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A Presumable Mechanism of the Separation of Diastereomeric and Enantiomeric Mixtures

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Abstract

Homo and heterochiral supramolecular associates with helical structure are formed in the solutions of mixtures of chiral compounds due to their self-disproportionation (SDE). These form homo and heterochiral double helices having eutectic composition. Pure enantiomers are obtained by the distribution of these associates between two immiscible phases.

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

Introduction

The chiral compounds, the pure enantiomers are ubiquitous in our everyday life, e.g., fragrances, in vitamins or in medicines. A main part of the medicines contains just one of the mirror image pairs, one of the enantiomers, because the biological activity of the two antipodes may be different or even opposite. So they have different or even opposite effect on the living organisms, built up by asymmetric molecules, by enantiomers. So, the enantiomeric separations are necessary and inevitable and the demand for pure enantiomers becomes higher and higher [1].

Even though several new methods and selective synthesis are known in the pharmaceutical practice, the most commonly and economic method remains the resolution, in other words the separation of racemic compounds (1:1 mixture of the two enantiomers), obtained in the chemical synthesis into pure enantiomers using another chiral compound, the so called resolving agent. In this case the separation of enantiomeric mixtures are 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].

Results and Discussion

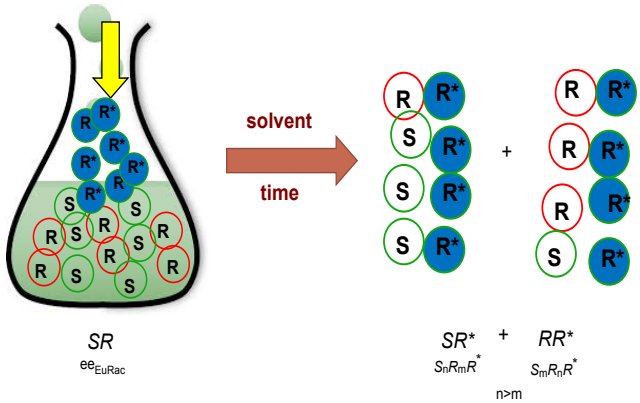
How does a resolution process work in general? To the solution of racemic compound obtained at the chemical synthesis, which is an equimolar mixture of mirror-image pairs of enantiomers, is added the resolving agent (Scheme 1). In the solution due to the self-organization of enantiomers (SDE), supramolecular associates are formed, and these will be distributed between two phases, according to the conditions, and circumstances of the process.

The distribution depends, mainly on the properties of the starting compounds, on the eutectic compositions of the racemic compound (ee_{EuRac}) and the resolving agent (ee_{EuRes}), respectively. The solvent applied, and the time of crystallization has a significant effect as well.

The behaviour of enantiomeric mixtures can be described as racemic-like, (about 80%), and conglomerate-like behaviour (about 20%) [3,4] A non-linear correlation can be seen between the purity of the crystallized mixture and the initial composition, both the melting point diagrams and purity-purity diagrams are specific for a given behaviour [5,6].

In both cases a specific composition of enantiomeric mixtures can be observed, the so-called eutectic composition, when the enantiomeric composition is the same in each phase. During the crystallization a purer mixture is obtained compared to the starting composition in case of enantiomeric mixtures having conglomerate-like behaviour. The composition of the crystalline phase depends on the eutectic composition in the case of enantiomeric mixtures having racemic-like behaviour, namely, if the starting composition is higher than the eutectic composition, a purer mixture can be obtained in the crystalline phase, while starting out from a lower composition than the eutectic composition, the crystallized part will have a near racemic composition.

How do the interactions work? If in the solution of an enantiomeric mixture homo chiral supramolecular associations are formed by self-organization and self-disproportionation (SDE), in the crystalline phase we can find the pure (purer) enantiomer. If we change the temperature



Scheme 1: The general scheme of the resolution processes. (R and *S* the pure enantiomers, *R** the resolving agent).

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the heterochiral associations become more stable and less soluble, so the crystalline phase will contain an enantiomeric mixture with near racemic composition (Scheme 2).

If in the solution only one of enantiomers is present, it was demonstrated, that the homo chiral self-organized supramolecular associates can have plus (P) and minus (M) helicity. For example, in the case of Threonine (a chiral proteinogenic amino acid), which crystallizes as a conglomerate, the deposited aggregates show an obvious right and left-handed configuration. It was observed at the same time, that in the *R* configuration the P helical structure is present in 85% amount, while in the *S* configuration the M helical structure was formed in crystalline phase in the same amount. This ratio between P and M helical structures is almost the same as the ee_{Eu} of the enantiomeric mixture of Threonine (Scheme 3) [7].

A similar right and left-handed configuration was observed in case of mirror-image pairs during the crystallization of quartz. In this case the ratio of P and M helical structures is equal because it is a helical but achiral molecule (Scheme 4).

A similar antiparallel double helical structure was also observed when non-covalent associates were formed by interactions of chiral molecules. The structure of DNA, which plays a decisive role in the inheritance of living organisms, is antiparallel double helix supramolecular structure. The backbone of this macromolecule is an enantiomer, the phosphate of deoxyribose monomer. This chiral molecule has a code in its structure (its eutectic composition), which influences the configuration and the helicity of the macromolecule formed. It is remarkable, that even though this chiral molecule has 8 isomers, just one of them takes part in the building up of this macromolecule [8].

In case of resolution processes small chiral molecules, the racemic compounds tend to form homo- and heterochiral associations due to their self-organization, and these groups have helical structures, where P and M helices are formed in a definite amount encoded by their own code. These helices tend to form homo and heterochiral double helices which will be distributed between two phases (Scheme 5).

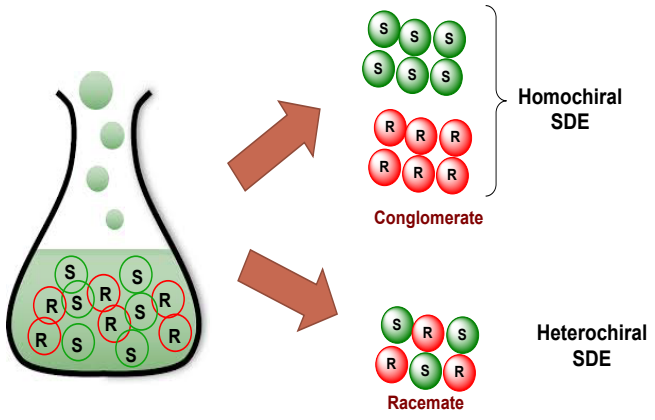
The homochiral helices can be transformed to helices, having eutectic composition. The heterochiral double helices racemic crystals are precipitated, if the starting enantiomeric ratio does not exceed the eutectic composition (Scheme 6).

Due the resolution processes the resolving agent, with its P and M double helices can react with the antiparallel P and M heterochiral double helices of racemic compound. The composition of the diastereomer in crystalline phase can be influenced by the applied solvent (Scheme 7). If the kinetic control of crystallization is determined by the eutectic composition of the racemic mixture, then the thermodynamic control may be determined by the eutectic composition of the resolving agent. Or contrarily, if the latter determines the kinetic control, then the thermodynamic control is determined by the eutectic composition of the racemic mixture.

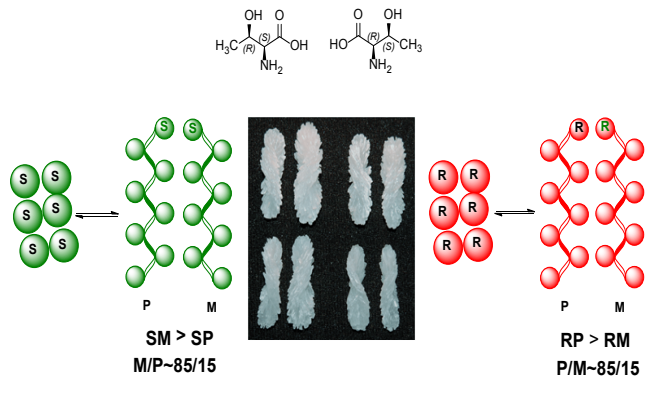
From different solvents, not the same diastereomers precipitate, most probably due to the different solubility of the double helix structures, however, their stoichiometry is decisively determined by the eutectic composition of the racemic compound. It is an adequate example the resolution of Flumequine intermediate in different solvents (Scheme 8) [9].

In the case of the resolution of FTHQ with DPTA, during the crystallization from ethyl acetate, both the kinetic and thermodynamic control is determined by the eutectic composition of the racemic compound. Although in the case of the thermodynamic control instead of the faster crystallizing diastereomer salt, the other one, of poorer solubility precipitates, the stoichiometry is determined by the eutectic composition of the racemic FTHQ.

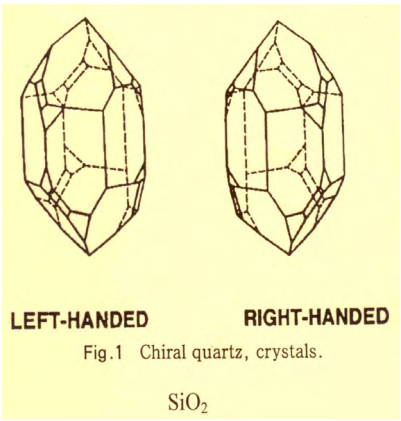
Three weeks of crystallization gives the evidence, that in this case undoubtedly the ee_{EU} code of the racemic compound determines the



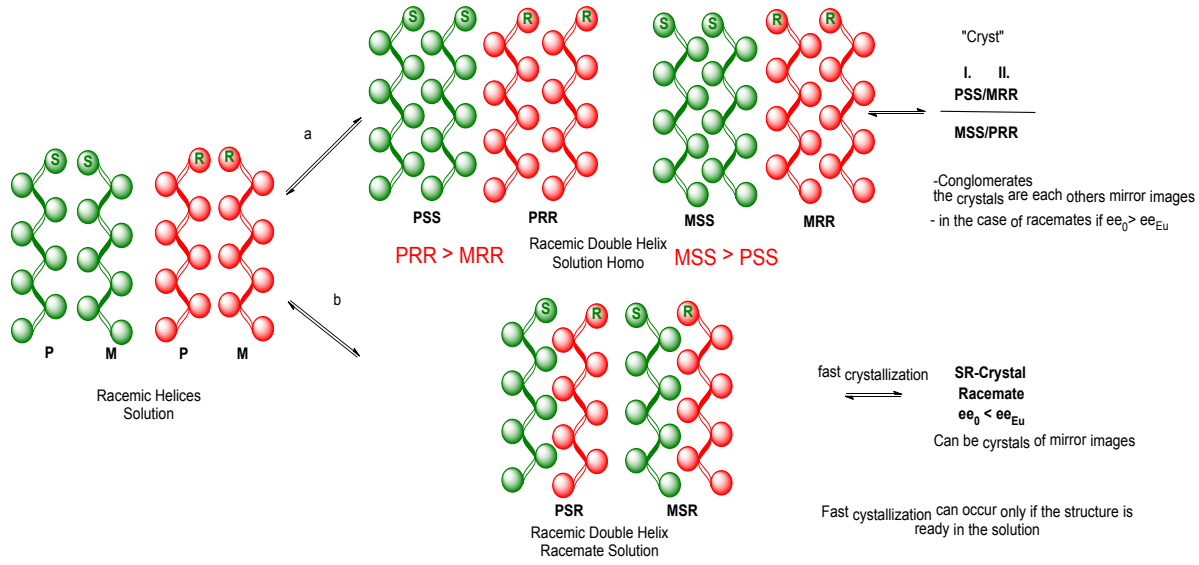
Scheme 2: The distribution of enantiomeric mixture into homo- and heterochiral supramolecular associations.



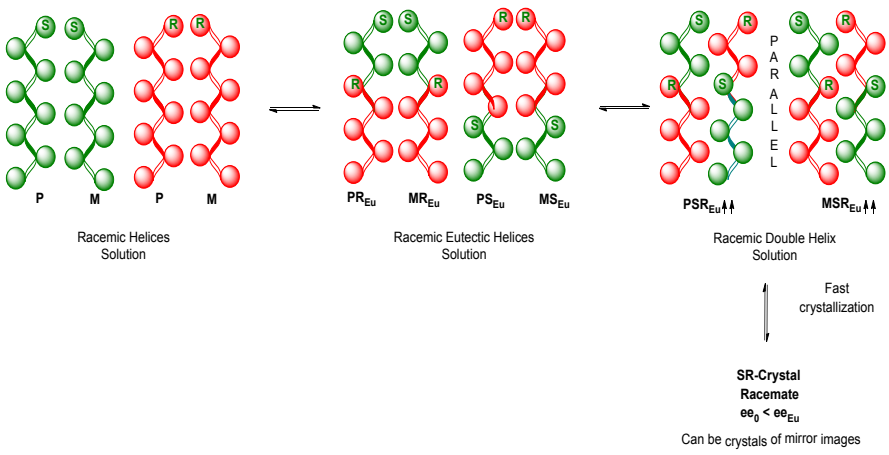
Scheme 3: The macroscopic helicity of threonine aggregates reveals their predominant molecular chirality.



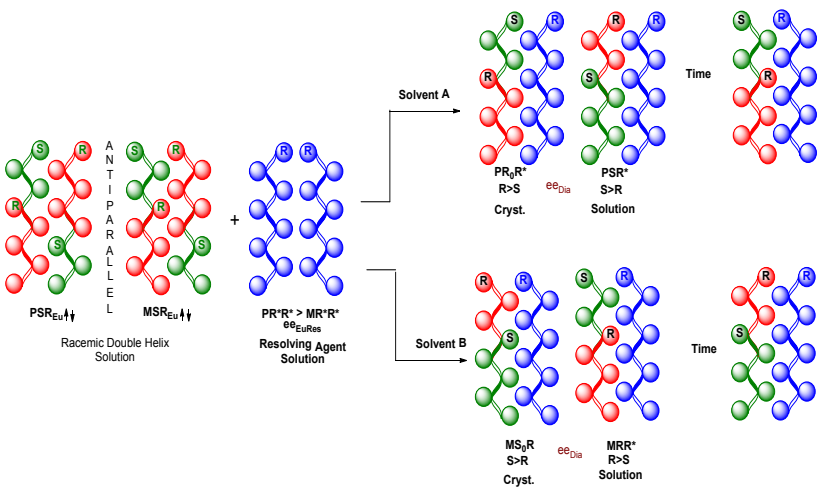
Scheme 4: The right and left-handed configuration observed in case of quartz crystals.



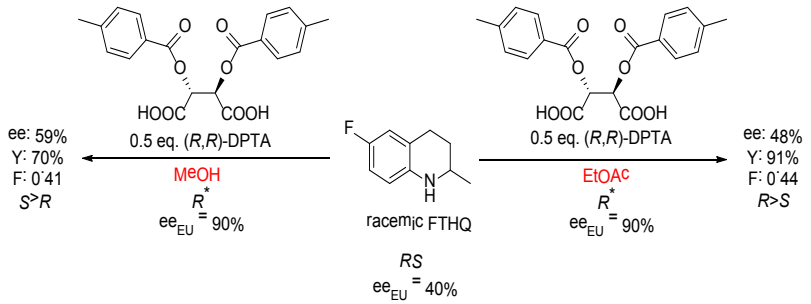
Scheme 5: Formation of double helices from the chiral helices.



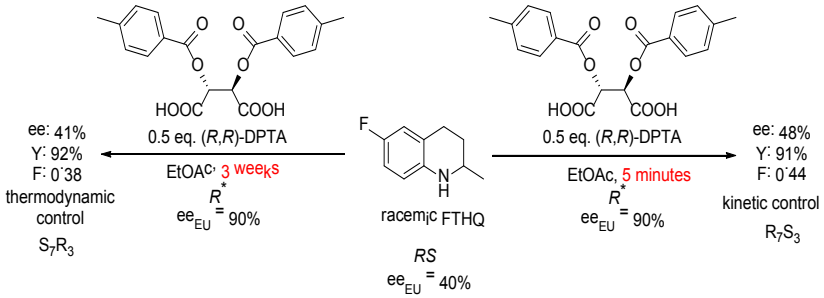
Scheme 6: Transformation of helices into helices having eutectic composition.



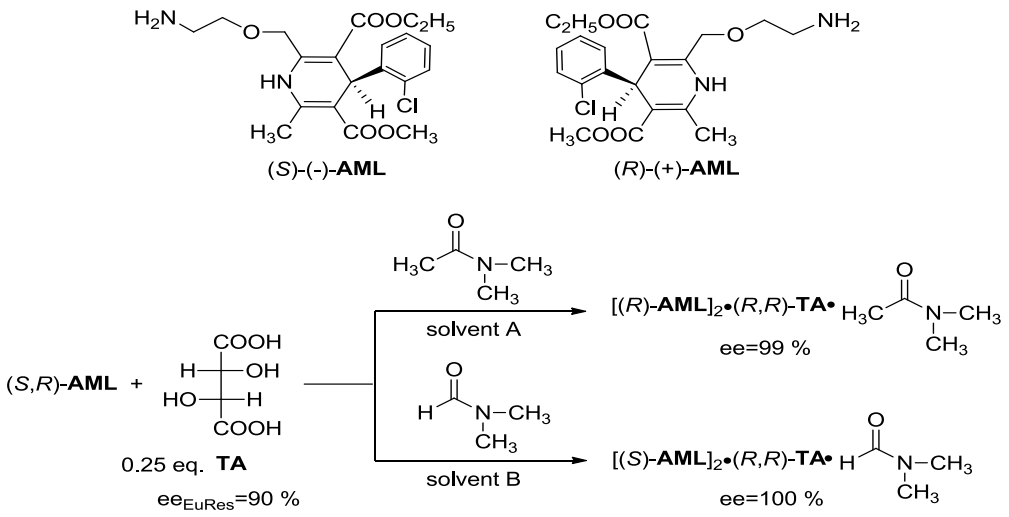
Scheme 7: Transformations due the resolution processes.



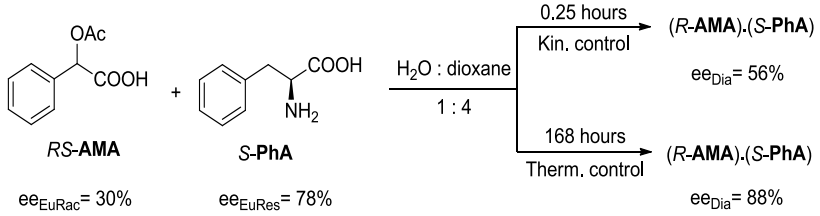
Scheme 8: Solvent dependency of the resolution of Flumequine intermediate.



Scheme 9: The kinetic and thermodynamic control is determined by the eutectic composition of racemic compound.



Scheme 10: A solvent-depended resolution when the stoichiometry of diastereomers is determined by the eutectic composition of resolving agent.



Scheme 11: A time-depended resolution when the stoichiometry of diastereomers is determined by the eutectic composition of one of starting compounds.

stoichiometry of the crystallization instead of DPTA (Scheme 9) [10].

The solvent-dependency can also be observed at the resolution of racemic Amlodipine (**AML**) by (*R,R*)-tartaric acid (**TA**) (Scheme 10) but in this case the stoichiometry of diastereoisomers is determined by the eutectic composition of the resolving agent [11-13].

When kinetic control is applied, the results are determined by the eutectic composition of the racemic compound. On the contrary, on thermodynamic control, the determining factor is the eutectic composition of the resolving agent (Scheme 11) [14].

Conclusion

Like DNA in the living organisms reproduces itself, as a result of its code, form supramolecular associates having double helical structure, so it is capable to reproduce itself and to catalyse the processes, in the resolution processes are also observed a self-reproduction of supramolecular associates having helical structure which tend to reproduce themselves.

While the self-reproduction of racemic compounds is encoded by its eutectic composition, the resolving agent pursues to reproduce itself from the enantiomers of racemic compound but in the ratio of its eutectic composition.

Acknowledgments

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