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CHIRAL RESOLUTION IN SUPERCRITICAL CARBON DIOXIDE BASED ON DIASTEREOMERIC SALT FORMATION

Thesis booklet

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1. Introduction

Chiral compounds play an important role in contemporary chemical industrial processes, especially in the pharmaceutical and food sectors. The economically and environmentally favourable production of pure enantiomers is a key aspect of modern chemical engineering.

Supercritical fluids are attractive for green chemistry applications, as their properties are tunable by physical parameters, increasing optimization possibilities. Their low viscosity and lack of surface tension improves their usability in diffusion-limited processes. By reducing their pressure, they become gaseous, precipitating dissolved components with low solvent residue levels.

Supercritical carbon dioxide is especially suited to green chemical applications, as it is non-flammable, non-explosive, non-toxic in trace amounts and easily obtainable. Its comparatively low critical temperature enables applications involving heat-sensitive materials.

The aim of this thesis was demonstrating that the use of supercritical carbon dioxide in the production of enantiomers offers viable results while reducing environmental impact. Two model compounds were chosen: ibuprofen (abbreviated as IBU), an over-the-counter analgesic drug, and *cis*-permethric acid (abbreviated as cPA), an intermediate in pesticide synthesis. Supercritical carbon dioxide was used as a solvent or antisolvent, as well as a separation medium.

2. Literature review

Supercritical carbon dioxide is applied in several sectors of the chemical industry. It is used as an extraction medium in the treatment of plant materials such as hops[1] and in aerogel drying.[2] Supercritical carbon dioxide is also used as a reaction medium[3] or a solvent or antisolvent in crystallization and particle formation.[4,5]

The possibility of chiral resolution with supercritical carbon dioxide via selective extraction of enantiomers was first reported[6] in 1994, with the first reported results published[7] in 1997. The resolution process involves the addition of half-equivalent quantities of a resolving agent to a racemate in an organic solvent, evaporating the organic solvent and separating the diastereomeric salts from the unreacted enantiomeric mixture by the extraction of the latter with supercritical carbon dioxide. This technique was successfully applied

[1] P. Hubert *et al.*, *Angew. Chem. Int. Ed. Engl.*, **17** *10* 710–715, **1978**
[2] Q. Tang *et al.*, *J. Supercrit. Fluids*, **35** *1* 91–94, **2005**
[3] X. Han *et al.*, *Chem. Soc. Rev.*, **41** *4* 1428–1436, **2012**
[4] J. Jung *et al.*, *J. Supercrit. Fluids*, **20** *3* 179–219, **2001**
[5] E. Reverchon, *J. Supercrit. Fluids*, **15** *1* 1–21, **1999**
[6] E. Fogassy *et al.*, *Tetrahedron Lett.*, **35** *2* 257–260, **1994**
[7] B. Simándi *et al.*, *J. Org. Chem.*, **62** *13* 4390–4394, **1997**

to the resolution of several racemates, including the model compounds investigated in this thesis, ibuprofen and *cis*-permethric acid.[7]

Supercritical carbon dioxide is widely applied as an antisolvent in crystallization or encapsulation processes. However, the application of these antisolvent technologies to chiral resolution has not been extensively investigated. The earliest reported result[8] describes the resolution of ephedrine with mandelic acid. The racemate and resolving agent was dissolved in methanol and co-pulverized with supercritical carbon dioxide through a nozzle. The resolution efficiency was found to be influenced by the density of carbon dioxide. Diastereomers produced using this technique had higher optical purity than those obtained via conventional crystallization, and required only one recrystallization step to achieve $> 99\%$ purity.

The resolution of mandelic acid with 1-phenylethanamine has been reported.[9] The racemate was dissolved in ethyl acetate and dimethyl sulfoxide (DMSO) and pulverized into a precipitator pressurized with supercritical carbon dioxide, followed by pulverization of the resolving agent. This approach yielded particles with a diastereomeric excess of 0.63, with 92% of (*R*)-(−)-mandelic acid recovered as particles.

A direct precursor to the antisolvent methods presented in this thesis, the resolution of ibuprofen using 1-phenylethanamine has been reported.[10] The racemate and resolving agent were dissolved in ethyl acetate–DMSO, then injected into a crystallizer maintained under pressure by a flow of supercritical carbon dioxide. The experiments suffered from either low recovery of ibuprofen ($< 10\%$) or low diastereomeric excess (< 0.20). No experiment yielded a diastereomeric excess of more than 0.40.

3. Experimental methods

Three resolution methods were investigated in this work: the novel, solvent-free *in situ* method, as well as the gas antisolvent (GAS) and supercritical antisolvent (SAS) methods. All three techniques are based on a modified version of the Pope–Peachey method: a resolving agent is added to the racemate in half mole equivalent ratio, forming diastereomers preferentially with one of the enantiomers. The polar salt-type diastereomers (the raffinate) are separated from the relatively apolar unreacted enantiomeric mixture (the extract) by extraction with supercritical carbon dioxide. The resolving agents used were 1-phenylethanamine (abbreviated as PhEA, both *R* and *S* configurations) and (*S*)-(+)-2-(*N*-benzylamino)butan-1-ol (abbreviated as (*S*)-BAB).

[8] A. Kordikowski *et al.*, *J. Pharm. Sci.*, **88** *8* 786–791, **1999**

[9] A. Martín *et al.*, *J. Supercrit. Fluids*, **40** *1* 67–73, **2007**

[10] S. Santarossa *et al.*, *Proceedings of 11th European Meeting on Supercritical Fluids*, (OC-BP-4), Barcelona, Spain, **May 4–7, 2008**

The *in situ* method involves measuring the racemate and the resolving agent into a batch reactor and pressurizing said reactor with supercritical carbon dioxide. In contrast with established methods applying carbon dioxide as a solvent (homogeneous-phase reactions in supercritical CO_2 or heterogeneous-phase reactions between liquid reactants and liquid CO_2), this technique involves the heterogeneous-phase reaction of solid/liquid reactants in supercritical carbon dioxide. The reactants dissolve into the CO_2 phase, while the formed diastereomeric salts precipitate from it. Unreacted enantiomers are removed from the reactor by extraction with a constant-pressure stream of supercritical CO_2 which is then expanded in order to precipitate the dissolved components. The main advantage of this method is that it forgoes the use of organic solvents completely, using supercritical carbon dioxide as the medium for diastereomer formation and separation.

In the GAS technique, a concentrated organic solution of racemate and the resolving agent is measured into a batch reactor and pressurized with supercritical carbon dioxide. The organic solution is dissolved into the CO_2, resulting in a solvent mixture with decreased solvent power, from which the diastereomers precipitate. During the extraction with supercritical CO_2, the organic solution is also removed. Although this method does not eliminate the use of organic solvents, it yields products comparable to or better than the *in situ* techniques at significantly reduced reaction times.

The SAS technique is the semi-continuous version of GAS, in which the concentrated organic solution of the racemate and resolving agent is injected into a crystallizer vessel, which is maintained under pressure with a stream of supercritical CO_2. A data acquisition and remote equipment control system was developed to automate the injection process. Upon injection, the diastereomers precipitate almost instantaneously, while the unreacted enantiomers and organic solvent are carried away by the CO_2 stream. An expansion valve drops the stream pressure below critical, precipitating the solvent and enantiomers in a separator vessel. Due to the characteristics of the SAS apparatus, this technique represents a tenfold size-up compared to the GAS method.

Optical purity was characterized by enantiomeric excess (ee). For brevity the terms $ee_{(R)}$ and $ee_{(S)}$ denote excesses of (*R*)-(−)-ibuprofen and (*S*)-(+)-ibuprofen, respectively (abbreviated as (*R*)-IBU and (*S*)-IBU), while the terms $ee_{(+)}$ and $ee_{(-)}$ denote excesses of (1*R*,3*R*)-(+)-*cis*-permethric acid and (1*S*,3*S*)-(−)-*cis*-permethric acid, respectively (abbreviated as (+)-cPA and (−)-cPA).

Yields were calculated using one of three approaches: relative to the total amount of material (Y), using an "ideal resolution" (see below) as a reference ($\mathring{Y}$), or modeling the reactor as an ideal continuous stirred tank reactor ($\hat{Y}$). The first approach calculates the extract and raffinate yields (Y_e and Y_r) from their respective masses (m_e and m_r) by division with the mass of racemate and resolving agent (m_{rac} and m_{res}): $Y_e = m_e/(m_{\text{rac}} + m_{\text{res}})$, $Y_r = m_r/(m_{\text{rac}} + m_{\text{res}})$. The second approach uses an "ideal resolution" as its reference,

i.e. a complete, irreversible reaction between the racemate and the resolving agent, a complete extraction of soluble components, and no decomposition of the diastereomers. In this case, the yields vary depending on the molar ratio (mr), defined as $\mathrm{mr} = n_{\mathrm{res}}/n_{\mathrm{rac}}$, and are given by $\mathring{Y}_e = m_e / \left[(1-\mathrm{mr}) \cdot m_{\mathrm{rac}} \right]$ and $\mathring{Y}_r = m_r / (\mathrm{mr} \cdot m_{\mathrm{rac}} + m_{\mathrm{res}})$. The third approach derives the theoretical masses of the extract ($\hat{m}_e$) from a differential equation describing an ideal continuous stirred tank reactor as a function of the volume of CO_2 used for extraction ($V_{\mathrm{extraction}}$) and the reactor volume (V_{reactor}): $\hat{m}_e = (1-\mathrm{mr}) \cdot m_{\mathrm{rac}} \cdot \left(1 - e^{-V_{\mathrm{extraction}}/V_{\mathrm{reactor}}}\right)$. Accordingly, the theoretical mass of raffinate was defined as $\hat{m}_r = m_{\mathrm{rac}} - \hat{m}_e + m_{\mathrm{res}}$, and the yields were calculated from these theoretical masses using $\hat{Y}_e = m_e/\hat{m}_e$ and $\hat{Y}_r = m_r/\hat{m}_r$.

The resolution efficiency for a single fraction (extract or raffinate) was described by the selectivity, defined as $\mathring{S} = \mathring{Y} \cdot \mathrm{ee}$. The overall resolution efficiency, taking both fractions into account, was calculated by two distinct definitions, depending on the yield calculation: $F = Y_e \cdot \mathrm{ee}_e + Y_r \cdot \mathrm{ee}_r$, or $\hat{F} = 0.5 \cdot \left(\hat{Y}_e \cdot \mathrm{ee}_e + \hat{Y}_r \cdot \mathrm{ee}_r\right)$.

Optical purities were determined by chiral gas chromatography. Qualitative compositional information was obtained by powder X-ray diffraction. The morphology of diastereomers was studied by scanning electron microscopy.

4. Results

4.1. Resolution of ibuprofen with 1-phenylethanamine

The *in situ* method was successfully applied to this system. A detailed investigation of pressure and reaction time at 40 °C was carried out at three pressure levels (100, 150 and 200 bar) and in the 1–100 h range. Resolution efficiency was characterized using $\hat{F}$. The values are shown in Figure 1 (each data point corresponds to a single experiment). Increasing either the pressure or reaction time exerts a positive effect on the resolution efficiency, with a strong interaction between parameters.

The effect of temperature on the optical purity of the CO_2 phase was studied at 200 bar by sampling the reactor with sufficiently small amounts of CO_2 that does not significantly alter the reaction mixture composition. It was found that the ee of the CO_2 phase increases according to a saturation curve, and that both the initial slope and final value were larger at 50 °C than at 40 °C. However, no resolution could be performed above 50 °C as no crystals could be recovered.

The effect of pressure, reaction time and temperature all indicate that the *in situ* resolution takes place according to an equilibrium reaction. The positive effect of pressure on $\hat{F}$ indicates that the reaction is shifted in the forward direction by an increase in pressure, suggesting that a negative activation volume. The changes in $\hat{F}$ shown in Fig. 1 are largely

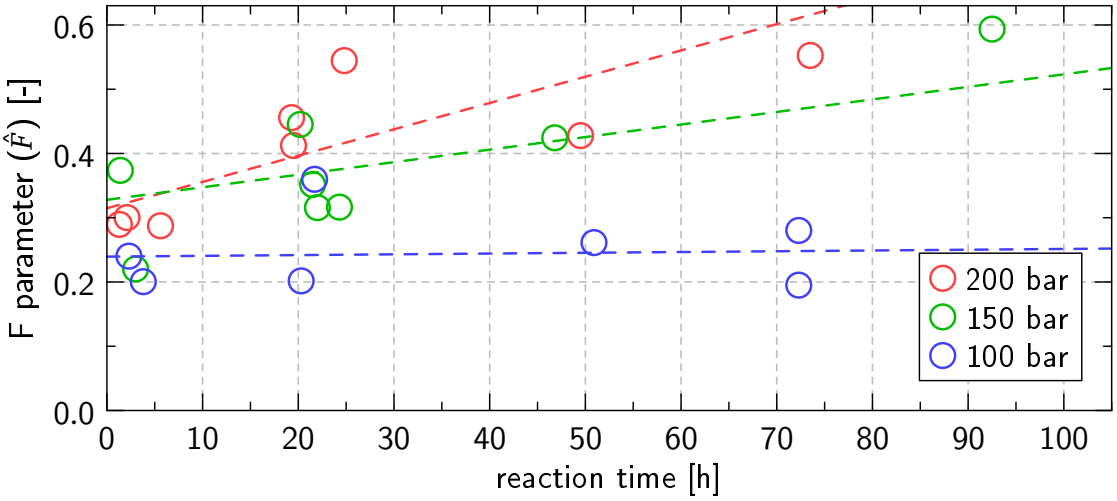

Figure 1: *In situ* resolution of IBU with (*R*)-PhEA at 40 °C. Dashed lines only indicate general trends and are not the results of mathematical modeling.

due to changes in ee, likely due to the differing crystallographic unit cell sizes of the diastereomers.[11] At higher temperatures, the initial reaction rate increases according to the Arrhenius equation (reflected by the increased initial slope), while the reaction is shifted in the forward direction according to the van 't Hoff equation (reflected by the increased final value).

The resolution could also be achieved using the GAS technique. The effect of pressure was investigated between 100–200 bar at 45 °C, using methanol as the organic solvent. The resolution efficiency F was found to decrease continuously from 100 to 200 bar due to decreasing raffinate yield and extract optical purity, while the raffinate optical purity remained constant between 0.7–0.8 $ee_{(R)}$. This suggested a decomposition of the diastereomers during the washing phase. Since the same amount of methanol was used at all pressures, and more CO_2 was required to obtain higher pressures, the CO_2:solvent mass ratio R decreased with increasing pressures. In order to separate the effects of R and pressure, experiments were carried out in which varying amounts of solvent were pressurized to 150 bar at 45 °C. In addition to methanol, ethanol and ethanol–methanol 1:1 were also investigated. All three solvents exhibited the same effect: with increasing R, raffinate yields increased linearly at first, then leveled off at a constant value, while raffinate optical purities were virtually unaffected. The trend for methanol is shown in comparison to that of the cPA–(*R*)-PhEA system in Figure 5 (p. 11). If raffinate yields were examined as a function of the CO_2:solvent mole ratio R_m (rather than the mass ratio), all three solvents (MeOH, EtOH, EtOH–MeOH 1:1) exhibited the same trend. Although SEM analyses showed significant differences between the raffinate crystal habits, their XRD patterns were the same, indicating that the crystalline structure was not affected.

[11] P. Molnár *et al.*, *Chirality*, **21** *6* 628–636, **2009**

If no significant decomposition of the diastereomers occurs, resolution efficiencies show a maximal trend as a function of the molar ratio.[12] The maximum occurs around mr = 0.5, while values tend to zero as mr approaches 0 or 1. In order to study how diastereomer decomposition alters this trend, experiments with mr varying between 0.3–1.25 were carried out at 130 bar and 45 °C. Due to the diastereomer decomposition, observed resolution efficiencies appear to reach zero around mr = 0.2, rather than mr = 0. Furthermore, instead of reaching zero around mr = 1, successful resolutions – albeit with relatively low F, around 0.2 – could be performed at mr ≥ 1. This hinted at the possibility of exceeding the optical purity limit of ee = 0.88, resulting from the eutectic phase behaviour[13] of IBU enantiomers, by submitting the raffinate of an antisolvent resolution to a second antisolvent resolution step. Assuming equimolar salt formation, the second step is carried out at approximately mr = 1, however, IBU in the diastereomer will not be racemic (as is the case with the first step). Therefore, a study of the initial ee (ee_0) on the raffinates was carried out by adding (*S*)-IBU to racemic IBU to achieve a desired ee_0. For these experiments, (*S*)-PhEA was used due to its affinity for (*S*)-IBU, which was in excess. The results are shown in Figure 2. The limitation was in fact circumvented: at $ee_0 = 0.776$, the raffinate $ee_{(S)}$ was in excess of 0.9.

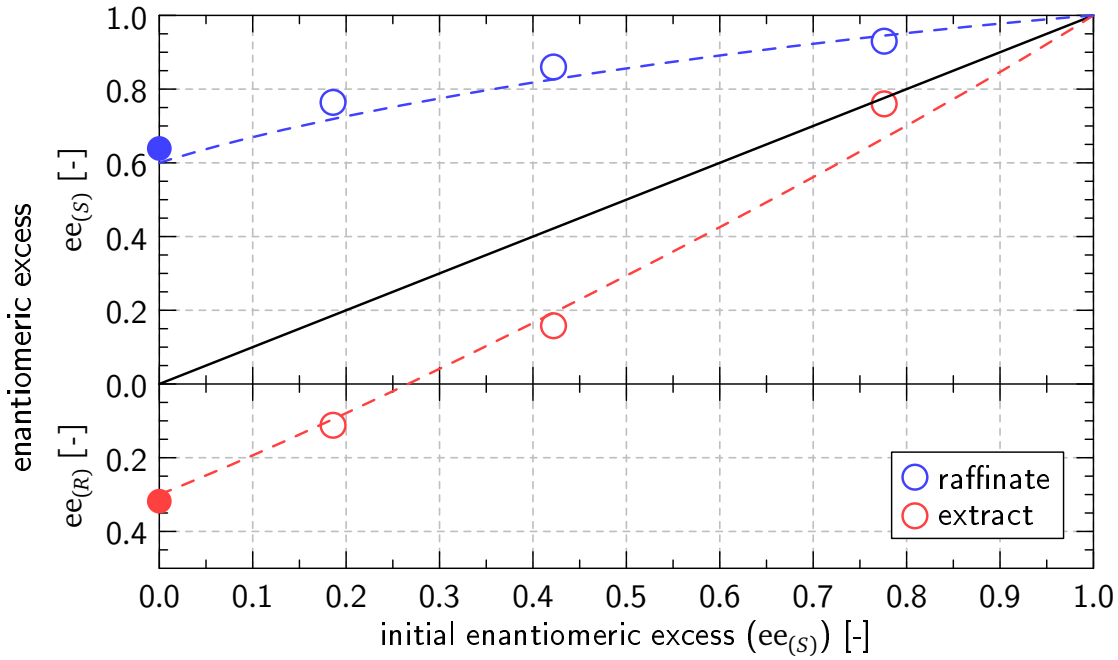

Figure 2: GAS resolution of IBU with (*S*)-PhEA. Thick line indicates diagonal. Dashed lines only indicate general trends and are not the results of mathematical modeling.

The resolution system was transferred to the SAS technique. Raffinate yields and optical purities were comparable to those obtained using GAS, albeit somewhat lower as the mass flow rate ratio values could not exactly reproduce the values of R used for GAS.

[12] E. Székely, PhD thesis, Budapest University of Technology and Economics, (Budapest, Hungary), **2004**
[13] F. Faigl *et al.*, *Org. Biomol. Chem.*, **8** *5* 947–959, **2010**

Two-step resolution was demonstrated by first performing a SAS resolution, then submitting the raffinate to a GAS resolution by dissolving it in methanol without additional PhEA. In two steps with no recrystallization, an IBU-(*R*)-PhEA salt with $ee_{(R)} = 0.900$ and nearly racemic IBU with $ee_{(R)} = 0.068$ were obtained. The overall yield was limited by the reduced capacity of the GAS apparatus, however, future experiments could use two SAS resolutions to avoid this.

4.2. Resolution of *cis*-permethric acid with (*S*)-(+)-2-(*N*-benzylamino)butan-1-ol

The *in situ* method was successfully implemented on this system. The effect of reaction time at 200 bar was not significant: extract optical purities indicated that the resolution proceeds to a large extent within 1 h, therefore, all subsequent experiments were conducted at this reaction time.

The effect of pressure was studied between 150–210 bar at 45 °C, results are shown in Figure 3. Raffinate yields were practically unaffected, while raffinate $ee_{(-)}$ dropped from 0.7 to 0 when decreasing pressure from 170 bar to 150 bar. XRD analyses showed that at 150 bar, both diastereomers are present in the raffinate, thus no resolution occurs as both salts form at equal rates. The crystalline structure of raffinates obtained at higher pressures, accrording to XRD, was different from that of standards prepared by vacuum evaporation.

The effect of temperature was investigated at 200 bar, at three levels: 35, 45 and 55 °C. In the raffinate, both in terms of yields and optical purities, 35 °C was found to be the optimal temperature in the range examined.

Antisolvent resolutions could not be carried out for this system. No crystallization was observed, the recovered extract and liquid raffinate were both racemic.

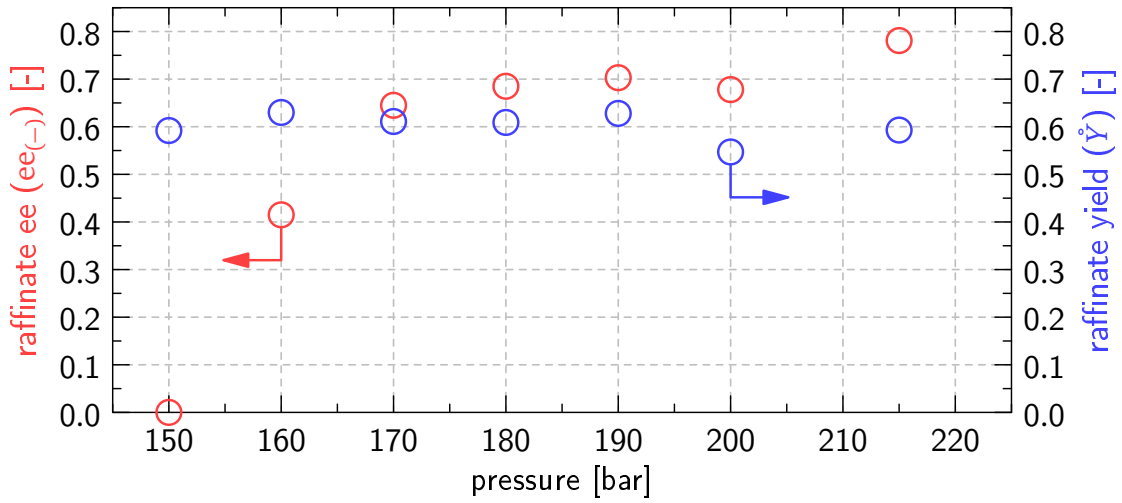

Figure 3: *In situ* resolution and purification of cPA with (*S*)-BAB at 45 °C.

4.3. Resolution of *cis*-permethric acid with (*R*)-(+)-1-phenylethanamine

The GAS method was successfully implemented on this system. A detailed investigation of the effects of pressure on the raffinates was carried out between 100–200 bar, at 45 °C using methanol. Figure 4 shows the results. Three distinct regions were observed: $ee_{(-)}$ is nearly zero between 100–120 bar, very high (> 0.8, reaching 0.940 at 150 bar) between 130–170 bar and medium between 180–200 bar. Yields decrease continuously between 100–170 bar, dropping to almost zero between 180–200 bar.

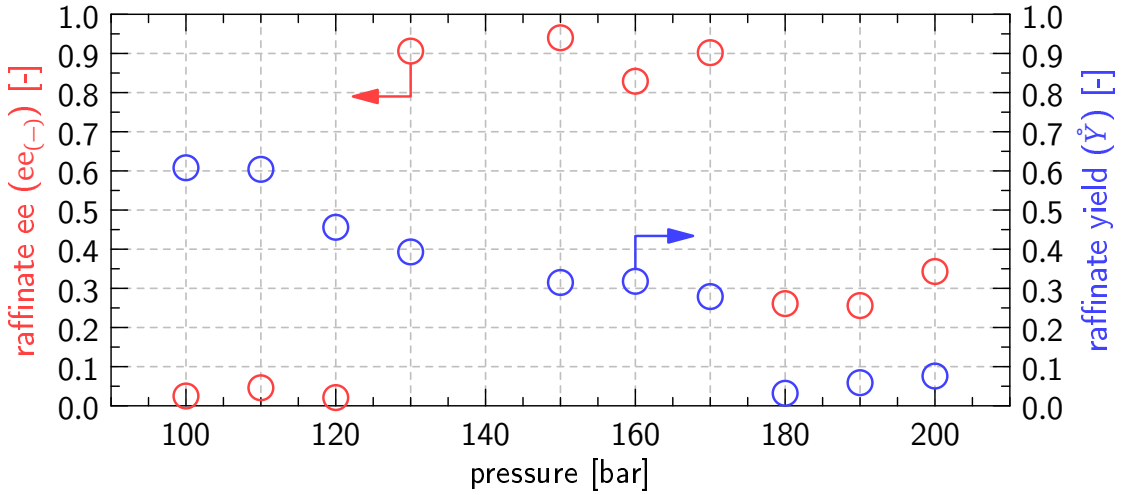

Figure 4: GAS resolution of cPA with (*R*)-PhEA at 45 °C and mr = 0.5.

These unusual, sharp changes prompted further studies. Experiments conducted with varying mr revealed that crystallization only occurs when cPA is in excess compared to (*R*)-PhEA. Substituting racemic cPA with pure enantiomers as starting material, it was found that the trends in both ee and yield are due to diasteromer dissociation. Specifically, (+)-cPA–(*R*)-PhEA dissociates above 120 bar, while (—)-cPA–(*R*)-PhEA only dissociates above 170 bar. Thus, the excellent ee between 130–170 bar is due to selective diastereomer dissociation, while the low yields above 170 bar are caused by the dissociation of both salts. XRD measurements revealed that between 100–120 bar, the absence of chiral discrimination is caused by the formation of a racemic salt.

The resolution was also realized using the SAS technique. The effect of the CO_2:methanol mass flow rate ratio *R* was investigated. Similar to results obtained with the IBU–(*R*)-PhEA system, *R* did not impact raffinate ee but altered raffinate yields according to a saturation-type curve. The results from the two systems are compared in Figure 5.

SEM images showed that the antisolvent resolution methods for both the IBU–(*R*)-PhEA and cPA–(*R*)-PhEA systems yielded fibrous diastereomers with fiber diameters between 700–1000 nm and fiber lengths of several tens of μm. A typical example is shown in Figure 6.

The resolution could not be carried out using the *in situ* method. Although large quantities of solid diastereomeric salts were recovered, these were found to be racemic, indicating a non-stereoselective diastereomer formation.

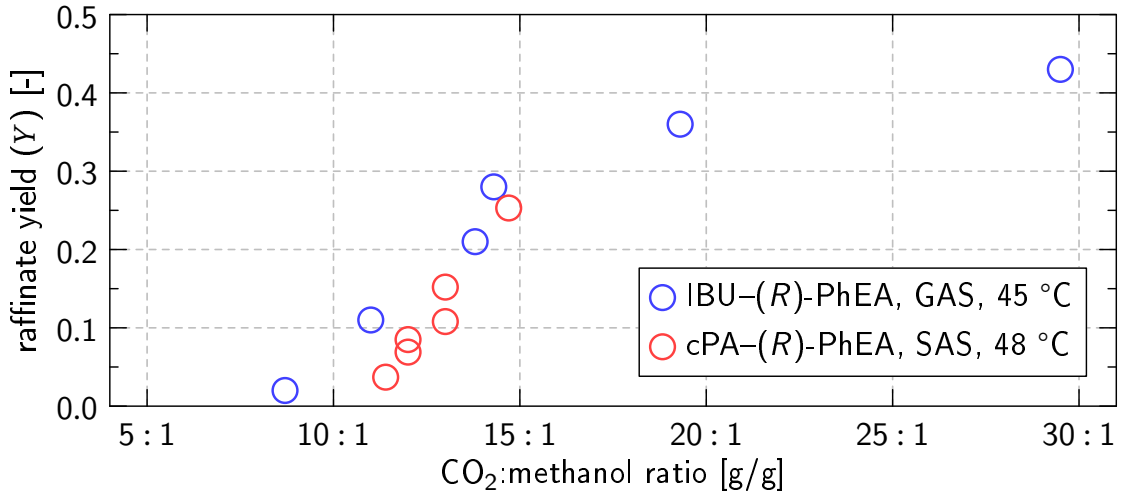

Figure 5: Comparison of SAS resolution of cPA and GAS resolution of IBU, at 150 bar.

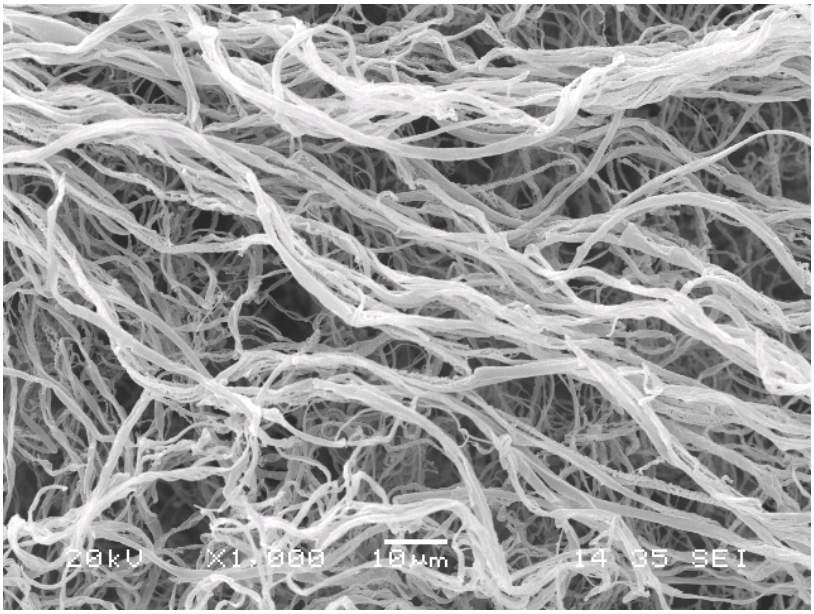

Figure 6: SAS resolution of cPA with (*R*)-PhEA. Scanning electron microscope image of raffinate obtained at 150 bar, 48 °C, $R = 14.7{:}1$.

5. Thesis statements

1. Chiral resolution based on diastereomeric salt formation can be carried out in an *in situ* system, using supercritical carbon dioxide as the only solvent for a batch reaction. The yields and optical purities of the products obtained with this technique are comparable to traditional resolution methods. [1]

2. The behavior of *in situ* chiral resolution systems are strongly influenced by the racemate–resolving agent pairing. In particular:

   (a) The effect of the batch reaction time is not significant if both the racemate and the resolving agent are soluble in supercritical carbon dioxide. If the resolving agent is poorly soluble or undergoes competing reactions with carbon dioxide [2], long reaction times are required for chiral resolution to occur.

   (b) Between 100–200 bar and 35–55 °C, the effects of pressure and temperature, on either the product optical purity or the product yield, can be highly significant or negligible, varying independently of each other based on the racemate–resolving agent pairing.

3. Chiral resolution based on diastereomeric salt formation, using carbon dioxide as an antisolvent in a batch process, is influenced by multiple parameters. [3, 4] In particular:

   (a) If using short-chain alkane alcohols as the solvent, the molar ratio between the solvent and antisolvent exerts a linear influence on the yield of the precipitated diastereomers, without impacting the optical purity thereof. The molar ratio is capable of influencing the crystal habit of the diastereomers without impacting the crystalline structure.

   (b) Between 100–210 bar and 35–50 °C, pressure and temperature both affect the product optical purity and/or the product yield, the specific effects being determined by the racemate–resolving agent pairing.

4. Conversion of batch antisolvent chiral resolution systems to semi-continuous systems retains major product features (optical purity, yield, microscopic structure) as long as significant process parameters (pressure, temperature, solvent–antisolvent mass ratio of mass flow rate ratio) are not altered. [3]

6. Potential applications

Techniques for the facile, environmentally friendly production of optically active compounds could find applications in virtually all areas of the chemical industry. Although this thesis focused on model compounds relevant to the pharmaceutical and pesticide sectors, chiral compounds are used in many other areas, such as food products, cosmetics or fine chemicals. Methods employing supercritical carbon dioxide have the potential to yield products with very low residual solvent content, making them especially attractive in cases where high product purity is required. Antisolvent techniques – as both demonstrated in this thesis and published in literature – are suitable for controlling product morphology, potentially enabling the consolidation of resolution and formulation into a single step, greatly simplifying downstream processing.

7. Publications

Publications related to the thesis

[1] Gy. Bánsághi, E. Székely, D. Méndez Sevillano, Z. Juvancz and B. Simándi: "Diastereomer salt formation of ibuprofen in supercritical carbon dioxide", *J. Supercrit. Fluids*, **69** 113–116 (IF: 2.732, 1 citation), **2012**

[2] J. Madarász, E. Székely, J. Halász, Gy. Bánsághi, D. Varga, B. Simándi and Gy. Pokol: "Ammonium carbamate type self-derivative salts of (*R*-)- and racemic α-methylbenzylamine", *J. Therm. Anal. Calorim.*, **111** *1* 567–574 (IF: 2.206, 1 citation), **2013**

[3] Gy. Bánsághi, L. Lőrincz, I. M. Szilágyi, J. Madarász and E. Székely: "Crystallization and Resolution of cis-Permethric Acid with Carbon Dioxide Antisolvent", *Chem. Eng. Technol.*, **37** *8* 1417–1421 (IF: 2.175), **2014**

[4] D. Varga, Gy. Bánsághi, J. A. M. Pérez, S. Miskolczi, L. Hegedűs, B. Simándi and E. Székely: "Chiral Resolution of Racemic Cyclopropanecarboxylic Acids in Supercritical Carbon Dioxide", *Chem. Eng. Technol.*, **37** *11* 1885–1890 (IF: 2.175), **2014**

[5] L. Hegedűs, S. Miskolczi, Gy. Bánsághi, E. Székely and F. Faigl: "Synthesis of (*S*)-(+)-2-(*N*-benzylamino)butan-1-ol from its Schiff base by catalytic hydrogenation over palladium", *Current Green Chemistry* (accepted for publication), **2015**

Other publications

[6] P. Molnár, P. Thorey, Gy. Bánsághi, E. Székely, L. Poppe, A. Tomin, S. Kemény, E. Fogassy and B. Simándi: "Resolution of racemic trans-1,2-cyclohexanediol with tartaric acid", *Tetrahedron: Asymmetry*, **19** *13* 1587–1592 (IF: 2.796, 7 citations), **2008**

[7] P. Molnár, P. Thorey, Gy. Bánsághi, E. Székely, A. Tomin, L. Poppe, S. Kemény, E. Fogassy and B. Simándi: "Transz-1,2-ciklo-hexándiol reszolválása szuperkritikus extrakcióval", *Olaj-Szappan-Kozmetika*, **58S** 88–92, **2009**

[8] E. Székely, Gy. Bánsághi, P. Thorey, P. Molnár, J. Madarász, L. Vida and B. Simándi: "Environmentally Benign Chiral Resolution of trans-1,2-Cyclohexanediol by Two-Step Supercritical Fluid Extraction", *Ind. Eng. Chem. Res.*, **49** *19* 9349–9354 (IF: 2.071, 2 citations), **2010**

[9] P. Thorey, P. Bombicz, I. M. Szilágyi, P. Molnár, Gy. Bánsághi, E. Székely, B. Simándi, L. Párkányi, Gy. Pokol and J. Madarász: "Co-crystal of (*R*,*R*)-1,2-cyclohexanediol with (*R*,*R*)-tartaric acid, a key structure in resolution of the (±)-trans-diol by supercritical extraction, and the related ternary phase system", *Thermochim. Acta*, **497** *1–2* 129–136 (IF: 1.899, 14 citations), **2010**

[10] Gy. Bánsághi, E. Székely, D. Méndez Sevillano, Z. Juvancz and B. Simándi: "Ibuprofén reszolválása diasztereomer sóképzési reakcióval szuperkritikus szén-dioxidban", *Olaj-Szappan-Kozmetika* (submitted), **2012**

[11] Gy. Bánsághi, D. Varga, L. Lőrincz, L. Hegedűs, J. Madarász, B. Simándi and E. Székely: "Cisz-permetrinsav diasztereomersó-képzésen alapuló reszolválási módszereinek összehasonlítása", *Olaj-Szappan-Kozmetika* (submitted), **2012**

PRESENTATIONS

[15] P. THOREY, P. MOLNÁR, GY. BÁNSÁGHI, E. SZÉKELY, A. TOMIN and B. SIMÁNDI: "Resolution of trans-1,2-cyclohexanediol by partial complex formation followed by supercritical carbon dioxide extraction", lecture presented at *Műszaki Kémiai Napok 2008*, Veszprém, Hungary, **Apr. 22–24, 2008**

[13] P. MOLNÁR, P. THOREY, GY. BÁNSÁGHI, E. SZÉKELY, J. MADARÁSZ, I. M. SZILÁGYI, L. POPPE, A. TOMIN, S. KEMÉNY, E. FOGASSY and B. SIMÁNDI: "Transz-1,2-ciklohexándiol reszolválása szuperkritikus szén-dioxiddal", lecture presented at *Szuperkritikus Oldószerek Műveleti és Analitikai Alkalmazása*, Budapest, Hungary, **May 22, 2008**

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