Sustainable Ways of Combining Reactions and Separations Using Ionic Liquids and Carbon Dioxide
Sustainable Ways of Combining Reactions and Separations Using Ionic Liquids and Carbon Dioxide

Proefschrift

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door

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Somayeh Kazemi

June 2013
Summary

Traditional chemical processes show shortcomings caused by using volatile organic compounds as solvents during reactions and separations. Therefore, it is necessary to address this issue by moving toward more environmentally friendly processes. This is possible by using less toxic and hazardous solvents, such as ionic liquids and supercritical carbon dioxide (scCO₂).

Ionic liquids have attracted a lot of attention as potential “green” solvents to replace conventional organic solvents due to their unique properties. Ionic liquids are molten salts, which are liquid below 373 K. They consist of organic cations with organic or inorganic anions. Typically, ionic liquids possess an extremely low vapor pressure, a high thermal stability, and a wide liquid range. Ionic liquids show high solubility for both polar and apolar compounds. As a result of these properties, there are many reports where ionic liquids have been used as solvents for chemical reactions.

Moreover, ionic liquids in combination with CO₂ show numerous advantages. For instance, ionic liquids do not dissolve in CO₂, but CO₂ is highly soluble in ionic liquids. Moreover, it is shown before that CO₂ is able to force two immiscible liquid phases to form one homogeneous phase as CO₂ pressure increases. This interesting behavior, which is known as the miscibility switch phenomenon, is generally applicable for ternary systems containing ionic liquids, CO₂ and organics. A new process set-up based on this phase behavior has been proposed, in which the reaction is carried out in a homogenous phase at high rate (no mass transfer limitations) by selection of a suitable pressure, temperature and CO₂ concentration. After completion of the reaction, a phase separation is induced by changing the conditions. The product can be recovered with high purity from one of the two phases that is substantially free of ionic liquid.

Two model reactions were studied to apply this new process concept. First, the epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol was studied in the
presence of ionic liquids as solvents. (2S,3S)-(−)-3-Phenylglycidol is an intermediate for a well-known potent active anti-inflammatory agent, Ibuprofen. In order to scale up the reaction in an ionic liquid/scCO₂ miscibility switch system, a study was started to select the optimum ionic liquid in this case. The catalytic epoxidation reaction of cinnamyl alcohol in the presence of ionic liquids was optimized with respect to various parameters: (i) type and amount of oxidizing agent, (ii) type and amount of catalyst, (iii) type of ionic liquids (ranging from hydrophobic to hydrophilic), and (iv) temperature. Optimization of the conditions revealed that product stability is the key factor in determining the reaction conditions. Optimum conditions were obtained using the ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][Tf₂N]) with 3 mol% vanadyl acetylacetonate as a catalyst and 1.5 equiv. of tert-butyl hydroperoxide as oxidant at 25 °C.

In order to design the subsequent separation step using CO₂ extraction, it is critical to have the knowledge on the phase behavior of the systems involved. Therefore, the high-pressure phase behavior of ternary systems containing epoxidation reaction compounds, ionic liquids and scCO₂ were measured. Phase behavior experiments were carried out using a synthetic method in the Cailletet apparatus at five different concentrations of CO₂, at temperatures and pressures up to 368 K and 12.1 MPa, respectively. Both ternary systems (cinnamyl alcohol + ionic liquid + CO₂ and (2S,3S)-(−)-3-phenylglycidol + ionic liquid + CO₂) only show one type of phase transition (liquid-vapor to liquid) at the highest pressures studied. A comparison between the two systems shows that both systems behaved similarly at low concentrations of CO₂ (less than 40 mol%). However, by increasing the concentration of CO₂ (more than 40 mol%) higher pressures are necessary to completely dissolve CO₂ in the system containing cinnamyl alcohol compared to (2S,3S)-(−)-3-phenylglycidol. Moreover, a comparison between the binary system of [bmim][Tf₂N] + CO₂ and the studied ternary systems indicates that the addition of organic compounds decreases the solubility of CO₂ in [bmim][Tf₂N]. Finally, using data obtained during this work, the conditions for carrying out the epoxidation reaction in a homogeneous phase and extracting the product with scCO₂ in the two-phase region are determined.
The second model reaction was Friedel-Crafts acylation reaction of ferrocene to acetylferrocene. Ferrocene, which is solid up to 445 K, is a building block for wide range of applications from homogeneous catalysis and material science to biology and medicine. Acetylferrocene is the product of the acylation reaction of ferrocene and has applications as an intermediate in the production of functional groups, combustion catalysts for propellants, and in medicinal chemistry. Recently, a comprehensive investigation of the acylation of ferrocene into acetylferrocene has been conducted in the presence of ionic liquids as solvents instead of conventional organic solvents. The promising results showed that up to 100% conversion and yield could be reached using imidazolium-based ionic liquids, specially [bmim][Tf₂N] as a solvent with scandium triflate (Sc(OTf)₃) as a catalyst.

In order to investigate the feasibility of the product extraction using scCO₂, the solubilities of ferrocene and acetylferrocene in scCO₂ were measured using an analytical method in a quasi-flow apparatus. High-performance liquid chromatography was applied through an online sampling procedure to determine the concentration of ferrocene and acetylferrocene in the scCO₂ phase. The experiments were performed within a temperature range of 308 to 348 K and at pressures ranging from 7.7 to 24.4 MPa. The molar solubilities at the applied conditions range from 8.9 to 31.2 × 10⁻⁴ for ferrocene and 2.5 to 79.2 × 10⁻⁴ for acetylferrocene. The existence of a cross-over area for acetylferrocene is detected at a pressure of around 15 MPa and for ferrocene at a pressure of around 10 MPa. The comparison between the experimental solubility data shows that ferrocene is more soluble in scCO₂ at lower pressures, while at higher pressures acetylferrocene was more soluble in scCO₂. The reason for this behavior is a trade-off between the lower polarity of ferrocene (more dominant at lower pressures) and the molecular structure of acetylferrocene (more dominant at higher pressures). Results obtained in this work show that the solubility of the reaction product acetylferrocene in scCO₂ was sufficiently high to use scCO₂ extraction at high pressures to separate it from its reactant ferrocene in Friedel-Crafts acylation processes.
Furthermore, to investigate the possibility of applying the miscibility switch phenomenon to perform Friedel-Crafts acylation reaction, the high-pressure phase behavior of the ternary system containing ferrocene or acetylferrocene, the ionic liquid [bmim][Tf$_2$N] and CO$_2$ were studied experimentally. The experiments were performed using a synthetic method in the Cailletet apparatus within a pressure range of 0.25 up to 10 MPa and in a temperature range of 278 up to 368 K. Five different concentrations of CO$_2$ (10, 20, 31, 40 and 50 mol% of CO$_2$) were investigated. While for the ternary systems containing ferrocene + ionic liquid + CO$_2$ three phase transitions (SLV → SL, SL → L and LV → L) were experimentally measured, for the ternary systems with acetylferrocene two different regions of liquid-vapor (LV) and liquid (L) were recognized. It is also shown that CO$_2$ acts as a co-solvent in all measurements in the presence of ferrocene, even at high CO$_2$ concentrations (50 mol%). Ferrocene is thus more soluble in the [bmim][Tf$_2$N] + CO$_2$ mixture than in pure [bmim][Tf$_2$N]. Removing CO$_2$ from the system by pressure release results in precipitation of the ferrocene, so that it can be recovered from the ionic liquid phase. This is contrary to many other ionic liquid + organic systems that show anti-solvency behavior in the presence of large amounts of CO$_2$, where it is possible to recover the organic compound as precipitate by the addition of supercritical CO$_2$.

The solute effect on the phase behavior was studied by comparing the experimental results of the binary system [bmim][Tf$_2$N] + CO$_2$ with those of the ternary system acetylferrocene/ferrocene + [bmim][Tf$_2$N] + CO$_2$. It is shown that addition of an acetyl group to the ferrocene molecule dramatically changes the phase behavior of the binary system. Finally, the homogeneous liquid phase region was determined experimentally. This study indicates that performing the acylation reaction of ferrocene to acetylferrocene in the presence of [bmim][Tf$_2$N] and CO$_2$ in a homogeneous liquid phase is feasible.

Finally, the benefits of applying new process set-up were investigated from economical and ecological point of view. For this purpose, the conventional production process is compared with the alternative process proposed in this study.
Summary

using ionic liquid/CO₂ for both model reactions. From an ecological point of view, the ionic liquid/CO₂ production process generates much less catalyst and solvent losses and consumes much less energy. From an economical point of view, there are capital expenditures associated with the purchase of new equipment for the ionic liquid/CO₂ production process, but the savings in operational costs for both reactions are much higher, making the new process overall more attractive than the conventional one. For the market of 100 ton per year 3-phenylglycidol production, new process saving will be 3.10 million euros per year. For the production of 100 ton per year of acetylferrocene, it is estimated that using ionic liquid/CO₂ process will save 0.94 million euros per year regarding variable and fixed costs for the production of acetylferrocene. In conclusion, even though the ionic liquid/CO₂ production process needs high start-up investment but the amount of the money saved each year is higher than this investment, and therefore it is economically and ecologically feasible to replace the current production process.
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Introduction
1. Introduction

1.1. Problem definition

The effects of climate change, such as temperature increase, heat waves, drought and precipitation, are becoming ever more evident. Growing human industrial activity is known as one of the key factors playing a role in these regards. It was calculated that in 2009, the cost related to air pollution from the 10,000 largest polluting facilities in Europe corresponded to an amount of 169 billion euro for the harm to the health and the environment. During the past decades, raising awareness of environmental issues emerging from industrial activities has included the need to move towards more efficient and sustainable processes. One of the major causes of air pollution is the presence of Volatile Organic Compounds (VOCs) in the atmosphere.

Solvents are mainly used to transfer heat and mass in chemical processes and enable the subsequent separation and purification steps. They traditionally consist of VOCs, such as benzene, hexane, acetone, etc. The main drawback of using VOCs is their high vapor pressure, resulting in emissions and polluting indoor and outdoor air quality. They are also often flammable and toxic, and represent performance, safety and health concerns [1]. It is estimated that around 20 million Tons of VOCs is released into the atmosphere each year due to industrial activities [2]. For instance, in the US, 2/3 of the all industrial emissions and 1/3 of all VOC emissions originate from solvent emissions [3].

Figure 1.1 shows the emissions of non-methane VOCs (NMVOCs) in 2009 in Europe (EU) indicating the sources for this class of emissions [4]. It can clearly be seen that the most polluting sector regarding NMVOCs emissions is “the solvent and product use sector” with a contribution of 35.8%.

It is expected that future chemical processes will use alternative environmentally benign and green solvents as reaction and separation media. In order to promote innovative environmentally benign chemical technologies, US Environmental
1. Introduction

Protection Agency (EPA) introduced the green chemistry principles in 1990, which are [5]:

1. **Prevention**: It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom Economy**: Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Syntheses**: Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

![Figure 1.1. Contribution to EU NMVOCs emissions from main source sectors in 2009 [4]](image)
4. **Designing Safer Chemicals**: Chemical products should be designed to effect their desired function while minimizing their toxicity.

5. **Safer Solvents and Auxiliaries**: The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. **Design for Energy Efficiency**: Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. **Use of Renewable Feedstock**: A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. **Reduce Derivatives**: Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**: Catalysis (as selective as possible) are superior to stoichiometric reagents.

10. **Design for Degradation**: Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time analysis for Pollution Prevention**: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention**: Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Therefore, the main focus of green chemistry is to reduce or eliminate the use or generation of hazardous substances in the design, manufacture and use of chemical products. In other words, pollution generation should be prevented instead of remediation. Green processes must be designed to be energy-efficient with minimum waste generation and no use of toxic and hazardous solvents. To reach this goal, many legislations as well as voluntary controls have already been introduced. Some examples of these legislations in Europe are the Environmental protection act 1990, the EU solvent Directive (1999/13/EC), the Control of Substances Hazardous to Health (COSHH) regulations, the Registration Evaluation and the Authorization of Chemicals (REACH) standard, among others [6].

The EU solvent Directive Commission is following the implementation of the VOC Solvents Emissions Directive in its Member States [7]. According to this Directive, Member States are obliged to report to the Commission periodically on the implementation of the Directive. As a consequence, the chemical industry is under considerable pressure to replace conventional organic solvents with more environmentally benign solvents.

As a result of these regulations and the joint effort from scientific and industrial sectors, NMVOCs emissions in EU dropped by 56% from 16740 Gg in 1990 to 7412 Gg in 2010 (see Figure 1.2).

In recent years, efforts have been made to replace VOCs with more environmentally friendly solvents. Some of the successful alternatives are discussed in the next pages.
1. Introduction

1.2. Alternative solvents

Many alternatives to organic solvents have been proposed over the last two decades. Ideally solvent-free conditions, or the use of water as the ultimate green solvent can be considered. However, many organic compounds do not dissolve in water, and especially solids cannot be processed without a solvent. Therefore suitable alternatives have been sought and found in the classes of (i) ionic liquids, (ii) supercritical fluids and (iii) fluorous media.

1.2.1. Ionic liquids

Ionic liquids have gained a lot of attention as emerging environmentally benign solvents [8]. They can replace conventional organic solvents in several applications due to their unique features. Ionic liquids are salts with melting points below 373 K. They consist of an organic cation combined with an organic or inorganic anion [8].
1. Introduction

Ionic liquids show, in general, a very interesting set of properties to be used for different applications in chemical industry.

- The melting points of these organic salts are frequently found below 150 °C [9], and occasionally as low as -96 °C [10]. Some ionic liquids are stable up to 500 K [11].

- At room temperature they have no measurable vapor pressure due to their ionic nature [8].

- They normally have high solvency power for polar and non-polar compounds.

- Billions of ionic liquids can be designed and synthesized by selecting different ion pair combinations, which enable them to possess specific properties. Furthermore, the ability to tune the solvent properties of the ionic liquids is one of their outstanding features, which makes them unique solvents for various reactions and separations [12-19].

- Moreover ionic liquids are almost nonflammable, highly thermally and (electro)chemically stable and present a large liquid range [8].

The main challenges to the large scale application of ionic liquids are their high costs, their high toxicity (many ionic liquids contain halogens), the unknown long term stability and their relatively high viscosity compared to most common molecular solvents. The latter decreases the mass transfer rate during reaction and separation processes [10]. However, the viscosity of ionic liquids can drop significantly by addition of co-solvents such as carbon dioxide (CO₂) [8]. An overall comparison between ionic liquids and organic solvents is presented in Table 1.1. [20].

Recently, deep eutectic solvents as a new class of ionic liquids analogues have been attracting a lot of attention. Deep eutectic solvents are mixtures of two or three solid compounds that form a liquid upon mixing. These mixtures are often based on choline chloride, metal chloride, carboxylic acids and/or urea [21-23].
1. Introduction

Table 1.1. Comparison between organic solvents and ionic liquids [24]

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<tr>
<th>Property</th>
<th>Organic solvents</th>
<th>Ionic liquids</th>
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<tbody>
<tr>
<td>Number of solvents</td>
<td>&gt; 1000</td>
<td>&gt; 1000000</td>
</tr>
<tr>
<td>Applicability</td>
<td>Single function</td>
<td>Multifunction</td>
</tr>
<tr>
<td>Catalytic ability</td>
<td>Rare</td>
<td>Common and tunable</td>
</tr>
<tr>
<td>Chirality</td>
<td>Rare</td>
<td>Common and tunable</td>
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<tr>
<td>Vapor pressure</td>
<td>Obeys the Clausius-Clapeyron equation</td>
<td>Negligible vapor pressure under normal conditions</td>
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<tr>
<td>Flammability</td>
<td>Usually flammable</td>
<td>Usually nonflammable</td>
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<td>Solvation</td>
<td>In many cases weakly solvating</td>
<td>Strongly solvating</td>
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<td>Polarity concept questionable</td>
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<tr>
<td>Tunability</td>
<td>Limited of solvents available</td>
<td>Virtually unlimited range means &quot;designer solvents&quot;</td>
</tr>
<tr>
<td>Cost</td>
<td>Normally cheap</td>
<td>Typically between 2 and 100 times the cost of organic solvents</td>
</tr>
<tr>
<td>Recyclability</td>
<td>Green imperative</td>
<td>Economic imperative</td>
</tr>
<tr>
<td>Viscosity (Pa.s)</td>
<td>0.0002 – 0.1</td>
<td>0.022 - 40</td>
</tr>
<tr>
<td>Density (kg m⁻³)</td>
<td>600 - 1700</td>
<td>800 - 3300</td>
</tr>
<tr>
<td>Refractive index</td>
<td>1.3 – 1.6</td>
<td>1.5 – 2.2</td>
</tr>
</tbody>
</table>

These solvents share many advantages with ionic liquids, such as the low volatility, but are also non-toxic and readily biodegradable. However, the lower thermal stability and high viscosity are their main drawbacks in this early investigation stage [25].
1. Introduction

1.2.2. Supercritical fluids

Fluids that are heated above their critical temperature and compressed beyond their critical pressure become supercritical [20]. In comparison to liquid solvents, supercritical fluids (SCFs) have similar density, higher diffusivity and mass transfer rate, and these properties can be tuned easily by temperature and pressure variation. In addition, the viscosity of SCFs is about 100-fold lower than that of liquid solvents [26]. Due to the mentioned advantages, SCF technology has emerged as an interesting technology for various applications such as new solvents for organic and catalytic reactions and also product extraction. The use of SCFs can result in high quality and pure final products.

Supercritical CO$_2$ (ScCO$_2$) is the most well-known SCF, and is an attractive alternative to replace the VOCs as an ideal green reaction mixture or extraction solvent due to the following advantages [27]:

- ScCO$_2$ possesses a mild critical temperature (304.25 K) and critical pressure (7.38 MPa), which can easily be reached in chemical processes.

- It is also known to be non-flammable, non-toxic, abundantly available, inexpensive and relatively inert [26].

- Additionally, the solvency power of scCO$_2$ can be tuned by changing the pressure or temperature, which makes it a good candidate for extraction processes.

- Finally, scCO$_2$ is easy to recycle.

Despite the mentioned advantages of using scCO$_2$ instead of VOCs, their low solvency power for polar compounds remains a drawback for their application.
1. Introduction

1.2.3. Fluorous media

Perfluorocarbons (PFCs) have attracted a lot of attention recently as solvents for many catalytic and thermal reactions \[28-31\]. The main advantages of PFCs is the ease of their separation from their hydrocarbon analogues. They have found application in gas/liquid reactions, liquid/liquid biphasic separations and product and catalyst purification due to the following properties:

- Many organics are immiscible with PFCs, whereas gases have good solubilities in PFCs.
- PFCs have low reactivity and high chemical stability.
- They have low viscosity and non-toxicity.

However, their low reactivity results in a longtime presence in nature, which restrict their application.

1.3. Aim of the thesis

The aim in this thesis is to investigate, whether the properties of scCO\(_2\) and ionic liquids, can be combined to achieve a truly green process. The main objective of the study presented in this thesis is therewith to investigate the feasibility of using ionic liquids and CO\(_2\) in reaction and separation processes. In spite of the mentioned advantages of using ionic liquids as reaction media, the subsequent extraction stage normally uses organic solvents. As a result, even though one step of the process is being performed in more environmentally benign solvent, the whole process cannot be considered as environmentally friendly, since it still suffers from the involvement of VOCs.

Furthermore, it has been shown that scCO\(_2\) can be used to extract a product from the reaction mixture with ionic liquids as solvents \[32\]. The reason is that the solubility of CO\(_2\) in ionic liquids is generally very high, but CO\(_2\) is not able to dissolve most ionic
1. Introduction

liquids [33]. The straightforward spin off of this finding is to extract an organic compound from an ionic liquid using scCO$_2$ as extractant without any contamination by the ionic liquid [34]. Furthermore, it is possible to tune the solvency power of scCO$_2$ by adjusting the pressure, which makes it a good candidate for the extraction process.

One of the interesting characteristics of CO$_2$ in ternary systems, which is known as the miscibility switch phenomenon, is that it can force two immiscible liquid phases to form one homogeneous phase upon pressure increase [35]. Based on this phenomenon, it is possible to combine reactions and separations in the presence of ionic liquids and CO$_2$ in a smart way. The reaction can be performed in the homogeneous phase and after completion of the reaction, the conditions can be changed, resulting in a phase split in which one of the phases is substantially free of ionic liquid, allowing the recovery of the product without any solvent contamination [36,37]. A schematic presentation of this process set-up is shown in Figure 1.3.

![Figure 1.3: A schematic presentation of novel process set-up [36]](image-url)
1. Introduction

Two representative industrial cases were used as model reactions for further study. In order to apply the above-mentioned process concept, it is important to study the kinetics of the desired reactions in ionic liquids instead of conventional organic solvents and also to optimize the conditions of these reactions with respect to the variables of the system in the presence of the new solvents. After gaining the knowledge on the optimized reaction variables, it is crucial to locate the homogeneous and heterogeneous region in the ternary system containing reactants and/or products in presence of ionic liquids and CO$_2$. Therefore, ternary phase behavior data are necessary to find the optimum reaction and separation conditions. It is also important to investigate the solubility of the reactant and product in scCO$_2$, since it will affect the extraction efficiency. Although there have been many studies on the measurement of the binary phase behavior of systems containing ionic liquids and CO$_2$ [38-41], studies on multicomponent systems containing ionic liquids are still very limited [42-49].

1.4. Scope of the thesis

The main idea behind this work is to study the feasibility of using ionic liquids and CO$_2$ according to miscibility switch phenomena as reaction and separation media instead of conventional organic solvents. Therefore, two model reactions of interest in pharmaceutical and material industry were selected. In order to introduce the field, a historical and theoretical background of ionic liquids and scCO$_2$ and miscibility switch phenomena is presented in Chapter 2. Also, recent applications of the miscibility switch phenomena are discussed.

The first model reaction in the ionic liquid/CO$_2$ system is the epoxidation reaction of cinnamyl alcohol into 3-phenylglycidol. Epoxides are key intermediates in the manufacture of functionalized fine chemicals and pharmaceutics. In order to optimize the reaction conditions in the presence of ionic liquids instead of conventional organic solvents, Chapter 3 presents a systematic study of the kinetics of this reaction and the optimization of the different variables.
1. Introduction

In order to determine the conditions for reaction in a homogeneous phase and separation in a heterogeneous system, the phase behavior of the epoxidation reaction system is investigated in Chapter 4. The phase behavior experiments were performed using a synthetic method in the Cailletet apparatus, which is introduced in detail in Chapter 4.

The second model reaction studied in an ionic liquid/CO\(_2\) system is the Friedel-Crafts acylation reaction of ferrocene into acetylferrocene, which is presented in Chapters 5 to 7. In Chapter 5 the Friedel-Crafts reaction is introduced and the possibility of extraction of the product using scCO\(_2\) is investigated based on solubility measurements of the reactant and product in CO\(_2\). In Chapter 6 the phase behavior of the ternary system consisting of ferrocene + ionic liquid + CO\(_2\) is presented, in which different phase transitions were observed. These data are compared with the data of the binary of ionic liquid + CO\(_2\) system. Chapter 7 contains the phase behavior investigation of the ternary system consisting of acetylferrocene + ionic liquid + CO\(_2\). A comparison is made on the effect of the solute on the phase behavior of the ternary system. Finally, the feasibility of applying miscibility switch phenomena is discussed for the Friedel-Crafts acylation reaction.

In Chapter 8 an economical and environmental study of the new process set-up based on miscibility switch phenomena is presented. The characteristics of this new process are compared to those of conventional processes, thus showing that the new process set-up has some economical and environmental advantages.

Finally, in Chapter 9 concluding remarks and an outlook for the future applications are discussed. Recommendations are given to make a proper selection of suitable systems (type of ionic liquid, type of reaction, etc.) for studying the miscibility switch phenomena. Moreover, the advantages and disadvantages of the new process set-up based on current knowledge are presented.
1.5. References


1. Introduction


1. Introduction


1. Introduction


2

Background
2. **Background**

2.1. **Ionic liquids**

2.1.1. *History of ionic liquids*

The field of ionic liquids started with a report on ethylammonium nitrate ([EtNH$_3$][NO$_3$]) in 1914, where the physical properties of this ionic liquid, such as its low melting point at 13-14 °C, were described [1]. In spite of the importance of this finding, it did not draw the attention of the scientific society until 1951, when ethylpyridinium bromide/AlCl$_3$ ionic liquid was used for the first time as electrolyte to electroplate aluminum [2]. The main drawback of chloroaluminate ionic liquids is their sensitivity to moisture, since they produce HCl in contact with water. Later on, in the 1990s, water-stable ionic liquids were discovered, which turned out to be promising ‘green’ solvents. The most well-known ionic liquids contain dialkylimidazolium based cations with water stable anions. Ionic liquids have since then attracted great interest both as material as well as reaction solvent, not only in the academia but also in the industry, with a growing number of the scientific publications and patents (>10000 and >2000, respectively) [3].

2.1.2. *Properties*

By definition, ionic liquids are salts, which are solely composed of ions and have a melting point below 373 K [4]. Some of the most common anions and cations are shown in Figure 2.1. Ionic liquids are mainly composed of large organic cations and small inorganic or organic anions. They form crystalline structures with low lattice energies. Consequently, ionic liquids have low melting points compared to conventional inorganic salts. Moreover, ionic liquids have negligible vapor pressure at room temperature [5].
2. Background

<table>
<thead>
<tr>
<th>Cations</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>+ R₁</td>
<td>+ R₃</td>
<td>+ R₁₂</td>
</tr>
<tr>
<td>R₂-N-R₄</td>
<td>R₃-N-R₂</td>
<td>R₃-P-R₄</td>
</tr>
<tr>
<td>Ammonium</td>
<td>Imidazolium</td>
<td>Pyrrolidinium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phosphonium</th>
<th>Pyridinium</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ R₁</td>
<td>+ R₁</td>
</tr>
<tr>
<td>R₂-P-R₄</td>
<td>R₂-N-R₃</td>
</tr>
</tbody>
</table>

R₁,R₂,R₃,R₄: H, methyl, ethyl, propyl, butyl, hexyl...

<table>
<thead>
<tr>
<th>Anions</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BF₄⁻</td>
<td>tetrafluoroborate</td>
<td>PF₆⁻</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>chloride</td>
<td>Br⁻</td>
</tr>
<tr>
<td>CH₃OSO₃⁻</td>
<td>methylsulfate</td>
<td>CF₃SO₃⁻</td>
</tr>
<tr>
<td>NO₃⁻</td>
<td>nitrate</td>
<td>N(CF₃SO₂)₂⁻</td>
</tr>
</tbody>
</table>

Figure 2.1. Some of the commonly used anions and cations to design an ionic liquid

Ionic liquids can have high thermal stabilities. For example some ionic liquids like 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) and 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([emim][Tf₂N]) have been heated up to 400°C with no sign of degradation [6]. Ionic liquids exhibit ionic interactions in addition to the interactions that also exist in conventional organic solvents, such as van der Waals interactions, dipole-dipole interactions and hydrogen bonding. Due to their ionic character, they are very miscible with polar substances. Moreover, the presence of the alkyl chain on the cation improves the solubility of the less polar compounds in ionic liquids. Consequently, ionic liquids exhibit high
2. Background

Solvency power for both organic, inorganic, polar and non-polar materials, which makes them good candidates for solvents in catalytic reactions [7]. Some of the physical properties of imidazolium-based ionic liquids are presented in Table 2.1.

<table>
<thead>
<tr>
<th>Cation</th>
<th>Anion</th>
<th>Melting point/ °C</th>
<th>Thermal stability/ °C</th>
<th>Density/ g cm⁻³</th>
<th>Viscosity/ cP</th>
</tr>
</thead>
<tbody>
<tr>
<td>emim&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BF₄⁻</td>
<td>6</td>
<td>412</td>
<td>1.24</td>
<td>37.7</td>
</tr>
<tr>
<td>bmim</td>
<td>BF₄⁻</td>
<td>-81</td>
<td>403</td>
<td>1.12</td>
<td>219</td>
</tr>
<tr>
<td>bmim</td>
<td>(CF₃SO₂)₂N⁻</td>
<td>-4</td>
<td>439</td>
<td>1.43</td>
<td>52</td>
</tr>
<tr>
<td>bmim</td>
<td>PF₆⁻</td>
<td>-61</td>
<td>349</td>
<td>1.36</td>
<td>450</td>
</tr>
<tr>
<td>hmim</td>
<td>PF₆⁻</td>
<td>-61</td>
<td>417</td>
<td>1.29</td>
<td>585</td>
</tr>
</tbody>
</table>

<sup>a</sup>emim: 1-ethyl-3-methylimidazolium, bmim: 1-butyl-3-methylimidazolium, hmim: 1-hexyl-3-methylimidazolium

2.1.3. Toxicity and biodegradability of ionic liquid

Because ionic liquids have negligible vapor pressure, they are often claimed to be environmentally friendly and are called “green solvents”. However, toxicity and biodegradability of ionic liquids are important factors to evaluate their environmental impact. Therefore, before considering their implementation in industry, it is necessary to determine their impact on the environment.

The toxicity of ionic liquids is mainly determined by the associated cation rather than by the anion. For example, in the case of imidazolium and pyridinium based ionic liquids, increasing the alkyl group chain length and increasing the number of alkyl groups on the cation ring increases toxicity; however, the type of the anion does not
2. Background

significantly affect toxicity [9]. Table 2.2 shows acute toxicity values of selected ionic liquids to *V. fischeri*, expressed as EC-50 (the lower the value of EC-50, the more toxic the ionic liquid is). It should be noted that in the case of anion, lipophilicity and vulnerability to hydrolytic cleavage can be leading factors in anion cytotoxicity [10]. Scientific research on the toxicity of ionic liquids is mainly restricted to common commercial ionic liquids. Due to the lack of a systematic study, it is still difficult to draw a definite conclusion for general trend in the toxicity of ionic liquids. Moreover, the information on the toxicity of ionic liquids in mixtures is necessary for their further applications [11].

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Log EC-50</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Octyl-3-methyl imidazolium bromide</td>
<td>0.07</td>
</tr>
<tr>
<td>1-Octyl-3-methyl pyridinium bromide</td>
<td>0.25</td>
</tr>
<tr>
<td>1-Hexyl-3-methyl imidazolium bromide</td>
<td>0.81</td>
</tr>
<tr>
<td>1-Hexyl-3-methyl pyridinium bromide</td>
<td>1.48</td>
</tr>
<tr>
<td>1-Butyl-3,5-dimethyl pyridinium bromide</td>
<td>2.08</td>
</tr>
<tr>
<td>1-Butyl-3-methyl pyridinium bromide</td>
<td>2.12</td>
</tr>
<tr>
<td>1-Butyl-3-methyl imidazolium bromide</td>
<td>3.35</td>
</tr>
</tbody>
</table>

More recently, studies on the biodegradability of ionic liquids have been carried out, taking into account the potential use and disposal methods of ionic liquids. The main opinion is that each anion and cation will undergo different pathways for decomposition [12]. It is believed that the presence of certain molecular features, such as esters, amides, hydroxyl groups, aldehydes, carboxylic acid groups or linear alkyl
chains, facilitate the biodegradability of ionic liquids. On the contrary, ionic liquids with alkyl chain of more than four atom carbons are poorly biodegradable [3, 13].

Although generalizing ionic liquids as completely ‘green’ solvents should be avoided, it should be also noted that ionic liquids can be specifically designed to meet the environmental requirements.

2.1.4. Applications of ionic liquids

Due to the unique properties of ionic liquids, they have been found advantageous in wide range of applications. Here, some of the present applications are briefly reviewed.

2.1.4.1. Ionic liquids as reaction media

Given the unique properties of ionic liquids, such as the high solvency power, the high chemical and the good thermal stability and catalytic properties [14], many attempts have been made to use them as solvents in organic, inorganic and polymer synthesis as well as in biocatalytic reactions instead of conventional solvents [15]. The enormous amount of synthetic procedures that have been carried out in ionic liquids has been reviewed in articles and books [14-18]. The addition of an ionic liquid can improve the reaction in several ways. It can lead to better yields, regioselectivities or enantioselectivities, higher reaction rates or easier separation and isolation processes.

Since ionic liquids have generally good solvency power for metal catalysts, the field of transition-metal-catalyzed reactions in ionic liquids have been the subject of extensive studies. Ionic liquids have successfully been applied as reaction media for hydrogenations, hydroformylations, isomerizations, dimerizations, alkylations, Diels-Alder reactions, Heck and Suzuki coupling reactions and enzyme-catalyzed reactions [1, 14, 15, 19]. Also, the application of ionic liquids as versatile solvents in the synthesis of nanomaterials has been recently studied [20]. Some examples of the organic reactions in ionic liquids are shown in Table 2.3.
Table 2.3. Some examples of organic reactions in ionic liquids [8]

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Reaction Details</th>
</tr>
</thead>
</table>
| Biocatalytic ammonolysis          | **Candida antarctica** Lipase B  
\[
\begin{array}{c}
\text{CH}_{3}\text{CH}(_2)_{14}\text{COOH} + \text{NH}_3 \\
\text{40 °C, 4 days} \\
\text{100%}
\end{array}
\] |
| Diels-Alder reaction              | \[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{0.2 mol% Sc(CF}_3\text{SO}_3)_3 \\
\text{[Bmim][PF}_6\text{]} \\
\text{20 °C, 2h} \\
\text{99%}
\end{array}
\] |
| Friedel-Crafts alkylation         | \[
\begin{array}{c}
\text{20 mol% Sc(CF}_3\text{SO}_3)_3 \\
\text{[Bmim][SbF}_6\text{]/C}_6\text{H}_6 \\
\text{20 °C, 12 h} \\
\text{92%}
\end{array}
\] |
| Heck reaction                     | \[
\begin{array}{c}
\text{4 mol% PdCl}_2 \\
\text{8 mol% P(o-tol)}_3 \\
\text{Et}_3\text{N (1.5 equiv.)} \\
\text{[Bmim][PF}_6\text{]} \\
\text{MW} \\
\text{180 °C, 5 min} \\
\text{95%}
\end{array}
\] |
2. Background

(Cont.) Table 2.3. Some examples of organic reactions in ionic liquids [8]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reaction Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroformylation</td>
<td>H₂/CO 20 bar 0.1 ml% [Rh(CO)₂(acac)]/PPh₃ [Bmim][PF₆]/heptane 80 °C, 2h</td>
<td>( \text{CH}_3\text{CHO} ) + ( \text{CH}_2\text{CHO} ) 99% n:iso, 3:1</td>
</tr>
<tr>
<td>Hydrogenation</td>
<td>H₂ 60 bar [( \text{H}_4\text{Ru}_4(\mu-\text{C}_6\text{H}_6)_4 )] [BF₄] [Bmim][BF₄] 90 °C, 2.5 h</td>
<td>91% TOF 364 mol mol⁻¹ h⁻¹</td>
</tr>
</tbody>
</table>

2.1.4.2. Separation using ionic liquids

The possibility of tailoring the solubility properties of the ionic liquids, makes them an attractive alternative solvent for separation and purification processes. Ionic liquids have been applied to separate or extract different types of components, including organic molecules, metal ions, gases and biomolecules [21-23]. Examples are liquid-liquid extraction [24], desulfurization of sour gas [25], gas chromatography [26], extraction of metal oxides [27], separation of azeotropic mixtures [28, 29], extraction of bioactive compounds from natural plants [30], ionic liquid based membranes for gas and organic compound separations [31, 32], and more recently biomass separation using ionic liquids and high-value pharmaceutical [33] and biomedical separations [34].
2. Background

### 2.1.4.3. Ionic liquids in electrochemistry

Ionic liquids, due to their wide potential window, water immiscibility, high conductivity and also high solubility of metal salts, are good candidates for electrodeposition and electrochemical applications. For example, they have been used as electrolytes in battery systems [35, 36], solar cells [37], electrochemical synthesis and electrodeposition of metals [38, 39]. Moreover, ionic liquids have been used for electropolishing to increase the optical reflectivity of metallic surfaces for high-tech applications [40]. Recently, electrochemical reduction and fixation of the carbon dioxide (CO₂) in ionic liquids have also been applied and could attract more attention in future [41].

### 2.1.4.4. Other applications of ionic liquids

In addition to the mentioned uses of ionic liquids, there are few other new emerging applications. These applications include their usage as gas sensors [42], lubricants [43], heat-transfer fluids [44], storage media and as liquid mirrors for a lunar telescope [45].

### 2.1.4.5. Industrial applications of ionic liquids

All of these remarkable advantages enable ionic liquids to rapidly find applications in the chemical industry. Some examples of commercial applications are [3]:

- **BASF**: BASIL [46], aluminum plating and cellulose dissolution [47]
- **Degussa**: paint additives [47]
- **Linde**: hydraulic ionic liquid compressor [48]
- **IFP**: difasol [49]
- **Pionics**: batteries [50]
- **G24i**: solar cells [51]
In addition, ionic liquids provide opportunities in the field of life science, such as enzymatic [52] and whole-cell biocatalysis [53] and as protein stabilization agents [54].

### 2.2. Supercritical carbon dioxide

Supercritical carbon dioxide (scCO$_2$) is one of the emerging solvents to meet the future demands for sustainable and environmentally friendly technologies. ScCO$_2$ possesses a mild critical temperature (304.25 K) and critical pressure (7.38 MPa), which can easily be reached in chemical processes. The discovery of critical phenomena can be tracked back to 1822, when two separate gas and liquid phases of an alcohol disappeared under formation of a single phase by increasing the temperature [55]. The phase transition of CO$_2$ around its critical point is demonstrated in Figure 2.2.

![Image of phase behavior](image)

(a) Two-phase liquid-gas system  
(b) Meniscus less well defined  
(c) Homogeneous scCO$_2$ phase

Figure 2.2. phase behavior of the scCO$_2$ around its critical point [56]

Before reaching the critical point, two separate (gas + liquid) phases with a well-defined meniscus can be observed (Figure 2.2(a)). By increasing the temperature and pressure of the system (Figure 2.2 (b)), the difference between the densities of the
2. Background

two phases decreases, and the meniscus starts to disappear. Finally, a homogeneous single phase can be observed at above the critical point (Figure 2.2 (c)) without any meniscus [56]. Thus the critical point for a pure compound exhibits the highest temperature and pressure at which both the liquid and the gas phase can exist in equilibrium. This can also be observed in the phase diagram of pure CO$_2$ in Figure 2.3.

One of the main advantages of scCO$_2$ over conventional solvents is its compressibility. Depending on the temperature and pressure, scCO$_2$ has a unique combination of properties, ranging from a gas-like to liquid-like behavior. It has high diffusivity and low viscosity like a gas at liquid-like densities. ScCO$_2$ exhibits a solvency power like a non-polar liquid. It is tunable by varying the density through changing the pressure (or temperature). Therefore, the solubility of different compounds in scCO$_2$ can be tuned and controlled by setting the pressure and temperature, which makes scCO$_2$ a good candidate as solvent for chemical reactions and extraction processes. In addition, scCO$_2$ is non-flammable, non-toxic, abundantly available, inexpensive, relatively inert, 

![Phase diagram of CO$_2$](image-url)

**Figure 2.3.** Phase diagram of CO$_2$ [8]
and easy to recycle [57].

Due to these advantages, scCO₂ is a well-established solvent in many chemical processes. The extraction of the caffeine from coffee is one of the best known and most important applications of scCO₂ [58]. Other examples are the extraction of natural products, such as essential oils and hops. It has many applications in reaction chemistry as a solvent, such as homogeneous catalysis, heterogeneous catalysis and chemical synthesis [59, 60]. One of the examples of scCO₂ application in polymer synthesis is production of fluoropolymers [61, 62]. ScCO₂ is also used in nanoparticle production [63], pharmaceutical production/formulation [64], dry cleaning [65], dyeing [66], foaming [67], spray painting [68] and coating of surfaces [69, 70].

2.3. Ionic liquid/carbon dioxide systems

As discussed before, ionic liquids exhibit many advantages over conventional organic solvents as reaction media; however, the subsequent extraction stage normally uses organic solvents. As a result, even though one step of the process is being performed in more environmentally benign solvent, the whole process cannot be considered as environmentally friendly due to the involvement of volatile organic solvents. One alternative is to use low-temperature distillation, which is possible because of the extremely low vapor pressure of ionic liquids. However, distillation it is not suitable for the recovery of thermally unstable products.

ScCO₂ and ionic liquids are both alternative solvents in chemical processing with contrasting properties. Ionic liquids are polar solvents with negligible volatility, while scCO₂ is a non-polar solvent with high volatility. Additionally, scCO₂ has high solubility in ionic liquids, while ionic liquids are almost non-soluble in scCO₂ [71, 72]. The solubility of CO₂ in ionic liquids is mainly determined by the anion type and its interactions with the CO₂ molecules [73]. A schematic illustration of the ionic liquid + CO₂ phase behavior is shown in Figure 2.4. Accordingly, it was found that scCO₂ can extract an organic compound from an ionic liquid without any contamination by the ionic liquid solvent [71, 74].
New biphasic systems were developed, where the reaction was carried out in the ionic liquids (whereby the catalyst remains in the ionic liquid phase) and the product was extracted using scCO₂ [17, 75]. In Figure 2.5, a continuous-flow operation of the biphasic systems with ionic liquids/scCO₂ is depicted. This concept has been applied to hydroformylations [76, 77], hydrogenations [78-80], dimerizations [81, 82], (enzyme-catalyzed) esterifications [83, 84] and the synthesis of cyclic carbonates [85, 86].

The main advantages of biphasic ionic liquid/CO₂ systems are 1) The suppression of catalyst leaching due to the extremely low solubility of metal-catalysts in CO₂, and 2) The absence of a-solvent removal step. Moreover, CO₂ can increase the diffusivity of the compounds in ionic liquids by dramatically decreasing the viscosity of ionic liquids. For example, the viscosity of the ionic liquid, [hmim][Tf₂N], decreases approximately 60% in the presence of CO₂ at 100 bar and 70 °C, which leads to 3-fold improvement in diffusivity in the ionic liquid at the same condition [76]. It should also be noted that the solubility of reaction gases (H₂ and O₂) can be increased in the ionic

Figure 2.4. Phase behavior of binary ionic liquid + CO₂ system
2. Background

liquid phase in the presence of low concentrations of CO$_2$ (co-solvency behavior) [87]. At high concentrations, CO$_2$ dilutes the system, lowering the solubilities (anti-solvency behavior).

However, there are also several disadvantages associated with the implementation of ionic liquid/CO$_2$ systems. Notably, the reaction rate in a biphasic system is lower than that in single phase reactions due to mass transfer limitations, and leads to slow product extraction [77, 88]. These limitations can be overcome by using miscibility switch phenomena in ionic liquid/CO$_2$ systems.

2.3.1. Miscibility switch

Previously, experimental and theoretical studies have shown that in ternary mixtures with liquid(1) + liquid(2)/solid + CO$_2$, the CO$_2$ pressure can adjust the number of the
phases present in the system [89, 90]. Using this phenomena, known as miscibility window, it is possible to pressurize a two-phase heterogeneous system to form a single homogeneous liquid phase. This phenomenon has been validated for many ternary systems containing organics and CO₂. The first achievement of a homogeneous phase in ternary systems containing ionic liquids and CO₂ was demonstrated during the phase behavior study of the system 1-hexyl-3-methylimidazolium tetrafluoroborate ([hmim][BF₄]) + isopropanol + CO₂ [91]. During this study, the concentration ratio between [hmim][BF₄]: isopropanol was kept constant and the mole ratio of CO₂ was varied from 0.1001 to 0.6023 (Figure 2.6). It can be seen from this figure that at low concentrations of the CO₂ (until 30.03%) a one-phase liquid (L) region and a two-phase liquid + vapor (L + V) exists. By increasing the CO₂ concentration, four more regions, i.e. two two-phase regions (L₁ + L₂) and two three-phase regions (L₁ + L₂ + V) appear. By further increasing the concentration of the CO₂, the two (L₁ + L₂) regions approach each other and minimize to a L homogeneous region. At a CO₂ concentration of 0.6023, the homogeneous phase disappeared. A simplified schematic representation of the phase transitions by increasing the pressure at 55.96 mol% CO₂ is depicted in Figure 2.7.

The location of the miscibility switch phenomena greatly depends on the interactions between the components and the composition of the mixture [90]. Recently, a new process set-up based on this phenomena has been proposed. In this process set-up, the reaction can be carried out in a homogenous phase in the presence of reactants as well as a catalyst [84]. Since the reaction takes place in a homogenous region without any mass transfer limitations, the expected reaction rates are higher compared to heterogeneous systems. The homogenous phase can be reached by selection of suitable pressures, temperatures and CO₂ concentrations. After completion of the reaction, a phase split is induced by varying the conditions.
2. Background

The homogenous phase splits into two phases by decreasing the pressure (or increasing the temperature). One phase is rich in ionic liquids and the other one is the organic-rich phase. The product can be recovered with high purity from one of the two

Figure 2.6. The phase behavior of the ternary system [hmim][BF₄] + isopropanol + CO₂ [91]
2. Background

phases that is substantially free of ionic liquid. The novel process set-up is depicted in Figure 2.8.

Therefore, the combination of scCO$_2$ and ionic liquids offers a versatile and unique system, which is applicable to many chemical processes. In order to apply this new process set-up, it is important to detect the homogeneous and heterogeneous phase conditions. To achieve this goal, a thermodynamic rationale of the molecular

Figure 2.7. Schematic presentation of the phase transition in the ternary [hmim][BF$_4$] + isopropanol + CO$_2$ system at a CO$_2$ mole fraction of 0.5596

Figure 2.8. Novel process set-up using miscibility switch phenomena in the presence of ionic liquids and CO$_2$ [106]
interactions between compounds, compositions of different compounds in the system, temperature, and pressure of the processes is necessary. These operational conditions can be identified on the basis of the phase behavior studies.

Although there have been many studies on the measurement of the binary phase behavior of systems containing ionic liquids and CO$_2$ [92-95], studies on multicomponent systems containing ionic liquids are still very limited. Few studies on ternary ionic liquid + CO$_2$ + organic solute systems have been performed [71, 91, 96-103]. It was shown that the location of the phase transitions is greatly affected by 1. the nature of the organic compound, 2. the type of ionic liquid and 3. their respective concentrations in the system [97, 100, 101, 104]. It was also shown that CO$_2$ at low concentrations acts as a co-solvent by increasing the solubility of organics into the ionic liquid phase. On the contrary, CO$_2$ at higher concentrations acts as an anti-solvent by decreasing the solubility of organics in the ionic liquid phase [101, 103, 105]. Solutes with similar molecular structures can have different influence on the phase behavior of the ternary systems [99, 100].

The number of reactions that have specifically been studied for the implementation of the new type of processing based on miscibility switch phenomena is low. The first successful case study was the enantioselective hydrogenation of methyl (Z)-α-acetamidocinnamate in the ionic liquid [bmim][BF$_4$] + CO$_2$ system (Figure 2.9) [106].

![Figure 2.9. Asymmetric hydrogenation of methyl (Z)-α-acetamidocinnamate in the [bmim][BF$_4$] + CO$_2$ system [106].](image)
This hydrogenation reaction of (Z)-α-acetamidocinnamate in the presence of hydrogen and Rh-catalyst yields the product N-acetyl-(S)-phenylalanine methyl ester. This is an intermediate reaction in the industrial manufacture of Levodopa, which is an anti-parkinson drug. The reaction rate and selectivity in the homogeneous ionic liquid + CO\textsubscript{2} system were shown to be comparable to those in methanol, which is the conventional solvent for this reaction [107].

Furthermore, phase behavior measurements were used to determine the reaction and separation conditions. The homogeneous reaction phase was reached at reasonable pressures (~5 MPa). The results showed that the addition of CO\textsubscript{2} and catalyst increased the solubility of the hydrogen in the ionic liquid. The subsequent separation step was carried out in the biphasic system. It was shown that the N-acetyl-(S)-phenylalanine methyl ester can be separated by CO\textsubscript{2} either as co-solvent in extraction or as anti-solvent in precipitation. A schematic representation of the process set-up is shown in Figure 2.10.

The further study of the new process set-up included a nucleophilic aromatic substitution in synthesis of Mirtazapine [108], which is the active ingredient in the anti-depressant Remeron\textsuperscript{®} (Figure 2.11).

The feasibility of applying the miscibility switch to series of hydrogenation reactions was studied (Figure 2.12) [108]. The Hydrogenation of 2-(6-methoxy-2-naphthyl)acrylic acid into (S)-(+)2-(6-methoxy-2-naphthyl)propionic acid (or naproxen) was investigated (Figure 2.12). Naproxen is a non-steroidal anti-inflammatory drug (Figure 2.12). The ternary phase behavior of the product, naproxen, in the presence of ionic liquid [bmim][BF\textsubscript{4}] + CO\textsubscript{2} was measured experimentally and the results indicated the possibility of the product extraction by precipitation from the ionic liquid using scCO\textsubscript{2}. The other model reaction was the hydrogenation of acetophenone into 1-phenylethanol (Figure 2.12), which is an important step in the fine chemical industry.
2. Background

Figure 2.10. Schematic representation of the process set-up for hydrogenation reaction of methyl (Z)-α-acetamidocinnamate in the [bmim][BF$_4$] + CO$_2$ (with permission from Kamarza Mulia)

Figure 2.11. Nucleophilic aromatic reaction step in synthesis of Mirtazapine [108]
2. Background

Synthesis of (S)-(+)naproxen

The hydrogenation of acetophenone into 1-phenylethanol

The hydrogenation of 4-isobutylacetophenone to 1-(4-isobutylphenyl)-ethanol

Figure 2.12. Hydrogenation reactions studied for miscibility switch phenomena [108]

The ternary phase behavior study of the reactant/product + [bmim][BF₄] + CO₂ showed that the homogenous reaction condition is reachable with CO₂ compositions up to 50 mol%. A liquid-liquid phase split was not observed for CO₂ concentrations up to 50 mol%. However, it was expected to occur at higher CO₂ concentrations. Finally, the hydrogenation of 4-isobutylacetophenone into 1-(4-isobutylphenyl)-ethanol was studied, which is a reaction step in the production of Ibuprofen (Figure 2.12). The homogeneous region for the reaction was identified using ternary phase behavior measurements of reactant/product + ionic liquid [bmim][BF₄] + CO₂ system, in which the presence of the miscibility switch phenomena was successfully demonstrated.
So far, with the exception of the examples above, mostly hydrogenation reactions were studied with respect to the miscibility switch phenomena. Thus, it is of great importance to study other classes of reactions [106, 108]. In addition, in these studies [bmim][BF₄] was mostly used. Because the [BF₄]⁻ anion can undergo hydrolysis (HF formation), we aim to use more moisture resistant ionic liquids in this study. In addition, all the previous studies used organic compounds as reactant or product. However, inorganic compounds also form an important part of chemical products.

The mentioned limitations in the previous studies underline the importance to extend the investigation using more environmentally benign solvents and miscibility switch phenomena to other systems. Therefore, two different classes of important reactions in chemical industry are chosen to study the miscibility switch and its application in combined reactions and separations. The main idea is to use an ionic liquid as a solvent and CO₂ as a co-solvent for reaction and subsequent separation by extraction or precipitation using scCO₂. The two model reactions that are studied in this thesis are: (i) Epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol (Figure 2.13), and (ii) Friedel-Crafts acylation reaction of ferrocene to acetylferrocene (Figure 2.14).

These reactions will be discussed in detail in Chapters 3-4 and 5-7, respectively.

![Epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol](image.png)

*Figure 2.13. Epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol*
2. Background

Figure 2.14. Friedel-Crafts acylation reaction of ferrocene to acetylferrocene.
2.4. References


2. Background


2. Background


2. Background


2. Background


2. Background


2. Background


93. Shiflett, M.B., et al., *Phase Behavior of N₂O and CO₂ in Room-Temperature Ionic Liquids [bmim][Tf₂N], [bmim][BF₄], [bmim][N(CN)₂], [bmim][Ac], [eam][NO₃], and [bmim][SCN]*. International Journal of Thermophysics, 2012: p. 1-25.
2. Background


2. Background


EPOXIDATION REACTION OF CINNAMYL ALCOHOL TO 3-PHENYLGLYCIDOL
Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

3.1. Introduction

Epoxides are key intermediates in the manufacture of functionalized fine chemicals and pharmaceutics. Due to their high susceptibility for nucleophilic attack, and their asymmetric nature, epoxides offer an easy route towards the synthesis of a wide range of important chiral products [1, 2]. Recently for large-scale production of epoxides, kinetic resolution of epoxides using chiral cobalt complexes has proven to be a valuable technology [3]. However, from a viewpoint of atom efficiency, the oxidation of a prochiral alkene into a chiral epoxide in one step, remains to be preferred. In this way 100% yield towards the desired product can be obtained, and potentially two chiral centers are created with one catalyst. For asymmetric epoxidation, a large catalytic toolbox has been developed to perform these reactions on small scale. This toolbox is dominated by chiral transition metals [4]. In addition organocatalytic methods, and notably the Shi epoxidation employing oxone as oxidant and a fructose derived catalyst, have shown to be successful [5]. For metal catalysis, a range of oxidants have been probed, but from a viewpoint of atom efficiency, the use of hydrogen peroxide (H$_2$O$_2$) or alkyl hydroperoxide (R-OOH) is preferred [6, 7]. Notably, some of transition metals, i.e. titanium (Ti), vanadium (V), molybdenum (Mo) and tungsten (W) which can all effectively activate peroxides via the so-called peroxometal pathway leading to MOOR type oxidants are the candidates of choice [8].

In the present study we were interested in studying large-scale catalytic concepts for the production of 3-phenylglycidol from the corresponding allylic, cinnamyl alcohol (Figure 3.1). (2R,3R)- and (2S,3S)-phenylglycidol and substituted phenylglycidols, serve as chiral precursors for important drugs such as reboxetine, toloxetine, fluoxetine and the taxol side chain [9-11]. Some applications of 3-phenylglycidol as an intermediate to produce other organics are shown in Figure 3.2.
Vanadium as metal has a key advantage as epoxidation catalyst for allylic alcohols, because of its high alcohol binding affinity [8, 12]. In 1977, Sharpless demonstrated that a combination of VO(acac)₂ and a chiral hydroxamic acid afforded optically active epoxides from the corresponding allylic alcohols and tert-butyl hydroperoxide (TBHP) with up to 50% ee [12]. Then a few years later, the well-known titanium-tartrate method was discovered by Sharpless, which turned out to be a versatile and reliable method for epoxidation both for allylic alcohols, as well as for non-functionalized alkenes [13]. However, in terms of catalyst loading and stability, the use of vanadium still offers many advantages [14]. In last decade major progress has been made in vanadium catalyzed asymmetric epoxidation using novel chiral hydroxamic acids as ligands [15]. Nowadays, two new protocols are available: Yamamoto and coworkers have reported a C₂-symmetric bishydroxamic acid, which, in combination with 1 mol% VO(O-iPr)₃ and TBHP as oxidant leads to 97% ee for 3-phenylglycidol [16, 17]. Malkov and coworkers, have developed amino-acid-derived hydroxamic acids as chiral ligands, also showing considerable potential for the V-catalyzed asymmetric epoxidation [18]. Some examples of hydroxamic acid ligands are shown in Figure 3.3.
Traditionally, epoxidation reactions are performed in the presence of volatile organic solvents. There is an increasing pressure to replace these volatile organic compounds with more green and environmentally benign solvents. During the past decades, ionic liquids and supercritical carbon dioxide (scCO₂) have been studied as alternative solvents for chemical reactions and separations [19-21]. In order to advance the use of vanadium catalyzed epoxidation technology towards up-scaling, we focused on a method to replace the solvent in these reactions, which is typically dichloromethane or toluene, with an ionic liquid process solvent [19, 20, 22].
3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

According to the guidelines of green chemistry \[23\], it is of great importance to use less volatile, less flammable and less toxic reaction solvents in the course of chemical reactions and processes to achieve new attractive industrial processes \[24\]. The last decade of studies on ionic liquids, have taught us that ionic liquids will have a potential as sustainable solvents because of their low volatility, low flammability, high thermal stability and excellent solubilizing properties. But their benefit has to be clearly demonstrated for each individual case because of their cost, potential toxicity and difficulties in separation afterwards \[25-27\]. In our case, an ionic liquid will be probed as process solvent, solubilizing the reactant and catalyst, and will be part of the process set-up. It will be applied in such a way that it will not leave the factory, nor end up in the product. The process is based on miscibility switch phenomena for carrying out a chemical reaction and separation in presence of ionic liquids and scCO\textsubscript{2} that have been proposed recently\(\textsuperscript{[28]}\). When using an ionic liquid as a solvent for the reaction, in combination with scCO\textsubscript{2} as co-solvent, the reaction can be performed in a homogeneous phase by selection of suitable pressure, temperature and CO\textsubscript{2} concentration. After the completion of the reaction, changing the conditions result in a multi-phase system. One of the phases is an ionic liquid, and one of the other phases is
3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

the CO₂-rich phase. From the latter phase the product is recovered substantially free of ionic liquid, because ionic liquids do not dissolve in CO₂ [29].

The use of ionic liquids in oxidation catalysis was recently highlighted and many pregnant examples have been published [30-32]. The first epoxidation reactions carried out in ionic liquids as solvents were performed only in 2000 [33]. This study involved the epoxidation of alkenes and allylic alcohols to their corresponding epoxides using urea H₂O₂ as the oxidant, methyltrioxorhenium (MTO) as the catalyst and 1-ethyl-3-methylimidazolium tetrafluoroborate, [emim][BF₄], as the ionic liquid. The experiment resulted in fairly high chemical yields for different olefin substrates and allowed efficient product recovery by extraction with an organic solvent. Later on, also vanadium complexes were used as epoxidation catalysts in ionic liquids, resulting in good reaction yields and selectivities [34, 35].

These latter studies motivated us to explore the V-catalyzed epoxidation reaction of allylic alcohols in the presence of miscibility-switch compatible ionic liquids as solvents. Therefore, in this study the catalytic epoxidation of cinnamyl alcohol to 3-phenylglycidol in oxidatively stable imidazolium-type liquids was studied with the aim of applying this novel process concept. Once successful, this technology can be extended to chiral products by involving a chiral ligand.

3.2. Experimental

3.2.1. Materials

Cinnamyl alcohol with a purity of 98%, tert-butyl hydroperoxide (TBHP) solution of ~5M in decane and trans-cinnamaldehyde with purity of 98% were purchased from Aldrich. (2S,3S)-(−)-3-Phenylglycidol (99%), benzaldehyde (>99.5%), 2-propanol (99%) and tetradecane (>99.5%, GC standard) were purchased from Fluka. H₂O₂ was purchased as a 30% weight solution in water from Merck. The quenching agent triphenylphosphine (99%) was used as received from Aldrich. The ionic liquids, 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][Tf₂N]) (>98%)
and 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([bmim][TfO]) (>98%) were purchased from Aldrich, and 1-butyl-3-methylimidazolium nitrate ([bmim][NO₃]) (>95.0%) from Fluka, and dried in a vacuum desiccator in the presence of phosphorus pentoxide before use. The first catalyst studied, vanadyl acetylacetonate (VO(acac)₂), was purchased from Aldrich with a purity of 98%. The second catalyst studied, vanadyl (3,5-salophen) trifluoromethanesulfonate (VO(3,5-Salophen)CF₂SO₃), was kindly provided by Prof. Valeria Conte from the Department of Chemical Sciences and Technology, University of Rome Tor Vergata [36]. The molecular structure of vanadium catalysts are shown in Figure 3.4.

![Figure 3.4. Vanadium catalysts. a) VO(acac)₂, b) VO(3,5-Salophen)TfO](image)

3.2.2. Method

The catalytic epoxidation experiments were carried out in a round bottom flask equipped with magnetic stirrer in a thermostatted water bath. The equipment to perform the experiments consists basically of a heating system combined with magnetic stirrer IKA RCT basic, and a temperature controller IKA ETS-D4 fuzzy. The standard reaction procedure consisted of dissolving 4 mmol of cinnamyl alcohol and a variable amount (1-5 mol%) of catalyst in 3 ml of ionic liquid. Once the solution had reached the desired temperature, the oxidizing agent was added to the solution to
Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

start the reaction. The type and amount of catalyst and oxidizing agent were systematically varied to find the optimum conditions. The experimental set-up and chemical are shown in Figure 3.5.

![Experimental set-up and chemicals](image)

Figure 3.5. Experimental set-up and chemicals

![Gas chromatography](image)

Figure 3.6. Gas chromatography
Samples were taken each 10 minutes after start of the reaction up to 1 h, and thereafter every hour (up to 5 h) in order to determine the reaction time. Triphenylphosphine was used to quench the remaining TBHP from the solution. Quantitative analyses to calculate the chemical yields and selectivities were carried out using gas chromatography (GC) (Figure 3.6) from CHROMPACK equipped with CP-Sil 5 CB column and using H₂ as the carrier gas with tetradecane as internal standard. Molar responses are calibrated against commercial samples. The software used for analyzing the results returned by the GC is Galaxy Varian Workstation. Prior to the experiments, calibration using 10 standard samples of a known concentration of each substance, cinnamyl alcohol, (2S,3S)-3-phenylglycidol, cinnamaldehyde and benzaldehyde, were carried out with the Gas Chromatography using 2-propanol as the solvent and tetradecane as an internal standard.

3.3. Results and discussions

3.3.1. Effect of solvent

The chiral vanadium catalyzed epoxidation reactions of allylic alcohols have been attracting a lot of attention after the outstanding publication by Yamamoto et al in 1999 [37]. The main advantages of using vanadium catalysts are their stability against moisture and the lower required catalyst loads compared to other catalysts [14]. With the aim of developing a green process approach for V-catalyzed epoxidation as described above, a suitable ionic liquid had to be found which is able to (i) dissolve and retain vanadium in the ionic liquid process solvent, (ii) be stable under oxidative conditions with TBHP and (iii) be compatible in the miscibility-switch region. Imidazolium based ionic liquids are interesting due to the fact that they display low melting points [36] moreover, cations with shorter alkyl chain lengths result in lower viscosity and lower toxicity compared to longer alkyl chain cations [38]. Previously, it was found that the solubility of CO₂ in an ionic liquid is mainly caused by the strong interactions between the CO₂ molecules and the anions of ionic liquids [39-41]. Some
of the common anions ranked according to their hydrophobicity are depicted in Figure 3.7.

Based on these criteria, three different anions for bmim-based ionic liquids i.e., (i) [bmim][Tf2N] 1, (ii) [bmim][TfO] 2 and (iii) [bmim][NO3] 3, were applied as solvents during the experiments, varying from hydrophobic 1, to hydrophilic 2, to more hydrophilic 3. It should be noted that the [PF6]− and [BF4]− anions decompose slowly leading to the formation of HF, which is a Lewis acid. This Lewis acid promotes the epoxide ring opening in the presence of water which is not desirable in this reaction.

![Hydrophobic Anions vs Hydrophilic Anions](image)

**Figure 3.7.** Some commonly used anions based on their water miscibility [25]

In initial studies, we performed the epoxidation reaction of cinnamyl alcohol at room temperature and 3 mol% VO(acac)2 as catalyst. Figure 3.8 and Figure 3.9 show the effect of the type of ionic liquid on the conversion and chemical yields of the epoxidation reaction of cinnamyl alcohol versus time, respectively.

The reaction is finished after 2 hours in all cases. For solvents 1 and 3 the maximum conversion is close to 90% while in case of solvent 2, only 62% conversion is reached. Apart from differences in conversion rate, the solvents have a large impact on the selectivity of the reaction (Table 3.1 and Table 3.2).
3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

Figure 3.8. Effect of different types of ionic liquids on the oxidative conversion of cinnamyl alcohol (3 mol% VO(acac)₂, 1.5 equiv. TBHP, 25 °C): ▲, [bmim][Tf₂N]; ●, [bmim][TfO]; ■, [bmim][NO₃]

Figure 3.9. Effect of different types of ionic liquids on the chemical yield of 3-phenylglycidol in the epoxidation reaction of cinnamyl alcohol (3 mol% VO(acac)₂, 1.5 equiv. TBHP, 25 °C): ▲, [bmim][Tf₂N]; ●, [bmim][TfO]; ■, [bmim][NO₃]
3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

Table 3.1. Selectivity\(^a\)(%) of epoxidation reaction of cinnamyl alcohol in different ionic liquids (3 mol% of VO(acac)\(_2\), 1.5 equiv. TBHP, 25 °C, 2 h)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>3-Phenylglycidol (%)</th>
<th>Benzaldehyde (%)</th>
<th>Cinnamaldehyde (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{bmim}]\text{Tf}_2\text{N})</td>
<td>65</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>([\text{bmim}]\text{TfO})</td>
<td>42</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>([\text{bmim}]\text{NO}_3)</td>
<td>8</td>
<td>14</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^a\)Selectivity is defined as the molar ratio of desired product to the total amount of products

Table 3.2. Epoxidation reaction of cinnamyl alcohol in different solvents (3 mol% of VO(acac)\(_2\), 1.5 equiv. TBHP, 25 °C, 2 h)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
<th>Selectivity to 3-phenylglycidol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{bmim}]\text{Tf}_2\text{N})</td>
<td>90</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>([\text{bmim}]\text{TfO})</td>
<td>62</td>
<td>26</td>
<td>42</td>
</tr>
<tr>
<td>([\text{bmim}]\text{NO}_3)</td>
<td>87</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Toluene</td>
<td>94</td>
<td>63</td>
<td>67</td>
</tr>
</tbody>
</table>

The hydrophobic solvent 1, gives the highest selectivity towards the desired product 3-phenylglycidol i.e. 65%. Solvents 2 and 3 lead to 42% and 8% selectivity, respectively. The two competing pathways are the oxidation of the alcoholic group leading to cinnamaldehyde, and oxidative cleavage of the double bond, leading to benzaldehyde. These two reactions are commonly catalyzed by homolytic, radical-type reaction pathways [42].

These results can be explained by the common notice that polar, non-coordinating solvents endow the best properties for electrophilic epoxidations [8]. The proposed
mechanism for vanadium catalyzed epoxidation of cinnamyl alcohol is shown in Figure 3.10. Peroxovanadates, can also endow competing homolytic radical-type pathways, depending on the nature of the substrate and the solvent. In this case, hydrophilic solvents apparently favor these pathways.

The epoxidation reaction of cinnamyl alcohol was also performed in toluene as benchmark, which is the conventional organic solvent for this reaction. When using toluene as solvent the chemical yield and selectivity to 3-phenylglycidol are 63% and 67%, respectively. These results are comparable to those in [bmim][Tf₂N], indicating that ionic liquids can be a suitable substitutes for organic solvents in epoxidation reactions. However, comparing the yields for the ionic liquid 1 and toluene
3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

(Figure 3.11), we noticed that the 3-phenylglycidol tended to decompose in toluene while it was stable in the ionic liquid 1. This means that the rate of product loss due to decomposition is lower in 1 compared to toluene. Therefore, the stability of the product in 1, makes this solvent an attractive alternative to toluene.

![Figure 3.11. Comparison of the chemical yield of 3-phenylglycidol in the epoxidation reaction of cinnamyl alcohol in ionic liquid [bmim][Tf$_2$N] and toluene (3 mol% VO(acac)$_2$, 1.5 equiv. TBHP, 25 °C): ▲, [bmim][Tf$_2$N]; ◆, Toluene](image)

In an attempt to improve the yield and selectivity, the temperature was increased, using 1 as solvent (Table 3.3). It could also be seen from Table 3.3 that the rate of reaction increased with increasing temperature. However, an almost linear decrease of selectivity from 65% at RT, to 39% at 55°C was observed. Therefore, in order to minimize the decomposition and to increase the stability of 3-phenylglycidol, it is advisable to carry out the epoxidation reaction at a moderate temperature of 25 °C.
3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

Table 3.3. Epoxidation reaction of cinnamyl alcohol at different temperatures (3 mol% of VO(acac)$_2$, 1.5 equiv. TBHP, 2 h, in [bmim][Tf$_2$N])

<table>
<thead>
<tr>
<th>Run</th>
<th>Temperature (°C)</th>
<th>Total Conversion (%)</th>
<th>Selectivity to 3-phenylglycidol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>98</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>99</td>
<td>39</td>
</tr>
</tbody>
</table>

3.3.2. Effect of catalyst

Loadings from 1-5 mol%, two types of vanadium catalysts at 25 °C and 1.5 equivalent of TBHP were studied (Figure 3.4). The results show that 3 mol% of VO(acac)$_2$ is an efficient amount of catalyst. Further increase of the load of VO(acac)$_2$ does not improve the chemical yield significantly, while at lower loading decrease of yield to 38% is observed (Figure 3.12). This seems to be due to the lower activity and thus stability of the catalysts. Therefore, there is no preferences from 3 to 5 mol% of catalyst loading. Apart from VO(acac)$_2$, the use of VO(3,5-salophen)(TfO) as stable V5+ catalyst [42] was studied for the epoxidation of cinnamyl alcohol. The results are presented in Table 3.4. Selectivity in both cases is almost similar, around 62-65%. However, VO(3,5-salophen)(TfO) shows albeit lower activities, with a flat activity profile: the vanadium catalyst is more stable, and overall less active. Currently, a rationale for this behavior is not clear and this aspect requires further study.

3.3.3. Effect of oxidant

Instead of using TBHP, hydrogen peroxide was also tested as oxidant. When using 1.5 equiv. of H$_2$O$_2$ (30% aqueous solution) as oxidant, only 20% yield of 3-phenylglycidol was observed, with a selectivity of 24%. This is in accordance with previous studies on the use of HOOH as oxidant in V-catalyzed epoxidation reactions [35]. TBHP has the
advantage, that it can be applied under non-aqueous solutions, thereby favoring electrophilic oxidation. Different ratios of TBHP to alcohol were applied ranging from 1-2.5 (Table 3.5). Increase of the TBHP concentration from 1 equiv. to 1.5 equiv. resulted in an increase in both chemical yield and selectivity of 3-phenylglycidol production. However, increasing the TBHP concentration to higher amounts is not effective and slightly decreases both the chemical yield and selectivity to 3-phenylglycidol. Probably, the product starts to decompose at higher amounts of oxidant. In an attempt to decrease the product decomposition, oxidant was added to the reaction solution slowly.

However, no difference in overall yield and selectivity was observed. Therefore, it is advisable to use 1.5 equiv. of TBHP as oxidant relative to cinnamyl alcohol in order to achieve optimum epoxide yield.
3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids

Table 3.4. Epoxidation reaction of cinnamyl alcohol in different vanadium catalysts (1.5 equiv. TBHP, 25 °C, 2 h, in [bmim][Tf₂N])

<table>
<thead>
<tr>
<th>Run</th>
<th>Catalyst</th>
<th>Catalyst load (mol%)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
<th>Selectivity to 3-phenylglycidol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VO(acac)₂</td>
<td>1</td>
<td>87</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>VO(acac)₂</td>
<td>2</td>
<td>87</td>
<td>54</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>VO(acac)₂</td>
<td>3</td>
<td>90</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>VO(acac)₂</td>
<td>4</td>
<td>95</td>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>VO(acac)₂</td>
<td>5</td>
<td>97</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>VO(3,5-Salophen)TfO</td>
<td>1</td>
<td>62</td>
<td>39</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>VO(3,5-Salophen)TfO</td>
<td>2</td>
<td>68</td>
<td>41</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>VO(3,5-Salophen)TfO</td>
<td>3</td>
<td>68</td>
<td>41</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>VO(3,5-Salophen)TfO</td>
<td>4</td>
<td>73</td>
<td>42</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>VO(3,5-Salophen)TfO</td>
<td>5</td>
<td>75</td>
<td>43</td>
<td>57</td>
</tr>
</tbody>
</table>

Table 3.5. Epoxidation reaction of cinnamyl alcohol in different oxidants (3 mol% of VO(acac)₂, 25 °C, 2 h, in [bmim][Tf₂N])

<table>
<thead>
<tr>
<th>Run</th>
<th>Oxidant</th>
<th>Molar ratio (oxidant : reactant)</th>
<th>Yield (%)</th>
<th>Selectivity to 3-phenylglycidol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBHP</td>
<td>1.0</td>
<td>48</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>TBHP</td>
<td>1.5</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>TBHP</td>
<td>2.0</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>TBHP</td>
<td>2.5</td>
<td>52</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>H₂O₂</td>
<td>1.5</td>
<td>20</td>
<td>24°</td>
</tr>
</tbody>
</table>

°Selectivity to cinnamaldehyde is 26% and to benzaldehyde is 50%
3.4. Conclusion

In this chapter a systematic investigation of the epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol in different ionic liquids has been carried out. The effect of three different ionic liquids as solvents i.e., (i) [bmim][Tf$_2$N], (ii) [bmim][TfO] and (iii) [bmim][NO$_3$], on the yield and selectivity were determined. Results clearly indicate that the use of hydrophobic [bmim][Tf$_2$N] is required to reach reasonable selectivities for 3-phenylglycidol. In that sense [bmim][Tf$_2$N] is the ideal substitute for toluene, the conventional organic solvent for this reaction, which shows similar results, both in terms of selectivity as well as reactivity. In contrast, the use of [bmim][NO$_3$] as hydrophilic solvent includes a homolytic reaction pathway and leads to mainly alcohol oxidation, with 78% selectivity to cinnamaldehyde as product.

Optimization of the conditions revealed that product stability is leading in this: Therefore, low temperatures and low TBHP loadings are required. Vanadium is therefore a very active catalyst that leads to fast epoxidation. The optimum conditions for the epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol were obtained using [bmim][Tf$_2$N] as solvent with 3 mol% VO(acac)$_2$ as catalyst and 1.5 equiv. of TBHP as oxidant at 25 °C.

Apart from VO(acac)$_2$, VO(3,5-salophen)(TfO) is an excellent source of vanadium (V) which is much more stable in solution. In this case 1 mol% of vanadium is sufficient to reach the maximum conversion and selectivity of 62% and 63% respectively. VO(3,5-salophen)(TfO) has been shown to be an excellent sulfide oxidation catalyst with tunable properties. Sulfoxide production under miscibility switch conditions can therefore be considered as a possibility as well.
3.5. References


3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids


3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids


3. Vanadium-catalyzed epoxidation reaction of cinnamyl alcohol in ionic liquids


Effect of carbon dioxide addition on the phase behavior of epoxidation reaction mixtures in ionic liquids

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4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction mixtures in ionic liquids

4.1. Introduction

Previously, the epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol (Figure 4.1) in the presence of ionic liquids as solvents was studied in Chapter 3 [1]. Due to their unique properties, ionic liquids have attracted a lot of attention as potential “green” solvents to replace conventional organic solvents. (2S,3S)-(-)-3-Phenylglycidol is an intermediate for a well-known potent active anti-inflammatory agent, Ibuprofen [2, 3]. In general, epoxides are versatile intermediates, which can be modified to produce a range of important building blocks. They are produced via epoxidation reactions [4-6].

![Figure 4.1. Molecular structure of studied chemical compounds. a) Cinnamyl alcohol, b) (2S,3S)-(-)-3-Phenylglycidol](image)

The catalytic epoxidation reaction of cinnamyl alcohol in the presence of ionic liquids has been optimized with respect to (i) type and amount of oxidizing agent, (ii) type and amount of catalyst, (iii) type of ionic liquids, and (iv) temperature [1]. Optimum conditions were obtained using the ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][Tf₂N]) with 3 mol% vanadyl acetylacetonate as a catalyst and 1.5 equiv. of tert-butyl hydroperoxide as oxidant at 25 °C. One of the main advantages of using ionic liquids as solvent for this epoxidation
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

reaction was the higher stability of the epoxides in ionic liquids compared to that in conventional organic solvents.

Due to the extremely low vapor pressure of ionic liquids, low-temperature distillation can be regarded as an option for product recovery. However, it is not suitable for thermally unstable products like (2S,3S)-(−)-3-phenylglycidol [7]. Another alternative is to use supercritical carbon dioxide (scCO₂) to extract the products from ionic liquids, because ionic liquids do not dissolve in CO₂, but CO₂ is highly soluble in ionic liquids [8, 9]. Moreover, it was shown before that CO₂ is able to force two immiscible liquid phases to form one homogeneous phase as CO₂ pressure increases [10, 11]. This interesting behavior of CO₂, which is known as the miscibility switch phenomenon, is generally applicable for ternary systems containing ionic liquids, CO₂ and organics [12]. In this process set-up, the reaction can be carried out in a homogenous phase at high rate (no mass transfer limitations) [13] by selection of a suitable pressure, temperature and CO₂ concentration. After completion of the reaction, a phase separation is induced by changing the conditions e.g. by reducing the pressure. The product can be recovered with high purity from one of the two phases that is substantially free of ionic liquid.

In order to apply this novel process principle, it is important to detect the homogeneous and heterogeneous phase conditions. Therefore, it is crucial to have the knowledge on the phase behavior of the ternary systems containing ionic liquids, CO₂ and the organic reactant/product of the chemical reactions.

In this chapter, we report the results of investigations on the phase behavior of the ternary systems containing CO₂, the ionic liquid [bmim][Tf₂N] and an organic compound from the epoxidation reaction mixture e.g., cinnamyl alcohol (reactant) or (2S,3S)-(−)-3-phenylglycidol (product). Phase behavior experiments were carried out in the Cailletet apparatus in a temperature range of 278 to 368 K and pressures up to 12.1 MPa. The CO₂ concentration was varied from 10 mol% to 50 mol%. The conditions at which the different phase transitions occur were measured.
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

4.2. Experimental

4.2.1. Materials

The ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)- imide ([bmim][Tf$_2$N]) (99%) was purchased from Iolitec. The ionic liquid was dried prior to use and the water content was measured by Karl-Fischer analysis to be less than 0.01%. Cinnamyl alcohol (98%) was supplied from Aldrich and (2S,3S)-(3)-3-phenylglycidol (99%) was purchased from Fluka. Both chemicals were used as received. High purity CO$_2$ (99.99%) was purchased from HoekLoos B.V.

4.2.2. Methodology

Phase behavior measurements were carried out according to the synthetic method using the Cailletet apparatus. A schematic representation of the set-up is shown in Figure 4.2. Depending on the heating fluid used in this apparatus, phase behavior measurements can be carried out within a temperature range from 255 to 470 K and a pressure range from 0.1 to 15 MPa. The principle of the measurements is that at constant overall composition, the temperature is fixed, and then pressure is varied until the phase change is observed visually. The main part of the Cailletet apparatus is a thick-walled Pyrex glass tube, also known as the Cailletet tube, which is an equilibrium cell (Figure 4.3). Essentially, the samples with known overall composition were placed in the Cailletet tube. The Cailletet tube has length of 50 cm and inner diameter of around 3 mm. It is closed at one end and open at the other end. From the open end, the necessary pressure was transmitted to the samples through the mercury column. Mercury acts also as a sealing liquid. The pressure is generated using a screw type hand pump through a hydraulic oil system.

Prior to phase behavior measurements, the samples were prepared. Samples were a solution of 20 mol% of cinnamyl alcohol (or (2S,3S)-(3)-3-phenylglycidol) in [bmim][Tf$_2$N]. The overall composition of the solution was kept constant during all the experiments.
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

Since the water content of solutions containing ionic liquid can change the phase behavior significantly, the mentioned solution was placed in the desiccator and left under vacuum for a few days in order to dry the sample. The dried solution (<100 ppm water) was injected into the Cailletet tube using a micro-syringe. Thereafter, the tube was connected to a gas-rack. The main purpose of gas-rack equipment is to inject a known amount of desired gas to the Cailletet tube and make it ready to be amounted to the Cailletet set-up.

Figure 4.2. The Cailletet apparatus: A, autoclave; B, magnets; C, capillary glass tube; D, drain; E, motor; H, rotating hand pump; Hg, mercury; I, thermostat liquid in; L, line to dead weight pressure gauge; M, mixture being investigated; Ma, manometers; O, thermostat liquid out; Or, hydraulic oil reservoir; P, closing plug; R, Viton O-rings; S, silicone rubber stopper; T, mercury trap; Th, glass thermostat; V, valve. [14]
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

An overall view of gas rack is shown in Figure 4.4, and a simplified schematic representation of the gas rack is shown in Figure 4.5 [14]. The sample was degassed using a vacuum pump, while kept frozen using liquid nitrogen in order to prevent the

Figure 4.3. The Cailletet tube

Figure 4.4. Gas rack
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

loss of material. Then, the CO₂ was injected to the system through the dosing bulb using mercury, which also worked as a sealing substance.

The amount of CO₂ injected was determined using the second virial equation of state at the known pressure, temperature and volume of the dosing bulb. Therefore, the gas rack consists of two parts: (i) vacuum branch, and (ii) gas dosing branch. Then, the tube containing the desired amount of solution was placed into the Cailletet apparatus.

Figure 4.5. A simplified schematic representation of the gas rack [14]
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

Finally, the Cailletet tube, which contained the solute + ionic liquid + CO₂ was sealed with mercury and mounted into the Cailletet apparatus. Using a double-walled glass thermostat jacket, a thermostat fluid circulated around sample and kept its temperature constant. The temperature of the sample was measured using a platinum resistance thermometer, which was located in the glass jacket.

In general, temperature was kept constant in the sample and pressure was varied until the phase transition was observed visually. In this case, bubble points were measured when the last bubble of the gas disappeared in the sample. This set of experiments were performed in a temperature range from 278 to 368 K and pressures up to 12.1 MPa were applied. The accuracy of the measurements for the temperature was ±0.01 K and pressures were taken with an accuracy of ±0.003 MPa.

4.3. Results and discussions

Experimental bubble point data for the ternary systems of cinnamyl alcohol + [bmim][Tf₂N] + CO₂ and (2S,3S)-(-)-3-phenylglycidol + [bmim][Tf₂N] + CO₂ are presented in the appendices (Tables A1-1 and A1-2). The data were measured within a temperature range of 278 to 368 K and pressures up to 12.10 MPa were applied. In total, five different concentrations of CO₂ (from 10 to 50 mol%) were investigated. For all systems studied, the concentration of solutes (cinnamyl alcohol and (2S,3S)-(-)-3-phenylglycidol) with respect to the ionic liquid [bmim][Tf₂N] was kept constant at 20mol%. The experimental data are plotted in pressure versus temperature graphs in Figure 4.6 and Figure 4.7, respectively.

From these figures, it can be noticed that both systems only show liquid-vapor to liquid transitions within the conditions studied. This is in contrast with what has been observed in other ternary “ionic liquid + CO₂ + organic” systems, in which also liquid-liquid, solid-liquid and three-phase regions have been identified [15, 16].
Moreover, it can be observed that increasing the temperature decreases the CO$_2$ solubility in both systems. In other words, by increasing the temperature higher pressures are necessary to dissolve the CO$_2$ in the ternary systems. An increase in CO$_2$ concentration results in an increase in pressure in order to reach a homogeneous liquid phase.

This can be better observed from Figure 4.8, where the pressure is plotted against the concentration of CO$_2$. A third-order polynomial fit of the experimental data is used to obtain the lines (isotherms) in Figure 4.8. In this figure also the bubble point data of the binary ionic liquid + CO$_2$ system are added as points for comparison [17]. It can be
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

Figure 4.7. Experimental bubble point data (LV → L) for the ternary system of (2S,3S)-(−)-3-phenylglycidol + [bmim][Tf₂N] + CO₂, at different concentrations of CO₂: ■, 9.98 mol% CO₂; ◇, 20.03 mol% CO₂; ○, 30.00 mol% CO₂; △, 40.03 mol% CO₂; □, 49.98 mol% CO₂

observed that both organic compounds (cinnamyl alcohol and (2S,3S)-(−)-3-phenylglycidol) decrease the solubility of CO₂ in the liquid phase, because higher pressures are needed to completely dissolve the same amount of CO₂. This behavior can be explained on basis of CO₂ – ionic liquid interactions. Previously, it was found that the solubility of CO₂ in an ionic liquid is mainly caused by the strong interactions between the CO₂ molecules and the anions of ionic liquids [18-20]. Because cinnamyl alcohol (or 3-phenylglycidol) competes with CO₂ in the ternary system for these interaction sites, the solubility of the CO₂ is lower in the ternary systems compared to the binary system. Moreover, this could be due to dilution effect which is caused by addition of organics.

From Figure 4.8, it can also be seen that both ternary systems show similar phase behavior at concentrations of CO₂ up to 40 mol%. This behavior can be explained by
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

Figure 4.8. Comparison between isotherms for the binary system [bmim][Tf$_2$N] + CO$_2$ (grey symbols), ternary systems of cinnamyl alcohol + [bmim][Tf$_2$N] + CO$_2$ (filled symbols connected with lines) and (2S,3S)-(·)-3-phenylglycidol + [bmim][Tf$_2$N] + CO$_2$ (open symbols connected with lines) at different temperatures: ◊, 313.15 K; ○, 333.15 K; △, 353.15 K.

the similarity of the molecular structure of the two components as shown in Figure 4.1. However, by further increasing the concentration of CO$_2$, the difference in the phase behavior of these two systems is more pronounced. At CO$_2$ concentrations higher than 40 mol%, higher pressures are necessary to completely dissolve CO$_2$ in the system containing cinnamyl alcohol compared to (2S,3S)-(·)-3-phenylglycidol. Reason is that (2S,3S)-(·)-3-phenylglycidol is more bulky, so that it can facilitate the uptake of larger amounts of CO$_2$. We have also checked the possibility of a chemical reactions occurring between epoxide ring and CO$_2$. For this purpose, the ternary system of (2S,3S)-(·)-3-phenylglycidol + IL + CO$_2$ was left under pressure for 24 hrs. After analyzing the samples from this solution using GC, there was no indication of chemical reaction.
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

In conclusion, the experimental data show the possibility for a homogeneous phase in these systems. Therefore it is possible to use the miscibility switch phenomenon to carry out epoxidation reactions in ionic liquid + CO$_2$ mixtures. For instance, at CO$_2$ concentrations of 40 mol%, a homogeneous phase can be reached at 298 K and pressures above 4 MPa. The temperature (298 K) is the optimum reaction temperature which was found by evaluation of the results of kinetic studies [1]. In order to extract the product using CO$_2$, it is necessary to induce a two-phase regime with CO$_2$ either in the liquid or in the supercritical state. This will lead to product recovery at a scCO$_2$ temperature of 333 K and pressures below 8 MPa.

4.4. Conclusion

In this chapter, experimental data for the phase behavior of ternary mixtures containing the ionic liquid [bmim][Tf$_2$N], CO$_2$ and two organic compounds are presented. The selected organic compounds are cinnamyl alcohol and (2S,3S)-(−)-3-phenylglycidol, which are the reactant and product in an epoxidation reaction, respectively. The solubility data were measured using a Cailletet apparatus from 278 to 368 K and pressures up to 12.1 MPa; five different concentrations of CO$_2$ ranging from 10 mol% up to 50 mol% were investigated. For both systems, only liquid-vapor to liquid transitions have been detected within the operational conditions of our experiments. It is shown that in both systems higher pressures are necessary to reach the homogeneous phase by increasing the temperature and the concentration of CO$_2$. At lower concentrations of CO$_2$ (below 40 mol%), both ternary systems have similar phase behavior due to the similarity in molecular shape of cinnamyl alcohol and (2S,3S)-(−)-3-phenylglycidol. However, at higher CO$_2$ concentrations (above 40 mol%), higher pressures are required to completely dissolve CO$_2$ in the ternary system of cinnamyl alcohol + [bmim][Tf$_2$N] + CO$_2$. One possible explanation is that (2S,3S)-(−)-3-phenylglycidol is more bulky than cinnamyl alcohol and can facilitate the uptake of larger amounts of CO$_2$. Finally, conditions for carrying out the reaction in a homogenous region and the separation in a heterogeneous region are determined. A homogeneous reaction phase can be reached at 298 K and at pressures higher than 4
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

MPa when the CO₂ concentration is 40%. Separation by extraction using scCO₂ is possible at 333 K and pressures lower than 8 MPa.
4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction

4.5. References


4. Effect of carbon dioxide addition on the phase behavior of epoxidation reaction


Friedel-Crafts acylation reaction of ferrocene to acetylferrrocene
Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

5. Solubilities of ferrocene and acetylferrrocene in supercritical carbon dioxide

5.1. Introduction

The Friedel-Crafts acylation is an important reaction with applications in material science, catalysis, bio-organometallic chemistry and in the pharmaceutical industry [1, 2]. In this chapter, the acylation reaction of ferrocene to acetylferrrocene is studied. Ferrocene and its derivatives are attractive organometallic compounds due to their sandwich structure which results in specific physical and chemical properties [3, 4]. Ferrocene has a high thermal stability and unusually high stability for an organometallic species when contacted with air, but shows a very high reactivity with other oxidizing agents [5]. Ferrocenes are increasingly applied for the production of fuel additives, polymers with semiconductor properties, pharmaceuticals and fine chemicals [6-10]. One of the well-known production methods in ferrocene chemistry is the acylation reaction by which ferrocenyl ketones, such as acetylferrrocene, are produced [11].

Traditionally, acetylferrrocene is synthesized from ferrocene by a classical Friedel-Crafts acylation reaction using dichloromethane or carbon disulfide as a solvent. Lewis acids (such as aluminum chloride and hydrogen fluoride) or Brønsted acids (such as polyphosphoric acid) are used as catalysts, while acetyl chloride is used as an acylation agent [3, 12, 13]. The draw-back of conventional reaction is that the catalyst (aluminum chloride) and the carbonyl part of the product can form a stable complex. Therefore an excess amount of catalyst is required, which results in a huge amount of waste [14]. Consequently, the conventional route of Friedel-Crafts acylation reaction suffers from by-product formation, release of toxic volatile organic solvents to the atmosphere, and corrosion issues [12, 13, 15].

Recently, a comprehensive investigation of the acylation of ferrocene into acetylferrrocene has been conducted in the presence of ionic liquids as solvents
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

(Figure 5.1) [5] Considering the numerous advantages of ionic liquids compared with organic solvents (see Chapter 2), such as insignificant vapor pressure, low flammability, and high solvency power [16], this would bring a significant advantage. On the first attempt, the ionic liquid 1-ethyl-3-methylimidazolium chloroaluminate was used as a solvent for ferrocene acylation. This reaction, however, suffers from the water sensitivity of the haloaluminate ionic liquids [17]. Later on, scandium triflate (Sc(OTf)$_3$), which is a Lewis acid and stable against water, was used as a Friedel-Crafts catalyst [18, 19]. Promising results were obtained using imidazolium-based ionic liquids and Sc(OTf)$_3$ as a catalyst in acylation reaction of ferrocene to acetylferrocene: up to 100% conversion and yield were reached using imidazolium-based ionic liquids, i.e. 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)-imide ([bmim][Tf$_2$N]) as solvent, Sc(OTf)$_3$ as a catalyst and microwave irradiation (Table 5.1)[5].

In spite of these promising results, which showed the superior performance of ionic liquids as solvents for the Friedel-Crafts acylation of ferrocene, the problem of volatile organic solvent emissions during the separation step still persists [5].

![Figure 5.1. Friedel-Crafts acylation reaction of ferrocene to acetylferrocene using a Sc(OTf)$_3$ catalyst in the ionic liquid [bmim][Tf$_2$N][5]](image-url)
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

Table 5.1. Acylation of ferrocene in [bmim][Tf2N]-catalyzed by Sc(OTf)3 with microwave irradiation (A: acylation agent, FcH: ferrocene, cat: catalyst) [5]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acylation agent</th>
<th>FcH:A:cat molar ratio</th>
<th>$T_{\text{bulk}}$ (°C)</th>
<th>Time (min)</th>
<th>Conversion (%)</th>
<th>GC yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac2O</td>
<td>1:5:0.05</td>
<td>80</td>
<td>3.5</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>Ac2O</td>
<td>1:10:0.05</td>
<td>105–110</td>
<td>3.5</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Ac2O</td>
<td>1:5:0.05</td>
<td>105–110</td>
<td>7.0</td>
<td>88</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>Ac2O</td>
<td>1:5:0.05</td>
<td>95</td>
<td>4.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Ac2O</td>
<td>1:5:0.05</td>
<td>115</td>
<td>1.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>(EtCO)2O</td>
<td>1:5:0.05</td>
<td>116–120</td>
<td>4.5</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>(EtCO)2O</td>
<td>1:5:0.05</td>
<td>92–96</td>
<td>2.0</td>
<td>&gt;99</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>(PhCO)2O</td>
<td>1:5:0.05</td>
<td>127–155</td>
<td>4.5</td>
<td>98</td>
<td>42</td>
</tr>
</tbody>
</table>

To overcome this problem supercritical carbon dioxide (scCO2) has been used to extract the product from ionic liquids mixtures [20]. It is known that scCO2 has a high solubility in ionic liquids, while most of the ionic liquids have negligible solubility in scCO2 [20, 21]. As a result, scCO2 can extract a pure product compound from an ionic liquid without any contamination [22]. In addition, scCO2, when combined with the ionic liquid, provides a reduction in viscosity and surface tension and promotes mass transfer [23]. ScCO2 possesses a mild critical temperature and critical pressure, which can be easily reached in chemical processes. Additionally, the solvency power of scCO2 can be tuned by manipulating the pressure (or temperature), which makes it a good candidate for extraction processes.

In this study, the aim is to use ionic liquids as solvents for the production of acetylferrocene without using volatile organic solvents during the separation step. In order to achieve this goal, the feasibility of acetylferrocene extraction with scCO2 from the reaction mixture should be studied. Therefore, phase behavior data of the binary
systems consisting of ferrocene/acetylferrocene + CO$_2$ are needed. To the best of our knowledge the solubility of acetylferrocene in scCO$_2$ has never been studied before. However, there are limited data points available for the solubility of ferrocene in scCO$_2$ [24]. The solubilities of ferrocene and acetylferrocene in scCO$_2$ were measured using an analytical method with a quasi-flow apparatus. High-performance liquid chromatography (HPLC) was applied through an online sampling procedure to determine the concentration of ferrocene and acetylferrocene in the scCO$_2$ phase. Finally, the solubilities of ferrocene and acetylferrocene are compared to each other, and differences are explained in terms of molecular structure and thermal properties.

5.2. Experimental

5.2.1. Materials

Ferrocene (melting point: 445 K) of >98 w% purity was purchased from Acros Organics N.V. Acetylferrocene (melting point: 354 K) with a purity of >95 w% was purchased from Merck Schuchardt OHG, however the certificate of analysis showed that the purity of the acetylferrocene was actually 99.4 w%. CO$_2$ with a purity of 99.7 vol% was supplied by Hoek Loos. HPLC grade $n$-hexane (97% purity) and ethanol (99.8% purity) were purchased from Sigma Aldrich. All materials were used without further purification.

5.2.2. Apparatus and procedure

The solubilities of ferrocene and acetylferrocene in scCO$_2$ were measured using an analytical method with a quasi-flow apparatus at (308, 318, 328, 338 and 348) K and pressures between 7.7 to 24.4 MPa. The set-up is schematically shown in Figure 5.2 [25]. In this apparatus, the solubilities in the scCO$_2$ stream were measured, using online sampling, by HPLC.
Prior to the measurements, samples of acetylferrocene or ferrocene were placed in the high pressure sapphire-cell. The sapphire-cell with an internal volume of 18 cm$^3$ has been designed to operate in the temperature range of 293 to 423 K and at pressures up to 35 MPa. Then, the cell was placed in an oven and the system was closed (Figure 5.3). Subsequently, the desired temperature was set at the oven. Once the desired temperature was reached, CO$_2$ was added to the system using an ISCO pump (model 260D), until the desired pressure was achieved. CO$_2$ circulation inside the solubility cell was started by means of a micropump (Micropump INC, model 380) after temperature and pressure conditions were stable.

The temperature was measured with an accuracy of ± 0.1 K and the pressure was measured with the accuracy of ± 0.05 MPa. However, the temperature measurements have an overall uncertainty of ± 0.5 K due to the temperature fluctuations in the oven. More detailed information on the apparatus and calibration can be found elsewhere [26].
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

After 3 hours, a sample was taken for HPLC using a sample loop fitted with an injection valve. This procedure was repeated successively every 45 min. Once the difference between two following measurements was less than $1 \times 10^{-4}$ mol$_{\text{solute}}$/mol$_{\text{CO}_2}$, it was presumed that equilibrium was reached. Then, the average concentration was registered as the solubility at the corresponding temperature and pressure.

The ultra-violet spectrophotometric (UV-Vis) profiles for HPLC were recorded at 323 nm, as the maximum electronic absorption of solutes in absolute ethanol and n-hexane occurred at this wavelength [27]. The analytical column used in this study was a chiral CHIRALPACK® (type AD-H, 4.6 × 250 mm) with amylose tris(3,5-dimethylphenylcarbamate) as adsorbent and coated on 5 μm silica-gel. The mobile phase consisted of a mixture of n-hexane and ethanol in the proportions of 85/15 (v/v). The flow rate was 1.0 mL·min$^{-1}$ and the total running time was 20 min.

According to Lambert-Beer’s law, the peak areas for a component are linearly related to their concentrations. Therefore, the solubilities at each pressure and temperature

Figure 5.3. Solubility cell set-up
were calculated from the peak areas in the UV-Vis profile. Prior to the measurements, calibration lines of the peak area as function of concentration for both ferrocene and acetylferrocene were obtained by analyzing six standard samples with different known concentrations of solute (in a mixture of n-hexane and ethanol in the proportions 85/15, v/v) in the range from (0 to 4) mg·mL⁻¹. The uncertainty of the final phase composition was ± 0.1 mg·mL⁻¹. Each standard sample was injected at least three times, and an average was taken to perform the linear regression. The correlation coefficient of the calibration line was equal to 0.999 and 0.991 for ferrocene and acetylferrocene, respectively.

5.3. Results and discussions

The solubilities of ferrocene and acetylferrocene in scCO₂ were measured at temperatures between 308 and 348 K and in the pressure range of 7.7 to 24.4 MPa. These data are presented in Table 5.2 and Table 5.3, respectively. It should be noted that each point was the average of at least two experimental measurements. From these data, it can be noticed that both solutes have the same order of magnitude of solubility in scCO₂. The experimental molar solubility of ferrocene in scCO₂ ranges from 8.9 to 31.2 × 10⁻⁴ and for acetylferrocene ranges from 2.5 to 79.2 × 10⁻⁴ mol_solute/mol_CO₂, which is sufficiently high (> 1-10 g/L) for separation using the scCO₂ extraction [28]. In order to better observe the results, the experimental data for ferrocene and acetylferrocene are graphically depicted in Figure 5.4 and Figure 5.5, respectively.

The error bars representing the standard deviations are also shown in these figures. The standard deviation is the square root of the variance. It can clearly be noticed that the solubility of both ferrocene and acetylferrocene in scCO₂ increases by increasing the pressure. The pressure does not significantly affect the size of the error bar. The effect of the temperature on the solubility of ferrocene and acetylferrocene in scCO₂ is more complex. For example, a decrease in acetylferrocene solubility is observed with an isobaric increase of temperature at pressures lower than around 15 MPa.
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

Table 5.2. Solubility (mol/mol) of ferrocene in scCO$_2$ at different pressures and temperatures.

<table>
<thead>
<tr>
<th>Pressure (MPa)</th>
<th>$T = 308$ K</th>
<th>$T = 318$ K</th>
<th>$T = 328$ K</th>
<th>$T = 338$ K</th>
<th>$T = 348$ K</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p / y \times 10^4$</td>
<td>$T = 308$ K</td>
<td>$T = 318$ K</td>
<td>$T = 328$ K</td>
<td>$T = 338$ K</td>
<td>$T = 348$ K</td>
</tr>
<tr>
<td>9.2</td>
<td>8.9 ± 0.4</td>
<td>11.0</td>
<td>8.7</td>
<td>8.0</td>
<td>8.2</td>
</tr>
<tr>
<td>12.9</td>
<td>10.0 ± 0.1</td>
<td>12.3</td>
<td>15.1</td>
<td>15.0</td>
<td>16.1</td>
</tr>
<tr>
<td>17.4</td>
<td>14.0 ± 0.5</td>
<td>19.1</td>
<td>16.8</td>
<td>17.1</td>
<td>19.6</td>
</tr>
<tr>
<td>20.1</td>
<td>15.6 ± 0.2</td>
<td>19.6</td>
<td>17.8</td>
<td>19.2</td>
<td>23.8</td>
</tr>
<tr>
<td>24.4</td>
<td>19.1 ± 0.5</td>
<td>22.1</td>
<td>21.5 ± 0.6</td>
<td>24.1</td>
<td>22.9 ± 0.9</td>
</tr>
</tbody>
</table>

Table 5.3. Solubility (mol/mol) of acetylferrocene in scCO$_2$ at different pressures and temperatures.

<table>
<thead>
<tr>
<th>Pressure (MPa)</th>
<th>$T = 308$ K</th>
<th>$T = 318$ K</th>
<th>$T = 338$ K</th>
<th>$T = 348$ K</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p / y \times 10^4$</td>
<td>$T = 308$ K</td>
<td>$T = 318$ K</td>
<td>$T = 338$ K</td>
<td>$T = 348$ K</td>
</tr>
<tr>
<td>7.7</td>
<td>2.5 ± 0.2</td>
<td>10.2</td>
<td>11.9</td>
<td>11.7</td>
</tr>
<tr>
<td>13.1</td>
<td>26.1 ± 1.8</td>
<td>11.5</td>
<td>16.0 ± 2.7</td>
<td>12.8</td>
</tr>
<tr>
<td>15.2</td>
<td>30.0 ± 1.1</td>
<td>14.9</td>
<td>47.9 ± 2.2</td>
<td>19.4</td>
</tr>
<tr>
<td>20.1</td>
<td>38.3 ± 1.0</td>
<td>18.4</td>
<td>67.0 ± 3.6</td>
<td>22.1</td>
</tr>
<tr>
<td>21.7</td>
<td>40.5 ± 3.2</td>
<td>19.1</td>
<td>42.8 ± 2.6</td>
<td></td>
</tr>
</tbody>
</table>
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

Figure 5.4. Molar solubility (mol/mol) of ferrocene in scCO$_2$ as a function of pressure at different temperatures: ◊, 308 K; □, 318 K; □, 328 K; ○, 338 K; △, 348 K. Lines are a guide to the eye.

Figure 5.5. Molar solubility (mol/mol) of acetylferrocene in scCO$_2$ as a function of pressure at different temperatures: ◆, 308 K; ■, 318 K; ○, 338 K; ▲, 348 K. Lines are a guide to the eye.
On the other hand, at pressures higher than around 15 MPa an isobaric increase in temperature increases the solubility of acetylferrocene in scCO₂. The pressure of 15 MPa is known as the cross-over pressure. The cross-over pressure is a characteristic of the solute-solvent system [29]. This behavior is a consequence of a trade-off effect between the solute vapor pressure and the solvent density on the solute solubility, and has been observed previously in other scCO₂ + solute systems [26, 29-31]. This means that the volatility of acetylferrocene is the dominant effect at pressures higher than 15 MPa (leading to an increase in solubility at increasing temperature), while the density of scCO₂ becomes the dominant factor at pressures lower than 15 MPa (leading to a decrease in solubility at increasing temperature). The same behavior can be observed for the temperature-dependence of the solubility of ferrocene in scCO₂. The cross-over pressure for ferrocene can be found around 10 MPa. Finally, it should be noticed that the standard deviation, which is the square root of the variance, of the experimental solubility data increases with increasing temperature. The experimental error for acetylferrocene is highest at 348 K (standard deviation = 7.2 × 10⁻⁴). The reason is that at 348 K the melting point of acetylferrocene (354 K) is approached.

In Figure 5.6 and Figure 5.7, the solubility of ferrocene in scCO₂ is compared to the solubility of acetylferrocene in scCO₂ at 308 K and 348 K, respectively. It can be seen that the solubility of ferrocene is higher than the solubility of acetylferrocene at low pressures, while the solubility of acetylferrocene is higher than the solubility of ferrocene at higher pressures.

This is a result of the differences in molecular structure and thermal properties of both solutes. Ferrocene has a lower molecular weight and polarity compared to acetylferrocene, and is therefore expected to be more soluble in scCO₂. On the other hand, acetylferrocene is more volatile than ferrocene, which enhances the solubility of acetylferrocene over ferrocene in scCO₂. Quadrupole moment of CO₂ and Lewis acid-Lewis base interactions between CO₂ and carbonyl group of the acetylferrocene are possible reasons for higher solubility of acetylferrocene in CO₂ compared to ferrocene.
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

[32-34]. Recent studies have also shown that addition of alkyl chain increases the solubility of organometallic compounds in CO$_2$ [35].

Figure 5.8 shows the comparison between the solubility data of ferrocene, which are obtained in this study, with the data available in the literature [24]. It can be seen from Figure 5.8 that there is a very good agreement between the two data sets at pressures higher than 15 MPa. However, the two data sets show different cross-over pressures. In our experiments it is apparent that the cross-over pressure can be found around 10 MPa, while the data from literature predict a cross-over pressure of around 15 MPa.

Figure 5.6. Comparison between molar solubilities (mol/mol) of ferrocene and acetylferrocene in scCO$_2$ at 308 K. Data points connected with solid line and dashed line are representing acetylferrocene and ferrocene, respectively. Lines are guide to the eye.
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

The reason for this difference could be due to the different experimental method used as well as the impurities in the materials (in ref. [24] supercritical fluid chromatography of a solution of ferrocene in heptane was used, while the method used in this work is extraction of pure ferrocene in scCO$_2$ with a quasi-flow apparatus). Moreover, it should be noted that the directly measured solubility data from literature are very limited [24], making it difficult to determine the cross-over pressure from these data. Since pure ferrocene (instead of a ferrocene solution in heptane) is used in this study, we believe that the obtained solubility data in this work have higher accuracy.

Finally, it should be noted that supercritical extraction is a potentially good method to

![Figure 5.7. Comparison between molar solubilities (mol/mol) of ferrocene and acetylferrocene in scCO$_2$ at 348 K. Data points connected with solid line and dashed line are representing acetylferrocene and ferrocene, respectively. Lines are guide to the eye.](image-url)
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

separate the product acetylferrocene from the Friedel-Crafts acylation reaction mixture with ferrocene. Particularly, when the reaction is carried out in an ionic liquid, the product acetylferrocene can be recovered without any solvent losses. Further CO\textsubscript{2} regeneration is possible by lowering the solubility of solutes in CO\textsubscript{2} through manipulating the pressure and temperature conditions, as shown in Table 5.2 and Table 5.3. Nevertheless, for more accurate evaluation additional data on the partition coefficient of acetylferrocene in [bmim][Tf\textsubscript{2}N] and CO\textsubscript{2} is needed.

Results showed that the selectivity for the extraction of acetylferrocene strongly depends on the conditions used. Therefore, the preference of the extraction switches

![Figure 5.8](image_url)

Figure 5.8. Molar solubility (mol/mol) of ferrocene in scCO\textsubscript{2} at different temperatures. Data connected with lines are measured in this work (for the legend please see Fig. 3). Data connected with dashed line are collected from literature [24]: *, 313.15 K; +, 323.15 K; ×, 333.15 K; ■, 343.15 K. Lines are guide to the eye.
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

Based on the operation conditions. ScCO₂ at pressures higher than 13 MPa should be used in order to show high selectivity (higher solubility of acetylferrocene compared to ferrocene). For instance, at 308 K and 20.1 MPa the selectivity for acetylferrocene solubility compared to ferrocene is 2.5 times higher. However, it should also be noted that in actual multicomponent mixture, acetylferrocene and ferrocene will affect one-another’s solubilities in ScCO₂. These observations indicate the importance of studying the solubility of both product and reactant in a ternary mixture with CO₂.

5.4. Conclusion

In this chapter, the solubilities of ferrocene and acetylferrocene in ScCO₂ are experimentally determined using an analytical method with a quasi-flow set-up. Acetylferrocene is the product of the Friedel-Crafts acylation reaction of ferrocene. The solubility data are measured within a pressure range of 7.7 MPa to 24.4 MPa and at temperatures between 308 and 348 K. The experimental molar solubility of ferrocene in ScCO₂ ranges from 8.9 to 31.2 × 10⁻⁴ (= 2.9 to 11.1 g/L) and for acetylferrocene ranges from 2.5 to 79.2 × 10⁻⁴ (= 0.8 to 26.2 g/L), which is sufficiently high for separation using the ScCO₂ extraction.

The solubility of ferrocene and acetylferrocene in ScCO₂ increases with increasing pressure. At low pressures the solubilities decrease with increasing temperature, while at high pressures the solubilities increase with increasing temperature. The cross-over pressure of ferrocene can be found around 10 MPa, while it is around 15 MPa for acetylferrocene.

In order to achieve high extraction selectivities, the solubility of acetylferrocene should be higher than the solubility of ferrocene in ScCO₂. It is shown that acetylferrocene is more soluble in ScCO₂ at higher pressures, while ferrocene is more soluble at lower pressures. This can be explained by the difference in molecular structure and the thermal properties of both components. This study stresses the importance of phase behavior measurements for designing separation processes using ScCO₂ extraction.
5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide

5.5. References


5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide


5. Solubilities of ferrocene and acetylferrocene in supercritical carbon dioxide


Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

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6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

6.1. Introduction

The phase behavior of a new ternary “ionic liquid + carbon dioxide (CO₂) + organics” system was measured, where the organic compound is a solid. Specifically, we are interested in the co- and anti-solvency behavior of CO₂ in the 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][Tf₂N]) + ferrocene system. Ferrocene (Figure 6.1) is an organometallic compound with the formula Fe(C₅H₅)₂, which is widely used as a reactant in the Friedel-crafts acylation reactions [1-3]. It has many applications in organometallic reactions and as a functional building block. Recently, the acylation reaction of ferrocene has been successfully carried out using ionic liquids as solvents [4]. These results motivated us to explore the applicability of the miscibility switch phenomenon for the acylation reaction of ferrocene. Therefore, it is important to measure the phase behavior of the mentioned system in the presence of CO₂ and ionic liquids.

![Figure 6.1. Molecular structure of ferrocene](image)

So far, several studies have been conducted to measure the phase behavior of ternary “ionic liquid + CO₂ + organics” systems [5-12]. Most of these studies involve an organic
compound in the liquid state (e.g., methanol), where different types of phase transitions (e.g. liquid-vapor to liquid$_1$-liquid$_2$-vapor (LV → L$_1$L$_2$V), liquid$_1$-liquid$_2$-vapor to liquid$_1$-liquid$_2$ (L$_1$L$_2$V → L$_1$L$_2$) and liquid$_1$-liquid$_2$ to liquid (L$_1$L$_2$→L$_1$)) were observed depending on the type of organic compound, type of ionic liquid and their concentrations [5-10]. Instead, there are only limited studies on ternary phase behavior of ionic liquid + CO$_2$ + organics systems, where the organic compound is a solid [11, 13, 14]. For example, the solubility of solid naphthalene in the binary 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF$_6$]) + CO$_2$ system was studied, where the concentrations of the naphthalene in CO$_2$-rich phase throughout the temperature and pressure range were determined [14]. Later on, the phase behavior of the ternary system containing the organic compound methyl-(Z)-α-acetamido cinnamate (MAAC) + the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]) + CO$_2$ was studied experimentally. The results indicated that CO$_2$ at low concentrations increases the solubility of MAAC in [bmim][BF$_4$], while at higher CO$_2$ concentrations it has a reverse effect and decreases the solubility of MAAC in [bmim][BF$_4$] [11]. Finally, the co-solvency behavior of CO$_2$ in the ternary system with solid (s)-naproxen + [bmim][BF$_4$] + CO$_2$ was reported [13].

It was previously found that CO$_2$ at low concentrations acts as co-solvent (increasing the solubility of organics in the ionic liquid phase), while CO$_2$ at higher concentrations works as anti-solvent (decreasing the solubility of organics in the ionic liquid phase) [11, 13]. Because supercritical CO$_2$ (scCO$_2$) is often used as extracting solvent at high concentrations, its anti-solvency behavior is dominantly observed, resulting in precipitation of the organic compound from the ionic liquid phase by CO$_2$ addition [15, 16].

Phase behavior experiments are carried out in a Cailletet apparatus in the temperature range of 278.38 to 368.47 K and at pressures up to 9.24 MPa. The CO$_2$ concentration is varied from 10% mol to 50% mol. The conditions at which the different phase transitions occur are measured.
6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

6.2. Experimental

6.2.1. Materials

The ionic liquid [bmim][Tf$_2$N] used in this study was purchased from Iolitec with 99% purity. This ionic liquid was further dried using a desiccator under vacuum supplied with molecular sieves as a drying agent for several days. The water content was measured by Karl-Fischer analysis to be less than 0.01%. Ferrocene of 98% purity was purchased from Acros Organics N.V. and was used without further purification. High purity CO$_2$ (99.99%) was supplied by HoekLoos B.V..

6.2.2. Experimental set up

The Cailletet apparatus was used to perform phase behavior measurements according to the synthetic method. This set-up is explained in detail in Chapter 4.

6.2.3. Experimental procedure

A solution of 5.0 mole% of ferrocene in the ionic liquid [bmim][Tf$_2$N] was prepared prior to the sample preparation, in order to keep the concentration of solute constant in all the experiments. Since the water content of solutions containing ionic liquid can change the phase behavior significantly, the mentioned solution was placed in the desiccator and left under vacuum for a few days in order to dry the sample. The dried solution (<100 ppm water) was injected into the Cailletet tube using a micro-syringe. In the data measurement procedure, the temperature was set to a desired value, and then the pressure was changed until the phase transition was observed visually. In other words, at a constant temperature, pressure is changed until the last bubble in the case of measuring liquid-vapor to liquid (LV $\rightarrow$ L) line or the last solid particle in the case of measuring solid-liquid to liquid (SL$\rightarrow$L) dissolves. By repeating this course of action at different compositions, the complete phase behavior of the desired system within the operational conditions was collected.
6.3. Results and discussion

The experimental data of the different phase transitions collected for the ternary system containing ferrocene + [bmim][Tf$_2$N] + CO$_2$ are presented in the appendices (Table A2-1). In all experiments the concentration of ferrocene in [bmim][Tf$_2$N] was kept constant at 5.0 mol%. Figure 6.2. presents the data at 20.00 mol% of CO$_2$ graphically, where three phase transitions (SLV → SL, SL → L and LV → L) were experimentally measured.

From Figure 6.2, one can clearly observe the existence of four different regions: (i) a homogeneous liquid (L) phase, (ii) a two-phase liquid-vapor (LV) region, (iii) a two-phase solid-liquid (SL) region, and (iv) a three-phase solid-liquid-vapor (SLV) region.

![Figure 6.2. Phase behavior of the ternary system of [bmim][Tf$_2$N] + CO$_2$ + ferrocene (5 mol% in ionic liquid) at 20.00 mol% of CO$_2$. The open symbols represent the SLV→SL transition, the solid symbols represent the SL→L transition, and the dotted symbols represent the LV→L transitions (the dotted line for the SLV→LV transition is not measured).](image)
6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

Similar phase behavior was found at other CO₂ concentrations. In order to study the effect of the CO₂ concentration in the ternary system of ferrocene + [bmim][Tf₂N] + CO₂, the five different isopleths (10, 20, 30, 40 and 50 mol% of CO₂) are presented in a pressure-versus-temperature diagram in Figure 6.3. In this figure SL → L and SLV→SL transitions of the ternary system of [bmim][Tf₂N] + CO₂ + ferrocene are presented. From this figure it can be observed that by increasing the concentration of CO₂, higher pressures are required to dissolve CO₂ in the ternary system.

![Figure 6.3. SL → L (solid symbols) and SLV→SL (open symbols) isopleths of the ternary system of [bmim][Tf₂N] + CO₂ + ferrocene, at different concentrations of CO₂: □, 10.00 mol% CO₂; ●, 20.00 mol% CO₂; ▲, 29.98 mol% CO₂; ◆, 39.97 mol% CO₂; ■, 50.05 mol% CO₂. (Lines are to guide the eye)
6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

In Figure 6.4, the LV → L and SL → L isopleths are plotted, so one can see when the homogeneous liquid phase is reached. From Figure 6.4, it can be noticed that the LV → L transition similar to the SLV→SL transitions (Figure 6.3) shifts to higher pressures with increasing CO$_2$ concentration. This means that a higher pressure is necessary to dissolve more CO$_2$ in the liquid phase. This is the common behavior for the solubility of CO$_2$ in ternary ionic liquid systems [8, 9, 12, 13]. Figure 6.4 also shows that the SL → L phase boundary shifts to lower temperatures as the CO$_2$ concentration increases in the system.

![Graph](image)

Figure 6.4. SL → L (solid symbols) and LV → L (dotted symbols) isopleths of the ternary system of [bmim][Tf$_2$N] + CO$_2$ + ferrocene, indicating the location of the homogeneous region at different concentrations of CO$_2$: □, 10.00 mol% CO$_2$; ●, 20.00 mol% CO$_2$; ▲, 29.98 mol% CO$_2$; ◆, 39.97 mol% CO$_2$; ■, 50.05 mol% CO$_2$. (Lines are to guide the eye)
6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

This behavior can be better observed by exploring the isobars of the ternary system as illustrated in Figure 6.5. These data are acquired by linear fit of the SL → L data at four different pressures (4, 5, 6, and 7 MPa). From this figure one can see that the addition of CO$_2$ decreases the temperature required to dissolve the solid ferrocene in the ternary ionic liquid system. Ferrocene is thus more soluble in the [bmim][Tf$_2$N] + CO$_2$ mixture than in pure [bmim][Tf$_2$N]. This behavior is also known as the co-solvency effect of scCO$_2$ and it is ascribed to higher chemical interaction between ferrocene and CO$_2$ [17, 18].

Figure 6.5. Isobars for the precipitation temperature versus the mole fraction of CO$_2$ in the ternary system of [bmim][Tf$_2$N] + CO$_2$ + ferrocene: 4 MPa (◊), 5 MPa (○), 6 MPa (□) and 7 MPa (△).
6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

The effect of addition of ferrocene to the binary mixture of [bmim][Tf₂N] + CO₂ is shown in Figure 6.6. at four different concentrations of CO₂. In this figure the LV→L experimental data for the ternary system ferrocene + [bmim][Tf₂N] + CO₂ are compared to those for the binary system of [bmim][Tf₂N] + CO₂ [19]. From this figure, it can be noticed that slightly higher pressures are necessary to dissolve CO₂ in [bmim][Tf₂N] in ternary system of ferrocene + [bmim][Tf₂N] + CO₂ compared to binary system of [bmim][Tf₂N] + CO₂. This is due to the fact that in ternary system CO₂ competes with the ferrocene to interact with the ionic liquid [bmim][Tf₂N], and here our results show that these interactions are slightly stronger for ferrocene and ionic liquid [bmim][Tf₂N] compared to non-polar CO₂ and ionic liquid [bmim][Tf₂N].

Figure 6.6. Comparison between the isopleths for LV → L ternary system [bmim][Tf₂N] + CO₂ + ferrocene (filled symbols) and binary system [bmim][Tf₂N] + CO₂ (open symbols with dashed lines) at different concentrations of CO₂: ○, 20.00 mol% CO₂; ▲, 29.98 mol% CO₂; ●, 39.97 mol% CO₂; ■, 50.05 mol% CO₂; ○, 18.86 mol% CO₂; △, 29.26 mol% CO₂; ◇, 38.18 mol% CO₂; ■, 48.66 mol% CO₂.
From literature it is known that CO\textsubscript{2} can act both as co-solvent and as anti-solvent. Generally, CO\textsubscript{2} at low concentrations works as co-solvent whereas CO\textsubscript{2} at high concentrations acts as anti-solvent [17]. Most research on ternary ionic liquid + CO\textsubscript{2} + organics systems involves high concentrations of CO\textsubscript{2}, because the CO\textsubscript{2} is used as extractant for the recovery of organics from the ionic liquid phase [5, 20]. In some cases the anti-solvency behavior of CO\textsubscript{2} at high concentrations is also used, where the organic compound is recovered from the ionic liquid phase as precipitate by the addition of sc\textsubscript{CO}\textsubscript{2} [15]. On the contrary, in this work we found that CO\textsubscript{2} at concentrations up to 50 mol\% acts as co-solvent in the ternary ferrocene + [bmim][Tf\textsubscript{2}N] + CO\textsubscript{2} mixture. This means that we can precipitate ferrocene out of the ionic liquid phase by removal of the CO\textsubscript{2} by pressure release. Thus, the phase behavior has a large impact on the design of the solute recovery step. It is expected, however, that CO\textsubscript{2} will also act as an anti-solvent in this system at higher concentrations, but it is not possible to measure this with our set up due to the limitations of the allowable pressure range.

6.4. Conclusion

The phase behavior of the ternary system containing the ionic liquid [bmim][Tf\textsubscript{2}N], the sc\textsubscript{CO}\textsubscript{2}, and the solid organometallic compound ferrocene has been studied experimentally. Measurements were carried out at five different concentrations of CO\textsubscript{2} (10, 20, 30, 40 and 50 mol\%), at temperatures ranging from 278 up to 368 K and pressures up to 9.24 MPa. The measured phase diagram showed four different regions (L, LV, SL and SLV) for all experiments, but the CO\textsubscript{2} concentration was found to have a large influence on the location of the phase boundaries. The LV \to L transition shifts to higher pressures with increasing CO\textsubscript{2} concentration. The SL \to L phase boundary shifts to lower temperatures as the CO\textsubscript{2} concentration increases in the system. It was observed that sc\textsubscript{CO}\textsubscript{2} acts as a co-solvent in all cases, even at high CO\textsubscript{2} concentrations (50 mol\%). Ferrocene is thus more soluble in the [bmim][Tf\textsubscript{2}N] + CO\textsubscript{2} mixture than in pure [bmim][Tf\textsubscript{2}N]. Therefore, ferrocene can be precipitated out of the ionic liquid by
6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

CO$_2$ pressure release. The results stress the importance of the availability of accurate phase behavior data for the design of new chemical processes.
6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene

6.5. References


6. Phase behavior of the ternary system ionic liquid + carbon dioxide + ferrocene


Phase behavior of the ternary system ionic liquid + carbon dioxide + acetylfierrocene

7. Phase behavior of the ternary system ionic liquid + carbon dioxide + acetylferrocene

7.1. Introduction

As mentioned in previous chapters, the Friedel-Crafts acylation is an important reaction with applications in many fields such as material science, catalysis, bio-organometallic chemistry and the pharmaceutical industry [1, 2]. One of the well-known examples is the acylation reaction of ferrocene to acetylferrocene. In order to apply miscibility switch phenomena, it is crucial to locate the homogeneous and heterogeneous regions in the ternary systems containing reactants or products in the presence of ionic liquids and CO$_2$. Therefore, ternary phase behavior data are necessary to find the optimum reaction and separation conditions. Although there have been many studies conducted on the measurement of the binary phase behavior of systems containing ionic liquids and CO$_2$ [3-6] studies on multicomponent systems containing ionic liquids are still very limited. A number of studies have been conducted to report the phase behavior of ternary ionic liquid + CO$_2$ + organics systems, where the organic compound is an alcohol, a ketone or an ether, either liquid or solid at room temperature [7-14]. Different types of phase transitions have been observed in the studied systems, of course, depending on the type of organic molecules, type of ionic liquid and their concentrations [7-12].

In the previous chapter the ternary phase behavior of the reactant which is ferrocene with ionic liquid and CO$_2$ has been presented. It is our intention in this chapter to measure the phase behavior of the ternary system containing the solid organometallic compound of acetylferrocene (Figure 7.1) in the presence of ionic liquid [bmim][Tf$_2$N] and CO$_2$. Acetylferrocene is an intermediate in the production of functional groups in polymers, combustion catalysts for propellants and in medicinal chemistry [2].
7. Phase behavior of ternary system ionic liquid + carbon dioxide + acetylferrrocene

7.2. Experimental

7.2.1. Materials

Acetylferrrocene of 98% purity was purchased from Acros Organics N.V. and was used as received. The ionic liquid [bmim][Tf₂N] was purchased from Iolitec with 99% purity and was further dried under vacuum in desiccator. Water content was measured to be less than 0.01% using Karl-Fischer. CO₂ was supplied by HoekLoos B.V., with 99.99% purity.

7.2.2. Sample preparation and measurements

To keep the concentration of the solute constant in all experiments, a solution of 5.0 mole% of acetylferrrocene in the ionic liquid [bmim][Tf₂N] was prepared prior to the sample preparation. A synthetic method using the Cailletet apparatus (Figure 7.2) was used to measure the phase behavior of the ternary system acetylferrrocene + [bmim][Tf₂N] + CO₂. A detailed explanation of the set-up and procedure are presented in Chapter 4. Experiments with water as a heat-transferring fluid were carried out in a
Phase behavior of ternary system ionic liquid + carbon dioxide + acetylferrocene temperature range of 278.15 to 368.15 K. The Cailletet apparatus allows pressure measurements up to 15 MPa.

Figure 7.2. The Cailletet apparatus
7. Phase behavior of ternary system ionic liquid + carbon dioxide + acetylferrrocene

7.3. Results and discussion

The phase behavior data for the ternary system containing acetylferrrocene + [bmim][Tf$_2$N] + CO$_2$ in a temperature range of 278.15 to 368.15 K and pressures up to 10.01 MPa are presented in appendices (Table A3-1). The concentration of acetylferrrocene in [bmim][Tf$_2$N] was maintained at a constant value of 5.0 mol% in all the measurements. These data are graphically depicted in Figure 7.3.

![Figure 7.3](image)

**Figure 7.3.** Experimental isopleths for the system acetylferrrocene + [bmim][Tf$_2$N] + CO$_2$ at different CO$_2$ concentrations: ◊, 10.10 mol%; □, 19.97 mol%; △, 30.76 mol%; +, 40.10 mol%; ○, 50.04 mol%.

This figure shows the five different isopleths (10, 20, 31, 40 and 50 mol% of CO$_2$) in a pressure-versus-temperature diagram. Also, it is possible to recognize two different regions of liquid-vapor (LV) and liquid (L) in the acetylferrrocene + [bmim][Tf$_2$N] + CO$_2$ system. From this figure, it can be seen that the LV → L transition moves to higher pressures with increasing CO$_2$ concentrations. In other words, a higher pressure has to be applied to achieve a homogeneous liquid phase when more CO$_2$ is added to the system. During these experiments and for the mentioned temperature and pressure conditions, no solid-liquid or solid-vapor transitions were observed.
In order to explore the effect of the addition of acetylferrocene to the binary system, Figure 7.5 illustrates the comparison between the binary system of [bmim][Tf₂N] + CO₂ [3] and the ternary system acetylferrocene + [bmim][Tf₂N] + CO₂. Third-order polynomial equations were used to fit the experimental data and interpolations at three different temperatures were used to plot isotherms. Figure 7.5 shows that the addition of acetylferrocene to the binary system of [bmim][Tf₂N] + CO₂ slightly decreases the solubility of CO₂ in the ternary system. Moreover, it indicates that higher pressures are necessary to dissolve CO₂ in the acetylferrocene + [bmim][Tf₂N] system compared to [bmim][Tf₂N] only.

This behavior could be due to the reason that the acetylferrocene molecule and the ionic liquid [bmim][Tf₂N] form stronger (polar) interactions compared to the interaction of [bmim][Tf₂N] with CO₂. This behavior of different organic compounds in the presence of ionic liquids and CO₂ has been reported previously in literature [10,
7. Phase behavior of ternary system ionic liquid + carbon dioxide + acetylferrrocene

Additionally, from this figure one can clearly see the effect of the CO$_2$ concentrations on the pressure necessary to obtain a homogeneous phase.

Previously, the phase behavior of ternary system ferrocene + [bmim][Tf$_2$N] + CO$_2$ was studied experimentally. As mentioned before, ferrocene is the reactant to produce acetylferrrocene in the acylation reaction. In order to establish the optimum conditions to carry out the reaction and separation, it is essential to collect and to compare the phase behavior data for both systems.

In Figure 7.6, a comparison between the ternary system of ferrocene + [bmim][Tf$_2$N] + CO$_2$, which data were obtained in our study [15] and the ternary system acetylferrocene + [bmim][Tf$_2$N] + CO$_2$ is shown graphically. It was found before that four different phase regions are detectable in the ternary system of ferrocene + [bmim][Tf$_2$N] + CO$_2$: (i) a homogenous liquid (L) phase, (ii) a two-phase liquid-vapor

![Figure 7.5. Comparison between isotherms for the binary system [bmim][Tf$_2$N] + CO$_2$ (filled symbols connected with dashed lines) and the ternary system acetylferrocene + [bmim][Tf$_2$N] + CO$_2$ (open symbols): □ and ■, 313.15 K; △ and ▲, 333.15 K; ○ and ●, 353.15 K. Dashed lines are polynomial fits to help the comparison.](image-url)
7. Phase behavior of ternary system ionic liquid + carbon dioxide + acetylferrocene

(LV) region, (iii) a two-phase solid-liquid (SL) region, and (iv) a three-phase solid-liquid-vapor (SLV) region [15].

However, only two regions were observed for the ternary system acetylferrocene + [bmim][Tf₂N] + CO₂. In other words, ferrocene precipitates as a solid by lowering the temperature while acetylferrocene is soluble in the solution at the same conditions. This behavior can be explained by the fact that acetylferrocene is more polar and has a lower melting point than ferrocene. Moreover, it can be seen from Figure 7.6 that higher pressures are necessary to dissolve CO₂ in the ternary system acetylferrocene + [bmim][Tf₂N] + CO₂ compared to the ternary system ferrocene + [bmim][Tf₂N] + CO₂.

![Figure 7.6. Comparison between isopleths for the ternary system acetylferrocene + [bmim][Tf₂N] + CO₂. △, 30.76 mol% CO₂; ○, 50.04 mol% CO₂ and the ternary system ferrocene + [bmim][Tf₂N] + CO₂[15] □, 29.98 mol% CO₂; ▲, 50.05 mol% CO₂. Open symbols represent SLV→SL transitions, solid symbols represent SL→L transitions, and dotted symbols represent LV→L transitions). Dashed lines are guide to the eye.](image)

This behavior indicates the importance of studying the phase behavior of both reactant and product simultaneously in order to find the homogeneous region for the acylation reaction. Consequently, the best conditions to carry out the acylation
reaction of ferrocene to acetylferrocene strongly depends on the CO$_2$ concentrations in the system. For example, for a CO$_2$ concentration of 30 mol% and temperatures higher than 330 K and pressures higher than 5 MPa should be applied to maintain a homogenous phase during the acylation reaction. Afterwards, during the separation process the phase split could be achieved by pressure reduction. In summary, it can be concluded that the miscibility windows principle provides a useful tool to perform the acylation reaction of ferrocene into acetylferrocene in the presence of ionic liquid [bmim][Tf$_2$N] and CO$_2$.

7.4. Conclusion

In this work, the phase behavior of the ternary system consisting of the organometallic compound acetylferrocene in the presence of the ionic liquid [bmim][Tf$_2$N] and CO$_2$ was studied for five different concentrations of CO$_2$, ranging from 10 mol% up to 50 mol%. Acetylferrocene is the product of the Friedel-Crafts acylation reaction of ferrocene. From the results it was possible to recognize two regions (LV and L). By increasing the CO$_2$ concentration the LV → L transition shifts to higher pressures. Comparison of the obtained ternary data with the binary data of [bmim][Tf$_2$N] + CO$_2$ indicated that addition of acetylferrocene decreases the solubility of CO$_2$ in the [bmim][Tf$_2$N]. The reason could be due to presence of stronger interactions between acetylferrocene and [bmim][Tf$_2$N] compared to interactions between CO$_2$ and [bmim][Tf$_2$N].

Comparison between the ternary phase behavior data of acetylferrocene + [bmim][Tf$_2$N] + CO$_2$ with the ternary data of the system ferrocene + [bmim][Tf$_2$N] + CO$_2$, which we measured in our previous study, clarified that ternary systems containing solutes with similar molecular structure may show a completely different phase diagram.

The experimental results of this study were also used to locate the homogeneous region for the reaction of ferrocene to acetylferrocene in ionic liquid + CO$_2$ systems according to miscibility switch phenomenon. For example at 30 mol% of CO$_2$, 

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temperatures higher than 330 K and pressures higher than 5 MPa should be applied to maintain a homogenous phase during the acylation reaction. In conclusion, the optimal operating conditions for the acylation reaction in ionic liquid + CO$_2$ systems were successfully determined.
7. Phase behavior of ternary system ionic liquid + carbon dioxide + acetylferricene

7.5. References


4. Shiflett, M.B., et al., *Phase Behavior of N$_2$O and CO$_2$ in Room-Temperature Ionic Liquids [bmim][Tf$_2$N], [bmim][BF$_4$], [bmim][N(CN)$_2$], [bmim][Ac], [eam][NO$_3$], and [bmim][SCN]*. International Journal of Thermophysics, 2012: p. 1-25.


7. Phase behavior of ternary system ionic liquid + carbon dioxide + acetylferrocene


Evaluation of sustainability and economics
8. Evaluation of sustainability and economics

8.1. Introduction

In this chapter the production process for two model reactions, i.e. (i) epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol and (ii) Friedel-Crafts acylation reaction of ferrocene to acetylferrocene, are evaluated from a green chemistry and economic perspective. In both cases, the conventional production process is compared with the alternative process proposed in this study using ionic liquid/carbon dioxide (CO$_2$). From a green chemistry standpoint, the ionic liquid/CO$_2$ production process has the potential to increase the stability and lifetime of the catalyst, does not generate solvent losses by means of evaporation, and possibly consumes less energy. From an economical standpoint, there are capital expenditures associated with the purchase of new equipment for the ionic liquid/CO$_2$ production process, but the savings in operational costs for both reactions could be much higher, making the new process overall more attractive than the conventional process. Within the future, increasing energy costs and a more pregnant legislation to replace existing production processes with environmentally benign processes (to reduce waste generation, solvent emission and energy consumption), there is a great need for environmentally friendly alternatives such as the ionic liquid/CO$_2$ production process described in this thesis.

8.2. Epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol

8.2.1. Environmental evaluation

waste production

As was mentioned in the first chapter, the main message of the 12 principles of the green chemistry is to reduce or eliminate the use or generation of hazardous substances in the design, manufacture and use of chemical products. Therefore, to evaluate the environmental impact of the two production processes, it is important to
8. Evaluation of sustainability and economics

calculate the waste production of both methods. Catalyst and solvent losses are the
main sources for waste generation in the epoxidation reaction of cinnamyl alcohol to
3-phenylglycidol. The formation of the by-products (benzaldehyde and
cinnamaldehyde) is also source of the waste production in this reaction. In the late
1980s, R.A Sheldon developed the E(nvironmental) factor, which measures amount of
waste (kg) that is produced per kilogram of product [1]. This is an important factor to
assess the environmental impact of manufacturing processes. Here, we calculate the
E-factor as summation of main wastes that are produced during both conventional
and ionic liquid/CO₂ production processes.

In the conventional production process, 5 mol% of VO(acac)₂ is used for the
production of 3-phenylglycidol. It has been reported that the turnover number (TON)
for this reaction is equal to 22 (mol product/mol catalyst) [2]. This means that 1 gr of
VO(acac)₂ catalyst produces 12.5 gr of 3-phenylglycidol before becoming inactivated.
In the other words, 80.3 g of VO(acac)₂ catalyst is used per kilo 3-phenylglycidol
produced as catalyst make-up. As mentioned before, the chiral 3-phenylglycidol is
produced using chiral ligands, which are explained in Chapter 3. Here, we assume that
same type and amount of chiral ligand is consumed in the ionic liquid/CO₂ production
process as conventional process, and therefore we do not proceed with the calculation
of these ligands since they will be eliminated in the comparison of two processes. It is
expected that ionic liquids protect the VO(acac)₂ catalyst against oxidation and
consequently, the VO(acac)₂ catalyst is more stable in ionic liquid/CO₂ system. This
assumption is supported by similar studies on the catalytic reactions in ionic liquids
[3, 4]. Thus theoretically the catalyst make-up in the ionic liquid/CO₂ would be ideally
zero. Since this would be an unrealistic assumption, we presume that the catalyst has
to be replaced every 10 cycles. Regarding the results from Chapter 3, this means that 1
gr of VO(acac)₂ catalyst produces 111.3 gr of 3-phenylglycidol before becoming
inactivated in ionic liquid/CO₂ production process. This corresponds to the catalyst
make-up of 9 gr per kg of 3-phenylglycidol production.
In order to calculate the solvent losses, first we need to calculate the amount of the solvent used to produce 1 kg of 3-phenylglycidol. According to the reaction procedure, 3 L of toluene is used to produce 1 mol of 3-phenylglycidol which means that 18.93 kg of toluene is consumed for the production of 1 kg of 3-phenylglycidol [2]. Approximately 80% of the toluene used in this process is assumed to be recovered by evaporation [5]. Therefore, the amount of toluene losses are $0.20 \times 18.93 = 3.78$ kg toluene per kilo of produced 3-phenylglycidol. There is no solvent losses associated with the ionic liquid/CO$_2$ production process since ionic liquids do not evaporate into vapor phase. Later on, in the economical evaluation section, it is assumed that it is necessary to replace the ionic liquid once a year which is more realistic assumption.

In the conventional production process, 0.38 kg of by-products (benzaldehyde and cinnamaldehyde) is produced per kg of produced 3-phenylglycidol. This value in the ionic liquid/CO$_2$ production process is 0.40 kg of by-products per kg of produced 3-phenylglycidol. It should be noted that these aldehydes are important products with many applications in industry and they can be used next to the main product.

**Energy consumption**

In order to recover the conventional solvent, which is toluene in this case, it is essential to evaporate the solvent. In the conventional epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol is carried out at 25 °C. Therefore, it is necessary to heat the toluene from 25 °C to its boiling point (110.6 °C) and then heat the toluene until it evaporates. After recovering toluene from reaction mixture, toluene is cooled down in order to use it again as solvent in the reaction. During the cooling process, almost the same amount of energy should be recovered from toluene to cool it down to 25 °C. The cooling process can be carried out by air or cooling water, which are much cheaper than steam or electricity, that are consumed in the evaporation process. Moreover, by implementing heat integration, it is possible to use the energy from gas toluene to evaporate liquid toluene. Therefore, the energy consumption is overall much less and in an ideal case close to zero. However, in order to have more realistic
8. Evaluation of sustainability and economics

estimation, the following equation is used to calculate the required heat to evaporate toluene [6]:

\[ \Delta H = C_{p,l} \cdot \Delta T + \Delta_{vap}H, \]  \hspace{1cm} (1)

where:

\[ \Delta H \] = Amount of energy [kJ·kg\(^{-1}\)]
\[ C_{p,l} \] = Specific heat of liquid [kJ·kg\(^{-1}\)·K\(^{-1}\)]
\[ \Delta T \] = Temperature difference [K]
\[ \Delta_{vap}H \] = Enthalpy of evaporation [kJ·kg\(^{-1}\)]

The enthalpy of evaporation for toluene at boiling point is \( \Delta_{vap}H = 360.10 \) kJ kg\(^{-1}\) and the specific heat of toluene is \( C_{p,l} = 1.71 \) kJ kg\(^{-1}\) K\(^{-1}\) [7]. Using equation (1) the total amount of 507 kJ/kg energy is required to evaporate 1 kg of toluene. In conventional process 18.93 kg of toluene is used to produce 1 kg of 3-phenylglycidol, therefore the amount of 9.59 MJ/kg energy is used per kg produced 3-phenylglycidol.

The main energy consumption step in the ionic liquid/CO\(_2\) process is the energy required for repressurizing CO\(_2\). In this thesis it is shown that the 3-phenylglycidol extraction is possible with scCO\(_2\) at 313 K and pressures lower than 120 bar (12.0 MPa). To maximize the amount of product extraction, it is important to apply the optimum pressure in which the product has high solubility in scCO\(_2\). Since there is no information on the solubility of the 3-phenylglycidol in scCO\(_2\), we used the data from similar molecules to 3-phenylglycidol. According to the available data, molecules with similar structure have solubility range of 1 to 10 g/kg CO\(_2\) [8]. For instance, it is
8. Evaluation of sustainability and economics

reported that the solubility of N-acetyl-(S)-phenylalanine methyl ester (APAM) in scCO$_2$ at 120 bar and 40 °C is 1.78 g/kg [9]. Since 3-phenylglycidol has a lower molecular weight compared to APAM, it is expected to have higher solubility in scCO$_2$. Based on this information, it is assumed that the solubility the 3-phenylglycidol in scCO$_2$ at 120 bar and 40 °C is 5 g/kg. It was also shown before that the solubility of the solids in the scCO$_2$ depends on the density of the scCO$_2$ and at pressures around critical pressure a sharp increase in the solubility of the solid solute in scCO$_2$ was observed [9]. Normally in the pressures lower than critical pressure (76 bar) there is a sharp decrease in the solubility of solutes is scCO$_2$. Based on this information and also the results from previous chapter on phase behavior of the ternary system of ionic liquid + CO$_2$ + 3-phenylglycidol, it is recommended to work at 120 bar for the scCO$_2$ extraction and to decrease the pressure until 80 bar to fully recover the product from the CO$_2$ phase.

In order to calculate the energy consumption for pressurizing CO$_2$ from 80 bar to 120 bar, one can use the following equation [10]:

\[
W = \frac{1}{\eta} \cdot \int \frac{1}{\rho} \cdot dp \approx \frac{\Delta p}{\eta \cdot \rho_{average}},
\]

(2)

where:

\[ W \quad = \quad \text{Work} \quad [\text{J}.\text{kg}^{-1}] \]

\[ \eta \quad = \quad \text{Compressor efficiency} \]

\[ \rho \quad = \quad \text{Density} \quad [\text{kg.m}^{-3}] \]

\[ \Delta p \quad = \quad \text{Pressure difference} \quad [\text{Pa}] \]
Table 8.1. Waste production and energy consumption of the 3-phenylglycidol production using conventional and ionic liquid/CO₂ production processes.

<table>
<thead>
<tr>
<th></th>
<th>Catalyst make-up (g/kg product)</th>
<th>Solvent make-up (kg/kg product)</th>
<th>By-product formation (kg/kg product)</th>
<th>E-factor (kg/kg product)</th>
<th>Energy for evaporating solvent (MJ/kg product)</th>
<th>Energy for pressurizing CO₂ (MJ/kg product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional process</td>
<td>80.3</td>
<td>3.78</td>
<td>0.38</td>
<td>4.24</td>
<td>9.59</td>
<td>-</td>
</tr>
<tr>
<td>Ionic liquid /CO₂ process</td>
<td>9</td>
<td>0</td>
<td>0.40</td>
<td>0.41</td>
<td>-</td>
<td>1.67</td>
</tr>
</tbody>
</table>

The average density of CO₂ in 80 - 120 bar range and 313.15 K is 628.6 kg/m³ and pressure difference is 40 bar. It is assumed that the efficiency of the compressor is 75%. Using equation (2) the amount of energy necessary to pressurize the CO₂ from 80 bar to 120 bar is \( W = 8.48 \text{ kJ/kg} \). The solubility of 3-phenylglycidol is estimated to be 5 g/kg in CO₂ at 120 bar. Therefore, for the production of 1 kg of 3-phenylglycidol 200 kg of CO₂ should be pressurized. Therefore, the total amount of energy consumed for production of 1 kg of 3-phenylglycidol is \( 200 \times 8.48 = 1696 \text{ kJ/kg} = 1.67 \text{ MJ/kg} \).

An overview of the waste production and energy consumption in the epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol is shown in Table 8.1. In this table a comparison between the conventional production process and the ionic liquid/CO₂ process is presented.

**8.2.2. Economical evaluation**

Previously, we have optimized the reaction and separation conditions of the epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol in ionic liquid/CO₂ system as an alternative to the conventional production process. Since the main goal of this study is to find the best possible alternative, it is important to estimate the difference in cost associated with conventional and ionic liquid/CO₂ production.
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processes. For both processes, the total costs consist of the fixed costs and variable costs. By fixed costs (CAPEX) we mean investment costs such as equipment, piping, instrumentation, control systems, building, maintenance, etc. Variable costs (OPEX) consist of costs for raw materials, energy, labor and utilities, etc [11].

**Variable costs**

The variable costs for both conventional and ionic liquid/CO$_2$ production processes of epoxidation reaction of 3-phenylglycidol consist of the costs for raw materials, i.e. costs for cinnamyl alcohol as reactant, TBHP as oxidant, the costs for catalyst and solvent make-up and the costs for energy, labor and utilities. As was shown before in this thesis, both production methods for 3-phenylglycidol have comparable conversions and yields. Therefore, it is expected that the costs for the reactant and oxidant are similar. It is also assumed that the labor costs in both processes are comparable since both cases have similar problems such as handling oxidants. Regarding this information, solvent and catalyst make-up costs as well as energy cost are the variable costs which will be included in the comparison analysis.

In order to calculate the costs for catalyst make-up, an inquiry was made from Sigma-Aldrich company for the large scale purchase of the VO(acac)$_2$ catalyst [12]. According to this inquiry, the price of VO(acac)$_2$ is 406 €/kg of catalyst. Catalyst make-up for conventional epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol was calculated before and is 80.3 g/kg product. Consequently, the cost for catalyst-make up is 32.60 €/kg of 3-phenylglycidol produced. For the calculation of the costs of solvent make-up, the price of toluene is 953.52 € per metric ton [13]. Since the solvent make-up in conventional process is 3.78 kg/kg 3-phenylglycidol produced, then solvent make-up costs 3.60 €/kg of 3-phenylglycidol produced.

In the ionic liquid/CO$_2$ process, the catalyst make up was calculated to be 9 gr/kg product. Therefore, the cost for catalyst make-up is 2.43 €/kg of 3-phenylglycidol produced. As pointed out before, it is expected to have zero solvent make-up for the
8. Evaluation of sustainability and economics

Table 8.2: Catalyst, solvent and energy consumption costs of the 3-phenylglycidol production using conventional and ionic liquid/CO\textsubscript{2} production processes (costs are per kg of 3-phenylglycidol).

<table>
<thead>
<tr>
<th></th>
<th>Costs for catalyst make-up</th>
<th>Costs for solvent make-up</th>
<th>Energy costs</th>
<th>Total variable costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional production process</td>
<td>€ 32.60</td>
<td>€ 3.60</td>
<td>€ 0.72</td>
<td>€ 36.92</td>
</tr>
<tr>
<td>Ionic liquid/CO\textsubscript{2} production process</td>
<td>€ 2.43</td>
<td>€ 0</td>
<td>€ 0.13</td>
<td>€ 2.56</td>
</tr>
</tbody>
</table>

The energy consumption of the conventional and ionic liquid/CO\textsubscript{2} production process were calculated previously. In order to estimate the costs for the energy consumption, it is assumed that 1 Nm\textsuperscript{3} of natural gas has the amount of 4.9 MJ exergy [14]. The price of the natural gas is 0.37 euro per Nm\textsuperscript{3} [15]. Therefore, the energy costs for conventional process are 0.72 euros per kg 3-phenylglycidol and for the ionic liquid/CO\textsubscript{2} process are 0.13 euros per kg 3-phenylglycidol.

In Table 8.2 an overview for the comparison of the variable costs of the 3-phenylglycidol production using conventional and ionic liquid/CO\textsubscript{2} processes are shown. It can be seen from Table 8.2 that the total variable costs for the production of 3-phenylglycidol in the conventional process are higher compared to the ionic liquid/CO\textsubscript{2} process. However, in order to be more realistic, it is assumed that the ionic liquid should be replaced one a year.

Fixed costs

The fixed costs mainly include the investments for the reaction and separation equipment, solvent and catalyst for the start-up of the process. Since such an
investment has already been made, there is no need for spending money in this part for the conventional production process. The same fixed costs are applicable for the ionic liquid/CO\(_2\) production process, however in this case, this investments should be made. It should be noted that the ionic liquid/CO\(_2\) process equipment is no more extensive than the one for the conventional process since there is no additional equipment for solvent and catalyst recovery is needed. In any case, it is necessary to invest for the high-pressure reactor in the ionic liquid/CO\(_2\) process.

The other difference for the establishment of the ionic liquid/CO\(_2\) process then would be costs for the purchase of the ionic liquid and CO\(_2\), since the rest of the materials, such as catalyst and oxidizing agent, are the same as conventional process. Since CO\(_2\) is cheap and abundant, we neglect the related costs. It was shown before in the kinetics study that for the production of 1 kg of 3-phenylglycidol, 9.69 kg of ionic liquid [bmim][Tf\(_2\)N] is used. Since the 3-phenylglycidol is an intermediate for number of chemicals, it is difficult to calculate the yearly market for this product. Therefore we based our calculations on the market of 100 ton per year, which is a reasonable estimate in pharmaceutical and fine chemicals industry. It is also assumed that reaction and separation time (residence time) is 12 hours. The operational time for one complete cycle is one day and a year has 600 operational days. Based on this assumption, an amount of 1.62 ton ionic liquid is required per year in the ionic liquid/CO\(_2\) production process. The current price for the ionic liquids are often based on a lab-scale production of a few kilos and therefore it is often expensive. However, by increasing the market size and competition between producing companies, it is expected that prices for the large scale production of ionic liquids will drop below 30 €/kg for standard quality ionic liquids [16]. Using straightforward calculations, the investment for the ionic liquid amounts to 0.05 million euros per year.

In order to estimate the cost associated with the high pressure reactor, first we need to calculate the volume of the reactor. As showed before, the amount of solvent in the epoxidation reaction is 1.62 ton of [bmim][Tf\(_2\)N], which has 1.25 m\(^3\) of volume. Based on this, we assume that the volume of reactor should approximately be 1.5 m\(^3\). Since
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this is a high pressure reactor (up to 10 MPa), and the oxidizing agent is present in the system, stainless steel is the chosen as fabricating material. According to an inquiry from De Heer BV., the high pressure reactor costs around 300,000 euros. Therefore, the fixed costs for the epoxidation reaction of cinnamyl alcohol using ionic liquid/CO₂ are 0.05 + 0.30 = 0.35 million euros.

In order to compare the conventional production process with the ionic liquid/CO₂ production process in the epoxidation reaction of the cinnamyl alcohol to 3-phenylglycidol, both variable and fixed costs should be considered. It was shown previously in Table 8.2 that using ionic liquid/CO₂ process will save 36.92 – 2.56 = 34.36 €/kg for 3-phenylglycidol production. For a 100 ton per year production of 3-phenylglycidol this saving will amount to 3.44 million euros per year. Comparing this value with 0.35 million euros per year, which is the investment for the ionic liquid and high pressure reactor in the ionic liquid/CO₂ process, new process will save up to 3.09 million euros per year. It is obvious that the amount of the saving is much higher. In conclusion, the yearly savings are expected to be higher than the initial equipment investment, and therefore it is economically and ecologically feasible to replace the current production process.

8.3. Friedel-Crafts acylation reaction of ferrocene to acetylferrrocene

For the economical and environmental evaluation of the conventional and ionic liquid/CO₂ production process of the acetylferrrocene, the same approach as above is used.

8.3.1. Environmental evaluation

Waste production

As was mentioned before, the main source for the waste production in conventional processes are the catalyst and solvent losses. In the conventional production process
of the acetylferrocene the aluminum chloride ($\text{AlCl}_3$) is used as catalyst and dichloromethane is used as solvent [17]. Since the $\text{AlCl}_3$ catalyst can form a stable complex with the product, it is necessary to use an excess amount (up to full stoichiometric quantities) of catalyst. Therefore, it is very difficult to recycle the catalyst and later in the process, the catalyst is hydrolyzed and destroyed. This increases the amount of corrosive waste during the acylation reaction [18]. In conventional process, 1.20 kg of $\text{AlCl}_3$ catalyst is used to produce 1 kg of acetylferrocene. For solvent make-up, a straightforward calculation shows that 37.97 kg of dichloromethane are used to produce 1 kg of acetylferrocene. It is assumed that 80% of the dichloromethane is recovered using evaporation afterwards. This means that $0.2 \times 37.97 = 7.59$ kg dichloromethane per kg produced acetylferrocene is lost during the production of 1 kg acetylferrocene.

In the ionic liquid/CO$_2$ production process, the catalyst Sc(OTf)$_3$ does not leach and it is expected to have reasonable stability in the presence of ionic liquids. Therefore, we assume that the catalyst replacement should happen every 10 cycles [19]. Therefore, catalyst make-up is 11gr of Sc(OTf)$_3$ per 1 kg of acetylferrocene production. Since ionic liquids have negligible vapor pressure, no solvent loss happen in this process. However, to have more realistic assumption, we estimate that the ionic liquid should be replaced each year.

**Energy consumption**

In order to calculate the energy consumption of the conventional process, equation (1) is used. As mentioned before, the energy that is needed for cooling, can be used for evaporation using heat integration. Therefore, here we only calculate the energy that is needed for evaporation. This means that the overall energy consumption can be less than the energy is needed. The specific heat of dichloromethane is $C_{p,l} = 1.20$ kJ kg$^{-1}$ K$^{-1}$ and the enthalpy of evaporation at its boiling point is $\Delta_{\text{vap}}H = 330.39$ kJ kg$^{-1}$ [7]. The conventional process is carried out at 25 °C and the boiling temperature of dichloromethane is 39.60 °C. Thus, 347.91 kJ/kg energy is required to evaporate 1 kg
of dichloromethane. Thus, the total energy that is required per kg of produced acetylferrocene is $347.91 \cdot 37.97 = 13210.14$ kJ/kg acetylferrocene = 13.21 MJ/kg acetylferrocene.

As was mentioned before, the main energy consumption step in the ionic liquid/CO$_2$ process is the pressurizing CO$_2$ step. During the extraction process, the pressure of the scCO$_2$ will decrease from 120 bar to 80 bar at 40 °C. The solubility of acetylferrocene in the scCO$_2$ at 120 bar and 40 °C is measured to be 4.8 g/kg. This means that 205 kg of CO$_2$ is used to produce 1 kg of acetylferrocene. The amount of energy which is necessary to pressurize CO$_2$ from 80 to 120 bar (assuming 75% efficiency for compressor) is calculated from equation (2) and is $W = 8.48$ kJ/kg. The total amount of energy used in pressurizing CO$_2$ for the production of 1 kg acetylferrocene is $8.48 \cdot 205 = 1738$ kJ/kg = 1.74 MJ/kg acetylferrocene.

Table 8.3 gives an overview of the catalyst and solvent losses as well as energy consumption for the conventional and ionic liquid/CO$_2$ production processes of the acylation of ferrocene to acetylferrocene.

8.3.2. Economical evaluation

Variable costs

In both conventional and ionic liquid/CO$_2$ production process, the costs for reactant, acylation agent, the catalyst and solvent make-up costs, the energy and labor costs are considered as variable costs. Reactant and acylation agent costs are considered as similar in both types of production processes. Also labor costs are regarded similar. Therefore, in this section, primarily catalyst and solvent make-up costs together with energy costs are compared.

The catalyst make-up is calculated to be 1.20 kg/kg of acetylferrocene. The price of the
Table 8.3. Waste production and energy consumption of the acetylferrocene production using conventional and ionic liquid/CO₂ production processes.

<table>
<thead>
<tr>
<th></th>
<th>Catalyst make-up (g/kg product)</th>
<th>Solvent make-up (kg/kg product)</th>
<th>E-factor (kg/kg product)</th>
<th>Energy for evaporating solvent (MJ/kg product)</th>
<th>Energy for pressurizing CO₂ (MJ/kg product)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional process</strong></td>
<td>1.20 kg/kg product</td>
<td>7.59 kg/kg product</td>
<td>8.79 kg/kg product</td>
<td>13.21 MJ/kg product</td>
<td></td>
</tr>
<tr>
<td><strong>Ionic liquid/CO₂ process</strong></td>
<td>11.00 g/kg product</td>
<td>0 kg/kg product</td>
<td>0.011 kg/kg product</td>
<td>-</td>
<td>1.74 MJ/kg product</td>
</tr>
</tbody>
</table>

AlCl₃ anhydrous catalyst is 0.71 €/kg [20]. This means that the catalyst make-up costs 1.20 . 0.71 = 0.85 €/kg produced acetylferrocene. The price for dichloromethane is 2 €/kg, thus, for production of 1 kg acetylferrocene, solvent make-up costs 7.59 . 2 = 15.18 € per kg acetylferrocene.

Previously, it was calculated that the conventional production process consumes 13.21 MJ/kg of produced acetylferrocene and ionic liquid/CO₂ consumes 1.74 MJ/kg of produced acetylferrocene. It is also assumed that 1 Nm³ of natural gas has the amount of 4.9 MJ exergy [14]. The price of the natural gas is 0.3696 euro per Nm³ [15]. Therefore, the total amount of energy consumed during the conventional production process is 1.00 €/kg and in the ionic liquid/CO₂ process is 2.56 €/kg. Table 8.4 shows the costs for the conventional production process compared to the ionic liquid/CO₂ production process.

It is apparent from Table 8.4 that the variable costs for the production of acetylferrocene using the ionic liquid/CO₂ production process are much lower than for the conventional production process. Assuming an annual market of 100 ton per year, the ionic liquid/CO₂ production process reduces the costs by 1.57 million euros per year.
8. Evaluation of sustainability and economics

**Fixed costs**

As mentioned before, the fixed costs mainly include the investments for the reaction and separation equipment, solvent and catalyst for the start-up of the process. For the conventional processes, these costs have already been made and therefore, there are no fixed costs associated with the conventional process. However, for the ionic liquid/CO$_2$ production process, fixed costs will be associated with the installment of new equipment. The main fixed cost here is to purchase the high pressure reactor. For the other equipments, most likely, there is a possibility to adopt the already existing equipments for the ionic liquid/CO$_2$ production process.

| Table 8.4. Waste production and energy consumption costs of the acetylferrocene production using conventional and ionic liquid/CO$_2$ production processes (costs are per kg of acetylferrocene). |
|---|---|---|---|
|  | Costs for catalyst make-up | Costs for solvent make-up | Energy costs | Total variable costs |
| Conventional production process | € 0.85 | € 15.18 | € 1.00 | € 17.03 |
| Ionic liquid/CO$_2$ production process | € 1.22 | € 0 | € 0.13 | € 1.35 |

The remaining costs are the expenses for the purchase of the ionic liquid and catalyst and CO$_2$. Using information from literature, for the production of the 1 kg of acetylferrocene 25.25 kg of ionic liquid [bmim][Tf$_2$N] and 107 g Sc(TfO)$_3$ is used [21]. The annual market of 100 ton is assumed for the production of acetylferrocene. The similar assumptions as previous calculation are made i.e. the operational time for one complete cycle is one day and a year has the 600 ($300 \cdot 2$) operational days. Therefore, the total amount of 4.21 ton ionic liquid and 17.83 kg of Sc(TfO)$_3$ is required in the
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ionic liquid/CO₂ production process. It is expected with a large scale production of ionic liquids prices will drop below 30 €/kg for standard quality ionic liquids [16]. The price for the Sc(TfO)₃ is 111 €/kg [22]. Using straightforward calculations, the investment for the ionic liquid is 0.125 million euros per year and for the catalyst is 0.002 million euros per year. Therefore, the total investment for ionic liquid and catalyst is approximately 0.13 million euros per year. Since CO₂ is cheap and abundant we neglect the related costs. The volume of 4.21 ton of [bmim][Tf₂N] ionic liquid is 3.2 m³. Based on this, we assume that the volume of the reactor is 3.5 m³. For the quick estimation of the price of the high pressure reactor, the rule of sixth-tenths is used [11]. The following equation, shows the rule of sixth-tenths:

\[ C_2 = C_1 \left( \frac{S_2}{S_1} \right)^{0.6} \]  

(3)

here \( C_2 \) is the approximate cost for the equipment with the size of \( S_2 \) and \( C_1 \) is the approximate cost for the equipment with the cost of \( S_1 \) [11]. The price and size of the high pressure reactor in the epoxidation reaction, that is calculated before, are used as \( C_1 \) and \( S_1 \), respectively. Using this equation, the cost for the purchase of high pressure reactor with 3.5 m³ volume is approximately 500,000 euros. This means that the total fixed costs in the ionic liquid/CO₂ production process of acetylferrocene is 0.13 + 0.50 = 0.63 million euros.

Previously, it was estimated that using an ionic liquid/CO₂ process will save 1.69 million euros per year regarding variable costs for the production of acetylferrocene. Comparing the amount of savings to the costs for the start-up investments, ionic liquid/CO₂ production process will save 1.57 – 0.63 = 0.94 million euros in the first year of production. In summary, even though the ionic liquid/CO₂ production process
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needs high start-up investment, it shows environmental and economical benefits over the conventional production method.
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8.4. References


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Conclusions and outlook
9. Conclusions and outlook

9.1. Conclusions

During the past decades, raising awareness of environmental issues emerging from industrial activities has increased the importance to move towards more efficient and sustainable processes. One of the significant causes of pollution is the use of volatile organic solvents. Future chemical processes will use alternative environmentally benign solvents as reaction and separation media, such as ionic liquids and supercritical carbon dioxide (scCO$_2$). The combined reactions and separations in the presence of ionic liquids and CO$_2$ also benefit from the miscibility switch phenomenon: in this case the reaction is carried out in a homogeneous phase while separation is performed under two-phase conditions. In order to apply this process concept, it is crucial to locate the homogeneous and heterogeneous region in the ternary systems containing reactants or products in the presence of ionic liquids and carbon dioxide. Two model reactions have been studied in the work described in this thesis with respect to this new process concept, i.e. (i) the epoxidation reaction of cinnamyl alcohol to 3-phenylglycidol, and (ii) the Friedel-Crafts acylation reaction of ferrocene to acetylferrrocene.

The first step to use ionic liquids as reaction media is to select appropriate ionic liquids to substitute conventional organic solvents. A reaction conditions study was performed to optimize the epoxidation reaction condition in the presence of ionic liquids. It was found that the use of the hydrophobic [bmim][Tf$_2$N] results in reasonable selectivities for 3-phenylglycidol, while using more hydrophilic ionic liquids leads to much lower yields, and results mainly in byproduct formation rather than 3-phenylglycidol production. Optimization of the conditions showed that product stability is a leading factor in determining reaction conditions. Therefore, low temperatures and low oxidant loadings are preferred. A catalyst study showed that the vanadium complex is a very active catalyst that leads to fast epoxidation reactions. The optimum conditions for the epoxidation reaction of cinnamyl alcohol to 3-
phenylglycidol were obtained using [bmim][Tf$_2$N] as solvent with 3 mol% VO(acac)$_2$ as catalyst and 1.5 equivalent of tert-butyl hydroperoxide as oxidant at 25 °C.

The oxidation reaction was further studied to obtain the phase behavior data. For both systems, only liquid-vapor to liquid transitions have been detected within the operational conditions of experiments. At lower concentrations of carbon dioxide (below 40 mol%), both ternary systems have similar phase behavior due to the similarity in molecular shape of cinnamyl alcohol and (2S,3S)-(-)-3-phenylglycidol. However, at carbon dioxide concentrations above 40 mol%, higher pressures are required to completely dissolve carbon dioxide in the ternary system of cinnamyl alcohol + [bmim][Tf$_2$N] + carbon dioxide. The reason is that (2S,3S)-(-)-3-phenylglycidol is a more bulky molecule and can facilitate the uptake of larger amounts of carbon dioxide. Finally, conditions for carrying out the reaction in a homogenous region and the separation in a heterogeneous region were determined. A homogenous reaction phase can be reached at 298 K and at pressures higher than 4 MPa, when the carbon dioxide concentration is 40 mol%. Separation by extraction using scCO$_2$ is possible at 333 K and pressures lower than 8 MPa.

The second model reaction studied was the Friedel-Crafts acylation reaction of ferrocene to acetylferrocene. In order to achieve high extraction selectivities, the solubility of acetylferrocene should be higher than the solubility of ferrocene in scCO$_2$. It was shown using solubility measurements that acetylferrocene is higher soluble in scCO$_2$ at higher pressures, while ferrocene is more soluble at lower pressures. This can be explained by the difference in molecular structure and the thermal properties of both components.

The ternary phase behavior study of the acylation reaction mixture in the presence of ionic liquid + CO$_2$ showed that four different phase regions are detectable in the ternary system of ferrocene + [bmim][Tf$_2$N] + CO$_2$: (i) a homogenous liquid (L) phase, (ii) a two-phase liquid-vapor (LV) region, (iii) a two-phase solid-liquid (SL) region, and (iv) a three-phase solid-liquid-vapor (SLV) region. However, only two L and LV regions are detectable for the ternary system acetylferrocene + [bmim][Tf$_2$N] + CO$_2$. In
other words, ferrocene precipitates as a solid by lowering the temperature while acetylferrocene is soluble in the solution at the same conditions. This behavior can be explained by the fact that acetylferrocene is more polar and has a lower melting point than ferrocene. Consequently, the ternary systems containing solutes with similar molecular structure may show a completely different phase diagram, which indicates the importance of the phase behavior studies. The optimal operating conditions for the acylation reaction in ionic liquid + CO$_2$ systems were successfully determined. For example, at 30 mol% of CO$_2$, temperatures higher than 330 K and pressures higher than 5 MPa should be applied to maintain a homogeneous phase during the acylation reaction.

In Chapter 8, it has been shown that using combined reactions and separations in ionic liquids and scCO$_2$ leads to lower waste generation and lower energy consumption compared to conventional processes. In the epoxidation reaction of the cinnamyl alcohol to 3-phenylglycidol and for the 100 ton per year production of 3-phenylglycidol, a new process set-up will save 3.10 million euros per year. In Friedel-Crafts acylation reaction of ferrocene to acetylferrocene and for the 100 ton per year production of acetylferrocene, the intensified process set-up will save 0.94 million euros per year. The reason for huge amount of savings are lower energy costs, lower solvent and catalyst make up. The ionic liquid/CO$_2$ production process generates much less catalyst and solvent losses and consumes much less energy, therefore it is an environmentally viable process concept. In summary, using ionic liquid/CO$_2$ production process not only results in environmental benefits, but also in economical benefits.

9.2. Outlook

Ionic liquids are high-potential solvents that provide a wide range of applications in chemical processes. Applying miscibility switch phenomena in the presence of ionic liquids and carbon dioxide results in a sustainable method, in which pure product recovery without solvent contamination is possible. However, it is difficult to implement the miscibility switch phenomenon, since high reaction rates and
selectivities should be obtained in ionic liquids. Moreover, homogeneous phase and heterogeneous phase detection using phase behavior measurements are time consuming and expensive.

Even under known miscibility switch conditions, problems can be encountered, such as the formation of solids, no phase split (in which case, extraction is necessary), and high temperature or pressure requirement (which is inconvenient and expensive). Moreover, reactions do not always improve by addition of carbon dioxide.

In addition, it is of great importance to predict the phase behavior of the multicomponent systems in the presence of ionic liquids and carbon dioxide in order to avoid cumbersome and time consuming phase behavior experiments. To achieve this goal developing or modifying current thermodynamic models should be considered.

Currently, the lack of systematic and unified investigations on the toxicology and biodegradability of the ionic liquids makes it difficult to draw a general conclusion on their “greenness”. On one hand, it is crucial to conduct the life cycle assessment to evaluate the environmental impact of ionic liquids at all the stages. On the other hand, information on the toxicity and biodegradability of the ionic liquids in mixtures is necessary for their further applications. Therefore, it is recommended to further investigate the greenness of ionic liquids and its mixtures by systematic toxicity and life cycle studies.
Appendices
Appendix 1

**Table A1-1**: Experimental bubble point data for different molar fractions of CO$_2$ ($x_{CO_2}$) in the system cinnamyl alcohol + [bmim][Tf$_2$N] + CO$_2$ (20.00 mole% solute with respect to ionic liquid)

<table>
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<th>$x_{CO_2}$</th>
<th>$T$ (K)</th>
<th>$P$ (MPa)</th>
<th>$T$ (K)</th>
<th>$P$ (MPa)</th>
<th>$T$ (K)</th>
<th>$P$ (MPa)</th>
</tr>
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## Appendices

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Appendices

Appendix 2

**Table A2-1:** Experimental \((p, T)\) data for different molar fractions of CO\(_2\) \((x_{\text{CO}_2})\) in the system [bmim][Tf\(_2\)N] + CO\(_2\) + 5.0 mol% ferrocene (with respect to the IL)

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</tr>
</tbody>
</table>

|                |       |       |       |       |
| SL → L         | 323.45 | 3.392 | 353.51| 5.214 |
|                | 328.47 | 3.692 | 358.54| 5.574 |
|                | 333.43 | 3.993 | 363.49| 5.875 |
|                | 338.43 | 4.273 | 368.40| 6.175 |
|                | 343.50 | 4.573 |       |       |

| SL → L         | 316.43 | 3.252 | 318.18| 6.054 |
|                | 317.14 | 5.054 | 318.42| 7.055 |

| LV → L         |       |       |       |       |
| SL → L         |       |       |       |       |
Appendices

Appendix 3

**Table A3-1:** Experimental bubble point data for different molar fractions of CO$_2$ ($x_{CO_2}$) in the system [bmim][Tf$_2$N] + CO$_2$ + 5.0 mol% acetylferrocene (with respect to the IL)

<table>
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<th>$x_{CO_2}$</th>
<th>$T$ (K)</th>
<th>$P$ (MPa)</th>
<th>$T$ (K)</th>
<th>$P$ (MPa)</th>
<th>$T$ (K)</th>
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Samenvatting

Veel traditionele chemische processen zijn niet volledig duurzaam als gevolg van het gebruik van vluchtige organische oplosmiddelen tijdens reacties en scheidingen. Dit probleem kan worden aangepakt door gebruik te maken van meer milieuvriendelijke processen. Dat is bijvoorbeeld mogelijk door toepassing van minder giftige en gevaarlijke oplosmiddelen, zoals ionische vloeistoffen en superkritisch koolstofdioxide (scCO$_2$).

Ionische vloeistoffen hebben door hun unieke eigenschappen veel belangstelling opgewekt als potentiële ‘groene’ oplosmiddelen om conventionele vluchtige organische oplosmiddelen te vervangen. Ionische vloeistoffen zijn gesmolten zouten, die vloeibaar zijn bij temperaturen onder de 373 K. Ze bestaan uit organische kationen en organische of anorganische anionen. Doorgaans bezitten ionische vloeistoffen een extreem lage dampspanning, een hoge thermische stabiliteit en een groot vloeistofbereik. Ionische vloeistoffen vertonen een hoge oplosbaarheid voor zowel polaire als apolaire stoffen. Deze eigenschappen maken ionische vloeistoffen geschikt als oplosmiddelen voor een grote verscheidenheid aan chemische reacties.

Bovendien vertonen ionische vloeistoffen in combinatie met CO$_2$ veel voordelen. Ionische vloeistoffen lossen niet op in CO$_2$, maar CO$_2$ is juist zeer oplosbaar in ionische vloeistoffen. Het is ook bewezen dat CO$_2$ in staat is om twee niet-mengbare vloeistoffasen te forceren om één homogene fase te vormen onder hoge druk. Dit interessante gedrag, dat bekend staat als het ‘miscibility switch’ fenomeen, is algemeen toepasbaar op ternaire systemen bestaande uit ionische vloeistoffen, CO$_2$ en organische stoffen. Een nieuw proces gebaseerd op dit fasegedrag wordt voorgesteld, waarbij de reactie snel kan worden uitgevoerd in de homogene fase (geen massa transport beperkingen) door selectie van een geschikte druk, temperatuur en CO$_2$ concentratie. Nadat de reactie voltooid is, zal een fasescheiding instantaan worden geïnduceerd door de condities te veranderen. Het zuivere product kan worden teruggewonnen uit de fase die geen ionische vloeistof bevat.
Twee modelreacties werden bestudeerd om dit concept op toe te passen. Als eerste werd de epoxidatie van cinnamyl alcohol naar 3-phenylglycidol in de aanwezigheid van ionische vloeistoffen als oplosmiddel bestudeerd. (2S,3S)-(S)-3-Phenylglycidol is een bestanddeel voor een bekend, krachtig ontstekingsremmend middel: ibuprofen. De katalytische epoxidatie van cinnamyl alcohol werd geoptimaliseerd met betrekking tot de volgende parameters: (i) type en hoeveelheid van de oxiderende stof, (ii) type en hoeveelheid van de katalysator, (iii) type van de ionische vloeistoffen (variërend van hydrofoob tot hydrofiel) en (iv) temperatuur. Uit de optimalisatie van de condities bleek dat de stabiliteit van het product de belangrijkste factor is bij het bepalen van de reactie condities. Optimale condities werden verkregen bij gebruik van de ionische vloeistof 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][Tf₂N]) met 3 mol% vanadyl acetylacetonate als katalysator en 1,5 equiv. of tert-butyl hydroperoxide als oxidant bij 25 °C.

Om de daaropvolgende scheidingsstap met CO₂ te kunnen ontwerpen, is er kennis nodig van het fasegedrag van de betrokken systemen. Daarom is het hoge-druk fasegedrag van de ternaire systemen, die epoxidatie reactieverbindingen, ionische vloeistoffen en scCO₂ bevatten, gemeten. Fasegedrag experimenten werden uitgevoerd met behulp van een synthetische methode in het Cailletet apparaat bij vijf verschillende concentraties van CO₂, en temperaturen en drukken tot respectievelijk 368 K en 12.1 MPa. De ternaire systemen {cinnamyl alcohol + ionische vloeistof + CO₂} en {(2S,3S)-(S)-3-phenylglycidol + ionische vloeistof + CO₂} tonen slechts één type faseovergang (vloeistof-damp naar vloeistof) bij de hoogste druk die bestudeerd werd. Beide systemen gedragen zich vergelijkbaar bij lage concentraties CO₂ (minder dan 40 mol%). Echter, bij hogere concentraties van CO₂ (meer dan 40 mol%) zijn hogere drukken nodig om CO₂ volledig op te lossen in het systeem dat cinnamyl alcohol bevat vergeleken bij (2S,3S)-(S)-3-phenylglycidol. Verder laat een vergelijking tussen het binaire systeem van [bmim][Tf₂N] + CO₂ en de bestudeerde ternaire systemen zien dat het toevoegen van organische verbindingen de oplosbaarheid van CO₂ in [bmim][Tf₂N] verlaagt. Ten slotte zijn de condities voor het uitvoeren van de...
epoxidatie reactie in een homogene fase en extraheren van het product met scCO₂ in het twee-fase gebied bepaald.

De tweede modelreactie was de Friedel-Crafts acyleringsreactie van ferroceen naar acetylferroceen. Ferroceen, dat vast is tot 445 K, is een bouwsteen voor een breed scala van toepassingen, van homogene katalyse en materiaalkunde tot biologie en geneeskunde. Acetylferroceen is het product van de acyleringsreactie van ferroceen en kent toepassingen als tussenproduct bij de productie van functionele groepen, verbrandingskatalisatoren van drijfgassen en in de farmaceutische chemie. Recentelijk is er veel onderzoek uitgevoerd naar de acylering van ferroceen naar acetylferroceen in de aanwezigheid van ionische vloeistoffen als oplosmiddel in plaats van conventionele organische oplosmiddelen. De veelbelovende resultaten toonden aan dat tot 100% omzetting en opbrengst kunnen worden gehaald door gebruik te maken van op imidazolium-gebaseerde ionische vloeistoffen, met name [bmim][Tf₂N], als oplosmiddel en met triflaat scandium (Sc(OTf)₃) als katalysator.

Om de haalbaarheid van acetylferroceen extractie met scCO₂ te onderzoeken, werd de oplosbaarheid van zowel ferroceen en acetylferroceen in scCO₂ gemeten met behulp van een analytische methode in een quasi-flow apparaat. Met behulp van vloeistofchromatografie werd de concentratie van ferroceen en acetylferroceen in de scCO₂ fase in verschillende monsters bepaald. De experimenten werden uitgevoerd bij temperaturen tussen 308 en 348 K en bij drukken variërend van 7.7 tot 24.4 MPa. De molaire oplosbaarheden bij de toegepaste condities variëerden van 8.9 tot 31.2 × 10⁻⁴ voor ferroceen en van 2.5 tot 79.2 × 10⁻⁴ voor acetylferroceen. Er werd een cross-over gebied voor acetylferroceen gedetecteerd bij een druk rond de 15 MPa en voor ferroceen bij een druk rond de 10 MPa. Ferroceen is meer oplosbaar in scCO₂ bij lagere drukken, terwijl bij hogere drukken acetylferroceen meer oplosbaar is in scCO₂. De reden voor dit gedrag is een wisselwerking tussen de lagere polariteit van ferroceen (meer dominant bij lagere drukken) en de chemische structuur van acetylferroceen (meer dominant bij hogere drukken). De resultaten laten zien dat de oplosbaarheid van het reactieproduct acetylferroceen in scCO₂ voldoende hoog is om
Samenvatting

scCO₂ extractie te kunnen gebruiken om het af te scheiden van het reactant ferroceen in Friedel-Crafts acyleringsprocessen.

Om te onderzoeken of het ‘miscibility switch’ fenomeen op Friedel-Crafts acyleringsreacties kan worden toegepast, werd het hoge druk fasegedrag van het ternaire systeem, dat de ionische vloeistof [bmim][Tf₂N] + CO₂ + ferroceen/acetylferroceen bevat, experimenteel bestudeerd. De experimenten werden uitgevoerd met gebruik van een synthetische methode in het Cailletet apparaat, waarbij de druk en de temperatuur een bereik hadden van respectievelijk 0.25 tot 10 MPa en 278 tot 368 K. Vijf verschillende concentraties van CO₂ (10, 20, 31, 40 en 50 mol% CO₂) werden onderzocht. Terwijl voor de ternaire systemen met ferroceen + ionische vloeistof + CO₂ drie fasenovergangen (SLV → SL, SL → L en LV → L) experimenteel werden gemeten, bevatte het ternaire systeem met acetylferroceen slechts twee verschillende regio's ((LV) en (L)). Er werd aangetoond dat CO₂ als een co-solvent werkt in alle metingen in de aanwezigheid van ferroceen, zelfs bij hoge CO₂ concentraties (50 mol%). Ferroceen is dus meer oplosbaar in het [bmim][Tf₂N] + CO₂ mengsel dan in zuiver [bmim][Tf₂N]. Het verwijderen van CO₂ uit het systeem door drukvermindering resulteert in precipitatie van ferroceen, zodat het kan worden gewonnen uit de ionische vloeistoffase. Dit in tegenstelling tot veel andere ionische vloeistof + organische systemen, die anti-solvent gedrag vertonen in de aanwezigheid van grote hoeveelheden CO₂, waarbij het mogelijk is om de organische verbinding terug te winnen als precipitaat door toevoeging van scCO₂.

Het effect van de opgeloste stoffen op het fasegedrag werd bestudeerd door vergelijking van de experimentele resultaten van het binaire systeem [bmim][Tf₂N] + CO₂ met die van het ternaire systeem acetylferroceen/ferroceen + [bmim][Tf₂N] + CO₂. Er werd aangetoond dat toevoeging van een acetylgroep aan de ferroceen molecuul het fasegedrag van het binaire systeem behoorlijk verandert. Ten slotte werd het homogene vloeistofgebied experimenteel bepaald. Deze studie laat zien dat het uitvoeren van de acyleringsreactie van ferroceen tot acetylferroceen in de aanwezigheid van [bmim][Tf₂N] en CO₂ in een homogene vloeistoffase mogelijk is.
Samenvatting

Tot slot werden de voordelen van de toepassing van de nieuwe procesopstelling onderzocht vanuit economisch en ecologisch perspectief. Voor dit doel werd het conventionele productieproces vergeleken met het alternatieve proces, zoals voorgesteld in deze studie, waarbij gebruik wordt gemaakt van de ionische vloeistof/CO₂ voor beide modelreacties. Vanuit het ecologische oogpunt genereert het ionische vloeistof/CO₂ productieproces veel minder katalysator- en oplosmiddelverliezen en verbruikt het veel minder energie. Vanuit het economische oogpunt zijn investeringen in verband met de aanschaf van nieuwe apparatuur voor het ionische vloeistof/CO₂ productieproces weliswaar hoger, maar er worden besparingen gerealiseerd op de operationele kosten. Hierdoor is het nieuwe proces over het algemeen aantrekkelijker dan het conventionele proces. Voor een markt van 100 ton 3-phenylglycidol per jaar zal het nieuwe proces een besparing van 3.1 miljoen euro op jaarbasis opleveren. Voor een productie van 100 ton acetylferroceen per jaar wordt geschat dat het gebruik van het ionische vloeistof/CO₂ proces een jaarlijkse besparing van 0.94 miljoen euro oplevert. Concluderend, ofschoon het ionische vloeistof/CO₂ productieproces een hoog startkapitaal nodig heeft, zijn de bedragen die jaarlijks bespaard worden hoger dan deze investering. Het is dus economisch en ecologisch rendabel om het huidige productieproces te vervangen.
Propositions
Propositions accompanying the thesis of Somayeh Kazemi

**Sustainable ways of combining reactions and separations using ionic liquids and carbon dioxide**

1. Ionic liquids cannot be classified as green solvents, since systematic and unified investigations on the toxicology and life cycle assessments of the ionic liquids and their mixtures are lacking.


2. Extraction of products from ionic liquids should not be done with ethers, since ethers are partially miscible with most ionic liquids.


3. Reliability of experimental results is as dependent on the analytical techniques as on the meticulousness with which the experiments are performed.

4. The use of shale gas limits the expansion of using clean and sustainable energy sources due to lower prices.

5. The main cause of the global energy problem is the increased consumption, not the lack of resources.

6. The transition from a non-democratic society to a democratic one cannot be achieved unless individuals are educated to choose wisely.

7. The willingness of Dutch people to speak English is one of the greater barriers for highly educated immigrants to integrate into the Dutch society.

8. Imposing quotas for women in higher levels of management is a superficial solution to avoid addressing the underlying fundamental issues.
9. People, who spend time doing sport only to live longer, spend a similar amount of time actually doing the sport.

10. New technological communication tools are not sufficient to develop emotional intelligence.

The propositions are considered opposable and defendable and as such have been approved by the promoters, Prof. dr. I.W.C.E. Arends, Prof. dr. ir. M.C. Kroon, and Prof. dr. G.J. Witkamp.
Stellingen behorend bij de het proefschrift van Somayeh Kazemi

Sustainable ways of combining reactions and separations using ionic liquids and carbon dioxide

1. Ionische vloeistoffen en hun mengsels kunnen niet worden geclasseerd als groene oplosmiddelen, omdat een systematische studie naar de giftigheid en een levenscyclusanalyse ontbreekt.


2. Men moet geen producten extraheren uit ionische vloeistoffen met behulp van ethers, omdat ethers deels mengbaar zijn met de meeste ionische vloeistoffen.


3. De betrouwbaarheid van experimentele resultaten is evenzeer afhankelijk van de gebruikte analytische technieken als van de zorgvuldigheid waarmee de experimenten zijn uitgevoerd.

4. Door de lage prijs van schaliegas wordt de expansie van de toepassing van schone en duurzame energiebronnen belemmerd.

5. De hoofdoorzaak van de mondiale energieproblematiek is niet de schaarste aan energiebronnen, maar de toegenomen consumptie.

6. De overgang van een niet-democratische naar een democratische samenleving kan niet worden bereikt tenzij de individuen opgeleid zijn om de keuzes op een wijze manier te maken.

7. De bereidheid van de Nederlanders om Engels te spreken is een voornam barrière voor hoogopgeleide immigranten om te integreren in de Nederlandse samenleving.
8. Het opleggen van vrouwenquota in de top is een oppervlakkige oplossing om het aanpakken van de onderliggende fundamentele aspecten te vermijden.

9. Mensen, die enkel sporten om langer te leven, besteden vrijwel evenveel tijd aan het sporten zelf als de tijd die zij ermee winnen.

10. Nieuwe communicatietechnologieën zijn niet afdoende om emotionele intelligentie te ontwikkelen.

Deze stellingen worden opponeerbaar en verdedigbaar geacht en zijn als zodanig goedgekeurd door de promotoren, Prof. dr. I.W.C.E. Arends, Prof. dr. ir. M.C. Kroon, en Prof. dr. G.J. Witkamp.
Curriculum Vitae
Personal Information

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Education

1997 - 2001    Student at the National Organization for Development of Exceptional Talents, Tabriz, Iran.

2001 - 2005    B. Sc. degree in Chemical Engineering, Sharif University of Technology, Department of Chemical and Petroleum Engineering, Tehran, Iran.

2005 - 2007    Master degree in Thermodynamics and Catalysis, Sharif University of Technology, Department of Chemical and Petroleum Engineering, Tehran, Iran.

2008 - 2013    PhD, Delft University of Technology, Department of Chemical Engineering, Delft, The Netherlands.

Graduate courses

June 2009    Supercritical Fluids - Green Solvents in Chemical Engineering, KOC University, Istanbul, Turkey.


August 2010    Ionic Liquid Science and Technology, Catholic University of Leuven, Belgium.

September 2011    Scientific Writing in English, Delft University of Technology, The Netherlands.
Publications
List of publications

Journal papers


S. Kazemi, C. J. Peters and M. C. Kroon, *Phase behavior of the ternary system acetylferrocene, the ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide and carbon dioxide to be applied in Friedel-Crafts acylation reactions*, Journal of Chemical Engineering Data, 58 (2013) 951-955.


Conference proceeding/ book of abstract

Publications


