Separation of non-racemic mixtures of enantiomers: an essential part of optical resolution

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Non-racemic enantiomeric mixtures form homochiral and heterochiral aggregates in melt or suspension, during adsorption or recrystallization, and these diastereomeric associations determine the distribution of the enantiomers between the solid and other (liquid or vapour) phases. That distribution depends on the stability order of the homo- and heterochiral aggregates (conglomerate or racemate formation). Therefore, there is a correlation between the binary melting point phase diagrams and the experimental ee_I *vs.* ee_0 curves (ee_I refers to the crystallized enantiomeric mixtures, ee_0 is the composition of the starting ones). Accordingly, distribution of the enantiomeric mixtures between two phases is characteristic and usually significant enrichment can be achieved. There are two exceptions: no enrichment could be observed under thermodynamically controlled conditions when the starting enantiomer composition corresponded to the eutectic composition, or when the method used was unsuitable for separation. In several cases, when kinetic control governed the crystallization, the character of the ee_0–ee_I curve did not correlate with the melting point binary phase diagram.

Introduction

There is an ever increasing demand, foremost by the pharmaceutical industry for enantiomerically pure (enantiopure) compounds. Except for transformations of enantiopure starting materials obtained from natural sources, enantioselective methods almost never yield the pure enantiomers. Even enzymic reactions, when not acting on their natural substrates often yield products of less than 100% enantiomeric excess (ee). Racemate resolution methods and enantioselective synthetic procedures are extensively covered in the literature.[1–11]

All this calls for methods by which non-racemic products, obtained by various procedures, can be upgraded. Most of such ee enhancement methods are based on the solid state behaviour of mixtures of enantiomers. However, application of solid–liquid or solid–vapour distribution systems remains largely an art that has not been systematically discussed. Numbers of enantiomeric enrichment processes are only mentioned in articles as a part of the experimental section.[12]

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Ferenc Faigl

Ferenc Faigl got his MSc diploma in 1977 from the Technical University of Budapest. He earned his first doctoral degree in 1981, Doctor of Sciences degree and Dr Habil. in 1996. He became Full Professor of the Department of Organic Chemical Technology, in 1997. He has been the Deputy Dean of the Faculty of Chemical Engineering and Biotechnology since 1999 and Head of the Research Group of Hungarian Academy of Sciences since 2003. He is the author and co-author of 107 papers, book chapters and booklets, and holds 32 patented procedures and patent applications. He received the gold degree of outstanding inventors in 1987 and 1989, the awards "Jedlik Ányos" and "Zemplén Géza" in 2007.

Elemér Fogassy

Elemér Fogassy graduated in 1957 at 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., PhD in 1974 and his DSc in 1986. He has been working in the pharmaceutical industry from 1957–1964. 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 319 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 in 2000–2003 he was recipient of the Széchenyi Professor's Stipend. He received the "Academy-Patent Award" in 2007.

Recently, experimental details and theoretical interpretations have been published on the amplification of ee starting from chiral compounds having small enantiomeric excess. These articles demonstrate that not only thermodynamically[13–16] but kinetically controlled[17] ee upgrading processes may be useful in the discussion on the origin of biomolecular homochirality on earth.

However, in laboratory or industrial scale preparation of enantiopure compounds, one has to consider the efficiency of the enantiomer separation processes. It means that for practical purposes, not only the enantiomeric purity of a product (ee), but also its yield also relevant. Therefore, it is advisable to use the parameter *S* characterizing the efficiency of the ee upgrade process.[18]

$$S = ee * yield$$

Here we report a systematically ordered series of practically useful enantiomer enrichment methods and strategies for the preparation of pure enantiomers.

Mihály Nógrádi

Professor Mihály Nógrádi (76) 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. He has published 140 research papers.

Emese Pálovics

Emese Pálovics was born in 1967 in Satmar (Rumania). She graduated in 1990 at the University of Technology "Traian Vuia" in Timisoara as a chemical engineer. Since 1994 she has been scientific assistant at the Research Group for Organic Chemical Technology, Hungarian Academy of Sciences (BUTE) working on crown ethers and organophosphorus compounds. Since 2004 she has worked with Prof. Elemér Fogassy in the field of optical resolution. She earned her PhD in 2009.

1. Solid state behaviour of mixtures of enantiomers: crystal structure, melting point, solubility

1.1 Homochiral and heterochiral interaction: conglomerate- and racemate-type crystals

Reducing the interaction of enantiomeric entities to two molecules, such interactions can be either homochiral, *i.e.* interaction between two chiral molecules of the same configuration ($R\cdots R$ or $S\cdots S$), or heterochiral, *i.e.* that between those of opposite configuration ($R\cdots S$). One of these interactions is necessarily of lower energy. Consequently, the difference between the stabilities of the crystal lattices built up from molecules of the same configuration (homochiral) and those from a 1 : 1 (racemic) mixture of molecules of opposite configuration can usually be observed. The only exception is the (very rare) case of *solid solutions* (or pseudoracemates) when the energy difference between the homochiral and heterochiral associates is so small that the enantiomers can replace each other in the crystal lattice in any ratio. To solid solutions none of the enrichment methods of upgrading described in this paper can, unfortunately, be applied.

Accordingly, chiral compounds basically form two types of crystals. When homochiral interactions are preferred over heterochiral ones, a so called *conglomerate* is formed, *i.e.* the individual crystals ideally contain molecules of the same configuration. When, in turn, heterochiral interactions are energetically more favorable, apart from the two mirror image homochiral crystals, a third kind of crystalline phase appears. The unit cell of that kind of crystals contain the optical isomers in 1 : 1 ratio. In other words, a *racemate*† can be formed.

A simple model of such behavior of enantiomeric mixtures can be demonstrated by the comparison of the simplest associates (the dimers), which exist in solution. Representing the enantiomers by ***R*** and ***S***, the following dimers can be envisaged:

$$\boldsymbol{S} + \boldsymbol{S} \rightleftharpoons \boldsymbol{SS}$$

$$\boldsymbol{R} + \boldsymbol{R} \rightleftharpoons \boldsymbol{RR}$$

$$\boldsymbol{S} + \boldsymbol{R} \rightleftharpoons \boldsymbol{SR}$$

† This term, firmly established in the chemical literature, is unfortunately often confused with racemic mixtures in general.

József Schindler

József Schindler was born in 1976 in Budapest. He graduated in 2001 at the Budapest University of Technology and Economics as a chemical engineer. At present he is scientific assistant in a research group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology and works with Prof. Elemér Fogassy on optical resolution.

The relationship of ***SS*** and ***RR*** is enantiomeric, while that of either ***RR*** and ***SR*** or ***SS*** and ***SR*** is diastereomeric. As a consequence, if such a system is subjected to any kind of phase partition, mostly between a solid and liquid phase, selection between diastereomeric dimers (or analogous higher associates) can be expected.

Models can be constructed by which non-bonding interactions of substituents around a chiral center can be assessed based on their σ* values. When the sum of such interactions is bigger (stronger interactions) for the heterochiral dimer than that is for the homochiral one, formation of a racemate can be expected. Data obtained in this way can be used to select the most efficient method of separation.[19–21]

Melting point *vs.* composition diagrams of the conglomerate- and the racemate-forming compounds are typical and different (see Fig. 1).

Solid phases of the pure enantiomers, as well as of the racemate, behave as different entities and show, when mixed, the well known phenomenon of melting point depression. Accordingly, mixtures of conglomerate-forming enantiomers show a melting point minimum at the racemic composition. With racemate-forming enantiomers in turn, with some rare exceptions, the melting point of the racemate is higher than that of the pure enantiomers, and the melting point *vs.*composition curve shows a maximum at the racemic composition. Moreover, two minima (positioned symmetrically on either side of the maximum, at the so called *eutectic composition*, see Fig. 1 (ii)) can be seen in the diagram. It was Roozeboom who first systematically studied melting point diagrams of enantiomeric mixtures at the very end of the 19th century.[22] A mathematical treatment of the diagrams was presented somewhat later by van Laar.[23]

Solubility isotherms of the ternary systems (comprising the two enantiomers and the solvent) are generally running parallel to the melting point diagrams. This fact was first observed by Pasteur,[24] but it was again Roozeboom who pointed out this correlation.[22]

Higher melting points of crystals are usually associated with lower solubility, not surprisingly since both reflect the strength of cohesion forces between molecules. As will be explained in detail later, methods for the purification of non-racemic mixtures are almost exclusively based on enantiomeric composition *vs.* solubility correlations. Theoretical and practical aspects of such correlations for crystalline chiral compounds were exhaustively discussed in the classical book by Jacques *et al*.[25]

The concept behind all the procedures to be discussed below is the same. The optical isomers form homo- and heterochiral associates in the liquid phase (melt or solution) and under supersaturation such associates are functioning as seeds for crystallization.[26]

Even though this review focuses on the solid–liquid systems, we have to mention that the same principles are responsible for solid–vapour or liquid–vapour distributions of enantiomers, but the effects of kinetic factors have to be taken into consideration when one wishes to rationalize the results of enrichments made by sublimation or distillation. An interesting example is the self-purification of enantioimpure (*S*)-2-(trifluoromethyl)lactic acid by sublimation in open air.[27] Surprisingly enough, the racemic part of the investigated sample sublimed out and an enriched fraction remained in the plate. In order to explain the phenomenon, the authors compared the hydrogen-bridge systems of the homo- and heterochiral crystals. While the pure enantiomer formed a zig-zag structure, the racemate was built up from heterochiral dimers. Furthermore, the trifluoromethyl groups were closer to each other in the racemate than in the homochiral crystals. The striking difference in molecular packing may explain the observed, quite unusual differences in the sublimation rates of the racemic and optically pure compounds.

1.2 Changing the type of crystals by derivatization or by changing the counter ion

Enrichment of conglomerate-forming enantiomeric mixtures is usually much more efficient than purification of racemate-forming mixtures; therefore, methods for changing that behaviour of the enantioimpure mixtures are of prominent practical significance.

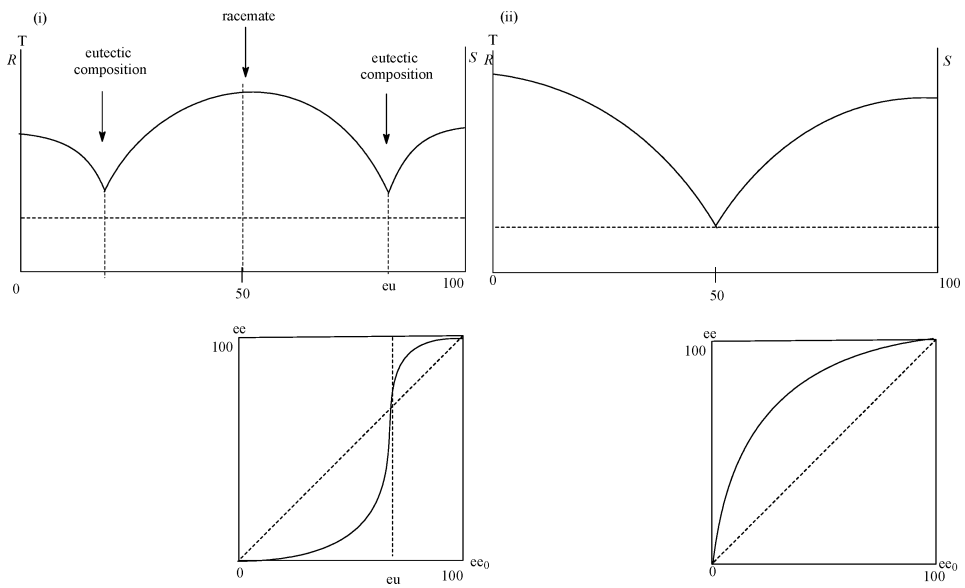
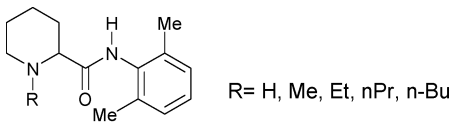


Fig. 1 Binary melting point *vs.* composition phase diagrams of (i) racemate-type crystals, (ii) conglomerate-type crystals. Below, changes in the ee values of the crystallized mixtures are shown as a function of the starting enantiomeric excess (ee_0) of a supersaturated solution of the mixture, respectively.

A study on various acidic salts of 1-phenylethylamine with achiral dicarboxylic acids revealed that while the succinate forms a conglomerate,[28] the malonate and the phthalate give racemates.[29] Extension of the investigation to the oxalate[30] and eight other dicarboxylic acids confirmed that efficient enantiomer separation can only be carried out with conglomerate-forming salts.

An interesting case is the crystallization of *N*-alkylpipecolylxylides (**APX**; Scheme 1). Among the investigated compounds, there is only one conglomerate-forming material, the *N*-butyl derivative. The others form racemates, representing the rare cases when the melting point of the racemate is lower than that of the pure enantiomers.[31]



APX

Scheme 1

Sometimes racemate-forming compounds can be transformed to conglomerate-type by derivatization. For example, the benzodioxane carboxylic acid (**DO**-CO_2H; Scheme 2) forms a racemate with an eutectic composition at 88% ee, but crystals of its methyl ester (**DO**-CO_2Me) are of conglomerate-type and can be enriched by recrystallization to 98.9% ee. Similarly, mesylation of the racemate-forming alcohol (**DO**-CH_2OH) gives the conglomerate forming derivative (**DO**-CH_2OMeS).[32]

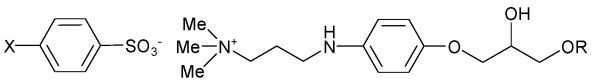
In the cases of several chiral ammonium sulfonates (**CAS**; Scheme 3), two complementary strategies were applied for the induction of preferential enrichment by controlling the mode of polymorphic transition.

One was the slight modification of the molecular structure (changing X and R in **CAS**) so as to prevent the undesired polymorphic transition. The other was the use of the appropriate seed crystals to induce the so called "epitaxial transition".[33]

2. Melting and recrystallization

2.1 Enrichment of mixtures of conglomerate forming enantiomers

2.1.1 Enrichment by melting or freezing. The method is similar to the gradual concentration of a solution of a non-racemic mixture of conglomerate-forming enantiomers. Gradual cooling of a melt of such a mixture results in the crystallization of the major enantiomer. When a certain point is reached, cooling is stopped and the phases are separated by filtration or centrifugation. An enriched solid phase can be obtained and the filtrate contains the melt of a lower enantiomeric purity mixture. Owing to technical problems (temperature control, *etc.*), this procedure is only practical on a larger scale.



CAS

X=Me, NO_2, Br, R=Me, Ph, p-FC_6H_4

Scheme 3

E.g., cooling a melt of a partially resolved sample of **PGL** (the lactone intermediate of prostaglandine synthesis) to 0–5 °C followed by separation of the solid and the liquid phases enrichments (shown in Fig. 2) could be achieved.[34]

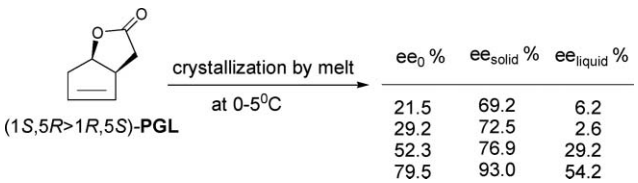
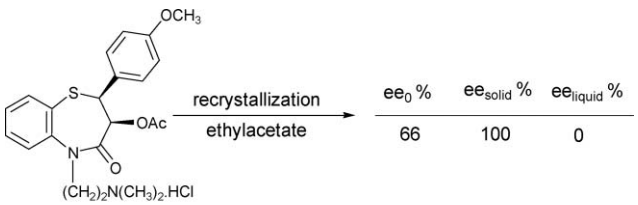


Fig. 2 Enantiomeric enrichment (ee_{solid}) of **PGL** starting from various enantiomer content (ee_0) samples, by partial solidification of its melt.

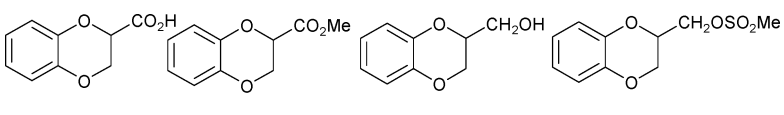
2.1.2 Enrichment by recrystallization. This is the simplest method, both from a practical and a theoretical point of view. Since the solubility of conglomerate-forming racemic mixtures is higher than that of the pure enantiomers, the enantiomeric excess can be, at least in principle, totally recovered by crystallization from such an amount of solvent that is sufficient to keep the racemic portion in solution. Examples for the application of this approach are numerous. The only problem is that, according to the compilation of Jacques *et al.*,[35] less than 20% of the chiral compounds crystallize as conglomerates.

As a single example, recrystallization of an enantiomeric mixture of dilthiazem hydrochloride (**DIL**·HCl, $ee_0 = 66\%$) from ethyl acetate may be quoted yielding the pure *S* enantiomer (Fig. 3).[36]



(*S*,*S* > *R*,*R*)-**DIL** . HCl

Fig. 3 Enrichment of a mixture of conglomerate forming **DIL**·HCl by recrystallization.



DO-CO_2H **DO**-CO_2Me **DO**-CH_2OH **DO**-CH_2OMeS

Scheme 2

2.2 Enrichment of enantioimpure mixtures of racemate-forming enantiomers

2.2.1 Enrichment by melting. We discuss this case first, because it is conceptually the simplest, involving only three components: the two enantiomers and the racemate.

It was mentioned in point 2.1.2 that enrichment of a conglomerate-forming mixture of enantiomers by partial solidification of a melt invariably leads to more or less pure crystals of the enantiomer in excess, although the yield depends on the initial composition.

The outcome of such a procedure involving racemate-forming mixtures of enantiomers depends on the initial composition (ee_0) related to the eutectic composition (ee_{eu}, see in Fig. 1). Starting from mixtures that are less pure than the eutectic composition ($ee_0 < ee_{eu}$), partial crystallization of the melt provides a crystalline phase of lower purity ($ee_{solid} < ee_{eu}$) and a liquid phase of higher enantiomeric purity ($ee_{liquid} > ee_0$) relative to ee_0. On the other hand, when the initial enantiomeric purity is higher than the eutectic composition ($ee_0 > ee_{eu}$) crystals enriched in the major enantiomer are obtained ($ee_{solid} > ee_0$), while the liquid phase will be less pure than the initial composition ($ee_l < ee_0$). Ideally, in the first case, racemic crystals and an enantiomerically enriched liquid should be obtained, and in the second case, the pure enantiomer should be crystallized and the eutectic mixture should be remain in the liquid phase. Owing to technical difficulties, such results in practice can only be approximated.

Enantiomers of *trans*-chrysanthemic acid (**TCA**) are forming a racemate; therefore, partial crystallization of a melt of **TCA** with ee_0 lower than the eutectic composition results in an enriched liquid phase (Fig. 4).[37]

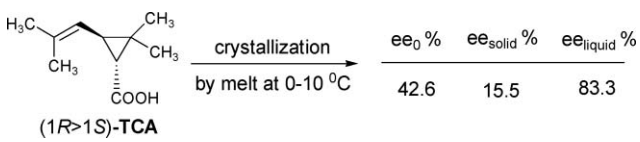


Fig. 4 Enantiomeric enrichment of a mixture of racemate-forming TCA by partial crystallization of a melt.

With the Flumequine intermediate (**FTHQ**), the eutectic composition is approximately at ee 40%. Therefore, no enrichment can be expected with an initial composition (ee_0) around 40%. However, by starting from a mixture of $ee_0 > 40\%$, significant enrichment can be achieved by separation of a partially solidified melt (Fig. 5).[38]

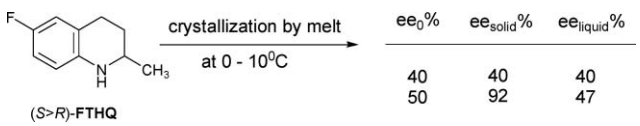
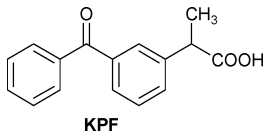


Fig. 5 Enantiomeric enrichment of a mixture of racemate-forming **FTHQ** by partial crystallization of a melt.

2.2.2 Enrichment by crystallization from a solvent. A higher melting point is usually associated with a lower solubility of racemates. Therefore, recrystallization of racemate-forming chiral compounds of moderate enantiomeric purity usually results in crystallization of the racemate, and the enantioenriched mixture can be recovered from the mother liquor. Its ee depends on the experimental conditions and with a judicial selection of the solvent, it can be quite high.

Recrystallization of mixtures with $ee_0 > ee_{eu}$ produces crystals of the enantiomer in excess. That was the case when mixtures of ketoprofen (**KPF**; Scheme 4) enantiomers of $ee_0 \geq 75\%$ were crystallized from *tert*-butyl methyl ether/petrol ether mixtures, yielding enantiopure crystalline products (up to ee > 99.9%).[39]



KPF

Scheme 4

In a hybrid process, preliminary enrichment of enantiomeric mixtures of mandelic acid was achieved with chromatography. When the enantiomer content became larger than the eutectic composition, preferential crystallization of the major enantiomer could be achieved.[40]

For resolutions on a larger scale it is advisable to construct a ternary phase diagram by measuring the solubility of mixtures of various compositions at a given temperature. The outcome of a recrystallization can be gleaned from such diagrams showing the eutectic composition. This can be illustrated by the recrystallization of an intermediate (**TOF**) of the tranquillizer tofizopam (Fig. 6) based on binary and ternary phase diagrams.[41]

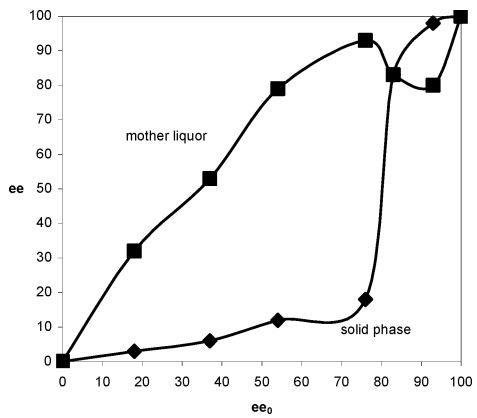


Fig. 6 Variation of the enantiomeric excess (ee) of **TOF** as a function of the initial enantiomeric composition (ee_0) during recrystallization from ethyl acetate (intersection of the two curves can be found around the eutectic composition).

The data in Fig. 7 demonstrate that almost pure racemate crystallizes when the initial purity $ee_0 < ee_{eu}$, while in the case of $ee_0 > ee_{eu}$, a practically pure enantiomer crystallizes. This figure also calls attention to the fact that in a practical process, ee values predicted by the phase diagrams can never be fully realized and, according to the kinetics of crystallization, the enantiomeric composition in the filtrate frequently differs from the theoretically expected composition (which could be achieved at thermodynamic equilibrium between the solid and liquid phases). In other words, in certain cases one can jump over the eutectic composition during crystallization of enantioimpure mixtures.

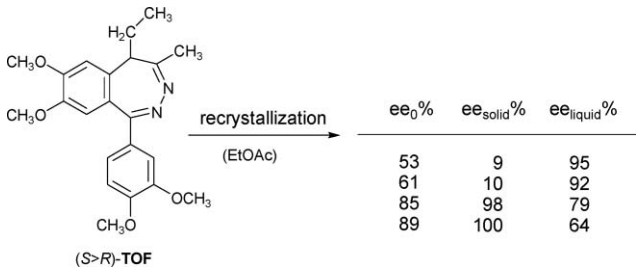


Fig. 7 Enrichment of a racemate-forming compound (**TOF**) by recrystallization as a function of the initial composition (ee_0).

A survey of twenty enantiomeric mixtures revealed that twelve of them formed racemates and recrystallization of the latter compounds resulted in the enrichment of the major enantiomer in the mother liquor, in all cases.[42]

An example for the situation when the enantiomer in excess can be recovered from the mother liquor in high purity is the recrystallization of a cylopentanopyrimidine (**CPP**) of ee_0: 65% (Fig. 8).[43]

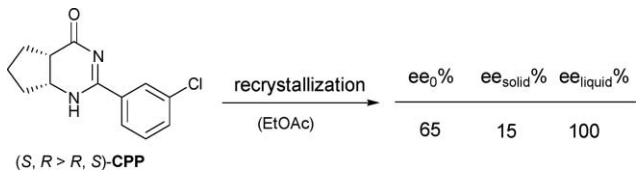


Fig. 8 An example when the optically pure enantiomer (**CPP**) was recovered from the mother liquor.

Upon crystallization of a mixture of the enantiomers of Citalopram (**CTP**) from heptane, the result depends again on ee_0. When it is less than the eutectic composition, crystals of the racemate can be filtered. When $ee_0 > ee_{eu}$, the enantiomer in excess crystallizes in practically pure form (Fig. 9).[44]

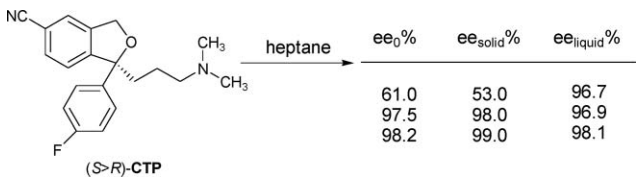


Fig. 9 Enantiomeric enrichment of a racemate forming **CTP** by recrystallization as a function of the initial composition (ee_0).

Resolution of the amino acid intermediate of the Dilthiazem (**TRA**) produces a mother liquor enriched in the desired *S*,*S* enantiomer. Evaporation of the solvent followed by recrystallization of the residue from ethanol was the method of purification. In this case, the crystalline fraction has the lower ee value while the mother liquor contains the almost pure (ee 98%) enantiomer (Fig. 10).[36]

The economics of the above mentioned purifications of racemate-forming enantiomers may depend on the ee_0 value and the position of the eutectic composition (ee_{eu}). Using this technique for the hydrochloride of flumequine intermediate **FTQH**·HCl, considerable enrichment could be realized with a starting material of low purity (Fig. 11), while almost no change of enantiomeric composition occurred during recrystallization of a sample of high purity (compare it with the crystallization of the free base **FTQH**, point 2.2.1).[38]

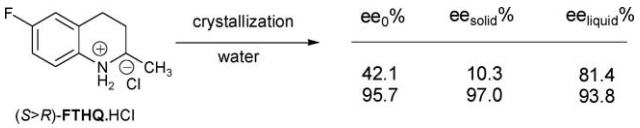


Fig. 11 Enantiomeric enrichment of **FTHQ**·HCl.

Solvate formation may also help enantiomer enrichment. A series of enantioimpure samples of 2-(4-aryloxyphenoxy)propionic acids have been upgraded in two steps using special solvate formation of the pure enantiomer. First, a close to racemic fraction of the given acid was crystallized from a dry organic solvent. Then, water was added to the filtrate and the pure enantiomer crystallized as a hydrate in good yields.[45]

2.2.3 Enantiomeric enrichment based on density differences. With racemate-forming chiral compounds, crystals of the racemate and those of the enantiomers should have different densities. Higher density of the racemate can be anticipated. By suspending a finely powdered mixture of optical isomers in a solvent or a solvent mixture of intermediate density, the lighter crystals float on the surface, while the heavier ones sink to the bottom.

This was the method by which poorly resolved phenylalanine (**PA**) could be enriched by sedimentation in a mixture of chlorobenzene and bromobenzene of $d = 1.35$ (Fig. 12).[46]

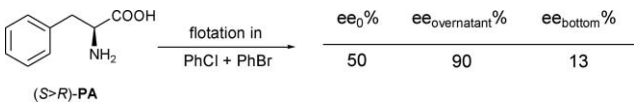


Fig. 12 An example for enantiomeric enrichment based on crystal density difference.

The density difference between the homochiral and heterochiral solids was used in the separation of alanine excess enantiomer crystals from racemate crystals on a preparative scale density gradient ultracentrifugation applying a 50 wt% Nycodenz gradient. The samples were recovered from the gradient material fractions by simple filtration.[47]

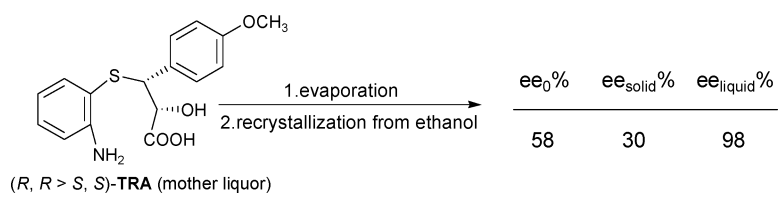


Fig. 10 Recrystallization of **TRA**: the almost pure enantiomer is recovered from the mother liquor.

2.2.4 Modification of the eutectic composition of racemate forming enantiomers by derivatization. Resolution sometimes gives rise to products with an eutectic composition or near to that. Such mixtures, in principle, cannot be enriched by recrystallization. Transformation of the compound to a derivative (into one of its salts as the simplest method) may shift the position of the eutectic composition. In this way, one can get the enriched enantiomer mixture by recrystallization.

An important example is that of ibuprofen (**IBU**), a classical anti-inflammatory agent.[48] Ibuprofen forms a racemate with ee_{eu} 88% as it is apparent from its binary melting point phase diagram also constructed with the aid of DSC measurements (Fig. 13).[49] Consequently, recrystallization of a mixture of enantiomers ($S > R$) with a composition around ee_{eu} failed to produce any enrichment.

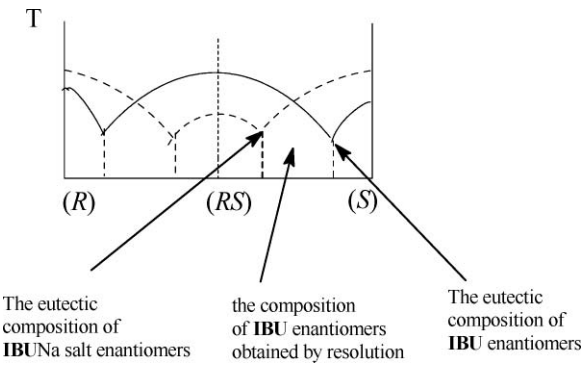
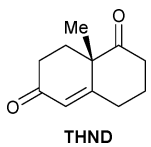


Fig. 13 Comparison of the binary phase diagrams of **IBU**Na salt and **IBU**.

The sodium salt of ibuprofen (**IBU**Na) also forms a racemate. However, the eutectic composition of this salt is at ee_{eu}: 24%. Therefore, separation of the pure enantiomer was possible starting from a mixture containing a 76% excess of the *S* enantiomer. Derivatization was accomplished by adding 0.5 equivalents of sodium hydroxide to an acetone solution of the acid (Fig. 14).

Essentially in a similar way, the mixtures of enantiomers of Naproxen (*S*)-**NAP** (R = H), an antiinflammatory agent that forms a racemate, were purified. However, the ethyl and methyl esters (Fig. 15, R = Me or Et) crystallize as conglomerates and are therefore suitable for enrichment by crystallization. Sodium salt formation shifted the eutectic point (ee_{eu}) to 32% (it is 56% for the free acid), improving the chances of enrichment by recrystallization. This behaviour can be interpreted by a closer racemic domain of the sodium salt. In this case, the eutectic composition can be found near to the racemic mixture resulting a wider range of conglomerate-like behaviour of enantiomer mixtures.

2.2.5 Separation of enantiomers by chromatography on an achiral adsorbent. The first example of ee upgrade by chromatography of enantioimpure mixtures on an achiral phase was the enrichment of a partially resolved diketone (**THND**; Scheme 5).[50]



Scheme 5

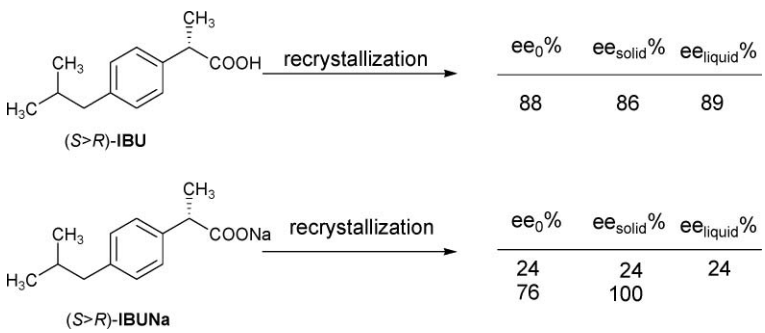


Fig. 14 Modification of the eutectic composition by derivatization of **IBU** and its effect on the ee upgrade.

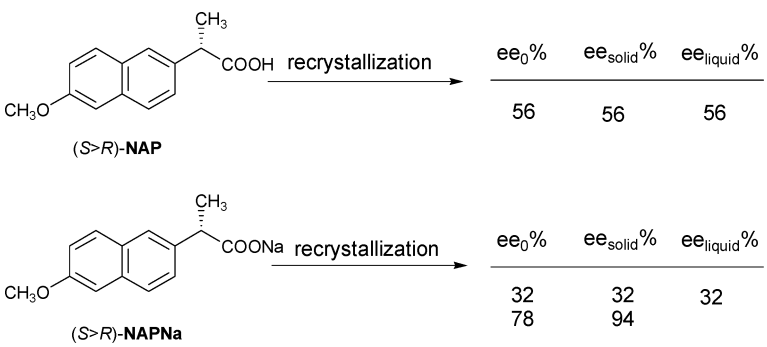


Fig. 15 Effect of salt formation on the enantiomeric enrichment in the case of **NAP** (ee_{eu} of **NAPNa** is closer to the racemic composition therefore there is a wider composition range for conglomerate like behaviour).

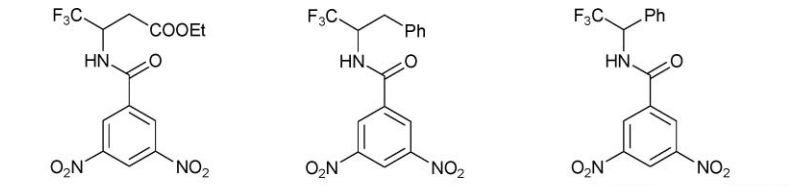


Fig. 16 Separation of the excess of an enantiomer from partially resolved mixtures of dinitrobenzamide derivatives by chromatography on an achiral adsorbent (ee_{max} and ee_{min} refer to the purest and the close to racemic fractions).

Enantioimpure mixtures of several different antihistamines were shown to undergo enantiomer enrichment under achiral conditions using an aminopropyl silica gel column with a hexane–isopropanol mobile phase. It has been demonstrated that the enrichment of antihistamine enantiomers is concentration-dependent, as very diluted samples are not resolved. The benzylic hydrogen on the chiral carbon appeared to play a major role in the chiral recognition process.[51]

The hypothesis that enantiomers form diastereomeric (homo- and heterochiral) associates finds corroboration by experiments in which partially resolved mixtures (ee_0 66%) of the dinitrobenzamide derivatives (**DNBA**1–3, shown in Fig. 16) could be enriched by passing them through a column filled with silica gel using a 5 : 1 mixture of hexane and ethyl acetate as eluent.[52,53]

A prerequisite for the success of this very simple method is a high stability of the associates. No wonder that its application seems to be rare.

3. Enrichment of enantioimpure samples by partial formation and/or decomposition of their salts

The use of half an equivalent of resolving agent, either in combination with half an equivalent of an achiral acid or base, or even without it, is an economic process and it is often used in optical resolutions carried out at industrial scale. In analogy, partial salt formation or partial decomposition of salts may be the right choice in enrichment procedures, too.

3.1 Enrichment *via* partial salt formation followed by distillation

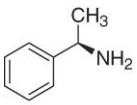
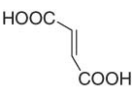
When the racemic portion of a racemate-forming volatile compound is transformed to a salt, the enantiomeric excess can be distilled off.[54]

Typical examples are the salts of 1-phenylethylamine (**PEA**) with dicarboxylic acids (oxalic acid, succinic acid, maleic acid or fumaric acid, see Table 1).

3.2 Enrichment by partial decomposition of a salt

When a solution of salts containing partially resolved acid or base are treated with less than an equivalent of a strong base or, respectively, a strong acid, the liberated part of the chiral acid or base precipitates frequently. In such cases, distributions of the homo- and heterochiral associates between the solid and liquid phases differ from the initial one. Depending on the type of the sample (conglomerate- or racemate-forming compound) the enantiomerically enriched or the racemic fraction can be isolated from the solid phase. With the proper choice of conditions, such an operation may lead to an almost enantiopure product.

Table 1 Enrichment of partially resolved 1-phenylethylamine (**PEA**) *via* partial salt formation with various dicarboxylic acids followed by distillation

	Distillation with	ee_0 (%)	$ee_{residue}$ (%)	$ee_{distillate}$ (%)
 (R>S)-**PEA**	 Oxalic acid	12.5	26.6	7.8
		25.0	44.6	15.5
		50.0	63.6	45.5
		75.0	65.7	78.1
		87.5	71.5	92.8
	 Succinic acid	12.5	27.3	7.6
		25.0	61.7	12.8
		50.0	75.2	41.6
		75.0	74.2	75.3
		87.5	83.6	88.8
	 Fumaric acid	12.5	41.8	2.7
		25.0	68.5	10.5
		50.0	95.5	34.9
		75.0	96.3	67.9
		87.5	97.5	84.1

3.2.1 Partial precipitation of conglomerate forming salts.

The situation is the simplest with compounds forming conglomerate-type crystals. In this case, one should dissolve the salt of the enantiomeric mixture and add a strong inorganic acid or base in an equivalent amount to the excess of the predominant enantiomer. The salt of the excess enantiomer should precipitate, at least in principle, in an enantiopure form.

Resolution of racemic tisercin (±)-**TIS** with half an equivalent of (*R*,*R*)-tartaric acid was carried out in the presence of hydrochloric acid. It was the desired (*S*)-enantiomer-containing salt that remained in solution. After concentration of the solution, aqueous sodium hydroxide solution (containing an equivalent amount of NaOH to the excess of (*S*)-**TIS**) was added into the reaction mixture and (*S*)-**TIS** precipitated, while an almost racemic hydrochloride salt remained in solution (Fig. 17).[55]

3.2.2 Partial precipitation of racemate-forming compounds.

In the series of racemate-forming compounds it is the racemate that is generally less soluble than the pure enantiomer. Therefore, the racemic fraction of these type of enantiomeric mixtures of chiral bases or acids can be liberated from the solution of their salt by addition of a strong inorganic acid or base (in an equivalent

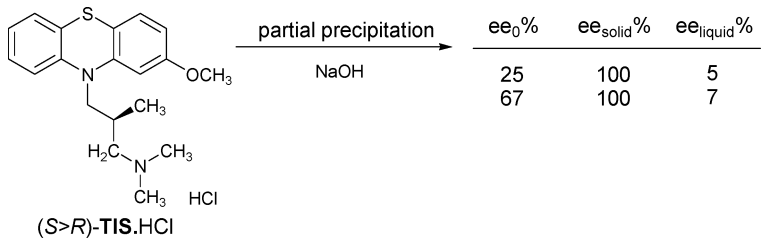


Fig. 17 Enantiomeric enrichment by partial precipitation of **TIS**.

amount to the racemic portion). The enriched isomer mixture (or the pure enantiomer) remains in solution as a salt and it can be recovered after filtration of the precipitated racemate.

An early example is the enantiomeric enrichment of the acid intermediate (**PRI**) of the analgesic (*S*)-Probon.[56,57] Partial precipitation (liberation) of the free acid from an aqueous solution of the **PRI** ammonium salt (with hydrochloric acid) gave a solid product containing the racemate fraction together with a small amount of the pure enantiomer. Complete acidification of the filtrate followed by extraction and distillation yielded the pure (*S*)-**PRI** enantiomer.

The example in Fig. 18 illustrates the high dependence of the efficiency of partial precipitation on ee_0 in the case of *N*-acetyl-4-fluorophenylglycine (**AcFPG**). Interestingly enough, starting from a higher enantiomeric excess (ee_0), a much better separation of the racemic fraction could be achieved (Fig. 18).

Fig. 18 Enrichment by partial precipitation of racemate forming **AcFPG** starting from the sodium salt of its enantioimpure mixtures.

Conditions are often less than ideal and considerable experimentation is required to achieve good results.

Upon resolution of a thiazoloimidazole derivative (**TET**), the remaining mother liquor contained a considerable amount of partially resolved material (ee_0 54%) as hydrochloride salt. First the racemic portion was precipitated by the addition of diluted sodium hydroxide solution, followed, after filtering off the racemic product, by precipitating the rest, enriched in the *R* enantiomer (see Fig. 19a).[58]

Using a similar strategy, acidification of a solution of the sodium salt of **TRAN** in two stages afforded the required enantiomer in almost pure form (see Fig. 19b).[59]

The outcome of selective precipitation depends on the initial composition (ee_0) of the mixture and its relation to the eutectic composition (ee_{eu}). This was studied in detail in the case of the two-stage precipitation of *cis*-permetric acid (**CPA**) from a solution of its sodium salt with hydrochloric acid (see Fig. 20).[60]

Starting from a mixture less pure than the eutectic composition (ee_{eu} 68%, determined by DSC measurements, *i.e.* $ee_0 < ee_{eu}$), the first fraction was closer to the racemic composition. When the initial composition was larger then the eutectic one ($ee_0 > ee_{eu}$), the first fraction contained the enantioenriched mixture ($ee_0 < ee_I$).

When recrystallization fails to bring about enrichment, fractionated precipitation may be the solution. This was the case with a series of the racemate forming *N*-acyl-phenylalanine and *N*-acyl-phenylgycine derivatives (**FPA**).[61] By selective, two-stage precipitation (starting from an aqueous solution of the sodium salts) of **FPA**, considerable enrichment could be achieved (Fig. 21). The procedure deserves to be discussed in more detail.

The binary melting point/composition phase diagram of *N*-formyl-phenylalanine (**FPA**) indicates racemate type behavior and an eutectic point at ee_{eu} = 75%. It is therefore not surprising that considerable enrichment could be attained with a mixture of ee_0 = 49.6%, while two stage precipitation starting from an aqueous solution of **FPA**·Na with ee_0 = 73.4% (composition near the eutectic point), did not resulted in significant enrichment (Table 2).[62]

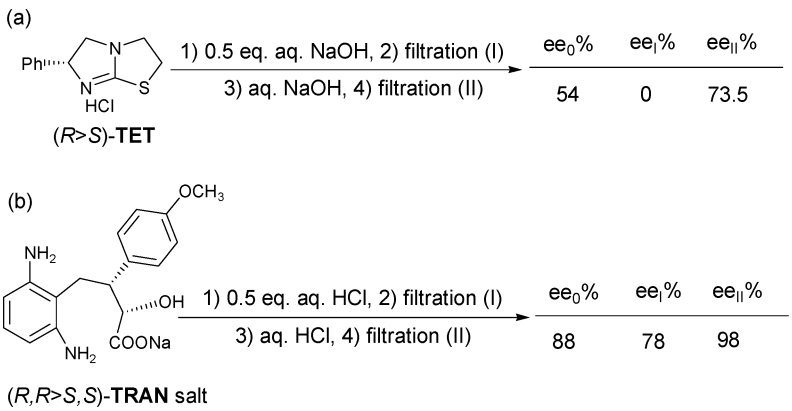


Fig. 19 Enrichment by partial precipitation of racemate-forming **TET** and **TRAN** starting from the salts of their enantioimpure mixtures.

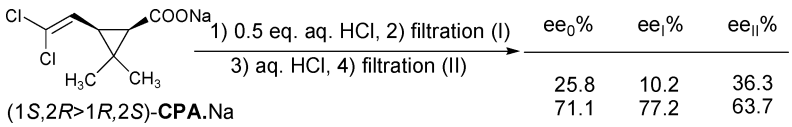


Fig. 20 Enrichment by partial precipitation of racemate-forming **CPA** starting from the sodium salt of its enantioimpure mixtures.

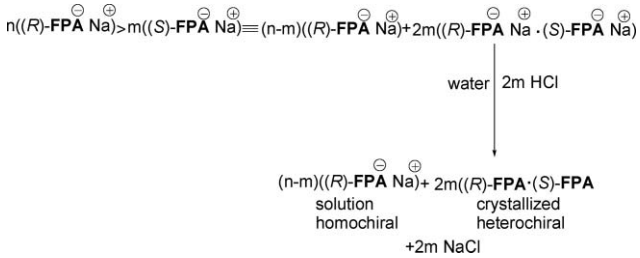
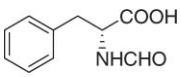


Fig. 21 The general scheme of selective precipitation of **FPA** from an aqueous solution of (*R*>*S*)-**FPA**·Na.

Table 2 Results (ee_I, ee_{II}) of the fractionated precipitation of enantioimpure mixtures (ee_0) of **FPA**

	ee_0 (%)	ee_I (%)	ee_{II} (%)
 **FPA** (*R*>*S*)	49.6	19.3	75.0
	73.4	70.8	75.2

The situation was almost the same in the cases of *N*-acetyl-phenylglycine (**AcPG**) (Table 3) and *N*-acetyl-4-fluorophenyl-glycine (**AcFPG**) (Table 4) where ee_{eu} could not be exceeded ($ee_{eu} \approx 86\%$ in both cases, according to the binary phase diagrams).[63]

In the case of *N*-propionyl-phenylalanine (**PPA**) the eutectic composition ($ee_{eu} = 58\%$) would indicate a rather low limit of enrichment. Nevertheless, owing to kinetic control of crystallization, enrichment up to ee = 90% could be realized.

Table 3 Results (ee_I, ee_{II}) of the fractionated precipitation of **AcPG** enantiomeric mixtures (ee_0)

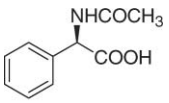
	ee_0 (%)	ee_I (%)	ee_{II}%
 **AcPG** (*S*>*R*)	63.6	52.6	86.2
	79.5	76.8	86.6

Table 4 Results (ee_I, ee_{II}) of the fractionated precipitation of **AcFPG** enantiomeric mixtures (ee_0)

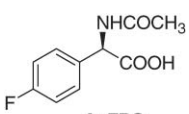
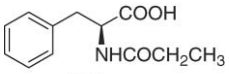
	ee_0 (%)	ee_I (%)	ee_{II}%
 **AcFPG** (*S*>*R*)	65.9	59.5	74.3
	77.7	5.0	86.5

Table 5 Fractionated precipitation of *N*-propionyl-phenylalanine from an aqueous solution of its sodium salt with hydrochloric acid in two stages (ee_I and ee_{II})

	ee_0 (%)	ee_I (%)	ee_{II} (%)
 **PPA** (*S*>*R*)	20	2.5	24.8
	25	47.7	–4.3
	35	39.0	24.3
	60	88.7	12.4
	85	99.9	83.8

3.3 An example of kinetic control during fractionated precipitation[61,63]

Induced crystallization is a very old, although severely limited method of classical resolution and the kinetics of such crystallization has been studied thoroughly.

On the other hand, the role of kinetic control in selective precipitations has largely remained obscure. Enrichment of the enantioimpure mixtures of *N*-propionyl-phenylalanine (**PPA**) and *N*-propionyl-phenylglycine (**PPG**) by fractionated precipitation (from aqueous solutions of their sodium salts with hydrochloric acid) were convenient models to study this phenomenon.

The binary melting point phase diagram of **PPG** indicated conglomerate-type behaviour, while that of **PPA** showed racemate type with $ee_{eu} = 59\%$. The results of selective precipitation contradict anticipations based on these findings. Owing to induced crystallization, enantiomeric enrichment in the first fraction exceeded the expected levels at small ee_0 values (see Tables 5 and 6, and Fig. 22 and 23).

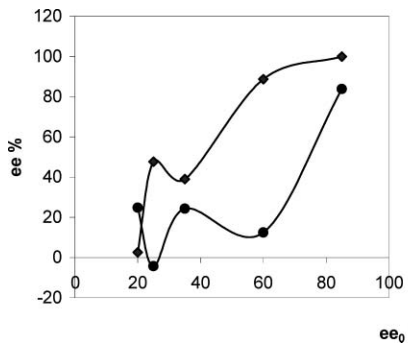
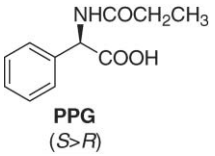


Fig. 22 Fractionated precipitation of *N*-propionyl-phenylalanine from an aqueous solution of its sodium salt with hydrochloric acid in two stages (fraction I –◆–◆–◆–: ee_I; and fraction II –●–●–●–: ee_{II}).

3.4 Enrichment of enantioimpure mixtures by salting out

The aminodiol intermediate (**AD**·HCl) of the synthesis of chloramphenicol was crystallized from aqueous solution, but a part remained in the solution. The amount of the crystallized racemic fraction could be increased by addition of the salt of the

Table 6 Fractionated precipitation of *N*-propionyl-phenylglycine from an aqueous solution of its sodium salt with hydrochloric acid in two stages (ee_I and ee_{II})

	ee_0 (%)	ee_I (%)	ee_{II} (%)
 PPG (*S*>*R*)	10	4	17
	12.5	27	–3.6
	15	38.2	–4.8
	25	27	1.2
	35	59	0.9
	50	84	–0.4
	75	90	16
	90	92	76

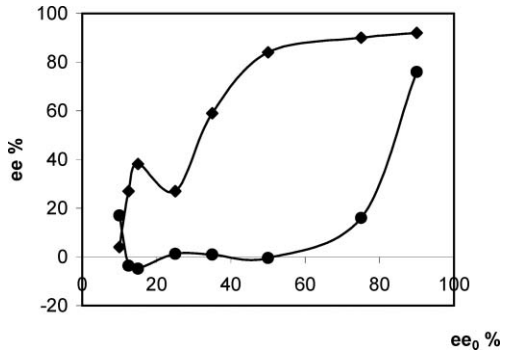


Fig. 23 Fractionated precipitation of *N*-propionyl-phenylglycine from an aqueous solution of its sodium salt with hydrochloric acid in two stages (fraction I –◆–◆–◆–: ee_I; and fraction II –●–●–●–: ee_{II}).

unfavourable enantiomer ((*S*,*S*)-**AD**·HCl), because displacement of the equilibrium could be promoted this way (Fig. 24).[64]

Classical resolution of 2-amino-3-(3,4-dimethoxyphenyl)-2-methylpropionitrile (**AN**) was performed by (*R*,*R*)-tartaric acid but the undesired (*R*)-**AN** crystallized in the diastereomeric salt. The filtrate contained the HCl salt of (*S*)-**AN**. The hydrochloride salt of the pure enantiomer precipitated from the mother liquor by adding sodium chloride into the aqueous solution (Fig. 25).[65]

3.5 Enrichment of enantiomeric mixtures by the aid of a non-resolving agent chiral reagent

Enantioimpure mixtures may be separated using a chiral reagent, which is not suitable for classical resolution of the racemic mixture.[66] When the (+) > (–)-*trans*-chrysantemic acid (**TCA**) mixture was treated with optically active *threo*-2-dimethylamino-1-phenyl-1,3-propanediol (**DMPP**) in diisopropyl ether, an interesting phenomenon was observed. Using one of the **DMPP** enantiomers, the racemic portion crystallised, and the other optical isomer of **DMPP** crystallised together with the enantiomeric excess of **TCA** (Fig. 26).

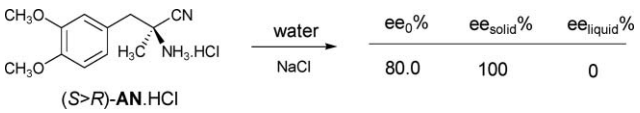


Fig. 25 Enantiomeric enrichment of **AN**·HCl by salting out with NaCl.

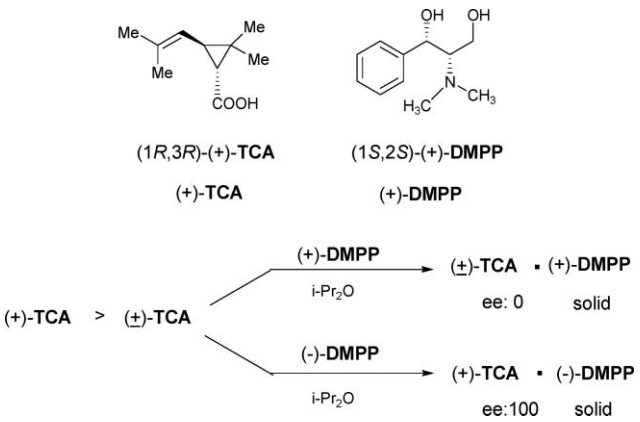


Fig. 26 Enantiomeric enrichment of **TCA** induced by a chiral agent (**DMPP**), which is not suitable resolving agent of **TCA**.

4. Strategies for the preparation of pure enantiomers.

Although the primary objective of enrichment of enantioimpure materials is to obtain the excess of the enantiomer in pure form, recovery of the racemic portion for resolution is also important (recycling).

Repeated resolution of such mixtures of enantiomers can be taken into consideration when the enantiomer content of the mixture is not too small.

Among the multitude of methods presented above, the simplest and most generally applicable ones are recrystallization and, when salt formation is possible, selective precipitation.

The type of the crystal, *i.e.* conglomerate- or racemate-forming, is crucial for the applicability of the method of choice. With conglomerate-forming compounds, initial composition (ee_0) is relevant only concerning the yield, but does not restrict the choice of methods. With racemate-forming compounds, however, the composition of the eutectic mixture (ee_{eu}), in other words the "broadness" of the racemate region, is of foremost practical importance. When this range is too wide, the prospects for recovering the enantiomer in excess in reasonable yields is poor. In this case, the search for a conglomerate-forming derivative or of one with a narrower range of racemate-forming composition is recommended. For large scale procedures experimentation with induced crystallization may pay off.

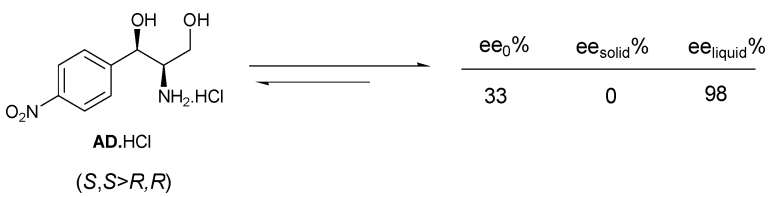


Fig. 24 Enantiomeric enrichment of **AD**·HCl by salting out using the unfavourable enantiomer of **AD**·HCl.

Kinetic control of crystallization may produce unexpected and sometimes welcome results contradictory to data derived from melting point phase diagrams.

Conclusions

Enrichment of enantioimpure chiral compounds is an important part of most API (active pharmaceutical ingredient) manufacturing processes. As shown in this perspective, the armoury of ee upgrading methods is extremely versatile and can be used independently of the origin (racemate resolution or enantioselective synthesis) of the optically active crude material. A systematic survey of the enantioenrichment methods demonstrated that the basis is the same for each one: namely, it is the presence of homo- and heterochiral associations in solid and liquid phases. Experimental results demonstrated that these diastereomeric associations might be responsible also for the evolution of biomolecular homochirality on earth.

In a laboratory or on an industrial scale the purification process design should start from the stability order of these diastereomeric associations. This can be determined by thermoanalytical methods or solubility measurements. In the case of conglomerate-forming compounds, the practical question is the yield of the enriched (or pure) enantiomer in the crystalline phase. One should choose the method that serves the sharpest separation of the enantiomer excess from the racemic mixture. Chiral purification of racemate-forming compounds is more complicated and the result strongly depends on the position of the eutectic composition. As a conclusion of the reviewed methods, we can say that combination of two methods (*e.g.* recrystallization and fractionated precipitation) may help to cross over the eutectic composition and this way efficiency of the enantioenrichment process can be improved. In certain cases, slight modification of the molecular structure completely changes the crystallization behaviour of the compound: the eutectic composition can be shifted significantly or conglomerate forming derivatives can be obtained.

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