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Separation of Mixtures of Chiral Compounds by their Distribution between Different Phases

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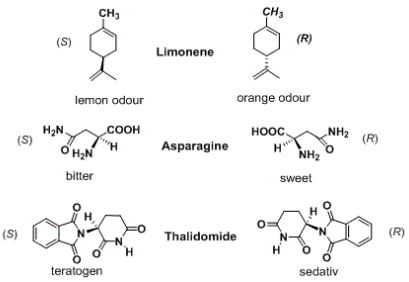
Abstract

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. The preparation of pure enantiomers due resolution is based on the formation of homo- and heterochiral supramolecular associations in the solutions of mixtures of chiral compounds. According to their self-disproportionation (SDE) [1] these are distributed between phases. In this paper some methods are described, which were developed by our research group for the separation of enantiomeric and diastereomeric mixtures. The examples are mainly based on the long experience of our research group in the resolution of industrially important molecules. A presumable mechanism is also presented, which assume that the distribution follows the equilibrium of homo- and heterochiral double helical structures formed due the interactions.

Keywords: Resolution; Diastereomeric mixture; Enantiomeric mixture; Supramolecular associates; Helical structure; Eutectic composition; Double helix

Introduction

The function of living organisms is determined by the behaviour of chiral compounds and their reactions. Not only the RNA and DNA influence this function, but the enantiomers of amino acids and sugars also have a dominant role. So, it is not surprising that an increasing number of drugs contain single enantiomers, which are often prepared by resolution of racemic compounds obtained due of chemical syntheses. The therapeutical effect of enantiomers can be different (Scheme 1) and it is not rare that these effects are opposite.



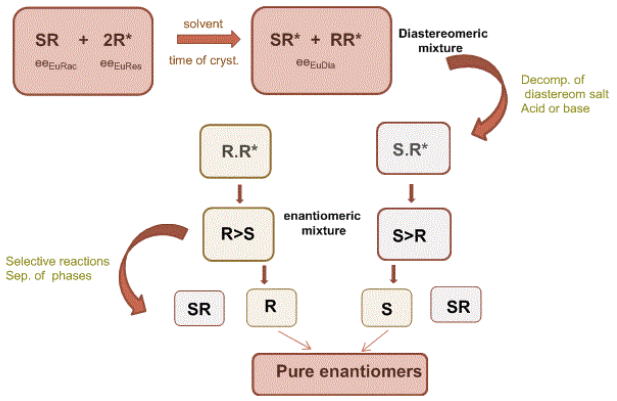
Scheme 1: The different properties of enantiomers.

A tragic reminder of the importance of chirality is thalidomide, in the early 1960s. So, the enantiomeric separations are necessary and inevitable and the demand for pure enantiomers becomes higher and higher [1].

Materials and Methods

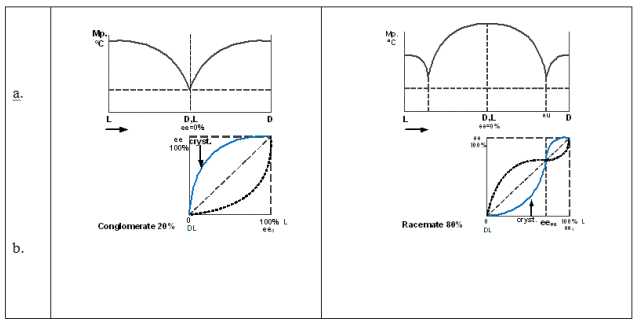
The resolution remains the most common and economical method for preparation of pure enantiomers, even though several new methods and selective syntheses are known. In this case, to the racemic compound obtained in the chemical syntheses, an other chiral compound, the so called resolving agent is added. In the solution diastereomeric salts are formed, and these will be distributed between two phases according to their self-disproportionation. So they can be separated from each other. The diastereomeric salts will be decomposed by adding an adequate acid or base. Due to the self-disproportionation of enantiomers, after the distribution between two phases, the pure enantiomer can be separated from the racemic portion by an adequate method from the enantiomeric mixture obtained in one of the phases (Scheme 2).

The stoichiometry of diastereomeric salt is determined by the properties of starting materials, but the distribution between phases can be influenced by the applied solvent, by the crystallization time, by using ultrasound irradiation, by the pH value of the solution. In this case the separation of enantiomeric mixtures is based on the exploitation of the distribution of hetero- and homochiral associates between two phases (most often between solid and liquid or vapour phases) [2].



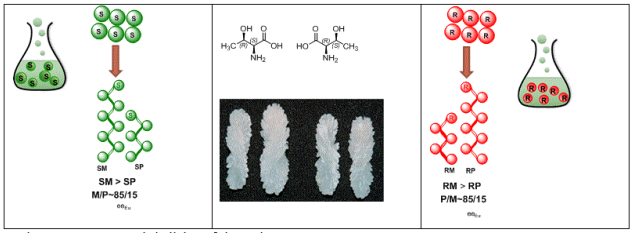
Scheme 2: General scheme of the resolution processes. Separation of pure enantiomers (S or R).

The distribution of enantiomeric and diastereomeric mixtures between phases depends on their self-disproportionation [3]. This is a defining characteristic for each mixture. The enantiomeric ratio received during crystallization depends on the enantiomer ratio of the starting mixture; however, this correlation is not linear. This non-linear correlation can be observed both on the melting point diagrams (Scheme 3a) [4] and purification curves (Scheme 3b) as well [5,6].



Scheme 3: Non-linear behaviour of conglomerates and racemates appearing on melting point diagrams (a) and purification curves (b).

It is assumed that in the solutions of enantiomeric mixtures homo- and heterochiral supramolecular associations are formed, having M and P helicity [7]. In this case, one of the enantiomers will be mainly M helical, while the other one will have P helicity. But to some extent, determined by their eutectic composition, both enantiomers are present also in the other helical structure. This was also confirmed by Videma when these helical structures were appeared macroscopically at the crystallization of threonine (Scheme 4) [8].



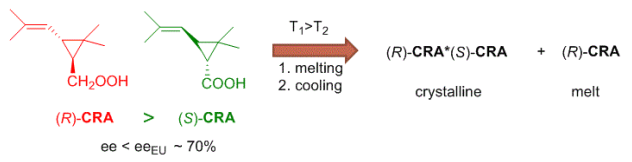
Scheme 4: Macroscopic helicity of threonine aggregates.

The distribution between phases is determined by the self-disproportionation (SDE) of enantiomers, that of helical structured supramolecular associations and their interactions in the solution are controlled by the eutectic composition.

Results and Discussion

Separation of enantiomeric mixtures by crystallization from melt

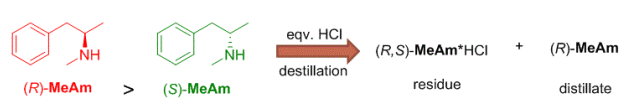
In the case of resolution of chrysanthemic acid (CRA), the enantiomeric mixture (R-CRA>S-CRA) obtained does not reach the eutectic composition ($ee<ee_{EuRac}$~70%). From the melted enantiomeric mixture part of the racemic fraction crystallized off, while the R-CRA enantiomer remained in the mother liquor (melt) (Scheme 5) [9].



Scheme 5: Separation of enantiomeric mixtures of chrysanthemic acid by crystallization from melt.

Separation of enantiomeric mixtures by distillation

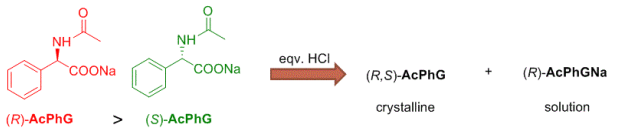
When the racemic portion of the enantiomeric mixture is converted to a salt, the enantiomeric excess can be distilled off [10]. For example, from the methyl anara (MAn) enantiomeric mixture (which is an intermediate of Jumex) when R-MAn>S-MAn, the excess R-MAn can be distilled off from beside of the hydrochloric acid salt of the racemic fraction (Scheme 6).



Scheme 6: Separation of enantiomeric mixtures by distillation.

Separation of enantiomeric mixtures by fractional precipitation

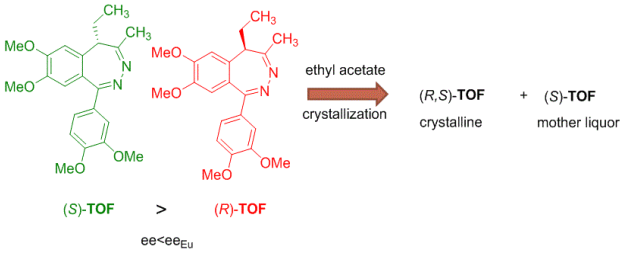
In case of enantiomeric mixture of Na salt of acetylphenylglycine (AcPhG), when the R-AcPhG>S-AcPhG, to the neutral (NaOH) aqueous solution of AcPhG HCl is added in equimolar amount to the racemic portion. In this case the hydrochloric salt of the racemic part ((R,S)-AcPhG.HCl) will be precipitated while the excess of R-AcPhG remains in the mother liquor (Scheme 7) [11].



Scheme 7: Separation of enantiomeric mixtures by fractional precipitation.

Separation of enantiomeric mixtures by recrystallization

The most common method for separation of enantiomeric mixtures is the recrystallization. For example, in the case of enantiomeric mixtures of Tofizopam (ee<eeEu), by the recrystallization of this enantiomeric mixture from ethyl acetate (Scheme 8) the composition of the crystalline phase approximated the racemic composition while the mother liquor enriched in the pure enantiomer [12].



Scheme 8: Separation of enantiomeric mixtures by recrystallization.

Distribution of diastereomeric mixtures

The diastereomeric mixtures behave similar to the enantiomeric mixtures, so for their separation (distribution between phases) similar methods can be used as in case of enantiomeric mixtures.

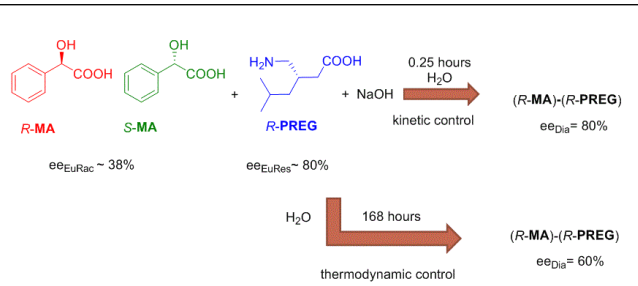
The effect of crystallization time on the distribution of diastereomeric salts between two phases

If the applied resolving agent is structurally similar to the racemic compound, the diastereomeric salts obtained due the resolution process can be considered as a quasi-enantiomeric mixture. In this case the influence of eutectic composition of both starting materials is observed on the resolution process, on the results of the separation.

When the racemic FoPhA (formyl-phenylalanine) is reacted with R-PhGMe (R-phenylglycine-methyl-ester), the eutectic composition of the racemic compound (eeEu~70%) also appears in the diastereomeric salt (ee_{Dia}~72%). In this case the quasi-enantiomer crystallizes and the composition of the crystalline diastereomeric salt correlate well to the eutectic composition of racemic compound (ee_{Dia}~ee_{EuRac}) (Scheme 9) [13].

Scheme 9: Effect of eutectic composition using structurally similar compounds.

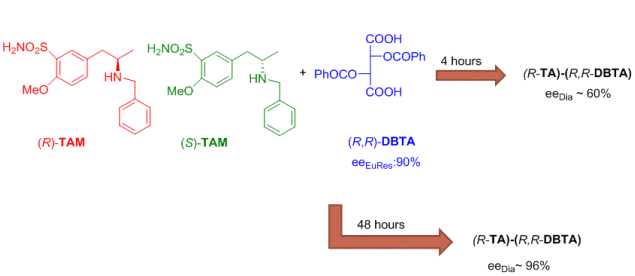
The influence of eeEu of starting materials was also recognized when the starting materials were structurally non related. Depending on the conditions, the resolving agent (with its M and P helicity) can enforce its code as well (ee_{Dia}~ee_{EuRes}). At the same time, it has been recognized that it can be advantageous to explore the effect of the crystallization time on the ee_{Dia} in case of crystalline diastereomeric salts. When the racemic mandelic acid (MA) is resolved with R-pregabalin (R-Preg), the kinetic control (short crystallization time) upon precipitation of the diastereomer gives the most favourable ee_{Dia} value (ee_{Dia}~ee_{EuRes}) (Scheme 10) [14].



Scheme 10: Effect ee_{Eu} at kinetic and thermodynamic control.

During the thermodynamic control, the eutectic composition of the racemic compound impairs the resolution (ee_{Dia}~ee_{EuRac}).

In other cases, however, the most favourable result is achieved by the application of thermodynamic control. For example, during the resolution of Tamsulosin intermediate (TAM), crystallized with RR-DBTA from a water-methanol solvent, ee_{Dia} is~60% over 4 hours but this result was improved (ee_{Dia}~96%) after 48 hours of crystallization (Scheme 11) [15].

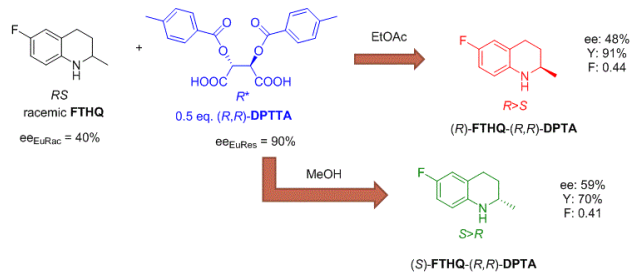


Scheme 11: Effect of thermodynamic control.

Effect of the applied solvent on the separation of diastereomeric mixtures

Not only the time of crystallization influences the result of the resolutions but the applied solvent may also have a great influence. If the crystallization of the diastereomers is carried out with identical crystallization time but from different solvents, the stoichiometry of the diastereomers obtained in the crystalline precipitate may be reversed [16].

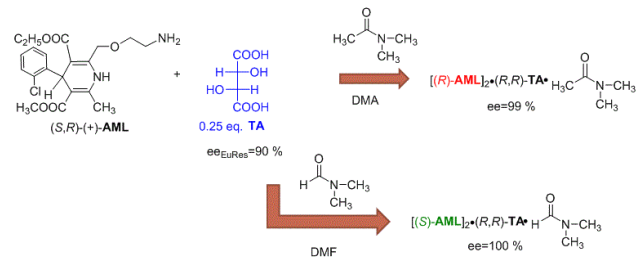
It was observed that the eutectic composition of the racemic compound determines the composition of the diastereomer in both solvents (Scheme 12).



Scheme 12: Effect of the applied solvent.

The effect of the solvent on the composition of the diastereomer can also be manifested by formation of a solvate [17].

For example, if the racemic amlodipine (AML) is resolved with tartaric acid (R-TA) in dimethylacetamide (DMA) then the neutral TA salt of the R-AML is precipitated, but in dimethylformamide (DMF) the S-AML can be separated from neutral TA salt DMF solvate. The high purity of the enantiomers can be attributed to the effect of the eutectic composition of resolving agent (TA). (ee$_{Dia}$~99%) (Scheme 13) [18,19].

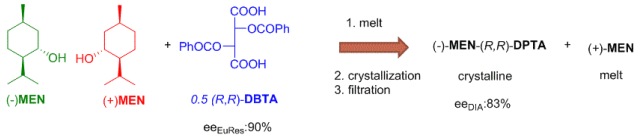


Scheme 13: Effect of the applied solvent by solvate formation.

Separation of diastereomers by crystallization from melt

Similarly to what has been seen for enantiomeric mixtures, separation of diastereomeric mixtures can be accomplished by melt crystallization.

The more stable diastereomer may be crystallized, if desired, by melting the racemic compound with a 0.5 molar equivalent resolving agent, then crystallizing and separating the two phases by filtration. For example, by reacting the racemic menthol (MEN) with 0.5 mole of dibenzoyl tartaric acid (RR-DBTA), the (-)-menthol crystallizes from the melt as molecule complex ((-)-MEN-(R,R)-DBTA) and it can be separated by filtration (Scheme 14) [20].

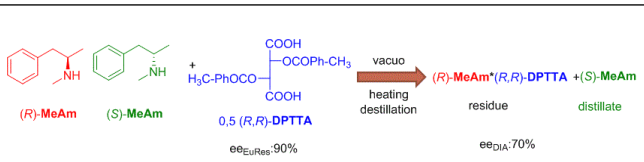


Scheme 14: Example for separation of diastereomeric mixtures by crystallization from melt.

Separation of diastereomers by distillation

In the case of suitable reagents, if the racemic compounds are reacted with 0.5 moles of resolving agent, the free enantiomer can be distilled off from the mixture [21].

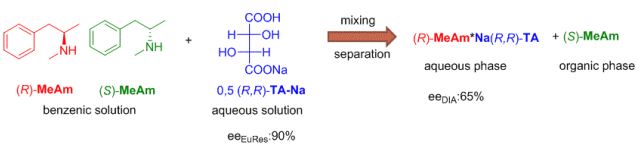
If the mixture obtained by reacting 0.50 mole DPTTA with ((R)-N-methyl-1-phenylpropan-2-amine (MAn) (the intermediate of Jumex) is distilled in vacuum, from the distillate the (S)-MA will be obtained while from the residue, containing the (R)-MA-(R, R)-DPTTA salt, the (R)-MA can be obtained with an enantiomeric excess of 70% (ee$_{Dia}$~70%) (Scheme 15).



Scheme 15: Example for separation of diastereomeric mixtures by distillation.

Separation of diastereomers without crystallization

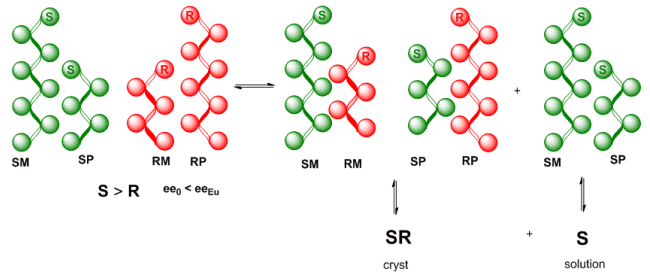
Separation of the mixture of diastereomers can also be carried out without crystallization using at least two immiscible solvents. For example, when 0.5 mole mono-sodium salt of (R,R)-TA dissolved in water is added to the benzenic solution of racemic intermediate of Jumex (MAm), after proper mixing, the aqueous phase contains the (R,R)-TA-Na-(R)-MAm, while the (S)-MAm will be isolated from the benzenic phase (Scheme 16) [22].



Scheme 16: Example for separation of diastereomeric mixture without crystallization.

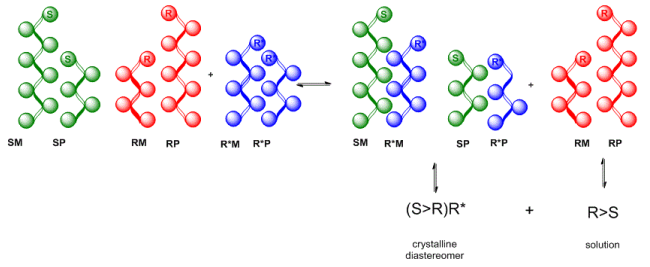
As a conclusion, at the separation of an enantiomeric mixture of a composition above eeEu, the enantiomeric excess crystallizes, while from a composition below the eutectic value, the racemic fraction will be obtained. Based on the observations introduced above, we presume

that at the separation of non-racemic mixtures, when the starting composition is lower than the eutectic composition (ee0<eeEu) and S>R, the crystallization follows the equilibrium of double helixes formed from the assumed supramolecular associations (Scheme 17) [23]. In order to the separation take place, the associates are formed already in the solution.



Scheme 17: Presumable mechanism for distribution of enantiomeric mixtures between phases which follows the equilibrium of double helixes formed.

At the same time, when the racemic compound is reacted with the resolving agent, the M and P helical structures of the corresponding enantiomers are reacted with the M and P helical structures of the resolving agent (R*). If the resolving agent's code is the dominant, the resolving agent reacts by its MR* and PR* ratio. In this case the crystallization also follows the equilibrium of the double helixes formed from the assumed supramolecular associations in the solutions of racemic compound (SR) and resolving agent (R*) if $ee_{DIA}>ee_{Res}$ (Scheme 18) [24].



Scheme 18: Presumable mechanism for distribution of diastereomeric mixtures between phases which follows the equilibrium of double helixes formed.

Conclusion

During the resolution processes the enantiomers tend to form a more stable, more symmetrical conformation, according to their own code. In course of interactions they tend to reproduce themselves enforcing their own code. While the self-reproduction of racemic compounds is encoded by their eutectic composition, the resolving agent pursues to reproduce itself from the enantiomers of racemic compound but in the ratio of its eutectic composition, of its stoichiometry.

The molecular structure of the single enantiomer is the code for reacting with other (foreign) chiral molecules.

Acknowledgments

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