CRYSTALLIZATION BASED SEPARATION OF ENANTIOMERS[*]
(REVIEW)

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ABSTRACT

Pure enantiomers are of large interest for several industries. Chemical synthesis is frequently not selective and provides racemic mixtures causing a large interest in efficient separation processes. Preparative chromatography is nowadays a powerful and flexible but expensive technology. As an alternative there exists the possibility to apply cheaper crystallization processes.

Based on classifying enantiomeric systems according to their type of solid-liquid equilibria, crystallization processes will be discussed which are capable to provide pure enantiomers. Two separation problems studied in our laboratory will be considered for illustration. Preferential crystallization was used to separate racemic threonine and an asymmetric partially enriched mixture of the mandelic acid enantiomers both from an aqueous solution. Using various operation modes and considering the effect of different seed characteristics and a tailor-made additive on the performance of preferential crystallization, the potential of this technique for enantioseparation is highlighted.

<u>*Keywords*</u>: *enantioseparation, crystallization, conglomerates, racemic compounds, preferential crystallization.*

INTRODUCTION

Enantiomers are stereoisomers that are non-superimposable mirror images of each other (optical isomers). On the basis of their opposite specific optical rotation a classification in (+)- and (-)-enantiomers is frequently used to distinguish between them. Another classification, common for amino acids and sugars, is the (D)-/(L)-system. 50:50-mixtures of enantiomers are called racemates. An introduction in the fascinating world of stereochemistry is given e.g. in [1].

Due to the fact that life is essentially constructed using L-amino acids as building blocks, there is tremendous interest in the pharmaceutical, food and agrochemical industries to produce pure enantiomers [2, 3]. Nowadays, there is a large amount of evidence available that in chiral drugs often only one enantiomer provides the desired physiological effect. In many cases,

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the other enantiomer has no effect or is even harmful. Regulators increasingly demand that chiral drugs are administered in optically pure form [4]. This has intensified efforts of industrial and academic research devoted to develop techniques which are capable to produce pure enantiomers. This goal can be achieved a) via the selective synthesis of just one enantiomer or b) via the separation of mixtures [5, 6].

In the last years remarkable progress has been achieved in the field of enantioselective catalysis [7, 8]. Nevertheless, highly selective reactions leading in an economical manner to a variety of pure enantiomers are still the exception and there is a demand in more generally applicable and cheap separation processes. Thus, below the typical situation is considered, that the product leaving the reactor is not optically pure so that subsequent enrichment (purification) steps are necessary.

The most versatile technique to perform enantioseparations is chromatography [9, 10]. Currently, there is a growing arsenal of selective chiral stationary phases available allowing to separate a large spectrum of racemates [11, 12]. A breakthrough in increasing the productivity of chromatographic enantioseparations was achieved in the last years due to the development of the simulated moving bed technology based on continuous countercurrent operation [13, 14]. However, chromatographic processes are expensive and there is an interest in developing alternative technologies. An overview regarding possible applications of a) transformations of enantiomers into diastereoisomers, b) chiral membranes, c) optically active solvents and d) kinetic resolutions using enzymes is given in [7, 8].

Since Pasteur's famous separation of the enantiomers of sodium ammonium tartrate by direct crystallization [15], immense activities have been devoted to study and to apply crystallization processes in order to obtain pure enantiomers. The feasibility of selective crystallization depends strongly on the whims of nature, specifically on the underlying solid-liquid equilibria. A first detailed classification of possible types of equilibria was published already in [16]. A recent and comprehensive analysis of the thermodynamics of enantiomeric systems is given in [17]. In this book also various possibilities to perform crystallization processes are discussed extensively. The state of the art of applying these techniques in the industry was summarized recently in [18].

In this paper two case studies of performing an enantioseparation by crystallization will be described. One of the systems investigated belongs to the group of conglomerates for which direct crystallization by entrainment is possible. The other system forms in the solid phase a racemic compound. In the latter case the racemate can only be separated by crystallization if there exists a sufficient enrichment in the feed solution. In the following first, the fundamental solid-liquid equilibria, i. e. the binary and ternary phase diagrams for the two chosen systems are presented. Second, the regions of metastability are considered determining (together with the solubility data) the regions where successful crystallization based enantioseparation can be performed. On the example of applying preferential crystallization classically to resolve conglomerates and in a challenging way to crystallize pure enantiomer(s) from partially enriched solutions in case of a racemic compound forming system, the potential of this direct crystallization technique for separation of enantiomers is highlighted afterwards. Finally, selected examples for optimization of such crystallization based separation processes are given.

SOLID-LIQUID EQUILIBRIA

The application of crystallization for the separation or purification of enantiomers requires a detailed knowledge of the corresponding phase diagrams describing the melting behavior of the two enantiomers ('binary' melting point phase diagram) and/or their solubility behavior in the presence of a suitable solvent ('ternary' solubility phase diagram). Comprehensive overviews regarding identified types of phase diagrams and their description have been published [17, 19-21].

Binary phase diagrams

Due to the type of the saturation curves in solid-liquid phase diagrams fundamental types of enantiomer systems can be identified, which have been firstly described in a pioneering work of Roozeboom [16]. The most frequently observed types of binary phase diagrams are those corresponding to conglomerates and racemic compound forming systems. These phase diagrams are presented schematically in Fig. 1.
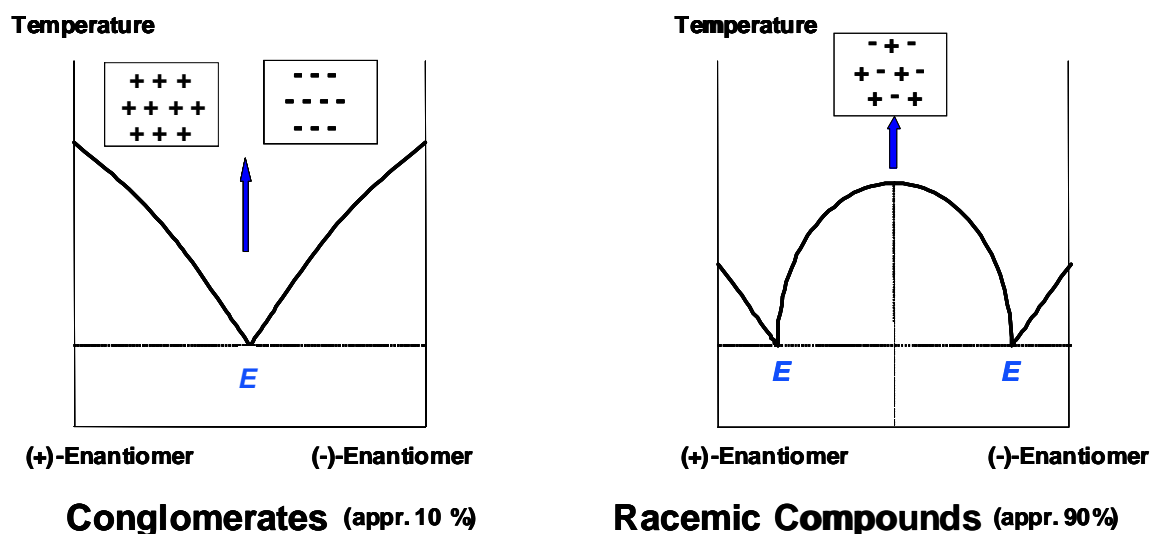
Fig. 1. Illustration of typical binary phase diagrams of enantiomeric systems ((+) and (-) indicate the two enantiomers).

Only 5 to 10 % of the racemates belong to the conglomerate forming group [17], which is the most favourable one for achieving a certain enantiomeric enrichment by fractional crystallization from a nonracemic mixture. Unfortunately, about 90 to 95 % of the racemates form a compound in the solid phase (racemic compound). In these cases the knowledge of the phase equilibria is even more important, because the existence region of the pure enantiomers in the phase diagram, which is defined by the position of the eutectic points E (see Fig. 1), is much smaller. A third type of systems, the solid solution forming racemates (or "pseudoracemates"), is relatively rare and will not be discussed in this paper. However, the formation of partial solid solutions is always feasible both for conglomerates and racemic compounds and can occur on the pure enantiomers and the racemic compound sides in the phase diagram. An example for the latter case is encountered for malic acid [22].

Binary phase diagrams can be measured e.g. using differential scanning calorimetry (DSC). Results for the enantiomers of mandelic acid are shown in Fig. 2. This substance obviously belongs to the racemic compound forming systems. The lowest melting point of about 115°C is found for an eutectic composition of about x = 0.7. More details including information regarding the possibility to describe this phase diagram mathematically and the existence of a metastable racemic phase are given elsewhere [23, 24].
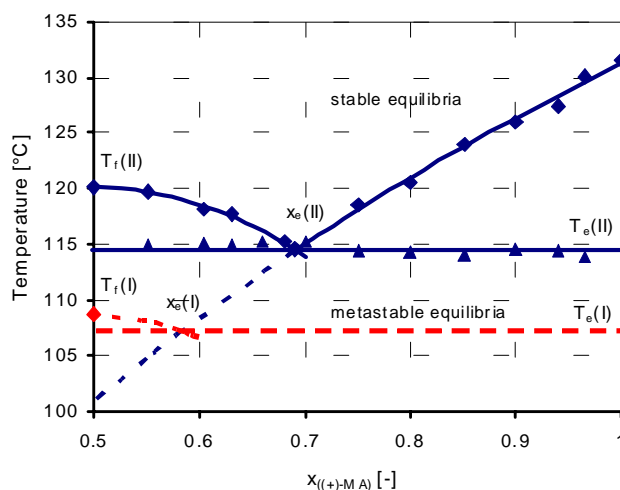

Fig. 2. Binary phase diagram of the mandelic acid enantiomers (only one half of the symmetric diagram is shown) [24].

It was known that threonine (Thr) belongs to the group of conglomerates [17, 25]. Own attempts to measure the binary phase diagram using DSC failed due to a steady decomposition process of both DL-Thr and L-Thr overlaying the fusion and finishing at about 232 °C and 239 °C, i. e. clearly below the melting point given in literature. Obviously, in case of systems that decompose before or during melting, reference melting data must be treated with care.

Ternary phase diagrams

Ternary (solubility) phase diagrams are closely related to the corresponding binary phase diagrams [17,
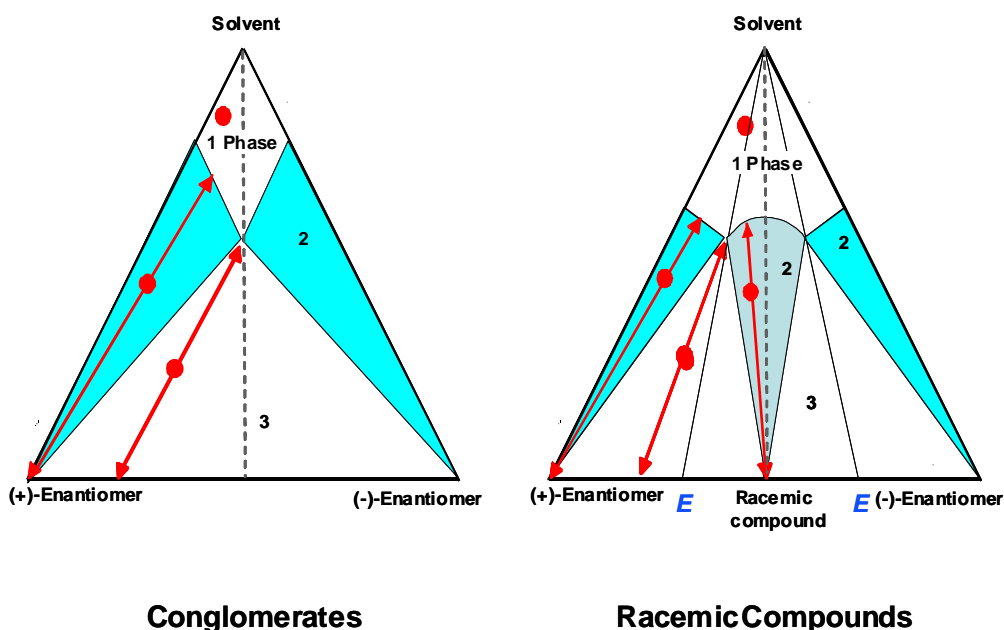
Conglomerates   **Racemic Compounds**

Fig. 3. llustration of typical ternary phase diagrams of enantiomeric systems under isothermal conditions (numbers just indicate the number of phases present in equilibrium) [21].

24]. Thus, a preliminary determination of the binary phase diagram is usually helpful to construct ternary phase diagrams.

Fig. 3 presents schematically typical solubility phase diagrams for conglomerates and racemic compound forming systems in an equilateral triangular form. The vertexes of the triangles represent the pure components: the solvent (on top), the (+)- and (-)-enantiomers (left and right). The triangle sides given in mole or weight fractions represent the binary systems (+)-enantiomer/solvent, (-)-enantiomer/solvent and (+)-/(-)-enantiomers. Each point inside the triangle describes a ternary mixture consisting of all three components. For conglomerates the diagram consists of a) an undersaturated 1-phase region close to the solvent corner, b) two 2-phase regions which will contain under equilibrium conditions an enantiopure solid phase and a saturated liquid phase with one or both enantiomers and c) a 3-phase region where under equilibrium conditions the liquid phase will be a saturated solution of a racemic mixture of the two enantiomers and the solid will be a mechanical mixture of the two enantiomers. Phase diagrams for racemic compound forming systems are more complicated. Due to the existence of two eutectic points (E) in the binary (+)-/(-)-enantiomer system the following main differences can be noticed in Fig. 3: a) the shape

of the 1-phase region changes, b) the 2-phase regions shrink, c) another 2-phase region appears where the solid phase will be the racemic compound and d) there are two separated 3-phase regions in which the solid phases will be mechanical mixtures of a pure enantiomer and the racemic compound. Obviously, the borders of the different regions shown in Fig. 3 will depend on temperature.

Fig. 4 presents the measured ternary phase diagram of the system (+)-mandelic acid/(-)-mandelic acid/water [26]. It contains the equilibrium data (measured in time consuming phase separation experiments) for different temperatures between 0 and 60°C. Most of the points measured refer to an excess of the (+)-enantiomer. For mixtures containing the (-)-enantiomer in excess only some experiments have been done to confirm the symmetry of the diagram. An exponential upward trend of the solubility with the temperature and a higher solubility of the racemic compound compared to the pure enantiomers were observed. Furthermore, between the pure enantiomer and the racemic composition a mixture with a solubility maximum can be identified at x = 0.7 (i.e. at the same composition as identified for the eutectic point in the binary phase diagram). In the range of the study the enantiomeric composition of this "eutectic line" does not depend on temperature.
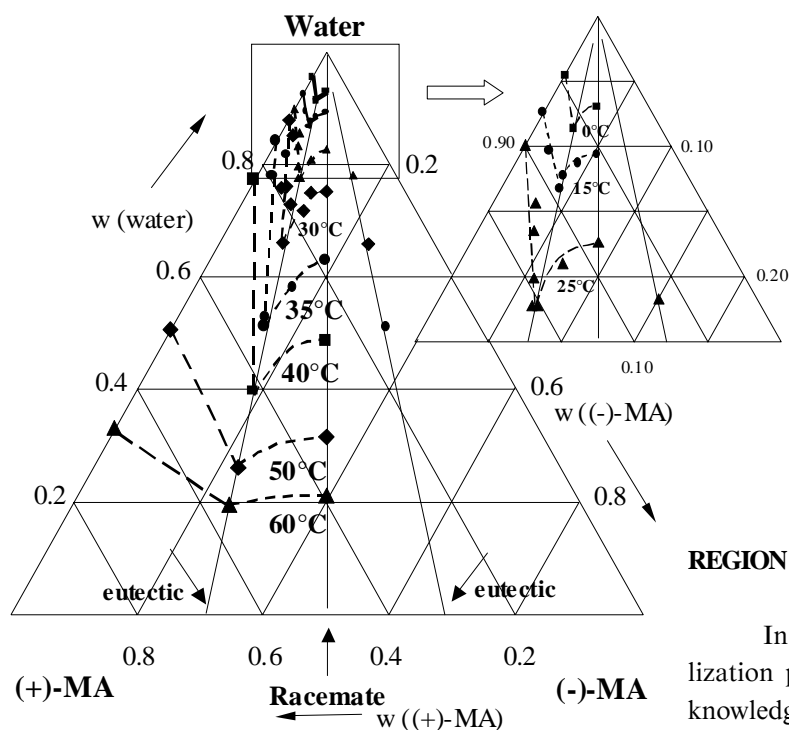
Fig. 4. Ternary solubility phase diagrams of the mandelic acid enantiomers in water (MA – mandelic acid) [26].
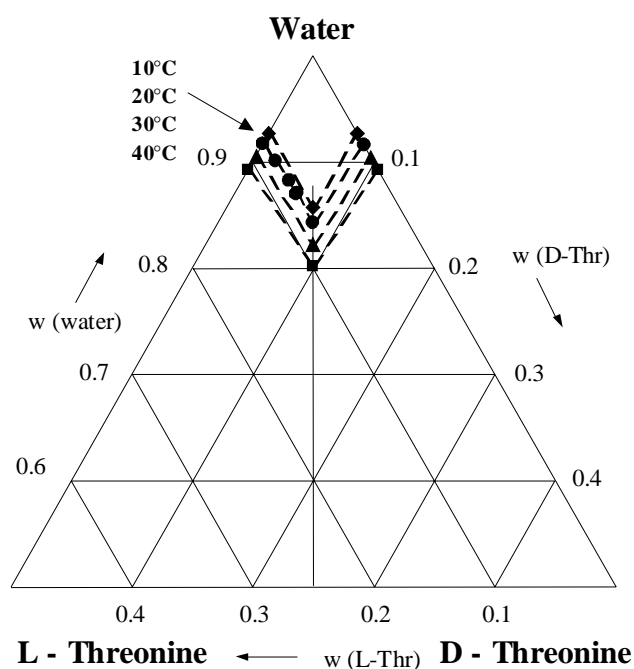

Fig. 5. Ternary solubility diagram of the threonine enantiomers in water for different temperatures [26].

This composition specifies a minimum enrichment required to enter the 2-phase regions allowing crystallization of just one enantiomer.

Fig. 5 shows the ternary phase diagram for the enantiomers of threonine in water. The results reveal that these components indeed form a conglomerate as reported in [17, 25]. Further, the solubility of one enantiomer is not affected by the presence of the other one, i.e. the solubility of the racemic mixture is just the superposition of the individual solubilities of the enantiomers. Thus, the system behaves ideally.

REGION OF METASTABILITY

In the field of designing and optimizing crystallization processes it is well known, that besides the knowledge about the phase diagrams, it might be important to take also into account the region of metastability (supersolubility) [27]. Often in systems close to the phase boundary a phase separation can be retarded quite a long time. There are various methods available to estimate the width of a metastable zone in terms of supersaturation.

Figs. 6 and 7 present experimental results regarding the width of the metastable zones for threonine and mandelic acid [28, 29]. These results were obtained using Nyvlt's polythermal method [30].

Fig. 6 shows supersolubility data of racemic threonine in water with regard to primary (heterogeneous) nucleation (without threonine crystals) and secondary nucleation (in the presence of a racemic mixture of threonine crystals) in comparison to the solubility. As expected the supersolubility with regard to secondary nucleation is smaller than in the case of primary nucleation [28].

Fig. 7 illustrates metastable zone width data with regard to secondary nucleation for three characteristic enantiomeric mixtures of mandelic acid in water (pure enantiomer, racemate and eutectic mixture of both enantiomers) in combination with the corresponding solubility data. Nucleation was detected in this study acoustically (LiquiSonic probe) and optically (fibre optical probe, turbidity) [28, 29]. While the pure enantiomer
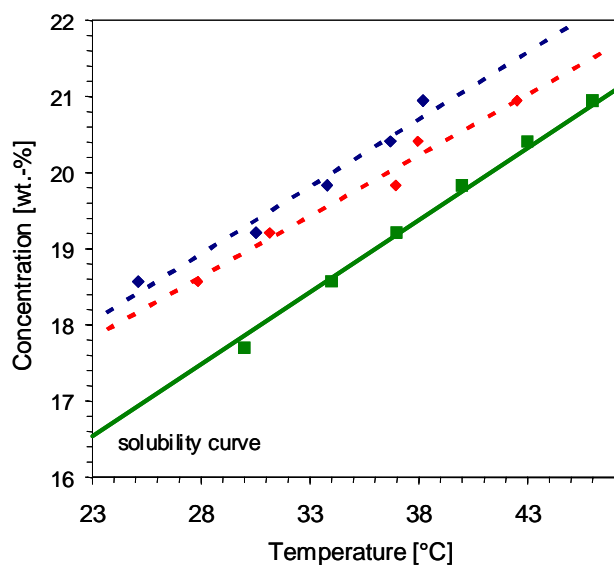
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Fig. 6. Solubility (solid line) and supersolubility (dashed lines) for DL-threonine in water embedding the metastable zone (upper dashed line: supersolubility with regard to primary (heterogeneous) nucleation, i. e. without crystals; lower dashed line: supersolubility with regard to secondary nucleation, i. e. in the presence of DL-threonine crystals) [28].
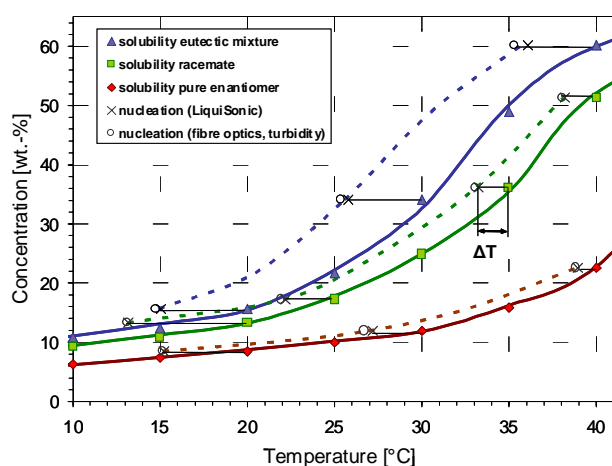

Fig. 7. Solubility and metastable zone width for secondary nucleation of mandelic acid species in water (in terms of the maximal achievable subcooling ΔT_{max}) [28, 29].

solution and the solution of the eutectic mixture were studied in the presence of pure enantiomer crystals, crystals of the racemic compound were present in case of the racemic solution. The difference in the metastable zone width for the three solutions can be explained by the compound forming character of the mandelic acid system and the different nucleating crystal species. In case of the enantiopure solution, nuclei are formed by

the pure enantiomer. In the case of the racemic solution, a recombination of heterochiral molecules is nessecary in connection with the formation of nuclei. For the eutectic mixture, a selective nucleation could be assumed, comparable with the selective seeding of the pure enantiomer in analogy to the preferential crystallization process described below.

RESOLUTION OF ENANTIOMERS VIA CRYSTALLIZATION

Based on the measured phase diagrams for threonine and mandelic acid, below the crystallization based separation of the enantiomers in these two systems will be explained applying preferential crystallization as the separation method. Mainly results obtained in our laboratory are considered. Thus, this section is concerned essentially with demonstrating the separation feasibility. More detailed aspects of practical realization, scale up and optimization of crystallization processes are summarized elsewhere [e. g. 31, 32].

Preferential crystallization of conglomerates

For conglomerates there exists an attractive possibility to directly crystallize pure enantiomers from a racemic solution. The principle of kinetically controlled crystallization by entrainment is shown in Fig. 8. Considering an initially undersaturated solution at a higher temperature T_1, the solution becomes supersaturated but remains clear, if it is rapidly cooled down to the lower
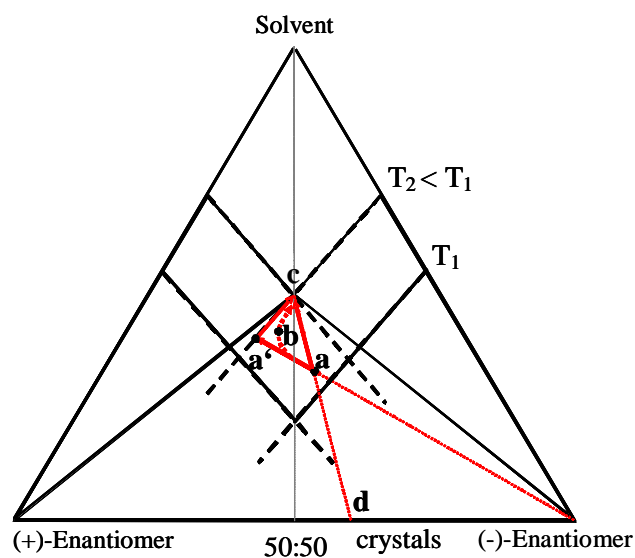

Fig. 8. Illustration of the principle of preferential crystallization [33].
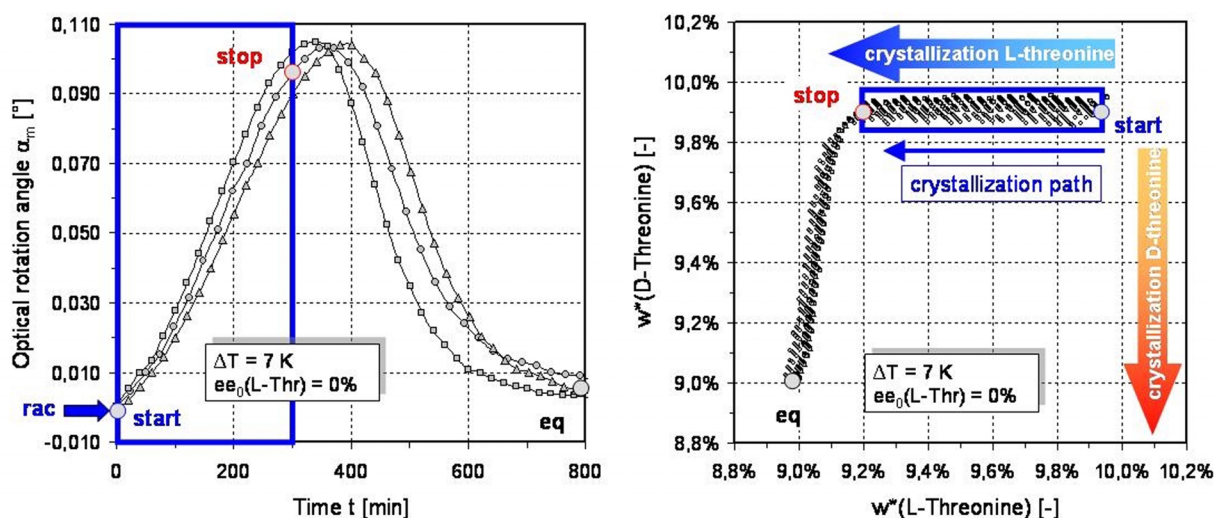
Fig. 9. Results of three runs of preferentially crystallizing L-threonine from a racemic mixture performed under identical experimental conditions. Left: Course of the polarimetric signals, Right: Process trajectories in the plane of threonine enantiomer liquid phase weight fractions. [35].

crystallization temperature T_2 within the metastable zone. Retarded, its composition would change in order to reach finally the thermodynamic equilibrium. In the equilibrium state the liquid phase will have racemic (i. e. eutectic) composition and the solid phase will consist of a mixture of crystals of both enantiomers. However, after seeding with homochiral crystals (e. g. the (-)-enantiomer in Fig. 8) it can be observed that the liquid phase composition does not move to point c directly but follows other trajectories (e. g. a → b → c). Thus, under particular conditions and in a restricted time interval it is possible to preferentially produce crystals of just one of the enantiomers. The feasibility of this process is due to the homochiral surface area offered initially and the specific driving forces. Detailed treatises of the process of crystallization by entrainment can be found in the literature, e. g. [17, 19].

An example proving the feasibility and the reproducibility of the process is shown in Fig. 9 for the threonine system which was already studied in [34]. Based on the determination of the metastable zone width (Fig. 6) the process could be performed for a subcooling ΔT of 7 K. Three consecutive runs realized at 33°C in a 2 L vessel delivered almost identical results. The profiles of the optical rotation angle without an initial enantiomeric excess and the evolution of the mother liquor composition are shown in a quasi-binary phase diagram (Fig. 9, left and right). The evolution of the liquid phase

composition represents the crystallization pathway, starting without an initial enantiomeric excess (i. e. at racemic composition), moving along a straight line and achieving a maximum enantiomeric excess of the counter-enantiomer D-threonine at the turning point. Then the solution tends to reach the equilibrium state (i. e. again racemic composition) by degradation of the excess of the counter-enantiomer. Before the pathway changes its direction, only L-threonine is obtained in the solid phase whereas behind the turning point D-threonine simultaneously crystallizes. Details regarding the experiments are given in [33, 35].

A possible cyclic process regime capable to produce periodically the two enantiomers is suggested in literature [e. g. 17, 19]. An applicable configuration might consist of two crystallizers connected in series where the separation of each enantiomer is performed. In Fig. 10 on the example of threonine the process trajectory obtained for two subsequent separation cycles crystallizing alternating L-threonine and D-threonine is presented. After seeding the racemic solution with L-Thr crystals, the resolution process starts providing L-Thr as crystallizing solid. The crystallization process is interrupted at a predefined rotation angle (here corresponding to 2% enantiomeric excess of the counter-enantiomer D-Thr, upper dashed line) in order to avoid nucleation of the counter-enantiomer and thus, contamination of the L-Thr gained. After filtering the solution,
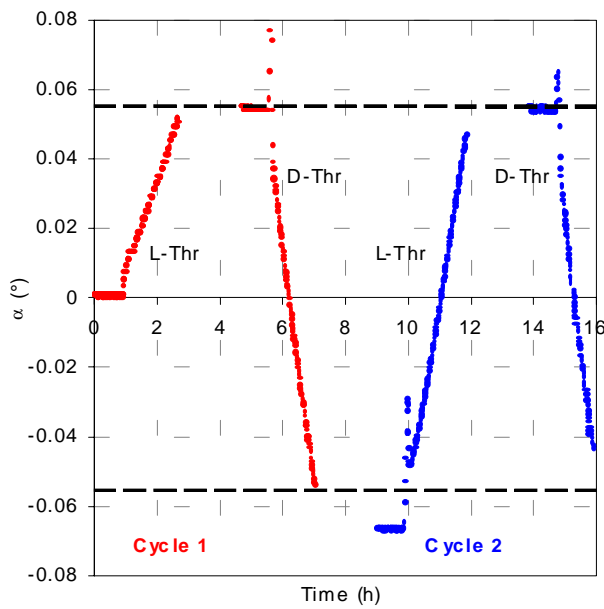
Fig. 10. Process trajectory for two subsequent separation cycles crystallizing alternating L-Thr and D-Thr [33, 35].

i. e. harvesting the solid pure enantiomer, fresh DL-Thr is fed to the mother liquor, dissolved and the D-Thr crystallization is started seeding with D-Thr crystals. The crystallization of D-Thr then is interrupted reaching again the predefined rotation angle (now 2% enantiomeric excess of L-Thr in the solution, lower dashed line), the solid D-Thr is harvested by filtration and the second cycle is started. It could be shown that online-monitoring the separation progress combining online-density with online-polarimetric measurements allows for control of the process in a "safe" and reliable manner. More detailed information also with regard to productivities obtained is given in [33, 35].

During the simple above mentioned cyclic crystallization process, the concentration of the desired enantiomer in the solution is decreasing, whereas the concentration of the counter-enantiomer remains constant (see Fig. 11, lower row). This phenomenon leads to an arrangement which might provide a better performance
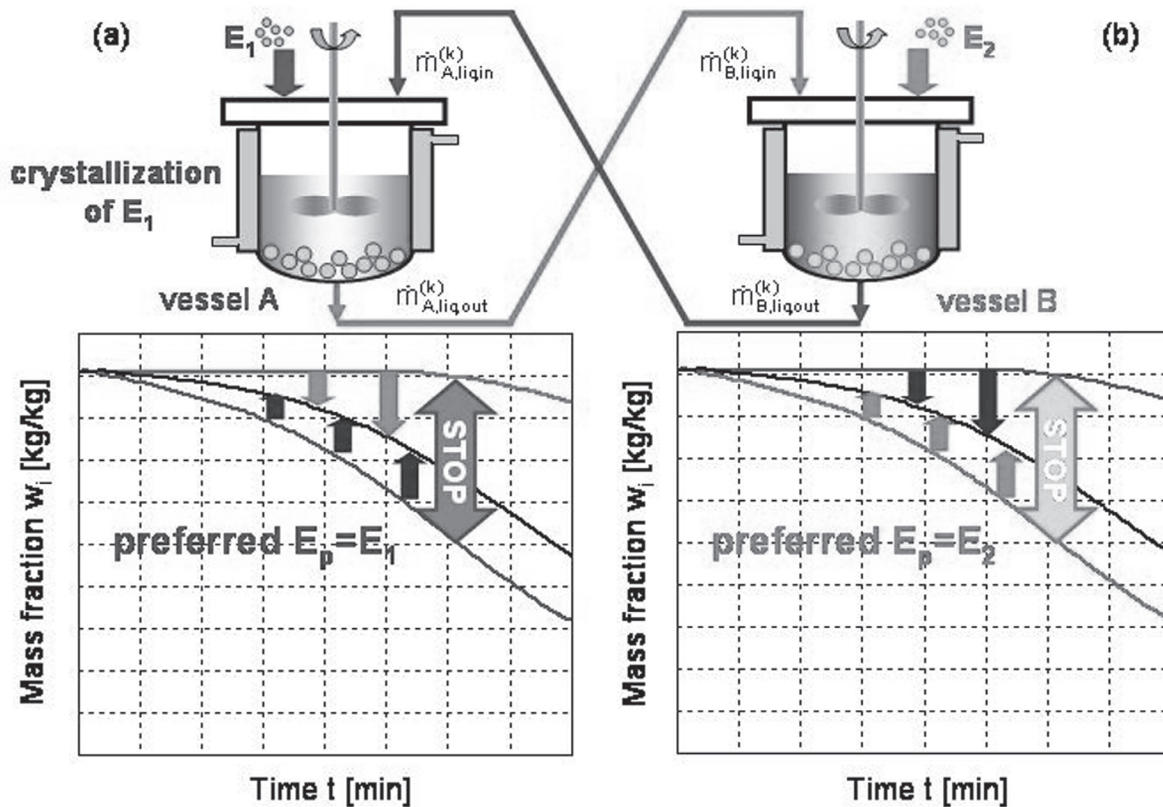

Fig. 11. Simultaneous preferential crystallization process: Concept of arrangement for two crystalli-zers coupled via liquid phase (upper row), concentration profiles (lower row).

where two crystallizers are coupled via the liquid phase, i. e., crystal-free mother liquor is exchanged between these two vessels [36, 37]. As result, the liquid phase shows a higher overall concentration of the preferred enantiomer in that vessel in which the preferred enantiomer was seeded. As it is shown in Fig. 11 (lower row), the supersaturation level which corresponds to the crystallization driving force is higher during the whole process compared to the case without an exchange (simple batch mode). Additionally, the concentration of the counter-enantiomer in the liquid phase for each of the vessels decreases. For the borderline case of infinite exchange flow rate racemic composition is reached in the fluid phase of both vessels. The described effect of decreasing the counter-enantiomer concentration in that crystallizer in which the preferred enantiomer shall be gained (i. e., vessel A in Fig. 11) reduces the probability for primary nucleation of the counter-enantiomer. This leads to a higher product purity at the end of the process and enhances also the productivity. More information, including an experimental validation is given elsewhere [38].

Preferential crystallization applied to racemic compound forming systems

As mentioned before, the majority of the chiral substances belong to the racemic compound forming type of systems. For these systems from thermodynamic point of view direct crystallization does not provide the pure enantiomers from racemic solutions. However, if a certain enantiomeric enrichment is achieved, providing a solution with a composition in one of the two 3-phase regions in the ternary phase diagram of the compound forming system (Fig. 3), the possibility to preferentially crystallize one of the enantiomers and/or the racemic compound is given. This idea bases on the fact that the stable solid phases in equilibrium are one of the enantiomers and the racemic compound. Thus, in a supersaturated solution, analogous to the conglomerate case (Fig. 8), after seeding selectively with enantiomer or racemate crystals the appropriate phase should preferentially crystallize for a certain time period. In a possible cyclic process (analogous to the conglomerate, Fig. 10) periodically one of the pure enantiomers and the racemic compound should be provided as seeds.

The feasibility of such a separation process was studied for the mandelic acid case where the enantio-
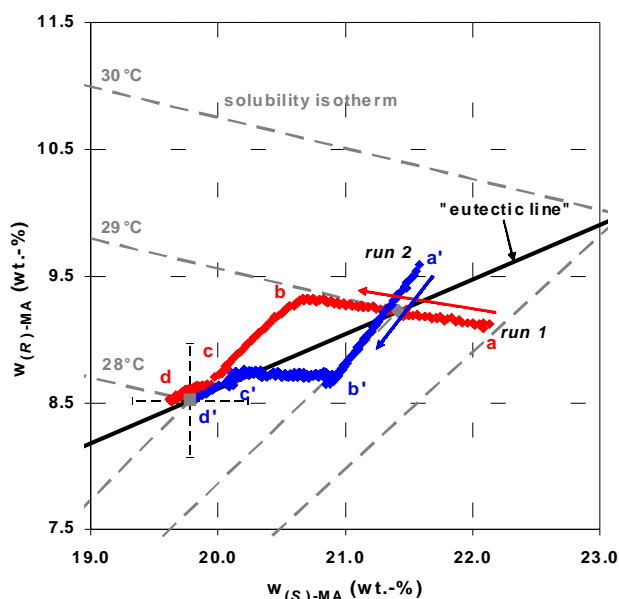

Fig. 12. Preferential crystallization in the mandelic acid system – proof of principle of a feasible separation (run 1: crystallization of (S)-mandelic acid, run 2: crystallization of the racemic compound) [39].

meric composition of the "eutectic line" was identified at x = 0.7, i. e. at an enantiomeric excess of ee = 40%. In Fig. 12 the results of two preferential crystallization experiments (run 1 and run 2) are presented as crystallization pathways in a quasi-binary phase diagram. In run 1, starting with an initial enantiomeric excess of the solution of $ee_0 = 41.5\%$ (S)-mandelic acid (point a), after seeding with (S)-mandelic acid (S)-mandelic acid crystallizes causing an exceeding of the "eutectic line" (a → b). Afterwards, the racemic compound (b → c) and a mixture of the racemic compound and (S)-mandelic acid (c → d) crystallize until the initial supersaturation is consumed and the remaining mother liquor has in equilibrium state eutectic composition. With run 2, where starting from a solution of an initial enantiomeric excess of $ee_0 = 38.5\%$ (point a') and seeding with racemic mandelic acid crystals racemic mandelic acid crystallized exceeding the "eutectic line" (a' → b'), the general feasibility of a (cyclic) preferential crystallization in a racemic compound forming system could be confirmed. More detailed results including the cyclic operation mode are published in [40]. Recently, the extension of the results to other pharmaceutical relevant systems ("Proof of Principle") could be demonstrated on the example of the propranolol hydrochloride enantiomers [39].

It should be mentioned again that, before an enantioselective crystallization of racemic compound

13

forming systems could be realized successfully, an enantiomeric enrichment step is needed. The possibility of using chromatography to achieve this goal and the combination of chromatography and crystallization for efficient separation of enantiomers are currently studied intensively [41-45].

Examples for improvement of productivity, process stability and product characteristics in preferential crystallization

In addition to novel crystallizer arrangements mentioned before, the influence of different process parameters like seed characteristics, initial enantiomeric excess and supersaturation, crystallization temperature and cooling profile in a polythermal process, were studied in order to optimize the crystallization outcome with regard to productivity, process stability and product properties.

In Fig. 13 are shown exemplarily the results of isothermal preferential crystallization experiments of threonine varying the seed size and applying glutamic acid (Glu) as a tailor-made stereoselective additive. L-Glu is known to selectively inhibit nucleation and growth processes of only the L-enantiomer of threonine ("Rule of Reversal") [46]. Shown are the profiles of the rotation angle as function of the time for four groups of measurements [47]. The seeds used were produced separately by growth from a supersaturated solution containing only a pure threonine enantiomer. "Not ground" seeds were taken as obtained after filtering and drying, "ground" seeds were ground before using.
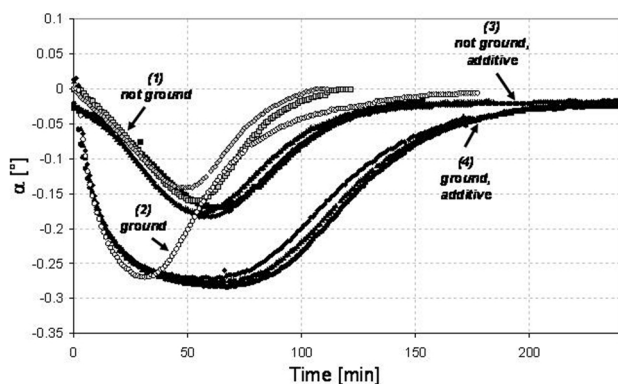

Fig. 13. Process trajectories as result of different seed characteristics (ground and not ground) and the application of a tailor-made additive to improve productivity, process stability and product characteristics in preferential crystallization of threonine [47].

Comparing the process trajectories for the experiments without additive (groups 1 and 2, Fig. 13), it can be easily seen that for the ground seeds due to the higher crystal surface offered the initial crystallization rate is much higher than for the coarser seeds (the slope of the curve is significantly steeper); further, the yield of the crystallized enantiomer is higher than for the coarse seeds. This enhanced entrainment effect is indicated by the lower level of the rotation angle obtained before crystallization of the counter-enantiomer. The same trend applies to the experiments in presence of the additive (experiment groups 3 and 4, Fig. 13). Grinding of the seed material also leads to an advantageous change in the product particle shape; the length/diameter ratio of the needle shaped crystals decreases significantly.

The application of the additive results in somewhat higher yields (comparison of experiments 1 with 3 and 2 with 4, respectively). In case of the ground seeds (experiments 4), a plateau phase of stagnating rotation angle is observed before nucleation of the undesired enantiomer occurs. Thus, a certain "safety region" is established where the kinetically driven preferential crystallization process might be performed in a more reliable manner. The growth kinetics of the crystallizing D-Thr and its purity are not influenced by the presence of the additive.

With regard to the case study and the process parameters discussed, finely ground seeds and the use of a stereoselective additive favor productivity, process stability and product characteristics. More details quantifying the described affects are published in [48].

CONCLUSIONS

Performing enantioselective crystallization processes requires a detailed knowledge regarding the underlying solid-liquid equilibria. If this information is available various process concepts can be realized. The specific features of an optimal process will depend strongly on the type of the phase diagram characteristic for the system under consideration. A detailed understanding of the phenomena related to nucleation and growth is complex. This still hinders the utilization of advanced concepts for modeling enantioselective crystallization processes [49, 50] which are more widely applied to describe the crystallization of single inorganic molecules. The development and application of reliable online ana-

lytical techniques is the precondition essential to allow for monitoring the separation progress directly and thus, to facilitate process optimization and control.

REFERENCES

1. E.L. Eliel, S. Wilen, M. Doyle, Basic organic stereochemistry, Wiley-Interscience, New York, 2001.
2. S.C. Stinson, Chiral pharmaceuticals, Chem. & Eng. News, 79, 2001, 56-61.
3. A.M. Rouhi, Chiral business, Chem. & Eng. News, 81, 2003, 45-55.
4. J. Blumenstein, Chiral drugs: regulatory aspects, in: J. Crosby, Introduction, in: A. Collins, G. Sheldrake, J. Crosby (Eds.), Chirality in industry II. Developments in the manufacture and applications of optically active compounds, John Wiley & Sons, Chichester, 1997, 11-18.
5. J. Crosby, Chirality in industry: An overview, in: A. Collins, G. Sheldrake, J. Crosby (Eds.), Chirality in industry. The commercial manufacture and applications of optically active compounds, John Wiley & Sons, Chichester, 1992, 1-66.
6. J. Crosby, Introduction, in: A. Collins, G. Sheldrake, J. Crosby (Eds.), Chirality in industry II. Developments in the manufacture and applications of optically active compounds, John Wiley & Sons, Chichester, 1997, 1-10.
7. A. Collins, G. Sheldrake, J. Crosby (Eds.), Chirality in industry. The commercial manufacture and applications of optically active compounds, John Wiley & Sons, Chichester, 1992.
8. A. Collins, G. Sheldrake, J. Crosby (Eds.), Chirality in industry II. Developments in the manufacture and applications of optically active compounds, John Wiley & Sons, Chichester, 1997.
9. G. Subramanian (Ed.), A practical approach to chiral separations by liquid chromatography, VCH, Weinheim, 1994.
10. G. Subramanian (Ed.), Chiral separation techniques - a practical approach, Wiley-VCH, Weinheim, 2000.
11. N.M. Maier, P. Franco, W. Lindner, Separation of enantiomers: needs, challenges, perspectives, J. Chromat. A., 906, 2001, 3-33
12. E. Francotte, Enantioselective chromatography as a powerful alternative for the preparation of drug enantiomers, J. Chromat. A., 906, 2001, 379-397.
13. M. Schulte, J. Strube, Preparative enantioseparation by simulated moving bed chromatography, J. Chromat. A., 906, 2001, 399-416.
14. M. Juza, M. Mazzotti, M. Morbidelli, Simulated moving-bed chromatography and its application to chirotechnology, Trends in Biotechnology, 18, 2000, 108-118.
15. L. Pasteur, Recherches sur les relation qui peuvent exister entre la forme crystalline et la composition chimique, et le sens de la polarisation rotatoire, Annales de Chimie et de Physique, 3, 1848, 442-459.
16. H.W.B. Roozeboom, Löslichkeit und Schmelzpunkt als Kriterien für racemische Verbindungen, pseudoracemische Mischkristalle und inaktive Konglomerate, Z. Phys. Chem. 28, 1899, 494.
17. J. Jacques, A. Collet, S.H. Wilen, Enantiomers, Racemates and Resolutions, Krieger, Malabar, 1994.
18. W.M.L. Wood, Crystal science techniques in the manufacture of chiral compounds, in: A. Collins, G. Sheldrake, J. Crosby (Eds.), Chirality in industry II. Developments in the manufacture and applications of optically active compounds, John Wiley & Sons, Chichester, 1997, 119-156.
19. A. Collet, Separation and purification of enantiomers by crystallization methods, Enantiomer, **4**, 1999, 157-172.
20. G. Coquerel, Review on the heterogeneous equilibira between condensed phases in binary systems of enantiomers, Enantiomer, **5**, 2000, 481-498.
21. H. Lorenz, A. Seidel-Morgenstern, Binary and ternary phase diagrams of two enantiomers in solvent systems, Thermochimica Acta, **382**, 2002, 129-142.
22. H. Kämmerer, H. Lorenz, A. Seidel-Morgenstern, Study of solubility equilibria in the chiral malic acid system, Proceedings 13th Int. Workshop on Industrial Crystallization (BIWIC 2006), Delft, 13.-15.09. 2006, P35, 1-2.
23. H. Lorenz, D. Sapoundjiev, A. Seidel-Morgenstern, Enantiomeric mandelic acid system - melting point phase diagram and solubility in water, Journal of Chemical and Engineering Data, 47, 2002, 1280–1284.
24. H. Lorenz, A. Seidel-Morgenstern, A contribution to the mandelic acid phase diagram, Thermochimica Acta, **415**, 2004, 55-61.
25. M. Matsuoka, H. Hasegawa, H.Ohori, Purity decrease of L-threonine crystals in optical resolution by batch preferential crystallization, ACS symposium series, **438**, 1990, 251-260.

26. H. Lorenz, D. Sapoundjiev, A. Seidel-Morgenstern, Solubility equilibria in chiral systems and their importance for enantioseparation, Eng. Life Sci., **3**, 2003, 132-136.

27. A. Mersmann, Crystallization technology handbook, Marcel Dekker, New York, 2001.

28. A. Perlberg, Ph.D. thesis, Otto-von-Guericke-Universität Magdeburg, Magdeburg 2006.

29. A. Perlberg, H. Lorenz, A. Seidel-Morgenstern, Crystal growth kinetics via isothermal seeded batch crystallization: evaluation of measurement techniques and application to mandelic acid in water, Ind. Eng. Chem. Res. **44**, 2005, 1012-1020.

30. J. Nyvlt, O. Söhnel, M. Matchova, M. Broul, The kinetics of industrial crystallizations, Elsevier, Amsterdam, 1985.

31. Mullin, Crystallization, Butterworth-Heinemann, Oxford, 2001.

32. A. S. Myerson (Ed.), Handbook of industrial crystallization, Butterworth-Heinemann, Oxford, 2002.

33. A. R. Alvarez, H. Lorenz, A. Seidel-Morgenstern, Online Monitoring of Preferential Crystallization of Enantiomers, Chirality, **16**, 2004, 499-508.

34. V.M. Profir, M. Matsuoka, Processes and phenomena of purity decrease during optical resolution of DL-threonine by preferential crystallization, Colloids and Surfaces A: Physicochemical and Engineering Aspects, **164**, 2000, 315-324.

35. M. P. Elsner, D. Fernández Menéndez, E. Alonso Muslera, A. Seidel-Morgenstern, Experimental study and simplified mathematical description of preferential crystallization, Chirality, **17**, 2005, 183-195.

36. M. P. Elsner, G. Ziomek, A. Seidel-Morgenstern, Investigation of simultaneous preferential crystallization for enantioseparation. Lecture # 13d, Annual Meeting of the American Institute of Chemical Engineers (AIChE), 12th-17th November 2005, San Francisco.

37. D. Polenske, M.P.Elsner, H. Lorenz, A. Seidel-Morgenstern, Alternative Einsatzmöglichkeiten der „Bevorzugten Kristallisation" zur Enantiomerentrennung, Chemie Ingenieur Technik, **78**, 2006, 1101-1110.

38. M.P. Elsner, G. Ziomek, A. Seidel-Morgenstern, Feasibility of simultaneous preferential crystallization, submitted to AIChE Journal.

39. H. Lorenz, D. Polenske, A. Seidel-Morgenstern, Application of preferential crystallization to resolve racemic compounds in a hybrid process, Chirality, **18**, 2006, 828-840.

40. D. Polenske, H. Lorenz, A. Seidel-Morgenstern, Separation of the propranolol hydrochloride enantiomers by preferential crystallization – thermodynamic basis and experimental verification, submitted to Crystal Growth & Design.

41. B.-G.Lim, C.-B. Ching, R. B. H. Tan, S.-C. Ng, Recovery of (-)-praziquantel from racemic mixtures by continuous chromatography and crystallization, Chem. Eng. Sci., **50**, 1995, 2289-2298.

42. H. Lorenz, P. Sheehan, A. Seidel-Morgenstern, Coupling of simulated moving bed chromatography and fractional crystallization for efficient enantioseparation, J. Chromat. A, **908**, 2001, 201-214.

43. K.Y. Fung, K.M. Ng, C. Wibowo: Synthesis of chromatography-crystallization hybrid separation processes, Ind. Eng. Chem. Res., **44**, 2005, 910-921.

44. M. Kaspereit, K. Gedicke, V. Zahn, A.W. Mahoney, A. Seidel-Morgenstern: Shortcut method for evaluation and design of a hybrid process for enantioseparations, J. Chromat. A, **1092**, 2005, 43-54.

45. K. Gedicke, W. Beckmann, A. Brandt, D. Sapoundjiev, H. Lorenz, U. Budde, A. Seidel-Morgenstern: Coupling chromatography and crystallization for efficient separations of isomers, Adsorption, **11**, 2005, 591-596.

46. L. Addadi, S. Weinstein, E. Gati, I. Weissbuch, M. Lahav, Resolution of conglomerates with the assistance of tailor-made impurities. Generality and mechanistic aspects of the "rule of reversal". A new method for assignment of absolute configuration, J. Am. Chem. Soc., **104**, 1982, 4610-4617.

47. F. Czapla, H. Lorenz, M.P.Elsner, A. Seidel-Morgenstern, Einfluss unterschiedlicher Prozessführungsstrategien auf die Produktivität und Produkteigenschaften bei der „Bevorzugten Kristallisation". In U.Teipel, (Hrsg.): Produktgestaltung in der Partikeltechnologie, Band 3, Fraunhofer-IRB-Verlag, Stuttgart, 2006, 219-235.

48. F. Czapla, H. Lorenz, M.P. Elsner, A. Seidel-Morgenstern, Model based experimental analysis for crystallization of DL-threonine in the presence of a chiral additive. Proceedings 13th Int. Workshop on Industrial Crystallization (BIWIC 2006), Delft, 2006, 98-104.

49. A.D. Randolph, M.A. Larson, Theory of particulate processes: Analysis and techniques of continuous crystallization, Academic Press, 1988.

50. D. Ramkrishna, Population Balances: Theory and applications to particulate systems in engineering, Academic Press, 2000.