Synthesis of Chiral Crystallization Processes

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A process synthesis procedure is presented for the resolution of racemic mixtures by crystallization. The phase behaviors of racemic mixtures and of those in the presence of solvents and resolving agents are discussed. The corresponding separation schemes are synthesized by considering the separation steps in a flowsheet as movements on a phase diagram. Separations with and without involving racemization and deracemization are considered. The procedure is illustrated with several examples, including the manufacture of ibuprofen and naproxen.

Introduction

Chirality plays an important role in biological activities. The pharmacological effects of the individual enantiomers of a drug can be strikingly different. With increasing awareness of the need for higher drug specificity, the worldwide market for chiral drugs grew 11% over the previous year to $96 billion in 1998 (Stinson, 1999). Similar albeit smaller growth is expected for the chiral agricultural chemicals sector where the impetus is reduction of environmental impact. If only one enantiomer of an insecticide or herbicide has potency, then marketing the product as a single isomer rather than as a racemate means a 50% reduction in the environmental loading for that particular product. Additionally, both raw material costs and waste generation can be reduced significantly when racemization or deracemization is possible. All of this has led to an increased demand for enantiopure intermediates and final products.

Crystallization, along with adsorption, is one of the two most important methods for the recovery of pure enantiomers (Eliel and Wilen, 1994; Lim et al., 1995; Ahuja, 1997; Collet, 1999). A large number of commercially important drugs and their precursors are manufactured by crystallization processes. The key reason is that most chiral compounds exist in solid form, and crystallization yields a pure, solid product. The various crystallization techniques for racemic resolution, as well as the related solid state chemistry, have been discussed from the chemist's viewpoint in the classic monograph by Jacques et al. (1981). An abbreviated version was presented by Sheldon (1993).

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Surprisingly little is available in the literature that examines chiral crystallization from the systems engineering perspective. This is a serious omission for three main reasons. First, there is enormous pressure to reduce time to market (Pisano, 1997). A systematic approach to chiral crystallization can significantly reduce the time for process development. Second, a systematic procedure can help identify process alternatives. While the capital cost of the processing plant is not an essential concern for a new drug, an economic process can help deter generic competition when the patent expires. Chiral crystallization processes tend to involve various expensive and environmentally sensitive solvents and resolving agents. A well designed process can significantly minimize waste disposal problems and operating costs related to such compounds.

Recently, systems engineering of achiral crystallization processes has received much attention. Rajagopal et al. (1991) and Dye and Ng (1995a) formulated design methods for extractive crystallization processes. Fractional crystallization was studied by Cisternas and Rudd (1993), Dye and Ng (1995b), Cisternas and Swaney (1998), Cisternas (1999), and Thomsen et al. (1998), among others. Design of crystallization processes for recovering pure solids from conjugate salt pairs was considered by Berry and Ng (1996); they showed that the same method could be used to resolve racemic mixtures.

This work extends these previous systems studies to chiral crystallization. The objective is to formulate a systematic procedure to identify process alternatives for resolving a given racemic mixture. The phase behaviors of racemates and those in the presence of resolving agents and solvents are presented, and the corresponding crystallization separation schemes are discussed. The procedure is illustrated with vari-

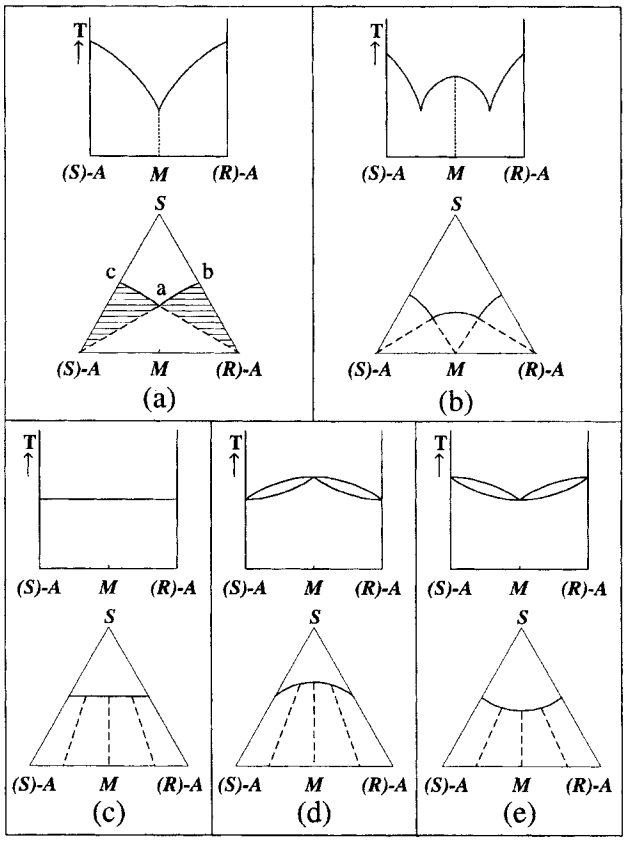


Figure 1. Binary and ternary phase diagrams of enantiomeric mixtures.

(a) Conglomerate; (b) racemic compound; (c) pseudoracemate with uniform melting point; (d) pseudoracemate with maximum melting point; (e) pseudoracemate with minimum melting point.

ous examples including two common analgesics—ibuprofen and naproxen.

Phase Behaviors of Enantiomeric Mixtures

Phase diagrams play a critical role in the synthesis of crystallization-based separation processes. Given the separation objectives and the phase diagram of the system on hand, flowsheet alternatives can be systematically constructed (Wibowo and Ng, 2000). Readers unfamiliar with representation of solid-liquid phase diagrams are referred to the aforementioned references for further details. We begin with a brief discussion of the classification of phase diagrams for enantiomeric mixtures (Figure 1). The pure enantiomers are represented as (*R*)-*A* and (*S*)-*A*, which indicate the chirality based on their absolute configuration. *M* indicates the racemic mixture between the two enantiomers.

The phase behavior depicted in Figure 1a features the formation of a *conglomerate*, which is an equimolar mixture of two crystalline enantiomers. In some cases, the crystals of a conglomerate are mechanically separable. Also shown in Figure 1a is an example of a three-component isothermal phase diagram for the racemate in the presence of a solvent *S*. This is a simple eutectic system consisting of two single saturation curves (ab and ac) and two crystallization compartments (shaded). A single pure product may be obtained by crystallization in each compartment. Conventional fractional crystallization techniques are not applicable for separating such a mixture because the racemate composition is the same as that of the double saturation point (point a), a barrier to traditional crystallization schemes. In Figure 1b, the phase behavior features the formation of a *racemic compound* which is a 1:1 solid compound. Also shown in Figure 1b is an example of a ternary isothermal phase diagram with a racemic compound. Figures 1c–e show the phase diagrams involving solid solutions. These mixtures feature a *pseudoracemate*, which is an equimolar mixture of two enantiomers that form solid solutions. Figure 1c shows an ideal solid solution while Figures 1d and 1e show maximum and minimum melting point phase diagrams, respectively. The racemic-compound type is the most common in nature, comprising of about 90% of all racemates (Jacques et al., 1981). Another 5–10% are conglomerates, while pseudoracemates are rare. Examples of systems exhibiting the three types of phase behaviors are given in Table 1.

Table 1. Examples of Enantiomeric Mixtures Exhibiting Phase Behaviors as Depicted in Figure 1

Phase Behavior	Phase Diagram	Example	Reference
Conglomerate	a	2-*p*-Nitrophenylbutane 2-Octanol α-Methylbenzylamine	Guetté et al. (1973)
Racemic compound	b	Malic acid Mandelic acid 2-Phenoxypropionic acid	Leclerq et al. (1976)
Pseudoracemic			
Uniform melting point	c	Isoborneol	Yager and Morgan (1935)
Max. melting point	d	Carvoxime	Jacques et al. (1981)
Min. melting point	e	2-Amylcarbamate	Melillo and Mislow (1965)

Synthesis Procedure for Chiral Crystallization Processes

Given the phase behavior of a racemate, one can synthesize a crystallization-based separation scheme for recovering pure enantiomers. We now present a 4-step synthesis procedure for generating suitable flowsheet alternatives (Table 2). Some accompanying heuristics for aiding decision-making are summarized in Table 3.

Step 1: identify separation objective

The separation objective identifies the desired product or products. Common objectives for racemate separation in-

Table 2. Procedure for Chiral Crystallization Process Synthesis

Step 1.	Identify separation objective
Step 2.	Identify physical/chemical basis for separation
Step 3.	Incorporate racemization or deracemization
Step 4.	Synthesize a complete separation flowsheet

Table 3. Heuristics for Decision-Making at Various Steps of the Synthesis Procedure

Step 2:
- Consider seeded crystallization in the melt or in solution for separating racemates having conglomerate phase behavior or a small racemic compound compartment.
- If seeded crystallization is used to recover enantiomers growing at different rates, recover the one with faster growth first.
- If salts are formed as dissociable compounds, consider using a polar solvent, such as water, acetone, or an alcohol (Collet, 1999).
- If an acid or base resolving agent is to be used to form stereomeric salts from the racemate mixture, choose an acid or base with small pK_a and pK_b in order to have near complete conversion.
- If the enantiomer can be sold as a salt, use a decomposition agent to recover the salt and to regenerate the resolving agent in one step.
- Consider using a second MSA to increase the solubility of the less desired product (Pope and Peachey, 1899).
- Consider multiple applications of a mixture of enantiomers as resolving agents if one of the enantiomers is not readily available but the mixture is (Ingersoll, 1925).
- Consider using a resolving agent in similar molecular shape and size to the solute (Kinbara et al., 1996).

Step 3:
- Consider racemization or deracemization if the separation objective is either recovery of a single enantiomer, or recovery of a primary product and partial recovery of a secondary product.
- Consider asymmetric transformation if the rate of racemization is faster than that of crystallization.
- Consider seed induced asymmetric transformation if the feed composition is not inside the compartment of (S)-A, but sufficiently close to the boundary of the (S)-A compartment.
- Do not use deracemization process if the overall process yield is low ($R_p < 0.5$).
- Consider using a bypass loop to reduce the crystallizer load in a deracemization process, if the product distribution ($\bar{X}$) in the deracemization unit is low while the yield is high.

Step 4:
- If the dissociable compounds (such as diastereomeric salts) have identical solubilities in the selected solvent, use seeded crystallization to separate them.
- If the relative composition of the dissociable compounds at the double saturation points on the ternary phase diagram is different at different temperatures, consider using fractional crystallization for separation.
- If the relative composition of the dissociable compounds at the double saturation troughs on the quaternary conjugate salt phase diagram is different at different temperatures, consider using fractional crystallization for separation. If not, consider using multiple MSA applications of different resolving agents.
- If the relative composition of the dissociable compounds at the double saturation points on the ternary phase diagram is different for different solvents, consider using selective dissolution and crystallization for separation (Bender et al., 1993).
- If the dissociable compounds that are salts are formed with a base (acid) and the product is soluble in water, consider using a strong acid (base) to recover the MSA.
- After dissociable compound decomposition, if some components of the dissociable compound are insoluble in the solvent, consider using liquid-liquid extraction or drowning out crystallization to separate the resolving agent and the product.
- After dissociable compound decomposition, if the relative volatility between the product and the resolving agent is greater than 1.5, consider using distillation for separation of the product and the resolving agent.
- If product recovery is performed using a strong base or acid, processing temperature and duration have to be chosen to avoid excessive racemization of the product.

clude: (a) complete recovery of both enantiomers; (b) recovery of a single enantiomer; and (c) complete recovery of one (the primary product) with partial recovery of the other (secondary product). For this article, we designate (S)-A as the primary product.

Step 2: identify physical/chemical basis for separation

Step 2 identifies the basic chemistry and physical phenomena for achieving separations. The different crystallization methods for racemic resolution are classified in Table 4 in order of increasing process complexity. There are two main groups: direct resolution, and resolution that employs a mass separating agent (MSA) which is used in the course of the process to deliberately change unfavorable phase behavior of the system. The specialized term for MSA in use for racemic mixtures is *resolving agent*. In general, the complexity of the process increases with the number of chemical entities in the process.

Without using a resolving agent, direct resolution frequently depends on the use of seed crystals. Seeded crystallization can be performed in the melt or in solution, and is generally applicable to racemates having conglomerate phase behavior (Figure 1a). Compared to techniques with an MSA, this method is simple, and requires fewer process units. However, it is not effective in separating racemic compounds (Figure 1b). For this reason, resolving agents are widely employed in industry to separate both conglomerates and racemic compounds (Liu, 1999). Table 5 lists examples of such MSA-utilizing processes. Figure 2 is a generic flowsheet that describes the basic steps for these types of separations. To bypass the eutectic (or 1:1 compound), dissociable compounds are formed between the racemate and the MSA. The solid-liquid phase behavior of these dissociable compounds is such that separation by crystallization is possible. The double saturation point of the dissociable compounds is often shifted away from the 50:50 racemate composition. Furthermore, 1:1 solid compound formation is less likely between the dissociable compounds. After separation, the dissociable compounds are decomposed to recover the products of interest. As the figure indicates, the resolving agent B is recycled. Table 6 gives a set of criteria for selecting a resolving agent. Throughout this article, the flowsheets are in the form of continuous processes. For batch processes, the flowsheet should be interpreted as a cycle of sequential operations.

Separations using resolving agents can be further classified into various categories (Table 4). Stoichiometric and nonstoichiometric resolutions refer to complete and incomplete transformation of racemates into dissociable compounds, respectively. One can use one single resolving agent or multiple resolving agents. The latter can be further classified in terms of the number of MSA applications. Thus, a one-application

Table 4. Classification of Crystallization-Based Resolution Techniques

Direct Resolution
- Seeded crystallization (melt or solution)

Use of Resolving Agents (stoichiometric or nonstoichiometric)
- Single mass separating agent
- Multiple mass separating agents (one or more applications)

Table 5. Racemic Resolution Processes Based on the Use of Resolving Agents

Product	Use	MSA	Company	Process Classification	Reference
(S)-Ibuprofen	Pain relief	(-)-α-Phenethylamine	Ethyl Corp.	Single MSA	Manimaran and Potter (1994)
(*S*)-Naproxen	Pain relief	An *N*-*n*-Alkyl-*D*-glucamine; triethylamine	Syntex	2 MSA, 1 application	Holton (1985)
Captopril	Hypertension treatment	L-(+)-2-Aminobutanol	Medichem S.A.	Single MSA	Stampa Díez Del Corral et al. (1994)
D-Phenylglycine	Antibiotics	Benzenesulfonic acid; H_2SO_4	Nippon Kayaka Kabushiki Kaisha	2 MSA, 1 application	Aoki et al. (1978)
D-Hydroxyphenylglycine	Antibiotics	Benzenesulfonic acid	Tanabe Seiyaku Co.	Single MSA	Chibata et al. (1982)
L-Homoalanin-4-yl-(methyl)phosphinic acid	Herbicide	(-)Quinine	Hoecht Schering AgrEvo GmbH	Single MSA	Knorr et al. (1999)
(+)-Permethric acids	Insecticide	1-(*p*-Isopropylphenyl)-ethylamine	Kuraray Co.	Single MSA	Nohira and Shinichi (1989)
L-Ambrox	Perfumery	(-)-1-(*p*-Tolyl)ethylamine	Kuraray Co.	Single MSA	Asanuma and Tamai (1994)

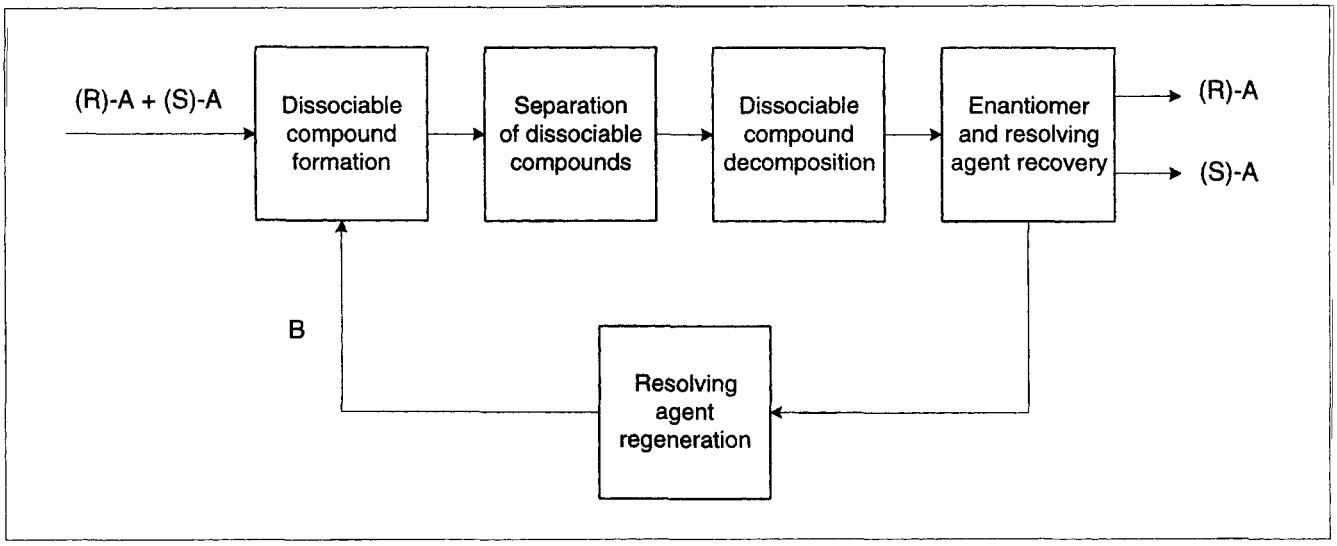


Figure 2. Generic flowsheet for racemic resolution via dissociable compound formation.

MSA-utilizing process forms dissociable compounds only once. A two-application MSA-utilizing process involves dissociable compound formation, separation, and decomposition steps twice in the separation scheme. In stoichiometric resolution, the total amount of resolving agent applied in the dissociable compound formation step is equal to the amount of racemate present. With a relatively smaller amount of resolving agent, nonstoichiometric processes have significant amounts of free enantiomer in the system. Since there are only a few specialized examples of nonstoichiometric resolution processes, it is not emphasized in this article.

Table 6. Criteria for Selection of Resolving Agents

- The resolving agent should be chemically stable under processing conditions, including high temperature and extreme pH.
- The resolving agent should eliminate any 1:1 compound between the enantiomers.
- The double saturation point should be shifted away from the 50:50 composition.
- The dissociable compounds should form and decompose easily under appropriate conditions.
- The resolving agent should be easily recoverable from the solvent using conventional techniques such as distillation, crystallization or adsorption.

Dissociable compounds may be formed with a chiral or achiral, organic, or inorganic agent. The use of dissociable compound formation is conceptually similar to separation processes based on reversible chemical complexation. The types of bonds formed between such complexes may be site-specific, such as hydrogen bonds or acid-base interactions, or nonsite-specific such as solid compound formation, or crystalline inclusion compounds (clathrates). Cyclodextrins are an example of the latter, which form rigid rings large enough for occupation by a smaller molecule. Although in some cases these molecules exhibit a lock-and-key type relationship with the solute, it has been shown that host-induced conformational changes may occur (Fujita et al., 1999). Resolutions using cyclodextrins have been carried out by Cramer and Dietsche (1959). As a general rule, dissociable compounds that have specific or nonspecific bond energies in the 10–50 kJ/mol range are expected to be suitable for separation processes based on reversible chemical complexation (King, 1986).

The most common method for racemic resolution is diastereomeric salt formation with the enantiomers and another chiral agent. Phase behaviors for diastereomeric mixtures in solution are typically simple eutectics or contain solid solutions. It is estimated that 20–25% of diastereomers in solution have simple eutectic phase diagrams (Collet, 1999). For systems with solid solutions, melt crystallization can be used in conjunction with fractional crystallization to effect resolution. However, such techniques have yet to be developed.

Laboratory procedures for screening resolving agents that form diastereomeric salts have been given in the literature (Collet, 1996; Vries et al., 1998); however, few heuristics are available for matching a resolving agent with a given solute. One study by Kinbara et al. (1996) suggests that resolving agents comparable in molecular size and shape to the solute would result in a greater recovery of the desired enantiomer or its salt.

A typical example of diastereomeric salt formation involves carboxylic acids and amines. Acid or base functional groups can be added to enantiomer molecules, if necessary. In general, the enantiomers possess multiple functional groups. One example is the diastereomeric salt formed between (R, R)-tartaric acid and a (-)(*S*)-3-methylamino-4-methylenepyrrolidine derivative (Okada and Tsushima, 1993). Some of these groups may have to be chemically modified to effect separations. For simplicity, only molecules having a single functional group are considered in this article. Examples in this article are configured such that the racemate is an acid, *HA*, and the resolving agent is a base *B*. Obviously, a process with the acid-base relationship reversed can be similarly designed using the same procedure.

In order to have near complete conversion from racemate to salt formation, the dissociation constants of the acid and base should be as large as possible. Typical *pK* values for resolving agents range from 2 to 8 and from 4 to 7 for acids and bases, respectively (Jacques et al., 1981). Some resolving agents are designed to have low pK_a or pK_b values. For example, chiral phosphoric acids have a pK_a in the 2–3 range (Sheldon, 1993). Figure 3 shows the degree of dissociation of

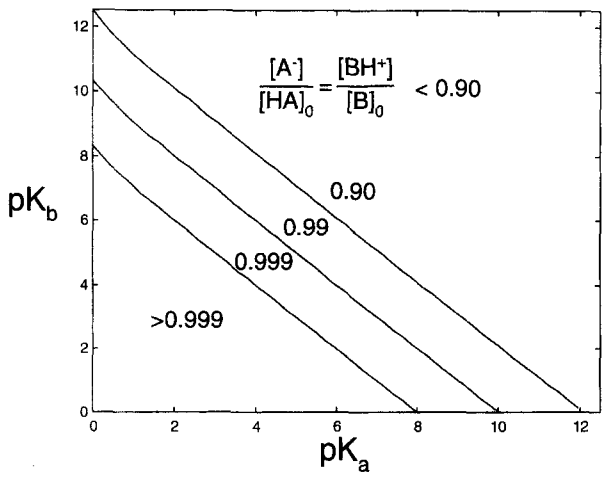


Figure 3. Degree of dissociation of *HA* as a function of pK_a and pK_b values.

Table 7. Equations and Input Data for a Simple Diastereomeric Salt Formation

Overall Reaction	*Dissociation Reactions*
$HA+B \leftrightarrow \{BH^+, A^-\}$	$[H^+][A^-]-[HA]K_a=0$
	$[BH^+][OH^-]-[B]K_b=0$
Material Balance Equations	$[H^+][OH^-]-K_w=0$
$[HA]+[A^-]-[HA]_0=0$	
$[BH^+]+[B]-[B]_0=0$	*Charge Balance*
	$[H^+]+[BH^+]-[A^-]-[OH^-]=0$
Input Parameters	
$K_w=1\times10^{-14}$ $[HA]_0=[B]_0=1$	

HA, $[A^-]/[HA]_0$, for a single acid-base pair in a dilute, aqueous solution. These values are approximately equal to $[BH^+]/[B]_0$ for this system. The equations used for this reaction and other input data are given in Table 7. For typical *pK* values, the amount of free (undissociated) enantiomer and free resolving agent in solution is negligible. This is not the case for a nonstoichiometric resolution.

While strong acids and bases are preferred in dissociable compound formation, the salt of a weaker acid and weaker base is easier to decompose in order to recover the desired enantiomer. If an acid such as HCl is used to decompose dissociable compounds, the products of the decomposition step are the free acid and the chloride salt of the base (Eq. 1). If a base such as NaOH is used, the products of the decomposition step are the free base and the salt of the acid (Eq. 2)

$$\{BH^+, A^-\} + \mathrm{HCl} \rightarrow HA + \{BH^+, \mathrm{Cl}^-\} \quad (1)$$

$$\{BH^+, A^-\} + \mathrm{NaOH} \rightarrow \mathrm{B} + \{Na^+, A^-\} + \mathrm{H_2O} \quad (2)$$

Figure 4 shows the percentage of free acid in solution relative to the initial total amount of salt $[HA]/[\{BH^+, A^-\}]_0$ for a range of pK_a and pK_b values for decomposition of a diastereomeric salt with HCl. The equations used for this reac-

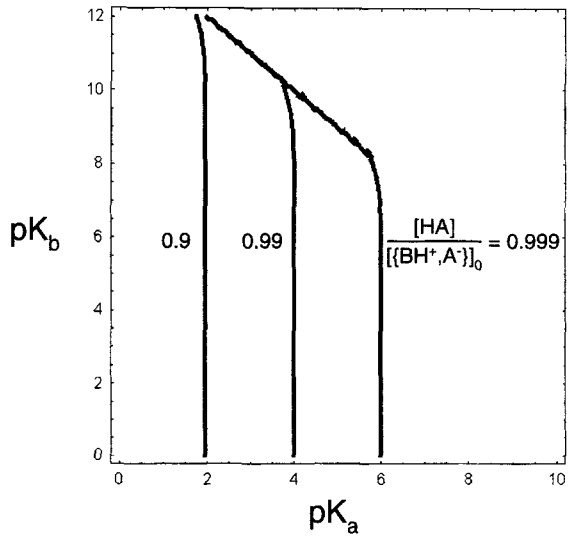


Figure 4. Percentage of free acid relative to the initial total amount of salt as a function of pK_a and pK_b values.

Table 8. Equations and Input Data for Diastereomeric Salt Decomposition using HCl

Overall Reaction

$$\{BH^+, A^-\} + \mathrm{HCl} \leftrightarrow \{BH^+, \mathrm{Cl}^-\} + HA$$

Material Balance Equations

$$[HA] + [A^-] - [\{BH^+, A^-\}]_0 = 0$$
$$[BH^+] + [B] - [\{BH^+, A^-\}]_0 = 0$$
$$[\mathrm{Cl}^-] - [\mathrm{HCl}]_0 = 0$$

Input Parameters

$$K_w = 1 \times 10^{-14} \quad [\{BH^+, A^-\}]_0 = [\mathrm{HCl}]_0 = 1$$

Dissociation Reactions

$$[H^+][A^-] - [HA]K_a = 0$$
$$[BH^+][OH^-] - [B]K_b = 0$$
$$[H^+][OH^-] - K_w = 0$$

Charge Balance

$$[H^+] + [BH^+] - [A^-] - [OH^-] - [\mathrm{Cl}^-] = 0$$

tion and other input data are listed in Table 8. The amount of free acid is very high, exceeding 99%, if pK_a of the acid is greater than 4. For this reaction, calculations also show that nearly all of the base B is converted to the chloride form of the base. Based on these results, we will assume complete dissociation of all ionic species in solution in order to simplify other analyses in this article. In practice, solvent selection is frequently made to aid the ionization process. About 80% of racemate resolutions reported in the literature used a polar or hydrogen bond donating solvent, such as water, acetone, or an alcohol, or mixtures of such solvents (Collet, 1999).

It is relatively easy to convert the product in salt form to the free form. However, one should beware of the possibility of racemization or impurity introduction to the product. The choice between the use of an acid or a base depends on the desired form of the product. For example, naproxen is sold in both free acid and sodium salt form. In this case, the use of a base is advantageous because both the base and the sodium salt are available after the conversion reaction (Eq. 2). If only the free acid form is desired, one has to trade the cost and effectiveness of recovering B from the salt in Eq. 1 off the cost of recovering HA from the sodium salt in Eq. 2.

Step 3: incorporate racemization or deracemization

If the separation objective is not to recover both enantiomers, chemical racemization or deracemization should be considered, provided that the chemistry for such a step is known. Racemization converts an unequal mixture of enantiomers into a 50:50 mixture. In contrast, deracemization moves the relative composition of enantiomers away from the 50:50 composition.

Racemization can be achieved in a number of ways. Some methods involve dissociable compound formation with a resolving agent. In a recent review, Ebbers et al. (1997) presented a classification of types of racemizations for organic compounds as well as the reported frequency of use. As can be seen in Figure 5, catalytic racemization is the most common technique, comprising of more than 50% of the reported cases. The thermal method, in which the mixture attains equilibrium at a high temperature, is about 14%. Racemization can also be performed using crystallization-induced asymmetric transformation (Scheme 1), which shifts the

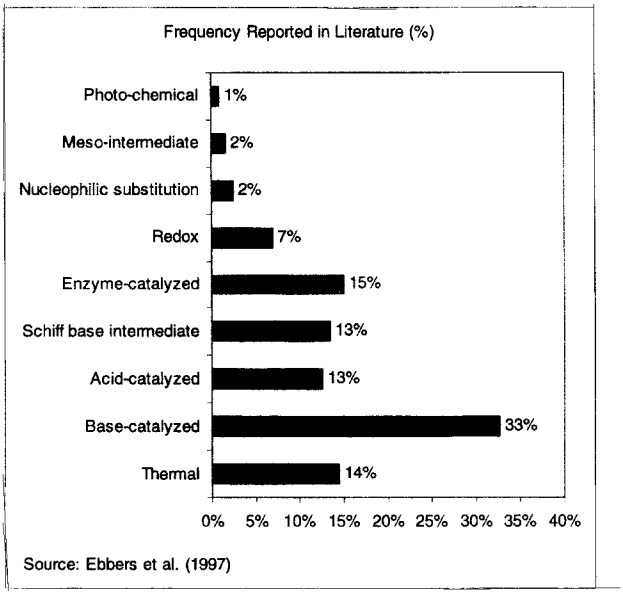


Figure 5. Frequency of use for various racemization methods.

relative amounts of enantiomers while simultaneously crystallizing the primary product

$$R_{(aq)} \rightleftharpoons S_{(aq)} \longrightarrow S_{(s)}$$

Scheme 1.

Although not as well organized as racemization, reviews of deracemization methods are available (Ward, 1995; Stecher and Faber, 1997). In general, there are two common schemes of deracemization. The first is kinetic resolution (Scheme 2a), where one of the enantiomers of a racemate is more readily converted to a product than the other. The second method is enantiospecific stereoinversions (Scheme 2b), where a catalyst selectively converts one enantiomer to another enantiomer

$$R \xrightarrow{\text{slow}} P$$
$$\uparrow\downarrow$$
$$S \xrightarrow{\text{fast}} Q$$

Scheme 2a.

$$R \xrightarrow{\text{cat.}} S$$

Scheme 2b.

Many deracemization processes are biocatalytic, though not necessarily. For example, α-substituted arylacetic acids can be deracemized by chemical techniques (Camps and Giménez, 1996).

Figure 6 presents the possible flowsheet structures at Step 3. Four generic unit operations are included: separation units are labeled with s, racemization units with an r, deracemization units with a d, and crystallization-induced asymmetric transformation units with AT. Note that the recycle loop associated with a unit signifies the possible use of internal recycle of solvent, resolving agent, or solute. Each box may consist of several unit operations to be synthesized in Step 4.

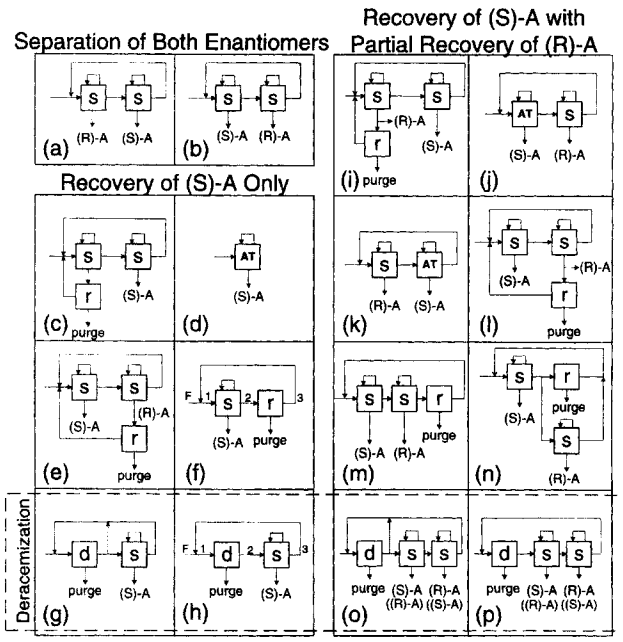


Figure 6. Flowsheet structures for racemic resolution processes with or without a racemization or deracemization step.

Figures 6a and 6b depict the flowsheet structures for alternatives without using racemization and deracemization, that is, when the separation objective is the recovery of both enantiomers. Figures 6f and 6h are the base-case flowsheet structures for racemization and deracemization, respectively. Note that a racemization unit always follows a separation unit while a deracemization unit precedes it. The remaining flowsheets in Figure 6 are alternatives using racemization or deracemization for different situations.

During racemization or deracemization, there may be product loss due to chemical decomposition, which is indicated by the purge streams in Figure 6. To take this into account, we define the yield y_d as the ratio of the flow rate of enantiomers leaving the unit to that entering the unit. For Figure 6f, the yield for racemization is

$$y_d = \frac{F_R(3) + F_S(3)}{F_R(2) + F_S(2)} \tag{3}$$

For a given feed (stream 2), y_d is the only parameter to be fixed in order to complete material balances around the racemization unit. For deracemization (Figure 6h), y_d is

$$y_d = \frac{F_R(2) + F_S(2)}{F_R(1) + F_S(1)} \tag{4}$$

Contrary to a racemization process where the product composition is 50:50, the product distribution must be specified in a deracemization unit in order to complete material balances around the unit. We define the product distribution $\bar{X}$ as the relative amount of (S)-A in the outlet of the deracemization unit. For the flowsheet in Figure 6h, we have

$$\bar{X} = \frac{F_S(2)}{F_S(2) + F_R(2)} \tag{5}$$

The deracemization process is completely fixed by specifying both y_d and $\bar{X}$.

As mentioned above, racemization and deracemization are used to improve the productivity of the entire process by converting the less desired (R)-A to the more desired (S)-A. As a measure of productivity, we define R_p as the ratio of (S)-A recovered to the total amount of (S)-A and (R)-A in the feed. In a process for resolving a racemic mixture without racemization or deracemization, the value of R_p obviously cannot exceed 0.5. With a racemization or deracemization unit, an increase in the amount of (S)-A will lead to a higher value of R_p. An R_p less than 0.5 indicates that too much product is lost and the racemization/deracemization process does not improve productivity. By performing material balances, R_p can be determined for the base-case flowsheets. For racemization (Figure 6f),

$$R_p = \frac{0.5 - X_S(2)}{1 - X_S(2) - 0.5y_d} \tag{6}$$

Here, $X_S(2)$ is the amount of (S)-A to the total amount of enantiomers in stream 2. As Eq. 6 indicates, when there is no loss in the racemization process ($y_d = 1$), R_p is always equal to unity. This means that all (R)-A in the feed is converted into (S)-A and the purge is nil. On the other hand, when there is total loss ($y_d = 0$), R_p is always less than 0.5. Note that due to crystallization of (S)-A, $0 < X_S(2) < 0.5$. Similarly, from material balances for deracemization (Figure 6h), we obtain

$$R_p = \frac{y_d\left(\bar{X} - X_S(3)\right)}{1 - X_S(3) - y_d + y_d\bar{X}} \tag{7}$$

When $y_d = 1$, Eq. 7 indicates that R_p is always equal to unity regardless of the conversion. Similarly, $y_d = 0$ yields $R_p = 0$, indicating that all product is lost in the deracemization unit, and therefore there is nothing to crystallize.

Table 9 outlines the decision process leading to the process alternatives presented in Figure 6. Depending on the separation objective and whether racemization or deracemization is a possibility, we move down the corresponding column. Some of the decision points are not relevant for a particular choice, and therefore should be skipped, as indicated by a dash in Table 9. Answering the questions in turn, we stop when the answer is in the affirmative. When this occurs, the flowsheet referred to in the corresponding slot is the initial flowsheet for Step 4.

We first consider the location of the feed in the phase diagram for the racemate-resolving agent-solvent system. If the feed composition is well inside the compartment boundary of the undesired product (R)-A, then (R)-A should be crystallized first (Figure 6a). Otherwise, the base case flowsheet is Figure 6b, which crystallizes (S)-A first. If only (S)-A is to be

Table 9. Decision Table for Incorporation of Racemization or Deracemization

Decision Points	Recovery of Both Enantiomers	Recovery of (S)-A Only		Recovery of (S)-A and Partially (R)-A	
	No reaction	*Racemization*	*Deracemization*	*Racemization*	*Deracemization*
Feed well inside compartment of (R)-A or its salt	Figure 6a	Figure 6c	—	Figure 6i	—
Potential asymmetric transformation $R_p < 0.5$	—	Figure 6d	—	Figure 6j or Figure 6k	—
	—	Figure 6e	infeasible	Figure 6l	Infeasible
Low conversion, but high yield	—	—	Figure 6g	—	Figure 6o
All other cases	Figure 6b	Figure 6f	Figure 6h	Figure 6m or 6n	Figure 6p

recovered, crystals of (R)-A are subjected to subsequent racemization and recycle (Figure 6c). If partial recovery of (R)-A is desired, a portion of these crystals is taken as a product (Figure 6i). Feed location is not a concern in deracemization because an excess amount of (S)-A will be formed anyway.

The second decision point deals with the possibility of using crystallization-induced asymmetric transformation for racemization. Here, two conditions need to be satisfied. First, crystallization of (S)-A would move the mother liquor composition away from a 50:50 mixture of enantiomers while racemization restores this composition. Asymmetric transformation is possible if the feed composition is inside the (S)-A crystallization compartment or sufficiently close to its boundary. In the latter, seed induced crystallization can be used for this purpose. (See Kelkar and Ng (1999) for a quantitative analysis.) Second, successful asymmetric transformation requires that the rate of racemization be faster than that of crystallization. When the separation objective is to recover (S)-A only, asymmetric transformation combines separation and racemization in one unit (Figure 6d). If (R)-A is to be partially recovered, an additional separation unit is necessary to recover (R)-A (Figure 6j or 6k). Removing the secondary product first (Figure 6k) is only possible if the double saturation point for the enantiomers (or their salts) is close to 50:50 in composition. This configuration may be preferred if it is difficult to interrupt the asymmetric transformation once the process has begun.

Next, we consider the overall yield from the racemization or deracemization process. At this decision point, we calculate R_p using Eqs. 6 and 7 for racemization and deracemization processes, respectively. The values of y_d, $\bar{X}$, and $X_S(2)$ or $X_S(3)$ are obtained from laboratory data or basic thermodynamics and kinetics. If the overall yield is low ($R_p < 0.5$), a maximum amount of (S)-A should be recovered before racemization of (R)-A (Figures 6e and 6l) to avoid destruction of the primary product. Deracemization should not be used if $R_p < 0.5$.

The fourth decision point concerns the conversion for the deracemization process. If the per-pass conversion is low, the composition of the stream leaving the deracemization unit will not be far away from 50:50. Therefore, a large recycle stream is necessary to achieve high overall conversion. To reduce the load to the crystallizer, we can create a bypass loop around the crystallizer (Figures 6g and 6o).

When the conditions in all decision points are not met, the base-case flowsheets (Figures 6f and 6h) are the best alternatives for complete recovery of (S)-A only. For partial recovery of (R)-A using racemization, there are two process alternatives to be considered (Figures 6m and 6n). In particular, the alternative of splitting the mother liquor between racemization and removal of (R)-A (Figure 6n) reduces the flow rate to the crystallizer in the (R)-A separation unit.

Step 4: synthesize a complete separation flowsheet

After the racemization/deracemization structure is determined, we synthesize the complete separation sequence by constructing basic movements on the phase diagrams. These techniques have been discussed extensively in the literature (Berry and Ng, 1996; Wibowo and Ng, 2000). For example, an isothermal ternary phase diagram with a solvent indicates whether separation by fractional crystallization is possible. An isothermal conjugate salt pair diagram shows the possibility of resolution by means of diastereomeric salt formation. While not repeated here, we will demonstrate these methods with examples.

We begin with the flowsheet identified in Step 3 by adding details to the separations unit. This should include recovery of the products, solvents and resolving agents, and recycle loops as well as connections among all unit operations. The next step is to add purge streams to eliminate wastes produced in the racemization or deracemization units, and impurities in the feed.

Finally, let us point out two options in which differences in solubility between solutes in different solvents are explored. One is the use of drowning-out agents to induce precipitation or liquid-liquid phase split (Berry et al., 1997). Another is the use of selective dissolution and crystallization to recover the product; specifically, solvent switching and crystallization was used to separate diastereomeric, 1-β-methylcarbapenem intermediates (Bender et al., 1993).

Example 1: A Single Resolving Agent Process

The use of a resolving agent leads to a multicomponent crystallization process. Proper selection and analysis of the appropriate phase diagrams is essential for synthesis of process alternatives. The necessary chemistry and other input data for this example are given in Table 10.

Step 1. The separation objective is to completely separate (R)-AH and (S)-AH.

Step 2. Since a racemic compound exists, a resolving agent is needed.

Step 3. We do not consider racemization or deracemization because both enantiomers are recovered, and Figure 6b is the basic flowsheet.

Table 10. Chemistry for Example 1: Single Resolving Agent Process

Dissociable Compound Formation
(R)-$AH + B \leftrightarrow \{BH^+,(R)\text{-}A^-\}$
(S)-$AH + B \leftrightarrow \{BH^+,(S)\text{-}A^-\}$
Solvent
Water
Dissociable Compound Decomposition
$\{BH^+,(R)\text{-}A^-\} + \text{NaOH} \leftrightarrow B + \{Na^+,(R)\text{-}A^-\} + H_2O$
$\{BH^+,(S)\text{-}A^-\} + \text{NaOH} \leftrightarrow B + \{Na^+,(S)\text{-}A^-\} + H_2O$

Step 4. Figure 7 shows the overall flowsheet structure. Dissociable compounds are formed between the racemic mixture (HA) and the recycled resolving agent (B) (stream 20) in a reactor (Rxr1). The two dissociable compounds, having different phase behavior from the racemate, are separated using a conventional crystallization scheme enclosed by the box with dashed lines. The phase diagram that shows the process paths for this subsystem is given in Figure 8a. The points on the phase diagram correspond to the stream numbers on the flowsheet. The feed for this subsystem stream 1 is mixed with a recycle stream 5. An evaporative crystallizer removes solvent from this mixture at temperature T_{C1}. As solvent is removed, the process path moves away from the solvent vertex (S) until it reaches the saturation curve for $\{BH^+,(S)\text{-}A^-\}$. Further solvent removal causes $\{BH^+,(S)\text{-}A^-\}$ to crystallize out of solution, which is removed with a filter (not shown). With simultaneous solvent removal and crystallization of $\{BH^+,(S)\text{-}A^-\}$, the process path follows the saturation curve for $\{BH^+,(S)\text{-}A^-\}$. The process path for crystallizer $C1$ stops at point 3, just short of the double saturation point, in order to prevent coprecipitation of the two salts. The mother liquor is diluted with solvent at temperature T_{D1} to prevent coprecipitation of solids in the next step (lines 3–4 in Figure 8a). A cooling crystallizer cools the mixture to temperature T_{C2} causing $\{BH^+,(R)\text{-}A^-\}$ to precipitate from the solution. The mother liquor (stream 5) is recycled and the process is repeated. After separation, the dissociable compounds are separately decomposed in Rxr2 and Rxr3 with NaOH to sodium salts of the enantiomers.

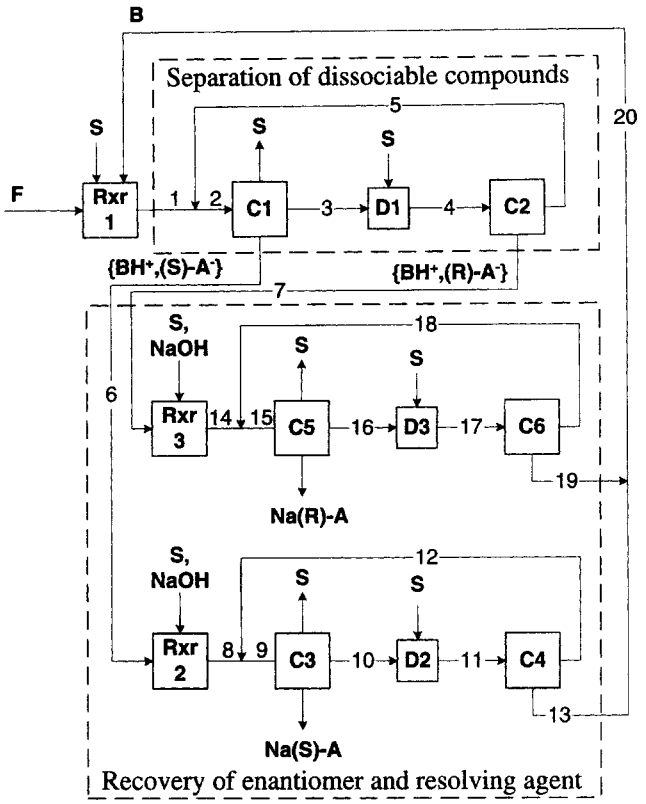


Figure 7. Example 1: single resolving agent process.

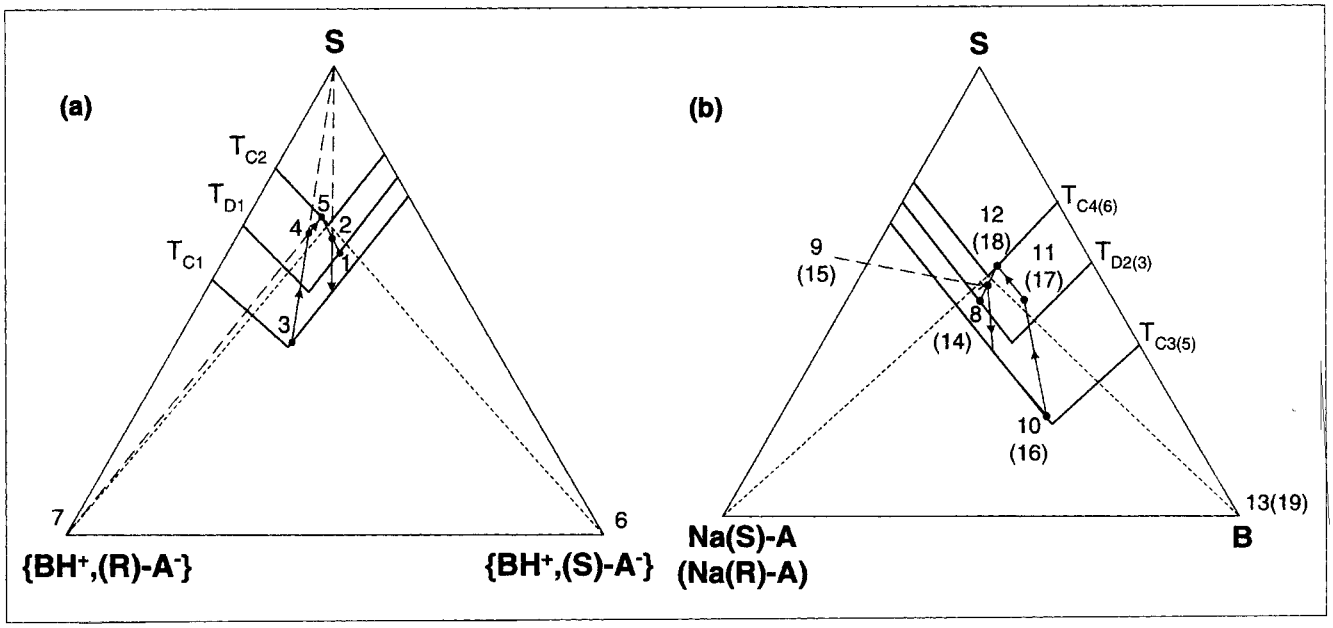


Figure 8. Example 1.

(a) Phase diagram for separation of dissociable compounds; (b) Phase diagram for enantiomer and resolving agent recovery.

In similar separation schemes the sodium salts and the resolving agent in free form are recovered by crystallization. A similar phase diagram (Figure 8b) is used for these subsystems, because we would expect the same phase behavior between *(R)-AH* and the resolving agent as *(S)-AH* and the resolving agent. It is topologically similar to Figure 8a; however, the relative solubilities of the sodium salt and B are different than for $\{BH^+,(R)\text{-}A^-\}$ and $\{BH^+,(S)\text{-}A^-\}$. The feed mixture, stream 8(14), is mixed with recycled mother liquor from crystallizer 4(6). The evaporative crystallizer *C3(C5)* removes solvent at $T_{C3}(T_{C5})$ precipitating the sodium salt of the enantiomer *Na(S)-A* (*Na(R)-A*). The mixture is diluted with solvent at temperature $T_{D2}(T_{D3})$ to prevent coprecipitation of solids in the next step. A cooling crystallizer cools the mixture to temperature $T_{C4}(T_{C6})$ causing B to precipitate from the solution. The mother liquor, stream 12(18) is recycled and the process is repeated.

Design variables and process tradeoffs for this example are now highlighted. We will begin with the material balances for crystallization system that separates the diastereomeric salts and expand outwards to cover the rest of the flowsheet. A degree of freedom analysis shows that after fixing the flow rate and composition of stream 1, four design variables are needed in order to calculate the material balances for this subsystem. We will choose these as $x_W(3)$ and $x_W(4)$, the mol fractions of solvent in streams 3 and 4, respectively, $X_S(3)$, the solventless mol fraction of $\{BH^+,(S)\text{-}A^-\}$ in stream 3, and $X_S(5)$, the solventless mol fraction of $\{BH^+,(S)\text{-}A^-\}$ in stream 5.

In the following equations, W represents solvent, S represents $\{BH^+,(S)\text{-}A^-\}$, and R is $\{BH^+,(R)\text{-}A^-\}$. Noting that the flow of $\{BH^+,(S)\text{-}A^-\}$ is constant in streams 3 through 5, we obtain the flow rate of $\{BH^+,(R)\text{-}A^-\}$ in stream 5, $F_R(5)$, in terms of $F_R(3)$, $X_S(3)$, and $X_S(5)$, as

$$F_R(5) = \frac{\left(\frac{X_S(3)}{1-X_S(3)}\right)}{\left(\frac{X_S(5)}{1-X_S(5)}\right)} F_R(3) \tag{8}$$

Because the flow of $\{BH^+,(R)\text{-}A^-\}$ is constant across the first crystallizer (*C1*), Eq. 8 can be combined with the balance of $\{BH^+,(R)\text{-}A^-\}$ around the mixing point between the feedstream and the recycle (stream 5), to get

$$F_R(3) = \frac{X_S(5)(1-X_S(3))}{X_S(5)-X_S(3)} F_R(1) \tag{9}$$

Substituting this back into Eq. 8, we get

$$F_R(5) = \frac{X_S(3)(1-X_S(5))}{X_S(5)-X_S(3)} F_R(1) \tag{10}$$

Using the definition of $X_S(5)$, the recycle flow rate of $\{BH^+,(S)\text{-}A^-\}$, $F_S(5)$ is solved using Eq. 10

$$F_S(5) = \frac{X_S(5)X_S(3)}{X_S(5)-X_S(3)} F_R(1) \tag{11}$$

The solvent flow in the recycle is now calculated using Eqs. 10 and 11

$$F_W(5) = \left(\frac{x_{W4}}{1-x_{W4}}\right) \frac{X_S(3)}{X_S(5)-X_S(3)} F_R(1) \tag{12}$$

The choice of values for the design variables are constrained by the features of the phase diagram, Figure 8a. The design variables $X_S(3)$ and $X_S(5)$ are limited by the locations of the double saturation points $X_{ds}(T_{C1})$ and $X_{ds}(T_{C2})$ at the crystallizer temperatures T_{C1} and T_{C2}. Based on the geometry of this example

$$X_S(3) > X_{ds}(T_{C1}) \tag{13}$$

$$X_S(5) < X_{ds}(T_{C2}) \tag{14}$$

From Eq. 12, in order for the recycle solvent flow rate to be positive we have $X_S(3) < X_S(5)$, giving,

$$X_{ds}(T_{C1}) < X_S(3) < X_S(5) < X_{ds}(T_{C2}) \tag{15}$$

A plot of the ratio recycle flow to this subsystem's feed flow $F(5)/F(1)$ for various values of $X_S(3)$ and $X_S(5)$ are given in Figure 9. In addition to the feed composition $x_R(1)$ (= 0.2), the only parameter needed for this figure is $x_W(4) = 0.7$. Large recycle flow rates, which generally require large equipment sizes, occur when $X_S(3)$ is nearly equal to $X_S(5)$. Large recycle flow rates correspond to the ratio $X_S(3)/X_S(5)$ being large. In terms of the phase diagram, this means phase diagrams which exhibit greater shifting of the relative amounts of *R* and *S* between double saturation points at different temperatures are more economic candidates for this type of crystallization system. In an ideal liquid mixture, the relative amount of *R* and *S* at the double saturation point is constant with changing temperature. Thus, nonideality in the liquid phase is a *desired* property of the solvent-resolving agent-enantiomer mixture. It is worthwhile noting that the more solvent added at dissolver D1 the more is recycled and subse-

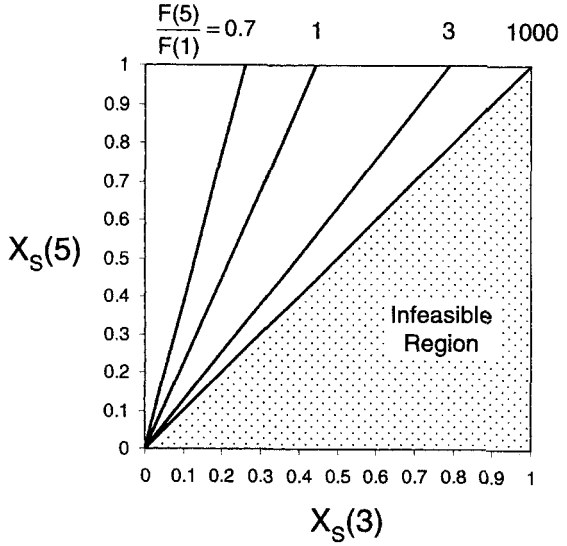


Figure 9. Dependence of recycle flow on design variables $X_S(3)$ and $X_S(5)$.

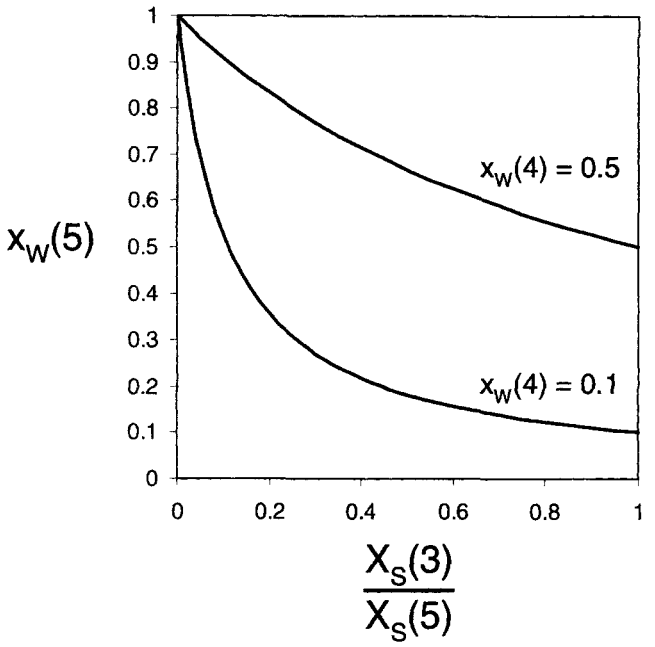


Figure 10. Dependence of molar fraction of solvent in recycle stream on the ratio $X_S(3)/X_S(5)$.

quently evaporated. Therefore, a solvent for which the solutes have high solubility is desired for this flowsheet configuration.

Figure 10 shows that the mol fraction of solvent in the recycle stream $x_W(5)$ decreases with an increase in the ratio of the design variables $X_S(3)/X_S(5)$. Recall that the total flow in stream 5 increases with increasing $X_S(3)/X_S(5)$. This signifies that more solute is being recycled. Figure 10 also shows the difference in $x_W(5)$ as the solubility of the solute is varied. High values of $x_W(4)$ mean that the solutes have lower solubility in the solvent, thereby demanding higher solvent content to prevent premature precipitation.

The separation systems for recovery of the enantiomer and resolving agent, shown in Figure 7, have the same equipment configuration as described above for separation of the dissociable compounds. The flows of NaOH and *B* are fixed by the specification that all reactants are fed in stoichiometric amounts. Thus, the only remaining design variables that need to be specified are the dissolver temperatures and the solvent flow rates to dissolver tanks D2 and D3. The design problem at this point is to find the least amount of solvent needed to run the process, given thermodynamic constraints and operability constraints. The analysis is similar to what we have done for the upstream separations system and is omitted.

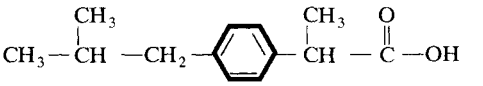
Example 2: Resolution of Ibuprofen Using (S)-lysine

Ibuprofen, α-methyl-4-(2-methylpropyl) benzeneacetic acid, is an analgesic normally used to relieve pain and inflammation, such as arthritic conditions, dental pain, and sports injuries. It is widely available without prescription under a variety of trade names including Advil, Nuprin, and Motrin. Sunshine and Laska (1989) found that the use of optically pure (S)-ibuprofen elicits a more potent and rapid analgesic response compared to the same dosage of ibuprofen in its racemic form. Indeed, (S)-ibuprofen has been recognized as the active form (Tung et al., 1991a; Schloemer et al., 1997) although ibuprofen is predominantly marketed as the racemic mixture. Accordingly, it is desirable to design a process for obtaining optically pure (S)-ibuprofen crystals from a racemic mixture. The necessary input information is given in Table 11.

Step 1. The separation objective is to recover a single enantiomer, namely (S)-ibuprofen.

Step 2. In this step, we choose a technique based on the input information. We first consider the possibility of using direct resolution methods (Table 3). The presence of a racemic compound leads to the conclusion that the phase diagram is of type (b) depicted in Figure 1. A feed containing a racemic mixture would lie in the compartment of the racemic

Table 11. Input Information for Example 2: Resolution of Ibuprofen using (S)-lysine

General Information of Ibuprofen (A)	
Chemical formula	
Solubility in water	Very low and identical for both enantiomers
pK_a (Janjikhel and Adeyeye, 1999)	4.8
Racemic compound	A racemic compound forms between (*R*)-*A* and (*S*)-*A*
General Information on (S)-lysine (B)	
Chemical formula	$H_2N(CH_3)_4CH(NH_2)COOH$
Solubility in water at 25°C, g/L	400
pK_a (Lide, 1997)	10.53
Resolution of (RS)-Ibuprofen-(S)-Lysinate	
Solvent	Ethanol in water (97% solution)
Crystallization temperature	23°C
Solubility in solvent at 23°C (Tung et al., 1991b)	(*R*)-*A*·(*S*)-*B*: 8 g/L (*S*)-*A*·(*S*)-*B*: 6 g/L
Racemic compound	No racemic compound
Crystallization kinetics	Racemization is much slower than crystallization; (*S*)-*A*·(*S*)-*B* grows 3 times faster than (*R*)-*A*·(*S*)-*B*
Racemization yield, y_d	100%

compound, making it impossible to recover any of the enantiomers in a pure form. Therefore, direct resolution is not recommended, and we should consider the use of a resolving agent.

Table 4 indicates that the next simplest method is to use stoichiometric resolution with a single MSA. The presence of a carboxylic group in the ibuprofen molecule opens the possibility of using a base to form diastereomeric salts. Among the compounds matching the criteria in Table 6, several have been proposed in the open and patent literature. For example, the use of (*S*)-α-methylbenzylamine has been proposed (Manimaran and Impastato, 1991). Optically active amino acids, such as lysine, arginine, and histidine, are also good candidates for MSA in ibuprofen resolution (Bhattacharya et al., 1994). In this example, we consider the use of (S)-lysine (*B*).

Step 3. The phase diagram of the ibuprofen-lysinate system with 97% solution of aqueous ethanol as the solvent at the crystallization temperature is depicted in Figure 11 (Tung et al., 1991b). The advantage of using such a high concentration of organic solvent is twofold: to reduce salt solubility and to prevent hydrate formation (Tung et al., 1991a). Given that the objective is to recover only (*S*)-*AH*, a racemization unit is considered, as pointed out in a heuristic in Table 3. To select a flowsheet structure, we follow Table 9. First, we consider the location of the feed. After addition of (*S*)-*B* and the solvent, the feed composition is located inside the compartment of the (*S*)-*AH*·(*S*)-*B* salt. Second, asymmetric transformation is considered. Since the rate of racemization is much slower than that of crystallization (Table 11), successful transformation is unlikely (Table 3). Third, the overall yield is evaluated. Assuming $y_d = 1$ (Table 11), we obtain $R_p = 1$ (Eq. 6). Therefore, the initial flowsheet structure is Figure 6f. The separation box (*s*) in this structure is expanded in the next step to give the complete flowsheet.

Step 4. Following the procedure described in Wibowo and Ng (2000), we obtain the flowsheet in Figure 12. Since there is only one product, (S)-ibuprofen, only one crystallizer is

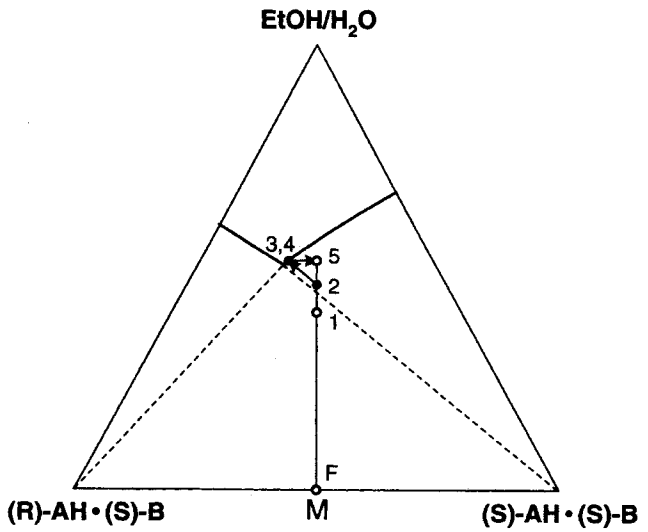


Figure 11. Phase diagram for Example 2: resolution of ibuprofen using (S)-lysine.

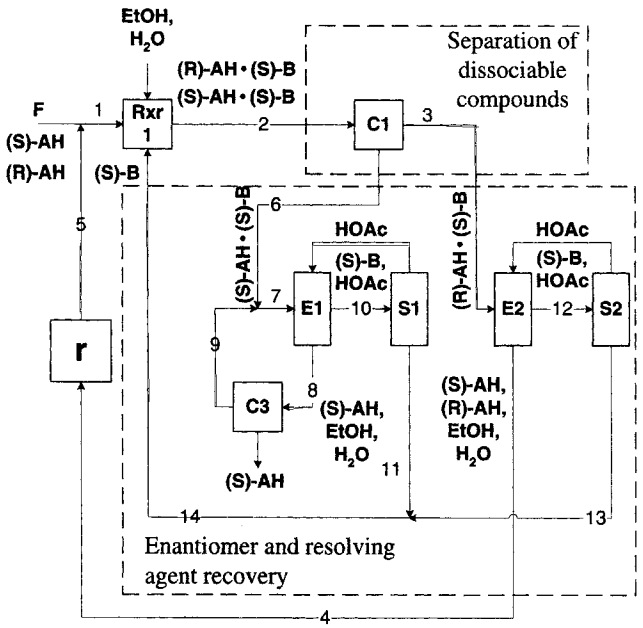


Figure 12. Example 2: resolution of ibuprofen using (S)-lysine.

needed for separation of the dissociable compounds. (*S*)-*B* is added to Rxr1 at the beginning of the separation train to form a mixture of lysinate salts, (*R*)-*AH*·(*S*)-*B* and (*S*)-*AH*·(*S*)-*B*. The latter is then removed as crystals in the crystallizer *C*1. The mother liquor (stream 3), enriched with (*R*)-*AH*·(*S*)-*B*, is sent to the racemization unit. However, the resolving agent in this stream and in the crystallizer product (stream 6) must be separated first. An option to free (S)-lysine from the salts is by adding an acid. Since ibuprofen is virtually insoluble in water, while (S)-lysine is very soluble, extraction using an aqueous acetic acid solution causes salt decomposition as well as separation of the lysine (Table 3). To enhance the solubility of ibuprofen in the organic phase, an alkane such as heptane, is added. The addition and removal of heptane is not shown in Figure 12 to maintain clarity. (S)-ibuprofen is then recovered as solid crystals from the organic phase (stream 8) in a crystallizer. The lysine can be regenerated from the lysine acetate solution (streams 10 and 12) using recovery methods such as distillation, and then recycled. The final flowsheet in Figure 12 is essentially the same as the one described in a patent assigned to Hoechst Celanese Corp. (Bhattacharya et al., 1994).

Other resolving agents can also be used for resolving ibuprofen. For example, Schloemer et al. (1997) disclosed the use of *N*-octyl-D-glucamine, which was found to give a system of diastereomeric salts having a similar phase behavior to the one depicted in Figure 11. Consequently, the resulting flowsheet is almost identical to that in Figure 12.

While there is no incentive to recover (*R*)-ibuprofen, let us recover both enantiomers for the sake of demonstration. An alternative is to replace the racemization block in Figure 12 with a separation scheme to recover (*R*)-ibuprofen. In principle, a resolving agent is added to form a dissociable compound *AH*·*D*, where (*R*)-*AH*·*D* is less soluble than (*S*)-*AH*·*D*. Another possibility of recovering both enantiomers is to

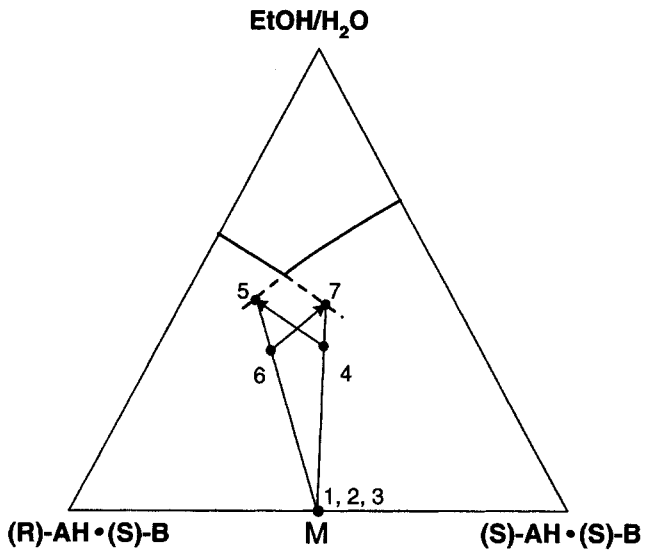


Figure 13. Process alternative for Example 2: phase diagram.

use seeded crystallization with (S)-lysine as the resolving agent. The heuristic in Table 3 suggests that the faster-growing (S)-$AH\cdot(S)$-B should be separated first. Following Table 9, the appropriate flowsheet structure is Figure 6b. Ibuprofen can be recovered from the diastereomeric salts using acetic acid, as described previously. Figure 13 shows the process paths on the phase diagram, while Figure 14 shows the final flowsheet for this process. The racemic mixture feed is combined with the resolving agent, (S)-B. Part of this mixture is mixed with a recycle stream (7) to give stream 4, which is fed to the first crystallizer to remove crystals of (S)-$AH\cdot(S)$-B. The mother liquor from the first crystallizer (stream 5) is combined with the remaining feed and fed to a second crystallizer where (R)-$AH\cdot(S)$-B is removed. The effluent from this crystallizer (stream 7) is recycled. The resolving agent is recovered from the crystal products (streams 8 and 14). The flowsheet in Figure 14 is similar to the one proposed by Tung et al. (1991b).

Table 12. Chemistry for Example 3: Mutual Resolution of Two Racemates

Dissociable Compound Formation

(R)-$AH + (R)$-$B \leftrightarrow \{(R)\text{-}BH^+, (R)\text{-}A^-\}$

(S)-$AH + (S)$-$B \leftrightarrow \{(S)\text{-}BH^+, (S)\text{-}A^-\}$

$\{(R)\text{-}BH^+, (R)\text{-}A^-\} + \{(S)\text{-}BH^+, (S)\text{-}A^-\} \leftrightarrow \{(R)\text{-}BH^+, (S)\text{-}A^-\} + \{(S)\text{-}BH^+, (R)\text{-}A^-\}$

Dissociable Compound Decomposition

$\{(R)\text{-}BH^+, (R)\text{-}A^-\} + HCl \leftrightarrow \{(R)\text{-}BH^+, Cl^-\} + (R)\text{-}AH$

$\{(S)\text{-}BH^+, (S)\text{-}A^-\} + HCl \leftrightarrow \{(S)\text{-}BH^+, Cl^-\} + (S)\text{-}AH$

Solvent

Water

Example 3: Mutual Resolution of Two Racemates

This is a demonstration of mutual resolution of two racemic mixtures using fractional crystallization. This is akin to the technique proposed by Marckwald (1896), who used the second enantiomer of a chiral resolving agent to obtain the other enantiomer of a racemate. In the classification of Table 4, it falls under the heading of stoichiometric resolution using a pair of enantiomers as mass separating agents. The chemistry of compound formation and decomposition is given in Table 12. The two racemates react to form a quaternary conjugate salt system. The phase diagram at two temperatures T_{C1} and T_{C2} is shown on a quaternary conjugate salt phase diagram in Figure 15. This diagram is plotted with its x-axis in $[(S)\text{-}A^-]/([(R)\text{-}A^-]+[(S)\text{-}A^-])$, and its y-axis in $[(S)\text{-}BH^+]/([(S)\text{-}BH^+]+[(R)\text{-}BH^+])$. $\{(R)\text{-}BH^+, (R)\text{-}A^-\}$ and $\{(S)\text{-}BH^+, (S)\text{-}$

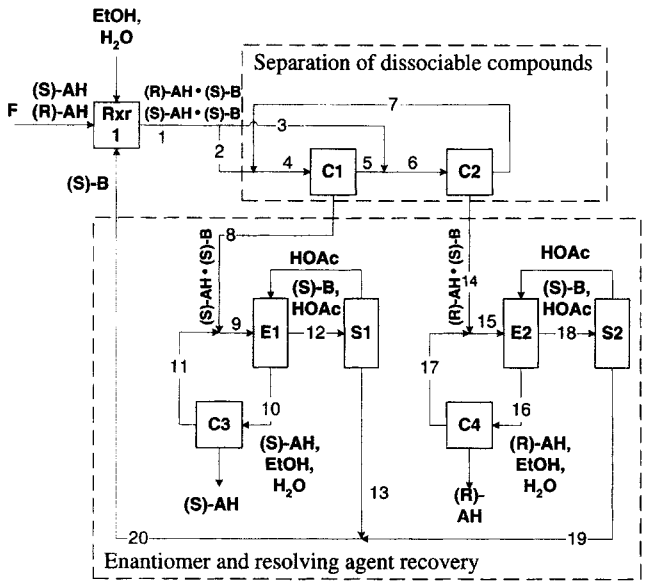


Figure 14. Process alternative for Example 2: process flowsheet.

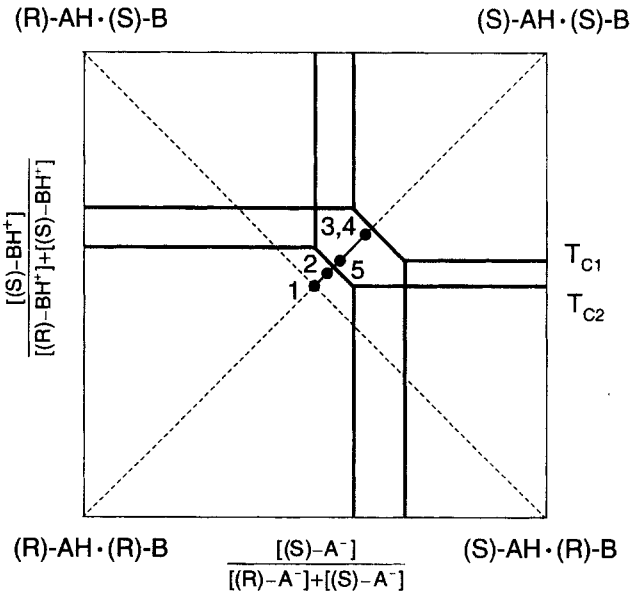


Figure 15. Quaternary salt phase diagram for Example 3: mutual resolution of two racemates.

$A^-\}$ form the compatible salt pair while $\{(R)\text{-}BH^+,(S)\text{-}A^-\}$ and $\{(S)\text{-}BH^+,(R)\text{-}A^-\}$ form the incompatible salt pair.

The flowsheet for this process is given in Figure 16. This process combines the two racemates in equal amounts to form the conjugate salt system. The compatible salts are separated by a fractional crystallization scheme described in Berry and Ng (1996). The process paths are also shown on the phase diagram in Figure 15. At T_{C1}, $\{(R)\text{-}BH^+,(R)\text{-}A^-\}$ is recovered as crystals in crystallizer $C1$. At T_{C2}, $\{(S)\text{-}BH^+,(S)\text{-}A^-\}$ is recovered as crystals in crystallizer $C2$. After separation, the salts are decomposed using hydrochloric acid in Rxr2 and Rxr3. This forms the free acid and the chloride salt of the base that are separated using another crystallization scheme. Phase diagrams with process paths for these processes are not explicitly given, but are expected to be qualitatively similar to Figure 8b.

It is interesting to note that which salt pair is compatible and incompatible is immaterial to achieving the separation objective. If the pairing were reversed (that is, $\{(R)\text{-}BH^+,(S)\text{-}A^-\}$ and $\{(S)\text{-}BH^+,(R)\text{-}A^-\}$ forming the compatible salt pair), separation of the compatible salt pairs and subsequent decomposition still gives the same four separate enantiomers. Another perspective of this method is presented in Figures 17a–17c, which show quaternary conjugate salt phase diagrams for different possible phase behaviors. The filled (unfilled) circle shows the feed composition for the process if (R)-B ((S)-B) is the resolving agent. By selecting either (S)-B or (R)-B as the resolving agent, one can engineer which crystallization compartment from which the separation will begin.

Example 4: Use of a Mixture of Resolving Agents

This is an example of separation using a two-component mass separating agent. Here we use one chiral resolving agent and one achiral resolving agent in a single application to separate a racemic mixture. The necessary chemistry for this example is shown in Table 13. The chiral resolving agent is denoted as B. The achiral MSA is potassium hydroxide. This

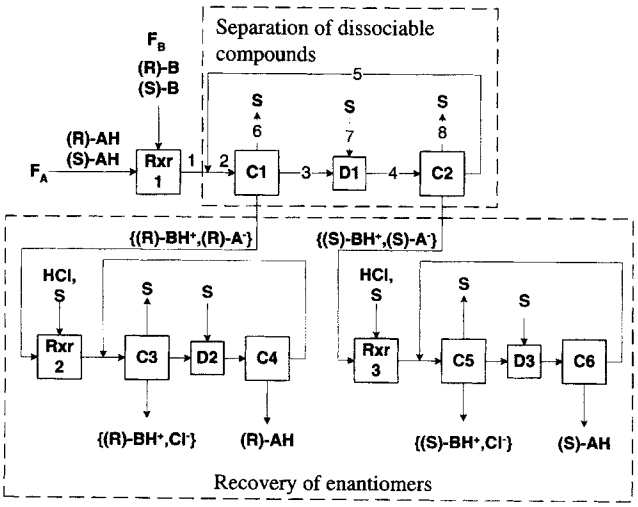


Figure 16. Example 3: mutual resolution of two racemates.

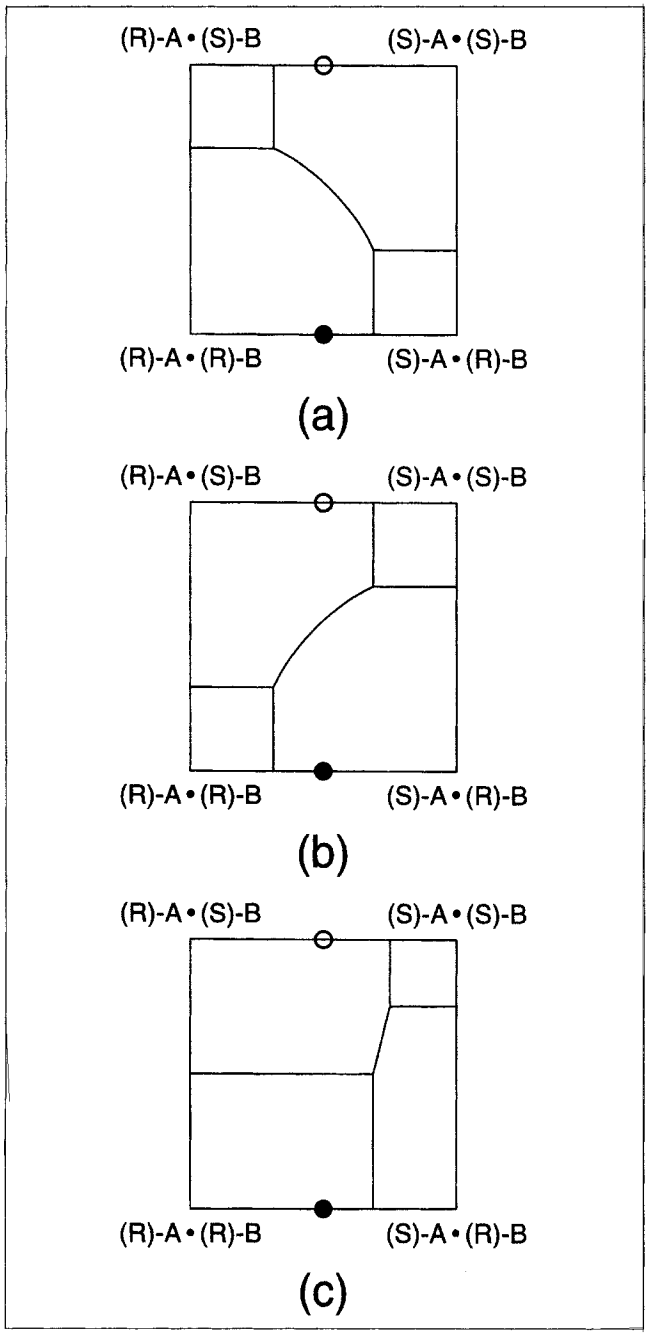


Figure 17. Effect of choice of resolving agent on the product at the first crystallizer for three phase behaviors.

mixture forms a quaternary conjugate salt system

$$\{BH^+,(R)\text{-}A^-\}+\{K^+,(S)\text{-}A^-\}\leftrightarrow\{K^+,(R)\text{-}A^-\}+\{BH^+,(S)\text{-}A^-\} \quad (16)$$

The corresponding phase diagram is shown in Figure 18 with its x-axis in $[(S)\text{-}A^-]/([(S)\text{-}A^-]+[(R)\text{-}A^-])$, and its y-axis in $[K^+]/([K^+]+[BH^+])$. Note that the potassium salts of the enantiomers are much more soluble than the diastereomeric

Table 13. Chemistry for Example 4: Use of a Mixture of Resolving Agents

Dissociable Compound Formation
$(R)\text{-}AH + B \leftrightarrow \{BH^+,(R)\text{-}A^-\}$
$(S)\text{-}AH + B \leftrightarrow \{BH^+,(S)\text{-}A^-\}$
$(R)\text{-}AH + KOH \leftrightarrow \{K^+,(R)\text{-}A^-\} + H_2O$
$(S)\text{-}AH + KOH \leftrightarrow \{K^+,(S)\text{-}A^-\} + H_2O$
Dissociable Compound Decomposition
$\{BH^+,(R)\text{-}A^-\} + KOH \leftrightarrow B + \{K^+,(R)\text{-}A^-\} + H_2O$
$\{BH^+,(S)\text{-}A^-\} + KOH \leftrightarrow B + \{K^+,(S)\text{-}A^-\} + H_2O$
Solvent
Water

salts. Thus, the double saturation troughs between the potassium salts and the diastereomeric salts are much closer to the side of the potassium salts. This gives a larger area over which $\{BH^+,(R)\text{-}A^-\}$ can crystallize out.

As a historical note, the method of adding half of an equivalent of a strong acid or base along with half of an equivalent of chiral resolving agent was first done by Pope and Peachey (1899). By illustration with the quaternary conjugate salt phase diagram, the utility of their method is clear. The second MSA, *KOH*, gives a much more soluble dissociable compound than that with the organic chiral MSA, that in turn allows greater single pass recovery of the latter.

The flowsheet is depicted in Figure 19. The dissolved racemate reacts with a 50:50 mixture of each of the MSAs. The resulting stream is mixed with a recycle stream (stream 5) and fed to crystallizer $C1$. The crystallizer $C1$ is an evaporative crystallizer operating at temperature T_{C1}. The diastereomeric salt $\{BH^+,(R)\text{-}A^-\}$ crystallizes from solution and is removed with a filter. The mother liquor (stream 3) from crystallizer $C1$ is diluted with solvent and fed to another

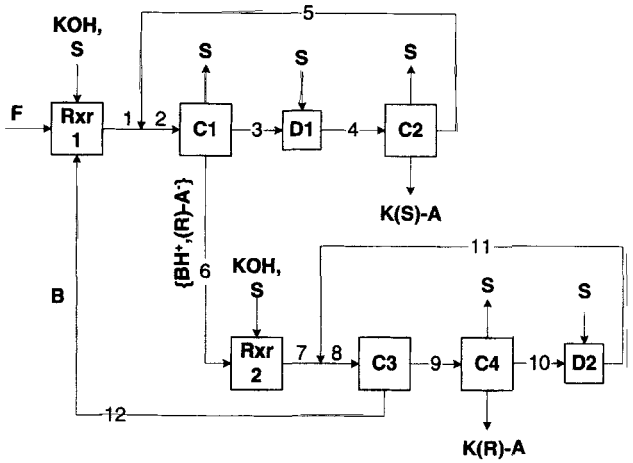


Figure 19. Example 4: use of a mixture of resolving agents.

evaporative crystallizer ($C2$) operating at a lower temperature T_{C2}. In crystallizer $C2$ the potassium salt of (S)-A is the least soluble solute and is crystallized and filtered. The mother liquor from the second crystallizer is recycled.

The diastereomeric salt $\{BH^+,(R)\text{-}A^-\}$ is redissolved and decomposed by adding additional potassium hydroxide. The phase diagram containing the process paths for this subprocess is given in Figure 20. The mixture (stream 7) is combined with a recycle stream (stream 11). The chiral MSA (B) is removed in a cooling crystallizer ($C3$). The product $K(R)$-A is subsequently removed in an evaporative crystallizer ($C4$) operating at a higher temperature T_{C4}. Solvent is added to the recycled mother liquor from crystallizer $C4$ (stream 10).

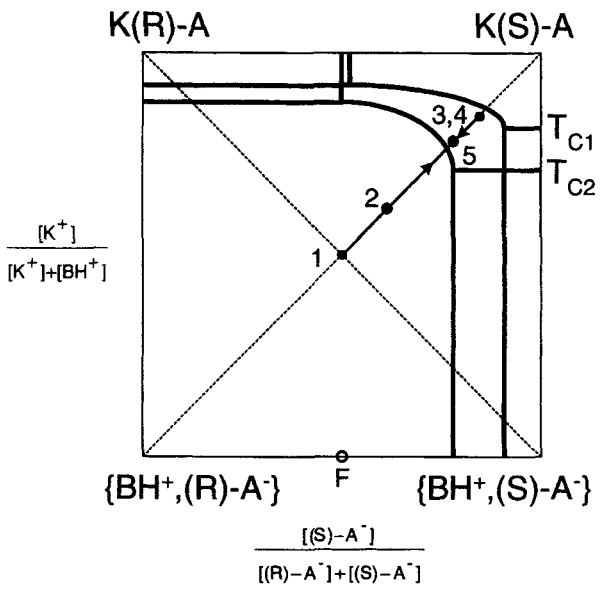


Figure 18. Quaternary conjugate salt phase diagram for Example 4: use of a mixture of resolving agents.

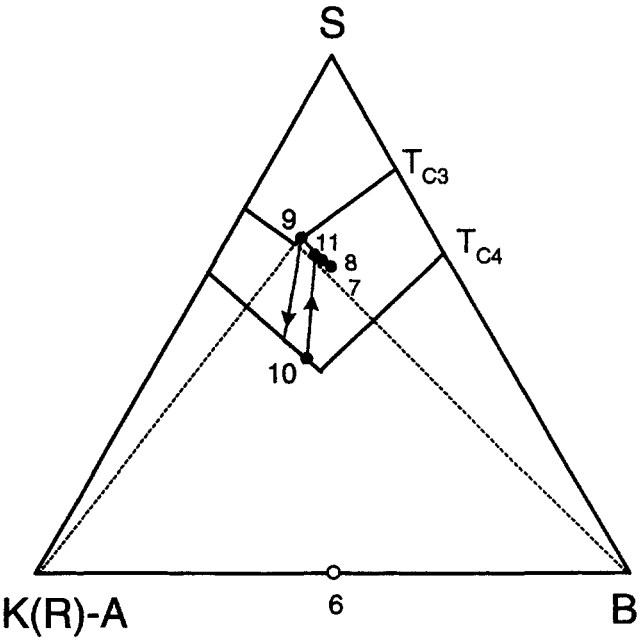
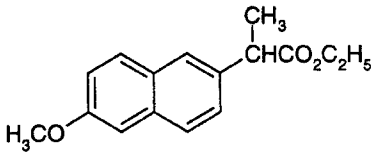


Figure 20. Product and resolving agent recovery in Example 4.

Table 14. Data for the Resolution of an (S)-Naproxen Intermediate (Source: Arai et al., 1983)

General Information of Ethyl α-(6-Methoxy-2-Naphthyl)Proprionate

Chemical formula



	(S)-form	Racemate
Melting points (°C)	81–82	50–52
Solubilities in ethanol at 21°C, kg/kg	0.038	0.126
Racemization		
Method	Base catalyzed using C_2H_5ONa	
Rate constant, 2% C_2H_5ONa, 21°C	$2.9x10^{-4}s^{-1}$	

Example 5: Direct Crystallization of a Naproxen Intermediate

Naproxen is an analgesic that is currently marketed in nonprescription form under the brand name Aleve. It has been found that the (*S*)-isomer has 28 times the anti-inflammatory activity as that of the (R)-isomer (van Eikeren, 1997). Nissan Chemical Industries has patented one route to (S)-naproxen by resolution of an intermediate, ethyl α-(6-methoxy-2-naphthyl)propionate, which is readily converted to (S)-naproxen (Arai et al., 1983). Table 14 shows available data concerning the process.

Step 1. Our objective is to recover 100% (S)-ethyl α-(6-methoxy-2-naphthyl)propionate.

Step 2. We want to try direct crystallization first. While the phase behavior is not known, the solubility data suggest that it is close to a conglomerate system. If a stable 1:1 compound were present in the phase diagram, we would expect the racemate to have a solubility comparable to twice that of the enantiomer. In this case, the racemate solubility of 0.126 kg/kg ethanol is much higher than the (S)-form solubility at 0.038 kg/kg ethanol. Therefore, direct resolution is a reasonable approach.

Step 3. For recovery of a single enantiomer, we should consider using racemization. Assuming a conglomerate system, our feed composition will be at the double saturation point, which is sufficiently close to the (S)-ethyl α-(6-methoxy-2-naphthyl)propionate crystallization compartment to use seeded crystallization. In addition, it is known that, in the presence of sodium ethoxide, the rate of racemization is fast. Thus, an asymmetric transformation process should be used and Figure 6d is the suitable flowsheet, which is identical to the process described by Arai.

Syntex has a process for resolution of naproxen using diastereomeric salt formation (Holton, 1985). This process is a two-component single MSA application process involving a mixture of resolving agents, triethylamine, an achiral agent, and an *N-n*-alkyl-D-glucamine, a chiral agent. One possible configuration according to the patent is given in Figure 21 which shows that Syntex chose flowsheet 6(e), which isolates the undesired enantiomer, (R)-naproxen, in the separation unit denoted by *s* before racemization for recycle (r). (S)-Naproxen is separated from the racemic mixture feed by diastereomeric salt formation with the *N-n*-alkyl-D-glucamine, shown in the subsystem enclosed by the dotted line (Figure 21). After the diastereomeric salt is recovered by crystallization (*C*1), it is decomposed by aqueous HCl (Rxr2) and the (S)-naproxen enantiomer is recovered in a second crystallizer (*C*2). The resolving agent is recovered by a combination of crystallization and distillation.

Without going over the details, our design procedure also shows that asymmetric transformation of diastereomers (flowsheet 6(d)) and mother liquor racemization (flowsheet 6(f)) are other possible alternatives. A Step 4 analysis suggests that within the chosen racemization scheme fractional crystallization of a conjugate salt system may also be an alternative (Figure 16). Again, our procedure identifies the possible alternatives, actual feasibility depends on the quaternary conjugate salt phase diagram of (R)- and (S)-naproxen and the two resolving agents, which has to be determined by experiments.

Example 6: Method of Ingersoll Extended

This example illustrates processes involving multiple MSA applications, and the fact that the mixture MSA may have any composition. Historically, Ingersoll (1925, 1928) performed the first successful racemate resolution by using such mixtures of chiral MSAs.

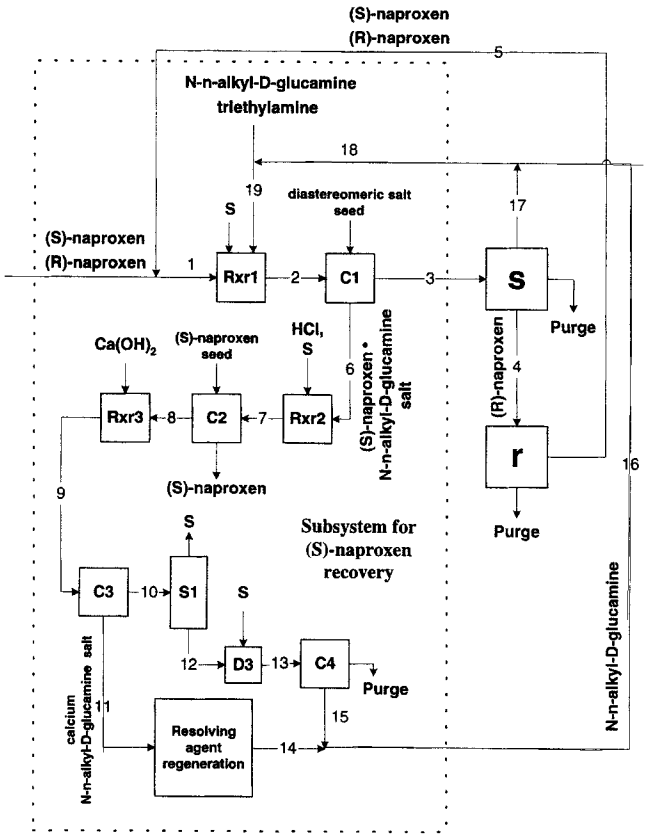


Figure 21. Resolution of naproxen using diastereomeric salt formation.

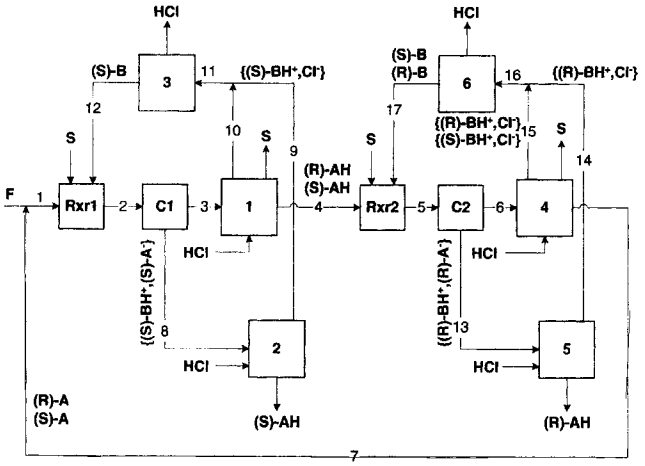


Figure 22. Example 6: method of Ingersoll extended.

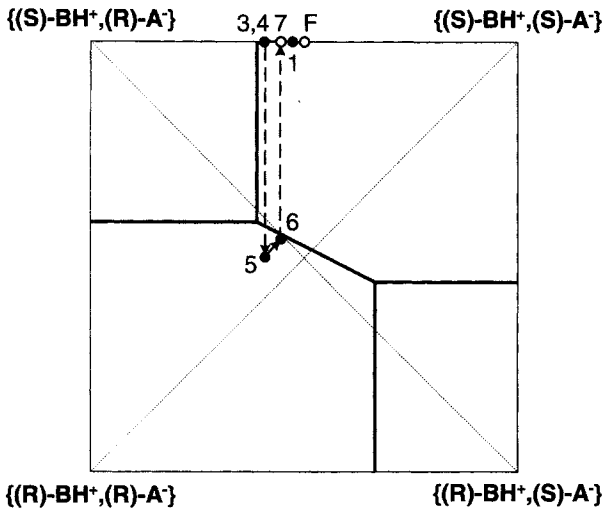


Figure 23. Example 6: method of Ingersoll extended.

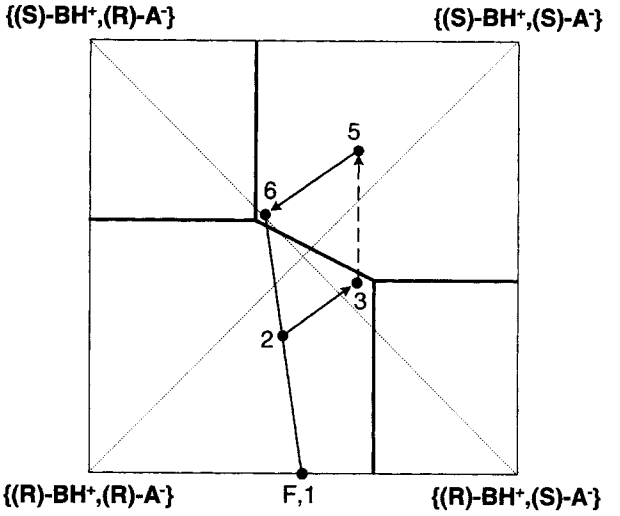


Figure 24. Example 6 with new recycle structure, phase diagram.

Figure 22 shows the overall flowsheet for racemate separation by first employing a chiral resolving agent ((*S*)-*B*) and second employing the racemic mixture of the same agent as the MSA. Figure 23 shows the phase diagram containing process paths for this process. The feed (*F*), recycled enantiomer, and resolving agent (*S*)-*B*, and solvent *S* are mixed in a reactor (Rxr1) where diastereomeric salts are formed. The mixture is cooled in a crystallizer (*C*1) precipitating the diastereomeric salt $\{(S)\text{-}BH^+,(S)\text{-}A^-\}$, which is sent to subsystem 2 to recover (*S*)-*AH*. Similarly, the dissociable compounds in the mother liquor are decomposed using HCl in box 1. Streams 9 and 10 containing the chloride salt of (*S*)-*B* are sent to subsystem 3 to recover the resolving agent.

Up to this point, we only operate along the upper edge of the phase diagram. Now, the enantiomers (stream 4) are redissolved in a reactor (Rxr2) to which a racemic mixture ((*R*)-*B* and (*S*)-*B*) of the resolving agent is added. The composition of this mixture (stream 5) is now in the crystallization region of $\{(R)\text{-}BH^+,(R)\text{-}A^-\}$ in Figure 23. This diastereomeric salt is precipitated by cooling in another crystallizer (*C*2) where the $\{(R)\text{-}BH^+,(R)\text{-}A^-\}$ is recovered. The free enantiomer (*R*)-*AH* is recovered (box 5) in the same manner as (*S*)-*AH* (box 2). The diastereomeric salts in the remaining mother liquor (stream 6) are decomposed and recovered (box 4) in the same manner as before (box 1). (Boxes 1, 2, 4, and 5 can be identical processes.) The spent resolving agent are recovered in box 6 as in box 3. This process may be used if the second enantiomer of the resolving agent is not readily available, but the racemate is. The key idea is that a crystallization boundary can be crossed by a change in resolving agent composition.

The phase diagram for a novel configuration for this process is given in Figure 24. The corresponding process flowsheet is given in Figure 25. This eliminates subsystem 4 from the flowsheet by direct recycle of the mother liquor from crystallizer *C*2, which contains a mixture of diastereomeric salts (stream 6). In order to maintain the proper resolving

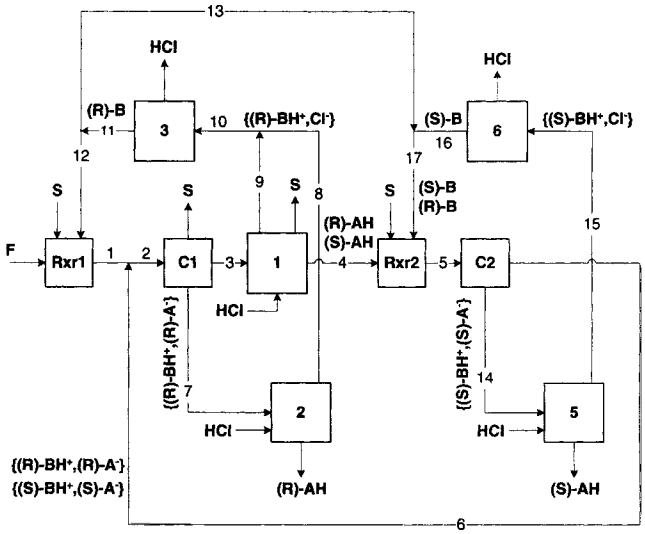


Figure 25. Example 6 with new recycle structure, flowsheet.

agent composition, some of the resolving agent (*R*)-*B* recovered from the first MSA application must be diverted to the Rxr2 via stream 13.

Conclusions

A procedure for the synthesis of crystallization processes for the resolution of racemic mixtures has been presented. In a step-by-step manner, it guides the user to identify the separation objective, to explore the chemical and physical basis for effecting resolution, and to generate the process flowsheet alternatives. The intent of this procedure is not to generate the actual chemistry for a specific racemic mixture; instead, it provides an overall framework for developing a resolution process.

Heuristics are used for each step of the procedure to aid in decision-making. For cases where racemization or deracemization is used, a decision table guides the choice of an appropriate flowsheet structure. Also emphasized is the use of various types of phase diagrams for generating the entire separation system. Changes in crystallization boundaries with changes in temperature, solvent, and resolving agent provide the basis for constructing a process flowsheet for separation of the enantiomers. It should be noted that it is not necessary to determine the entire phase diagram to use this procedure. With the foresights developed in this procedure, one can focus on the portion of the phase diagram that is relevant to the flowsheet, thereby reducing the amount of experimental effort.

Examples are provided to illustrate the various methods in this synthesis procedure. In addition to direct crystallization, one can use a single enantiomer, a racemic mixture of a resolving agent, or a mixture of resolving agents. The effects of design variables on process flows are also discussed.

Not all types of phase equilibrium phenomena are included. Not considered is the possibility of using melt crystallization for the separation of solid solutions, the effects of pressure on phase behaviors, liquid-liquid phase split (oiling out) upon addition of MSA, the formation of hydrates, or structurally ordered solid compound formation. Also, crystallization is one of the techniques used for racemate resolution. While we focus on crystallization-based separations in this study, it is advantageous to consider hybrid systems where crystallization is used along with other techniques such as adsorption and extraction. Similar ideas have been proposed for distillation-crystallization hybrids for separation of achiral compounds (Berry and Ng, 1997).

In addition, the effects of mass transfer and kinetics were not given treatment in detail, but are clearly of importance. Some treatment has been given for reactive systems (Kelkar and Ng, 1999), but further research is needed in this area.

Acknowledgment

We express our appreciation to the National Science Foundation, Grant No. CTS-9908667, for support of this research.

Notation

A = racemate
B = resolving agent
$D \cdot E$ = dissociable compound formed between D and E
$F_i(j)$ = molar flow rate of component i in stream j
HA = acid form of A
$[I]$ = concentration of I in solution (molarity)
$\{I,J\}$ = ionic salt of I and J
K = dissociation constant
M = racemic composition
$pK = -\mathrm{Log}_{10}(\mathrm{K})$
R_p = productivity ratio
$(R),(S)$ = denote chirality according to Cahn-Ingold-Prelog notational system
S = solvent
T = temperature
$x_i(j)$ = mol fraction of component i in stream j
$X_i(j)$ = solventless mol fraction of component i in stream j
$\bar{X}$ = product distribution
y_d = yield

Subscripts

C = crystallizer
ds = double saturation
R = (R)-enantiomer or diastereomer
S = (S)-enantiomer or diastereomer
W = solvent
0 = initial

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