



A fast, new method to enhance the enantiomeric purity of non-racemic mixtures: self-disproportionation of enantiomers in the gas antisolvent fractionation of chlorine-substituted mandelic acid derivatives



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ABSTRACT

Gas antisolvent precipitation is a particle formation technique, when typically pressurized carbon dioxide is added to an organic solution resulting in immediate and high oversaturation and precipitation of fine particles. Provided that a reasonable share of the originally dissolved material remains dissolved in the carbon dioxide – organic mixed solvent, these components can be extracted during the washing phase. This method is called gas antisolvent fractionation. Gas antisolvent fractionation has been applied for the first time to enantiomeric enrichment of non-racemic mixtures, and demonstrated on the example of chlorinated mandelic acid derivatives. Due to self-disproportionation of enantiomers, the precipitated solid and the extracted fractions have different enantiomeric excesses if gas antisolvent fractionation is carried out on a non-racemic mixture. However, there is a limit in the enantiomeric excess (*ee*) that can be achieved correlating strongly with the atmospheric melting eutectic behavior of the compounds. Thus, if initial enantiomeric mixtures have a higher than eutectic *ee*, a >99% *ee* can be reached in the crystalline product. The strong correlation between the high-pressure experiments and the atmospheric melting eutectic behavior suggest that despite the very large oversaturation during the antisolvent precipitation, the composition of the products (i.e., the crystalline and the extracted phases) is thermodynamically determined. Technological advantages such as short operational time, or the possibility of controlling the crystal morphology suggest that the development of an efficient technique of enantiomeric purification is possible based on gas antisolvent fractionation.

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1. Introduction

The need for the production of enantiopure compounds in the pharmaceutical industry, manufacturing of agrochemicals and in the food industry is the driving force for the development of new methods of enantiomeric enrichment.

Enantiomeric enrichment of non-racemic mixtures can be carried out without the addition of any chiral selector. When the *ee* values of the separated products differ from each other and that of the starting material, we talk about self-disproportionation of enantiomers.^{1,2} This phenomenon has been observed in separation techniques such as sublimation³ or high-performance liquid chromatography (HPLC) with achiral moving and stationary phases.⁴

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Among the techniques aimed at the enhancement of the enantiomeric purity of non-racemic mixtures, recrystallization is a very simple way to improve the enantiomeric purity of the target compound. Self-disproportionation of enantiomers can also be observed under these circumstances. In the case of racemic compounds, the atmospheric recrystallization-based enantiomeric enrichment process is limited by the eutectic behavior of dissolution, which is close to the eutectic composition observable in the melting point phase diagrams. The crystalline phase formed in a solution of a lower than eutectic enantiomeric purity (i.e., $ee_0 < ee_{eu}$) typically has lower enantiomeric purity than the initial *ee*, while the mother liquor contains the enantiomerically enriched material. Starting from over the eutectic composition ($ee_0 > ee_{eu}$) the opposite happens. Conglomerate forming compounds do not exhibit such boundaries. The strong correlation of the limiting *ee* value in enantiomeric enrichment with the eutectic *ee* of the

binary melting point phase diagram was described by Faigl et al. through several recrystallization processes. The authors explain their results as the consequence of thermodynamic control during the recrystallization experiments.⁵

Traditional recrystallization processes are often slow, and use large amounts of organic solvents. Gas antisolvent precipitation and supercritical antisolvent precipitation both using supercritical carbon dioxide as an antisolvent have been widely studied and applied techniques to recrystallize various compounds. Antisolvent processes are not only fast and eco-friendly (reducing the amount of organic solvent needed), but also offer the possibility to produce fine powders with narrow particle size distribution in the micrometer main particle diameter range. The morphology (i.e., the crystal habit) can also be influenced by the operational parameters, however, this advantage can only be exploited in a scaled-up equipment. Besides the advantages, safety issues and higher investment costs regarding the high pressure unit operations have to be taken into consideration.^{6–9} Gas antisolvent fractionation is a combination of the gas antisolvent precipitation and separation of the impurities by the following supercritical fluid extraction, it is also referred to in the literature as supercritical antisolvent extraction,^{10–12} supercritical antisolvent fractionation¹³ etc. Gas antisolvent and supercritical antisolvent precipitation have already been used as separation methods in chiral resolutions carried out by diastereomeric salt formation.^{14,15} This technique is now presented for the first time for enantiomeric enrichment based on self-disproportionation of enantiomers.

During the gas antisolvent fractionation process (Fig. 1), the aim is to achieve partial precipitation of a compound dissolved in an organic solvent. First, a nearly saturated solution of the starting material needs to be prepared, and filled into a suitable high pressure vessel (Fig. 1a). Carbon dioxide is then introduced and is dissolved by the organic solvent. Thus, because of the expansion and polarity drop of the solvent, its solvent power is sharply reduced, resulting in (partial) precipitation of polar components (Fig. 1b). By choosing appropriate operational parameters (i.e., pressure, temperature and organic solvent concentration), a homogenous fluid phase can be achieved over the precipitate. The dissolved portion of the starting material together with the organic solvent can be extracted using pure carbon dioxide (Fig. 1c). After depressurization of the equipment, the crystalline product can be recovered (Fig. 1d).

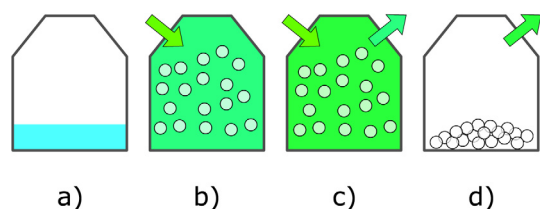


Figure 1. Stepwise depiction of the gas antisolvent fractionation process. (a) The compounds to be precipitated (and separated) are filled into the autoclave as a solution. (b) Carbon dioxide is introduced, resulting in a polarity change and precipitation. (c) The dissolved components are extracted using pure supercritical carbon dioxide and can be collected in a solvent trap (not pictured). (d) The crystalline product can be recovered after depressurization.

We aimed to develop a method to enhance the enantiomeric purity of non-racemic mixtures of chlorinated mandelic acid derivatives (Fig. 2) based on their recrystallization by gas antisolvent fractionation. Mandelic acid derivatives are often used as resolving agents or intermediates in the pharmaceutical or agrochemical industries to introduce stereoselectivity stereogenic centers in the molecules.^{16–20} We also investigated the possible correlation between the limits of enantiomeric enrichment observable in the

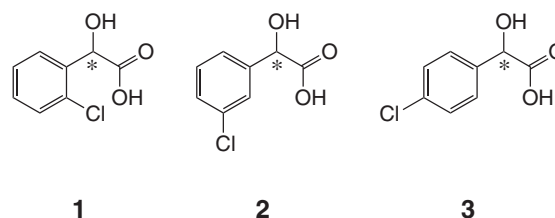


Figure 2. The studied mandelic acid derivatives 2-chloromandelic acid **1**, 3-chloromandelic acid **2**, 4-chloromandelic acid **3**.

products' *ee* – initial *ee* diagrams and the atmospheric melting point phase diagrams in order to gain further understanding in the mechanism of the chiral discrimination.

2. Results and discussion

Melting point phase equilibria diagrams of **1** and **2** have already been reported in the literature.^{21,22} DSC measurements were carried out to confirm the data obtained from the references. The experimental phase equilibria diagram of 4-chloromandelic acid was however not available in the literature, and only the melting points and fusion enthalpies of the single enantiomers and of the racemate have been published.^{23,24} Experimental and literature data of atmospheric melting temperatures and fusion enthalpies are summarized in Table 1. Our own experimental values were used for the modelling of the melting point phase equilibrium curves pictured in the upper sections of Figs. 3–5.

To model the phase equilibrium behavior of the acids, the Prigogin–Defay Eq. (1) was used at *ee* values lower than the eutectic *ee* and the Schröder–van-Laar Eq. (2) was used at *ee* values higher than the eutectic *ee* of the corresponding acid.²²

$$\ln[4 \cdot X_R \cdot (1 - X_R)] = \frac{2 \cdot \Delta H_{rac}}{R} \cdot \left(\frac{1}{T_{rac}} - \frac{1}{T} \right) \quad (1)$$

$$\ln X_R = \frac{\Delta H_R}{R} \cdot \left(\frac{1}{T_R} - \frac{1}{T} \right) \quad (2)$$

where X_R denotes the molar fraction of the (*R*)-enantiomer. ΔH_{rac} and ΔH_R stand for the fusion enthalpy of the racemic and the enantiopure compounds respectively. T denotes the melting point in K. T_{rac} and T_R represent the melting points of the racemic and the enantiopure (*R*) compound respectively, in K units. R is the universal gas constant. Although the calculations were carried out using the molar fractions of the enantiopure acid, the obtained models were plotted against the enantiomeric excess, in order to achieve a similar scaling with the ee_0 – ee_1 diagrams.

In the cases of **1** and **2**, the phase diagrams calculated based on our measurements are in good agreement with those obtained from the literature. In case of **1**, the measured points were also

Table 1
Melting temperature and fusion enthalpy data of racemic and enantiopure **1**, **2**, and **3**. Indices *rac* and *R* refer to racemic and enantiopure, respectively.

Compound	1	2	3
<i>Measured data</i>			
T_{rac} [K]	362	387	393
T_R [K]	393	378	393
ΔH_{rac} [J/mol]	21,588	24,609	25,749
ΔH_R [J/mol]	24,033	23,251	21,345
<i>Data obtained from the literature</i>			
T_{rac} [K]	363 ²²	390 ²¹	393 ²⁴ ; 394 ²³
T_R [K]	392 ²²	379 ²¹	393 ²⁴ ; 394 ²³
ΔH_{rac} [J/mol]	23,137 ²²	27,980 ²¹	16,200 ²⁴ ; 27,200 ²³
ΔH_R [J/mol]	24,947 ²²	26,240 ²¹	27,100 ²⁴ ; 23,000 ²³

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