may be adjusted according to the selective transformation of the specific group present in a polyfunctional substrate.

The usefulness of electrochemical methodology in organic synthesis is related to its power to improve the reactivity of organic molecules by selective reversal of functional groups. This aim can be achieved by modifying (via an initial electron transfer between the electrodic surface and the substrate) the functional groups present in the original structure of the substrate. According, highly reactive intermediates (radicals, cations, anions) could be produced selectively, in mild conditions, and generally at room temperature. These intermediates evolve via intra- or intermolecular reactions. The intermolecular reactions can involve the 'parent' molecule, the solvent, the supporting electrolyte as well as electroinactive substrates purposely added to the solution [15–21].

Accordingly, the generation of the intermediates must be regarded as the heart of an electrochemical procedure of organic synthesis. Therefore, a correct planning of an electrochemical synthetic process requires a deep knowledge of the conditions of formation and of the reactivity of the intermediates.

Classical organic electrosyntheses are frequently performed in a solvent-supporting electrolyte system containing the dissolved electroactive substrate at a moderate concentration. The reactivity of the electrogenerated intermediates as well as the rate of the electron transfer process (from the electrode to the substrate) can be significantly affected by the nature of the solvent and of the supporting electrolyte.

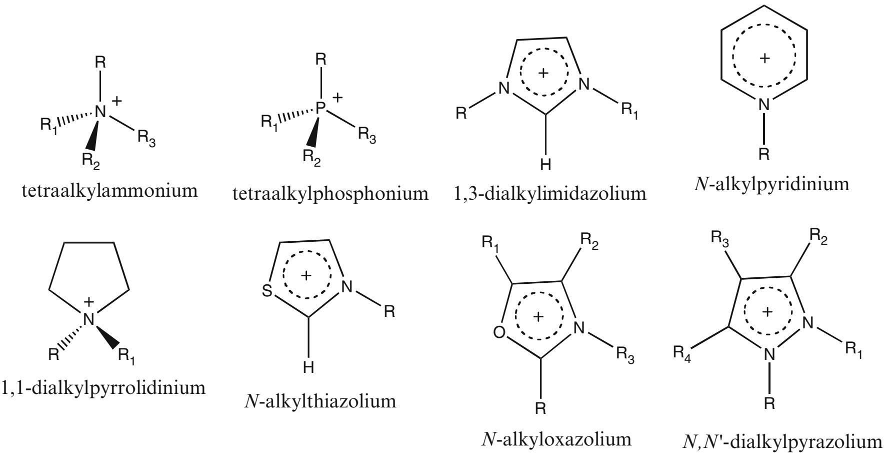
Factors as proton activity, usable potential range, dielectric constant, ability to dissolve electrolytes and substrates, ion pair formation, vapour pressure, viscosity, toxicity (as regards the solvents) and solubility, dissociation constant, mobility and discharge potential (as regards the supporting electrolytes) must be carefully evaluated.

Frequently volatile and toxic solvents (VOCs: DMF, DMSO, MeCN, hexamethylphosphoramide HMPA, N-methylpyrrolidone, pyridine, etc.) containing a large amount of salts (e.g. nitrate, perclorate, tetrafluoroborate, hexafluorophosphate of lithium, magnesium, sodium, tetraalkylammonium, etc.) have been used as solvent-supporting electrolyte systems. The large amounts of salts, comparable or greater than the one of the electroactive substrate, can create problem for the isolation and purification of the product of the electrochemical procedure. In addition, the use of VOCs involves a serious responsibility as concerns the recovering and/or the disposal of the solvents.

16.3 Room Temperature Ionic Liquids (RTILs) as Possible Green Solvents

As previously emphasized by other authors, the definition of ionic liquids given by Paul Walden is still acknowledged: *they are materials composed of cations and anions, that melt around 100°C or below as an arbitrary temperature limit* [22]. Although the first ionic liquid (ethylammonium nitrate) with melting point below the room temperature was reported in 1914, only half a century later, a class of ionic liquids (chloroaluminate-based ionic liquids) was extensively investigated according to a possible utilization in electrochemical technologies [23, 24]. At present, air- and moisture-stable room temperature ionic liquids (RTILs) are regarded as a class of salts resulting from the association of large organic cations (Fig. 16.1) (tetraalkylammonium, tetraalkylphosphonium, 1,3-dialkylimidazolium, N-alkyl-pyridinium, 1,1-dialkylpyrrolidinium, N-alkylthiazolium, N-alkyloxazolium, N,N-dialkylpyrazolium, etc.) with weakly coordinating anions (BF_4, PF_6, SbF_6, $ZnCl_3$, $N(Cf_3SO_2)_2$, $N(C_2F_5SO_2)_2$, $N(FSO_2)_2$, $C(CF_3SO_2)_3$, etc.).

The unique and attractive physico-chemical properties of RTILs are well known and have been reported by many authors, which include negligible vapour pressure, low combustibility, broad solubility range, high thermal and chemical stabilities, catalytic properties (they act both as solvents and as catalysts), large electrochemical window, high electrical conductivity, possible recycling, ability to increase the reactivity as well as the selectivity of some processes and facile product separation, etc. A lot of applications in different fields have been suggested: energy (battery, fuel cell, heat storage), chemistry (organic synthesis, polymerization, analytical chemistry, surfactants), biotechnology (biocatalysis, protein



tetraalkylammonium tetraalkylphosphonium 1,3-dialkylimidazolium *N*-alkylpyridinium

1,1-dialkylpyrrolidinium *N*-alkylthiazolium *N*-alkyloxazolium *N,N'*-dialkylpyrazolium

Fig. 16.1 Structures of organic cations of the most extensively utilized RTIL in organic synthesis purification), chemical engineering (extraction, separation, liquid membrane), new materials (liquid crystal, nanoparticles), coating (surfactant, lubricant, metal deposition), etc. [25–32].

The peculiarities of several RTILs, with different cation–anion combinations, have been carefully evaluated. This investigation shows that, as the properties of RTILs are affected by the nature of the anion and/or cation, it is possible to synthesize new RTILs with target properties, suitable for a specific application, varying the structure of the constituent ions. Accordingly, RTILs have been classified as 'designer solvents'. Nevertheless, owing to the complexity of the interionic interactions in RTILs, this design may not be always easy. Recently, possible correlations between ionic structures and physico-chemical properties have been reviewed and discussed [33–36].

Because of their specific properties, RTILs have been frequently used as green reaction media in clean organic synthetic processes as well as substitutes for conventional toxic and volatile solvents (VOCs). A lot of reactions have been re-examined and discussed using RTILs, instead of VOCs, and the results have been reported in papers and reviews [37–42].

As regards the organic electrosyntheses, owing to the wide electrochemical window, high intrinsic conductivity, recyclability and facile product separation, RTILs (in spite of the large viscosity and the related slow rate of diffusion) have been identified as alternative solvents, with respect to the VOC-supporting electrolyte systems, in which electrochemical processes (specifically, electro-organic syntheses) are being carried out [22, 43–46].

16.3.1 The Non-'innocent' Nature of Room Temperature Ionic Liquids (RTILs)

According to their negligible vapour pressure, low flammability, chemical and thermal stability, etc., ionic liquids have been frequently proposed as green solvents to replace volatile and toxic organic solvents (VOCs). Due to owing to the peculiar properties of every RTIL, related to the structure and to the specific combination cation/anion, the features of RTILs as green solvents cannot be generalized. Extensive investigations have been carried out to ascertain the effective chemical stability, environmental fate, toxicity and biodegradation. The results have been reported and carefully discussed in recent reviews [47–49].

Actually, because of the altered reactivity of some substrates dissolved in RTILs and the unexpected catalytic activity and unforeseen by-products formation, the possible non-innocent nature of many ionic liquids has been hypothesized by some authors [37].

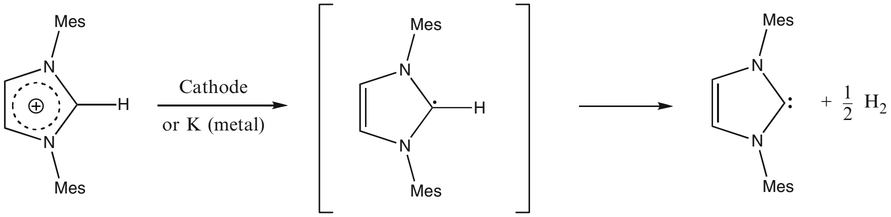
As regards imidazolium-based ionic liquids (the most extensively utilized RTILs in organic synthesis), their non-innocent nature may spring from the acidity of the C2-H group. Values of the pKa have been evaluated in the range 21–24

(H_2O, DMSO as solvents) [37, 47]. Recently, the peculiarities of the imidazolium cation have been extensively discussed [33, 50, 51].

Owing to the acidity of the C2-H, some bases are able to trigger under the deprotonation of 1,3-dialkylimidazolium cations yielding stable N-heterocyclic carbenes (NHCs) [37, 52]. The first stable N-heterocyclic carbene (1,3-di-1-adamantylimidazol-2-ylidene) was obtained by Arduengo et al. via deprotonation of imidazolium salts (NaH, dimsyl anion $^{-}CH_2S(O)CH_3$, THF as base, catalyst and solvent, respectively) [53, 54].

The basic nature of N-heterocyclic carbenes, stabilized by the presence of two adjacent N atoms, has been emphasized by several authors [38]. Therefore, the yield and the selectivity of any organic synthesis (driven by the reactivity of a substrate vs. appropriate bases and carried out in imidazolium salts as solvents) can be affected by side reactions related to the acidity of C2-H unit in 1,3-dialkylimidazolium cation and to the basicity and nucleophilicity of the resulting N-heterocyclic carbene. On this subject, noticeable work (related to the Baylis–Hillman, Knoevenagel and Claisen condensation, Horner reaction, etc.) carried out in RTILs has been reported and discussed [37].

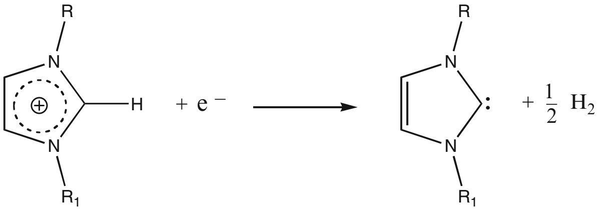
The chemical (via potassium metal) or electrochemical (via a glassy carbon cathode) reduction of 1,3-dialkylimidazolium cations was investigated by J. A. C. Clyburne et al. [55, 56]. The chemical reduction was carried out by refluxing a THF suspension of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride treated with a lump of potassium metal. The electrochemical reduction was investigated by cyclic voltammetry of DMF–dialkylimidazolium chloride solutions. The authors have suggested, in any case, a monoelectronic reduction of imidazolium cation to a radical intermediate and the following decomposition of the radical to N-heterocyclic carbene and dihydrogen (Scheme 16.1).



Scheme 16.1 Chemical and electrochemical reduction of 1,3-bis(2,4,6-trimethylphenyl)imidazolium cation (Reprinted from Ref. [55] with kind permission of © The Royal Society of Chemistry)

Accordingly, the large electrochemical window of 4.9 V evaluated via voltammetric measurements and constant current electrolyses in liquid Bmim-BF_4 in the absence of any organic classical solvent has been related to the cathodic reduction of imidazolium cation to carbene and to the anodic oxidation of BF_4^- to F_2 and fluorocarbons [57] (Scheme 16.2).

At the cathode:



At the anode:

$BF_4^- - e^- \longrightarrow BF_3 + \frac{1}{2} F_2$

$BF_3 + BF_4^- \longrightarrow B_2F_7^-$

$F_2 + \text{Bmim}^+ \longrightarrow$ fluorocarbons

Scheme 16.2 Cathodic and anodic behaviour of 1,3-dialkylimidazolium-BF_4 ionic liquids (Reprinted from Ref. [57] with kind permission of © The Electrochemical Society)

Therefore, a remarkable reactivity of the C2-H group versus reducing agents, in addition to the one versus bases, must be kept in mind: 1,3-dialkylimidazolium cations may be reduced to N-heterocyclic carbenes and dihydrogen. The reduction can be performed by chemical as well as by electrochemical (i.e. by the innocent cathodic surface) agents [55–59].

Recently, the reactivity (base, nucleophile, catalyst) and the role in modern organic synthesis of N-heterocyclic carbenes (cyclic carbenes bearing at least one amino substituent) has been set-up by Ender et al. [60, 61]. The possible utilization of NHCs as ligands for transition-metal catalyst [62, 63] and as organocatalyst has been emphasized [61]. The inversion of the normal reactivity (umpolung) induced via NHCs has been extensively discussed. Classical carbon–carbon-bond-forming reactions (benzoin condensation, Stetter reaction, etc.) have been re-examined using ionic liquids as pre-catalysts in the presence of bases.

According to the hypothesis of Clyburne et al. [55–59], concerning the electrochemical behaviour of imidazolium ions, the physico-chemical properties of an imidazolium-based ionic liquid can be strongly modified inducing (via a simple green cathodic reduction) the presence of N-heterocyclic carbenes.

The concentration of NHCs in RTILs can be easily prefixed via the control of the number of Faradays supplied to the electrodes during the electrochemical reduction. The complex reactivity of the N-heterocyclic carbene (strong bases, nucleophilic agent, catalysts) is affected by the particular structure and may be pre-arranged by a thorough design of the parent RTIL.

Therefore, RTILs may be considered versatile reaction media and a more extensive utilization in electro-organic synthesis must be supported. The possible utilization of

RTILs in the double role of green solvents and parents of electrochemically generated intermediates (bases and catalysts) to trigger a prefixed reaction of synthesis must be evaluated.

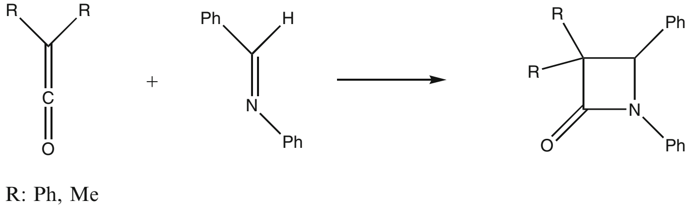
16.4 Synthesis of β-Lactams

Owing to their high antibiotic activity, β-lactams, natural and synthetic compounds containing the azetidin-2-one nucleus (a four-membered cyclic amide), have played an irreplaceable role in the fight against pathologic bacteria [64–67]. Recently, the possible anti-cancer activity of some β-lactams has been emphasized [67]. Because of the development of many resistant strains of bacteria, the synthesis of new β-lactamic structures (able to overcoming the increasing efficient defence mechanisms of bacteria) has become a necessity [68]. In addition to their significance as antibiotic agents, β-lactams are used as synthetic building blocks for a lot of transformations related to the selective bond cleavage (enhanced by the ring strain) of azetidin-2-one nucleus (β-lactam synthon method) [69–75]. Consequently, the set-up of new and more efficient strategies for the synthesis of the azetidin-2-one nucleus has been regarded as a significant target in organic chemistry and a large number of methodologies have been developed [76–83].

The Staudinger reaction, i.e. the [2+2] ketene–imine cycloaddition, is the most frequently employed procedure of synthesis of the azetidin-2-one nucleus. Base-promoted cyclization of suitable linear substrates is another frequently employed procedure. We wish to report the electrochemical methodologies of synthesis of β-lactams, according to both procedures, and the possible utilization of RTILs (as solvents and/or as parent of intermediates).

16.4.1 The Staudinger Reaction

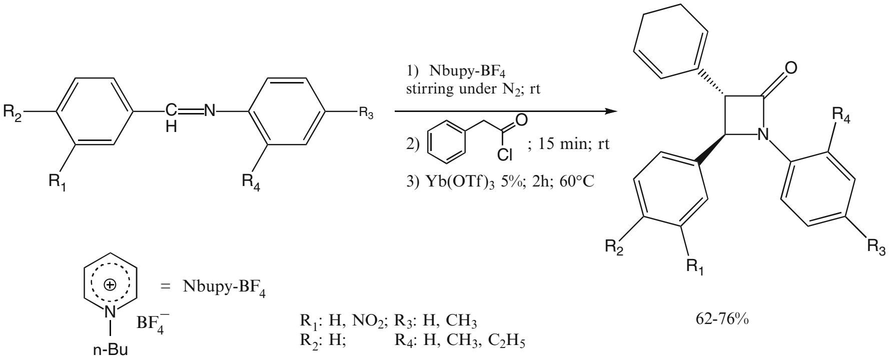
The understanding of the mechanism of the Staudinger reaction (Scheme 16.3) [84] is still a not completely resolved problem [85–89].



Scheme 16.3 Synthesis of the azetidin-2-one nucleus via the Staudinger reaction: the [2+2] ketene–imine cycloaddition

Therefore, some conclusions have been generally accepted and have been summarized as follows: 'the cycloaddition reaction is a stepwise reaction rather than a concerted one; the reaction is initiated by nucleophilic attack of an imine to a ketene, giving rise to a zwitterionic intermediate; a conrotatory electrocyclic ring-closure of the zwitterionic intermediate produces the final 2-azetidone product' [85]. As the stereochemistry of the structure of the β-lactams strongly affects their biological activity, the stereoselectivity of the process must be carefully considered. Uncatalysed as well as catalysed processes have been reported; organometallic and organic catalysts have been utilized in procedures oriented to the syntheses of enantiopure β-lactams [90–92].

The synthesis of the azetidin-2-one nucleus, via the classical annulation of acetylchlorides with imines, requires more than stoichiometric amounts of triethylamine (about 3 equivalent), which cannot be recovered and reused. In addition, the procedure needs a large amount of organic solvents (VOCs) and, as a consequence, causes a large amount of waste. To overcome these difficulties, the possible ytterbium (III) triflate–catalysed stereoselective synthesis of β-lactams via [2+2] cyclocondensation in ionic liquids has been investigated by Su et al. (Scheme 16.4) [93].

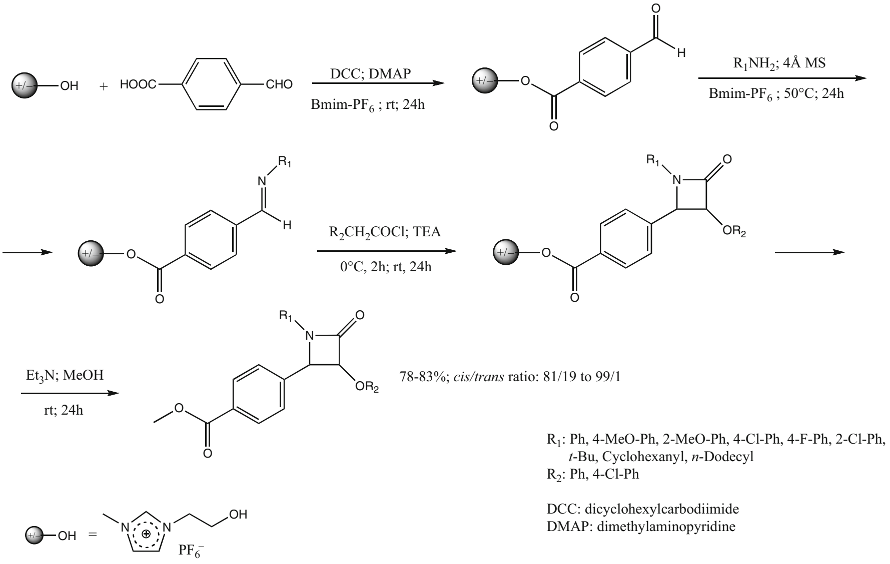


Scheme 16.4 Ytterbium (III) triflate–catalysed synthesis of β-lactams via [2+2] cyclocondensation in ionic liquids (Reprinted from Ref. [93] with kind permission of © Taylor & Francis)

The use of triethylamine and VOCs has been avoided. All products have trans-stereochemistry and are racemic mixture. Good yields of isolated β-lactams have been achieved (62–76%) only when R_1 is an electron-withdrawing group and R_3 and R_4 electron-donor groups. In the other cases, acylamides are the main products. Nevertheless, β-lactams have been isolated (at a lower yields, 34% vs. 62%) even if the procedure is carried out in RTILs in the absence of the catalyst. Entirely convincing explanations (one side of RTIL was alkaline) have not been reported by the authors.

The synthesis of β-lactams in ionic liquids, using functionalized ionic liquid as soluble supports, has been reported. β-Lactams have been isolated in elevated yields and high *cis/trans* ratio, according to a rather wearisome procedure and long reaction times.

Bmim-PF_6 (1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate) was used as solvent and hydemim-PF_6 (1-(2-hydroxyethyl)-3-methyl-1*H*-imidazolium hexafluorophosphate) was used as functionalized ionic liquid (so-called task-specific ionic liquid) (Scheme 16.5) [94].



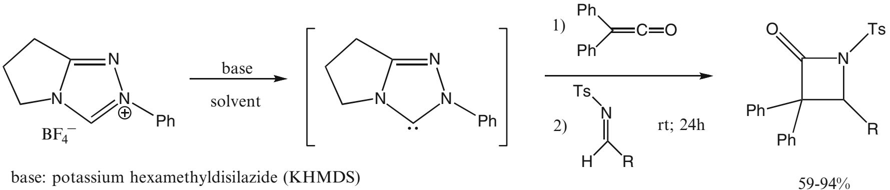
78-83%; *cis/trans* ratio: 81/19 to 99/1

R_1: Ph, 4-MeO-Ph, 2-MeO-Ph, 4-Cl-Ph, 4-F-Ph, 2-Cl-Ph, *t*-Bu, Cyclohexanyl, *n*-Dodecyl
R_2: Ph, 4-Cl-Ph

DCC: dicyclohexylcarbodiimide
DMAP: dimethylaminopyridine

Scheme 16.5 Synthesis of β-lactams using functionalized ionic liquid as soluble supports (Reprinted from Ref. 94 with kind permission of © Elsevier)

Recently, the ability of N-heterocyclic carbenes to promote the Staudinger reaction has been investigated using ionic liquids, in the presence of suitable base as pre-catalysts. According to the procedure suggested by Smith et al., a solution of base (potassium hexamethyldisilazide KHMDS, toluene as solvent) was added to the suspension of ionic liquid (triazolium salt) in Et_2O and stirred under N_2. Subsequently, the mixture was added of diphenylketene and of imine and stirred at room temperature before concentration in vacuo (Scheme 16.6). The order of addition of reactants is critical for the success of the synthesis [95].



base: potassium hexamethyldisilazide (KHMDS)
solvent: toluene, THF, CH_2Cl_2, $E_{t2}O$
R: Ph, 2-naphthyl, 2-furyl, 4-MeO-Ph, 4-Br-Ph, (E)-CH=CHPh

Scheme 16.6 Ionic liquids, in the presence of bases, as pre-catalysts in the Staudinger reaction (Reprinted from ref. [95] with kind permission of © The Royal Society of Chemistry)

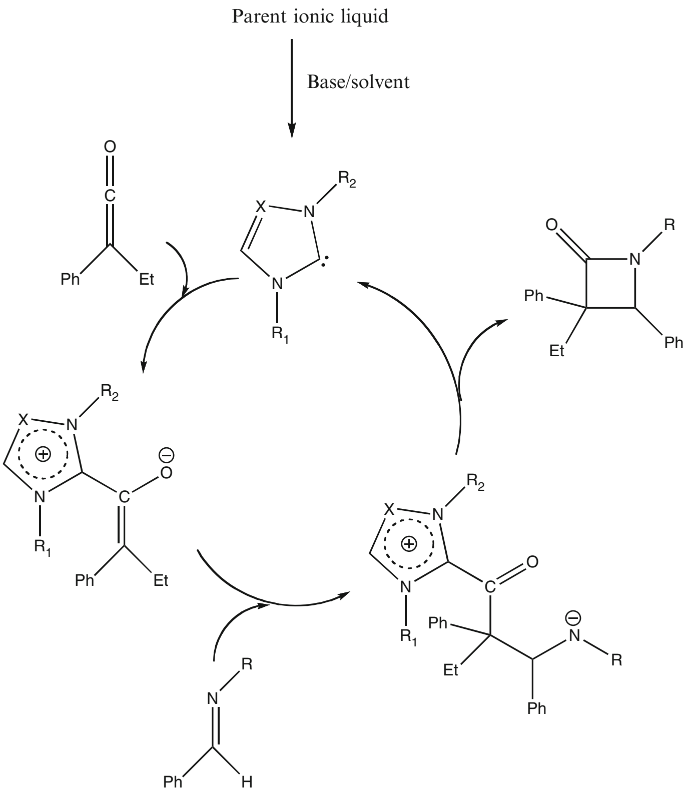


Fig. 16.2 1,3-Dialkylimidazol-2-ylidene as catalyst in the Staudinger reaction: a possible mechanism (Reprinted from Ref. [96] with kind permission of © The American Chemical Society)

N,N′–Bis(2,6-diisopropylphenyl)imidazol-2-ylidene (obtained at room temperature via base-promoted deprotonation of the parent imidazolium ionic liquid using THF as solvent) was utilized by Ye et al. to catalyse the Staudinger reaction of phenylethylketene with N-tosylphenylimide. The corresponding β-lactam has been isolated in good yield (87%; *trans/cis* ratio = 76/24) [96].

A possible mechanism has been suggested, based on the initial deprotonation of the parent ionic liquid and on the following nucleophilic addition of N-heterocyclic carbene to diphenylketene to generate the enolate intermediate (Fig. 16.2) [95, 96].

An alternative mechanism based on the nucleophilic activation of the imine has been proposed (‘imine first’ pathway) (Fig. 16.3) [96, 97].

Subsequently, the ability of enantiomerically pure N-heterocyclic carbenes (NHCs) to catalyse the enantioselective Staudinger reaction has been tested. Different NHCs, obtained via deprotonation by potassium hexamethyldisilazide KHMDS in Et_2O of the respective parent ionic liquids, are able to promote the cycloaddition of diphenylketene and N-tosylimide giving β-lactams in elevated yields and 55–75% e.e. (Scheme 16.7) [95].

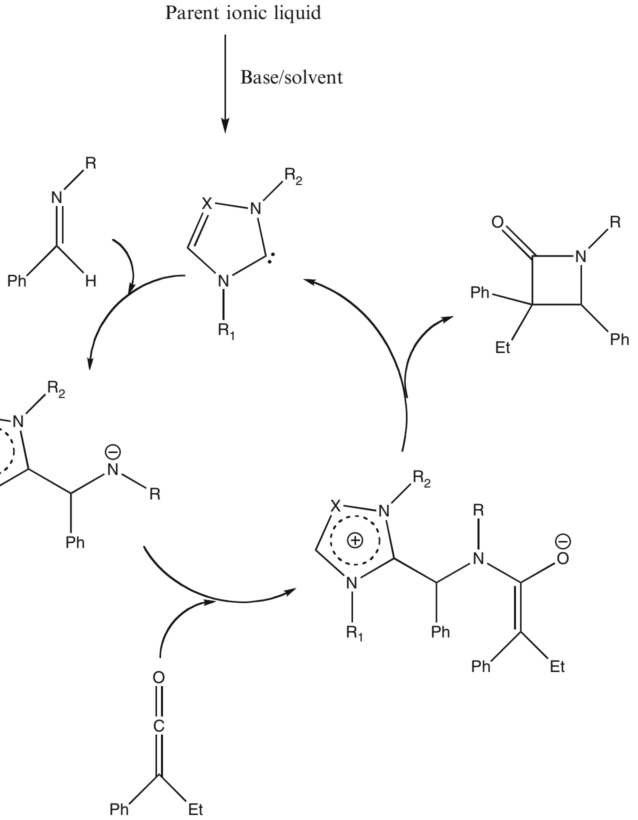
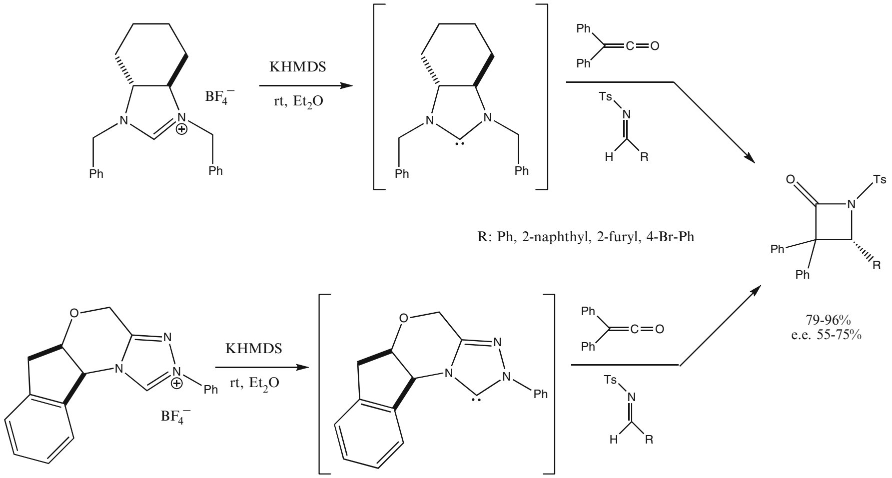
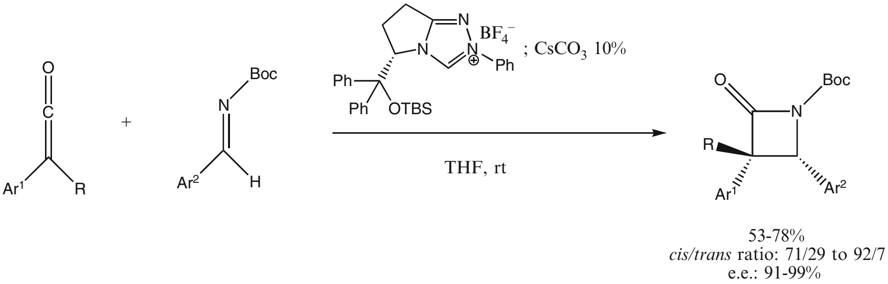


Fig. 16.3 1,3-Dialkylimidazol-2-ylidene as catalyst in the Staudinger reaction: an alternative mechanism (Reprinted from Ref. [96] with kind permission of © The American Chemical Society)



Scheme 16.7 NHCs as catalyst in the cycloaddition of diphenylketene and N-tosylimide giving β-lactams (Reprinted from ref. [95] with kind permission of © The Royal Society of Chemistry)

Ionic liquids have been proved to be efficient pre-catalysts (in solution of THF, containing 10% Cs_2CO_3) in the Staudinger reaction of arylalkylketenes with a variety of N-*t*-butoxycarbonyl arylimines to give the corresponding β-lactams in good yields with good diastereoselectivity and enantioselectivity (Scheme 16.8) [96].

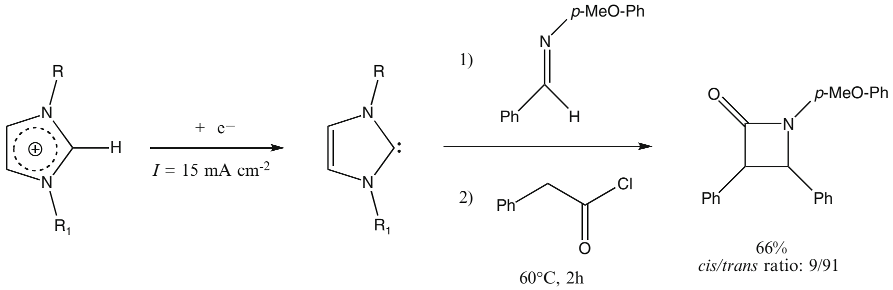


Scheme 16.8 Ionic liquids as pre-catalysts in the Staudinger reaction of arylalkylketenes with N-*t*-butoxycarbonyl arylimines (Reprinted from Ref. [96] with kind permission of © The American Chemical Society)

Finally, the enantioselective bicyclo-β-lactam formation, via direct annulation of enals and unsaturated N-solfonyl ketimines using N-mesityl-substituted triazolium chloride (in the presence of bases in organic solvents) as pre-catalyst, has been investigated by W. Bode et al. [98].

16.4.2 Electrochemically Promoted Staudinger Reaction in Room Temperature Ionic Liquids (RTILs)

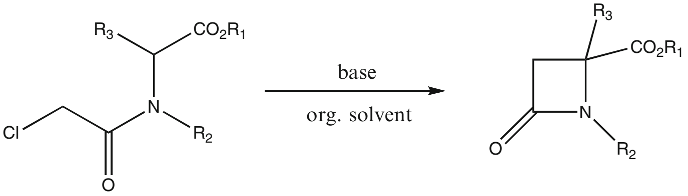
Recently, an electrochemical methodology for the synthesis of β-lactams, from imine and acyl chloride, using RTILs in the double role of pre-catalyst (i.e. of parent of N-heterocyclic carbene) and solvent, has been suggested. Bmim-BF_4 was electrolyzed under galvanostatic condition in a two compartment home-made cell. Electrolyses were carried out at 60°C, under nitrogen atmosphere, using Bmim-BF_4 as anolyte and catholyte. After the consumption of a prefixed number of Faradays (0.5 per mol of imine), the current was switched off and imine was added to the catholyte under stirring; when the dissolution was complete, phenylacetyl chloride was added. The mixture was kept at 60°C for 2 h. β-Lactam was isolated in good yield (66%; *cis/trans* ratio: 9/91). The use of organic solvents (VOCs) as well as the addition of base are not required (Scheme 16.9) [99].



Scheme 16.9 RTILs, as pre-catalyst and solvent, in the electrochemical synthesis of β-lactams (Reprinted from Ref. [99] with kind permission of © the Royal Society of Chemistry)

16.4.3 Base or Electrochemically Promoted Cyclization in Volatile Organic Compounds (VOCs)

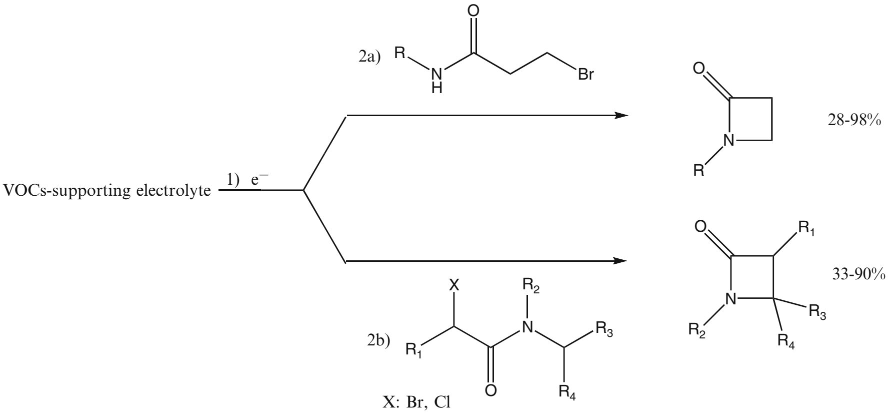
The possible cyclization of linear substrates to β-lactams has been investigated by many authors [100–108]. The cyclization, promoted by bases (NaH, Et_3N, Cs_2CO_3, etc.), has been carried out in classical VOCs (MeCN, DCM) solvents (Scheme 16.10).



Scheme 16.10 Base-promoted cyclization of linear substrates to β-lactams

Recently, the stereoselective cyclization of optically pure *N*-(*p*-methoxybenzyl)-*N*-(2-chloro)propionylamino acid derivatives to 1,3,4,4,-tetrasubstituted β-lactams has been discussed [106, 107]. The stereochemical control is fully dictated by the configuration of the 2-chloropropionyl group in the linear precursors, and it is totally independent of the configuration of the starting amino acid.

A simple electrochemical synthesis of β-lactams has been developed by constant current electrolysis of suitable VOC-supporting electrolyte solutions and subsequent addition of haloamides. The utilization of bases (NaH, Et_3N, Cs_2CO_3 etc.), purposely added to the solutions, has been avoided. The yields and the stoichiometry of the process are affected by the nature of the substituents and the solvent-supporting electrolyte solutions (Scheme 16.11) [109–111].

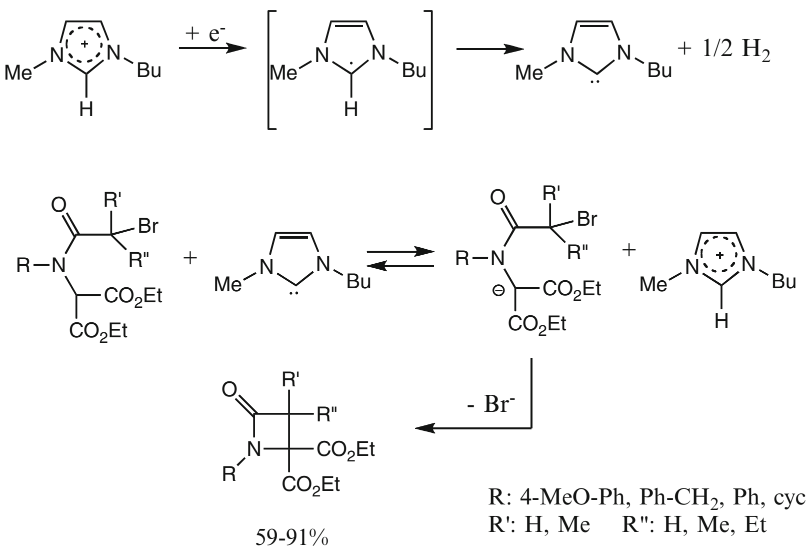


Scheme 16.11 Electrochemically promoted cyclization of linear substrates to β-lactams

16.4.4 Electrochemically Promoted Cyclization in Room Temperature Ionic Liquids (RTILs)

To evaluate the possible electrochemically induced cyclization of haloamides to β-lactams, avoiding the use of toxic organic solvent, the behaviour of haloamides has been investigated in previously electrolyzed RTILs.

1-Butyl-3-methyl-1*H*-imidazolium tetrafluoroborate (Bmim-BF_4) was initially electrolyzed, in the absence of bromoamide, in a divided cell (Pt cathode and anode), under a nitrogen atmosphere, at 45°C, at a constant density current of 25 mA cm^{-2}. This simple electrochemical procedure is able to modify the reactivity of imidazolium-based ionic liquids causing the presence in the solvents of 2-butyl-3-methylimidazol-2-ylidene, via the monoelectronic reduction of the 2-butyl-3-methylimidazolium cation. After the consumption of a prefixed number of Faradays, the current was switched off and the bromoamide was added to the cathodic compartment. In electrochemically activated RTILs, N-heterocyclic carbenes are stable bases strong enough to deprotonate bromomides, yielding the azetidin-2-one ring via C3–C4 bond formation (Scheme 16.12) [112].



59-91%

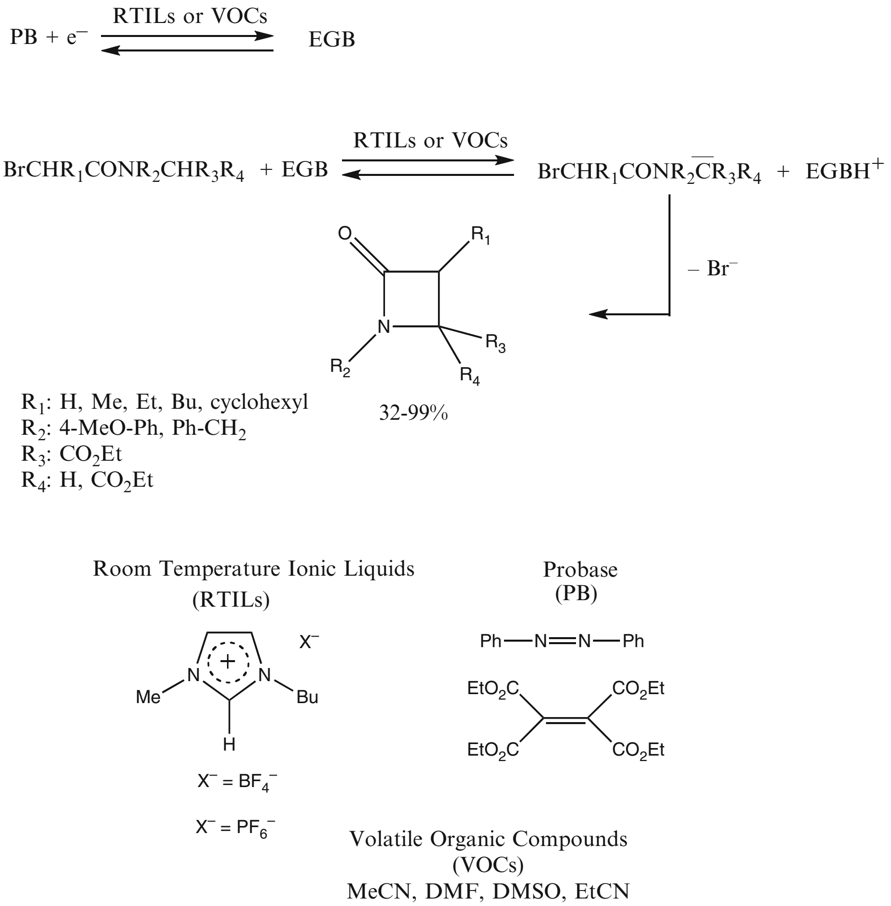
R: 4-MeO-Ph, Ph-CH_2, Ph, cyclopentyl
R': H, Me R": H, Me, Et

Scheme 16.12 Synthesis of β-lactams, via deprotonation of bromoamides by electrogenerated N-heterocyclic carbenes, in RTILs

β-Lactams have been synthetized in elevated yields (59–91%) avoiding the use of VOCs as well as of bases. After the workup of the cathodic solution, the ionic liquid was recovered and reused for five subsequent syntheses. In each case, β-lactams were isolated without any decrease of the yields (e.g. yield: 82%, 94%, 92%, 89%, 93%) [112].

A comparison, concerning the cyclization of haloamides between the electrochemical methodology in ionic liquids and the classical procedures (employing organic solvents: benzene and acetonitrile, and bases: Et_3N and Cs_2CO_3), has been performed. The yields of β-lactams, isolated according to the classical procedures, proved to be equal or smaller than the ones isolated according to the electrochemical methodology in RTILs. In conclusion, the electrochemical synthesis of β-lactams in ionic liquids, while avoiding the use of toxic and environmentally unfriendly organic solvents, does not involve any decrease in the yields of the isolated products [112].

These results are in consistent with a reaction pathway involving a preliminary deprotonation, induced by the electrogenerated carbene, of the acidic group C4-H, followed by intramolecular bromide displacement of the resulting C4-carbanion, i.e. a C3–C4 bond formation. The efficiency of the procedure was strongly affected by the acidity of the C4-H group as well as by the basicity of the N-heterocyclic carbene. To test the generality of the procedure, the reactivity of bromoamides (containing groups $-CHR_3R_4$, with different pK_a) versus suitable electrogenerated bases has been investigated in RTILs as well as in VOCs (Scheme 16.13). β-Lactams have been isolated in good to elevated yields (32–99%). The efficiency of the procedure, carried out in RTILs, has been compared with the one carried out in VOCs and the pK_b of NHCs and the ones of electrogenerated bases confronted [113].

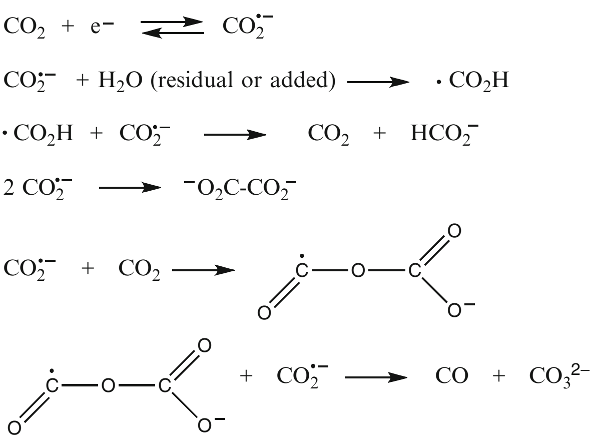


Scheme 16.13 Synthesis of β-lactams, via deprotonation of bromoamides by electrogenerated bases, in RTILs and in VOCs (Reprinted from Ref. [113] with kind permission of © Elsevier)

16.5 Carbon Dioxide as Raw Material in Organic Synthesis

In recent years, the utilization of carbon dioxide (harmless, inexpensive and available on large-scale reagent) as renewable carbon source in organic synthesis has been extensively investigated. The setting up of procedures suitable for the transformation of carbon dioxide into useful chemical intermediates (organic carbonates, carbamates, urethanes, esters, lactones, etc.) has been considered an attractive goal [114–116]. Therefore, the thermodynamic stability and kinetic inertness of carbon dioxide may cause remarkable troubles as regards its utilization as possible raw material. As a consequence, great deals of efforts have been devoted to solve the problem of its activation. Many catalytic procedures (homogeneous as well as heterogeneous catalysis) for the chemical transformation of carbon dioxide have been reported [117, 118].

Recently, the main methodologies for the utilization of carbon dioxide in organic synthesis have been reported by Sakakura et al. [114]: (a) to use high-energy starting materials (hydrogen, unsaturated compounds, small-membered ring compounds, etc.), (b) to choose oxidized low-energy synthetic targets, (c) to shift the equilibrium to the products by removing a particular product and (d) to supply energy such as light or electricity. As regards the last point (d), the electrochemical activation of carbon dioxide, in organic solvents [119–121] as well as in RTILs [122], is related to the cathodic monoelectronic reduction of CO_2 to radical anion $(CO_2)^-$ which evolves oxalate, carbonate and formate ions (Scheme 16.14).



Scheme 16.14 Electrochemical reduction of carbon dioxide (Reprinted from Ref. [119] with kind permission of © The American Chemical Society)

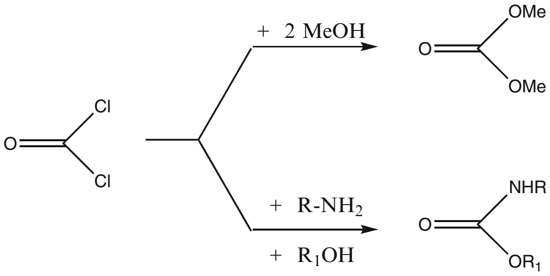
Owing to the rising demand of organic carbonates and carbamates, extensive investigations have been carried out to set up new eco-friendly procedures for synthesis of these intermediates.

16.5.1 Synthesis of Organic Carbonates and Carbamates

The increasing interest in organic carbonates [123–125] and carbamates [126–128] is related to the leading role played by these classes of compounds in the synthesis of pharmaceuticals and agricultural chemicals and in the chemical industry (medical drug, pesticides, fungicides, herbicides, intermediates, solvents, etc.). In addition, they are frequently used as versatile and efficient protecting groups for alcohols, diols, amine function, etc. [129].

The classical syntheses of organic carbonates and carbamates involve the direct or indirect utilization of phosgene or its substitutes (Scheme 16.15).

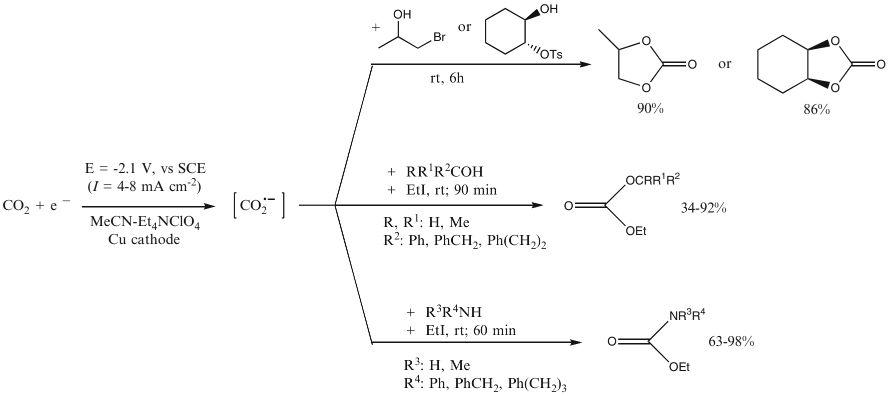
Scheme 16.15 Utilization of phosgene in the synthesis of carbonates and carbamates



To avoid the use of these toxic and harmful reagents, many authors have suggested the utilization of carbon dioxide in place of phosgene. The most common synthetic methodologies (using carbon dioxide) leading to the formation of carbamates [130] and carbonates [117, 131], via homogeneous or heterogeneous catalysts, have been reported extensively in reviews. Here, we will discuss the procedures of synthesis of carbonates and carbamates carried out via electrochemical activation of carbon dioxide (or of the co-reagents). We will compare the results obtained using VOCs as solvents with those obtained using RTILs.

16.5.2 *Electrosynthesis in Volatile Organic Compounds (VOCs)*

The electrochemical activation of carbon dioxide, directed to the synthesis of carbonates and carbamates, has been achieved via electrolyses (under potentiostatic, $E = -2.1$ V vs SCE, or under galvanostatic conditions) of VOC-supporting electrolyte solutions with continuous CO_2 bubbling, according to the monoelectronic reduction of CO_2 to CO_2^{-}, followed by addition of suitable substrates. The electrochemically activated CO_2 reacts with (a) primary and secondary alcohols, bearing a leaving group at the α-position, affording the corresponding cyclic carbonates in high yields (86–90%) and (b) unsubstituted alcohols or amines affording, after addition of EtI, unsymmetrical ethyl carbonates (in moderate to good yields, 34–92%) or carbamates (in excellent yields 63–98%) (Scheme 16.16). The yields of the isolated products are strongly affected by the nature of the cathodic material and of the solvent-supporting electrolyte as well as by the number of Faradays per mole of substrate supplied to the electrodes. Best results were obtained using Cu cathode, MeCN–Et_4NClO_4 solutions, 2.0–3.0 Faradays per mole of substrate supplied to the electrodes [132, 133].



Scheme 16.16 Electrochemically activated carbon dioxide in the synthesis of cyclic carbonates and unsymmetrical carbonates and carbamates (Reprinted from Ref. [132] and [133] with kind permission of © Elsevier)

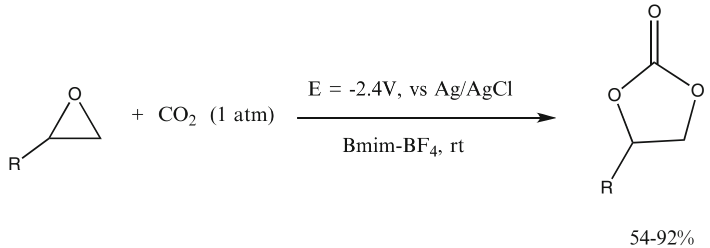
In order to increase the yields of the isolated products, simplified procedures (e.g. galvanostatic vs. potentiostatic conditions) utilize a more favourable work potential (E = −1.1 V vs. −2.1 V), and alternative methodologies were set up. The electrolyses were carried out by cathodic reduction of a mixture O_2/CO_2 (E = −1.1 V) [134, 135], or of suitable probases [136, 137], or of the solvent-supporting electrolyte system [138], followed by addition of alcohols or amines and, if necessary, of EtI. In this way, carbonates and carbamates have been isolated in good to high yields. Nevertheless in all these procedures, the large amounts of supporting electrolyte make it difficult to isolate the synthetic products. In addition, the utilization of volatile and toxic solvents should be avoided, according to the growing demand of eco-friendly technologies.

These troubles have spurred to investigate the electrochemical activation of carbon dioxide in RTILs, aimed to set up new electrochemical methodologies of synthesis of carbonates and carbamates in the absence of VOCs, supporting electrolytes, catalysts and co-solvents.

16.5.3 Electrosynthesis in Room Temperature Ionic Liquids (RTILs)

The synthesis of cyclic carbonates in RTILs, via cycloaddition of cathodically activated carbon dioxide to epoxide, has been reported by Deng et al. [139]. Ionic liquids, saturated with CO_2 by bubbling at normal pressure and containing the epoxidic substrate, were electrolyzed in an undivided cell (Cu as cathode, Mg or Al as sacrificial anode). The electrolyses were carried out under potentiostatic conditions at a potential negative enough to the selective reduction of CO_2 to CO_2^- (E = −2.4 V vs.

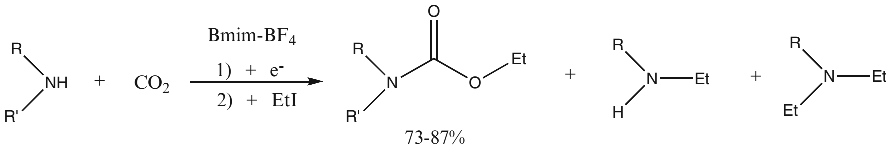
Ag/AgCl, according to the voltammetric indications) (Scheme 16.17). The authors suggested that, in the presence of the substrate, the radical anion CO_2^- should rapidly react with the intermediate of the desired product, which was activated with ionic liquid electrocatalytic system, rather than to react with solvent or itself. The behaviour of many ionic liquids has been investigated. The conversion, selectivity and current efficiency of the addition reaction was influenced by the nature of the ionic liquid (the structure of the cation as well as of the anion), the temperature and the substituent group on the substrate molecule. The best performance was achieved using Bmim-BF_4 at room temperature.



R: CH_3, $ClCH_2$, Ph

Scheme 16.17 Synthesis of cyclic carbonates in RTILs, via cycloaddition of cathodically activated carbon dioxide to epoxide (Reprinted from Ref. [139] with kind permission of © The Royal Society of Chemistry)

A new simple electrochemical procedure for the synthesis of carbamates from amines, using carbon dioxide as C1-building block, has been established by selective cathodic reduction of carbon dioxide in a CO_2-saturated ionic liquid solutions containing amines, followed by the addition of an alkylating agent. Accordingly, a solution of amine in Bmim-BF_4, maintained under constant bubbling of CO_2, was electrolyzed in a divided cell under potentiostatic condition (E = −2.4 V vs. Ag, Pt as anode and cathode, 55°C). At the end of the electrolysis, the cathodic solution was stirred at room temperature for 2 h added with ethyl iodide (EtI). After workup, the carbamates were isolated in good to elevated yields (Scheme 16.18) [140, 141].



R: $PhCH_2$, cycloheptyl, cyclohexyl, cyclopentyl, $Ph(CH_2)_3$, cyclohexylmethyl, allyl, Ph, 4-Cl-Ph
R': H, Me

Scheme 16.18 Synthesis of carbamates, from amines and electrochemically activated carbon dioxide, in ionic liquid solutions (Reprinted from Ref. [140] with kind permission of © The American Chemical Society)

This electrochemical synthesis of carbamates is related to the direct cathodic reduction of CO_2, carboxylation of amine via carbonate anion yielding the carbamate anion and the alkylation of the carbamate anion. For the last step of the whole synthetic process, two possible routes are possible: the N-alkylation of the carbamate anion (yielding nitrogen-derived products and CO_2 elimination) and the O-alkylation of the carbamate anion (yielding the carbamates). Both the routes (O-alkylation and N-alkylation) are affected by the nature of the ion pair: carbamate anion–non-metal cation, carbamate anion–metal cation. The last ion pairs give predominantly N-alkylation, and, in this case, the presence of crown ethers is necessary to obtain acceptable values of isolated carbamates.

Therefore, the efficiency of a procedure of synthesis of carbamates from carbon dioxide and amines needs an effective activation of CO_2 as well as a reaction medium suitable to promote the O-alkylation versus the N-alkylation. Ionic liquid Bmim-BF_4 is able to enhance the nucleophilicity of the oxygen centre of the carbamate anion promoting the O-alkylation versus the N-alkylation. In Bmim-BF_4 solutions, the carbamate anion has been identified as a 'naked' anion, characterized by a strong oxygen nucleophilicity versus alkylating agents. In fact, the interaction between the carbamate anion and $Bmim^+$ cation (a highly polarisable organic counterion) is not significant enough to depress the oxygen nucleophilicity [140 and 5–8 therein]. In Bmim-BF_4 solutions, the selectivity of O-alkylation versus N-alkylation is affected by the nature of the cathode and the number of Faradays supplied to the electrodes. In the electrosynthesis of carbamates, the role of Bmim-BF_4 as reaction medium is to affect the selectivity of the procedure, in addition to being a green solvent.

Successively, a similar electrochemical procedure of synthesis of organic carbonates was undertaken using carbon dioxide as C1-building block in a solution of alcohols in Bmim-BF_4 (Scheme 16.19).

$$\mathrm{ROH} + \mathrm{CO_2} \xrightarrow[\text{2) R'I}]{\text{Bmim-BF}_4\ \text{1) + e}^-} \underset{33\text{-}74\%}{\mathrm{ROCO_2R'}}$$

R: Me, Et, *n*-Bu, *s*-Bu, *t*-Bu, $PhCH_2$, $Ph(CH_2)_2$, Ph
R': Me, Et

Scheme 16.19 Synthesis of carbonates, from amines and electrochemically activated carbon dioxide, in ionic liquid solutions (Reprinted from Ref. [141] with kind permission of © the Royal Society of Chemistry)

The yield of the isolated carbonates was affected by temperature, cathodic material, working potential, alcohol concentration and the current density. Primary and secondary alcohols were converted in good yields, but tertiary alcohols and phenols were unreactive. The possibility of recycling the ionic liquid

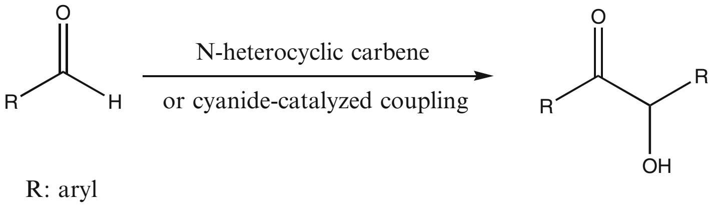
Bmim-BF_4 was investigated. Bmim-BF_4 was recovered and reused for five subsequent syntheses, and the yield of the isolated carbonate was found to decrease from 74% to 50% [141].

16.6 Carbon–Carbon-Bond-Forming Reactions

The need to promote the formation of new carbon–carbon bonds has been always felt in organic chemistry. Therefore, to set up efficient procedures capable to generate these bonds has been considered as the backbone of organic synthesis. Among various carbon–carbon-bond-forming reactions, the benzoin condensation, the Stetter and the Henry reactions are some of the most versatile procedures.

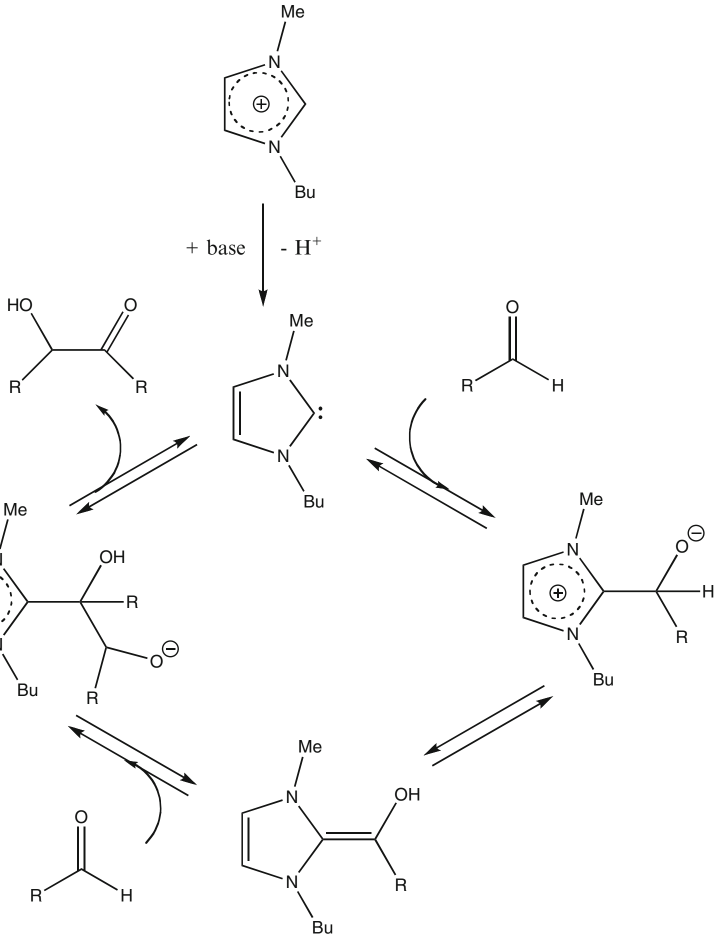
16.6.1 Benzoin Condensation

The benzoin condensation is the coupling reaction of two molecules of aldehydes to form the corresponding α-hydroxy ketones (Scheme 16.20). Owing to its ability to promote the formation of new carbon–carbon bonds as well as the creation of stereogenic centres, different procedures based on the N-heterocyclic-carbene-catalysed (in the past cyanide-catalysed) benzoin condensation have been set up [60, 61, 142–148]. A wide variety of heteroazolium salts, in the presence of bases that are capable to deprotonate at C2 carbon atom and the corresponding cation yielding N-heterocyclic carbene, have been reported as pre-catalysts for the benzoin condensation.



Scheme 16.20 The benzoin condensation: synthesis of α-hydroxy ketones

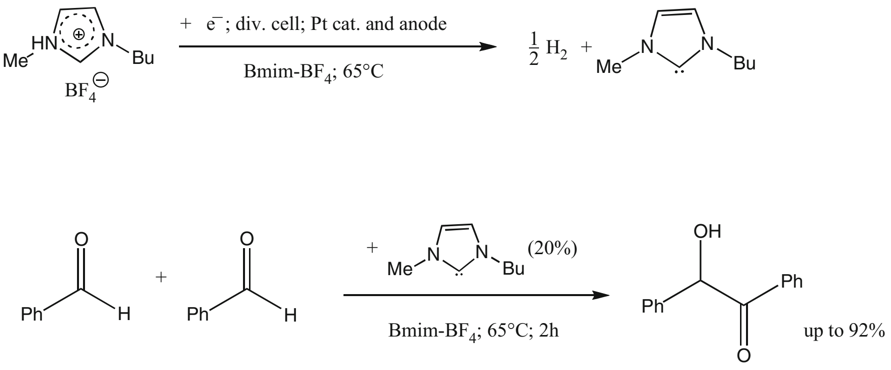
The mechanistic model, proposed by Breslow, has been extensively discussed [149]. The core of the benzoin reaction is the polarity reversal (umpolung) of the carbonyl, initiated by nucleophilic attack of NHC to the aldehyde yielding an acyl anion equivalent that triggers the carbon–carbon bond formation. The α-hydroxy ketone results from the addition of the acyl anion equivalent to another aldehyde (Scheme 16.21).



Scheme 16.21 Benzoin condensation: the mechanistic model, proposed by Breslow (Reprinted from Ref. [149] with kind permission of © The American Chemical Society)

Generally, the benzoin condensation has been achieved in organic solvents (THF, MeCN, CH_2Cl_2, EtOH, etc.), in the presence of heteroazolium salts and bases (NaH, KH, Et_3N, K_2CO_3 etc.) as pre-catalysts. Some problems related to the solubility and selectivity of the bases have been emphasized [52].

Recently, the benzoin condensation of aromatic or heteroaromatic aldehydes (in the absence of VOCs and bases) catalysed by NHCs, obtained by cathodic reduction of RTILs, has been reported. α-Hydroxyketones have been isolated in good to elevated yields, in short reaction time. No α-hydroxyketones have been obtained from linear or short-branched aldehydes; instead aldol products and carbene–aldehyde adducts have been isolated in elevated yields (Scheme 16.22) [150, 151].



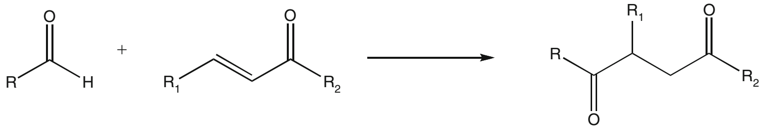
R: Ph, 4-MeO-Ph, 4-Me-Ph, 4-F-Ph, 2-Me-Ph, 2-naphthyl, 2-furyl, 2-thienyl

Scheme 16.22 Benzoin condensation catalysed by NHCs obtained by cathodic reduction of RTILs (Reprinted from Ref. [151] with kind permission of © Elsevier)

The efficiencies of the procedures performed in RTILs or in VOCs have been compared. Benzaldehyde was added to electrolyzed solutions of Bmim-BF_4 or Bhmt-Cl (3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride) in VOCs (DMSO, MeCN, DMF) or in electrolyzed Bmim-BF_4 (in the absence of VOCs). The yield of the benzoin isolated from VOCs solutions, strongly affected by the nature of the solvents (12–75%), was lower with respect to that one of benzoin isolated from RTIL (85%) [150].

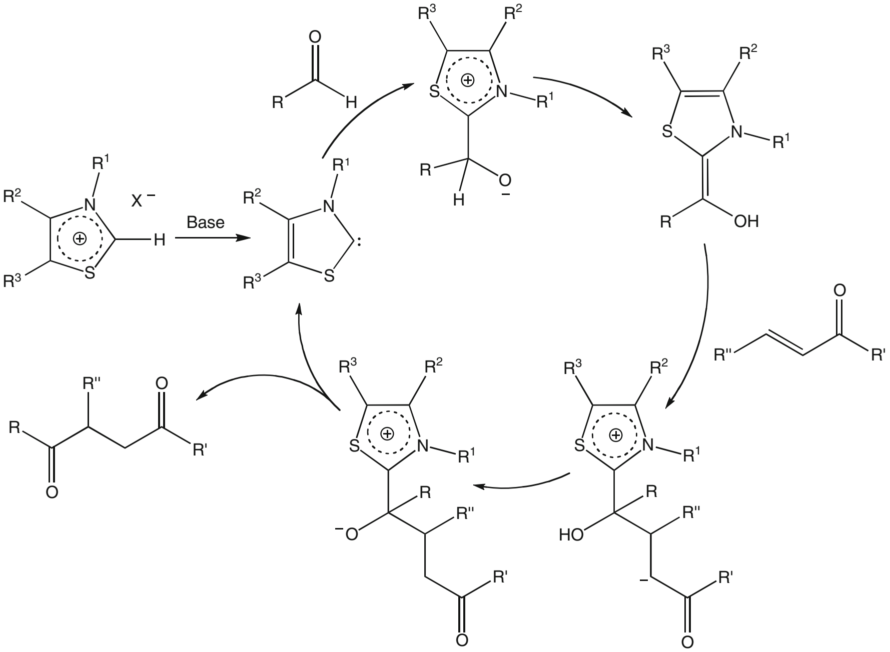
16.6.2 Stetter Reaction

The Stetter reaction provides an atom-economical entry to 1,4-bifunctional molecules (1,4-diketones, 4-ketoesters, 4-ketonitriles etc.) via 1,4-addition, catalysed by cyanide ion or N-heterocyclic carbenes, of an activated aldehyde to suitable Michael acceptor (Scheme 16.23) [152–154].



Scheme 16.23 Stetter reaction: synthesis of 1,4-bifunctional molecules

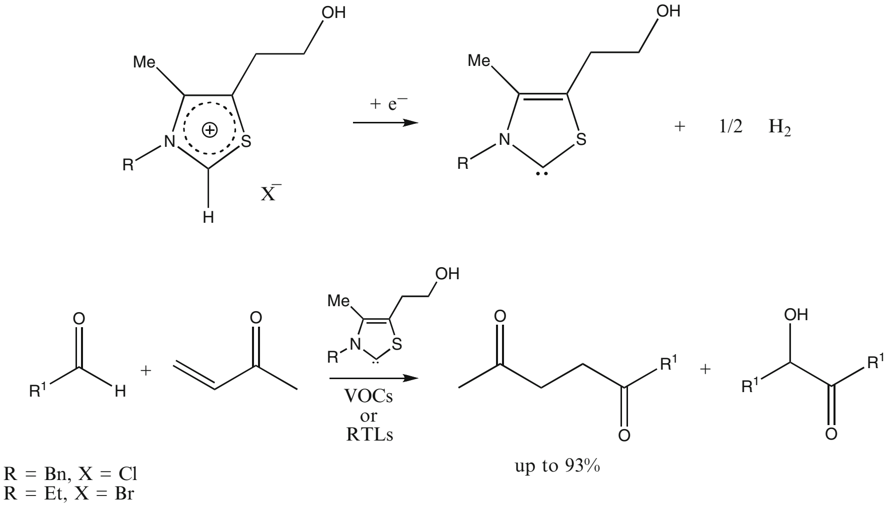
In the classical procedures, the Stetter reaction is performed in VOCs or in RTILs as solvent, using thiazolium salts (in the presence of bases) as pre-catalysts (i.e. in the presence of thiazolium-2-ylidenes) [60, 61, 142, 155–158]. The formation of the 1,4-dicarbonyl compounds has been related to the nucleophilic attack of the acyl anion equivalent to the Michael acceptor (Scheme 16.24).



Scheme 16.24 Stetter reaction: the mechanistic model (Reprinted from Ref. [159] with kind permission of © Elsevier)

Possible competitive nucleophilic attack of the acyl anion equivalent to the parent aldehyde molecule, yielding benzoin as by-product, must be considered.

With the aim to avoid the utilization of VOCs and/or bases, an alternative electrochemical procedure has been studied. To the solutions of thiazolium salts in organic solvents or in RTILs, previously electrolyzed under galvanostatic conditions, were added of aldehydes and 1-buten-3-one and stirred at controlled temperature for a prefixed interval of time. Conventional workup of the resulting solutions afforded 1,4-dicarbonyl compounds and α-hydroxyketones as by-products (Scheme 16.25) [159].



R = Bn, X = Cl
R = Et, X = Br

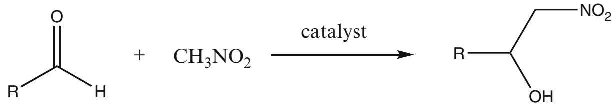
R^1: Ph, $CH_3(CH_2)_4$, $CH_3(CH_2)_6$, C_6H_{11}, $PhCH_2CH_2$, $Ph(CH_3)CH$, 4-F-Ph, 4-Me-Ph, 2-furyl, 2-thienyl

Scheme 16.25 Stetter reaction catalysed by NHCs obtained by cathodic reduction of RTILs (VOCs or RTILs as solvents) (Reprinted from Ref. [159] with kind permission of © Elsevier)

The yields of the isolated 1,4-dicarbonyl compounds and their selectivity were affected by the nature of the solvent, the molar ratio of catalyst to substrate and the reaction time. The different relativities of the aliphatic aldehydes (yields of isolated product 73–93%, selectivity 100%) versus the one of aromatic (yield 34–49%, sel. 100%) and heteroaromatic (yield 37–62%, sel. 62–79%) aldehydes have been emphasized.

16.6.3 Henry Reaction

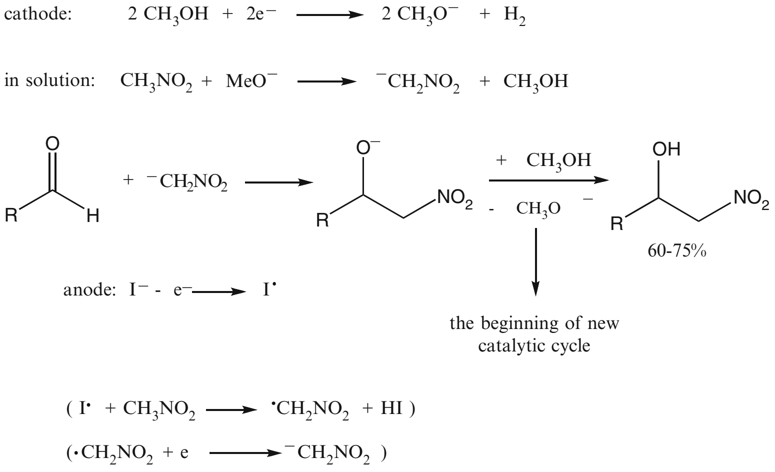
The Henry (or nitro-aldol) reaction is one of the powerful carbon–carbon bond formation reactions frequently used in organic synthesis, providing access (via coupling between a carbonyl compound and an alkylnitro compound) to β-nitroalcohols, useful synthons in organic synthesis (Scheme 16.26) [160].



Scheme 16.26 Henry reaction: synthesis of β-nitroalcohols

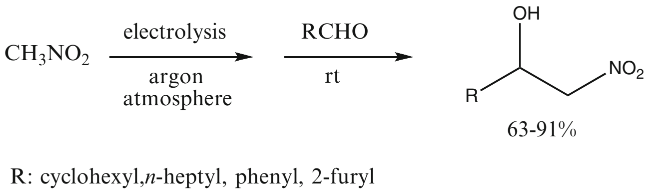
The Henry reaction is performed, in the presence of catalysts (organic or inorganic bases, quaternary ammonium salts, etc.), protic and aprotic organic solvents [161], water [162], supercritical fluids [163] or ionic liquids [164]. Nitroalkenes can be obtained as by-products, via dehydration of β-nitroalcohols. Considerable efforts have been made to increase the yield and selectivity and to control the basicity of the medium and the reaction time.

An electrochemical-induced Henry reaction has been achieved by Elinson et al. via electrolysis (undivided cell) of solutions of carbonyl compounds and nitromethane in methanol or in methanol–DMF mixture containing alkali metal iodide as supporting electrolyte. β-Nitroalcohols have been isolated in 60–75% yields. The authors suggest that the Henry reaction could be induced by the deprotonation of methanol at the cathode and by the oxidation of the iodide anion at the anode (Scheme 16.27) [165].



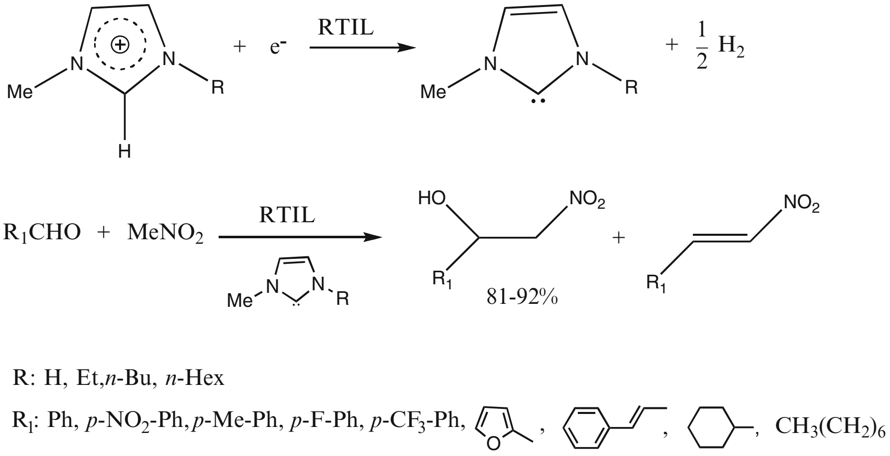
Scheme 16.27 The electrochemical-induced Henry reaction in methanol (Reprinted from Ref. [165] with kind permission of © Elsevier)

An electrosynthetic approach to 2-nitroalcohols via activation of nitromethane by electrogenerated superoxide anion has been reported by Evans et al. [166–168]. Recently, the electrochemically induced Henry reaction has been performed via direct cathodic reduction of nitromethane (Scheme 16.28) [169, 170].



Scheme 16.28 Henry reaction performed via direct cathodic reduction of nitromethane (Reprinted from Ref. [170] with kind permission of © John Wiley and Sons)

Finally, the electrosynthesis of β-nitroalcohols has been performed, under mild conditions and in high yields and selectivity, by stirring nitromethane and aldehydes in previously electrolyzed RTILs in total absence of VOCs and supporting electrolyte. The effects of the number of Faradays per mole of aldehyde supplied to the electrode, the reaction time, temperature and the structure of the RTILs on the yield and selectivity have been extensively investigated. After the workup of the catholyte, RTILs were recovered and reused. In every case, β-nitroalcohols were isolated in good yields (81–92%) (Scheme 16.29) [171].



Scheme 16.29 Henry reaction performed in previously electrolyzed RTILs (Reprinted from Ref. [171] with kind permission of © Elsevier)

16.7 Conclusions

The significant selected examples reported in this article emphasized the possibility of utilizing RTILs as solvents in the electrochemical procedures of organic synthesis and the consequent increase of the eco-friendliness of the methodologies. The electrochemical syntheses carried out in RTILs have been compared with those in VOC-supporting electrolyte systems. The results, related to the synthesis of β-lactams, the activation of CO_2 and the C–C bond formation reactions (i.e. some extensively investigated electrochemically induced processes), prove that the utilization of RTILs, while avoiding the presence of volatile and toxic solvents and of large amount of supporting electrolyte, simplifies the workup of the reaction mixtures and allows the recovery and the reutilization of the reaction media.

In addition, a simple pre-electrolysis is able to modify the physico-chemical properties of the RTILs by inducing the formation, at a prefixed concentration, of N-heterocyclic carbenes. According to this modification, the RTILs can be utilized in the electrochemical syntheses in the double role as green solvent and parent of reactive intermediates or catalysts. The benzoin condensation, the Stetter reaction (electrogenerated carbenes as nucleophilic catalysts) and the Henry reaction (electrogenerated carbenes as basic catalysts) are the recent examples of the considerable and unexpected potentiality of RTILs in organic electrosynthesis.

In our opinion, the combination of the electrochemical methodology and the RTILs, especially as regards the double role of RTILs as green solvents and precatalysts, could open a new area for the investigation concerning the setting up of eco-friendly procedures of organic electrosynthesis.

Both the structures of a specific RTIL (the cationic and the anionic structure) can affect the solubility of the substrates, the yield and the selectivity of the overall procedures and the efficiency of the electrogenerated carbenes as catalysts. In addition, changing the structure of the RTIL, unexpected products can be isolated according to a considerable variation of the reactivity of the substrates. These effects have been emphasized in publications related to both classical and electrochemical methodologies. Nevertheless, owing to the complexity of the interactions (cation/anion, cation/substrate and anion/substrate), the rationalization and the prediction of these effects are not always easy. Probably, this target needs further extensive investigations. The electrochemical methodology, owing to its ability to generate N-heterocyclic carbenes in mild conditions, at a prefixed concentration, by cathodic reduction of the parent RTIL in the total absence of classical organic solvents and bases, could provide a meaningful share.

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Chapter 17
Organic Ionic Liquids: Ultimate Green Solvents in Organic Synthesis

Mohammed Abid Shaikh and Xudong Huang

Abstract Over the years, ionic liquids have gained significant attention in organic synthesis and other areas of chemistry as environmentally benign solvents. Unlike traditional solvents, ionic liquids offer several advantages such as being nonvolatile, noncorrosive, immiscible in organic solvents, easily stored and handled, producing less hazardous waste, and easily recovered in terms of materials during the reaction work-up. Their role in enhancing reaction rates and selectivity is well documented in the literature. Ionic liquids have proved to be an important alternative over traditional solvents in a variety of synthetic transformations. In this account, we highlight some of the advancements over the last decade in the development of ionic liquids as solvents in organic synthesis.

17.1 Introduction

Ionic liquids (IL) are organic salts that can be stored in a liquid state at room temperature, a breakthrough achieved only recently when imidazolium and pyridinium derivatives were introduced [1–4]. In early 1900s, alkylammonium nitrates were found to have a melting temperature of 12°C [5]. However, till 1980, there was no

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significant interest in ionic liquids [6–9]. Most of the research on ionic liquids was carried out before 1992 using chloroaluminate anions that have limited scope due to water sensitivity and necessity to be handled in a dry atmosphere [10–12]. In 1992, a dramatic change occurred when a new generation of ionic liquids was reported. These ionic liquids were insensitive to water and made from 1-ethyl-3-methylimidazolium cation [emim] and tetrafluoroborate and acetate anions [13–17]. Ionic liquids consist of a salt where one or both the ions are large, and the cation has a low degree of symmetry; such factors tend to reduce the lattice energy of the crystalline form of the salt and lower the melting point [1–4, 18–20]. Ionic liquids have two main categories: simple salts, such as $[EtNH_3]NO_3$, and binary ionic liquids that include aluminum(III)chloride and 1,3-dialkylimidazolium chlorides.

Ionic liquids are ground-breaking green alternatives to the highly toxic solvents that are hazardous to the environment and human health. When employed as media for promoting organic synthesis or catalytic reactions, ionic liquids offer certain advantages as alternatives to conventional solvents. Ionic liquids can be safely reused, make product recovery easier, and allow for catalyst recycling. Recently, the synthesis of functionalized ionic liquids according to the requirement of a specific reaction has become an attractive area for development, including ionic liquids that have been developed for specific synthetic problems, thereby giving ionic liquids the name “designer solvents” [21, 22]. Due to their tunable features for various targeted chemical transformations, their advantages are as reusable homogenous supports, reagents, and catalysts with green features. Studies show the possibility of designing suitable catalysts for targeted chemical transformation [23–25]. These specific ionic liquids often serve the dual role of catalyst and reaction medium. Functional ionic liquids have been developed and successfully applied to catalyze a number of chemical transformations; such ionic liquids maintain the unique properties of ionic liquids; therefore, they can be easily recycled and reused as homogenous small molecular catalysts.

The use of ionic liquids in numerous organic transformations ranging from one-step to one-pot multicomponent reactions had been documented in the literature. In this account, we will provide a brief overview of some of the recent advancements in this area and depict that ionic liquids are indeed versatile green solvents in organic synthesis.

17.2 Solvent Properties

Ionic liquids are organic molten salts that can be kept in a liquid state at room temperature and dissolve many organic compounds to produce reactions. Their properties such as melting point, viscosity, density, and hydrophobicity can be regulated by simple changes to the structure of ions. For example, the melting points of 1-alkyl-3-methylimidazolium tetrafluoroborates and hexafluorophosphates are a function of the length of the 1-alkyl group and form liquid crystalline phases for alkyl chain lengths over 12 carbon atoms [26, 27]. The miscibility of water in these ionic liquids also depends on the structure of the alkyl chain. For example, 1-alkyl-3-methylimidazolium tetrafluoroborate salts are miscible with water at 25°C when the alkyl chain length is less than 6, but at or above six carbon atoms, and they form a separate phase when mixed with water [28, 29]. Such a capacity is beneficial for carrying out solvent extractions or product separations as the relative solubilities of the ionic and extraction phase can be adjusted to make the separation as easy as possible.

Ionic liquids are aprotic but polar, and this property is essential for solubilizing compounds, such as proteins and carbohydrates that are sparingly soluble in common organic media. The water-miscibility of ionic liquids varies greatly; 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 is water soluble, but does not dissolve simple sugars. On the other hand, 1-butyl-3-methylimidazolium chloride [bmim]Cl dissolves cellulose and other complex compounds, such as sugars and proteins. The investigation revealed that the ionic liquids could be considered to be polar phases with the solvent properties being largely determined by the ability of the salt to act as a hydrogen-bond donor and/or acceptor and the degree of localization of the charge on the anions. However, the ammonium and phosphonium salts that were used would not have had large differences in the delocalization of the charge on the cation, and this may be an important effect for other salts, such as the pyridinium- and imidazolium-based ionic liquids. Furthermore, it was found that increasing the chain length of alkyl substituents on both cations and anions leads to greater lipophilicity of the ionic liquids. Also, the influence of hydrogen bonding can be diminished by fluorinating the ionic liquids [30–32].

Current ionic liquids are stable under air and moisture, and some are even hydrophobic, which eliminates the hydrolysis problem. Most ammonium and imidazolium salts are hygroscopic, and if used in open vessels, hydration will almost certainly occur. The degree to which this is a problem will depend on the use to which the ionic liquid is being put and what solutes are being used. Handling of these salts under inert atmosphere is recommended.

17.3 General Methods for Preparation of Ionic Liquids

The most common ionic liquids include alkylammonium, alkylphosphonium, *N*-alkylpyridinium, and *N*,*N*′-dialkylimidazolium cations. Two general methods for their preparation are acid–base neutralization reactions and metathesis of halide salts with a metal or ammonium salts. Alkylammonium, pyridinium, and imidazolium halides can be prepared by the reaction of the appropriate alkyl halide and amine. Preparation of 1-ethyl-3-methylimidazolium chloride [emim]Cl requires a sealed tube since it has a low boiling point. On the other hand, synthesis of [bmim]Cl can be achieved under conventional reflux conditions [33, 34].

Salts like [emim]BF_4 can be prepared by metathesis of 1-ethyl-3-methylimidazolium iodide [emim]I with silver tetrafluoroborate Ag[BF_4] that offers greater moisture stability and immiscibility with a number of organic solvents. Similarly, 1-ethyl-3-methylimidazolium hexafluorophosphate [emim]PF_6 can be prepared by reaction of

[emim]Cl with hexafluorophosphoric acid HPF_6 [35, 36]. The metathesis method is advantageous for the preparation of a variety of salts such as, thiocyanate, nonafluorobutanesulfonate, bis(trifluoromethylsulfonyl)imide, tris(trifluoromethylsulfonyl) methide, trifluoroacetate, and heptafluorobutanoate. Tetraalkylammonium tetraalkylborides are also prepared by the metathesis reaction of tetraalkylammonium bromide and lithium tetraalkylboride [37, 38]. The reaction of a trialkylborane with the appropriate alkyllithium reagent in dry hexane yields the required lithium tetraalkylboride. Alkylammonium nitrate salts are prepared by the neutralization of aqueous solutions of the amine with nitric acid. Similarly tetraalkylammonium sulfonates have been prepared by mixing equimolar amounts of the sulfonic acid and the tetraalkylammonium hydroxide [39]. Another direct method involves the combination of a halide salt with a metal halide, which is how the halogenoaluminate(III) and the chlorocuprate(I) ionic liquids are prepared. Chloroaluminate(III) ionic liquids are excellent catalysts and solvents in many processes but suffer from several disadvantages, such as moisture sensitivity and a difficulty in separation of products containing heteroatoms from the ionic liquid while leaving ionic liquid intact [40].

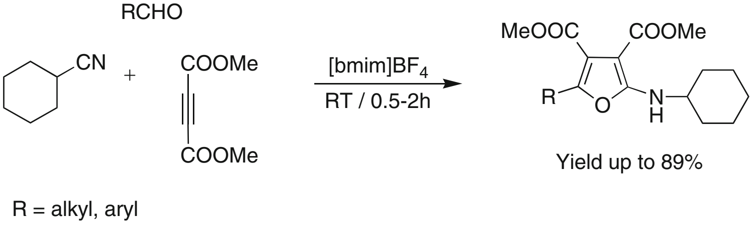
17.4 Applications of Ionic Liquids in Organic Synthesis

Ionic liquids have attracted considerable attention due to their numerous applications in synthetic chemistry. The various synthetic methods reported in the literature need to be relooked due to strengthening environmental regulations and safety concerns. Thus, the development of novel environmentally benign and energy-efficient synthetic methods to modernize or replace these well-performing methods is in great demand. To address this important issue, various new eco-friendly synthetic procedures have been designed that rely on the use of benign reagents or recyclable catalysts and novel solvent systems and that address the energy consumption/reaction time issue by using nonconventional activation methods. Over the years, ionic liquids have found various applications in organic synthesis, and various review articles have been published, highlighting their importance. We wish to demonstrate a general and brief overview of some of the important ionic liquid–based processes.

17.4.1 Multicomponent Reactions

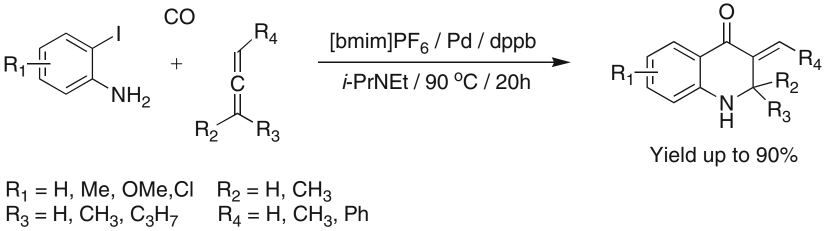
Due to their high atom economy, multicomponent reactions have emerged with a high potential in the fine chemicals and pharmaceutical industries [41]. These reactions are usually not concerted; rather, they are tandem or domino processes in which multiple reactions are combined into one synthetic operation. This significantly reduces reaction time as well as the amount of waste in comparison to an alternative multistep synthetic process. The first step produces an intermediate that need not be isolated, but it must undergo a sequence of reactions until the stable product is formed. Careful design of substrates with predetermined functionalities often results in products that are difficult to obtain otherwise in traditional multistep syntheses [42]. Ionic liquids have been proven to be useful in multicomponent reactions as a catalyst and as reaction media.

Yadav and coworkers [43] have reported a three-component coupling of aldehyde, dimethyl acetylenedicarboxylate, and cyclohexyl isocyanide in [bmim]BF_4 ionic medium under extremely mild conditions to obtain the corresponding 2-aminofuran derivatives (Scheme 17.1). The reaction went to completion in a short time of 2 h with a yield of about 89%. The products obtained were isolated by simple extraction with ether. The remaining ionic liquid was further washed with ether and reused several times without further purification. The reaction was studied in both hydrophilic [bmim]BF_4 and hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6 ionic liquids; however, [bmim]BF_4 was found to give the best results. In contrast, the use of organic solvents such as acetonitrile and tetrahydrofuran gave poor yields under refluxing conditions with long reaction times from 8 to 12 h. This work clearly highlights the importance of ionic liquids as catalysts and reusable solvents in organic synthesis.



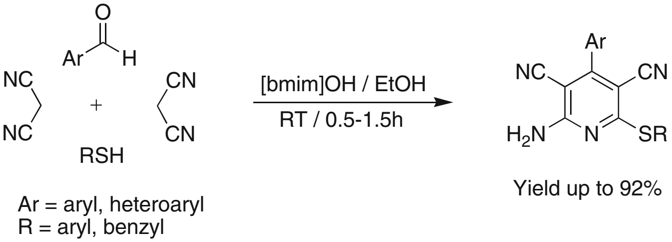
Scheme 17.1 Synthesis of 2-aminofuran derivatives using [bmim]BF_4

The palladium-catalyzed cyclocarbonylation reaction of *o*-iodoanilines with allenes and CO in 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6 afforded 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones in yields of up to 90% under a low pressure (5 atm) of CO (Scheme 17.2). The ionic liquid, as the solvent and promoter, enhanced the efficiency of the cyclocarbonylation reaction. In this work, Ye and group demonstrated the recyclability of the system of ionic liquids and their use as catalysts [44].



Scheme 17.2 A three-component domino approach for the synthesis of quinolinones using [bmim]PF_6

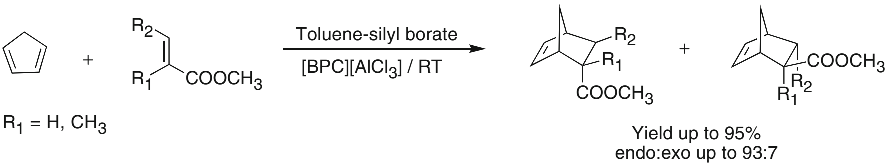
Recently, Ranu and coworkers [45] used basic ionic liquid, 1-butyl-3-methylimidazolium hydroxide [bmim]OH, in place of conventional bases to provide a selective, high-yielding one-pot synthesis of highly substituted pyridines through a three-component condensation of aldehydes, malononitrile, and thiophenols at room temperature (Scheme 17.3). The other advantages of this procedure are a lack of hazardous organic solvents in the reaction and the reusability of ionic liquids.



Scheme 17.3 A one-pot synthesis of highly substituted pyridines under [bmim]OH ionic liquid

17.4.2 *Cyclization/Cycloaddition Reactions*

Cycloaddition reactions are one of the most pioneering transformations carried out in the history of organic chemistry. They require activation energy either photochemically or through heat/high temperatures. Cycloaddition reactions, in general, represent an important tool for the formation of C–C bonds. The Diels–Alder cycloaddition is a well-known strategy for the synthesis of cyclic materials and was accelerated by Lewis acid catalysts. Kumar and group [46] documented that the acidic chloroaluminate ionic liquid can enhance the catalytic power of silyl borate catalyst for carrying out the Diels–Alder reactions. The cycloaddition reaction of cyclopentadiene with methyl acrylate was carried out in the presence of various catalyst systems; however, the silyl borate and *n*-butylpyridinium chloride/aluminum chloride [BPC]AlCl$_3$ catalyst combination provided excellent yield of 98% in 1 h reaction time with 93% selectivity of endo product (Scheme 17.4). The authors also reported the reusability of acidic chloroaluminate by extracting the product with Et$_2$O. The catalyzed reaction in the recycled condition gave a 91–95% yield for up to seven recycles, thus confirming the active role of the ionic liquid in promoting the reaction.



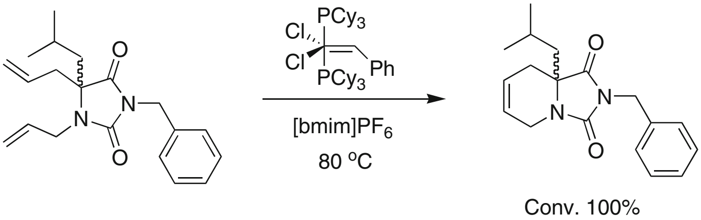
Scheme 17.4 Cycloaddition reaction of cyclopentadiene using [BPC]AlCl$_3$

In another attempt, Song et al. reported that ionic liquids [bmim]PF$_6$ act as powerful media in scandium triflate catalyzed Diels–Alder reactions not only for the facilitating of catalyst recovery but also for the accelerating of the reaction rate and improving of selectivity (Scheme 17.5). Various dienes and dienophiles provided excellent yields and selectivity at room temperature in 4 h [47].

Scheme 17.5 Scandium triflate catalyzed Diels–Alder reaction under [bmim]PF$_6$

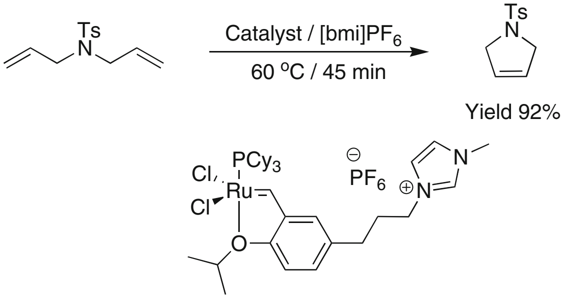
17.4.3 Metathesis

Ring-closing metathesis (RCM) has been established as a powerful and effective tandem method for the construction of many functionalized compounds from diene precursors [48, 49]. Many useful transformations have been reported for industrial applications as well as for the synthesis of complex molecules due to major advances in catalyst design. The Grubbs ruthenium catalysts have been used most extensively in RCM because of their high reactivity, air stability, and remarkable functional group tolerance [50, 51]. However, the fact that these catalysts are nonrecyclable and can only be removed from the product by repeated chromatography severely hampers their use in industrial processes. Buijsman and coworkers [52] performed RCM in the most frequently used ionic liquid 1-butyl-4-methylimidazolium hexafluorophosphate [bmim]PF$_6$ using alkene as a substrate and 5 mol% of a Grubbs catalyst (Scheme 17.6). Product was obtained in 98% yield at 80°C in 24 h. However, a low conversion was obtained during the catalyst recycling due to the slow decomposition of the catalytic system.



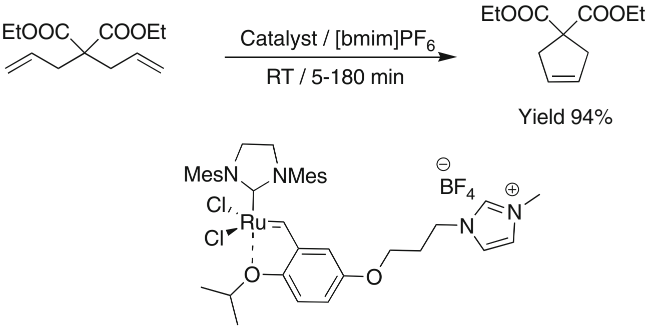
Scheme 17.6 Ring closing metathesis of alkenes under [bmim]PF$_6$

To overcome the problem of catalyst decomposition, Audic and coworkers [53] designed a novel alkyl imidazolium salt-supported ruthenium carbene complex (Scheme 17.7). The resulting ionic catalyst is completely soluble in ionic liquid and allows the RCM reaction to be carried out under standard homogeneous conditions. This new catalyst system provided high conversion and yields (92–98%). Moreover, the recycled catalyst solution was used for the metathesis, and similar results were obtained up to the tenth cycle. The catalyst has shown high activity with a remarkable recyclability and can be stored in [bmi]PF_6 for several months without loss of activity.



Scheme 17.7 Ring closing metathesis of alkenes under [bmi]PF_6

Further modification in support of the ruthenium carbene complex with ionic liquid media was described by Wakamatsu et al. [54]. The RCM of diethyl diallylmalonate using a new catalyst was carried out under an argon atmosphere in the presence of 5 mol% catalyst in CH_2Cl_2/[bmim]BF_4 (9:1) at room temperature. The starting material was consumed after 0.5 h to provide a product with 94% yield (Scheme 17.8). Continuous fast conversion was observed, and reliable reusability was realized by the fifth cycle.

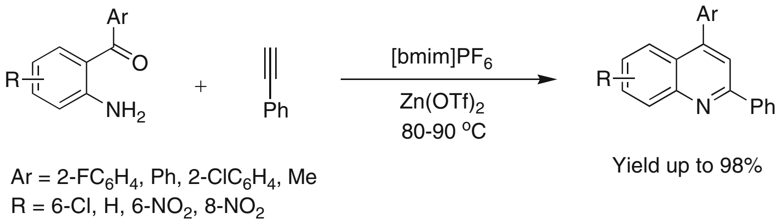


Scheme 17.8 Ring closing metathesis of alkenes under [bmim]BF_4

17.4.4 Synthesis of Heterocyclic Compounds

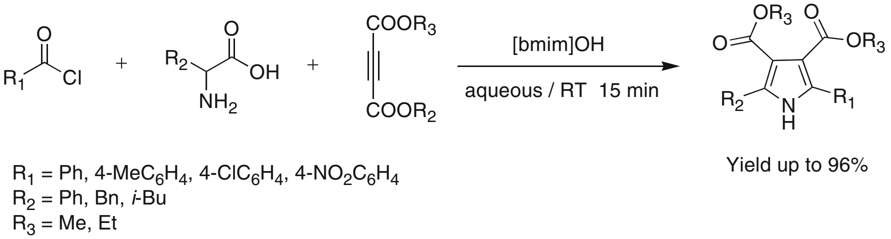
Heterocycles have attracted considerable attention due to their numerous applications in pharmaceutical and synthetic chemistry. These heterocyclic moieties are also found in a variety of biologically active synthetic and natural products. For example, heterocyclic alkaloids were the active ingredients in many natural remedies long before the development of modern chemistry, and some are still in use today, such as pyridine derivatives, quinoline, and coumarins. The majority of current synthetic drugs have a heterocyclic structural component. Given their wide applications, heterocyclic compounds have a long and extensive history of syntheses within which many classic syntheses have been developed. However, significant challenges still exist because the preparation of certain compound classes is still difficult.

Sarma and Prajapati [55] reported an efficient, simple, and recyclable protocol for the synthesis of 2,4-disubstituted quinolines using [bmim]PF_6 as a recyclable ionic liquid in the presence of 1 mol% zinc triflate. This method eliminated the usage of harmful organic solvents, high reaction temperatures, prolonged reaction times, low yields, tedious workup procedures, and the use of stoichiometric and/or relatively expensive reagents (Scheme 17.9). Consequently, there is great current interest in assembling quinoline systems from acyclic precursors and an ever increasing demand for selective, cheap, eco-friendly, and low-cost protocols for their synthesis. The synthesis of 2,4-disubstituted quinolines was achieved through the treatment of 2-amino-5-chloro-2′-fluorobenzophenone with phenylacetylene in [bmim]PF_6 and in the presence of 1 mol% zinc triflate when heated at 80–90°C for 2.5 h, a process that resulted in the formation of 2-phenyl-4-(2′-fluorophenyl)-6-chloroquinoline at a 98% yield.



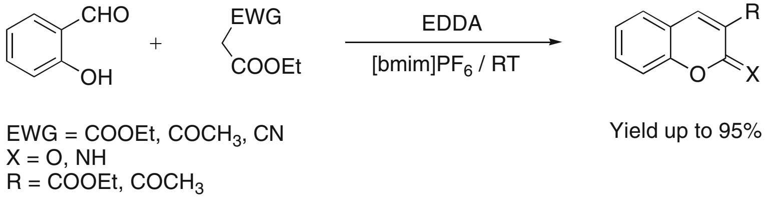
Scheme 17.9 Synthesis of substituted quinolines in [bmim]PF_6

A three-component, one-pot condensation reaction was described by Yavari and Kowsari [56] by using the [bmim]OH–H_2O system to give the functionalized pyrroles in excellent yields. When the benzoyl chlorides, L-phenylalanine, and acetylenedicarboxylates were allowed to react under an organic alkali catalyst, [bmim] OH-H_2O provided highly functionalized pyrroles (96% yield) within 15 min (Scheme 17.10).



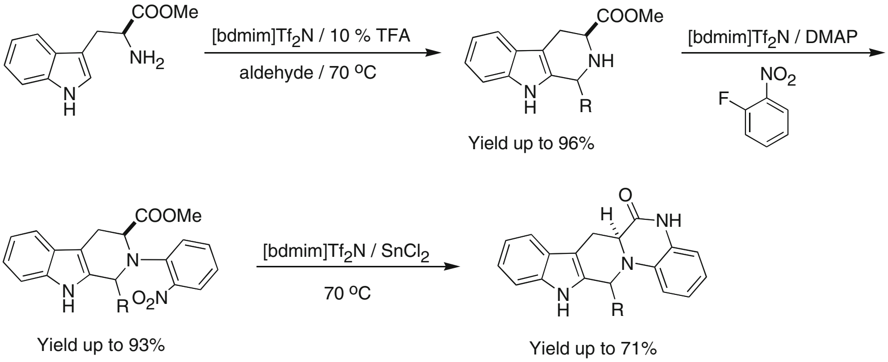
Scheme 17.10 A one-pot condensation using the [bmim]OH–H_2O system to synthesize the functionalized pyrroles

The moisture- and air-stable ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6, were used as "green" recyclable alternatives to volatile organic solvents for the ethylenediammonium diacetate-catalyzed Knoevenagel condensation between aldehydes or ketones with active methylene compounds. As described by Su et al. [57], the ionic liquids containing a catalyst were recycled several times without decrease in yields and reaction rates. In the case of 2-hydroxybenzaldehyde, the reactions led to the formation of 3-substituted coumarin derivatives in high yields of up to 95% (Scheme 17.11). When ethyl cyanoacetate was used, 2-imino-2*H*-1-benzopyran-3-carboxylic acid ethyl ester was formed.



Scheme 17.11 Knoevenagel condensation between aldehydes or ketones using [bmim]PF_6

Tseng and colleagues [58] reported a three-step synthesis of fused tetrahydro-β-carbolinequinoxalinones, solely based on the use of ionic liquids as solvents. Tetrahydro-β-carboline is a central core for many biologically important indole alkaloids, and the moiety of quinoxalinone often exhibits a wide spectrum of biological activities such as being anti-HIV, antihypertensive, and a ligand for a number of protein receptors. As a first step, tryptophan methyl ester was reacted with an aldehyde to form tetrahydro-β-carboline by Pictet–Spengler cyclization that further reacted with 1-fluoro-2-nitrobenzene to form *N*-aryl-tetrahydro-β-carboline. Intramolecular cyclization upon a reduction reaction in step three provided the desired tetrahydro-β-carbolinequinoxalinones. The entire process was based on the use of 1-*n*-butyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)-imide [bdmim]Tf_2N and 1-*n*-butyl-2,3-dimethylimidazolium perfluorobutylsulfonate [bdmim]$PFBuSO_3$ salts and provided good-to-excellent yields in all of the steps (Scheme 17.12).



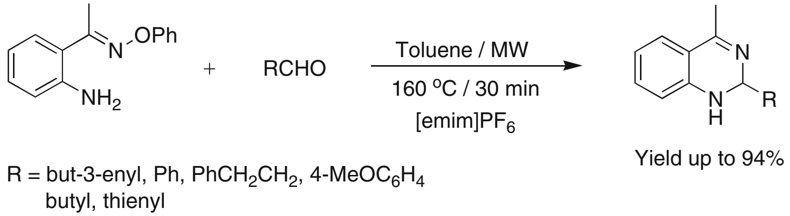
Scheme 17.12 A three-step synthesis of fused tetrahydro-β-carbolinequinoxalinones

17.4.5 Combination of Ionic Liquids and Microwave Irradiation

Microwave-assisted organic synthesis has recently gained significant attention since microwave (MW) heating could substantially accelerate the rate of reactions. The initial development of microwave technology was relatively slow for various reasons, mainly safety concerns, temperature control, and reproducibility [59, 60]. However, in the 1990s, the gradual availability of commercial microwave instruments, specifically designed for synthetic applications, resulted in explosion-like developments in this area. These state-of-the-art instruments are easy to use and provide accurate temperature and pressure control to critically enhance the reproducibility of the work. More importantly, the increased interest in microwave-assisted organic synthesis is due to sometimes astonishingly short reaction times that significantly contribute to revolutionizing this field in industry. This useful technology has been utilized in various organic transformations ranging from one-step to one-pot multicomponent reactions.

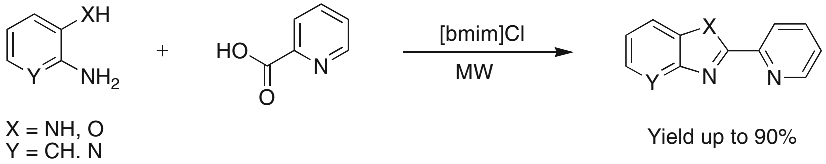
The uses of ionic liquids as solvent, additive, and/or catalyst in microwave-assisted organic syntheses have gained popularity as indicated by huge number of publications. Due to the ionic nature, the catalytic properties of ionic liquids accelerate many organic reactions using conventional organic synthesis methodologies. These compounds can also absorb microwave irradiation very efficiently and can increase the rate of organic reactions even those involving low polarity reaction media. In this section, the more relevant results describing the innovative applications of ionic liquids will be reviewed.

Portela-Cubillo et al. [61] have described the synthesis of a wide range of biologically active compounds containing the quinazoline ring system. This method utilizes the free-radical-based method that relies on microwave-promoted reactions of o-phenyl oximes with aldehydes. 2-Aminoarylalkanone *o*-phenyl oximes were prepared which produce dihydroquinazolines when mixed with an aldehyde in toluene and subjected to microwave heating under [emim]PF_6. When $ZnCl_2$ was included in the reaction mixture, fully aromatic quinazolines were produced in high yields of up to 94% over short reaction time of 30 min (Scheme 17.13). The method worked well with alkyl, aryl, and heterocyclic aldehydes and for a variety of substituents in the benzenic part of the molecule.



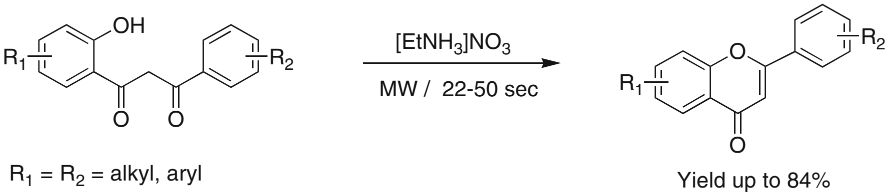
Scheme 17.13 Synthesis of dihydroquinazolines under microwave heating and [emim]PF_6

An efficient and fast procedure for the synthesis of 2-(2-pyridyl)azoles, from *o*-substituted aromatic amines and picolinic acid, was described by Likhanova and coworkers using ionic liquid [bmim]Cl as a catalyst under microwave irradiation (Scheme 17.14) [62]. These compounds were evaluated as corrosion inhibitors for oil refinery environments.



Scheme 17.14 Synthesis of 2-(2-pyridyl)azoles using ionic liquid [bmim]Cl under microwave irradiation

Recently, the applications of ionic liquids and microwave technology have resulted in developing of new environmental friendly technology, such as the aqueous [bmim]BF_4 as a green solvent in the microwave-assisted clean synthesis of 1*H*-benzo[f]chromene derivatives. A high-yielding and fast method for the conversion of substituted 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones under microwave irradiations was achieved. This methodology provides higher yield in short reaction times (i.e., seconds), using ethyl ammonium nitrate $[EtNH_3]NO_3$ as solvent and catalyst. The catalyst can be recycled and reused for several times (Scheme 17.15) [63].



Scheme 17.15 Synthesis of 1*H*-benzo[f]chromene derivatives using $[EtNH_3]NO_3$ as solvent and catalyst

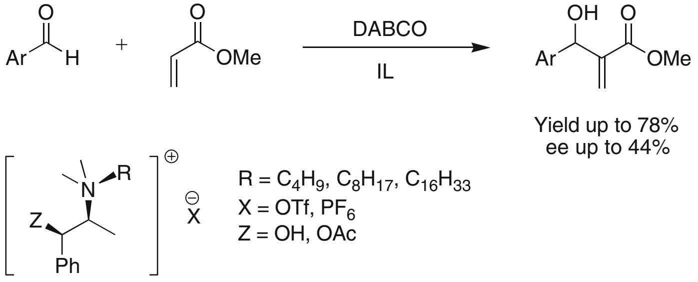
The above examples clearly demonstrate the potential of microwaves in ionic liquids as solvent and/or catalyst. Many well-known and new reactions have been discovered by this technology with evident advantages in most of the cases. The synergism arising from the combined use has enormous potential to meet the increasing demand for environmentally benign chemical processes.

17.5 Design and Synthesis of Chiral Ionic Liquids

One of the important properties of ionic liquids is that they can be fine-tuned to meet specific solvation requirements to influence reaction outcomes. In recent years, the use of chiral ionic liquids as reaction media for asymmetric organic reactions and chiral discrimination as well as the optical resolution of racemic mixtures has dramatically increased. Unfortunately, there are only a few chiral ionic liquids that are designed, synthesized, and used as solvents for asymmetric reactions, leaving open an important area with huge potential and scope for further development.

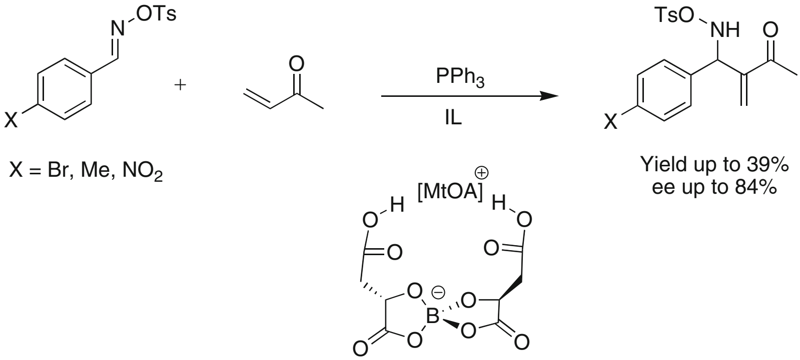
Though various modifications of cations such as ammonium, pyridinium, oxazolinium, and thiazolium have occurred, the imidazolium-cation-derived chiral ionic liquids have gained widespread usage due to their facile preparation, low melting points, and relatively favorable viscosity. The best-known imidazole-derived salts that have been reported so far contain the chiral moieties bonded to one or both of the nitrogen atoms on positions 1 and 3 of the imidazolium cation. Also, there are several chiral ionic liquids in which the chiral moiety is contained in the anion.

Groundbreaking work in this area was reported by Pegot and coworkers, who designed an ephedrinium cation and used it as reaction media for an asymmetric Baylis–Hillman reaction between aromatic aldehyde and methyl acrylate (Scheme 17.16) [64]. A large excess of methyl acrylate and a catalytic amount of 1,4-diazabicyclo[2.2.2]octane DABCO did not improve the yield or enantioselectivity. However, the best enantioselectivity (up to 44%) was obtained when the reaction was performed for 7 days. These results were exciting enough to motivate other researchers to explore this important area.



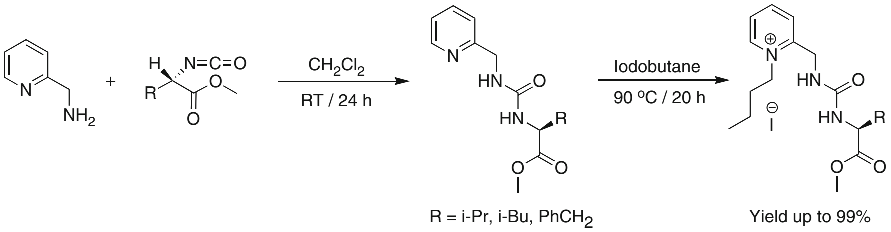
Scheme 17.16 Ephedrinium cation as reaction media for an asymmetric Baylis–Hillman reaction

Another excellent piece of work in this area on the aza-Baylis–Hillman reaction was published by Gausepohl and coworkers [65]. In this process, a C–C bond occurs between an activated alkene and imine. For this purpose, a new malic-acid-based ionic liquid (sodium dimalatoborate salt) was designed and synthesized (Scheme 17.17). To assess the efficacy of it for chiral induction, the aza-Baylis–Hillman reaction between methyl vinyl ketone and *N*-(4-bromobenzylidene)-4-toluenesulfonamide was examined. In this model reaction, a reasonable conversion of 39% and high enantiomeric excess of up to 84% were obtained.



Scheme 17.17 Aza-Baylis–Hillman reaction using malic acid-based ionic liquid

Recently, Ni and group [66] introduced a new type of chiral ionic liquid based on pyridinium cation having a chiral moiety tethered to a urea unit. The synthesis of salt involves a reaction of 2-aminomethyl pyridine with chiral 2-isocyanate-3-methylbutyrate and then heating in the presence of alkyl halide to form salt (Scheme 17.18). In total, nine chiral pyridinium salts were synthesized with varying amino acids. Currently, the authors are using these salts for asymmetric induction in organic transformation.



Scheme 17.18 Synthesis of chiral ionic liquid based on pyridinium cation having a chiral moiety tethered to a urea unit

Ionic liquids have numerous applications in organic synthesis. Some of the important reactions have proved that ionic liquids are truly versatile catalysts. Reaction media include, esterification reaction [67, 68], aldol condensation [69, 70], hydrogenation [71], Friedel–Crafts reactions [72, 73], oxidation [74–76], Henry reaction, cross-coupling reactions [77, 78], and some enzyme reactions [79, 80].

17.6 Conclusions and Future Outlook

Over the past two decades, ionic liquids have become a solvent of choice as well as catalyst in organic synthesis. The early progress made in this area prompted chemists to design better, safer, and general methods for the synthesis. Today, a broad range of such salts is readily available either commercially or could be easily synthesized from common starting materials, providing a boost for synthetic applications. In fact, a large number of laboratories in academia as well as industry have adapted their use. Because the properties and behavior of the ionic liquid can be adjusted to suit an individual reaction type, they can truly be described as "designer solvents." We have demonstrated through this chapter that by choosing the correct ionic liquid, high product yields can be obtained. Further, the ionic liquid can be recycled, reducing processing costs. It must be emphasized that reactions in ionic liquids are not difficult to perform and usually require no special apparatus or methodologies. The reactions are often quicker and easier to carry out than those using conventional organic solvents, which is of exceptional importance due to strengthening environmental regulations and safety concerns. Recent trends include significant efforts in several areas of organic synthesis. For example, synthesis development research most likely in the green chemistry areas will dominate in the foreseeable future. These include, but are not limited to, the ionic liquid–based multistep one-pot processes, asymmetric synthesis, and the development of chiral ionic liquids.

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