Resolution of Enantiomers by Non-Conventional Methods

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Abstract: Despite unprecedented advances in enantioselective synthesis and separation techniques, large scale production of enantiopure substances, such as required by the pharmaceutical and pesticide industries, is still heavily dependent upon the separation of diastereomers obtained from the enantiomers and an optically active resolving agent. Economy of the process can be much enhanced when only a half-equivalent of the resolving agent is used. Substitution of the other half-equivalent by some achiral compound, as well as separation of the unreacted portion of the substrate from the diastereomer by various physical methods, is discussed. Methods for selecting optimal conditions of resolution and for the purification of partially resolved mixtures are also discussed.

1 Introduction and Historical Background

Louis Pasteur was probably the first to recognize the biological significance of chirality1 when he observed in 1848 that only the natural (R,R)-tartaric acid was digested Penicillium glaucum. Investigations triggered by the dismal thalidomide affair in the 1960s have shown that its tranquilizing effect is associated only with the S enantiomer, while its antipode is responsible for its atorogenicity. This and several other developments led to the current situation where unless it cannot be proved that both enantiomers of a chiral drug or pesticide are biologically equivalent, registration of racemic compounds may run into serious difficulties. The challenge of manufacturing a chiral compound in an enantiomerically pure form can be met in three ways: enantioselective synthesis, exploiting the natural chiral pool, and resolution of racemates. Despite the spectacular progress in enantioselective methods, the high cost of reagents and extreme reaction conditions (low temperature, strict exclusion of moisture, etc.) have rendered some of their application to industrial processes prohibitively expensive. The availability of chiral natural products is also rather limited. Resolution of racemates, however, usually requires relatively cheap reagents and simple reaction conditions. Resolution has therefore not lost its significance, least of all for the pharmaceutical and pesticide industry. The most elegant, though unfortunately also quite expensive, method to separate enantiomers, i.e. chromatography on chiral media, is only suitable for the preparation of very expensive compounds. Enzymatic methods are becoming ever more efficient, but still require considerable knowledge and strictly controlled conditions. In this review, we intend to present the state of the ‘art of resolution’ via diastereomer formation with special emphasis on methods using a half-equivalent of the resolving agent.

In his pioneering work, Louis Pasteur formed salts from enantiomers of tartaric acid with (R,R)-quinotoxine, an optically active base, and observed that one of them, namely the R,R-enantiomer, gave a crystalline salt while its antipode did not. More importantly, when racemic tartaric acid was reacted with the same base, the salt of (R,R)-tartaric acid crystallized, while the other salt remained in solution. All this was done well before the tetrahedral orientation of the carbon valence, and thereby the secret of chirality, was discovered by van’t Hoff and Le Bel in 1874.

In modern terms, the essence of Pasteur’s experiments is that a mixture of mirror image entities, identical in all their scalar properties (solubility, melting point, etc.), is transformed by interactions with a single enantiomer of a chiral compound (called the resolving agent) to a pair of products (salts, complexes, covalently bound compounds, etc.) called diastereomers. These diastereomers exhibit different scalar properties and can therefore be separated using achiral methods (typically fractional crystallization).

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Biographical Sketches

Elemér Fogassy (70) graduated in 1957 from the Technical University of Budapest (now University of Technology and Economics) as a chemical engineer. He earned his Dr.Techn. in 1965, his C.Sc. in 1973, his Ph.D. in 1974 and his D.Sc. in 1986. He worked in the pharmaceutical industry from 1957–64. In 1964, he joined the Department of Organic Chemical Technology at TUB and became a professor in 1987. He is author or co-author of 250 papers and patents. He received the József Varga Medal in 1999, the Dénes Gábor Prize in 2000, the Albert Szent-Györgyi Prize in 2004 and from 2000–2003, he was recipient of the Széchenyi Professor’s Stipend.

Professor Mihály Nógrádi (71) graduated from the Technical University of Budapest as a chemical engineer in 1957. From 1956–1960, he worked on industrial-scale countercurrent liquid-liquid extraction at the Research Institute for Organic Chemical Industry. After spending two years in the pharmaceutical industry, he joined the Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences at the Institute for Organic Chemistry of the Technical University of Budapest. He acquired his Ph.D. with a thesis on the synthesis of natural flavonoids, which remained one of his main interests for a long time. In 1968–69, he was a postdoctoral fellow at the Department of Chemistry of Sheffield University, studying the conformation of medium-sized rings by dynamic NMR methods. His latter interest prompted him to write a textbook on stereochemistry that was published in Hungarian, English and Polish (1975), and a monograph on stereoselective synthesis in English (1987, 2nd edition 1995) that was also translated to Russian. Since 1990, he has published several papers on the synthesis of natural macrocyclic bibenzyls. His cooperation with the pharmaceutical industry resulted in several patents, among them one for Ipriflavone, which is marketed in Japan, Italy and Hungary for the treatment of osteoporosis. He has published 140 research papers.

Emese Pálovics was born in 1967 in Satmar (Rumania). She graduated in 1990 from the University of Technology ‘Traian Vuia’ in Timisoara as a Chemical Engineer. Since 1994, she has been a scientific assistant at the Budapest University of Technology and Economics in a research group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology, working on crown ethers and organophosphorus compounds. She currently works with Professor Elemér Fogassy, in the field of optical resolution.

József Schindler was born in 1976 in Budapest. He graduated in 2001 from the Budapest University of Technology and Economics as a chemical engineer. In 2004, he obtained his Ph.D. He is presently a scientific assistant in a research group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology, and works on optical resolution with Professor Elemér Fogassy.
The range of commonly used resolving agents is rather narrow; some of the most important ones are shown in Figure 1.

The most common resolving agents

2 Resolution Methods Using a Half-Equivalent of Resolving Agent

Allowing a racemic mixture to react with an equimolar amount of a single enantiomer of a chiral agent, and separating the resulting diastereomeric mixture (salts, complexes, or compounds) by scalar physical methods remains the method of choice when only a small amount of the pure enantiomers is needed. When, however, one of the enantiomers turns out to be useful for some practical purpose, usually as a drug, the cost of the resolving agent becomes an important factor. This prompted a search for methods where part of the precious resolving agent is replaced with some inexpensive achiral compound. These efforts, continuing to the present day, resulted in the methods known as the ‘half-equivalent’ methods.

2.1 Resolution with a Half-Equivalent of Achiral Acid or Base

In 1899 (the same year when kinetic resolution was discovered), Pope and Peachey reacted racemic 2-methyltetrahydroquinoline with a half-equivalent of (+)-3-bromocamphor-8-sulfonic acid ammonium salt. The other half-equivalent was replaced with hydrochloric acid. The same diastereomeric salt crystallized as before, i.e. the one which proved to be less soluble in the conventional experiment using one equivalent of the chiral acid (Scheme 1).5

This was a logical proposition since salts formed with a strong inorganic acid or base are usually more soluble than those involving a bulky organic partner. A further advantage of using a half-equivalent of resolving agent is that the unwanted diastereomer becomes less oversaturated, and is thus less likely to precipitate.

The practical importance of this approach is illustrated in three examples taken from drug manufacturing.

When aqueous solutions of the hydrochloride of the racemic chloramphenicol synthetic intermediate (shown in Scheme 2) and a half-equivalent of the ammonium salt of the resolving agent \((R,R)-DBTA - \cdot NH_4^+\) are combined, it is the salt of the desired \((R,R)-DBTA - \cdot NH_4^+\) which crystallizes.6 \((\pm\)-cis-CPA is an important intermediate in the synthesis of several prostaglandins. When a half-equivalent of \((R)-PEA\) is added to an aqueous solution of the sodium salt of the racemic carboxylic acid, the amine salt of the desired acid crystallizes, while the other remains dissolved (Scheme 3).7

The amine \((\pm\)-AN is an intermediate in the synthesis of the important antihypertensive \(\alpha\)-methyl-DOPA. To a solution of the racemic intermediate, a half-equivalent of \((R,R)-TA\) and a half-equivalent of hydrochloric acid are added. In this case, it is the hydrochloride of the required enantiomer that stays in solution (Scheme 4).8

Scheme 4 Resolution of an intermediate of α-methyl-DOPA synthesis using a half-equivalent each of the resolving agent and hydrochloric acid

An important application of the method is the resolution of 1,1′-bi-2-naphthol, a common starting material of several chiral reagents and catalysts (Scheme 5).9 From the mother liquor, the S enantiomer can be isolated in 89–93% yield (99% ee), while decomposition of the solid with hydrochloric acid gives (R)-BIN in 85–88% yield (ca. 100% ee).

Scheme 5 Resolution of (±)-1,1′-bi-2-naphthol with a half-equivalent of N-benzylcinchonidinium chloride (NBNC-CI+)

A variant of the method was used for the resolution of (±)-S-methyl-S-phenylsulfoximine with a half-equivalent of (S)-CSA.10 The salt of the (+)-sulfoximine precipitated, optically pure, in 80% yield, while the addition of another 0.1 equivalent of (S)-CSA precipitated the rest of the (+)-sulfoximine and left a solution from which the (−)-sulfoximine could be isolated in 74% yield (97–99% ee).

2.2 Resolution with a Half-Equivalent of Resolving Agent in Two-Phase Systems

Addition of an achiral acid or base is unnecessary when the solvent keeps the unreacted enantiomer in solution. Sometimes, however, a pair of immiscible solvents must be used. For example, if water is favorable for the crystallization of the diastereomeric salt, but is a poor solvent for the substrate, then using a pair of immiscible solvents may result in efficient separation of the enantiomers.

This was exploited in the resolution of the tranquilizer tofizopam (DBA) in a water–chloroform system with (R,R)-DBTA (Scheme 6).11

If the diastereomeric salt is also soluble in one of the immiscible solvents, solid–liquid distribution may be replaced by liquid–liquid distribution. An example of this case is the resolution of the amine (±)-PPA, an intermediate of the anti-Parkinson’s disease drug selegiline. The salt of the R enantiomer preferentially forms a salt with monosodium tartrate that remains in the aqueous phase, while the S enantiomer resides in the benzene phase as the base (Scheme 7).12

Scheme 6 Resolution of tofizopam with a half-equivalent of (R,R)-DBTA in a chloroform–water system

The reason for using monosodium tartrate is that the neutral salts of four-carbon dicarboxylic acids are usually more soluble in water than the acid salts, thus the diastereomeric salt remains in the aqueous phase.

Scheme 7 Resolution with a half-equivalent of the resolving agent in a two-phase system. Both the diastereomeric salt of one of the enantiomers and the free base of the other remain in solution, but in different phases.

An interesting example is the resolution of the diaryl sulfoxides (±)-SO when two salts are distributed between chloroform and water. The salt of one of the enantiomers formed with quinine, a hydrophobic base, goes preferentially to the organic phase, while the potassium salt of the other enantiomer stays in the aqueous phase (Scheme 8).13

Scheme 8 Resolution in a two-phase system with a half-equivalent of a hydrophobic base combined with an inorganic base

2.3 Resolution with a Half-Equivalent of Resolving Agent Combined with Extraction Using a Supercritical Fluid

The technique of supercritical fluid extraction can also be successfully applied to resolution. The racemic mixture and a half-equivalent of the resolving agent are mixed in a solvent. The solvent is then evaporated and the free
enantiomer is extracted with a supercritical fluid, usually with carbon dioxide. Resolution of the anti-inflammatory drug ibuprofen \((\pm)-\text{IBU}\) with \((R)-\text{PEA}\) was realized in this way (Scheme 9).14

\[
\text{Scheme 9} \quad \text{Resolution with a half-equivalent of the resolving agent and extraction of the free enantiomer with supercritical carbon dioxide}
\]

2.4 Resolution with a Half-Equivalent of Resolving Agent by Melting the Components Followed by Filtration

Resolution of liquid racemates can sometimes be accomplished in a way that a half-equivalent of the resolving agent is added to the racemate and the mixture is brought to melting. A salt is preferentially formed with one of the enantiomers, while the other can be removed by filtration or by extraction with an appropriate solvent.

In this manner, \((-\)-menthol forms a crystalline complex with \((R,R)-\text{DBTA}\) and crystallizes readily when racemic menthol is melted with a half-equivalent of the resolving agent. Uncomplexed \((+)-\text{menthol can then be separated by filtration. Addition of some hexane facilitates the operation (Scheme 10).}\)15

\[
\text{Scheme 10} \quad \text{Resolution of a liquid racemate with a half-equivalent of the resolving agent in the melt [(–)-MENT = (1R,2S,5S)-menthol]}
\]

A similar example that borders on resolution and is based on inclusion phenomena16 is the cocrystallization of the diphenylaminoalcohol \((1S,2R)-\text{AA}\) with one equivalent of benzoic acid and a series of 20 racemic 1-arylethanols. The result was 1:1:1 crystalline complexes which included the alcohols in 24–98% ee. The predominant configuration varied \((R:S = 14:6)\) (Scheme 11).17

\[
\text{Scheme 11} \quad \text{Resolution of 1-arylethanols by cocrystallization with (1R,2S)-2-amino-1,2-diphenylethanol and benzoic acid}
\]

2.5 Resolution with a Half-Equivalent of Resolving Agent Combined with Removal of the Free Substrate by Sublimation or Distillation

Resolution of racemic \(\text{trans-2-iodocyclohexanol was also based on the formation of a molecular complex, again with (R,R)-DBTA, but in this case the separation of the free enantiomer was performed by fractional sublimation (Scheme 12).}\)18

\[
\text{Scheme 12} \quad \text{Resolution by molecular complex formation with a half-equivalent of the resolving agent followed by fractional sublimation}
\]

When the free enantiomer is a distillable liquid, it can be removed from its mixture with the diastereomeric salt by distillation. Thus, the racemic amine \((\pm)-\text{PPA}\) was reacted with a half-equivalent of \((R,R)-\text{DBTA}\) and the free amine was recovered by vacuum distillation (Scheme 13). This example is, in fact, only an operational variant of the one shown in Scheme 7.

\[
\text{Scheme 13} \quad \text{Resolution with a half-equivalent of the resolving agent followed by separation of the free enantiomer by distillation}
\]

More complicated is the process illustrated in Scheme 14. First the racemic amine \((\pm)-\text{PA}\) was reacted, without solvent, with a half-equivalent of hemiphthalyl-\((S)-1\)-phenylethylamine \([\text{(S)-PHT}]\). The salt of the \(R\) enantiomer was preferentially formed and the \(S\) antipode was recovered by vacuum distillation at a moderate temperature. On
raising the temperature, the salt decomposed and the \( R \) enantiomer could be distilled off, while the resolving agent ended up as a phthalate.\(^{19}\)

Scheme 14 Resolution of a racemic amine with a half-equivalent of an acidic derivative of \((S)-\text{PEA}\) involving a two-stage distillation process

Resolution by two-stage fractional distillation can also be successful when the resolving agent forms a molecular complex with the substrate. This was exemplified by resolution of the same amine with the so-called Seebach ligand \([(R,R)-\text{SL}]\) (Scheme 15).

Scheme 15 Resolution of an amine by formation of a molecular complex with a half-equivalent of Seebach ligand followed by fractional distillation at two temperatures

This example differs from the previous one inasmuch as the resolving agent can, at least in principle, be recovered.

3 Selection of the Optimal Resolving Agent and Solvent

3.1 Selection of the Solvent

An important practical issue is how to find, for a given task, the most efficient resolving agent and how its enantiomer-recognizing potential can best be exploited. A sensible approach is to first try with a particular compound that has been used to resolve similar compounds. A recent monograph may be very useful in this respect.\(^{20}\) When, after consulting the relevant literature and performing some preliminary experiments, a hopeful candidate has been found, the task of finding the optimal solvent has to be addressed. The ideal solvent is one in which the solubility difference of the products (the two diastereomers, or, with a half-equivalent methods, the diastereomer and the unreacted substrate) is as great as possible. Although the discovery of the ideal solvent for one particular system is typically a case of trial and error, the following examples may illuminate that experimenting with the solvent can yield substantial dividends.

Resolution of racemic trans-chrysanthemic acid, an important building block of synthetic pyrethroid insecticides, can be best performed when some methanol is added to the ether-type solvent (Scheme 16).\(^{21}\) Interestingly, the resolving agent \([(R,R)-\text{AD}]\) is a derivative of the unwanted enantiomer obtained in the course of resolving the key intermediate of an industrial chloramphenicol synthesis.

Scheme 16 Resolution of trans-chrysanthemic acid \([(\pm)-\text{CHR}]\) in a mixture of solvents, one of which forms a crystalline solvate with the diastereomeric salt

Selecting a solvent that forms a crystalline solvate with one of the diastereomeric salts is also crucial in the resolution of amlodipine, an important antihypertensive drug (Scheme 17).\(^{22}\) When the wrong solvent is used, the salt is contaminated with the racemic base.

Selection of the solvent may influence not only the degree of enantiomer separation, but also the configuration of the
enantiomer contained in the preferentially crystallizing diastereomeric salt. For example, when the racemic tetrahydroquinoline intermediate of flumequine, an antimicrobial agent, is resolved with a half-equivalent of \((R,R)\)-DTTA in acetic acid, the precipitating salt contains the \(R\) base, whereas in isopropanol, it contains the \(S\) base (Scheme 18).\(^{23}\)

**Scheme 18**  Solvent-dependence of the enantiomer that forms the less soluble diastereomeric salt

Experimentation with solvent–water mixtures of adjustable dielectric constant in the resolution of 3-aminocapro lactam \([\pm]\)-ACL with \(N\)-tosyl-(S)-phenylalanine \([(S)\text{-TPhA}]\) led to the determination that if \(\varepsilon\) was in the range of 30–60, a crystalline hydrate was formed with the \(S\) enantiomer, while when \(\varepsilon\) was outside this range, the diastereomeric salt contained the \(R\) enantiomer (Scheme 19).\(^{24–26}\)

**Scheme 19**  Influence of solvent dielectric constant on the enantiomer that forms a crystalline diastereomer

Sometimes, formation of a crystal solvate can be essential for successful resolution. When racemic 1,1‘-binaphthol is resolved with \((R,R)\)-1,2-diaminocyclohexane, a crystalline toluene solvate containing the \(R\) enantiomer precipitates, while the salt of the \(S\) enantiomer stays in solution.\(^{27}\)

With \((S)\)-mandelic acid \([(S)\text{-MA}]\), the thienyl-aminoalcohol \((\pm)\)-TAA gives crystals of poor diastereomeric excess \((S = 0.30)\) in water, while in 2-butanol, crystallization failed. When, however, two equivalents of water was added to the 2-butanol, a crystalline hydrate of a salt of much higher purity \((S = 0.63)\) could be isolated (Scheme 20).\(^{28}\)

**Scheme 20**  Enhancement of resolution efficiency \((S)\) by crystal hydrate formation

### 3.2 Selection of the Resolving Agent

To aid in the selection of the optimal resolving agent, computational methods based on substituent constants of the ligands around the chiral center have been elaborated.\(^{29}\) Other methods exploited experimental data established from binary and ternary phase diagrams.\(^{30}\) All this can be complemented with practical experience. It is often rewarding when one of the enantiomers to be resolved is derivatized in a way that it can also serve as a resolving agent.\(^{31}\) For instance, chiral acids obtained by acylation of natural amino acids can be very useful for the resolution of racemic amino acids or bases.\(^{32,33}\) Thus, racemic phenylalanine \([\pm]\)-PhA can be successfully resolved with a half-equivalent of \(N\)-benzoyl-(R)-phenylalanine \([(R)\text{-BzPhA}]\) (Scheme 21). Note that the precipitating salt is of a quasi-racemate character.

**Scheme 21**  Resolution of racemic phenylalanine with a half-equivalent of \(N\)-benzoyl-(S)-phenylalanine

### 3. Selection of Resolving Agents for Structural Analogues

It is a logical proposition, and in fact it often works, to apply the same resolving agent and solvent for structural analogues. Though rather different in structure, the liquid-crystal-forming compounds shown in Figure 2 are similar in shape and can both be resolved with \((R,R)\)-DBTA.\(^{34}\)

**Figure 2**  Compounds of similar shape that can be resolved under similar conditions
Unfortunately, with small molecules, even a slight structural modification may preclude the use of the same resolving agent. Thus, while phenylglycine can be well-resolved with (1R)-CSA, the latter fails to resolve 4-hydroxyphenylglycine. It is surprising, however, that if a mixture of the two racemic amino acids is treated in water with (1R)-CSA, a salt that contains the R enantiomer of both crystallizes (Scheme 22).\(^3\)

Scheme 22 Cooperative resolution of two closely related compounds

The reason for this particular behavior is unclear, but is probably connected with the crystal structure of the diastereomeric salt. In trivial terms, the salt of phenylglycine may invite its hydroxyl analogue to participate in crystal formation.

3.4 Resolution with a Mixture of Resolving Agents (The Dutch Approach)

It seems that sometimes, the presence of an almost indifferent third component may contribute to the formation of a properly crystallizing diastereomeric salt. A congener of the compound to be resolved may serve this purpose. One example of this peculiar behavior is the ‘Dutch resolution’ (Scheme 23).\(^4\)

Scheme 23 Resolution with a mixture of two structurally related resolving agents of the same configuration

In this example, a 1:1 mixture of (R)-PA and (R)-CIPA was used for the resolution of (±)-ephedrine, whereas it failed with (R)-PA and was less efficient with (R)-CIPA alone. The method has been reviewed and complemented by several new examples reported recently by Kellogg et al.\(^5\)

3.5 Resolution with Chiral Metal Complexes or Metal Salts

Preparation of diastereomeric metal complexes can also be exploited for the resolution of certain types of compounds.\(^6\) For example, the non-trivial task of resolving chiral phosphines can be accomplished using an optically active dinuclear palladium complex \([\{R\}-PD\}_2\) (Scheme 24).

Scheme 24 Resolution of a chiral phosphine with an optically active palladium complex

With some reservation, one can ascribe the resolution of tetrahydrofurfuryl alcohol \([\{\pm\}FuOH]\) with a half-equivalent of the calcium salt of \((R,R-)DBTA\) to this category. From ethanol, it is the complex of the R-alcohol \([\{\pm\}FuOH-(R,R-)DBTA-Ca^{2+}]\) that preferentially crystallizes.\(^7\) The very charm of this procedure is that the complex itself can serve as a resolving agent, and was used for the resolution of tetrahydrofurfuryl carboxylic acids \([\{\pm\}FuAc]\) (Scheme 25).

Scheme 25 Resolution via complex formation: (i) resolution of tetrahydrofurfuryl alcohols with the calcium salt of \((R,R-)DBTA\); (ii) Resolution of tetrahydrofurfuryl carboxylic acids with the diastereomeric complex formed

4 Phase Transformations of Diastereomeric Salts or Complexes (Kinetic and Thermodynamic Control)

It should be reasonable to assume that after the termination of crystallization during a resolution procedure, the composition of the precipitate remains constant; however, there are some exceptions. In these cases, during prolonged contact with the liquid phase, the composition of the solid phase changes and even a reversal, to a diastereomer containing the opposite enantiomer, can happen. In
this situation, the thermodynamically less stable diastereomeric product crystallizes more rapidly than the other (kinetic control), but changes gradually to the more stable one on standing (thermodynamic control). This phenomenon is illustrated by the resolution of the previously mentioned flumequin intermediate (±)-FMQ with di-p-tolyl-(R,R)-TA (Scheme 26).23

5 Resolution by Formation of Covalently Bound Diastereomers

5.1 Resolution Using a Pure Chiral Reagent (Kinetic Resolution)

A less common method for resolution, mostly used when the substrate is not amenable to salt formation, is linking the resolving agent to the enantiomers by a covalent bond, whereupon a pair of diastereomers is formed. These are then separated by conventional methods, most conveniently by fractional crystallization. An example is the acylation of racemic timolol, a β-receptor blocker, with the anhydride of (R,R)-DBTAH followed by fractional crystallization of the diastereomeric half-esters (Scheme 27).40

While salt formation is an instantaneous process where kinetics do not play a role (for an exception, see Scheme 26), the diastereomeric nature of the transition states leading to the diastereomers ensures that their rate of formation is different. If this difference is large enough, the half-equivalent strategy can be invoked. It is the more reactive enantiomer that is preferentially transformed to the product, and the latter can be separated from the unreacted antipode owing to its different solubility.21

5.2 Resolution Using a Mixture of Two Reagents

A special case of kinetic resolution is when a racemate is reacted with a mixture of reagents, one or both of which are chiral. An example for this rather special method is shown in Scheme 28.42 A mixture of acylating agents, (R)-PMe and (S)-PBn, prepared from quasi-enantiomeric pyridine compounds, was reacted with racemic 2-naphthylpropanol [(±)-NOH]. After separation, two carbonates are obtained in high yield and high enantiomeric purity, and can then be hydrolyzed to the corresponding alcohols.

6 Racemization of an Unwanted Enantiomer

There is an ever stronger pressure on the industry to produce the more effective, or the only effective, enantiomer of chiral drugs and pesticides. If these are obtained by resolution of racemates, the formation of an equal amount of the useless enantiomer cannot be avoided. The best way to utilize the latter is racemization, then recycling the racemate through the resolution process. Unfortunately, in practice, racemization can rarely be accomplished with compounds that have more than a single chiral center.

In some lucky instances, the resolution process is accompanied by racemization of the unwanted enantiomer (second-order asymmetric transformation). A fine example is the resolution of a key intermediate in the synthesis of chloramphenicol, the amino alcohol (±)-AA, with one equivalent of the hemi-phthalate (R,R)-FT, a derivative of the unwanted aminodiol enantiomer. While the salt of (R)-AA crystallizes, the (S)-AA racemizes, and eventually the whole racemate is transformed to the salt that contains the R enantiomer (Scheme 29).43
7 Deracemization

The ratio of equilibrating enantiomers can be shifted in favor of one of the enantiomers by the addition of an optically active reagent that preferentially forms a loose complex with one of the enantiomers. If the reaction is quenched after reaching equilibrium, an optically active product can be isolated.

For example, the equilibrium between the cyclohexanones (S)-\( \text{CH} \) and (R)-\( \text{CH} \), which racemize in alkaline media via the enol form, is shifted towards the R enantiomer in the presence of a diol [(R,R)-\( \text{DIOL} \), prepared from (R,R)-\( \text{TA} \)] (Scheme 30).44

The modification consists of transforming the acid to the neutral calcium salt, then adding the solvate of the R salt with methoxyethanol, whereupon 43% of the same enantiomer crystallizes. Thereafter, an amount of racemic salt equal to the amount of product that separated is added, and the solution is inoculated with the S,S salt. At this point, the yield of the S,S antipode is 41%.

8 Resolution of Conglomerate-Forming Racemates by Induced Crystallization

8.1 Resolution by Alternating Inoculation with the Pure Enantiomers

Pasteur’s method of racemate resolution by sorting enantiomorphic crystals is of purely historical interest; not only is it extremely painstaking, but according to an estimate by Jacques et al.,45 only about 10% of racemic chiral compounds form a conglomerate of enantiomeric crystals. The remainder form a separate racemic phase (racemat or racemic molecular compound) besides the mirror image crystals of the pure enantiomers. In other words, a racemic mixture contains a single phase (the ‘racemate’), while a non-racemic mixture consists of the crystals of the racemic phase and those of the enantiomer in excess. Since the very reason for the formation of a racemic phase is its higher stability, with few exceptions, it has a higher melting point and a lower solubility.

Alternating inoculation of oversaturated solutions is therefore only applicable, with rare exceptions (see Section 8.2), to conglomerate-forming racemates, but in this case it might be quite economical. The method consists of inoculating an oversaturated solution of the racemate with seed crystals of one of the pure enantiomers, whereupon crystals of the same enantiomer separate. If these are removed before their kinetic advantage is lost, a non-racemic solution is left, which can be again concentrated to oversaturation and inoculated now with the other enantiomer, and so on. This method can also be credited to Louis Pasteur.47 A modern, somewhat modified version of the method is illustrated in Scheme 31.48

The modification consists of transforming the acid to the neutral calcium salt, then adding the solvate of the R,R salt with methoxyethanol, whereupon 43% of the same enantiomer crystallizes. Thereafter, an amount of racemic salt equal to the amount of product that separated is added, and the solution is inoculated with the S,S salt. At this point, the yield of the S,S antipode is 41%.

8.2 Spontaneous Resolution Combined with a Second-Order Asymmetric Transformation

A unique case of resolution by induced crystallization of a racemic-phase-forming compound is that of 1,1′-binaphthyl.49 Here, induced crystallization is combined with a second-order asymmetric transformation. Since the rotation barrier of this compound is rather low, it readily racemizes on melting. Another exceptional feature of this system is that the melting point of the enantiomers is higher than that of the racemic phase. Therefore, on seeding with crystals of one enantiomer, crystals of the same start to separate, accompanied by racemization in the remaining melt, until the entire amount is transformed to the enantiomer added as seed.
Purification of Partially Resolved Mixtures by Crystallization of Conglomerate-Forming and Racemic-Phase-Forming Compounds

9.1 Crystallization from Solution

The upgrading of partially resolved mixtures by repeated fractional crystallization is a well-established practice. With conglomerate-forming enantiomers, the upper limit for the yield of the predominant enantiomer is its initial enantiomeric excess.

With compounds that form a racemic phase, the position of the composition on the binary phase diagram (i.e. the eutectic composition) determines whether it is the racemate that can be obtained pure by crystallization while the enantiomer in excess stays in solution, or vice versa.

The benzodiazepine-type tranquilizer tofizopam forms a racemic phase and, even with quite high initial ee values (eeo), it is the racemic phase that crystallizes; the pure enantiomer can only be obtained in crystalline form from a mixture of eeo > 85% (Scheme 32).50

Sometimes, the range covered by the racemic phase is extremely broad, and makes purification beyond a certain level impossible. For example, the eutectic composition of the dioxan carboxylic acid DX is at 94.6% ee. In this case, however, the problem can be circumvented by transforming the acid to its methyl ester, which forms a conglomerate and yields an almost pure product upon recrystallization (Scheme 33).51

Working with a series of racemic-phase-forming long molecules intended for liquid crystal applications, Tamura et al. studied the mechanism of induced crystallization52 and found that upon recrystallization, the crystals always contain an excess of one of the enantio-
9.2 Crystallization from Melt

If the melting point of the compound to be resolved is not too high, upgrading of the optical purity of the enantiomer in excess in a partially resolved mixture can also be performed by partial crystallization after melting. The process is similar to that used for the (R,R)-DBTA complex of racemic menthol (Scheme 10). An example is the purification of a partially resolved mixture of the lactone LA, an intermediate of prostaglandin synthesis, by crystallization if its melt (Scheme 35). Enantiomers of this lactone crystallize as a conglomerate.

Scheme 35 Separation of a partially resolved mixture of a conglomerate-forming compound by crystallization of its melt

The behavior of racemic-phase-forming chiral compounds is more complicated, as exemplified by the flumequine intermediates FMQ. When the ee of one of the enantiomers exceeds the eutectic composition (in this case, 50%), on cooling the melt, that particular enantiomer crystallizes; otherwise, it is the racemic phase that crystallizes (Scheme 36).

Scheme 36 Influence of ee on the results of crystallizing the melt of a racemic-phase-forming compound

10 Purification of a Partially Resolved Mixture of Racemic-Phase-Forming Enantiomers by Fractional Precipitation

If a salt of an achiral acid or base with a non-racemic mixture of racemic-phase-forming enantiomers is partially decomposed, the composition of the products (free base or acid and the remaining salt) is different. For example, when a water-soluble hydrochloride of a water-insoluble base is partially decomposed by the addition of alkali, the ee of the precipitating base deviates significantly from ee (Scheme 37).

![Scheme 37](image)

Scheme 37 Partial decomposition of a salt of a non-racemic mixture of enantiomers forming a racemic phase

The hydrochloride of levamizol, an anthelmintic, is water-soluble but the corresponding base is not. If ee is less than the eutectic composition and sodium hydroxide equivalent to the amount of racemate is added, first a racemic base precipitates. Upon addition of more alkali, the enantiomer in excess separates, and can be obtained in high purity in this way.

11 Resolution by Supercritical Fluid Extraction or Distillation

If an enantiomeric mixture is partially transformed to a salt and then the solvent is evaporated, the unreacted portion can be separated from the salt either by extraction with a supercritical fluid or, more conventionally, by distillation. The enantiomeric purity of the two phases will be different. With conglomerates, it is always the salt which shows the higher ee value.

For racemic-phase-forming compounds, the result depends on ee, and if the latter is less than the eutectic composition, the remaining crystals are of lower enantiomeric purity than the distillate. Scheme 38 illustrates this procedure for the purification of the often-used resolving agent 1-phenylethylamine (PEA). The efficiency of the method depends, of course, on ee.

![Scheme 38](image)

Scheme 38 Separation of a partially resolved mixture of a racemic-phase-forming compound by partial salt formation and removal of the free component by distillation or supercritical extraction (data are for distillation)
12 The Non-Linear Character of the Resolution Processes

So far, it has been assumed that resolving agents are pure enantiomers. In practice this is not always the case – even some natural products, such as α-pinene, may be optically impure. With such resolving agents, correlation of the ee of the resolving agent \( (\text{ee}_\text{cat}) \) and resolved substrate \( (\text{ee}_\text{prod}) \) is an intriguing problem. A logical supposition would be that this correlation should be linear. That this is not always true was demonstrated in studies of enantioselective catalytic reactions in the presence of enantiomerically impure catalysts carried out by Noyori,56 Kagan57 and others. Apart from a linear correlation \( (\text{ee}_\text{cat} = \text{ee}_\text{prod}) \), either a positive \( (\text{ee}_\text{cat} < \text{ee}_\text{prod}) \) or negative \( (\text{ee}_\text{cat} > \text{ee}_\text{prod}) \) deviation from linearity is often observed, as shown in Figure 3. In a detailed analysis, Girard and Kagan58 demonstrated that the effect can be explained by the different reactivity of homochiral and heterochiral dimers of the catalyst. A kinetic advantage of a homochiral species results in a (+)-NLE, while that of a heterochiral species results in a (−)-NLE.

In the authors’ opinion, non-linearity in chiral–chiral interactions may be a more general phenomenon than has been recognized. For example, two distinct hydrated crystal forms of the diastereomeric salts of mandelic acid with cinchonine, of ee 25.3% and 90.1% respectively, have been identified by thermal analysis and X-ray powder diffraction.58 Non-linear correlations were found in resolutions with the distillation method58 and by molecular complex formation.59 In another case, when salts were formed from \((R)-\text{PEA}\) and 0.75 equivalent of various achiral dicarboxylic acids, strong non-linear correlation of \( \text{ee}_0 \) and ee values of the distillate was observed.60 This phenomenon is illustrated in Figure 4.

Experimental verification of the generality of this hypothesis is still incomplete and a detailed discussion would go beyond the scope of this review.

![Figure 3](image-url)  
**Figure 3** Correlation between the enantiomeric purity of a chiral catalyst \( (\text{ee}_\text{cat}) \) and that of the product \( (\text{ee}_\text{prod}) \): linear (A), positive effect (B) and negative (C) non-linear

It should be understood that some of the methods reviewed are of rather limited scope, and before trying to apply them, one should consult the original literature.

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References

(1) Present-day nomenclature will be used throughout this review.
(3) Catalog prices, 2004: \((R)-1,1\text{-}\text{binaphthyl}: \text{€} 44/g; (R)-2,2\text{-}\text{bis(diphenylphosphino)}-1,1\text{-}\text{binaphthalene (BINAP)}: \text{€} 335/g; (−)-α-pinene: \text{€} 12/g; (+)-α-pinene: \text{€} 13/g; (+)-1,4\text{-}\text{bis(diphenylphosphino)}-1,4\text{-}\text{dideoxy-2,3-}O\text{-}\text{isopropylidene-}D\text{-}\text{threitol ([+]-DIOP]}: \text{€} 118/g; (R,R)\text{-}\text{tartaric acid}: \text{€} 46/100 g; (S,S)\text{-}\text{tartaric acid}: \text{€} 70/100 g; dibenzoyl-(R,R)\text{-}\text{tartaric acid}: \text{€} 81/100 g; (S)-lactic acid: \text{€} 33/kg; (−)-1\text{-}\text{phenylethylamine}: \text{€} 82/100 mL; (R)-1\text{-}\text{phenylethylamine}: \text{€} 84/100 g; brucine hydrate: \text{€} 83/100 g; quinine: \text{€} 112/100 g.
(4) Pasteur, L. C. R. Hebd. Seances Acad. Sci. 1853, 37, 162.