1. Introduction

Reaction of a racemic acid or base with an optically active base or acid gives a pair of diastereomeric salts. Members of this pair exhibit different physicochemical properties (e.g., solubility, melting point, boiling point, adsorption, phase distribution) and can be separated owing to these differences. The most important method for the separation of enantiomers is the crystallization. This is the subject of this chapter.

Preparation of enantiopure (ee~100%) compounds is one of the most important aims both for industrial practice and research. Actually, the resolution of racemic compounds (1:1 mixture of molecules having mirror-imagine relationship) still remains the most common method for producing pure enantiomers on a large scale. In these cases the enantiomeric mixtures or a sort of their derivatives are separated directly. This separation is based on the fact that the enantiomeric ratio in the crystallized phase differs from the initial composition. In this way, obtaining pure enantiomers requires one or more recrystallizations. (Figure 1).

The results of these crystallizations (recrystallizations) of mixtures of chiral compounds differ from those observed at the achiral compounds. Expectedly, not only the stereoisomer in excess can be crystallized, because the mixture of enantiomers (with mirror image relationship) follows the regularities established from binary melting point phase diagrams, and ternary composition solubility diagrams, respectively, as a function of the starting enantiomer proportion. According to this fact, we talk about conglomerate behaviour when the enantiomeric excess is crystallized, and racemate behaviour when it remains in the mother liquor.1

At the same time, there are some enantiomeric mixtures having racemate properties (based on binary phase diagram) which show conglomerate behaviour during its purification by fractionated precipitation. Always the enantiomeric excess is crystallized independently from the starting isomeric composition. This is explained by the kinetic crystallization of the enantiomeric excess.2 Consequently, if the enantiomeric purity obtained after recrystallization or by other partial crystallization (as the result of splitting between the two phases) is
plotted against the initial enantiomeric composition, either racemate or conglomerate behaviour is expected, or a conglomerate like curve is obtained (hereinafter: kinetic-conglomerate) (Figure 2).3

Fig. 1. The essential processes of enantiomeric separation starting from the racemic compound

Fig. 2. The composition of enantiomeric mixtures obtained by crystallization (ee) in function of starting enantiomeric purity (ee0). a). conglomerate melting point diagram; b). racemate melting point diagram; The diagrams of expected results of c). conglomerate crystallization, d). racemate crystallization, e) kinetic-conglomerate like crystallization
The above mentioned behaviour depends on the substituents of the base skeleton of the racemic compound. It means that different substituents can determine the change in behaviour. For example, the formyl-, acetyl- and propionyl-derivatives of phenyl alanine (FoPA, AcPA, PPA, see below) show different behaviour.

\[
\begin{align*}
\text{FoPA} & \quad \text{NHCHO} \quad \text{COOH} \\
\text{AcPA} & \quad \text{NHCOCH}_3 \quad \text{COOH} \\
\text{PPA} & \quad \text{NHCOCH}_2\text{CH}_3 \quad \text{COOH}
\end{align*}
\]

At separations based on the distribution between solid and another (liquid or melt) phase formation of a crystalline material is needed. The chiral discriminating effect can be explained by the presence and reactions of homo- and heterochiral aggregates (the simplest members of them are the dimers), and by their different physical and chemical properties. Thus in the solution or in the melt of racemic mixtures of enantiomers (S and R) two homodimers (SS and RR) and one heterodimer (SR) should be present, while in a hypothetical enantiomeric mixture (S>R, ee = 50%) presence of two dimers, namely SS and SR, is expected. Considering that homo- and heterodimers are in diastereoisomeric relation with each other, their solubility and reactivity are different.

\[
3S_2R \leftrightarrow S.S + R.R + S.R
\]

\[
3S_2R \leftrightarrow S.S + S.R
\]

The behaviour of a mixture of chiral compounds, in which the resolving agent is a substituted derivative of one of the enantiomers (which are also present in the mixture in racemic form) is similar to the behaviour of the above mentioned enantiomeric mixtures. Under such conditions real diastereoisomeric pairs are formed containing an enantiomer and the structurally similar resolving agent, respectively.

If the racemic compound (mixture of enantiomers in 1:1 ratio) is reacted with equimolar amount of a derivative of one of the enantiomers (e.g. R*, having opposite chemical character) a quasi-enantiomeric mixture is formed.

\[
\begin{align*}
\text{S.R} + \text{R*R*} & \leftrightarrow \text{SR*} + \text{RR*} \\
\text{ee}_0 & \sim \text{quasi 50}\% \quad \text{diastereomers}
\end{align*}
\]

In these cases non-symmetric conglomerate or racemate biner phase diagrams are expected and „quasi-conglomerate“ (RR*) or „quasi-racemate“ (SR*) precipitate may be obtained. In the former case the enantiomeric purity of R or S in the crystalline diastereoisomeric salt (RR* or SS*) can be anything, but in the latter (“quasi-racemate”) case an enantiomeric purity (ee) usually reflects the eutectic composition for the enantiomeric mixture of original racemic compound.
The resolving agent has a decisive role at the separation of diastereoisomers. Previously, we referred to the fact that the resolving agent (having related structure with one of the enantiomers of the racemic compound) may form well-crystallizing diastereoisomer. But usually separations based on crystallization of diastereoisomers obtained from chiral reagents with significantly different structures are performed. One of these frequently used reagents is the dibenzoyltartaric acid (DBTA), which is suitable for the resolution of racemic bases. It was observed, that it has also an ability to form relatively stable molecular complexes with racemic alcohols, and its Ca and Mg salts form coordinative complexes both with alcohols and phospholenes. In these cases pure enantiomers can also be obtained by fractionated precipitation of the diastereoisomeric complexes.5,6

It is assumed based on the results of the resolutions (both via salt-formation, and complex-formation) that the composition of the crystalline diastereoisomer is determined by the properties of the enantiomeric mixture of the racemic compound even if the resolving agent has not a similar structure to the racemic compound.

The enantiomeric mixture obtained by recrystallization (fractionated precipitation) and decomposition of diastereoisomers usually needs further purification to obtain the pure (single) enantiomer. The above mentioned behaviour of the stereoisomeric mixtures is expected at these enrichment processes, too.

However, during the purification of enantiomeric mixtures (having diastereoisomeric relationship and –behaviour of the homo- and heterochiral aggregates) both the kinetic and thermodynamic control can be observed, and certainly these phenomena can be observed at the (re)crystallization of diastereoisomers as well.7 At the same time in case of reciprocal resolution (one of the enantiomers of the original racemic compound is applied as resolving agent for resolution of the racemic mixture of the initial chiral agent) the former behaviour is expected inevitably (namely the previously experienced kinetic- or thermodynamic control can be observed).

So, the crystallization rules (based on expected chiral-chiral interaction) of enantiomeric mixtures can be applied even if two or more chiral compounds are present.

However, the mode of separation of the crystalline fraction is very important. For example, the separation of enantiomers can be effectuated even if a mixture from the melt of enantiomeric mixtures is crystallized. The crystalline material can be separated from the residue by filtration, distillation, sublimation or extraction.8

A similar separation can be achieved even if the amount of the resolving agent applied is less than an equivalent to the racemate. Then the enantiomeric mixture can be separated from the crystalline diastereoisomer by sublimation or distillation, in accordance with the above mentioned methods.

The dielectrical constant of the solvent (if solvent is used at the resolutions) changes the formation, composition and enantiomer recognition of the crystals.9 The composition of crystalline diastereoisomers is also influenced by the pH of the reaction mixture.10

The purity (de) of the diastereoisomer can be improved using a mixture of structurally related resolving agents. It is often referred as “Dutch resolution” in the literature.11
If the diastereoisomeric salt can not be separated by fractionated precipitation, it is feasible to get its crystalline solvate by fractionated precipitation from a solvate forming solution. When the solvent, unsuitable for separation of the diastereoisomers, contains structurally (partly) similar compound(s) to the solvate forming solution, the separation of enantiomers became feasible by fractionated precipitation of the diastereoisomeric salt. It is particularly striking, when the wanted crystal composition is obtained by using a structurally similar (either with racemic compound or resolving agent) achiral compound.

It is possible that the recrystallization from an adequate solvent does not give pure enantiomers, but a good enrichment can be often achieved by fractionated precipitation.

The racemate and conglomerate like behaviour of enantiomers can also be observed both at the recrystallization and at the liberation of the enantiomers from their salts formed with achiral compounds.

Based on own and other's experimental results some conclusions can be drawn according to the fractionated crystallization of chiral compounds.

The regularities of crystallization of the systems containing at least two chiral compounds can not be described by linear correlations. At the same time, the behaviour of the enantiomeric mixtures of the racemic compound will be one of the determining factor of the behaviour of the systems containing chiral compounds.

To characterize the obtained fractions not only their yield (Y), but the enantiomeric purity of the products (ee) is also relevant. Therefore it is advisable to use the parameter F characterizing the efficiency of the procedure (F=ee*Y). This factor is actually the yield of enantiomeric excess separated. (Earlier this factor was marked with the letter S, but it could refer to the configuration even if it was marked by a different font.)

Hereinafter, the possibilities of enantiomer and diastereoisomer separations based on crystallization are shown by known examples.

At first examples will be given for separation of mixtures, containing two or more chiral compounds in solventless conditions or using solvent, respectively.

Among the next examples we refer to the results derived from earlier considerations, too. We demonstrate that behaviour of these enantiomeric and diastereoisomeric mixtures raised from interactions between chiral compounds are not always the expected ones. The shown examples relate mainly to calculable regularity, but often a minor modification in the molecular structure can induce significant change of results. For justification, the two essential perception of Pasteur, are shown at first, then the consequences of the „slight changing” of the molecular structures will be presented in the light of our present knowledge.

It was recognized by Pasteur, that the enantiomers of racemic tartaric acid can be separated by induced crystallization, if the supersaturated aqueous solution of its sodium-ammonium salt was seeded with the crystals of a pure enantiomer. In this case significant amount of the pure enantiomer could be find in the solid phase and a mixture of enantiomers remaind in the saturated solution in which the other enantiomer was in excess. That other enantiomer
could be crystallized in pure form from the supersaturated solution of this latter enantiomeric mixture. This experiment demonstrated the fact, that the excess of an enantiomer can crystallize from an enantiomeric mixture of the above mentioned tartaric acid salt. According to our present knowledge, it means that the enantiomers of sodium-ammonium salt of tartaric acid form a conglomerate in their mixtures.

When the same experiment, namely crystallization of the non-racemic enantiomeric mixture of sodium-ammonium tartarate, was effectuated at a temperature above 27 °C, the racemic fraction (the racemate) crystallized, because the sodium-ammonium salts of racemic tartaric acid have a racemate like behaviour at around 30 °C. In this case the derivative of tartaric acid (the mixed salt) was suitable for fractioned enantiomeric separation, but only at a lower temperature than 27 °C (influence of temperature).

Pasteur also recognized, that more efficient separation of the enantiomers of racemic tartaric acid could be achieved by application of another chiral base (Quinotoxine (Q)) as resolving agent to the enantiomers of tartaric acid was obtained a better enantiomeric separation. In this case a diastereoisomeric salt ((R,R)-TA.Q.6H2O) crystallized while the better soluble diastereoisomeric salt((S,S)-TA.Q) remained in solution.

When cinikotoxine (a chiral base, similar to quinotoxine, without CH3O- substituent) was used, the other tartaric acid enantiomer ((S,S)-TA) crystallized in the diastereoisomeric salt.

It is supposed that the crystal solvate was a decisive role during crystallization of the first salt or the lack of methoxy substitution (H-bridge acceptor) on common molecular configuration of the resolving agent changed its enantiomeric recognition ability in the second case. Keeping these experimental results in mind, the known methods of enantiomer separation via crystallization will be discussed in the next sections.

2. Crystallization without any solvent

Both the enantiomeric mixtures and the mixtures of true diastereoisomeric pairs and free enantiomers can form crystalline and melt fractions, which are separable by an adequate method.

2.1 The crystallization of the enantiomeric mixtures

When the non-racemic mixture of enantiomers may be melted without decomposition, depending on whether the homochiral or the heterochiral associations are more stable, the
enantiomeric excess (conglomerate type) or the racemic fraction (racemate type) crystallizes from the melt. Sometimes these phases may be separated by filtration.

2.1.1 Separation with filtration

2.1.1.1 Conglomerates

In such cases the enantiomeric excess is crystallized with a higher purity than that of in the initial composition, in a certain range of temperature. For example, the common intermediate of the synthesis of several prostaglandines is a lactone (PGL). Its enantiomeric mixtures (ee\textsubscript{0}) can be enriched by crystallization (ee\textsubscript{solid}) from melt, while the racemic ratio (liquid residue, ee\textsubscript{liquid}) can be recovered for repeated resolution.\textsuperscript{20}

\[
\begin{array}{ccc}
\text{ee}_0 \% & \text{ee}_{\text{solid}} \% & \text{ee}_{\text{liquid}} \% \\
21.5 & 69.2 & 6.2 \\
29.2 & 72.5 & 2.6 \\
52.3 & 76.9 & 29.2 \\
79.5 & 93.0 & 54.2 \\
\end{array}
\]

(1S,5R>1R,5S)-PGL

2.1.1.2 Racemates

In racemate forming enantiomeric mixtures the enantiomeric excess with a higher enantiomeric purity than that the initial composition remains in the melt and the crystalline phase formed has a lower ee. For instance, at the crystallization of the enantiomeric mixture of trans-chrysanthemic acid (CHRA) from melt the liquid phase contains a higher purity fraction than the ee\textsubscript{0} value of the initial mixture.\textsuperscript{21}

\[
\begin{array}{ccc}
\text{ee}_0 \% & \text{ee}_{\text{solid}} \% & \text{ee}_{\text{liquid}} \% \\
42.6 & 15.5 & 83.3 \\
\end{array}
\]

(1R>1S)-CHRA

At the crystallization of melts of racemate forming enantiomeric mixtures the eutectic composition usually determinates the composition of the crystallized mixture and the oily residue. That eutectic composition can be known from the binary melting point phase diagram. When the initial isomeric composition (ee\textsubscript{0}) is higher than the eutectic composition, the pure optical isomer can be crystallized. By way of illustration the eutectic composition (it is approximately at ee 40%) of flumequine intermediate (FTHQ) cannot be enriched, but by starting from a mixture of ee\textsubscript{0} > 40%, significant enrichment can be achieved, especially because it has a “conglomerate like” behaviour.\textsuperscript{22}
2.1.2 Partial crystallization, distillation

When a part of an enantiomeric mixture is transformed into a crystalline salt and the residue can be distilled, the solid phase may contain either the racemic composition or the excess of the enantiomer. In the former case the distilled fraction should be the enriched mixture relative to $ee_0$, but the less pure mixture can be found in the distilled fraction when the $ee_0 > ee_{Eu}$. This is applied even if the salt of the enantiomeric excess proportion is the more stable, as well. An example for this phenomenon is the purification of the enantiomeric mixture of phenylethylamine (PEA). The mixture was treated with less than an equivalent amount of dicarboxylic acid (oxalic acid, succinic acid, fumaric acid or phthalic acid = DCA) (see Table 1, the molar ratio: PEA/DCA~ 3,3/1,25), and the excess of the amine was distilled. The PEA-DCA salt behaved as a racemate because $ee_{desalt} > ee_0$ In case of the salts of oxalic- and malonic acids this is changed above of eutectic composition.23

| Salt forming acid | $ee_0$ (%) | $ee_{distillate}$ (%) | $ee_{residue}$ (%) |
|-------------------|------------|-----------------------|-------------------|
| COOH COOH Oxalic acid | 12.5       | 26.6                  | 7.8               |
|                   | 25.0       | 44.6                  | 18.5              |
|                   | 50.0       | 63.6                  | 45.5              |
|                   | 75.0       | 65.7                  | 78.1              |
|                   | 87.5       | 71.5                  | 92.8              |
| CH$_2$COOH CH$_2$COOH Succinic acid | 12.5       | 51.2                  | 0.0               |
|                   | 25.0       | 63.1                  | 12.3              |
|                   | 50.0       | 62.7                  | 45.8              |
|                   | 75.0       | 57.4                  | 82.9              |
|                   | 87.5       | 49.9                  | 100               |
| HOOC
| COOH
| Fumaric acid | 12.5       | 41.8                  | 2.7               |
|                   | 25.0       | 68.5                  | 10.5              |
|                   | 50.0       | 95.4                  | 34.9              |
|                   | 75.0       | 96.3                  | 67.9              |
|                   | 87.5       | 97.6                  | 84.1              |
| HOOC
| COOH
| Phthalic acid | 12.5       | 42.5                  | 2.5               |
|                   | 25.0       | 84.2                  | 5.3               |
|                   | 50.0       | 94.6                  | 35.1              |
|                   | 75.0       | 94.4                  | 68.5              |
|                   | 87.5       | 95.0                  | 85.0              |

Table 1. The enrichment of enantiomeric mixtures of (R>S) – PEA via partial salt formation followed by distillation.
2.2 Crystallization of diastereoisomers

In this chapter we discuss on such separations in which the racemic compound is reacted with a resolving agent, so the mixture contains three chiral compounds: the two enantiomers and another chiral compound. At this time the more stable diastereoisomer crystallizes and it can be separated from the non racemic enantiomeric mixture by several methods.

2.2.1 Separation by filtration

In this case the resolving agent should be added to the racemic compound and the mixture should be warmed until it melted then is should be cooled while one of the diastereoisomers crystallizes from the melt. The crystalline material can be separated by filtration from the residue of the melt (as in case of enantiomeric mixtures). An example for this method is the resolution of racemic menthol (MEN) with O,O’-dibenzoyl-(R,R)-tartaric acid ((R,R)-DBTA). The crystalline molecular complex (diastereoisomer) contains the (1R,2S,5R)-menthol (the L-menthol (L-MEN)), while the remained melt is enriched in the other enantiomer.

\[
\begin{align*}
(1R,2S,5R)\text{-MEN} & \quad + \quad (R,R)\text{-DBTA} \\
(1S,2R,5S)\text{-MEN} & \quad \text{crystallized diastereomer}
\end{align*}
\]

2.2.2 Separation by distillation

If the racemic compound is reacted with half an equivalent amount of resolving agent, the enantiomeric mixture remained after crystallization can be separated by distillation. Such a method was accomplished at the resolution of N-methyl-phenylisopropylamine (MA) by (R,R)-dibenzoyl-tartaric acid ((R,R)-DBTA). In this case the (S)-MA was distilled off beside of crystalline (R)-MA (R,R)-DBTA salt.

\[
\begin{align*}
(\text{S})\text{-MA} & \quad + \quad (R,R)\text{-DBTA} \\
(\text{R})\text{-MA} & \quad \text{distillated} \quad \text{crystallized residuum}
\end{align*}
\]
When the racemic phenylisopropylamine (A) is resolved with (S)-N-phthaloyl-phenylethylamine (PPEA) according to the above mentioned method, further separation can be accomplished starting from the residue of the first distillation. When the temperature is increased, the residual crystalline diastereoisomeric salt decomposes and the liberated enantiomer ((R)-A), constituting the diastereoisomer salt) can also be distilled off while the resolving agent is transformed into a phthalimide derivative. 

The situation is essentially the same when the racemic A is resolved by (R,R)-TADDOL (TAD). The first crystalline residuum is the molecular complex of (R)-A.(R,R)-TAD. At higher temperature this complex is decomposed and the regenerated TAD remains in the flask as the final residuum.

2.2.3 Separation by sublimation

Sublimation method for indirect separation of enantiomers is very similar, in principle to the above mentioned distillation-based procedure. In the next example the diastereoisomeric molecular complexes could be separated using the significant difference between their thermal stability.

The solid phase reaction between the racemic compound (trans-2-iodo-cyclohexanol = IC) and the resolving agent ((R,R)-DBTA) occurs during a long-term staying. Then the enantiomers could be separated from the mixture by two sublimation steps.
2.2.4 Separation by a supercritical fluid (carbon dioxide)

We think that this method for separation of the crystalline diastereoisomeric salt and the enantiomeric mixture can also be placed to the methods where the crystallization is accomplished without a solvent, and based on the instantiated examples we can declare that both the diastereoisomeric salt and molecular complexes may be separated by supercritical carbon dioxide.

When the racemic acid or base is treated with less than an equivalent amount of chiral compound (resolving agent) one can obtain a good enantiomer separation if crystallization occurs in the mixture. For example, at the resolution of racemic ibuprofen (IBU) with (R)-PEA, the free enantiomer (S)-IBU can be separated from the salt ((R)-IBU,(R)-PEA) by extraction with a supercritical fluid, most often with carbon dioxide.28

The pure enantiomers of racemic 1,2-cyclohexane-diol (CHD) could be obtained with the same method using (R,R)-Tartaric acid (TA) as resolving agent. In this case the (S,S)-CHD isomer could be extracted and the crystalline molecular complex of (R,R)-CHD and (R,R)-TA remained in the solid phase.29
3. Crystallization from a solvent

The majority of the enantiomer separation methods based on crystallization involves solvent or solvent mixtures. Crystallizations from supersaturated solutions can be used both at the separation of enantiomeric mixtures, and at the separation of diastereoisomeric mixtures.

Comparison of the variable parameters of that method with the conditions of the above outlined solventless processes show that one have to take into consideration the characteristics of the applied solvent or solvent mixtures during optimization of such a resolution process. Furthermore, chiral or achiral additives can also be applied which improve without exception the efficiency of the resolution (F=ee*t).

3.1 Crystallization of enantiomeric mixtures

The most frequently applied versions of the classical enantiomeric enrichment method (effectuated by crystallization from a solution) are presented below.

3.1.1 Recrystallization

The optical isomers exist in the supersaturated solutions as a mixture of homochiral and heterochiral associations. Therefore both the conglomerate or the racemate like behaviour can be observed during the crystallization, similar to the before discussed solventless crystallization methods

3.1.1.1 Conglomerates

When a nonracemic enantiomeric mixture is recrystallized from a solvent, and the enantiomeric excess (ee) of crystalline phase is always higher than the initial composition (ee0), then the compound (or its crystallized derivative) is conglomerate forming material. For example, when the enantiomeric mixture of dilthiazem hydrochloride (DIL.HCl) is recrystallized from ethyl acetate, the enantiomeric excess crystallizes in a very high purity.30
3.1.1.2 Racemates

At the recrystallization of racemate forming (the most common) enantiomeric mixtures the enriched enantiomeric mixture usually can be recovered from the mother liquor after filtration of the crystalline fraction having near to racemic composition. However, the composition of the crystalline material can be changed when the initial enantiomeric purity is higher than the eutectic composition. A certain example is the recrystallisation of the enantiomeric mixtures of tofizopam (TOF) from ethyl acetate. Almost racemic composition crystallized from small or medium pure enantiomeric mixtures. However the sole enantiomer crystallized from the solution when the initial composition was higher than the eutectic one ($ee_0 > 85\%$).

The above example demonstrates that one can prepare the enantiomerically pure product from almost any samples having medium $ee_0$, with two recrystallizations if the enantiomeric mixture recovered from the filtrate of the first crystallization is applied as starting material of the second recrystallization. This technique was adapted at the purification of the hydrochloride salt of a flumequine intermediate (FTHQ.HCl), too.
3.1.2 Fractionated precipitation.

In several cases the recrystallization fails to result in enantiomeric enrichment. The solution for the purification of such enantiomeric mixtures may be the fractionated precipitation. In order to carry out such a purification step the enantiomeric mixture or its derivative (e.g. its salt formed with an achiral reagent) is dissolved in a solvent. Then a part of the dissolved material is liberated from its salt (or a salt is prepared from a part of it) with a reagent in a way that the liberated fraction (or salt) can precipitate from the solution, while the other proportion of the initial mixture remains in the solution. For example, the salts (e.g. watersoluble) of acids or bases are dissolved and a part of the free acid or base is precipitated by addition of less than equimolar achiral acid or base.

3.1.2.1 Conglomerates

Similar to the experiences shown at the recrystallization of enantiomeric mixtures, the conglomerate behaviour can also be observed at fractioned precipitation. An application of this method was effectuated at the resolution of racemic tisercine (TIS) with half an equivalent of (R,R)-tartaric acid. The (S)-TIS enantiomer, the active pharmaceutical ingredient, remained in the filtrate of the diastereoisomeric salt formation process. Consequently, it contaminated with its mirror image isomer. The enantiomeric enrichment was accomplished by selective precipitation. The (S,R)-TIS mixture was dissolved in water as a hydrochloric acid salt, then less than an equivalent amount of potassium hydroxide was added to the solution in order to liberate the excess of (S)-TIS. The pure (S)-TIS base precipitated from the solution and an almost racemic hydrochloride salt remained in the solution.

The conglomerate-like behaviour during the fractionated precipitation was observed in case of several chiral acids, too. A good example is the enantiomeric enrichment of N-acetylphenylalanine (AcPA). The pure (R)-AcPA isomer was obtained in two steps from its nonracemic enantiomeric mixtures.
3.1.2.2 Racemates

As it was already discussed in the above cases, enantiomeric enrichment of racemate forming enantiomeric mixtures result in an almost racemic crystalline phase when the starting enantiomer purity is smaller than the eutectic composition \( (e_0 < e_{eu}) \), but highly enriched mixture or the sole enantiomer can be crystallized when the initial composition is bigger than the eutectic one \( (e_0 > e_{eu}) \).

This type of selective precipitation was applied in the cases of \( N \)-acyl-aminoacids when their recrystallization from water failed. However, addition of less than an equimolar amount of hydrochloric acid to the solution of their sodium salt get good enrichment. It is therefore not surprising that considerable enrichment could be attained with a mixture of \( e_0 = 49.6 \% \), while two stage precipitation starting from an aqueous solution of \( \text{FoPA.Na} \) with \( e_0 = 73.4 \% \) (composition near the eutectic point), did not resulted in significant enrichment.

3.1.2.3 Kinetic control

The above mentioned examples (\( \text{FoPA} \) and \( \text{AcPG} \)) demonstrated both the conglomerate and racemate behaviour during fractionated precipitation of enantiomeric mixtures under thermodynamic control. However a new type of crystallization order was observed when the propionyl derivatives of phenylalanine and phenylglycine (\( \text{PPA} \) and \( \text{PPG} \), respectively) were examined. This type of compounds presented different behaviour during the enantiomeric enrichment processes than expected on the basis of their binary (melting point/composition) phase diagrams. Binary phase diagram of \( N \)-propionyl-phenylglycine (\( \text{PPG} \)) indicated conglomerate type behavior, while that of \( N \)-propionyl-phenylalanine (\( \text{PPA} \)) was a racemate type with \( e_{eu} = 86 \% \) in both cases, according to the binary phase diagrams.\(^{34}\)

\[
\begin{array}{c|c|c|c}
\text{ee}_0 \% & \text{ee}_\text{solid} \% & \text{ee}_\text{liquid} \% \\
45.0 & 59.6 & 6.0 \\
78.2 & 100 & 6.7 \\
\end{array}
\]

\[
\begin{array}{c|c|c|c}
\text{ee}_0 \% & \text{ee}_\text{solid} \% & \text{ee}_\text{liquid} \% \\
49.6 & 19.3 & 75.0 \\
73.4 & 70.8 & 75.2 \\
\end{array}
\]

\[
\begin{array}{c|c|c|c}
\text{ee}_0 \% & \text{ee}_\text{solid} \% & \text{ee}_\text{liquid} \% \\
63.6 & 52.6 & 86.2 \\
79.5 & 78.8 & 86.6 \\
\end{array}
\]
Selective precipitation of (R>S)-N-propionyl-phenylalanine (PPA) was effectuated starting from the aqueous solution of its sodium salt. Addition of less than equimolar amount of hydrochloric acid resulted in the crystallization of the excess of (R)-PPA to such an extent, that in certain cases the usually remaining racemic composition become unbalanced, too (therefore the (S) enantiomer is enriched in the filtrate)

\[
\begin{array}{ccc}
\text{ee}_0 & \text{ee}_{\text{solid}} & \text{ee}_{\text{liquid}} \\
20 & 2.5 & 24.8 \\
25 & 47.7 & -4.3 \\
35 & 39.0 & 24.3 \\
60 & 88.7 & 12.4 \\
85 & 99.9 & 83.3 \\
\end{array}
\]

Essentially the same phenomenon was observed at the fractionated precipitation of the enantiomeric mixture of (R>S)-N-propionyl-phenylglycine (PPG).

\[
\begin{array}{ccc}
\text{ee}_0 & \text{ee}_{\text{solid}} & \text{ee}_{\text{liquid}} \\
10 & 4 & 17 \\
12.5 & 27 & -3.6 \\
15 & 38.2 & -4.8 \\
25 & 27 & 1.2 \\
35 & 59 & 0.9 \\
50 & 84 & -0.4 \\
75 & 90 & 16 \\
90 & 92 & 76 \\
\end{array}
\]

In light of these experimental data it should be mentioned, that during the purification of enantiomeric mixtures of N-acyl-aminoacids not only the suitable methods but also the substituent on the molecule skeleton (acyl group) may determine the productivity of enrichment.

### 3.2 Crystallization of diastereoisomers

The similarities between the enriching processes starting from enantiomeric mixtures or diastereoisomeric mixtures were already discussed above at the presentation of the solvent free methods. It is an interesting question: whether the widely used fractionated precipitation from a solvent will change this trend at the diastereoisomeric mixtures?

The diastereoisomeric systems discussed bellow contain salts, molecular complexes and coordinative complexes as well.

#### 3.2.1 The salt-forming resolving agents

##### 3.2.1.1 Structurally similar resolving agents

Comparison of the results of the enantiomeric enrichments mentioned above let us to conclude that the difference between the enantiomeric excesses of the crystalline and the liquid phases is the greatest when the starting enantiomeric purity is near 50% (ee$_0$ ≈ 50%). In the cases of ten separtions made by crystallization this enrichment (\(\Delta\text{ee} = \text{ee}_{\text{cryst}} - \text{ee}_{\text{liq}}\)) was
between 34-95%, (on the average 60%), while the average of the six greatest difference was 70%. This means that the purification of enantiomers by crystallization is a very fruitful route (independently from the method applied (from melt to using a solvent) to enantiopure materials.

Another approach is the resolution of an enantiomeric mixture with a structurally similar resolving agent. It is the situation when one of the enantiomers of the racemic compound is transformed (with a minimal chemical transformation) into a reagent able to form diastereoisomeric salt with the initial racemic compound. It can be done if the aminoacid is N-acylated and one of the pure enantiomers is esterified, or if its carboxylic group is transformed into an amide, or changed with methyl group, respectively.

For example, the racemic N-acetyl-phenylglycine (AcPG) can be reacted with methyl (S)-phenylglycinic acid (MePG). The resolution can be treated as a recrystallization of a quasi enantiomeric mixture with ee=50% from water when the less soluble diastereoisomeric salt (namely, the heterochiral quasi-racemic mixture) crystallized containing (R)-AcPG in good enantiomeric excess (ee: 79%).

If the substituents of the compounds would be removed (Ac from AcPG → R and S and Me from MePG → S), the composition of the mixture would be

\[ 1R + 3S \equiv RS + SS \]

Namely, the starting mixture would be an “enantiomeric mixture with ee= 50%”. Therefore the above shown crystalline diastereoisomeric salt is a quasi-racemate.

The situation was almost the same when the N-acetyl-phenylalanine (AcPA) was reacted with methyl (S)-phenylalaninate (MePA) according to the preceding resolution. The obtained crystalline diastereoisomeric salt also will be a quasi-racemate, but its enantiomeric excess (ee: 93%) was even higher than that of the former case.

It was also observed, that the average ee and F values of diastereoisomeric salts obtained at the resolutions (in number 28 resolutions) of racemic N-acetyl-phenylalanine and -phenylglycine (AcPA and AcPG) with structurally similar bases (resolving agents) correspond to the eutectic composition (eeE value) of the adequate racemate (in these cases the enantiomers of the racemic compounds form racemates). Consequently, if the resolution of a racemic compound is accomplished with structurally similar resolving agents (in water) the purity of the enantiomer obtained from the crystalline diastereoisomeric salt corresponds to the biner phase diagram of the enatiomeric mixture or converge to the
(experimental) eutectic composition. In other words, the characteristics of the resolved compounds strongly influence or even determinate the composition of the diastereoisomeric salts crystallized during the resolutions.\textsuperscript{36}

In five cases among the resolutions of six racemic compounds with structurally similar resolving agents the crystallized diastereoisomeric salts have shown quasi-racemate behaviour (thus these were quasi-resolutions). At the same time in one case, during the resolution of \textit{N}-formyl-phenylalanine (\textit{FoPA}), crystallization of a quasi-homochiral diastereoisomer was observed. The observed quasi-racemate/quasi-conglomerate = 5/1 ratio has also been in accordance with the earlier described data on the similar ratio of the racemates and conglomerates among the true enantiomeric mixtures.\textsuperscript{37}

On the basis of the above discussed experimental data we concluded, that the behaviour of diastereoisomers follows the behaviour of their constituent enantiomeric mixtures. We have also observed that the similarity between the molecular structures of a racemic compound and a resolving agent has a positive effect on the enantiomeric separation. It also may be established, that a „derivative resolving agent” (use of optically active derivatives of the racemate as resolving agent) would be the optimal agent for separation of any racemic compound, but the best derivative should be found on experimental way.

\subsection*{3.2.1.2 Resolving agents with diverse molecular structures}

According to the previously mentioned, the appropriate resolving agents for a racemic compound should be found among the structurally similar compounds because of the higher probability of the formation of well-fitting associates (salts or complexes) from that type of resolving agents and one of the isomers of racemic compound.

Of course, such a well-fitting chiral compound may be found among several other compounds, as well. They are the well-known and traditional resolving agents. Such a universal resolving agent is the O,O’-dibenzoyl-(\textit{R,R})-tartaric acid (\textit{DBTA}) (mentioned several times previously). Presumably the above discussed findings, that the efficiencies of resolutions using structurally similar resolving agents may be determined by the behaviour of the enantiomeric mixtures of the racemic compound, may also be expanded on that diastereoisomeric salts forming resolutions where the resolving agent has „non-similar” molecule structure (particularly in cases of crystallizations from water).

In the simplest cases the generally used methods follow the first ever resolution by salt formation accomplished by Pasteur (fractionated precipitation method). In this case the racemic compound and the resolving agent are dissolved in a solvent, in a molar equivalent amount. The less soluble diastereoisomeric salt crystallizes (during cooling) and it can be separated from the other diastereoisomeric salt (remained in solution) by filtration. The enantiomeric mixtures are isolated from the diastereoisomers and they are enriched to the desired \textit{ee} values by applying one of the previously discussed methods.

It has to be mentioned, that the enantiomeric mixture found in the crystalline diastereoisomer is usually much purer than that is isolated from the filtrate.

Pope and Peachey\textsuperscript{38} have been recognized that if the half of the resolving agent necessary for the better soluble diastereoisomer is replaced by an achiral reagent (having the same chemical character as it is for the resolving agent) the less soluble diastereoisomer will be
crystallized and the other isomer remains in the solution as a salt of the applied achiral additive. This method not only economizes a half part of the resolving agent, but the efficiency of resolution can also be improved.

Hereafter some examples of the above mentioned procedures, used in the pharmaceutical industry, will be presented.

The racemic intermediate of chloramphenicol \((\text{AD}.\text{HCl})\) is obtained as a hydrochloride salt during the synthesis, and it is dissolved in water (the free base is low-soluble in water). In this case the resolving agent \((\text{O,O'}-\text{dibenzoyl-}(R,R)-\text{tartaric acid} \text{ N,N-dimethylamamide (DBTADA)})\) is practically insoluble in water but its ammonium salt is well soluble and it can be prepared easily. The two aqueous solutions are mixed so that the molar ratio between the racemic compound and the resolving agent should become 1/0.5. The diastereoisomeric salt containing the desired enantiomer \((R,R)-\text{AD}\) crystallizes while the hydrochloride salt of \((S,S)-\text{AD}\) remains in solution.

\[
\begin{align*}
\text{(S,S)-AD.HCl} & \\
\text{(R,R)-AD.HCl} &
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N}.\text{HOOC}\text{PhOCO}^{-}\text{CON(CH}_3)_2\text{NH}_3 + \text{water} & \rightarrow \text{(R,R)-AD. (R,R)-DBTADA.HCl} + \text{(S,S)-AD.HCl in solution}
\end{align*}
\]

The next example one is of the first resolutions of a racemic intermediate of prostaglandines. During the synthesis it is isolated as the water-soluble sodium salt \(((R,S)-\text{cis-Na})\). Half an equivalent amount of \((R)-1\)-phenylethylamine \((\text{PEA})\) neutralized with hydrochlorid acid is added to the aqueous solution of \((R,S)-\text{cis-Na}\). The \((S)-\text{cis.(R)-PEA}\) crystallizes while \((R)-\text{cis-Na}\) remains in the solution.

\[
\begin{align*}
\text{(S)-cis-Na} & \\
\text{(R)-cis-Na} &
\end{align*}
\]

\[
\begin{align*}
\text{OH} + \text{CH}_3\text{COONa} & \rightarrow \text{(S)-cis.(R)-PEA in solution}
\end{align*}
\]

It may happen frequently, that only one enantiomer of the resolving agent is available, or one of the two enantiomers is significantly cheaper. For this reason mainly \((R,R)-\text{tartaric acid}\) is used industrially among of tartaric acid enantiomers and their derivatives. It is the case, for example, at the resolution of a racemic intermediate \((\text{AN})\) of \(\alpha\)-methyl-\text{DOPA}. The resolution of racemic \(\text{AN}\) is performed in the aqueous solution of its hydrochloric acid salt.
(AN.HCl) by half an equivalent amount of mono sodium salt of (R,R)-tartaric acid (TA.Na). The crystalline salt of undesired (R)-AN.TA precipitates. After filtration of the diastereoisomeric salt the pure (S)-AN.HCl can be crystallized from the mother liquor by salting out (addition of sodium chloride into the filtrate) while the racemic AN.HCl remains in solution. Since the enantiomeric excess crystallized from the filtrate we can speak about conglomerate behaviour. However, the compound may be a racemate forming material, if the purity of the (S>R)-AN.HCl enantiomeric mixture is higher than the eutectic composition (ee\textsubscript{eu} for AN.HCl).

3.2.1.3 Mixture resolving agents

The so called “Dutch resolution” \textsuperscript{39} utilize the recognition whereas a part of the original resolving agent can be replaced by another chiral compound with similar chemical character and under such circumstances (when the resolving agent really is a mixture of structurally related molecules) a diastereoisomer (containing usually an enantiomer of the racemate in very high purity) crystallizes from the supersaturated solution. The advantage of this resolution method is that the efficiency may often be superior to the use of any of the resolving agent components alone, and sometimes it works even if one of the reagents alone is unsuitable to form crystallizing diastereoisomeric salt.
In the following example three kinds of resolution of racemic ephedrine (EPh) via diastereoisomeric crystallization will be presented, as before. The favourable resolving agent is a chiral diester of phosphoric acid containing 2-chloro-phenyl substituent (CPH), while the structurally similar phosphoric acid containing unsubstituted phenyl group (PH) is an unsuitable resolving agent.

### 3.2.1.4 Mixture of a resolving agent and a structurally related achiral molecule

The above-mentioned observation, namely a part of the resolving agent can be replaced by a structurally related compound which is unsuitable for separation of the enantiomers means in general, that the presence of a structurally similar but achiral reagent may also improve the results of a resolution.

For example, when N-acetyl-phenylalanine (AcPA) is resolved with half an equivalent amount of (R)-phenylglycine amide (PGA) in presence of sodium hydroxide both the enantiomeric purity and the productivity were lower than when instead of sodium hydroxide half an equivalent amount of benzylamine (BA) was applied (BA has a more related structure with the resolving agent than sodium hydroxide). Its presence improved significantly the crystallization of (S)-AcPA. (R)-PGA diastereoisomeric salt, as well as the efficiency of the resolution.

\[
\text{COOH} \quad \text{COOH} \\
\text{NHCOCH}_3 \quad \text{NHCOCH}_3 \\
\begin{array}{c}
\text{(R)-AcPA} \\
\text{(S)-AcPA}
\end{array} \\
\begin{array}{c}
\text{CONH}_2 \\
\text{NH}_2
\end{array} + \begin{array}{c}
\text{CONH}_2 \\
\text{NH}_2
\end{array} + \text{NaOH} \rightarrow \begin{array}{c}
\text{(S)-AcPA. (R)-PGA} \\
\text{crystalline}
\end{array} + \begin{array}{c}
\text{(R)-AcPA. Na} \\
\text{in solution}
\end{array}
\text{ee: 74\%, F: 0.42}
\]

\[
\text{COOH} \quad \text{COOH} \\
\text{NHCOCH}_3 \quad \text{NHCOCH}_3 \\
\begin{array}{c}
\text{(R)-PGA} \\
\text{BA}
\end{array} \\
\begin{array}{c}
\text{CONH}_2 \\
\text{NH}_2
\end{array} + \begin{array}{c}
\text{CONH}_2 \\
\text{NH}_2
\end{array} + \text{BA} \rightarrow \begin{array}{c}
\text{(S)-AcPA. (R)-PGA} \\
\text{crystalline}
\end{array} + \begin{array}{c}
\text{(R)-AcPA. BA} \\
\text{in solution}
\end{array}
\text{ee: 100\%, F: 0.81}
\]

The use of an achiral compound with related molecular skeleton may also be advantageous, if its structure is related with structure of the racemic compound. For example, if the resolution of racemic AcPA is carried out using (R)-PEA, the crystallized diastereoisomeric salt contains almost racemic AcPA, but addition of the achiral analogous phenoxy-acetic acid (POAA) to the racemic compound, result in a very good enantiomdiscrimination. The achiral additive crystallizes quickly together with resolving agent and, during the long standing, the POAA is exchanged for (S)-AcPA enantiomer in the crystal.
3.2.2 Influence of solvents

In the majority of the above discussed fractionated precipitations or crystallizations of diastereoisomeric salts water was used as a solvent. The experimental observation of decades is that the dissociation in solvent of diastereoisomeric salts and of salts formed with achiral auxiliaries in water or in other protic solvents, is considerably influenced by the proton concentration (pH value). Naturally this value influences both the quantity and the isomeric purity of the crystallized salt, namely the efficiency of the resolution. There are also examples in the literature, when the configuration of the enantiomer in the crystalline diastereoisomeric salt and/or the efficiency of the resolution are determined by the polarity of solvent (the dielectric constant characteristic for this), respectively.

In other cases, the use of solvent mixtures could influence which diastereoisomer can be found in the crystalline phase. In such cases, either the crystallizing diastereoisomer or the one remained in the mother liquor form stable solvate with one of the solvents. After a short summary of the theoretical background, it will be shown via examples, how can we use the influence of pH, solvent polarity, and solvate formation, respectively, to improve the efficiency of enantiomeric separation.

3.2.2.1 The influence of pH

The pH dependence of resolutions based on fractionated crystallization of diastereoisomeric salts was described by a thermodynamical equilibrium model.33

The equilibrium model of a resolution of DL racemic base with an acidic resolving agent (RH) can be outlined below.
Separation of the Mixtures of Chiral Compounds by Crystallization

\[
\begin{align*}
\text{solid} & \quad \text{liquid} \\
\text{DL + 2RH} & \quad \text{DHR} \quad + \quad \text{LHR} \\
\text{DL} + 2\text{RH} & \quad \text{DHR} \quad + \quad \text{LHR} \\

\text{D} + \text{H}^+ & \quad \text{DH}^+ \quad + \quad \text{R}^+ \quad + \quad \text{R}^- \\
\text{DL} & \quad \text{DHR} \quad + \quad \text{LHR} \\
\text{PD} & \quad \text{PL} \\
\text{K}_d \text{L} & \quad \text{K}_d \text{D} \\
\text{K}_b \text{L} & \quad \text{K}_b \text{D} \\
\text{K}_a & \quad \text{+ 2H}^+ \\
\text{2RH} & \quad \text{K}_s \text{D} \quad \text{K}_s \text{L} \\
\end{align*}
\]

Where \( K_s = \) salt solubility constant, \( K_d = \) salt dissociation constant, \( K_b = \) base dissociation constant, \( K_a = \) acid dissociation constant, \( P_D \) and \( P_L \) are the precipitated diastereoisomeric salts, respectively.

The efficiency of the resolution (\( S = F \), see above in point 1) can be calculated by means of the next formula, using the known thermodynamic constants data, and the concentrations of the starting compounds (\( c_o = \) concentration of the racemic compound, \([\text{RH}]_o = \) concentration of resolving agents) and of \([\text{H}^+] = \) proton concentration, as well.

\[
0.5c.os = K_{sl} - K_{sd} + \left(1 + \frac{K_b}{[\text{H}^+]} + \frac{K_{hb}}{K_{RH}} + \frac{K_{hb}K_{dh}}{[\text{RH}]_0 - 0.5c_0y - (K_{sl} + K_{sd})}\right) \]

From the relationship deduced on basis of the model the regularity of several „rule of thumb” based on experimental observations were justified. A fundamental conclusion is that the efficiency of resolution is the function of both the hydrogen ion concentration and the initial concentration of the resolving agent.

a. With derivation of the equation, describes the thermodynamic equilibrium model, can be justified that in so far as \( K_{dl} > K_{dd} \), the minimum value (\( S_{\text{min}} \)) of the \( S = f(\text{H}^+) \) function at \( [\text{H}^+] = \sqrt{K_bK_{RH}} \) that corresponds to the proton concentration provided by hydrolysis of the neutral diastereoisomeric salt; namely that concentrations occur at the equivalent resolution discovered by Pasteur: It means that this type of resolution results in the smallest separation efficiency. It is worth to mention, that the essential condition, whereas the dissociation constant of the rather soluble salt is bigger, is
realized at the majority of resolutions. (If $K_{dL} > K_{dD}$ is not valid, application of the equivalent amount of resolving agent gives the best result.)

In the light of the above deduction the experimental observation, that the tartaric acid (TA, as a dibasic acid) is an efficient resolving agent is not surprising because in the most cases the hemitartarates crystallize and one carboxylic group remains "free". This additional acidic group increases the proton concentration compared to the proton concentration of the solution of a neutral salt (salt of a monobasic acid).

In practice, an excess (10-20%) of the resolving agent used to be added to the racemic compound and, of course, the excess shifts the pH value of the solution as well.

b. Based on the equation of the thermodynamic equilibrium model, the optimum relative concentration of the resolving agent can be determined. It means that the efficiency of $S$ is maximal when the denominator of the second member of multiplication in the equation tends to zero, namely $S \rightarrow S_{\text{max}}$ if $[RH]_o = 0.5c_o y + (K_{sL} + K_{sD})$. If the solubility constants of the diastereoisomers are low, and we tend to obtain the highest yield ($y \approx 1.0$), then $[RH]_o \sim 0.5c_o$, consequently using half an equivalent amount of resolving agent will result in the highest efficiency. At the same time it is the theoretical argument of the successfulness of the method disclosed by Pope-Peachey.

The dramatic influence of the pH of the medium was first encountered at the separation of optical isomers of cis-permethrinic acid carried out with half an equivalent amount of (S)-2-benzylaminobutanol ((S)-BAB). The resolution started in the presence of a 25 mol % excess of sodium hydroxide. In such a medium the diastereoisomeric salt containing the almost pure (S)-CPA crystallized (ee: 96%) with a yield of 27% counted to the amount of racemic acid. After removal of the precipitate by filtration, the excess alkali was neutralized with a counted amount of hydrochloric acid. That time the resolving agent remained in the filtrate crystallized with (R)-CPA enantiomer as diastereoisomeric salt and in the second mother liquor an almost racemic CPA-Na salt was found (it can be recycled into the resolution).

The resolution of trans-permethrinic acid was carried out in analogue mode.

![Diagram of the resolution process](image-url)
Separation of the Mixtures of Chiral Compounds by Crystallization

The behaviour of racemic compounds may also be influenced with the choice of pH value of the aqueous solution. The isoelectronic point of 2-phenylglycine (PG) is at neutral pH value (Ip = 7.0). The free racemic aminoacid with (S)-camphorsulfonic acid (CSA) forms a well crystallizing salt in water, but the amino acid in the precipitated diastereoisomer have almost racemic composition. When the crystallization is started from an aqueous solution containing half an equivalent amount of CSA and equivalent amount of hydrochloric acid (total 50% excess of acid to the PG as base!), the crystalline salt contains (S)-2-phenylglycine in high enantiomeric purity (and in good yield), while the almost pure (R)-2-phenylglycine was obtained from filtrate by crystallization of its hydrochloric acid salt.\(^{44}\)

![Diagram of the reaction](image)

The resolution of racemic free phenylalanine (PA) was also carried out with high efficiency, if near the half an equivalent amount of resolving agent (O,O'-dibenzoyl-(R,R)-tartaric acid (DBTA) or the optically active N-benzoyl-d-phenylalanine (BPA)) was applied in aqueous methanolic solution which contained more than 0.5 equivalent amount of hydrochloric acid, too.\(^{45}\)

### 3.2.2.2 Influence of dielectric constant

In the previous chapter the crucial role of the pH value has been shown via examples.

It was also recognized that the polarity of the solvents or solvent mixtures (quantified by the dielectric constant of solvents) can also determinate the composition of the crystallized diastereoisomeric salt.\(^4\) For example, in the resolution of \(\alpha\)-aminocaprolactam (AC) with (S)-N-tosylphenylalanine ((S)-TsPA) in various solvents the (S)-AC was predominant when the dielectric constant of the solvent was \(\varepsilon<27\) or \(\varepsilon>62\). However, the salt of the antipode (R)-AC crystallized when the solvent was in medium polarity (29<\(\varepsilon\)<58).\(^{46,47,48}\)

![Diagram of the reaction](image)
That observation can be generalized: systematic variation of the solvent, the diastereoisomer containing the desired enantiomer can be brought to crystallization. (Using the adequate solvent one of the diastereoisomers is crystallized from the mixture of diastereoisomers, and the other one can be crystallized from another solvent.)

For example, if the resolution of flumequine intermediate (FTHQ) is resolved with O,O’-di-para-toluoyl-(R,R)-tartaric acid ((R,R)-DPTTA) in presence of acetic acid the (R)-FTHQ enantiomer crystallizes in the salt, while the (S)-FTHQ enantiomer forms a better crystallizing salt when isopropyl alcohol is used as a solvent.\textsuperscript{49}

\textbf{3.2.2.3 Resolution in two immiscible solvents}

One variant of the resolution methods is that salt formation is carried out in a system of two immiscible solvents (e.g. water and dichloromethane). In this case the more stable diastereomeric salt separates, while the free enantiomer dissolves in one of the phases (usually the organic one).\textsuperscript{50,51}

This manner was used at the resolution of the anxiolytic tofisopam (TOF) with half equivalent of (R,R)-DBTA. It was accomplished in a water–chloroform system. The diastereomeric salt containing the (R)-TOF enantiomer was crystallized from the biphase solvent, while free (S)-TOF was recoverable from organic phase.\textsuperscript{52,53}
3.2.2.4 Presence of solvates and compounds with similar effect

It can be frequent observed at the fractionated crystallization of diastereomeric salts that the crystalline diastereomer forms solvate with the solvent. As an example can be mentioned the first ever resolution by salt formation accomplished by Pasteur where the “d-quinotoxine-d-tartrate” obtained was a hexahydrate. Of course it can be found numerous similar examples in the literature.

It is not rare the phenomenon that the selective solvate formation of diastereomers gives a much better separation or the solvate formation is essential for successful resolution. It is true because only in this case crystallizes the diastereomer. E.g. in methanol trans-(R)-chrysanthemic acid (trans-(R)-CHRA) forms with (R,R)-2-N,N-dimethylamino-1,3-propanediol [(R,R)-DMAD] crystals containing the solvent. If the resolution was carried out in another solvent (e.g. in methyl isobutyl ether) best results were obtained if some methanol was added, because it permitted the precipitation of the methanol solvate (is crystallized the (R)-CHRA.(R,R)-DMAD.CH3OH).

3.2.2.4.1 When the separation of diastereomers is possible just from solvate forming solvent

The separation of enantiomers of racemic amlodipine (AML) with (R,R)-tartaric acid by fractionated crystallization of diastereomers from the common solvents was without success, but in DMSO, however, the salt of (S)-AML crystallizes as a DMSO solvate. Even more surprisingly, in N,N-dimethyl-acetamide it is the solvate of the (R)-AML salt which crystallizes in good yield and high purity.
3.2.2.4.2 Presence of achiral compound

It is well known separation of diastereomers when the enantiomeric purity reachable using a resolving agent may be significantly improved if the crystallization of diastereomeric salt is promoted by crystallization of an achiral compound having analogue molecular structure with a part of the resolving agent molecules.

This phenomenon was observed at the resolution of racemic $\alpha$-phenylethylamine (PEA) using (R)-N-(1-phenyl-ethyl)-glutaric acid ((R)-PEGA) as resolving agent. From acetone was crystallized diastereomeric salt containing (S)-PEA with ee: 58%. If is added an equivalent of carbamide to the mixture the enantiomeric excess of the isolated (S)-PEA was 90%.58

\[
\begin{align*}
{(S)}\text{-PEA} + \text{HOOC}-\text{N}^{-}\text{-CH}_3 \rightarrow \text{(S)}\text{-PEA.(R)}\text{-PEGA} \quad \text{ee: 58% F: 0.36} \\
{(R)}\text{-PEA} + \text{HOOC}-\text{N}^{-}\text{-CH}_3 \rightarrow \text{(R)}\text{-PEGA} \quad \text{ee: 90% F: 0.49}
\end{align*}
\]

3.2.3 Resolving agents forming diastereomeric complexes

The difference between solubility of diastereomeric salts, their solvent dependence justify that although the ions of salt establish strong interactions, nevertheless the formation of secondary interactions between the compounds containing these ions (formation of diastereomeric molecular complexes) is the reason of differential solubility of diastereomeric salts in the respective solvent. Naturally, it is not by chance that the diastereomeric salt of dibenzoyltartaric acid (DBTA) are well separable and it is a very suitable resolving agent for a wide range of racemic basis. It means that the enantiomers of racemic compounds which do not contain either acidic or basic functional groups form diastereomerically related molecular complexes with DBTA. These complexes can be separated by fractionated crystallization. Such several alcohols with various molecular structures could be resolved, e.g. the resolution of racemic menthol (MEN) was carried out with (R,R)-DBTA in solution, too. In hexane insoluble reagent contacting the dissolved racemic menthol forms crystalline diastereomeric molecular complex.59 (as was shown earlier at the crystallization of diastereomers from melt).

\[
\begin{align*}
{(1S,2R,5S)}\text{-MEN} + \text{HOOC}_{\text{PhOCO}}^{-}\text{COOH} & \rightarrow 1.\text{hexane} \rightarrow 2.\text{crystallization} \rightarrow 3.\text{filtration} \rightarrow \text{(1R,2S,5R)}\text{-MEN.(R,R)}\text{-DBTA crystalline} \\
{(1R,2S,5R)}\text{-MEN} + \text{HOOC}_{\text{PhOCO}}^{-}\text{COOH} & \rightarrow 1.\text{hexane} \rightarrow 2.\text{crystallization} \rightarrow 3.\text{filtration} \rightarrow \text{(1S,2R,5S)}\text{-MEN in solution}
\end{align*}
\]
From the crystalline diastereomer could be isolated the L-MEN with a good enantiomeric purity (ee: 83%).

The widely applied **TADDOL (TAD)** was also a suitable reagent of several diastereomeric molecular complex, for example enantiomers of phospholene oxides (**PHO**) could be obtained with high optical purity after the fractionated crystallization and decomposition of the precipitated diastereomers.\(^8\)

\[
\begin{align*}
\text{HOOC} & \quad \text{OCOCa}_{1/2} \\
\text{PhOCO} & \quad \text{COOCa}_{1/2} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH}
\end{align*}
\]

3.2.4 Resolving agents forming coordinative complexes

It is well known that the coordinative complex of several metal is well crystallize. The calcium salt of dibenzoyltartaric acid (**DBTAC**), was used be quite a few for separation of diastereomeric coordinative complex by fractionated crystallization. For example the separation of derivatives of phospholene oxides (previously mentioned) was carried out using (**DBTAC**).\(^9\)

\[
\begin{align*}
\text{HOOC} & \quad \text{OCOCa}_{1/2} \\
\text{PhOCO} & \quad \text{COOCa}_{1/2} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

3.2.5 Time of crystallization

Although the methods based on fractionated crystallization suggest that during crystallization the less soluble diastereomer is crystallized, but at the enantiomeric separations realized by fractionated crystallization, or precipitation, respectively, was observed in some cases that instead of expected racemate behaviour was crystallized the
enantiomeric excess (conglomerate like behaviour), namely its faster crystallization determines the separation (kinetic conglomerate).

3.2.5.1 Thermodinamic control

In general, at the fractionated precipitation if is expected a conglomerate like behaviour on base of binary phase diagram of diasteroemeric mixture, the filtration is effectuated when the quantity of crystalline precipitate is constant. However if the difference between the crystallization rate of diastereomers is not large enough, can be occured that both diastereomers are crystallized in near similar quantity. In this case we cold not talk about enantiomeric enrichment. If instead of quick filtration is given time for stabilition of thermodynamic equilibrium, in turn is obtain a separation with good result. This can be demonstrate via resolution of tamsulosin intermediate (TAI) using as resolving agent DBTA in the mixture of water and ethanol, when at the end of crystallization was not carried out enantionwmeric enrichment, but if the crystalline mixture was allowe to stand for 2 days, was reached a very high enantiomeric excess.\(^60\)

![Chemical structure of TAI and DBTA](image)

Similar phenomenon was also observed at the resolution of racemic oxirane derivatives, containing two terciary aminogroups.\(^61\)

3.2.5.2 Kinetic controlled crystallization

Accordingly to the previously examples would appear to be advantageous that the time of crystallization to be more longer but if one of the diastereomers crystallizes quickly and the other is wrong solvable, then nevertheless its opposite is also favourable.

Thus in the resolution of the intermediate of flumequine (FTHQ) in ethyl acetate with di-paratoluyl-tartaric acid \((R,R\)-DPTTA\), after a crystallizing of 5 minutes the \((R\)-FTHQ\,(R,R\)-DPTTA\) salt predominates, but on standing 3 weeks its antipode \((S\)-FTHQ\,(R,R\)-DPTTA\) will be in excess in the crystals.\(^48\)

![Chemical structure of FTHQ and DPTTA](image)
In the most cases it is not necessary to effectuate so quickly the filtration of crystals, because the stabilization of thermodynamic equilibrium need a longer period. This is so even if the racemic compound of resolving agent is resolved using one of enantiomers of racemic compound.\(^\text{62}\)

The resolution of \(N\)-formyl-phenylalanine (\(\text{FoPA}\)) with \((S)\)-phenylethylamine (\(\text{PEA}\)) in water after 2 hours gave diastereomeric salt with high purity, but this enantiomeric excess diminished when the filtration of the precipitated salt was carried out after a longer standing (1 week).

If the resolution of racemic \(\text{PEA}\) is accomplished with \((S)\)-\(\text{FoPA}\) (reciprocal resolution), in function of crystallization time practically the same thing was happened as expected on basis of the foregoing, but the results were not identical because at the normal and the reciprocal resolutions the systems are in diastereoisomeric relationship.

4. Conclusions

The behaviour of the enantiomeric mixtures can be interpreted by formation of their homo- and heterochiral aggregates having diastereomeric property. Due to spontaneous formation of these aggregates the non-racemic mixtures of enantiomers can be enriched by processes required some selective crystallization. The running of biner meltingpoint/composition phase diagrams (conglomerate or racemate), and the kinetic controlled crystallizations (kinetic conglomerates), respectively, determine the fact, that the crystalline phase contains the enantiomer or the racemic proportion. These regularities are also reflected by the running of curves where the enantiomeric purity of the product obtained (ee) during the selective crystallizations and precipitations were plotted against the initial composition (\(\text{ee}_0\)).

At the separation of racemic compounds using another chiral material (namely resolution) the behaviour of enantiomeric mixture forming the racemate determines the efficiency of
resolution. If the racemic compound and resolving agent have similar molecule structure, the diastereomers form quasi-racemate, and quasi-conglomerate respectively.

If the structures of racemic compound and resolving agent are not considered structurally related compounds, at separation of the diasteremers also exist the complementarity between compounds form the diastereomer, which is in advanced insured in case of structurally similar compounds. In all probability the results of separation of diastereomers are also determined by the behaviour of enantiomeric mixtures of racemic compound and resolving agent.

The probability of this statement is underlined near the experimental data, the fact that the conditions, separation methods, typical behaviours observed at the separation of diastereomers based on the fractionated crystallization were similar to the experienced one at the separation of mixtures containing only enantiomers.

The rulings of chiral-chiral recognitions are valid even if the aim is to isolate by crystallization a chiral compound, having a higher purity than the initial one (ee > ee₀
eq), from a mixture containing more than two chiral component.

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6. Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| A            | phenylisopropylamine |
| AC           | aminocapro lactam |
| AcPA         | acetyl-phenylalanine |
| AcPG         | acetyl-phenylglycine |
| AD           | aminodiol |
| AML          | amlodipine |
| AN           | aminonitrile |
| BA           | benzylamine |
| BAB          | benzylaminobutanol |
| BPA          | benzoyl-d-phenylalanine |
| CHD          | cyclohexane-diol |
| CHRA         | chrysanthemic acid |
| CPA          | permetric acid |
| CPH          | chloro-phenyl substituent |
| CSA          | camphorsulfonic acid |
| DBTA         | dibenzoyltartaric acid |
| DBTAC        | calcium salt of dibenzoyltartaric acid |
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|   |   |
|---|---|
| DCA | dicarboxylic acid |
| DIL | diltiazem |
| DMAD | dimethyamino-1,3-propanediol |
| DPTTA | di-para-toluoyl-tartaric acid |
| EPh | ephedrine |
| FoPA | formyl-phenylalanine |
| FTHQ | flumequine |
| IBU | Ibuprofen |
| IC | Iodo-cyclohexanol |
| MA | methyl-phenylizopropylamine |
| MEN | menthol |
| MePA | phenylalanine methyl ester |
| MePG | phenylglycine methyl ester |
| PA | phenylalanine |
| PEA | Phenylethylamine |
| PEGA | phenyl-ethyl-glutaric acid |
| PG | phenylglycine |
| PGA | phenylglycine amide |
| PGL | Prostaglandine |
| PHO | phospholene oxides |
| POAA | phenoxy-acetic acid |
| PPA | propionyl-phenylalanine |
| PPEA | phthaloyl-phenylethylamine |
| PPG | propionyl-phenylglycine |
| Q | Quinotoxine |
| TA | Tartaric acid |
| TAD | Taddol. |
| TAI | tamsulosin intermediate |
| TIS | Tisercine |
| TOF | Tofizopam |
| TPA | tosylphenylalanine |

7. References

[1] a) Eliel, E. L.; Wilen, S. H.; Stereochemistry of Organic Compounds Eds.; Wiley New York, 1994 b). Roozeboom, H. W. B.; Z. Physik. Chem. 1899, 28, 494.

[2] Bereczki, L.; Pálovics, E.; Bombicz, P.; Pokol, G.; Fogassy, E.; Marthi, K.: Tetrahedron: Asym. 2007, 18, 260

[3] Faigl, F., Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J.; Tetrahedron: Asymm., 2008, 4, 519

[4] Scheldon, R. A. Chirotechnology, Marcel Dekker Inc. N.Y 1993

[5] Novák, T; Schindler, J; Ujj, V; Czugler, M; Fogassy, E; Keglevich, Gy: Tetrahedron: Asymmy. 2006, 2599.

[6] Ujj V; Schindler J; Novák T; Czugler M; Fogassy E; Keglevich Gy: Tetrahedron: Asymm. 2008, 1973-1977

www.intechopen.com
[7] a). Blackmond, D.G., Klussmann, M.: *Chem. Commun.*, 2007, 3990-3996. b). Perry, R.H., Wu, C., Neefiu, M., Cooks, R.G.: *Chem. Commun.*, 2007, 1071-1073. c). S. I. Goldberg, *Orig Life Evol Biosph.*, 2007, 37, 55-60.

[8] Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J.: *Organic & Biomolecular Chemistry* 2010, 8, 347-359.

[9] Sakai, K.; Sakurai, R.; Yuzawa, A.; Hirayama, N. *Tetrahedron: Asymmetry*, 2003, 14, 3716

[10] Fogassy, E.; Faigl, F.; Ács, M.; Grofcsik, A. *J. Chem. Res.*, 1981, 31, 346. Fogassy, E.; Faigl, F.; Ács, M.; Simon, K.; Kozsda, É.; Podánya, B.; Czegler, M.; Reck, G. *J. Chem. Soc. Perkin Trans. 2*, 1988

[11] Kellogg, R.M.; Nieuwenhuijzen, J.W.; Prouwer, K.; Vries, T.R.; Broxterman, Q.B.; Grimbergen, R.F.P.; Kaptein, B.; La Crois, R.M.; de Wever, E.; Zwaagstra, K.; van der Laan, A.C. *Synthesis*, 2003, 1626.

[12] Schindler, J.; Egressy, M.; Bereczki, L.; Pokol, G.; Fogassy, E.; Marthi, K. *Chirality*, 2007, 19, 239.

[13] a). Hung. Pat. no. 214720, *Chem. Abs.* 1995, 124, 117097; b). US Pat. 02133894 2001, *Chem. Abs.* 2001, 139, 90595

[14] a). Weissbuch, I., Lahav, M., Leiserowitz L. *Advances in Crystal Growth Research*, Page: 381-400, 2001. b). Fogassy, E.; Faigl, F.; Pálovics, E.; Schindler, J. *11th International Conference of Chemistry Cluj*, ed. Hung. Techn. Sci. Soc. of Transylvania 2005, 357.

[15] Pálovics, E.; Schindler, J.; Borsodi, J.; Bereczki, L.; Marthi, K.; Faigl, F.; Fogassy, E.: *Műszaki Szemle*, 2007, 39-40, 48

[16] a). Kozma, D.; Böcskei, Zs.; Simon, K.; Fogassy, E.: *J. Chem. Soc. Perkin Trans 2*, 1994, 1883 b). Nemák, K.; Ács, M.; Kozma, D.; Fogassy, E.: *J. Therm. Anal.* 1997, 48, 691.

[17] Pálovics, E.; Fogassy, E.; Schindler, J.; Nógrádi, M.: *Chirality*, 2007, 19, 1

[18] Fogassy, E.; Lopata, A.; Faigl, F.; Darvas, F.; Ács, M.; Tőke, L.: *Tetrahedron Lett.* 1980, 21, 647.

[19] Pasteur, L. *Acad. Sci.*, 1848, 26, 535.

[20] Ács, M.; Pokol, G.; Faigl, F.; Fogassy, E.: *Termal. Anal.* 1988, 33, 1241.

[21] Kozsda, K.R.; Keserü, Gy.; Böcskei, Zs.; Szilágyi, J.; Simon, K.; Bertók, B.; Fogassy, E.: *J. Chem. Soc. Perkin Trans 2*, 2000, 149.

[22] Bálint, J.; Egri, G.; Vass, G.; Schindler, J.; Gajáry, A.; Friesz, A.; Fogassy, E.: *Tetrahedron: Asym.* 2000, 11, 809.

[23] Kozma, D.; Simon, H.; Kassai, Cs.; Madarász, J.; Fogassy, E.: *Chirality* 2001, 13, 29.

[24] Simon, H.: PhD disz. 2003

[25] a). Kozma, D.; Madarász, Z.; Kassai, Cs.; Fogassy, E.: *Chirality*, 1999, 11, 373.b). Hung. Pat. no. 212 667

[26] Ács, M.; Mravik, A.; Fogassy, E.; Böcskei, Zs. *Chirality*, 1994, 6, 314

[27] Kassai, Cs: PhD disz. BME 2000

[28] Fogassy, E.; Ács, M.; Szili, T.; Simándi, B.; Sawinsky, J.: *Tetrahedron Letters*, 1994, 35, 257-260

[29] Molnár, P.; Thorey, P.; Bánsághi, Gy.; Székely, E.; Poppe, L.; Tomin, A.; Kemény, S.; Fogassy, E.; Simándi, B.: *Tetrahedron: Asymmetry*. 2008, 19, 1587.

[30] Gizur, T.; Harsányi, K.; Fogassy, E.; *J. Pract. Chem.* 1986, 336, 628.
Separation of the Mixtures of Chiral Compounds by Crystallization

[31] Fogassy, E.; Ács, M.; Tóth, G.; Simon, K.; Láng, T.; Ladányi, L.; Párkányi, L.: J. Mol. Structure 1986, 147, 143.
[32] Fogassy, E.; Faigl, F.; Ács, M.: Tetrahedron, 1985, 41, 2841.
[33] Jacob, R.M.; Reginier, G.L.: DE 1050035 1958
[34] Pálovics, E.: PhD theses.
[35] Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J.: Organic & Biomolecular Chemistry 2010, 8, 347-359.
[36] Pálovics, E., Faigl, F., Fogassy, E.: New Trends and Strategies in the Chemistry of Advanced Materials (eds.: Tudose, R., Muntean, S.G.), Mirton, Timisoara, 2010, pp 20-26
[37] Jaques, J.; Wilen, S.H.; Collet, A.: Enantiomers racemates and resolution, John Wiley-and Sons, New York, 1981
[38] Pope, W.J.; Peachey, S.J.: J. Chem. Soc., 1899, 75, 1066.
[39] Kellogg, R.M.; Nieuwenhuizen, J.W.; Pouwer, K.; Vries, T.R.; Broxterman, Q.B.; Grimbergen, R.F.P.; Kaptein, B.; La Crois, R.M.; de Wever, E.; Zwaagstra, K.; van der Laan, A.C.: Synthesis, 2003, 1626.
[40] Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J.: Tetrahedron: Asymmetry 2008, 19, 519-536.
[41] Fogassy, E.; Faigl, F.; Ács, M.; Grofcsik, A.: J. Chem. Res. (S) 1981, 11, 346 (1981); (M) 1981, 11, 3981. pg. 9
[42] Fogassy, E.; Faigl, F.; Ács, M.; Simon, K.; Koszda, É.; Podányi, B.; Czugler, M.; Reck, G.: J. Chem. Soc. Perkin Trans. 2, 1988, 1385-1392. Hung. Pat. no. 188.255.
[43] Simon, K.; Koszda, É.; Faigl, F.; Fogassy, E.; Reck, G.: J. Chem. Soc. Perkin Trans. 2, 1990, 1395. Hung. Pat. no. 197.866, 1985.
[44] Töke, L.; Lonyai, P.; Fogassy, E.; Ács, M.; Csermely, Gy.; Szenttornyai, A.; Faigl, F.: Hung. Pat HU 24599, 1983, CAN 99:140389
[45] Ács, M.; Faigl, F.; Fogassy, E.: Pat. No. WO 8503932, 1985, CAN 104:168835.
[46] Sakai, K.; Sakurai, R.; Yuzawa, A.; Hirayama, N.: Tetrahedron: Asymmetry, 2003, 14, 3716.
[47] Sakurai, R.; Sakai, K.: Tetrahedron: Asymmetry, 2003, 14, 411.
[48] Sakai, K.; Sakurai, R.; Hirayama, N.: Tetrahedron: Asymmetry, 2004, 15, 1073.
[49] Bálint, J.; Egri, G.; Kiss, V.; Gajáry, A.; Juvancz, Z.; Fogassy, E.: Tetrahedron: Asymmetry, 2001, 12, 3435.
[50] Ács, M.; Fogassy, E.; Faigl, F.: Tetrahedron, 1985, 41, 2465.
[51] Kozma, D.; Fogassy, E.: Synth. Comm., 1999, 29, 4315.
[52] Hung. Pat. no. 179452, 1978, Chem. Abs. 1978, 97 6331
[53] Fogassy, E.; Ács, M.; Toth, G.; Simon, K.; Láng, T.; Ladányi, L.; Párkányi, L.: J. Mol. Struct., 1986, 147, 143.
[54] Woodward, R.B.; Doering, W.E.: J. Chem Soc., 1945, 67, 860.
[55] Jaques, J.; Wilen, S.H.; Collet, A.: Enantiomers racemates and resolution Wiley-Interference, N.Y. 1991
[56] Hung. Pat. no. 214720, Chem. Abs. 1995, 124, 117097
[57] US Pat. 02133894 2001, Chem. Abs. 2001, 139, 90595
[58] Schindler, J.; Eggers, M.; Bereczki, L.; Pokol, Gy.; Fogassy, E.; Marthi, K.: Chirality 2007, 19, 239-244.
[59] Kassai, Cs.; Juvancz, Z.; Bálint, J.; Fogassy, E.; Kozma, D.: Tetrahedron, 2000, 56, 8355.
[60] Gizur, T.: Hun Pat. 202963 2002, CAS 140 253341
[61] Faigl F.; Thurner A.; Farkas F.; Proszenyák Á.; Valacchi M.; Mordini A.: Arkivoc, 2004 (vii), 53-59.
[62] Pálovics, E.; Schindler, J.; Faigl, F.; Fogassy, E.: Tetrahedron: Asymm.y.2010. 21,2429-2434
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