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Chiral separation of systems of high eutectic composition by a combined process: Case study of serine enantiomers

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ABSTRACT

A concept for the chiral resolution of racemic compounds by a combination of chiral pre-enrichment by continuous multi-column chromatography and final purification using selective crystallization is presented. The system of serine enantiomers in water represents a typical racemic compound-forming system with very high eutectic compositions in the chiral system, which is generally considered as unfavorable for selective crystallization. It is shown exemplarily, how the solvent and temperature-dependent formation of hydrates can be exploited to allow efficient chiral resolution by a combined process for this and similar systems.

1. Introduction

Changes in the regulative framework [1] and the rising awareness of commercial advantages of enantiopure products have provoked intensive research in the area of asymmetric synthesis, in biotechnology and in the development of physical separation techniques. Amino acids belong in this context to a prominent class of compounds, as firstly the market for feed and food additives made of L-amino acids is significant and keeps on growing and secondly, both L- and D-amino acids belong to the chiral pool [2,3] and are important precursors in the synthesis of enantiopure pharmaceutical drugs. Often, the D-form of amino acids is by far more expensive, since only the L-form can be obtained in a single step through e.g. large-scale fermentation processes.

The enantiomers of serine are a typical example. Different synthesis pathways towards the racemic DL-serine are known for long, among others starting with methyl acrylate [4,5]. While the L-amino acid is produced as a few hundred tons per year by fermentation [3], competitive direct entirely synthetic pathways towards the D-form are not published. Apparently, approaches based on either racemization of the comparatively cheap L-enantiomer followed by separation of racemic mixtures [6] or transformation/conversion of the unwanted L-enantiomer [7] remain most promising. This contribution focuses on the former, on the physical separation of racemic mixtures of serine.

In view of pharmaceutical drug development and production, chiral chromatographic separation techniques and selective crystallizations based on the formation of diastereomers are found most frequently. The application of crystallization techniques is usually restricted to the removal of remaining side products and to the final product formulation. Crystallization is not considered as the primary step for direct chiral resolution of a pair of enantiomers, although a number of efficient separation methods are known [8–12]. One reason might be the requirement to quantify crystal growth kinetics and probabilities of nucleation events of the counter-enantiomer, which necessitates comprehensive experiments. This is often avoided for e.g. reasons of limited process development time and uncertainties in further scale-up.

Thermodynamically controlled techniques are designed more quickly and the possible process yield can be estimated a priori. However, the majority of racemic systems of enantiomers (so called 'racemic compound-forming systems') cannot be separated directly by Thermodynamically controlled techniques, a pre-enrichment of the target enantiomer is needed [9]. The corresponding initial degree of asymmetry for a pair of enantiomers is substance specific and can range between >50% (most favorable) up to >99% content of the target enantiomer [13]. Very high values render those processes increasingly unattractive from an economic perspective. The minimal degree of asymmetry needed

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to conduct successfully a selective crystallization step corresponds to the eutectic composition of the chiral system, which in turn depends among others on the solution temperature and the choice of solvent [13–15]. Within this contribution the dependency of the eutectic composition of serine enantiomers on solvent and temperature was analyzed exemplarily while aiming to design and validate a crystallization-based chiral separation process. The symmetry of the initial racemic solution was broken by a preliminary chiral continuous multi-column process as shown by other authors and in an earlier contribution [16–19]. Instead of purifying a given asymmetric solution above the very-high eutectic composition and subsequent selective crystallization of the target compound, an alternative way based on 'preferential enrichment' was proposed. Hereby, the eutectic composition was shifted above the purity requirements for the amino acid and a thermodynamic equilibration step, originating from an only slightly enriched solution, yielded a liquid phase, which was enriched sufficiently in the target enantiomer.

2. Solid–liquid equilibria in aqueous methanol solutions

The knowledge of the underlying solid–liquid equilibria (SLE) of a system of interest is very relevant for process design. The chiral system of serine enantiomers in water is known to feature a characteristic eutectic composition very close to 100% [13]. Comprehensive solubility data for the racemic compound are available from Dalton et al. [20] and for L-serine by Ferreira et al. [21]. Ternary solubility data of a single solubility isotherm were published by Klussmann et al. [13]. Further, different solubility models considering either the racemic compound or the single enantiomer were parameterized by several authors [22,23].

Here, it was intended to introduce firstly a thermodynamic consistent model for the description of ternary phase equilibria of serine enantiomers in water. Therefore, additional solubility data became necessary to determine in the course of this work.

2.1. Experimental-determination of SLE

Solubilities of pure L-serine and mixtures of both enantiomers in water were determined by thermodynamic equilibration and for temperatures within a range of 288.15–340.15 K. Defined amounts of serine enantiomer(s) in excess were given to preweighted amounts of water. A magnetic stirrer was added and the vials were properly sealed and temporized in water baths using double-walled compartments for >2 days. Afterwards, the stirrers were switched off allowing the solids to settle. Samples of the liquid phase were withdrawn through filters of 0.45 μm using a syringe. The enantiomeric ratio was analyzed by analytical chiral chromatography (eluent flow rate: 0.5 mL/min; 60/40 (v/v, methanol/water); column: Chirobiotic T, Astec, ICZ Chemietechnik GmbH, 250 mm × 4.6 mm, 5 μm; injection volume: 5 μL; T = 293.15 K; detection wavelength 205 nm), the dissolved amount of amino acid was determined by drying and gravimetry. All solid phases were filtered off and analyzed by X-ray powder diffraction (XRPD). Eutectic compositions in aqueous methanol and aqueous ethanol, respectively, were measured analogously by thermodynamic equilibration of slurries of both enantiomers in solution.

TG-DSC was performed in order to evaluate weight losses upon heating of hydrates.

2.2. Solid phase analysis and modeling of SLE

The simplified equation by Schröder and van Laar (Eq. (1)) and the equation by Prigogine and Defay [24] (Eq. (2)) were used to describe the solubilities of serine enantiomers $x^l_{(D)}$ and $x^l_{(D)}$ in solution.

$$\ln(\gamma^l_{(L)} x^l_{(L)}) = \frac{\Delta h^f_{(L)}}{R}\left(\frac{1}{T^f_{(L)}} - \frac{1}{T}\right) \quad (1)$$

$$\ln(4\gamma^l_{(L)} x^l_{(L)} \gamma^l_{(D)} x^l_{(D)}) = \frac{\Delta h^f_{(DL)}}{R}\left(\frac{1}{T^f_{(DL)}} - \frac{1}{T}\right) \quad (2)$$

The non-random two liquid model (NRTL) [25] expresses non-idealities in solubility behavior by activity coefficients $\gamma^l_{(L)} = f(T, x^l_{(L)}, x^l_{(D)}, x_{(water)})$, with T being the solution temperature and $x_{(water)}$ being the solvent (here: water) fraction. The model was applied as described in previous papers [14,26–28]. Suitable model parameters were found by fitting the model against binary solubility data using the commercial Matlab™ (MathWorks, USA) software package and an integrated Nelder–Mead optimizer. The heat and temperature of fusion, $\Delta h^f_{(L)}$ and $T^f_{(L)}$, of the amino acid were not available, since it decomposes prior to the melting. The proposed values in the literature range from melting points of 375 K for the enantiomer [21] up to 776 K for the racemic compound [22] and highlight the difficulty in their proper estimation. It is known from a database [29] that decomposition of L-serine occurs at 493 K and thus, the melting point was expected to be close by or above this value. The group contribution method by Marrero et al. [30] yielded a melting point of 588.9 K and a heat of fusion of 33.273 kJ mol^{-1} for the single enantiomer. These values were used as initial values and it was attempted to optimize them further during the parameterization procedure within the given method accuracy by Marrero of 16%. The initial values for the racemic compound ($\Delta h^f_{(DL)}$, $T^f_{(DL)}$) were taken as identical to the single enantiomer. Physical reasonable limits set the boundaries for the solver. Proper correlation of the solubilities of the single enantiomer with the NRTL model was generally possible. It is obvious, that the NRTL model with 3-parameters for the solvent–solute interactions and another 4 parameters for the two heats and temperatures of fusion allow numerous possible parameter sets, that represent well the given solubility data. Surprisingly, it was not possible to describe the solubility of the racemic compound even after adjustment of its heat and temperature of fusion in addition. Apparently, heterochiral interactions, i.e. interactions among the L- and the D-enantiomer are relevant. The attempt to fit simultaneously 6 parameters for the NRTL model (3 for solvent–solute interactions and 3 for heterochiral solute–solute interactions) together with 4 values for the heats and temperatures of fusion to the solubility data of the single enantiomer and the racemic compound failed. No suitable set of parameters was found for the model applied.

An X-ray power diffraction (XRPD) analysis of the solid phase of the single enantiomer clarified the situation with identification of a monohydrate of the serine enantiomer. Its presence is also known from the literature [31], but described to occur above 303 K only. However, the conducted XRPD analysis proved the existence of the monohydrate at any temperature within the investigated range.

In Fig. 1 the patterns of the racemic compound (no. 1), the anhydrous enantiomer (no. 2) and patterns from the time-resolved analysis of a sample of the single enantiomer (nos. 3–6), crystallized from water at 283 K, are summarized. The result of the first XRPD analysis directly after recrystallization (no. 3) showed distinct preferred orientation of the crystals at ∼15° 2θ. The characteristic reflections of the anhydrate of the enantiomer (no. 2) at ∼6° 2θ and around 10° 2θ are not present. The reflections indicate the presence of the monohydrate (compare [31]), which was stable for about 20 h. The patterns undergo a time-resolved development until the latest analysis of the sample (no. 6) appears identical to the ones of