Chemical Bulletin of "Politehnica" University of Timisoara, ROMANIA
Series of Chemistry and Environmental Engineering
Chem. Bull. "POLITEHNICA" Univ. (Timisoara) *Volume 61(75), 1, 2016*

Influence of Helical Structured Supramolecular Associates and that of Eutectic Composition on the Distribution of Enantiomeric and Diastereomeric Mixtures between Phases

E. Pálovics[*,**], Z. Szeleczky[**] and E. Fogassy[**]

[*] MTA-BME Organic Chemical Technology Research Group, University of Technology and Economics, Budapest, H-1521, P.O.B. 91 Budapest, Hungary, Fax +36(1)4633648, e-mail: epalo@mail.bme.hu,

[**] Department of Organic Chemistry and Technology, University of Technology and Economics, Budapest

Presented at the 9th Edition of the Symposium "NEW TRENDS AND STRATEGIES IN THE CHEMISTRY OF ADVANCED MATERIALS WITH RELEVANCE IN BIOLOGICAL SYSTEMS, TECHNIQUE AND ENVIRONMENTAL PROTECTION", June 09-10, 2016, Timisoara

Abstract: The driving force [1-3] 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. The mixtures of chiral molecules self-organize to supramolecular associations (SDE) [4] that can have homo- and heterochiral compositions. The helical and double helix-like structures that provide higher complementarity are produced in the equilibrium processes between these polymer-like associations. The isolated crystals are formed by these structures. The chiral molecules that take part in the processes are organized according to their CODEs, borne by their chemical properties and structure (eutectic composition) and this way they provide the stoichiometry of the crystalline diastereomer precipitating from the solution.

Keywords: resolution, distribution between phases, eutectic composition, supramolecular associates, helical structure.

The most commonly used methods for 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 vapor phases) [5, 6].

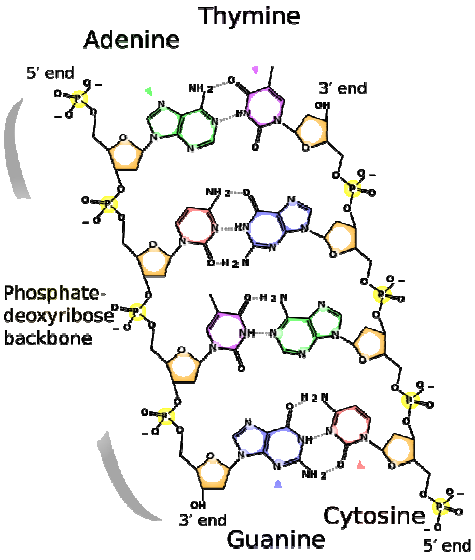
In many cases, living organisms contain only one of the two enantiomers of the chiral molecules, but often racemic compounds (1:1 mixture of the two enantiomers) are obtained in the chemical syntheses. The biological activity of the two antipodes may be different or even opposite, so enantiomeric separations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

The structure of the DNA (Scheme 1), which plays a crucial role in the heritance of the living organisms, was clarified in 1953 by Watson and Crick: an anti-parallel double helix, linked together by hydrogen bond systems, which is typical for supramolecular structures [7].

The backbone of this biopolymer is composed of deoxyribose enantiomer phosphate monomers. This causes and allows that the order of the four bases linked to the backbone bears the code of its operation. Thus, the key compound is an enantiomer, which is able to form a racemic compound with its mirror image pair, but only one enantiomer is produced in the chiral environment of the nature.

Like in the case of quartz, other chiral molecules can be capable of forming chiral crystals. It can be explained by the helical, or even with the double-helix like structure of the associations formed during the crystallization both in the case of achiral and chiral molecules. Furthermore, the mixtures of chiral molecules – enantiomers or diastereomers – show non-linear correlations as well, mainly during their phase distribution. In the contiguous phases the ratio of the two enantiomers is different.

The phases are separate from each other, thus the ratio of the two enantiomers are different in them. This can have a connected ion with the eutectic composition of the molecules that are present in the solution and can be regarded as a code that determines the stoichiometry of the diastereomers.



Scheme 1. DNA structure

At the same time, until the reach of the eutectic composition the crystalline phase attempts to have racemic composition, while after this point the enantiomeric excess will be enriched according to the self-disproportion.

According to the kinetic and thermodynamic control during crystallization, the stoichiometry of the crystallizing diastereomer can be determined by the constituent enantiomers pair that is present in the diastereomeric mixture. The crystallizing diastereomer formed from the racemic compound and the resolving agent is determined by the applied solvent. The reason behind for this can also be explained by the helicity of the double helix structure forming during crystallization. The phase distribution of the chiral compounds is characterized by the diastereomer-like properties of the mixtures of enantiomers and diastereomers. The mixtures of the enantiomers or their derivatives try for attempt to have a more and a less symmetrical distribution.

Achiral molecules and their mixtures can form crystals, having P and M helicity, linked to each other by hydrogen bonds [11]. From the mixtures of achiral molecules, crystals of mirror image having double helix structure (of opposite helicity can be formed. Of course, the mirror image crystals of Sodium-ammonium tartrate (Pasteur) are formed from supramolecular associations having opposite double helicity

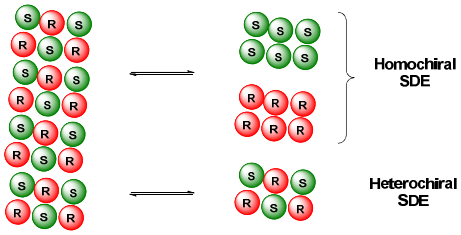
Thus, the supramolecular double helix, composed of deoxyribose monomers linked to each other by covalent bonds, can also be found in the case of polymer-like, non-covalent molecular associations, moreover in this latter case the mirror-image M and P helicity can be a significant property. The first enantiomeric separation starting from a racemic compound, i.e. the assortment of the mirror-image crystals of the racemic tartaric acid salt carried out by Pasteur, and later on, the enantiomeric separation of racemic compounds was assured by the crystallization of double helix structures of opposite helicity.

In solutions of enantiomeric mixtures groups of homo- and heterochiral self-organized associations of supramolecular structure are formed (Scheme 2).

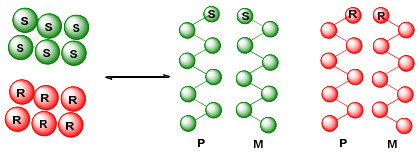
The homo- and heterochiral groups of enantiomers, due to their self-organization, form homo- or heterochiral associations of plus or minus (P and M) helicity (Scheme 3). From the heterochiral associations, only those having eutectic composition will be presented (In the case of the presented examples, the enantiomeric ratio of the eutectic composition is 3:5) The groups of enantiomers self-organize to helical structures (self-reproduction?) Their length is unknown, but certain units have to be repeated.

Homochiral double helices can be formed from the chiral helices (Scheme 4 a), from which enantiomeric pure crystals were formed in the case of conglomerates, as well as in the case of racemates, if the purity of the starting mixture is higher than the eutectic composition. Heterochiral double helices can also be formed from the chiral helices if the starting composition does not exceed the eutectic one (Scheme 4 b).

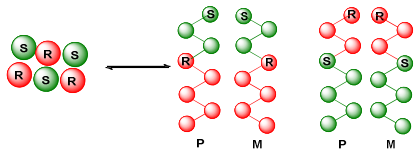
The homochiral helices can be transformed to helices, having eutectic composition. The heterochiral double helices racemic crystals are precipitated, if the starting enantiomeric ratio does not exceed the eutectic composition (Scheme 5).



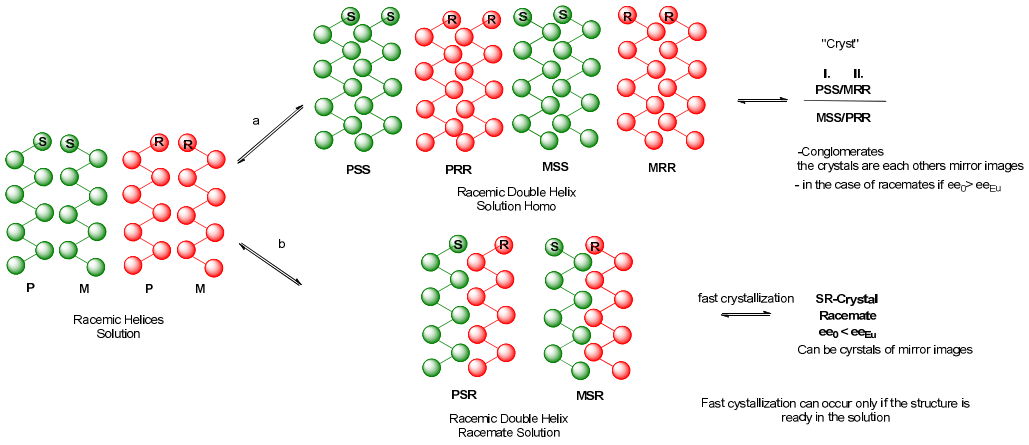
Scheme 2. Groups of homo- and heterochiral self-organized associations of supramolecular structure



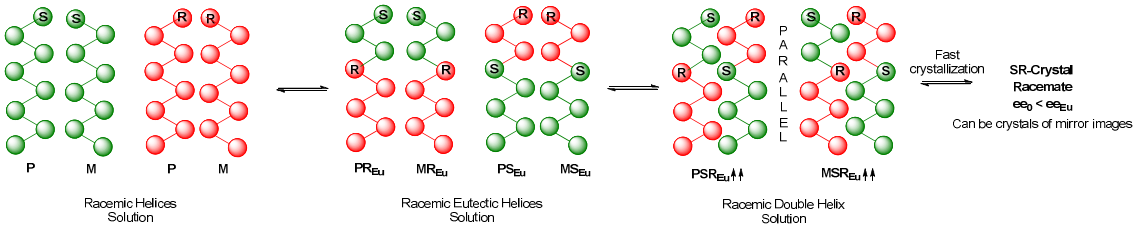
Scheme 3. Homochiral helices



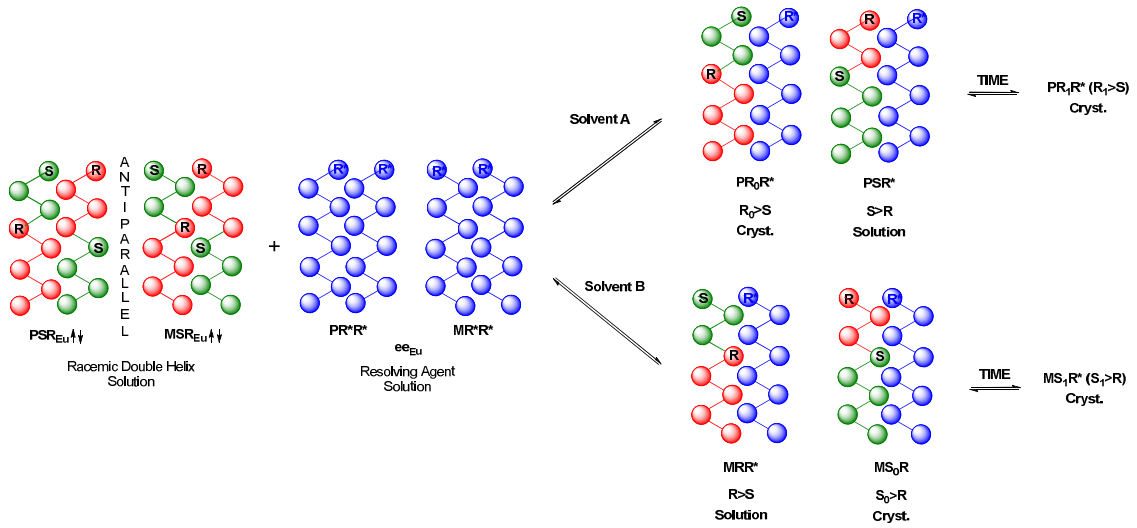
Heterochiral helices; the enantiomeric ratio of the eutectic composition is 3:5



Scheme 4. Formation of double helices from the chiral helices



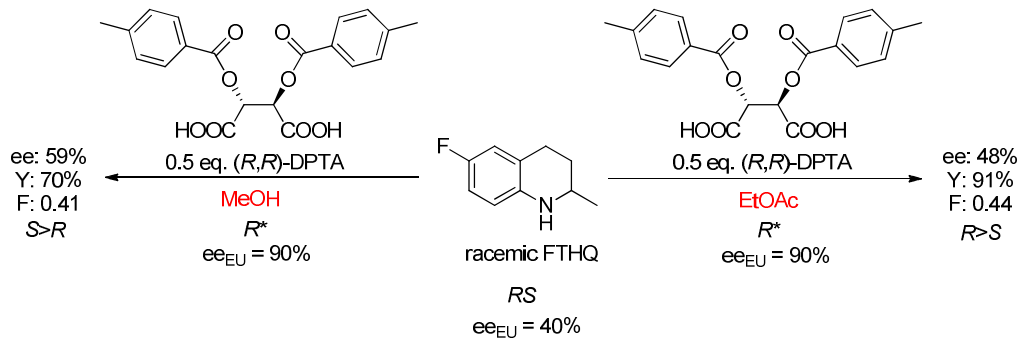
Scheme 5. Transformation of helices into helices having eutectic composition



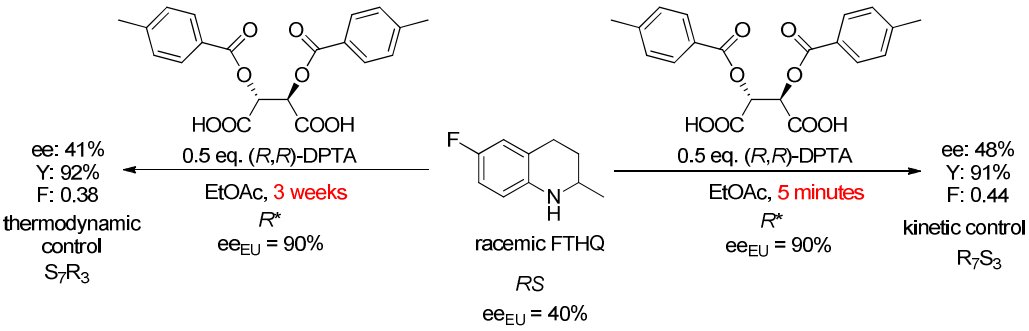
Scheme 6. Transformations due the resolution processes

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. If a diastereomer having for example P helicity and containing either of the enantiomers in excess, crystallize from Solvent A, most probably the diastereomer having M helicity and containing the other enantiomer in excess will crystallize from another Solvent B (Scheme 6). If the kinetic control of a 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 (Scheme 7).



Scheme 7. Solvent dependency of the resolvation of Flumequine intermediate



Scheme 8. The kinetic and thermodinamic control is determined by the eutectic composition of racemic compound

In the case of the resolution of **FTHQ** with **DPTA**, during the crystallization from ethyl acetate, both the kinetic and thermodynamic control are 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 stoichiometry of the crystallization instead of **DPTA** (Scheme 8). [12]

Like DNA in the living organisms reproduces themselves, in the resolution processes are also observed a self-reproduction of supramolecular associates having helical structure. 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.

ACKNOWLEDGMENT

The authors are grateful for the financial support of the Hungarian Scientific Research Found (OTKA grant number K 104769 for E. Fogassy).

REFERENCES

1. Jacques J., Wilen S.H. and Collet A., Enantiomers racemates and resolution, Wiley-Interf., N.Y., **1881**.
2. Kozma D. and Fogassy E., Optical resolutions via diastereomeric salt formation**.** CRC Press; London, **2002**.
3. Soloshonok V.A., *Angewandte Chemie International Ed*., 45, **2006**, 766-769.
4. Faigl F., Fogassy E., Nógrádi M., Pálovics E. and Schindler J., *Org. Biomol. Chem*., 8, **2010**, 947–959.
5. Pálovics E., Szeleczky Zs., Fődi B., Faigl F. and Fogassy E., *RSC Advances*, 4, **2014,** 21254-21261.
6. Watson J.D., Molecular Biology of the gene Ed: W.A Benjamin INC., USA, **1965**.
7. Hargittay I. and Hargitati M, *Struct. Chem*. 19, **2008**, 697-717.
8. Sommerdijk N.A.J.M., Buynsters P.J.J.A., Akdemir H., Geurts D.G., Pistorius A.M.A., Feiters M.C., Nolte R.J.M. and Zwanenburg B., *Chem. Eur. J*., 4(1), **1998**, 127–136.
9. Kobayashi Y., Kodama K. and Saigo K., *Org. Lett*., 6(17), **2004**, 2941–2944.
10. Daniels D.S., Petersson E.J, Qui J.X. and Schepart Z., *JACS*, 129, **2007**, 1532-1533.
11. Koshima H., Nakagawa T, Matsuura T., Miyamoto H. and Toda F., *J. Org. Chem.*, 62, **1997**, 6322-6325.
12. Balint J., Egri G., Kiss V., Gajary A., Juvancz Z. and Fogassy E., *Tetrahedron:Asymmetry*, 12, **2002**, 3435-3439.

Received: 23 June 2016
Accepted: 27 July 2016