the two zones, i.e.:

\[
\Delta \text{pH}_{Z \pm} = \log \left( \frac{[\text{CS}]_{\text{org}}Z_+ K_{t+} + 1 - D_0/K_t}{[\text{CS}]_{\text{org}}Z_- K_{t-} + 1 - D_0/K_t} \right)
\]

where \([\text{CS}]_{\text{org}}Z_+ \) and \([\text{CS}]_{\text{org}}Z_- \) are the free CS concentrations in the A_+ and A_- zones, respectively. When \(K_{t+} > K_{t-}, [\text{CS}]_{\text{org}}Z_+ < [\text{CS}]_{\text{org}}Z_- < [\text{CS}]_{\text{initial}}\). Eqn [13] indicates that chiral resolution can be improved by increasing \(D_0/K_t\) and/or choosing the CS with a large \(K_{t+}/K_{t-}\) value. It also implies that increasing the CS concentration will yield higher peak resolution.

**Advantages of Chiral CCC**

Countercurrent chromatography can be applied to the separation of enantiomers by dissolving a suitable chiral selector in the liquid stationary phase in analogy to binding the CS to the solid support. The HSCCC technique has the following advantages over the conventional chromatographic technique using a solid stationary phase:

1. The method permits repetitive use of the same column for a variety of chiral separations by choosing appropriate chiral selectors.
2. Both analytical and preparative separations can be performed in a standard CCC column by adjusting the amount of CS in the liquid stationary phase. The method is cost effective especially for large scale preparative separations.
3. The separation factor and peak resolution can be improved by increasing the concentration of CS in the stationary phase.
4. The method is very useful for investigation of the enantioselectivity of the chiral selector including determination of formation constant and separation factor.
5. pH-Zone-refining CCC can be applied to chiral separation allowing a large scale separation in a shorter separation time.

See also: II/Chromatography: Chromatography: Instrumentation. III/Chiral Separations: Amino Acids and Derivatives; Capillary Electrophoresis; Cellulose and Cellulose Derived Phases; Countercurrent Chromatography; Cyclodextrins ad Other Inclusion Complexation Approaches; Gas Chromatography; Ion-Pair Chromatography; Liquid Chromatography; Molecular Imprints as Stationary Phases; Protein Stationary Phases; Supercritical Fluid Chromatography; Synthetic Multiple Interaction (‘Pirkle’) Stationary Phases; Thin-Layer (Planar) Chromatography. Zone Refining Countercurrent Chromatography.

**Further Reading**


**Crystallization**

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Methods for obtaining optically active compounds in enantiopure form are commonly classified into three categories: utilization of chiral pool starting materials (stereoselective multistep synthesis), creation of chirality from achiral precursors (asymmetric synthesis) and separation of racemates into their enantiomer constituents (resolution). This last method can be carried out in a variety of ways: crystallization processes, chromatography of racemates on chiral stationary phases and kinetic resolution mediated by chiral reagents or enzymes.

The crystallization methods comprise several variants: (1) direct crystallization of enantiomer mixtures, (2) separation of diastereoisomer mixtures – the so-called classical resolution – and (3) crystallization-induced asymmetric transformation. The first two were discovered by Louis Pasteur in 1848 and 1853, respectively. The third was first reported in 1913. At the turn of the 21st century, these methods are in wide use in laboratory-scale separations as well as in industry for the preparation of pharmaceutical and agrochemical active principles. To cite but a few examples, hundreds to thousands of tonnes of commercially important materials such as (-)-menthol, (S)-(+-)naproxen, 1,2-methylodopa, D-phenylglycine and the pyrethroid insecticide deltamethrin are produced by such methods.
In the context of enantiomer separations crystallization techniques are attractive for several reasons. Firstly, in many instances they are more straightforward and more economical than any other method. Secondly, these methods, once considered old-fashioned, have, during the past two decades, been greatly improved in their rationale and efficiency, as a consequence of a better knowledge of the properties upon which separations by crystallization are based: identification of racemate types, utilization of phase diagrams describing solid–liquid equilibria. Thirdly, these methods apply not only to the resolution of racemates (i.e. 1:1 mixtures of d and l enantiomers), they can also be used for obtaining pure enantiomers from nonracemic (partially resolved) mixtures, regardless of their origin. And finally, the so-called crystallization-induced asymmetric transformation overcomes the inherent 50% yield limitation of a resolution, permitting up to 100% of a racemic material to be converted into one enantiomer in a single stage.

**Enantiomer Mixtures**

This section deals with crystallization methods allowing pure enantiomers to be prepared from partially resolved mixtures or from racemates without the help of any chiral auxiliary reagent.

**Phase Diagrams of Enantiomer Systems**

We call enantiomer systems mixtures containing the two mirror-image d and l components in any ratio, either without solvent (binary (d, l) mixtures), or in the presence of a solvent (ternary (d, l, Σ) mixtures). Depending on the nature of the crystal phases which may coexist with the liquid (melt or solution), three categories of enantiomer systems have been identified.

In the first category, which represents 5–10% of cases, the enantiomers crystallize separately from one another (homochiral crystallization, spontaneous resolution). A solid (d, l) system then consists of a mechanical mixture of d and l crystals in a ratio corresponding to their respective mole fractions (x; 1 − x). The melting point phase diagram shows a simple eutectic at x = 0.5 (racemate composition). Such a (d, l) system is said to be a conglomerate of enantiomers (Figure 1A). In a conglomerate, the racemate has a melting point about 30 K lower than those of its pure enantiomers. Its solid-state infrared spectrum is identical with the solid-state spectrum of a pure enantiomer, because the infrared spectrometer does not make a difference between right- and left-handed crystals. Since most binary mixtures of enantiomers behave ideally in the liquid state, the liquidus curves of a conglomerate phase diagram can generally be accurately calculated by means of the Schröder–van Laar equation, where TA and ΔH_A are the temperature and enthalpy of fusion, respectively, of a pure

---

**Figure 1** Binary melting point phase diagram for enantiomer systems. (A) Conglomerate; (b) racemic compound with T_R < T_A, eutectic at x = 0.3 and 0.7; (c) racemic compound with T_R > T_A, eutectic at x = 0.1 and 0.9. On recrystallization, a solid mixture M in which the mole fraction of the major enantiomer (here d) is 0.8 (enantiomeric excess ee = 60%) can give this enantiomer in pure form in cases (A) and (B), the maximum yield being given by the ratio NA/EA; in case (C) only the racemic compound can be obtained (see text).
enantiomer, and \( R \) is the gas constant. This equation gives the melting temperature \( T \) of a mixture in which \( x \) represents the mole fraction of the major enantiomer:

\[
\ln x = \frac{\Delta H_A}{R} \left( \frac{1}{T_A} - \frac{1}{T} \right)
\]

In the second, main category of enantiomer systems, representing 90–95% of cases, the \( d \) and \( l \) enantiomers crystallize together to form an ordered 1:1 compound, called a racemic compound (heterochiral crystallization). Typical binary phase diagrams corresponding to this case are shown Figure 1(B) and (C). The melting point \( T_R \) of the racemic compound can be either lower or higher than that of the pure enantiomers (however, on average, the difference between \( T_R \) and \( T_A \) rarely exceeds \( \pm 20 \) K). The solid-state infrared spectrum of a racemic compound is different from that of a pure enantiomer. This is a simple way of distinguishing between a racemic compound and a conglomerate (in addition to the melting point criterion). In such systems, a partially resolved solid consists of a mechanical mixture of two crystal phases, the racemic compound, in amount \( r = 2(1 - x) \), and the enantiomer in excess, in amount \( ee = 2x - 1 \). In Figure 1(B) and (C) the liquidus curves for the enantiomer branches are calculated by means of the Schröder–van Laar equation, while the racemic compound branch is calculated by a similar equation first given by Prigogine and Defay, where \( T_R \) and \( \Delta H_R \) are the temperature and enthalpy of fusion, respectively, of the racemic compound:

\[
\ln 4x(1 - x) = \frac{2\Delta H_R}{R} \left( \frac{1}{T_R} - \frac{1}{T} \right)
\]

In the last category of enantiomer systems, called pseudoracemates, there is almost no chiral discrimination between the \( d \) and \( l \) species which co-crystallize more or less at random within the same lattice to form a solid solution. In a pseudoracemate, a partially resolved sample consists of a single crystal containing the \( d \) and \( l \) enantiomers in a ratio \( (x; 1 - x) \). Such systems are, fortunately, not common. They may occur with rod-shaped or quasi-spherical molecules (e.g. camphor). They do not lend themselves easily to separation by crystallization techniques, and for this reason they will no longer be considered here.

**Solubility Rules Derived from Binary-phase Diagrams**

In the absence of temperature- or solvent-dependent polymorphism, the solubility rules that govern the behaviour of enantiomer mixtures on crystallization can be simply derived from the binary phase diagrams depicted in Figure 1. The component which can be obtained upon crystallization will be either the racemic compound, or the enantiomer in excess, depending on the composition of the starting mixture with respect to the closest eutectic of the phase diagram. Thus, recrystallization of mixture \( M \), having \( x = 0.8 \) (\( ee = 60% \)) can give the major enantiomer in pure form in cases (A) and (B). The maximum possible yield is given by \( NE/EA = 60% \) in case (A), and only 33% in case (B). In case (C), recrystallization of \( M \) can only afford the racemate in a maximum yield \( NE/RE \). In this case the enantiomeric enrichment takes place in the liquid, but under equilibrium conditions the highest attainable purity is that of the eutectic. In other terms, in a partially resolved conglomerate, it is always possible to recover the major enantiomer in a yield equal to the \( ee \) of the starting material, whereas in a racemic compound the outcome of the crystallization will depend on the enantiomeric composition of the starting material and on that of eutectic; even in relatively favourable cases such as that depicted in Figure 1(B), the maximum possible yield will be lower than the \( ee \) of the starting material.

**Ternary Phase Diagrams**

For applications in which accurate quantitative data are required (e.g. optimization of large-scale recrystallizations), it is preferable to utilize ternary (solubility) phase diagrams \( (d, l, \Sigma) \). Solubility phase diagrams are 3D triangular prisms where each face is a binary melting point phase diagram, \( (d, l) \), \( (d, \Sigma) \) and \( (l, \Sigma) \). It is customary to convert this 3D representation into a 2D one by keeping one of the variables fixed, most often the temperature. Accordingly, a horizontal slice of the prism generates the usual triangular isotherm describing the solid–liquid phase equilibria at given \( T \). This is illustrated in Figure 2(A), for a conglomerate. In order to facilitate the use of such triangular isotherms, it is convenient to adopt a system of cartesian axes \( (C, E) \), where \( C \) represents the concentration and \( E \) the excess of enantiomer, expressed in the same dimensionless unit (generally in weight %); \( C \) and \( E \) are defined as follows:

\[
C = \frac{d + l}{d + l + \Sigma} \times 100 \quad E = \frac{d - l}{d + l + \Sigma} \times 100
\]

Typical ternary isotherms for a conglomerate and a racemic compound are shown in Figure 2(B) and (C), respectively. In a conglomerate the solubility of the racemate is normally twice the solubility of each
Figure 2 (A) 3D-representation of a \( [d, l, \Sigma] \) system and the corresponding 2D-isotherm, for a conglomerate. The composition of a ternary system \( X \) is conveniently defined by its cartesian coordinates \((C, E)\). Note that \( E/C = ee \), the usual enantiomeric excess, defined as \( ee = (d - l)/(d + l) \); (B) and (C) represent ternary isotherms that correspond roughly to the binary phase diagrams (A) and (B) of Figure 1. On recrystallization, mixture \( M \) will only afford the major enantiomer in pure form if the composition of the ternary system is comprised between \( N \) and \( P \), the maximum yield being obtained for system \( N \) (see text). In diagram (C), \( e \) represents the \( ee \) of the ternary eutectic \( E \).

individual enantiomer, unless special circumstances, such as common ion effects or aggregation phenomena, decrease or increase the solubility ratio with respect to its normal value. Figure 2(B) and (C) roughly correspond to the binary phase diagrams of Figure 1(A) and (B), respectively. On recrystallization of mixture \( M \), the major enantiomer \( d \) can be obtained between \( N \) and \( P \), for instance from system \( O \). However, the best yield \( Y \) in pure \( d \) will be obtained from system \( N \), at concentration \( C_N \) (in weight %):

\[
Y = \frac{NE}{AE} \times \frac{100}{C_N}
\]

For a conglomerate the above calculated yield is the same as that derived from the binary phase diagram, \( Y = NE/AE \). For a racemic compound, \( Y \) calculated from the ternary isotherm is usually very close to that derived from the binary phase diagram because in such systems the \( ee \) of the eutectic does not change significantly with temperature, except in the case of polymorphism or of solvation.

This is why information on the type of enantiomer system and, in particular, on the location of the eutectics in racemic compound phase diagrams is of great importance when the purification of partially resolved mixtures by crystallization techniques is undertaken. When the phase diagram of the considered system is not favourable (e.g. as in Figure 1C), recrystallization should be avoided and it may be advisable to postpone the purification to a next step, or to seek derivatives having more favourable phase diagrams. These concepts are particularly useful for the final purification of enantiomers prepared by asymmetric synthesis or chiral chromatography.

**Direct Crystallization of Racemates**

Separation of enantiomers by direct crystallization of their racemate is an attractive method, because no
rently two main types of methods are then available. In the first of these the two enantiomers are allowed to crystallize simultaneously from a solution or melt which is always close to the racemic composition. In the second, called entrainment, the crystallization of a single enantiomer is promoted from a supersaturated solution or supercooled melt which is not allowed to come to equilibrium.

**Simultaneous Crystallization**

Although hand-sorting of the \( d \) and \( l \) crystals (as originally performed by Pasteur on sodium ammonium tartrate) can occasionally be a useful technique, the localization of the crystallization of each enantiomer on suitably disposed \( d \) and \( l \) seeds represents an improvement of greater practical interest. In small-scale preparations, one can utilize a small number of \( d \) and \( l \) seeds sufficiently separated from one another in the same crystallizer, and the large crystals which are eventually formed are collected manually. Large-scale applications utilize pairs of crystallization chambers, each one being loaded with a large amount of seeds of one enantiomer. The system is then continuously fed with a circulating, slightly supersaturated, racemic solution. Such processes have been proven to be valuable for continuous large-scale productions such as those developed by Haarmann & Reimer for \((-\))-menthol (resolved as its benzoate), and Merck for \(L\)-\(\alpha\)-methyldopa (resolved as its nitrile precursor).

**Entrainment**

The entrainment method takes its origin in experiments performed by Gernez in 1866, showing that a supersaturated solution of sodium ammonium tartrate, when seeded with a particle of \((+\)) salt, only yielded crystals of that salt. The resolution by entrainment is a batch process, which rests on the control of the crystallization rates of the two enantiomers, and implies the utilization of ternary phase diagrams, such as that shown in Figure 3. A solution \( M \), supersaturated with respect of both enantiomers, and containing a small excess \((E\) g\%\) of one of them (here, \(l\)) is seeded with crystals of that enantiomer. Crystallization is then allowed to proceed until the solution has reached composition \( N \). At this point, the rotation of the solution is approximately equal and opposite in sign to that of the starting solution, and the \(l\) enantiomer that has crystallized amounts to twice its excess in the original solution \( M \) (i.e. \(\approx 2E\) g\%). At this stage, the crystals are separated off, and the same weight of racemic material is added to the filtrate and dissolved by heating. This results in a new supersaturated systems of composition \( P \), symmetrical to \( M \), where the \(d\) enantiomer is now in the same excess as was the \(l\) in the previous experiment. Seeding with the \(d\) form and crystallization up to \( Q \) then yields \(\approx 2E\) g\% of \(d\), and addition of the same weight of racemate allows the return to \( M \), and so forth.

In practice, the economics of the process depends on the amount of material collected after each crystallization, which should represent at least 10–15% of the solute, and on the number of cycles which can be performed; this number is limited by the build-up of impurities which follows the addition of fresh racemate at each step, and which may eventually disturb the crystallization kinetics. The Roussel-Uclaf and Zambon processes for the manufacture of the chloramphenicol and thiamphenicol intermediates shown in Figure 3 are well-known industrial applications of resolution by entrainment. The method is also of great value for laboratory-scale resolutions, especially at the 100 g to kg scale.
For low-melting conglomerates, the entrainment can also be effected without solvent, in a supercooled melt. Such processes are easily understood by means of the melting point phase diagrams, by considering the metastable extension of the liquidus curves below the eutectic temperature.

**Diastereoisomers**

The most widely used method for the separation of enantiomers, often called classical resolution, rests on the crystallization of diastereoisomers formed from a racemate (dl) and an enantiopure reagent (say, D), called a resolving agent:

\[
dl + D \rightarrow dD + ID
\]

It is convenient to designate with letters \( p \) (positive) and \( n \) (negative) the diastereoisomers resulting from reaction of the two constituents of like sign and opposite signs, respectively. In this convention, no account is taken of the sign of rotation of the diastereoisomers themselves, which, if needed, can be specified by adding a + or − subscript to the \( p \) and \( n \) descriptor. Accordingly, the above reaction yields a mixture of \( p \) (\( d \)) and \( n \) (\( ID \)) diastereoisomers, which, for instance, can both be dextrorotatory, i.e. \( p_+ \) and \( n_+ \). The opposite enantiomer (\( L \)) of the resolving agent would then afford with the same racemate the diastereoisomer pair \( p_- \) (\( IL \)) and \( n_- \) (\( dL \)), mirror image of \( p_+ \) and \( n_+ \) (Markwald principle). Note that the reciprocal resolution of \( DL \) by, for instance, \( d \), would yield a mixture of \( p_+ \) (\( dD \)) and \( n_- \) (\( dL \)).

Diastereoisomeric salts, formed from simple acid-base reactions, are central to such resolutions, although covalent diastereoisomers (esters, amides, etc.) are also occasionally resolvable by crystallization. To cite but a single example, the DSM company resolves \( DL \)-phenylglycine by crystallization of its diastereoisomeric salts with \((+)-10\)-camphorsulfonic acid, to produce the \( p \)-enantiomer required for the manufacture of the antibiotic ampicillin, at a scale of more than 1000 tonnes per year.

Diastereoisomeric inclusion complexes, in which the resolving agent is a chiral crystalline host lattice, represent an interesting alternative for the resolution of substances that cannot form salts, or do not possess functional groups suitable for formation of covalent diastereoisomers.

**Phase Diagrams and Solubility Rules**

Diastereoisomers \( p \) and \( n \) are distinct compounds and exhibit different structures in the crystal state. It follows that all physical properties involving the crystal themselves and the crystal/liquid or crystal/gas equilibria, such as melting points, solubilities, sublimation properties, crystal densities, etc., are different for the \( p \) and \( n \) species of a given pair. However, the possibility of separating \( p \) and \( n \) diastereoisomers by crystallization of their 1:1 mixture, resulting from the reaction of a racemate with a resolving agent, does not depend only on the properties of the pure \( p \) and \( n \) compounds: it rests primarily on the existence of favourable solid–liquid phase equilibria for the binary \((p, n)\) or ternary \((p, n, \Sigma)\) systems. The phase diagrams of diastereoisomer systems (Figure 4) are basically similar to those of enantiomer systems. There exist, however, several important differences between them: (1) the phase diagrams of diastereomer mixtures are not symmetrical; (2) in contrast to enantiomers, diastereoisomers preferentially form eutectics or solid solutions (Figure 4(A) and (C), respectively); (3) the occurrence of 1:1 \((pn)\) addition compounds depicted in Figure 4(B) is by far less than that of \((dl)\) racemic compounds.

Only diastereoisomer systems forming eutectic phase diagrams are suitable for resolution by crystallization. In the solubility isotherm of Figure 4(A), 1:1 \((p, n)\) mixtures will afford the pure less soluble diastereoisomer (here \( p \)) if the crystallization is carried out between \( N \) and \( P \), for instance from solution \( O \). The best yield however will be obtained from solution \( N \). This yield is given by:

\[
Y = \frac{NE}{Ep} \times 100\% \quad \text{C}_N
\]

where \( C_N \) is the concentration of solution \( N \). Since the \( p/n \) ratio in the ternary eutectic is usually close to that of the binary eutectic, \( Y \) is not very different from \( RE/AE \) in the melting point phase diagram. The best systems are those in which the eutectic is close to the edge of the phase diagram, and the maximum value of \( Y = 50\% \) is approached when \( E \) is closed to one of the pure components. The occurrence of such good systems has been estimated at 20–25% of diastereoisomer mixtures. It is important to recognize that in such cases one or two crystallizations are normally sufficient to obtain the less soluble diastereoisomer in pure form.

Systems in which a 1:1 \([p, n]\) compound exists, as in Figure 4(B), are totally unsuitable for resolution because crystallization of a 1:1 mixture will afford the 1:1 compound. Some resolution is possible with systems forming a solid solution, as shown in Figure 4(C), providing that the solubility difference between the pure components is sufficiently large. Most
often, however, the enrichment is very modest and utilization of systematic fractional crystallization techniques is required. These techniques are very tedious and time-consuming and this is why resolution of \((p, n)\) systems forming solid solutions is not recommended unless alternative methods cannot be found. Note that diastereoisomeric lattice inclusion complexes are more prone to form solid solutions than the other types of diastereoisomers and often need repeated crystallizations to reach good enrichments. In such cases rather than purify the diastereoisomers, it may be advisable to complete the purification on the partially resolved enantiomers, along the lines indicated above.

**Resolving Agents**

In order to set up practical process for the separation of diastereoisomeric salts, initially a system forming a eutectic must be selected. This leads to the choice of the resolving agent and of the solvent. Next the crystallization conditions are optimized by means of phase diagrams along the lines discussed above. A classical resolving agent is a chiral acid or base available in bulk quantities at low price, and which has a propensity to form crystalline diastereoisomers when combined with racemic bases or acids. Table 1 lists some of the most common resolving agents for salt formation. Other, more specialized, resolving agents for the separation of
diastereoisomers by chromatography or for analytical purposes (nuclear magnetic resonance spectroscopy) are not mentioned here. For important commercial applications, it may be appropriate to design new resolving agents: for example, the N-alkyl-D-glucamine family (prepared from D-glucose) has been developed by Syntex as a substitute for cinchonidine for the large-scale resolution of naproxen (over 1000 tonnes per year). There are no clear guidelines allowing the prediction of a good resolving agent for a given substrate. This is not really a serious problem because the number of available resolving agents, being very limited, generally allows systematized protocols to identify the best ones very quickly.

Salts usually need polar solvents to crystallize, and a statistical survey of solvents used in over 800 such resolutions indicate that anhydrous or aqueous acetone and alcohols (ethanol, methanol, 1- and 2-propanol, 1-butanol), and water feature in 80% of cases. The presence of water may be necessary whenever the salts crystallize as hydrates. This is why 95% ethanol (rather than absolute ethanol) is to be preferred during the selection of a resolving agent.

Interesting achievements in the area of chiral host lattices have been reported during the last decade. A small number of chiral substances that form diastereoismeric crystalline inclusion complexes with a variety of guests have been identified. In addition to the alkaloid brucine, which has been utilized for resolving, at least partially, chiral halogenoalkanes (including CHFClBr) and, more recently, acetylenic alcohols and cyanohydrins, several new hosts have been discovered, among which readily available diols prepared from tartaric acid seem to have the greatest potential as resolving agents.

### Crystallization-induced Asymmetric Transformations

The 50% yield limit of a resolution can be exceeded if the diastereoisomers can be equilibrated in the solution (i.e. $dD \Rightarrow lD$) at a rate faster than the crystallization of the least soluble one. Such a phenomenon was first reported by Leuchs in 1913; he isolated in 94% yield a single diastereoisomeric salt after reaction of an easily racemizable racemic acid with brucine. In addition to the requirement that the diastereoisomers must epimerize easily, processes of this type can only be successful if the diastereomer system belongs to the eutectic type. In Figure 5, the starting material has composition $O$ (overall concentration $C_0$). In the liquid phase, the composition of the diastereoisomer mixture in chemical equilibrium is indicated by $L$, which in the case shown is slightly shifted towards the $n$ species. The final equilibrium state is featured by $N$, representing the overall composition of the system at the end of the process. System $N$ consists of pure solid $p$ in equilibrium with liquid $L$. The yield in diastereoisomer $p$ is proportional to $LN/Lp$, and can be derived from $C_0$ and the composition of the liquid in equilibrium ($C_{eq}$):

$$Y = \frac{(C_0 - C_{eq})}{(100 - C_{eq})} \times \frac{100}{C_0}$$

Accordingly, yields approaching 100% can only be obtained in poor solvents, in which $C_{eq}$ is very small. Typically, $C_{eq} = 2\%$ and $C_0 = 20\%$ would give a $Y$ of nearly 92%. In contrast to the case of a classical resolution, the yield does not depend directly on the location of the eutectic. However, it is the distance between the eutectic $E$ and the equilibrium solution $L$ which provides the driving force for the process, and this is why, again, a eutectic close to the edges of the phase diagram is preferable.

There are many examples of such processes in industry. They can be performed on diastereoisomeric salts (e.g. phenylglycine camphorsulfonate) as well as on covalent diastereoisomers (e.g. in the Roussel-Uclaf synthesis of the insecticide deltamethrin).

### Table 1 Common resolving agents

<table>
<thead>
<tr>
<th>Acids</th>
<th>Bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tartaric acid (+), (−)</td>
<td>α-Methylbenzylamine (+), (−)</td>
</tr>
<tr>
<td>Dibenzoyltartaric acid (+), (−)</td>
<td>Ephedrine (+), (−)</td>
</tr>
<tr>
<td>Mandelic acid (+), (−)</td>
<td>2-Amino-1-butanol (+), (−)</td>
</tr>
<tr>
<td>Malic acid (+)</td>
<td>Quinine (−)</td>
</tr>
<tr>
<td>10-Camphorsulfonic acid (+), (−)</td>
<td>Quinidine (+)</td>
</tr>
<tr>
<td>γ-Bromo-α-camphorsulfonic acid (+), (−)</td>
<td>Cinchonine (+)</td>
</tr>
<tr>
<td>Glutamic acid (+), (−)</td>
<td>Cinchonidine (−)</td>
</tr>
<tr>
<td>Aspartic acid (+), (−)</td>
<td>Brucine (−)</td>
</tr>
<tr>
<td>α-Camphamic acid (+), (−)</td>
<td>Yohimbine (+)</td>
</tr>
<tr>
<td>1,1′-Binaphthyl-2,2′-diyl-hydrogen phosphate (+), (−)</td>
<td>Dehydroabietylamine (+)</td>
</tr>
<tr>
<td>N-Methyl-D-glucamine (+)</td>
<td>N-Methyl-D-glucamine (−)</td>
</tr>
</tbody>
</table>
Crystallization-induced asymmetric transformations of diastereoisomers. In the solubility isotherm shown, $L$ represents the composition of the liquid in which the two diastereoisomers are in chemical equilibrium (here with a slight excess of $n$). This liquid is itself in physical equilibrium with the solid, consisting of pure $p$. After completion of the chemical and physical equilibrations, the starting system $O$ will be converted into the final system $N$, consisting of solid $p$ in equilibrium with liquid $L$.

Crystallization-induced asymmetric transformations of enantiomers forming conglomerates can also be carried out by combining entrainment techniques with simultaneous racemization of the substrate in the solution. Although a number of examples have been described, and a number of patents have been filed, only a few processes of this type have reached commercial application.

**Future Prospects**

The understanding of phase equilibria in enantiomer and diastereoisomer systems is a central question, not only in view of its practical relevance to separation processes, but also because it may shed light on some of the mechanisms governing molecular recognition in condensed matter. Among the numerous unsolved questions, that of the prediction of racemate types is perhaps one of the most challenging. Recently, it has been shown that, in theory, conversion of racemic compounds into conglomerates could be achieved for some racemates by crystallization under high pressure. An experimental verification of this prediction would be of great importance in extending the possibilities of resolving racemates by direct crystallization.

See Colour Plate 67.

**Further Reading**


