Chapter 6

Separation of Chiral Compounds: Enantiomeric and Diastereomeric Mixtures

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Additional information is available at the end of the chapter

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Abstract

Despite the dramatic development of enantioselective synthesis and chromatographic separation methods, optical resolution still remains the cheapest and operationally simplest method for producing pure enantiomers on a larger scale. No extreme conditions or expensive reagents are required, and the eventually expensive resolving agents can be recovered. This chapter is based mainly on the authors' long experience in the resolution of industrially important molecules, and it presents new observations and establishments as well. Several methods for separation of chiral mixtures, enantiomeric and diastereomeric mixtures, are shown, and possibilities for predicting the efficiency of resolution based on the analysis of physico-chemical properties of the reactants are also described.

Keywords: enantiomeric mixtures, resolution, eutectic composition, helical structure

1. Introduction

Due to both practical and theoretical reasons, the properties and the possible preparation techniques of chiral compounds are investigated in ever widening fields of research, applying various examination methods [1, 2]. It is a great challenge for some researchers if the goal is to find a simple, inexpensive, economical and also patentable preparation of a given chiral compound (single enantiomer), for example according to the demands of the industrial production or drug discovery. Although nowadays several alternative synthetic pathways can be found for the preparation of a given single enantiomer, most probably in most cases the break-up of a certain racemic composition [3], leading to the synthesis of the final product,

followed by the purification of the mixture, is applied [1, 2, 4]. In most cases, mixtures of diastereomers received with appropriate resolving agents, or mixtures of enantiomers isolated thereof, have to be separated. It is common in the two separation methods, that the distribution of the mixtures between two phases, and the phase separation can be applied [4–6]. However, the phase distribution of the mixtures of chiral compounds is not linear, but the distributions follow the binary melting phase diagrams of the mixtures, or the ternary phase diagrams characteristic also for the applied solvent [7, 8].

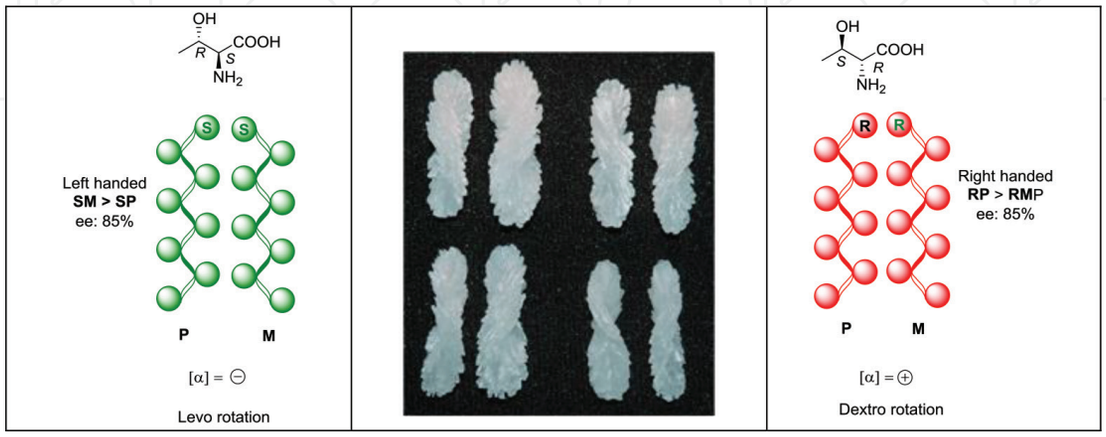
Besides the effect of the applied solvents, the phase distribution of the mixtures is also determined by kinetic or thermodynamic control [9]. The phase distribution is also determined by the eutectic composition of the chiral molecules in the mixtures [10, 11]. The equilibrium of the supramolecular helical structures, which participate in the phase distribution, determines the formation of the phase equilibriums [12]. A remarkable consequence of the effect of the helical structures is that the mirror-image macroscopic enantiomers form not only mirror-image crystals, but by attaching together, mirror-image helical crystals are formed [13, 14]. At the same time, mainly one of the helicities can be attributed to a given enantiomer, most probably this is the reason behind the results of separations. In the followings, the most characteristic examples of the above-mentioned methods will be discussed.

2. Separation of enantiomeric mixtures without chiral reagent

2.1. Formation of macroscopically helical crystals

The enantiomeric mixtures form crystals of a given helicity corresponding to the major configuration (**Scheme 1**).

In case of purification of enantiomeric mixtures of threonine was observed, that the majority of crystals have a convolution corresponding to the helical structure of the excess, while the minor enantiomer, crystallized near the excess, have the opposite convolution. The ratio between the major and minor helical crystals is in good correlation with the eutectic composition



Scheme 1. Purification of enantiomeric mixtures of threonine from water ($ee_0 \neq 0$).

of the enantiomeric mixture of threonine. So the eutectic composition (ee_{Eu}) precipitates during evaporation, dominated by the helicity of the excess, along with the crystallization of the minor enantiomer as well.

Mirror-image crystals are formed from the supramolecular helical structures, which contain one of the enantiomer in excess. The helicity of the crystals is determined by the optical rotation of the enantiomer in excess [13, 14].

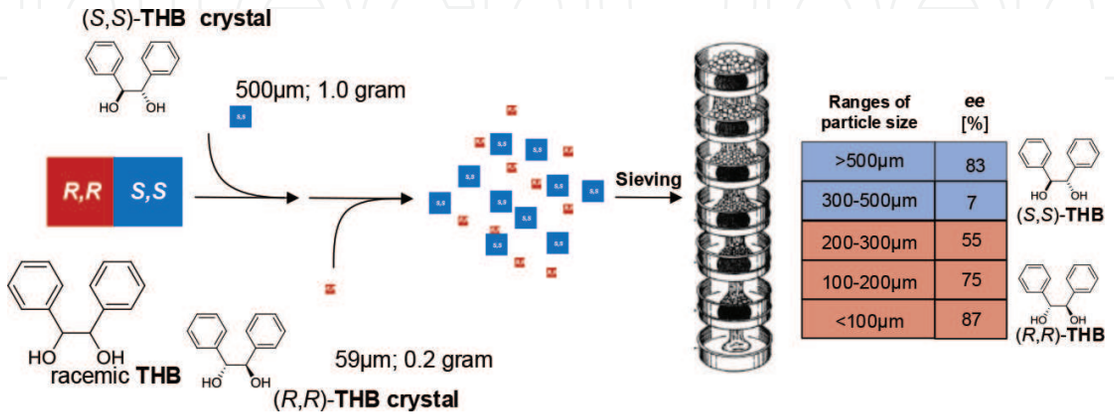
2.2. Particle-size-controlled crystallization

The ethanol solution of the conglomerate racemic *trans*-hydrobenzoin [15] (**THB**) was seeded with different amounts of (*S,S*)-**THB** and (*R,R*)-**THB** seeds of different particle size during a specified cooling program. After crystallization, the received crystals were separated to different ranges of particle size by sieving. Thus, enantiomeric mixtures of (*S,S*)-**THB** and (*R,R*)-**THB** of 83% and 87% enantiomeric excess were gained, respectively (**Scheme 2**) [16].

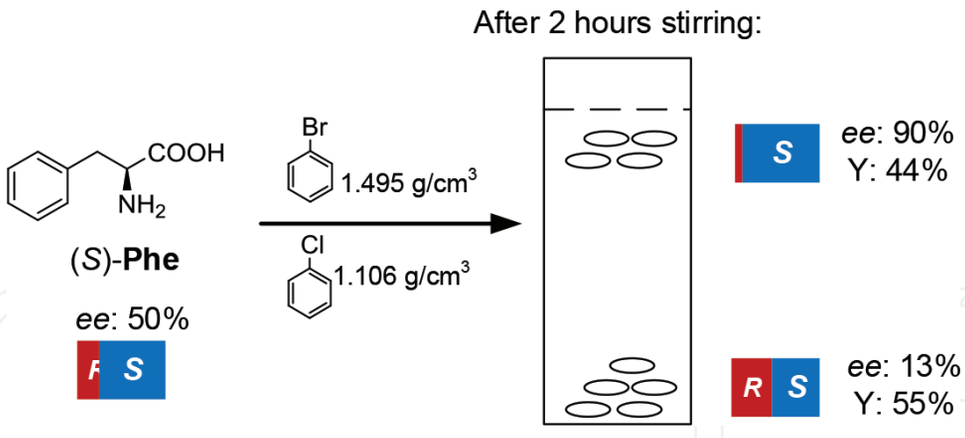
2.3. Gravity-based enantiomer separation

According to Soloshonok et al., the SDE (self disproportionation of enantiomers) appears in three main areas: gravitational field, phase transition, and the achiral chromatography [17]. Basically, the gravity-based SDE applies the differences in crystal density. The racemate enantiomeric mixture can be considered as the mechanical mixture of the racemic and enantiopure crystals, which can have different crystal densities. This difference can be applied for the separation of the racemic and enantiopure fraction. For example, from a enantiomeric mixture of phenylalanine (**Phe**) having 50% enantiomeric purity, two phases of 90 and 13% enantiomeric purity, respectively, could be separated after stirring in an inert solvent of appropriate density, set between the densities of the racemic and enantiopure crystals (**Scheme 3**) [18, 19].

Based on these results, separation of amino acid enantiomeric mixtures was carried out via density gradient ultracentrifugation, applying an iodinated gradient (*Nycodenz*) used in the isolation of nucleic acids and proteins. Recently, the density difference between the racemic and enantiopure Ibuprofen was utilized in an apparatus based on principle of magnetic levitation [20].



Scheme 2. Application of particle-size-controlled crystallization for resolution.



Scheme 3. Application of density difference for the purification of enantiomeric mixtures.

2.4. Distribution between phases, enantiomeric separation

In the case of phase transitions, the SDE phenomenon is not uniform, it highly depends on the type of the phase transition [17].

2.4.1. Fractionated crystallization

In the case of the recrystallization of enantiomeric mixtures, by plotting the enantiomeric purity of the solid phase in function of the starting enantiomeric purity, a curve similar to binary and ternary phase diagrams can be obtained (ee_0-*ee* curve) (**Scheme 4**). Regarding a racemate enantiomer mixture, by recrystallizing a mixture having lower purity than the eutectic composition, in any case increased purity will be gained in the solution/melt phase, while above the eutectic composition, the enantiomeric enrichment is expected in the solid phase [2]. The recrystallization is not successful in all the cases to reach enantiomeric enrichment, for example the recrystallization experiments of the enantiomer mixtures of *N*-formyl-phenylalanin (*N*-formyl-**Phe**) and *N*-acetyl-phenylalanin (*N*-Ac-**Phe**), were unsuccessful [21].

A possible mechanism of the recrystallization of racemate-type enantiomeric mixtures is described by Tamura [24–28].

2.4.2. Distribution between solid and gas phases, enantiomer separation

In the case of mandelic acid, the vapor phase has a eutectic composition, which is independent from the composition of the starting mixture and this composition will sublimate [29]. Independently from the preparation of the starting mixture, enantiomeric mixtures of mandelic acid of 30–54% enantiomeric purity were received as sublimates (**Scheme 5**), which approximates well the eutectic composition determined from the binary and ternary phase diagrams of mandelic acid (ee_{eu}: 32% [30, 31]). In the case of the sublimation of several racemate-type amino acids, the purities received in the sublimates [32–34] were identical to the eutectic compositions determined from the ternary phase diagrams [35].

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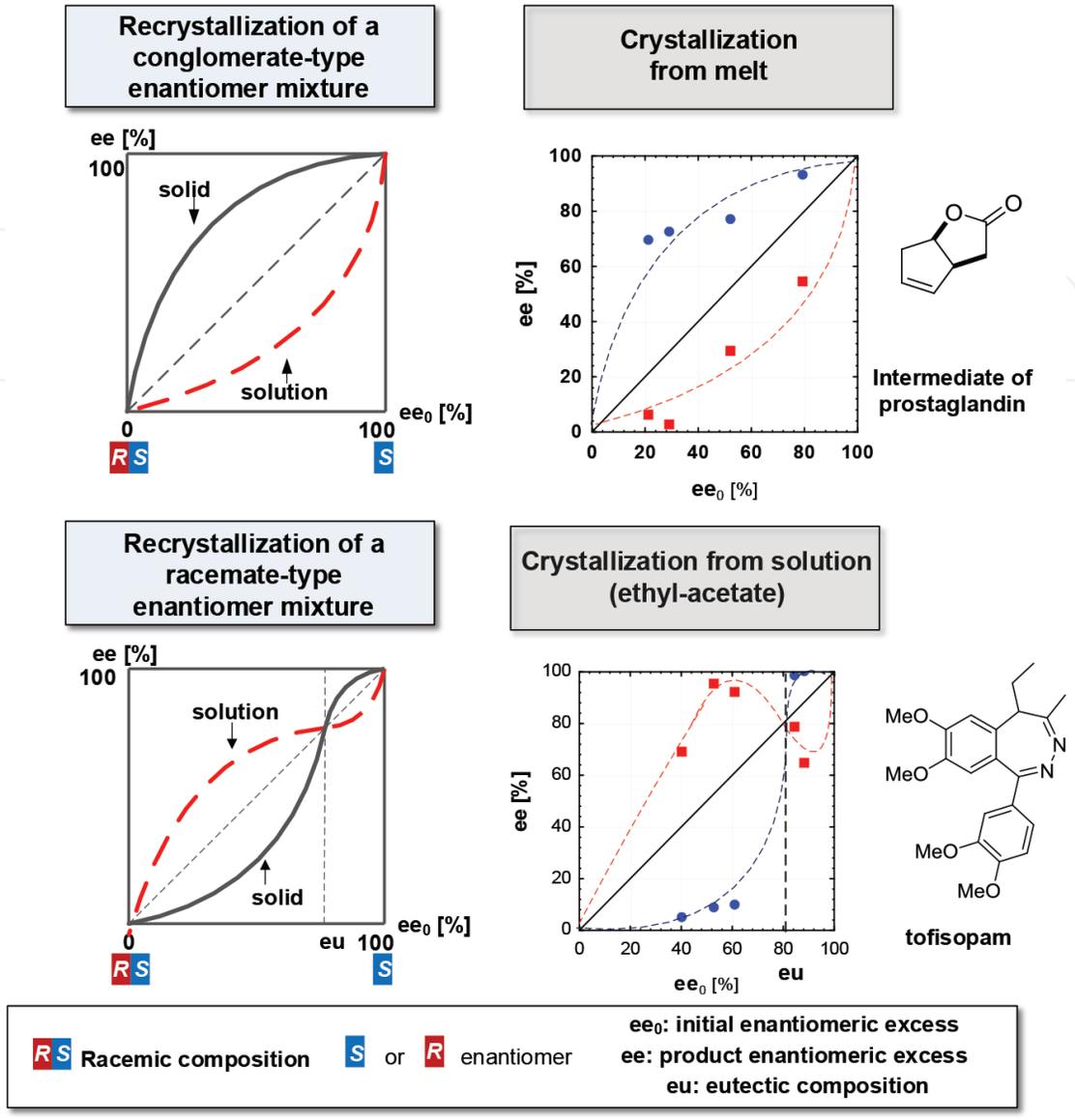
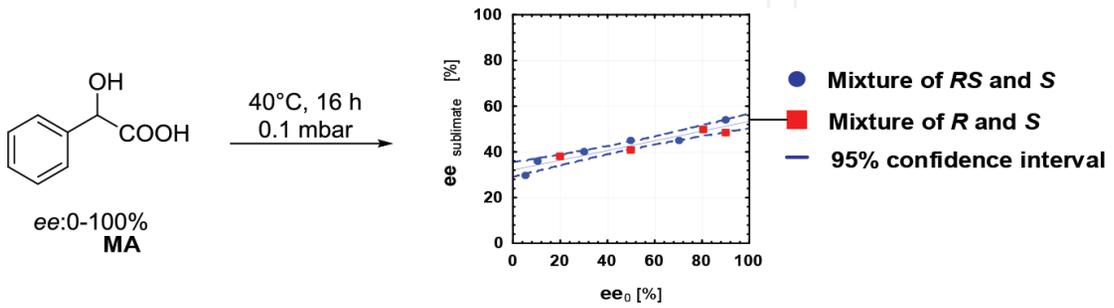


Scheme 4. Typical curve received from the recrystallization of a conglomerate-type enantiomer mixture (ee_0-ee diagram) and an example of ee_0-ee diagram for crystallization from melt [22] (upper diagrams); and a typical curve received from the recrystallization of a racemate-type enantiomer mixture (ee_0-ee diagram) and an example of ee_0-ee diagram for crystallization from solution (lower diagrams) [23].



Scheme 5. Sublimation of enantiomer mixtures of mandelic acid (MA).

2.4.3. Distribution between liquid and gas phases, enantiomer separation

During the distillation of enantiomer mixtures of isopropyl-(*S*)-trifluorlactate (isopropyl-(*S*)-**TLAK**), the purity of the enantiomer mixtures gained in the distillate and in the residue was different from the starting composition (**Scheme 6**) [36, 37]. Another example for the enantiomer enrichment received by fractionated distillation is that an enantiomeric mixture of 91% enantiomer purity of *N*-trifluoracetyl-(*S*)-valine-methyl-ester (*N*-trifluoracetyl-**Val-Me**) could be further separated to two parts of 88.0 and 97.6% enantiomeric excess, respectively [38].

2.4.4. Separation of enantiomeric mixtures by achiral chromatography

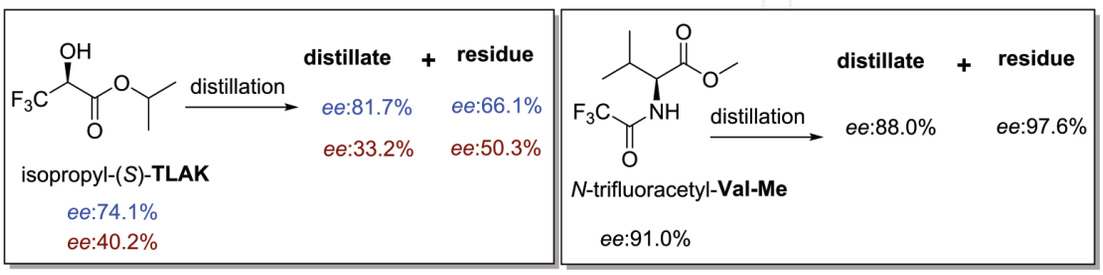
The SDE phenomenon prevails in the case of enantiomeric enrichment by achiral chromatography. Applying achiral stationary phase and an appropriate eluent, the enantiomeric mixtures can be separated to a polar and a less polar phase, which have different enantiomer purity from the staring composition due to the formation of homo- and heterochiral associations. For example, an enantiomeric mixture of *N*-acetyl-1-phenylethylamin (*N*-Ac-**PhEA**) having 71% enantiomeric excess could be further separated on silica gel stationary phase to two fractions of 99 and a 28% *ee* values, respectively (**Scheme 7**) [39].

Such a separation was first described by Cundy and Crooks [40], but this method is applied by others as well, for the purification of enantiomeric mixtures [17, 41].

2.4.5. Separation of enantiomers by fractionated precipitation

After partial liberation of the achiral salt of the enantiomeric mixtures, the purity of the received enantiomeric mixture may be different from the starting composition. By the addition of base equivalent to the enantiomeric excess to the hydrochloric salt of the conglomerate *Tisercin* (Levomepromazine) (**TIS**) in every case the liberating enantiomeric mixture is purer than the starting composition (**Scheme 8**) [42, 43].

By the resolution of the racemic *cis*-permethric acid (**CPA**), a mixture enriched in (*S,S*)-enantiomer was received. Further purification of the **CPA** was carried out by precipitation from its *Na*-salt with hydrochloric acid (**Scheme 9**) [44].



Scheme 6. Separation of enantiomer mixtures by distillation.

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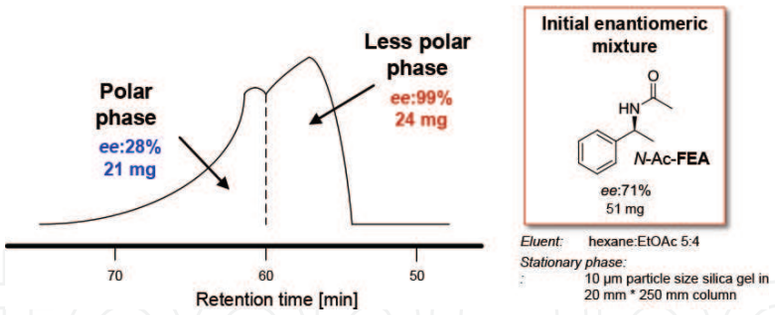
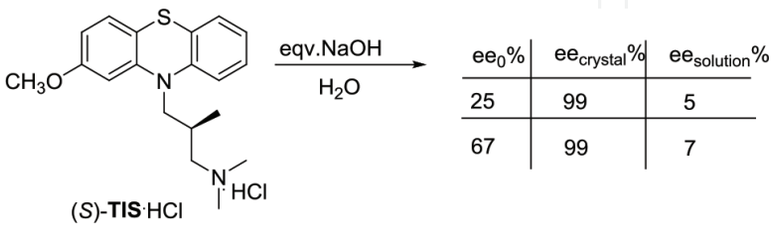


Scheme 7. Purification of enantiomeric mixture of *N*-acetyl-phenylethylamine applying achiral chromatography [45].



ee_0%	$ee_{crystal}$%	$ee_{solution}$%
25	99	5
67	99	7

Scheme 8. Fractionated precipitation of enantiomer mixture of Tisercin.

2.4.6. Kinetic control at the fractionated precipitation

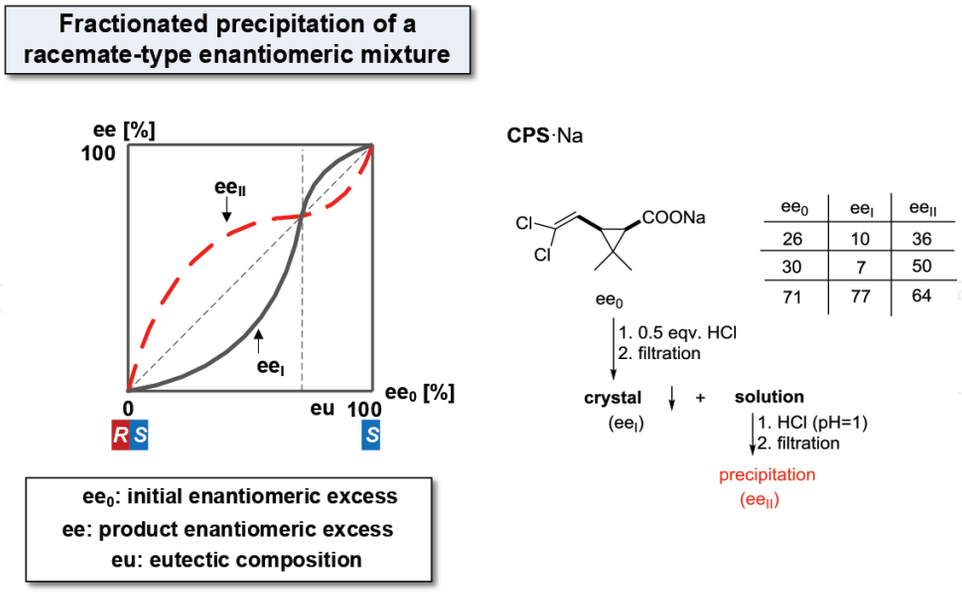
In the case of the fractionated precipitation of the enantiomer mixtures of *N*-propionyl-phenylalanine (*N*-propionyl-**PhA**), the curve expected from the binary phase diagram is significantly different from the received one. The crystals of the enantiomeric excess catalyze (instead of the separation of a low enantiomeric excess, expected under thermodynamic control) the separation of much higher enantiomer purity. For example, in the case of a starting composition around ee_0: 20%, in the first fraction one of the enantiomers is enriched, while the second fraction will be enriched in the other one (**Scheme 10**) [21].

2.4.7. Precipitation and extraction

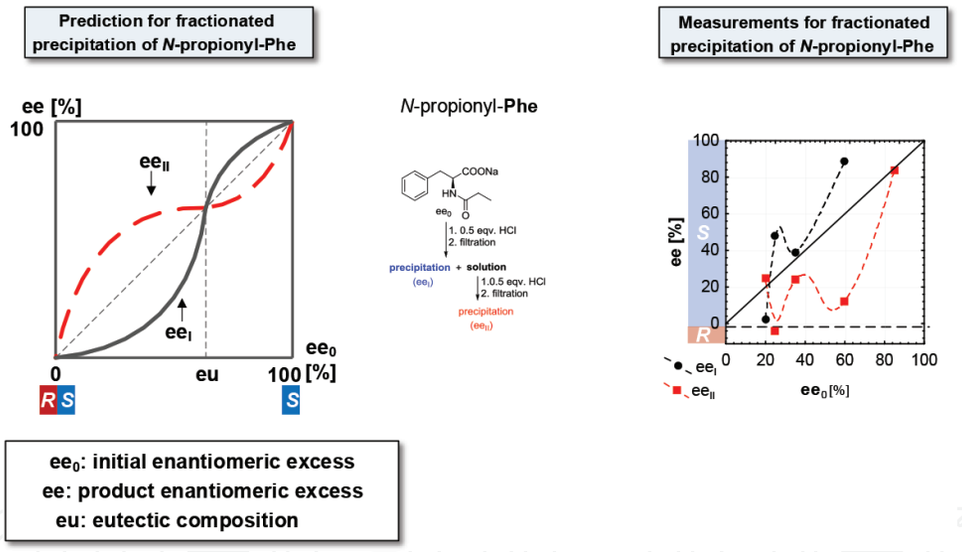
With the combination of precipitation and extraction, for example by liberating a part of the enantiomer mixture in the mixture of water and a water-immiscible solvent, the free enantiomer will stay in the organic phase, while the salt in the water [45].

2.4.8. Precipitation and distillation

The purification of enantiomer mixtures can also be carried out by the transformation of the racemic percentage of the enantiomer mixture into solid phase as salt, followed by the distillation of the free enantiomeric excess [46, 47]. This method was applied in the case of enantiomer mixtures of salts of 1-phenylethyl-amine (**PhEA**) composed with nonequivalent amounts of dicarboxylic acids. By plotting enantiomer purity of the distillate and the residue in the function of the starting enantiomer purity, a diagram similar to the ee_0-*ee* curve, received in



Scheme 9. Fractionated precipitation of *cis*-permethric acid.



Scheme 10. Fractionated precipitation of N-propionyl-phenylalanine.

course of recrystallizations, can be obtained, and also, the joins are in accordance with the eutectic composition of the ternary phase diagram [48].

2.4.9. Precipitation of neutral salts of dicarboxylic acid

The racemic amlodipine with the chiral dicarboxylic tartaric acid crystallizes as the neutral salt of the racemic compound from solvents, without the presence of solvates or solvate-like molecules. Consequently, in the case of enantiomeric mixtures with achiral dicarboxylic acids, the crystallization of the neutral salt of the racemic percentage seemed to be logical.

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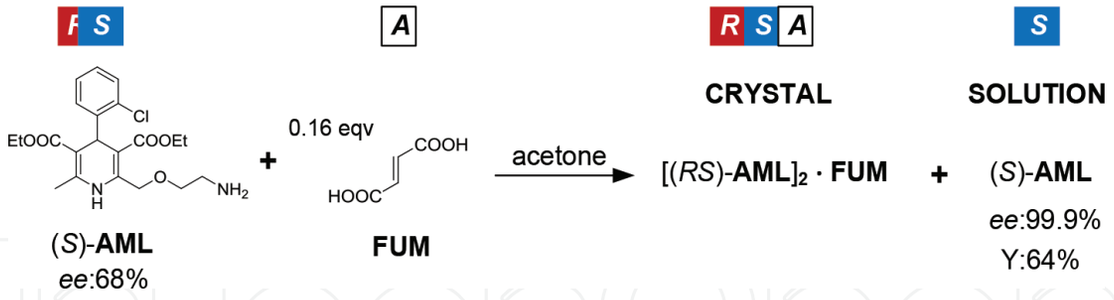


Scheme 11. Purification of enantiomeric mixture of amlodipine.

To the enantiomeric mixture of AML in solution (in acetone), achiral fumaric acid (**FUM**) was given in equal amount to the racemic percentage. The mixture was dissolved by heating. After cooling, the fumaric acid salt of the racemic percentage was filtered out, while the residue was evaporated, resulting in enantiopure (*S*)-**AML** and (*R*)-**AML** base, respectively. From a starting **AML** enantiomeric mixture of *ee*: 68%, reacted with 0.16 equivalent fumaric acid (equivalent to the racemic percentage), after the filtration of the precipitated crystalline neutral fumaric acid salt, (*S*)-**AML** of *ee*: 99.9% enantiomeric excess can be separated from the mother liquor (**Scheme 11**).

3. Separation of diastereomeric mixtures (recent results)

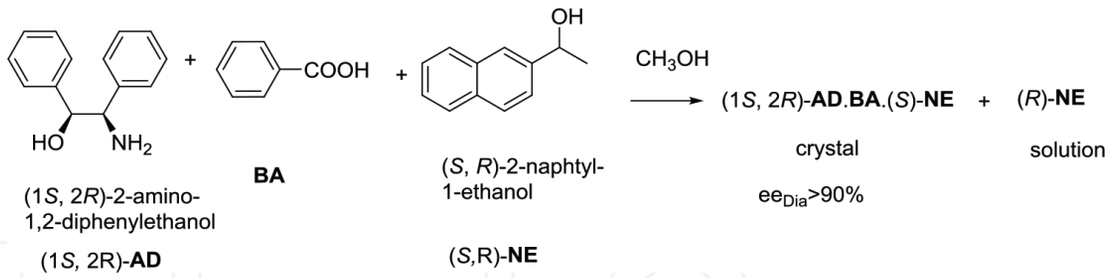
3.1. Chiral salt of helical supramolecular structure as resolving agent (separation of diastereomeric molecular complex)

The salt of a chiral amine of supramolecular helical (double helix) structure and an achiral acid precipitates from the solvent (methanol) containing racemic alcohol as well, in the form of supramolecular helical crystals, which are composed of chiral amine, acid and one enantiomer of the racemic alcohol (**Scheme 12**) [49].

According to Kinbara, the most suitable resolving agent of a racemic molecule can be selected by the design of a stable hydrogen bond system [50]. Saigo et al. concluded after the analysis of several single crystals of pairs of diastereomeric salts, that the formed CH/π interactions play a significant role in the solubility difference of the diastereomers, which clearly influences the chiral recognition and thus the result of the separation [51, 52].

Others estimated well by quantum chemical computations the difference between the lattice energies of the pairs of diastereomeric salts, without preliminary knowledge on the crystal structure [53, 54]. However, it is confessed by the authors that these calculations need to be upgraded in order to be safely applicable in the search of resolving agents.

The conclusions drawn from the preparative results can facilitate the choice of the resolving agent. For example, it is already trivial, that very good separations can be reached with the application of a resolving agent of similar molecular structure (structurally related) to the racemic compound [10, 21, 55–58].



Scheme 12. The salt of chiral base and achiral acid crystallizes with the appropriate enantiomer of racemic alcohol.

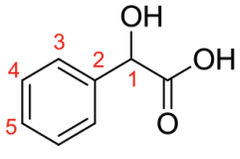
3.2. Ratio of the molecules composing the diastereomer

Another approach construes the importance of the ratio of molecular lengths of the racemic molecule and the resolving agent instead of the structural similarity. According to Sakai, the author of the "space-filler concept," the crystal-lattice of the less soluble diastereomer salt is influenced by the structural properties of the constituents of the salt (i.e., the enantiomer and the resolving agent), such as the molecular size. Sakai et al. investigated the relative molecular length of the racemic molecule and the resolving agent in course of resolutions of 1-aryl-alkyl-amines with 2-hydroxycarboxylic acids and vice versa (**Scheme 13**). Based on the results of 20 resolutions, the best separations of the racemic mixtures can be reached with the application of a resolving agent of similar molecular length [59].

Other researchers considered the longest carbon-chain as the length of a molecule (**Scheme 14**). Based on the average of the results of 21 resolutions (*ee*, F), almost linear correlation was found between the difference of the molecular length of structurally related racemic mixtures and resolving agents, and the result of the resolution (**Schemes 15** and **16**) [10].

Besides the abovementioned 21 resolutions [10], carried out with structurally related resolving agents, the results of 28 additional resolutions [8, 18, 60–74] applying structurally non-related resolving agents were systematized (most of them were industrialized).

Based on the results of 49 resolutions, by plotting the average enantiomeric excess and efficiency of resolution values in function of the difference of molecular length, respectively, the following diagrams are received (**Schemes 17** and **18**). Accordingly, higher enantiomeric excess can be reached in case of higher difference of molecular length of the racemic compound and the resolving agent [75].



Scheme 13. Calculation of molecular length according to Sakai.

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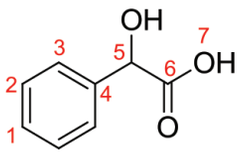
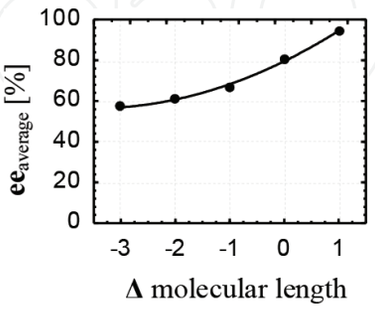
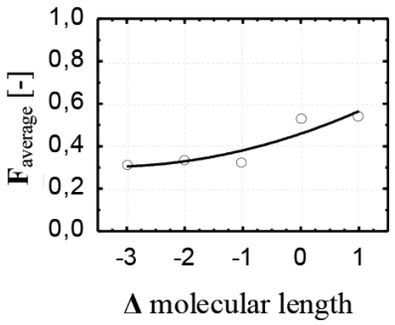


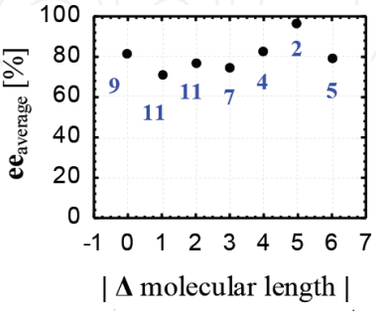
Scheme 14. Calculation method of molecular length used by other researchers.



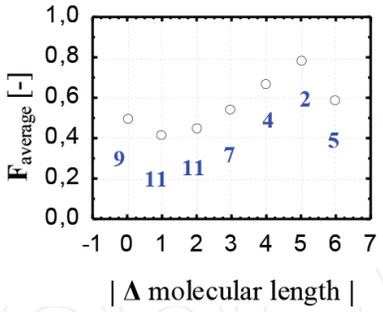
Scheme 15. Average of enantiomeric excess values of enantiomeric mixtures separated from diastereomeric salt in function of the difference of molecular length.



Scheme 16. Average of efficiency of resolution values of enantiomeric mixtures separated from diastereomeric salt in function of the difference of molecular length.



Scheme 17. $ee_{average}$ values of 49 resolutions in function of the difference of molecular lengths (blue numbers represent the number of samples).



Scheme 18. $F_{average}$ values of 49 resolutions in function of the difference of molecular lengths (blue numbers represent the number of samples).

4. Amino acids and their mixtures as resolving agents

4.1. Amino acid resolving agents

1-Aminoindane was successfully resolved with the application of nearly 0.5 equivalent aspartic acid (**Asp**) and the (*R*)-enantiomer was separated (**Scheme 19**) [76].

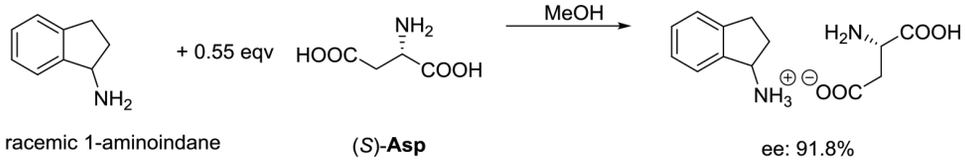
For the resolution of racemic acids basic amino acids were also applied, for example (*S*)-lysine (**Lys**) (**Scheme 20**) [77, 78].

4.2. Mixtures of amino acids as resolving agents

With the application of equivalent amount of (*S*)-**Phe**, (*S,S*)-**AP** and (*S*)-**PG** resolving agents or their mixtures in course of the resolution of racemic mandelic acid (**Scheme 21**), the most effective resolving agent was the (*S*)-**PG**. In the case of resolutions carried out using the mixtures of resolving agents in 1:1 ratio, the most effective combination was the mixture of (*S*)-**Phe** and (*S*)-**PG.**

Among the half-equivalent resolving agents, (*S*)-**Phe** was the most effective, while from the half-equivalent resolving agent combinations, the mixture of (*S*)-**Phe** and (*S,S*)-**AP** was the most effective [8].

The racemic mandelic acid (**MA**) cannot be resolved from water with the application of (*S*)-**Ala**, however, a diastereomeric salt of *ee*: 23% enantiomeric excess was received using (*S*)-**Phe** as resolving agent. Applying mixtures of the two resolving agents in different ratios, (*S*)-**MA** of significantly increased enantiomeric excess could be separated from the precipitated diastereomeric mixture when the resolving agent consisted of 0.35 mol (*S*)-**Phe** and 0.65 mol (*S*)-**Ala** [8]. This is the application of the Dutch resolution method in the case of amino acid mixture resolving agents (**Scheme 22**).



Scheme 19. Resolution of Rasagilin intermediate with (*S*)-aspartic acid.

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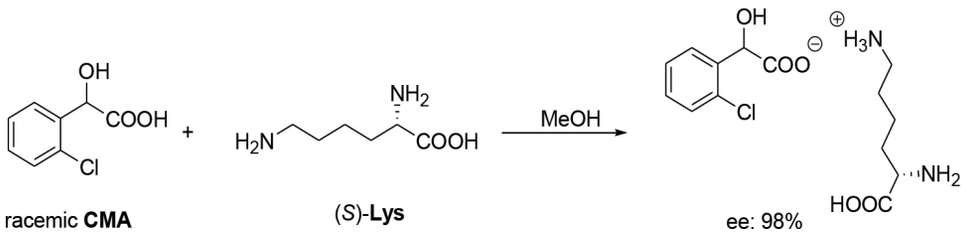
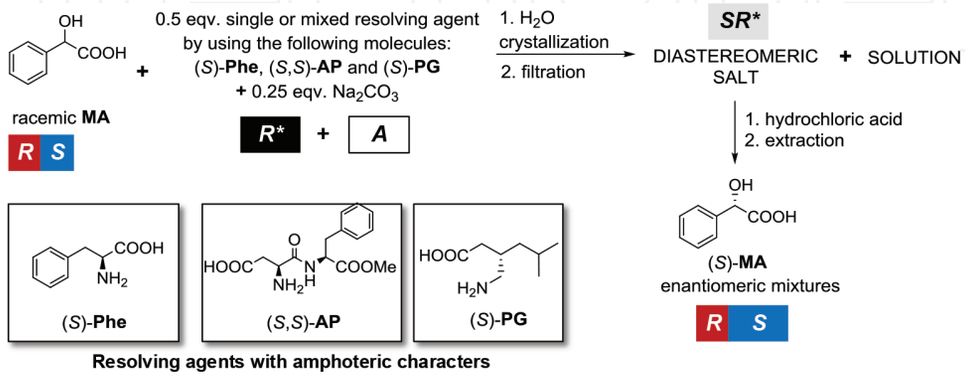
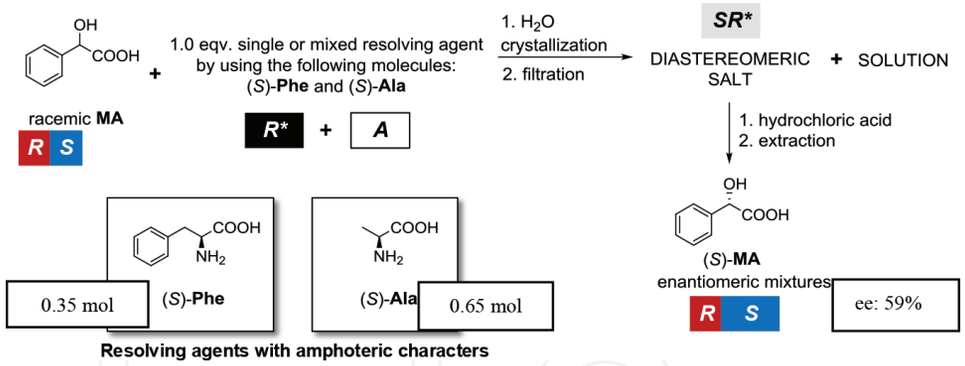


Scheme 20. Resolution of 2-chloro-mandelic acid with (S)-lysine.



Scheme 21. Resolution of mandelic acid with the application of mixtures of resolving agents according to the Pope-Peachey half-equivalent method.

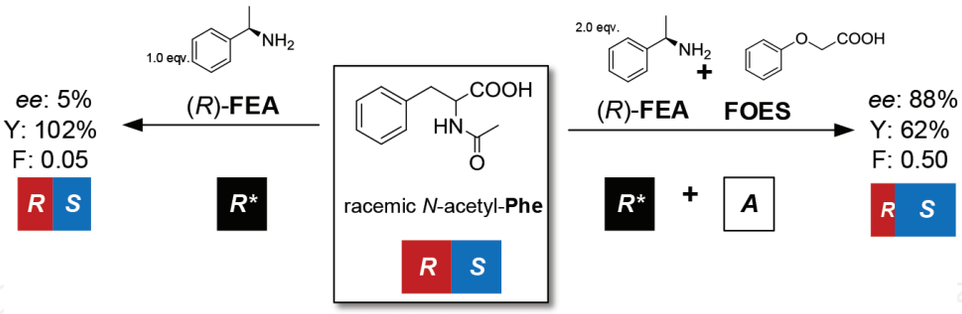


Scheme 22. Resolution of mandelic acid with the mixture of (*S*)-**Phe** and (*S*)-**Ala** resolving agents.

5. Presence, role, and effect on the diastereomer separation of achiral additive

5.1. Achiral additive structurally related to the racemic compound

After the resolution of *N*-acetyl phenylalanine (*N*-acetyl-**Phe**) with 1.0 equivalent (*R*)-1-phenylethylamine ((*R*)-**PhEA**), (*S*)-*N*-acetyl phenylalanine of 5% enantiomer purity could be separated from the diastereomeric salt. However, when equivalent amount of the structurally related phenoxy acetic acid (**PhOAA**) was given to the racemic *N*-acetyl-phenylalanine and this mixture was resolved with 2 equivalents of (*R*)-1-phenylethylamine, (*S*)-*N*-acetyl-phenylalanine of 88% enantiomeric excess was enriched in the diastereomeric salt (**Scheme 23**) [79].



Scheme 23. Resolution of *N*-acetyl-phenylalanine in the presence of phenoxy acetic acid.

5.2. Achiral additive structurally related to the resolving agent

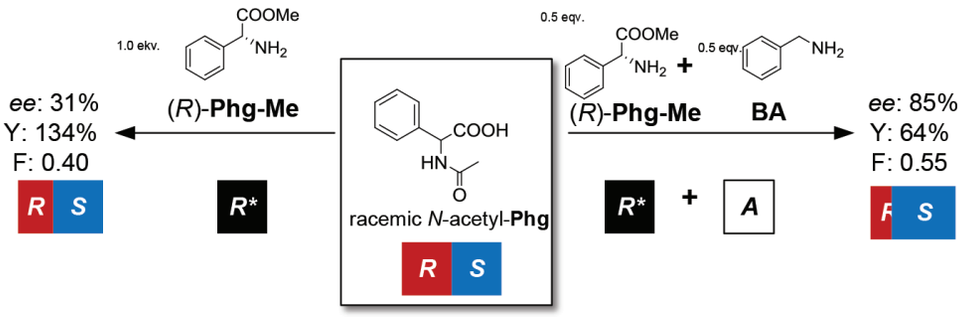
With the application of achiral additives, which are structurally related to the resolving agent, the efficiency of the enantiomer separations was significantly improved.

By changing the half of the phenylglycine methyl ester (**PhG-Me**) enantiomer resolving agent to the structurally related benzylamine (**BA**) in course of the resolution of *N*-acetyl phenylglycine (*N*-Ac-**PhG**), the enantiomer purity of the diastereomer salt of *N*-Ac-**PhG** increased by 54%, compared to the results of the 1 equivalent **PhG-Me** resolving agent (**Scheme 24**). Also in the case of 1-phenyl-ethyl amine (**PhEA**) resolving agent, by exchanging the half of **PhEA** to benzylamine, both the enantiomer purity and the efficiency of resolution values increased [79].

The resolution of racemic ibuprofen (IBU) with (*R*)-1-phenylethylamine ((*R*)-PhEA) and benzylamine (BA) as structurally related achiral additive was investigated. The unreacted enantiomer mixture of IBU was removed by $scCO_2$ extraction from the received diastereomeric salt. The addition of the achiral benzylamine resulted in higher efficiency of resolution (F_{SCS}) values compared to the experiments without additive (**Scheme 25**) [80].

5.3. Additive of similar structure to the polar part of the resolving agent

Racemic 1-phenylethylamine (**PhEA**) was resolved with *N*-glutaryl-1-phenylethylamine (**PhEA-GA**) applying urea and its derivatives and thiourea additives of neutral character, which show structural similarity with a part of the resolving agent. Although the enantiomer purity of the **PhEA** received from the diastereomeric salt decreased (from *ee*: 62% to *ee*: 51–54%), the increased yields led to higher efficiency of resolution values (from F: 0.36 to F: 0.37–0.49) in all cases (**Scheme 26**). The urea was



Scheme 24. Resolution of N-acetyl-phenylglycine with 1-phenylethylamine and with benzylamine as achiral additive.

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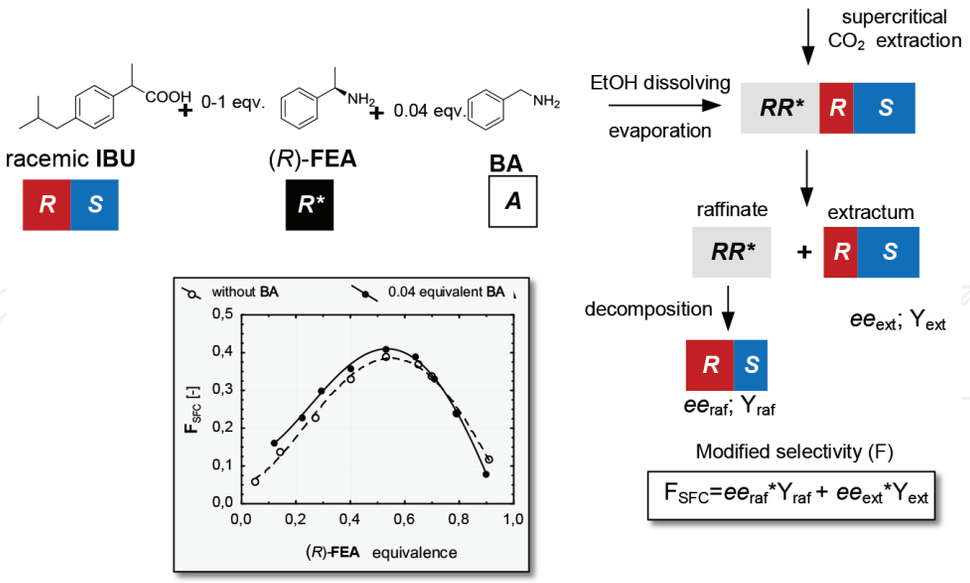
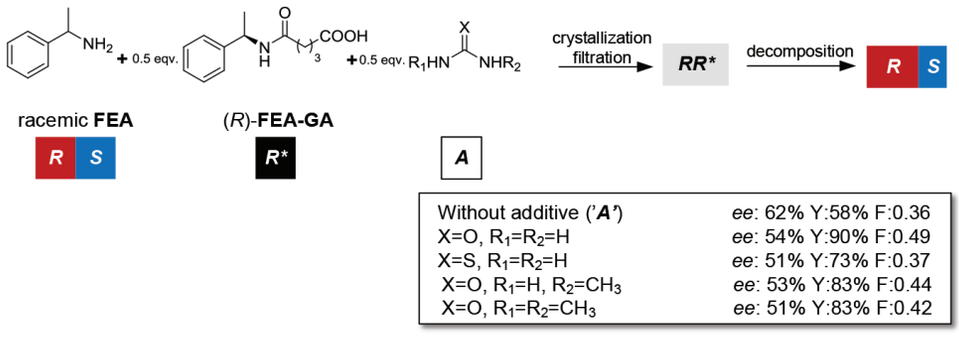
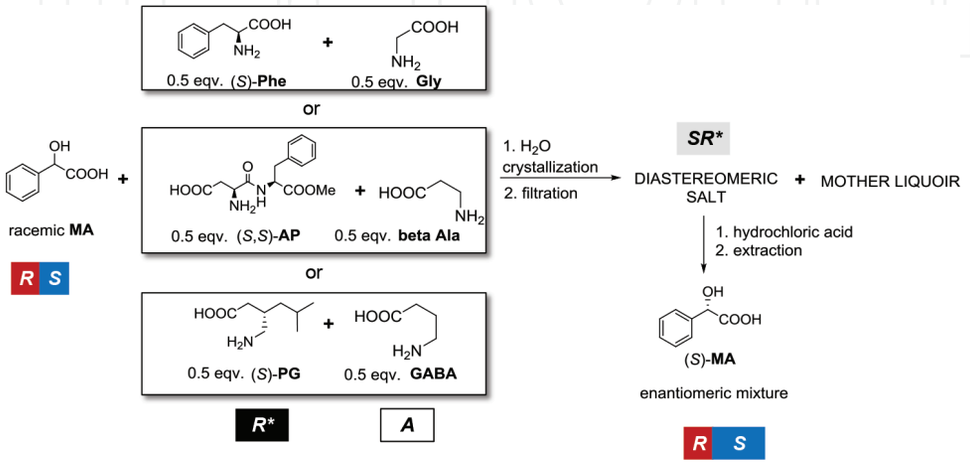


Scheme 25. Effect of benzylamine on the resolution of racemic ibuprofen by $scCO_2$ extraction.

proven to be present in the solid phase; therefore the process of the crystallization was investigated by polarization microscopy. According to the results, the nucleation of the diastereomer salt of (*S*)-**PhEA**·(*R*)-**PhEA-GA** starts on the surface of the initially appearing needle-like urea crystals [81].



Scheme 26. Resolution of racemic 1-phenylethylamine in the presence of urea and its derivatives.



Scheme 27. Resolution of mandelic acid with the application of amphoteric achiral additives.

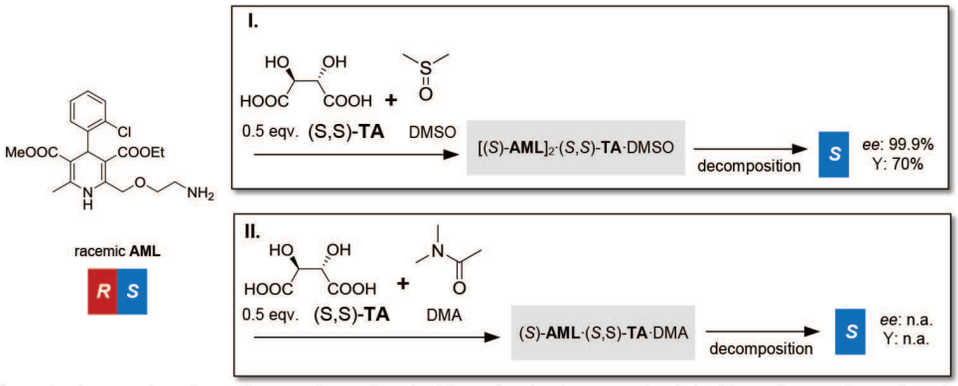
5.4. Application of achiral additives structurally related to amino acids [19]

The resolution of racemic mandelic acid (**MA**) was carried out with mixtures of amphoteric resolving agents and structurally similar achiral compounds in 1:1 ratio, namely with the mixtures of (*S*)-**Phe** and **Gly**, (*S,S*)-**AP** and β-**Ala**, and (*S*)-**PG** and **GABA**, respectively (**Scheme 27**).

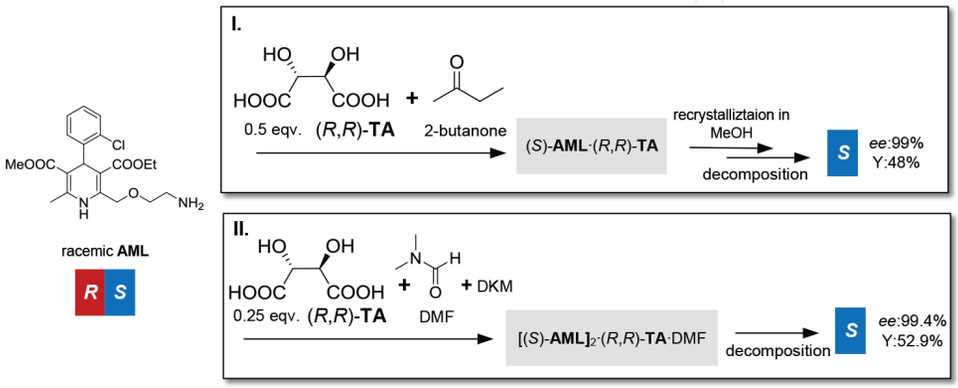
The results were compared to experiments carried out with the application of solely half-equivalent resolving agent. In the case of (*S*)-**Phe**, the addition of achiral glycine resulted in Δ*ee* = 15%, in the case of aspartame ((*S,S*)-**AP**), the achiral β-Ala led to Δ*ee* = 38%; while the combination of (*S*)-pregabalin ((*S*)-**PG**) and γ-aminobutyric acid (**GABA**) led to an increase of Δ*ee* = 9% in enantiomeric purity.

6. Effect of solvate forming solvents and molecules having similar structure on the results of diastereomer separation

In the case of resolution of amlodipine with (*S,S*)-tartaric acid ((*S,S*)-**TA**) from dimethyl-sulfoxide solvent, the dimethyl-sulfoxide solvate of (*S*)-amlodipine-hemi-(*S,S*)-tartrate salt crystallizes with high purity (**Scheme 28I**) [82]. The diastereomer salt enriched in (*S*)-amlodipine precipitates also from *N,N*-dimethylacetamide (**DMA**) solvent (**Scheme 28II**) [83] from 2-butanone solvent, the diastereomer salt of (S)-amlodipine crystallized applying (R,R)-tartaric acid as resolving agent



Scheme 28. Resolutions of amlodipine with (*S,S*)-tartaric acid.



Scheme 29. Resolution of amlodipine with (*R,R*)-tartaric acid.

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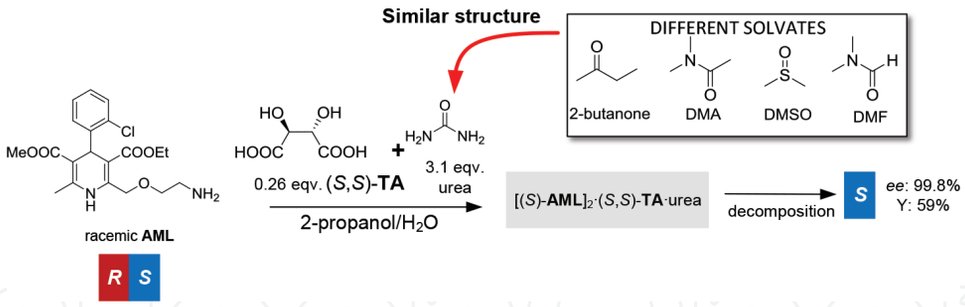

Scheme 30. Resolution of amlodipine with (*S,S*)-tartaric acid in the presence of urea.

(**Scheme 29I**) [84]. From the mixture of N,N-dimethylformamide and cosolvents, the DMF solvate of ((S)-**AML**)$_2$·(R,R)-**TA** crystallized, with high enantiomeric purity (**Scheme 29II**) [85].

With the addition of urea, which has similar structure to the different solvates, to the resolving agent (*S,S*)-tartaric acid, from the mixture of 2-propanol and water enantiopure *S*-amlodipine can be received with good yield (**Scheme 30**) [86]. The reason of the selection of urea as additive is not explained by the inventors, but the structural similarity is easily recognizable, thus this patent can be considered as the first published form of the application of achiral additive having similar structure as the solvate.

7. Conclusion

One of the possibilities for the separation of mixtures of chiral compounds (enantiomers, diastereomers) is their nonlinear distribution between two phases. The phase-distribution depends on the starting mixture, which follows well the curves of the binary and ternary phase diagrams. The equilibrium processes between the supramolecular associates, formed from the chiral molecules, as well as the solubility equilibriums and the catalytic interactions of the formed crystals lead to the phase distribution of the mixtures. Most probably the helical structure of the associates, resulting in another mirror-image relation, determines their phase-distribution.

In the case of enantiomeric mixtures, the macroscopic manifestation of the helical associates is the formation of crystals of helical structure, related to the configuration of the enantiomer in excess. The phase-distribution is determined by the eutectic composition of one of the present chiral molecules through the effects of the solvent and the time-dependence of the phase equilibriums. The equilibriums can be affected by the partial replacement of the chiral compounds by structurally related chiral or achiral molecules.

It has a more beneficial effect, if the molecules composing the diastereomer have different size and bond lengths.

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