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Ionic Liquids for Better Separation Processes

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Preface

These early years of the twenty-first century have witnessed a formidable burgeoning of research in ionic liquids across a good range of disciplines. Due to their special and versatile characteristics, these low-melting salts have been proposed and are currently under investigation, for many and widely varied applications. A number of these applications have already taken off and have become a scaled-up reality in industrial processes, constituting a proof of the potential competitiveness of ionic liquid technology against current state-of-the-art technologies.

One of the main drivers of research on ionic liquids has been their utilisation in separation processes. The need to perform separations, in its different variations (purification of products, fractionation of multicomponent streams, elimination of contaminants, etc.), is practically ubiquitous in the industrial framework of our society. Thus, the continued search for better alternatives to carry out these separations is a transversal motivation to reach improved processes for a more sustainable world. Ionic liquids have the potential to play a relevant role in some of those alternatives. This volume, *Ionic Liquids for Better Separation Processes*, brings together a selection of topics on separation processes, in which ionic liquids have demonstrated or look promising for superior performance over the currently utilised strategies.

The chapters of this book analyse the advances to date and the future potential in the involvement of ionic liquids in new approaches for diverse separation applications of industrial or analytical interest, covering a range of different unit operations (distillation, liquid-liquid extraction, leaching, chromatography, etc.). In some cases, the ionic liquids act as direct replacements of other auxiliary substances, whereas in other cases they imply the consideration of a novel technological strategy to carry out the desired separation if compared to the benchmark approaches currently in use. These are straightforward indicators of the tremendous versatility of ionic liquids for better separation processes. The limitation is likely lying in our ability to combine our knowledge on ionic liquids with our knowledge of the separation problems to be addressed and get the most out of this suggestive marriage.

The authors of the chapters are reputed experts in their respective fields and have extensive experience in the work with ionic liquids. In my opinion, these characteristics have enabled them to set each separation topic with an equilibrated focus and to impregnate the different chapters with their valuable experience and critical insight. I believe that this volume will be found useful by researchers and practitioners involved in the development of separation processes, who may discover in it new alternatives based on ionic liquids and, in general, the potential of these appealing substances in the separation field. It will also be a valuable source for those with a general interest in ionic liquids from an applied perspective.

I would like to close these lines by acknowledging the contributing authors, who kindly accepted to join me in this enterprise and showed the most favourable disposition along the way. Also, I would like to express my gratitude to the Springer support personnel, for their patience and help with all technical issues.

Santiago de Compostela, Spain Héctor Rodríguez

Contents

Chapter 1
Ionic Liquids in the Context of Separation Processes

Héctor Rodríguez

Abstract The unique characteristics of ionic liquids (salts which are liquid at or near-ambient temperature) open new horizons in the development of improved processes to carry out the separation of compounds from multicomponent feedstreams or feedstocks. The utilisation of ionic liquids can facilitate improvements in the performance of state-of-the-art technologies, and it can also represent the basis for the development of new technological strategies leading to the separations of interest. The potential usage of ionic liquids in separation processes is not exclusive of a particular operation unit; in fact, several ones can benefit from ionic liquids, both at industrial and analytical levels.

Keywords Separation process • Ionic liquid • Tunable solvent • Industrial separation • Analytical separation

1.1 Introduction

The development of separation processes dates back to the early civilisations of humankind. Among other examples, they managed to extract metals from ores or different valuable compounds (aromas, dyes) from plants; to obtain salt by evaporation of sea water; or to get liquors by distillation [1]. With the evolution of history, the separation techniques have been perfected, expanded and industrialised. Nowadays, separation operations are present at some or many stages of virtually all industrial processes of relevance. They may play, for example, a fundamental role in taking an efficient advantage of most key fractions of feedstocks that nature offers us in the form of complex multicomponent matrices, such as petroleum or biomass. They are also typically needed to recycle unreacted substances to reaction units, to get products with the required degree of purification or to remove contaminants from residual streams prior to their discharge to the environment.

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To carry out a targeted separation, the selected unit operation will involve the utilisation of energy or auxiliary substances or materials. It is in this context that the emergence of ionic liquids [2] since the late 1990s has boosted the possibilities for improvement of the current state-of-the-art of separation processes. After years of active research in the field, this book intends to provide an ample perspective of the progresses made to date in the arena of separation processes through the involvement of ionic liquids and an estimation of the prospects for the near future in this regard.

1.2 Ionic Liquids and Their Unique Characteristics

From a lexical point of view, an ionic liquid would be any substance constituted by ions and in a liquid state – including classical, high-temperature molten salts. However, the term *ionic liquid* has come to refer more specifically to salts with low melting or glass transition temperatures, typically (and arbitrarily) considering a mark of 100 °C [2]. For a salt to be liquid at so low temperatures, at least one of its constitutive ions must be large and with a low degree of symmetry. These factors tend to frustrate packing and to reduce the lattice energy of the crystalline form of the salt, therefore lowering the melting temperature [3].

Substances meeting the present definition of ionic liquid have been known for over a century [2]. Nevertheless, it can be said that the modern era of ionic liquids has its inception in a series of research programmes over the second half of the twentieth century, aimed at obtaining molten salts at the lowest temperatures possible for their use in electrochemical applications, and ending up with room-temperature molten salts [4]. A drawback of the ionic liquids developed at that stage was the need to protect them from moisture, as well as their tendency to react with many substrates. A step forward occurred with the report, in 1992, of air- and water-stable ionic liquids [5]. As prognosticated by Welton [6], this easiness of handling has facilitated the approach to ionic liquids of those without specialist knowledge of the field, thus causing a tremendous expansion of the community of researchers involved in ionic liquid investigations. Together with other concurrent factors [2], this led to the burgeoning of research on ionic liquids in academia and industry since the late 1990s, as exemplified in Fig. 1.1 with the number of research articles published per year. For those interested in a deeper description of the history of ionic liquids, more detailed accounts can be found elsewhere [2, 4, 7].

By 2010, more than 1500 ionic liquids had already been reported in the scientific literature, and many more combinations of cation and anion are presumed to lead to ionic liquids [2]. Given the large number of members of this family of substances, it is difficult to generalise any common property to all ionic liquids, apart from those that are implicitly included in their definition: they exhibit ionic conductivity because they are constituted by ions, and they are liquid at some temperature below 100 °C, as agreed by convention [8]. In spite of this, many ionic liquids will often exhibit an appealing set of other properties [2], including extremely low

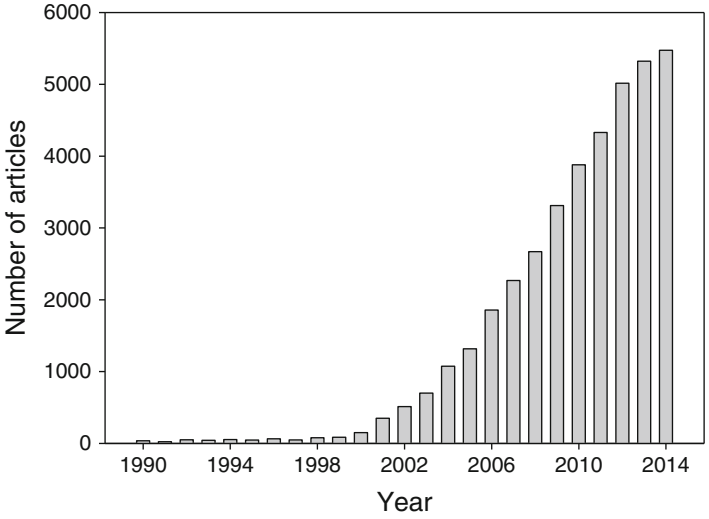

Fig. 1.1 Evolution of the annual number of research articles on ionic liquids over the last 25 years. (Search carried out in July 2015 with SciFinder® using the term 'ionic liquid' as research topic and refining by the document type 'Journal')

vapour pressure, good thermal and chemical stabilities, wide liquid range, non-flammability and great solvation ability for a broad range of compounds. These are interesting properties that suggest the consideration of ionic liquids as potentially better solvents in safer and more environmentally friendly processes [9]. It must be added that the properties of ionic liquids can be tuned to a good extent by the judicious combination of cations and anions and the tailoring of their chemical structures (e.g. by modification of the number and/or length of alkyl substituents) [7]. This tunability, in conjunction with the above-mentioned set of properties, led to the coinage of the term *designer solvents* to emphasise the possibility of 'designing' an ionic liquid to match the characteristics required by a specific application [9, 10].

The characteristics of ionic liquids render them attractive not only for their use as solvents but also for alternative roles in a broad range of varied applications. A thematic symposium held at the 231st ACS National Meeting in Atlanta in 2006 was already entitled 'Ionic Liquids: Not Just Solvents Anymore' [11]. In a compilation of industrial applications of ionic liquids at a level of pilot or commercial scale (as of ca. 2006), Maase [12] identified three types of role for the ionic liquid: process chemical (where the classical use as solvent would be included), performance chemical and engineering fluid. A similar conclusion would be achieved from an analysis of the applications listed in a nearly contemporary review on industrial applications of ionic liquids by Plechkova and Seddon [13]. Other interesting developments in ionic liquid research in more recent years have expanded the portfolio of potential applications. As an example, it may be worth mentioning the utilisation of a biological property as the primary driver in the design of ionic liquids

(in contrast to the physical and chemical properties previously emphasised) [14], which has recently been an active topic of research towards, e.g. the application of ionic liquids as pharmaceuticals.

Although Fig. 1.1 indicates an ever-increasing interest in ionic liquids since the beginning of the present century, it also shows for the very recent years what could be possible first signs of deceleration of the growing rate of the field (at least in the terms in which a number of research publications can represent a field as a whole). Is the ionic liquid field reaching the top part of the S-curve of growth? Evidently it is too early to answer this question at present, and more years to come are necessary in order to provide a better perspective. Recent developments both at scientific and industrial levels invite to think of a promising outlook for the future. Eventually the key to keep the formidable growing pace of the field of ionic liquids will be the sustained generation of new and attractive ideas, together with the successful development of the corresponding projects and subsequent progress towards practical implementation.

1.3 Ionic Liquids in Separations

The versatility of ionic liquids in general terms is transferable to their application in separations in particular. Their tunability allows customisation of the ability to preferentially interact (or not) with specific substances in mixtures, thus enabling their use to perform separations of widely varied nature. This possibility of tailoring the properties of ionic liquids by judicious combination of cation and anion has led to their consideration in many separation strategies that involve solvents or materials as auxiliary elements. Without intending to be exhaustive in reviewing all the applications for which ionic liquids have been proposed in the field of separations, this section will try to emphasise the diversity of roles that ionic liquids can play in separation processes and the broad set of separation techniques in which they have impacted.

Early approaches to the exploration of (what we would understand nowadays as) ionic liquids for separations date back from several decades ago and were related to their use as supported stationary phases in gas-liquid chromatography. A recent publication by Haumann [15] includes a summary of those first steps and the relevant references associated. Since those early works, ionic liquids have been further proposed for application in this and many other chromatographic, spectroscopic and electrophoretic techniques [16, 17], and indeed this is a lively topic at present.

Outside the framework of analytical chemistry separations, the first report of ionic liquids for separations was published in 1998, and it proposed their use as replacements of volatile organic solvents in liquid-liquid extraction processes involving an aqueous phase [18]. Other uses of ionic liquids as novel solvents in different applications of liquid-liquid extraction have followed, for example, in the separation of aromatic and aliphatic hydrocarbons [19, 20] or in the extraction

of metals [20], among others. In addition to liquid-liquid extraction, similar suggestions of replacement of conventional volatile solvents with ionic liquids have reached other industrial separation techniques that utilise solvents, such as absorption of gases or extractive distillation [19, 20].

Beyond the mere replacement of volatile organic solvents in already configured solvent-based processes, it is interesting to note that the special solvation capacity of ionic liquids has also given rise to new solvent-based technologies for applications in which non-solvent processes are the benchmark in the current state-of-the-art. This is the case, for example, of the selective extraction of sulfur compounds from fuels with ionic liquids [20, 21].

A further strategy involving ionic liquids in liquid-liquid extractions has consisted on their use as co-solutes for the generation of aqueous biphasic systems [22, 23], of special interest for the extraction and purification of biomolecules and other substances that require an aqueous medium.

In a broad sense, the first dedicated industrial-scale ionic liquid-based process, the so-called BASIL™ process established by BASF in 2002 [12], would even be susceptible of consideration as example of ionic technology for an extraction process. BASF developed this process for the synthesis of alkoxyphenylphosphines, which are formed along with HCl in the reactive step, obtaining product and by-product together in a homogeneous liquid phase. For the necessary scavenging of the acid in order to get the purified product, the organic compound 1-methylimidazole is added, which combines with HCl to form the ionic liquid 1-*H*-3-methylimidazolium chloride as a distinct liquid phase. This innovative approach improved enormously the productivity of the overall synthesis process as compared to the previous state-of-the-art. With generation of the ionic liquid in situ for removal of a substance from a homogeneous liquid phase, the BASIL process is illustrative of the formidable versatility of approaches that ionic liquid technology can adopt for application in separations.

Another separation area in which ionic liquids have made an impact in the last years is the processing of biomass, via a solid-liquid extraction (leaching) approach. Works in this area relate mostly to either extraction of value-added compounds from plants [24] or to dissolution and fractionation of lignocellulosic materials for the recovery of the major constituent biopolymers [25]. The solvent can be the ionic liquid alone, but in the particular case of extraction of value-added compounds from plant, hybrid solvents constituted by a combination of ionic liquid and molecular solvent have been frequently used. With volatile solutes, a recovery of the product and of the solvent is possible by a distillation strategy, but quite often the solutes of interest are non-volatile. Given also the negligible vapour pressure of ionic liquids, the recovery of the desired product and recycling of the solvent require alternatives to distillation. Among others, a common procedure involves the use of (molecular) antisolvents to precipitate the solutes out of the solution, although this may pose a significant energy penalty at the stage of distilling off the antisolvent from its mixture with the ionic liquid for their recycling to the process.

In addressing the issue of recovering non-volatile solutes from non-volatile ionic liquids, the combination with supercritical fluids, in particular supercritical CO_2,

was suggested [26]. The supercritical fluid and the ionic liquid can form a biphasic system in which the solute will partition between phases (with the ionic liquid not entering the supercritical fluid phase), then isolating easily the desired product by diminishing the pressure to transform the supercritical fluid to a gas. Unfortunately, this strategy implies the investment and operation costs typically associated with processes involving supercritical fluids. Nevertheless, it is a paradigmatic example of the combination of ionic liquids with other solvents (viz. supercritical fluids) with the potential to be the basis of new technologies to develop more sustainable processes.

The use of ionic liquids in combination with solid supports is also present in the efforts of application of ionic liquids to large-scale separation processes. One of the negative characteristics of ionic liquids for their use in many processes is their relatively high viscosity compared to that of conventional molecular solvents at typical process temperatures. A way of overcoming this problem consists in the utilisation of supported ionic liquid phases (SILPs) instead of the bulk ionic liquid [27]. These SILPs have been explored for separations of different nature both in gas phase and in liquid phase [15, 28, 29], leading in a particular case to another paradigmatic application of ionic liquids in a scaleup industrial separation process recently implemented in PETRONAS, namely, for the removal of mercury from natural gas [29]. Also, the properties of ionic liquids are excellent for their use in membranes of varied morphologies [30]. Supported ionic liquid membranes, gelled membranes and other morphological configurations have been investigated for the separation of mixtures of gases, especially CO_2 separation, and, to a lesser extent, some research has been carried out for separations in the liquid phase too [30].

Summing up, given the portfolio of possibilities and advances in so varied fronts, it can be stated that separation processes can benefit from ionic liquids through many different avenues. Either via replacement of other substances in consolidated technologies or through the development of alternative technologies, ionic liquids have gradually gained presence in the separation arena, with some ionic liquid technology processes accordingly making the transition to real implementation in the industry [12, 13, 29]. The growth of interest in ionic liquids for separations has mimicked, in general terms, the growth of the ionic liquid field in general, with an impressive increase over the last decade and a half, as shown by Fig. 1.2 via an estimation of the number of research articles published annually on this specific topic. Among the enormously diverse world of ionic liquids, their application for separations has been (and will likely continue to be) a relevant section, representing about one third of the total number of research articles published annually.

1.4 Ionic Liquids for Better Separation Processes?

The experience accumulated so far constitutes a proof that ionic liquids can be the basis for the technology of improved separation processes, and simultaneously, it provides us with valuable knowledge towards a better envisioning of the ways

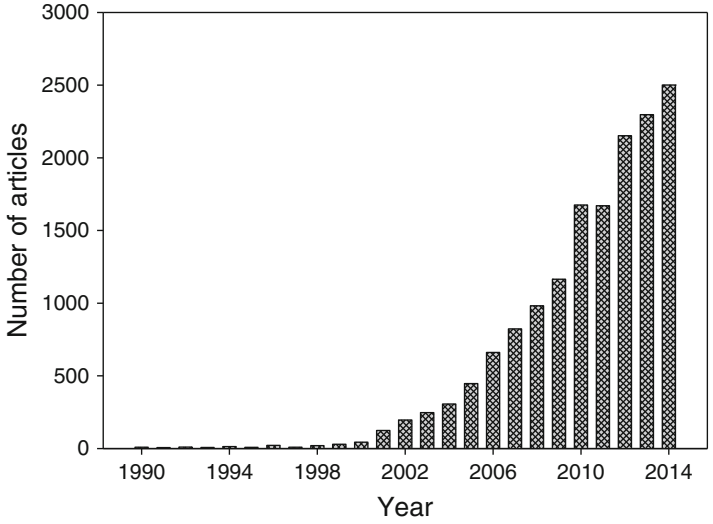

Fig. 1.2 Estimated evolution of the annual number of research articles on ionic liquids for separations over the last 25 years. (Search carried out in July 2015 with SciFinder®. First, several data sets were generated using the term 'ionic liquid' and refining the initial number of hits with a second term: 'separations', or 'extraction', or 'absorption', or 'distillation', or 'membrane', etc. Then, all these data sets were combined in a single one, and a refining by the document type 'Journal' was made)

to succeed in achieving such improvements. With this background, the versatility and tunability of ionic liquids are key characteristics to be exploited, allowing this appealing family of substances to adapt to the specific circumstances of virtually any separation problem. The limitation of what ionic liquids can do for us in the field of separations is perhaps bounded just by our capacity to challenge our own thinking and taking the most of their set of properties towards fulfilment of the desired targets. In this regard, the present book aims at condensing, in a single volume, the main advancements to date and the real potentialities of ionic liquids and their particular characteristics in a number of varied separation processes of industrial interest, supported by different unit operations. Without aiming at being an exhaustive coverage of all the (numerous) areas and applications in which ionic liquids can do a significant contribution, this book will provide the reader with the broad perspective of the roles that ionic liquids can play in the search of better separation processes for the future, ranging from improved state-of-the-art technologies to newly developed processes with alternative technological fundamentals.

Eventually ionic liquids will be one more tool that scientists and engineers working in the field of separations will have available to reach their objectives. It may not be the appropriate tool, or other tools may be more suitable for what we want, but in order to judiciously decide that, first we have to be well acquainted

with ionic liquids and their possibilities. Hopefully this book will help in that direction, contributing to optimise the benefit that ionic liquids can offer to our future separation processes.

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Chapter 2
Extractive Distillation with Ionic Liquids: Pilot Plant Experiments and Conceptual Process Design

G. Wytze Meindersma, Esteban Quijada-Maldonado, Mark T.G. Jongmans, Juan Pablo Gutiérrez Hernandez, Boelo Schuur, and André B. de Haan

Abstract Ionic liquids (ILs) can replace conventional solvents in separation processes, such as extractive distillation (ED), because of their ability to selectively separate azeotropic/close boiling mixtures. Four case studies were selected: ethanol/water (1-ethyl-3-methylimidazolium dicyanamide, [emim][$N(CN)_2$], and ethylene glycol, EG), 1-hexene/*n*-hexane (no suitable IL found), methylcyclohexane/toluene (1-hexyl-3-methylimidazolium tetracyanoborate, [hmim][$B(CN)_4$], and *N*-methyl-2-pyrrolidone, NMP), and ethylbenzene/styrene (4-methyl-*N*-butylpyridinium tetrafluoroborate, [4-mebupy][BF_4], and sulfolane). Pilot plant experiments proved that the developed models for ED could well describe the experimental results.

Conceptual processes were designed for the ED of three case studies. The ethanol/water process with [emim][$N(CN)_2$] reduced the energy requirements with 16 % compared to the process with EG, provided that proper heat

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integration is implemented. The methylcyclohexane (MCH)/toluene process with [hmim][$B(CN)_4$] required about 50 % less energy with heat integration than the conventional process with NMP with heat integration.

The IL [4-mebupy][BF_4] reduced the energy requirement most compared to the conventional distillation for the ethylbenzene/styrene process (43.2 %), which is 5 % lower than with extractive distillation with sulfolane. However, the capital expenditures were about 23 % higher than for the sulfolane process. It can be concluded from the total annual costs that all studied ED processes outperform the current distillation process to obtain high purity styrene, but that ILs do not perform better than sulfolane.

The general conclusion of these four examples is that only in some special cases ILs can be more advantageously applied than conventional solvents in extractive distillation. The key performance points for ED are a high selectivity and high capacity, next to the solvent recovery and heat integration.

Keywords Conceptual process design • Energy requirement • Heat integration • Sulfolane • Ionic liquids

2.1 Introduction

In the history of chemical separations, conventional distillation has been applied to more commercial processes than all other techniques combined. This well-known operation takes advantage of the difference in volatility of chemical compounds, and it is suitable for separating a variety of mixtures. However, not all liquid mixtures can be applied for the separation with ordinary fractional distillation. For instance, low relative volatility mixtures (including azeotropic mixtures) are difficult or economically unfeasible to separate by ordinary distillation. In the separation of ethylbenzene and styrene, for example, deep vacuum distillation in the pressure range of 5–20 kPa is generally used to separate unreacted ethylbenzene from styrene, and the vacuum is applied to limit the polymerization of styrene. The

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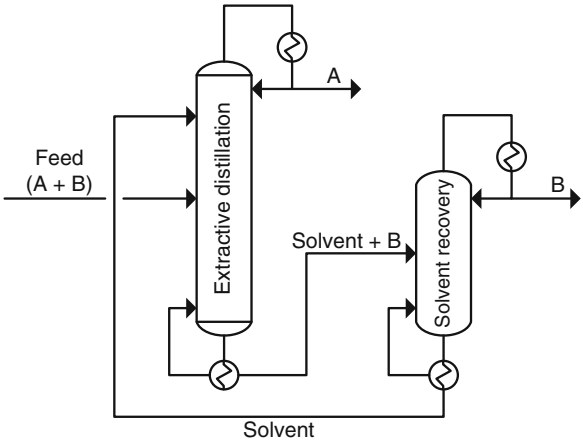

Fig. 2.1 Extractive distillation process

distillation of ethylbenzene from styrene accounts for 75–80 % of the total energy use in the distillation section of a typical styrene plant, due to the low relative volatility, 1.3–1.4 [1, 2]. Extractive distillation could lead to a dramatic decrease in both capital and operational expenses.

Extractive distillation has several advantages over other separation technologies: it is operated like a conventional distillation process, using two key variables such as polarity and boiling point difference, and, except for the solvent recovery operation, it does not require additional steps to purify products [3, 4]. Figure 2.1 shows a conventional extractive distillation process [5, 6].

One of the most useful ways to obtain chemicals that cannot be separated by conventional distillation is to employ selective solvents. They exploit the non-ideality of a mixture of components having different chemical structures. Extractive distillation is widely used in the chemical and petrochemical industries for separating azeotropic, close boiling, and low relative volatility mixtures. In extractive distillation, an additional solvent is used in order to interact with the components of different chemical structure within the mixture. Ionic liquids as solvents combine the advantages of both organic solvents and salts: increasing the relative volatility of one of the components and reducing the solvent-to-feed (S/F) ratio by the salting-out effect without the disadvantages of a solid salt [3, 7–13].

Since an ionic liquid has a low or negligible vapor pressure, the recovery of an IL could bring advantages for its recovery, compared to the recovery of conventional solvents. Suitable regeneration processes are, for example, evaporation, stripping with hot gas, precipitation, or a combination of these processes. The best option for the solvent regeneration will probably be a flash column or a multi-effect evaporator, which requires a low amount of energy, possibly followed by a strip column for the removal of last traces of products.

ILs are suggested by a large number of authors for a broad range of separations, but studies including process design and pilot plant experiments are scarce [14–26]. However, these studies are needed to indicate whether ILs can indeed be applied successfully compared to conventional solvents. Hence, our studies comprise

several different systems, including a large number of ILs, and the approach spanned the whole range from laboratory experiments, molecular simulations to pilot plant experiments, and conceptual process designs, including one economic evaluation.

Keywords Conventional distillation, Extractive distillation, Selective solvents, Azeotropic mixtures, Close-boiling mixtures, Ionic liquids, Regeneration processes

2.2 Objectives

Four case studies were selected for separation with extractive distillation: organic/water (ethanol/water), olefin/paraffin (1-hexene/*n*-hexane), aliphatic/aromatic hydrocarbons (methylcyclohexane/toluene), and aromatic/aromatic hydrocarbons (ethylbenzene/styrene). The conventional solvent is ethylene glycol for the ethanol/water separation, *N*-methyl-2-pyrrolidone (NMP) for the 1-hexene/*n*-hexane and the methylcyclohexane/toluene separations, and sulfolane for the ethylbenzene/styrene separation. The objectives of this project are:

- Screening and selection of suitable ionic liquids for each separation system
- Scale-up of the separation process (ethanol/water and methylcyclohexane/toluene) from laboratory scale to pilot plant scale
- Regeneration/recovery of the ionic liquids
- Economic evaluation of the separation process with ionic liquids

The objective was to find ILs with high selectivities for the separations in study, in combination with a solvent capacity that is as high as possible. These features (selectivity and capacity) are crucial for the capital and operational expenditures of an extractive distillation process: the larger the selectivity of the solvent, the lower the annual costs [27, 28]. This can be explained by the fact that, if the selectivity of the solvent increases, the relative volatility of the mixture to be separated also increases, resulting in a reduction in the number of equilibrium stages and the reflux ratio. This decreases the operational as well as capital expenditures. The capacity of the solvent also has a significant effect on the total annual costs for systems in which the solvent has a miscibility gap with the feed mixture, particularly for solvents that are relatively expensive, such as ILs [28]. The main conclusion is that, next to the selectivity, the capacity also should be sufficiently high, to keep the total costs of an extractive distillation unit economical. If the solvent capacity is large, less solvent is required to obtain a homogeneous liquid phase in the extractive distillation column. If less solvent is needed, the energy required for heating the solvent in the extractive distillation and solvent recovery columns decreases. No phase separation is to be expected for the ethanol/water separation with extractive distillation, but this could occur for the organic/organic separations. Because of the low solubility of ILs in aromatics [29], many ILs do not form a homogeneous liquid phase with many aromatics over the full composition range [26, 30, 31]. Therefore, it also is important to examine the capacity.

Keywords Ethanol/water, 1-hexene/hexane, Methylcyclohexane/toluene, Ethylbenzene/styrene, Screening, Selection, Scale-up, Regeneration, Economic evaluation

2.3 Methods

Suitable ionic liquids were screened for the ethanol/water, 1-hexene/*n*-hexane, and the methylcyclohexane/toluene separations by means of the software COSMO-RS/COSMOTherm [32]. The results of this screening were validated with experiments. Both binary and ternary equilibrium data were determined for the selected system with a conventional solvent and an ionic liquid. Suitable ionic liquids for the ethylbenzene/styrene separation were selected by liquid-liquid equilibrium (LLE) experiments, because they all formed biphasic LLE systems, and LLE measurement is much less laborious than vapor-liquid equilibrium (VLE) measurement. The correlation between the LLE selectivity and the VLE relative volatility demonstrated the feasibility of this screening method [33]. Several physical properties, such as density, viscosity, surface tension, and heat capacity, were determined for the selected ionic liquids. A rate-based model was developed for the separation of ethanol/water in an extractive distillation column. Finally, two separation systems (ethanol/water and methylcyclohexane/toluene) were tested in the pilot plant. The energy requirements of the separations were determined and compared to those of the conventional separation. Equilibrium-based models were used for the development of the conceptual process designs using Aspen Plus V7.2 and for the economic evaluation.

Keywords COSMO-RS, Screening, Equilibrium data, Physical properties, Pilot plant

2.4 Laboratory Experiments

2.4.1 Separation of 1-Hexene and n-Hexane

The conventional solvent for the separation of 1-hexene and *n*-hexane is *N*-methyl-2-pyrrolidone (NMP). There are also several ionic liquids suitable for this separation, as is shown in Fig. 2.2.

It is clear from this figure that only the ionic liquid [hmim][$B(CN)_4$] performs slightly better than the conventional solvent NMP. Since the increase in relative volatility is only 5 % and since the capacity of this IL is too low (required S/F = 20), replacement of the conventional solvent by an IL in an extractive distillation process for the separation of 1-hexene and *n*-hexane will not be economically feasible. Therefore, no further research was carried out for this separation.

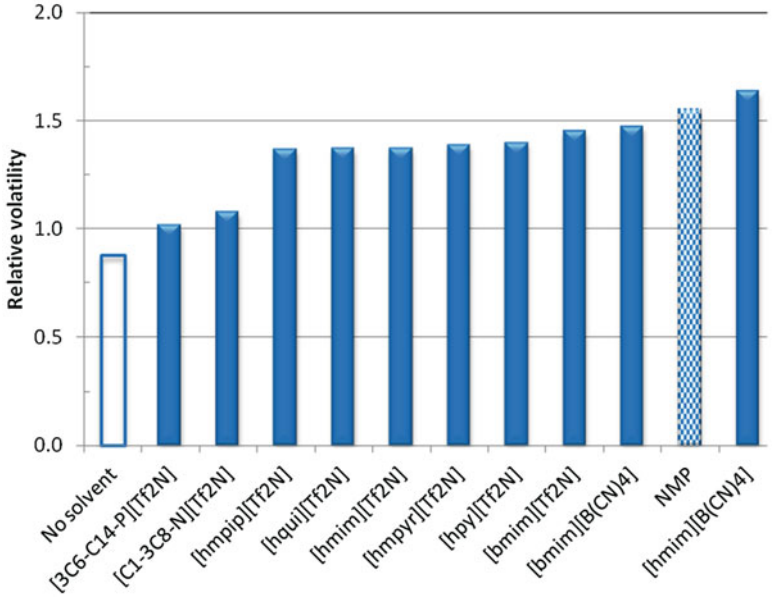

Fig. 2.2 Relative volatility of 1-hexene and *n*-hexane for several solvents: trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)amide ($[3C_6\text{-}C_{14}\text{-}P][Tf_2N]$), methyltrioctylammonium bis(trifluoromethylsulfonyl)amide ($[C_1\text{-}3C_8\text{-}N][Tf_2N]$), 1-hexyl-1-methylpiperidinium bis(trifluoromethylsulfonyl)amide ($[hmpip][Tf_2N]$), 1-hexylquinolinium bis(trifluoromethylsulfonyl)amide ($[hqui][Tf_2N]$), 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide ($[hmim][Tf_2N]$), 1-hexyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)amide ($[hmpyr][Tf_2N]$), 1-hexylpyridinium bis(trifluoromethylsulfonyl)amide ($[hpy][Tf_2N]$), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide ($[bmim][Tf_2N]$), 1-butyl-3-methylimidazolium tetracyanoborate ($[bmim][B(CN)_4]$), N-methyl-2-pyrrolidone (NMP), 1-hexyl-3-methylimidazolium tetracyanoborate ($[hmim][B(CN)_4]$). S/F = 20, $T = 303.15$ K

2.4.2 Separation of Ethanol/Water

There are several ionic liquids investigated for the extractive distillation of ethanol/water mixtures, and the most used conventional solvent in extractive distillation is ethylene glycol (EG). We have screened a large number of cations and anions with COSMO-RS/COSMOTherm in order to select suitable combinations for the ethanol/water separation [32]. The results of the COSMO screening were validated by experiments. Figure 2.3 shows the selected solvents for the ethanol/water separation. The ILs show comparable or slightly higher relative ethanol/water volatilities than EG.

The best ILs for this separation are 1-ethyl-3-methylimidazolium acetate ([emim][OAc]) and *N*-butyl-*N*,*N*,*N*-trimethylammonium acetate ($[C_4\text{-}3C_1\text{-}N][OAc]$). However, the last IL is a solid at the process conditions used and is, therefore, not suitable. The IL 1-ethyl-3-methylimidazolium lactate ([emim][Lac])

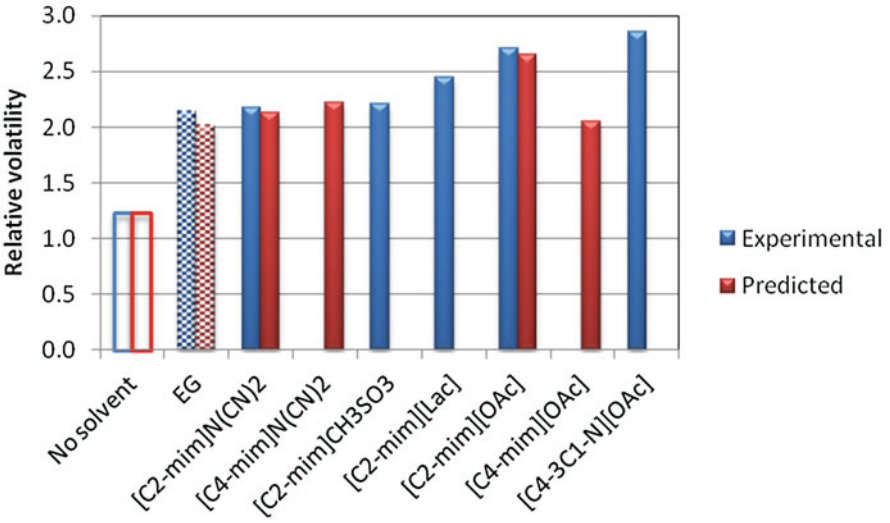

Fig. 2.3 Relative volatilities of ethanol/water with several solvents: ethylene glycol (EG), 1-ethyl-3-methylimidazolium dicyanamide ($[C_2\text{-mim}]N(CN)_2$), 1-butyl-3-methylimidazolium dicyanamide ($[C_4\text{-mim}]N(CN)_2$), 1-ethyl-3-methylimidazolium methanesulfonate ($[C_2\text{-mim}]CH_3SO_3$), 1-ethyl-3-methylimidazolium lactate ($[C_2\text{-mim}][Lac]$), 1-ethyl-3-methylimidazolium acetate ($[C_2\text{-mim}][OAc]$), 1-butyl-3-methylimidazolium acetate ($[C_4\text{-mim}][OAc]$), tributylmethylammonium acetate ($[C_4\text{-}3C_1\text{-N}][OAc]$). S/F ≈ 1, $P = 0.1$ MPa

was not suitable because the IL proved to be unstable during our experiments and 1-ethyl-3-methylimidazolium methanesulfonate ($[emim][CH_3SO_3]$) was discarded because of its comparable relative volatility regarding EG and its high viscosity: 149.9 mPa.s at 25 °C. The ILs [emim][OAc] and $[emim][N(CN)_2]$ were used in the process simulations. However, due to the strong interactions between water and [emim][OAc], the recovery and purification of this IL appeared to be challenging and energy intensive. Besides that, the lower thermal stability of the IL [emim][OAc], the regeneration of this IL required very low pressures (1×10^{-4} Pa) at the maximum allowable temperature for this IL, 160 °C, and, therefore, the process using this IL becomes unfeasible. Even though the relative volatility of the mixture ethanol/water using $[emim][N(CN)_2]$ is lower, this IL is a more suitable solvent than [emim][OAc], considering the overall process. Therefore, this IL was selected and evaluated in our extractive distillation pilot plant for the separation of ethanol/water and compared with the benchmark solvent EG.

2.4.3 Separation of Methylcyclohexane and Toluene

There are several ionic liquids investigated for the extractive distillation of methylcyclohexane/toluene mixtures, and the most important conventional solvent used in extractive distillation is NMP. We have screened a large number of cations and

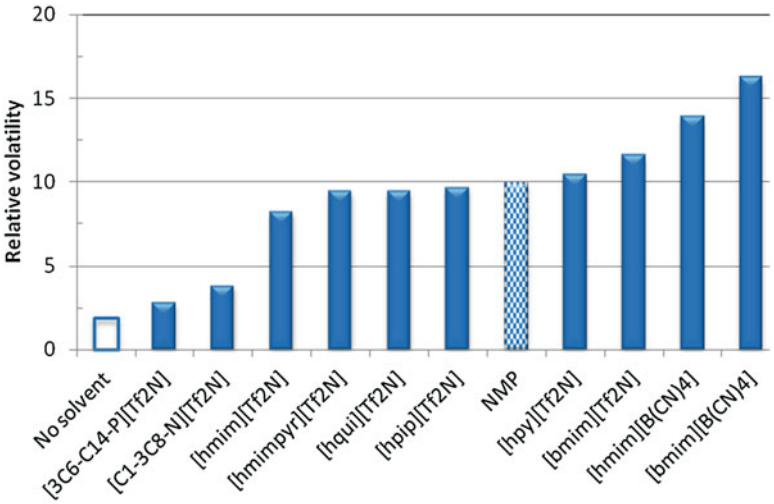

Fig. 2.4 Relative volatilities of methylcyclohexane/toluene with several solvents: trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)amide ($[3C_6\text{-}C_{14}\text{-}P][Tf_2N]$), methyltrioctylammonium bis(trifluoromethylsulfonyl)amide ($[C_1\text{-}3C_8\text{-}N][Tf_2N]$), 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide ($[hmim][Tf_2N]$), 1-hexyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)amide ($[hmimpyr][Tf_2N]$), 1-hexylquinolinium bis(trifluoromethylsulfonyl)amide ($[hqui][Tf_2N]$), 1-hexyl-1-methylpiperidinium bis(trifluoromethylsulfonyl)amide ($[hpip][Tf_2N]$), N-methyl-2-pyrrolidone (NMP), 1-hexylpyridinium bis(trifluoromethylsulfonyl)amide ($[hpy][Tf_2N]$), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide ($[bmim][Tf_2N]$), 1-hexyl-3-methylimidazolium tetracyanoborate ($[hmim][B(CN)_4]$), and 1-butyl-3-methylimidazolium tetracyanoborate ($[bmim][B(CN)_4]$). S/F = 15, $T = 303.15$ K

anions with COSMO-RS/COSMOTherm in order to select suitable combinations for this separation [32]. The results of the COSMO screening were validated by experiments. Figure 2.4 shows the selected solvents for the methylcyclohexane/toluene separation. Some ILs show comparable and others higher relative methylcyclohexane/toluene volatilities than NMP [34].

It becomes clear from this figure that four ILs perform better than NMP: 1-hexylpyridinium bis(trifluoromethylsulfonyl)amide ($[hpy][Tf_2N]$), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide ($[bmim][Tf_2N]$), $[hmim][B(CN)_4]$, and 1-butyl-3-methylimidazolium tetracyanoborate ($[bmim][B(CN)_4]$). The IL $[hmim][B(CN)_4]$ was selected for the simulation of the extractive distillation process because of its high selectivity and higher miscibility with both toluene and methylcyclohexane than $[bmim][B(CN)_4]$.

2.4.4 Separation of Ethylbenzene and Styrene

Because of the relevance of the selectivity as well as the capacity, these two properties were investigated for a range of 37 ILs using LLE measurements

[33]. LLE measurements were performed, because only the selectivity (S) can be determined from VLE experiments, but not the capacity (D). In addition, the LLE measurements are much less labor intensive than VLE measurements. The selectivities obtained from the LLE experiments were subsequently validated by performing VLE measurements for three ILs. There are no data available in the literature about the screening of ILs for the separation of close boiling aromatic mixtures with ILs. However, much data is already known for several other hydrocarbon/hydrocarbon separations [15–26]. The reported solvent capacities and selectivities for those separations were used to make a first estimate on promising cation-anion combinations. For example, it is known that ILs containing anions with large electron delocalization, such as $[N(CN)_2]^-$ and $[B(CN)_4]^-$, have a high solvent capacity for aromatics [14].

Figure 2.5 shows the relative styrene/ethylbenzene volatility and the styrene capacity for a selection of the solvents investigated for the separation of ethylbenzene/styrene. It is clear from this figure that there are several ILs that have a higher relative volatility than the benchmark solvent sulfolane. However, from the results of the LLE experiments, it was concluded that there is a clear trade-off between

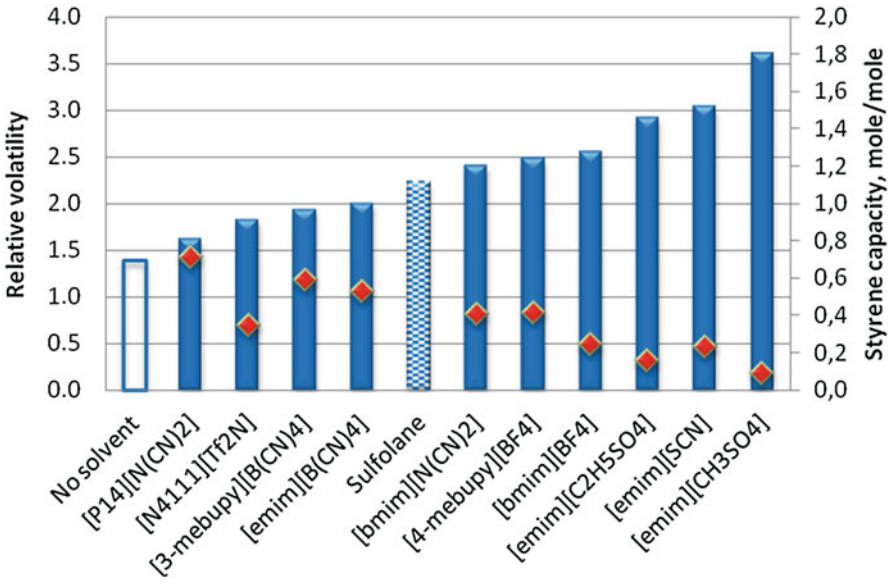

Fig. 2.5 Relative volatilities of ethylbenzene/styrene (bars) and styrene capacity (♦) with several solvents: trihexyl(tetradecyl)phosphonium dicyanamide ($[P_{14}][N(CN)_2]$), butyltrimethylammonium bis(trifluoromethylsulfonyl)amide ($[N_{4111}][Tf_2N]$), 3-methyl-N-butylpyridinium tetracyanoborate ($[3\text{-mebupy}][B(CN)_4]$), 1-ethyl-3-methylimidazolium tetracyanoborate ($[emim][B(CN)_4]$), sulfolane, 1-butyl-3-methylimidazolium dicyanamide ($[bmim][N(CN)_2]$), 4-methyl-N-butylpyridinium tetrafluoroborate ($[4\text{-mebupy}][BF_4]$), 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim][BF_4]$), 1-ethyl-3-methylimidazolium ethyl sulfate ($[emim][C_2H_5SO_4]$), 1-ethyl-3-methylimidazolium thiocyanate ([emim][SCN]), 1-ethyl-3-methylimidazolium methylsulfate ($[emim][CH_3SO_4]$). $T = 348.15$ K

capacity and selectivity [33]. The IL with the highest relative volatility, 1-ethyl-3-methylimidazolium methylsulfate ([emim][CH_3SO_4]), is not suitable because of its low styrene capacity ($D_{styrene} = 0.086$ mol/mol). Three ILs were selected for further study: 3-methyl-*N*-butylpyridinium tetracyanoborate ([3-mebupy][$B(CN)_4$]), [4-mebupy][BF_4], and 1-ethyl-3-methylimidazolium thiocyanate ([emim][SCN]). The IL [3-mebupy][$B(CN)_4$] shows a high capacity and a relative low LLE selectivity ($D_{styrene} = 0.592$ mol/mol, $S_{S/EB} = 1.38$); the IL [emim][SCN] has a high LLE selectivity, but a rather low capacity ($D_{styrene} = 0.229$ mol/mol, $S_{S/EB} = 2.18$); and the IL [4-mebupy][BF_4] has an average LLE selectivity and solvent capacity ($D_{styrene} = 0.414$ mol/mol, $S_{S/EB} = 1.77$).

A conceptual process design was carried out with these three ILs and with sulfolane, in order to determine which of the solvents is the most efficient to use in an extractive distillation process.

Keywords Liquid-liquid equilibrium, Selectivity, Capacity, Ionic liquids, Ethylene glycol, NMP, Sulfolane

2.5 Pilot Plant

The extractive distillation pilot plant consists of three packed column sections, a reboiler, and a condenser. The packing in the pilot plant is Sulzer Mellapak™ 750Y-structured packing; see Fig. 2.6.

Due to the excellent performance in columns with diameters up to 15 m, the Mellapak™ packing is the most used structured packing worldwide. The minimum load ($u_{l,min}$) of a Sulzer Mellapak™ 750Y packing is 0.2 $m^3/(m^2.h)$, and the minimum liquid flow is 0.28 kg/h for the ethanol-water distillation, 0.33 kg/h for the extractive distillation with EG as solvent, and 0.31 kg/h with the IL as solvent.

Fig. 2.6 Sulzer Mellapak™ 750 Y, ©Sulzer Chemtech Ltd

Table 2.1 Pilot plant dimensions and information

Pilot plant column	Value	Unit
Total height	3.12	Meter
Section height	1.04	Meter
Section diameter	0.049	Meter
Number of column sections	3	
Number of distributors	3	
Feed entry	1.04	Meter
Solvent entry	3.12	Meter
Reboiler duty (max.)	2.04	kW
Sampling points	11	
Temperature indicators	17	
Packing diameter of Sulzer Mellapak™ 750Y Standard material	0.049	Meter

The dimensions and other characteristics concerning the column are summarized in Table 2.1. The column sections and the reboiler are connected to each other by distributors for the redistribution of the liquid over the next section.

Figure 2.7 shows the pilot plant column during construction and a schematic drawing of the column. The feed enters the column between the first and second section of the column, at a height of 1.04 m, and the solvent enters the column at the top, at 3.12 m. The low boiling compound is collected from the condenser as distillate and the solvent/high boiling compound mixture from the bottom. The pilot plant has four tanks of each 100 L for the feed, solvent, distillate (ethanol or methylcyclohexane), and heavy product.

2.5.1 Ethanol/Water Separation

2.5.1.1 Experimental Conditions

The conditions (concentration and temperature) of the feed and solvent streams were kept constant during all experiments. The feed flow remained constant at 3 kg/h throughout the experiment, and the solvent stream is dependent on the desired solvent-to-feed (S/F) ratio. The feed composition was 70 % water and 30 % ethanol. The key part in extractive distillation is the use of the solvent, and, therefore, the S/F ratio is an important parameter in the experiments. The solvent extracts the high boiling component from the mixture and, hence, helps to purify the low boiling component. By changing the S/F ratio, the efficiency of the solvent in the stripping section of the column will change. Thus, the capacity of the column can be altered: a higher amount of stages is needed at a lower S/F ratio. However, a higher solvent flow generates more bottom flow, and, consequently, a higher capacity is required for the stripping section. During the experiments, the S/F ratio is set at 0.5 (1.5 kg/h solvent) and 2 (6 kg/h solvent).

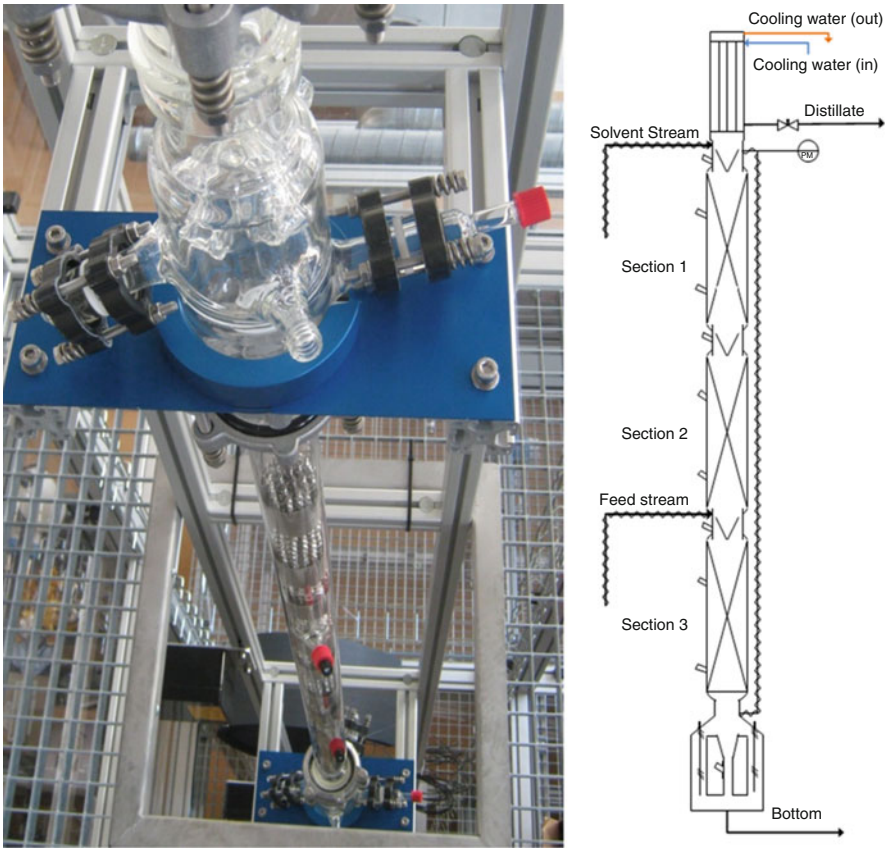

Fig. 2.7 Column section (*left*) and schematic drawing (*right*) of the pilot plant column

Determination of feed temperature in a distillation process is also essential for the efficiency of the column itself. The temperature of the feed entering the column does not have to be equal to the temperature inside the column. However, an equality of the temperatures will increase the energy efficiency (second law of thermodynamics) of the process. Therefore, the feed streams in the pilot plant are preheated in the storage tanks and in the transportation lines. The mixture (ethanol-water) feed is preheated to 50 °C and the solvent feed to 70 °C.

The purity and amount of product can be controlled by changing the distillate rate. The distillate rate influences the reflux ratio and, therewith, the vapor to liquid ratio. A decrease in the distillate rate would result in an increase of the reflux ratio and vice versa. The purity will decrease with decreasing reflux ratios. The distillate rate in these experiments was set at 0.7 and 0.9 kg/h. The last distillate rate is 100 % of the introduced ethanol.

2.5.1.2 Modeling of the Extractive Distillation of Ethanol/Water Separation [35]

The extractive distillation was modeled in Aspen V7.2 using a rate-based model, RadFrac, which requires reliable predictions of mass transfer coefficients, interfacial areas, and diffusion coefficients to predict the performance of the column. The physical properties of the IL needed to model this process were determined by us [36, 37]. Aspen Rate-Based Distillation uses state-of-the-art mass and heat transfer correlations to predict column performance, eliminating the need for efficiency factors or HETP (height equivalent of a theoretical plate). The mass transfer correlation depends on the type of packing used in the pilot plant. Aspen gives a few correlations for packed columns to choose from: Bravo, and Billet and Schultes. The Billet and Schultes correlation needs additional mass transfer correlation parameters in order to converge, and, therefore, only the Bravo correlation is used.

Bravo, Rocha, and Fair first developed a generalized correlation for mass transfer in packed distillation columns and later a theoretical model for structured packing [38–40]. The first method is based on the assumption that the surface is completely wetted and that the interfacial area density is equal to the specific packing surface. The liquid phase mass transfer coefficients are predicted by the penetration model. The generalized correlation is used to model the extractive distillation column.

2.5.2 Extractive Distillation with EG and [emim][N(CN)$_2$] [35]

There is one run carried out with ethanol and water only, three with EG, and three with [emim][N(CN)$_2$] as the extractive solvent. The experiment with ethanol and water was carried out in order to test the pilot plant and to record the performance of the pilot plant. The purity of the product should be higher with the use of the extractive solvents. The experimental performance of the pilot plant is compared with the results of the model of the extractive distillation. The operational conditions are summarized in Table 2.2.

Table 2.2 Operational conditions of extractive distillation experiments (ethanol/water separation)

Experiment	Solvent	Feed flow kg/h	Solvent flow kg/h	Distillate rate kg/h	Reboiler duty kW
1.1	–	3	–	0.9	2.04
2.1	EG	3	1.5	0.7	2.04
2.2	EG	3	6	0.9	2.04
2.3	EG	3	6	0.7	2.04
3.1	[emim][N(CN)$_2$]	3	1.5	0.7	2.04
3.2	[emim][N(CN)$_2$]	3	6	0.9	2.04
3.3	[emim][N(CN)$_2$]	3	6	0.7	2.04

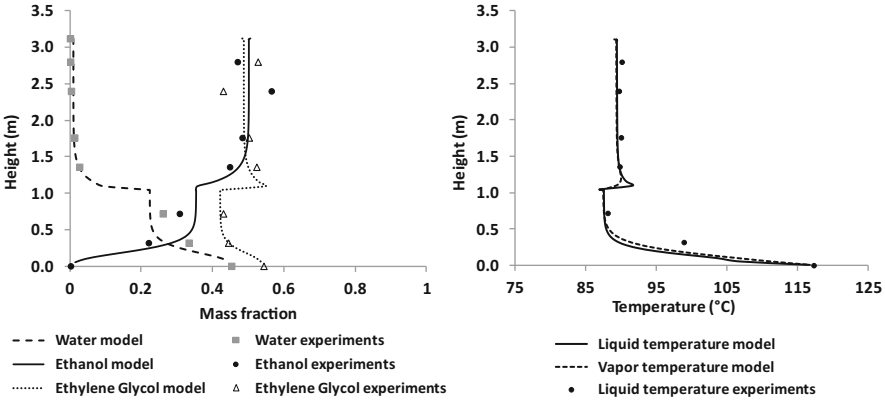

Fig. 2.8 Composition (*left*) and temperature (*right*) profiles for ethanol/water distillation with EG as solvent. S/F = 2, distillate rate 0.9 kg/h

Samples taken from the feed flow, sampling ports, distillate, and bottom flows were analyzed. Most samples consisted of ternary mixtures of water-ethanol-solvent, and the concentration of ethanol in the mixtures was obtained by gas chromatography (GC), using 1-butanol as an internal standard. Water could not be analyzed in the gas chromatograph, and, therefore, the Karl Fischer titration for an accurate analysis of the water content was used. Since the ionic liquid has no vapor pressure, it could not be analyzed by GC and was collected in a pre-column and a cup-liner to protect the column. The IL concentration was then calculated by means of a mass balance. The EG concentration was also calculated by means of a mass balance.

The profiles of the concentrations and temperatures over the height of the column for the ethanol/water separation are well described by the developed model. The profiles of the concentrations and temperatures over the height of the column of experiment 2.2, extractive distillation with EG as the solvent, are shown in Fig. 2.8. This figure shows that the model describes the experiments adequately. The water content decreases from 2.7 % at 1.36 m to 0.13 % at 3.12 m. The temperature in the upper part of the column is around 90 °C. The other runs with EG as solvent show comparable results.

The compositions and the temperature profile of an extractive distillation with [emim][$N(CN)_2$] as solvent are shown in Fig. 2.9 (run 3.2).

Figure 2.9 shows that also for [emim][$N(CN)_2$] as solvent, the model describes the experiments very well. The water content decreases from 2.3 % at 1.36 m to 0.087 % at 3.12 m. Also for the IL as solvent, the other runs show comparable results. The temperature in the upper part of the column is around 85 °C. The temperature in the upper part of the column is around 5 °C higher for EG as solvent than for the IL as solvent, and this is caused by the higher heat of mixing when EG is used.

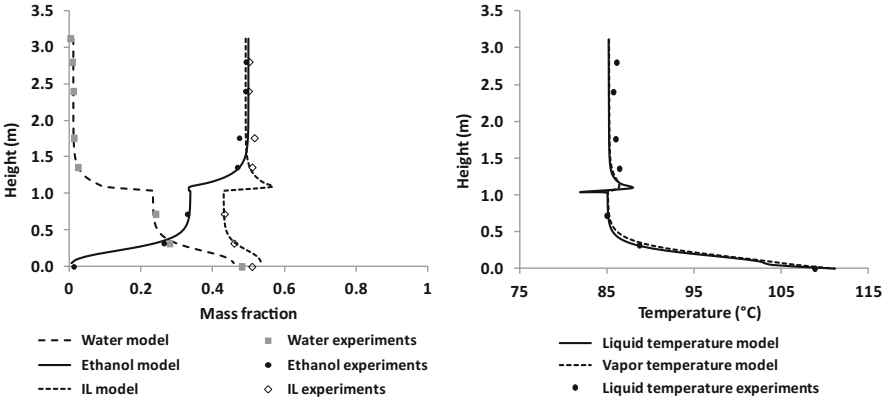

Fig. 2.9 Composition (*left*) and temperature (*right*) profiles for ethanol/water distillation with [emim][$N(CN)_2$] as solvent. S/F = 2, distillate rate 0.9 kg/h

Table 2.3 Product purity, water content, and reflux ratio of all experiments (ethanol/water separation)

Run	Solvent	S/F	Dist. rate kg/h	Product purity %	Water content %	Reflux ratio
1.1	–	–	0.9	93.5	6.5	7.43
2.1	EG	0.5	0.7	98.37	1.63	9.81
2.2	EG	2	0.9	99.87	0.13	6.34
2.3	EG	2	0.7	99.88	0.12	8.62
3.1	IL	0.5	0.7	98.76	1.24	10.32
3.2	IL	2	0.9	99.91	0.087	7.10
3.3	IL	2	0.7	99.92	0.077	4.55

The product purity, water content, and the reflux ratio of all experiments are given in Table 2.3. The ethanol content of the distillate of the extractive distillation is calculated via the water content, because the analysis of ethanol at high ethanol concentrations, above 95 %, was not accurate enough.

The lowest purity was obtained for the normal distillation of ethanol/water mixture, 93.5 % at the highest reboiler duty, as was to be expected. Extractive distillation of ethanol/water mixtures provides higher purities, up to 99.92 % with S/F ratios of 2, as can be seen in Table 2.3. A higher distillate rate requires a higher reflux ratio. The IL [emim][$N(CN)_2$] achieves slightly higher purities than ethylene glycol. The conclusion is that the pilot plant performs well and that a high purity of the ethanol product can be achieved. The developed model describes the extractive distillation experiments with both EG and [emim][$N(CN)_2$] well.

Table 2.4 Operational conditions of extractive distillation experiments (methylcyclohexane/toluene separation). Feed flow 2 kg/h, S/F = 5

Solvent	Distillate rate kg/h	Reboiler duty kW
NMP	0.3	1.02
IL	0.3	0.61
IL	0.3	1.02
IL	0.6	1.02

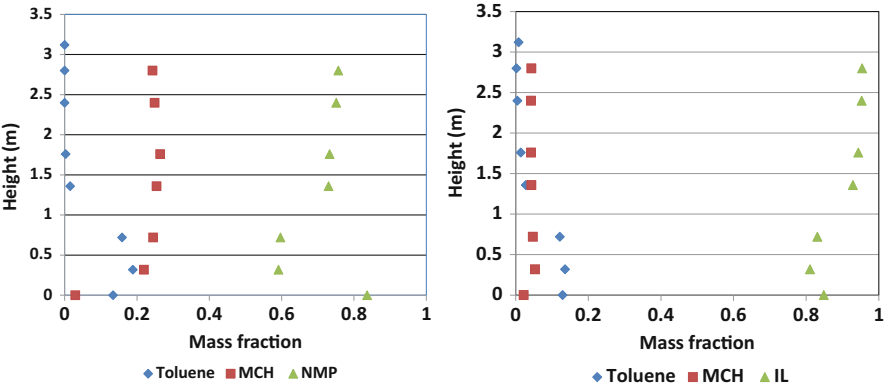

Fig. 2.10 Composition profiles for MCH/toluene distillation with NMP (*left*) and [hmim][B(CN)$_4$] (*right*) as solvent. Reboiler duty 1.02 kW, S/F = 5, distillate rate 0.3 kg/h

2.5.3 Methylcyclohexane/Toluene Separation

2.5.3.1 Experimental Conditions

The conditions (concentration and temperature) of the feed and solvent streams were kept constant during all experiments. The feed flow remained constant at 2 kg/h throughout the experiment, and the solvent-to-feed ratio was 5 for all experiments. The feed composition was 30 % MCH and 70 % toluene, and the feed temperature was 90 °C. There were four runs carried out, one with NMP as the solvent and three with the IL [hmim][B(CN)$_4$] as the solvent. The operational conditions of all experiments are shown in Table 2.4.

2.5.4 Extractive Distillation with NMP and [hmim][B(CN)$_4$]

The profiles of the experimental runs for the separation of methylcyclohexane and toluene with NMP and [hmim][B(CN)$_4$] as solvent are shown in Fig. 2.10. The reboiler duty in both runs was 1.02 kW, the S/F ratio was 5, and the distillate rate was 0.3 kg/h. The profiles of the runs with the IL with different reboiler duties and distillate rates are depicted in Fig. 2.11. The temperature in the column was around 100 °C near the condenser in all runs.

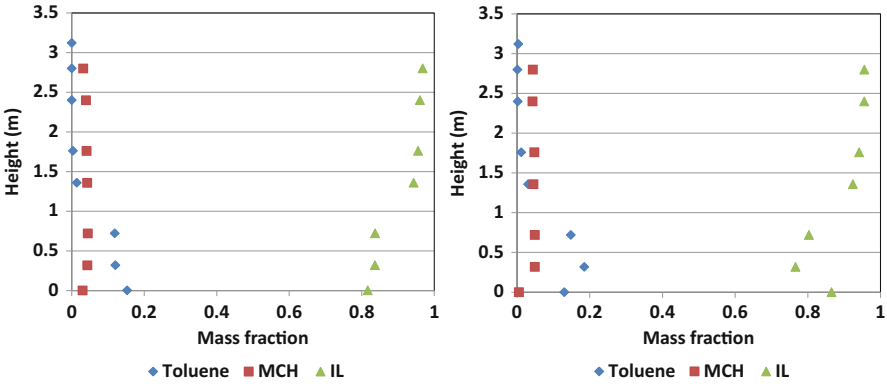

Fig. 2.11 Composition profiles for MCH/toluene distillation with [hmim][$B(CN)_4$] as solvent. S/F = 5. Reboiler duty 0.61 kW, distillate rate 0.3 kg/h (*left*). Reboiler duty 1.02 kW, distillate rate 0.6 kg/h (*right*)

Table 2.5 Product purity, reboiler duty, and distillate rate of all experiments (methylcyclohexane/toluene separation)

Solvent	Reboiler duty kW	Distillate rate kg/h	Concentration of MCH %	Concentration of toluene %	Concentration of solvent %
NMP	1.02	0.3	96.5	0	3.5
IL	0.61	0.3	100	0	0
IL	1.02	0.3	99.82	0.08	0
IL	1.02	0.6	99.67	0.03	0

The results of the analyses of the top product of all runs are shown in Table 2.5.

The lowest MCH purity was obtained with NMP as solvent and the highest MCH purity with the IL as solvent. A lower reboiler duty is apparently better for the separation: the product purity is 100 % with 0.61 kW and 99.82 % with 1.02 kW with the same distillate rate of 0.3 kg/h. A higher distillate rate results in lower product purity, as was to be expected. The conclusion is that the pilot plant performs well and that a very high purity of the product (MCH) can be achieved with [hmim][$B(CN)_4$] as solvent.

Keywords Packed column, Extractive distillation, Solvent/feed ratio, Pilot plant, Modeling, Sulzer Mellapak

2.6 Conceptual Process Design

2.6.1 Ethanol/Water Separation

A model feed mixture of 200 kmol/h composed of 160 kmol/h of ethanol and 40 kmol/h of water at 35 °C and 100 kPa was used for a conceptual process design of

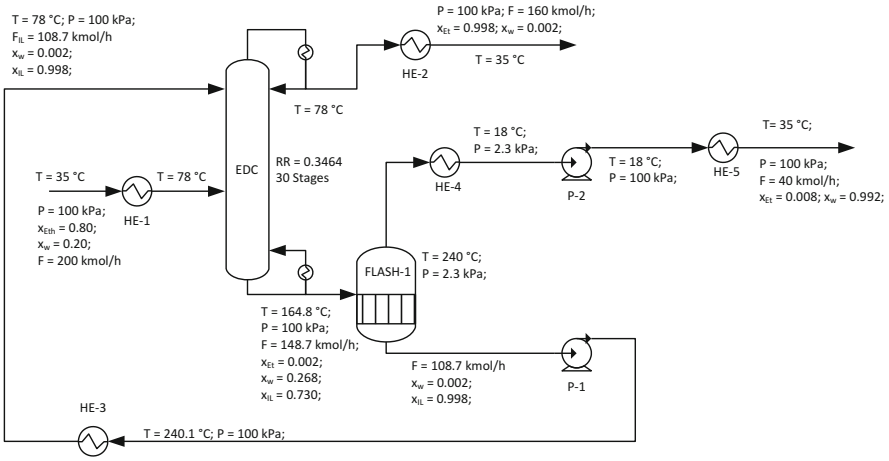

Fig. 2.12 ED process using [emim][$N(CN)_2$]. Recovery of IL with flash drum at 240 °C

the extractive distillation of ethanol/water with both EG and the IL [emim][$N(CN)_2$] as solvents. Ordinary distillation is not a suitable technology to recover ILs due to their nonvolatility, which would lead to unacceptable high temperatures in the reboiler. Processes like flash vaporization, stripping with N_2, and a combination of both technologies are taken into account. For none of the regeneration technologies considered, the energy requirements for the process using the IL could compete with the process using ethylene glycol.

The process with the lowest energy requirements is flash evaporation at 240 °C of the bottom stream of the extractive distillation column. This process consists of a simple evaporation flash drum, which removes the water from the ionic liquid due to the decrease in pressure and a simultaneous increase of temperature. Figure 2.12 shows the complete extractive distillation process with [emim][$N(CN)_2$] as solvent and with flash evaporation of the water.

Replacing the conventional solvent EG with [emim][$N(CN)_2$] yields 6.6 % lower energy duties in the extractive distillation column. However, the recovery of the IL is more energy intensive than the recovery of EG, due to the higher heat capacity of the IL. Therefore, no energy savings are achieved when an IL replaces the conventional solvent. Hence, heat integration is an essential requirement for a feasible extractive distillation process with an ionic liquid.

The total energy requirements of the recovery technologies combined with the extractive distillation column and including heat integration are summarized in Fig. 2.13.

The extractive distillation process without heat integration using [emim][$N(CN)_2$] as solvent requires about 11 % more energy than the process using EG as solvent. However, the IL process with heat integration requires 16 % less energy than the EG process with heat integration.

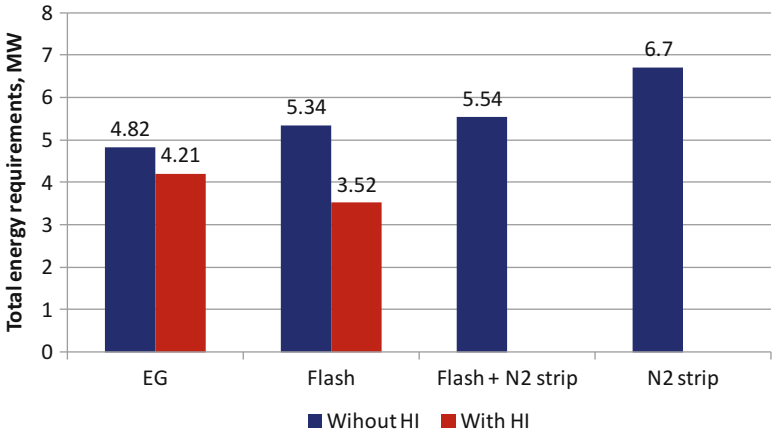

Fig. 2.13 Total energy requirements for the ED process using [emim][$N(CN)_2$] (ED column + recovery technology), without and with heat integration (HI). Feed: 200 kmol/h

2.6.2 Methylcyclohexane/Toluene Separation

A model feed mixture of 1000 kmol/h composed of 300 kmol/h of MCH and 700 kmol/h of toluene at 35 °C and 100 kPa was used for a conceptual process design of the extractive distillation of MCH and toluene with both NMP and the IL [hmim][$B(CN)_4$] as solvents. There are several options to recover the IL, i.e., flash vaporization at 150 °C, stripping with hot N_2, combination of flash vaporization and hot N_2-stripping, a combination of flash vaporization and stripping with hot methylcyclohexane, and recovery by supercritical CO_2 ($scCO_2$). The extractive distillation process with the first four options for the recovery of the IL required less energy than the extractive distillation process using NMP. Only the process using $scCO_2$ to recover the IL required a higher amount of energy, i.e., 98 MW compared with 30.6 MW of the NMP process. The best option is flash vaporization at 150 °C and stripping with hot methylcyclohexane. This process requires about 50 % less energy than the ED process with NMP. A conceptual process design, including the recovery of the IL with flashing of the bottom stream of the EDC and stripping the IL with hot methylcyclohexane, is shown in Fig. 2.14.

When heat integration is applied, even more energy can be saved. The total energy requirements of the recovery technologies combined with the extractive distillation column and including heat integration are summarized in Fig. 2.15. The process with the lowest energy consumption with heat integration is the recovery process using flash vaporization and stripping of the IL with hot methylcyclohexane. This process has a 50 % lower energy requirement than the ED process with NMP with heat integration.

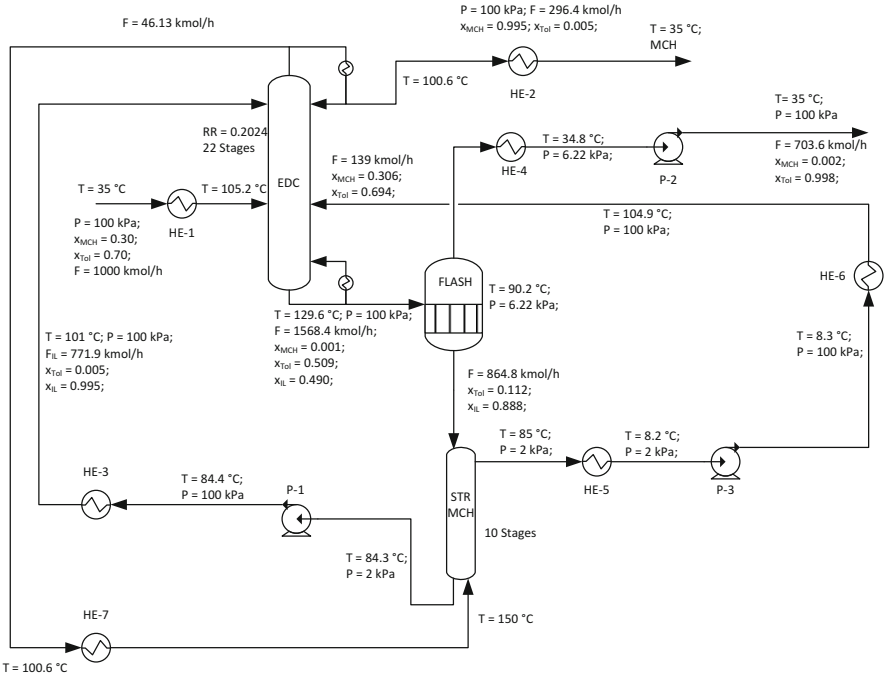

Fig. 2.14 Conceptual process design of ED process of methylcyclohexane/toluene with [hmim][$B(CN)_4$]

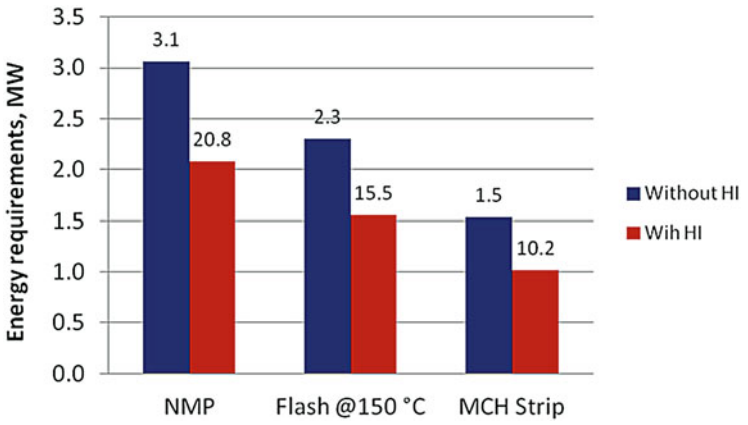

Fig. 2.15 Total energy requirements for the ED process for the separation of methylcyclohexane/toluene using [hmim][$B(CN)_4$] (ED column + recovery technology), without and with heat integration (HI). Feed: 1000 kmol/h

2.6.3 Ethylbenzene/Styrene Separation [41]

The saturated ethylbenzene/styrene feed to the extractive distillation process was 100 metric ton/h, with a styrene concentration of 60 mol% [2] at 57.3 °C and 5.43 kPa (feed stage pressure). Sulfolane and three ILs were used as extractive solvents: 4-methyl-*N*-butylpyridinium tetracyanoborate ([4-mebupy][$B(CN)_4$]), [4-mebupy][BF_4], and [emim][SCN]. The conceptual design study should determine whether the use of ILs is beneficial compared to the benchmark solvent sulfolane, and whether it is more efficient to have an IL with a higher selectivity and lower capacity, or an IL with lower selectivity and higher capacity.

The feed entered the extractive distillation column in all processes as a saturated liquid. The ethylbenzene product obtained at the top of the distillation/extractive distillation columns was set to 98.3 mol% [2]. The final styrene product was modeled for several ethylbenzene impurity levels, i.e., 100, 10, and 1 ppm. A mass balance was applied to calculate the top and bottom flows of the columns. The temperatures at which sulfolane and the three ILs enter the extractive distillation column were set to the temperature of the tray at which they are fed. The condenser pressures in the distillation/extractive distillation columns were set to 50 mbar to keep the temperature in the column low and thereby minimize styrene polymerization.

There are several options to recover the IL, i.e., evaporation under mild conditions with a maximum temperature of 130 °C and using cooling water of 20 °C, flash evaporation at $P < 10$ mbar, evaporation followed by stripping with N_2, evaporation followed by stripping with hot ethylbenzene, distillation with a sulfolane/IL blend, and distillation with NMP/IL blend. Evaporation under mild conditions could be applied for the IL [3-mebupy][$B(CN)_4$]. This process could not be applied for the other two ILs, because the required IL purity of >99.6 % could not be reached with single-stage evaporation and the constrained temperature of 130 °C. The heat duty requirements for the other regeneration processes, two-stage evaporation at low pressures, N_2-stripping, EB stripping, sulfolane/IL (SF) distillation, and NMP/IL distillation were comparable, between 24 and 25 MW.

The best options are two-stage evaporation and evaporation followed by EB stripping, as can be seen in Fig. 2.16, showing the total annual costs for these regeneration methods.

Figure 2.17 shows the total extractive distillation process with the IL [3-mebupy][$B(CN)_4$] as solvent, and Fig. 2.18 shows the ED process with the ILs [4-mebupy][BF_4] and [emim][SCN].

The total energy requirements and operational costs (OPEX) are presented in for all processes. The conclusion can be drawn from Fig. 2.19 that all extractive distillation processes have lower energy requirements (40–45 %) compared to the current distillation process. However, the extractive distillation processes using ILs hardly outperform the extractive distillation process using sulfolane. Compared to the extractive distillation processes with sulfolane, the ILs [3-mebupy][$B(CN)_4$] and [4-mebupy][BF_4] save only ∼1 % and ∼5 %, respectively, on the energy

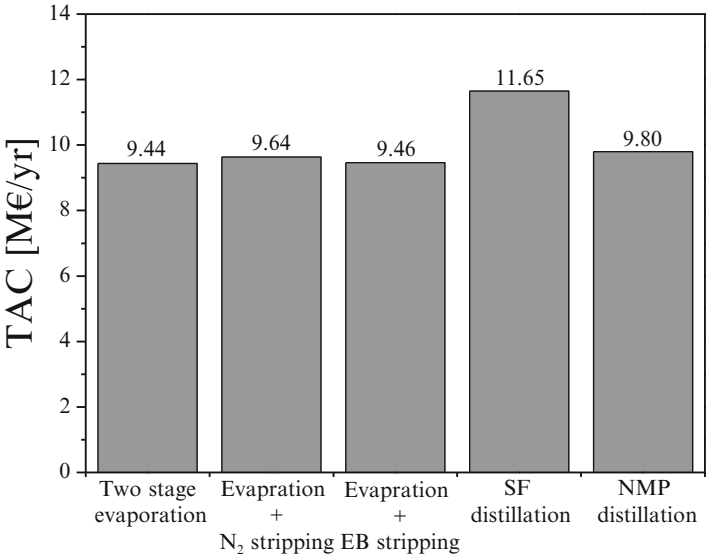

Fig. 2.16 Total annual costs (TAC) of the different regeneration processes [41] (ethylbenzene/styrene separation)

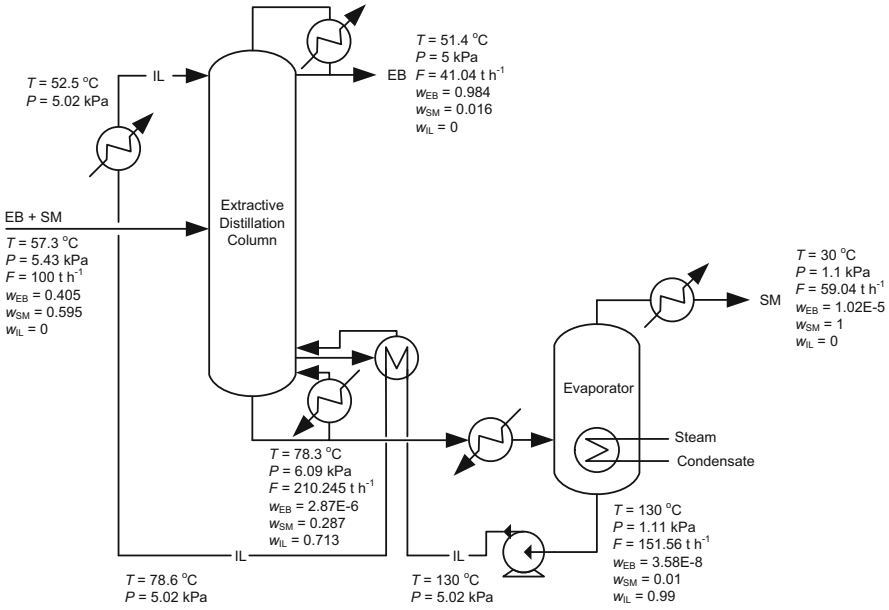

Fig. 2.17 Process scheme for extractive distillation process with an evaporator with the IL [3-mebupy][$B(CN)_4$] (ethylbenzene/styrene separation)

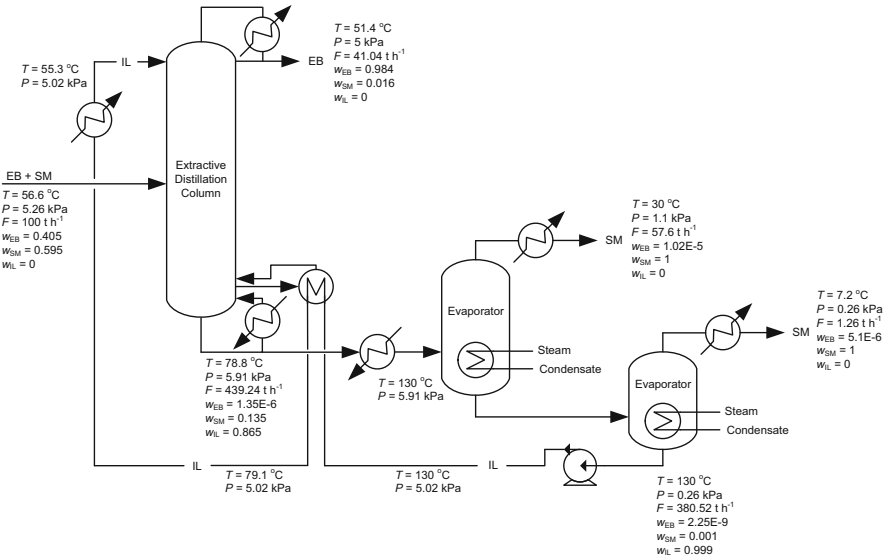

Fig. 2.18 Process scheme for extractive distillation process with two evaporators as regeneration technology with the ILs [4-mebupy][BF_4] and [emim][SCN] (ethylbenzene/styrene separation). First evaporator is operating at mild conditions ($T = 130$ °C, $T_{condenser} \geq 20$ °C), the second evaporator at very low vacuum pressures ($P < 10$ mbar)

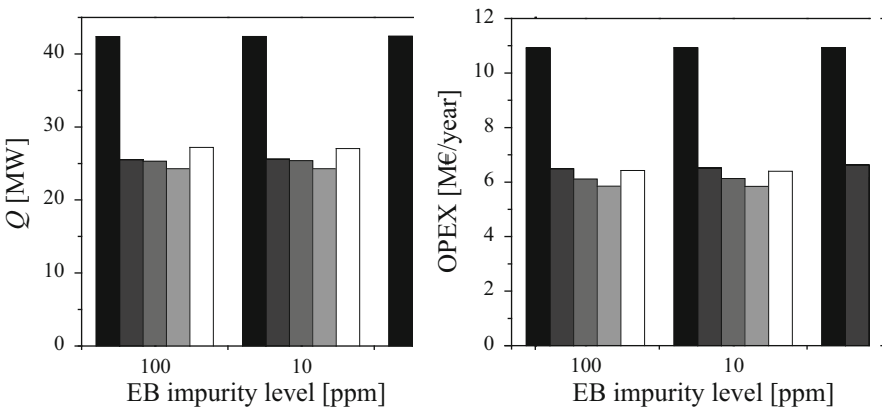

Fig. 2.19 (**a**) Total energy requirements of the different processes for the different ethylbenzene impurity levels. (**b**) Operation expenditures (OPEX) of the different processes for the different ethylbenzene impurity levels. *Black bars*, distillation; *dark gray bars*, sulfolane; *gray bars*, [3-mebupy][$B(CN)_4$]; *light gray bars*, [4-mebupy][BF_4]; *white bars*, [emim][SCN] [41]

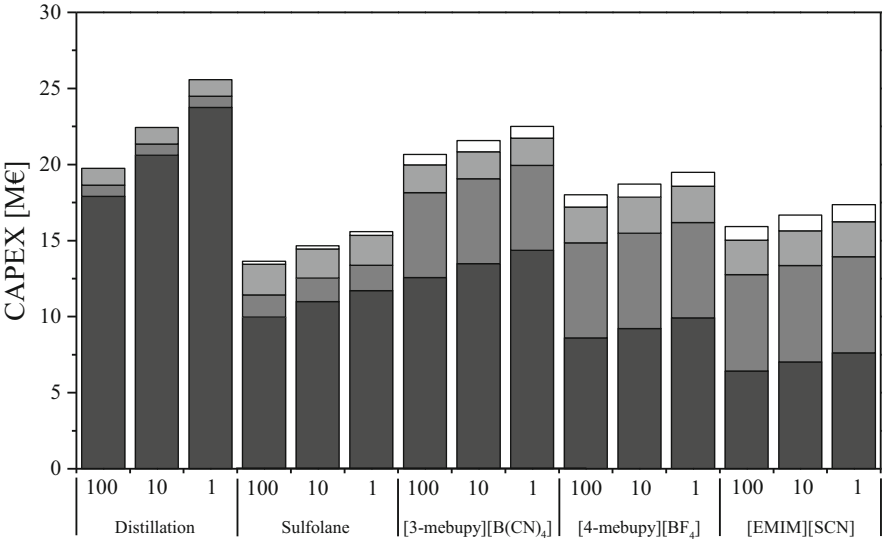

Fig. 2.20 Capital expenditures (CAPEX) for the different processes and ethylbenzene impurity levels. *Dark gray bars*, (extractive) distillation column; *gray bars*; solvent recovery unit; *light gray bars*, heat exchangers; *white bars*, solvent investment [41]

requirements, while the IL [emim][SCN] has ∼5 % higher energy requirements.The IL [4-mebupy][BF_4] outperformed the other ILs. The process with [4-mebupy][BF_4] has 46.5 % and ∼10 % lower OPEX compared to the distillation and sulfolane extractive distillation processes, respectively.

The capital expenditures (CAPEX) were also calculated for the different processes, which are presented in Fig. 2.20. The CAPEX are a summation of the investment requirements for the (extractive) distillation column, solvent recovery unit, heat exchangers, and solvent investment. Figure 2.20 shows that the largest investment is required for the (extractive) distillation column for all processes.

The extractive distillation column is by far the largest equipment in size, and the costs for the structured packing Mellapak 250X contribute significantly to the total column investment (∼50 %). The IL processes require all a lower CAPEX than the current distillation process, except for the process with the IL [3-mebupy][$B(CN)_4$] at an ethylbenzene impurity level of 100 ppm. However, the sulfolane extractive distillation process requires clearly the lowest CAPEX. The large difference between the extractive distillation processes using ILs and sulfolane originates mainly from the difference in investment for the solvent recovery unit. The solvent recovery unit is the second largest contributor to the total CAPEX of the extractive distillation processes with the ILs. The forced circulating evaporator (∼5.5 M€) and falling film evaporator (∼0.9 M€) are both relatively expensive. The differences in CAPEX between the IL processes are dominated by the different investments for the extractive distillation column. The column investments are clearly the lowest for the IL [emim][SCN], because for this IL the lowest amount

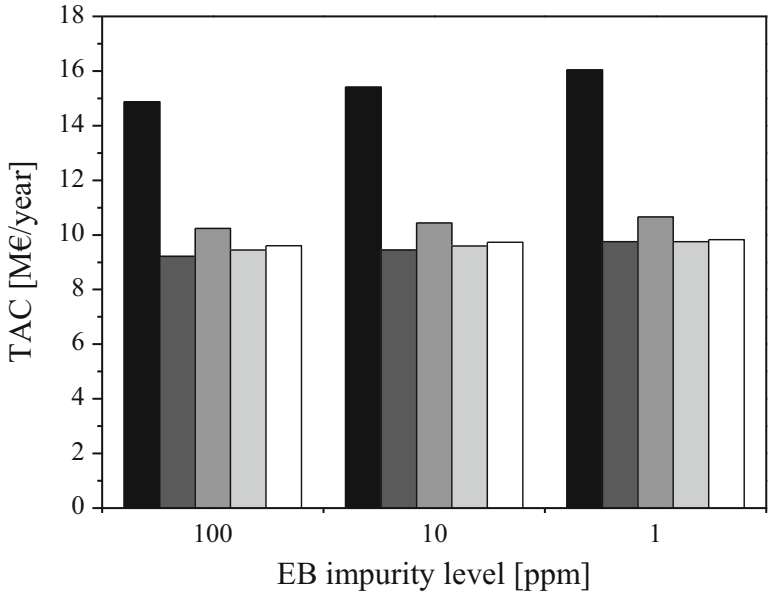

Fig. 2.21 Total annual costs (TAC) for the different processes and ethylbenzene impurity levels. *Black bars*, distillation; *dark gray bars*, sulfolane; *gray bars*, [3-mebupy][$B(CN)_4$]; *light gray bars*, [4-mebupy][BF_4]; *white bars*, [emim][SCN] [41]

of stages (column height) is required and the lowest reflux ratio (column diameter). The solvent investment contributes only 3–7 %, depending on the IL, to the CAPEX of the extractive distillation processes at an IL price of 25 €/kg. At an IL price of 200 €/kg, the solvent investment would contribute about 23 % to the total investment. Finally, the TAC were calculated, which are depicted in Fig. 2.21.

The conclusion can be drawn from this figure that all extractive distillation processes have lower TAC compared to the current distillation process. However, sulfolane gives slightly lower TAC than the ILs. ILs can thus not outperform sulfolane to separate ethylbenzene from styrene by extractive distillation.

Keywords Energy requirements, Heat integration, Regeneration processes, CAPEX, Total annual costs

2.7 Conclusion

For the separation of methylcyclohexane and toluene with extractive distillation, the best IL was [hmim][$B(CN)_4$]. A MCH purity of 100 % could be achieved in the pilot plant. The ED process using this IL and with the recovery of the IL by flash vaporization and stripping with hot methylcyclohexane required less energy than

the ED process using NMP as solvent. When applying heat integration, the energy requirements could be further decreased. The total energy consumption using the IL as solvent is 50 % of that of the ED process using NMP.

The best ionic liquid for the separation of ethanol/water is [emim][$N(CN)_2$], which shows comparable relative ethanol/water volatility as ethylene glycol. Experiments in the pilot plant showed that the experimental results could very well be described by the developed model. An ethanol purity of 99.91 % could be achieved. Besides the performance in the ED column, the IL should be easily recoverable. The recovery of the IL using flash evaporation at 240 °C required the lowest amount of energy, but the extractive distillation process using the IL required 11 % more energy than the benchmark solvent EG. After implementing heat integration, the total energy requirements of both processes can be decreased, and the use of the IL becomes more attractive, yielding 16 % of energy savings compared with the heat-integrated conventional process.

All extractive distillation processes for the separation of styrene/ethylbenzene outperform the current distillation process, but ILs do not perform better than sulfolane as solvent. The IL [4-mebupy][BF_4] outperformed [3-mebupy][$B(CN)_4$] and [emim][SCN] with up to 11.5 % lower energy requirements in the separation of styrene and ethylbenzene with extractive distillation. The operational expenditures of the ED process using [4-mebupy][BF_4] are 43.2 % lower than the current distillation process and 5 % lower than extractive distillation with sulfolane as solvent. However, the capital expenditures for ED were about 23 % lower for the sulfolane process compared to the ED process with the IL as solvent.

Extractive distillation is not a feasible option for the separation of 1-hexene and *n*-hexane, because the increase in relative volatility with an IL is only 5 % compared to that with the benchmark solvent NMP, while the capacity is too low for a feasible separation process.

The general conclusion of these four examples is that only in some special cases ionic liquids can be more advantageously applied than conventional solvents in extractive distillation. The key performance points for extractive distillation are a high selectivity and high capacity, next to the recovery of the solvent and heat integration in the whole process.

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Chapter 3
Ionic Liquids for Extraction Processes in Refinery-Related Applications

Ana Soto

Abstract Ionic liquids are being investigated to improve many of the petrochemical industry stages, ranging from the extraction of crude oil from wells to the obtaining of added value products. The goal is to get more efficient, safe and environmentally benign processes. In this chapter, the possible role of ionic liquids to improve the extraction units in refinery-related applications is considered. These salts are being tested to improve the current separation processes of refineries (deasphalting, metal removal, aromatics extraction, etc.) or as alternatives to other processes (desulfurisation, denitrogenation, etc.). The most recent studies are considering the possibility of using ionic liquids for enhanced oil recovery, for instance, the recovery of bitumen from oil sands or the use of surfactant ionic liquids in chemical oil recovery. Most of the studies consist, at this moment, of only theoretical research. However, it is expected that they become an industrial reality, as it has been the case with the Hycapure-Hg process for mercury removal from natural gas.

Keywords Ionic liquids • Extraction • Refinery • Upstream • Refining

3.1 Introduction

Nowadays, the world's major sources of energy are crude oil and natural gas. Crude oil is a mixture of hydrocarbon compounds (paraffins, naphthenes and aromatics) of different chemical composition and molecular structures with some impurities (1–5 wt.%). Most of these impurities, such as sulphur, nitrogen, vanadium and nickel, are chemically bounded to the hydrocarbon structures. Others, such as sand/clay, water and water-soluble salts of zinc, chromium and sodium, are present as inorganic material. Natural gas is methane which, leaving the reservoir, can contain other heavier hydrocarbon vapours.

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In its raw form, crude oil is practically useless. Before it has any real value, it must be processed into products like fuels, lubricants, waxes, coke, asphalt and innumerable stocks that are the basis of petrochemical industry. Petrochemical plants generate thousands of chemical compounds used in the production of plastics, adhesives, detergents, dyes, fertilisers and many other useful products for society. The composition and the types of impurities of the crude oil are key factors in determining its cost and in establishing the number and intensity of operations that the oil needs to be going through to obtain products of quality. Thus, different processes are implemented in refineries to optimise the output of different crude oils. The refining industry is strategically important but faces many challenges. Continuous adaptation and improvement are needed, and ionic liquids can considerably help to obtain more efficient and environmental benign processes.

3.2 Crude Oil Processing

Many stages are developed from extracting crude oil from a well to obtaining an everyday product. They can be classified as follows [1]:

- Exploration: searching for potential oil fields.
- Upstream: production and stabilisation of oil. This stage includes the separations carried out in the field, near the well, to remove the gases, water and dirt that accompany crude oil coming from the reservoir.
- Midstream: transportation and storage of crude oil.
- Refining: downstream processes accomplished in the refinery to transform crude oil into marketable products.
- Petrochemical: the industrial processing of chemicals from petroleum (synthesis gas, olefins, aromatics, etc.) to obtain derived products of added value.

Ionic liquids are showing interesting applications in all the stages cited above. Figure 3.1 shows a simplified diagram of the crude oil processing, including the operations where these liquid salts are being tested as alternatives to conventional processes. It is not intended to be a rigorous flow diagram; in fact there is not only one refinery scheme [2]. The number and position of treatment processes change according to the raw material and objectives of the refinery (obtaining fuels or feedstock for petrochemical industry). The aim of this draft is just to facilitate the understanding of the activities or processes where current research on ionic liquids is being focused.

After a desalting process to avoid the presence of corrosive salts in the oil, the atmospheric distillation separates the crude oil into fractions according to their different boiling ranges. Naphtha has to be submitted to a catalytic hydrogenation process to reduce its concentration of sulphur, nitrogen, oxygen, metals and other contaminants. C4 or C5 fractions, obtained from light naphtha, can be used for the

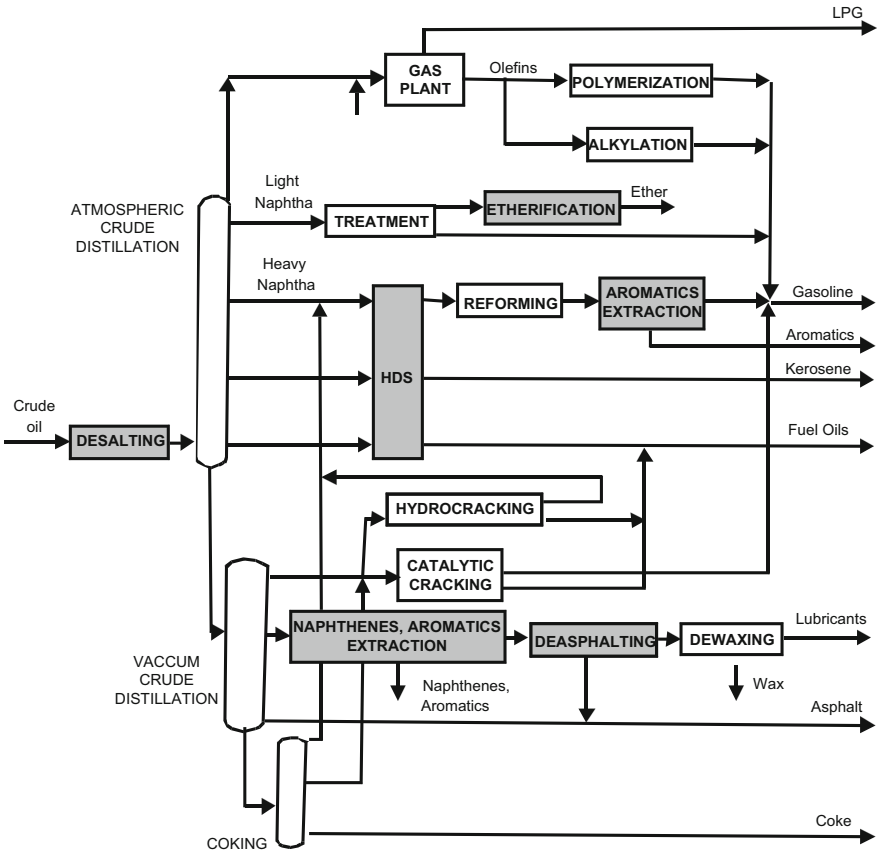

Fig. 3.1 Simplified flow diagram of a refinery. *Shaded boxes* indicate processes where ionic liquids have been tested

synthesis of ethers, needed as additives for gasoline. In the case of heavy naphtha, its catalytic reforming allows the production of an aromatic-rich liquid used in gasoline blending. A prior extraction of aromatics is required.

The heavier fraction of atmospheric distillation goes to a vacuum distillation column. A vacuum gas oil is obtained. It can be processed by hydrocracking or catalytic cracking to obtain additional sources of light products. An intermediate fraction of this distillation can be used to obtain lubricants; nonetheless, several operations are previously required: extraction of aromatic and naphthenic compounds, deasphalting and wax separation. The two heavier fractions of the vacuum column are used in asphalt and coke production. Several fractions leaving the coking unit can also be treated by a severe thermal cracking process, which transforms residual fuel oil into transportation fuels.

3.3 Ionic Liquids in Upstream Operations

Increasingly, there is an imbalance between the demand and supply of petroleum products, thus rendering necessary the recovery of hard-to-access oil. Technological development plays an important role in terms of the challenges facing the better exploitation of the oil world resources. Ionic liquids can facilitate the oil recovery from tar sands or be used as chemicals in recovering the remaining oil from reservoirs that have lost drive during the application of conventional recovery methods.

3.3.1 Bitumen Recovery from Oil Sands

Oil sands, also known as tar sands, are part of the solution to declining conventional oil reserves. They are a complex mixture of sands, clays, water and a black viscous mixture of hydrocarbons called bitumen. Canada (Alberta), Venezuela, USA (Utah) and various countries in the Middle East have deposits; nonetheless, only Canada has a large-scale commercial tar sands industry. Oil sand processing includes mining (sometimes assisted with steam injection), bitumen extraction and upgrading it by dilution with lighter hydrocarbons to make it transportable by pipelines prior to refining.

In the extraction plant, steam, hot water and additives (usually caustic soda) are added to the oil sands to form a slurry which is stirred. By flotation, bitumen droplets rise to the top of the separation vessel, where the bitumen is skimmed off, and sands settle to the bottom. Additionally, the middle phase (mainly water) is processed to recover residual bitumen. Further bitumen processing removes water and residual solids, and the product is sent for upgrading. The process needs a significant amount of water and energy (for heating and stirring) and poses several environmental challenges in relation to water contamination. Cutting-edge processes are being developed to be more environmentally friendly and to substantially reduce water and energy requirements per unit of bitumen produced.

Painter et al. [3] patented a method for the separation and recovery of hydrocarbons from particulate matter by using ionic liquids or ionic liquid analogues. When the particulate matter is contacted with the ionic liquid, the hydrocarbon dissociates from the solid particulate to form a multiphase system. The process can be carried out at a relatively low temperature (25–55 °C). The selected ionic liquids are soluble in water and insoluble in non-polar hydrocarbon solvents. Moreover, they can be contained or reacted into innocuous amino acids if they are released to the environment. Some examples are: 1-butyl-3-methyl-imidazolium trifluoromethanesulfonate, [bmim][CF_3SO_3]; 1-butyl-2,3-dimethyl-imidazolium tetrafluoroborate, [bmmim][BF_4]; and 1-butyl-2,3-dimethyl-imidazolium trifluoromethanesulfonate, [bmmim][CF_3SO_3] [4]. The patent also proposes the use of ionic liquid analogues

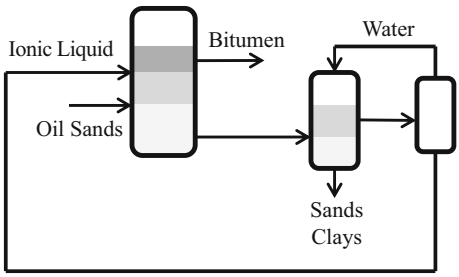

Fig. 3.2 Bitumen recovery from oil sands

composed by two components which form a eutectic with a melting point much lower than either of the individual components. For example, mixtures of tetralkyl ammonium salts and organic hydrogen-bond donors are suggested.

Figure 3.2 shows a process flow diagram to carry out the separation proposed in the patent [3]. Oil sands and the ionic liquid are fed to a vessel. When mixed with the ionic liquid, the bitumen separates from the oil sands and a three-phase system is formed. The bottom phase consists of a slurry containing sands and ionic liquid, the middle phase is mainly ionic liquid (with some bitumen and minerals) and the top phase consists of bitumen. The bitumen is recovered from the upper phase. The middle phase can be retained in the mixing vessel or extracted to separate ionic liquid which would be recycled to the mixing vessel. The bottom phase is sent to another vessel where it is mixed with water to form a solution of ionic liquid, water and suspended sand and clay particulates. The sands and clays are filtered from the ionic liquid and water, and the ionic liquid is recovered by separating the water, e.g. in an evaporator. Water is recycled to the secondary mixing vessel and the ionic liquid to the primary mixing vessel.

As an alternative, Painter et al. [3] propose the addition of an organic solvent immiscible with the ionic liquid in the first mixing vessel. The organic solvent dissolves non-polar hydrocarbons and lowers their viscosity, optimising the separation. In this case, the upper phase shown in the primary mixing vessel of Fig. 3.2 would be a mixture of the bitumen and organic solvent, which after withdrawal has to be separated to recycle the corresponding phases. Because of the complete recycling of the ionic liquid, water and organic solvent if it is used, this process has the potential for ameliorating many of the environmental problems associated with current extraction methods.

Preliminary studies carried out by these researchers [4, 5] show that bitumen can be separated, free of ionic liquid, from the consolidated Utah oil or tar sands using, for example, [bmim][BF_4] in conjunction with toluene at ambient temperatures (∼25 °C). It appears that yields in excess of 90 wt.% can be obtained. However, the separation is more difficult than in the case of Canadian tars.

3.3.2 Enhanced Oil Recovery (EOR)

During the primary recovery in the exploitation of an oil field, the oil is either drained naturally, due to the pressure gradient between the bottom of the wells and the surface or by pumping it until the pressure in the well has decreased substantially. The secondary recovery methods consist of injecting, inside the oil field, a fluid cheaper than oil (e.g. water) to keep a pressure gradient. Tertiary or enhanced oil recovery (EOR) is oil recovery by injection of gases or chemicals and/or thermal energy into the reservoir. It has been proven that such methods are effective in recovering the remaining oil (approximately a 60–80% of the original crude) from reservoirs that have lost drive during the application of the primary and secondary recovery methods. This advanced recovery technique improves the extraction when oils are retained due to capillary forces or because of immobilisation due to high viscosity (heavy oils and tar sands).

Chemical EOR processes use a displacing fluid with optimal chemical formulation, which promotes a decrease in mobility ratio and/or an increase in the capillary number [6]. The mobility control process is based on maintaining a favourable displacing mobility ratio to improve sweep efficiency. The capillary number is a dimensionless ratio of viscous-to-local capillary forces. An increase in the capillary number implies a greater oil mobilisation. The most effective way to achieve this is reducing the interfacial tension by using an adequate surfactant. The main chemical flood processes are polymer, surfactant, alkaline flooding and their combinations [7].

Surfactant flooding is based on injecting into the reservoir a slug of surface-active chemicals added to water with the aim of reducing the capillary forces that trap the oil in the pores of the rock. The principal factors that influence the surfactant slug design are interfacial properties; mobility of the slug in relation to the mobility of the oil-water bank; the persistency of acceptable slug properties and slug integrity in the reservoir; and cost [8]. A slug of water containing polymer solution usually follows the surfactant slug for mobility control. In the case of microemulsion or micellar flooding, higher concentrations of surfactant are used and an oil is incorporated on the core of the droplets promoting miscibility in the overall system. The relatively high viscosity of the microemulsion is also an advantage [9]. The main disadvantage of the surfactant flooding EOR methods lies in the difficulty of finding an optimal chemical formulation (surfactant, cosurfactant, electrolyte, thickening agents for viscosity control, etc.) with a surfactant capable of producing a drastic interfacial tension reduction, low adsorption to the reservoir rock and low cost.

Ionic liquids (ILs) are salts that, because of the steric mismatch of the cation or/and anion, have melting points lower than a conventional threshold (100 °C). The steric mismatch is generally due in large part to the attachment of alkyl side chains to the charged head group of the ions. At least one of the ions of an ionic liquid is thus amphiphilic and therefore a potential surfactant. Collins et al. [10] showed a number of surfactant ionic liquids capable of forming stable microemulsions without any need for a cosurfactant or salt. A great number of applications have been proposed

for traditional surfactants where the possibilities of ionic liquids are being studied, among others, foaming and antifoaming agents, demulsification of petroleum oil, extraction of natural products, analytical techniques, synthesis of new materials and, of course, surfactant flooding.

Ionic liquids have been tested in preliminary studies for their use in both surfactant and microemulsion flooding. Hezave et al. [11, 12] propose 1-dodecyl-3-methylimidazolium chloride as an interfacial tension reducing agent through tests with Iranian crude oil. They found also that the named ionic liquid, unlike traditional surfactants, is more effective for higher saline formation water and that the interfacial tension decreases with temperature. These authors have also carried out interfacial tension measurements between crude oil and other imidazolium and pyridinium chlorides, showing that these ionic liquids are successful in reducing this property and therefore possible chemicals to be used in EOR [13]. Benzagouta et al. [14] found that the interfacial tension values between Saudi oil and brine were smaller when using a surfactant ionic liquid, Ammoeng™ 102, than the typical Triton X-100. Bin-Dahbag et al. [15] have tested the possibilities of nine ammonium- and phosphonium-based ionic liquids for this application. They were screened according to their solubility in brines of different compositions, thermal stability and ability to reduce the aqueous-oleic phase interfacial tension. Again, the ionic liquid superiority, in comparison with traditional surfactants, in high-salinity reservoirs is pointed out.

In the case of microemulsion flooding, a stable solution of oil, water, surfactants, cosurfactants, salts, etc. is injected into the reservoir. The optimal formulation of this surfactant system is associated with a three-phase behaviour in which the interfacial tension becomes significantly low. It has been recently shown [16, 17] that some surfactant ionic liquids in the presence of water and oil (dodecane) form a Winsor type III system where a three-phase region is found. In this domain, a microemulsion (middle phase) coexists with an excess-water phase (consisting of practically pure water) and an excess-dodecane phase (consisting of practically pure dodecane). The water/oil interfacial tension reduction corroborates the ability of the ionic liquids to act as a surface active agent, as desirable for their use in an EOR process. Several advantages can be highlighted. Some of them are intrinsic to the character of the ionic liquids. If room temperature ionic liquids are selected, the manipulation of these surfactants will be easier in comparison to the solid surface-active agents. Moreover, the surfactant ionic liquids can be designed for specific oil and reservoir types and conditions, while being non-toxic and biodegradable. Further advantages are being shown. For instance, the three-phase system (associated with a considerable interfacial tension reduction) generated when adding the ionic liquid trihexyl(tetradecyl)phosphonium chloride ($[P_{6\,6\,6\,14}]Cl$) to a water-oil mixture remains stable in a wide range of temperatures as well as in the presence of salt (Fig. 3.3). No cosurfactant or additive was needed to get this Winsor type III phase behaviour, and the high viscosity of ionic liquid increases the viscosity of the microemulsion [16, 17].

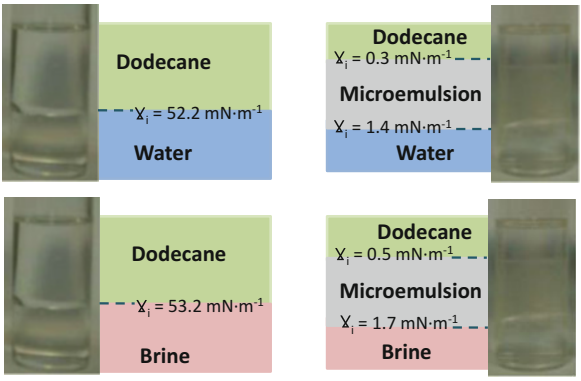

Fig. 3.3 Water/brine-oil interfacial tension reduction at 25 °C due to the presence of the ionic liquid $[P_{6\,6\,6\,14}]Cl$

3.3.3 Demulsification

The output from a well is a mixture of oil, water and gas. For economic and operational reasons, they must be separated, in the same production site, prior to sending the oil to the refining process. This dehydration is usually carried out by gravity separators, allowing the gas to bubble out, the water to settle at the bottom and the oil to be taken out at the middle.

However, stable water-in-oil emulsions are formed in oil wells due to the presence of natural surfactants such as asphaltenes and resins. More effective dehydration practices are needed, and the chemical removal of water is one of the most promising methods. It consists of the addition of small amounts of demulsifiers (1–1000 ppm) to crude oil stored in tanks of separation, just before being pumped, to break the water-in-oil emulsion [18]. Polymeric surfactants, alkylphenol-formaldehyde resins or mixing of surface-active compounds are used for this task.

Flores-Oropeza et al. [19], from the Instituto Mexicano del Petroleo, patented a method where ionic liquids are applied individually or in formulation to dry and desalt median, heavy and extra-heavy crude oils. Among others, proposed ionic liquids include trioctylmethylammonium with chloride, methylsulfate or ethylsulfate and trihexylmethylammonium methylsulfate. Formulations consist of ionic liquids dissolved in typical solvents like dichloromethane, chloroform, aromatic compounds, alcohols, etc. The inventors kept the crude oil at 80 °C for 20 min, and at the end of that time, a predetermined amount of the ionic liquid (individual or formulation), or a formulation of commercial copolymers, was added. Samples were stirred for 3 min, purged and placed again in the temperature-controlled bath.

Evolution of dehydration and desalting was followed with time. The adequate selection of the ionic liquid, depending on the crude oil, allowed dehydration of up to 95 %, also being greater than those formulations prepared with commercial products.

Guzmán-Lucero et al. [20] propose, for oils with higher API gravities, the combined use of ionic liquids with microwave energy to facilitate the breakdown of the water-in-oil emulsions. This source of energy accelerates and increases the efficiency of the demulsification.

3.4 Ionic Liquids for Extraction Processes in Refining

Crude oil is the source of a huge variety of mainly organic molecules, which exist as mixtures in the natural state. The target aim of refineries is to separate these complex mixtures into products that meet our needs. For this objective, several mass transfer processes are developed in this chemical industry: distillation, absorption, liquid-liquid extraction, leaching, adsorption, membrane separation, etc. Along with distillation, liquid-liquid extraction is one of the separation processes most used in refineries.

In liquid-liquid extraction, a liquid feed of two or more components is contacted with a second liquid phase, called the solvent, which is immiscible or partly miscible with the feed. The solvent preferentially dissolves one or more components of the feed, effecting at least a partial separation of the feed components. The extract is the exiting liquid phase, rich in solvent, which contains the extracted solute. The raffinate is the exiting liquid phase that contains compounds not extracted. In its simplest form, solvent extraction would involve a ternary system, with the separation of one of the components (solute) of a binary mixture (solute and carrier) using a solvent partially miscible with the other component, i.e. the carrier.

Liquid-liquid extraction is generally employed when distillation is not an economically satisfactory solution (azeotropic and close-boiling mixtures, thermolabile compounds, etc.). As a mass-separating agent is used to create a second phase in equilibrium, after the extraction itself, a solvent regeneration step (usually distillation) is required to separate the solvent from the solubilised components. The extraction can be implemented in different ways – one stage, crosscurrent, countercurrent and countercurrent with reflux – but the implementation most frequently used in refineries is countercurrent.

From a thermodynamic point of view, the two main factors that define an ideal solvent are a high capacity for dissolving the solute (minimising solvent-to-feed ratio) and a high selectivity for the solute relative to the inert (facilitating the separation). Capacity can be defined as the quantity that is extracted from the feed by a given quantity of solvent. Capacity is straightforwardly related to solute distribution ratio (β) defined as:

$$\beta = \frac{x_s^{II}}{x_s^{I}} \tag{3.1}$$

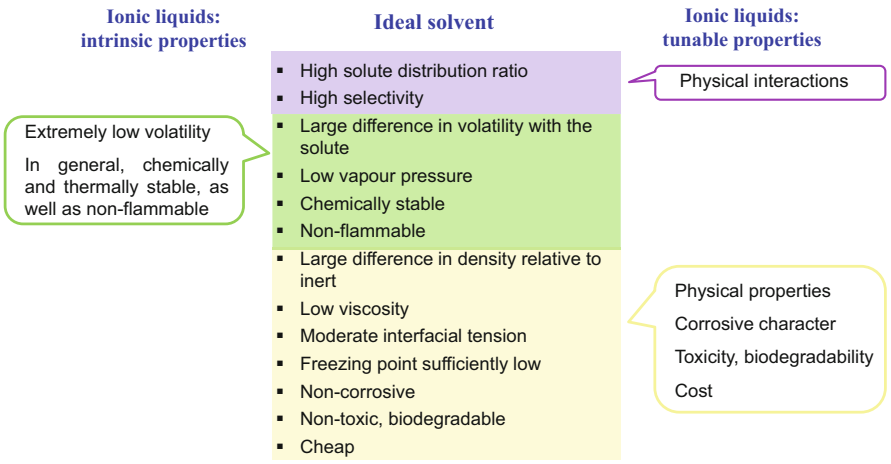

Fig. 3.4 Required properties for an ideal solvent in comparison with ionic liquids properties

where x stands for molar fraction, subscript s refers to the solute and superscripts I and II refer to the raffinate and extract phases, respectively.

Selectivity (S) is definable as the degree to which the solvent extracts the solute in the feed with regard to the carrier. It represents a measure of the ease of separation of the solute and the carrier and is mathematically expressed as:

$$S = \frac{x_s^{II}}{x_s^{I}} \cdot \frac{x_c^{I}}{x_c^{II}} \tag{3.2}$$

where subscript c indicates the carrier and the other symbols have the same meaning as in Eq. (3.1).

Figure 3.4 shows the properties that define an ideal solvent and the properties of ionic liquids that adhere to those requirements. Some of the general properties are intrinsic to those of ionic liquids, since they have negligible volatility and most of them are chemically and thermally stable, as well as non-flammable. Other properties of ionic liquids can be tuned, to a good extent, by the appropriate choice of the type of ions and their chemical structure. Thus, these salts can be tailored to obtain certain physical properties, solvation ability, cost, etc. with the aim of designing an optimal extraction solvent. For this reason, a huge number of extraction processes with ionic liquids have been investigated as an alternative to classic and traditional separation processes.

In order to replace a conventional separation process by a process that utilises ionic liquids, this process must be more economic, meaning a lower energy demand, lower use of feedstock, less waste and so on [21]. The solvent regeneration is crucial to obtain a technically and economically feasible process. Because ionic liquids have a negligible vapour pressure, usually a simple flash distillation allows

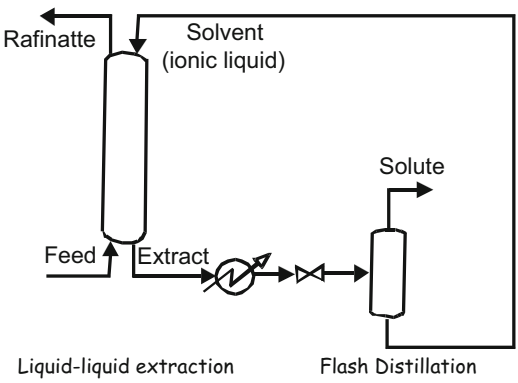

Fig. 3.5 Liquid-liquid extraction and solvent regeneration

its regeneration (Fig. 3.5). However, relatively extreme conditions in terms of temperature and pressure could be required to obtain high ionic liquid purities.

3.4.1 Desalting

Salts contained in crude oil lead to corrosion, fouling and poisoning of catalyst, as well as other problems in downstream processes. Desalting is carried out in refineries and/or among separators in upstream operations. After preheating (100–150 °C), the crude oil is washed with fresh or pre-used water (to minimise water consumption), following a water separation step. This dehydration can be carried out by adding demulsifier chemicals, as explained in Sect. 3.3.3, and/or more frequently by introducing the emulsion into a high-voltage electrostatic field inside a gravity settler. The electrostatic field helps to break the emulsion of water in oil. Two streams leave the settler, a desalted crude oil ready to be refined and a water flow that contains salts (sodium calcium, magnesium chloride, etc.), minerals and water-soluble impurities.

Desalting processes are used to eliminate inorganic salts. However, they are not useful to remove large organic salts such as naphthalic acid which require specific methods (adsorption, extraction, etc.). Anderson et al. [22] discovered that a desalter can be modified in its operation to enable the removal of an ionic liquid and an organic acid (for instance, naphthenic acid) from a crude oil. In the process, water and a mixture containing crude oil with an organic acid and ionic liquid are heated and mixed. Unlike traditional desalters, a high volume percentage in water is used. The formation of an oil-in-water emulsion enhances the transfer of organic acids to the aqueous phase. In a second step, a deacidified crude oil is separated from one or more liquid phases that are comprised of the water, ionic liquid and organic acid. An electrostatic field can be used for easier settling. Tributyl(methyl)ammonium methyl carbonate or other basic ionic liquids are proposed for this method [22].

3.4.2 Metal Removal

Small quantities of metals occur naturally in crude oils. Besides the presence of these elements as inorganic salts, they can be found in the form of salts of carboxylic acids or more typically as porphyrin chelates or organo-metal complexes. Usually Ni and V are found in the highest concentrations in the heaviest crude oils, but in ppm or lower concentrations, many other metals are present such as Al, Co, Cu, Fe, Hg, Mg, Zn, etc.

After atmospheric and crude distillation, the metals tend to concentrate in the heavier hydrocarbon fractions. These fractions are subjected to several operations, such as coking or visbreaking, to reduce the content in these metallic elements.

Serban et al. [23] propose a method for removing one or more metals from a crude oil using a crude-immiscible ionic liquid by liquid-liquid extraction in several removal steps. A crude oil effluent having a reduced metal content relative to the crude oil feed and an extract that contains the ionic liquid and the separated solute are obtained. Optionally, a de-emulsifier can be added to at least one of the extracting steps. Tested ionic liquids for this task were, for example, 1-ethyl-3-methylimidazolium with chloride, ethyl sulphate or bis(trifluoromethylsulfonyl)imide anions; 1-butyl-3-methylimidazolium with hydrogen sulphate, hexafluorophosphate or tetrafluoborate anions; tetraethylammonium acetate; tetrabutylphosphonium methanesulfonate; and 1-butyl-4-methylpyridinium hexafluorophosphate (temperatures between 50 and 70 °C).

The Queen's University Ionic Liquids Laboratories (QUILL) in collaboration with Petronas developed a system for removing metals, particularly mercury, from hydrocarbon fluids. The mercury is toxic, corrosive, reactive with aluminium components and poisonous to catalysts. The patent [24] shows that certain metal-containing ionic liquids are capable of extracting elemental, ionic and organic forms of mercury from hydrocarbon fluids with high levels of efficiency. In the process, the mercury-containing hydrocarbon fluid feed is contacted with an ionic liquid (as a liquid or supported into a solid) having the formula $[Cat^+][M^+][X^-]$. $[Cat^+]$ and $[X^-]$ represent the common cations and anions of the ionic liquids, and $[M^+]$ represents one or more transition metal cations having an oxidation state of $+2$ or greater. The ionic liquids oxidise elemental mercury and organomercury species to highly soluble mercury ions and extract them. The exiting hydrocarbon fluid has a reduced mercury content.

For gas treatment, the process (called Hycapure-Hg) has been shown to have better efficiency than the traditional process used in refineries (molecular sieves). It has been installed in full-scale commercial onshore gas terminals in Malaysia (Kerteh, Bintulu, etc.), successfully producing sales-quality natural gas.

3.4.3 *Etherification*

Ethers are introduced as additives to gasoline to meet the oxygen requirements and the vapour pressure limits. Currently, the most common ethers used for this purpose are ETBE (ethyl *tert*-butyl ether) and TAME (*tert*-amyl methyl ether), due to the decay of the use of MTBE (methyl *tert*-butyl ether), which was found responsible for a significant amount of pollution of aquifers due to leakage from underground petrol tanks.

MTBE and ETBE are obtained from the reaction of isobutylene with methanol and ethanol, respectively. TAME is obtained from isoamylene and methanol. These exothermic reactions take place over acidic ion exchange resin catalysts under controlled temperature and pressure. The reaction is very selective towards the isoolefins and is carried out with excess of alcohol to cause the chemical equilibrium to shift towards the formation of the ether. As a result, a mixture of unreacted olefin, excess alcohol and the produced ether has to be separated.

A generic process for ether production is shown in Fig. 3.6a [25]. The separation section consists of a fractionating column (usually comprising a catalytic section to improve the yield of the reaction) where the ether is obtained as bottom product. The unreacted olefin is obtained at the top normally with an important quantity of the alcohol used in excess. However, the proportion of this compound in the distillate and the bottoms depends on the nature of the hydrocarbon and alcohol used, as well as on the operation conditions in the column. The top stream from the distillation column is fed to a liquid-liquid extraction column. In the refinery processes, water is used as solvent. The raffinate is the unreacted hydrocarbon that can be recycled back to the reactor. The extract (the phase rich in solvent, to which most of the solute is transferred) is a mixture of water and alcohol and is azeotropic in the case of ethanol. The separation of the ethanol-water mixtures is carried out in a new fractionating column. In the case of ethanol, water and the azeotropic mixture (95.6 wt.% ethanol, 4.4 wt.% water) are obtained. Consequently, when the ethanol is recycled to the reaction section, several problems appear such as deactivation of the resins or formation of unwanted alcohols.

The IFP proposes an enhanced method [26] of producing ether, which avoids the use of water, comprising of at least one stage of separation of the excess alcohol by an ionic liquid. Simply, the inventors suggest the possibility of feeding one or several streams of the process into a liquid-liquid extraction column, which uses ionic liquid as solvent, followed by a flash distillation. The locations of where the extraction would take place are illustrated in Fig. 3.6b, by means of a square, and the process that is to be added to the flow diagram is shown in Fig. 3.5. The alcohol can be separated from the hydrocarbon and/or the ether by putting it in contact with the ionic liquid that preferably solubilises the alcohol. Due to the negligible vapour pressure of the ionic liquid, it may be easily separated from the alcohol in a single vapour-liquid equilibrium stage. The separated and condensed alcohol can be recycled to the process. This method, according to the invention, advantageously

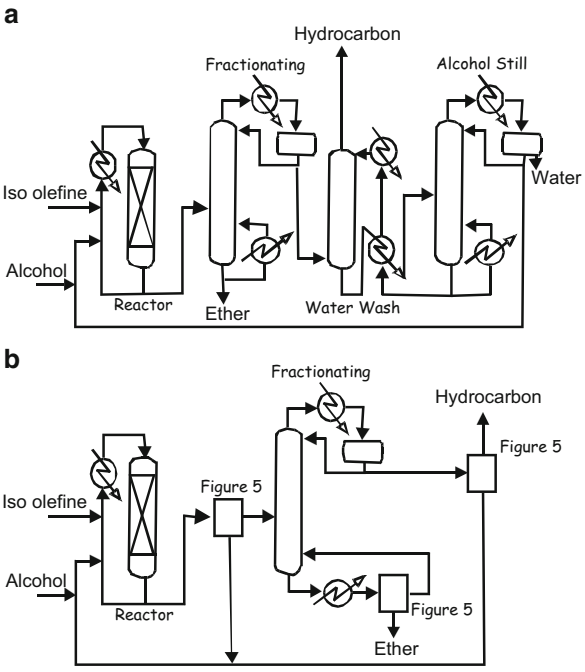

Fig. 3.6 Generic process for ether production: (a) traditional method, (b) with ionic liquids

allows the recycling of an alcohol whose purity level and low water content favour the etherification reaction in terms of selectivity and activity of the etherification catalyst.

Arce and collaborators have shown that ionic liquids can efficiently extract the alcohol from the ether. For instance, in the case of ETBE, the ionic liquids 1-ethyl-3-methylimidazolium methanesulfonate, 1-ethyl-3-methylimidazolium trifluoromethanesulfonate, 1-ethyl-3-methylimidazolium ethylsulfate and 1-butyl-3-methylimidazolium trifluoromethanesulfonate were tested [27–29]. Figure 3.7 shows solubilities and selectivities obtained from the liquid-liquid equilibria of ETBE + ethanol + ionic liquid at 298.15 K. The ability of the mentioned ionic liquids to carry out the separation of mixtures of ETBE and ethanol by solvent extraction is supported by the high values obtained for these parameters, being 1-ethyl-3-methylimidazolium methanesulfonate the most promising ionic liquid from the point of view of thermodynamics.

Other ionic liquids such as mono-, di- or tri-ethanolamine salts of acetic, caproic or valeric acid are also proposed by The Academician Y.H. Mamedaliyev Institute of Petrochemical Processes for selective purification of alkyl-tert-alkyl ethers [30].

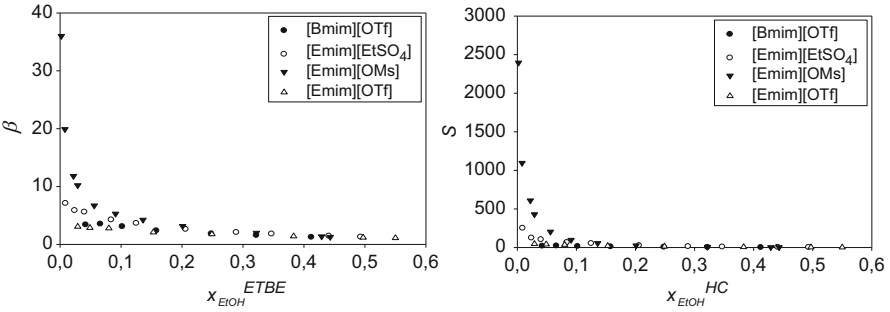

Fig. 3.7 Solute distribution ratios and selectivities (molar basis) for the system ETBE + ethanol + ionic liquid at 298.15 K

3.4.4 Aromatics Extraction

Aromatics are extracted from an oil cut either to give added value to the cut itself or to the aromatics that it contains [31]. Many oil refinery processes require the separation of aromatics from aliphatic hydrocarbons. For example, dearomatisation is used to obtain the BTX (benzene-toluene-xylene) fraction from catalytic reforming and naphtha steam cracking effluents. BTX are basic raw materials in the petrochemical industry for the manufacture of plastic, synthetic rubber and synthetic fibre. Aromatics extraction is also used to obtain kerosene with a better smoke point, a diesel oil with a higher cetane number or a lube oil with a better viscosity number. Moreover, this extraction can also be used to reduce the sulphur- and nitrogen-aromatic compounds, but these processes of desulphurisation and denitrogenation will be considered in the following section.

Concerning the BTX production, not only solvent extraction, but also processes based on azeotropic distillation, extractive distillation, crystallisation by freezing and adsorption on solids were developed, each one having different requirements for efficient and economical operations. Solvent extraction is, by far, more widely applied than either of the other mentioned methods. Industrial processes for the aromatics extraction from light oil cuts can be classified in two types, according to whether they operate with a single solvent, which can be a homogeneous mixture of solvents, or a pair of solvents that are immiscible with each other. The operation sequence for single solvent processes can be generalised into an extraction step, purification of aromatics by extractive distillation and solvent regeneration by conventional distillation. In the case of processes using two solvents, unlike the former, after the aromatics extraction, a re-extraction with a secondary solvent is carried out. The problem of separating the aromatics from the solvent by distillation no longer exists, but the recovery of two solvents can be an important drawback in the cost of energy [31]. Among the solvents used, several ethylene glycols, sulfolane, dimethyl sulfoxide, N-formylmorpholine, N-methyl-2-pyrrolidone or mixtures of some of them with water can be cited. Sulfolane (or,

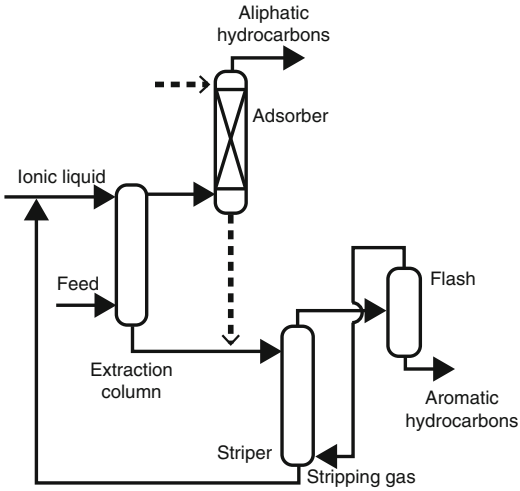

Fig. 3.8 Aromatics extraction with ionic liquids

more systematically, 2,3,4,5-tetrahydrothiophene 1,1-dioxide), used in UOP and Shell processes, is in a preferential position because it offers a good balance of solvent properties.

Regarding the treatment of lube oil stocks to produce lubricants, the paraffinic hydrocarbons with a high viscosity index must be separated from the naphthenic and aromatic hydrocarbons with a low viscosity index. One more time, due to the close-boiling points, liquid-liquid extraction is the process used for this aim. A number of different solvents can be used: furfural, N-methyl-2-pyrrolidone, phenol or liquid sulphur dioxide (where the first is the most widely used). After the extraction, flash distillation and steam stripping are the commonly used processes to recover the solvent from the oil-rich raffinate and aromatic-rich extract streams.

Harmsen et al. [32] address the design of a commercial scale process for the separation of aromatics compounds from a mixture using ionic liquids as solvents. Figure 3.8 shows a simplified flow diagram of the proposal of these inventors. The main unit is a countercurrent extraction column where the aliphatic-aromatic mixture is kept in contact with the ionic liquid. From the top of the column, the raffinate phase, containing basically aliphatic hydrocarbons with traces of aromatic compounds and ionic liquid, is fed to a column with an adsorbent bed. The trace compounds are retained and the effluent of this adsorber is a purified aliphatic compound stream. There are two parallel fixed-bed adsorbers operating in a cyclic manner. One is operating at the same time that the other is being regenerated by passing a heated aromatic liquid product stream, with the effluent being recycled to the extract stream of the extraction column. The combined streams are fed to a stripping column and put into contact with a stripping hydrocarbon gas (e.g. methane). The purified ionic liquid is recycled to the extraction column, and the stream comprised of stripping gas and aromatic compounds is sent to a condenser. The condensate contains the aromatics (final product), and the volatile fraction (basically butane) is passed to the stripping column as stripping gas.

There are many publications in the literature analysing the ability of different ionic liquids for the aromatics extraction. The study is carried out through the liquid-liquid equilibrium determination of ternary mixtures of the type aliphatic hydrocarbon + aromatic hydrocarbon + ionic liquid. The most studied systems are *n*-hexane + benzene + ionic liquid and *n*-heptane + toluene + ionic liquid for the case of *n*-alkanes and cyclohexane + benzene + ionic liquid and methylcyclohexane + toluene + ionic liquid for the case of cycloalkanes. An excellent overview on the current state of the art can be found in the reviews published by Ferreira et al. [33] and by Meindersma et al. [34] for cyano-containing ionic liquids.

Ferreira et al. [33] collected the information published in the literature for these ternary systems to analyse the effect of various structural features on both the ionic liquid and the hydrocarbon in their phase behaviour. In all the studied cases, selectivities have been clearly found to be much higher than one, thus confirming the ability of ionic liquids to carry out the targeted separation. In the best cases, solubilities are only slightly higher than one, whereas in most of the cases they are lower than the unity. That means that large quantities of solvent may be required for efficient separation. Concerning this point, ionic liquids can be advantageous if we assume that they can be easily recovered due to their negligible vapour pressure. However, the authors establish their conclusions analysing β and S in terms of mole fractions, and the results are clearly less favourable in terms of mass fractions. Ferreira et al. [33] concluded that, based on selectivity, the preferred ionic liquid cations are *ammonium* > *imidazolium* > *pyridinium* > *phosphonium* and, according to solubility, *pyridinium* > *imidazolium* > *ammonium* > *phosphonium*. Cations with shorter alkyl chains decrease solubility, but increase selectivity. Concerning the ion families, the aromatic nitrogen-based cations and anions with low hydrogen-bond basicity, such as $[EtSO_4]^-$, $[MeSO_4]^-$, $[SCN]^-$ and $[DCA]^-$, are preferred. As usual in liquid-liquid extraction, the increase in temperature does not favour the separation, thus reducing energy requirements.

Considering not only β and S but also physical properties, Meindersma et al. [34] suggest the ionic liquids 1-butyl-3-methylimidazolium tricyanomethanide ($[C_4mim]C(CN)_3$), 1-butyl-3-methylpyridinium dicyanamide ($[C_4mpy]N(CN)_2$), 1-butyl-3-methylpyridinium tricyanomethanide ($[C_4mpy]C(CN)_3$), 1-butyl-3-methylpyridinium tetracyanoborate ($[C_4mpy]B(CN)_4$) and 1-butyl-3-methylpyrrolidonium tetracyanoborate ($[C_4mpyrr]B(CN)_4$). They have tested and found that the ionic liquid $[C_4mpy]N(CN)_2$ is a better extractant for the separation of toluene from their mixtures with *n*-heptane in a pilot plant Rotating Disc Contactor (RDC) than sulfolane. However, they emphasise that in order to apply these cyano-containing ionic liquids in industrial extraction processes, the cost of the ionic liquids has to drastically decrease.

A comparison between the performance of sulfolane [35] (currently the leading solvent used in industry) and several ionic liquids to extract benzene from *n*-hexane is carried out in Fig. 3.9. This figure shows the solute distribution ratio and selectivity as a function of the solute mass fraction in the hydrocarbon phase at 298.15 K. Mass fraction was selected to compare the effects, due to the large

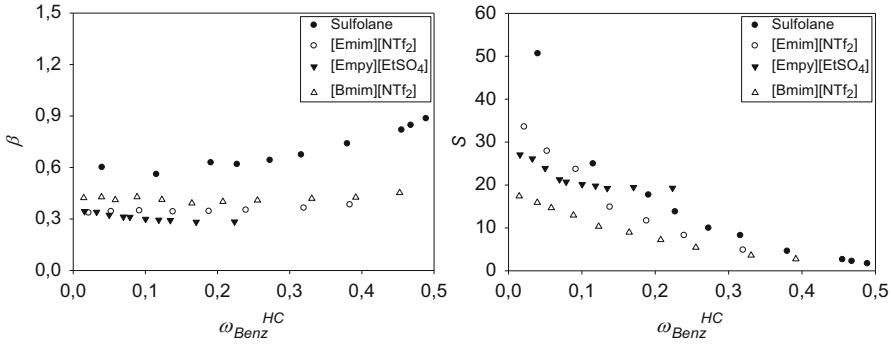

Fig. 3.9 Solute distribution ratios and selectivities (mass basis) at 298.15 K for the system *n*-hexane + benzene + ionic liquid

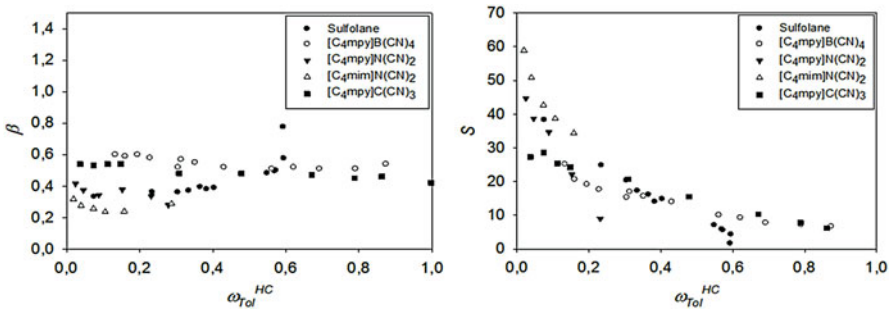

Fig. 3.10 Solute distribution ratios and selectivities (mass basis) at 303.15 K for the system *n*-heptane + toluene + ionic liquid

molecular weight differences among sulfolane and ionic liquids. Salts leading to high values for these parameters were taken from literature [36–38].

As it can be seen, even when selecting the most favourable ionic liquids, they show lower solubilities and selectivities than sulfolane, so in terms of these parameters the replacement does not seem to be feasible. Similar conclusions have been obtained by Meindersma and de Haan [21]. These authors suggest four ionic liquids for the targeted separation: $[C_4mim]C(CN)_3$, $[C_4mpy]N(CN)_2$, $[C_4mpy]C(CN)_3$ and $[C_4mpy]B(CN)_4$. For some of them, Fig. 3.10 shows the solute distribution ratio and selectivity as a function of the solute mass fraction in the hydrocarbon phase for *n*-heptane + toluene + ionic liquid at 303.15 K [39–42].

These ionic liquids reach values more favourable for the dearomatisation. At low concentrations of toluene, $[C_4mim]N(CN)_2$ and $[C_4mpy]N(CN)_2$ have bigger selectivities than sulfolane; however, their solubilities are lower. At medium concentrations, all these ionic liquids and sulfolane present similar values of selectivities, but $[C_4mpy]C(CN)_3$ and $[C_4mpy]B(CN)_4$ present higher solubilities. In any case, the comparison must also take into account other parameters such as physical

properties, environmental impact, no loss of the solvent, energy requirements to regenerate the solvent and cost. Meindersma and de Haan [21] have carried out a preliminary economic evaluation for the separation of aromatic compounds from the feed of a naphtha cracker with several ionic liquids, concluding that the process can be competitive. A lower investment in the ionic liquid process mainly results from the easy regeneration of the solvent.

3.4.5 Desulphurisation and Denitrogenation

With the industrialisation and development of many countries, serious atmospheric pollution incidents have started to appear worldwide. Emission levels of sulphur play a critical role in the chemistry of the atmosphere, as it is a major component in the production of acid rain. Sulphur dioxide emissions arise from the oxidation, during combustion, of the sulphur contained within fossil fuels. For these reasons, it is evident that there is a necessity to diminish the presence of sulphur in fuels and many countries have established directives to this effect. The current trend is focused on the production of ultra-low-sulphur fuels.

In refineries, the hydrotreating process can be divided into a number of reaction categories: hydrodesulphurisation, hydrodenitrification, saturation of olefins and saturation of aromatics [25]. A hydrotreater unit specifically employed to remove sulphur is usually called a hydrodesulphurisation (HDS) unit. Many refinery streams, such as naphtha, gasoline, diesel oil and residue, are processed by hydrotreating. In the case of diesel oil deep desulphurisation, the specific name of the process is hydrofining.

All these processes take place over a metal catalyst in a hydrogen atmosphere, working at high pressures (20–70 atm) and temperatures (between 260 and 450 °C). The catalyst is, typically, a sulphide of molybdenum supported on alumina and promoted by either cobalt or nickel. With this process, it is expected to remove the organic sulphur compounds (mercaptans, sulphides and disulfides, thiophenes, dibenzothiophenes and their alkyl-substituted derivatives) present in the fuels due to the natural formation of the crude oil. The presence of each compound varies in each type of fuel, and their reactivity in the HDS process diminishes when increasing the size of the molecule. Thus, the most difficult components to remove by the HDS process are the refractory dibenzothiophenes, especially those with substitutions in the positions 4 and 6.

The progressive adaptation of refineries to gradually more strict legislative requisites is being carried out through changes in their processes. Several desulphurisation steps, recycling, more severe pressure and temperature conditions, new catalysts, higher hydrogen consumptions, etc. are the pathways being used to achieve the required desulphurisation levels. Nonetheless, these approaches imply high operation costs and less safe processes.

With the aim of solving these limitations and enhancing the extraction of sulphur from fuels, several alternative techniques were studied during the last few years

to either replace or be combined with the HDS process. Among them, extractive desulphurisation and also oxidative extractive desulphurisation (which improves the extraction oxidising the sulphur compounds) are promising alternatives.

There are many works in the literature focused on the study of the use of ionic liquids as solvents in extractive desulphurisation processes. However, all of them suffer from important drawbacks that need to be solved prior to incorporating the process into a real refinery. There is an alarming absence of studies concerning the content of the other compounds of the fuels during the desulphurisation process. Denitrogenation and dearomatisation are also important parameters that must be taken into account, since they will directly affect the properties of the fuel. Moreover, even in most of the published patents, there are no suggestions as to how the extraction using ionic liquids can be integrated in the existing hydroprocessing systems.

Bhattacharya et al. [43] propose a process for removing sulphur and nitrogen compounds from a vacuum gas oil feed, using ionic liquids, based on a liquid-liquid countercurrent extraction column. The invention encompasses a variety of flow scheme embodiments: an optional washing step of the vacuum gas oil, to recover the remaining ionic liquid, before being fed to a hydrocarbon conversion process; an optional ionic liquid regeneration by extraction with a hydrocarbon fraction lighter than the vacuum oil; and an optional ionic liquid drying step (distillation or stripping with a dry inert gas).

The Saudi Arabian Oil Company proposes an ionic liquid desulphurisation process incorporated in a tank [44] or in a low-pressure separator [45]. The layout implies integration within refineries, without the need for integration of substantially new equipment, with existing hydroprocessing reactors. Figure 3.11 shows a simplified flow diagram of the proposal of these inventors [45]. The effluent from a typical hydrotreating system is mixed with water and a nonaqueous ionic liquid and sent to a low-pressure cold separator (225–275 °C) where, after contact, two phases are separated. The hydrocarbon phase, containing ionic liquid, is passed through a fractionator to obtain the ionic liquid (which can be recycled) from the bottom and the desulphurised hydrocarbon from the top. The combined stream of wastewater and ionic liquid is passed to a phase separation vessel. The water is separated, and the ionic liquid is sent to a vacuum distillation unit for regeneration prior to its recycling. The distilled diesel fraction, which is rich in sulphur, is sent to a sulphur reduction process.

A similar process is presented [44] for the case of ionic liquids that have less efficacy for sulphur extraction in the presence of water. Instead of mixing the feed simultaneously with water and ionic liquid, the process is carried out in two steps. The hydrocarbon is first washed and, after separation, treated with the ionic liquid.

Another proposal integrated in the refineries comes from Chevron [46], but in this case the ionic liquid is supported. In the process, a hydrocarbon feed is put into contact with an adsorbent, consisting of an ionic liquid deposited onto a porous support, and placed to eliminate sulphur and nitrogen compounds before the hydroprocessing step. The adsorbent can be also placed prior to an isomerisation dewaxing step as a method to produce a lube oil.

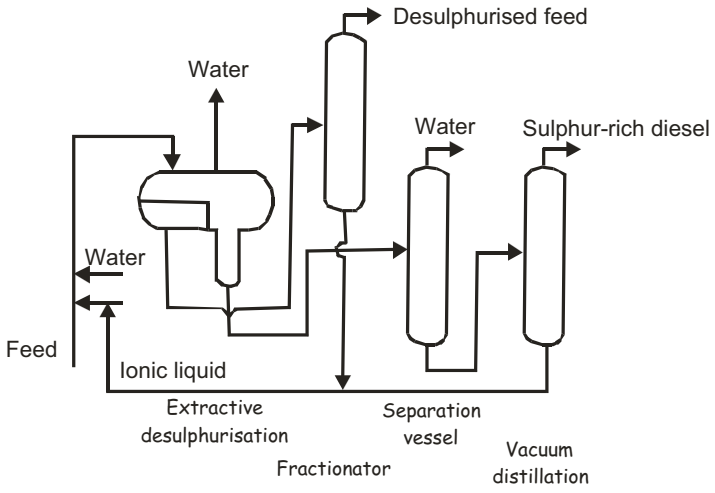

Fig. 3.11 Desulphurisation with ionic liquids

Regarding the most suitable ionic liquid to be used in a desulphurisation process, most of the studies in the literature are just based on the solubility of a sulphur compound (normally dibenzothiophene) in the ionic liquid. Other studies focus on the liquid-liquid equilibrium of systems composed of an ionic liquid, a sulphur-containing compound and an aliphatic hydrocarbon. The development of the ionic liquids proposed for this aim [47, 48] coincides with the evolution of ionic liquids itself. The first tested ionic liquids for the selective extraction of sulphur from fuels were haloaluminates, which react with water, being unstable in air. Subsequent studies corresponded to imidazolium ionic liquids with hexafluorophosphate and tetrafluoroborate anions. Nevertheless, these anions imply the possible formation of their hydrolysis products, such as hydrofluoric acid, under certain conditions. Halide-free ionic liquids were then thought to be the solution to these decomposition problems. The high prices and toxicity of the bis(trifluoromethylsulfonyl)imide anion can potentially be limiting factors for its use. Many of the subsequently proposed ionic liquids for desulphurisation have sulphur atoms in the anion. This would not be a problem if the ionic liquid content in the oil phase after the separation were negligible. Nevertheless, since a really small amount of contamination with the salt (several ppms) can be decisive, there is a high risk of the use of these kinds of anions as desulphurising agents. Other anions such as acetate or dialkyl phosphate, being environmentally benign and cheap ions, are interesting alternatives. Also, task-specific ionic liquids can be considered. These complex ionic liquids can balance out the results achieved with traditional ones, but they are usually more expensive and difficult to synthesise or purchase.

An important step in the screening of ionic liquids for this specific task was carried out by Holbrey et al. [49], who studied different anions and cations for the extraction of dibenzothiophene from dodecane, being able to establish a ranking

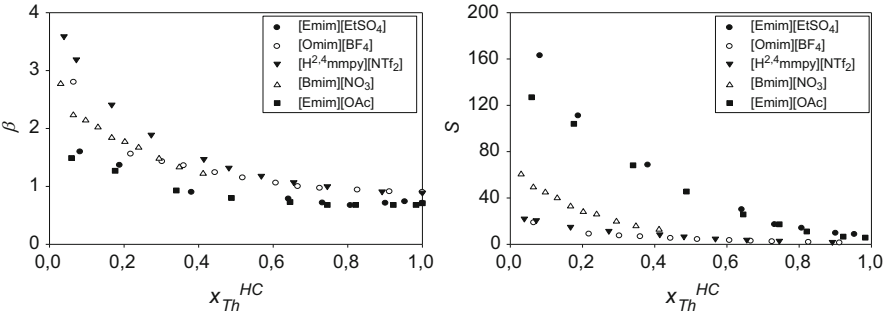

Fig. 3.12 Solute distribution ratios and selectivities (molar basis) at 298.15 K for the system *n*-hexane + thiophene + ionic liquid

of these salts for desulphurisation depending on the cation: alkylpyridinium ≥ pyridinium ≈ imidazolium ≈ pyrrolidinium. However, this is a classification based only on solubility, while neglecting a more important parameter such as selectivity.

Figure 3.12 shows solubilities and selectivities obtained from the liquid-liquid equilibria of *n*-hexane + thiophene + ionic liquid at 298.15 K [50–54]. Selected ionic liquids correspond to those found in the literature with the highest values of these parameters. The high values obtained, for solubilities and selectivities, indicate that all of them are able to separate thiophene from hexane. As it was explained in the dearomatisation section, assuming that the recovery of ionic liquids could be carried out, the selectivity can be considered as the criteria to select the best ionic liquid (always from a thermodynamic point of view). If $[C_2mim][EtSO_4]$ is not considered, because it has a sulphur-containing anion, the $[C_2mim][OAc]$ would be the best option. Rodríguez-Cabo et al. [55] have shown that this ionic liquid has a great desulphurisation capacity and a high selectivity; however, in the process, a large extraction of aromatic hydrocarbons also takes place. For that reason, the implementation of the extraction process with ionic liquids in the refinery, a step practically ignored in the literature, is a critical point to be considered.

One way to improve the solubility of the sulphur-containing compounds in a solvent is to oxidise these components, so that they can be more easily separated. This is the basis of oxidative desulphurisation. The selection of a suitable oxidising agent to convert the sulphur compounds into sulfoxides and then to sulfones is a critical factor. To make the process more efficient, a catalyst for the oxidation reaction is usually needed. An important feature for the application of the oxidative desulphurisation is to have its relative efficiency different from that of HDS. The oxidative reactivity increases when the electron density of the sulphur species is higher: dibenzothiophene > 4,6-dimethyldibenzothiophene > benzothiophene ≫ thiophene. As a consequence, refractory sulphur compounds in traditional HDS are easily removed by oxidative desulphurisation.

The use of the most common oxidising system, H_2O_2 and acetic acid, seems to be one of the most suitable choices for the oxidative desulphurisation with

ionic liquids. Polyoxometalates have also been tested as possible catalysts. Another alternative is the use of acidic ionic liquids working simultaneously as solvents and catalysts. Among them, the choice of anions such as hydrogen sulphate or dihydrogen phosphate is an option to be considered and preferable to the more problematic Fenton-like or Brønsted acidic ionic liquids. Moreover, the advantage of being able to design the ionic liquid is that it allows the introduction of typical catalytic groups (e.g. polyoxometalates or carboxylates) as functional groups in the solvent, avoiding the need of the catalyst. But, as it was previously commented, usually these are alternatives more expensive and difficult to synthesise.

The oxidative desulphurisation enhances the simple extraction with ionic liquids when the fuel has heavy sulphur compounds. However, there are implicit problems associated: reduction of sulphur extraction capacity of the ionic liquid, operation with strong oxidants, selection of an optimal temperature, separation of catalyst and oxidant from the reaction products that limits their recyclability, contamination of the oil, etc.

There is not a unique solution to the desulphurisation problem (it greatly depends on the stream to be desulphurised), and the sulphur extraction ability is not the only parameter to take into account. Co-extraction of (un)desired compounds, pilot plant experiments, integration of the process in the refinery and life cycle analyses, among others, are further aspects to carefully study prior to the implementation of the proposed alternatives in refineries.

3.4.6 Deasphalting

Solvent deasphalting produces lubricating oil base stocks, with a certain viscosity index, by extracting high-boiling lighter paraffinic and naphthenic hydrocarbons (asphaltenes and resins) from the vacuum residue of the vacuum distillation unit [25]. Propane or butane mixtures are usually used as solvents. The process can also be a step for the preparation of catalytic cracking feeds (with or without an intermediate hydrorefining unit), and then solvents heavier than propane are used (butane to hexane). The deasphalting operation is carried out in an extractor with a precipitation zone. It operates with a temperature gradient between the top and the bottom to promote precipitation of the asphaltic fraction.

Traditional processes are energy intensive because they require the refrigeration and compression of propane or butane to liquefy them for their use as solvents in the deasphalting process. In the regeneration of the solvent after the process, they are evaporated, and consequently they have to be refrigerated and compressed for reuse. Moreover, non-asphaltenic molecules co-precipitate in the process due to a lack of selectivity for these solvents.

The ExxonMobil research and engineering company is an applicant for a patent [56] for upgrading heavy hydrocarbons by the separation of asphaltenes using ionic liquids. These salts are proposed as solvents for liquid-liquid extraction to remove asphaltenes, heavy resins and polycyclic hetero (N) aromatics from vacuum residue,

bitumen or heavy oils. Heating or the addition of an aromatic diluent can be used to reduce the viscosity and to facilitate the process. The ionic liquid could be recovered by the addition of an anti-solvent (water or alcohols) or by vacuum distillation.

Liu et al. [57] found that ionic liquids based on the cations containing a conjugated aromatic core, or the anions which are strong hydrogen-bond acceptors, are more effective for deasphalting processes. Also, increasing the effective anion charge density enhances the ability of the salt to break the asphaltene associations, thus enhancing the solubility of these compounds in the ionic liquid.

3.5 Final Remarks

Ionic liquids can be interesting alternatives for extraction processes in refinery-related applications. However, currently there are important bottlenecks to be solved prior to seeing these processes come to an industrial reality. One of them is the incorporation of the process in an existing refinery without involving drastic changes or unaffordable costs. Another challenge is the regeneration of the ionic liquid. Although they have a negligible vapour pressure, sometimes this step is not easy, requiring relatively extreme conditions in terms of temperature and pressure. Another aspect to consider is that the cost of the ionic liquids is still an important problem that limits their competitiveness. Moreover, an important lack of experiments carried out at a pilot plant level, studies about integration of the process in the refinery, life cycle analyses and rigorous economic evaluations, among others, currently place the ionic liquids far from refineries.

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Chapter 4
Ionic Liquids for Metal Ion Separation

Yu Liu and Ji Chen

Abstract Ionic liquids (ILs) as important green solvents and extractants have showed potential application in separation of metal ions. In this chapter, we present new developments in our lab and others to use ILs for green separation of metal ions, such as rare earths (REs) and heavy metal ions, especially by the IL-functionalized solid adsorption materials. The important fundamentals and applied studies on metal ion separation are commented, which include the synthesis of ILs, the new separation systems of ILs, new task-specific ILs (TSILs), and complex materials composed of ILs and inorganic and organic polymers as adsorption materials for liquid-liquid and liquid-solid separation. This chapter only discusses frequently used ILs for metal ion separation; for more information of ILs, some reviews may be referred.

Keywords Task-specific ionic liquids • Ionic liquid extractant • Ionic liquid immobilized adsorbent • Strongly basic anion exchange resin • Rare earths • Heave metal ions

4.1 Introduction

The recovery of high-value metal ions, such as rare earth (REs) [1], Mo [2], Re [2], and heavy metal ions [3], such as Cr [4], Pb [5], Hg [6], Cd [7], and As [8], from ores and waste products has been widely studied in recent years. Many conventional extractants, such as phosphorus-based extractants, carboxylic acids, tertiary and quaternary amines, etc., are used for the separation of metal ions in the metallurgical industry. The early process of metal separation and recovery was mainly concerned with economic benefits, which led to severe environmental problems. To limit the environmental pollution, the Emission Standard of Pollutants from Rare Earth Industry (GB 26451-2011) in China was set up and implemented on October 1, 2011. It was the first REs national emission standard not only applied in

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China but also to the world, aiming to set higher emission standards and reduce the environmental pollution significantly. The separation and recovery technology of metal ions will face serious environmental challenges. Therefore, the development of green separation method and process for metal ion is of great significance.

ILs have been studied extensively as green solvents in the separation processes due to their negligible vapor pressure, high thermal and chemical stabilities, nonflammability, and high solvent capacity. ILs can be used in several processes involving dissolution, extraction, and recovery of metal ions for liquid-liquid extraction. There are some obvious advantages of ILs in extraction and separation processes, such as high separation efficiency. Several excellent reviews on these topics have been published recently [9–14].

As the most familiar and widely used extractant, commercially available Aliquat® 336 or [A336]Cl [5] is a typical extractant used as ionic liquid in the separation of metal ions, even though it was not recognized as "IL" earlier. Recently, phosphonium-type compounds with similar structure of Aliquat® 336 were named as a series of Cyphos® IL. Among them, Cyphos® IL 101 [15] presents high extraction ability for the extraction of Pd (II). Phosphonium-based ILs also have been used as extractants for the selective separation of Co(II) and Ni(II), in chloride medium [16].

In our lab, ILs were used as highly efficient extractants and environmentally benign solvents for the separation of various metal ions, for example, RE(III), rare metals, heavy metals, etc. Several typical applications are presented as follows.

As an extractant, pure ionic liquid $[C_8mim][PF_6]$ has good extractability for Ce(IV) from HNO_3 medium [17] and form insoluble complex. The unique extraction behavior of Ce(IV) by pure $[C_8mim][PF_6]$ was mainly due to the formation of new IL of $[C_8mim]_n{\cdot}Ce(NO_3)_m$. To avoid IL loss during the extraction process, $[C_8mim]^+$ was added to the initial $Ce(NO_3)_4$ solutions and/or KPF_6 solution was used as stripping agent. The increasing $[C_8mim]^+$ concentration may prompt the formation of $[C_8mim]_n{\cdot}Ce(NO_3)_m$ in the IL phase and thus increase the partition of Ce(IV) to the IL.

Imidazolium-based ILs are the most widely used IL solvents and applied in the separation of metal ions. However, there are still some drawbacks of the IL, especially the loss of IL due to the ion exchange mechanisms and the difficulties in recovering metal ions from IL phase [18]. These limitations were especially serious for 1-alkyl-3-methylimidazolium hexafluorophosphate $[C_nmim][PF_6]$, one of the most commonly used ILs.

In the four common categories of ILs, i.e., imidazolium, pyrrolidinium, ammonium, and phosphonium [19], ammonium-type IL attracts more attention for the lowest cost [20] and the least toxicity [21]. As a kind of important compounds, quaternary ammonium salts have been widely used as phase-transfer catalyst, surfactant, and bactericide for a century [22–24].

Sun [25] prepared a series of novel ammonium-based bifunctional IL extractants (bif-ILEs) with different anions by acid-base neutralization reaction and used them for the selective separation of REs(III) and metal ions (Fig. 4.1). These bif-ILEs were prepared through three steps: anion exchange, hydrolysis, and

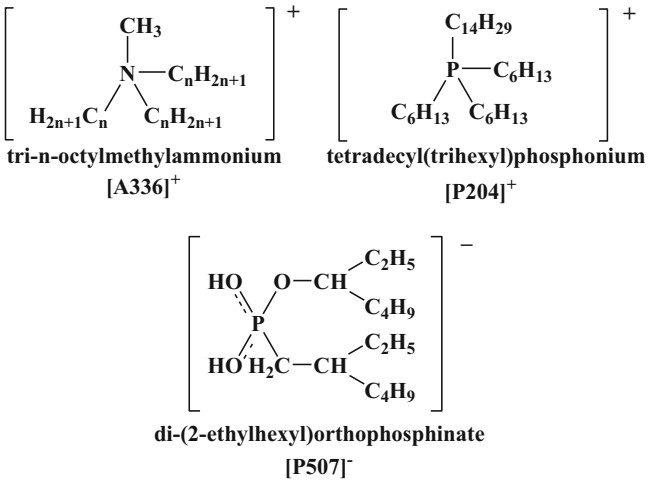

Fig. 4.1 Typical structures of ions constitutive of novel bif-ILEs

acid-base neutralization. The bif-ILEs include [A366][CA-12], [A336][CA-100], [A336][P204], [A336][P507], [A336][C272], and [A336][C302] [25]. Such bif-ILEs are found to exhibit an inner synergistic effect and steric effect, which provide higher extraction ability than those corresponding precursors for the separation of metal ions [26]. It was found that [A336][P204] is not the simple mixture of two extractants but the combination of $[A336]^+$ with $[P204]^-$ (deprotonation anion of P204) by the interionic interactions. Bif-ILEs [A336][P507], [A336][P204], and [A336][C272] have high selectivity for extracting Ce(IV) in H_2SO_4 solution [27] and H_2SO_4/H_3PO_4 system [28]. In HNO_3 system [A336][P507] as the extractant could recover REs (Y, Eu, La, Ce, and Tb) from waste fluorescent lamps [29]. Ammonium-type ILs combining carboxylic acid such as [A336][CA-12] and [A336][CA-100] have prominent extraction ability for REs [30] from HNO_3 medium. [A336][CA-12] could separate La(III) from other REs(III) [31] in the chloride medium and extract Co(II) or Ni(II) [32] in H_2SO_4 solution.

Cyphos IL 104 containing quaternary phosphonium cation and phosphonic acid anion was also explored as novel extractant. The protonated form of the Cyphos IL 104 anion, Cyanex 272, is a well-known extractant of Co(II), Ni(II), and RE(III) [33, 34]. Cyphos IL 104 [35] together with biodiesel as diluent was studied in the extraction of Y(III), showing high extractability and selectivity and low acid and base consumption.

Although IL's application for metal ion liquid-liquid extraction is exciting, the potential use of a large amount of ILs at industrial scale still has some uncertain factors. In the exploration of ILs for economical application, a new kind of IL functional adsorption materials has been prepared by immobilizing ILs on various kinds of supports (e.g., polymers) with the advantages of low consumption and low cost. In this chapter, we will summarize the applications of IL functional adsorption material in the separation and recovery of metal ions recently.

4.2 Preparation and Characterization of IL Immobilized Adsorbents

Various types of ILs could be immobilized on different support materials by physical and chemical techniques. The solid support materials used for immobilization include inorganic porous materials and polymer, such as polymer resin [4], silica gel [36], polymer membranes [37], Al_2O_3 [38], and activated carbon [38].

4.2.1 Preparation and Characterization of Polymer Supported Strongly Basic Anion Exchange Resin

Merrifield resin is a kind of polymer-based chloromethylated styrene divinylbenzene resin, which includes gel type and macroporous type. Zhu et al. synthesized a series of N-alkylimidazolium-functionalized strongly basic anion exchange resins (AIM-AER) by anchoring N-methylimidazolium onto gel-type resin via covalent bonds in the Cl^- form (RCl), SO_4^{2-} form (R_2SO_4) [4], NO_3^- form (RNO_3) [39], and PF_6^- form (RPF_6)[40]. The preparation route is shown in Fig. 4.2. The Merrifield resin sample was reacted with N-methylimidazole in dimethylformamide (DMF) at 80 °C for 36 h. The resin was then filtered and washed with ethanol for 24 h at 65 °C and dried in vacuum to afford N-methylimidazolium-functionalized anion exchange resin in the Cl^- form denoted as RCl, which can transform into other forms (R_2SO_4, RNO_3, or RPF_6) by reacting with Na_2SO_4, $NaNO_3$, or

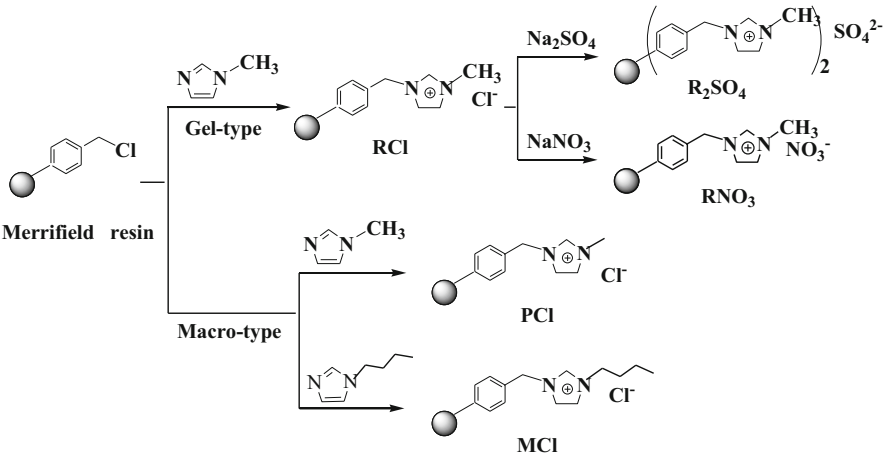

Fig. 4.2 Synthesis route of polymer-supported AIM-AER: RCl, R_2SO_4 and RNO_3, and PCl and MCl (Reprinted from ref. [43], copyright 2008, and ref. [45], copyright 2012, with permission from Elsevier)

Table 4.1 Properties and characteristics of strongly basic anion exchange resins

Resin	RCl	R_2SO_4	RNO_3	RPF_6	PCl	MCl
Resin type	Strongly basic anion exchange resin					
Matrix	Gel type				Macroporous type	
Cation form	N-Methylimidazolium					N-Butylimidazole
Anion form	Cl^-	SO_4^{2-}	NO_3^-	PF_6^-	Cl^-	Cl^-
Decomposition temperature (°C)	220	220	258	304	251	213
Max adsorption capacity (mg/g)	132	125	/	/	139	111

Fig. 4.3 SEM pictures of XAD-7 resin (**a**), $[C_8mim][PF_6]$/Cyanex 923 impregnated XAD-7 resin (**b**), and Cyphos IL 104 impregnated XAD-7 resin (**c**) (Reprinted from ref. [43]. Copyright 2008, with permission from Elsevier; Reprinted from ref. [45]. Copyright 2012, with permission from Elsevier)

HPF_6 solution. The macroporous-type copolymer strongly basic anion exchange resins coupled with N-alkylimidazolium was synthesized by a similar strategy. The N-methylimidazole-immobilized resin was denoted as PCl [41], and the N-butylimidazole-immobilized resin was denoted as MCl [42]. Their properties are summarized in Table 4.1.

Amberlite XAD resin is a kind of frequently used resin with uniform pore size distribution, high surface area, and chemical stability. Solvent-impregnated resin has been prepared by direct impregnation method. The XAD-7 resins were immersed into IL solution ($[C_8mim][PF_6]$/Cyanex 923 [43], [A336][NO_3] or [A336][CA-100] [44], Cyphos IL 104 [45]) for 12 h, and then the resins were separated through a porous filter in vacuum, washed with deionized water, and dried at 50 °C.

As shown in Fig. 4.3, the surface morphology of XAD-7 resin (a) was obviously changed after immobilization by $[C_8mim][PF_6]$ containing Cyanex 923 (b). The surface of b was coated with a homogeneous film of IL containing extractant. Electrostatic interaction should be a dominant force for explaining the existence of IL film since both of the IL and XAD-7 were polar. The phenomenon of Cyphos IL 104 impregnated on XAD-7 resin (c) was quite different, and Cyphos IL 104 was not coated on the surface of resin, while it existed in the inner channel of XAD-7 resin, because the surface of resin was smooth and IL was not observed on the surface. The mass transfer between extractant and metal ions could be accelerated, and the loss of ionic liquid and extractant may be reduced.

4.2.2 Preparation and Characterization of Silica Supported Strongly Basic Anion Exchange Resin SBA-15

Mesoporous silica is considered to be an attractive adsorbent for metal ions, due to its high thermal and chemical stabilities, well-ordered periodic pore structure, and controllable pore diameter. Zhu et al. synthesized N-methylimidazolium-functionalized mesoporous SBA-15 anion exchangers by a template-directed hydrolysis-polycondensation of tetraethoxysilane (TEOS) with 1-methyl-3-(triethoxysilylpropyl)imidazolium chloride (MTICl) (Fig. 4.4) [46]. Pluronic P123 and NaCl were dissolved in water and HCl, and then TEOS and MTICl were sequently added. The molar ratio of MTICl and controlled quantities of silica, x = MTICl/(MTICl+TEOS), were ranged from 0.1 to 0.25. A series of SBA-15 resin was prepared with the similar procedure in different prehydrolysis time and designated as SBA15Im$_x$Cl-t; $x = 0.1, 0.15, 0.2, 0.25$; and $t = 1, 2, 3, 4$ h.

4.2.3 Preparation of ILs Functionalized Solvent-Impregnated Resins

The AIM-AER RPF_6 has been used as polymeric support to prepare solvent-impregnated resins with extractant (Cyanex 923) and/or IL ($[C_8mim][PF_6]$). RPF_6 was reacted with Cyanex 923 and/or $[C_8mim][PF_6]$ in ethanol solution [40]. Then the solvent was removed and the resin was dried in vacuum. Compared with RCl, Cyanex 923 exhibited relatively stronger affinity to RPF_6. The interactions between Cyanex 923 and RPF_6 were nonpolar interaction due to the nonpolar groups and electrostatic interaction. Therefore, RPF_6 was more stable than RCl and suitable to be used as polymeric support of solvent-impregnated resins (SIRs).

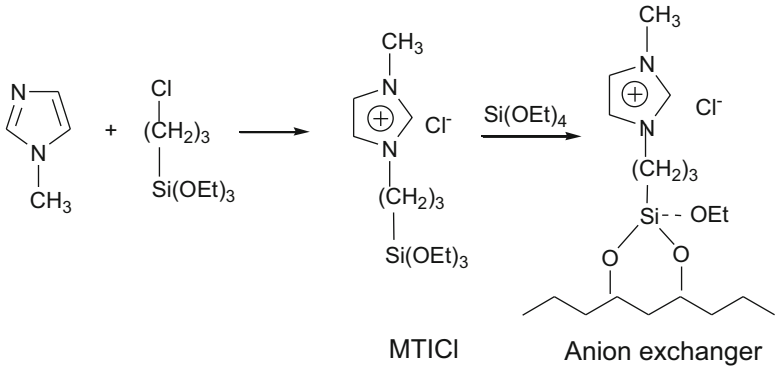

Fig. 4.4 Synthesis route of functionalized SBA-15 anion exchanger resin SBA15ImxCl-t (Reproduced from Ref. [46] by permission of The Royal Society of Chemistry)

4.2.4 Preparation and Characterization of Polymer Inclusion Membranes

Polymer inclusion membranes (PIMs), which are composed of polymers, plasticizers, and ion carriers, have gained considerable attention since their outstanding abilities to remove metal ions selectively from dilute solution [37, 47]. PIM represents an alternative way to immobilize extractants, reduce the use of volatile organic compounds, and enhance the efficiency of extractants for metal extraction.

Poly(vinylidene fluoride) (PVDF) was dissolved in DMF and carrier with plasticizers, e.g., $[C_4mim][PF_6]$, $[C_8mim][BF_4]$, or $[C_8mim][NTf_2]$, was added. The mixture was stirred for 5 min at room temperature, kept for 72 h, and then stirred for 30 min. The final solution was used for casting membranes. The nascent membrane was evaporated, then immersed into deionized water, and washed several times in order to remove DMF.

In order to compare the effect of different carriers on Cr(VI) transport, the permeability coefficient (P) with $[C_nmim][PF_6]$ or $[BF_4]$ ($n = 4, 8$) as IL plasticizers and Cyphos 104 (Fig. 4.5a), [A336][C272], [A336][P204], and [A336][P507] (Fig. 4.5b) as carriers was enhanced. As shown in Fig. 4.5, with the amount of $[C_8mim][BF_4]$ in the membrane increased, the P of Cr(VI) changed greatly. The maximum P of Cr(VI) transport was 12.00 μm/s for $[C_8mim][PF_6]$ ILP, 15.57 μm/s for $[C_8mim][BF_4]$ ILP, 17.48 μm/s for [A336][C272] ILP, 18.35 μm/s for [A336][P204] ILP, and 15.45 μm/s for [A336][P507] ILP, respectively.

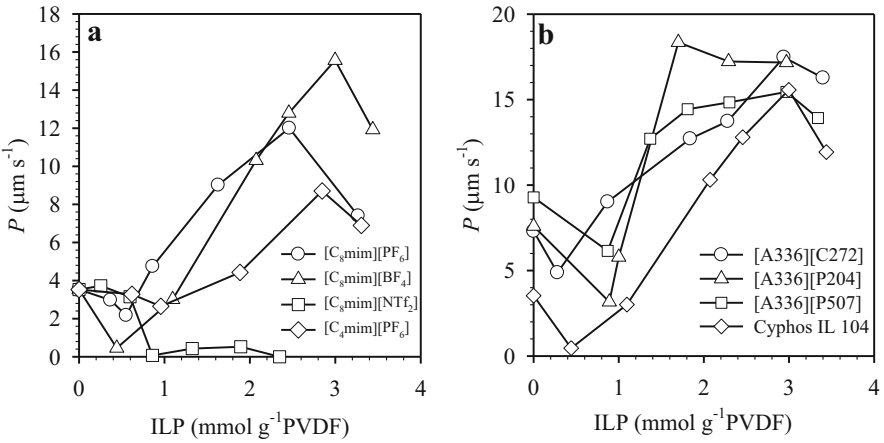

Fig. 4.5 Permeability coefficient (P) of Cr(VI) versus different carriers. Feed phase: 100 mg/L Cr(VI), 0.10 mol/L HCl; stripping phase: 0.05 mol/L NaOH; PIM: 0.4 mmol/g carriers. *Left* (Reprinted from ref. [37], copyright 2011, with permission from Elsevier; *Right*: Reprinted from ref. [47] copyright 2012, with the permission from the American Chemical Society)

4.2.5 *Preparation and Characterization of Sol-Gel Materials Containing ILs*

TEOS, formic acid, and deionized water were mixed together at room temperature, then extractant (Cyanex 923 or Cyphos IL 104) with or without N-methylimidazolium IL [$C_n$mim][PF_6] ($n = 4$, 8) was added (Fig. 4.6), and then the mixture gradually coagulated. After aging for 2 h, the resulting solid material was dried in vacuum. The sol-gel materials are referred to as 923SG (without IL) and IL923SG (with IL) [48]. This synthesis strategy was also applied on quaternary phosphonium and quaternary ammonium ILs [49]. Cyphos IL 104, Aliquat 336, Cyanex 272, and [A336][C272] were used, and the silica adsorbents were referred to SG-2, SG-3, SG-4, and SG-5, respectively.

N,*N*,*N*′,*N*′-tetra(*n*-octyl)diglycolamide (TODGA)-doped silica composites were also prepared by acid-catalyzed sol-gel process [50]. TODGA was dissolved in [$C_n$mim][NTf_2] ($n = 2$, 4, 6, 8, 10), and then the mixture of tetramethylorthosilicate (TMOS) and formic acid (HCOOH) dropped into the solution. The final products consisting of [$C_n$mim][NTf_2] and TODGA were denoted as C_nSG ($n = 2$, 4, 6, 8, 10).

Figure 4.7 shows the scanning electron microscopy (SEM) image of the pore morphology and structure of blank material and modified silica materials. It can be noticed that more mesopores and channels are possessed in the structure of IL

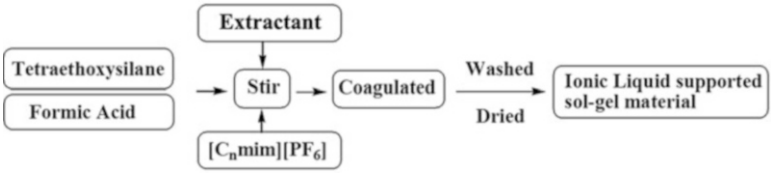

Fig. 4.6 Synthesis route of sol-gel material

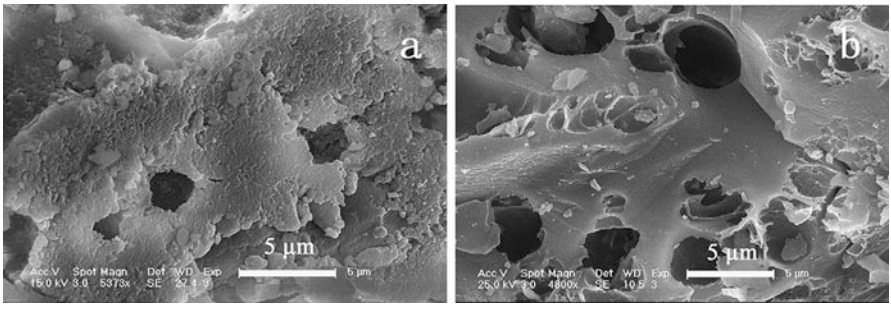

Fig. 4.7 SEM images of (**a**) the blank sorbent and (**b**) IL923SG-3(4800 × magnification) (Reprinted from ref. [48], copyright 2007, with permission from Elsevier)

modified sorbents (b) compared with the blank sorbent. The channel size is large enough for free transportation of reactant and product. High surface area and large pore sizes are believed to enhance the metal ion adsorption capacity. ILs act as both solvent and template, leading to the formation of a macro-mesoporous silica structure.

4.2.6 *Preparation and Characterization of Chitosan Biosorbents Containing ILs*

With higher requirement of environment, the use of renewable feedstocks and less hazardous and degradable chemicals arouses public attentions. Among the numerous biosorbents, chitin is one of the most abundant biopolymers in nature. Chitosan, obtained by deacetylation of chitin, possesses excellent metal-binding capability, but it has a tendency to agglomerate or to form a gel in aqueous solution, so the active binding sites are not readily available for adsorption. The introduction of ILs could enhance the adsorption capacities and reduce the solubility of chitosan.

Carboxymethyl chitosan (CMCTS) [51, 52] was prepared by adding sodium hydroxide solution to the suspension containing chitosan and water/isopropanol to swell for 1 h at 50 °C (Fig. 4.8). Then, monochloroacetic acid was added dropwise into the reaction mixture and stirred for 4 h at 50 °C. The resulting suspension was filtered and washed with ethanol and vacuum-dried at room temperature overnight. [A336][OH] was added dropwise to chitosan solution (mole ratio 1.1:1) and the reaction was stirred at 50 °C for 24 h. The precipitate in the reaction mixture was filtered, washed with a solution of acetone/water, and freeze-dried to yield the Aliquat 336 functionalized chitosan adsorbent [A336][CMCTS].

[A336][CMCTS] presents a coarse structure in comparison to the particles of chitosan shown in the SEM images in Fig. 4.9. The formation of such coarse structure is associated with interactions between cations and anions. Moreover, the surface area of [A336][CMCTS] was measured to be 2.43 m^2/g, larger than that of chitosan (1.72 m^2/g). Therefore, [A336][CMCTS] is superior to those composites that are prepared via cross-link route.

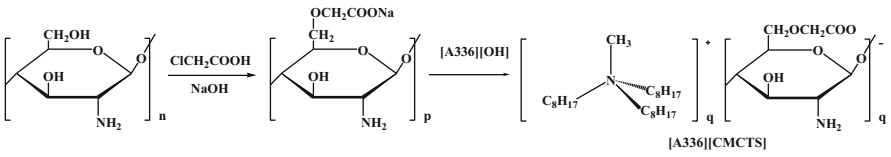

Fig. 4.8 Synthetic route for preparation of [A336][CMCTS]

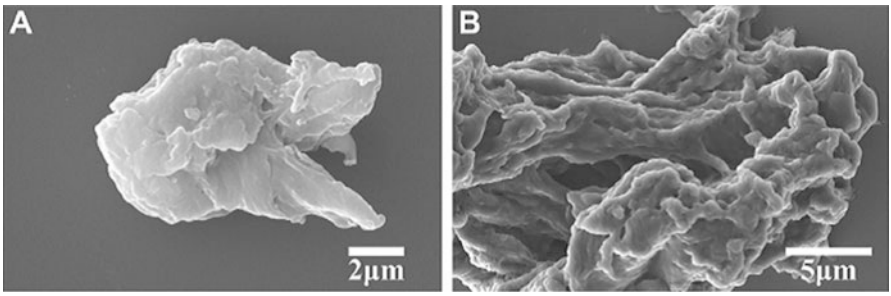

Fig. 4.9 SEM images of (**a**) chitosan and (**b**) [A336][CMCTS] (Reprinted from ref. [51], copyright 2013, with permission from Elsevier)

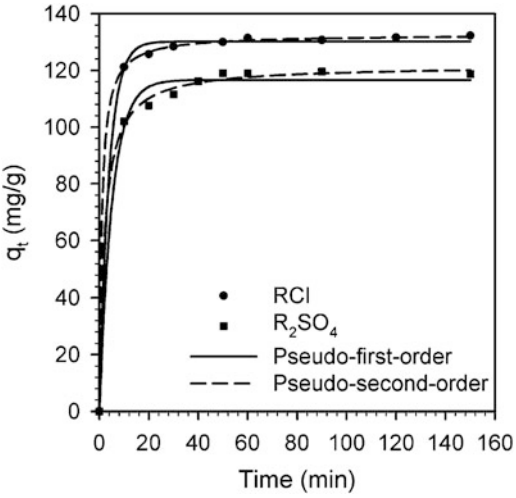

Fig. 4.10 Pseudo-first-order and pseudo-second-order kinetic model for Cr(VI) adsorption on RCl and R_2SO_4. Adsorption conditions: initial Cr(VI) concentration, 100 mg/L; resin amount, 0.01 g; volume of Cr(VI) solution, 15 mL; pH, 4.6 (Reprinted from ref. [4], copyright 2009, with the permission from the American Chemical Society)

4.3 Adsorption Mechanism of Metal Ion Separation

The adsorption kinetics and isotherm mechanism of the above adsorption materials were investigated, and the regeneration and reusability of the new anion exchange resin are discussed in this section.

4.3.1 Adsorption Kinetics of Metal Ions

The adsorption kinetics experiments of Cr(VI) were carried out using strongly basic anion exchange RCl and R_2SO_4. As shown in Fig. 4.10, Cr(VI) adsorption increases rapidly with increasing reaction time in the first 10 min and then increased slowly with contact time.

The pseudo-first-order and pseudo-second-order kinetic models were used to investigate the adsorption kinetic mechanism by fitting the experimental data obtained from the batch method. The Lagergren pseudo-first-order model is expressed as Eq. (4.1):

$$\log(q_e - q_t) = \log q_e - \frac{k_1}{2.303}t \tag{4.1}$$

where q_t and q_e are the amounts of adsorbed Cr (VI) at the time of t and equilibrium, respectively. k_1 is the rate constant of pseudo-first-order adsorption. It can be rearranged as Eq. (4.2):

$$q_t = q_e\left(1 - e^{-k_1 t}\right) \tag{4.2}$$

The q_e and k_1 were calculated by plotting q_t versus t.

The pseudo-second-order model of Cr (VI) is given as Eq. (4.3):

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e} \tag{4.3}$$

where k_2 is the rate constant of pseudo-second-order adsorption. It can be rearranged as Eq. (4.4):

$$q_t = \frac{q_e^2 k_2 t}{1 + q_e k_2 t} \tag{4.4}$$

The q_e and k_2 were attained by plotting q_t versus t.

Table 4.2 shows the fitted results according to the pseudo-first-order and pseudo-second-order models. It could be seen that both the pseudo-first-order and pseudo-second-order models fitted the data well, yielding high regression values. However, the regression value of the pseudo-second-order model was a little higher than that of the pseudo-first-order model. The q_e calculated from the pseudo-second-order model fitted the experimental data very well, especially for RCl anion exchange resin. Therefore, the pseudo-second-order model could describe the adsorption kinetics of Cr(VI) on RCl and R_2SO_4 better.

Table 4.2 Pseudo-first-order and pseudo-second-order kinetic parameters for Cr(VI), As(V), and Re(VII) adsorption on RCl and R_2SO_4

Resin	Metal ion	Pseudo-first order			Pseudo-second order			Ref.
		q_e (mg/g)	k_1 (min^{-1})	R^2	q_e (mg/g)	k_1 (min^{-1})	R^2	
RCl	Cr(VI)	130	0.260	0.998	133	0.00760	0.999	[4]
R_2SO_4	Cr(VI)	117	0.190	0.991	122	0.00390	0.998	[4]
RCl	As(V)	44.7	0.229	0.982	46.0	0.0109	0.938	[8]
R_2SO_4	Re(VII)	139	0.515	0.796	141	0.0165	0.945	[2]
PCl	Cr(VI)	141	0.0230	0.997	161	0.000195	0.995	[41]

4.3.2 Adsorption Isotherms of Metal Ions

The effect of initial metal ion concentration on the adsorption of metal ion by resins was analyzed using the Langmuir and Freundlich isotherm models. The Langmuir isotherm (Eq. 4.5) assumes monolayer coverage of the adsorption surface and no interaction among adjacent adsorbed molecules:

$$q_e = \frac{bq_m C_e}{1 + bC_e} \tag{4.5}$$

where q_e is the equilibrium amount of metal ions adsorbed on resin (mg/g), C_e is the equilibrium concentration of metal ions remained in the solution (mg/L), q_m is the maximum loading capacity of resin, and b is the Langmuir constant related to the energy of adsorption (L/mg).

The Freundlich equation (Eq. 4.6) is derived to model multilayer adsorption and adsorption on heterogeneous surfaces.

$$q_e = kC_e^{1/n} \tag{4.6}$$

where k is Freundlich constant related to the adsorption capacity.

The sorption parameters of Langmuir and Freundlich isotherm models are shown in Fig. 4.11. It reveals that the uptake of metal ions increased with increasing equilibrium concentration and reached saturation very quickly for Cr(VI) adsorption and the Langmuir model has better correlation over the whole concentration range than the Freundlich data. But for Cr(III) adsorption, Freundlich provided a better fit than the Langmuir model. The maximum adsorption capacity of metal ions on different anion exchangers is listed in Table 4.3.

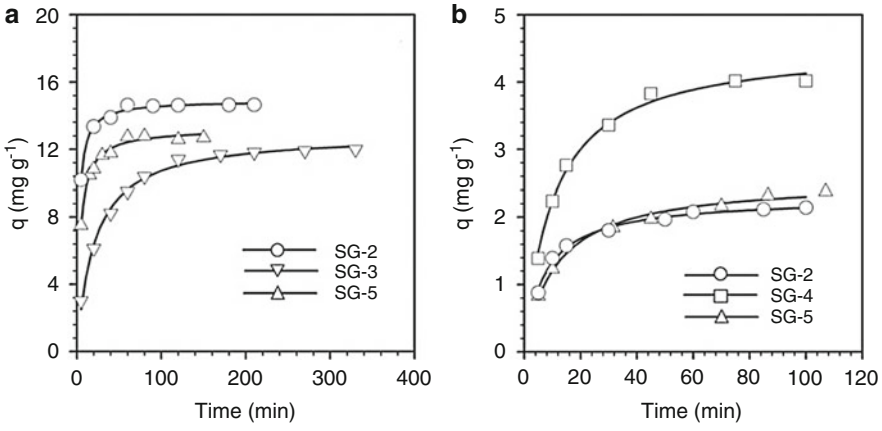

Fig. 4.11 Pseudo-second-order kinetic data of (**a**) Cr(VI) (1.0 mol/L HCl) and (**b**) Cr(III) (initial pH: 4.6), at 25 °C (solid/liquid ratio: 4.0 g/L; contact time: 4 h) (Reprinted from ref. [49], copyright 2010, with permission from Elsevier)

Table 4.3 Langmuir and Freundlich isotherm constants for metal ion adsorption by resins

Entry	Resin type		Resin	Metal ion	Langmuir isotherm		Freundlich isotherm		Ref.
					q_m (mg/g)	B (L/mg)	k	n	
1	Polymer-supported resin	Merrifield resin	RCl	Cr(VI)	132	3.80			[4]
2			R_2SO_4	Cr(VI)	125	0.500			[4]
3			RCl	As(V)	67.2	0.355	43.3	11.8	[8]
4			R_2SO_4	Re(VII)	462	0.0345	86.7	3.50	[2]
5			PCl	Cr(VI)	139	5.22	103	12.1	[41]
6		Amberlite resin	XAD-7/Cyphos IL 104	Cr(VI)	44.8	0.0530			[45]
7	Mesoporous silica-supported resin		SBA15	Cr(VI)	90.5	1.10			[46]
8	Sol-gel-type resin	Sol-gel/Cyphos IL 104	SG-2	Cr(III)	2.96	0.0450	0.316	2.07	[49]
9		Sol-gel/Cyanex 272	SG-4		5.83	0.0450	0.556	1.92	
10		Sol-gel/[A336][C272]	SG-5		2.31	1.27	1.68	11.8	
11		Sol-gel/Cyphos IL 104	SG-2	Cr(VI)	19.1	2.19	13.0	10.3	
12		Sol-gel/Cyanex 272	SG-3		12.2	0.130	3.95	4.30	
13		Sol-gel/[A336][C272]	SG-5		15.5	1.13	8.04	6.46	
14		Sol-gel/[C_2mim][NTf_2]	C2SG	La(III)	3.06	0.390	2.02	10.4	[50]
15		Sol-gel/[C_4mim][NTf_2]	C4SG		3.79	0.160	1.41	4.30	
16		Sol-gel/[C_6mim][NTf_2]	C6SG		3.46	1.06	2.67	14.9	
17		Sol-gel/[C_8mim][NTf_2]	C8SG		3.64	1.65	2.97	19.2	
18		Sol-gel/[C_{10}mim][NTf_2]	C10SG		3.14	0.270	1.55	5.80	

The adsorption parameter values of the Langmuir and Freundlich isotherm models, together with the correlation coefficients (R^2), are summarized in Table 4.3. The Freundlich model has better correlation than the Langmuir model for the adsorption of Cr(VI) by RCl, R_2SO_4, PCl, SBA-15, and As(V) by RCl. Freundlich isotherm provided a satisfactory fit with R^2 values for the adsorption of Re(VII) by R_2SO_4 and Cr(VI) by XAD-7/Cyphos IL 104 resin.

The equilibrium data of adsorption of Cr(VI) and Cr(III) by sol-gel-type resin have been shown in Fig. 4.11. The maximum amounts of Cr(VI) adsorbed were 19.31, 11.05, and 15.29 mg/g for SG-2, SG-3, and SG-5, respectively. It is clear from Table 4.3 (entries 8–13) that the Langmuir model could fit all the experimental data well for Cr(VI) adsorption, as R^2 values (0.990–0.992) are higher than the Freundlich model (0.852–0.897). The maximum adsorption capacities of Cr(VI) on SG-2, SG-3, and SG-5 were 19.16, 12.21, and 15.49 mg/g, respectively. For the adsorption of Cr(III), Freundlich provided a satisfactory fit with R^2 values ranging from 0.991 to 0.997. Freundlich also provided a better fit for the extraction of La(III) by a series of CnSG sol-gel sorbents than the Langmuir model (Table 4.3, entries 14–18).

4.3.3 Resin Regeneration and Reusability

The metal ion-loaded anion exchange resin was usually regenerated by NaCl, NaOH, HCl, NH_3H_2O, NH_4Cl, and their mixed solutions with different concentrations (Table 4.4)

Aliquat 336 functionalized chelating adsorbent [A336][CMCTS] [52] was investigated for enrichment and separation of Y(III), Pb(II), and Cd (II) (Fig. 4.12). The kinetics and isotherm parameters were plotted as amount adsorbed (mg/g) versus time (min). The adsorption is fast over the first 40 min and then increased slowly from 60 to 240 min until it reaches the equilibrium after 360 min. All of the three adsorptions of Pb(II), Y(III), and Cd(II) on [A336][CMCTS] fit better to the pseudo-second-order equation with R^2 of 0.991–0.999 as presented in Table 4.5. Therefore,

Table 4.4 Type and concentration of desorption solutions of metal ion-loaded anion exchange resin

Resin	Metal ion	Elution reagents (mol/L)	Desorption percentage (%)	Ref.
RCl	Cr(VI)	0.3 M NaOH + 0.3 M NaCl	100	[4]
RCl	As(V)	0.1 M HCl	99.5	[8]
R_2SO_4	Re(VII)	1 M HNO_3	100	[2]
PCl	Cr(VI)	0.1 M NH_3H_2O + 0.5 M NH_4Cl	95.0	[41]
SBA15	Cr(VI)	0.2 M NaOH + NaCl	90.5	[46]
XAD-7/Cyphos IL 104	Cr(VI)	0.05 M NaOH	95.0	[45]
MCl	Phenol-Cr(VI)	0.5 M NaOH + 0.5 M NaCl	99.1	[42]

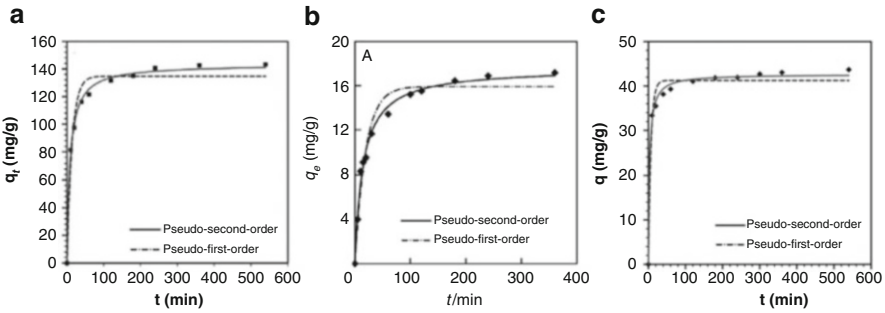

Fig. 4.12 Adsorption kinetics of (**a**) Pb(II), (**b**) Y(III), and (**c**) Cd(II) in [A336][CMCTS] using pseudo-first-order and pseudo-second-order equations (Reprinted from ref. [51], copyright 2013, with permission from Elsevier)

Table 4.5 Pseudo-first-order and pseudo-second-order model parameters for Y(III), Pb(II), and Cd(II) adsorption on [A336][CMCTS]

		Pseudo-first order			Pseudo-second order		
Metal ion	Adsorbent	q_e (mg/g)	k_1 (min^{-1})	R^2	q_e (mg/g)	k_2 (g/(mg·min))	R^2
Y(III)	[A336][CMCTS]	15.9	0.0500	0.964	17.6	0.00400	0.991
Pb (II)	[A336][CMCTS]	53.5	0.0120	0.983	147	0.000600	0.999
Cd (II)	[A336][CMCTS]	68.0	0.862	0.926	23.5	4.72	0.996

the adsorption reaction proceeds mainly according to pseudo-second-order kinetics model. Similar results are observed for metal ion adsorption by chitosan-based adsorbents.

Figure 4.13 shows the relationship between the adsorption amount of Pb(II), Y(III), and Cd(II) on [A336][CMCTS] and the equilibrium concentration results using the Langmuir and Freundlich models. Obviously the total amount of Y(III) and Cd(II) adsorbed always increases with the increasing of initial metal ion concentrations. Equilibrium data in Table 4.6 were well described with the Freundlich model for the adsorption of Pb(II) and Cd(II) by [A336][CMCTS] and the Langmuir model for Y(III). The maximal adsorption capacity was 184.5 mg/g for the adsorption of Pb(II), higher than other chitosan-based adsorbents. For comparison, carboxymethyl chitosan prepared as intermediate was also used to investigate the adsorption of Pb(II), and the adsorption capacity is 56.5 mg/g. Therefore, the incorporation of $[A336]^+$ in chitosan backbone makes the as-prepared adsorbent very promising for Pb(II) removal in real waste water.

4.4 Separation of Metal Ions by Supported Ionic Liquid

AIM-AER RCl, R_2SO_4, RNO_3, and R_2SO_4 were employed for adsorption of metal ions and Cr(VI) [41], As(V) [8], and Re(VII) [2] from aqueous solution. In the study of metal ion recovery from real copper arsenic filter cake sample [2], R_2SO_4

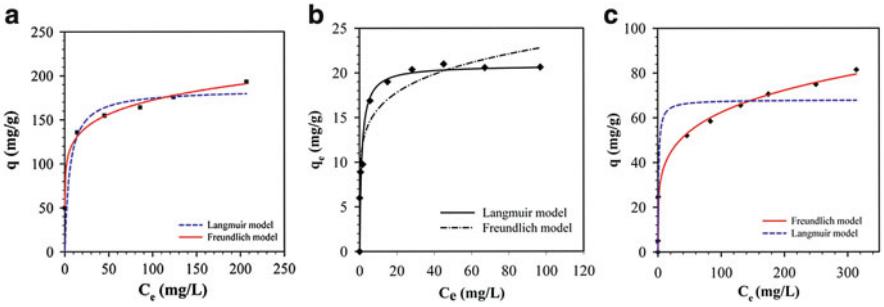

Fig. 4.13 Experimental adsorption isotherms of (**a**) Pb(II), (**b**) Y(III), and (**c**) Cd(II) on [A336][CMCTS] and modeled results using the Langmuir and Freundlich models (Reprinted from ref. [51], copyright 2013, with permission from Elsevier)

Table 4.6 Langmuir and Freundlich adsorption isotherm constants for Pb(II), Y(III), and Cd(II)

		Langmuir constants			Freundlich constants		
Metal ion	Sorbent	q_{max} (mg/g)	b	R^2	K_f	n	R^2
Pb (II)	[A336][CMCTS]	185	0.175	0.783	90.3	7.12	0.996
Y(III)	[A336][CMCTS]	20.8	0.846	0.992	11.1	6.39	0.952
Cd (II)	[A336][CMCTS]	68.0	0.862	0.926	23.5	4.72	0.996

resin performs high selectivity for Re(VII) from Mo(VI)-containing solution. The recovery of Re(VII) is up to 93.3 %, but only 5.1 % for Mo(VI), and the ratio $\beta_{Re/Mo}$ was 25.64 when the concentration of Mo(VI) was 200 times greater than that of Re(VII). R_2SO_4 can be used to efficiently adsorb Re(VII) from real copper arsenic filter cake sample with adsorption rate of 89.1 %.

The effects of Cyanex 923 extractant or [C_8mim][PF_6] IL impregnated on RCl and RPF_6 were studied for extraction of Sc(III) [40]. Cyanex 923 and [C_8mim][PF_6] exhibited stronger affinity to RPF_6 than to RCl. RPF_6 with Cyanex 923 had higher extraction efficiency for Sc(III) than Tm(III), Yb(III), and Lu(III). The extraction mechanisms of SIRs containing RPF_6 and Cyanex 923 with or without [C_8mim][PF_6] were cation exchange and neutral complexation, respectively.

XAD-7 containing IL has remarkable adsorption behavior of metal ions, including RE(III) and heavy metal ions. Y(III) could be selectively extracted from the Sc(III), Er(III), Tm(III), and Yb(III) mixtures since its least stability constant with the complexing agent EDTA [43]. XAD-7 containing [A336][NO_3]/[A336][CA-100] was used for the separation of Sc(III) from other RE(III) [44]. The β value of [A336][CA-100]-XAD-7 for Sc(III) to Y(III), Eu(III), and Ce(III) could reach 16.49, 62.73, and 87.12, respectively, which indicated that Sc(III) can be effectively separated from Y(III), Eu(III), and Ce(III). XAD-7 containing Cyphos IL 104 was applied on Cr(VI) removal with other metal ions in HCl solution at pH value of 0–2, and the adsorption rate of Cr(VI) was 99.24 %, much higher than other ions[45].

SBA-15 [46] anion exchangers had high surface areas (>400 m^2/g), well-ordered pores (>58 Å), and excellent thermal stability up to 387 °C. The anion exchangers had high adsorption capacity on Cr(VI) ranging from 50.8 to 90.5 mg/g over a

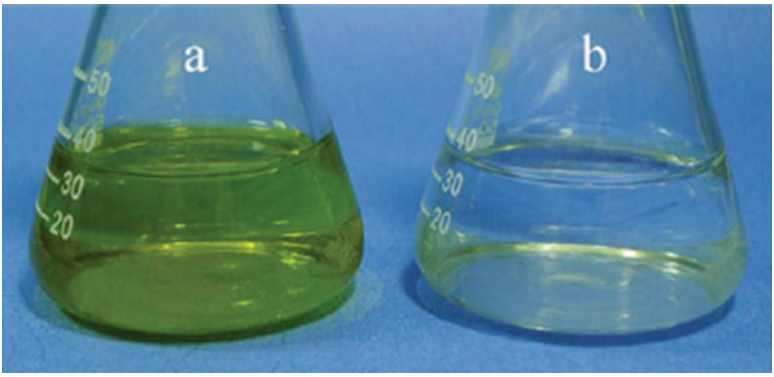

Fig. 4.14 Picture of electroplating wastewater before (**a**) and after treatment (**b**) (Reprinted from ref. [41] by permission of Taylor & Francis Ltd)

wide pH range. The adsorption mechanism was mainly anion exchange. PCl [41] was used for the separation and recovery of Cr(VI) with coexisting Cr(III), Fe(III), Cu(II), Zn(II), Ni(II), and Al(III) from electroplating wastewater (Fig. 4.14). The adsorption capacities of PCl for Cr(VI) are above 139 mg/g at pH range of 2.0–5.0. Cr(VI) was separated and precipitated as a valuable industrial product $BaCrO_4$ with purity higher than 99 %.

In some industrial wastewater, Cr(VI) and phenol may coexist and have some difficulties to separate from polluted water. It is important for an adsorbent to simultaneously remove Cr(VI) and phenol. The competitive adsorption of Cr(VI) from mixture solution was studied by N-butylimidazolium-functionalized strongly basic anion exchange resin (MCl) at two different pH values (pH 5.0 and pH 11.0) [42]. The results are shown in Fig. 4.15. At pH 5.0, the adsorption amount of Cr(VI) had a slight decrease (4.2 %) with the increase in phenol concentration from 0 to 200 mg/L, which indicated that phenol had little influence on Cr(VI) adsorption at pH 5.0. The adsorption of phenol was mainly molecular adsorption at pH 5.0, and there was almost no competitive anion exchange reaction between phenol and MCl. At pH 11.0, the adsorption amount of Cr(VI) was lower than that at pH 5.0 because the main Cr(VI) species changed to CrO_4^{2-} at pH 11.0 [42]. At pH 11.0, the adsorption amount of Cr(VI) also decreased 24.3 % with increasing concentration of phenol from 0 to 200 mg/L. It indicated that phenol has greater influence on Cr(VI) adsorption at pH 11.0 for the competitive anion exchange reaction of phenolate.

The silica materials prepared by the chemical method combined the advantages of liquid-liquid extraction and solid-liquid separation. In the studies of Y(III) extraction by sol-gel materials that contain 20.0 % $[C_8mim][PF_6]$ and 1.4 % Cyanex 923, it was found that 92.9 % of Y(III) was removed [48]. The silica materials doped with Cyphos 104 and imidazolium IL (O104SG-1) can separate RE(III) with good β values for Yb/Dy (37.82), Yb/Ho (20.83), Y/Dy (18.64), Y/Ho (10.27), and Er/Dy (7.71) in the medium of HNO_3. Another kind of silica materials prepared with quaternary phosphonium and quaternary ammonium ILs was applied for the removal of both Cr(III) and Cr(VI) from aqueous solution [49]. Cr(VI) is quite

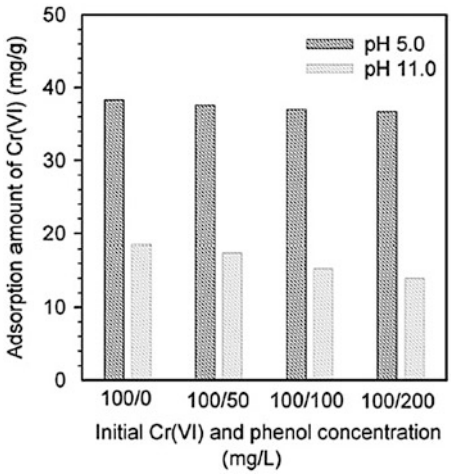

Fig. 4.15 Adsorption amount of Cr(VI) by MCl resin at an initial Cr(VI) concentration of 100 mg/L in the presence of different concentrations of phenol (0, 50, 100, and 200 mg/L) at an initial solution pH of 5.0 and 11.0 (Reprinted from ref. [42], copyright 2011, with permission from Elsevier)

soluble in aqueous solution over almost the entire pH range and mainly in the anionic form of H_2CrO_4, $HCrO_4^-$, CrO_4^{2-}, $Cr_2O_7^{2-}$, and $HCr_2O_7^-$. Cr(III) is less toxic than Cr(VI) and mainly in the anionic form of $Cr(OH)^{2-}$. Both of Cr(VI) and Cr(III) are the main pollutants of wastewater, and the emission concentration of Cr(VI) and total Cr (including Cr(III), Cr(VI), and other forms) should be limited below 0.5 and 1.5 mg/L based on the Emission Standard of Pollutants for Electroplating in China (GB 21900–2008). The concentration of extractant doped in sol-gel sorbents was 0.39, 0.45, 0.45, and 0.39 mmol/g for Cyphos IL 104, Aliquat 336, Cyanex 272, and [A336][C272] functional silica resin denoted as SG-2, SG-3, SG-4, and SG-5, respectively. SG-5 and SG-2 can effectively remove Cr(III) and Cr(VI) from aqueous solution by adjusting pH values. The maximum adsorption amounts of Cr(III) and Cr(VI) were 2.14 and 19.31 mg/g for SG-2 with complex mechanism under the undissociated form (H_2CrO_4) through H-bond coordination, and the complex with the ratio of 1:1 was formed. Cr(VI) was extracted by Aliquat 336 doped SG-3 with anion exchange mechanism. SG-4 sorbents doped with Cyanex 272 extract Cr(III) by complex mechanism. The maximum adsorption amounts of Cr(III) and Cr(VI) were 2.32 and 15.29 mg/g for SG-5 by anion exchange and ion association process.

Guibal investigated the adsorption of Cd(II) by Cyphos IL resins before and after metal uptake; the cross-section cartography of C, O, F, P, Cl, and Cd elements in the whole mass of the resin is shown in Fig. 4.16. Cd(II) was homogeneously dispersed in the whole particle [7]. The O element could be regarded as a marker of the immobilization particle for which it only appeared in the encapsulating matrix. Cd(II) was only incorporated with the P element of Cyphos IL; therefore, the distribution of Cd(II) is related to the dispersion of P.

The removal of Pb(II) by [A336][CMCTS][51] from the wastewater of Sichuan RE ore of bastnasite process was investigated. The adsorption rate of [A336][CMCTS] toward Pb(II) was 143.3 mg/g. About 97.71 % of Pb(II) could be removed, whereas the metal ions such as Ca, Mg, and Na are insignificantly

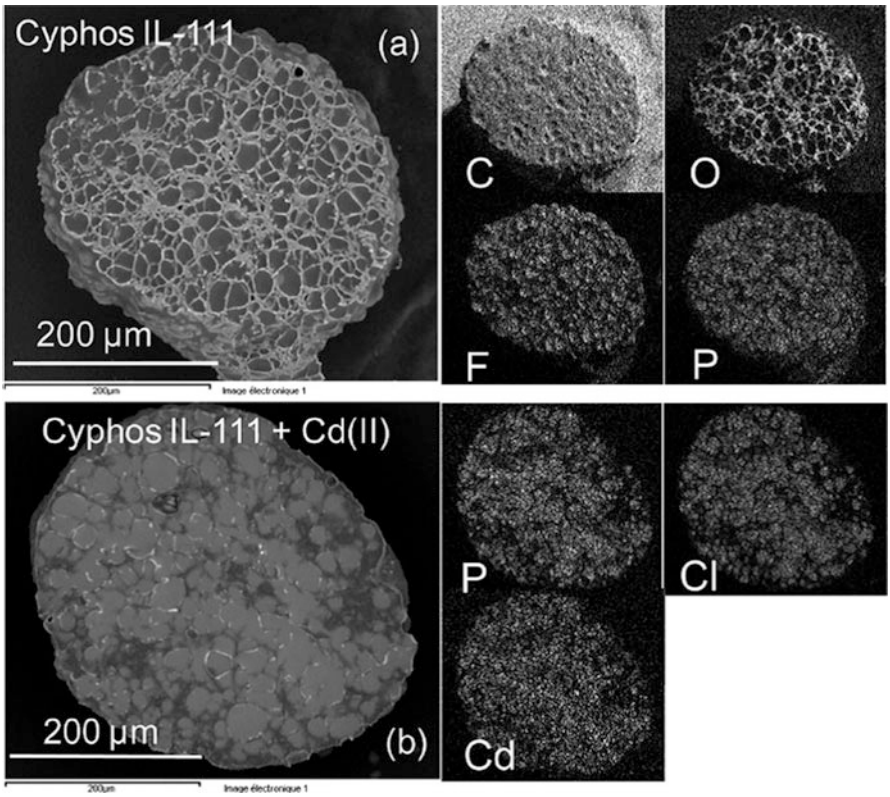

Fig. 4.16 Cyphos IL-111-immobilized resin before (**a**) and after (**b**) Cd(II) sorption – cross-section view and cartography of C, O, F, P, Cl, and Cd elements (SEM-EDAX analysis) (Reprinted from ref. [7] by permission of Taylor & Francis Ltd)

adsorbed. The adsorption rates of La and Ce were 15.74 % and 22.50 %, respectively. The preferential adsorption behavior could be probably explained by the steric effect, that is, ionic radii of the metal ions affect the adsorption. [A336][CMCTS] was also used for the enrichment and separation of REs from waste phosphor [52]. A significant recovery for Y(III) and Eu(III) (71.2 % and 63.4 %, respectively) in the HCl leaching system was observed depending on the amine groups and deprotonated carboxylic groups; a small amount of Al(III) (14.4 %) and Fe(III) (25.8 %) was adsorbed and insignificant Mg (II) and Ca(II) were obtained.

4.5 Conclusion

In this chapter, the preparation of various IL-based adsorption materials and their applications in the separation of different metal ions were reviewed, and it was found that ILs play a unique role in the adsorption of metal ions. ILs are a

rather new class of compounds, and they provide an advanced method to prepare new separation materials. The exchanged metal ion separation mechanism will create new separation techniques to meet the current demands, especially for the environmental protection in hydrometallurgy and related fields.

Appendix: List of Abbreviations

List of abbreviations	Full name
ILs	Ionic liquids
REs	Rare earths
TSILs	Task-specific ILs
[A336]Cl	Aliquat® 336, tricaprylmethylammonium chloride
[C_8mim][PF_6]	1-Methyl-3-octylimidazolium hexafluorophosphate
bif-ILEs	Bifunctional IL extractants
[A366][CA-12]	Tricaprylmethylammonium sec-octylphenoxyacetate
[A336][CA-100]	Tricaprylmethylammonium sec-nonylphenoxyacetate
[A336][P204]	Tricaprylmethylammonium di-2-ethylhexylphosphinate
[A336][P507]	Tricaprylmethylammonium di-(2-ethylhexyl)orthophosphinate
[A336][C272]	Tricaprylmethylammonium bis(2,4,4-trimethylpentyl)phosphinate
[A336] [C302]	Tricaprylmethylammonium bis(2,4,4-trimethylpentyl) monothiophosphinate
[A336][TS]	Tricaprylmethylammonium thiosalicylate
DMF	Dimethylformamide
AIM-AER	*N*-Alkylimidazolium-functionalized strongly basic anion exchange resins
[A336][NO_3]	Tricaprylmethylammonium nitrate
TEOS	Tetraethoxysilane
MTICl	1-Methyl-3-(triethoxysilylpropyl)imidazolium chloride
PIMs	Polymer inclusion membranes
PVDF	Poly(vinylidene fluoride)
TODGA	*N*,*N*,*N*′,*N*′-tetra(*n*-octyl)diglycolamide
Cyphos IL-101	Trihexyl(tetradecyl)phosphonium chloride
Cyphos IL-105	Trihexyl(tetradecyl)phosphonium dicyanamide
Cyphos IL-109	Trihexyl(tetradecyl)phosphonium bistriflamide
Cyphos IL-111	Trihexyl(tetradecyl)phosphonium tetrafluoroborate
SEM	Scanning electron microscopy
CMCTS	(Carboxymethyl) chitosan
[A336][CMCTS]	Tricaprylmethylammonium (carboxymethyl)chitosan
MCl	*N*-Butylimidazolium-functionalized strongly basic anion exchange resin

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Chapter 5
Aqueous Biphasic Systems Based on Ionic Liquids for Extraction, Concentration and Purification Approaches

Isabel M. Marrucho and Mara G. Freire

Abstract During the past decade, ionic-liquid-based aqueous biphasic systems (IL-based ABS) have been the focus of a significant amount of research, and excellent and comprehensive reviews are nowadays available. Rather than focusing on the phase equilibria and the phase separation mechanisms of ABS, this chapter provides an assessment of the current status of implementation of this liquid-liquid approach in the extraction, concentration and purification of biomolecules/solutes/products from real matrices.

Examples on the successful use of IL-based ABS in the extraction/purification of value-added compounds from plant matrices and from extracellular media are provided. The use of IL-based ABS as an extraction and concentration methodology is also discussed, focusing on two main approaches: control of environmental samples and monitoring of human health or abuse of drugs. Finally, and due to the rapid development and design of extraction processes based on ILs, the use of IL-based ABS for the treatment of aqueous effluents contaminated with ILs is also presented.

Keywords Aqueous biphasic systems • Ionic liquids • Real samples • Extraction • Purification • Concentration • Recovery

5.1 Introduction

In many biotechnological processes, downstream processing methods for the recovery of the final product are a key problem and represent the highest contribution in the overall process costs. In 1958, Albertsson [1] proposed aqueous

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biphasic systems (ABS) as cost-effective separation, purification and concentration platforms in downstream processing.

ABS fall within the liquid-liquid techniques and involve the partitioning of biomolecules/solutes/products from one aqueous phase to another. Usually, these systems are formed by different pairs of solutes (polymer-polymer, polymer-salt or salt-salt) and where above specific concentrations of these solutes in water the system undergoes a two-phase separation [2]. Because of the nonvolatile nature of polymers and salts, these phase-forming components can be recovered and recycled and are a more benign alternative to traditional liquid-liquid extraction systems which use volatile and hazardous organic compounds. Furthermore, the large amount of water, being both phases water-rich, makes of such systems more benign and biocompatible extraction routes when dealing with biologically active biomolecules.

Traditional polymer-based ABS have been widely investigated [2]. However, these systems usually require a long equilibration time to achieve the phases' separation, either due to the high viscosity or small difference in the density of the coexisting phases. In the past decade, ABS composed of ionic liquids (ILs) have been proposed by Rogers and co-workers [3]. One of the most important features of ILs, and that has attracted both academy and industry, is their "designer solvents" aptitude. It is theoretically possible to form at least one million of different ILs [4], which is further transferred to novel ABS with different characteristics [5]. In fact, IL-based ABS have been studied in a variety of applications [5], namely, for the recycling and concentration of ILs from aqueous solutions, for carrying out metathesis reactions in the formation of new ILs and as new separation techniques, as originally suggested by Rogers and co-workers [3].

Up to date, circa 179 scientific manuscripts regarding IL-based ABS were published. Figure 5.1 depicts the number of manuscripts published per year under the topic of IL-based ABS. In the last few years, there was an exponential growth in the number of published articles, showing the interest by the scientific community on exploring these systems. It is quite clear that the study of IL-based ABS was complemented by an exponential growth in the research of their applications, namely, for extraction purposes. There are several main classes of extracted solutes: alkaloids, amino acids and proteins, most of them with pharmacological relevance [5]. Additional classes of solutes have also been studied and include steroid hormones, pharmaceuticals and phenolic compounds, among others. On the other hand, it has been demonstrated that IL-based ABS can be formed with a wide plethora of organic/inorganic salts, carbohydrates, polymers and amino acids [5–8].

IL-based ABS present several advantages over the typical polymer-based systems, namely, a low viscosity, which favours the metabolite mass transfer and reduces energetic inputs, and confirmed enhanced and tailored extraction efficiencies for a wide variety of biomolecules [5]. Since polymer-based ABS present a restricted difference in polarities between the coexisting phases, selective extractions are difficult to achieve. Due to the inherent tailoring ability of ILs, IL-based ABS cover a wider hydrophilic-hydrophobic range, and remarkable extractions and selectivities can indeed be attained [9]. In this context, IL-based ABS meet all

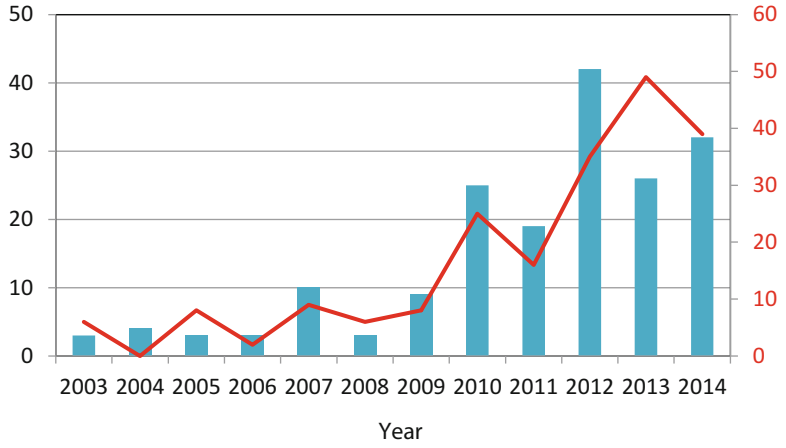

Fig. 5.1 Published manuscripts on "IL-based ABS" from 2003 to 2014: number of articles per year regarding the characterization of IL-based ABS (*blue bars*/primary scale), number of articles per year on the application of IL-based ABS for extraction processes (*red line*/secondary scale). Values based on a search on ISI Web of Knowledge in the 24th of October, 2014, with the following topics: "aqueous biphasic system", "aqueous two-phase system", "ionic liquid" and "extraction compound", "partition coefficient" and "extraction efficiency"

the requirements for an easy design and scale-up of a wide range of separation processes, becoming a target of high interest in industrial separation steps.

IL-based ABS are a promising alternative, offering the possibility to extract, purify and concentrate (with tailored ability on the extraction efficiencies and selectivities) a variety of solutes, in a single-step procedure. This feature opens new horizons to implement such processes in several areas of research, such as in biotechnology, analytical chemistry, food chemistry and chemical engineering, among others, to real applications at an industrial level.

5.2 IL-Based ABS in the Extraction/Purification of Value-Added Compounds

5.2.1 Extraction/Purification of Value-Added Compounds from Plant Matrices

Herbal drugs have been described in ancient medicine for the treatment of different diseases. The production of natural extracts from plants has been finding a wider demand since they are generally considered safe by users mainly because they are "natural". However, their consumption may lead to adverse reactions and/or undesired clinically significant interactions when taken in concomitance with

pharmacological treatments or when used under certain clinical conditions. On the other hand, very often it is argued that the dose of supposed active constituents is too low to exert any therapeutically relevant effect. Also, the difficulty in the production of the most diverse natural products at high purity levels is behind the high cost of analogous synthetic products, and thus, simple, cost-effective and an easy-to-scale-up method is in crucial demand. In this way, the extraction of active ingredients from plant matrices, either considered in herbal medicine or just from other less noble biomass, is gaining attention of the researchers and also of the industries [10].

Two examples were selected from the literature in order to illustrate the advances on the use of ABS composed of ILs for the extraction and purification of value-added compounds from plant matrices. In the first example, the extraction of pharmaceutical ingredients, namely, anthraquinones derivatives, and polysaccharides is described, while the second example focuses on the extraction of saponins and polyphenols from biomass.

Tan and co-workers published two papers [11, 12] on the extraction of value-added compounds from *Aloe vera* L. (family: Liliaceae) [13] employing ILs. Aloe contains two major active materials: aloe polysaccharides, present in the aloe fillet, and aloe anthraquinones derivatives, existent in the leaves of different aloe plants [14]. Aloe polysaccharides are the major active ingredients in the aloe gel and are responsible for the pharmacological activities of wound healing, anti-inflammation and immune-modulating properties, while aloe anthraquinones have multiple pharmacological actions, including laxative, antibacterial, anti-inflammation, hemostatic and antispasmodic [14, 15].

There are many methods currently used for the extraction and separation of aloe anthraquinone derivatives. Unfortunately, these methods are time-consuming and of high cost, and the apparatus and procedure are difficult to scale up. In the same line, several methods have been used for the separation and purification of aloe polysaccharides. Again, all these methods have major drawbacks, such as the low purity of the final compounds coupled to a high complexity and high cost of the methodologies which have been preventing their implementation in industry [11, 12].

When working with plant matrices, a plant extract or a crude plant material is usually produced, generally following well-established procedures depending on the plant under study. In the present case, aloe pulp was obtained from the aloe peel [11, 12], and the homogenized pulp was soaked in a 60 % ethanol solution for 24 h. The water and ethanol were separated from the residue by centrifugation, leaving behind a reddish-brown colloid. For the aloe polysaccharide study, the colloid was just dried and used. For the anthraquinone extraction, sulphuric acid and chloroform were added into the extract and the mixture was refluxed. After evaporating the solvent, a yellowish-brown colloid was obtained as the crude extract, which was then dissolved in methanol and used as the stock solution. In both cases, ABS were implemented using 1-butyl-3-methylimidazolium tetrafluoroborate ($[C_4mim][BF_4]$) and sodium-based inorganic salts: in the case of the anthraquinone extraction, the best results were obtained for the systems where Na_2SO_4 was used (extraction efficiency of 88 %); for the polysaccharide extraction, enhanced extractions were obtained with ABS composed of NaH_2PO_4 (extraction efficiency of 90 %) [11, 12].

These correspond to the optimized conditions and are the result of a series of experiments with other ABS formed by ILs based on the $[C_n mim]^+$ cation ($n = 2$, 4 and 6) combined with different anions such as $[N(CN)_2]^-$ and Br^-, as well as formed by a large battery of inorganic salts [11, 12]. The chemical structures of the ILs investigated, as well as their definition, are depicted in Fig. 5.2.

In the case of the anthraquinone extraction, one of the limiting factors for the choice of the salt was the pH of the ABS, since weakly acidic or neutral pH was required [11, 12]. As for the aloe polysaccharides, the choice of the system was based, on top of the weakly acidic media, on the absence of reaction with H_2SO_4 used in the quantification of aloe polysaccharides. Interestingly, while the anthraquinones preferred the IL-rich phase, and were recovered by pH adjustment, the aloe polysaccharides preferentially migrated to the inorganic-salt-rich phase, separating thus from the contaminant proteins, and were further recovered through dialysis. The optimization of the experimental conditions was also researched by changing external conditions, such as temperature, pH and equilibration time [11, 12]. Under the optimal conditions, this novel method was indeed capable of purification of the target materials while removing majority impurities in a single-step extraction. In order to truly evaluate the potential of the proposed IL-based ABS, the authors [11, 12] also studied other ABS combining polyethylene glycol (PEG) polymers and inorganic salts. The obtained results rather than showing the superiority of the IL-based ABS also demonstrated the fine-tuning capacity and selectivity afforded by ILs [11, 12].

Although the authors [11, 12] did not propose a simultaneous extraction of both added-value compounds, the results clearly indicate that it would be possible to separate and to recover, in a single step, both the anthraquinones and the aloe polysaccharides. Both the aloe anthraquinones and the polysaccharides can be easily extracted from the preferential ABS phase, underlying the great potential of this method for large-scale purification of aloe anthraquinones and other active ingredients in natural plants. Finally, and although not commonly found in literature [5], in an era where we are being claimed by the sustainability concept, the authors recovered the salt and the IL for further use [11, 12].

Ribeiro et al. [16] focused on the extraction of saponins and polyphenols from mate and tea matrices using IL-based ABS. Saponins are a structurally diverse class of compounds that are largely distributed in the plant kingdom and associated to defence functions in plants. Many different saponins have been isolated from a variety of plant sources and display interesting physicochemical (foam production, emulsification, solubilization, sweetness and bitterness) and biological (haemolytic, antimicrobial, insecticide and molluscicide) properties. Therefore, they are commercially explored in many applications, such as by the food, cosmetic and pharmaceutical industries [17–19].

Ribeiro et al. [16] performed the direct extraction of the desired compounds from dried leaves and aerial parts of tea and mate matrices with aqueous solutions of ILs. Contrarily to the works by Tan et al. [11, 12], where only few ILs were tested, a large list of ILs was rehearsed in this work [16], ranging from imidazolium-based ILs with variable length in the side chains to more sustainable ILs, such as those based on

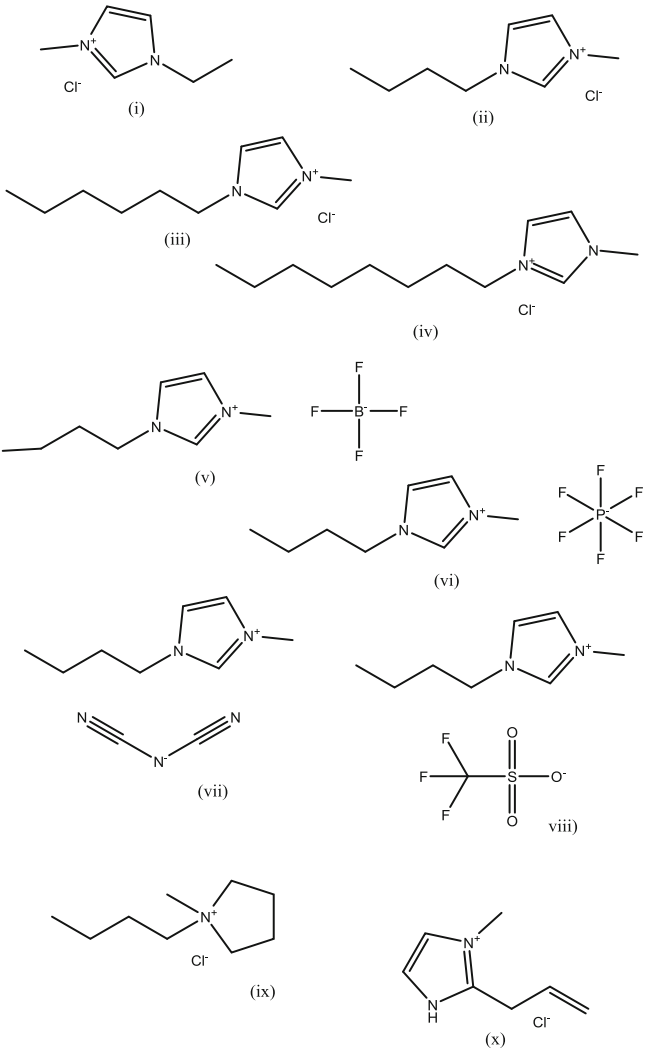

Fig. 5.2 Chemical structure of the studied ILs [11, 12]: (*i*) 1-ethyl-3-methylimidazolium chloride ([C_2mim]Cl); (*ii*) 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl); (*iii*) 1-hexyl-3-methylimidazolium chloride ([C_6mim]Cl); (*iv*) 1-methyl-3-octylimidazolium chloride ([C_8mim]Cl); (*v*) 1-butyl-3-methylimidazolium tetrafluoroborate ([C_4mim][BF_4]); (*vi*) 1-butyl-3-methylimidazolium hexafluorophosphate ([C_4mim][PF_6]); (*vii*) 1-butyl-3-methylimidazolium dicyanamide ([C_4mim][$N(CN)_2$]); (*viii*) 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([C_4mim][CF_3SO_3]); (*ix*) 1-butyl-1-methylpyrrolidinium chloride ([C_4mpyr]Cl); (*x*) 1-allyl-3-methylimidazolium chloride ([amim]Cl)

the cholinium cation. These ILs cations were combined with several anions in order to infer on the IL anion effect on the extraction efficiencies. External experimental variables, such as temperature, agitation speed, extraction time and solvent to raw

material ratio, were also evaluated [16]. It is interesting to note that under the tested conditions, most of the ILs investigated yielded higher extraction efficiencies than the method traditionally used (aqueous solution of 30 wt.% of ethanol) [16].

Some authors have already reported the use of ABS as an efficient method for saponin concentration: Han et al. [20] employed a polyethylene glycol (PEG 4000) and K_2HPO_4 ABS with an aqueous extract of *Momordica charantia* to concentrate saponins in the saline-rich phase. In this line of thought, Ribeiro et al. [16] described the concentration of saponins and phenolic compounds from the aqueous solutions of cholinium chloride (containing the target compounds) using IL-based ABS. The performance of two inorganic salts, Na_2CO_3 and K_3PO_4, was also evaluated. The results obtained revealed that the highest tea saponin extraction coefficients were obtained with the ABS constituted by cholinium chloride ([Ch]Cl), while for mate saponins, the ABS formed by ethanol and Na_2CO_3 leads to better results [16]. In the case of tea and mate polyphenols, the best results were obtained with the ABS composed of [Ch]Cl and Na_2CO_3 [16]. A summary of these results is provided in Fig. 5.3.

Finally, and taking advantage of the complete miscibility of most ILs, the saponins and phenolic compounds existent in the IL-rich phase were recovered through the addition of a second and more hydrophobic IL (cholinium bistriflimide) promoting the formation of two immiscible liquid phases. By this approach, both the saponins and the phenolic compounds were recovered in the aqueous phase [16].

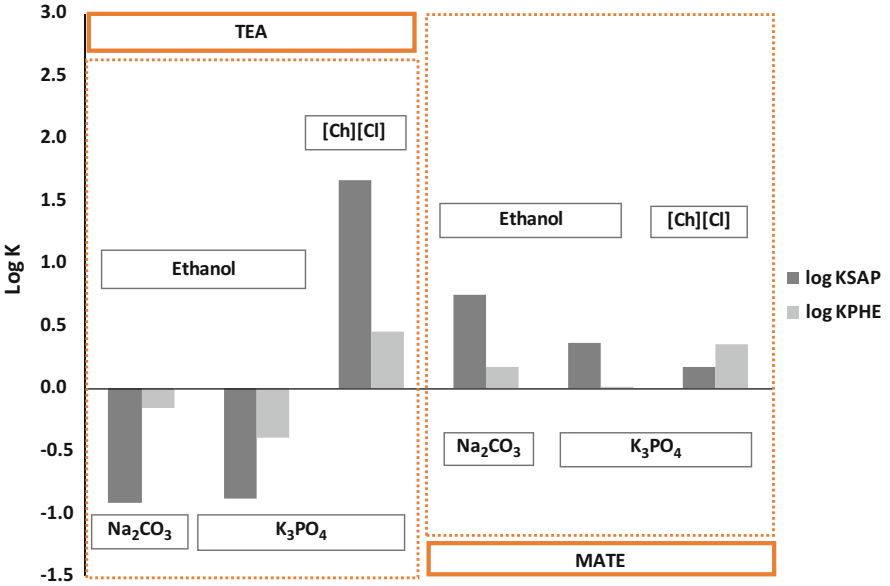

Fig. 5.3 Partition coefficients of tea and mate saponins in several aqueous biphasic systems (Data taken from Ribeiro et al. [16])

5.2.2 *Extraction/Purification of Value-Added Compounds from Extracellular Media*

The production of biochemicals has been motivated by the modern genetic tools available nowadays for metabolic pathway engineering. Despite this progress, several bio-based processes still suffer from limited productivity, mainly due to product inhibition, leading thus to substantial downstream processing costs, high waste water volumes and an increased substrate cost in the case of a decreased yield. Consequently, the development of recovery technologies that allow the selective in situ product recovery (ISPR) in cell biotechnology is mandatory. Several ISPR techniques, including ABS, have been proposed, depending on the biochemical production [21]. In the past 10 years, about 140 papers have been published which describe fermentations coupled with ISPR technology [21]. From these, only one work [22], focusing on the bioproduction of 2-phenylethanol, used ILs to recover the product through the implementation of a two-phase system. Nevertheless, only hydrophobic ILs, based on the bistriflimide and hexafluorophosphate anions, and that form two phases with water at ambient conditions, were investigated [22]. However, several reviews have been published on the use of polymer-salt or salt-salt ABS for the recovery of bioproducts, clearly showing the great potential of this technique [23, 24]. In this context, this field represents a huge avenue to be still explored with IL-based ABS.

Due to the lack of maturity of the field, in this section, we selected the first available examples of in situ product recovery, where the fermentation broth is pre-purified, and only then the extraction/purification of the bioproduct is performed. The selected articles describe the extraction of biopharmaceutical compounds, in particular tetracycline from *Streptomyces aureofaciens* and penicillin G, and of enzymes, namely, lipase produced by *Bacillus* sp. ITP-001, and two different alcohol dehydrogenases from *Escherichia coli*.

Liquid-liquid or solid-liquid extractions, usually carried out using organic and volatile solvents, are generally employed for the extraction and purification of common antibiotics from the fermentation broth [25]. Although these techniques are simple, are of low cost and lead to a high purity level, the use of organic compounds displays major drawbacks, mainly due to their volatile and hazardous nature prejudicial to the environment and human health. Consequently, the development of more benign liquid-liquid extraction is required. Pereira et al. [26] demonstrated the use of IL-based ABS for the extraction/purification of tetracycline from the fermented broth of *Streptomyces aureofaciens*. At the end of the fermentation process, the fermented broth was filtrated and then centrifuged. The supernatant obtained from this process presented a final pH of 4.27 and a tetracycline concentration of 0.175 g/L – used in the partitioning studies described below.

The ABS implemented in this work [26] were based on ILs combining the common cholinium cation with several anions, such as chloride, bicarbonate, dihydrogencitrate, acetate and dihydrogen phosphate. The chemical structures of

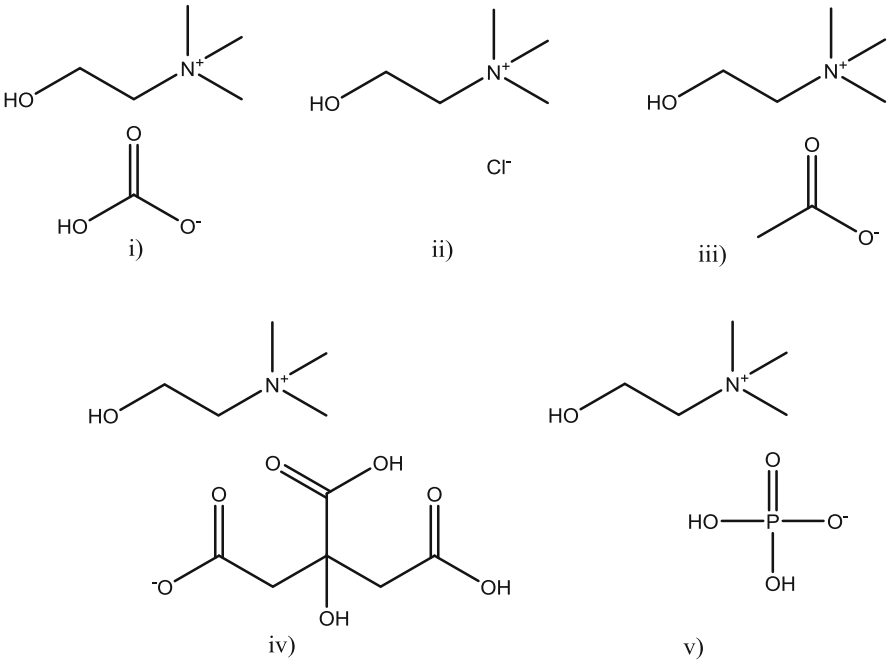

Fig. 5.4 Chemical structure of the studied ILs [26]: (*i*) cholinium bicarbonate ([Ch][Bic]); (*ii*) cholinium chloride ([Ch]Cl); (*iii*) cholinium acetate ([Ch][Ac]); (*iv*) cholinium dihydrogencitrate ([Ch][DHCit]); (*v*) cholinium dihydrogen phosphate ([Ch][DHP])

the ILs investigated are depicted in Fig. 5.4. Polyethylene glycol (PEG 600) was used to promote the phase separation and ABS formation [26].

The authors [26] justified the choice of cholinium-based ILs based on their benign and biocompatible features, supporting therefore their applicability in the recovery of an antibiotic for further human consumption. In addition, these ILs are of easy preparation, relatively cheap, stable in water and biodegradable.

The optimization of the tetracycline partitioning was achieved by testing different concentrations of cholinium-based ILs [26]. In most cases, tetracycline preferentially migrates to the PEG-rich phase, leading to the conclusion that the salting-out capacity of the IL is responsible for this migration pattern. The effect of the tie-line length was also researched, yet no direct correlation was perceived between the partition coefficient and this parameter, except for the cholinium bicarbonate-containing system [26]. Since tetracycline is an amphoteric drug, the pH effect on the drug partition was also studied and its importance was attested. The highest partition coefficient in the extraction of tetracycline using cholinium-based ILs from the purified fermented broth was obtained with the ABS formed by cholinium bicarbonate and PEG 600. These results were compared with those obtained using ABS based on PEG/Na_2SO_4 and [Ch]Cl/K_3PO_4. The highest partition coefficients were obtained for the system composed of [Ch]Cl (20.1 wt.%) + K_3PO_4 (35.02 wt.%).

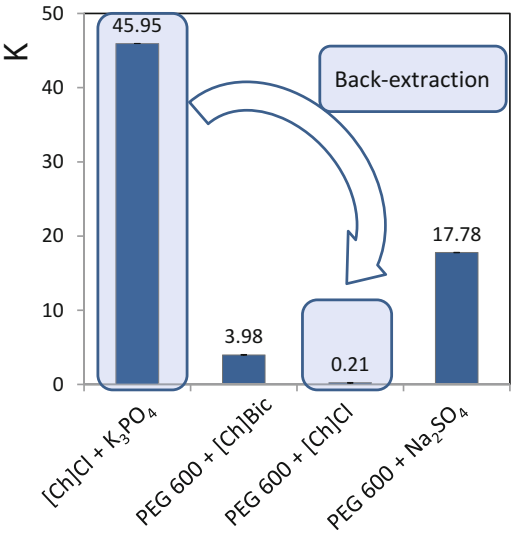

Fig. 5.5 Partition coefficients of tetracycline from the fermented broth in several ABS (Data taken from Pereira et al. [26])

Nevertheless, some inversions on the preferential migration of tetracycline were observed, making the authors [26] to suggest the back extraction of the antibiotic and the recycling of both phases.

The partitioning dependence on the pH of the medium can be used to trigger the back extraction of tetracycline (due to its speciation). For example, in the PEG 600/Na_2SO_4 ABS, tetracycline is mainly in its neutral form ($5.30 < pH < 6.25$), whereas in the [Ch]Cl/K_3PO_4 system, it is completely deprotonated (pH of the phases > pKa_3). Hence, in the polymer-salt system, tetracycline is recovered in the top phase (PEG-rich phase) with K values in the order of 18, while in the [Ch]Cl/K_3PO_4 system, the antibiotic preferentially migrates for the [Ch]Cl-rich phase (with $K \approx 46$). A summary of these results is provided in Fig. 5.5.

Liu and co-workers presented a series of four papers [27–30] on the extraction/purification of penicillin G from its fermentation broth. The traditional way to obtain penicillin includes the extraction with organic solvents at low pH, back extraction into an aqueous phase at high pH and crystallization of the pure product [31]. Nevertheless, the emulsification due to the existence of proteins in the fermentation broth and the decomposition of penicillin at low pH values severely hamper the success of this technology.

Contrarily to the previous work [26], where several ILs were tested, Liu et al. [27] chose one IL, namely, [C_4mim][BF_4], and one inorganic salt, NaH_2PO_4, to implement the ABS and researched the effect of the IL, inorganic salt and penicillin concentration on the drug extraction efficiency and partition coefficient. A high extraction yield of 93.7 %, in the extraction of penicillin G from aqueous solution at a pH between 4 and 5, was obtained [27]. The authors stated that this new method does not lead to the degradation of penicillin and that no emulsification and protein denaturation occur [27]. Afterwards, the extraction of penicillin from

its filtrate fermentation broth, supplied directly by the industrial manufacture, was carried out. Batches between 20,000 and 30,000 μ/mL of penicillin G at pH = 5.8–6.0 were used together with the optimized conditions, with an ABS composed of $[C_4mim][BF_4]$ (20 wt.%)+ NaH_2PO_4 (40 wt.%), and an extraction efficiency around 90 % was obtained. Penicillin G was recovered in the IL-rich phase of the ABS, leaving miscellaneous proteins in the opposite layer. Subsequently, the hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate ($[C_4mim][PF_6]$) was mixed with the $[C_4mim][BF_4]$-rich phase leading to the formation of two new phases: a hydrophobic phase, rich in both the ILs, and a hydrophilic phase, rich in water and penicillin G [27]. The chemical structures and definitions of the ILs investigated are provided in Fig. 5.2. In comparison with the traditional liquid-liquid butyl-acetate-water system or polymer-based ABS, IL-based ABS showed two main advantages: penicillin is efficiently extracted at neutral pH, while avoiding the protein emulsification, and the IL can be recycled for further use. However, as $[C_4mim][BF_4]$ is unstable in aqueous acidic solutions [32], in a subsequent work, Liu et al. [28] tested a new ABS formed by 1-butyl-3-methylimidazolium chloride ($[C_4mim]Cl$) + NaH_2PO_4. Again, the IL, salt and penicillin concentrations were evaluated to trigger the maximum extraction yields and partition coefficients for penicillin [28].

In a further work, Liu et al. [30] studied the implementation of the previous procedure in the enzymatic hydrolysis of penicillin G, obtaining 6-aminopenicillanic acid and a by-product, phenyl acetic acid. The penicillin G hydrolysis by penicillin acylase takes place in the water-rich phase in equilibrium with the IL-rich layer, and the 6-aminopenicillanic acid conveniently precipitates at the working pH = 5 as it is being produced, while phenyl acetic acid migrates into the IL-rich phase. As a result, the removal of the two products from the enzyme environment at relatively high pH values is permitted in this in situ product recovery approach, which is beneficial for both enzymatic activity and stability [30].

In addition to the interest in pharmaceutical compounds, a special focus has been given to the extraction of enzymes from extracellular media using aqueous biphasic systems. The traditional methods to purify macromolecules involve several steps, such as ammonium sulphate precipitation, dialysis, ionic and affinity chromatography [33] or electrophoresis [34]. These methodologies increase the cost of the enzyme production and are difficult to implement at a large scale [35]. In recent years, liquid-liquid extractive bioconversion processes, in particular ABS, have shown a great potential to extract and purify enzymes and other biologically active macromolecules. Worthwhile noting the fact that in both the following described works, an indirect ISPR approach was carried out since the separation and purification steps were performed using the fermentation broth after the end of the production stage, aiming to avoid toxicity and biocompatibility problems derived from the direct contact of the ILs with the bacterium [36–42]. This is also a consequence of the lack of knowledge on the IL toxicity, indicating a field that needs to be explored. It should be highlighted that in addition to the well-studied imidazolium-based fluids, a vast plethora of ILs are available nowadays, revealing that studies using more biocompatible ILs are of crucial interest.

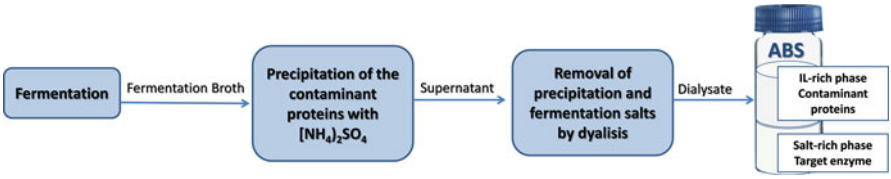

Fig. 5.6 Representative scheme of the different stages applied in the purification of the lipolytic enzyme produced by *Bacillus* sp. ITP-001 via submerged fermentation (Information taken from Ventura et al. [42])

Ventura et al. [42] reported the purification of a lipolytic enzyme produced by *Bacillus* sp. ITP-001. A scheme depicting the purification steps carried out by the authors is provided in Fig. 5.6. Four ILs, namely, 1-butyl-3-methylimidazolium dicyanamide ($[C_4mim][N(CN)_2]$), 1-butyl-1-methylpyrrolidinium chloride ($[C_4mpyr]Cl$), $[C_4mim]Cl$ and 1-methyl-3-octylimidazolium chloride ($[C_8mim]Cl$), together with a phosphate buffer solution at pH = 7, were used to prepare ABS to carry out the lipase extraction at ambient conditions. The chemical structures and definitions of the investigated ILs are presented in Fig. 5.2. The compositions of the extraction system (25 wt.% of IL + 30 wt.% of phosphate buffer solution at pH 7.0) were the same for all the ILs studied to exclude the influence of the IL and salt concentrations [42]. The separation data suggest that the purification of the enzyme is mainly controlled by the cation alkyl chain length, followed by the cation core and, finally, by the anion nature. The increase in the alkyl chain length leads to a stronger increase in the purification factor and in the partition coefficient rather than in the enzyme activity partition coefficient, which remains consistently very low [42]. This is due to an increase in the hydrophobic nature of the ILs from $[C_4mim]Cl$ to $[C_8mim]Cl$, which increases the dispersive forces between the enzyme and the ILs at the IL-rich phase. Due to its very low isoelectric point (pI = 3.0) [43], the lipase is negatively charged at pH = 7.0, favouring thus its partition to the salt-rich phase while simultaneously increasing the partitioning of the contaminant proteins into the IL-rich phase. The obtained results were compared with literature values for PEG 800/K_3PO_4 ABS [43] supporting the high potential of IL-based ABS for the purification of enzymes from a complex matrix.

Dryer and Kragl [44] described the application of IL-based ABS for the purification of two different alcohol dehydrogenases, one produced from crude cell extracts of *Escherichia coli* and other produced by *Lactobacillus brevis* (LB ADH) and by *Thermophilic bacterium* (T ADH). One IL, commercially available under the AMMOENG110™ designation, composed of a quaternary ammonium cation, with oligoethylene glycol units of different chains, combined with the chloride anion, was used for the formation of ABS with the buffer KH_2PO_4/K_2HPO_4 (pH = 7). Two temperatures, 20 and 4 °C, were tested, and the temperature of 4 °C was chosen to carry out the purification steps. In order to facilitate the optimization process and to limit the number of experiments, experimental design was used [44]. The optimal composition derived from the partition coefficients data for ABS implementation

for the purification of the two alcohol dehydrogenases is very similar. However, the specific activity of the LB ADH in the IL-rich phase was increased up to 200 %, while for the T ADH an increase of around 400 % was observed. This indicates that the IL has a stabilizing effect on both the enzymes investigated, which is also confirmed by the enhancement in the enzymes' half-life. The authors [44] also carried out the reduction of acetophenone as a substrate in the presence of aqueous solutions of 10 wt.% of AMMOENG110™, which increased the solubility of the substrate. However, both conversions are limited, 87 % for LB ADH and 4.8 % for T ADH, as a result of the increased substrate concentration [44].

5.3 IL-Based ABS in the Concentration of Drugs or Biomarkers

The use of IL-based ABS as a concomitant extraction and concentration methodology has been focused on two main approaches: control of environmental samples and monitoring of human health or abuse of drugs. With the evolution of medicinal- and pharmacy-related science, the improvement on healthier life conditions and athletic performance has been complemented by an increase in the consumption of a wide diversity of drugs. Nevertheless, the excessive ingestion of pharmaceutical compounds or drugs has raised serious apprehensions within the human health as well as within aquatic resources. Conventional techniques for identifying and quantifying human pollution tracers in environmental-related samples and (bio)markers in biological fluids present major drawbacks, mainly due to the complex real matrices and the high lower detection limits of the more accessible equipment. Moreover, a complex pretreatment process using volatile and hazardous organic solvents is usually required, being also time-consuming and expensive. Therefore, significant efforts have been carried out on the development of pretreatment technologies, which allow a simultaneous extraction and concentration, using IL-based ABS [5].

Before the use of ABS as concentration techniques, the corresponding ternary phase diagrams must be determined aiming at establishing the monophasic and biphasic regions. Figure 5.7 illustrates the representation of a hypothetical ternary system phase diagram composed of IL + salt + H_2O. A ternary phase diagram consists of a binodal or solubility curve that separates the monophasic region from the biphasic region and depends on several conditions (such as pH and temperature). The knowledge of the biphasic region, the initial mixture composition and the composition of the individual phases is crucial to any extraction process and to predict the mechanism allied to the partitioning of a solute between the two immiscible aqueous phases. For an initial mixture composition (E) at the biphasic region, the composition of the two immiscible phases, the bottom and top phases in equilibrium, is represented by two extreme points corresponding to the respective tie line (TL), nodes D and F, respectively. Different TLs lay in a phase diagram

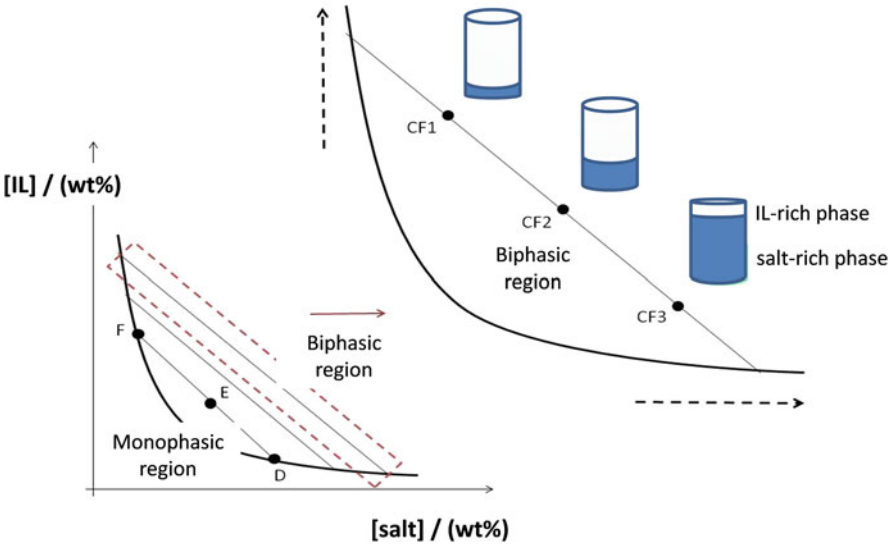

Fig. 5.7 Ternary phase diagram (*orthogonal representation*) for a hypothetical system composed of IL + salt + H_2O (*left image*). Schematic representation of the concentration factor analysis process through the variation of the initial mixture composition along the same TL (*right image*); CF1, CF2 and CF3 correspond to increased concentration factors at the IL-rich phase

with different tie-line lengths (TLLs). Higher TLL values lead to higher differences between the bottom and top phase compositions. The manipulation of the initial compositions along the same tie line allows obtaining liquid-liquid systems with the same composition at the coexisting phases while differing in the volume or weight ratio (Fig. 5.7). These principles correspond to the basis for the development of concentration platforms carried out with ABS.

As can been ascertained from Fig. 5.7, the development of concentration approaches in ABS is better achieved using higher TLL values. Even though it is mathematically possible to apply concentration factors up to infinite, only with higher TLLs it is possible to experimentally apply concentration factors at fixed values without significant experimental oscillations. The procedure of the concentration factor analysis, in an ABS, consists in the scanning on the compositions of an initial mixture in order to gradually decrease the volume or the weight of the phase in which the solute is being extracted, in this case, the IL-rich phase. For that purpose, a successive decrease of the concentration of the IL amount accompanied by an increase of the concentration of salt must be carried out. The decrease of the extractive phase volume leads to an increased concentration of the solute. By applying the lever-arm rule, it is possible to determine the corresponding concentration factor (CF) value corresponding to a given mixture point composition (CF1 < CF2 < CF3). A prerequisite of the concentration procedure consists on the selection of a TL able to afford complete extraction efficiencies, in order

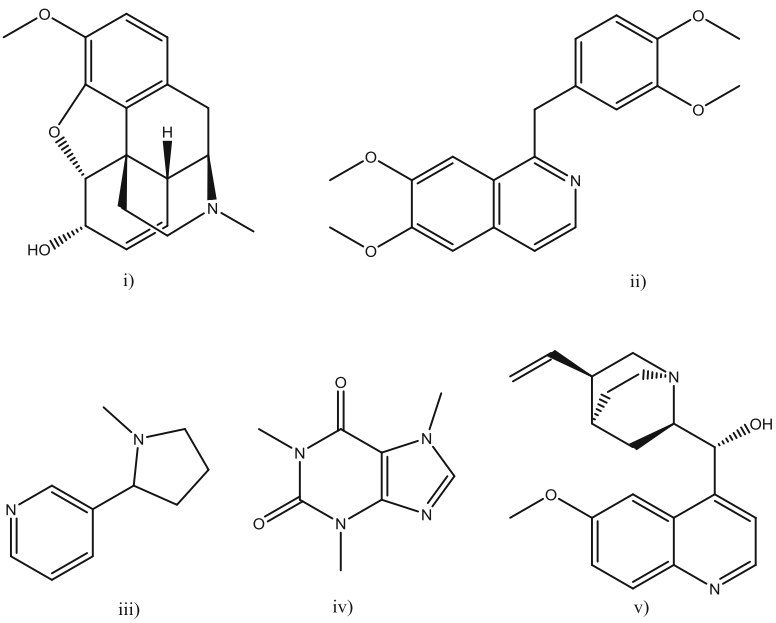

Fig. 5.8 Chemical structure of alkaloids investigated in IL-based ABS: (*i*) codeine, (*ii*) papaverine, (*iii*) nicotine, (*iv*) caffeine, (*v*) quinine

to obtain higher CFs and without the saturation of the extractive phase. This concentration process resulting from the manipulation of the ABS compositions will allow the concentration of target analytes from real matrices and their proper identification/quantification by conventional analytical apparatus.

In addition to legal concerns (e.g. the use of doping agents and/or other illicit drugs), the development of methods for the recovery and concentration of drugs able to allow their adequate identification and quantification still remains a challenge either in academia or in health monitoring/abuse of drugs. Alkaloids are one of the major classes of such drugs and include codeine, papaverine, caffeine, nicotine, morphine, etc. The chemical structures of the alkaloids used in IL-based investigations are depicted in Fig. 5.8. Quantitative determinations are regularly accomplished by chromatographic and spectroscopic methods, which inherently require the pretreatment of samples by the application of extraction methods (mainly to increase the metabolites and drug concentration from the original sample); hydrolysis and/or derivatization steps may also be performed [45]. Nowadays, the two most common methods for sample pretreatment comprising alkaloids are liquid-liquid extraction (LLE) [46] and solid-phase extraction (SPE) [47]. Although SPE presents good purification and concentration effects, it requires a relatively time-consuming solvent desorption step (using traditional volatile organic solvents) and pretreatment processes. LLE inherently involves the use of toxic volatile organic compounds, and the sample recovery is not always adequate. Accordingly,

the development of cost-effective and more environmentally friendly pretreatment methods is of great interest.

Li et al. [48], in 2005, reported the pioneering application of IL-based ABS as a pretreatment/extraction strategy in the analysis of opium alkaloids (codeine and papaverine). The ABS investigated was composed of [C_4mim]Cl and a phosphate-based salt (K_2HPO_4), while the alkaloids present at the coexisting phases were quantified by HPLC (high-performance liquid chromatography). The researchers reported optimized extraction efficiencies of 93 % for papaverine and 65 % for morphine. Later, Freire and co-workers [49] demonstrated the complete extraction of archetypal alkaloids, such as caffeine and nicotine, achieved in a single step, by a proper tailoring of the IL employed in the ABS formulation and respective composition. Although not prohibited by the World Anti-Doping Agency, the use of these simpler alkaloids is still limited to specific levels. For instance, threshold urinary levels of 12 mg/mL of caffeine have been established by several sport federations [50, 51]. In the work addressed by Li et al. [48], only one IL ([C_4mim]Cl) was investigated, while the optimization on the extraction efficiencies and enrichment factors was carried out through the manipulation on the composition of the coexisting phases. However, the efficiency of IL-based ABS extractions should also be planned taking into account the correct choice of the IL-constituting ions. The wide plethora of ILs available nowadays allows the tailoring of the IL chemical structure which better fits a target extraction, and this could result in a significantly lower consumption of ILs and salts.

The study of Freire et al. [49] focused on 17 imidazolium-based ILs which yield ABS in the presence of K_3PO_4 aqueous solutions. In general, nicotine presented higher partition coefficients (when compared to caffeine) in the studied IL-based ABS; this trend was justified based on the higher hydrophobicity of nicotine (with a methyl-pyrrolidine ring) and its preferential affinity for the most hydrophobic (IL-rich) phase. The partitioning of both alkaloids was shown to be strongly dependent on the IL employed in the formation of ABS, whereas a close relation to the IL salting-in/-out behaviour was also highlighted. A summary of the major results collected by the authors is provided in Fig. 5.9.

After the fine tuning of the IL chemical structure and respective compositions with aqueous solutions, the direct extraction of alkaloids from human urine was evaluated [49]. The gathered results revealed that the extraction effectiveness for both alkaloids is even more enhanced with human urine samples, i.e. the presence of a more complex matrix, which now includes NaCl and urea, favours the alkaloids migration for the IL-rich phase. Indeed, the authors found particular examples showing the complete extraction of both alkaloids which were not observed with simpler aqueous phases.

Subsequent works by Louros et al. [52], Freire et al. [6] and Domínguez-Pérez et al. [8] demonstrated the ability of less-conventional ABS composed of phosphonium-based ILs and inorganic salts, imidazolium-based ILs and carbohydrates and imidazolium-based ILs and amino acids to extract caffeine. In general, the highest extraction efficiencies for the IL-rich phase are obtained with ABS formed

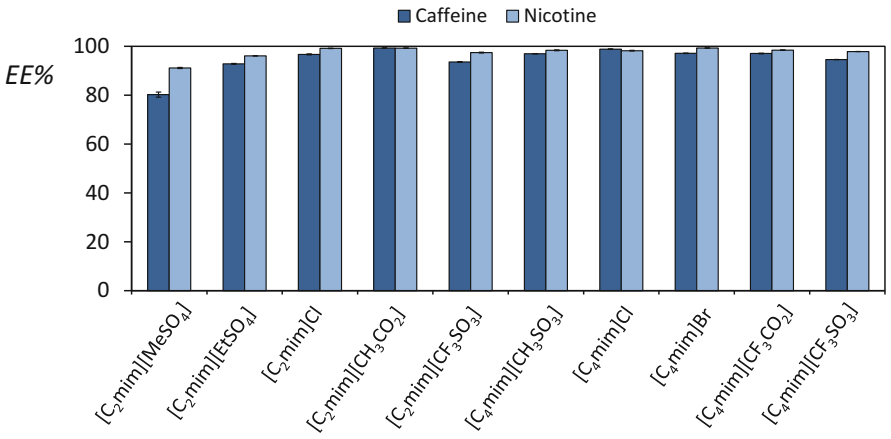

Fig. 5.9 Extraction efficiencies (*EE%*) of caffeine and nicotine in ABS formed by different ILs (25 wt.%) and K_3PO_4 (15 wt.%) (Data taken from Freire et al. [49])

by ILs and K_3PO_4 due to its strong salting-out nature which improves the migration of the alkaloids for the opposite phase [49].

Quinine (6′-methoxycinchonan-9-ol) is a naturally occurring alkaloid usually extracted from the bark of cinchona tree growing in India, South America and Indonesia. Quinine has been used in medicine in the treatment of malaria and is commonly added as an additive in soft drinks as a flavouring agent [53]. Nevertheless, in high dosages, quinine is a potential toxic compound due to its dangerous side effects, including chest pain, asthma and disturbed vision, among others [54]. The adverse effects of quinine in humans are directly correlated with its concentration in plasma. So far, several analytical methods have been described for its determination in biological fluids, namely, LLE and SPE [55, 56]. Although these methods allow the determination of the quinine concentrations considered as dangerous, these are time-consuming and require the use of volatile organic solvents and specific and expensive equipment. Moreover, some interference of major proteins in plasma is usually found. To overcome these drawbacks, Flieger and Czajkowska-Żelazko [57] demonstrated the potentiality of an ABS composed of [C_4mim]Cl and K_3PO_4 or KH_2PO_4. Quinine was identified and quantified in the IL-rich phase after the extraction from plasma samples of volunteers that ingested tonic water containing quinine. Although no enrichment factors were provided, the proposed strategy provided a suitable purification of the samples with extraction yields in the range of 89–106 % [57]. Based on these results, ABS display the potential either for achieving highly concentrated samples of alkaloids for further quantitative analysis or for engineering strategies aiming at obtaining contaminant-free matrices.

Steroid hormones, namely, testosterone and epitestosterone, were also identified and quantified in human urine after pretreatment with IL-based ABS [58]. Anabolic androgenic steroids are commonly used to improve the athletic performance. In fact,

testosterone is already forbidden in sports since 1983 by the International Olympic Committee. Liu and co-workers [58] employed an ABS formed by $[C_4mim]Cl$ and K_2HPO_4, coupled with reversed-phase high-performance liquid chromatography (RP-HPLC), to simultaneously concentrate and quantify testosterone and epitestosterone in human urine. Under the optimal conditions, the extraction efficiencies, attained in a single step, ranged between 80 and 90 %. The proposed approach only requires 3.0 mL of urine and allowed a 10-fold enrichment factor for both analytes, which according to the authors is sufficient for their analysis by HPLC [58].

The content of proteins present in human urine is useful either in diagnosis or prognosis, for instance, in kidney transplant recipients and acts also as markers of chronic nephropathy and cardiovascular diseases [59]. Recently, microalbuminuria, identified by the presence of low levels of albumin (albumin excretion in the order of 300 mg/day) in a urine sample, is indicative of pathological alterations in blood capillaries and the earliest sign of diabetes mellitus [60]. In the presence of high amounts of proteins in the samples, these can be quantified (as a total of proteins) by spectroscopic techniques. Nevertheless, when the protein content is very low, more sensitive methods, such as radioimmunoassay or enzyme-linked immunosorbent assays, are required [61]. Even so, the complex nature of the real matrices frequently leads to serious interferences through the protein quantification. Therefore, the development of pretreatment techniques for the accurate quantification of proteins in body fluids plays a vital role. Based on this prerequisite, Du et al. [62] proposed the use of an IL-salt ($[C_4mim]Cl + K_2HPO_4$) ABS for the extraction and concentration of proteins from body fluids. After phase separation, the proteins mainly concentrate at the IL-rich (upper) phase, while the majority of contaminants remained in the salt-rich (bottom) layer. Fourier transform infrared (FTIR) spectroscopy and UV spectroscopy confirmed the inexistence of chemical (covalent) interactions between the proteins and the IL, settling thus the preservation of the protein structure. By the increase on the amount of inorganic salt, the volume of the IL-rich phase was progressively decreased allowing the authors to establish a maximum enrichment factor of 20 (attained by a second phase separation) [62].

Vitamin B12 (cyanocobalamin) is an essential nutrient formed by a tetrapyrrole complex and which contains a cobalt (Co) atom. A high demand for specific and simple methodologies to monitor vitamins in human fluids is growing because of their importance in human health. In most situations, vitamin B12 is determined as total Co, assuming that no free Co exists. Still, the applicability of these techniques for VB12 quantitation in complex samples is somewhat more restricted since conventional methods cannot distinguish between free inorganic Co and Co bonded to VB12 forms [63]. One of the most widely used techniques for VB12 identification and quantification is HPLC. However, HPLC has some limited sensitivity and selectivity, making it unsuitable for determining trace levels of VB12 in complex matrices, reinforcing the requirement of a prior extraction methodology. Aiming the separation and enrichment of vitamin B12 from urine samples, the use of an ABS composed of $[C_6mim]Cl$ and K_2HPO_4 was suggested by Berton et al. [64]. Vitamin B12 was extracted from pretreated urine samples and enriched in the upper IL-rich phase, followed by a direct injection into the HPLC system for analysis.

The composition of the biphasic mixtures, the pH of the aqueous medium and temperature were optimized by the authors, leading to an extraction efficiency of 97 %. In summary, the authors [64] demonstrated that only 5.0 mL of a urine sample and a single hydrolysis/deproteinization/extraction step were required before the direct determination by the quantitative method.

Macrolide antibiotics, such as azithromycin and mydecamycin, are largely employed in veterinary and medicinal practices to treat a wide range of diseases. However, their extensive consumption and therapeutic activities on humans and animals can lead to a main persistence of these compounds in the aqueous environment. In this context, simple and accurate pretreatment techniques and analytical methods are required to a proper monitoring of aqueous streams. To this end, IL-based ABS composed of $[C_4mim][BF_4]$ and a salt (Na_2CO_3, Na_2SO_4, NaH_2PO_4 or $(NH_4)_2SO_4$) were suggested to separate and to further determine trace azithromycin and mydecamycin in real water samples [65]. The type and concentration of salts, as well as the temperature of extraction, were investigated. With real samples, the recovery of azithromycin and mydecamycin ranged between 91.8 and 96.2 % and from 89.6 to 92.2 %, respectively. The effect of interfering substances was also addressed, where the coexistence of organic compounds, such as lactose, glucose, fructose, sucrose, starch and magnesium stearate, does not significantly interfere with the antibiotic detection and quantification. Nevertheless, no enrichment or concentration factors were explored by the authors [65]. Similar works were reported by the same group of researchers in the extraction of trace roxithromycin from real water samples using a $[C_4mim][BF_4]$-Na_2CO_3 ABS (extraction efficiency up to 90.7 %) [66], of acetylspiramycin from aqueous samples using a $[C_4mim][BF_4]$-NaH_2PO_4 ABS (extraction efficiency up to 90.14 %) [67].

Han et al. [68] used a liquid-liquid extraction approach based on ABS formed by $[C_4mim][BF_4]$ and an organic salt, $Na_3C_6H_5O_7$, aiming an easier identification and quantification of chloramphenicol in water, milk and honey samples, using HPLC as the analytical method. Chloramphenicol is an effective antibiotic against a wide range of Gram-positive and Gram-negative bacteria [68]. Nonetheless, due to its toxicity, this antibiotic was already banned in food-producing animals within the EU [69], and an appropriate monitoring of trace levels of chloramphenicol is still a significant challenge. Again, two main pretreatment methods are commonly used, namely, LLE [70] and SPE [71]. The recovery of the antibiotic from aqueous samples of real feed water, milk and honey samples ranged between 90.4 and 102.7 %. Later on, the same group of researchers [72] used an ABS constituted by $[C_4mim]Cl$ and K_2HPO_4 combined with solvent sublation to quantify chloramphenicol in the same type of samples. The authors investigated either the characteristic conditions of ABS-mediated extractions, such as the type of phase-forming components, their concentration and solution pH, as well as the conditions inherent to sublation, namely, the nitrogen flow rate and sublation time. Under the optimized conditions, the recovery of chloramphenicol was from 97.1 to 101.9 %, while revealing a satisfactory reproducibility and performance afforded by sublation. Moreover, no significant interferences were verified in the presence of excipients. The authors [72] successfully demonstrated that the proposed method can be widespread applied

on the quantitative determination of chloramphenicol in environment samples and food.

Still worthwhile mentioning is the work of Domínguez-Pérez et al. [8] who used an ABS composed of 1-butyl-3-methylimidazolium trifluoromethanesulfonate ($[C_4mim][CF_3SO_3]$) and one amino acid (lysine) to promote phase separation and the extraction of a synthetic antibiotic – ciprofloxacin. A partition coefficient of 2.7 was obtained in a single-step process in a fixed mixture composition [8]. This value is much lower than those obtained for the abovementioned antibiotics using IL-based ABS formed with inorganic salts. However, it should be pointed out that amino acids have a lower salting-out ability than high-charge density inorganic salts, thus leading to lower extraction efficiencies to the IL-rich phase. Nevertheless, and although often used, IL-salt ABS are highly ionic media and might not be compatible with the extracted product, since many biomolecules present narrow tolerance limits of ionic strength – if the recovery and reuse of the extracted compounds is envisaged. The use of amino acids as potential substitutes of salts to form more environmentally benign and less aggressive IL-based ABS has been therefore suggested [8]. In the same line, Shahriari et al. [73] proposed the use of more benign ABS composed of biodegradable and biocompatible cholinium-based ILs for the extraction of tetracycline and ciprofloxacin from aqueous media. After the tailoring of the IL chemical structures and amount of salt employed, the complete extraction of tetracycline was achieved in a single step [73]. The major results accomplished by the authors are summarized in Fig. 5.10.

The remarkable results attained with cholinium-based ABS reveal that they are actually improved alternatives to traditional extraction methods and certainly deserve further attention from the biotechnology and analytical fields. The use of cholinium-based ILs combined with other inorganic/organic salts, as well as with gentler and more biodegradable species, such as carbohydrates or polymers, was suggested by the authors [73] as more environmentally friendly and benign extraction routes. Some other ABS composed of cholinium-based ILs and biodegradable polymers have been demonstrated [74].

Passos et al. [75] also employed IL-based ABS for the extraction of an endocrine disruptor (bisphenol A) from water and artificial human urine. Bisphenol A (4,4′-(propane-2,2-diyl)diphenol), or BPA, is a key monomer in the production of epoxy resins and the most common form of polycarbonate plastics. The leaching of BPA, and particularly from food storing items, became a matter of concern after its recognition as an endocrine disruptor. It exerts hormone-like properties leading to altered immune functions, imbalanced hormone ratios, decreased semen quality, obesity, diabetes, heart disease and behavioural alterations in children [76]. It has been identified in air, water, sediments, food items and human biological fluids (serum, plasma, placenta, semen and breast milk) [77]. However, the low content of bisphenol A in human fluids is the major obstacle towards its identification, quantification and a proper monitoring of its impact in human health. With the goal of developing a concentration technique, the authors [75] tested a wide range of ILs combined with K_3PO_4 as a strong salting-out agent aiming at finding a proper ABS able to completely extract and further concentrate bisphenol A in the IL-

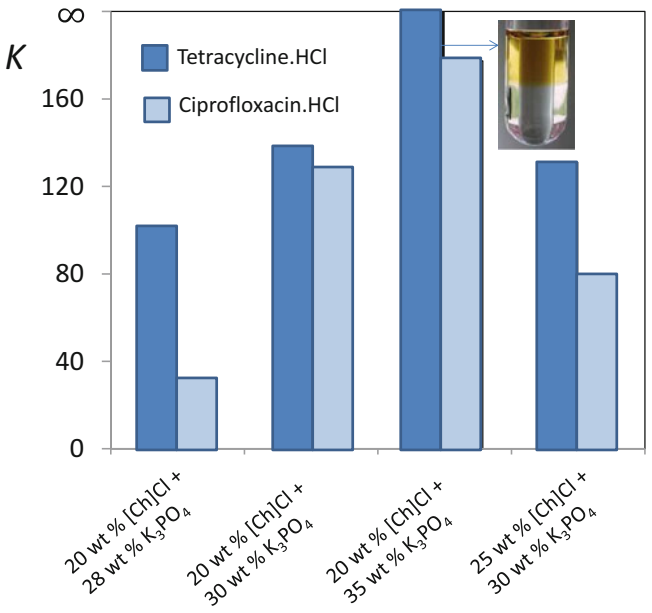

Fig. 5.10 Tailoring of the partition coefficients (K) of tetracycline and ciprofloxacin using ABS formed by [Ch]Cl and K_3PO_4 by changing the system composition and where the complete extraction of tetracycline is highlighted (Data taken from Shahriari et al. [73])

rich phase. Different chloride-based ILs were investigated comprising imidazolium, pyrrolidinium, phosphonium, ammonium or cholinium cations. In all situations, the obtained extraction efficiencies were higher than 98.5 %. After fine-tuning the ILs and respective compositions with model systems composed of water, artificial human urine was further used to ascertain on their applicability to real samples. In general, the presence of a more complex matrix favoured the partitioning of the endocrine disruptor for the IL-rich, achieving 100 % of extraction in most of the systems investigated [75].

After the initial screening, the authors [75] deeply studied the concentration factors achievable, by carrying out extractions at mixture compositions along the same tie line aiming at decreasing the volume of the IL-rich phase, while keeping the complete extraction performance in a single step. A schematic representation of the procedure adopted as well as the extraction efficiencies of BPA obtained with different ABS at different mixture compositions is provided in Fig. 5.11.

The authors [75] found that the concentration of BPA can be increased at least up to 100-fold by the reduction of the total volume of the extractive phase (making use, e.g. of the following mixture compositions: 2.5–2.7 wt.% of IL + 45 wt.% of K_3PO_4). Certainly, by obtaining a complete extraction and possible concentration up to 100-fold, human fluid samples can be effortlessly checked for their bisphenol A content (or other substances of interest) [75]. Indeed, 100-fold is the highest concentration factor reported in the literature using IL-based ABS.

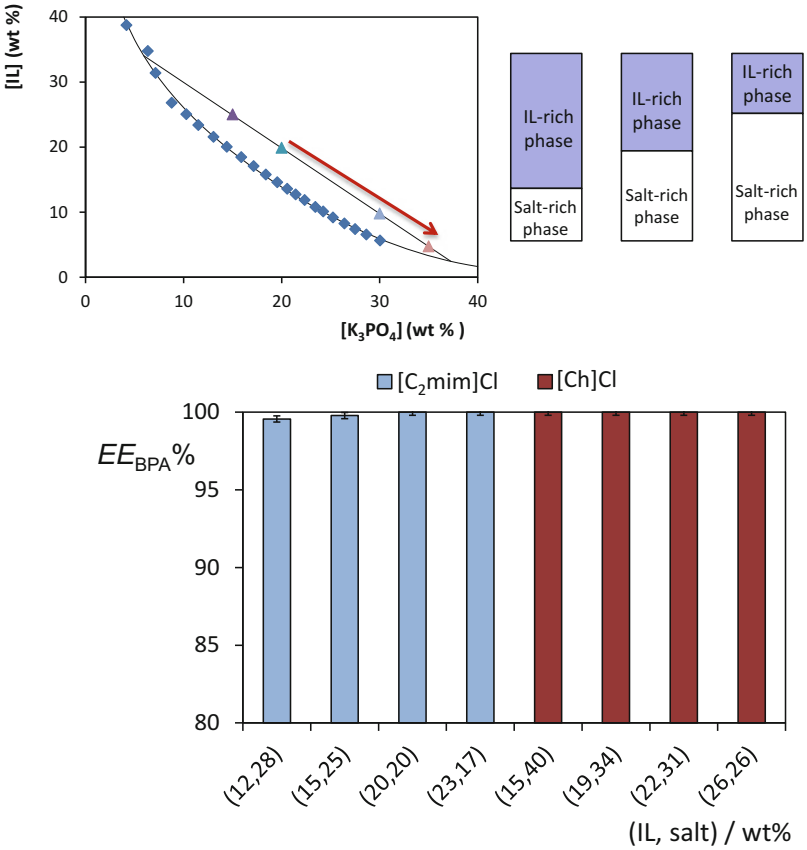

Fig. 5.11 Concentration procedure adopted and extraction efficiencies of BPA (EE_{BPA} %) obtained with several ABS and at different mixture compositions (Data taken from Passos et al. [75])

Since concentration factors up to infinite can be attained, further studies aiming at exploring higher concentration factors attained by IL-based are of crucial need.

The results described above confirm that IL-based ABS are real and improved alternatives to the traditional extraction-concentration methodologies, offering simpler, greener, quicker and more efficient procedures. Actually, when coupled with a suitable analytical method, IL-based ABS represent viable pretreatment and cleanup techniques and allow operating with aqueous solutions containing analytes in trace amounts. Furthermore, compared to conventional LLE and SPE approaches, ABS avoid the use of volatile organic solvents, replacing them with relatively small amounts of nonvolatile and recyclable ILs and salts.

5.4 IL-Based ABS in the Treatment of Aqueous Effluents

The use of IL-based ABS for the treatment of aqueous effluents contaminated with ILs was suggested in the pioneering work of Rogers and co-workers [3]. Although IL-based ABS are mostly used in the development and design of extraction processes [5], they can also be used as an effective route for the recovery and/or concentration of hydrophilic ILs from aqueous solutions.

The number of applications involving ILs has dramatically increased in the past few years, and their production and use in a large scale will inevitably lead to their dispersion into water streams (either by wastewater disposal or accidental leakage). Although ILs have been claimed as "green solvents", mainly due to their negligible vapour pressures, not all of them are benign, biocompatible and biodegradable. Indeed, the environmental impact of ILs is still an open issue. Therefore, the development of methods for their removal from water or wastewater streams is especially important when envisaging their application at a large scale. In addition to their removal, where degradation methods can be applied, their recovery and recycling are preferred strategies within the sustainability concept. The application of IL-based ABS for the recycling and recovery of hydrophilic ILs has been clearly demonstrated as described below.

Deng and co-workers [78] studied ABS composed of 1-allyl-3-methylimidazolium chloride ([amim]Cl) and three inorganic salts (K_3PO_4, K_2HPO_4 or K_2CO_3). The chemical structure of the investigated IL is depicted in Fig. 5.2. The authors [78] verified that the recovery efficiency of the IL increased with the concentration of inorganic salt. As previously discussed, higher amounts of salt lead to larger TLLs and lower contents of IL at the salt-rich phase and vice versa. In general, the recovery efficiencies follow the order $K_3PO_4 > K_2HPO_4 > K_2CO_3$ [78]. High-charge density salts are stronger salting-out agents leading to a better exclusion of the IL to the IL-rich phase. A maximum recovery efficiency of 96.80 % of IL was reported by the authors [78]. Li and co-workers [79] also demonstrated that $[C_4mim][BF_4]$ can be recovered from aqueous solutions by the addition of Na_3PO_4, Na_2CO_3, Na_2SO_4, NaH_2PO_4 or NaCl by the creation of ABS, while the maximum recovery efficiency reported was 98.77 %. Again, salts with a stronger salting-out ability allow for higher recovery efficiencies of the IL.

Despite the largely explored phosphate- and carbonate-based salts, Coutinho and co-workers [80] have proposed the use of aluminium-based salts to form ABS aiming at removing and recovering ILs from aqueous environment. In addition to the strong salting-out aptitude of these salts, thus leading to an easy phase separation and high recovery efficiencies, aluminium-based salts are already used in water treatment processes. According to the USEPA (United States Environmental Protection Agency), alum, chlorine, lime and coagulant aids can be added directly into the public water storage and distribution systems while keeping it suitable for public consumption [80]. Neves et al. [80] studied a large array of ILs (imidazolium, pyridinium and phosphonium based) combined with the inorganic salts $Al_2(SO_4)_3$ and $AlK(SO_4)_2$. The minimum recovery efficiency found was 96 %, whereas in most

of the ABS investigated recovery efficiencies of 100 % were attained. The addition of aluminium-based salts allowed to reduce the IL concentration at the aqueous phase from circa 45 wt.% to values around 1 wt.%. The authors [80] also applied several cycles in the process to guarantee that the salt can be recycled, and the IL was completely recovered. It should be highlighted that the possibility of ion exchange between the coexisting phases was also explored while concluding that, at least up to the detection limits of the analytical equipment used, no ion exchange was observed between the aluminium-based salts and the several ILs investigated [80].

Albeit the previous works [78–80] made use of strong salting-out salts, which usually contain high-charge density anions, these comprise further environmental risks given the high concentrations of salt required. To overcome this drawback, ABS composed of ILs and carbohydrates were also proposed [81, 82]. Carbohydrates are non-charged, biodegradable, nontoxic and a renewable feedstock, guarantying therefore the use of safer and more benign approaches. ILs such as [amim]Cl, 1-allyl-3-methylimidazolium bromide ([amim]Br) and [C_4mim][BF_4] were recovered from aqueous solutions by the addition of appropriate amounts of carbohydrates (sucrose, glucose, xylose, fructose) through the formation of ABS. However, only recovery efficiencies up to 74 % were obtained [81, 82]. Even though studies involving carbohydrates show the potential of a more environmentally friendly recovery process, which can be further improved by the optimization of a variety of conditions, we must be aware that we are adding now a large amount of organic matter to the aqueous medium that can give rise to other concerns.

5.5 Conclusions and Future Trends

Taking into account the vast amount of literature published over the last decade, it can be affirmed that the combination of the unusual properties displayed by ILs, with those of ABS, greatly boosted the potential of this technique allowing for novel approaches in extraction, separation and concentration of a wide variety of solutes (ranging from simple molecules, such as caffeine, to more complex solutes, such as proteins and pharmaceuticals). This renewed interest in ABS is well understood if one takes into account the impressively enhancement in the efficiency and recovery yields provided by IL-based ABS for a large variety of solutes. These results are due not only to the different phase splitting mechanisms, allowed by the use of ILs combined with other phase promoters, but also by the possibility of tuning the IL's affinity for a specific solute.

In contrast to the vast body of fundamental knowledge built on IL-based ABS, their application in real systems is currently giving the first steps. The aim of this *critical review* is to disclose the effective potential of this methodology, which we believe is largely unexplored. Examples of extraction and purification of compounds with different chemical and biological activities, from complex natural matrices and biological media, are here presented. Although the proof of concept of IL-based ABS as key tools in downstream processing of biotechnological processes has been

made over the last few years, the development of suitable and robust processes has not yet been fully approached. The crucial step is, now, the choice of adequate technological solutions for IL-based ABS industrial implementation, encompassing the recognition of the different levels where these systems can be integrated. The recycling of the phases allowing the design of continuous processes is also vital for their wide application. In this context, several examples are presented in this review where the recycling of the phases is successfully achieved, eliminating the question of the IL cost and simultaneously opening the door to the implementation of continuous processes.

The use of IL-based ABS to improve the detection limit of several analytical techniques is of high relevance in different fields. In this review, examples regarding human health issues and environmental contamination control are described. We foresee that IL-based ABS will continue to be further explored in the future in the early diagnosis of diseases and on the detection of micropollutants in the environment and food as they are being pushed forward by the modern society regulations. The development of commercial kits for concentration of specific compounds might also play a significant role in the dissemination of the implementation of this technique which can be of commercial value.

Regarding the potential trend in the application of IL-based ABS for the recovery of biological products, and due to the fact that ABS based on polyethylene glycol and inorganic salts have already been industrially implemented in the extraction and purification of biopharmaceuticals, it is expected that the high value of this market combined with the excellent extraction indicators obtained for some simple extraction/purification steps of these compounds will provide the drive to extend this technology to IL-containing systems. The food and the cosmetic industries are also other parallel areas where IL-based ABS will certainly gain acceptance due to market demand for the addition of natural products and the high sophistication level of technology present in these industries.

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Chapter 6
Extraction of Sandalwood Oil Using Ionic Liquids: Toward a "Greener" More Efficient Process

Arvind Kumar, Hui Wang, and Robin D. Rogers

Abstract We have demonstrated that sandalwood can be dissolved in the ionic liquid 1,3-diethylimidazolium acetate ($[C_2C_2im][OAc]$) and that sandalwood oil can then be extracted from the sandalwood/$[C_2C_2im][OAc]$ solutions using diethyl ether, which forms a biphasic system with the ionic liquid. The main components of the obtained sandalwood oil, as confirmed by GC–MS, NMR, and FTIR, are (*Z*)-α-santalol and (*Z*)-β-santalol. Pretreatment of the sandalwood with microwave irradiation or poly(ethylene glycol), the presence of polyoxometalate as the catalyst, and higher dissolution temperature all led to increased essential oil yield. After the extraction of the essential oil, carbohydrate-rich material and free lignin were regenerated from the wood/$[C_2C_2im][OAc]$ solution, thus allowing an integrated process of separating all the major components of sandalwood, the biopolymers and the oil.

Keywords Sandalwood oil extraction • (Z)-α-santalol • (Z)-β-santalol • Lignin extraction • Carbohydrate-rich material extraction • Ionic liquid

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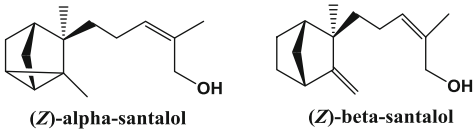
6.1 Introduction

Sandalwood oil is best known as a sweet, warm, and woody essential oil used as a body fragrance and as an ingredient in fragrant products such as incense, perfumes, aftershaves, aromatherapy oil, and other cosmetics [1]. This essential oil is obtained from sandalwood which is a commercially and culturally important plant species belonging to the family Santalaceae and the genus *Santalum* [2]. The yield (typically 2.5–6.2 %) and quality of sandalwood oil depends on the age, soil, climatic, and genetic factors associated with the tree [3].

Sandalwood oil is a complex mixture, and more than 300 constituents have been identified from the extracts of heartwoods of various sandalwood species, with (*Z*)-α-santalol and (*Z*)-β-santalol (Fig. 6.1) as the major components [4]. Standards suggest that *S. album* essential oil should contain no less than 90 wt.% free alcohols [5], in particular, (*Z*)-α-santalol falling in the range of 41–55 % and (*Z*)-β-santalol in the 16–24 % range. Other compounds such as nuciferol, bisabolol, or farnesol are also normally detected in small amounts in sandalwood oil [6, 7].

Currently, sandalwood oil is extracted from sandalwood by hydrodistillation, steam distillation, supercritical fluid extraction (e.g., supercritical carbon dioxide ($scCO_2$)), or by solvent extraction (e.g., benzene, ethyl ether, ethyl alcohol) [8, 9]. Extraction using $scCO_2$ has been shown to be the best method to get sandalwood oil with higher santalol content in a relatively shorter processing time (1 h vs. 16–48 h for the other methods) [9]. However, extraction of sandalwood oil with $scCO_2$ or steam distillation needs to be carried out under high pressure (e.g., 35.7 MPa [8]) and is energy intensive, while solvent extraction is associated with the risk of handling large quantities of combustible and often toxic solvents. Greener and more energy-efficient methods to get the essential oil from sandalwood could therefore be commercially viable.

Ionic liquids (ILs, salts with melting points below 100 °C [10]), such as 1-butyl-3-methylimidazolium chloride ([C_4mim][Cl]) and 1-ethyl-3-methylimidazolium acetate ([C_2mim][OAc]), can efficiently dissolve lignocellulosic biomass [11, 12], including bagasse [13], poplar [14], pine [15], oak [14, 15], and switch grass [16], under mild conditions. Recently, the extraction of essential oils from natural sources using ILs has also been demonstrated. For instance, orange essential oil, mainly limonene, was distilled from orange peels dissolved in IL media, with oil yield ranging from 1.5 to 5.0 % [17], in comparison with an isolated yield of ∼1 % of limonene from orange peel after steam distillation and successive extraction of limonene with dichloromethane or diethyl ether [18].



(*Z*)-alpha-santalol (*Z*)-beta-santalol

Fig. 6.1 Structures of (*Z*)-α-santalol and (*Z*)-β-santalol

IL-based microwave-assisted extraction has been successfully applied in extracting essential oil and four kinds of biphenyl cyclooctene lignans from *Schisandra chinensis* Baill [19]. With this method, the extraction time was shortened to 40 min (vs. 3.0 h for hydrodistillation of essential oils and 4.0 h for reflux extraction of lignans), and the extraction efficiency was improved with reduced environmental pollution. Usuki et al. efficiently extracted and isolated shikimic acid, the starting material in the commercial synthesis of oseltamivir phosphate (Tamiflu), from *Ginkgo biloba* leaves utilizing [C_4mim][Cl] [20].

The successful application of ILs in essential oil extraction motivated us to expand the use of ILs to extract the essential oil from sandalwood. In this work, 1,3-diethylimidazolium acetate ([C_2C_2im][OAc]), which has a higher decomposition temperature than [C_2mim][OAc] [21], was used to dissolve sandalwood, and the essential oil was extracted from the resulting solution using diethyl ether. The extracted oil was characterized by gas chromatography–mass spectrometry (GC–MS), ^{1}H NMR, and FTIR. After oil recovery, the biopolymers from the sandalwood were regenerated by adding anti-solvent, e.g., a mixture of acetone/water (1:1, v/v), to the IL solution. The influences of various parameters on the essential oil yield, including cooking time and temperature, pretreatment with microwave heating, use of polyoxometalate catalyst, and swelling with poly(ethylene glycol) (PEG-300), were also investigated.

6.2 Experimental

6.2.1 Materials

The ionic liquid [C_2C_2im][OAc] was purchased from BASF (Ludwigshafen, Germany). PEG-300, standard sandalwood oil, decane, farnesol, and microcrystalline cellulose (MCC) with a degree of polymerization of 270 were purchased from Sigma-Aldrich Inc. (Milwaukee, WI). Indulin AT (lignin from the kraft pulping process) was provided by MeadWestvaco Corporation (Glen Allen, VA). Root Vanuatu Premium Sandalwood was received from Seaman Timber Co. (Montevallo, AL), and before dissolution the sandalwood was ground into powder with particle sizes less than 0.25 mm and dried overnight in an oven (Precision Econotherm Laboratory Oven, Natick, MA) at 90 °C. Acidic polyoxometalate (POM), $H_5[PV_2Mo_{10}O_{40}]$, was donated by Japan New Metals Co. (Akita, Japan). Diethyl ether was supplied by EMD Chemicals, Inc. (Gibbstown, NJ). Deuterated chloroform ($CDCl_3$) was purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA). Deionized (DI) water was obtained from a commercial deionizer (Culligan, Northbrook, IL) with specific resistivity of 16.82 MΩ cm at 25 °C. HPLC grade methanol was from Fisher Scientific (Pittsburgh, PA). All other solvents and reagents, e.g., acetone, were obtained from Sigma-Aldrich (St. Louis, MO) and used as received.

6.2.2 Dissolution of Sandalwood and Extraction of the Oil and Biopolymers

Dissolution in oil bath Dissolution of sandalwood in $[C_2C_2im][OAc]$, an IL with a melting point of 30 °C [21], followed our previous work on dissolution of southern yellow pine in IL [15]. Briefly, 1.0 g of sandalwood was added to 20.0 g IL (in the solid state) in a 50 mL beaker covered with aluminum foil, and the mixture was put in an oil bath preheated to a certain temperature (100 or 170 °C) for 6 or 24 h while being subjected to vigorous magnetic stirring. After dissolution, the sandalwood/IL solution was cooled to room temperature, and 20 mL diethyl ether, which can form a biphase with $[C_2C_2im][OAc]$, was added to the mixture to extract the oil from the IL solution with continuous stirring at room temperature for 1 h. Upon standing for 1 h, a biphasic system was formed. The top diethyl ether phase was separated from the IL phase using a pipet, and the IL phase was extracted with diethyl ether twice more to make sure all the oil was removed. The diethyl ether solutions were combined, and sandalwood oil was obtained by exposing the solution to air to evaporate diethyl ether at room temperature.

After the extraction of the oil from the sandalwood/$[C_2C_2im][OAc]$ solution, the remaining wood/IL solution was subjected to filtration for the removal of undissolved wood residue. The biopolymers (e.g., cellulose, lignin) in the homogeneous IL solution were recovered following our previous procedure [15]. Briefly, the IL solution was poured into a 300 mL beaker containing 200 mL of a 1:1 (v/v) mixture of acetone/water and stirred at room temperature for 1 h followed by centrifugation. The supernatant was transferred to a 500 mL beaker for lignin recovery. The precipitated carbohydrate-rich material (CRM) was further washed with an acetone/water (1:1 v/v) mixture twice more and then with DI water to ensure all of the lignin and IL were washed out before subjecting the material to vacuum filtration using a ceramic funnel with nylon filter paper (20 μm).

The lignin was precipitated from the supernatant and combined wash solutions by allowing the acetone to evaporate while the material was stirred at room temperature. The recovered lignin was separated from the remaining aqueous IL solution by vacuum filtration as above, but 0.8 μm nylon filter paper was used because of the smaller lignin particle size. The lignin and CRM were dried overnight in an oven (Precision Econotherm Laboratory Oven, Natick, MA) at 90 °C.

Microwave-assisted pretreatment Microwave irradiation was used to pretreat the sandalwood/IL solution to facilitate the oil extraction. The sandalwood and IL mixture, prepared as above, underwent 40 pulses of 3 s (2 min total) in a domestic microwave oven (SHARP Carousel R-209KK, Mahwah, NJ) at full power (800 W), with vigorous stirring using a glass rod for *ca.* 20 s between pulses. (Caution: Care must be taken when using microwave heating because ILs are good microwave absorbers and heating occurs rapidly which can easily lead to degradation of the ILs and biopolymers or even explosions.) The microwave-pretreated sandalwood/$[C_2C_2im][OAc]$ solution was then heated in an oil bath, and the oil extraction followed the procedure described above.

Pretreatment of sandalwood with polyethylene glycol To enhance the extract yield, the sandalwood was also pretreated by swelling 1 g sandalwood in 5 g PEG-300 for 24 h at room temperature. Twenty grams of $[C_2C_2im][OAc]$ was then added to the sandalwood/PEG-300 mixture, and the resulting mixtures were processed by either the oil bath heating or microwave heating methods noted above, followed by oil extraction.

6.2.3 Characterization

^{1}H NMR spectra of the fresh and recovered $[C_2C_2im][OAc]$, the extracted sandalwood oil, and the commercial sandalwood oil were collected using a Bruker Avance 500 NMR spectrometer at 25 °C by dissolving the samples in $CDCl_3$. The ground sandalwood, regenerated CRM, MCC, Indulin AT, and precipitated lignin, were characterized by FTIR spectroscopy using a PerkinElmer Spectrum 100 FTIR spectrometer equipped with an attenuated total reflectance (ATR) cell with 24 scans at a resolution of 2 cm^{-1}.

GC–MS analysis of the extracted oil was performed using a HP 6890 GC series equipped with an Rtx-Wax column (30 m length × 250 μm i.d. × 0.5 μm film thickness) connected with a Micromass AutoSpec-Ultima™ NT Mass spectrometer with electron ionization (EI) mode operating at 70 eV. The initial oven temperature was 40 °C and increased to 200 °C at a rate of 2 °C/min. The oil samples were dissolved in HPLC grade methanol, and the methanol solution was mixed with decane, as the internal standard for santalol, in a 1:10 (v/v) ratio. 0.3 μL of the oil solutions (10:1 decane/oil methanol) were injected into the GC–MS system (split 1:30) at an inlet temperature of 220 °C. Helium was used as the carrier gas (1 mL min^{-1}). The identification of the sesquiterpene alcohols was achieved by comparing the MS spectra with published data [22], and confirmed by the NIST standard mass spectrometry library. The calibration curve for quantification was obtained by analyzing the mixtures of decane and farnesol at various mole ratios (1:1, 1:2, 1:4, and 1:8), and it was assumed that the response of the santalols to GC was the same as that of farnesol since pure α-santalol or β-santalol is not commercially available. The quantities of sandalwood oil's main components, (*Z*)-α-santalol and (*Z*)-β-santalol, were calculated using the calibration curve based on the equation: $y = 0.587x + 0.573$ ($R^2 = 0.994$), where x is the concentration ratio of farnesol/decane and y is the chromatographic peak area ratio of farnesol/decane.

6.3 Results and Discussion

In a typical experiment, 1.0 g dried sandalwood powder (<0.25 mm) was added to 20 g of $[C_2C_2im][OAc]$ in a 50 mL beaker. The biomass/IL solution was heated in an oil bath at 100 °C with vigorous magnetic stirring (350 rpm) for a specific period

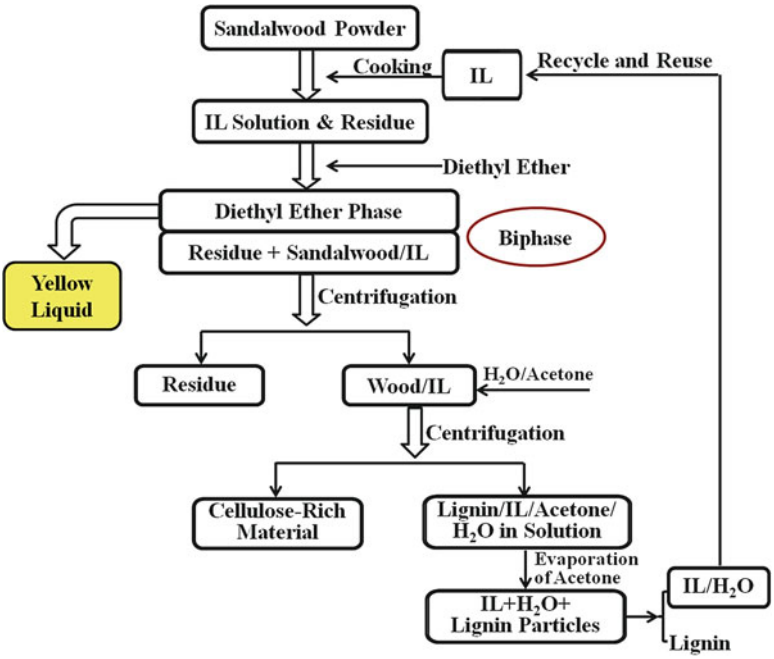


Fig. 6.2 Schematic of integrated process for extracting sandalwood oil and biopolymers from sandalwood using $[C_2C_2im][OAc]$

of time. After the dissolution, diethyl ether was used to extract the essential oil from the wood/IL solution as described in the Experimental. The detailed procedure is shown in Fig. 6.2.

Qualitative analysis of the oils Analysis of the obtained sandalwood oil was performed by GC–MS, followed by comparing its NMR and FTIR spectra with those of an authentic sandalwood oil. A typical GC chromatogram is shown in Fig. 6.3. The identification of the sesquiterpene alcohols was achieved by comparing the MS spectra with published data [22], and it was found that the compounds with retention times of 23.25 min and 23.45 min were (*Z*)-α-santalol and (*Z*)-β-santalol, respectively. The (*Z*)-α-santalol and (*Z*)-β-santalol in the oil extracts obtained under varying experimental conditions were quantified based on the peak area obtained by GC.

Figure 6.4 compares the ^{1}H NMR spectrum of sandalwood oil obtained using the conditions of Entry 3 in Table 6.1 (discussed below) with that of a commercial sandalwood oil sample. The spectrum matches that of the authentic oil reasonably well with only minor differences, and the differences can be attributed to the complexity of the sandalwood oil, which is dependent on the extraction methods, wood sources, etc. [3]. The absence of peaks around 7.30 and 10.80 ppm corresponding

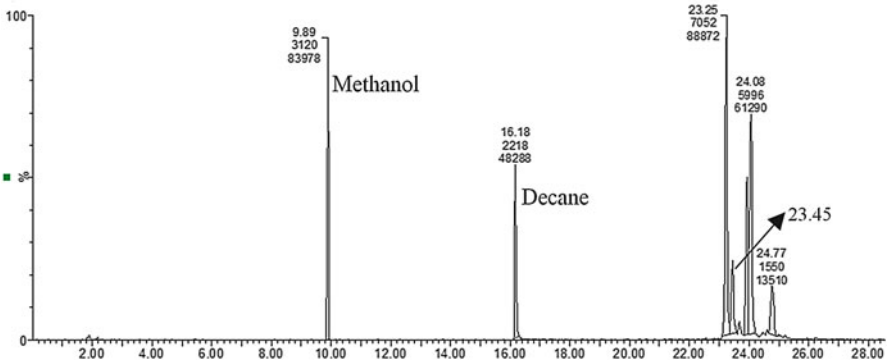


Fig. 6.3 Representative (Table 6.1, Entry 3, discussed below) GC chromatogram of sandalwood oil extracted using $[C_2C_2im][OAc]$. Methanol was the solvent to dissolve the essential oil, and decane was added to the oil solution as the internal standard

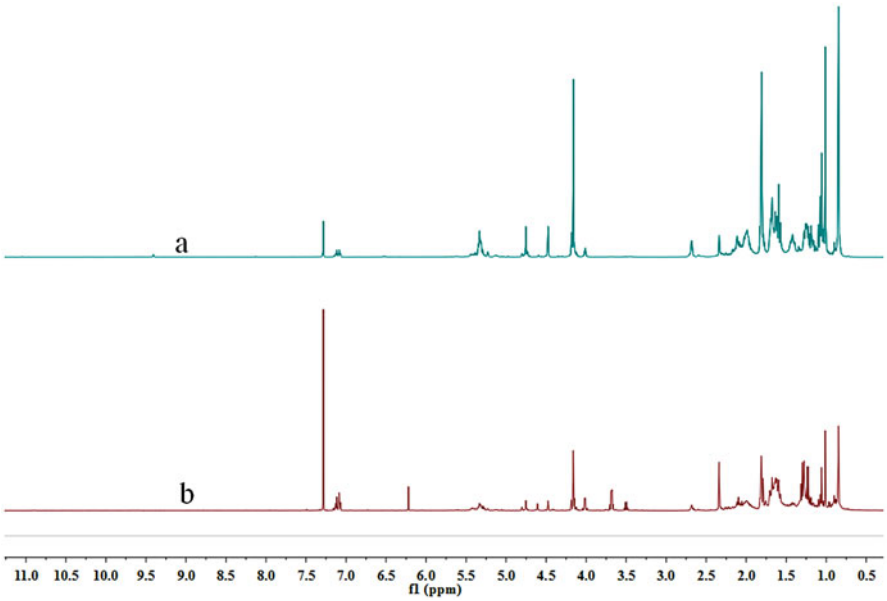


Fig. 6.4 ^{1}H NMR spectra of (*a*) commercial sandalwood oil and (*b*) representative sandalwood oil obtained from the IL dissolution method (Table 6.1, Entry 3)

to the imidazolium protons in $[C_2C_2im]^+$ indicates that no trace of IL was found in the extracted essential oil at the level of ^{1}H NMR detection.

A comparison of the FTIR spectrum of extracted sandalwood oil with that of an authentic sample is shown in Fig. 6.5. The peak at 3300 cm^{-1} indicates the presence of -OH, and the peaks at around 2975 cm^{-1}, 1640 cm^{-1}, 1455 cm^{-1}, and 1010 cm^{-1} are attributed to the presence of C = CH_2 (C–H stretches), C = C, a methylene

Table 6.1 Sandalwood oil yields and santalol contents obtained under varying experimental conditions

Entry	Conditions	Extracted oil yield (%)	(*Z*)-α-santalol (%)	(*Z*)-β-santalol (%)
1	100 °C, 6 h	3.9	7.9	3.0
2	100 °C, 24 h	3.7	8.2	3.1
3	MW[a] 100 °C, 6 h	5.0	16.0	5.1
4	POM, 100 °C, 6 h	4.8	15.9	6.2
5	POM, MW, 100 °C, 6 h	5.9	20.4	9.3
6	PEG-300, 100 °C, 24 h	7.1	10.6	5.6
7	PEG-300, 100 °C, 6 h	7.0	9.8	5.3
8	PEG-300, MW, 100 °C, 6 h	7.5	21.8	10
9	170 °C, 5 min	7.2	14.1	3.6

[a]*MW* microwave treatment for 2 min with 3 s pulses (3 s × 40 pulses)

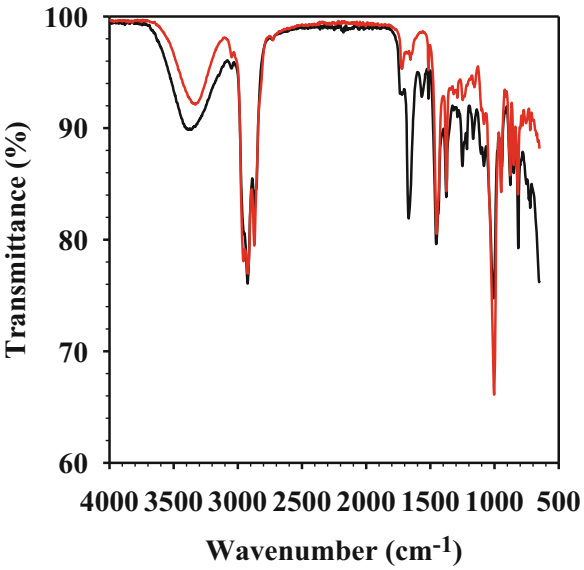


Fig. 6.5 FTIR spectra of a representative sandalwood oil extracted using the IL strategy (*black*, Table 6.1, Entry 3) and the commercial sandalwood oil (*red*)

group, and C–O in alcohols [23]. The close similarity of these spectra indicates that the sandalwood oil obtained from IL dissolution is of good purity.

Comparison of cooking methods, pretreatment, and catalyst Having shown the nature and quality of the sandalwood oils obtained, we investigated four different processing methods to determine the effects on oil composition and yields. The sandalwood oil yields (the mass percentage of extracted oil to the mass of the added wood) are obtained by (a) cooking in an oil bath, (b) initially heating the mixture under microwave irradiation followed by oil bath heating, and pretreating the sandalwood with PEG-300 followed by either the (c) oil bath method or (d) microwave irradiation method which are listed in Table 6.1.

When the sandalwood/[C_2C_2im][OAc] solution was cooked in an oil bath at 100 °C for 6 h, the oil yield was 3.9 % of the added wood mass, comparable with the yield (typically 2.5–6.2 %) of current techniques [3]. Increasing the cooking time to 24 h had little effect on the extraction yield (Table 6.1 Entry 2 vs. 1). However, pretreatment of the sandalwood under microwave irradiation (40 × 3 s pulses with *ca.* 20 s stirring between each pulse for a total irradiation time of 2 min) before oil bath heating (Table 6.1 Entry 3 vs. 1) led to an increase in the extraction yield from 3.9 to 5.0 %, with twice the (Z)-α-santalol content.

The addition of acidic polyoxometalate (POM), $H_5[PV_2Mo_{10}O_{40}]$ at 0.5 wt.% of IL as a catalyst (which has been used to improve the dissolution of lignocellulosic biomass in IL by breaking bonds within lignin [24]) led to increased oil yield (4.8 %) and α-santalol concentration over oil bath heating alone (3.9 %, Table 6.1 Entry 4 vs. 1). The combination of both microwave-assisted pretreatment and addition of the POM catalyst led to even higher extraction yields of 5.9 % (Table 6.1 Entry 5).

To further enhance the extraction yields, sandalwood samples were swelled in PEG-300 which has been reported to absorb into the walls of wood cells swelling them for easier penetration of liquids [25]. In a pretreatment step, 1 g of sandalwood was soaked in 5 g of PEG-300 for 24 h prior to being added (with the PEG) to 20 g of the IL and processed as noted above. In each case, higher yields of sandalwood oil were obtained (7.0–7.5 %; Table 6.1 Entries 6–8). Here again, the highest yield was obtained using the combination of microwave irradiation and oil bath heating (Table 6.1 Entry 8). However, despite the benefit of the higher yields when pretreating with PEG-300, the oil extracts were contaminated with PEG because of its miscibility with both the oil and diethyl ether.

To improve yields without adding a swelling polymer, we also considered using a higher temperature above the glass transition temperature of lignin, guided by our previous work which demonstrated higher pulp yield with lower lignin content in much shorter times when using this approach [13]. The sandalwood/[C_2C_2im][OAc] mixture was cooked in an oil bath at 170 °C for only 5 min (Table 6.1 Entry 9) and yet provided one of the highest oil yields of 7.2 %. The reduced time (5 min vs. 6 h) and reduced chemical load (no POM or PEG-300) could make this an attractive option for scaling up this process.

Recovery of solubilized biopolymers After recovery of the sandalwood oil, the remaining wood/IL solution (Table 6.1 Entry 1) was subjected to filtration for removal of the undissolved wood residue. The biopolymers dissolved in the IL were regenerated following procedures developed in our previous report [15]. Briefly, the resulting homogeneous wood/IL solution was poured into 200 mL of a mixture of acetone/water (1:1, v/v) to regenerate carbohydrate-rich material (CRM), which was then separated by centrifugation. The supernatant was transferred to another beaker for lignin recovery. The precipitated CRM was further washed with an acetone/water mixture twice more and then with DI water to ensure all of the lignin and IL were washed out before subjecting the material to vacuum filtration. The lignin was precipitated from the supernatant and combined wash solutions by allowing the acetone to evaporate while the material was stirred. The recovered lignin was

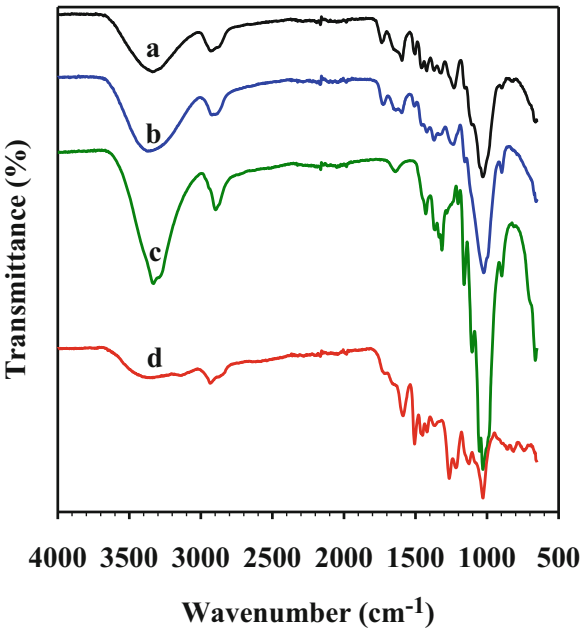


Fig. 6.6 Comparison of FTIR spectra of (*a*) ground sandalwood, (*b*) regenerated carbohydrate-rich material, (*c*) microcrystalline cellulose, and (*d*) Indulin AT

separated from the remaining aqueous IL solution by vacuum filtration. FTIR of the regenerated CRM (Fig. 6.6) and lignin (Fig. 6.7) indicate that the CRM contains some lignin, while the lignin is pure, in accordance with our previous studies [15, 24].

After the filtration of the coagulated lignin, water in the IL solution was removed using a rotovap, and the recovered IL was dried under high vacuum for 8 h. Comparison of the ^{1}H NMR spectrum of recycled IL with that of the fresh IL in Fig. 6.8 indicates no apparent difference between the recovered and fresh IL except that more water (the peak around 5.2 ppm) was present in the recovered IL.

6.4 Conclusions

In this work, we have demonstrated an efficient process for extraction of sandalwood oil by dissolving sandalwood in [C_2C_2im][OAc] followed by extraction with diethyl ether. Sandalwood oil yields ranged from 3.9 to 7.5 %, higher than the typical yields (2.5–6.2 %) of traditional techniques. Increasing the cooking time from 6 to 24 h had no effect on the extraction yield. Pretreatment of sandalwood with microwave irradiation before oil bath heating led to an increase in the oil yield, with twice the (Z)-α-santalol content in the oil. The presence of POM catalyst also led to increased

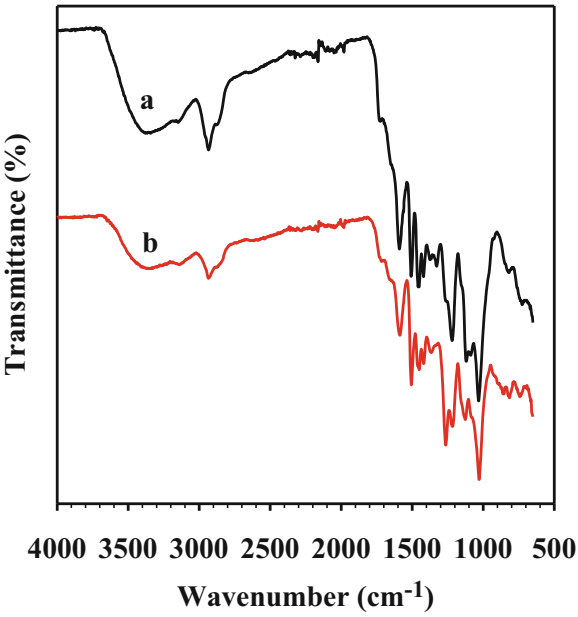


Fig. 6.7 Comparison of FTIR spectra of (*a*) lignin regenerated from sandalwood and (*b*) Indulin AT

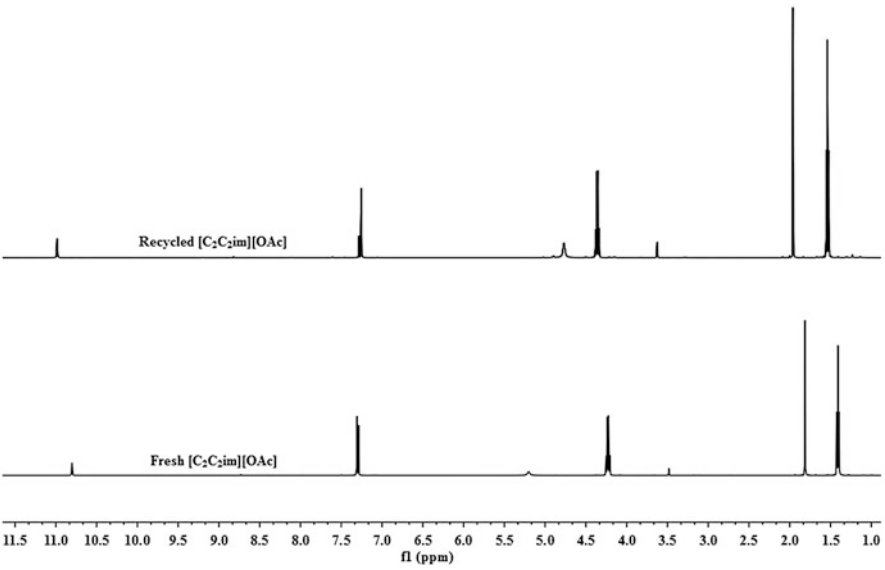


Fig. 6.8 Comparison of ^{1}H NMR spectra of recycled IL and fresh IL

oil yield and α-santalol concentration. Swelling the sandalwood in PEG-300 prior to oil bath or microwave heating also resulted in higher oil yield. The highest yield was obtained when PEG swelling, microwave irradiation pretreatment, and oil bath heating were combined to treat the sandalwood.

Dissolving the sandalwood in the IL above the glass transition temperature of lignin led to enhanced oil yield with reduced extraction time from 6 h to only 5 min. This rapid dissolution, even at higher temperature, might be an energy-saving process; however, a complete energy study will be needed to prove this.

After oil extraction, biopolymers, including CRM and lignin, could be recovered from the wood/IL solution. The IL extraction process thus might be integrated with separation of biopolymers such as carbohydrate-rich material and lignin. The utilization of all components of the sandalwood might help the economics of developing a commercial extraction process.

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Chapter 7
Leaching of Active Ingredients from Plants with Ionic Liquids

Anna K. Ressmann and Katharina Bica

Abstract Recently, there was a tremendous interest in the use of ionic liquids for cost-effective and environmentally friendly dissolution and processing of biomass as diverse as cellulose, chitin, and wood. There are several aspects of ionic liquids that are potentially advantageous for the leaching of active ingredient isolation: Ionic liquids are not only a suitable extraction media for valuable components from plant matter but do allow a better access to the active ingredient via dissolution of the biomass that cannot be obtained with traditional solvents. We report the benefits of ionic liquids for the extraction of valuable ingredients including important pharmaceutical intermediates and essential oils from plant materials and discuss different isolation strategies as well as the recovery of the ionic liquids.

Keywords Biorefinery • Natural products • Extraction • Fine chemicals • Essential oils • Lignocellulose • Pharmaceutically active ingredients

7.1 Introduction

Biomass feedstocks have become a unique and indispensable resource for various fields: Apart from the use for alternative energy production, e.g., bioethanol, biomass including pre-consumer waste can be used for the manufacturing of high-value fine chemicals [1–3]. Bioactive compounds obtained from biomass are of tremendous importance for the pharmaceutical industry, as they provide a diverse and unique source of active ingredients for drug manufacturing [4]. Current estimation of the pharmaceutical market indicate that between 25 and 50 % of drugs are derived from natural products, and the extraction of a drug or its precursor can be the bottleneck in the manufacturing process [5]. According to the worldwide sell in

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the early 2000, natural product-derived drugs are frequently found in top position, and 8 out of 29 small molecule drugs launched in the 2000s owe their origins to natural products [6, 7].

The typical commercial extraction process for pharmaceutical active ingredients from plant materials is based on the use of volatile organic compounds (VOCs) as extraction media, despite often fairly low overall efficiencies. After long periods of refluxing and separation of by-products, e.g., waxes, essential oils, and chlorophylls from the raw extract, the purification of active ingredients typically requires several additional crystallization stages. The large amounts of VOCs may often cause a threat to the environment and a risk of exposure to hazardous chemical compounds. Consequently, modern extraction media for the extraction of active ingredients from plant materials such as pressurized hot water or supercritical fluids have become popular as an alternative to conventional reflux methods [8–12]. However, only recently research started to focus on the use of ionic liquids as leaching media for pharmaceutically valuable compounds from plant components, as they provide benign and efficient solvents for the isolation of active ingredients.

7.2 Biomass Dissolution with Ionic Liquids

Biomass dissolution in molten salts dates back to 1934 when Graenacher partially dissolved cellulose using the molten salt *N*-ethylpyridinium chloride [13]. In the early 1980s, Seddon et al. found that chloroaluminate ionic liquids could dissolve kerogen, a fossilized organic material present in sedimentary rocks which had been insoluble in all known solvents except for hydrofluoric acid [14]. In 2002 Rogers et al. reported a groundbreaking paper on the dissolution of cellulose in the imidazolium-based ionic liquids 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl) in high concentrations without derivatization [15]. Cellulose hardly dissolves in conventional solvents due to its strong hydrogen bonding between the polymers, and current dissolution processes require expensive reagents, e.g., *N*-methylmorpholine-*N*-oxide monohydrate (NMMO). Novel ionic liquid-based technologies for improved processing of cellulose that take advantage of the direct dissolution of biomass are therefore of considerable interest [16, 17]. Since Rogers's pioneering publication in 2002, a number of papers have been published on the dissolution of cellulose in ILs, on the use of ILs as reaction medium for the functionalization of cellulose, or on the preparation of cellulose fibers, films, beads, and cellulose composite materials [16–18]. Cations based on methylimidazolium and methylpyridinium including allyl, ethyl, or butyl side chains are all suitable for the dissolution of biomass, and the best dissolution results were obtained with the C_4 side chain. Considering the anions, chloride, acetate, and formate are all anions with good prospects, the solubility of cellulose was found to increase in following order: $OAc^- < Cl^- < Br^-$ [16]. The dissolution process of cellulose has even been commercialized by BASF, and 5 wt.% solutions of cellulose in 1-ethyl-3-methylimidazolium acetate ([C_2mim]OAc) are commercially available through Sigma-Aldrich under the trade name CELLIONIC™.

Several tentative mechanisms for the dissolution process of cellulose in ILs have been proposed: NMR experiments showed that the high chloride concentration and activity in [C_4mim]Cl break the extensive hydrogen-bonding network, thus allowing the dissolution of higher concentrations of cellulose [15]. However, open questions on the dissolution process remain, and a detailed mechanism at the molecular level is an open research area.

The processing of biomass with ionic liquids is not limited to the dissolution of cellulose, and biopolymers as diverse as wood [19–23], lignin, chitin [24–27], silk fibroin [28], wool keratin [29], starch and zein protein [30], cotton and bamboo [31], chitosan [24], and cork biopolymers [32] have been reported to be at least partially soluble in various ionic liquids. While biomass dissolution for the purpose of (ligno-)cellulose processing or biofuel production has attracted tremendous interest, less attention has been paid to active ingredient isolation using ionic liquids. However, the number of papers and patents on the extraction and isolation of valuable ingredients is rapidly increasing, thereby clearly demonstrating the potential of ionic liquids in this area.

7.3 Extraction of Active Ingredients Using Ionic Liquids

Apart from the advantages in biomass processing or functionalization with ionic liquids, it was only recently that research in this area started. Yet, there are several aspects of ionic liquids that are potentially advantageous. Additionally to their unique solvent properties and potential environmental benefits compared to organic solvents, the ability of ILs to swell or dissolve biomass can lead to a better access to the valuable ingredient embedded in biopolymer matrices (Fig. 7.1) [12].

Pioneering work in this area was reported for the extraction of the anti-malaria drug artemisinin from plant material by alternative solvents including ILs [34–36]. To date, most examples for active ingredient leaching from biomass are performed on analytical scale, and HPLC analysis has been established as method of choice for the quantification of the valuable ingredient in the presence of ionic liquids. Only 18 % of all papers deal with the actual isolation of the active ionic liquids, thus indicating that the separation of ionic liquid, active ingredient, and biomass, as well as the recovery and possible recycling of the ionic liquid, is the real challenge (Fig. 7.2, left).

Although ionic liquids can improve extraction yield and efficiency compared to volatile organic compounds, biomass dissolution often requires long reaction times at elevated temperature that are always associated with high energy consumption. Consequently, different extraction technologies apart from conventional solvent extraction have evolved (Fig. 7.2, right). Considering the ionic nature of ionic liquids that makes them susceptible to interaction with electromagnetic fields, it is obvious that the application of microwave energy might be a highly useful tool not only for synthesis in or of ionic liquids but also for the dissolution of biomass and for the extraction of valuable ingredients from plant materials [37]. Many

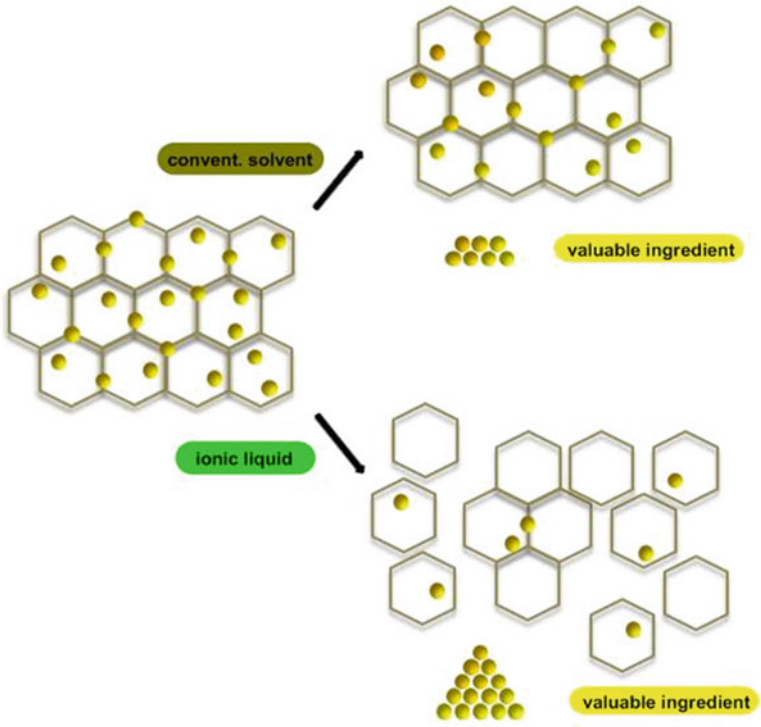


Fig. 7.1 Ionic liquid strategy for the leaching of valuable ingredients from plant matter (Reproduced from Ref. [33] by permission of The Royal Society of Chemistry)

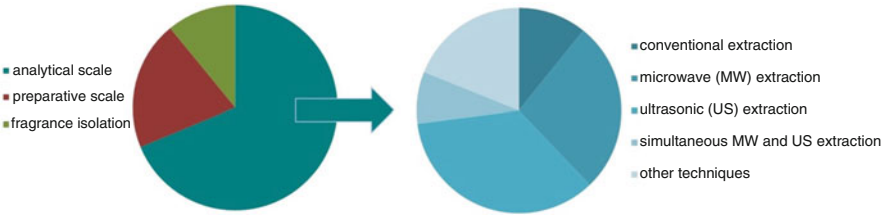


Fig. 7.2 *Left*: overview of active ingredient isolation from biomass using ionic liquids. *Right*: methods used on analytical scale in details

examples successfully demonstrated the advantageous application of microwave irradiation (MW) for the extraction of active ingredients resulting in shorter reaction times and higher efficiency. Apart from the use of microwave energy, ultrasound (US) can be applied for the extraction of active ingredients. US can break plant tissue, and the solvent can therefore penetrate through plant tissue. It has already been demonstrated that US is a suitable technique for the extraction of organic compounds from solid matrices [38–42].

7.3.1 Extraction with Pure Ionic Liquids

In the past years, HPLC-based strategies for the extraction and quantification of several active pharmaceutically ingredients with ionic liquids have been reported. Typically, a sample of ground or powdered biomass is completely or partially dissolved in the ionic liquid and stirred for a certain time at elevated temperature. After dilution with a cosolvent – typically methanol, ethanol, or H_2O – biopolymers precipitate and can be separated. The remaining solution containing both ionic liquid and the active ingredient is further analyzed to quantify the active ingredient.

Table 7.1 provides an overview of the experiments performed using pure ionic liquids without additional cosolvents. In a benchmark contribution in 2006, the British company Bioniqs Ltd. extracted the important antimalarial drug artemisinin from *Artemisia annua* and compared several alternative isolation techniques including ionic liquids, supercritical carbon dioxide, VOCs, and fluorinated solvents for the extraction. Although artemisinin is reasonably soluble in organic solvents, its

Table 7.1 Extraction of valuable ingredients using pure ionic liquids

Entry	Active ingredient	Biomass	Ionic liquid[a]	Conditions[b]	Reference
1	Artemisinin	*Artemisia annua*	[DMEA]oct, $[BMOEA]N(Tf)_2$	Conv., 30 min	Lapkin [35]
2	Different alkaloids	Various biomass of plant or fungal origin	[BMOEA]Cl	Conv., r.t., 4 h, slr. 3:20	Walker [43]
3	Anthraquinone	*Rheum officinale*	$[C_n mim]Y$ $n = C_1 - C_{10}$. $Y = BF_4^-$, PF_6^-, OAc^-, $CF_3SO_3^-$	Conv.	Pei [44]
4	Paeonol	*Cynanchum paniculatum*	$[C_4 mim]Cl$	MW, 70 °C, 1 min, slr. 7.3:1	Jin [45, 46]
5	Shikonin, dimethylacryl-shikonin	*Arnebia euchroma* (Royle) Johnst.	$[C_6 mim]BF_4$	US, 20 °C, 5 min	Xiao [47]
6	Glabridin	*Glycyrrhiza glabra* L.	$[C_6 mim]N(Tf)_2$	US, 30 °C, 40 min, pH = 7	Li [48]

[a]Only the best performing ionic liquid is listed (key for abbreviations: dimethylethanolammonium octanoate ([DMEA]oct), bis(2-methoxyethyl)ammonium bis(trifluoromethylsulfonyl)imide ($[BMOEA]N(Tf)_2$, bis(2-methoxyethyl)ammonium chloride ([BMOEA]Cl), 1-alkyl-3-methylimidazolium-based ILs ($[C_n mim]Y$, with n being the number of carbon atoms in the alkyl chain and Y a generic anion), 1-butyl-3-methylimidazolium chloride ($[C_4 mim]Cl$), 1-hexyl-3-methylimidazolium tetrafluoroborate ($[C_6 mim]BF_4$), and 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($[C_6 mim]N(Tf)_2$)), aqueous solution = aq

[b]Solid/liquid ratio = slr. [g/mL]; *MW* microwave irradiation, *US* ultrasound

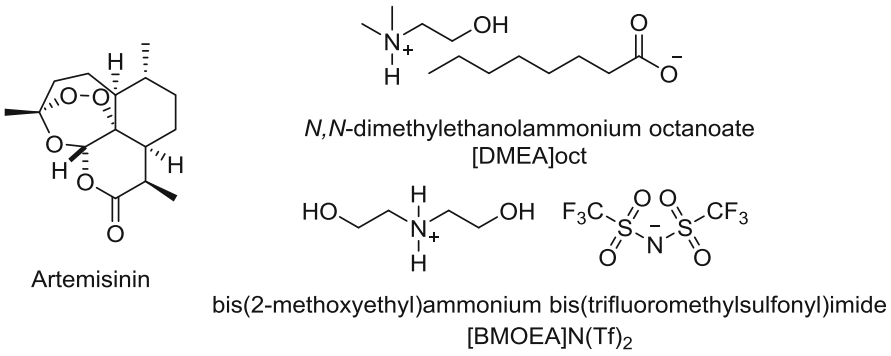


Fig. 7.3 Ionic liquids used for the extraction of artemisinin [35]

extraction with nonpolar solvents suffers from the co-extraction of essential oils, chlorophylls, and waxes that it must be separated afterward. It was shown that extraction with the ionic liquids *N*,*N*-dimethylethanolammonium octanoate and bis(2-methoxyethyl)ammonium bis(trifluoromethylsulfonyl)imide (Fig. 7.3) gave higher extraction efficiencies compared to the conventional solvents ethanol and hexane and thus proved that ionic liquids are a promising class for the extraction [35].

7.3.2 *Extraction of Active Ingredients Using Aqueous-Ionic Liquid Systems*

The concept of aqueous-ionic liquid systems for biomass dissolution has been only sparingly explored, although promising work on the cellulose pretreatment with aqueous solutions of ionic liquids has been reported by Welton et al. [49]. While ionic liquids often proved to be superior to conventional solvents in terms of extraction yield and purity, their usage is still associated with a major drawback: Ionic liquids are relatively expensive – at least compared to conventional organic solvents – which may restrict their large-scale application as a bulk solvent. As a compromise between economic and environmental criteria, the use of aqueous-ionic liquid systems as reaction media for synthesis and catalysis has recently attracted interest [50]. Investigations on the behavior of ionic liquids in the presence of water showed that certain ionic liquids can form aggregates in aqueous solution [51–54]. This is the case for long-chain 1-alkyl-3-methylimidazolium chloride salts [$C_n$mim]Cl with $n = 8$–18, where the apolar side chain stays in contact with other cations and micelles are formed.

The use of aqueous-ionic liquid solutions or micellar systems is particularly prominent in combination with microwave-assisted extraction. Apart from the reduction of ionic liquid required for extraction, the application of aqueous-ionic

liquid solution can reduce problems associated with the high viscosity of some ionic liquids that can hinder their application as bulk solvent in microwave-assisted extraction processes. Consequently, a surprisingly large number of leaching procedures of active ingredient from plant materials with aqueous-ionic liquids exist that are summarized in Table 7.2.

An elegant way was presented by Bi et al. (Table 7.2, entry 17) for the extraction of cryptotanshinone, tanshinone I, and tanshinone II A from *Salvia miltiorrhiza* Bunge. After extraction using aqueous solution of $[C_8mim]Cl$, HPF_6 was added to form 1-methyl-3-octylimidazolium hexafluorophosphate ($[C_8mim]PF_6$) and the active ingredients remained in the ionic liquid phase. A second small layer consisting of proteins was formed above the ionic liquid layer [55].

7.3.3 Other Extraction Strategies

Apart from conventional solvent extraction, or microwave-assisted heating and ultrasound treatment for biomass dissolution with ionic liquid, some other techniques have been reported for the leaching of valuable ingredients from biomass (Table 7.3).

7.3.3.1 Ionic Liquid-Based Aqueous Two-Phase Systems (ATPS)

Aqueous two-phase systems (ATPS) are typically generated by mixing aqueous solutions of two structurally different polymers or by mixing one polymer with certain salts at high concentration. ATPS are often considered as environmentally friendly separation systems where large amounts of organic solvents for purification, extraction, and enrichment are avoided and provide an interesting strategy for active ingredient isolation from plant materials.

Hydrophilic ionic liquids can form aqueous two-phase systems when contacting with concentrated solutions of water-structuring salts [85]. In 2005, Li et al. used a $([C_4mim]Cl)/K_2HPO_4$ system for the extraction of opium alkaloids from *Pericarpium papaveris*, a traditional Chinese medicine. After extraction of codeine and papaverine with aqueous $[C_4mim]Cl$ solution, K_2HPO_4 was added as it led to effective phase separation and to the appropriate that allowed determination of the opium alkaloids. With higher temperatures, the concentration of $[C_4mim]Cl$ in top phase decreased without reducing the extraction efficiencies, thus allowing a wide temperature range for the extraction of codeine and papaverine. The extraction yields were compared with those from liquid-liquid extraction (LLE) showing similar extraction yields and shorter extraction times without use of nonvolatile solvents [78].

ATPS were also applied by Lin et al. in 2012 for the microwave-assisted extraction of the blood pressure lowering and anti-inflammatory hyperin and isoquercitrin from *Apocynum venetum* [86, 87]. The system $[C_4mim][BF_4]/NaH_2PO_4$ was chosen

Table 7.2 Aqueous ionic liquid solution for the extraction of active ingredients

Entry	Active ingredient	Biomass	Ionic liquid[a]	Extraction parameters[b]	Reference
1	*Trans*-resveratrol	*Rhizma Polygoni* Cuspidati	Aq. $[C_4mim]Cl$	MW, 60 °C, 10 min., slr. 1:20	Du [56]
2	Polyphenolic alkaloids	*Nelumbo nucifera* Gaertn.	Aq. $[C_4mim]BF_4$ and $[C_6mim]BF_4$	MW 0.5 M, 90 s, slr. 1:10	Lu [57]
3	Polyphenols	Psidium guajava leaves, Smilax china tubers	Aq. $[C_4mim]Br$	MW; 60–70 °C, 10 min, slr. 1:20	Du [58]
4	Rutin	*S. chinensis*, *Flos Sophorae*	Aq. $[C_4mim]Br$ and $[C_4mim]OTs$	MW, 2.5 M, 70 °C, 12 min, slr. 1:25 for *S. chinensis* and 1.5 M, 60 °C, 8 min, slr. 1:35 for *Flos Sophorae*	Zeng [59]
5	3 alkaloids: *N*-nornuciferine, *O*-nornuciferine, and nuciferine	Lotus leaf *Nelumbo nucifera* Gaertn.	Aq. $[C_6mim]Br$	MW; 1.0 M, 280 W, 2 min, slr. 1:30	Ma [60]
6	Dehydrocavidine	*Corydalis saxicola*	Aq. $[C_6mim]Br$	MW; 70 °C, 10 min, slr. 20:1	Du [61]
7	Myricetin, quercetin	Myrica rubra leaves	Aq. $[C_4mim]HSO_4$	Hydrolysis via MW, 2.0 mol/L $[C_4mim][HSO_4]$ slr. 30:1 70 °C, 10 min	Du [62]
8	Camptothecin, 10-hydroxycamptothecin	*Camptotheca acuminata*	Aq. $[C_6mim]Br$	MW; 0.8–1.2 M, 8–12 min, slr. 1:8–1:12	Wang [63]
9	Podophyllotoxin	Chinese herbal medicine	Aq. $[C_4mim]BF_4$, $[C_{10}mim]BF_4$ (*D. versipellis*/*S. hexandrum*); $[amim]BF_4$ (D. sinensis)	MW; for *D. versipellis*/*S. hexandrum*: c = 0.8 g/mL, 60 °C, 10 min, slr. 1:100. For *D. sinensis*: c = 0.6 g/mL, 50 °C, 15 min, slr. 1:100	Yuan [64]
10	Glaucine	*Glaucium flavum*	Aq. $[C_4mim]$ acesulfamate	Conv., 1 M, 80 °C, 1 h, slr. 1:40	Bogdanov [65]
11	Piperin	White pepper	Aq. $[C_4mim]BF_4$	US; 2 M, 30 min, slr. 1:15	Cao [66]
12	Tanshinones	*Salvia miltiorrhiza* Bunge	Aq. $[C_{14}mim]Br$	US; 50 mM, r.t., 30 min	Wu [67]

(continued)

Table 7.2 (continued)

Entry	Active ingredient	Biomass	Ionic liquid[a]	Extraction parameters[b]	Reference
13	Fangchinoline and tetrandrine	*Stephaniae tetrandrae*	Aq. solutions of $[C_4mim]BF_4$	US; 150 W, pH = 9.8	Zhang [68]
14	Aesculin and aesculetin	*Cortex fraxini*	Aq. $[C_4mim]Br$	US; 0.5–1 M, 250 W, 30–50 min, slr 2:3,	Yang [69]
15	Three terpenoid indole alkaloids vindoline, catharanthine, and vinblastine	*Catharanthus roseus*	Aq. [amim]Br	US; 0.25–0.75 M, 250 W, 30 min, slr. 1:10,	Yang [70]
16	Biphenyl cyclooctene lignans	*Schisandra chinensis* Baill	Aq. $[C_{12}mim]Br$	US, 0.8 M, 150–250 W, 30 min, slr. 1:12	Ma [71]
17	Cryptotanshinone, tanshinone I, and tanshinone II A	*Salvia miltiorrhiza* Bunge	Aq. $[C_8mim]PF_6$ /in situ ion exchange to $[C_8mim]PF_6$	US; 0.5 M, 105 W, 80 min, slr. 1:40, 20 μL/mL HPF_6	Bi [55]
18	Phenolic compounds	*Laminaria japonica* Aresch	Aq. $[C_4mim]BF_4$	US; 0.5 M, 200 W, 60 min, pH = 1.25	Han [72]
19	Carnosic acid, rosmarinic acid	*Rosmarinus officinalis*	Aq. $[C_4mim]BF_4$	US; 1 M, 150–250 W, 30 min, slr. 1:20	Zu [73]
20	Different phenons	*Cynanchum bungei* Decne	Aq. $[C_6mim]BF_4$	US; 175 W, 25 °C, 50 min, slr. 1:35	Sun [74]
21	Anthraquinone	Rhubarb	Aq. solutions $[C_4mim]Br$	US/MWAE; 2 M, 500 W MW, 2 min, slr.1:15	Lu [75]
22	Phenolic compounds	*Arctium lappa* L., burdock leaves	Aq. solutions $[C_4mim]Br$	US/MWAE; 1.5 M, 50 W US, 400 W MW, 30 s, slr. 1:20,	Lou [76]
23	Tannins	*Galla chinensis*	Aq. $[C_4mim]Br$	US/MWAE; 2.5 M, 400 W MW, 1 min, slr. 1:15	Lu [77]

[a]Only the best performing ionic liquid is listed (key for abbreviations: 1-butyl-3-methylimidazolium chloride ($[C_4mim]Cl$), 1-alkyl-3-methylimidazolium tetrafluoroborate ($[C_nmin]BF_4$), 1-alkyl-3-methylimidazolium bromide ($[C_nmim]Br$), 1-butyl-3-methylimidazolium tosylate ($[C_4mim]OTs$), 1-butyl-3-methylimidazolium hydrogensulfate ($[C_4mim]HSO_4$), 1-allyl-3-methylimidazolium tetrafluoroborate ($[amim]BF_4$), 1-butyl-3-methylimidazolium acesulfamate ($[C_4mim]$acesulfamate), 1-methyl-3-octylimidazolium hexafluorophosphate ($[C_8mim]PF_6$)), aqueous solution = aq

[b]Solid/liquid ratio = slr. [g/mL]; *MW* microwave irradiation, *US* ultrasound, *conv*. convective heating, *MWAE* microwave-assisted extraction

Table 7.3 Other strategies for ionic liquid-assisted extraction of active ingredients

Entry	Active ingredient	Biomass	Ionic liquid/technique	Reference
1	Opium alkaloids	*Pericarpium papaveris*	$[C_4mim]Cl$/ATPS	Li [78]
2	Hyperin, isoquercitrin	*Apocynum venetum*	$[C_4mim]BF_4$/ATPS	Lin [79]
3	Rutin and quercitrin	*Flos sophorae Immaturus*, *Crataegus pinnatifida* Bunge, *Hypericum japonicum* Thunb., and *Folium Mori*	$[C_4mim]Cl$/IL-PLE	Wu [80]
4	Anthraquinone derivatives	*Radix et Rhizoma Rhei*	$[C_6mim]PF_6$/DLLME	Zhang [81]
5	Liquiritin, glycyrrhizic acid	Licorice	Imidazolium-based IL/SPE	Tian [82]
6	Different tanshinones	*Salvia miltiorrhiza* Bunge	Imprinted functionalized IL-modified silica	Tian [83]
7	Different tanshinones	*Salvia miltiorrhiza* Bunge	IL-modified porous polymer	Tian [84]

and compared to conventional ATPS technology. Initially, the extraction efficiency of aqueous solutions of $[C_4mim]BF_4$ and $[C_8mim]BF_4$ was investigated, indicating a strong influence on the concentration of the aqueous solution as well as of the temperature. Comparison with water, methanol, and ethanol-water mixtures showed that aqueous-ionic liquids solutions gave higher extraction yields. After microwave-assisted extraction of the herb with aqueous-ionic liquid solution for 10 min at 30 °C, the extract was centrifuged and the supernatant liquid separated. The preconcentration of hyperin and isoquercitrin from extract in ATPS was investigated using $[C_4mim]BF_4$ and NaH_2PO_4. While adding more ionic liquid increased the extraction yield, it also decreased the preconcentration of the active ingredients in the upper phase. The optimal concentration was 0.2 g ml^{-1} ILs aqueous solution with preconcentration efficiencies of 66.4 % for hyperin in 65.7 % for isoquercitrin [79].

7.3.3.2 Ionic Liquid-Based Pressurized Liquid Extraction (IL-PLE)

The active components rutin and quercetin were extracted from *Flos sophorae Immaturus*, *Crataegus pinnatifida* Bunge, *Hypericum japonicum* Thunb., and *Folium Mori* using ionic liquid-based pressurized liquid extraction. Dried sample, diatomaceous earth as supporting material, and 1-alkyl-3-methylimidazolium-based ionic liquid-aqueous solution were heated to 120 °C and pressurized at 1500 psi for 5 min. After dilution of the obtained extract with water, the solution was filtered and an aliquot was analyzed via HPLC equipped with chemiluminescence detection. Compared with conventional solvent extraction or with ultrasound-

assisted strategies, this technology using [C_4mim]Cl aqueous solutions achieved the highest extraction efficiency in the shortest time and could also outperform conventional solvents such water and methanol [80].

7.3.3.3 Solid-Phase Extraction (SPE) and Dispersive Liquid-Liquid Extraction (DLLE)

Tian et al. used solid-phase extraction (SPE) for the extraction of liquiritin and glycyrrhizic acid from licorice with an ionic liquid-based silica sorbent prepared from chloropropyl silica and 2-ethyl-4-methylimidazol. After extracting licorice with methanol, the extracts were loaded onto the SPE cartridge consisting of the ionic liquid-absorbed silica particles, successively washed and eluted for HPLC analysis. Comparison with conventional C18 sorbent showed that the ionic liquid-modified material exhibited higher selectivity for the two active ingredients.

In a related paper, ionic liquid-modified silica materials were developed for the extraction of different tanshinones from the traditional medicinal herb *Salvia miltiorrhiza* Bunge [83]. Molecular imprinted ionic liquid-modified silica was prepared with 9,10-phenantrenequinone as imprinting template and used for the separation of cryptotanshinone, tanshinone I, and tanshinone II A in the herb extract with high selectivity of the three compounds.

Later on, this group also used ionic liquid-modified porous polymers for the extraction of tanshinones from the *Salvia miltiorrhiza* Bunge [84]. Different side-chain functionalized imidazolium-based ionic liquids were used for the preparation of ionic liquid-modified polymers that were again imprinted with 9,10-phenantrenequinone as template. The obtained polymers were then applied as sorbents for tanshinones from a methanol herb extract. It was shown that ionic liquid-modified molecular imprinted polymers provide good absorbents for the tanshinones, and the sorbent with carboxylic acid functionalities in the side chain showed the highest selectivity for the target compounds.

Dispersive liquid-liquid microextraction for active ingredient isolation was applied by Rezaee et al. [88] and is based on a ternary component solvent system which consists of disperser solvent, extraction solvent, and aqueous sample containing an analyst. *Radix et Rhizoma Rhei* consist of anthraquinone derivatives emodin, chrysophanol, rhein, aloe-emodin, physcion, and their glucosides which are regarded as the major active compounds with antifungal [89], antiviral [90], antioxidant [91], anticancer [92], and antimutagenic [93, 94] activities. Hydrophobic ionic liquids, e.g., [C_6mim]PF_6, were used to replace conventional organic solvents as extraction solvent, and the active ingredients were transferred from aqueous solution to the ionic liquid phase by assistance of temperature [81].

Molecular imprinted anion-functionalized poly(ionic liquids) were also used for the separation and quantification of flavonoids myricetin, quercitrin, and amentoflavone with antihypertensive, anti-inflammatory, and antiviral activities from *Chamaecyparis obtusa*. The poly(ionic liquid)-based sorbents were functionalized with different anions, e.g., BF_4^-, PF_6^-, $N(Tf)_2^-$, lactate, or

sulfonate, via anion metathesis and applied as sorbent for multiphase dispersive extraction (MPDE). Plant powder and molecular imprinted anion-functionalized poly(ionic liquids) were placed in an empty cartridge, rinsed and eluted to finally analyze the content of flavonoids in *C. obtusa*. In a similar manner, Bi et al. could also apply hybrid poly(ionic liquid)-bonded silica in combination with an ionic liquid solution for MPDE for extraction, separation, and quantification of the flavonoids myricetine and amentoflavone from *Chamaecyparis obtuse*.

7.4 Isolation, Scale-Up, and Recycling Strategies

While many ionic liquids can readily dissolve biomass and are thus able to efficiently extract active ingredients, the previous section focused on the extraction of different active ingredients using ionic liquids on an analytical scale. The scaled isolation of the valuable ingredient remains challenging and fewer examples exist in literature. The scale-up and isolation of active ingredients face the problem of separating the ionic liquid from the bioactive component, but also the challenge of recovery and recycling of the ionic liquid that might be mandatory for a future application on industrial scale. Different strategies for the separation of the active ingredient and recovery of the ionic liquid have been developed that typically rely on extraction or precipitation of the active ingredient with cosolvents. Other technologies include the use of ion exchange resins, macroporous resins, or silica-confined ionic liquids for the adsorption and separation of the active ingredient. The ionic liquid is typically recovered as solution in water or in water/ethanol mixtures and has to be isolated via evaporation of the volatile cosolvents (Fig. 7.4) (Table 7.4).

7.4.1 Crystallization/Precipitation of the Active Ingredient

Already in 2008, Bioniqs Ltd. developed an isolation strategy for artemisinin from *Artemisia annua*. An approximate 10 wt.% solution of choline acetate/biomass was mixed at room temperature. The extraction efficiency was 71 % of artemisinin per pass, which can be precipitated by the addition of water. Furthermore, artemisinin can be isolated from this precipitate in 97 % which means an overall yield of 69 %. By the removal of water, the solvent can be recycled. The conventional isolation is performed using hexane at reflux conditions, which suffers from many coextractions of impurities. In comparison to the conventional extraction with hexane, the ionic liquid process represents a safer, higher-yielding process with a fully biodegradable ionic liquid [36].

Betulin is a naturally occurring triterpene alcohol with a lupane skeleton found in birch bark, but also in roots or leaves of some ash trees [105, 106]. Like many members of the lupane family, betulin exhibits versatile pharmaceutical

Table 7.4 Isolation strategies of active ingredients using ionic liquids

Entry	Active ingredient	Biomass	Ionic liquid[a]	Extraction conditions	Isolation strategy	Reference
1	Artemisinin	*Artemisia annua*	Choline acetate	Conv.; r.t. 30 min	Prec.	Bioniqs Ltd. [36]
2	Betulin	Birch bark	$[C_2mim]OAc$	MW; 15 min, 100 °C	Prec.	Ressmann [95]
3	Artemisinin	*Artemisia annua*	Aq. $[C_2mim]X$, =Br, Cl, I	US; 20–60 °C, 5–60 min 1slr. 1:5–1:70	Extr.	Zhao [96]
4	Shikimic acid derivatives	*Illicium verum*, star anise	Brønsted acidic ILs; $[HSO_3C_4mim]HSO_4$	Conv.; 80 °C, 24 h, MW; 30 min, 100 °C	Extr.	Ressmann [97]
5	Various lactones	*Ligusticum chuanxiong* Hort.	Protic ILs, DMCEAP, DMHEEAP	MW; 300 W, 160 °C, 10 min	Extr.	Yansheng [98]
6	Caffeine	Guaraná seeds	Aq. $[C_4mim]Cl$	Conv.; 2.34 M, 70 °C, 30 min	Extr.	Claudio [99]
7	Piperine	Black pepper	Aq. solution of biodegradable IL, $[C_nmim]Cl$, n = 10,12,14	Conv.; r.t., 3 h	Extr.	Ressmann [100]
8	Shikimic acid	*Ginkgo biloba* leaves	$[C_4mim]Cl$	Conv.; 100–150 °C, 1 h	Anion exchange resin	Usuki [101]
9	Shikimic acid	*Illicium verum*, star anise	$[C_2mim]OAc$	MW; 15 min, 100 °C	Anion exchange resin	Zirbs [33]
10	Tannins	*Galla chinensis*	$[C_4mim]Br$		Adsorption	Lu [102]
11	Oxymatrine, matrine	*Sophora flavescens* Ait	Silica-confined ILs		Adsorption	Bi [103]
12	Tannins	*Acacia catechu*, *Terminalia chebula*	DIMCARB	Conv.; r.t. 16 h	Distillation of IL	Chowdhury [104]

[a]Only the best performing ionic liquid is listed (key for abbreviations: 1-ethyl-3-methylimidazolium acetate ($[C_2mim][OAc]$, 1-alkyl-3-methylimidazolium halide ($[C_nmim]X$), 1-methyl-3-(4-sulfobutyl)imidazolium hydrogensulfate ($[HSO_3C_4mim]HSO_4$), *N*,*N*-dimethyl(cyanoethyl)ammonium propionate (DMCEAP), *N*,*N*-dimethyl-*N*-(2-hydroxyethoxyethyl)ammonium propionate (DMHEEAP), *N*,*N*-dimethylimidazolium *N*′,*N*′-dimethylcarbamate (DIMCARB)), *aq* aqueous solution, *conv.* convective heating, *MW* microwave irradiation, *US* ultrasounds, *prec.* precipitation, *extr.* extraction, *r.t.* room temperature

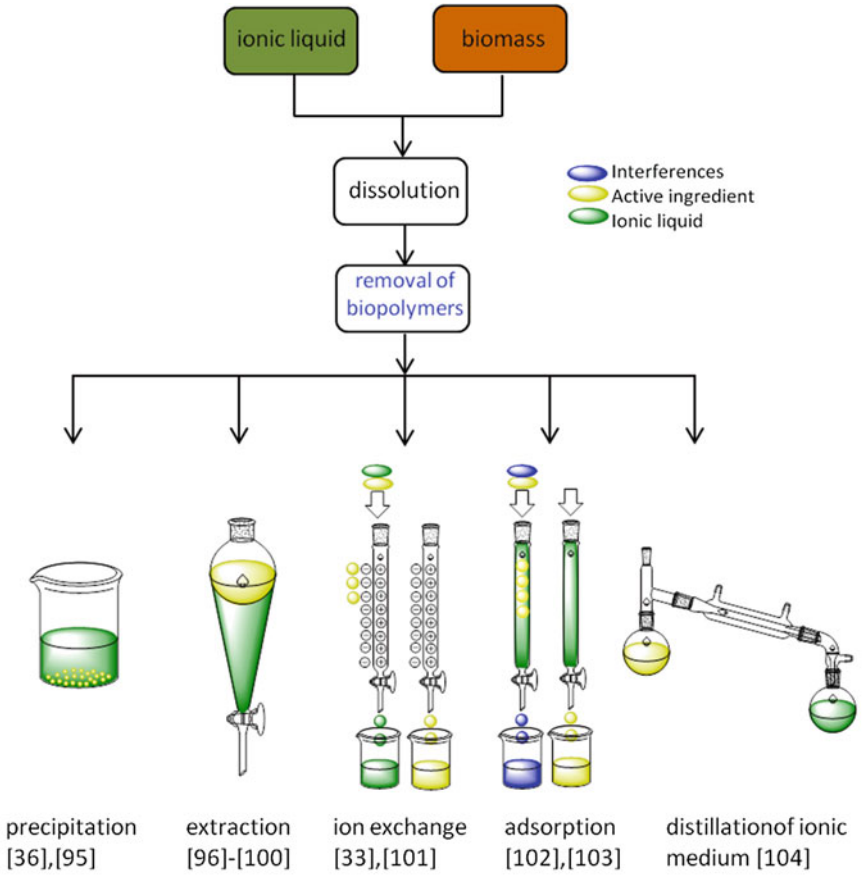


Fig. 7.4 Different isolation strategies for active ingredients after biomass dissolution in ionic liquids

activity, including antitumor, anti-HIV, antiviral, antibacterial, anti-inflammatory, and antimalarial properties [107, 108]. In the current industrial isolation processes, betulin is extracted with high-boiling hydrocarbon solvents, chlorinated solvents, or with water azeotropes of alcohols [109–112]. This is not only a rather time-consuming process with a limited yield of 10–20 % but suffers from co-extraction of many impurities thus requiring several tedious purification steps to obtain betulin in pharmaceutical purity.

Comparison of organic solvents and ionic liquids for the extraction of the pharmaceutically active steroid betulin from birch bark showed significantly improved extraction yield for a range of ionic liquids. A simple and scalable isolation procedure allowed isolating betulin in excellent purities of up to 98 % and recovery of the ionic liquid. Based on the high purity and isolation yield, this strategy

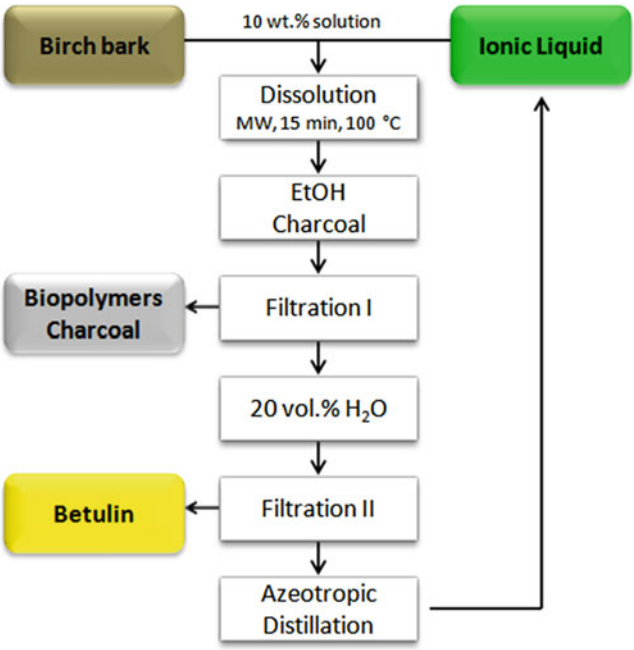


Fig. 7.5 Isolation procedure for the pharmaceutically active ingredient betulin (Reproduced from Ref. [113] by permission of The Royal Society of Chemistry)

provides a single-step, higher-yielding, and efficient strategy for the isolation of betulin (Fig. 7.5) [95].

7.4.2 Extraction of the Active Ingredient with a Cosolvent

In 2009, Zhao et al. invented a patent which describes the isolation of artemisinin from *Artemisia annua* using aqueous [C_2mim]X (X=Br, Cl, I) solutions and ultrasonic irradiation. The extract was further treated with organic solvents to obtain artemisinin and purified via column chromatography and recrystallization while the ionic liquid was recovered [96].

In the current manufacturing process, the synthesis of Tamiflu™ involves the formation of shikimic acid ethyl ester followed by a ketal intermediate that is further transferred into the final drug [114]. The initial step in the industrial process is typically done using stoichiometric amounts of toxic and corrosive thionyl chloride for the generation of anhydrous hydrochloric acid as catalyst. The toxicity of thionyl chloride and the formation of greenhouse gases after hydrolyzation do not only raise serious safety and environmental concerns, but require a more involved manufacturing process. The group of Bica et al. developed an ionic liquid-based

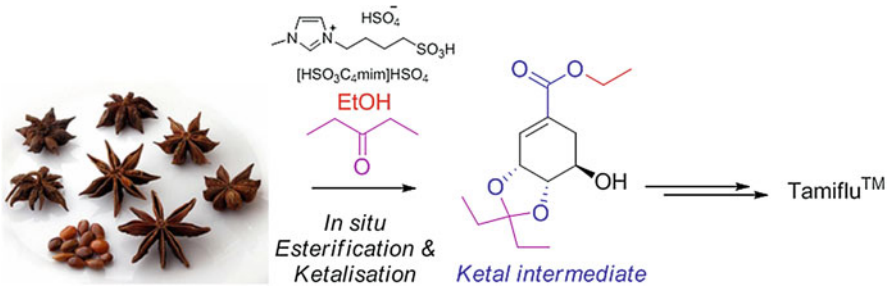
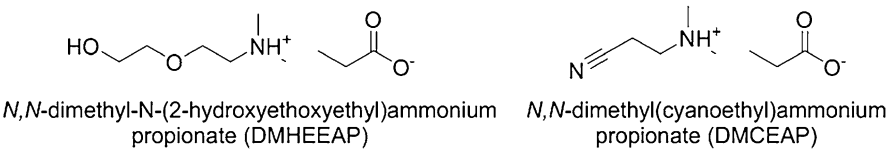


Fig. 7.6 In situ extraction and derivatization of shikimic acid from star anise powder (Reproduced from Ref. [97] by permission of The Royal Society of Chemistry)



N,N-dimethyl-N-(2-hydroxyethoxyethyl)ammonium propionate (DMHEEAP)

N,N-dimethyl(cyanoethyl)ammonium propionate (DMCEAP)

Fig. 7.7 Ionic liquids used for the extraction of *Ligusticum chuanxiong* Hort

strategy for the reactive dissolution of star anise seeds using different Brønsted acidic ionic liquids as solvent and reaction media toward the isolation of important pharmaceutical intermediates (Fig. 7.6) [97]. Based on Brønsted acidic ionic liquids, this procedure provides a single-step, higher-yielding, and environmentally benign strategy toward the synthesis of the anti-influenza drug Tamiflu™.

The lactones which are pharmaceutically active senkyunolide I, senkyunolide H, and *Z*-ligustilide have been extracted from *Ligusticum chuanxiong* Hort. using two protic ILs, *N*,*N*-dimethyl-*N*-(2-hydroxyethoxyethyl)ammonium propionate (DMHEEAP), and *N*,*N*-dimethyl(cyanoethyl)ammonium propionate (DMCEAP) by Yansheng and coworkers (Fig. 7.7). After microwave irradiation of the crude plant material with the ionic liquids for 1–5 min, the sample was diluted with methanol and the methanol phase filtered and analyzed via HPLC. The recovery of DMHEEAP was performed according to following procedure: The reaction mixture was diluted by methanol and filtered. Methanol was evaporated and the recovered IL reused. After the third cycle, the extraction yield decreased dramatically due to higher viscosity caused by co-extraction of contaminants and coproducts [98]. An additional back extraction of the ionic liquid with *n*-hexane could improve the concentration of senkyunolide I and senkyunolide H hardly decreased, but the concentration of *Z*-ligustilide still decreased by 39.7 %[98].

In 2013, Claudio et al. reported an enhanced and selective extraction of caffeine from guaraná seeds using aqueous solutions of ionic liquids based on imidazolium or pyridinium cations combined with the chloride, acetate, and tosylate anions. A response surface methodology allowed identifying optimal conditions for the extraction process such as the ionic liquid concentration, the contact time, the

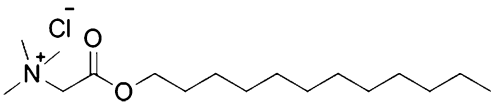


Fig. 7.8 Betaine-based biodegradable and surface-active ionic liquid

solid-liquid ratio, and the temperature. Outstanding extraction yields (up to 9 wt.% of caffeine per guaraná dry weight) were obtained at a moderate temperature and in a short-time, thus showing that aqueous solutions of ionic liquids are superior alternatives for the solid-liquid extraction of caffeine from biomass. The recyclability and reusability of the ionic liquids was realized via back extraction conventional solvents; however, the toxic organic solvent chloroform had to be used for a complete removal of caffeine of the ionic liquid-aqueous solution [99].

Ressmann et al. used ionic liquid-aqueous micellar solutions as isolation media for the pharmaceutically active ingredient piperine from black pepper [100]. Several surface-active ionic liquids including a biodegradable betaine derivative (Fig. 7.8) were used for the extraction of piperine, and a strong correlation between extraction yield and the critical micelle concentration of the respective ionic liquid was found.

A scaled strategy for the isolation of piperine based on back extraction of aqueous solutions with a small volume of environmentally benign *n*-butyl acetate was developed. This strategy allowed recovery and recycling of the aqueous-ionic liquid micellar solution for five runs without any loss in extraction efficiency.

The importance of the aqueous-ionic liquid solution compared to pure water was also visible from electron microscopy that was performed on the recovered biomass after extraction. Although micellar solution of 1-alkyl-3-methylimidazolium-based ionic liquids [$C_n$mim]Cl cannot completely dissolve biomass as it would be the case with neat ionic liquids, some changes in biomass morphology can be observed in electron microscopy that are not present when pure water was used as extraction media [100]. A similar effect was observed by Coutinho et al. reported an increase in the ratio of broken cells to intact cells of guaraná seed in the presence of ionic liquid-aqueous mixtures, although the biomass was not completely dissolved [99].

7.4.3 Separation of Active Ingredient and Ionic Liquid via Exchange Resins/Macroporous Resins

The importance of active ingredient isolation for the pharmaceutical industry is particularly true for the case of shikimic acid, the major starting material for the production of the neuraminidase inhibitor Tamiflu™ (oseltamivir phosphate) which is well known for the treatment and prevention of influenza [115, 116]. The production of Tamiflu™ is still dependent on the isolation of shikimic acid from Chinese star anise seeds, and the low isolation yield of 3–7 % was held responsible for the worldwide shortage in Tamiflu™ in 2005 [117–119].

The Tamiflu™ precursor shikimic acid was also extracted from *Ginkgo biloba* leaves with [C_4mim]Cl. Their HPLC analysis indicated that at 150 °C the IL yielded 2.5 times as much shikimic acid than methanol at 80 °C and that the IL performed better than H_2O and DMF. An ion exchange resin was used for the isolation of shikimic acid. An extract containing 7.1 mg of shikimic acid was charged to the resin column, washed with water to obtain the recovered IL (99 %). Washing with 25 % acetic acid released shikimic acid that could be isolated in 87 % yield.

In 2013, Zirbs et al. reported that the dissolution of star anise seeds from *Illicium verum* in imidazolium-based ionic liquids can lead to better access to the valuable ingredient embedded in the biopolymer and thus to a higher extraction yield. Different imidazolium-based ionic liquids were investigated, and the extraction yield of shikimic acid was correlated with their hydrogen-bonding properties via polarizable molecular dynamic simulations, indicating that the hydrogen bonding of the anion to shikimic acid is responsible for a good extraction performance. A scale-up strategy for the isolation of shikimic acid with the ionic liquid 1-ethyl-3-methylimidazolium [C_2mim]OAc was developed based on ion exchange resins, thus allowing to isolate shikimic acid in up to 10 wt.% yield with complete recovery of the ionic liquid [33].

Lu et al. presented an interesting strategy for extraction of *Galla chinensis* which contains the hydrolyzable tannins gallotannins using [C_4mim]Br solutions and macroporous resins for the removal of the ionic liquids [102]. After extraction of crude biomass with microwave- and ultrasound-assisted extraction with aqueous [C_4mim]Br solutions, macroporous resin adsorption technology was further employed to purify the tannins and remove the ionic liquid from crude extract. Initial adsorption and desorption experiments identified that XDA-6 resin was identified as best adsorbent, as it had higher separation efficiency than other tested resins. With XDA-6 resin adsorption, isotherms at different temperatures were obtained for tannins, showing a saturation plateau at tannins concentration of 24 mg mL^{-1} and 28 °C as ideal temperature. More parameters were adjusted to optimal conditions and optimum conditions were as follows: The ratio of column height to diameter bed was 1:8, the flow rate was 1 BV/h (bed volume per hour), and 85 % ethanol was used as eluent, while the elution volume was 2 BV. Under the optimized conditions, the adsorption and desorption rates of tannins in XDA-6 were 94.81 and 91.63 %, respectively. Furthermore, the result of ultra-performance liquid chromatography analysis showed that [C_4mim]Br could be removed from extract.

7.4.4 Silica-Confined Ionic Liquids

In 2012, Bi et al. extracted *Sophora flavescens* Ait. using silica-confined ionic liquids (SiILs) for the isolation of the active ingredients oxymatrine and matrine [103]. The evaluation of the SiILs was performed via measurement of the adsorbed active ingredient: SiIL was placed in a flask, standard solutions of the active

ingredients added, the mixture was shaken for 30 min, and the supernatant collected and filtered. The sample was analyzed via HPLC, and the amount of unadsorbed active ingredients was detected. With increasing alkyl chain length, the extraction yield decreased, and best results were obtained with a protic derivative. Different anions were tested with the best cation and Cl^- still gave the highest extraction yield compared to BF_4^-, PF_6^-, and $N(Tf)_2^-$ which might be related to its good water miscibility. Furthermore, conventional adsorbents such as C18 and $SilprNH_2$ were applied, but gave lower yield than the Cl^- SiIL.

The extraction of the roots was performed using 50 mL of water for 4 h. The extract was mixed with the SiIL to absorb the active ingredients. Finally, the separation of oxymatrine was achieved by washing the cartridges with 1 mL water for the removal of interferences. The active ingredient was then eluted using either methanol or acetonitrile or ethanol. The SiIL was regenerated after washing with triethylamine/methanol and drying at 60 °C and could be reused for 4 cycles with only a slight loss in performance.

7.4.5 Distillation of the Ionic Medium

The group of MacFarlane presented an elegant strategy for the extraction of biomass using the distillable ionic liquid, *N*,*N*-dimethylammonium *N*′*N*′-dimethylcarbamate (DIMCARB), to extract hydrolyzable tannin materials from plant sources such as catechu (*Acacia catechu*) and myrobalan (*Terminalia chebula*) [104]. Tannins are generally defined as water-soluble organic substances present in plant extracts that effect the transformation of animal hide into leather. Typically, vegetable tannins are phenol-rich compounds that show antitumor, anticarcinogenic, antimicrobial, and antiviral effects [120]. In the leather industry, tannins can replace the problematic "chrome tanning" process and therefore avoid the handling with Cr(VI), which is considered as highly toxic, mutagenic, and carcinogenic. Conventional extraction methods for tannins require harsh conditions and a high solvent/solid ratio resulting in poor extraction yields. DIMCARB is a distillable, protic ionic liquid and is formed by combining CO_2 and dimethylamine in an approximately 1:2 ratio. Figure 7.9 represents the dynamic equilibria in the DIMCARB system showing a two-step proton transfer for the formation of the dimethylammonium ion and the dimethylcarbamate ion. In contrast to conventional ionic liquids, the formation of DIMCARB is reversible, and distillation at 45 °C reforms CO_2 and dimethylamine.

A mixture of 5.0 g of either myrobalan nut or catechu was treated with 25.0 g of DIMCARB ionic liquid and stirred at room temperature for varying times (Fig. 7.10). After filtration of undissolved plant material and evaporation

Fig. 7.9 The distillable ionic medium DIMCARB

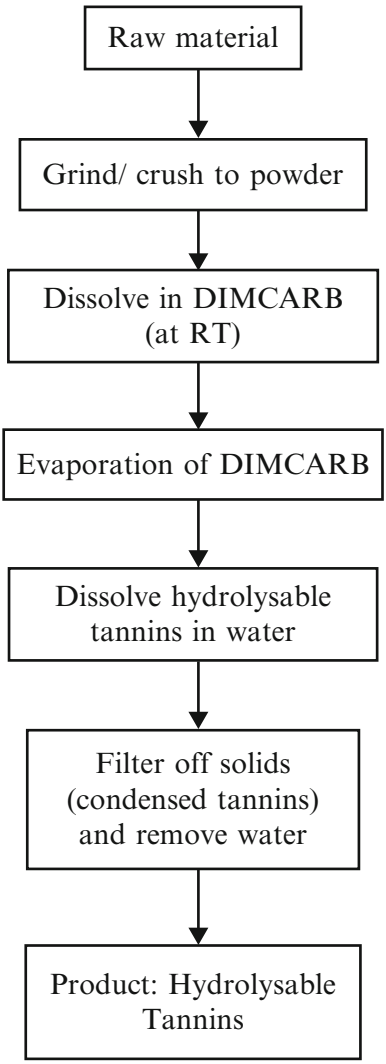


Fig. 7.10 Isolation procedure of tannins using DIMCARB (Reproduced from Ref. [104] by permission of The Royal Society of Chemistry)

of DIMCARB, water was added, and the aqueous solution was filtered to remove the so-called condensed tannins. The filtrate consisting of so-called water-soluble tannins could be directly used for the leather tanning process or evaporated to yield the pure hydrolysable tannins such as ellagic acid. In contrast to conventional solvents, ellagic acid was obtained in higher yields, and the products are more stable against bacterial molds as evidenced by microbial analysis. Furthermore, only a third of water was necessary compared to the conventional process [104].

7.5 Fragrance Isolation

Apart from active ingredients, plant matter may also consist of a variety of fragrances and essential oils. Valuable essential oils are typically a complex mixture of individual fragrance components obtained from plant material and are widely used in various domains of human activities including perfumery, cosmetics, nutrition, and pharmaceuticals [121]. According to the United Nation's COMTRADE database, global imports of essential oils stood at US$ 2 billion in 2005.

Essential oils are traditionally obtained by steam distillation, solvent extraction, or cold pressed from crude fragrance materials. Solvent extraction is always associated with the risk of handling large quantities of combustible and often toxic solvents, and the products suffer from contamination. Steam distillation is not only a highly energy-consuming process but can induce thermal degradation, hydrolysis, and water solubilization, thus often requiring expensive waste water redistillation for fragrance recovery [122].

The versatile features of ionic liquids do not only allow the dissolution of plant materials for efficient fragrance release but enable the direct and mild distillation directly from the IL media without excessive steam production, solvent contamination, or losses from water solubilization. Figure 7.11 represents the general isolation scheme for fragrances and essential oils (Table 7.5).

In 2008, Zhu et al. disclosed a method for extracting essential oil from leaves of *Diospyros kaki* and of pine needles using imidazolium-based hydrophilic ionic liquids, e.g., [C_4mim]OAc, [C_4mim]Cl, and [amim]Cl under microwave conditions. For the isolation and ionic liquid recovery, they either applied conventional steam distillation or ion exchange resins [124, 125].

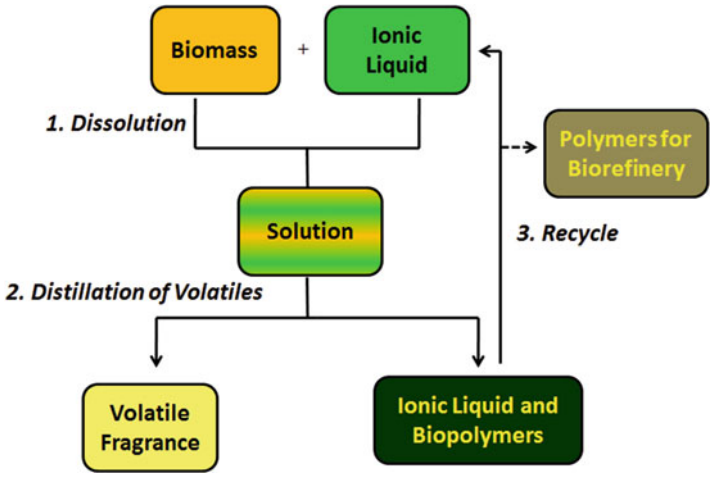


Fig. 7.11 General procedure for the isolation of fragrances and essential oils (Reproduced from Ref. [123] by permission of The Royal Society of Chemistry)

Table 7.5 Fragrance isolation using ionic liquids

Entry	Fragrance	Biomass	Ionic liquid	Reference
1	Pine needle oil	Pine needles	Hydrophilic methylimidazolium-based	Zhu [124]
2	Essential oils	Diospyros kaki	Hydrophilic methylimidazolium-based	Zhu [125]
3	Essential oils	*Illicium verum* Hook. f. and *Cuminum cyminum* L.	$[C_4mim]PF_6$	Zhai [126]
4	Orange essential oil	Orange peels	$[C_2mim]OAc$	Bica [123]
5	Biphenyl cyclooctene lignans	*Schisandra chinensis* Baill	Aqueous solution of $[C_{12}mim]Br$	Ma [127]
6	Carnosic acid, rosmarinic acid, and essential oil	*Rosmarinus officinalis*	Aqueous solution of $[C_8mimBr]$	Liu [128]
7	Essential oil	Dryopteris fragrans	$[C_2mim]OAc$	Jiao [129]

Zhai et al. extracted the bioactive essential oils from *Illicium verum* Hook. f. and *Cuminum cyminum* L. that are widely used for their flavors and pharmaceutical characters with the ionic liquid $[C_4mim]PF_6$ as microwave absorption media [126]. The distillate was concentrated continuously by a cooler outside the microwave oven, dried and analyzed via GC-MS. The ionic liquid-assisted microwave extraction process was compared to hydrodistillation (HD). The authors did not observe any obvious difference between main constituents in essential oils obtained by ionic liquid-assisted extraction or hydrodistillation; however, the extraction time was considerably shortened to 15 min only using microwave-assisted extraction with ionic liquids, whereas 180 min were required for complete extraction with conventional hydrodistillation.

Bica et al. presented the dissolution of orange peel in various ionic liquids and compared direct distillation and solvent extraction for the isolation of orange essential oil [123]. Only partial dissolution was observed for $[C_4mim]Cl$ and [amim]Cl after 24 h, whereas complete dissolution of orange peels was obtained using $[C_2mim]OAc$ after 3 h. The dissolved biomass was immediately subjected to vacuum resulting in a two-layer distillate consisting of limonene and water from the orange peel. Limonene was obtained in approx. 5 wt.% after phase separation in excellent purity, and no traces of the ionic liquid or its degradation products were found. As an alternative to direct distillation, liquid-liquid extraction was applied using ethyl acetate, but the isolated limonene suffered from low purity and yield. For recycling of the ionic liquid, $[C_2mim]OAc$ water was added and filtration of the coagulated biopolymers and evaporation of water allowed a simple recovery of the IL in spectroscopically pure form but dark in color. For further purification, the recovered ionic liquid was refluxed over charcoal and could be isolated in excellent purity at 90–95 %.

Ma et al. extracted essential oils as well as cyclooctene lignans which show antioxidant, antimicrobial, antitumor activities [130] from *Schisandra chinensis* Baill fruits using aqueous solutions of [$C_n$mim] ionic liquids under microwave irradiation [127]. Starting with a $[C_4mim]^+$ backbone, different anions were investigated. Since the bromide anion showed the highest extraction efficiency, the alkyl chain of [$C_n$mim] was varied ($n = 2$, 4, 6, 8, 10, 12). With increasing chain length, the extraction yield increased and [C_{12}mim]Br was therefore chosen for further investigations. Compared to conventional extraction strategies which required 180 min for complete extraction, the microwave-assisted strategy suing ionic liquids shortened the reaction time to 20 min. However, the authors found that a longer extraction time led to a decrease of lignans indicating that carbonization or isomerization of lignans took place.

Liu et al. simultaneously extracted carnosic acid, rosmarinic acid, and essential oil from *Rosmarinus officinalis* with aqueous solutions of ionic liquid using a combined microwave dissolution-hydrodistillation approach [128]. The essential oils containing in rosemary species are not only used in foodstuffs, perfumes, or cosmetic product, but exhibit biological activities such as antioxidant, antimicrobial, anti-inflammatory, antitumor, and chemopreventive activities [131]. Starting with the $[C_4mim]^+$ cation, the anions Br^- and NO_3^- showed the highest extraction yield for carnosic acid, whereas BF_4^- and Br^- were the most efficient anions for rosmarinic acid. For further studies, a 1 M [C_8mim]Br aqueous solution was chosen, and the optimization of parameters led to 15 min irradiation time at 700 W and a solid-liquid ratio of 1:12. The present method showed slightly higher extraction yield carnosic acid and rosmarinic acid than microwave-assisted extraction with ethanol and significantly higher extraction yields than conventional hydrodistillation and could reduce the reaction time to 20.

Dryopteris fragrans was extracted by Jiao et al. using MW irradiation and different 1-alkyl-3-methylimidazolium-based ionic liquids, since the essential oil has antioxidant potential in terms of the free radical scavenging and lipid peroxidation inhibitory activities [132]. After pretreating the plant material using 300 W irradiation power, the dark slurry was mixed with 100 ml water, and hydrodistillation was applied to isolate the essential oil. Recovery of the IL was successfully achieved by filtration of the ionic liquid-aqueous solution and successive azeotropic distillation of EtOH/H_2O. Different ILs were tested and the extraction of essential oil decreased in the order [C_2mim]OAc > [amim]Cl > [C_4mim]Cl > [C_4mim]Br > pure water. The recovered [C_2mim]OAc could be reused for five cycles; however, a loss of performance from 0.9 % essential oil after the first run to 0.5 % after the fifth cycle was observed.

7.6 Conclusion

The direct dissolution of biomass is one of the most attractive features of ionic liquids and makes them outstanding in many ways. While the immense potential of this process has been early recognized for areas such as lignocellulose processing,

the leaching of active ingredients from plant precursors did not receive as much attention.

However, a rapidly increasing number of papers clearly demonstrate that ionic liquids are not only suitable but often superior solvents for the extraction and isolation of active ingredients. Valuable ingredients from plant matter that include pharmaceutically active compounds, drug precursors, or essential oils and fragrances have been successfully extracted with ionic liquids. It was shown that even a partial dissolution of biopolymers can lead to a better access to the valuable ingredient resulting in fast and clean extraction process.

The extraction of active ingredients with ionic liquids or their aqueous solutions on analytical scale is particularly well established and offers novel opportunities, e.g., for quality control. In contrast, the scale-up of the process and the actual isolation of the active ingredient remain challenging: Fewer examples exist in literature describing the entire isolation process. Better strategies for the separation of the valuable ingredients, but also for ionic liquid recovery and recycling might have to be developed to allow the implementation on industrial scale.

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Chapter 8
Chiral Ionic Liquids in Separation Sciences

Maria Vasiloiu and Katharina Bica

Abstract Chiral ionic liquids (chiral ILs) have been recognized for years as an alternative strategy to carry out chiral transformation, especially in areas such as synthesis, catalysis, and separations. While many successful applications in asymmetric synthesis are known to date, the important field of chiral separations was only recently identified as novel playground for ionic liquids. In here, we discuss the role of chiral ionic liquids for the resolution of racemic compounds covering analytical strategies, e.g., chiral ILs as shift reagents or stationary phases, but also the use of chiral ILs for the preparative separation of racemic compounds including liquid-liquid extraction techniques.

Keywords Chirality • Diastereomeric interactions • Chiral recognition • NMR spectroscopy • Capillary electrophoresis • Enantiomer separations

8.1 Introduction

The structural variability in ionic liquids is a valuable tool for the design of functionalized and tailor-made solvents. This can be particularly useful for chiral ionic liquids, since both cation and anion can be easily functionalized to bear chiral structural motifs. Since the first example of a chiral ionic liquid was reported in 1997 by Howarth et al., the number of publications dealing with chiral ionic liquids grew rapidly, and nowadays a large pool of chiral ionic liquids bearing either chiral cations, anions, or seldom both with a wide variety of functionalities is available [1] (Fig. 8.1).

It was soon realized that enantiopure natural products from the so-called chiral pool provide a unique and indispensable source for ionic liquids and allow the resource-efficient design of chiral ionic liquids. Consequently, the overwhelming majority of all chiral ionic liquids owe their existence to natural amino acids that can be easily functionalized to form the cation or anion of ionic liquids [2]. Similarly,

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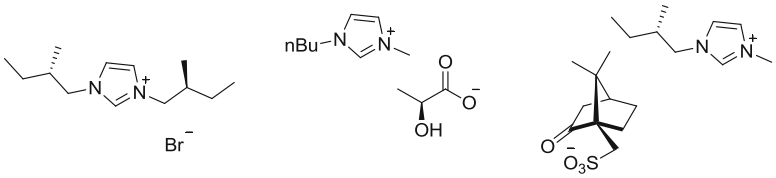


Fig. 8.1 Examples for chiral ionic liquids with chiral cation (*left*), chiral anion (*middle*), or both (*right*)

chiral alcohols such as menthol, terpenes (e.g., camphor or camphorsulfonic acid), chiral amines, or alkaloids provide a common source for the design of chiral ionic liquids, whereas about a third of all chiral ionic liquids reported in literature are derived from non-chiral pool sources.

The ionic structure, high degree of organization, and hydrogen-bonded supramolecular network inherent ionic liquids early promoted as novel aspect of chiral solvents that might allow a significant transfer of chirality for asymmetric synthesis as well as for separations [3]. It was particularly the wide field of asymmetric organocatalysis that gave access to highly enantioselective reactions catalyzed by chiral ionic liquids, with the special benefits of a simple recycling of the chiral catalyst [4]. Soon, applications in other asymmetric reactions followed, and successful example for the use of chiral ionic liquids as catalyst, solvent, or ligand include reactions as diverse as asymmetric hydrogenation [5], sulfoxide oxidations [6], or in alkylation reactions [7].

The application of chiral ionic liquids in separation sciences was mostly focused on the analytical scale, and chiral ionic liquids have been successfully used for as shift reagents in NMR spectroscopy, as stationary phases or in chromatography or as additives in capillary electrophoreses. Only few examples exist for the separation of racemic compounds on preparative scale, indicating that the potential in this important area still has to be explored (Fig. 8.2).

8.2 Chiral Ionic Liquids in Spectroscopy

8.2.1 Chiral Recognition Properties in NMR Spectroscopy

Chiral ionic liquids (CILs) have been recognized for years to affect the outcome of an asymmetric reaction or a separation process, although the prediction of any chiral ionic liquids' performance is difficult. In 2002, Wasserscheid et al. presented a new evaluation method for the chiral recognition properties of chiral ionic liquids that allowed a quantitative comparison for the strength of recognition properties between chiral ionic liquids and a racemic substrate (Fig. 8.3) [8]. The authors performed ^{19}F NMR spectroscopy of a mixture of racemic Mosher's acid sodium salt and the chiral ionic liquid in a common NMR solvent. Depending on the ratio of

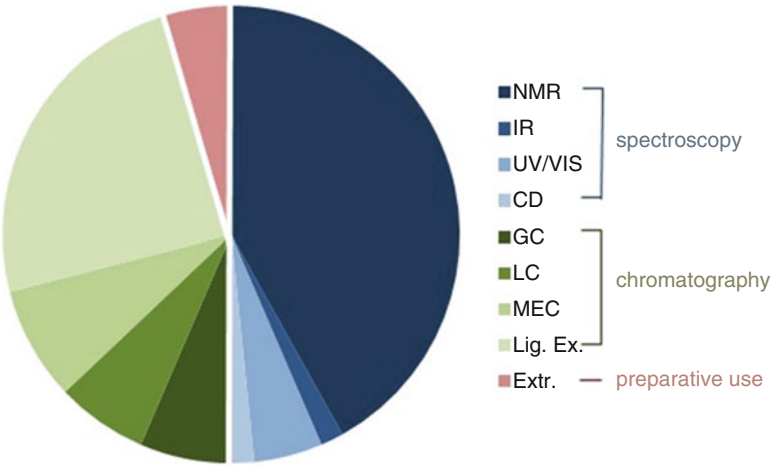


Fig. 8.2 Applications of chiral ionic liquids in separation sciences

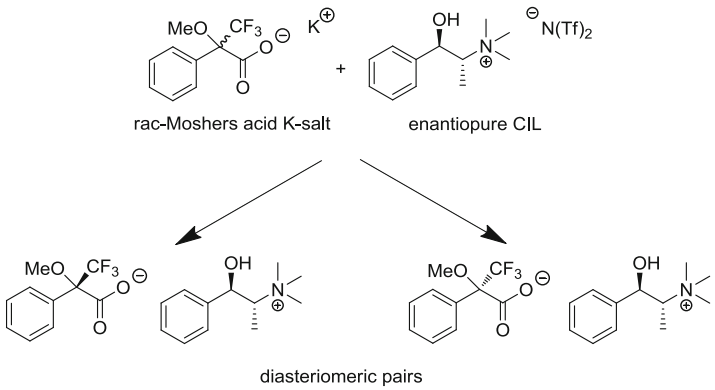
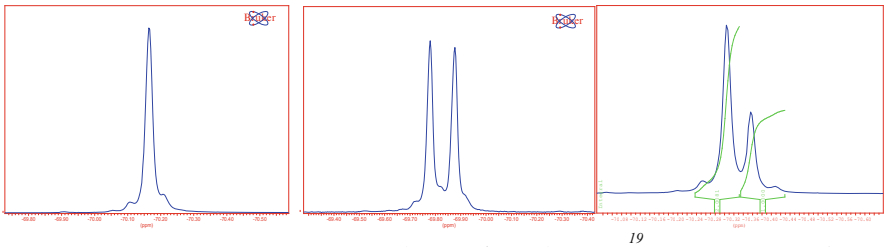


Fig. 8.3 Formation of diastereomeric ion pairs between chiral ionic liquid and racemic Mosher's acid potassium salt

the chiral ionic liquid applied in the experiment, a splitting of the ^{19}F signal of the CF_3 group was observed, thus giving evidence for the environment and the presence of a diastereomeric pair of the chiral cation and the two enantiomers of Mosher's acid (Fig. 8.4). The formation of the diastereomeric salts can be further enhanced by the addition of crown ether to trap the potassium cation or by the application of Mosher's acid silver salt in combination with halide-based chiral ionic liquids. Since 2002, this method has found a very broad application range and is often used for the evaluation and quantification of the chiral recognition properties of novel chiral ionic liquids.

The group of Wasserscheid reported a splitting of the ^{19}F signal of 11 Hz using an ephedrine-based chiral ionic liquid in CD_2Cl_2 as solvent [8]. The strongest



rac-Moshers acid K-salt in CD_2Cl_2 / 18-crown-6

rac-Moshers acid K-salt + chiral ionic liquid in CD_2Cl_2 / 18-crown-6

^{19}F NMR spectrum of an (S)-enantioenriched sample of Mosher's acid potassium salt in the presence of chiral ionic liquid

Fig. 8.4 Splitting of the ^{19}F signal of Mosher's acid potassium salt in the presence of a chiral ionic liquid

interactions were observed when the ionic liquid was used in a large excess of eight equivalents. Interestingly, a strong influence of the water content was observed indicating the importance of solvent composition (Table 8.1).

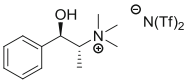
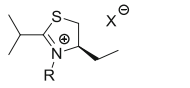
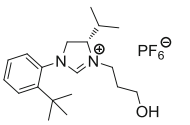
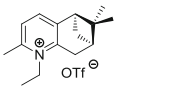
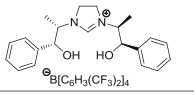
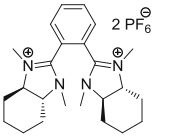
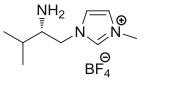
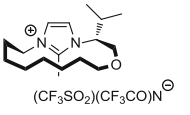
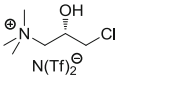
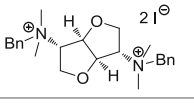
Remarkable results were obtained by Clavier et al. (Table 8.1, entry 3) using imidazolium salts derived from (*L*)-valine achieving a splitting of 63 Hz of the ^{19}F signal [10]. By changing the counterion to the bulkier potassium ion, the tightness of the anion pair could be decreased, leading to an increased diastereomeric interaction. In addition, the group around Clavier could demonstrate the importance of the aromatic system in the CIL leading to a $\pi-\pi$ stacking with the racemic substrate and enhanced recognition properties.

So far, the highest Δppm value was obtained by Jurčík et al. (Table 8.1, entry 5) who specifically design imidazolinium salts bearing two hydroxy-containing substituents as chiral shift reagents [12]. Starting from chiral pool-derived amino alcohols, the incooperation of a bidentate hydroxy structure amplified the splitting of the NMR signal and indicating the importance of the hydrogen bonding abilities. A shift difference of up to 151 Hz was observed in ^{19}F NMR for an ephedrine-derived bidendate chiral ionic liquid which is still the largest value ever reported in literature. The authors also reported a strong dependence on the anion: Whereas good Δppm values were also obtained with the weekly coordinating $N(Tf)_2^-$, the change to BF_4^- resulted in the disappearance of the splitting and no measureable interactions.

In comparison with ionic liquids bearing chiral cations, fewer examples exist in literature that have a chiral anion, and only few examples evaluating their chiral recognition properties via ^{19}F NMR are reported. Typically, 2,2,2-trifluoro-1-phenylethanol is chosen as racemic substrate (Table 8.2).

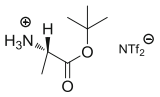
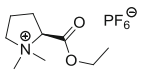
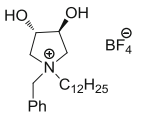
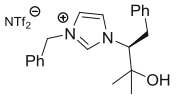
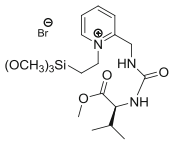
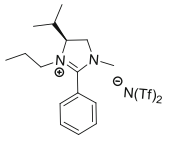
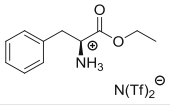
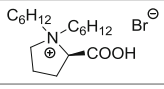
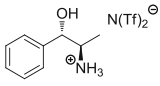
The group of Winkel investigated the recognition properties of different ionic liquids with chiral sulfonate-based anion containing chiral anions such as the common anion camphor sulfonate and observed a splitting of up to 7 Hz [26]. In principle, the authors observed better results in [d_8] toluene as solvent compared

Table 8.1 Chiral recognition properties of different chiral ionic liquids (CILs) in ^{19}F NMR spectroscopy

Entry	Chiral ionic liquid	ΔHz	Conditions	Reference	Year
1		11	CD_2Cl_2 + water, 8.2 eq. CIL, Mosher acid-Na^+ salt	Wasserscheid [8]	2002
2	 R= n-C_4H_9, n-$C_{12}H_{25}$ X= PF_6^-, BF_4^-, NTf_2^-	11	C_6D_6 + water, 5 eq. IL, Mosher acid-Ag^+ salt	Levillain [9]	2003
3		63	CD_2Cl_2, 3.3 eq. CIL, Mosher acid-K^+ salt	Clavier [10]	2004
4		4	CD_2Cl_2, 10 eq. CIL, Mosher acid-$N(Bu)_4^+$ salt	Drahonovsky [11]	2005
5		151	Acetone-d_6, 1 eq. CIL, Mosher acid/ K^+ salt	Jurčík [12]	2006
6		53	Acetone-d_6, 1 eq. CIL, Mosher acid-K^+ salt	Jurčík [13]	2006
7		35	C_6D_6 + water, 3.7 eq. IL, Mosher acid-Ag^+ salt	Luo [4]	2006
8		7	$CDCl_3$, 3 eq. CIL, Mosher acid-K^+ salt	Ishida [14]	2006
9		25	CD_2Cl_2 + water, 3.7 eq. CIL, Mosher acid-Na^+ salt	Tran [15]	2006
10		15	CD_3CN, 1 eq. CIL, Mosher acid-Ag^+ salt	Kumar [16]	2008

(continued)

Table 8.1 (continued)

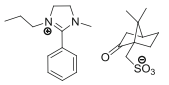
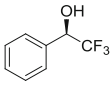
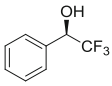
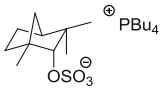
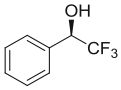
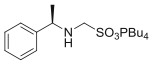
Entry	Chiral ionic liquid	ΔHz	Conditions	Reference	Year
11		n.d.[a]	DMSO, Mosher acid-Na^+ salt	Bwambok [17]	2008
12		n.d.[a]	Mosher acid-Ag^+ salt	Gao [18]	2008
13		8	$CDCl_3$, 3 eq. CIL, Mosher acid-K^+ salt	Bonnani [19]	2009
14		13	CD_3CN, 3 eq. CIL, Mosher acid-K^+ salt	Altava [20]	2009
15		15	$CDCl_3$, 3 eq. CIL, Mosher acid-K^+ salt	Li [21]	2009
16		15	$CDCl_3$, 2 eq. CIL, Mosher acid-K^+ salt	Winkel [22]	2009
17		11	CD_2Cl_2 + 30 % DMSO, Mosher acid-Na^+ salt	Bwambok [23]	2010
18		11	$CDCl_3$, 20 eq. CIL, Mosher acid-K^+ salt	Yu [24]	2010
19		13	$CDCl_3$, 5 eq. CIL, Mosher acid-K^+ salt	De Rooy [25]	2011

[a]No exact ΔHz values reported

to $CDCl_3$, which might be explained by enhanced hydrogen bonding due to the decreased polarity of the solvent. In order to improve the interaction between the chiral ionic liquid and the racemic substrate they also developed chiral ionic liquids with Brønsted basic sulfonate anions, and comparable Δppm values were obtained with 2,2,2-trifluoro-1-phenylethanol. Surprisingly, larger Δppm values of up to 41 Hz were obtained with racemic Mosher acid in [d_8] toluene (Table 8.2, entry 4).

A more detailed look on cation-anion interactions was published by Schulz et al., who investigated the diastereomeric interactions and the aggregation

Table 8.2 Chiral recognition properties of different ionic liquids with chiral anion in ^{19}F NMR spectroscopy

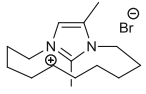
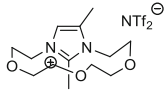
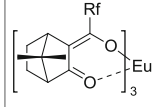
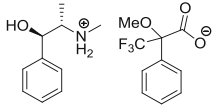
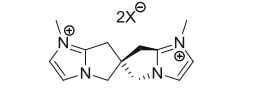
Entry	Chiral ionic liquid	ΔHz	Conditions	Analyte	Ref.	Year
1		7	[d_8]toluene		Winkel [22]	2009
2		4	[d_8]toluene		Winkel [22]	2009
3		7	[d_8]toluene		Winkel [26]	2010
4		41	[d_8]toluene	*rac*-Moshers acid	Winkel [26]	2010

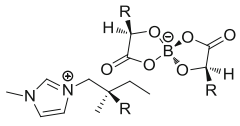
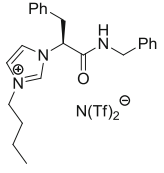
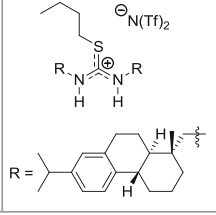
behavior of ephedrine-based chiral ionic liquids (Table 8.3, entry 3) [29]. In order to rationalize the concentration range for efficient chirality transfer diffusion coefficients and signal split of the diastereomeric ionic liquid, (1*R*,2*S*)-ephedrinium (*RS*)-methoxytrifluorophenylacetate were determined. Diffusion-ordered NMR spectroscopy (DOSY-NMR) was measured depending on the concentration in dichloromethane and gave aggregation numbers of cations and anions. In parallel, a significant peak splitting of the CF_3 group in ^{19}F NMR was only observed at a concentration >0.04 mol/L, which corresponds to the concentration range were aggregates are formed.

In 2013, Foreiter et al. published an elegant paper on enantiodiscrimination of racemic oxoanions with chiral thiouronium ionic liquids (Table 8.3, entry 7) [33]. A series of chiral thiouronium salts was synthesized from commercially available chiral amines (*S*)-methylbenzylamine and (+)-dehydroabietylamine. A detailed study on the chiral recognition properties revealed that a strong hydrogen bonding and a rigid conformation between oxoanions, e.g., mandelates, but also between sulfonates and phosphonates. The influence of the anion of the chiral ionic liquid was further investigated, and best enatiodiscrimination was observed in case of anions with poor hydrogen-bond acceptor abilities such as $N(Tf)_2^-$. A 1:1 ratio between chiral thiouronium salt and an oxoanion guest was identified as ideal ratio, and chiral discrimination was superior to the uncharged chiral thiourea precursor. The importance of hydrogen bonding between the thiouronium unit and the carboxylate moiety of the guest molecule was further visualized in DFT studies and X-ray crystal structure.

The chiral discrimination of racemic carboxylate salts has been also studied by Gonzalez et al., who used amino acid-derived chiral ionic liquids (Table 8.3, entry 6) [32]. Room-temperature liquid imidazolium-based chiral ionic liquids were

Table 8.3 Chiral recognition properties of different chiral ionic liquids in ^{1}H NMR spectroscopy

Entry	Chiral ionic liquid	ΔHz	Conditions	Analyte	Ref.	Year
1		7	$CDCl_3$, 1 eq. CIL	Ag-camphorsulfonate	Ishida [27]	2002
2		19	$CDCl_3$, 10 eq. CIL, 10 eq. Et_3NCl	 Rf = C_3F_7, CF_3	Ishida [28]	2004
3		24	CD_2Cl_2 as 6.4×10^{-1} mol/L	–	Schulz [29]	2009
4	 X=$N(CF_3SO_2)_2$, $N(CF_3(CF_2)_2SO_2)_2$	n.d.[a]	20 % DMSO-d_6-$CDCl_3$ 18-crown-6	Mosher acid-K^+ salt	Patil Mahesh [30]	2006

5	 R = methyl, isopropyl, phenyl, phenylmethyl, cyclohexanyl	11	$CDCl_3$ 0.1 mol/L	–	Yu [31]	2008
6		13	$CDCl_3$, 4 eq. CIL	Triethylammonium mandelate	Gonzalez [32]	2012
7		33	$CDCl_3$, 1 eq. CIL	Tetrabutylammonium mandelate	Forreiter [33]	2013

[a]No exact ΔHz values reported

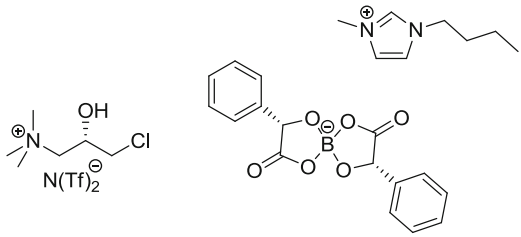


Fig. 8.5 Chiral ionic liquids used in IR spectroscopy (*left*), fluorescence spectroscopy (*left*), and UV-vis spectroscopy (*right*)

obtained from chiral α-amino acids in three steps and applied as chiral shift reagent for racemic triethylammonium mandelate in ^{1}H NMR. The largest splitting was observed with chiral ionic liquids obtained from l-phenylalanine functionalized with a benzyl amide group, and the aromatic amide moiety was found to be crucial for chiral recognition. The NMR studies were further extended to include the triethylammonium salts of racemic ibuprofen, *p*-methoxy mandelic acid, and Cbz-protected phenylalanine and always showed a non-equivalence of the α-methyl signal or the Cbz-methyl signal of the guest in ^{1}H NMR.

Yu et al. reported chiral ionic liquids with either chiral cation, chiral anion, or both (Table 8.3, entry 5) [31]. Based on a chiral boronate anion that was easily obtained from enantiopure α-hydroxy acids, the intramolecular recognition with the racemic (*R*,*S*)-1-methyl-3-(2-methyl-butyl)imidazolium cation was investigated. Differences in the NMR shifts of the cation enantiomers were observed that were dependent on the solvent dielectric constant, concentration, and structural modifications of the ionic liquid. The strongest chiral recognition was observed with chiral anions bearing large substitutes as 50 mM solution in $CDCl_3$. The further evaluation of intermolecular chiral recognition was investigated with a racemic quinine derivative and a chiral ionic liquid composed of a chiral anion and the achiral 1-ethyl-3-methylimidazolium cation.

8.2.2 Enantiodiscrimination with Chiral Ionic Liquids in IR Spectroscopy

In 2006, the group of Tran presented a novel technique for the determination of the enantiomeric composition of atenolol that relies on near-infrared spectroscopy in the presence of enantiopure chiral ionic liquids [34]. A chiral ionic liquid based on the $N(Tf)_2^-$ anion and commercially available (*R*)- and (*S*)-(3-chloro-2-hydroxypropyl)triethylammonium chloride (Fig. 8.5, left) was used. Solutions of different enantiomeric compositions of atenolol in the chiral ionic liquid were prepared, and absorption spectra were measured. The recognition properties of the chiral ionic liquid led to a characteristic change in the NIR spectra that could be used to determine the enantiomer composition of the pharmaceutical substrates via multivariate data analysis.

8.2.3 Enantiodiscrimination with Chiral Ionic Liquids in Fluorescence/UV-Vis Spectroscopy

The same chiral ionic liquid (*S*)-(3-chloro-2-hydroxypropyl)triethylammonium bis(trifluoromethylsulfonyl)imide was applied as chiral selector in fluorescence spectroscopy (Fig. 8.5, left) [15]. Fluorescence spectra of the pharmaceutically active propranolol, warfarin, and naproxen fluorescence spectra were recorded in the presence of chiral ionic liquids. Depending on the concentration of the drugs in the chiral ionic liquids, significant changes in the fluorescence spectra of the enantiomers were observed, thus indicating that the chiral ionic liquid can differentiate between the enantiomers. Multivariate method of analysis was used to develop calibration models that allowed the subsequent determination of the enantiomeric purity of unknown samples.

In 2012, Absalan et al. presented the application of ionic liquid composed of a chiral boronate anion as chiral selector in UV-vis assisted spectroscopy [35]. The chiral ionic liquid 1-butyl-3-methylimidazolium (T-4)-bis[(αS)α-(hydroxyl-O)benzeneacetato-KO]borate could be easily synthesized from enantiopure mandelic acid and was applied for chiral recognition of the common beta-adrenergic blocking agent propranolol (Fig. 8.5, right). The addition of enantiopure ionic liquid to the both enantiomers resulted in significant changes of absorbance at 259 nm, indicating stronger interactions of the chiral ionic liquid with (*S*)-propranolol hydrochloride. After optimization of conditions, e.g., concentration and temperature, the ionic liquids were applied for the determination of the enantiomeric excess of samples with different composition.

8.2.4 Enantiodiscrimination with Chiral Ionic Liquids in Circularly Polarized Luminescence

In 2012, the group of Kroupa reported a chiroptical luminescence technique for the evaluation of chiral discrimination ability ionic liquids [36]. Five amino acid-derived chiral ionic liquids were chosen based on alanine, proline, and leucine, and the amino acid was located either in the cation or anion of the ionic liquid. A racemic mixture of a luminescent lanthanoid complex europium complex Λ- vs. Δ-Eu(dpa)$_3^{3-}$ (dpa =2,6-pyridinedicarboxylate) was dissolved in the enantiopure chiral ionic liquids. Chiral discrimination of the amino acid-derived chiral ionic liquids was measured by their ability to perturb the equilibrium population of Λ- vs. Δ-Eu(dpa)$_3^{3-}$ from racemic to non-racemic. The authors observed emission dissymmetry factors $g_{em}(\lambda)$ with opposite signs for *L*- vs. *D*-amino acid-derived ILs, thus indicating that the preference of the discrimination is dictated by the handedness of the chiral cation. While discrimination was observed with chiral ionic liquids composed of alanine or proline, leucine-derived ionic liquids failed to induce any enthalpic chiral discrimination.

8.3 Chiral Ionic Liquids in Chromatography

8.3.1 Chiral Ionic Liquids as Stationary Phases in Gas Chromatography

The thermal stability, ability to form multiple solvation interactions, and low volatility of ionic liquids make them ideal candidates for use as stationary phases in gas chromatography [37]. Remarkable separation behavior has been found for some ionic liquids, since they display a high affinity toward dipolar solutes similar to polar stationary phases but also retain nonpolar solutes (e.g., alkanes and alkenes) in a manner that is comparable to stationary phases with low polarity [38]. This unique selectivity has been described as a result of a "dual-nature" retention mechanism. Additionally, many IL stationary phases also have the advantage of high temperature stability, whereas most conventional polar stationary phases cannot be used at temperatures greater than 280 °C [39]. This is a particular challenge for the resolution of enantiomers since there are hardly any commercially available chiral stationary phases which are stable over 280 °C. Additionally, the synthetic origin of many chiral ionic liquids provides another major advantage that is not possible with the commonly used cyclodextrin phases: The rather simple synthesis of chiral ionic liquids in both enantiomeric forms allows easily switching the handedness of a chiral stationary column when the reverse elution order is needed.

In 2004, Armstrong et al. presented the first application of chiral ionic liquids as stationary phase in gas chromatography using an ephedrine-based chiral ionic liquid (Fig. 8.6) [40]. After coating a fused-silica capillary tube with the chiral ionic liquid, they managed to separate racemic alcohols, sulfoxides, epoxides, and acylated amines into their enantiomers. However, when further investigating the long-term stability of the stationary phase, the separation performance of the stationary phase was decreasing, and a water-induced racemization process of the chiral ionic liquid was held responsible.

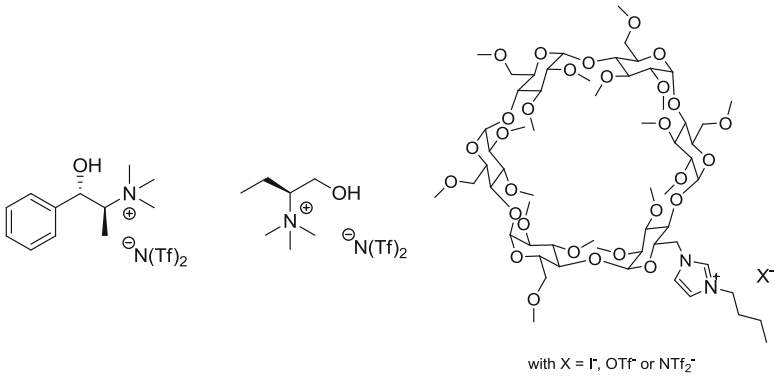


Fig. 8.6 Different chiral ionic liquids applied as chiral selectors in gas chromatography

Zhao et al. compared the separation characteristics of fused-silica capillary column that were either directly coated with a chiral amino alcohol-derived ionic liquid or further modified with single-walled carbon nanotubes before the coating process (Fig. 8.6) [41]. Twelve racemic substrates including amino acids, terpenes, alcohols, amines, and camphor were separated indicating that the single-walled carbon nanotubes improve the enantioseparation on the chiral ionic liquid stationary phase. This effect was attributed to the enhanced surface wettability of the inner wall of the capillary column, since the single-walled carbon nanotubes formed a layer with a skeletal network structure in the capillary tube.

The same chiral ionic liquid (*R*)-*N*,*N*,*N*-trimethyl-2-aminobutanol bis(trifluoromethylsulfonyl)imide was applied as stationary phase for gas chromatography by Yuan et al. An untreated fused-silica capillary column was coated with a 0.45 % (w/v) acetone solution of chiral ionic liquid; evaporation of the solvent and conditioning gave access to an ionic liquid-coated chiral stationary phase that was applied for the separation of nine racemic compounds including racemic citronellal [42].

Although not strictly a chiral ionic liquid technology, chiral separation using ionic liquids as stationary phases has also been achieved via dissolution of cyclodextrins in room-temperature ionic liquids. A first approach was published by Berthod et al. in 2001 when two cyclodextrin/ionic liquid columns were compared with two commercially available cyclodextrin columns containing the similar chiral selector [43]. The ionic liquids 1-butyl-3-methylimidazolium chloride ([C_4mim][Cl]) and 1-butyl-3-methylimidazolium hexafluorophosphate ([C_4mim][PF_6]) were used for dissolution and coating. In summary, Berthod et al. observed lower retention factors for the ionic liquid-containing phases but higher peak efficiencies. Unfortunately, a third of all tested analytes that were separated on the commercially available columns where not separated on the ionic liquid-based columns. This was probably due to the imidazolium cation used, which is blocking the cyclodextrin cavity through complexation and is therefore inhibiting chiral recognition. However, despite the fact that many of the substrates could not be separated on the ionic liquid-containing columns, the observations made could contribute to the better understanding of ionic liquid interactions.

In 2010, Huang et al. came up with a modified strategy to improve this behavior [44]. In comparison to the work of 2001, they used functionalized ionic liquid matrices for the dissolution of the chiral selector to hinder the interaction of the imidazolium core with the cyclodextrin cavity. Typically di-cationic ionic liquids based on imidazolium or phosphonium head groups were used in combination with a triflate (OTf) or bis(trifluoromethylsulfonyl)imide ($N(Tf)_2$) anion. Furthermore, the cyclodextrin units were modified to incorporate a permanent cationic group thus leading to stronger solute-solvent interactions and to an enhanced solubility of the chiral selector in the ionic liquid. With this novel technology, Armstrong et al. could improve the efficiency of the column, the enantioseparation, as well as the peak shape in comparison to commercially available cyclodextrin phases. Furthermore, they were able to separate all test substances that where tested on the commercial columns, thus providing a new and very promising method for chiral separation.

8.3.2 *Liquid Chromatography with Chiral Ionic Liquids*

Chiral ionic liquids can play different roles to support or improve separations in liquid chromatography: Apart from the use as stationary phases, they can be added as chiral mobile-phase additives and dynamically coat the stationary phase.

The first application of chiral ionic liquids in liquid chromatography was published in 2006 by the group of Yuan [42]. A chiral ionic liquid based on (*R*)-2-aminobutanol was as additive to the mobile phase consisting of H_2O and CH_3CN (10 mmol/L CIL) in combination with a commercially available C18 ODS column. Eight different analytes, e.g., the pharmaceutically active propranolol, could be separated thus showing the potential of this chiral ionic liquid in enantioselective separation.

In 2010, Zhou et al. presented novel stationary phases for liquid chromatography based on silica-bonded cyclodextrins that were further functionalized with 1,2-dimethylimidazolium or 1-amino-1,2,3-triazolium cations and variable anions [45] (Fig. 8.7). A series of racemates including α-nitroalcohols, α-hydroxylamines, alcohols, as well as two racemic drugs was chosen. With this novel chiral stationary phases and acetonitrile-based polar mobile phases, they were able to separate up those analytes with good to excellent resolution factors and attributed these results to the presence of both cationic and anionic moieties on the chiral selector.

When investigating the effect of the cationic moiety, the authors claimed that the imidazolium cation, with its lower pK_a value (triazole pK_a 11.8 vs. imidazole pK_a 7.9), was able to form tighter ion pairs. This seems to be beneficial for chiral recognition since both the cation and anion moieties interact with the analyte. Additionally, they investigated the effect of the anion and found the nitrate anion was the better choice since it is a weaker base and consequently more ready to participate in ion exchange. For increasing the recognition abilities of the chromatography system, the authors varied the composition of the mobile phase and found that increasing the acidity or basicity can lead to stronger interactions between selector and analytes and therefore enhanced resolution.

In 2009, Liu et al. applied amino acid-based chiral ionic liquids for the separation of racemic amino acids based on the ligand-exchange principles [46]. Pure *L*-proline, *L*-proline dissolved in $[C_4mim]Br$, and four 1-alkyl-3-methylimidazolium *L*-prolinate ionic liquids with different alkyl chain length were used as chiral

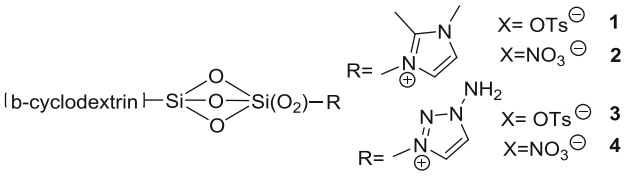


Fig. 8.7 Ionic liquid-modified silica-bonded cyclodextrins as stationary phases in liquid chromatography

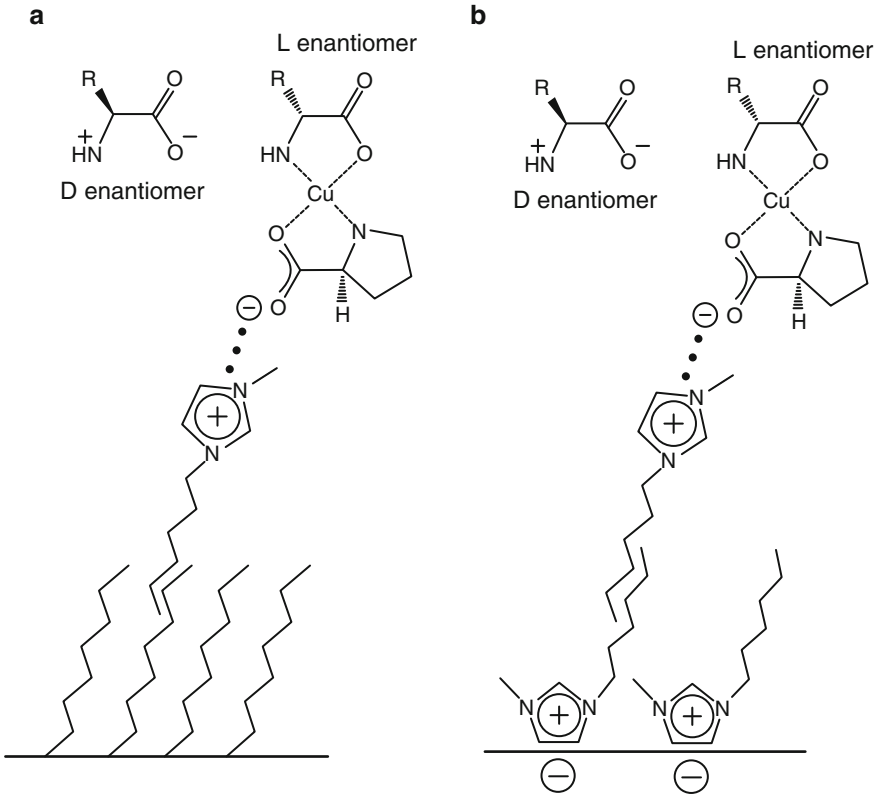


Fig. 8.8 Proposed retention mechanism in ligand-exchange chromatography with amino acid-derived chiral ionic liquids on (**a**) HPLC column and (**b**) capillary wall (Reproduced from Ref. [46] by permission of John Wiley & Sons Ltd.)

mobile-phase additive, and good baseline separation was obtained for racemic phenylalanine with all four amino acid-derived ionic liquids. Interestingly, the chiral recognition and hence the resolution were significantly increased by lengthening of the alkyl chain in imidazolium head group from C_2 to C_8, indicating the importance of the achiral cation which is substantially involved in the complex formation. The strong interaction of a long-chain imidazolium cation with the hydrophobic C18 column resulted in the formation of a stable complex which was able to separate enantiomers even at low concentrations of amino acid-derived chiral ionic liquid (Fig. 8.8). It should be noted that the use of *L*-proline as chiral ligand also led to baseline separation; however the observed separation factor was significantly lower than that of all amino acid-derived chiral ionic liquids.

In 2011, Bi et al. used chiral ionic liquid-assisted ligand exchange chromatography to separate racemic ofloxacin, a fluorinated quinolone with antibacterial activity [47]. Different amino acid-derived chiral ionic liquids as well as achiral ionic liquids

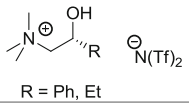
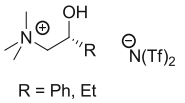
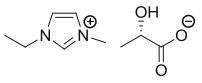
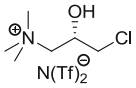
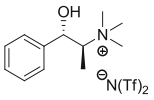
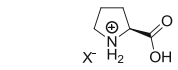
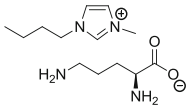
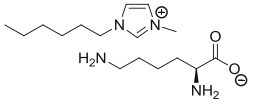
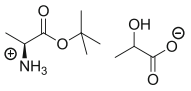
in combination with *L*-amino acids were used in combination with $CuSO_4.5H_2O$ as mobile-phase additive in HPLC. In the case of achiral cations as additives, the separation of ofloxacin enantiomers could be improved when ionic liquids with short alkyl chains where used. This is due to the competition of the imidazolium cations with the copper complexes for the adsorption onto the alkyl silica surface, which is in favor of copper when short alkyl chains are used. When chiral amino acid-based ILs were used as additives, the authors observed a different trend than previously reported by Liu et al.: Enantioseparation decreased with increasing chain length of the 1-alkyl-3-methylimidazolium cation, and weaker electrostatic interactions with Cu^{2+} as well as a steric hindrance of larger cations were held responsible for this decrease. Among different chiral ionic liquids based on alanine, valine, phenylalanine, and leucine, 1-butyl-3-methylimidazolium *L*-leucinate ([C_4mim][*L*-leucinate]) was found to be the most successful, so that the developed strategy could be applied for the determination of ofloxacin enantiomer distribution in various medicines.

8.3.3 Chiral Ionic Liquids in Capillary Electrophoresis and Micellar Electrokinetic Chromatography

Based on the work of François et al. with achiral ionic liquids as additives for capillary electrophoresis (CE), this group evaluated the effect of chiral ionic liquids as additives in CE for the enantioseparation of different profens in 2007 (Table 8.4, entry 1) [48]. Two chiral ionic liquids (ethyl- and phenylcholine bis(trifluoromethylsulfonyl)imide) were chosen as background electrolytes; however, no enantioselectivity was for the two anti-inflammatory 2-arylpropionic acids as racemic model compounds. The authors then switched to study the influence of different chiral ionic liquids in the presence of cyclodextrins (CD) that are commonly used chiral selectors. Variation of the electroosmotic flow, the total salt concentration, and the structure of the chiral ionic liquids in the separation of three model profens (naproxen, carprofen, and suprofen) did not help to establish a general trend concerning the nature of the chiral ionic liquid. However, in nine cases, a simultaneous increase of selectivity and resolution was observed indicating a synergistic effect of the two selectors.

Similar results were obtained by Rousseau in 2010, where the same chiral ionic liquids (ethyl- and phenylcholine) were used as additives to the background electrolyte cyclodextrins (2,3-di-O-methyl-6-O-sulfo)-β-CD) (Table 8.4, entry 2) [49]. With this system, racemic mixtures of two racemic pharmaceutical intermediates were successfully separated, describing the same effects as previously observed by François et al.: Adding chiral ionic liquid to the CD system led to a significantly higher enantiomeric resolution, again indicating a synergistic effect with the cyclodextrin. This was related to the decrease of the electroosmotic flow when the ionic liquid cation was adsorbed on the capillary wall. To exclude a simple

Table 8.4 Application of chiral ionic liquids ion capillary electrophoreses

Entry	Chiral ionic liquid	Co-electrolyte/ additive	Analyte	Reference	Year
1	 R = Ph, Et	β-cyclodextrin	2-arylpropionic acids	François [48]	2007
2	 R = Ph, Et	Carboxymethyl-β-cyclodextrin	Benzopyran derivative	Rousseau [49]	2010
3		β-cyclodextrin	Different drugs	Zuo [50]	2013
4		Cholic acid, 1-S-octyl-β-D-thioglucopyranoside	Profens	Tran [51]	2008
5		no additive	Rabazol, omeprazol	Ma [52]	2010
6	 with X = CF_3COO^-, NO_3^-, BF_4^-, SO_4^{2-}	Cu(II)	Dansylated amino acids	Mu [53]	2012
7		Zn(II)	Dansylated amino acids	Mu [54]	2012
8		Zn(II)	Dansylated amino acids	Zhang [55]	2013
9		no additive	1,1′-binaphthyl-2,2-dihydrogen-phosphate	Stavrou [56]	2013

salt effect, the same experiment was repeated with achiral ionic liquids as additive, and no improvement of the chiral resolution was observed.

Chiral ionic liquids in combination with cyclodextrins were also applied by Zuo et al. in 2013 to separate enantiomers of several pharmaceuticals including the actives zopiclone, repaglinide, and chlorphenamine [50]. The anion-chiral ionic liquid 1-ethyl-3-methylimidazolium *L*-lactate ($[C_2mim][L\text{-lactate}]$) was chosen, and the influence of ionic liquid concentration, chain length, and pH dependence of the system on the resolution were investigated (Table 8.4, entry 3). The evaluation

of optimum conditions allowed the considerably improved enantioseparation of 12 racemic compounds compared to conventional cyclodextrins as sole background electrolytes. Finally, this method could be applied for high-precision measurements of the enantiomeric purity of eszopiclone in commercial tablets.

Synergistic effects of ionic liquids with cyclodextrin as background electrolyte in CE were also reported by Zeng et al., who used 1-ethyl-3-methylimidazolium tetrafluoroborate in a glass microchip electrophoresis device [57]. The group was able to show a tremendous improvement and broadening of the separation window for two enantiomeric dipeptides with the achiral ionic liquid as additive in comparison to the commonly used boric acid buffer. The enantioseparation of three β-blockers via capillary electrophoresis in the presence of an achiral ionic liquid was also achieved by the group around Jin [58]. Glycidyltrimethylammonium chloride in combination with cyclodextrin was used background electrolyte. A remarkably low detection limit ranging from 0.1 to 0.65 mM was observed with this ionic liquid-cyclodextrin approach system, suggesting that this system might be applicable for the analysis of spike urine samples.

In 2008, Tran et al. demonstrated that the chiral ionic liquid *S*-3-(chloro-2-hydroxypropyl)trimethylammonium bis(trifluoromethylsulfonyl)imide is able to improve separation and enantioseparation in CE and can be used as co-electrolyte or chiral selector for several racemic profens including naproxen, ibuprofen, and flurbiprofen (Table 8.4, entry 4) [51]. When the chiral ionic liquid was used as background electrolyte and as single source of chirality, no separation of the substrates could be achieved. However, when the chiral anionic surfactant cholic acid was added to the aqueous solution, baseline separation of seven pharmaceutics including ibuprofen was observed. In the absence of chiral ionic liquid with cholic acid as sole additive in the mobile phase, the resolution was worse, and no separation of the ibuprofen enantiomers could be achieved. In some cases, the separation could be further improved by the addition of a third chiral and neutral component (1-*S*-octyl-β-D-thioglucopyranoside).

The ephedrine-based ionic liquid (+)-*N*,*N*-dimethylephedrinium bis(trifluoromethylsulfonyl)imide that has already been successfully applied in NMR spectroscopy and gas chromatography was used as background electrolyte and chiral selector in nonaqueous capillary electrophoresis to separate enantiomers of the antiulcer drugs rabeprazole and omeprazole by Ma et al. (Table 8.4, entry 5) [52]. The mechanism of enantioseparation was investigated suggesting that ion-pair interaction and hydrogen bonding are primarily responsible for the separation characteristics.

Mu et al. could present a different approach for the use of chiral ionic liquids in CE. Amino acid-derived chiral ionic liquids were used as chiral ligands in ligand-exchange capillary electrophoresis for the separation of dansylated amino acids using Cu(II) as complexation reagent (Table 8.4, entry 6) [53]. Based on (*L*)-proline, several protic ionic liquids were obtained via protonation with strong acids such as HNO_3, HBF_4, CF_3COOH, and H_2SO_4. After optimization of the separation conditions, [*L*-proline][CF_3COO] was identified as best chiral ionic liquid and applied for the separation of nine dansylated amino acids. When the use of this

protic ionic liquid was compared to the use of sole proline or proline in the presence of trifluoroacetic acid, the enantioseparation was inferior, indicating that the chiral ionic liquid played a special role whose exact mode of actions still has to be explored.

In the same year, this group presented the successful enantioseparation of derivatized amino acids using chiral ligand-exchange capillary electrophoresis with Zn(II) as complexation metal and *L*-ornithine as chiral cation (Table 8.4, entry 7) [54]. After optimization of key parameters such as buffer pH, concentration of Zn(II), and concentration of the chiral ionic liquids, Mu et al. were able to achieve baseline separation of 11 pairs of dansylated amino acids and could apply this strategy to investigate the inhibition efficiency of *D*-amino acid oxidase inhibitors. Related experiments were performed by the group around Zhang, who used different *L*-lysine-derived ionic liquids as chiral ligands and Zn(II) complexes in ligand-exchange CE [55]. Based on imidazolium cations with variable chain length and lysinate as anion, baseline separation of seven pairs of dansylated amino acids was obtained.

In 2013, the group around Stavrou presented the use of a chiral ionic liquid in CE as single source for chiral recognition without metal complexation (Table 8.4, entry 9) [56]. Five chiral ionic liquids based on an alanine esters with variably ester chain length and lactate or bis(trifluoromethylsulfonyl)imide as anion were synthesized. The chiral ionic liquids were used as additives in the background electrolyte to resolve racemic 1,1′-binaphthyl-2,2-dihydrogenphosphate. A strong influence of the ester type in the cation was observed since the enantioresolution improved with increasing bulkiness of the alkyl group. Consequently, the best resolution was obtained with alanine-*tert*-butyl ester as cationic moiety. Furthermore, variation of ionic liquid concentration, pH value, and anion revealed that optimum conditions were present with the hydrophilic lactate anion at a pH of 8–8.5. At these conditions, baseline separation of the chiral analyte could be obtained with chiral ionic liquids as single source of enantioselectivity. Additionally, it could be shown that the elution order of the two enantiomers of the analyte could be inverted when the other enantiomer of the chiral ionic liquid was used.

Achiral ionic liquids in combination with chiral polymeric surfactants and common CE buffers have been successfully applied in the separation of racemic analytes, and the ionic liquids resulted in improved resolution [59]. Already in 2006, Rizvi and Shamshi applied two chiral ionic liquids based on leucinol and prolinol for the separation of α-bromphenylacetic acid and 2-(2-chlorophenoxy)propanoic acid in micellar electrokinetic chromatography [60] (Fig. 8.9). The chiral amino alcohol precursors *N*,*N*-dimethylleucinol and *N*-methylprolinol were functionalized with an undecenoxycarbonyl moiety to obtain surface-active chiral ionic liquids with critical micelle concentrations (CMC) at 1.15 mM and 0.84 mM. These chiral ionic liquids as well as their polymerized derivatives were applied as pseudostationary phase in micellar electrokinetic chromatography, and a strong influence of concentration and pH value on the enantioseparation was observed. Electrostatic interactions between the acidic analytes and the cationic head groups were found to play a profound role

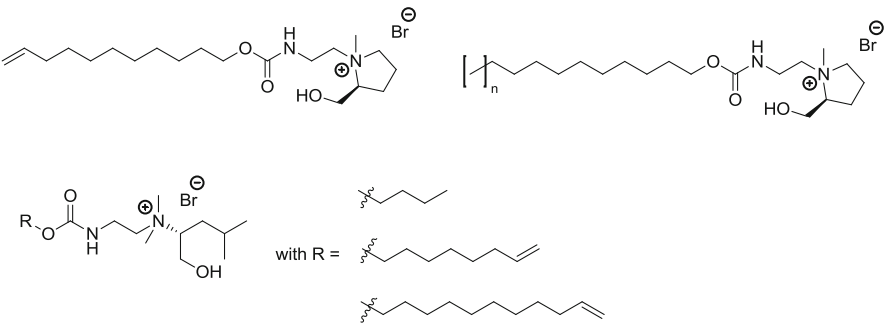


Fig. 8.9 Prolinol and leucinol derived chiral ionic liquids for micellar electrokinetic chromatography

in the separation process; baseline separation of 2-(2-chlorophenoxy)propanoic acid could be obtained with the polymerized leucine derivative at low pH values.

The combination and synergistic effects of chiral ionic liquids with cyclodextrins are not limited to capillary electrophoresis but have been also observed in micellar electrokinetic chromatography. In 2009, Wang et al. reported the enantioseparation of profen drugs in micellar electrokinetic chromatography using amino acid-derived surface-active chiral ionic liquids [61]. The combined use of the chiral ionic liquid and cyclodextrin derivatives allowed enantioseparation of the racemic drugs. Detailed investigation toward the separation of fenoprofen revealed different binding constants for the two isomers due to the synergistic effect of the chiral selectors.

8.4 Preparative Liquid-Liquid Extractions with Chiral Ionic Liquids

Although recognition and resolution abilities of chiral ionic liquids have been investigated systematically for analytical purposes, preparative application in separation sciences remains rare to date.

In 2010, Tang et al. presented the first application for preparative liquid-liquid separation of racemic amino acids via ligand exchange [62]. Based on proline-derived chiral ionic liquids and copper acetate as complexing agent, one enantiomer of the racemic amino acid substrate was selectively extracted and concentrated in the chiral ionic liquid phase (Fig. 8.10). With this strategy, the authors could obtain an enrichment of up to 36 %ee of *L*-phenylalanine in the chiral ionic liquid 1-butyl-3-methylimidazolium *L*-prolinate ([C_4mim][*L*-prolinate]) using ethyl acetate as immiscible organic solvent. The effect of copper ion concentration and amino acid concentration was further investigated, and a possible recycling strategy for the chiral ionic liquid was developed. Furthermore, the influence of the cation was

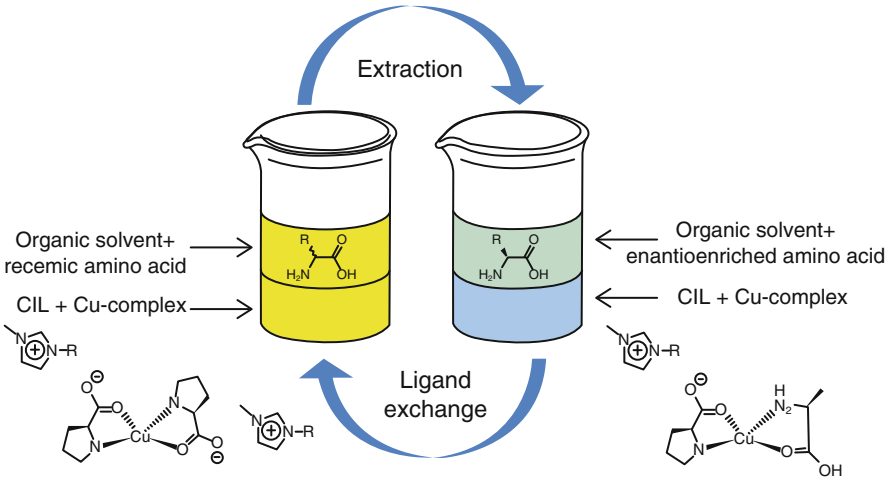


Fig. 8.10 Liquid-liquid separation of racemic amino acids with amino acid-derived chiral ionic liquids

investigated, and it turned out that an increase in chain length of the 1-alkyl-3-methylimidazolium cation lead to an increase of enantioselectivity from 38 %ee to 51 %ee, which might be explained by the reduced solvent polarity and the enhanced stability of the copper complex.

Zgonnik et al. [63] were able to apply and evolve this concept for enantioselective liquid-liquid extraction (ELLE process) [64] and came up with a new eco-friendly method without metal complexation but requiring two different ionic liquids whose ions differ in hydrophilicity. This strategy for the enantioselective extraction of racemic amino acids from an aqueous system relies on the aggregation behavior of ionic liquids where a hydrophilic cation combines with hydrophilic anion in the water phase and vice versa. The biphasic system in this enantioselective extraction process was obtained by mixing the chiral ionic liquid tetrabutylphosphonium *R*,*R*-tartrate ($[PBu_4]_2[R,R\text{-tartrate}]$) and a racemic cationic substrate dissolved in the hydrophobic ionic liquid 1-octyl-3-methyl-imidazolium bis(trifluoromethylsulfonyl)imide ($[C_8mim][N(Tf)_2]$). As a result of aggregation, the ions combine in an enantioselective way and are concentrated in the water layer, whereas the hydrophobic liquid layer contains $[PBu_4][N(Tf)_2]$ and the remaining enantiomer. A high dependence on temperature and incubation time was observed; the authors reported up to 30 % enantiomeric enrichment of the pharmaceutically active pipecoloxylidide at 50 °C (Fig. 8.11).

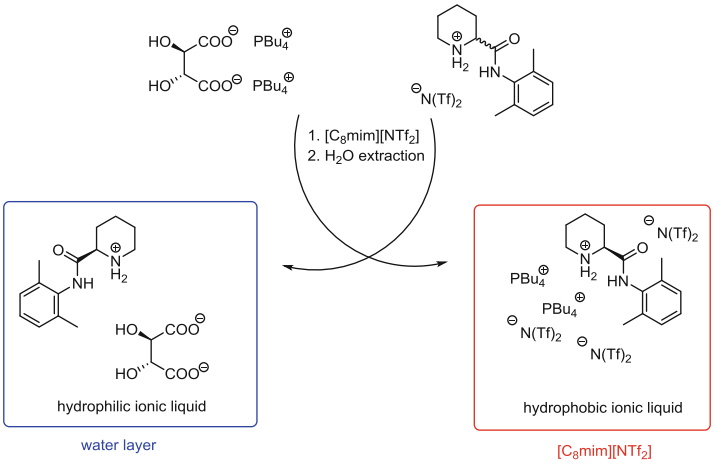


Fig. 8.11 Enantioselective liquid-liquid extraction with the chiral ionic liquid $[PBu_4]_2$[*R*,*R*-tartrate]

8.5 Conclusion

In the last 15 years, considerable effort has been put into the design and application of chiral ionic liquids in diverse areas. Based on their ionic structure and special properties, chiral ionic liquids are of particular interest for separation sciences. It has been shown that they provide separation characteristics that have not been observed with conventional substrates. Consequently, chiral ionic liquids offer novel separation methodologies and solutions to difficult separation problems.

Most of the work published to date on the application of chiral ionic liquids in separations originated from the analytical area. The utilization of ionic liquids as chiral selector in NMR spectroscopy but also in chromatography has been established. Numerous applications demonstrate the potential of chiral ionic liquids and provide a better understanding of the unique interactions between chiral ionic liquids and diverse analytes.

When it comes to separation on preparative scale, the field is less explored, and only few examples exist that demonstrate the potential of chiral ionic liquid in this area. This is surprising, since ionic liquids have been well established for separations of all kinds even in large scale. Clearly, knowledge gained on analytical range still has to be transferred to the preparative scale: A plethora of novel separations and resolution strategies for racemic compounds might be the award.

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Chapter 9
Analytical Applications of Ionic Liquids in Chromatographic and Electrophoretic Separation Techniques

María J. Trujillo-Rodríguez, Ana M. Afonso, and Verónica Pino

Abstract The synthetic tunability of ionic liquids (ILs), their structural versatility, and the wide range of interest properties that can present (from water soluble to water insoluble, from low density to high density, etc.), together with their impressive solvation abilities for different organic compounds, make their use in chromatographic and electrophoretic separation techniques an obvious approach of enormous interest. In fact, the studies of ILs have covered a number of topics in chromatographic and electrophoretic methods, from basic studies of performance to the development of complete analytical methods. Thus, they have been used in high-performance liquid chromatography (HPLC) as modifiers of mobile phases, as additives of mobile phases to improve the separation of basic analytes, as novel HPLC stationary phases, and even as pseudo-stationary phases in HPLC when utilizing ionic liquid-based surfactants, in a mode of micellar liquid chromatography (MLC). They have also experienced applications in counter-current chromatography (CCC), in which all phases involved have a liquid nature, acting as mobile phases or as stationary phases. In gas chromatography (GC), ILs have experienced an important application for developing novel stationary phases, characterized by their ability to separate polar and nonpolar compounds simultaneously, which is a problem in conventional GC columns. Moreover, they have been employed in capillary electrophoresis (CE) as background electrolytes in capillary zone electrophoresis (CZE), as pseudo-stationary phases in micellar electrokinetic chromatography (MEKC) if using IL-based surfactants at concentrations ensuring micelle formation and also in on-line CE preconcentration techniques based on the use of IL-based surfactants micelles such as sweeping-MEKC or micelle to solvent stacking, among others.

Keywords Ionic liquids • Ionic liquid-based surfactants • Polymeric ionic liquids • High-performance liquid chromatography • Counter-current chromatog-

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raphy • Gas chromatography • Capillary electrophoresis • Stationary phases • Micellar liquid chromatography • Micellar electrokinetic chromatography

9.1 Introduction

The synthetic tunability of ionic liquids (ILs), their structural versatility, and the wide range of interest properties that can present (from water soluble to water insoluble, from low density to high density, etc.), together with their impressive solvation abilities for different organic compounds, make their use in chromatographic and electrophoretic separation techniques an obvious approach of enormous interest.

In fact, the studies of ILs have covered a number of topics in chromatographic and electrophoretic methods, from basic studies of performance to the development of complete analytical methods. Thus, they have been used in high-performance liquid chromatography (HPLC) as modifiers of mobile phases, as additives of mobile phases to improve the separation of basic analytes, as novel HPLC stationary phases, and even as pseudo-stationary phases in HPLC when utilizing ionic liquid-based surfactants, in a mode of micellar liquid chromatography (MLC). They have also experienced applications in counter-current chromatography (CCC), in which all phases involved have a liquid nature, acting as mobile phases or as stationary phases. In gas chromatography (GC), ILs have experienced an important application for developing novel stationary phases, characterized by their ability to separate polar and nonpolar compounds simultaneously, which is a problem in conventional GC columns. Moreover, they have been employed in capillary electrophoresis (CE) as background electrolytes in capillary zone electrophoresis (CZE), as pseudo-stationary phases in micellar electrokinetic chromatography (MEKC) if using IL-based surfactants at concentrations ensuring micelle formation and also in on-line CE preconcentration techniques based on the use of IL-based surfactants micelles such as sweeping-MEKC or micelle to solvent stacking, among others.

In this chapter, the most common abbreviations for ILs will be utilized. For example, alkyl substituents of the IL cation will first be written showing their length (i.e., C_8 for octyl, C_2 for ethyl, Vi for vinyl, or M for methyl), followed by the terms Im for imidazolium, Pyrr for pyrrolidinium, and Py for pyridinium, and finally by the anion (e.g., $–PF_6$ for hexafluorophosphate, –Br for bromide, –Cl for chloride, $–CF_3SO_3$ for trifluoromethanesulfonate, $–BF_4$ for tetrafluoroborate, and $–NTf_2$ for bis(trifluoromethylsulfonyl)imide). In the case of Im-based ILs, the substituent located in position 1 will be written first, followed by the substituent in position 3.

9.2 ILs in High-Performance Liquid Chromatography (HPLC)

High-performance liquid chromatography constitutes one of the main analytical tools to perform complex separations of analytes. In HPLC, ILs have been used as organic modifiers, as mobile phase additives, as pseudo-stationary phases (for IL-based surfactants), and as novel stationary phases, as described in Fig. 9.1. Clearly, they have been tried in all main modes of HPLC, showing particular success as mobile phase additives, and also when forming novel surface-confined IL stationary phases (SCILs). Each application mode will be described in detail in the following subsections.

9.2.1 ILs as Organic Modifiers

ILs have been used as organic modifiers in high-performance liquid chromatography (HPLC), substituting partially conventional organic modifiers such as acetonitrile, methanol, or tetrahydrofuran (THF). In comparison with these organic solvents, ILs present important advantages: they have a tunable viscosity, and they can be miscible with water or with nonvolatile solvents depending on the specific IL nature.

Poole et al. were the first to study the suitability of different alkylammonium-based ILs as chromatographic solvents, mainly by characterizing their physical

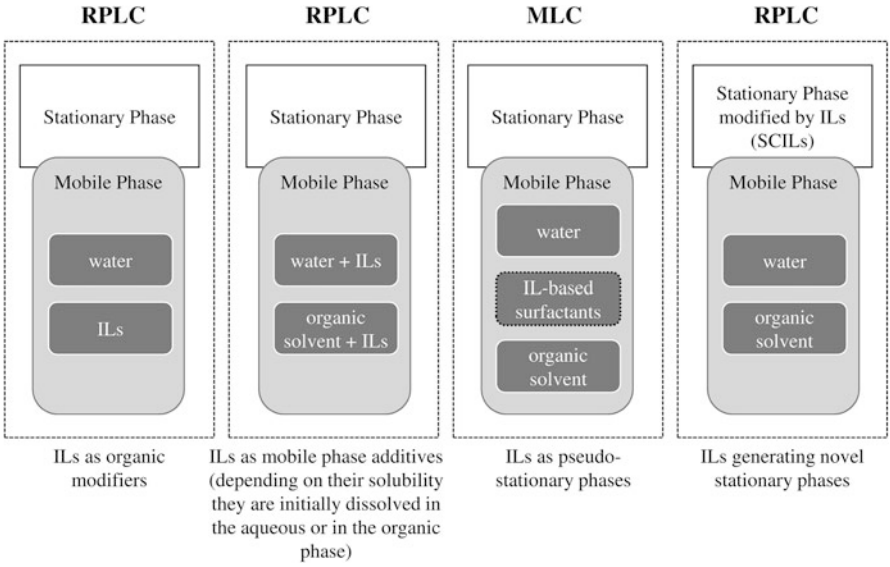

Fig. 9.1 Different application modes of ILs in HPLC

properties [1]. For the group of ILs tested, the main problem was their high viscosity. This problem was solved when mixing such ILs with other low-viscosity solvent (mainly acetonitrile or methanol).

The first practical use of ILs as organic modifiers in HPLC was carried out by Shetty et al. also from Poole's group [2]. These authors combined conventional solvents with alkylammonium nitrate- and thiocyanate-based ILs for the separation of organic compounds. Nevertheless, the pressure of the system was too high, even when operating at low flow rates.

Since then, several works have used ILs as organic modifiers in HPLC [3–5], but using alkylammonium formates and acetates instead of thiocyanates.

However, higher pressures, less transparency in ultraviolet detection, and lower efficiencies have been obtained for ILs in comparison with conventional organic modifiers. As a matter of fact, ILs have not been able to perform successfully as organic modifiers in HPLC up to date. Besides, the reported applications with ILs do not replace totally conventional solvents, because some amounts are still needed to decrease pressures in the HPLC system.

Nevertheless, it is worthy of mentioning that quite recently the IL isopropylammonium formate has been used successfully as organic modifier (also aiding in the stabilization of proteins) when working in reversed-phase liquid chromatography (RPLC) and using a PRP-3 polymeric column [6]. The IL showed even better performance than acetonitrile. It must be considered that a polymeric column rather than a classical silica-based column is used in this recent report, what perhaps opens a window for new analytical opportunities.

9.2.2 ILs as Mobile Phase Additives

One of the main outstanding applications of ILs in HPLC is related to their use (at low concentration levels) as mobile phase additives. It is used with the purpose of suppressing the well-known "silanol effect."

Silica is probably the most common stationary phase employed in RPLC, due to its versatility and wide list of favorable features for chromatography [7]. Nevertheless, it is also important to mention that, in some cases, strong interactions are established between the free silanol groups of the silica-based stationary phase and the analytes under chromatographic separation, especially when basic compounds are analyzed [8]. These interactions, the so-called silanol effect, lead to poor separation performance: asymmetry of the peaks, high retention times, low efficiency, and poor reproducibility [9–11].

There are three main possibilities to reduce such silanol interactions: to work with mobile phases possessing high percentages of water (what it is not always possible for practical separations), to employ low pH values (what it is not quite convenient either), or to add an additive into the mobile phase possessing higher affinity than basic analytes for the free silanol groups of the silica-based stationary phase [9, 12]. In fact, the addition of an additive capable to interact with residual

silanol groups of the stationary phase is the most common approach in the majority of the separations [13]. Conventional compounds employed as suppressors or masking agents of silanol effects are tertiary amines: triethylamine (TEA) [14, 15], cyclohexylamine [16], or dimethyloctylamine [12].

Within this approach, ILs have also been applied as suppressor agents in RPLC. Certainly, when ILs are added in the mobile phase, they act as salts (cations and anions in solution), but in some cases they may keep several of their intermolecular interactions. Once in the mobile phase, several interactions are established between the IL cations and anions and the surface of the stationary phase. First, a competition for the residual silanol groups of the silica surface takes place between the cations of the IL and the polar groups of the analytes [9]. In addition, ion pairing can be formed between IL anions and basic cationic solutes [17]. Both IL anions and cations can also suffer sorption on the C_{18} stationary phases. It has been shown that the sorption of anions depends on the Hofmeister series [13, 18–20]: $PF_6^- > SCN^- > ClO_4^- \sim BF_4^- > NO_3^- > I^- > Br^- > Cl^- > F^- > H_2PO_4^- > SO_4^{2-}$. Regarding cations, sorption on C_{18} stationary phases is related to the length of the alkyl chain bonded to the IL cation [18]. Besides, a weak bilayer electronic structure is formed on the surface of the stationary phase [21, 22]. A number of works in the literature discuss about the mechanism of interaction between the ILs and the silica [20, 23, 24] and the interaction between the analyte, the IL, and the silica [8].

In any case, an important feature is that all of these interactions have positive effects on the separations of basic analytes. Thus, the addition of an IL onto the mobile phase normally causes a decrease of the band broadening, best resolutions, and a reduction of retention times of the basic analytes [13, 25, 26].

It is also worthy of mentioning that many works have compared the obtained results using ILs with those of conventional additives such as triethylamine [17, 27, 28], ammonium acetate [29], or sodium dodecyl sulfate [29], showing a significant chromatographic improvement in all cases, also with lower requirements of ILs compared to the amount required of conventional masking agents. A representative example for the separation of six heterocyclic aromatic amines on a commercial ODS HPLC stationary phase is shown in Fig. 9.2.

He et al. and Zhang et al. were the first to report the use of ILs as mobile phase additives, specifically employing $C_4MIm\text{-}BF_4$ as additive for improving the separation of ephedrines and catecholamines, respectively [20, 21]. In both cases, retention factors were modified with the addition of the IL to the aqueous phase, and good chromatographic separations were achieved.

Since the appearance of these initial works, an enormous interest grew regarding the use of ILs as additives in RPLC, mainly because the improvements in the separation performance were normally achieved requiring really low amounts of ILs (down to 1 $mmol \cdot L^{-1}$). There are currently a number of reviews and book chapters in the literature which cover this important topic [7, 30–32].

Table 9.1 includes several examples of the applications of ILs as mobile phase additives to improve the chromatographic separation of basic compounds [8, 13, 17, 20–29, 33–42]. In all the cases, it can be observed that imidazolium-based ILs are

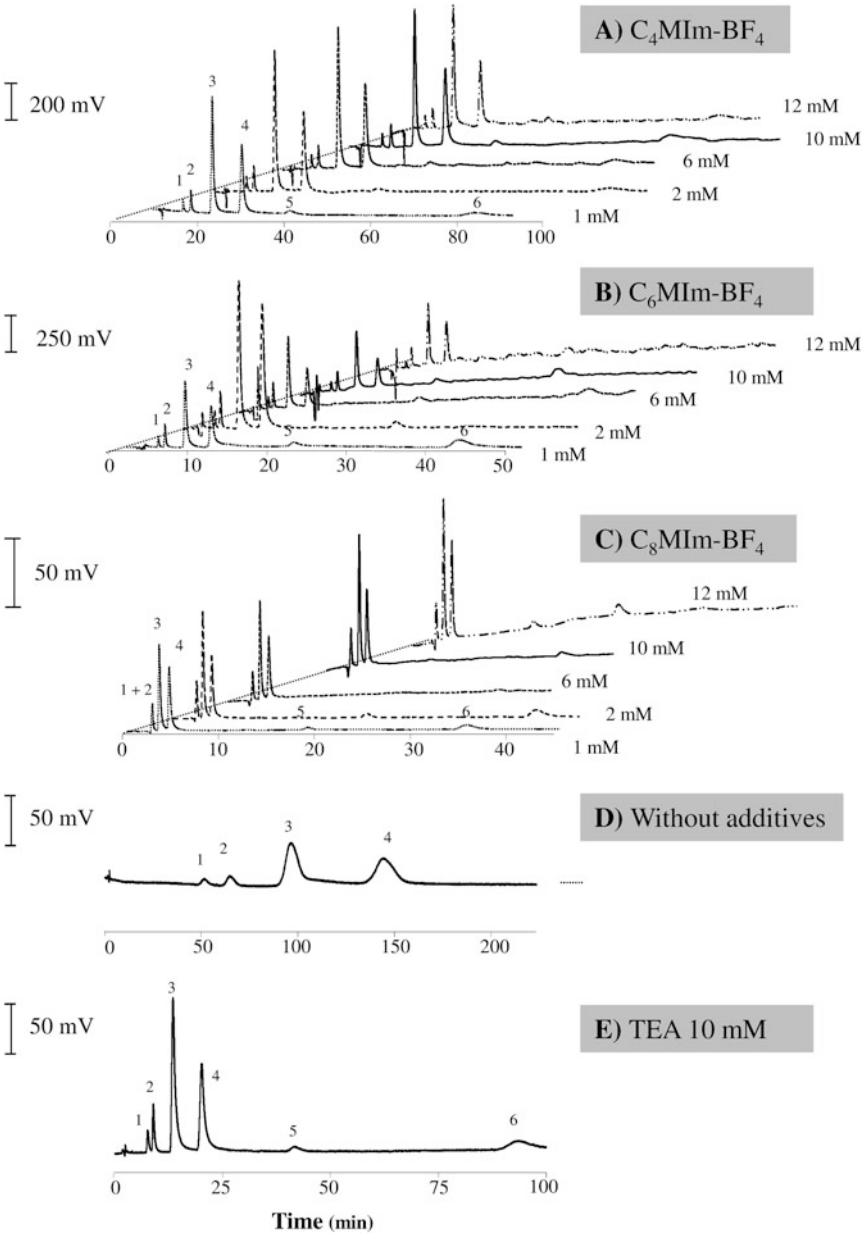

Fig. 9.2 Chromatograms obtained for six heterocyclic aromatic amines using different ILs as mobile phase additives: (**a**) $C_4MIm\text{-}BF_4$, (**b**) $C_6MIm\text{-}BF_4$, and (**c**) $C_8MIm\text{-}BF_4$; (**d**) without additives; and (**e**) TEA 10 mM as conventional additive. The analysis was conducted using HPLC with fluorescence detection (*FD*) and the commercial ODS column. The elution order was (1) 9H-pyrido[4,3-*b*]indole, (2) 1-methyl-9H-pyrido[4,3-*b*]indole, (3) 3-amino-1-methyl-5H-pyrido[4,3-*b*]indole, (4) 3-amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole, (5) 2-amino-9H-pyrido[2,3-b]indole, and (6) 2-amino-3-methyl-9H-pyrido[2,3-*b*]indole. For the rest of conditions, see reference [28]. Note the significant different scales in both x-axis and y-axis (Reprinted with permission from ref. [28]. Copyright © 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

Table 9.1 Examples of HPLC applications involving the utilization of ILs as mobile phase additives

ILs (conc. in mobile phase)	Analytes (number)	Mobile phase	Detector	Comments	Ref.
C_2MIm-BF_4; C_4MIm-BF_4; C_6MIm-BF_4 (50 mmol·L^{-1})[a]; C_6MIm-Cl	Fangchinoline and tetrandrine	MeOH/water (pH 3.0)/isocratic (80:20, v/v)	DAD (280 nm)	–	[13]
C_4MIm-PF_6; C_4MIm-Cl; C_4MIm-BF_4; C_8MIm-BF_4 (1–30 mmol·L^{-1})	Analgesic active urea derivatives (20)	ACN/water	DAD (265 nm)	Octanol-water partition coefficients were calculated	[33]
C_2MIm-Cl; C_2MIm-Br; C_2MIm-HSO_4; C_2MIm-BF_4; C_2MIm-PF_6 (30 mmol·L^{-1})[a] C_4MIm-PF_6; C_6MIm-PF_6; C_8MIm-PF_6; C_4Py-PF_6	Thiamine	Water (with ammonium formate 10 mmol·L^{-1}, pH 3.5)	DAD (254 nm)	Comparison with official analytical methods	[34]
C_6MIm-Br (0.4 %, v/v) with Au-NPs (8.27 mg·L^{-1})	Phenolic acids (5)	MeOH/water (with formic acid 1 % v/v)/gradient	ECD	–	[35]
C_4Py-BF_4; C_4MIm-Cl; C_2MIm-BF_4; C_4MIm-BF_4 (25 mmol·L^{-1})[a]	Catecholamines (3)	Water (pH 3)	DAD (280 nm)	Discussion of interactions IL-analyte	[20]
C_4MIm-Cl; C_2MIm-BF_4; C_3MIm-BF_4; C_4MIm-BF_4 (5.2–20.8 mmol·L^{-1})[a]	Ephedrines (4)	Water (pH 3)	UV (252 nm)	–	[21]
C_4MIm-Br; C_2MIm-BF_4; C_4MIm-BF_4 (30 mmol·L^{-1})[a]; C_6MIm-BF_4	Amines (4) and phthalic acids (3)	Water (pH 3)	UV (254 nm)	–	[36]
C_2MIm-BF_4 (1.5 %, v/v)[a]; C_6MIm-BF_4; C_6C_7Im-BF_4	Basic drugs (8)	MeOH/water (pH 2.87)/gradient	DAD (254 nm)	TLC studies	[25]
MMIm-MSO_4; C_2MIm-BF_4; C_6MIm-BF_4; (C_7OM)C_6Im-BF_4 (0.05–1.5 %, v/v)[a, b]	Drugs (9)	ACN/water (with phosphate buffer, pH 3)	DAD (254 nm)	TLC studies	[26]
C_4MIm-BF_4 (2–10 mmol·L^{-1})	Amino acids (2)	ACN/water	DAD (254 nm)	–	[22]
C_2MIm-BF_4; C_4MIm-BF_4; C_2MIm-MSO_4 (1–8 mmol·L^{-1})[a]; C_8MIm-MSO_4 (2–8 mmol·L^{-1})[a]	Amino benzoic acids (3)	MeOH/water/isocratic (25:75, v/v)	UV (254 nm)	–	[37]

(continued)

Table 9.1 (continued)

ILs (conc. in mobile phase)	Analytes (number)	Mobile phase	Detector	Comments	Ref.
$C_4MIm\text{-}BF_4$ (6 mmol·L^{-1})[a]; $C_8MIm\text{-}BF_4$	Basic β-blockers (6)	ACN/water (pH 3)/isocratic (30:70, v/v)	UV (254 nm)	Comparison with triethylamine	[17]
$C_4MIm\text{-}BF_4$ (0.5–15 mmol·L^{-1})	Amino acids (2) and nucleic acids (3)	MeOH/water (pH 3)/isocratic (65:45, v/v)	UV (254 nm)	–	[38]
		Or			
		MeOH/water (with Na_2HPO_3 10 mmol·L^{-1})/isocratic (95:5, v/v)			
$MMIm\text{-}MSO_4$; $C_2MIm\text{-}C_2SO_4$; $C_4MIm\text{-}C_8SO_4$; $C_2MIm\text{-}MC_6H_5SO_2$[c]; $C_2MIm\text{-}Cl$; $C_4MIM\text{-}Cl$; $C_8MIm\text{-}Cl$; $C_4Py\text{-}Cl$;$C_2MIm\text{-}Br$; $C_4MIM\text{-}Br$; $C_2MIm\text{-}BF_4$; $C_3MIm\text{-}BF_4$; $C_4MIm\text{-}BF_4$; $C_6MIm\text{-}BF_4$; $C_8MIm\text{-}BF_4$ (3.2–128 mmol·L^{-1})	Basic drugs (7)	ACN/water (pH 3)/isocratic (50:50, v/v)	DAD (254 nm)	Estimation of the silanophilic binding constant	[39]
$C_2MIm\text{-}MSO_4$; $C_2MIm\text{-}BF_4$; $C_4MIm\text{-}BF_4$ (13 mmol·L^{-1})[a]	Nucleotides (4)	MeOH/water/isocratic (10:90, v/v)	UV (254 nm)	Study of the effect of ILs on the separation mechanism	[23]
$(C_2)_4N\text{-}BF_4$; $C_2MIm\text{-}BF_4$; $C_4MIm\text{-}BF_4$ (5 mmol·L^{-1})[a]; $C_6MIm\text{-}BF_4$; $C_8MIm\text{-}BF_4$	Fluoroquinolone antibiotics (7)	ACN/water (with ammonium acetate 10 mmol·L^{-1}, pH 3)/isocratic (13:87, v/v)	FD (280/450 nm)	–	[40]
$C_4MIm\text{-}BF_4$ (1 mmol·L^{-1})	Heterocyclic aromatic amines (6)	ACN/water (pH 3.6)/gradient	FD (264/410 nm)	Comparison with triethylamine	[27]

C_4MIm-Cl (20 mmol·L^{-1})[a]; C_8MIm-Cl; C_{10}MIm-Cl	Herbicides (3) and phenols (3)	ACN/water (pH 7)/gradient	UV (280 nm)	Discussion of interaction IL-analyte	[24]
C_4MIm-BF_4 (1 mmol·L^{-1})[a]; C_6MIm-BF_4; C_8MIm-BF_4	Heterocyclic aromatic amines (6)	ACN/water (with KCl 2 mmol·L^{-1}, pH 3.6)/isocratic (19:81, v/v)	ECD	Comparison with ammonium acetate	[29]
C_4MIm-BF_4 (1 mmol·L^{-1})[a]; C_6MIm-BF_4; C_8MIm-BF_4	Heterocyclic aromatic amines (6)	ACN/water (pH 3.6)/isocratic (18:82, v/v)	UV (263 nm) and FD (264/410 nm)	Comparison with triethylamine	[28]
C_2MIm-BF_4; C_4MIm-BF_4 (5 mmol·L^{-1})[a]; C_6MIm-BF_4 (1 – 5 mmol·L^{-1})[a]; C_4MIm-PF_6	β-blockers (7)	ACN/water (pH 3)/isocratic (15:85, v/v)	UV (254 nm)	Comparison with triethylamine and with sodium dodecyl sulfate	[8]
				Discussion of interaction IL-analyte	
C_4MIm-Cl (0.4 %, v/v)[a]; C_4MMIm-BF_4 (0.4 %, v/v)[a]; C_2MIm-BF_4; C_4MIm-BF_4	Selenium species (6)	Water (pH 6)	ICP-MS	Best separation was achieved with a mixture of ILs	[41]
C_2MIm-Br; C_4MIm-Br; C_6MIm-Br; C_8MIm-Br; C_4MIm-Cl; C_4MIm-BF_4; C_4MIm-Ala[d, e]; C_4MIm-Val[d, e]; C_4MIm-PhAla[d, e]; C_2MIm-Leu[d, e]; C_4MIm-Leu (4.0 mmol·L^{-1})[a, d, e]; C_6MIm-Leu[d, e]; C_8MIm-Leu[d, e]	Ofloxacin enantiomers (2)	MeOH/water ($CuSO_4$, 3 mmol·L^{-1})/isocratic (20:80, v/v)	UV (293 nm)	Comparison with the use of achiral and chiral ILs	[42]

[a]IL selected (others were also tested)
[b]1-heptoxymethyl-3-hexylimidazolium tetrafluoroborate
[c]1-ethyl-3-methylimidazolium tosylate
[d]Chiral ILs
[e]Amino acid-based ILs

the preferred ones. Among them, probably C_4MIm-BF_4 is the IL of choice in the majority of applications, in all cases for reversed-phase silica-based C_{18} stationary phases [8, 17, 21–24, 27–29, 36, 38, 40]. It is also important to note that low concentrations of ILs are needed in these works.

Different groups of compounds have also been analyzed with this approach. There is only one application regarding the separation of inorganic compounds (selenium species) [41]. In this particular case, best results were obtained when mixing two ILs as additives: C_4MIm-Cl and C_4MMIm-BF_4. In the rest of applications, organic compounds are better separated in the presence of ILs as additives in the mobile phase. Among them, basic drugs [8, 13, 17, 20, 21, 23, 25, 26, 33, 34, 39, 40] and basic organic contaminants [24, 27–29] constitute the main type of analytes studied.

In the reported applications, the chromatographic separations are normally carried out in combination with diode array detection (DAD) or ultraviolet detection (UV) [8, 13, 17, 20–26, 28, 33, 34, 36, 38, 39]. Several works also employ fluorescence detection (FD) [27, 28, 40], electrochemical detection (ECD) [29, 35], or inductively coupled plasma-mass spectrometry detection (ICP-MS) [41]. Unfortunately, there are no works which use light-scattering detection (ELSD) or mass spectrometry (MS), probably because the ILs may cause posterior interferences with these detectors [43].

Horváth et al. have proposed a model (∼two-retention site model) to evaluate the silanol suppressing ability of masking agents [44, 45]. This model has been tested considering imidazolium-based ILs as masking agents [8, 28, 39]. The final equation derived from the method is the following:

$$\frac{[A]}{k_0 - k} = \frac{1}{k_2 K_A} + \frac{[A]}{k_2} \tag{9.1}$$

where k_0 and k are the retention factors of the analyte in the absence (k_0) or in the presence (k) of the masking agent (additive, A) at a concentration of $[A]$; k_2 is the silanophilic contribution to the retention mechanism of the analytes studied; and K_A is the binding constant between the silanol and the additive. High K_A values involve low retention times of the analytes and so more stable interactions between the free silanol groups of the stationary phase and the masking agent [7, 28].

It is possible to estimate the best IL to be selected as mobile phase additive from the plots of $[A]/(k_0 - k)$ versus $[A]$, by obtaining K_A through the intercept (these plots are straight lines). From this K_A value, it is also possible to estimate the optimum IL concentration (C_{IL}) needed to suppress the effect of free silanol groups of the stationary phase up to 95 % [7]. C_{IL} can be calculated as $29/K_A$ [45]. It is important to highlight that values higher than 10 mmol·L^{-1} are commonly obtained for conventional additives, whereas those obtained for ILs are much lower, around 1 mmol·L^{-1} [28, 39].

Chiral ILs have also been employed in HPLC as mobile phase additives with the purpose of improving the enantioseparation of chiral compounds. Thus, Bi et al. have studied the separation of ofloxacin enantiomers by HPLC using different

amino acid ILs containing chiral anions [42]. A comparison was also established with achiral ILs, and it was observed clearly superior enantioseparation efficiency when the chiral C_4MIm-Leu was used as additive.

Among other interesting approaches, Jia et al. have studied the separation of five phenolic acids in the presence of C_6MIm-Br and gold nanoparticles (Au-NPs) in the mobile phase [35]. The addition of the IL reduced retention of the analytes on the stationary phase, whereas the Au-NP catalysis power enabled peak areas of the analytes.

Despite the wide number of advantages that ILs offer as mobile phase additives, particularly when compared with common masking agents such as TEA, they present one disadvantage, and it is that they can cause interference during detection [43]; thus, proper selection of the wavelength detection and/or tailored IL is advisable prior to the establishment of the analytical method.

9.2.3 IL-Based Surfactants as Pseudo-stationary Phases

It has been observed that those ILs possessing long alkyl chains are able to form micelles in water when their concentration reaches a critical concentration value: the critical micelle concentration (CMC). When these ILs with surfactant properties are dissolved in water, they act as salts in water, but they do still retain several of their intermolecular interactions. This group of ILs has been termed as ionic liquid-based surfactants [46–48]. IL-based surfactants can also be easily modified like ILs, and more importantly, simple modifications in their structures lead to important variations in the micellar properties of their solutions. This behavior is hardly observed with conventional cationic surfactants such as cetyltrimethylammonium bromide (CTAB). Moreover, micelles formed by ILs exhibit characteristically low CMC values if compared to conventional cationic surfactants with similar structures [46–48], and this means that lower amounts of ILs are required to take advantage of the micelle properties.

Micellar liquid chromatography (MLC) is a mode of HPLC which utilizes surfactants in the mobile phase at concentrations above the CMC [49]. These micelles, once formed in the aqueous phase of the HPLC mobile phase, do not act exactly as additives, but they really comprise a pseudo-stationary phase [50]. In fact, a three-phase model is required to understand the mechanisms involved in all partition equilibria [51]. Figure 9.3 includes main equilibria taking place when MLC is utilized with IL-based surfactants.

It is important to consider that most applications of MLC require the utilization of hybrid micellar mobile phases which contain micelles in water and involve the formation of ternary systems upon addition of organic solvents (which are required to decrease analysis times). Thus, detailed studies of organic solvent influence on IL-based surfactants micelle behavior are quite important in the field [52].

One criterion to select an adequate surfactant for MLC is the requirement of a low CMC value, which is fulfilled by the majority of IL-based surfactants. Thus,

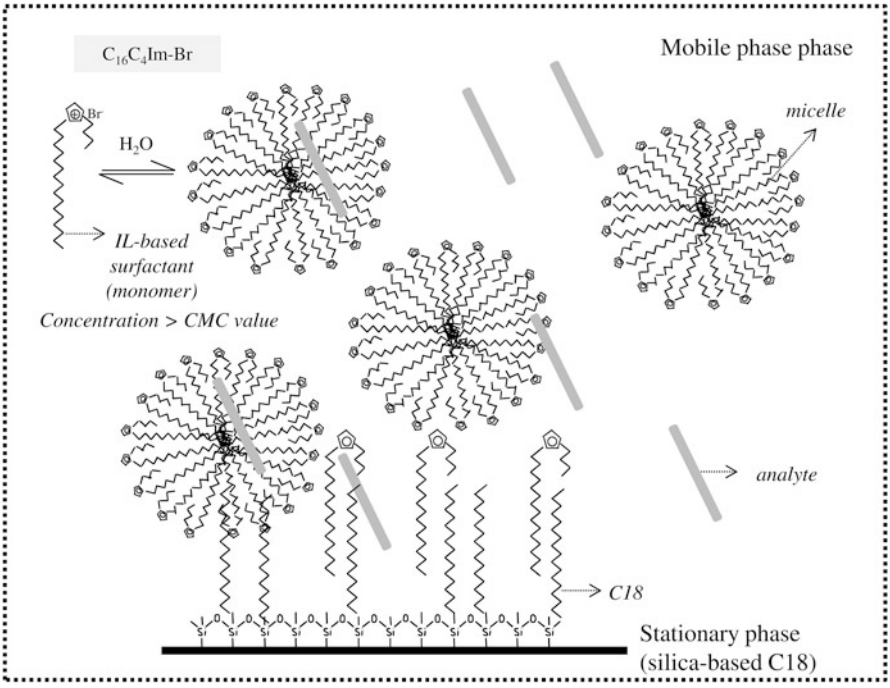

Fig. 9.3 Complex equilibria taking place in MLC when IL-based surfactants are utilized

our group studied the MLC behavior of $C_{16}C_4$Im-Br with the target analyte benzene and three different stationary phases, getting results totally comparable to those of CTAB [52]. More recently, Flieger et al. also studied the MLC behavior of C_{12}MIm-Cl with eight derivatives of 1,4-thiosemicarbazides and different stationary phases, obtaining in this case performance results in the separation comparable to that of the anionic surfactant sodium dodecyl sulfate (SDS), which is the most widely used in MLC [53]. While the studies of IL-based surfactants on MLC are still limited, it is expected that more applications will flourish.

9.2.4 ILs as Stationary Phases

ILs have also been tried as structural modifiers of HPLC stationary phases, constituting surface-confined ionic liquids (SCILs) [54–56]. This trend is particularly novel in analytical chemistry, and a number of works are being currently undertaken. Thus, a number of improvements are still expected in the literature.

Liu et al. were the first to report, in 2004, the utilization of a SCIL stationary phase for the separation of four ephedrines [57]. The SCIL column integrated the IL 1-(mercaptopropyl)alkyl-3-hexyl-imidazolium tetrafluoroborate.

Since then, a large number of works has reported the development of new stationary phases in which ILs are covalently attached to silica sorbents. The advantages of the use of these SCILs columns are derived from the tunability of the ILs [43, 58]. To sum up, they have the potential for truly multimodal retention properties, that is, the ability to interact with analytes through different mechanisms: hydrophobic, electrostatic, and hydrogen bonding, despite the presence of a neat positive charge on the SCIL stationary phase.

Zhang et al. recently reviewed the different synthetic routes most commonly employed to prepare SCIL stationary phases [43]. In all the cases, a coupling agent is needed to attach the silica substrate to the IL.

Propyltrimethoxylsilane (PTMS) derivatives have been commonly selected as coupling agents and, depending on the type of PTMS, two different routes of synthesis can be distinguished: (1) the monomeric route, in which γ-halo-PTMS are normally employed, and (2) the polymeric route, in which γ-mercapto-PTMS (MPS) is needed.

In the monomeric route (Fig. 9.4), the most employed γ-halo-PTMS as coupling agent is γ-chloro-PTMS (CPTMS) [43]. Two synthetic pathways can be distinguished in the monomeric route. There is a *heterogeneous* process (Fig. 9.4a), in which silica is first modified by the coupling agent, and then, a substituted or non-substituted imidazole is attached in situ to the modified silica. There is also a *homogeneous* process (Fig. 9.4b), in which the coupling agent is reacted first with the imidazole, and then, the silica is added. Although monomeric heterogeneous processes are easier to carry out, the homogeneous route is commonly selected if greater bindings are desired (higher coverage of IL over the silica surface) [59, 60].

Very recently, Zhang et al. described the preparation of a SCIL stationary phase by co-immobilization of two silane coupling agents (CPTMS and octadecyltrichlorosilane) to silica, followed by quaternization of methylimidazole to form polar-spaced phase [61].

The monomeric route for obtaining SCILs stationary phases has only been reported for two pyridinium-based SCILs [62, 63]. Liu et al., in 2002, also reported the preparation of a quaternary ammonium-based SCIL stationary phase, which was successfully employed in the separation of 22 alkaloids [64]. The rest of the reported applications for SCILs and the monomeric route are devoted to imidazolium-based SCILs. These SCILs included imidazolium cations containing aliphatic chains like methyl [65–67], butyl [68], hexyl [69], octyl [70–72], decyl [69], or octadecyl [61, 73], containing benzyl groups [72] or containing sulfonate groups [72, 74].

In the polymeric route (Fig. 9.4c), SCILs are prepared from ILs containing vinyl or allyl groups as substituents. This route also requires a MPS coupling agent and, in the majority of cases, goes through a *heterogeneous* process. Silica is first modified with MSP, followed by the immobilization of the vinyl- or allyl-IL via a surface-initiated radical chain-transfer reaction using azobisisobutyronitrile (AIBN) as radical initiator [75, 76]. The already formed polymeric SCILs could suffer further modifications by the substitution of the halide anion with other anions such as BF_4^-, by means of a metathesis reaction [77]. Recently, co-polymerization techniques in which both cation and anion suffer binding on silica have also

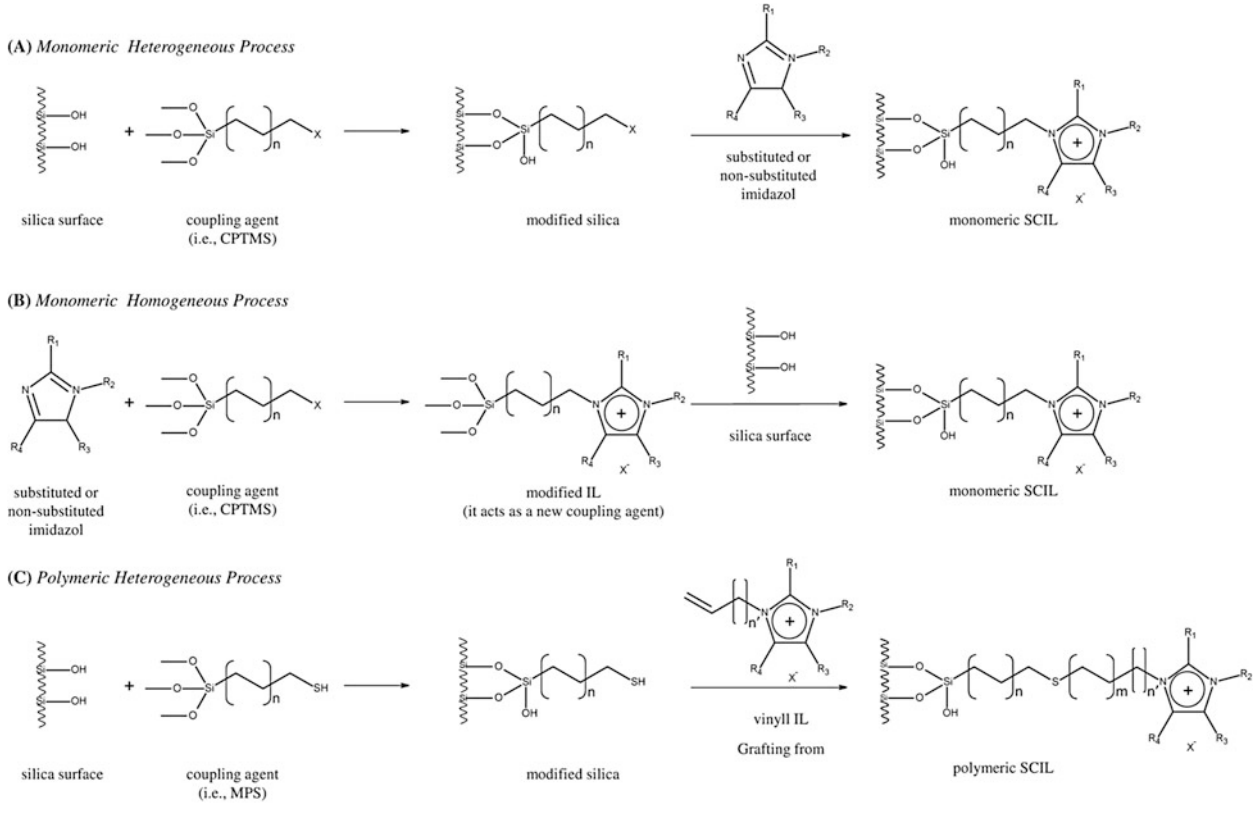

Fig. 9.4 Common synthetic procedures of surface-confined ionic liquid stationary phases

been reported [78], being in this case necessary an IL possessing polymerizable (vinyl/allyl) groups in both cation and anion.

Up to date, all works in polymeric SCILs stationary phases are based on imidazolium cations containing aliphatic chains [73, 75, 79, 80] or sulfonate groups [76, 81]. Recently, Qiao et al. reported the utilization of two dicationic ILs, 1,4-bis(3-allylimidazolium)butane and 1,8-bis(3-allylimidazolium)octane, in combination with Br^- or NTf_2^- anions to synthesize SCIL stationary phases, achieving column efficiencies as high as 130,000 plates·m^{-1} [77].

New methodologies of synthesis are appearing in the recent literature. For example, those involving the use of different coupling agents: γ-glycidoxypropyl-trimethoxysilane (GPTMS) [82] or γ-aminopropyltrimethoxysilane (APTMS) [83].

One of the main interesting characteristics of SCILs stationary phases is their multimodal behavior. This term refers to the ability of the stationary phase to interact with analytes through a combination of mechanisms (as it was mentioned above: hydrophobic or hydrophilic interactions, dipole-dipole interactions, electrostatic interactions, hydrogen bonding, π- π stacking, and shape and planar recognitions). In addition to this, the interest in obtaining separations for anions, cations, and neutral molecules within the same chromatographic run is obvious. SCIL phases have proved to be valid when used in reverse mode, normally requiring low amounts of organic modifiers [57, 62, 63, 65–76, 79, 80, 83–87] and under normal conditions [57, 65–68]. In other words, these phases had a reversed-phase chromatographic behavior for neutral aromatics, and at the same time, SCIL phases have also shown to behave like strong anion exchange stationary phases. They have also been successful when utilized in supercritical fluid chromatography (SFC) [88] and are showing promising results in hydrophilic interaction liquid chromatography (HILIC) [57, 65–68, 76, 77, 81, 83, 85].

These complex intermolecular interactions have been deeply studied by testing the separation performance of the SCILs phases with analytes of different nature and under different separations conditions. Also, the application of the linear solvation energy relationship (LSER) approach has been particularly useful. This linear method, also known as the Abraham model, is widely used to probe the type and relative importance of the interactions that govern solute retention in chromatography [89, 90]. The LSER model is defined by Eq. 9.2:

$$\log SP = c + eE + sS + aA + bB + lL \tag{9.2}$$

where e is the contribution of lone pair electron interactions (π –π or n – π interactions), s indicates the dipole-type interactions (polarizability or dipolarity), a the hydrogen-bond acidity, b the hydrogen-bond basicity, and l the cavity formation and dispersion interactions. The five system constants of Eq. 9.2, namely, E, S, A, B, and L, are determined by the multiple linear regression analysis of the numerous solute descriptors and the retention factor of the probes. The results obtained from the LSER model to SCILs phases also support their multimodal character approach [63, 70, 72, 91–93].

To summarize, a growing number of works are focusing on the development of novel SCIL phases (with different synthetic approaches) due to their inherent multimodal behavior, and this research area for ILs is expected to keep on generating successful results in chromatography.

9.3 ILs in Counter-Current Chromatography (CCC)

CCC is a separation technique in which both the mobile and the stationary phase have a liquid nature [94]. Thus, biphasic liquid systems are involved in the separation process. CCC presents several advantages over HPLC; for example, it allows very high concentration of analytes and so it has been widely used as a preparative technique.

There are important instrumentation differences between CCC and HPLC. Thus, centrifugation fields are required to maintain the liquid stationary phase in the CCC system, while the mobile phase passes through [95]. There are two main types of CCC columns: hydrodynamic and hydrostatic, both with inherent advantages and disadvantages depending on the specific application [96].

The most common polar systems used in CCC are the so-called aqueous two-phase systems (ATPSs), possessing two aqueous liquid phases. One of them normally contains a polymer, typically polyethylene glycol (PEG), and the second one contains a salt. Nonpolar systems in CCC do not contain water but proper mixture of organic solvents [95].

ILs, as novel solvents with unique solvation abilities, have also found an application field in CCC [96], as it has been summarized in Table 9.2 [97–101]. For nonpolar systems, a proper mixing of the selected IL with other solvents to favor their usability in CCC (given usually their high viscosities) is required.

The first report studying the theoretical applicability of IL as solvents in CCC was carried out by Berthod and Cardá-Broch in 2003 [102]. The authors obtained the fully ternary diagrams of the mixtures: methanol/water/C_4MIm-PF_6, ethanol/water/C_4MIm-PF_6, 1-propanol/water/C_4MIm-PF_6, 2-propanol/water/C_4MIm-PF_6, and acetonitrile/water/C_4MIm-PF_6, to characterize possible biphasic systems with adequate properties for CCC. The authors also obtained the partition behavior of up to 38 substituted aromatic compounds in these systems.

A year later, Berthod and Cardá-Broch carried out the first practical application [101]. Since then, the majority of applications of ILs in CCC have been undertaken using nonpolar systems containing ILs [97, 98, 100, 101], but an interesting application using an ATPS based on an IL has also been developed [99], as it can clearly be observed from Table 9.2.

Table 9.2 Examples of CCC applications involving the utilization of ILs in two-phase systems

Analytes (number)	Solvents system with ILs to form a 2 phases system	CCC column	Comments	Ref.
Flavonoids (2)	n-butanol/water/C_2MIm-Cl (5/5/0.1–0.5, v/v/M)	Hydrodynamic	Preparative separation from pollen	[97]
	n-butanol/water/C_3MIm-Cl (5/5/0.1–0.5, v/v/M)		Macroporous adsorption resins were used to separate ILs from target compounds	
	n-butanol/water/C_4MIm-Cl (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_5MIm-Cl (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_2MIm-BF_4 (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_3MIm-BF_4 (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_4MIm-BF_4 (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_5MIm-BF_4 (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_2MIm-Br (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_3MIm-Br (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_4MIm-Br (5/5/0.1–0.5, v/v/M)			
	n-butanol/water/C_5MIm-Br (5/5/0.1–0.5, v/v/M)			
Flavonoids (2)	Ethyl acetate/water/C_4MIm-PF_6[a] (5:5:0.2, v/v/v)	Hydrodynamic	Preparative extraction from traditional herbal medicine	[98]
	Ethyl acetate/water/C_6MIm-PF_6[a] (5:5:0.2, v/v/v)			

(continued)

Table 9.2 (continued)

Analytes (number)	Solvents system with ILs to form a 2 phases system	CCC column	Comments	Ref.
	Ethyl acetate/water/C_8MIm-PF_6[a] (5:5:0.2, v/v/v)			
Proteins (4)	ATPS: water/K_2HPO_4/C_4MIm-BF_4 (61.3/23.1/15.6 %, w/w)	Hydrodynamic and hydrostatic	The full phase diagram of this ATPS was obtained	[99]
			Comparison with PEG phases	
Bioactive analytes (2)	Ethyl acetate/water/C_4MIm-PF_6[a] (5:5:0.2 v/v/v)	Hydrodynamic	Preparative extraction from traditional herbal medicine	[100]
	Ethyl acetate/water/C_6MIm-PF_6 (5:5:0.1–0.6) v/v/v)		Ethanol-water in stepwise elution mode was employed to remove the IL from CCC peak fractions by D-101 macroporous resin column	
	Ethyl acetate/water/C_8MIm-PF_6 (5:5:0.1–0.6 v/v/v)			
Aromatic analytes (12)	Acetonitrile/water/C_4MIm-PF_6 (20/40/40 % w/w)	Hydrodynamic	The full phase diagram of this system was obtained	[101]
			Different aromatic solutes, including bases, acids, and neutral compounds, were injected into the CCC column to estimate their distribution constants between the IL-rich phase and the aqueous phase	

[a]This solvent system was the most adequate to work with

9.4 ILs in Gas Chromatography (GC)

Gas chromatography (GC) constitutes the technique of choice for the separation and determination of volatile and semivolatile compounds. ILs have been used successfully as stationary phases in GC capillary columns, mainly due to a number of adequate properties such as high thermal stability, high melting points, low to

negligible vapor pressure even at high temperatures, moderate to high viscosity, and tunable selectivity, among others [103].

High thermal stability is an important requirement for GC stationary phases, and in general, ILs have high thermal stability. This property depends on the nature of anions and cations constituting the IL. As an example, nucleophilic anions are normally more thermally stable [104]. In fact, the upper temperature of the capillary columns is normally set by the thermal decomposition of the ions.

The tunable selectivity refers to the high number of possible ILs that can be a priori synthesized, simply selecting different combinations of cations/anions. This provides a wide range of stationary phases able to interact with analytes through different solvation mechanisms.

As it happened with SCILs in HPLC, the studies of performance of ILs in GC have been widely undertaken utilizing the LSER method. The system constants obtained for most of the current IL-based GC stationary phases have been summarized in different review articles [30, 104, 105], which have helped not only in gaining knowledge about the performance of these novel phases but even also to design best ILs to perform selectively certain separations.

The first reported application involving the utilization of a molten salt as stationary phase in GC was due to Barber et al. [106]. The authors used molten stearates of manganese, cobalt, nickel, copper, and zinc supported on Celite® for the separation of 36 organic compounds. IL stationary phases of the type commonly used in GC were first published by Gordon et al. [107]. The authors studied the separation of 25 organic compounds with quaternary ammonium picrate and bromide ILs. Poole et al. were also pioneers in studying these first IL stationary phases, mainly based on alkylammonium and alkylphosphonium cations and nucleophilic anions [105, 108–118]. All these works are devoted to applications of IL-based stationary phases for packed columns.

However, most publications in GC involve the utilization of wall-coated open-tubular (WCOT) capillary columns, which provide higher efficiency than packed columns [104]. First studies of the applications of ILs in capillary columns were conducted by Poole et al. [110, 111, 114, 119]. The stationary phases were formed by tetraalkylammonium- and alkylpyridinium-based ILs. Since then, several works proposed the utilization of different types of ILs in GC stationary phases. One of the initial interests of IL-based stationary phases was directly related to the possibility of separating polar and nonpolar compounds within the same chromatographic run, due to the inherent solvation abilities of ILs [120].

As GC stationary phases, not only monocationic-based ILs have been used but multicationic, polymeric, hybrid, and chiral ILs, as shown in Fig. 9.5. The utilization of IL-based stationary phases has even extended to multidimensional gas chromatography (GC × GC), ensuring an exciting future applications [121–124].

It is extremely important to mention that the wide interest on IL-based stationary phases has resulted in the commercialization of some of these capillary columns [121].

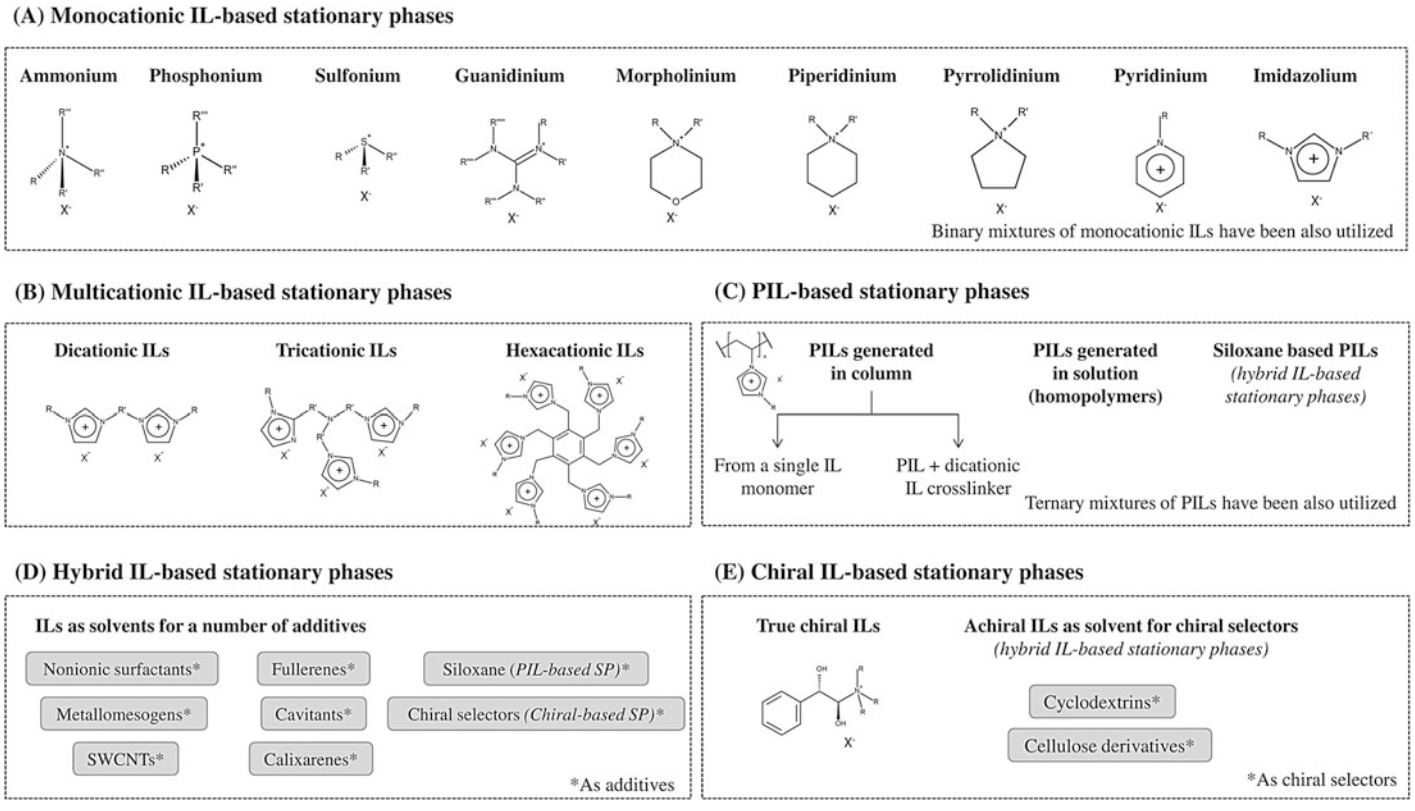

Fig. 9.5 Types of ILs employed as stationary phases in GC

9.4.1 Monocationic IL-Based Stationary Phases

Several cations have been employed to design and develop IL-based capillary columns: ammonium [111, 125–127], phosphonium [119, 128–131], sulfonium [129], guanidinium [128, 132], morpholinium [127], piperidinium [127], pyrrolidinium [127, 129, 133, 134], pyridinium [119, 127, 129], and imidazolium [127–129, 131, 133–136], as summarized in Fig. 9.5a.

Phosphonium-based ILs are characterized by a higher chemical and thermal stability than other ILs containing nitrogen atoms [123]. For example, the stationary phase trihexyl(tetradecyl)phosphonium trifluoromethanesulfonate can operate until 405 °C [131]. In addition, a wide range of anions can be utilized at high temperatures [104, 130, 131]. Guanidinium-based ILs are also quite thermally stable and able to operate up to 250 °C [132]. On the other hand, sulfonium-based ILs exhibited poor thermal stability.

With regard to morpholinium-, piperidinium-, pyrrolidinium-, and pyridinium-based ILs stationary phases, it has been observed that the hydrogen-bond acidity can be regulated by the anion [133, 137].

Nevertheless, the majority of applications that involve IL-based stationary phases for GC utilize imidazolium cations. They have good thermal stability (between 280 and 320 °C [30]), especially those with charge-delocalized anions.

Besides, imidazolium-based ILs normally exhibit lower melting points than pyridinium- and pyrrolidinium-based ILs, thereby decreasing their usefulness as stationary phases [123].

Column possessing a monocationic IL-based stationary phase is not clearly described in the literature. In any case, at first it is necessary to carry out sequences of pretreatment steps to achieve inertness, hydration level, adequate silanol content, and roughness in the fused-silica column [104]. The next step is the column coating. There are two routes for the coating: (1) the direct static coating method [120, 133–135] or (2) the coating with a layer of sodium chloride previous to the static coating method [126–129, 131, 138]. The static coating method enables to prepare columns with variable film thickness.

Binary mixtures of monocationic ILs have also been employed as GC stationary phases, particularly when a separation is not achieved with a single stationary phase [139, 140]. It is important to note that the selected (two) ILs must be miscibles in order to form a single and stable film of stationary phase.

9.4.2 Multicationic IL-Based Stationary Phases

Dicationic and tricationic ILs are currently the most multicationic-based ILs employed as GC stationary phases. Dicationic and tricationic ILs are constituted by two or three cations, respectively, linked by a spacer (see Fig. 9.5b) [141–143]. They are characterized by being liquids in a wide range of temperatures

and by a superior thermal stability to analogous monocationic-based ILs [123]. Thus, capillary columns can operate up to 350 °C when multicationic-based ILs are utilized for GC stationary phases [141, 142, 144].

Dicationic ILs are normally constituted by imidazolium [141–144] or pyrrolidinium [141] cations and alkyl chains as spacers [141]. In some cases, the methylene group in the alkane spacer is replaced by a $–CH_2OCH_2–$ group [141–144]. Regarding anions, NTf_2^- is the most employed. In other cases, the $CF_3SO_3^-$ anion substituted NTf_2^- to minimize the tailing of hydrogen-bonded compounds [141, 143, 144].

Tricationic ILs are constituted by a core structure (the spacer) linked to the cations. Payagala et al. (belonging to Armstrong's group) tested trigonal tricationic ILs formed by mesitylene, benzene, triethylamine, or tris(2-hexanamido)ethylamine cores linked to imidazolium or phosphonium cations [145], in all cases with NTf_2^-. At this point, it is important to mention that monocationic and analogous dicationic ILs possess identical polarities, solvation properties, and chromatographic selectivity. Nevertheless, these trigonal tricationic ILs possess different solvation parameters, higher polarities, and the ability to retain positive charges in some cases. Mutelet et al. studied the performance of trigeminal tricationic IL-based stationary phases for separation of different volatile organic compounds (VOCs) [146]. These tricationic ILs were formed by a $–OCH(CH_2)_2–$ group core linked to imidazolium or pyridinium cations and NTf_2^- or BF_4^- as anions. In these cases, good capacity was obtained by a moderate lengthening in the alkyl chain grafted to the imidazolium cation.

The work of González-Álvarez et al. reports the use of hexacationic ILs [147]. They were composed by a benzene core linked by ethyl groups to six imidazolium cations with different substituents, all derived from the cycloalkanol family, and NTf_2^- or $CF_3SO_3^-$ as anions. The hexacationic IL-based stationary phases also exhibited a dual nature, being able to separate both polar and nonpolar analytes.

9.4.3 Polymeric IL-Based Stationary Phases

Polymeric ionic liquids (PILs) have also been employed as GC stationary phases due to two main advantages: (1) the use of PILs ensures the homogeneity of the IL-coated film at high temperatures, and (2) an improvement of the thermal stability with respect to the monocationic IL-based stationary phases is achieved [30, 104].

Two different approaches have been utilized for preparation of PIL-based stationary phases: (1) the polymerization of a single-cation IL monomer and (2) the grafting of a single-cation structure onto a polysiloxane polymer [104] (Fig. 9.5c).

The polymerization of a single-cation IL monomer can also be performed by two routes: "in column" and "in solution prior to coating." Polymerization in column is carried out via free radical initiator, requiring a vinyl- or alkenyl-IL. The IL normally belongs to the imidazolium family [120, 148–150]. However, columns prepared using phosphonium ILs, polymerized in column, presented higher thermal

stability [150]. In some cases, a dicationic-vinyl-IL can be used as cross-linker to generate more stable and flexible PIL-based stationary phases. Thus, cross-linked PIL-based columns can operate between 300 and 380 °C [120, 148], whereas those without cross-linker can do it between 220 and 285 °C [104].

If the polymerization of a single-cation IL is conducted in solution prior to coating, a solution reaction of the IL monomer and the radical initiator takes place [151–154]. Thereby, homopolymers are generated with higher thermal stability and more rigidity than cross-linked-based PILs.

In addition, siloxane-based PILs can be obtained via the grafting of the IL onto a polysiloxane polymer. In these cases, the resultant column constitutes a hybrid IL-based stationary phase (see Sect. 9.4.4). Two reactions can be used to synthesize them. The first one is the *hydrosilylation* of a poly-hydrosiloxane with the vinyl-imidazolium IL [155]. By contrast, the second reaction is the *quaternization* of a polysiloxane by the addition of an imidazolium salt [156, 157]. The concentration of the IL monomer introduced in the polymer depends on the relative concentration of reactive groups and the molecular weight of the polymer [104].

Studies of binary and ternary mixtures of PILs have also been carried out for the separation of alcohols and carboxylic acids as well as selected ketones, aldehydes, and aromatic compounds [149].

9.4.4 Hybrid IL-Based Stationary Phases

Several reported applications involve the utilization of hybrid IL-based stationary phases. The term "hybrid" refers to phases formed by an additive dissolved in an IL. The IL acts as an adequate solvent for the additive and in turn to form a homogeneous and stable film onto the capillary column.

Siloxane-based PILs (see Sect. 9.4.3) can also be included in this group of hybrid IL-based stationary phases. Other additives utilized to form hybrid IL-based stationary phases include nonionic surfactants [158], metallomesogens [159], single-walled carbon nanotubes (SWCNTs) [160, 161], fullerenes [162], cavitants [163], and calixarenes [164]. They have been added to the stationary phase to obtain desired interactions with analytes during separation.

ILs utilized as solvents are normally of the imidazolium type with different anions: Cl^- [158], PF_6^- [158], $CF_3SO_3^-$ [159], BF_4^- [160, 164], NTf_2^- [162], and CF_3CO^- [162].

Mixtures of ILs can be used too. For example, Tran et al. utilized three different ILs, namely, C_4MIm-BF_4, C_8MIm-NTf_2, and C_2Py-CF_3CO. These ILs were combined with cavitants, formed by complex polar compounds with deep open-ended cavities that can participate in the interactions [163].

9.4.5 Chiral IL-Based Stationary Phases

Chiral IL-based stationary phases have been utilized in GC for the separation of racemates. In these cases, two types of stationary phases have been developed: (1) true chiral ILs with cations containing one or various enantiomeric centers [161, 165] or (2) chiral selectors dissolved in achiral ILs [166–169].

Ding et al. (belonging to Armstrong's group) were the first to report the utilization of two true chiral ILs based on ephedrinium and pseudo-ephedrinium for the separation of alcohols, diols, sulfoxides, epoxides, and acetylated amines [165]. In addition, the true chiral IL *N*,*N*,*N*-trimethyl-2-aminobutanol bis(trifluoromethylsulfonyl)imide has been utilized as GC stationary phase [161]. In the latter application, the IL was coated on a film of SWCNTs for the separation of enantiomers.

Nevertheless, although numerous chiral ILs can be potential stationary phases, their nature tends to favor multiple interaction sites with analytes, disfavoring the separation of enantiomers. Thus, there are more applications that involve the utilization of stationary phases in which the IL only acts as a solvent of a chiral selector. In these cases, the IL is achiral, and for that, the separation of the racemates is due to the chiral selector. Chiral selectors employed are mainly cyclodextrins [166, 167] but also cellulose derivatives [169]. The advantage of using an IL as solvent is that many chiral selectors are difficult to dissolve in conventional polysiloxane columns.

Among other combinations, Sun et al. have described the use of two types of chiral IL-based stationary phases by the development of a column in which a chiral imidazolium-based IL is dissolved in a PIL [168].

9.4.6 Commercial IL-Based Stationary Phases

Commercially available IL-based columns are much smaller than other conventional nonionic columns, which is an important advantage. Besides, they are more stable due to the absence of active hydroxyl groups, and they can operate at high temperatures, producing good peak shape and resolution for a variety of compounds [170].

The first commercial ionic liquid column was introduced by Supelco in 2008 [121]. Today, seven IL-based GC column have been commercialized, namely, SLB-IL59, SLB-IL60, SLB-IL61, SLB-IL76, SLB-IL82, SLB-IL100, and SLB-IL111. They are constituted by four types of IL cations based on phosphonium or imidazolium. All of them contain NTf_2^- except SLB-IL61, which contains NTf_2^- and $CF_3SO_3^-$ in a 1:1 ratio. These new columns range from those who present a PEG equivalent polarity, and with improved thermal stability (SLB-IL59), to phases with extremely high polarity (SLB-IL111) [170].

9.4.7 *Analytical Applications of IL-Based Stationary Phases in GC*

The majority of works published on IL-based stationary phases are focused in their synthesis, preparation, and characterization, but little attention has been paid so far in developing complete analytical applications. There are several works in which a comparison of different IL-based stationary phases is presented [127].

González-Álvarez et al. utilized the IL poly-1-(2-cyclohexanol)-3-(4-vinylbenzyl) imidazolium bis(trifluoromethylsulfonyl)imide to separate effectively a fragrance mixture containing 15 compounds in less than 10 min [150]. The results show retention times and efficiencies comparable to polysiloxane or PEG commercial columns.

On the other hand, the commercialization of IL-based stationary phases has allowed an increase of the interest and acceptance of these types of GC columns. Thereby, many reviews summarized these applications with commercial ones [30, 104], together with the undoubted interest of these commercial IL-based stationary phases for multidimensional separations [170].

Several literature works involve the utilization of commercial IL-based columns in many applications: analysis of essential oils [171–173], biological fluids [174], fuel and petrochemical analysis [175–178], environmental analysis [179–182], lipids [183–188], etc.

As an example to be highlighted, Mondello et al. utilized the SLB-IL59 stationary phase in bidimensional gas chromatography-mass spectrometry (GC × GC-MS) for the analysis of lemon essential oil with successful results [171].

9.5 ILs in Capillary Electrophoresis (CE)

Capillary electrophoresis (CE) is another important analytical separation technique. It requires high electric fields applied in narrow silica-based capillaries to accomplish the separation of analytes [189].

ILs have been used in different modes of CE, such as in nonaqueous CE (NACE) or traditional CE [46, 47, 190], either as supporting electrolytes, as additives to running buffers, or as dynamic coatings. IL-based surfactants have also been used in CE as pseudo-stationary phases in MEKC or in on-line preconcentration techniques based on the use of micelles.

Their applications as stationary phases in capillary electrochromatography (CEC) [191, 192] or as additives to decrease the harmful silanol effect in CEC [193–196] should also be highlighted.

9.5.1 ILs in CE or NACE

Ionic liquids have been utilized as main electrolytes solution or as electrolyte additives in capillary zone electrophoresis (CZE) for a number of applications [197–201]. In these applications, they perform as common salts in aqueous solutions, but with improved behavior due to the maintenance of several intermolecular interactions. Reversed CE electroosmotic flow (EOF), low modifications of the background current, and increased resolution between analytes can be cited among main interesting features of reported applications for ILs in CZE. ILs have also been employed to achieve chiral separations in CE, generally in combination with cyclodextrins [202–206].

They have also been utilized as ionic additives in nonaqueous media to form running buffers [207–210]. It must be noted that ILs influence the electrophoretic mobility of the buffer system, while acting simultaneously as supporting electrolytes [190].

In addition, it is evident that ILs are able to modify the capillary dynamically [211]. ILs bonded to CE capillary have also been used in complex applications, for example, to enhance the separation of drugs in human samples [212]. Similarly, the PIL poly-ViC$_4$Im-Br was physically absorbed on the silica capillary for the separation of basic proteins and anionic analytes [195].

9.5.2 ILs and IL-Based Surfactants in MEKC

Up to date, the most successful application of IL-based surfactants in CE is linked to MEKC. Schnee and Palmer performed a theoretical study using the LSER model [213], which demonstrated that cationic surfactants with the largest and most hydrophobic head groups were the best candidates to provide a very cohesive environment and strongest interactions with polar compounds in CE. This clearly points out to IL-based surfactants, mainly imidazolium-based IL-based surfactants. Since then, IL-based surfactants have found an important application field as pseudo-stationary phases in MEKC. Table 9.3 [214–218] summarizes several of these applications. From the examples listed in Table 9.3, it can be observed that imidazolium-based and pyrrolidinium-based ILs perform better than conventional cationic surfactants like CTAB in such separations, also requiring low amounts.

IL-based surfactants have also been utilized in MEKC as modifiers of the medium, which already contains a conventional surfactant [219–221]. In these applications, they perform as modifiers of buffers, in the same fashion as conventional molecular organic solvents, but with improved resolution while maintaining adequate background current.

Table 9.3 Examples of MEKC applications involving the utilization of IL-based surfactants as pseudo-stationary phases

IL-based surfactant	Conc (mM)/CMC in water (mM)	Application	Comparison with a conventional surfactant	Ref.
C_{12}MPyrr-Br	50/13.6	LSER model with 35 probes separation of 4 neutral benzene-type solutes	Yes (CTAB)	[214]
C_{14}MPyrr-Br	25/3.30			
C_{16}MIm-Br	15/0.83			
C_{18}MIm-Br	10/0.25			
C_{16}MIm-Br	10/0.84	Separation of 7 phenolic compounds	Yes (CTAB)	[215]
C_{12}MIm-Cl	15–20/13.17	Separation of resorcinol and 3 methylresorcinol isomers and 3 neutral benzene derivatives	No	[216]
C_{14}MIm-Cl	15–20/2.98			
C_{16}MPyrr-Br	20/0.83	Separation of 7 benzodiazepines	Yes (CTAB)	[217]
C_{16}MIm-Br	20/0.84			
C_{14}MIm-Br	20/2.6	Separation of 7 urinary nucleosides	Yes (TTAB)	[218]

9.5.3 IL-Based Surfactants in On-Line Preconcentration Techniques

IL-based surfactants have been utilized in several CE on-line preconcentration techniques based on the use of micelles.

Su et al. were the first to report the successful utilization of C_{16}MPyrr-Br over CTAB in sweeping-MEKC for the separation of seven benzodiazepines [217]. More recently, C_4MIm-Br has proved to be efficient in sweeping-MEKC for the preconcentration of methotrexate, folinic acid, and folic acid from biological fluids [222]. The overall technique was more sensitive than analyte focusing by micelle collapse (AFMC).

IL-based surfactants have also been tried in micelle to solvent stacking (MSS). Quirino et al. used the IL-based surfactant C_{12}MIm-BF_4 for the preconcentration and separation of a group of profens and herbicides [223]. The authors obtained up to ten times better performance with this IL-based surfactant compared to the conventional cationic surfactant CTAB as MSS carrier. The superior performance was attributable to several reasons, such as higher affinity between the analytes and the IL-based surfactants, and good solubility of the IL-based surfactant in high percentages of organic solvent, which in turn facilitated a more effective reversal of mobility.

Wang et al. have also reported a two-step stacking method by sweeping and micelle to solvent stacking using the IL-based surfactant C_{16}MPyrr-Br for the CZE separation of bisphenol-A, 2-nitrophenol, and 4-chlorophenol [224]. The CE

column was also conditioned with poly(1-vinyl-3-butylimidazolium) bromide (a PIL) to obtain the anodic EOF.

9.6 Conclusion and Future Trends

Chromatographic and electrophoretic separation techniques have benefited enormously from the incorporation or addition of ILs (and derivatives) in both the mobile phase and the (pseudo or neat) stationary phase. The tunability of ILs and their impressive solvation abilities, among many other interesting physicochemical properties, are the main reasons behind this success.

ILs, IL-based surfactants, and PILs, as well as hybrid materials incorporating them, are expected to continue expanding their applications in chromatographic and electrophoretic techniques, particularly as surface-confined stationary phases in HPLC and as novel stationary phases in GC.

Glossary

ACN	Acetonitrile
AFMC	Analyte focusing by micelle collapse
AIBN	Azobisisobutyronitrile
APTMS	γ-aminopropyltrimethoxysilane
ATPS	Aqueous two-phase system
Au-NPs	Gold nanoparticles
CCC	Counter-current chromatography
CE	Capillary electrophoresis
CEC	Capillary electrochromatography
CMC	Critical micelle concentration
CPTMS	γ-chloro-propyltrimethoxylsilane
CTAB	Cetyltrimethylammonium bromide
CZE	Capillary zone electrophoresis
DAD	Diode array detection
ECD	Electrochemical detection
ELSD	Light-scattering detection
EOF	Electro-osmotic flow
FD	Fluorescence detection
GC	Gas chromatography
GC × GC	Multidimensional gas chromatography
GPTMS	γ-glycidyloxypropyltrimethoxysilane
HILIC	Hydrophilic interaction liquid chromatography
HPLC	High-performance liquid chromatography
ICP-MS	Inductively coupled plasma-mass spectrometry detection

IL	Ionic liquid
Im^+	Imidazolium
LSER	Linear solvation energy relationship
MEKC	Micellar electrokinetic chromatography
MeOH	Methanol
MLC	Micellar liquid chromatography
MPS	γ-mercapto-propyltrimethoxylsilane
MS	Mass spectrometry
MSS	Micelle to solvent stacking
NACE	Nonaqueous capillary electrophoresis
NTf_2^-	Bis(trifluoromethylsulfonyl)imide
ODS	Octadecyl silica
PEG	Polyethylene glycol
PIL	Polymeric ionic liquid
PTMS	Propyltrimethoxylsilane
Py^+	Pyridinium
$Pyrr^+$	Pyrrolidinium
RPLC	Reversed-phase liquid chromatography
SCIL	Surface-confined IL stationary phase
SDS	Sodium dodecyl sulfate
SFC	Supercritical fluid chromatography
SLB-IL59	Commercial IL-based stationary phase 1,12-di(tripropylphosphonium)dodecane bis(trifluoromethylsulfonyl)imide
SLB-IL60	Commercial IL-based stationary phase 1,12-di(tripropylphosphonium)dodecane bis(trifluoromethylsulfonyl)imide
SLB-IL61	Commercial IL-based stationary phase 1,12-di(tripropylphosphonium)dodecane bis(trifluoromethylsulfonyl)imide trifluoromethylsulfonate
SLB-IL76	Commercial IL-based stationary phase tri(tripropylphosphoniumhexanamido)triethylamine bis(trifluoromethylsulfonyl)imide
SLB-IL82	Commercial IL-based stationary phase 1,12-di(2,3-dimethylimidazolium)dodecane bis(trifluoromethylsulfonyl)imide
SLB-IL100	Commercial IL-based stationary phase 1,9-di(3-vinylimidazolium)nonane bis(trifluoromethylsulfonyl)imide
SLB-IL111	Commercial IL-based stationary phase 1,5-di(2,3-dimethylimidazolium)pentane bis(trifluoromethylsulfonyl)imide
SWCNT	Single-walled carbon nanotube
TEA	Triethylamine
THF	Tetrahydrofuran
UV	Ultraviolet detection
VOC	Volatile organic compound
WCOT	Wall-coated open-tubular capillary columns

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