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RESEARCH ARTICLE

Regularities between Separations of Enantiomeric and Diastereoisomeric Mixtures. Prediction of the Efficiency of Diastereomeric/ Enantiomeric Separations on the Basis of Behaviour of Enantiomeric Mixtures

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Abstract

The driving force of the formation of the homo- and heterochiral associates in the mixtures of chiral compounds is, probably, the effort of the system to separate the most symmetric associates from the less symmetric ones. A possible way to achieve separation of these associates is the distribution between two phases. Therefore, during the separation of (a certain part) diastereoisomers similar trends can be observed as in course of the distribution of enantiomeric mixtures between two phases, although in the first case a third chiral compound (namely the resolving agent) is present. Of course in this case the formation of symmetrical associate is not so obvious as in case of enantiomeric mixtures. It should be noted that thus the outcome may be modified by the intervention of kinetic control. It can be concluded that the structure of chiral compounds encodes the result of the (optical) resolution.

Keywords

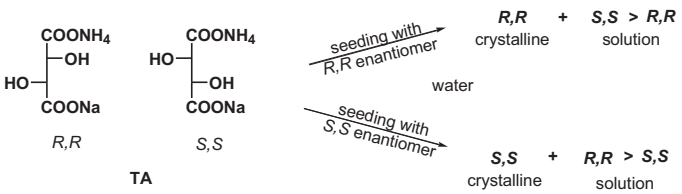
resolution, resolving agents, racemic compounds, eutectic composition, conglomerate- and racemate behaviour, SDE

1 Introduction

In many cases, living organisms contain only one of the two enantiomers of the chiral molecules, but often racemic compounds (1:1 mixture of the two enantiomers) are obtained in the chemical syntheses. The biological activity of the two antipodes may be different or even opposite, so enantiomeric separations are necessary and inevitable.

The resolution methods of racemic mixtures and enantioselective synthetic methods are extensively covered in the literature. [1]

Our statements are based on the fundamental recognition of Pasteur, who has recognized in 1848, that racemic mixtures can be separated into enantiomers by crystallization. [2] He also established that the crystallization can be controlled selectively by adding pure enantiomers into the supersaturated solution of the racemic compound (Scheme 1).



Scheme 1 Separation of enantiomers by induced crystallization

During the separation of racemic compounds, always a mixture of enantiomers is obtained. This enantiomeric mixture can be separated into pure the enantiomer and racemic proportion by further separations (Scheme 2).

$$\mathbf{D}_n \geq \mathbf{L}_m \rightarrow \mathbf{DD}_{n-m} + \mathbf{DL}_m$$

Scheme 2 The general scheme for „Self disproportion of enantiomers" (SDE) [3]

The behavior of enantiomeric mixtures has already been discussed by Rooseboom [4] in 1899, who has established that in case of conglomerates (approximately 20% of the enantiomer mixtures) always the pure enantiomer crystallizes, while in case of racemate type compounds (about 80% of the enantiomer mixtures) [5] the crystalline phase have almost

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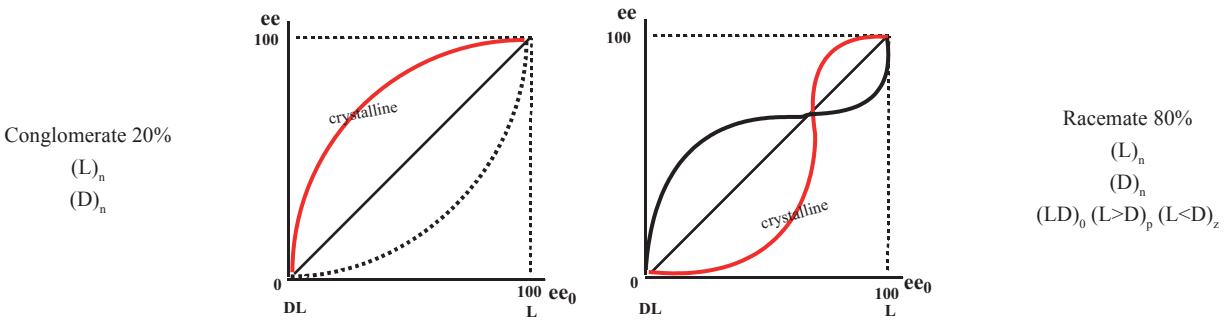
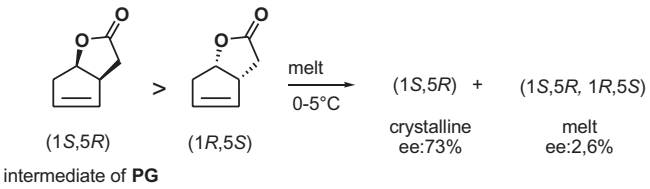
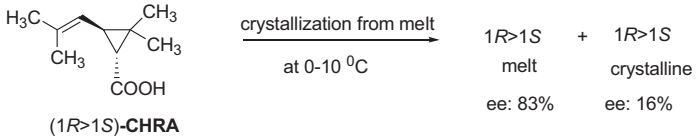


Fig. 1 The ee-ee$_0$ diagrams obtained by preparative separation of enantiomeric mixtures, and the supramolecular associates presumable in solvent



Scheme 3 The separation of enantiomeric mixtures of **PG** intermediates



Scheme 4 The separation of the non-racemic enantiomeric mixture of CHRA by crystallization from melt.

racemic composition when the starting enantiomeric excess of the enantiomeric mixture is below the eutectic composition. The eutectic composition is characterized by the fact that both solid and molten phases contain same ennatiomeric composition. The enantiomeric mixtures having an ee above the eutectic composition behave similarly to the conglomerates.

Our research group utilizes the ee-ee$_0$ diagrams (where ee is the enantiomeric purity of the crystalline phase and ee$_0$ is the initial enantiomeric composition) for the presentation of results (Fig. 1). In this manner not only the distribution between solid-liquid phases, but the distribution between any two phases can be shown.

These diagrams are in good correlation with the corresponding melting point diagrams of conglomerates or racemates. This similarity is expected because the distribution between the solid and the liquid phase is the key in both cases.

2 Separation of enantiomeric mixtures

2.1 Crystallization from melt

In case of conglomerates, enantiomeric enrichment is expected by the separation of theb crystalline phase from the melt of an enatiomeric mixture. The resolution of an intermediate of Prostaglandin (**PG**) is shown on Scheme 3 as an example.

In this case the enantiomeric mixture separated from the mother liquor6 of the resolution contains the enantiomer in excess (1*R*,5*S*)-**PG** that is inadequate to produce Prostaglandins. (Scheme 3). That is why the separation of the unwanted enantiomer and the racemic portion was necessary.

During the crystallization of the enantiomeric mixture of *trans*-chrysanthemic acid (**CHRA**) (racemate behaviour) from melt (Scheme 4), the enantiomer in excess with higher enantiomeric purity than the initial composition remains in the melt and the crystalline phase with a lower *ee* is formed at the same time. [7]

2.1.1 Crystallization from solvent

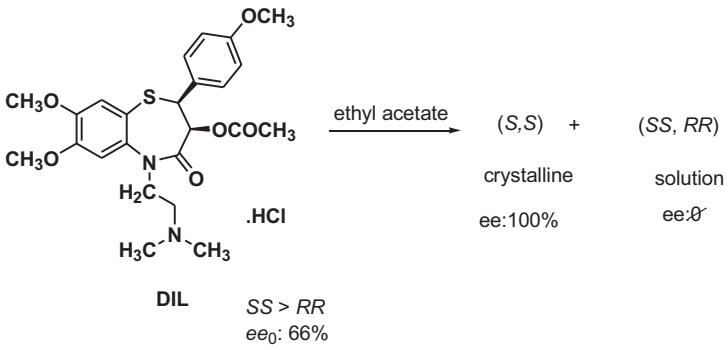
The separation of enantiomeric mixtures can be carried out by crystallization from an adequate solvent. For example, the separation of the non-racemic mixture of Diltiazem hydrochloride (**DIL**) was accomplished by crystallization from ethyl acetate (Scheme 5).

As the Diltiazem hydrochloride (**DIL**) is a conglomerate, the enantiomer in excess with an ee of 100% can be totally recovered from the crystalline phase, and the racemic portion may be separated from the solution.

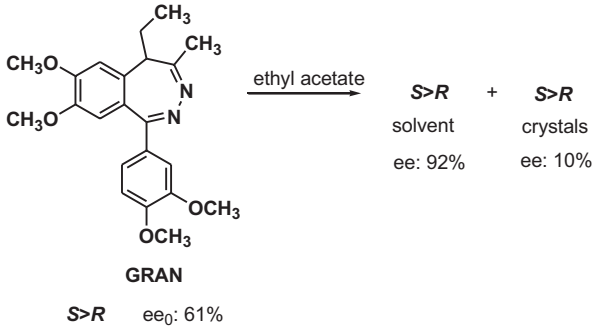
During the recrystallization of enantiomeric mixture (Scheme 6) of the Grandaxine (**GRAN**) from ethyl acetate, [9] the racemic proportion crystallizes and an enantiomeric mixture with a higher ee than the initial composition remains in the mother liquor (racemate behaviour).

2.1.2 Partial precipitation

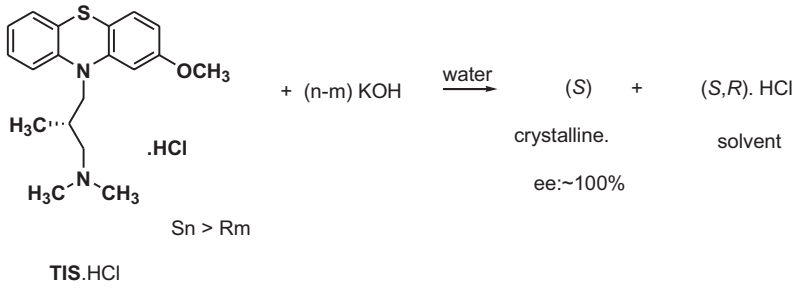
It is well known that solubility differences exist between derivatives of a given compound. This property may be exploited for the separation of enantiomeric mixtures into a more and a less pure fraction during partial precipitation.



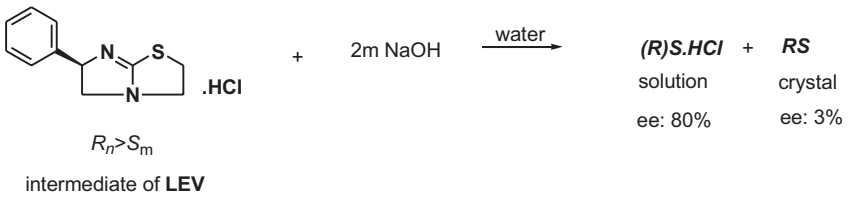
Scheme 5 Separation of non-racemic mixture of **DIL** by recrystallization from the solvent



Scheme 6 Separation of non-racemic enantiomeric mixture of **GRAN** by crystallization from the solvent



Scheme 7 Separation of non-racemic mixture by partial precipitation



Scheme 8 The separation the enantiomeric mixture of LEV by partial precipitation

The enantomeric mixtures of Tisercin hidrochloride (**TIS**-HCl) (Levomepromazine) are water-soluble, but the **TIS** in neutral form is insoluble in water (Scheme 7). If the aqueous solution of KOH is added in equivalent amount to enantiomeric excess, the pure enantiomer crystallizes [10], and the racemic proportion may be recovered from mother liquor (conglomerate behaviour).

The faster reaction of a derivative may also be exploited for separation in case of non-racemic mixtures having racemate behavior.

As it is shown on Scheme 8, the racemic proportion of Levamisole (**LEV**) can be separated by the addition of calculated quantity of NaOH to the aqueous solution of **LEV**.HCl (it is water-insoluble). In this case, the racemic portion crystallized, while the enantiomeric excess of the free base (**LEV** soluble in water) may be precipitated from the mother liquor as the second fraction. [11]

2.2 The effect of the kinetic control during partial precipitation

According to the binary melting point phase diagrams, the *N*-propionyl-phenylalanine (**PPA**) and the *N*-propionyl-phenylglycine (**PPG**) are racemates, but these compounds (**PPA** and **PPG**) behave like conglomerates [12] during partial precipitation (Fig. 2).

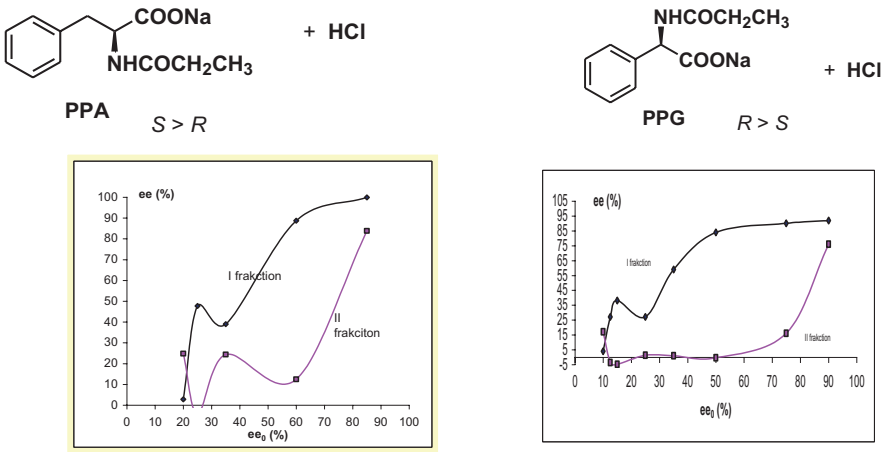
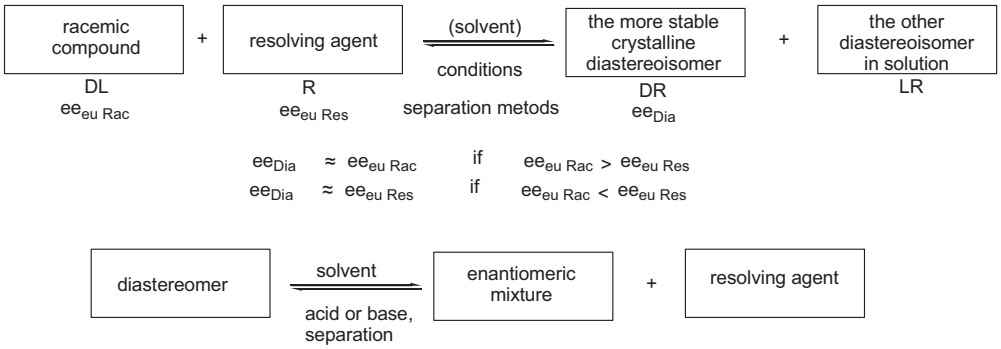
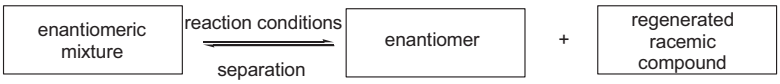


Fig. 2 The separation of **PPA** and **PPG** enantiomeric mixture by partial precipitation



Composition of the salt crystallized during the fractionated precipitation of diastereoisomeric salts and enantiomeric mixtures is determined by the SDE[3] capacity (self disproportion of enantiomers) of the involved chiral compounds.



Scheme 9 General scheme for the preparation of pure enantiomers via the formation of the diastereoisomeric salt (eeeuRac: ee of an enentiomer at the eutectic composition of the racemate; eeEuRes: ee of a resolving agent enantiomer (R or Я) at the eutectic composition; eeDia: ee of an enantiomer of the original racemate at the eutectic composition of the diastereoisomeric salt).

This unusual behavior is underlined by their ee_0-ee diagrams, as well. This phenomena can be explained by kinetic control. Namely, the enantiomer in excess precipitates faster by the addition of hydrochloric acid to the aqueous solutions of the corresponding sodium salts, although the faster crystallization of the racemic proportion was expected.

It means that the kinetic control is also useful for the separation of enantiomeric mixtures.

3 The separation of diastereoisomers

Many methods described in the literature for the separation of enantiomers involve the formation of diastereoisomers followed by liberation of the separated enantiomers. These enantiomeric separation methods are discussed and systematized in several articles. [1c-h, 5,13-16]

In the course of the resolution processes, racemic compounds are reacted with another chiral reagent (resolving agent). The diastereoisomers so obtained are separated, and their decomposition affords the corresponding enantiomeric mixtures. Usually, pure enantiomers can only be obtained by further purification of these enantiomeric mixtures (Scheme 9).

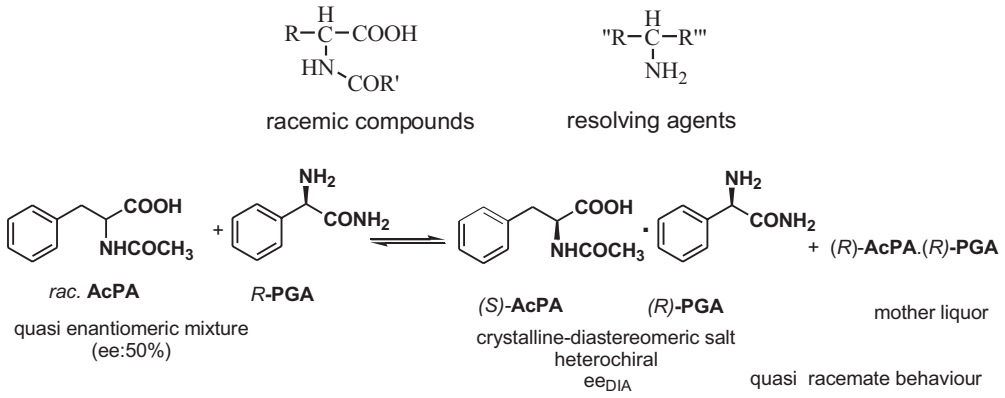
If we want to examine how the phenomena observed at the separation of enantiomeric mixtures (see Chapter 2) affect the distribution of diastereoisomers between two phases, resolving agents with slightly different structure from one of enantiomers should be chosen.

$$\underset{\substack{ee_{mixt}: 50\% \\ \text{quasi-enantiomeric mixture}}}{\mathbf{DL} + 2\mathbf{D}^*} \quad \leftrightarrow \quad \underset{\substack{ee_{DIA} \\ \text{diastereomeric mixture}}}{\mathbf{DD}^*\downarrow} + \quad \mathbf{LD}^*$$

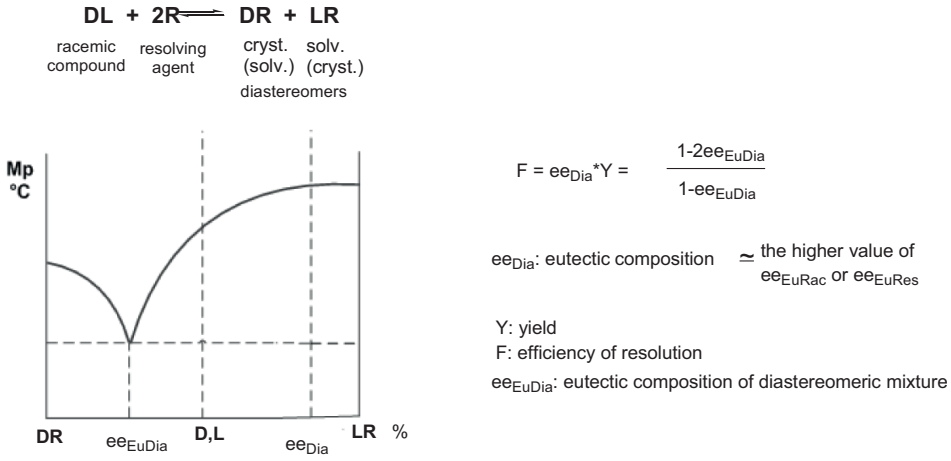
Scheme 10 General scheme for the crystallization of quasi-enantiomers

If the racemic compound is reacted with a derivative of one of the enantiomers having opposite chemical character in equimolar amount, a quasi-enantiomeric mixture is formed with quasi-enatiomeric purity of 50% (Scheme 10). In this case either quasi-racemate or quasi-conglomerate behavior may be expected.

The phenylglicine (**PG**) and phenylalanine (**PA**) were converted to their structurally related resolving agents by the



Scheme 11 Separation of quasi enantiomeric mixtures of **AcPA** and **PGA** by fractionated crystallization.



Scheme 12 A representative melting point/composition diagram of a diastereoisomer. The relation between the eutectic composition of diastereoisomeric mixture and efficiency of resolution.

acylation of the amino group with different carboxylic acids. Then these racemic compounds (acids) were reacted with the derivatives of „structurally related" enantiomers (bases) having opposite chemical character. (Scheme 11).

The enantiomeric purity (the purity of the enantiomeric mixtures isolated from diastereomers) and the yield of the diastereoisomers obtained were measured.

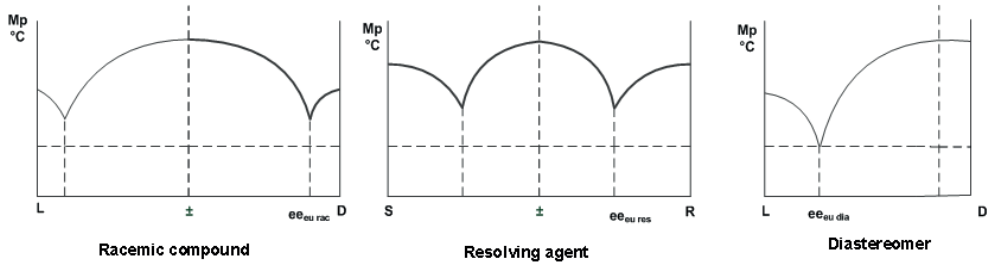
According to this series of experiments, resolutions of racemic compounds with bases having similar structure [17], affords diastereomers with either homo- or heterochiral structure.

The resolution of six racemic compounds using structurally related resolving agent was accomplished. In only one case (essentially 20% of the racemic compounds investigate), namely in case of the *N*-formyl-phenylalanine (**FoPA**), the crystallization of homochiral diastereomer was observed.

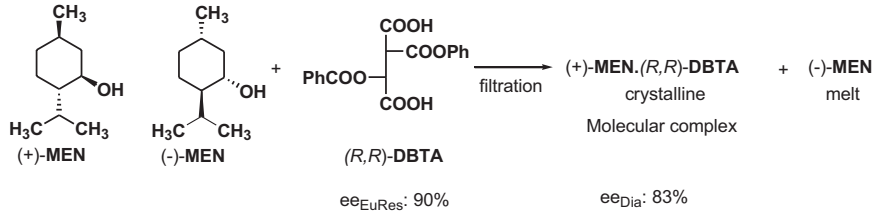
In all other cases the crystalline diastereoismeric salts had heterochiral configurations. Consequently, it is another evidence that the structurally similar compounds show the behavior of quasi-enantiomeric mixtures at the resolution with resolving agent having related molecular structure to them, because either heterochiral or homochiral diastereomers are obtained during the separations by fractional crystallization.

The question was arisen, if the eutectic composition of the racemic compound has an effect on enantiomeric purity of the enantiomeric mixture isolated from the diastereomeric salt formed in the resolution experiments when a resolving agent is used which is not structurally related to the racemic compound. A correlation between the eutectic composition of biner melting point diagrams of diastereoisomeric mixtures (eeEuDia) and efficiency of resolution (F) was established by us (Scheme 12). [18]

Furthermore, it was found by analyzing the results of 45 resolutions, that the average enantiomeric purity (ee_{EuDia} = 78%) of enantiomeric mixtures isolated from crystalline diastereoisomers correlates to the average value of the measured eutectic composition of the starting racemic compounds (ee_{EuRac} = 73%). At the same time, when the eutectic composition of the resolving agent is higher than the eutectic composition of the racemic compound (in 29 cases), a better correlation was observed between the average value of enantiomeric purities (ee_{EuDia} = 80%) of enantiomeric mixtures isolated from the crystalline diastereoisomers and the average value of eutectic compositions of enantiomeric mixtures of the resolving agent (ee_{EuRes} = 78%) (Table 1). [19]



Scheme 13 The affect of eutectic composition of racemic compound and resolving agent on the eutectic composition of diastereoisomers obtained (see also Scheme 12).



Scheme 14 The separation of diastereomers from melt

Table 1 The average ee data of the investigated resolutions

Number of resolutions	$ee_{eu\ Rac}$ (average)%	ee_{euRes} (average) %	ee_{euDia} (average)%	F (average)
45	73	-	78	0.56
29	-	78	80	0.54

Based on these observations, we suppose that the composition of crystalline diastereoisomer is determined either by the eutectic composition of the racemic compound or that of the resolving agent and the higher ee value has the more dominant effect (Scheme 13).

Consequently, a correlation can be found between the binary melting point/composition phase diagram of the diastereoisomeric mixtures and the phase diagrams of the enantiomers which are the constituents of the diastereoisomers.

If we wish to separate the enantiomers of a racemic mixture using structurally related resolving agent (equivalent or half equivalent amount), the enantiomers of the racemic compound are transformed into "quasi enantiomeric mixtures". In the course of the separation of these "quasi enantiomeric mixtures" (of diastereoisomers) the same methods can be used which are suitable methods for the separation of enantiomeric mixtures (also diastereoisomeric related supramolecular enantiomeric associates).[1f]

4 Separation of diastereoisomers

4.1 Separation of diastereoisomers from melt

The mixture of the racemic compounds and the resolving agents can be considered as the mixture of diastereoisomeric supramulecular structures. These diastereomer supramolecular structures exist in solutions and in melts, therefore these diastereoisomeric associates can be separated by crystallization from melt. During these experiments the mixture of the racemic compound and the resolving agent is melted, then the crystalline phase - obtained by controlled cooling - can be separated by filtration (if it is possible).

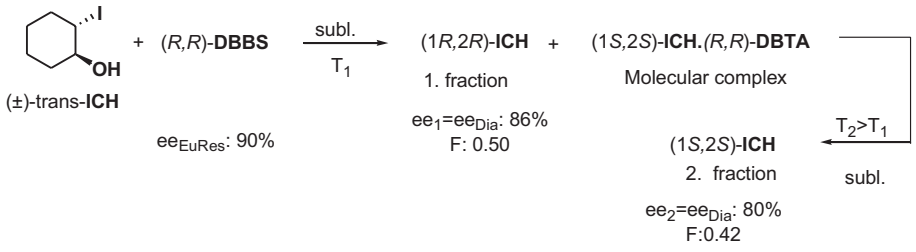
An example for such separation is the crystallization from melt of diastereoisomeric mixture of **MEN-DBTA** molecular complex incorporating menthol (**MEN**) and (*R*,*R*)-dibenzoyl-tartaric acid ((*R*,*R*)-**DBTA**) (Scheme 14). [20]

It can be seen from the above example that the behavior of mixture of the chiral compounds mentioned in the previous Chapters is valid not only for diastereoisomeric salts but for diastereoisomers in general. During the resolution of racemic menthol (**MEN**) with (*R*,*R*)-**DBTA** the molecules forming the diastereoisomeric complex are kept together by weak second order interactions, only. Formation of the more stable molecular complex that crystallizes more quickly makes the separation possible.

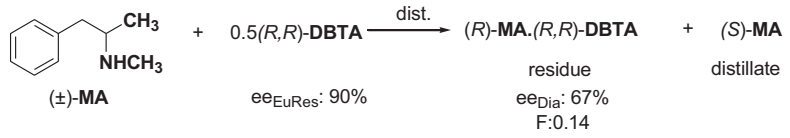
4.2 Separation of diastereoisomers by sublimation of enantiomeric mixtures

Enantiomeric separations can be effectuated even if the mixture of diastereoisomers is obtained in a solid-solid reaction. The reaction of solid 2-iodo-*trans*-cyclohexanol (**ICH**) and solid (*R*,*R*)-**DBTA** for three months is an example for this separation (Scheme 15).

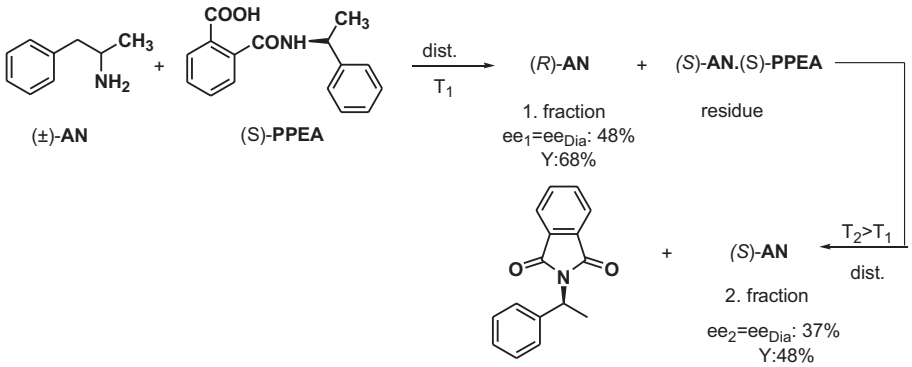
It was observed in the course of the fractionated vacuum sublimation [21] of the above mentioned mixture of compounds, that one of the enantiomers of **ICH** sublimated in the first fraction at relatively low temperature (T_1, Scheme 15). The other **ICH** enantiomer sublimated at higher temperature (T_2),



Scheme 15 The separation of diastereoisomers by fractional vacuum sublimation.



Scheme 16 Separation of diastereoisomers by distillation of enantiomeric mixture.



Scheme 17 Resolution of racemic **AN** *via* fractionated distillation of a mixture of free **AN** and **AN.**(*S*)-**PPEA** diastereoisomeric salt.

after thermal decomposition of the molecular complex formed previously in the solid-solid reaction.

4.3 Separation of diastereoisomers by distillation of enantiomeric mixtures

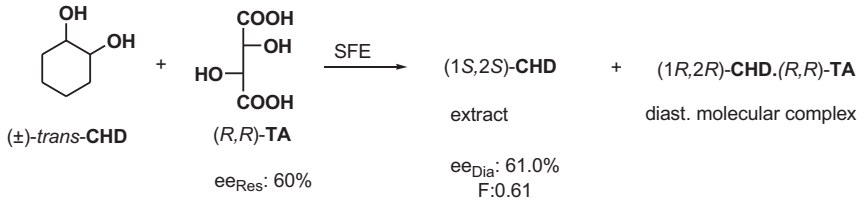
It can be expected in case of resolutions using half equivalent of resolving agent that the enantiomeric proportion of racemic compound may be separated from the corresponding diastereoisomer formed (distributed between two phases). In the reaction of methylanara (2-methylamino-1-phenylpropane, **MA**) and (*R*,*R*)-**DBTA**, after the precipitation of the diastereoisomeric salt, the residual free amin, namely (*S*)-**MA** could be obtained by distillation under vacuum [22], while the other enantiomer was obtained by the separation of the solid diastereoisomer residue (Scheme 16).

4.4 Separation of diastereoisomers by fractionated distillation of enantomeric mixtures

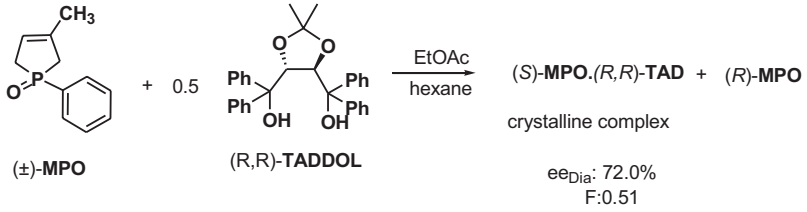
This method is also suitable for fractional separations if the resolving agent forms salt that can decompose without any side reaction. An adequate example for this is the resolution of racemic anara (2-amino-1-phenilpropane, **AN**) by half equivalent of the structurally related (*S*)-*N*-phtaloyl-α-phenylethylamine (**PPEA**) [23] (Scheme 17). Again, the free, optically active base ((*R*)-**AN**) could be distilled off at T_1, then the solid diastereoisomeric salt could decomposed at higher temperature (T_2, by ring closure of phtaloilic derivative), so the other enantiomer of the amine ((*S*)-**AN**) could be distilled off in the second stage.

4.5 Separation of diastereoisomers by extraction of enantomeric mixtures with a supercritical fluid (carbon dioxide)

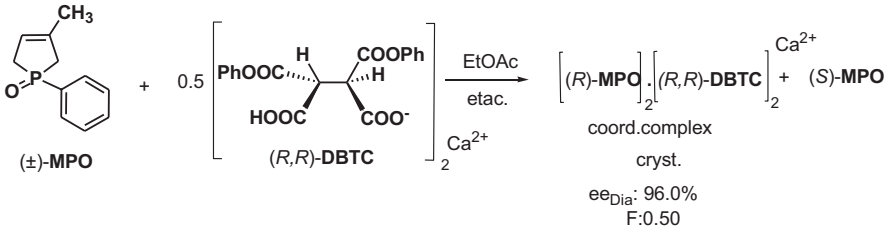
In the course of a half equivalent resolution, the remaining free enantiomer may also be removed by extraction from the reaction mixture after the crystallization of the diastereoisomeric salt. This extraction can be accomplished using supercritical fluid, most often supercritical carbon dioxide. In case of resolution of *trans*-cyclohexane-1,2-diol (*trans*-**CHD**)24 by (*R,R*)-tartaric acid ((*R,R*)-**TA**), the free enantiomeric portion was separated by extraction with supercritical CO_2 from the mixture of the excess of *trans*-**CHD** and the crystalline diastereoisomeric complex (Scheme 18). The other enantiomer can be recovered from the diastereoisomeric complex, as well.



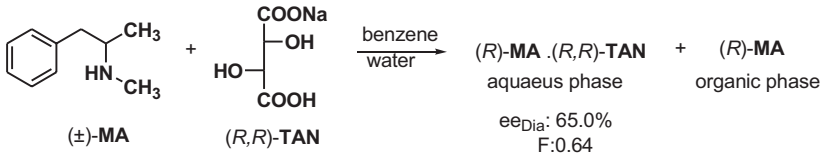
Scheme 18 Separation of enantiomers of the *trans*-**CHD** via molecular complex formation with **TA** followed by supercritical fluid extraction.



Scheme 19 Separation of diastereoisomeric molecular complexes of **MPO** by fractional crystallization



Scheme 20 Resolution **MPO** *via* diastereoisomeric coordination complex formation and fractional crystallization.



Scheme 21 Resolution of MA using two immiscible solvents.

4.6 Separation of diastereoisomeric molecular complexes by fractionated crystallization

The above demonstrated methods can be applied for the separation of enantiomers having asymmetric center on a phosphorous atom. For example, the resolution of several racemic alkyl-, alkoxy-, and aryl-substituted 3-methyl-3-phospholene oxides were accomplished via molecular complex formation with (*R*,*R*)-**TADDOL** (α,α,α′,α′-tetraphenyl-1,3-dioxolan-4,5-dimethanol) as the resolving agent (Scheme 19). If half equivalent of (*R*,*R*)-**TADDOL** was used, the more stable diastereoisomer crystallized which could be isolated by conventional methods, such as filtration. [25]

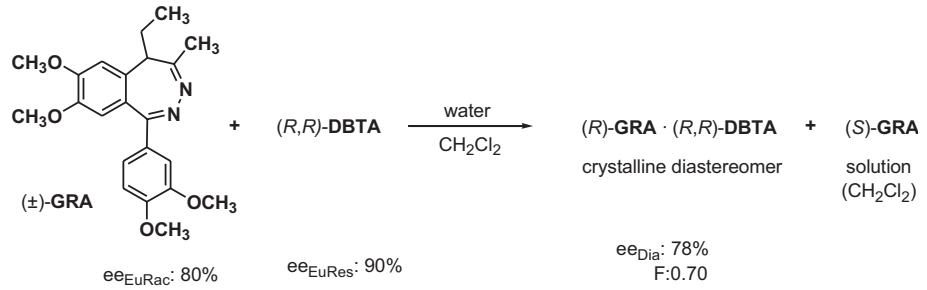
4.7 Separation of diastereoisomeric coordination complexes by fractionated crystallization

In other cases, the cyclic P-chiral 3-phospholene oxides were separated into their enantiomeric mixtures by resolution with the Ca^{2+} or Mg^{2+} salts of **DBTA** (**DBTC**). As it is shown on Scheme 20, when half equivalent of resolving agent was used, the favorable diastereoisomer was precipitated. After filtration and decomplexation of the diastereoisomeric complex, the enantiomeric mixture of the 3-phospholene oxide (**MPO**) was obtained. The antipode of the first isolated **MPO** enantiomer was recovered from the mother liquors of the resolutions. [26] Effectiveness of the method was demonstrated on several other cyclic P-chiral 3-phospholene oxides. [27]

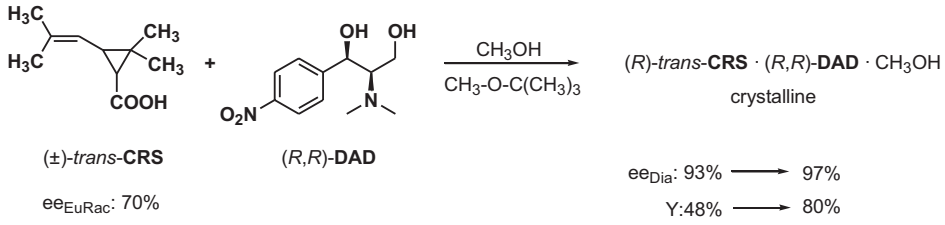
4.8 Separation of diastereoisomers from enantiomeric mixtures using mixtures of two immiscible solvents

Based on the above examples, the formation of solid phase, solid-liquid phases or solid-gas phases systems is always necessary for the separation of diastereoisomers. The question is if chiral separation between two immiscible liquid phases can be achieved. The answer yes, of course. Diastereoisomers may be separated by distribution between two liquid phases.

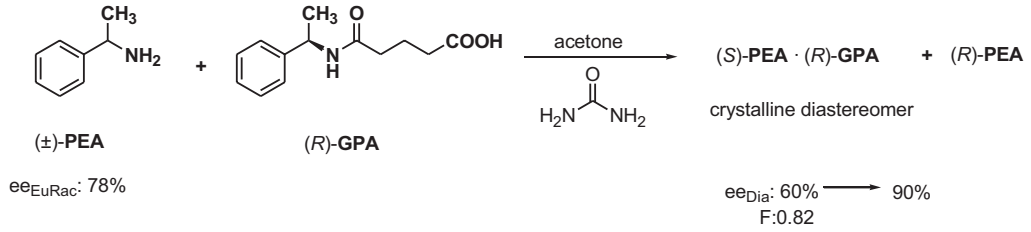
If the racemic methylanara (**MA**) is reacted with half equivalent of sodium salt of (*R*,*R*)-tartaric acid ((*R*,*R*)-**TAN**) in a mixture of water and benzene (Scheme 21), the enantiomer and diastereoisomer distributed between the two liquid phases. [28]



Scheme 22 The separation of diastereoisomers by crystallization from immiscible solvents



Scheme 23 Separation of diastereoisomers by crystallization involving the formation of solvates



Scheme 24 Separation of diastereoisomers by crystallization involving the formation of solvates

The aqueous phase contains the neutral salt of **TAN-MA**, while the other enantiomer can be found in the organic layer. So the separation of diastereoisomers or enantiomers can be accomplished without crystallization, using two immiscible solvents. The two solvent phases can also provide particularly good separation if the diastereoisomer can crystallize due to its insolubility in the two solvents applied.

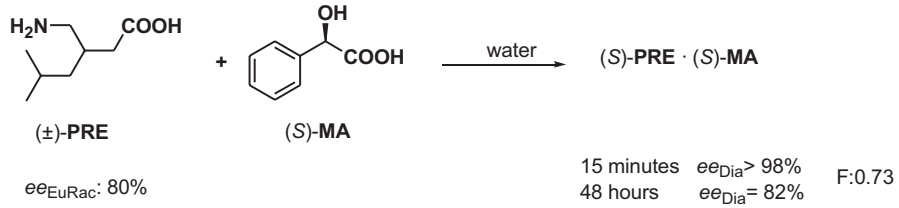
The resolution of racemic Grandaxine (**GRA**) with half equivalent of **DBTA** in mixture of water and chloroform, or water and dichloromethane is an example for the separation of diastereoisomers by crystallization from two immiscible solvents. [29] The crystallization started on the boundary of solvent phases, then it is accelerated. The diastereoisomeric salt formed was filtrated, and the two phases were separated. The enantiomeric mixture containing one of the enantiomers in excess was obtained from diastereoisomeric salt, while the other enantiomer was recovered in neutral form from the organic phase. In addition, a small amount of **GRA** with racemic composition was isolated from the aqueous solution (Scheme 22). Form the ee data shown in Scheme 22. One can conclude that in this case, the eutectic composition of the racemic compound governed the efficiency of separation.

4.9 Separation of diastereoisomers by crystallization involving the formation of solvates

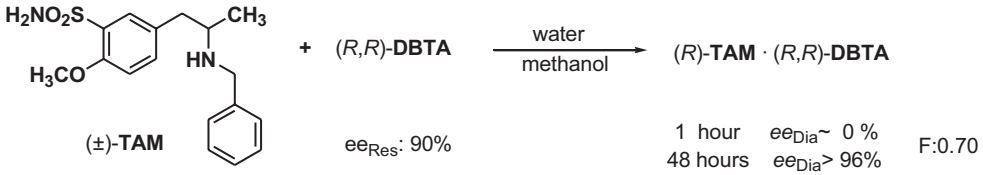
It is very common during the separation of diastereoisomers, that the enantiomeric purity and yield of separation is increased when solvates were formed during the crystallization of the diastereoisomers. For example, if *trans*-chrysanthemic acid (**CRS**) is resolved with *N,N*-dimethyl-aminodiol (obtained by the transformation of an intermediate of chloramphenicol) in methanol, a methanol solvate of the diastereoisomer could be isolated in very good diastereoisomeric purity, but the yield was 52%, only (Scheme 23). Whereas the resolution was accomplished in diisopropyl ether, or methyl-isobutyl ether in the presence of methanol, the methanol solvate of the diastereoisomer crystallized, but both the purity and the yield increased significantly. [30]

4.10 Separation of diastereoisomers by crystallization in the presence of a structurally related achiral reagent

Frequently, the resolution can be accomplished only via solvation. In the previous example the resolution could be carried out using another solvent. When the racemic α-phenylethylamine (**PEA**) was resolved using half equivalent of a derivative of



Scheme 25 The affect of kinetic control on the separation of diastereoisomers



Scheme 26 The effect of thermodynamic contol on the separation of diastereoisomers

a **PEA** enantiomer, a diastereoisomer was isolated which contained (*S*)-**PEA** in 60% excess in acetone (Scheme 24). [31] When an achiral compound (such as urea) with related structure to one part of the resolving agent was added to the solution before crystallization, much purer diastereoisomer was isolated with an (*S*)-**PEA** enantiomer excess of 90%.

So the achiral solvate forming reagent - which is structurally related to either the resolving agent or the racemic compound – promoted the crystallization of diastreomer, and increased enantiomeric excess of the diasteromer.

4.11 Crystallization of diastereoisomers based on kinetic and thermodynamic control

The decisive role of kinetic and thermodynamic control may be observed in the separation of enantiomeric mixtures. This phenomenon can also be found at both the separation of quasi-enantiomeric mixtures and conventional resolutions. [32,33] For example, the effect of kinetic control was observed in the resolution of Pregabalin (**PRE**) with mandelic aid [(*S*)-**MA**] (Scheme 25). When the crystalline diastereoisomeric salt was isolated after 15 minutes crystallization, enantiomeric excess of (*S*)-**PRE** isolated from the salt was 98%, while the ee decreased significantly if the crystallization was carried out over 48 hours.

It means that the thermodynamic control has a disadvantageous effect on this process.

The same phenomenon was observed in the course of the reciprocal process, when racemic **MA** was resolved by (*S*)-**PRE**. Namely, crystallization of the diastereoisomeric salt was controlled kinetically.

In other cases, it is necessary to wait until thermodynamic equilibrium, because in these cases the process is controlled thermodynamically. An adequate example is the resolution of an intermediate of Tamsulosin (**TAM**) with (*R,R*)-**DBTA** (Scheme 26). In this case, the diastereoisomeric salt contained the (*R*)-**TAM** enantiomer in excess. However, after an hour crystallization, practically racemic **TAM** was found in the salt, but excellent enantiomeric excess could be achieved when the diastereoisomer was crystallized for 48 hours. [34]

5 Conclusion

The above mentioned examples demonstrate that the properties of the enantiomeric mixtures determine the enantiomer (diastereoisomer) distribution between two phases and the behavior of the chiral compounds used determine the efficiency of the process during enantiomer or diastereoisomer separations in this way. There are numerous methods of choice (solid-solid, solid-liquid, solid-gas, liquid-liquid distributions) and the most favourable method should be chosen (if there are more possibilities).

We have recognized that in the resolution processes, the diastereoisomers behave similarly to their constituent enantiomeric mixtures, if the resolving agent was structurally related to the racemic compound.

We demostrated that the eutectic composition of the racemate and/or the resolving agent determines the composition of the (crystalline) diastereoisomers formed even if the chiral compounds forming diastereoisomer are not structurally similar. Comparison of the average ee values of the obtained enantiomeric mixtures from series of resolutions with the average eutectic compositions of the involved chiral compounds (racemate and resolving agent) confirmed the above observation, namely the higher eutectic composition governs the enantiomer separation (Table 2).

Table 2 The average ee data of the examined resolutions

Nr. of experiments	average value of ee_{EuRac}/ee_{EuRes} [b]	average value of ee_{Dia} [b]	average value of F
13 (10[a])	80%	78%	0.58

[a] the used compounds are not structurally related

[b] eee_{uRac}: ee of an enentiomer at the eutectic composition of the racemate; ee_{EuRes}: ee of a resolving agent enantiomer (R or Я) at the eutectic composition; ee_{Dia}: ee of an enantiomer of the original racemate at the eutectic composition of the diastereoisomeric salt.

We also think that the eutectic composition of the enantiomers forming diastereoisomer determines the efficiency of the resolutions in cases of crystalline diastereoisomeric salt, molecular- or coordination complex formations and these governing effects are valid when the separation is based on the distribution between two liquid phases.

On the bases of all this we can conclude that the structure of chiral compounds encodes the results of the (optical) resolutions.

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