AIChE

Efficient Separation of Enantiomers by Preferential Crystallization in Two Coupled Vessels

Martin Peter Elsner and Grzegorz Ziomek
Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstr. 1, 39106 Magdeburg, Germany

Andreas Seidel-Morgenstern
Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstr. 1, 39106 Magdeburg, Germany, and
Chair for Chemical Process Engineering, Otto von Guericke University, Universitätsplatz 2, 39106 Magdeburg, Germany

DOI 10.1002/aic.11719
Published online February 4, 2009 in Wiley InterScience (www.interscience.wiley.com).

The focus of this work is to study the enantioseparation of conglomerate forming systems using an innovative configuration for preferential crystallization. Two batch crystallizers are coupled by an exchange of their liquid phases. In each vessel one of the two enantiomers is seeded initially and crystallizes subsequently. Compared with conventional single batch crystallization the exchange of the crystal free liquid phases between two crystallizers leads to an increase of the concentrations of the preferred enantiomers and therefore to an increase of the driving forces for the crystallization. This enhances the productivity of the process compared with the conventional operation. © 2009 American Institute of Chemical Engineers *AIChE J,* 55: 640–649, 2009
Keywords: enantioseparation, crystallizer configurations, productivity, conglomerates, compound forming systems, threonine, mandelic acid

Introduction

The geometric property that is responsible for the nonidentity of an object with its mirror image is called chirality. In the context of chemistry, chirality usually refers to molecules. A chiral molecule may exist in two stereoisomeric forms which are nonsuperimposable mirror images of each other—the so-called enantiomers. Such enantiomers have, when present in a symmetric environment, identical chemical and physical properties except for their ability to rotate plane-polarized light in opposite directions. A mixture of equimolecular parts of an optically active isomer and its counter enantiomer is called racemate which is usually produced in a conventional, nonenantioselective reaction.

An increasing number of drug molecules is chiral and the single enantiomers of such drug molecules may have different effects on biological entities. There are cases in which the inactive enantiomer may be harmful and has to be removed on the API-level*. Biologically active enantiomers are also called eutomers, whereas those inactive ones are denominated as distomers. There is a growing need in pure enantiomers in pharmaceutical, agrochemical, food and allied industries as well as in cosmetic and fragrance industries. In principle the manufacturing of a chiral compound in an enantiopure form can be realized by the following three different methods[1–3]: (a) exploitation reactants from the chiral pool, (b) enantioselective chemical synthesis, (c) resolution of racemates. The exploitation of the chiral pool, which means the use of chiral substances available in nature, is limited to some compounds. Because the requirements in special catalysts and conditions necessary (usually a larger number of reaction steps) application of enantioselective chemical synthesis is still restricted in an industrial scale. The resolution of racemic (50:50) mixtures into its enantiomers is widely applicable and can be cheaper than a selective synthesis.

Correspondence concerning this article should be addressed to M.P. Elsner at mpelsner@mpi-magdeburg.mpg.de.

*API = active pharmaceutical ingredient.

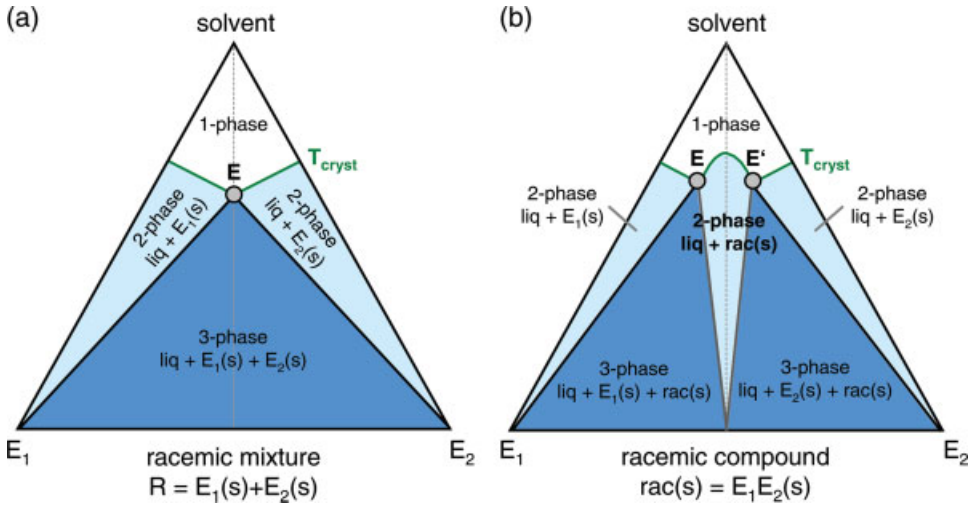

Figure 1. Ternary phase diagrams for (a) conglomerates, and (b) compound forming systems.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

However, because enantiomers behave identically in conventional physical separation processes, special efforts have to be made to isolate optically pure components. There are various methods for the resolution of racemates available like classical diastereoisomeric crystallization,[4] chiral chromatography,[5] chiral membrane technologies[6] or kinetic resolution using enzymes.[7] In the present paper the so-called preferential crystallization for the direct separation of enantiomers[8] will be considered and an efficient improvement using two coupled crystallizers will be presented.

Roozeboom characterized three fundamental types of enantiomeric mixtures by their melting point diagrams[9]: (1) ***conglomerates*** with a higher affinity to the same enantiomer, which are just a mechanical mixture of pure crystals of each enantiomer, (2) ***racemic compounds*** with a higher affinity to the opposite enantiomer and with an ordered 1:1 ratio within the elementary cell, and (3) ***solid solutions*** in which the molecules of the two enantiomers coexist completely randomly distributed within the crystal lattice. These different categories of enantiomer mixtures can be also identified in the solubility diagrams characterizing the ternary system consisting of the two enantiomers E_1, E_2, and a solvent. In the following contribution we will just focus on the first two types of enantiomeric mixtures which represent the majority of all chiral organic compounds (conglomerates: approximately 5–10%, racemic compound: approximately 90–95%[10]). The ternary phase diagrams of these two types are illustrated in Figure 1. For a nonsolvated conglomerate the solubility diagram at a given temperature T_{cryst} is illustrated in Figure 1a. The corresponding phase diagram shows one eutectic point E at racemic composition. The two branches of the solubility curve separate the domain of the unsaturated solution (one-phase region) from the regions where one or two solid phases coexist with the saturated solution. In comparison to conglomerate systems, the ternary phase diagram of a compound forming system (Figure 1b) reveals an additional two-phase region in the center of the diagram with the racemic compound as stable solid phase. Therefore, two eutectic points E and E′ exist. Although the racemic compound forming systems represent the majority of all chiral compounds, conglomerates are interesting, because they offer a cheap and simple way for direct separation by preferential crystallization which is the topic of the following section.

Preferential crystallization

Single Batch Operation. Conventional batchwise preferential crystallization is applicable for systems which crystallize as conglomerates.[10] The principle of a preferential crystallization process for conglomerates can be illustrated in a ternary phase diagram (Figure 2a). Starting from a saturated solution at a temperature $T_{cryst}+\Delta T$, the solution becomes supersaturated if the system is rapidly cooled down to the crystallization temperature T_{cryst}. Within the so-called metastable zone ($\Delta T < \Delta T_{max}$), i.e., in a thermodynamically unstable state which is kinetically inhibited, the liquid phase will remain free of particles for a certain period until nucleation will occur. In Figure 2a, point **A** represents an initial (50:50) mixture of the two enantiomers E_1 and E_2 and the solvent where the solution is supersaturated at the crystallization temperature T_{cryst}. In case that at point **A** the same amounts of seed crystals of both enantiomers E_1 and E_2 are introduced into the crystallizer, the two crystal types will start to grow simultaneously (and may also induce secondary nucleation depending on the nature of the compound and on the experimental conditions). The composition of the mother liquor is then displaced along a straight line directed to point **E** which is the equilibrium point for the temperature T_{cryst}. Otherwise, if at point **A** homochiral seeds (e.g., of type E_1) are introduced into the crystallizer, the liquid phase composition tends initially towards point **Z**. After a certain time (corresponding to the induction time of primary heterogeneous nucleation), spontaneous crystallization of the unseeded enantiomer (here E_2) is observed, and therefore the trajectory is attracted again towards the common equilibrium point **E**[17]. The best resolution conditions will be attained if the trajectory remains as close as possible to Z. This means that the difference in the overall crystallization rates between the two

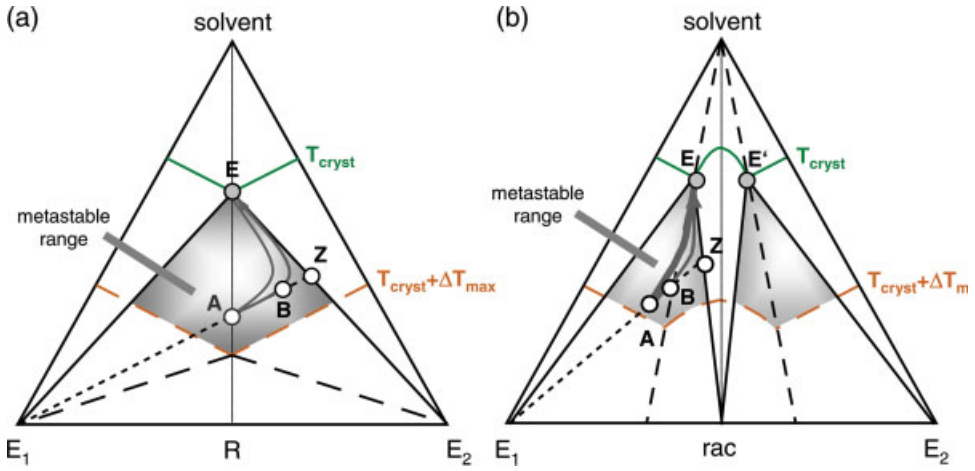

Figure 2. Illustration of the principle of preferential crystallization performed in the three-phase region for (a) conglomerates, and (b) compound forming systems.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

enantiomers is maximal during the whole process. For this reason the crystallization conditions have to be designed carefully and the process must be stopped before significant nucleation of the unseeded (counter) enantiomer occurs, (for example at point **B**). More detailed information about the process of preferential crystallization for conglomerates (or crystallization by entrainment) can be found in Ref. 10 to 21.

Recently, it has been shown that the principle of preferential crystallization can be also extended to compound forming systems in a simple batchwise mode. After generating an enantiomeric excess for example by a partially selective synthesis or by a chromatographic and a following evaporation step, the state **A** in Figure 2b located within the three-phase region can be reached.[22,23] As it is also depicted in Figure 2b seeding with crystals of the enantiomer E_1 initializes the crystallization of merely this enantiomer and the mother liquor composition tends towards point **Z**. Up to a certain time pure E_1 can be gained until the spontaneous nucleation of the racemic compound (rac) will occur and the trajectory will be attracted to the eutectic point **E**. The same considerations are valid for the crystallization of E_2 in the right-hand side three-phase region after seeding the enantiomerically enriched solution with E_2. More details about the batchwise and cyclic preferential crystallization of compound forming systems in a single vessel were presented recently.[22,23]

Coupled Batchwise Preferential Crystallization. The degree of supersaturation is the driving force for crystallization. Considering the described simple batch preferential crystallization, the concentration of the desired enantiomer in the solution is typically decreasing during the process, whereas during successful operation the liquid phase concentration of the counter enantiomer remains constant. Consequently, the driving force for the crystallization of the seeded, target enantiomer decreases with progress of the simple batch process (compare the trajectories of the liquid phase in Figure 4a for two decoupled vessels where in each vessel one enantiomer can be produced preferentially up to a specific turning point). As an alternative the possibility of simultaneous crystallization of both enantiomers in two separated vessels with an exchange of crystal-free mother liquor is depicted in Figure 3. It should be mentioned that a similar concept focusing on a connection of crystallizers can be found in Matsuoka.[14] Up to now no experimental validation was reported.

Because the two crystallizers are coupled via the liquid phase, higher values of the supersaturation of the specific preferred enantiomers can be achieved in each of the two

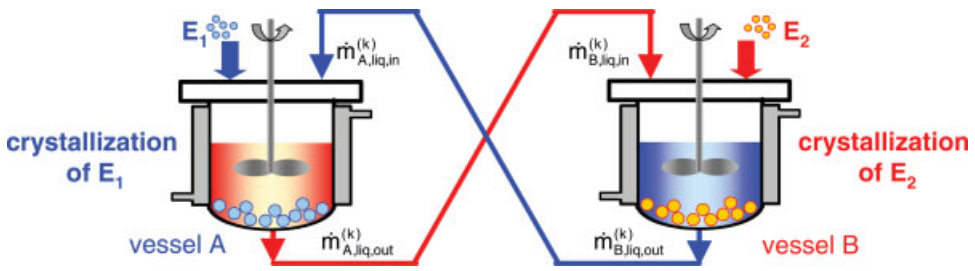

Figure 3. Simultaneous preferential crystallization process.

Concept of arrangement for two crystallizers coupled via the liquid phase where both enantiomers E_1 and E_2 have been seeded. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

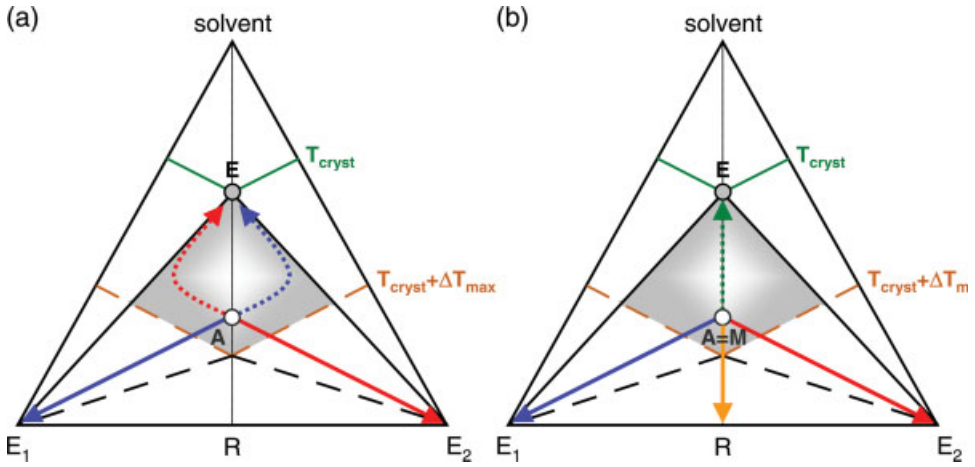

Figure 4. Trajectories during preferential crystallization performed for conglomerates (a) in two decoupled vessels and (b) in two vessels coupled via the liquid phase.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

vessels, whereas the supersaturation of the specific counter enantiomers is lowered in each vessel so that the probability of (primary) nucleation of the unwanted enantiomers is decreased or may be even suppressed completely. Obviously, this approach allows increasing the process productivity. Theoretical trajectories in the phase diagram for this coupled mode are shown in Figure 4b where for the most beneficial case, i.e., infinitely high exchange rate, the composition in the liquid phase is racemic during the whole process. The effect of mimicking a "racemization" by exchanging the fluid phases allows favorable manipulation of the concentration profiles and seems to be a suitable approach to enhance the process performance in case of conglomerates. A theoretical analysis of the influence of the most essential parameters like exchange flow rates, process duration time, initial enantiomeric excess switching time, etc. on the productivity of the described mode of the preferential crystallization has been recently published.[24]

Unfortunately, with respect to the above considerations an analogous exchange of crystal-free mother liquors should have a destructive effect in case of compound forming systems. In Figure 5a, the trajectories (compare Figure 2b) are depicted for two decoupled vessels starting in the three-phase regions from points A and A′, respectively. The supersaturated solution A in the first vessel was seeded with homochiral crystals of enantiomer E_1, whereas A′ in the second vessel was seeded with homochiral crystals of enantiomer E_2. An exchange of the mother liquors should also lead to a racemic composition in the liquid phase. For compound forming systems this state is already in the two-phase region where in equilibrium just liquid phase with racemic composition and the racemic compound (rac) coexist. Thus the initial seed crystals of each enantiomer in each vessel should dissolve as they are not stable and primary nucleation of the racemic compound (rac) should occur. This means a preferential crystallization of the pure enantiomers is not possible.

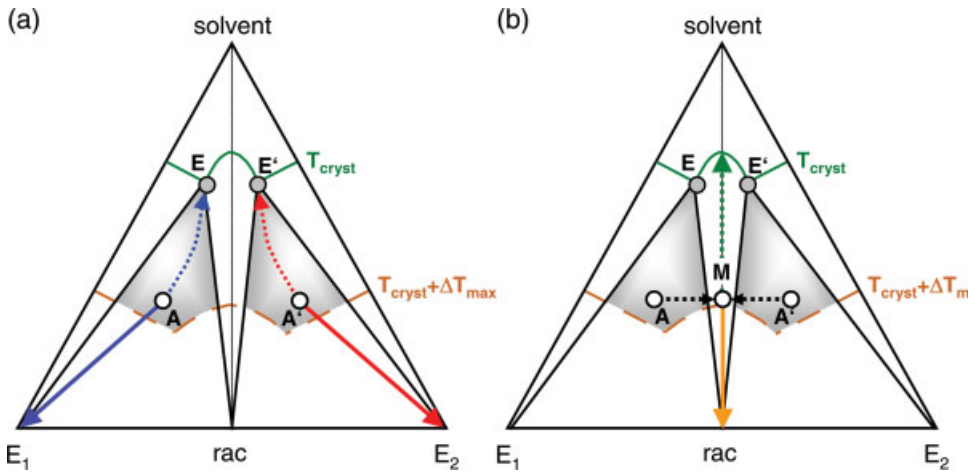

Figure 5. Trajectories during preferential crystallization performed for compound forming systems (a) in two decoupled vessels and (b) in two vessels coupled via the liquid phase.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

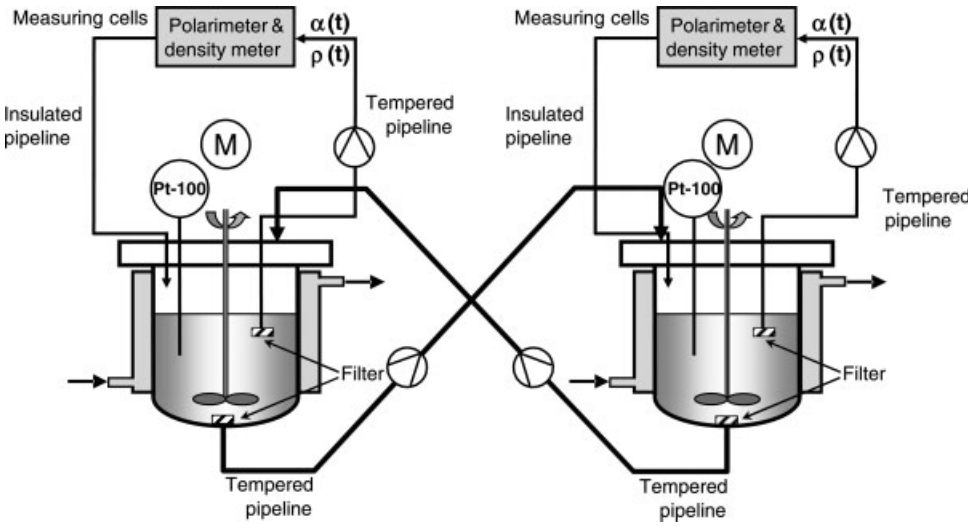

Figure 6. Schematic illustration of the experimental set-up.

Such process is only interesting for academic studies and will not have economic potential.

Experiments

Materials

For the experimental validation of the preferential crystallization process performed in two coupled vessels, DL-threonine (Merck, DL-threonine: purity $>$ 98%) dissolved in water has been used. This system is known to belong to the class of conglomerates.[19] In an additional experiment RS-mandelic acid (Aldrich, RS-mandelic acid: purity $>$ 98%) was used as a compound forming system to confirm the hypothesis of unfeasibility mentioned above.

Experimental set-up and procedure

Simple batches and coupled experiments have been performed in vessels of 450 ml volume. The temperature was controlled by Pt-100 resistance thermometers (resolution 0.1 K). An exchange of crystal-free solution between the tanks was performed using circulation pumps (Heidolph PD 5201, SP Quick 1.6). The liquid phase was separated from the solid phase by sintered glass filters (Dionex GmbH, external diameter: 9.8 mm, pore width: 0.45 μm) introduced into the exchanging pipes. All pipes used for exchanging the liquid phase were thermostated at solubility temperature. The exchanging flow rate has been set as high as possible according to theoretical results obtained by ELSNER et al.[24] Additionally, the process was controlled by online measurements of the optical rotation angle and the density using polarimeters (POLARmonitor, IBZ Messtechnik, Hanover, cell length: 5 cm) and density meters (Mettler Toledo DE40). A schematic representation of the experimental set-up is shown in Figure 6.

Experimental conditions of the runs for the conglomerate forming system are summarized in Table 1. The solution used for the crystallization experiment was prepared based on the solubility data of DL-threonine.[25] To guarantee complete dissolution of the all particles, the tanks were heated up to 50°C and maintained for about 1 h at this temperature. After that the solution was cooled down to saturation temperature $T_{sat} = 40$°C and subsequently sub-cooled up to the crystallization temperature with a constant cooling rate (14°C/h). The chosen constant crystallization temperature $T_{cryst} = 33$°C guarantees that the supersaturated solution remains in the metastable zone quantified already in Elsner et al.[17] At this temperature homochiral crystals (sieve fraction: 150–200 μm, purity: $\geq$ 98%) were added to the solution to initiate the preferential crystallization. After the time t_{end}, the process was stopped and the solution was filtrated and the solid phase has been washed with 10 ml of ice cold water and 10 ml of ice cold ethanol.

The experimental procedure for mandelic acid has been chosen according to Lorenz et al.[23] The solution used for the crystallization experiment was prepared according to the solubility data of RS-mandelic acid at 40°C.[25] Initial masses of substance and water and experimental conditions were summarized in Table 2. A sieve fraction of 212–300 μm was used for the seeding procedure. To measure the optical rotation angle a shorter cell (2.5 cm length) has been used for mandelic acid which reveals a higher specific optical rotation angle than threonine.[23]

Process quantification

For a quantification of the preferential crystallization process and a comparison of different crystallizer configurations,

Table 1. Experimental Conditions for the Crystallization Experiments with the Conglomerate Forming System. Solubility Data Based on 27

	Tank 1	Tank 2	Unit
Mass of water	383.7	383.7	g
Mass of DL-threonine	96.3	96.3	g
Saturation temperature	40	40	°C
Crystallization temperature	33	33	°C
Mass of seeds	1.0	1.0	g

Table 2. Experimental Conditions for an Additional Crystallization Experiment (Coupled Mode) with the Compound Forming Systems. Solubility Data Based on 27

	Tank 1	Tank 2	Unit
Mass of water	307.8	307.8	g
Mass of RS-mandelic acid	83.19	83.19	g
Mass of R-mandelic acid	59.01	–	g
Mass of S-mandelic acid	–	59.01	g
Saturation temperature	40	40	°C
Crystallization temperature	28	28	°C
Mass of seeds	1.125	1.125	g

a productivity Pr was applied. Based on Elsner et al.[17] following definition was used:

$$\mathrm{Pr}_{\mathrm{m}}^{(\mathrm{p})}(t_{\mathrm{end}}) = \frac{m_{\mathrm{s,end}}^{(\mathrm{p})} - m_{\mathrm{seeds}}^{(\mathrm{p})}}{(t_{\mathrm{end}} + t_{\mathrm{dead}}) \cdot 0.5 \cdot m_{\mathrm{rac}}}, \quad (1)$$

where p corresponds to the preferred enantiomer and c to the *c*ounter enantiomer. Equation 1 signifies the mass of product $m_{\mathrm{s,end}}^{(\mathrm{p})}$ gained without the mass of the enantiomer introduced at the beginning as seeds $m_{\mathrm{seeds}}^{(\mathrm{p})}$ per time unit and mass of used enantiomer (factor 0.5 in denominator is used to recalculate the mass of the enantiomer from the mass of racemate m_{rac} as no initial enantiomeric excess has been used in these experiments). In the calculations performed the dead time t_{dead} has been set as 200 minutes because of the time needed for dissolution, subcooling, and cleaning of crystallizers after experiments.

As an additional performance criterion for a comparison of the crystallizer configurations studied in this work, the purity of the solid phase has been used. The crystal purity for each enantiomer is defined as follows:

$$\mathrm{Pu}^{(\mathrm{p})} = \frac{m_{\mathrm{end}}^{(\mathrm{p})}}{m_{\mathrm{end}}^{(\mathrm{p})} + m_{\mathrm{end}}^{(\mathrm{c})}}. \quad (2)$$

The purity has been determined experimentally by HPLC analysis of the dissolved solid products.

Results and Discussion

Single vessel experiment for the conglomerate forming system

To evaluate and understand preferential crystallization of D- and L-threonine first of all conventional simple batch experiments have been performed. L-threonine has been chosen as the preferred enantiomer for the investigation (it is less expensive and better commercially available). The mass fraction profiles of both enantiomers for the simple batch process are presented in Figure 7. It is shown that after seeding with L-threonine crystals, for a certain time period just this enantiomer is crystallizing. Profiles depicted in Figure 7 shows that the mass fraction of L-threonine in the liquid phase decreases whereas the mass fraction of D-threonine increases in the initial period of the process. After approximately 300 minutes (primary) nucleation of the D-threonine occurs and its significant crystallization can be observed. At this time in principle the process has to be interrupted to obtain pure enantiomer in the solid phase. However, as it is depicted in Figure 7 the experimental run has been performed further until equilibrium between solid and liquid phase has been reached ($t_{\mathrm{end}} = 720$ minutes). After this time the obtained solid phase was found to have the expected equilibrium composition. To gain pure enantiomer a repetition of the same experiment has been performed, where crystallization of L-threonine was performed just for 300 minutes and the process was stopped before nucleation of the counter enantiomer occurred. In Table 3 the results of this experiment are summarized. It is worth to note that an exact time of the primary nucleation of the unseeded enantiomer for the simple batch preferential crystallization is difficult to predict therefore the product purity might change slightly from batch to batch. It was possible to obtain 3.16 g of L-threonine (excluding mass of seeds), with a productivity of 1.31×10^{-4} g/(g min). These results obtained in single batch operation serve subsequently for a comparison with the results obtained using two crystallizers coupled via the liquid phase.

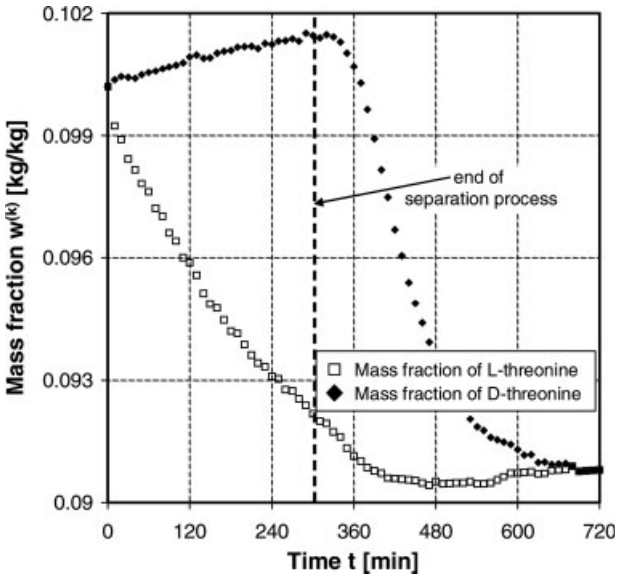

Figure 7. Mass fraction profiles for an isothermal simple batch experiment after seeding with L-threonine crystals.

Process parameters: $t_{\mathrm{end}} = 720$ min, $m_{\mathrm{seeds}} = 1.0$ g, $T_{\mathrm{cryst}} = 33$°C. Up to approximately 300 minutes just the seeded enantiomer, i.e., L-threonine, is crystallizing which is confirmed by HPLC analysis of the gained solid phase.

Coupled crystallizer mode for conglomerate forming systems (isothermal)

The concept for the coupled batch mode is based on the exchange of the crystal-free mother liquors between the crys-

Table 3. Experimentally Determined Productivity and Purity for the Resolution of DL-Threonine in a Simple Batch Operation Mode

Parameter	Used Symbol	Value	Unit
Mass of L-threonine	m_{L}	3.16	G
Productivity	Pr	1.31×10^{-4}	g/(g min)
Purity	Pu	0.96	–
Duration time	t_{end}	300	min

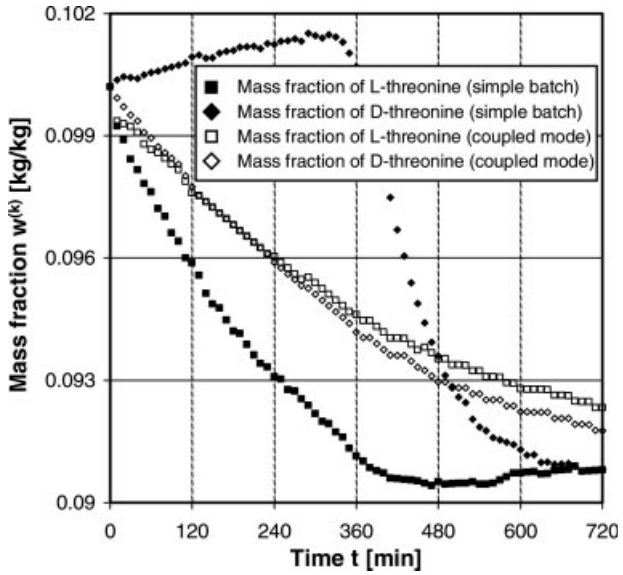

Figure 8. Comparison of mass fraction profiles for simple batch and for coupled batch mode experiments (both isothermal) after seeding with L-threonine crystals in tank 1.

Process parameters: $t_{end} = 720$ minutes, $m_{seeds} = 1.0$ g, $T_{cryst} = 33°C$.

tallizers where in each of the vessels one of the enantiomers is seeded. Figure 8 shows a comparison between the experimental mass fraction profiles for the simple batch and the coupled batch modes under identical isothermal experimental condition. The figure reveals that the exchange of the liquid phase indeed lead to an increase of the concentration of the seeded enantiomer (L-threonine) and at the same time to a decrease of the concentration of the counter enantiomer (D-threonine) in the tank where L-threonine was seeded before. It can be seen that the liquid phase has nearly racemic composition during the whole process. A higher concentration in the liquid phase of the preferred enantiomer corresponds to a higher supersaturation level. Because the supersaturation level is the driving force for the crystallization process, for the same duration time an increase of the gained mass of product has to be achieved in comparison with the simple batch process. In the first section of Table 4, the results for the coupled batch mode achieved after 300 minutes are presented. As expected the productivity for the preferential crystallization performed in the coupled mode is higher than in the case of decoupled vessels. Similar trends were observed in the tank where D-threonine was seeded. Additionally, a decrease of the counter enantiomer concentration allows suppressing its nucleation (i.e., the driving force for nucleation of the unwanted enantiomer is lowered by reduction of its supersaturation level). Therefore, pure product can be obtained for a longer time in each of the vessels. As it is shown in Table 4, after 720 minutes 6.91 g of L-threonine and 7.28 g of D-threonine has been obtained with a purity of 100%. All obtained results in the tank where D-threonine and in that tank where L-threonine, respectively was seeded are summarized in Table 4. Because it is impossible to guarantee entirely identical conditions in both vessels during the coupled process the crystallization and secondary nucleation rate might differ slightly. Therefore, small differences in the mass of gained product have been observed. However, it is remarkable that the mass of the product (L-threonine) for the coupled crystallizer mode is 114% higher than in the case of the simple batch mode.

Coupled crystallizer mode for conglomerate forming systems (polythermal)

The previous results for isothermal operation have shown that the liquid phase had nearly racemic composition in both vessels during the whole process and the experiment could be performed up to very low supersaturation levels (values c/c_{sat} close to 1.0) for both enantiomers because of the manipulation of the concentration profiles. A further possible degree of freedom is the temperature which can be also modified to enhance the process performance. The main idea for such polythermal process is that with decreasing crystallization temperature a further increase of the driving force can be realized. This is due to the fact that with decreasing crystallization temperature, the supersaturation level increases. As a result of that a higher mass of the wanted enantiomer should be achieved in each vessel. Mass fraction and temperature profiles obtained during such a polythermal experiment

Table 4. Comparison of Experimentally Determined Mass of Product, Productivity, and Purity for the Crystallization of D- and L-threonine in an Isothermal with the Polythermal Coupled Batch Mode

Parameter	Used Symbol	Value (L-threonine)	Value (D-threonine)	Unit
Isothermal Mode				
Mass of product	m	4.22	6.11	g
Productivity	Pr	1.75×10^{-4}	2.54×10^{-4}	g/(g min)
Purity	Pu	1.00	1.00	–
Duration time	t_{end}	300	300	min
Isothermal Mode				
Mass of product	m	6.91	7.28	g
Productivity	Pr	1.56×10^{-4}	1.64×10^{-4}	g/(g min)
Purity	Pu	1.00	1.00	–
Duration time	t_{end}	720	720	min
Polythermal Mode				
Mass of product	m	9.07	12.04	g
Productivity	Pr	2.05×10^{-4}	2.72×10^{-4}	g/(g min)
Purity	Pu	1.00	1.00	–
Duration time	t_{end}	720	720	min

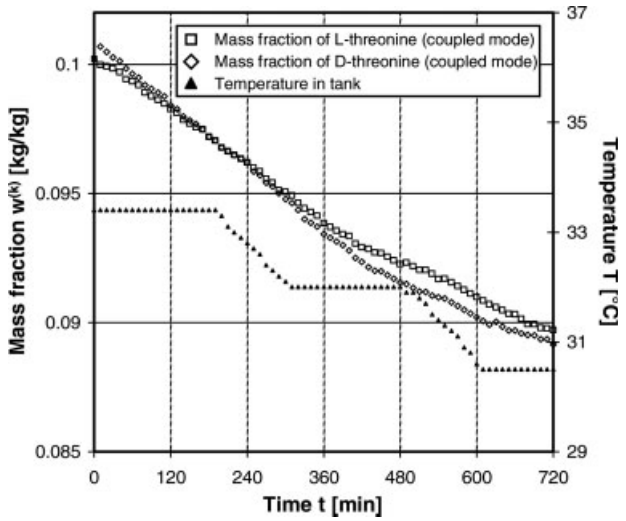

Figure 9. Mass fraction and temperature profiles for the coupled crystallizers in polythermal operation mode after seeding with L-threonine crystals (Tank 1).

Process parameters: $t_{end} = 720$ minutes, $m_{seeds} = 1.0$ g.

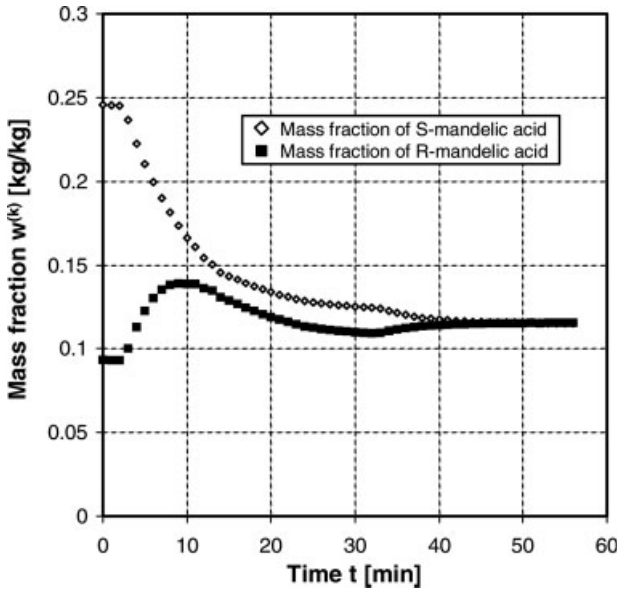

Figure 10. Mass fraction profiles for an isothermal coupled batch experiment providing mandelic acid in the tank where S-mandelic acid has been seeded.

Process parameters: $t_{end} = 55$ minutes, $m_{seeds} = 1.125$ g, $T_{cryst} = 28°C$.

are depicted in Figure 9. It is obvious that the mass fraction profiles show similar trends as in case of the experiment performed under isothermal conditions. Again permanent racemic composition of the liquid phase has been obtained. As presented in Figure 9 the temperature has been reduced from 33°C to 30°C in two steps. The final temperature and the cooling profile for the polythermal experiment have been determined based on the preliminary polythermal experiments performed for the simple batch mode. Obviously, cooling down of the solution results in a significant increase of the supersaturation level not only of the wanted but also of the unseeded enantiomer for the batch preferential crystallization process. Because of that, relatively fast nucleation of the unwanted enantiomer was observed and an enhancement of the process performance was not possible. However, a decreasing temperature profile should be feasible for the coupled batch mode and even beneficial for its productivity, because by exchanging the mother liquors of both tanks the actual concentration of the unwanted enantiomer in solution is lowered. For this reason a premature nucleation can be avoided. Results obtained for this polythermal coupled mode are summarized and compared with the isothermal mode in Table 4. One can see that the polythermal mode delivers a higher mass of the product ($m = 9.07$ g) and a higher productivity ($Pr_L = 2.05 \times 10^{-4}$ g/(g × min)) comparing with the isothermal mode. In comparison to the isothermal simple batch operation an increase of 184% concerning the mass of pure L-threonine could be achieved. The presented results show that the polythermal operation can be successfully applied for coupled batch crystallizer mode. The presented results reveal a high potential of the polythermal mode for the coupled crystallizer operation. Aim of future work is to find an optimal temperature profile that might lead to an enhancement of the process productivity and to an improvement of the product properties like final crystal size distribution.[26]

Preliminary investigation for compound forming systems

Preferential crystallization can be also performed for compound forming systems if the initial solutions have a

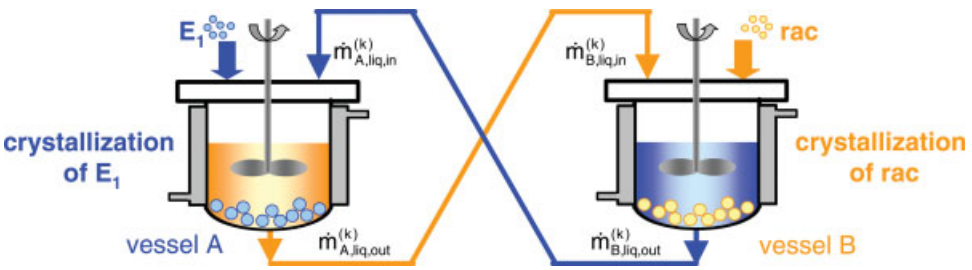

Figure 11. Simultaneous preferential crystallization process.

Possible concept of arrangement for two crystallizers coupled via liquid phase where one enantiomer E_1 and the racemic compound (rac) have been seeded. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

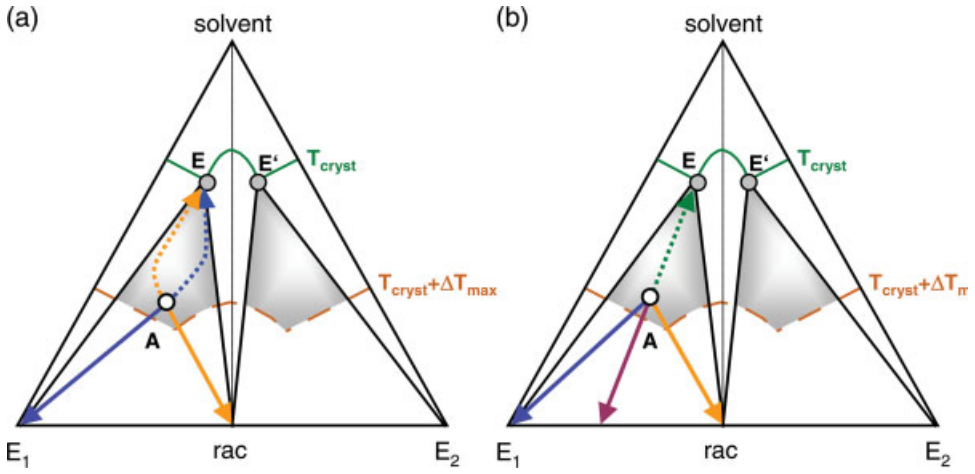

Figure 12. Trajectories during preferential crystallization performed for compound forming systems (a) in two decoupled vessels and (b) in two vessels coupled via the liquid phase where enantiomer E_1 and racemic compound (rac) have been seeded.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

composition located in one of the 3-phase regions of the phase diagram [compare Figure 2b]. A description of the preferential crystallization for mandelic acid dissolved in water using simple batch experiments was given recently.[19,22] This system has been also investigated in this work to perform a run using the coupled crystallizer mode. It is worth to note that for the mandelic acid a ternary phase diagram has already been investigated and can be found in the literature.[27] The liquid phases have been exchanged from the time when homochiral seeds were added into the tanks. Figure 10 shows the mass fraction profiles obtained during this experiment. It can be observed that an exchange of the liquid phases results in 50:50 mixtures in both vessels. After starting an exchange of the liquid phase, as it was expected, seeds which have been added before to each tank dissolved and crystallization was initialized later just by nucleation. A resolution of these enantiomers by crystallization which have the tendency to form compounds in the solid phase is not possible if the liquid phase has racemic composition. HPLC investigation of the obtained solid phase confirmed that the harvested crystals had racemic composition. Thus it has been shown that process symmetry gives only advantage in case of conglomerate forming systems but is detrimental in case of compound forming systems.

A conceivable alternative for compound forming systems is illustrated in Figure 11 where two vessels with an exchange of crystal-free mother liquor are coupled. Opposite to the above arrangement for conglomerates it should be possible to increase the overall crystallization rate and thus the productivity if in one vessel the pure enantiomer E_1 and in the second vessel the racemic compounds (rac) are seeded and subsequently crystallizing[†]. The corresponding trajectories are depicted schematically in Figure 12. This coupled mode should also result in a higher overall driving force and therefore a higher productivity in comparison to the simple batch mode cited in the literature.[22,23] Taking into consideration that the pure enantiomer and the racemic compound are showing different physical properties (especially with respect to the crystallization kinetics, i.e., growth and nucleation) an adjustment of the experimental conditions to guarantee 'process symmetry' will be indispensable. This promising and challenging configuration mode for compound forming systems is currently investigated. However, it should be mentioned that for compound forming systems just one enantiomer can be produced in a single step by means of this innovative coupled crystallizer configuration, whereas for conglomerate systems a resolution of both enantiomers in a single step is possible.

Conclusions

In this work the main idea and first experimental results of an innovative crystallizer configuration for preferential crystallization using two coupled vessels have been presented and compared with the standard single batch process. For both investigated crystallizer configurations, the productivities Eq. 1 and purities Eq. 2 have been determined and compared. The coupled mode exploits the fact that by exchanging the liquid phase, in comparison to the simple batch mode, the concentration of the preferred enantiomer increases and the concentration of the counter enantiomer decreases.

The results obtained for the crystallization of the conglomerate forming system (threonine) reveal that the coupled mode outperforms the simple decoupled crystallizer mode with regard to productivity and purity. It has been shown that the process performed in the coupled mode can be performed close to equilibrium providing in each of the two tanks pure enantiomers. According to the experimental results shown in this paper, the mass of the product gained in the end of the coupled batch process is significantly higher than in the simple batch mode.

In addition to the investigations under isothermal conditions, a decreasing temperature profile has been applied to

[†]The same circumstances might be also valid for E_2 in the second three-phase region on the right-hand side of the phase diagram.

the coupled crystallizer configuration. This polythermal operation led to a further enhancement of the gained mass of pure product, which was for this specific case study 184% higher in comparison to the simple batchwise operation.

Acknowledgments

The authors thank Luise Borchert and Jacqueline Kaufmann for their help in performing the HPLC analyses.

Notation

Latin symbols

E_k = enantiomer k
m = mass, g
Pu = purity
Pr = productivity, g/(g·min)
t = time, min
T = temperature, °C
$w^{(k)}$ = mass fraction (mass component k/total mass solution), kg/kg

Subscripts and superscripts

c = counter
D = D-threonine
cryst = crystallization, crystallizer
k = component index
L = L-threonine
p = preferred
rac = racemate
s = solid
w = water

Literature Cited

1. Collins AN, Sheldrake GN, Crosby J. *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds*. Chichester: Wiley, 1994.
2. Collins AN, Sheldrake GN, Crosby, J. *Chirality in Industry II: Developments in the Manufacture and Applications of Optically Active Compounds*. Chichester: Wiley, 1997.
3. Fogassy E, Nógrádi M, Pálovics E, Schindler J. Resolution of enantiomers by non-conventional methods. *Synthesis*. 2005;10:1555–1568.
4. Rouhi AM. Chiral business. *Chem Eng News*. 2005;81:45–55.
5. Maier NM, Franco P, Lindner W. Separation of enantiomers: needs, challenges, perspectives. *J Chromatogr A*. 2001;906:3–33.
6. Brice LJ, Pirkle WH. *Enantioselective Transport through Liquid Membranes,* in S. Ahaja (Ed.), Chiral Separations Applications and Technology. Washington DC: American Chemical Society, 1996: 309–334.
7. Coffen DL. *Enzyme-Catalyzed Reactions, Chiral Separations Applications and Technology*. Washington DC: American Chemical Society, 1996:59–91.
8. Sakai K, Coquerel G. *Novel Optical Resolution Technologies*. Berlin: Springer, 2007;3–51.
9. Roozeboom HWB. Löslichkeit Und Schmelzpunkt Als Kriterium Für Racemische Verbindungen, Pseudoracemische Mischkristalle Und inaktive Konglomerate. *Z Phys Chem*. 1899;28:494–517.
10. Jacques J, Collet A, Wilen SH. *Enantiomers, Racemates and Resolutions*. Malabar: Krieger, 1994;223–241.
11. Collet A, Brienne M-J, Jacques J. Optical resolution by direct crystallization of enantiomer mixtures. *Chem Rev*. 1980;80:215–230.
12. Matsuoka M, Hasegawa H, Ohori K. Purity decrease of L-threonine crystals in optical resolution by batch preferential crystallization. In: Myerson AS. (Ed.), *Crystallization as A Separation Process*. American Chemical Society. 1990:251–260.
13. Shiraiwa T, Miyazaki H, Kurokawa H. Successive optical resolution by replacing crystallization of DL-Threonine. *Chirality*. 1994;6:654–657.
14. Matsuoka M. Purity drop in optical resolution of racemic mixtures. In: Botsaris GD, Toyokura K. (Eds.), *Separation and Purification by Crystallization*. American Chemical Society. 1997;667:59–72.
15. Profir VM, Matsuoka M. Processes and phenomena of purity decrease during the optical resolution of DL-Threonine by preferential crystallization. *Colloids Surf A*. 2000;164:315–324.
16. Beilles S, Cardinael P, Ndzié E, Petit S, Coquerel G. Preferential crystallisation and comparative crystal growth study between pure enantiomer and racemic mixture of a chiral molecule: 5-ethyl-5-methylhydantoin. *Chem Eng Sci*. 2001;56:2281–2294.
17. Elsner MP, Fernández Menéndez D, Alonso Muslera E, Seidel-Morgenstern A. Experimental study and simplified mathematical description of preferential crystallization. *Chirality* 2005;17:S183–S195.
18. Angelov I, Raisch J, Elsner MP, Seidel-Morgenstern A. optimization of initial conditions for preferential crystallization. *Ind Eng Chem Res*. 2006;45:759–766.
19. Lorenz H, Perlberg A, Sapoundjiev D, Elsner MP, Seidel-Morgenstern A. Crystallization of enantiomers. *Chem Eng Process*. 2006;45: 863–873.
20. Lorenz H, Czapla F, Polenske D, Elsner MP, Seidel-Morgenstern A. Crystallization based separation of enantiomers. *J Univ Chem Technol Metallurgy*. 2007;42:5–16.
21. Angelov I, Raisch J, Elsner MP, Seidel-Morgenstern A. Optimal operation of enantioseparation by batch-wise preferential crystallisation. *Chem Eng Sci*. 2008;63:1282–1292.
22. Polenske D, Elsner MP, Lorenz H, Seidel-Morgenstern A. Alternative Einsatzmöglichkeiten Der Bevorzugten Kristallisation. *Zur Enantiomerentrennung Chem-ing-Tech*. 2006;78:1101–1110.
23. Lorenz H, Polenske D, Seidel-Morgenstern A. Application of preferential crystallization to resolve racemic compounds in a hybrid process. *Chirality* 2006;18:828–840.
24. Elsner MP, Ziomek G, Seidel-Morgenstern A. Simultaneous preferential crystallization in a coupled, batch operation mode–part I: theoretical analysis and optimization. *Chem Eng Sci*. 2007;62:4760–4769.
25. Lorenz H, Sapoundjiev D, Seidel-Morgenstern A. Solubility equilibria in chiral systems and their importance for enantioseparation. *Eng Life Sci*. 2003;3:132–136.
26. Ziomek G, Elsner MP, Seidel-Morgenstern A. Simultaneous preferential crystallization in a coupled, batch operation mode. part II: experimental investigation. *Chem Eng. Sci*. 2009 (in preparation).
27. Lorenz H, Sheehan P, Seidel-Morgenstern A. Coupling of simulated moving bad chromatography and fractional crystallization for efficient enantioseparation. *J Chromatogr A*. 2001;908:201–214.

Manuscript received Apr. 23, 2008, and revision received Sept. 11, 2008.