Gas Antisolvent Fractionation: A New Approach for the Optical Resolution of 4-chloromandelic Acid

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Abstract

A new, rapid optical resolution method of 4-chloromandelic acid is presented using (*R*)-1-phenylethanamine as the resolving agent. Gas antisolvent fractionation was investigated as the separation method, studying the effect of pressure, temperature and carbon dioxide to organic solvent mass ratio in details. Generally, the method offers green operation using supercritical carbon dioxide as the precipitative agent, and can be less time- and organic solvent-intensive than conventional processes. By upscaling, the possibility of controlling the crystal-morphology might also be improved. At 16 MPa, 40 °C and 7.5 carbon dioxide to methanol ratio 72 % enantiomeric excess was reached in the crystalline product, along a 73 % yield. The resolution efficiency was not affected by any of the operational parameters. Enantiomeric enrichment beyond 90 % can be carried out by repeated resolution of a scalemic mixture of the acid. Solid products were investigated using differential scanning calorimetry, powder X-ray diffraction and scanning electron microscopy confirming the formation of a crystalline (*R*)-1-phenylethanammonium-4-chloromandelate salt.

Keywords

chiral, enantiomer, supercritical, carbon dioxide, optical resolution

1 Introduction

The investigation of modern separation processes making highly valuable products accessible provides hard and popular challenges for today's researchers. Supercritical carbon dioxide is widely used as an extraction solvent, but it is known to be used as a solvent in chemical and enzymatic transformations as well [1]. Particle forming techniques utilizing this alternative solvent are also intensively investigated [2]. In antisolvent processes the non-flammable and non-toxic compound is used as a precipitative agent. Although such techniques have not found wide industrial applications yet, the scaled-up, semi-continuous variants offer considerable advantages. In many cases it is possible to form crystalline products of exceptional purity and even influence the main particle size also achieving a very narrow particle size distribution, or to achieve composites with special properties [3–5]. As antisolvent precipitation processes are very sensitive to operational parameters i.e.

pressure, temperature and the amount of the organic solvent (mixture), by setting appropriate conditions they can be used as separation processes based on fractionated crystallization. In our study the batch-type gas antisolvent fractionation (GASF) is presented as the separation method [6].

In the extraction step of the gas antisolvent fractionation technique, a homogenous fluid phase above the crystalline product is needed. Phase equilibrium measurements need to be carried out to determine the minimum pressure at a specific temperature and composition that is necessary to achieve a two phase (solid and fluid) system. An easy way to obtain the needed information about the phase behavior of a specific mixture (the carbon dioxide − methanol − 4-chloromandelic acid system in our case) is cloud point measurement. Another way of obtaining accurate data on phase equilibrium is taking samples from two fluid phases in equilibrium and analyzing their

composition [7]. However, this latter method takes more time to perform and its accuracy is above the needs to proceed with the GASF experiments.

Although the traditional ways of chiral separation have a wide literature coverage, methods for producing optically active – or even enantiomerically pure – compounds are still intensively researched [8, 9]. Due to the potentially different biological and pharmacological effects of the antipodes, there is a large demand for them in high purity in the chemical industry, mostly in the pharmaceutical, agricultural, and cosmetic sectors. Diastereomeric resolution is a popular and simple way to obtain optically active acids and bases. The racemate (acid or base) is reacted with an enantiopure compound of the opposite chemical character (base or acid), diastereomers are formed that can be separated based on their physical-chemical properties. Resolving agents are often selected on the basis of the structural similarity to the racemate i.e. similar molecular shape and size [8]. 1-Phenylethanamine (PhEA) is a popular synthetic resolving agent, often used for chiral separations of acid enantiomers.

Diastereomeric resolution is suitable for investigations of supercritical carbon dioxide-involving processes as optically active, or enantiopure compounds bear the high added value needed to make such techniques economical. Béla Simándi, Elemér Fogassy and colleagues studied resolution carried out by extraction with supercritical carbon dioxide for the first time [10–12]. This new method allowed substantially higher selectivity than the crystallization from organic solvents [13]. Carbon dioxide-involving experiments have even been conducted using the supercritical fluid as an antisolvent and as a reaction medium in diastereomeric salt formation as well [14–19]. Antisolvent methods have been studied in the production of enantiomerically pure compounds too [6, 14, 20–22]. Also, supercritical carbon dioxide was used as the reaction medium of enzymatic kinetic resolutions [23].

4-Chloromandelic acid, the model compound chosen for investigation in this study, is widely used as a platform molecule and chiral intermediate in various pharmaceuticals [24]. It has also been resolved using 1-phenylethanamine under atmospheric conditions [25].

2 Experimental
2.1 Materials
Racemic 4-chloromandelic acid (purity > 98 % CAS 7138-34-3) was purchased from TCI Ltd. Belgium, as well as enantiopure (R)-4-chloromandelic acid. Enantiomeric forms of 1-phenylethylamine (CAS 3886–69-9 for R

and 2627–86-3 for S enantiomer, > 99 %) were bought from Merck. Methanol was also supplied by Merck Ltd. (Darmstadt, Germany) and CO_2 (99.5 %) was ordered from Linde Gas Hungary Co. (Budapest, Hungary). Carbon dioxide was used freshly distilled.

2.2 Methods
2.2.1 Cloud point measurements
Solubility measurements of racemic 4-chloromandelic acid were conducted in a high-pressure view cell (Pickel's cell, New Ways of Analytics GmbH.) having a variable volume. The apparatus is schematically depicted in Fig. 1.

Methanol was used as a co-solvent. First, the acid was dissolved in the organic solvent. The mass of the acid was chosen to approximately match that to be filled later into the laboratory autoclaves. The solution was filled into the tempered view cell, then carbon dioxide was introduced into the apparatus. A Teledyne ISCO 260D syringe pump was used during pressurization, allowing density-based calculation of the amount of carbon dioxide filled into the cell. Pressurization was finished after achieving a homogenous, single phase system. Continuous mixing and a high-performance light source helped to determine when the mixture was completely clear. Then, cloud points were observed visually by moving the piston of the cell backwards (thus increasing its volume) and decreasing pressure. After recording data, the apparatus was heated to a different temperature and the measurement was repeated without any change in the composition and amount of the mixture.
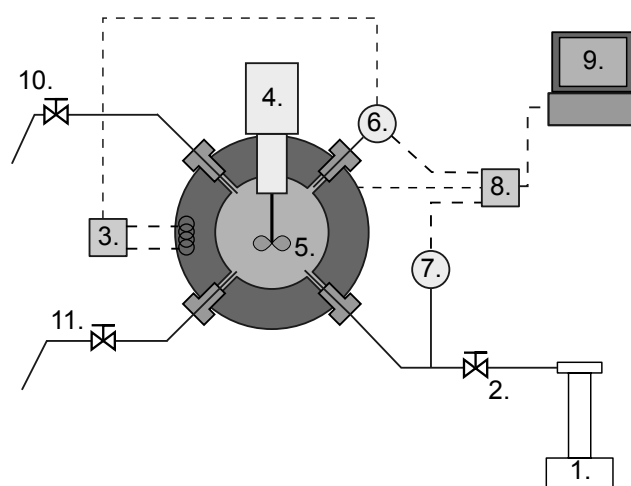

Fig. 1 Schematic cross-section drawing of the Pickel's cell. 1. Teledyne ISCO 260D syringe pump; 2. Valve; 3. Temperature regulator with heating rods; 4. Magnetically coupled stirrer; 5. Variable volume cell; 6. Temperature transducer; 7. Pressure transducer; 8. Analog-digital converter; 9. Data logging computer; 10. Sampling port for the upper phase; 11. Sampling port for the lower phase

2.2.2 Gas antisolvent fractionation

A simple laboratory autoclave having an approximate volume of 37 ml was used in the gas antisolvent fractionation (GASF) experiments. A schematic depiction of it can be found in a previous communication [6].

In a general experiment, 100 mg of 4-chloromandelic acid and half molar equivalent of the resolving agent (enantiopure (*R*)-1-phenylethanamine) were dissolved in a specific amount of methanol. The amount of organic solvent was specified by the experimental setting to be investigated. The solution was then filled into the tempered autoclave. The vessel was pressurized using a Teledyne ISCO 260D syringe pump, allowing density-based calculation of the amount of carbon dioxide filled into the reactor. The magnetic stirrer was switched on after reaching the desired pressure. One hour long equilibration followed. Then, the organic solvent and the dissolved components were washed out using pure carbon dioxide (maintaining constant pressure). The total amount of the supercritical fluid used in the extractive step is roughly equal to 3 times the volume of the high pressure vessel. The exiting, expanded gas bubbled through a solvent trap. After depressurization a solid product could be collected from the autoclave, this is referred to as the raffinate. The extract could be recovered by rinsing the outlet piping with a small amount of organic solvent into the solvent trap, then evaporating the solvent from the latter.

The scheme of the chemical reaction is shown in Fig. 2. The racemic 4-chloromandelic acid is reacted with half molar equivalent of enantiopure (*R*)-1-phenylethanamine in methanol. In an ideal case, only one of the enantiomers of the acid ((*R*)-acid) forms a salt with the enantiopure amine which precipitates in the autoclave upon addition of carbon dioxide. The (*S*)-acid remains dissolved in the solvent mixture. Most often, using the half molar equivalent method (here, a modified Pope-Peachy method without the achiral additive) results in the most efficient separation [8].

2.2.3 Capillary electrophoresis

Capillary electrophoretic analyses were performed on the raffinate and extract samples in order to determine the ratio of the enantiomers of 4-chloromandelic acid in them.
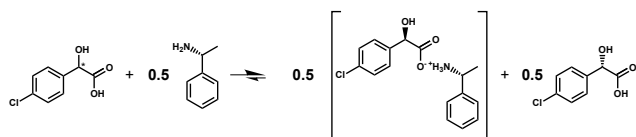
Fig. 2 The idealized scheme of the chemical reaction.

Measurements were carried out on an Agilent 7100 3DCE system (Agilent, Waldbronn, Germany) equipped with a diode array UV detector. Uncoated fused-silica capillaries of 58.5 cm effective and 50.0 cm total length (Agilent) were applied throughout the study. Samples and capillaries were tempered at 25 °C; analytes were detected at 200 nm. The capillary was flushed with 0.1 M NaOH solution, and purified water for 0.30 minutes each subsequently and finally with the running buffer for 1 minute before every analysis. Samples were injected using 50 mbar pressure for 0.50 minute, the applied voltage was +20 kV. Peaks were evaluated using the software "Chemstation".

Britton-Robinson buffer (BRB, containing 50 mM boric, acetic and phosphoric acid) was used as a background electrolyte. pH was set to 9.0 by adjusting with 0.1 M NaOH. The final running buffers were filtered through 0.22 μm Millex-GV syringe filters (Millipore, Bedford, USA). Diastereomeric salt mixture samples were dissolved in methanol to obtain 1 mg/ml stock solutions (related to dry material) and diluted further with ethanol: water 50 % V/V 100-fold to achieve optimal peak areas. As a chiral selector, 10 mM of 6-monodeoxy-6-monoamino-β-cyclodextrin (Cyclolab, Hungary) was applied in all experiments.

2.2.4 Powder X-ray diffraction

The XRD measurements were carried out on a PANalytical X'Pert Pro MPD powder X-ray diffractometer (PANalytical, Almelo, The Netherlands), equipped with an X'celerator detector, in Θ-Θ arrangement. Scans were performed at the Cu Kα wavelength (1.5408 Å), with a Ni filter, applying 40 kV (DC) voltage and 30 mA current. Diffractograms were recorded in the 2Θ ranges of 4 to 42°.

2.2.5 Scanning electron microscopy

Scanning electron microscopy (SEM) images were recorded by a JEOL JSM 5500-LV scanning electron microscope using 20 kV acceleration voltage and a secondary electron detector. For SEM studies, the samples were covered with a 510 nm Au Pd layer to make their surfaces conductive.

2.3 Calculation methods

Generally, chiral resolution processes are sharply influenced by the molar ratio (*MR*) between the resolving agent and the racemate. It can be calculated with Eq. (1):

$$MR = n_{res} / n_{rac} . \tag{1}$$

In the formula n_{res} denotes the molar amount of the resolving agent while n_{rac} stands for that of the racemate. In our experiments its value was set to 0.5.

Antisolvent precipitation processes, including the presented GASF process are sensitive to the amount of organic solvent in the carbon-dioxide – organic mixed solvent. Thus, the mass ratio of the two solvents was defined as the "solvent ratio" (R). m_{MeOH} stands for the mass of methanol used during the dissolution of the original components, while m_{CO_2} denotes the mass of carbon dioxide used to pressurize the reactor. The mass of methanol could be determined by direct weighing but the mass of carbon dioxide was calculated based on the volume change in the syringe pump and the density of liquid carbon dioxide at the pressure and temperature of the pump.

$$R = m_{CO_2} / m_{MeOH} \qquad (2)$$

Separation processes are usually evaluated based on the purity and the quantity of the product (or products obtained). In chiral separation processes the enantiomeric excess (ee) is suitable to describe the purity of the products. In our experiments, the raffinate (i.e. the crystalline product) consists of the diastereomeric salt of 4-chloromandelic acid and (R)-1-phenylethanamine, so, its composition could be described with the diastereomeric excess. But, the salt dissociates under the circumstances of the electrophoretic analysis, thus the average ee of the acid in the raffinate samples can be determined. In the following formula, Q_R and Q_S denote the quantities of (R)- and (S)-4-chloromandelic acid in the samples respectively. Quantities can be expressed as molar or mass concentrations, but as electrophoretic peak areas as well.

$$ee = |Q_R - Q_S| / (Q_R + Q_S) \qquad (3)$$

In the calculation of the yields the masses of the products were compared to a theoretical maximum. In the calculation of these hypothetical masses the diastereomeric salts were assumed to be formed with a conversion of 100 %, and also to be completely insoluble in the carbon dioxide – methanol mixed solvent. Unreacted 4-chloromandelic acid is supposed to be fully extracted from the high pressure vessel during the washing phase. Thus, the hypothetic, idealised raffinate mass is the maximal mass of the diastereomeric salt while the idealised extract mass is the mass of the unreacted scalemic mixture of 4-chloromandelic acid. These quantities are represented in the denominator of the raffinate yield (Y_{raff}) and the extract yield (Y_{extr}), using the molar ratio:

$$Y_{raff} = m_{raff} / \left[(m_{rac} \cdot MR) + m_{res} \right], \qquad (4)$$

$$Y_{extr} = m_{extr} / \left[m_{rac} \cdot (1 - MR) \right]. \qquad (5)$$

m_{raff} denotes the mass of the crystalline product (raffinate), m_{extr} denotes the mass of the extract. m_{rac} and m_{res} stand for the mass of the racemate (4-chloromandelic acid) and the resolving agent ((R)-1-phenylethanamine) respectively.

By multiplying the two quantities defined above, selectivity (S) is obtained. It is used to characterise chiral resolution based on purity and yield at the same time, and it can be calculated for both the raffinate and extract samples. This allows an evaluation without a preference on high purity or large product quantity:

$$S = Y \cdot ee. \qquad (6)$$

3 Results and discussion

Antisolvent processes are usually very parameter-sensitive [6, 16, 26]. Our aim in this study was not only to apply the process as a separation method in chiral resolution but also to present a detailed investigation process from preliminary measurements to a high purity compound.

3.1 Cloud point measurements

First, cloud point measurements were carried out to determine the applicable pressure range in the planned temperature range in order to achieve a single fluid phase above the solid product for the successful extraction steps. This fluid phase must contain the unreacted acid and the organic solvent. Cloud points observed in two measurements on systems containing 4-chloromandelic acid in a 0.003 mass fraction are shown in Fig. 3.

Two series of measurement points were recorded at two different solvent ratios. Cloud point pressures can be estimated as linear functions of temperature in the studied range. Above the specified pressure at a certain temperature, a single phase, homogenous mixture could be observed. But, underneath the line, a multiphase system is represented. An increase in temperature results in an increase in the cloud point pressure values, meaning a decrease in solubility. Comparing cloud point pressures at a certain temperature shows a sharp dependency on the solvent ratio. To a smaller amount of organic solvent in the system, a lower solubility corresponds.

As it was mentioned before, the high pressure reactor had to be operated at pressures above the determined cloud points in order to achieve successful extraction.
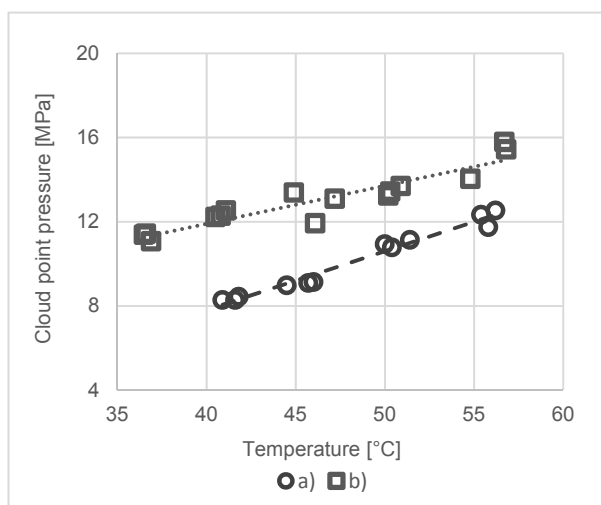
Fig. 3 Cloud point pressures of the carbon-dioxide – methanol – (*RS*)-4-chloromandelic acid mixture measured in the high-pressure view cell are plotted against temperature. 4-chloromandelic acid had a mass fraction of 0.003. a) *R* = 17.4; b) *R* = 21.7

3.2 Resolution via gas antisolvent fractionation

After investigating the possible ranges of operational parameters, their effect on the chiral resolution of 4-chloromandelic acid was studied. Pressure, temperature and solvent ratio (one at a time) were varied in the ranges of 12-20 MPa, 35-45 °C and 7.5-25, respectively. Repeatability was investigated at 16 MPa, 40 °C and 12.5 solvent ratio. The diagrams in Fig. 4 and Fig. 5 have two vertical axes. Yields and enantiomeric excesses are plotted simultaneously for the raffinates and extracts. The characterizing quantities can be distinguished by the matching color of the markers and axes while the product can be identified by the shape of the markers. Results of the study on the effect of pressure are shown in Fig. 4. Temperature and solvent ratio were kept approximately constant, at 40 °C and 12 respectively.

A decrease in the raffinate yield can be observed on increasing pressure, which is followed by the extract yields in a mirror-like way, according to the mass balance. At higher pressure, the density of the solvent mixture is increased, resulting in higher solubility. (A constant volume of organic solvent was used to prepare initial samples. This means that at a higher pressure, a slightly higher solvent ratio was achieved. This would result in a lower solubility, but, apparently, the change in the density of the solvent mixture overcame this effect.) Having the extract in higher than 100 % yield means that not only the unreacted amount of 4-chloromandelic acid is extracted from the reactor, but also some of the diastereomeric salt. This can happen by dissolution but it is more likely to be the effect of the salt-like compound
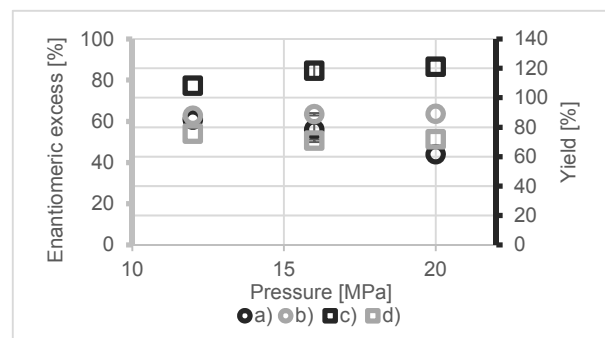

Fig. 4 The effect of pressure on the diastereomeric resolution of 4-chloromandelic acid with (*R*)-1-phenylethanamine. a) Raffinate yield; b) Enantiomeric excess measured in the raffinate; c) Extract yield; d) Enantiomeric excess in the extract
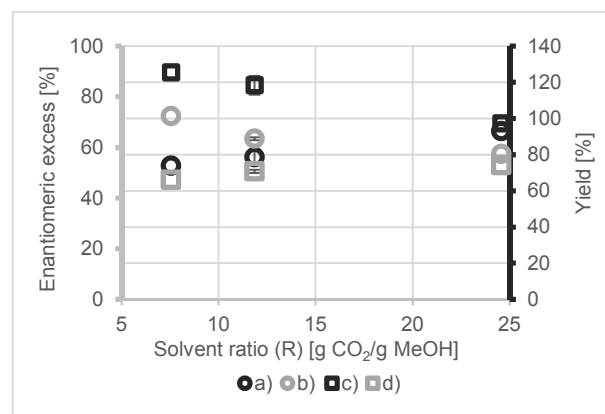

Fig. 5 The effect of the carbon dioxide to methanol mass solvent ratio on the GASF experiments. a) Raffinate yield; b) Enantiomeric excess of the 4-chloromandelic acid in the raffinate; c) Extract yield; d) Enantiomeric excess of the extract

(*R*)-1-phenylethanammonium-4-chloromandelate dissociating under high pressure. In either case, the significant dissolution of salt-like substances in solvent mixtures containing high pressure carbon dioxide as the major component is a rarely experienced phenomenon. Supposedly, the unreacted, and dissolved amount of 4-chloromandelic acid prevents dissociation of the diastereomeric salt. With the extraction progressing, dissociation can take place due to the lower-and-lower concentration of the acid in the system. As there is a difference in the solubility of the diastereomeric salts, this effect also contributes to achieving a higher purity product. At 16 MPa, 40 °C and a solvent ratio of 12, three repetitions were carried out showing excellent reproducibility. Standard deviations of the raffinate and extract yields are 4 % and 5 % respectively while those of the enantiomeric excesses are approximately 0.6 % in case of both products.

Fig. 5 shows the effect of the solvent ratio at 16 MPa and 40 °C.

Seemingly, this parameter had the strongest effect on both yields and enantiomeric excesses. These resolution experiments were the first, where a solvent ratio-dependency of the purity of the products was also observed along with the more easily explainable changes in the yield. Having a lower solvent ratio means a higher concentration of organic solvent, and also a more polar solvent mixture, that allows a higher amount of the polar compounds to be dissolved and washed out during the extraction step.

Changes in temperature in the investigated range did not have any significant effect on either the yields or the purities of the product. Thus, its value was set to 40 °C.

In Fig. 6 selectivity (both that of the raffinates and the extracts) is plotted against the solvent ratio. As neither temperature, nor pressure had a very strong effect on Y and ee, all of the measurements were plotted in one diagram.

No tendency can be observed in the case of either of the products. This means that the efficiency of the resolution is practically independent of the operational parameters in the studied range, the only possibility is to choose between crystals of higher ee or higher yield. (Of course, the raffinate and the extract would show mirror-like tendencies according to the total mass and component balance equations.) The highest enantiomeric excess in the raffinate was achieved at 16 MPa, 40 °C and 7.5 solvent ratio. The raffinate of this experiment had an ee of 72 %, accompanied with a yield of 73 %. The ee of the extract was 47 % and its yield was 125 %.

The possibility of enhancing the enantiomeric purity of the acid was investigated starting from scalemic 4-chloromandelic acid of 65 % ee. Half molar equivalent of (R)-1-phenylethanamine was used in the repeated resolution experiment, which resulted in a slightly higher than 90 % ee in the crystalline product.
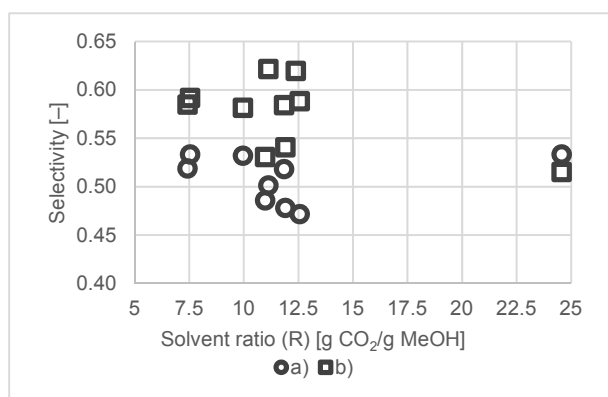
3.3 Powder X-ray diffraction

In Fig. 7 the powder X-ray diffraction patterns of the raffinates obtained at 16 MPa, 40 °C and 7.5 solvent ratio are shown, both in case of a racemic acid and the scalemic mixture as the initial compound (Fig. 7 c) and d)). They are compared to the diffractograms of 4-chloromandelic acid and the self-derivative carbamate-type salt that is formed from 1-phenylethanamine and carbon dioxide [27]. Based on the 2Θ angles and relative intensities of the characteristic peaks of the compounds, one can conclude that the possible carbamate-type by-product is not formed and that unreacted 4-chloromandelic acid cannot be found in the samples. (This is in good agreement with the supposition that the latter is dissolved in the high pressure solvent mixture, thus being completely extracted.)

Single crystal atomic coordinates of both diastereomeric salts [28–31] can be found in the Cambridge Structural Database [32]. They were obtained using the program Mercury [33]. It can be easily noticed that the diffraction patterns of our raffinates match those of the more stable (less soluble) (R)-1-phenylethanammonium-(R)-4-chloromandelate salt [30, 31], meanwhile its diastereomeric pair probably remained amorphous.

3.4 Scanning electron microscopy

In many cases, antisolvent precipitation processes offer the possibility of controlling the morphology and/or the size of the formed particles [2]. We intended to get an insight into the shapes and sizes of the crystals formed in the batch-type technique. The scanning electron microscopy images obtained are shown in Figs. 8 and 9.
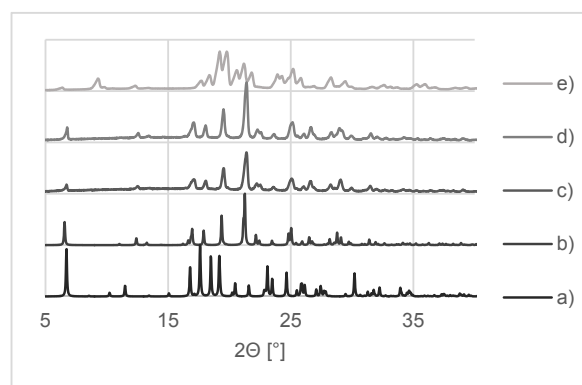
Fig. 7 Comparison of the powder X-ray diffraction patterns. a) The less stable (R)-1-phenylethylammonium (S)-4-chloromandelate salt [28, 29]; b) The more stable (less soluble) (R)-1-phenylethanammonium (R)-4-chloromandelate [30, 31]; c) A raffinate of ee = 72 %; d) A raffinate of 90 % ee; e) The self-derivative carbamate salt of (R)-1-phenylethanamine, a possible side-product

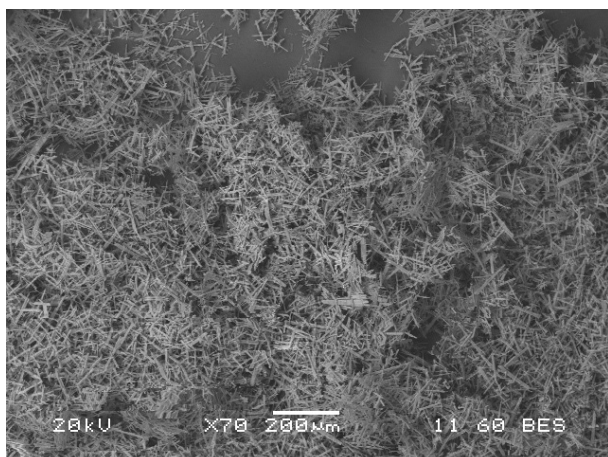**Fig. 6** Selectivity plotted against the solvent ratio.
a) Raffinate; b) Extract

Fig. 8 Scanning electron microscopy image of the raffinate formed from racemic 4-chloromandelic acid (the scale bar corresponds to 200 μm)

Fig. 9 Scanning electron microscopy image of the raffinate formed from a scalemic mixture of 4-chloromadelic acid having an *ee* of 65 % (the scale bar corresponds to 500 μm)

The raffinate obtained at 16 MPa, 40 °C and 7.5 solvent ratio (Fig. 8), starting from a racemate formed elongated crystals with lengths of 30-50 μm. Under the same circumstances, but starting from 65 % *ee* 4-chloromandelic acid the raffinate (Fig. 9) contained much larger, elongated, sheet-like particles. This finding is counter-intuitive because in the latter case, the higher ratio of the less soluble salt in the starting material results in higher oversaturation during the process. It would generally mean the formation of more crystal nuclei and smaller crystals.

4 Conclusion

Gas antisolvent fractionation was presented as the separation method in the chiral resolution of racemic 4-chloromandelic acid using half molar equivalent of (*R*)-1-phenylethanamine as the resolving agent. Detailed investigations on the effect of pressure, temperature and solvent ratio (the mass ratio of the organic solvent and carbon dioxide) were conducted in the ranges of 12-20 MPa, 35-45 °C and carbon dioxide to methanol mass ratio of 7.5-25 respectively. Although the solvent mass ratio had an effect on yield an enantiomeric excess, selectivity remained
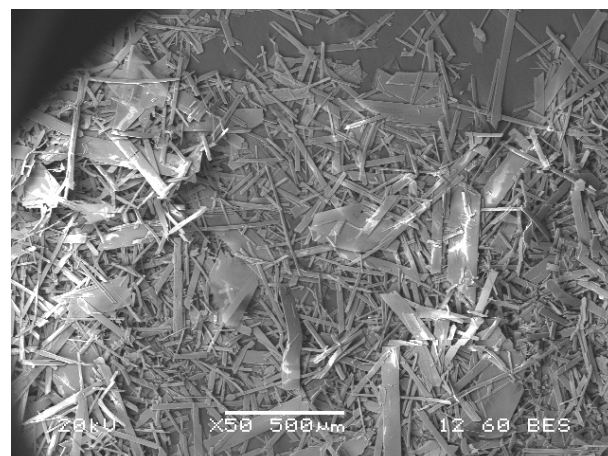
unaffected by this parameter as well. 72 % enantiomeric excess (*ee*) was achieved in the raffinate at 16 MPa, 40 °C and 7.5 solvent ratio, while a 65 % *ee* acid was purified to over 90 % by another resolution step with half molar equivalent of the amine. Generally, antisolvent precipitation processes offer a faster production than atmospheric crystallization methods. Although similar purities were achieved compared to the atmospheric method cited [25], the micronization capabilities of antisolvent methods can promote rapid dissolution of its products, also meaning a significant advantage. Highly scalene crystal formation of the (*R*)-(*R*) salt was confirmed using powder X-ray diffraction while crystal habit was investigated by scanning electron microscopy. The crystalline samples contained crystals in the maximum 200 μm range.

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