

CHIRAL IONIC LIQUIDS: APPLICATIONS IN CHEMISTRY AND TECHNOLOGY

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FOREWORD

Ionic liquids are novel solvents having a wide range of applications due to their tailored properties. Numerous books exist about the synthetic protocols, physicochemical properties, and the chemical and industrial uses of ionic liquids. Ionic liquids having an element of chirality, or chiral ionic liquids, are a sub-class of ionic liquids that play a key role in chiral recognition and separation as well as in asymmetric synthesis and catalysis. Despite an exponential surge in research articles over the past ten years, there are extremely few books on this topic. I am, therefore, very grateful to the editors and publishers for this book.

This book is organized into ten chapters and aims to provide the readers a thorough understanding of the design, synthesis, and significant applications of chiral ionic liquids.

The basics of chirality and ionic liquids are covered in Chapter 1, along with a brief overview of the synthesis, structural design, and uses of ionic liquid systems in chiral transmissions.

Chapter 2 and Chapter 3 give detailed insight into the design, synthesis, and important applications of carbohydrate, amino acid, and terpenoid-based chiral ionic liquids

Chapter 4 to Chapter 7 are very important and can be considered the backbone of this book. These chapters provide insight into the applications of chiral ionic liquids in chiral recognition and separations using capillary electrophoresis, gas and liquid chromatography, and various spectroscopic techniques

Chapter 8 discusses the organocatalytic applications of functionalized chiral ionic liquids

Chapter 9 is about the utility of chiral ionic liquids in aqueous two-phase separations (ATPS)

The final chapter extensively covers the synthesis and applications of chiral-supported ionic liquids

I firmly believe that this book will benefit the students as well as the researchers working in academia and industries. I extend my congratulations to the editors and all of the authors who have contributed to the current format of this book

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PREFACE

Ionic liquids (ILs) are compounds with some privileged properties like non-volatility, task specificity, electrochemical potential, tuneable density and viscosity, less (or non-) toxic nature, recyclability, etc. They have potential applications in different fields like synthesis and catalysis, energy materials, analytical chemistry, separation technologies, biotechnology, etc. Ionic liquids can be divided into several classes, such as protic ionic liquids, room temperature ionic liquids, chiral ionic liquids, Lewis acidic ionic liquids, etc. Among the various classes of ionic liquids, chiral ionic liquids (CILs) gained considerable attention from the research community in the past few decades as these compounds possess all the inherent properties of simple ionic liquids and are particularly significant in the field of asymmetric synthesis, organo-catalysis, enantiomeric separations and chiral recognition by spectroscopic and chromatographic methods due to the presence of chirality in their structures. The growing demand for pure enantiomers in the pharmaceutical and food industries sparks further development in the field of extraction and separation systems modified with CILs, highlighting them as affordable and environmentally friendly chiral selectors and solvents. In recent years, exponential growth in research publications has been observed in the field of synthesis and applications of CILs.

Our research group has been working on the synthesis and applications of CILs since 2013. The analysis of the existing literature shows that there are numerous books on the synthesis, catalytic, analytical, biotechnology, and industrial applications of ionic liquids, but to the best of our knowledge, there is no book about the synthesis and applications of CILs. In view of this, it was thought to edit a book specifically on these aspects of the CILs. This book is aimed at providing an insight into recent methodologies for the synthesis and applications of CILs in chemistry and technology. The main topics covered in the book (having 10 chapters) include Basic concepts of ionic liquids and chirality; Design, synthesis, and applications of chiral carbohydrate ionic liquids; Chiral ionic liquids from amino acids and terpenoids: synthesis and applications; Role of chiral ionic liquids in enantio-separation using capillary electrophoresis; Chiral ionic liquids stationary phases in electrophoretic separations; Chiral ionic liquids and chromatography: synergistic effects in enantio-separations; Chiral ionic liquids in chiral recognition methods using spectroscopic techniques; Design, synthesis and organo-catalytic applications of functionalized chiral ionic liquids; Chiral ionic liquids based biphasic systems in enantio-separations and Chiral-supported ionic liquids in asymmetric synthesis.

Overall, the book has been written to be a useful resource for academia as well as industry, particularly for students/researchers working in the areas of organic synthesis, engineering materials, and environmental and applied chemistry.

We, as Editors, would like to thank one and all who have been involved in the publication of this book. All our authors have done a prodigious job in formulating their chapters, and it has been a pleasure to read their contributions. All our colleagues have met their obligations in the most timely and passionate manner. We are truthfully indebted to them for making our task so effortless. The editors would also like to thank Ms. Humaira Hashmi, editorial project manager (EPM), and Ms. Sheikh Maryam Rehman, Publications Manager, for their support and help during this project. Finally, in a project like this, someone must take accountability for any mistakes that have crept in. Eventually, we are the editors, and this responsibility is ours. So, we tender an unreserved apology for any mistakes that have been found in the book.

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CHAPTER 1

Basic Concepts of Ionic Liquids and Chirality

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Abstract: The current chapter describes the basic concepts, selected physicochemical properties, and general structural supramolecular organization of ionic liquids. The concepts and importance of ion pairs, supramolecular aggregates, and the organization of neat ionic liquids are also addressed in this chapter. These ionic fluids have also been used as chiral inductors, and the basis for this application is also evaluated in this chapter. The main objectives of this opening chapter of the book are to highlight selected examples showcasing the significance of chiral ionic liquids and their applications in chemistry, particularly in promoting chiral transmission.

Keywords: Application, Chirality, Ionic liquids, Ion pairs, Induction, Organization.

INTRODUCTION

The importance of ionic liquids (ILs) in modern chemistry is undisputed. In the 1990s, the chemistry associated with ILs experienced growing interest, and since the dawn of this century, ILs have returned to prominence. The discovery of ILs is typically attributed to the pioneering work of Paul Walden, who described the synthesis and properties of ethylammonium nitrate in 1914 [1]. However, some have directly questioned whether this was the first report and suggested that this substance was described three years earlier [2]. Indeed, at that time, no one could have predicted that almost a century later, ILs would emerge as a significant and essential area of study. Apart from the controversy, no one doubts the importance and impact that the chemistry associated with ILs has on modern chemistry. This status is easily noticeable by the large number of important reviews recently published describing several applications, specific properties and trends in the use

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of these ionic fluids. Due to their industrial applications, the interest in ILs chemistry and technologies has increased, as reviewed elsewhere [3 - 7]. In almost every field of technology, ILs are currently being utilized due to their exceptional, appealing and tunable physicochemical properties, which are primarily responsible for their immense success. By carefully selecting both the cation and anion, it is possible to obtain an IL with properties tailored to a specific process.

ILs (examples in Fig. 1) may be defined as molten salts with melting points down to 100 °C. They are composed entirely of ions, typically with an organic cation and an anion, which may be organic or inorganic [8]. Among the attractive physicochemical properties observed for these salts, it is possible to highlight their negligible vapor pressure, thermal and chemical stabilities, typically a large electrochemical window, and relatively elevated ionic conductivity.

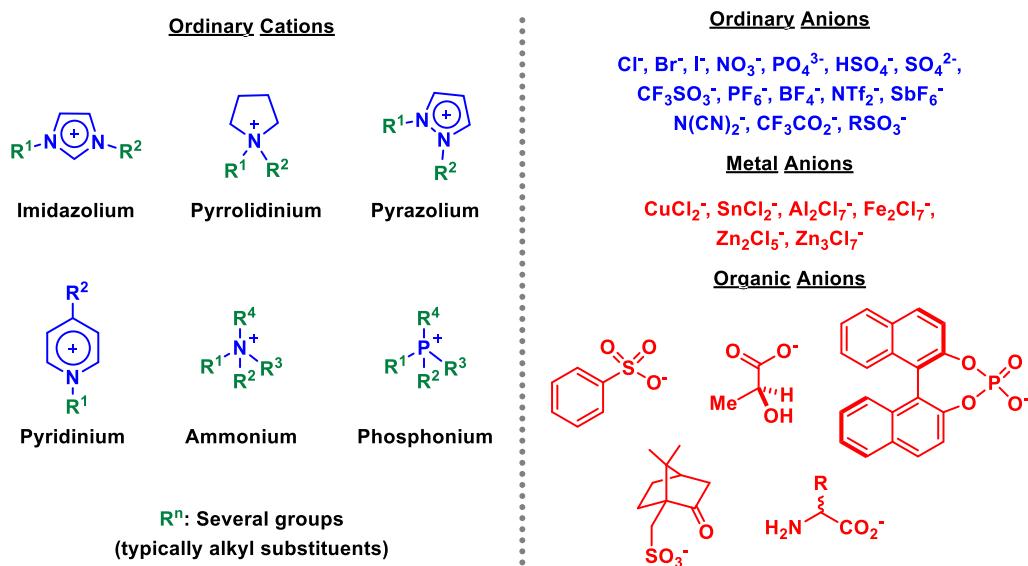


Fig. (1). Structures of some cations and anions used to afford ionic liquids.

Due to the success observed in the application of ILs in several areas of technology, the class of task-specific ILs (also known as TSILs) naturally emerged. TSILs (examples in Fig. 2) arise from a reaction to incorporate a functional group covalently tethered to either the cation, the anion, or both of an otherwise ordinary IL. The first example of a TSIL was described in 1999, and it was applied to promote the benzoin condensation reaction [9]. A few years later, the concept of TSILs was coined and summarized [10]. TSILs aim to harness the beneficial physicochemical properties of ordinary ILs with any property of the functionalization incorporated in the final structure.

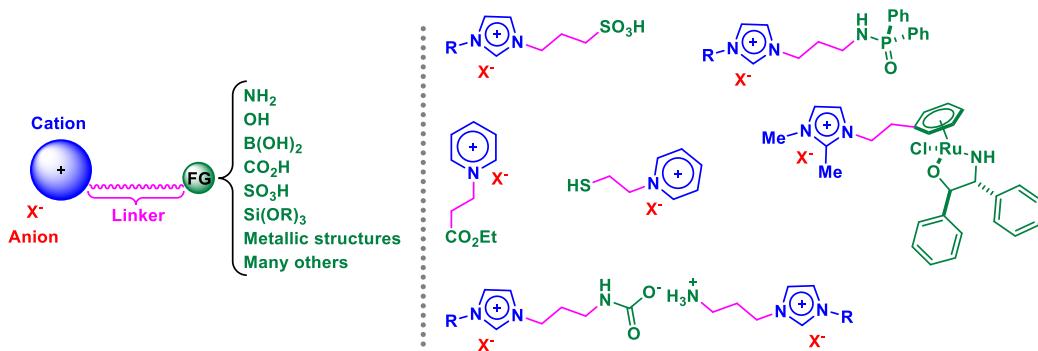


Fig. (2). Examples of task-specific ionic liquids. (Left) General molecular architecture of a TSIL and (Right) examples of some TSILs already described in the literature.

The evolution of IL chemistry naturally led to the development of chiral ILs (CILs) and chiral TSILs (CTSILs), as shown in Fig. (3).

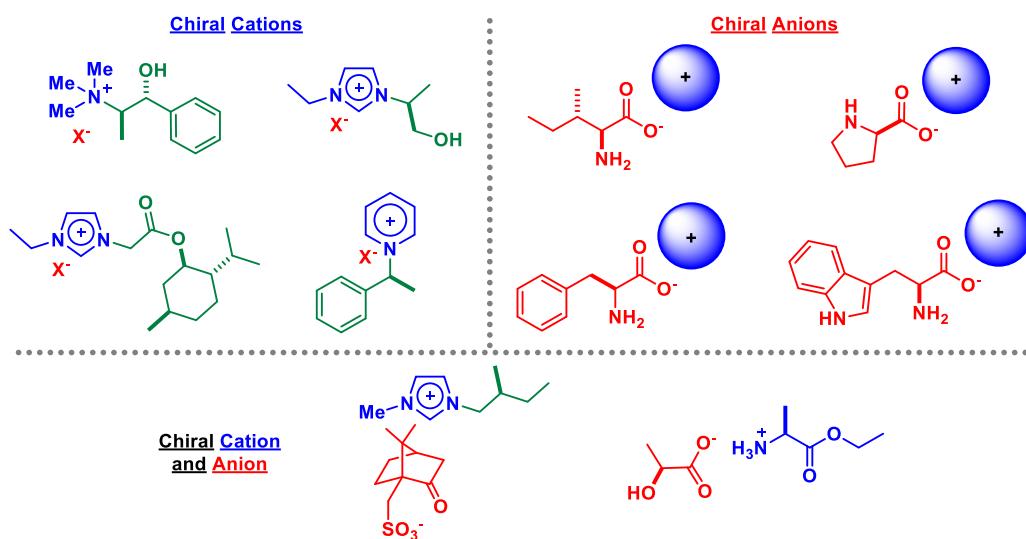


Fig. (3). Examples of chiral ionic liquids include those utilizing chiral groups on the cation (blue), on the anion (red), or combining them on both.

The first IL bearing two stereogenic centers was reported in 1996 [11], but the C-2 symmetry axis renders the structure achiral. A few years later, Seddon and co-workers reported the first example of a chiral imidazolium-based IL [12]. The anion was derived from lactic acid, and the lactate-containing structure was applied as the solvent to perform Diels-Alder reactions with reasonable diastereoselectivities (endo/exo). CILs may have their chirality held in the cation, in the anion, or both [13]. The development of the chemistry of ILs and their chiral

CHAPTER 2

Design, Synthesis, and Applications of Chiral Carbohydrate Ionic Liquids

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Abstract: Carbohydrates are nature's most prevalent bio-organic substance. Because of their benign nature and ubiquitous availability, the most relevant field of research is examining these chemicals for value-added uses. Although carbohydrate-derived chiral ionic liquids have shown promise in asymmetric synthesis, carbohydrate-based chiral auxiliaries, catalysts, and reagents have received little attention. Only CILs derived from isomannide and isosorbide proved useful for a variety of sustainable catalysis and asymmetric reactions. As a result, numerous research groups have recently developed carbohydrate-derived chiral ionic liquids from a naturally available chiral pool and evaluated their application in asymmetric synthesis and sustainable applications. This book chapter will cover the design, synthesis, and applications of chiral carbohydrate ionic liquids.

Keywords: Asymmetric synthesis, Carbohydrates, Catalysis, Sustainable, Synthesis.

INTRODUCTION

Ionic liquids have gained significant attention in recent years due to their unique properties and diverse applications in various fields of science and technology. These remarkable liquids are composed entirely of ions and have melting points below 100°C [1]. Unlike traditional organic solvents, which consist of molecules, ionic liquids are made up of large organic cations and inorganic or organic anions. This distinctive molecular arrangement results in their intriguing properties and provides a platform for innovative applications [2].

Ionic liquids possess several distinct properties that make them attractive for various applications. Some key properties include:

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Low Volatility

Ionic liquids have low vapor pressures, making them non-volatile and less prone to evaporation compared to conventional solvents.

Wide Liquid Temperature Range

Ionic liquids can remain liquid over a wide temperature range, including room temperature, which allows for their practical use.

High Thermal Stability

Ionic liquids are generally thermally stable, even at elevated temperatures, making them suitable candidates for high-temperature processes.

Good Solvating Power

Ionic liquids exhibit excellent solvating capabilities for both polar and non-polar compounds, enabling efficient dissolution of a wide range of substances.

High Ionic Conductivity

Ionic liquids can possess high ionic conductivity, making them potential candidates for use as electrolytes in energy storage and conversion devices.

Tunable Properties

By modifying the cation and anion constituents, the physicochemical properties of ionic liquids can be tailored to meet specific requirements.

However, the toxicity of certain ILs has raised concerns regarding their environmental impact and potential health hazards [3]. To address these concerns, researchers have turned their attention to developing biobased ionic liquids as a more sustainable and environmentally friendly alternative. Biobased ionic liquids derived from renewable biomass sources offer the potential to overcome the toxicity issues associated with traditional ILs while retaining their beneficial properties [4].

The development of biobased ionic liquids provides a promising approach to mitigate the toxicity concerns associated with traditional ILs. By utilizing renewable biomass sources, these ILs offer improved biocompatibility, reduced environmental impact, and enhanced biodegradability. The use of biobased ILs can contribute to the development of more sustainable and environmentally friendly solvents for various applications, ensuring a greener future for the utilization of ionic liquids.

The development of carbohydrate-based ionic liquids arose from the desire to explore sustainable and biocompatible alternatives to traditional ionic liquids. Carbohydrates, being renewable and abundant natural resources, offer a green and accessible starting material for the synthesis of these ionic liquids. Moreover, carbohydrate-based ionic liquids can exhibit unique properties and compatibility with biological systems, making them attractive for various applications in pharmaceuticals, biocatalysis, and separation sciences. Carbohydrate-based ionic liquids offer several advantages over their conventional counterparts [5 - 7].

Renewable and Sustainable

Carbohydrates are derived from renewable sources, making carbohydrate-based ionic liquids more environmentally friendly and sustainable compared to other ionic liquids derived from fossil fuels.

Biocompatible

Carbohydrate-based ionic liquids are generally biocompatible and have lower toxicity, making them suitable for applications involving living systems, such as biocatalysis and pharmaceuticals.

Chirality

Carbohydrate-based ionic liquids can possess inherent chirality due to the asymmetric nature of carbohydrates. This chirality can be harnessed for chiral discrimination, enantioselective synthesis, and chiral separation processes.

Versatility

Carbohydrate-based ionic liquids can be chemically modified to fine-tune their properties, allowing for a wide range of applications in different fields.

Chirality plays a fundamental role in chemistry, particularly in pharmaceuticals, biology, and materials science. Chirality refers to the property of asymmetry in a molecule, where a molecule and its mirror image are not superimposable. Enantiomers, the two mirror-image forms of chiral molecules, often exhibit different biological activities, pharmacological effects, and chemical reactivity. Understanding and controlling chirality is crucial in drug design, asymmetric synthesis of pharmaceuticals, enantioselective catalysis, and chiral separation techniques. Carbohydrate-based ionic liquids, with their inherent chirality, offer a valuable platform to study and exploit the importance of chirality in various chemical processes and applications [8]. Scientists have leveraged the chiral nature of carbohydrates to develop and utilize carbohydrate-based ionic liquids in various applications. By incorporating chiral carbohydrates into the ionic liquid

CHAPTER 3

Chiral Ionic Liquids from Amino Acids and Terpenoids: Synthesis and Applications

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Abstract: Ionic liquids (ILs) are widely useful as catalysts or as a medium for reactions in varied chemical processes since they possess environment-friendly chemical/physical properties. Ionic liquids (ILs) are those chemical entities that consist of a cation and an anion having melting points less than 100 °C. Since the last decade, there has been an increase in the number of chiral ionic liquids (CILs) and their applications. Most chiral ILs have either a chiral cationic or chiral anionic center. There are also some CILs with both chiral cationic and chiral anionic centers. Molecules obtained from nature (biomolecules) are mostly degradable; a number of them are not toxic and are sustainable in nature. So, the development of CILs from biodegradable biomolecules provides an opportunity to further improve their greener aspects. Amino acids are a special kind of biomolecule due to their easy conversion into both anions and cations; the diverse functionalities in their side chains make them chiral and also enhance their properties. In comparison to various other chiral molecules, amino acids are cheaper and plentiful. In the last few years, an array of novel chiral ionic liquids were synthesized from simple, economical, naturally occurring terpenoids. In this chapter, very recent developments about the amino acids and terpenoid-based CILs have been reported and reviewed.

Keywords: Amino acids, Biomolecules, Catalysts, Chirality, Chiral ionic liquids, Chiral pool, Environmentally benign, Green credentials, Ionic liquids, Sustainable, Terpenoids.

INTRODUCTION

Due to the growing environmental concern, the need for greener solvents for organic transformations has sparked the evolution of novel substitutes for toxic, volatile organic solvents [1]. Amongst them, room temperature ionic liquids (RTILs) appeared as potential candidates, and their prominent features include

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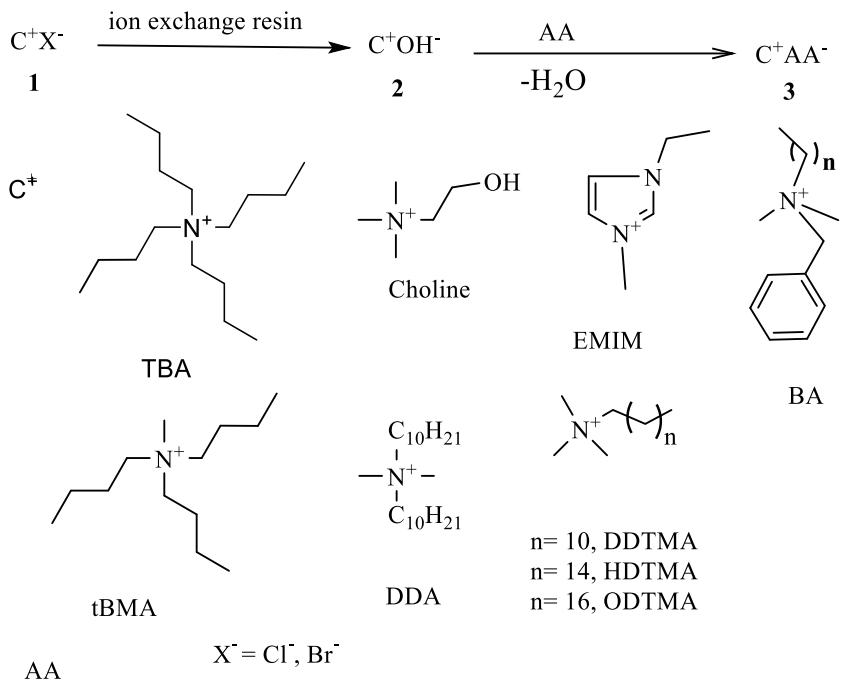
low vapor pressure, tunable properties, and recyclability [2]. These ionic liquids (ILs) can be easily synthesized and are useful as solvents in synthesis [3].

There had been an enormous increase in reaction yields/selectivity in comparison to the identical reactions using conventional organic solvents. Due to the presence of ions, they are polar and are able to dissolve a variety of organic and inorganic reactants. In the last ten years, another interesting group of ionic liquids, namely chiral ionic liquids, had emerged [4 - 6]; they have at least one chiral center. These chiral ionic liquids have stereogenic atom/atoms in the cation, anion, or in both the ions [7]. Chiral ionic liquids are widely used in chiral synthesis [8], chiral extraction [9], and as stationary phases in chiral chromatography [10a]. Flieger *et al.* [10b], in their recent interesting review, described the structures, properties, and applications of CILs in liquid chromatography, countercurrent chromatography, and various extraction techniques developed in recent years. Biomolecules are organic substances that form the basis of life. The union of ILs and biomolecules [11 - 14] opens opportunities in various fields like organic synthesis, electrochemistry, nanotechnology, biochemistry, pharmacology, food science, *etc.* Out of these biomolecules, amino acids (AAs) and terpenoids are the most abundant biomaterials in the nature and are well established since they are non-toxic, biocompatible and biodegradable [15]. In the present chapter, recent work on the development of CILs using amino acids/terpenoids is reported. Apart from that, work on new applications of amino acid/terpenoid-based chiral ionic liquids has also been reported.

Chiral Ionic Liquids from Amino Acids

Amino acids provide a renewable substitute for the development of ILs, having less toxicity and better biodegradability, which are the most important characteristics of “green” ILs.

Rozwadowski *et al.* [16] synthesized amino acid ionic liquids (AAILs) **3** using different L-amino acids and cations like tetrabutylammonium (TBA), choline, alkyl, 1-ethyl-3-methylimidazolium (EMIM), *etc.* (Scheme 1). NMR and FTIR spectra were taken; properties like specific rotation, thermal stability, glass transition temperature, and surface activity studies were reported. Many analyzed salts were thermally stable (in the range of 150–200 °C) and were liquids at room temperature. Out of the reported compounds, only 1-ethyl-3-methylimidazolium salts could dissolve cellulose.



glycine, L-valine, L-leucine, L-isoleucine, L-histidine, L-methionine, L-tyrosine, L-tryptophan, L-arginine, and L-threonine

Scheme (1). Synthetic route to amino acid-based ionic liquids (AAILs).

Nobuoka and coworkers [17] synthesized (S)-proline-based chiral ionic liquids **4** (Fig. **1**) and evaluated them as a chiral catalyst in Michael reaction of styrene derivative with cyclohexanone.

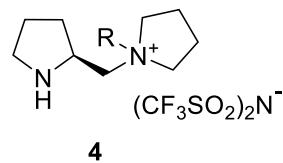


Fig. (1). (S)-proline-based chiral ionic liquids **4**.

The chiral ionic liquid catalyst showed excellent yields, good diastereoselectivities, and enantiomeric excess and was used for three cycles without any reduction in its activity and selectivity.

Zong group [18] carried out toxicity studies on cholinium-based ionic liquids toward a variety of microorganisms and enzymes. These ILs were found to be less

CHAPTER 4

Role of Chiral Ionic Liquids in Enantioseparations Using Capillary Electrophoresis

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Abstract: Ionic liquids (ILs) are low-melting compounds composed entirely of ions that exist as liquids at room temperature. Chiral ionic liquids (CILs) are a subclass of ILs that possess chiral characteristics. CILs are gaining immense attention as additives in enantioseparation techniques, such as capillary electrophoresis (CE). Capillary electrophoresis is a powerful analytical technique used for the separation of chiral compounds. CILs can affect the separation process through several mechanisms, including chiral recognition, modification of electrophoretic mobility, acting as a unique solvent system, and providing a chiral stationary phase. The use of CILs in the CE system offers several advantages for enantioseparation, including enhanced separation selectivity, improved resolution, and expanded applicability to a wide range of chiral compounds. However, the selection of an appropriate CIL and optimization of experimental conditions are critical to achieving the desired enantioseparation performance. Taking into account the blossoming research in the field, the present chapter summarizes the advancement in the application of CILs in capillary electrophoretic separations, taking examples from recent literature.

Keywords: Chiral ionic liquids, Chiral recognition, Capillary electrophoresis, Chiral selectors, Enantioseparations.

INTRODUCTION

Enantioseparation is the process involving the separation of enantiomers, which are optical isomers that are non-superimposable mirror images of each other. This process is significant across several scientific and industrial fields, such as the pharmaceutical industry [1], food industry [2], agrochemicals [3], environmental

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analysis [4], and chemical synthesis [5]. For example, enantioseparation is of prime importance in the field of pharmaceuticals. The enantiomers of a racemic drug can exhibit markedly different pharmacological, toxicological, pharmacokinetic, and metabolic properties [6]. Therefore, it is important to ensure the enantiomeric purity of drugs to control their efficacy and safety while minimizing or eliminating the side effects. Enantioseparation can also enable understanding and control of the properties of chiral compounds, thus helping to develop new drugs with improved efficacy and safety profiles [7]. The most widely used techniques for enantioseparation are high-performance liquid chromatography (HPLC), gas chromatography (GC), capillary electrophoresis, *etc.* [8]. However, the recent progress in the capillary electrophoresis technique has made this a preferred technique for enantioseparations, as evident from an increasing number of publications in this field [9]. Capillary electrophoresis (CE) involves the separation of analytes based on their electrophoretic mobility in the presence of an electric field. As compared to HPLC and GC, capillary electrophoresis offers several advantages for enantioseparation, including simple instrumentation, low consumption of solvents, high separation efficiency, and good resolution. CE offers high flexibility based on the use of a variety of separation modes, such as Electrokinetic Chromatography (EKC), Micellar Electrokinetic Chromatography (MEKC), Microemulsion Electrokinetic Chromatography (MEEKC), Non-aqueous CE (NACE), Ligand-Exchange CE (LECE), or Capillary Electrochromatography (CEC) [10, 11]. Among them, EKC is the most popular mode for chiral separations.

The process of chiral separation requires a chiral selector that can discriminate among the enantiomers, enabling their separation. A great variety of molecules, such as surfactants, antibiotics, chiral crown ethers, polysaccharides, and cyclodextrins, have been employed as chiral selector molecules in enantioseparation [12]. Though many of them have proved effective in enantioseparations, some drawbacks, such as low solubility, complex synthesis, high cost, temperature instability, low resolution, *etc.*, may limit their use [13]. The search for new chiral selectors capable of achieving higher resolution is still the most relevant topic in the field of enantioseparation. In this respect, chiral ionic liquids (CILs) recently attracted attention for achieving enantioseparations [14, 15]. Ionic liquids (ILs) are molten salts composed of organic cations and inorganic or organic anions. ILs have drawn the interest of the scientific community due to lucrative properties such as low melting point, low vapor pressure, high stability, reusability, *etc.* [16]. CILs are a subclass of ILs that possess a chiral moiety in their structure. CILs can provide chiral recognition and interact selectively with enantiomers, leading to their differential migration in the capillary. In comparison to traditional chiral selectors, the advantageous properties of CILs that make them desirable for use in enantioseparations include

low melting points, low volatility, high thermal stability, wide temperature range, tunability, high selectivity, versatility, and reusability [17]. Moreover, the CILs can also act as non-molecular solvents, dissolving compounds of a broad range of polarity. Thus, they are capable of acting both as chiral solvents and chiral selectors, having the potential to discriminate between the enantiomers with high target specificity [12]. This simplifies the separation process by eliminating the need for separate additives or solvents. The dual functionality of providing optical resolution and acting as solvent is an advantage over traditional chiral selectors, as the use of traditional chiral selectors may require one or more solvents as mobile phase additives. In CE, CILs can be used as background electrolyte additives in a system with a chiral selector, or they can be used as sole chiral selectors for the separation of a wide range of chiral compounds [18]. Several review articles concerning the use of CILs in chiral separations have been published in recent years, indicating interest in the field [12, 13, 19].

The present chapter reviews the recent applications of CILs in capillary electrophoretic separations as chiral selectors in dual systems or as sole chiral selectors. Along with discussing the classification and synthesis of CILs involved in enantioseparations, it also throws light on the mechanisms involved in enantioseparation. The factors affecting the selection and design of CILs for electrophoretic separations, along with strategies for their design and synthesis, have also been discussed. Furthermore, the challenges and future prospects in the use of CILs for electrophoretic separations have been deliberated.

Classification and Synthesis of Chiral Ionic Liquids

The ionic liquids generally contain bulky organic cations (ammonium, alkylimidazolium, and pyridinium) and organic or inorganic anions (hexafluorophosphate (PF_6^-), tetrafluoroborate (TFB), *etc.*). The type and size of cations and anions influence the unique physicochemical properties of ILs, namely high conductivity, low volatility and vapor pressure, good thermal stability, high miscibility in water and organic solvents, *etc* [12]. The new group of ILs having a chiral center was generated with the discovery of imidazole-based quaternary salt by Herrmann *et al.* in 1996 [20]. However, the term 'chiral ionic liquids' was first used by Howarth *et al.* in 1997, who reported the synthesis of chiral dialkyl imidazolium bromide and its application as the catalyst in the Diels–Alder reaction [21]. In CILs, the chirality is endowed by the cation or the anion or sometimes by both the cation and anion. The chiral cation is often an ammonium, imidazolium, phosphonium, pyridinium, or piperidinium cation. The chiral anions can be amino acids, mandelic acid, lactic acid, borates, or camphorsulfonic acid [19]. The anion may also be a simple non-chiral ion Cl^- and Br^- . The CILs used for enantioseparation can be classified into three categories

CHAPTER 5

Chiral Ionic Liquids as Stationary Phases in Electrophoretic Separations

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Abstract: Ionic liquids (ILs) are exceptional solvents having melting points at or below 100 °C. They are completely made up of ions, often consisting of an organic cation and an inorganic or organic anion. ILs having chiral moiety are referred to as chiral ionic liquids (CILs). Cations, anions, or both can be chiral in CILs. A CIL can have chiral azolinium, imidazolium, ammonium, or pyridinium as its chiral cationic component. Lactic acid, borate, or camphor sulfonate are some examples of the chiral anion. CILs have recently been used in electrophoretic techniques in different forms, such as chiral ligands, background electrolyte (BGE) additives, chiral selectors, and chiral stationary phases for the separation of chiral compounds. As they integrate the benefits of ILs and the features of a chiral moiety, they are thought to be particularly fascinating in chiral investigation. Notably, the use of CILs as chiral selectors offers advantages over other chiral selectors whose employment is typically constrained by a few issues, such as high-temperature instability, high UV absorptivity, complex synthetic methodologies, low solubility, and expensive nature. Therefore, it is crucial to consider how CILs can be used as solvents and chiral selectors. In this chapter, the diverse applications of chiral ionic liquids as stationary phases in electrophoretic separations are discussed in detail.

Keywords: Chiral ionic liquids, Chirality, Chiral molecules, Chiral selectors, Electrophoretic separations, Stationary phases.

INTRODUCTION

Ionic liquids (ILs) are exclusive solvents having melting temperatures at or below 100 °C [1]. They are completely made up of ions, often consisting of organic cations and organic or inorganic anions [2]. ILs started gaining attention in the 1980s due to their unique properties, such as viscosity, non-flammability, minimal

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vapor pressure, conductivity, and miscibility in a range of solvents [3]. Some properties of ILs are governed primarily by the anion, while others are impacted by the cation shape, symmetry, or length of the alkyl chain. Analytical chemistry has shown a lot of interest in the development and application of ILs [4 - 6].

The subclass of ILs having chiral moiety is known as chiral ionic liquids (CILs) [7]. Azolinium, pyridinium, imidazolium, or ammonium molecules can be a chiral cationic component in CILs. On the other hand, amino acid, lactic acid, borate, or camphor sulfonate can act as a chiral anionic component in CILs [8]. CILs have grown at an exponential rate because of their chiral discrimination capabilities. As they combine the benefits of ILs with those of a chiral moiety, they are regarded as particularly promising in chiral analysis. Moreover, CILs are easy to synthesize and stable at high temperatures and their production is straightforward. For more than ten years, numerous CILs have been used as chiral discrimination tools in extractions, gas chromatography (GC), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), mass spectrometry (MS), infrared (IR), Raman, and nuclear magnetic resonance (NMR) spectroscopy [4]. Among these techniques, CE demonstrates outstanding chiral recognition power owing to high separation efficiency, minimal sample and solvent consumption, quick migration periods, adaptability, and straightforward instrumentation [9]. In CE, CILs have been used as chiral ligands, chiral selectors, background electrolyte (BGE) additives, and chiral stationary phases for electrophoretic separations of chiral molecules. The use of CILs in electrophoretic separations is important due to their thermal robustness and non-flammability. In this chapter, the diverse applications of CILs as stationary phases in electrophoretic separations are discussed in detail. Even though CILs have only been utilized in a few studies for electrophoretic separations, it is clear from the encouraging outcomes discussed in this chapter that CILs have a bright future in this area and that their use will continue to grow significantly.

Principle of Capillary Electrophoresis (CE)

CE is the most prevalent analytical methodology as a superb alternative to the widely utilized HPLC to carry out the electrophoretic separations of enantiomers, proteins, and nucleic acids based on their binding affinity, charge, and size under an electric field [10]. In this technique, the separation of different species is mainly based on their effective mobilities in a narrow silica capillary having an interior width of 50 mm when subjected to an electric field. The effective mobility is the vector addition of the electrophoretic mobility, which is regarded as electroosmotic flow (EOF) [11]. A fused-silica capillary inner surface silanol group ionizes above pH 3. Positive ions from the electrolyte solution, also known as background electrolyte (BGE), will be drawn by the negative wall created by

the silanol groups at this or higher pH, generating a double layer. When an electric voltage is applied to the capillary ends, cations flow towards the cathode. This flow, or the EOF, will pull the bulk solution in this direction. In light of this, positively charged molecules will enter the detector first in a cathodic detection, followed by neutral species, and then negatively charged molecules. It is worth noting that the molecule size and charge will both affect its effective mobility, as electrophoretic mobility is directly proportional to effective charge and inversely proportional to the molecular size. Negatively charged species can only be detected if the EOF can prevent them from moving electrophoretically toward the anode. Although it is obvious that this is the most straightforward approach, CE's vast versatility opens up a myriad of other options. If, for example, coated capillaries are utilized, this straightforward scenario can be further altered. The coating may be permanent, covalently linked to the inner surface of the capillary, or it may be temporary, requiring replacement after each analytical run. Additionally, electrophoretic-based in-capillary pre-concentration techniques can be used to improve the sensitivity of the proposed procedures, which can also be improved by utilizing detection systems like mass spectrometry (MS) or fluorescence, among others.

Notably, because enantiomers have equal physicochemical properties, their electrophoretic mobility will be identical, and enantioseparation is possible only in a chiral atmosphere, like interactions with a chiral selector. Instead of covalent bonding, these interactions often include van der Waals forces or hydrogen bonding. As a result, diastereoisomer complexes are momentarily formed, and depending on their different mobilities, they are subsequently detached in a process known as direct methodology. Numerous chiral selectors, such as chiral metallic complexes, crown ethers, cyclodextrins, and chiral surfactants (such as bile acids), have been utilized in the CE [12]. Because of their remarkable structural features, thermal stability, and adjustable polarity, CILs have emerged as efficient chiral selectors in CE. Also, it is possible to synthesize a variety of task-specific CILs with different anion-cation combinations.

Overall, two mechanisms—one chromatographic and the other electrophoretic—are used to achieve chiral separations in CE. The different complexation constants between the enantiomers and the chiral selector give birth to the chromatographic mechanism. For instance, if an analyte is strongly “embedded” in the chiral selector, it results in the formation of two enantiomer-chiral selector complexes with slightly different sizes. Due to this difference, they have dissimilar electrophoretic mobilities and form the basis of the electrophoretic mechanism.

CHAPTER 6

Chiral Ionic Liquids and Chromatography: Synergistic Effects in Enantioseparations

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Abstract: Chiral ionic liquids (CILs) are a subcategory of ionic liquids that possess a chiral moiety. The need for chiral separations in several industries, including pharmaceutical, food, and chemical industries, has led to an increasing search for materials capable of performing such separations. CILs have emerged as effective candidates for the separation of enantiomers because of their advantageous properties like low melting point, little vapor pressure, high thermal stability, good electrical conductivity, and low cost. They are being employed in chromatographic methods as chiral ligands, stationary phases, and chiral selectors for the separation of chiral compounds. As compared to other chiral selectors (cyclodextrins, polysaccharides, surfactants, and crown ethers), CILs show better solubility, easy synthesis, and low cost. They represent an intriguing opportunity for use in chromatography because of their wide range of solubility in organic and inorganic solvents, as well as their miscibility with common solvents (methanol and acetonitrile). Considering the flourishing research in the field, the present chapter summarizes the advancement in the application of CILs as chiral ligands, stationary phases, and chiral selectors in liquid and gas chromatographic techniques. Furthermore, the chiral recognition mechanism and prospects for the use of CILs in enantioseparations have been examined.

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Keywords: Amino acids, Chiral mechanism, Chiral ionic liquids, Chiral molecules, Chiral cation, Chiral anion, Chiral ligands, Chiral selectivity, Diastereomers, Enantiomers, Gas chromatography, Green precursors, Liquid chromatography, Mobile phase additives, Racemic drugs, Stereoselective, Stationary phases.

INTRODUCTION

Ionic liquids (ILs) comprise salts having a melting point below 100°C. These have piqued the interest of researchers in several disciplines of the chemical industry during the last several years. The earliest mention of the production of salts with the qualities of today's "ionic liquids" emerged in the nineteenth century, between 1888 and 1914 [1, 2]. ILs partially substituted organic solvents and are gaining recognition due to their environmentally friendly nature and the ability to synthesize task-specific ILs [3]. ILs have the capacity to dissolve both polar and nonpolar substances, and their most important attribute is that they cannot evaporate at high temperatures. Typically, ILs are primarily composed of cations that contain nitrogen and are rich in alkyl groups, paired with various anions like halides, tetrafluoroborate, hexafluorophosphate, triflimide, *etc.* As ILs consist of large inorganic anions along with charged organic cations that are not closely packed in the lattice, the melting points of ILs are generally low. Recently, ILs have attracted considerable attention in analytical chemistry and have been used in gas and liquid chromatography, extractions, capillary electrophoresis, and spectroscopy [4 - 7]. The particular properties of ILs can be expanded according to the task and can create a new type of ILs [8].

CILs constitute a type of ILs with a chiral moiety that has IL-like features, including low melting and boiling points, thermal stability, minimal vapor pressure, and excellent electrical conductivity [9, 10]. The first chiral quaternary salts were N-heterocyclic carbenes of imidazole, which were prepared by Herrmann *et al.* in 1996 [11]. However, these chiral imidazolium chlorides were not known as CILs at the time. Howarth *et al.* introduced the term "chiral ionic liquids" for the first time in 1997, when they characterized stable chiral dialkyl imidazolium bromide as Lewis acid, which was applied as the catalyst in the Diels-Alder reaction, affording great enantiomeric purity of the product [12]. CILs have lately been recognized as non-molecular solvents as well as chiral agents with chiral discrimination abilities and high selectivity towards selected enantiomers. This growing relevance is due to the CILs group's unique structural characteristics, in which either the cationic or anionic component, or both, can be chiral, making them enantioselective. In addition to the common properties of ILs, CILs have the advantages of easy synthesis and functionalization, making them

widely used in a wide range of applications such as chiral recognition [13, 14], organocatalysis [15, 16], background electrolytes in capillary electrophoresis [17, 18], stationary phase additives in liquid and gas chromatography [5, 19, 20], high-performance liquid chromatography [8, 21], liquid-liquid extraction [22] and stereoselective polymerization [23, 24]. The two of the most extensively studied uses of CILs at present are chiral molecule recognition and asymmetric organocatalysis. Both concepts incorporate the term 'chirality' in their definitions and are extremely beneficial for the isolation and synthesis of a wide range of key enantioselective chemicals. Various spectroscopic and chromatographic methods can be employed to analyze the separation of enantiomers of molecules. These techniques include NMR spectroscopy, fluorescence spectroscopy, circular dichroism, liquid or gas chromatography, capillary electrophoresis, capillary electrochromatography, micellar chromatography, and supercritical chromatography [7, 25]. The combination of these systems has yielded significantly improved outcomes in resolving enantiomers, thanks to the synergistic effects they offer when used together. However, the given chapter mainly focuses on the application of CILs as efficient chiral selectors in chiral recognition combined with chromatographic techniques mainly liquid and gas chromatography.

Structural and Synthetic Aspects of Chiral Ionic Liquids

CIL molecules can have a chiral cation, chiral anion, or both ions (Fig. 1). CILs can dissolve a wide range of polar and nonpolar analytes while also providing chiral selectivity. Furthermore, CILs are simple to synthesize and stable at high temperatures. There are two synthetic approaches for CILs: asymmetric synthesis and the use of a "chiral pool" as precursors [26, 27]. There has been significant progress in synthesizing CIL precursors from natural sources, direct synthesis from homochiral materials, and asymmetric catalysis employing prochiral precursors as starting materials [28]. Chiral recognition capabilities are frequently harnessed by utilizing a wide range of chiral selectors, such as cyclodextrins, cyclofructans, linear oligo- and polysaccharides, branched polysaccharides, monomeric and polymeric surfactants, macrocyclic and lincomycin antibiotics, crown ethers, etc. These diverse selectors are commonly employed in various applications [29, 30]. The chiral cationic part of a CIL may be a chiral imidazolium, pyridinium, ammonium, or azolinium. The chiral anion may contain a substance such as amino acid, lactic acid, borate, or camphor sulfonate [31]. Many CILs have been synthesized using α -amino acids as starting ingredients, owing to the low cost and high enantiomeric purity of these starting substances. In comparison to imidazolium and quaternary ammonium ILs, which are synthesized from fossil fuel, amino acid-derived ILs are thought of as bio-renewable and hence a greener family of solvents. Because amino acids (AAs) have both a

CHAPTER 7

Chiral Ionic Liquids in Chiral Recognition Methods Using Spectroscopic Techniques

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Abstract: Chiral recognition and separation methods have received a lot of attention due to the growing need for pure enantiomeric forms of substances. The separation of enantiomers is usually done with the aid of a chiral selector. Numerous chiral selectors, such as crown ethers, polysaccharides, antibiotics, etc., are extensively used in enantiomeric recognition studies; nevertheless, each one of them has limitations of its own. Recently, chiral ionic liquids (CILs), having inherent chirality due to the presence of a chiral cation or anion, have emerged as inexpensive and lucrative chiral selectors for enantiomeric recognition procedures. This article discusses the application of CILs in chiral recognition methods through spectroscopic techniques like UV-visible, NMR, and fluorescence spectroscopy. It also focuses on the mechanism behind chiral recognition.

Keywords: Chiral recognition, Chiral selectors, Chiral ionic liquids, Enantiomers, Fluorescence spectroscopy, NMR spectroscopy, Separation methods.

INTRODUCTION

Chiral recognition and separation methods are very crucial in analytical chemistry as well as in drug design and discovery. Since the two enantiomeric forms of a drug molecule can have different physiological actions and pharmacokinetic activities, the enantiopurity of the drug molecules must be asserted before their marketing. After the thalidomide tragedy, strict rules and regulations are imposed by the various agencies/governments regarding the enantiopurity of drugs. So, as of now, the separation and identification of enantiomers is a crucial step in the

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pharmaceutical, food, agriculture, and other allied industries [1 - 3]. The ever-increasing demand for the different enantiomeric forms of a substance has pushed the scientific fraternity in quest of easy, affordable, and efficient separation methodologies [4, 5].

The fundamental idea guiding chiral recognition and separation is the difference in the free energies of the two diastereomeric complexes formed by the chiral selector with the different enantiomers of the analyte. At least three distinct interactions between the selector and the analyte enantiomers in space exhibit the diastereomeric complex formation. Hence, the enantiomeric separation is feasible in a 'chiral environment' only (*i.e.* the chiral selector must be enantiopure). So, the structure of the chiral selector must have three different groups to interact with the enantiomers; the interactions can be attractive or repulsive [6, 7]. Mostly, the interactions involved are hydrogen bonding, electrostatic, hydrophobic, dipole-dipole, *etc.* It may be noted here that achiral counter anions like BF_4^- , PF_6^- , NTf_2^- , and I^- are also important in the enantioseparation process, as they also interact with the analyte molecules. To analyze the diastereomeric pairs formed between the chiral selector and enantiomers, chromatographic and spectroscopic techniques are commonly used. NMR spectroscopy is one of the most widely used techniques in this context since it makes it very simple to evaluate and differentiate between the NMR signals of the diastereomeric complexes generated with the chiral selector. It is very easy to evaluate the difference between NMR signals of the diastereomeric complexes formed with the chiral selector and, hence, differentiate them. Fluorescence spectroscopy is also an efficient technique for enantiodifferentiation as the fluorescent enhancement/quenching can be measured easily.

For the past three decades, ionic liquids have emerged as very efficient materials with applications in separation and purification methods, catalysis, energy sciences, biotechnology, *etc.* The ionic liquids having any kind of chirality in their structural motifs are called chiral ionic liquids (CILs). The chiral ionic liquids can be tailored/functionalized as per the structural requirements for a particular application. The cationic and anionic moieties can be designed to give CILs that are well famed for their far and wide applications in diverse fields like chiral separation and recognition, analytical techniques, organocatalysis, *etc.* Details of the synthesis, catalytic, and other applications of CILs are beyond the scope of the present chapter and can be found somewhere else [8 - 10]. Herein, we have showcased the multidimensional applications of these scaffolds in the chiral recognition and separation methodologies. Basically, the CILs can be studied in enantiomeric recognition by using chromatographic and spectroscopic techniques. The role of CILs in chromatographic separations has already been reviewed in the

previous chapters. The applications of CILs in spectroscopic techniques, particularly NMR and fluorescence spectroscopy, are discussed in this chapter.

To make the discussion more informative and concise, only the representative reports are discussed, with a special focus on the mechanistic aspects of chiral recognition.

CILS IN CHIRAL RECOGNITION

Chiral Recognition Using NMR Spectroscopy

The assessment of the chiral recognition potential of CILs by using NMR spectroscopy is an easy, energy-efficient, and fastest technique. Numerous methods, including derivatization, lanthanide shift reagents, *etc.*, are commonly used for the enantiomeric separation of racemic analytes using NMR spectroscopy. A myriad variety of chiral salts having chirality in cationic or anionic parts have been utilized for the recognition of *rac*-Mosher's acid and mandelic acid salts by ^{19}F and ^1H NMR spectroscopy, as obvious from the literature findings. The CILs can interact differently with the enantiomeric forms of Mosher's acid salt and lead to the formation of different diastereomeric complexes with both the enantiomeric forms [11, 12]. Some of the representative examples of the use of CILs in enantiomeric recognition using NMR spectroscopy are presented in the following sections.

Luo and co-workers [13] synthesized a series of CILs by employing different amino acid precursors viz. (*S*)-alanine, (*S*)-valine, (*S*)-leucine, (*S*)-isoleucine, and (*S*)-proline. After characterization, these were tested for their potential in chiral recognition of racemic Mosher's acid salt using ^{19}F NMR. The CIL derived from (*S*)-valine (Fig. 1) has shown the maximum enantioseparation capability, and the NMR coupling constant for the peaks was found to be 34.998 Hz.

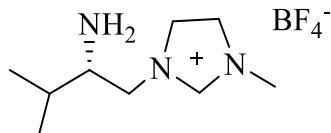


Fig. (1). (*S*)-valine based CIL.

Imidazolium-based CILs derived from the chiral precursors (*S*)-valinol, shown in Fig. (2), have been reported by Ishida *et al.* [14]. These CILs were tested as chiral selectors for the recognition of *rac*- α -methoxy- α -(trifluoromethyl)phenylacetic acid (MTPA) and *rac*-*O*-ethylphenylphosphonothioate (OEPT) enantiomers. The authors found that CIL with a rigid cyclic structure was effective in the enantiomeric recognition, and the CIL having an acyclic structure did not induce

CHAPTER 8

Design, Synthesis, and Organocatalytic Applications of Functionalized Chiral Ionic Liquids

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Abstract: The functionalized chiral ionic liquids (FCILs) can be considered a sub-class of chiral ionic liquids containing special functional groups for their use in fields like organo-catalysis, separation, purification, *etc.* The use of FCILs in the field of organo-catalysis is particularly important because of the recyclability and high efficiency of these systems. In the current chapter, the applications of functionalized chiral ionic liquids in asymmetric organo-catalysis are summarized with a special emphasis on synthetically important organic reactions like asymmetric Michael reaction, aldol reaction, epoxidation, asymmetric transfer hydrogenation, and Diels-Alder reaction.

Keywords: Aldol reaction, Diels-Alder reaction, Epoxidation, Functionalized chiral ionic liquids, Michael reaction, Organocatalysis, Transfer hydrogenation.

INTRODUCTION

Ionic liquids (ILs) are a class of organic compounds composed of ions with melting points below 100 °C [1]. These compounds are generally liquid at room temperature and polar in nature. ILs have much lower melting points as compared to inorganic salts due to the larger sizes of either the cations, the anions, or both [2]. Additionally, their molecular structures possess a high degree of asymmetry, which affects the ionic packing and thus decreases the Coulombic attraction between the ions. This non-coordinating behavior of ions enables them to remain in a liquid state. They show unique properties like high polarity, negligible volatility, high thermal stability, high ionic conductivity, low melting point, and structural designability that render them versatile materials [3]. They are immiscible with organic solvents and have remarkable air and moisture stability [4]. These unique characteristics contribute to the wide range of applications and

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practical uses of ionic liquids, making them ideal candidates for environmentally friendly and recyclable alternatives to volatile organic compounds; they are often used as industrial solvents [5]. Ionic liquids have proven to be highly versatile and eco-friendly substances extensively used in organic syntheses as catalysts or reaction media [6]. Their remarkable design flexibility allows for a wide range of anion-cation combinations, as well as the introduction of diverse functional groups into their structures, resulting in the creation of specialized “task-specific” ionic liquids. Among these task-specific ionic liquids, chiral ionic liquids have attained significant interest and attention across the globe [7]. The CILs are important not only in chiral synthesis and chiral extraction but also in chiral chromatography and chiral NMR shift reagents [8]. The exceptional properties of chiral ionic liquids make them vital tools for achieving enantioselective transformations and facilitating chiral separations in various scientific disciplines [9]. Their broad range of applications and potential for enhancing stereochemistry have positioned them as promising candidates in the quest for greener and more efficient chemical processes.

Chiral Ionic Liquids

Chiral ionic liquids form a unique subgroup within the category of ionic liquids, distinguished by the presence of chiral ions that possess non-superimposable mirror images. The name “chiral ionic liquids” was used for the first time by Howarth *et al.* in 1997; they described stable chiral dialkyl imidazolium bromide **1** (Fig. 1) as a Lewis acid and applied it as the catalyst in the Diels–Alder reaction, leading to high enantiomeric purity of the target product [10] (Scheme 1).

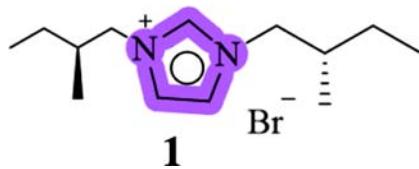
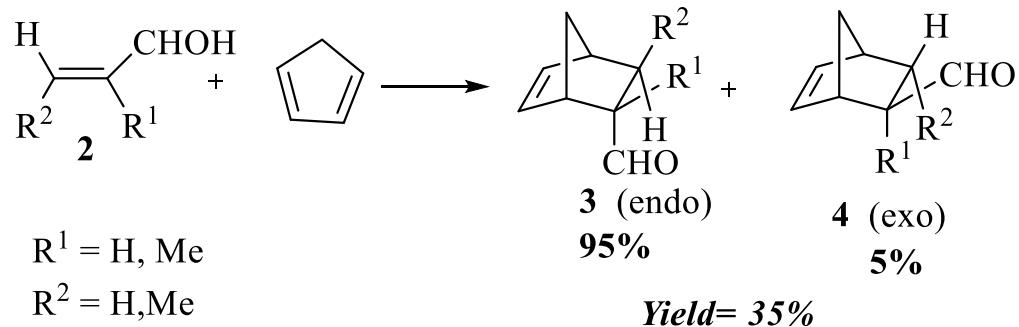


Fig. (1). Chiral dialkyl imidazolium bromide used in Diels–Alder reaction.

Chiral ionic liquids consist of cations and anions that possess chiral centers, resulting in a stereoisomeric structure. The chirality of these ionic liquids plays a significant role in determining their physicochemical properties, including characteristics such as melting point, viscosity, and solubility. Moreover, it influences their reactivity and selectivity in chemical reactions. A notable advantage of chiral ionic liquids lies in their dual role as solvents and chiral catalysts in asymmetric synthesis. This unique capability allows them to control the stereochemistry of chemical reactions, making them valuable tools in

achieving desired enantiomeric outcomes. Additionally, chiral ionic liquids can serve as chiral selectors in chromatography, enabling the efficient separation of enantiomers. It should be noted that simply having a chiral cation or anion in an ionic liquid does not inherently guarantee that it will exhibit enantioselective properties. For effective enantioseparation, the chiral ionic liquid must possess a suitable structure with an adequate number of binding sites for the enantiomer. The specific arrangement of the chiral components within the ionic liquid is essential for its effectiveness in enantioseparation and other chiral applications.



Scheme (1). CIL catalyzed Diels-Alder reaction.

Designing the Functionalized CIL

The catalytic properties of ionic liquids may be traced back to the frequently observed synergistic effect on catalysis when ionic liquids are used as reaction media. The further elaboration of the simple ILs with covalently connected catalytically active functional groups has significantly expanded the avenue of ionic liquid catalysis, leading to versatile functionalized ionic liquid catalysts.

Functionalized chiral ionic liquids (FCILs) are emerging as a new type of asymmetric organocatalysts and nonclassical chiral ligands. By judiciously anchoring functional groups onto chiral ionic liquids,

The design of FCILs involves the incorporation of specific functional groups into the ionic liquid structure, which can impart desired properties such as increased solubility, enhanced selectivity, or specific reactivity [11]. The development of FCILs represents a significant advancement in the pursuit of greener and more efficient chiral catalysis. A wide range of FCIL catalysts have been developed by strategically incorporating catalytic functional groups into the chiral ion pair skeletons.

The following general strategies are employed for the design and synthesis of FCILs:

CHAPTER 9

Chiral Ionic Liquid Based Biphasic Systems in Enantioseparations

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Abstract: Aqueous two-phase separation (ATPS) is a powerful, greener tool for the partitioning-based extraction and concentration of compounds in a mixture. ATPS is characterized by the separation of the biphasic layers upon the addition of the aqueous salt solution to aqueous ionic liquids. The aqueous biphasic system using chiral ionic liquids (CILs) has been studied for the resolution of the chiral molecules and their enantioseparation. Thus, in this chapter, a brief introduction to the ATPS formation thermodynamics for the polymer-polymer, polymer-salt, and salt-salt type ionic liquid is given. Apart from this, the effect of the salt, pH, and temperature on the physicochemical behavior of aqueous biphasic systems is discussed. The chiral ionic liquid-based ATPS is further categorized as tetrabutylammonium, choline, imidazolium, tropine, and quinine-based ionic liquids for enantioseparation. The study includes the effect of salts, cation of IL, anion of IL, temperature, pH, and Cu²⁺ ions. The chiral resolution of molecules and biomolecules is studied using these ionic liquids for amino acids and proteins.

Keywords: Aqueous two-phase system (ATPS), Aqueous biphasic system (ABS), Chiral ionic liquids (CILs), Chiral resolution, Chiral separation, Enantiomeric excess, Ionic liquid, Tie line length.

INTRODUCTION

Extraction is a very old and most acceptable technique commercially for industrial separation processes. Pharmaceutical industries have the potential application for the separation of chiral molecules relevant to pharmaceutical and personnel care applications [1]. Chiral ionic liquids have found application in chiral resolution

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With phase partitioning of the components being envisaged for a biphasic extraction, which may be liquid-liquid or solid-liquid [2]. The aqueous two-phase system (ATPS) is a promising liquid-liquid extraction (LLE) method for the separation of biological molecules [3]. ATPS was discovered in 1896 by Beijerinck, who observed the biphasic system by partitioning a mixture of gelatin and agar in water [4]. However, further development came in 1956, when Albertson proposed ATPS as a powerful method for biomolecular separation, including peptides, proteins, nucleic acid, *etc.*, using polyethylene glycol (PEG) and a dextran-based polymer-polymer biphasic system [4]. ATPS are biphasic systems comprising two water-rich phases formed by mixing two solutes above a critical concentration. The two solutes can be selected from polymers, salts, sugars, alcohols, or surfactants. These solutes partition into two phases in such a manner that one of the phases is in high quantity and the second solute is in minor quantity. The ATPS phases are both hydrophilic in nature with a lower interfacial tension having applications in biotechnological processes. Apart from this advantage, the ATPS technique is simple, adaptable, biocompatible, and easily scalable [4 - 6]. Using the combinatorial aspects of various types of ATPS, processing technologies could be formulated to achieve selective extractions, preconcentration of dilute solutes, removal of contaminants to a significant level, and denaturation of compounds. Despite the advantages that ATPS has, it is confined to academic research and laboratory use [5, 7 - 9] without significant industrial use. A large number of reviews have appeared in recent years, updating the concepts, advances, and applications of ATPS-based platforms [6, 8 - 30]. The preceding section provides an overview of the thermodynamic fundamentals and key properties of ATPS.

Phase Diagram of ATPS

The ATPS is most commonly prepared by both solutes, *i.e.*, a pair of hydrophilic polymers or salts and a polymer with a salt [31]. The combinations of polymer-polymer, salt-salt, or polymer-salt generate ATPS within a certain concentration range, wherein the phase separation would be controlled by the solvation of the major components of the phases.

Phase diagrams, as depicted in Fig. (1), show a potential working region for an ATPS that happens to be the starting point of an ATPS. ATPS are ternary systems composed of two phase-forming solutes and water. However, ATS systems are depicted in a two-dimensional plot, with the water concentration omitted and pure water corresponding to the origin of the plot. Based on the compositions (weight or molar) of ATPS-forming agents (solute 1 and 2), information about the system is as follows:

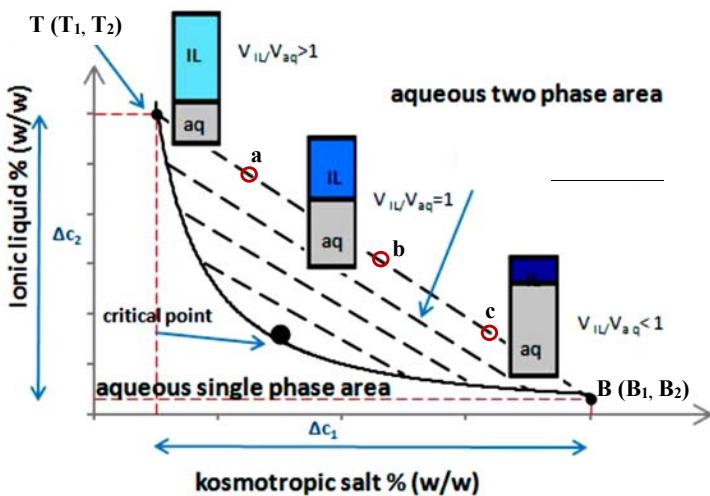


Fig. (1). Depicting a schematic for ATPS formation (Reproduced from [30]).

- Concentration of the solutes 1 and 2 necessary to create a biphasic system,
- The concentration of phase solutes in the lighter (top) and denser (bottom) phases, and
- The ratio of the phase volumes.

The ternary phase diagram, depicted in Fig. (1), is constituted by two phase-forming agents (solutes 1 and 2) and water. A solubility curve (binodal) divides the two-phase region (above the curve) from the single-phase region (below the curve). The composition of the phases in equilibrium is related by the tie-lines (TLs) that connect two points on the binodal curve, which correspond to the concentration of solutes 1 and 2 in the top-lighter and bottom-heavy phases. For example, a, b, and c correspond to three ATPS that have the same composition at equilibria, represented by $T(T_1, T_2)$ and $B(B_1, B_2)$, respectively, for the top and bottom phases. Upon moving along the TL connecting the T and B, the concentration of the solutes in the two phases remains the same. However, total compositions and ratio of the phase volumes *i.e.*, (V_T/V_B) , change on moving along the same TL. Thus, the feature of change in the ratio of phase volumes in ATPS is suitably utilized for the concentration of the analytes by a reduction in the volume of a particular phase by just moving along the associated TL.

TLs are nearly parallel to the adjacent points on the binodal curve, evaluating parameters like tie-line length (TLL) and slope of the tie-line length (SLT). This, in turn, helps predict other TLs in the vicinity. TLL has the same units as the concentration, and it is used to express the influence of the system composition on the partition of solutes. TLL and SLT are related according to Eqs. (1) and (2):

CHAPTER 10

Chiral-Supported Ionic Liquids in Asymmetric Synthesis

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Abstract: Supported ionic liquids (SILs) have been engaged in asymmetric synthesis, providing better recoverability, enantioselectivity, catalytic action, and economical and environmentally benign paths. SILs have minimized the limitations of previous homogeneous and heterogeneous systems and also opened new routes to design chiral heterogeneous systems with improved catalytic efficiency, including stability and recyclability. To carry out asymmetric reactions, both chiral catalysts and ILs have been supported onto a single support material, generally through a physical immobilization approach. In some cases, chiral ionic liquids have been grafted onto supports to obtain chiral SIL. The chirality has also been transferred into the resulting heterogeneous catalyst by covalently grafting chiral catalysts onto catalytic centers of supports by using ionic liquids as linkers. In this chapter, the potential catalytic role of all types of chiral SILs in several asymmetric organic reactions, such as hydrogenation, Mannich, epoxidation, Michael addition, Strecker, Diels-Alder reaction, etc., has been discussed.

Keywords: Asymmetric synthesis, Asymmetric reactions, Anantiomeric excess, Chiral catalysts, Chemical transformations, Chirality, Diastereoselective, Eco-friendly, Enantioselectivity, Grafting, Heterogeneous systems, Immobilization, IL-chiral catalysts, Reusability, Supported ionic liquids.

INTRODUCTION

Stereoisomers are organic molecules that have dissimilar atomic arrangements in three-dimensional space but possess similar connectivity of atoms [1]. In a chiral environment, these molecules can possess different physical or chemical properties from each other [2]. Therefore, enantioselective or asymmetric synthesis provides stereoisomeric products with unequal amounts [3]. Asymmetric synthesis is an approach to synthesize single enantiomeric products

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[4]. Biological systems give different responses to both enantiomers [5]. Generally, to form biologically active drugs or compounds, enantiomeric pure organic molecules are used as starting materials [6].

In an enantioselective transformation, asymmetric induction can be achieved through different strategies such as chiral auxiliaries, chiral solvents, chiral reagents or substrates, chiral enzymes or catalysts, *etc* [7 - 9]. Asymmetric synthesis plays an important role in organocatalysis [10, 11]. In recent years, asymmetric organocatalysis has been considered an excellent approach for the synthesis of enantiomeric pure organic species under mild operating conditions [12]. Chiral catalysts do not interfere in asymmetric reaction processes, and also, their sub-stoichiometric quantity used may improve catalytic efficiency, avoid the production of waste materials, and reduce cost (in comparison to expensive auxiliaries, reagents, and substrates) [13 - 15]. Asymmetric catalysis can be achieved by using heterogeneous or homogeneous chiral catalysts [16, 17].

Although several developments have been found in homogeneous asymmetric catalysis, the high cost of chiral catalysts/ligands encourages the researcher to move toward the designing of easily recoverable heterogeneous chiral catalysts [18]. However, in contrast to homogeneous catalytic systems, heterogeneous systems containing immobilized chiral catalysts onto particular support material provided low enantioselectivity and catalytic efficiency because of their lesser interactions with substrates [19]. Also, the nature of the solvent influences enantioselectivity, stability, and catalytic performance during asymmetric chemical transformations [20]. To overcome all these issues, chiral catalysts have been replaced by chiral ionic liquids in heterogeneous systems, which play an amazing role in asymmetric synthesis [21]. In another route, both chiral catalysts and ionic liquids have been immobilized onto supports to obtain heterogeneous catalysts [22].

Room temperature ionic liquids (ILs) are molten organic ionic compounds that exhibit melting points below 25°C and are composed of asymmetric organic/inorganic anions and organic cations [23]. Their structural variations, such as different sizes of cation or anion, delocalized charge in the cationic part, *etc.*, are responsible for their excellent physicochemical properties like low vapor pressure, high thermal/chemical stability, high density, high ionic conductivity, high viscosity, non-flammable character, and good solvation power [24, 25]. With the functionalization of cationic moiety or by varying anion/cation in IL structures, some chemical as well as physical properties can be easily tuned like acidity/basicity, solubility, coordinating power, and hydrophobic or hydrophilic character [26]. Therefore, ILs are considered designer liquids/solvents [27].

Hence, ILs have explored new opportunities in several fields, such as sensors, catalysis, electrochemistry, bio-catalysis, *etc* [28 - 32].

It is already documented that ILs showed several benefits in important chemical transformations [33]. The properties like vapor pressure and good solvation ability make them good green alternatives to traditional organic solvents [34]. In a variety of organic reactions, especially in asymmetric transformations, ILs act as a reaction medium [35]. ILs also have a tendency to dissolve several inorganic, organic, and complex substrates [36]. In addition, these stabilize distinct metal complexes/catalysts during organic transformations [37]. Besides, the use of ILs as a reaction medium in asymmetric reactions offers facile recycling of expensive chiral catalysts, increases turnover numbers, and improves the enantioselectivity and activity of catalysts in comparison to organic solvents [38]. Although ILs show strong interactions with substrates, thus improving enantioselectivity, in many cases, the high viscosity of ILs creates mass transfer issues [39].

In recent years, IL-tagged chiral catalysts have also gained significant attention in asymmetric synthesis [40, 41]. It was concluded that in an asymmetric reaction, a combination of IL and the chiral backbone of catalysts may strengthen the synergistic interactions among two participated components and, hence, may improve the impact of counter-ions of IL on the catalytic performances [42]. This approach provides a route for reusing the chiral catalysts by using a biphasic liquid-liquid system, which consists of two phases: one phase contains reactants/products, while the other has IL-chiral catalysts. However, this system improves several reaction parameters such as environmental, economic, and sustainability path, but many ligands/chiral catalysts are toxic and expensive [43].

ILs show effectiveness in asymmetric synthesis, but their large content is required for catalysis [44]. Also, most ILs are expensive, and some show a toxic nature, which restricts their use in several practical applications [45]. In addition, due to the highly viscous nature of ILs, only the diffusion layer (small portion) acts as reaction media while more content remains unusable or inaccessible; thus, to overcome these limitations, the new heterogeneous materials *i.e.*, supported ionic liquids (SILs), have been explored [46, 47]. These show amazing catalytic performance in asymmetric reactions [48]. The heterogenization of chiral catalysts with ILs offers a new class of SIL catalyst systems that possess excellent characteristics of ILs and provide easy recoverability of chiral catalysts [49]. The main reason behind the development of heterogeneous catalysts was some limitations associated with homogeneous catalysis, such as difficult recovery of catalyst, deactivation of catalysts, and difficult separation of products from reaction mixture [50]. However, biphasic organic liquid/IL systems have been used to solve recovery and separation problems, but they need large IL content,

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