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New Opportunities to Improve the Enantiomeric and Diastereomeric Separations

Emese Pálovics, Szeleczky Zsolt, Szolnoki Beáta, Bosits Miklós and Fogassy Elemér

Additional information is available at the end of the chapter

Abstract

The preparation of single enantiomers (ee ~100%) is one of the most important demands both for industrial practice and research. Actually, the resolution of the racemic compounds still remains the most common method for producing pure enantiomers on a large scale. To obtain the pure enantiomers, it is necessary to find the appropriate conditions and resolving agents. During the separation of diastereomeric mixtures, similar trends can be observed as in course of the distribution of enantiomeric mixtures between phases, because just the presence of one-third chiral compound (namely the resolving agent) is the difference. This chapter presents new observations and establishments about the new opportunities to optimize the separation of chiral mixtures, especially the diastereomeric mixtures.

Keywords: diastereomeric mixtures, pH, solvent, crystallization time, temperature, ultrasound irradiation

1. Introduction

In many cases, living organisms contain only one of the two enantiomers of chiral molecules, but often racemic compounds (1:1 mixture of the two enantiomers) are obtained in the chemical syntheses. The biological activity of enantiomers may be different or even opposite, so the enantiomeric separations are necessary and inevitable. Many methods described in the literature for the separation of enantiomers involve the formation of diastereomers followed by decomposition. These enantiomeric separation methods are discussed and systematized in several articles [1–10].

In most cases, the mixtures of diastereomers received by adequate resolving agents, or the mixtures of enantiomers isolated thereof, have to be separated. It is common in the separation methods, that the distribution of the mixtures between two phases is necessary, and the phase separation have to be applied [11–13].

Besides the effect of the applied solvents, the phase distribution of the mixtures is also determined by kinetic or thermodynamic control [14]. The phase distribution is also determined by the eutectic composition of the chiral molecules in the mixtures [15, 16].

Besides, the distribution between the phases is pH-dependent [17]. It seems that the effect of the kinetic control between two phases can be stabilized with the application of ultrasound [18]. The formation of solvates can also determine the distribution and the crystallization-based separation of diastereomers [19, 20]. By the incorporation of compounds of similar structure to the solvate-forming molecules, the fractionated crystallization can be successful in other solvents as well [21]. In the case of the crystallization of diastereomers, better separation can be reached, if the resolving agent is partially replaced by an achiral reagent of similar structure compared to the cases without replacement [22]. In the following, the most characteristic examples of the above-mentioned methods will be discussed.

2. pH dependence of the separation of diastereomeric mixtures

2.1. pH dependence in course of resolution of racemic acid with chiral base

A thermodynamic model has been elaborated [23] for the salt-salt resolution of racemic *cis*-permethric acid (**CPA**) with half-equivalent (*S*)-*N*-benzyl-2-aminobutanol ((*S*)-BAB) [24]. The amount of the base was systematically changed to investigate the pH dependence of the resolution. The calculated and measured *ee* and T curves are plotted in **Figure 1**. After the separation of the diastereomeric salt, by neutralizing the mother liquor with hydrochloric acid, the (*R,R*)-**CPA**·(*S*)-**BAB** diastereomer was precipitated.
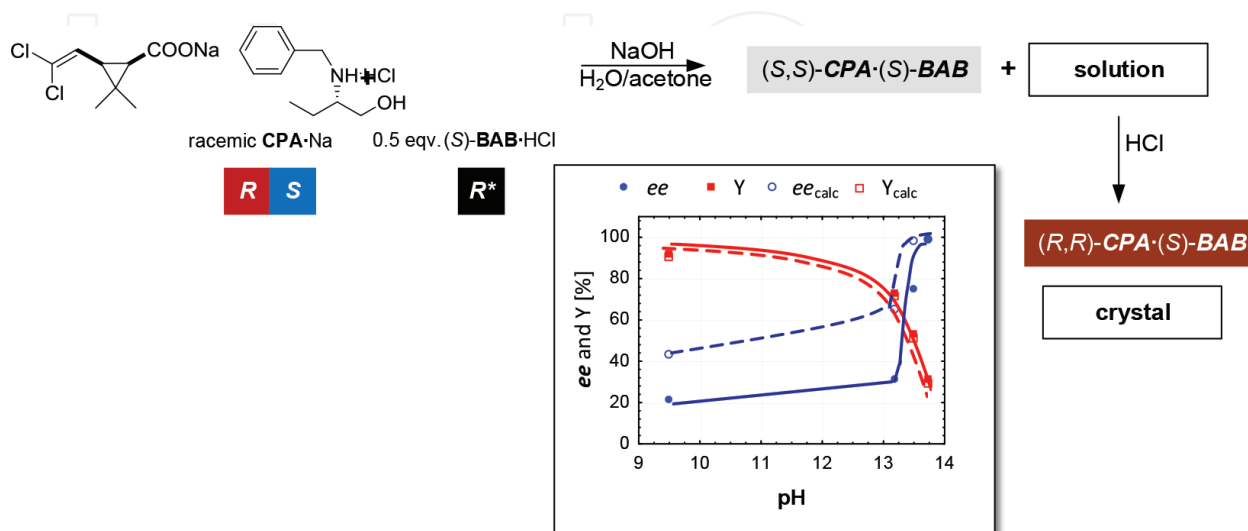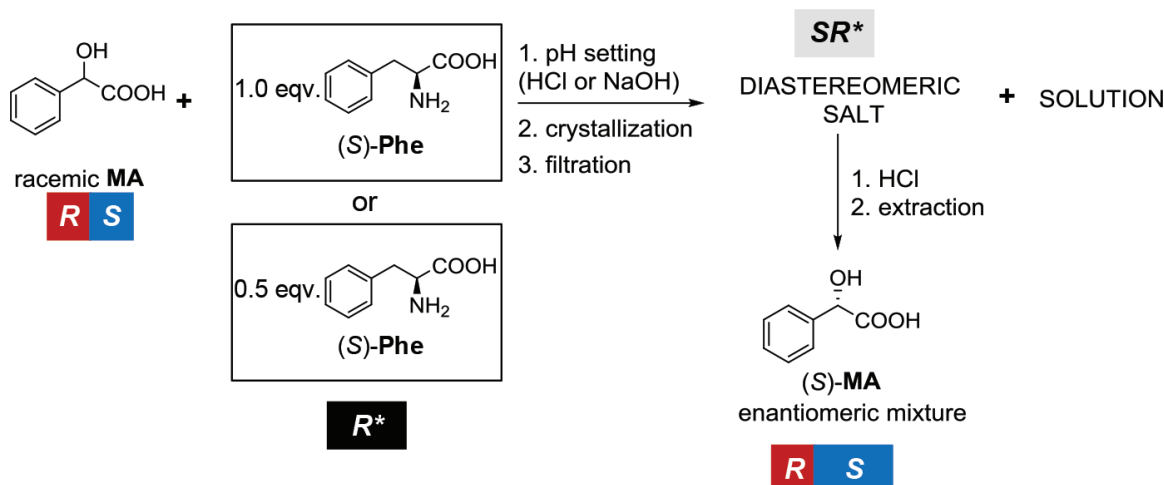

Figure 1. pH-dependent resolution of racemic cis-permethric acid with (S)-N-benzyl-2-aminobutanol.

Scheme 1. pH dependence during the resolution of mandelic acid with (*S*)-Phe.

2.2. pH dependence during the resolution of racemic mandelic acid with (S)-phenylalanine

In the case of (*S*)-**Phe**, experiments were carried out both with equivalent and half-equivalent amount of resolving agent relative to racemic mandelic acid (**MA**). The adjusting of the pH was accomplished with NaOH and cc. HCl (**Scheme 1**) [17].

In the case of the application of 1.0 equivalent resolving agent, the enantiomeric purity (44–51%) and yield of the crystalline salt are almost the same between pH 1.3 and 2.3. This pH range matches well the pK_a value of the carboxyl group of **Phe** (1.83). The time of crystallization was 15 min in all cases (**Figures 2** and **3**).

The pH dependence of the diastereomeric salt was also investigated after 2 weeks, when the thermodynamic equilibrium was reached (**Figure 4**).
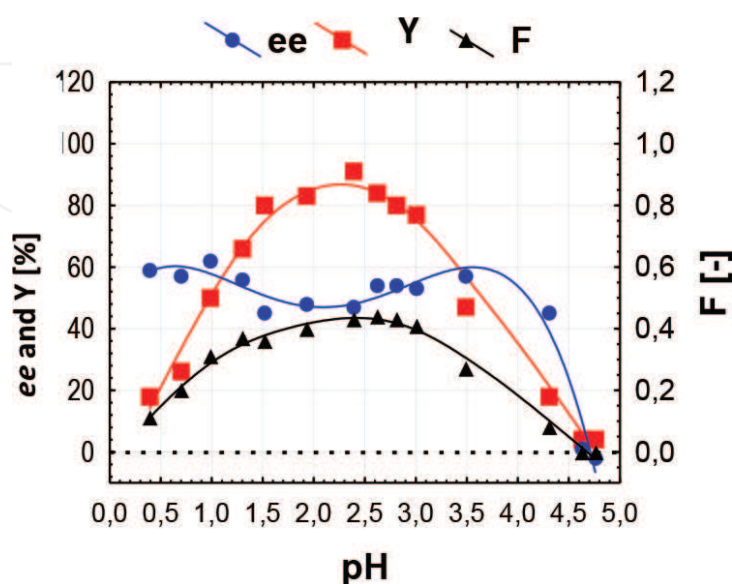

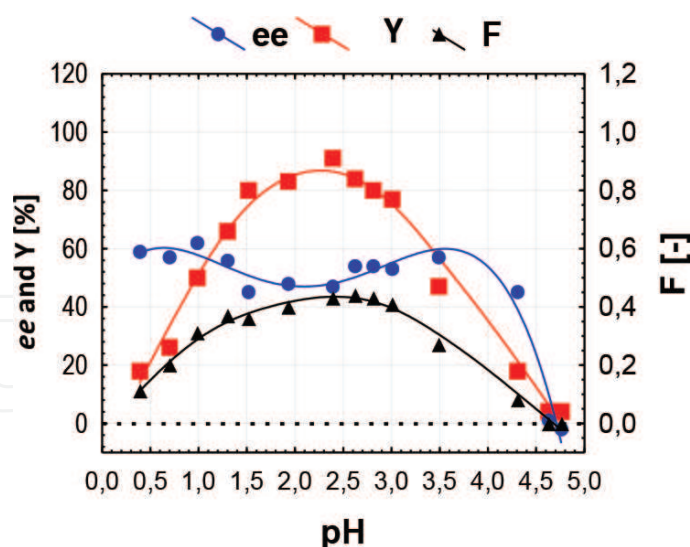**Figure 2.** pH dependence in course of the resolution of mandelic acid with 1.0 equivalent (*S*)-**Phe.**

Figure 3. pH dependence in course of the resolution of mandelic acid with 0.5 equivalent (*S*)-**Phe.**
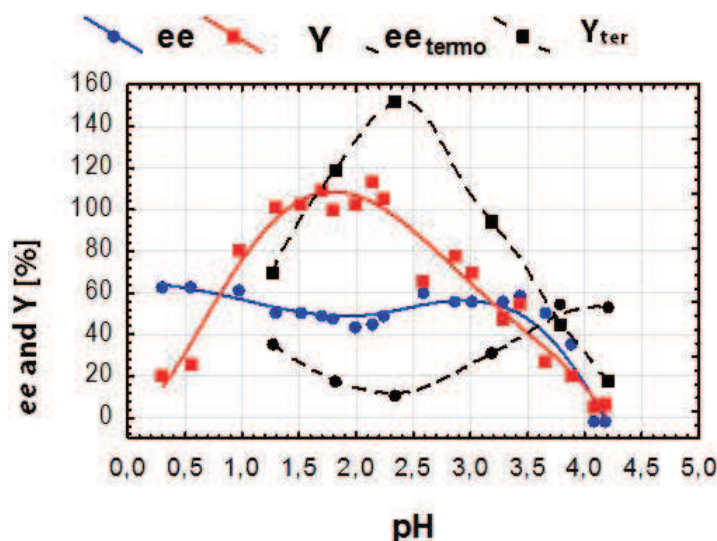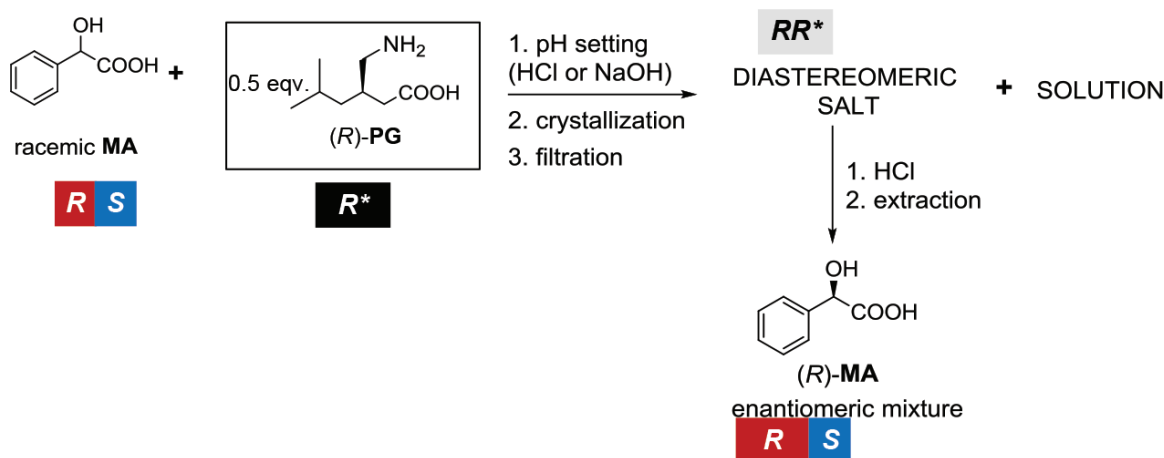

Figure 4. pH dependence in course of the resolution of mandelic acid with 1.0 equivalent (S)-Phe after 2 weeks of crystallization (the denotation thermo is applied for the results of the resolutions after 2 weeks of crystallization).

The purity of the enantiomeric mixtures separated from the crystalline phase became highly pH-dependent. At pH 1.2, the enantiomeric purity received during fast crystallization (*ee*: 52%) decreased to 36%, while at pH 2.3 from 49 to 11%. The optimum of the pH dependence can be reached in the case of kinetic control.

2.3. pH dependence in course of the resolution of racemic mandelic acid with (*R*)-pregabalin

The pH dependence of the resolution of racemic mandelic acid with (*R*)-pregabalin ((*R*)-**PG**) was carried out by kinetic control (crystallization time: 15 min) (**Scheme 2**).

The (*R*)-**MA** enantiomer mixtures can be received with almost identical enantiomeric purities (43–50%) and yields in the range of pH 3.0–4.4. The maximal value of the efficiency of the

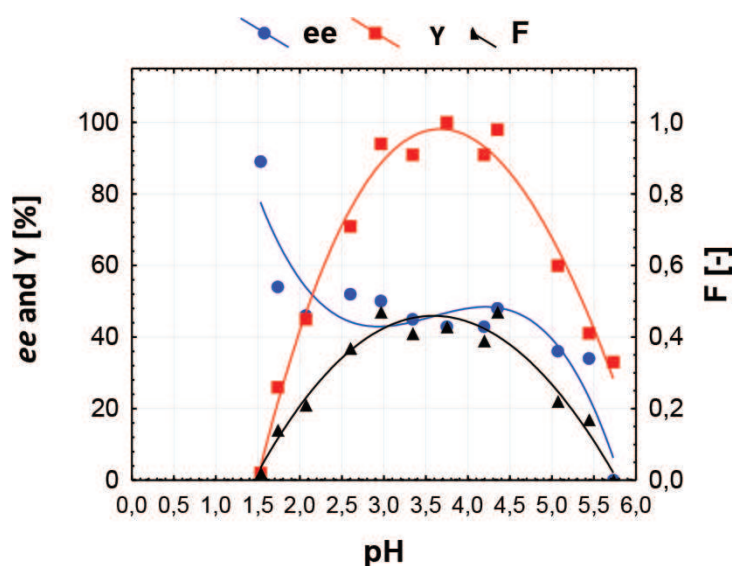**Scheme 2.** pH dependence of the resolution of mandelic acid with (*R*)-PG.

Figure 5. pH dependence in course of the resolution of mandelic acid with 0.5 equivalent (*R*)-**PG.**

resolution was reached in a pH range similar to the pK_a value of the carboxyl group of the resolving agent (**Figure 5**).

3. Role of eutectic compositions, crystallization time and solvent in case of diastereomer separation

3.1. Role of the solvent

The right choice of the solvent is crucial in course of the fractionated crystallization of diastereomers. The composition of the crystalline phase received during resolution is often changed in case of solvate or hydrate formation. The dominant configuration can also change, depending on the applied solvent. For example, by changing the solvent in case of resolution of racemic 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (FTHQ) with half-equivalent (*R,R*)-di-*p*-toluoyl-tartaric
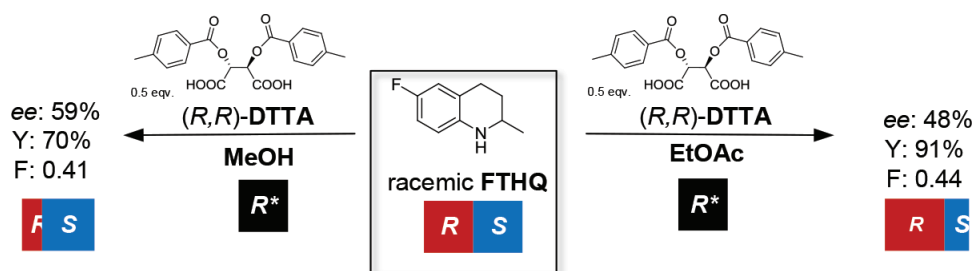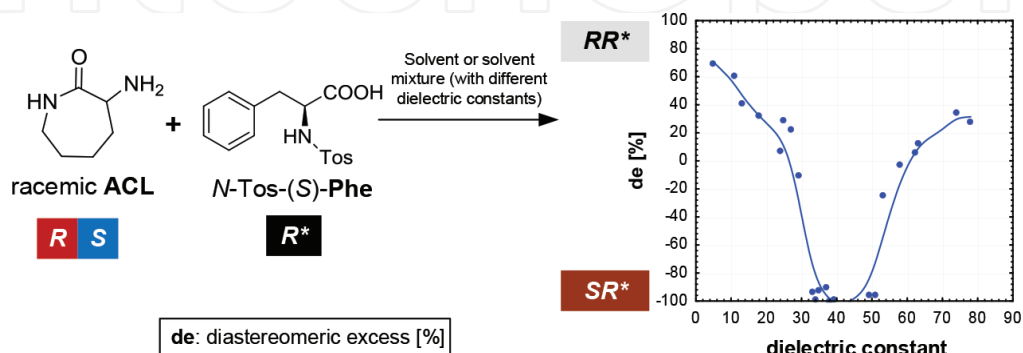
Scheme 3. Resolution of flumequine intermediate.

Figure 6. The first dielectric constant-dependent resolution was carried out by *Sakai.*

acid [(*R*,*R*)-DTTA)] resolving agent, the crystalline phase is enriched in different enantiomer, even without solvate formation [25]. When applying ethyl acetate as solvent, (*R*)-FTHQ with 48% enantiomeric excess, while with the application of methanol (*S*)-FTHQ with 59% enantiomeric excess can be separated from the filtrated diastereomer salt (**Scheme 3**).

Correlation was found between the composition of the diastereomeric salt and the dielectric constant of the solvent/mixture of solvents in course of the resolution of α-3-amino-ε-caprolactame (ACL) with *N*-tosyl-(*S*)-phenylalanine (*N*-Tos-(*S*)-**Phe**) [26]. In the ranges of 5–27 and 62–78 of the dielectric constant, the (*R*)-**ACL**·*N*-Tos-(*S*)-**Phe** diastereomer was in excess in the crystalline phase, while between the two ranges the (*S*)-**ACL**·*N*-Tos-(*S*)-**Phe** diastereomer was enriched (**Figure 6**).

According to the single-crystal studies, the dielectric constant of the solvent [27] also influences the hydrogen bonding system thus forming the chiral recognition process. This phenomenon was demonstrated *via* several other resolution experiments [28–32].

3.2. Role of the crystallization time

The effect of different crystallization times on the enantiomeric mixtures separated from the crystalline phase was investigated in course of the resolution of the racemic 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (**FTHQ**) with half-equivalent (*R*,*R*)-di-*p*-toluoyl-tartaric acid ((*R*,*R*)-**DTTA**)) [25]. When the mixture was filtrated after 5 min of crystallization, the solid phase composed mainly of the (*R*)-**FTHQ**·(*R*,*R*)-**DTTA** diastereomer, while after 3 weeks of crystallization, the (*S*)-**FTHQ**·(*R*,*R*)-**DTTA** diastereomer became the main component (**Scheme 4**). The kinetic control resulted in (*R*)-**FTHQ**·(*R*,*R*)-**DTTA** diastereomer, while the thermodynamic control gave (*S*)-**FTHQ**·(*R*,*R*)-**DTTA** diastereomer in the solid phase.
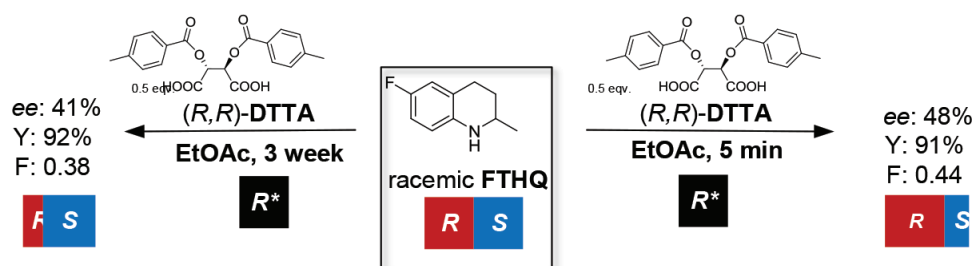
Scheme 4. Time dependence of the resolution of flumequine intermediate.
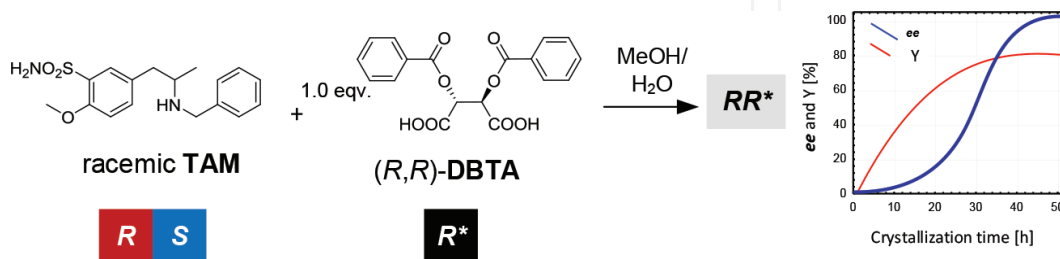

Figure 7. Time dependence of the resolution of tamsulosin intermediate.

By reacting the tamsulosin (**TAM**) intermediate with equivalent (*R,R*)-dibenzoyl-tartaric acid ((*R,R*)-**DBTA**), racemic enantiomer mixture could be separated from the crystalline phase; however, after 2 days of crystallization, the solid phase enriched in the required (*R*)-enantiomer (**Figure 7**) [33]. The thermodynamically preferred composition resulted in the best separation.

3.3. Effect of the eutectic composition of the enantiomeric mixtures of either the racemic compound or the resolving agent

In course of the fractionated crystallization of the mixtures of diastereomeric salts, the effects of the applied solvent and the crystallization time, and thus the enantiomeric ratio of the crystalline diastereomer, are determined by the eutectic compositions of the racemic compound or the resolving agent [11, 13]. At the same time, in the case of the organocatalysis, the eutectic composition of the catalyst determines the enantiomer purity of the product [34].

Consequently, in processes with the participation of chiral compounds, the enantiomer purity of the formed new chiral molecule is determined by the eutectic composition of the enantiomeric mixtures of the starting chiral compounds [12–14].

3.3.1. Effect of the eutectic composition of the resolving agent (ee$_{EUres}$) in course of kinetic control

At the resolutions of racemic mandelic acid (**MA**) and 2-chloro-mandelic acid (**CMA**) with (*R*)-pregabalin, the purity of the recoverable enantiomeric mixture (ee$_{DIA}$) is determined by the eutectic composition of the resolving agent (ee$_{EUres}$) in course of kinetic control 13.
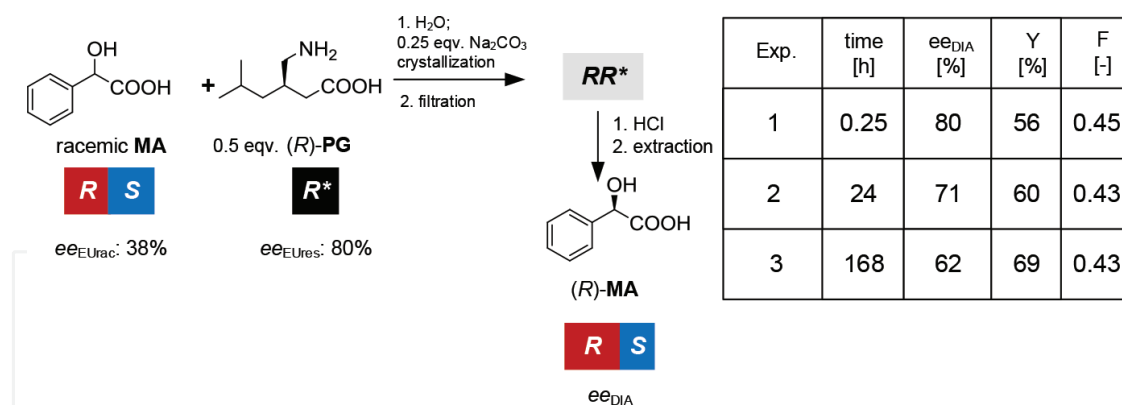
Scheme 5. Time-dependent resolution of racemic mandelic acid with (*R*)-pregabalin.
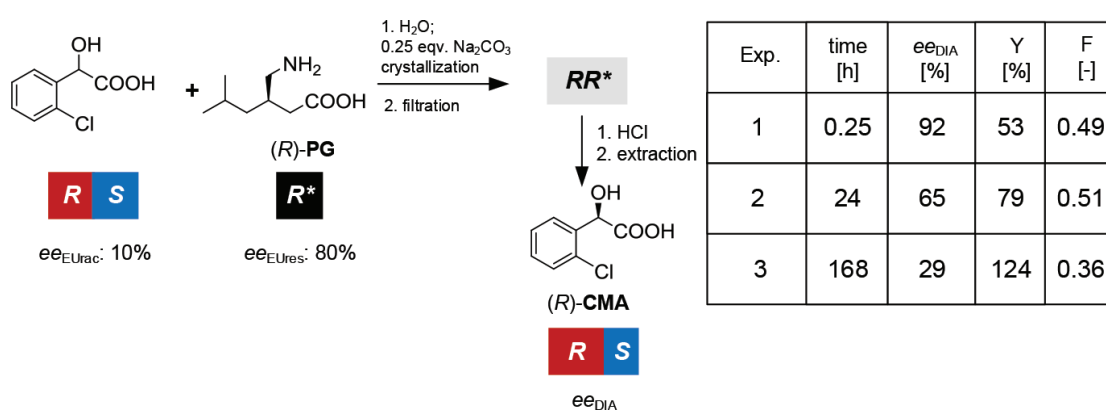
Scheme 6. Time-dependent resolution of racemic 2-chloro-mandelic acid with (*R*)-pregabalin.

By plotting the ee_{DIA} enantiomeric purity values of the enantiomeric mixtures of mandelic acid (**MA**) and 2-chloro-mandelic acid (**CMA**), recovered from the crystallized diastereomeric salt after the resolution with pregabalin (**PG**) (**Schemes 5** and **6**, respectively), in the function of time, it can be clearly seen that in the case of both **MA** and **CMA,** by increasing the time of the crystallization, the enantiomeric purity decreases (**Figure 8**). The highest enantiomer purity was reached by immediate filtration after crystallization. Regarding the eutectic compositions of **MA**, **CMA** and **PG** (ee_{EUrac} and ee_{EUres}), it seems that in course of kinetic control, the eutectic composition of the resolving agent (**PG**) affects the enantiomer purity of the recoverable enantiomeric mixtures of **MA** and **CMA**.

3.3.2. Effect of the eutectic composition of eutectic composition of the resolving agent (ee_{EUres}) in course of thermodynamic control

The resolution of 2-chloro-mandelic acid (**CMA**) was carried out using (*S*)-phenylalanine ((*S*)-**Phe**) as resolving agent (**Schemes 7** and **8**) [13] was observed the effect of thermodynamic control. In this case the eutectic composition of the resolving agent (ee_{EUres}) had a great influence on the purity of the obtained enantiomeric mixture (ee_{DIA}).
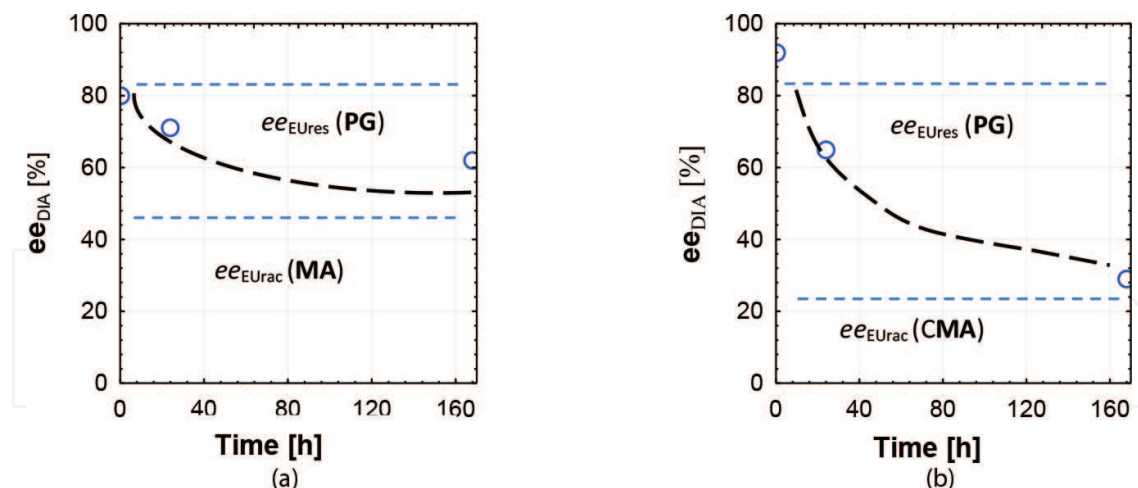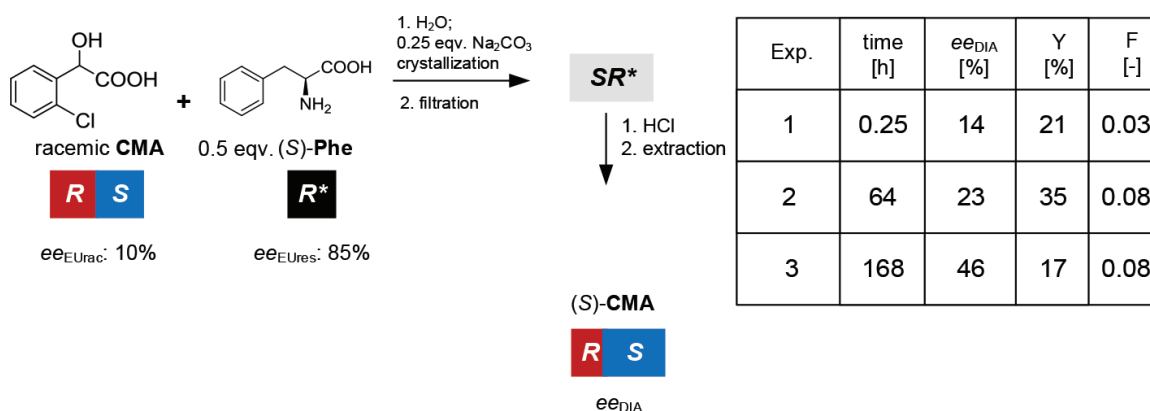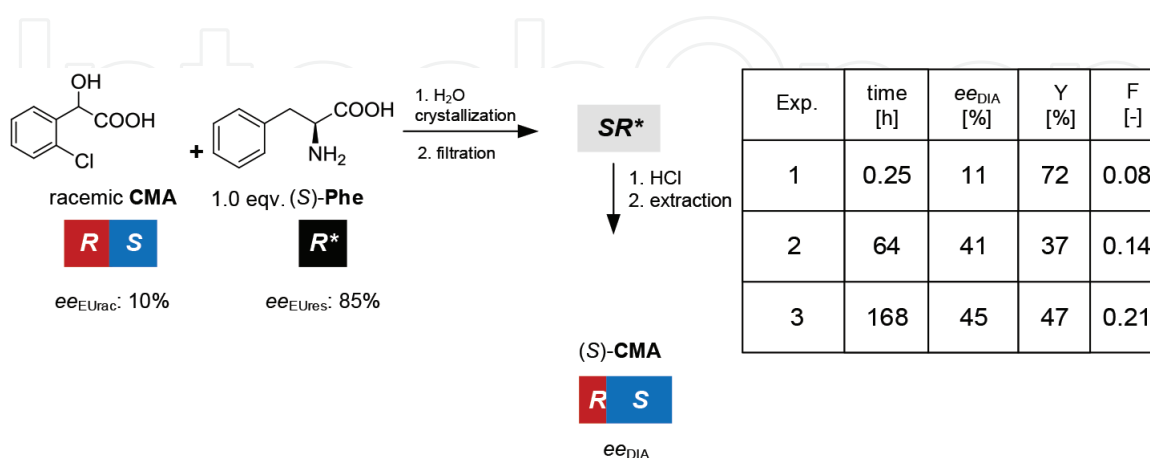
Figure 8. Effect of the crystallization time on the enantiomeric purity (ee_{DIA}) of the enantiomeric mixtures of **MA** (A) and **CMA** (B), recovered from the diastereomeric salt. The resolving agent was PG.

Exp.	time [h]	ee_{DIA} [%]	Y [%]	F [-]
1	0.25	14	21	0.03
2	64	23	35	0.08
3	168	46	17	0.08

Scheme 7. Resolution of racemic 2-chloro-mandelic acid with half-equivalent (*S*)-phenylalanine.

Exp.	time [h]	ee_{DIA} [%]	Y [%]	F [-]
1	0.25	11	72	0.08
2	64	41	37	0.14
3	168	45	47	0.21

Scheme 8. Resolution of racemic 2-chloro-mandelic acid with equivalent (*S*)-phenylalanine.
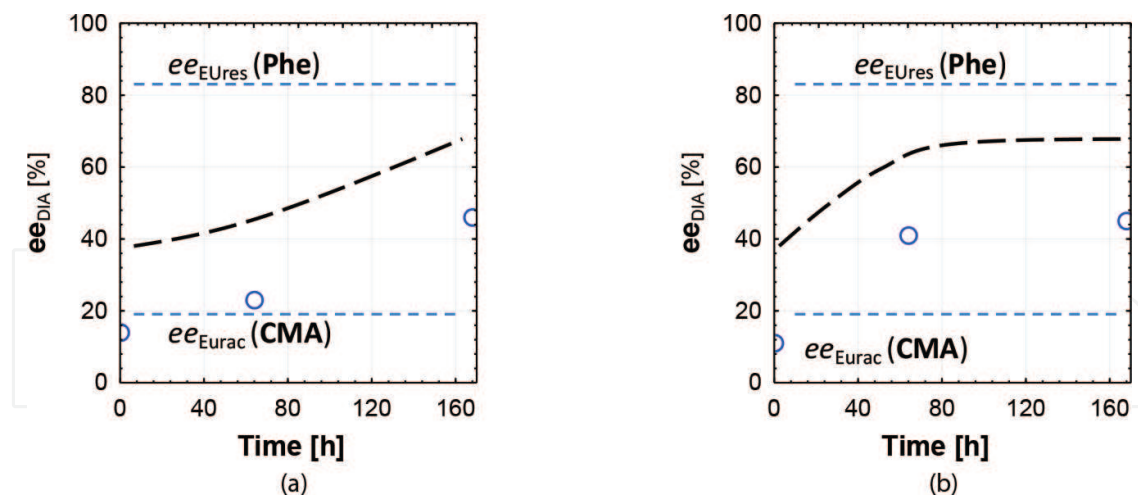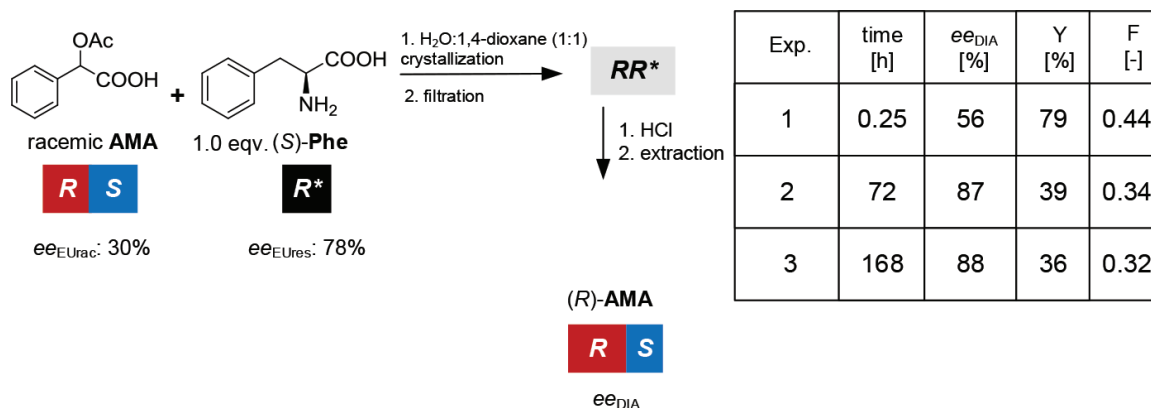
Figure 9. Effect of crystallization time on the enantiomer purity (ee_{DIA}) of **CMA** enantiomeric mixtures separated from the diastereomer salt after resolution with (S)-Phe, applying the methods of Pope-Peachey (a) and Pasteur (b).

Exp.	time [h]	ee_{DIA} [%]	Y [%]	F [-]
1	0.25	56	79	0.44
2	72	87	39	0.34
3	168	88	36	0.32

Scheme 9. Time-dependent resolution of the racemic O-acetyl-mandelic acid with 1.0 equivalent (S)-phenylalanine.

By plotting the time dependence of the resolutions, increasing enantiomeric purities can be seen with increasing crystallization times (**Figure 9**).

As the eutectic compositions are known (ee_{EUrac}: 10% and ee_{EUres}: 85%), it can be stated that in course of thermodynamic control, the enantiomer purity of the recoverable (S)-**CMA** enantiomeric mixture is determined by the eutectic composition of the resolving agent (ee_{EUres}) [14].

The resolving agent was the determinant for thermodynamic control when the enantiomers of racemic O-acetylmandelic acid (**AMA**) were separated by (S)-phenylalanine ((S)-**Phe**). (**Scheme 9**) [14].

By increasing the time of the crystallization, the (R)-**AMA** content of the crystalline phase increases. The thermodynamic equilibrium is determined by the eutectic composition of the resolving agent (**Figure 10**) [14].
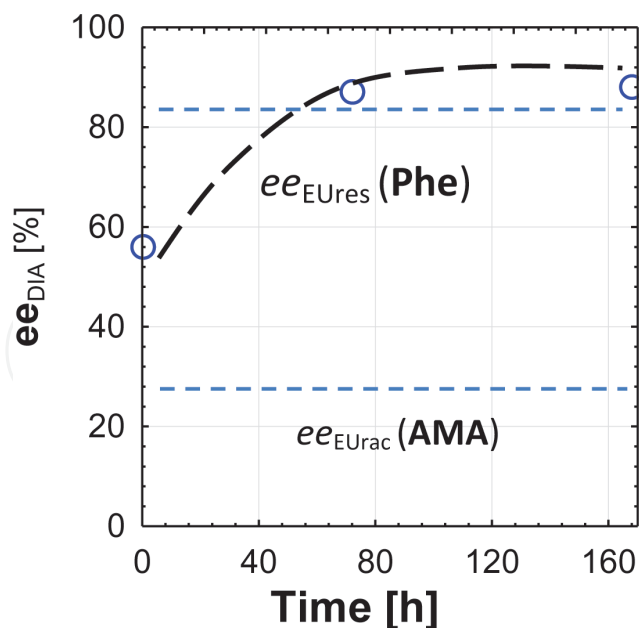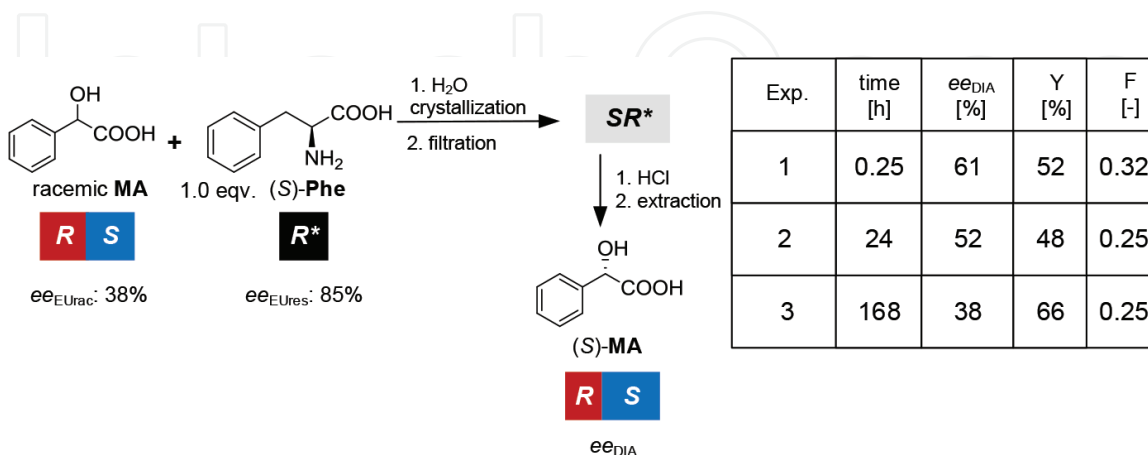
Figure 10. Effect of crystallization time on the enantiomer purity (ee_{DIA}) of enantiomeric mixtures of **AMA** separated from the diastereomer salt.

3.3.3. Effect of the eutectic composition of the racemic component (ee_{EUrac}) in course of thermodynamic control

The resolution of the racemic mandelic acid (**MA**) was carried out with (*S*)-phenylalanine [(*S*)-**Phe**] as resolving agent (**Scheme 10**). In this case, the purity of the recoverable enantiomeric mixture (ee_{DIA}) is determined by the eutectic composition of the racemic component (ee_{EUrac}) in course of thermodynamic control.

By plotting the enantiomer purity (ee_{DIA}) in the function of the crystallization time (**Figure 11**), it seems that in course of thermodynamic control, the enantiomer purity of the **MA** separated from the diastereomer salt decreases until the eutectic composition of the racemic mixture (ee_{EUrac}: 38%).

Scheme 10. Resolution of racemic mandelic acid (**MA**) with 1.0 equivalent (*S*)-phenylalanine [(*S*)-**Phe**].
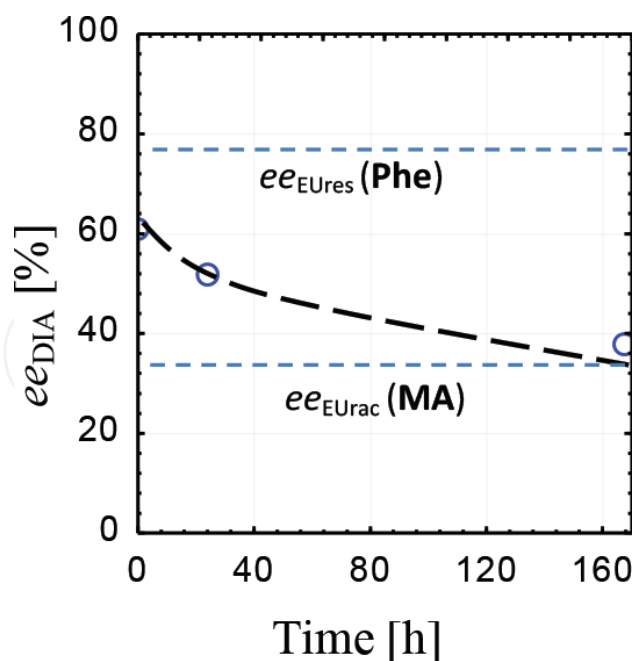
Figure 11. Effect of crystallization time on the enantiomer purity (ee_{DIA}) of the enantiomer mixtures of **MA** separated from the diastereomer salt.

4. Crystallization of diastereomers at different temperatures

The results of the resolutions based on salt formation can be influenced by changing the parameters. In order to reach higher purities, the temperature of the crystallization can be altered. The racemic mandelic acid has been resolved with (R)-pregabalin in water. The crystalline segregate was stirred for 168 hours at 26 and at 40°C. After filtration, the diastereomer salt was broken down, resulting in the enantiomeric mixtures of (R)-**MA** (**Scheme 11**).

The enantiomer purity of (R)-**MA** mixture was 81% at 26°C, while 93% enantiomeric excess was received at 40°C. The temperature-dependent solubility tests of the diastereomers have shown that by increasing the temperature, the difference in the solubility of the diastereomers may increase (**Figure 12**) [33, 35, 36].

Exp.	time [h]	T [°C]	ee_{DIA} [%]	Y [%]	F [-]
1	168	26	81	84	0.68
2	168	40	93	50	0.47
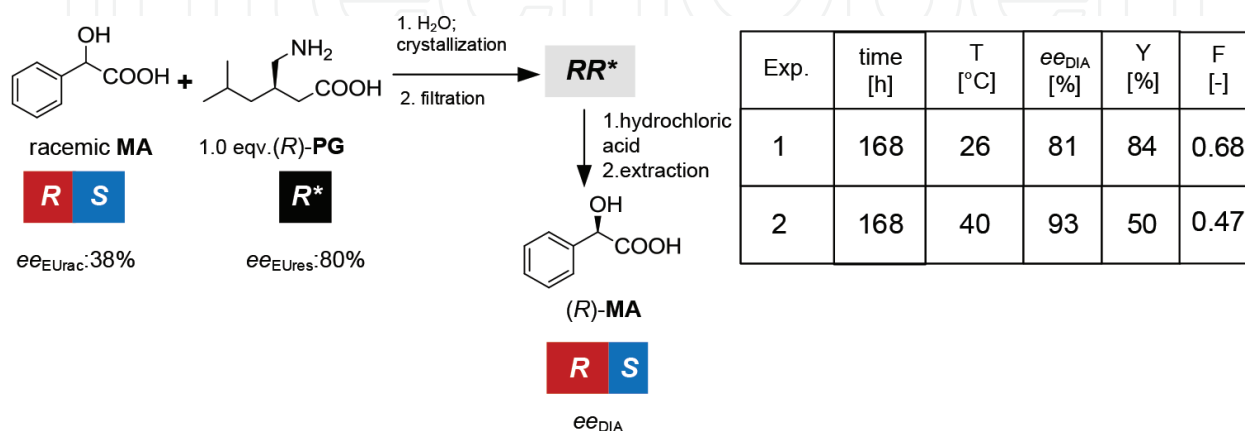
Scheme 11. Resolution of mandelic acid with pregabalin enantiomer at different temperatures.
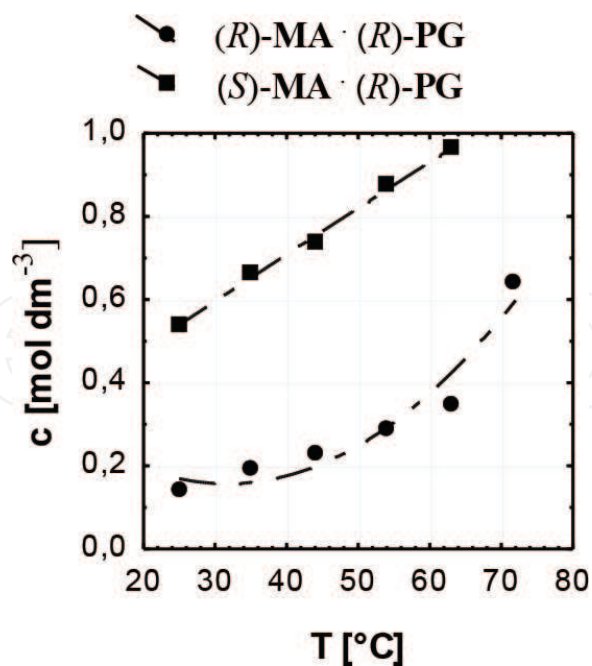
Figure 12. Temperature-dependent solubility of (S)-**MA**·(R)-**PG** and (R)-**MA**·(R)-**PG** diastereomers.

5. Effect of ultrasound on the composition of the diastereomeric salt

The resolution of the racemic etodolac (**ETO**) was carried out using cinchonidine (**CIN**) as resolving agent, with the application of seed and ultrasound. During the experiment, the ethanol solution was heated until complete dissolution of the components, followed by a crystallization of 4 hours at 0°C. During cooling, the reaction mixture was seeded with (R)-**ETO.CIN** diastereomer, which was then sonicated for 5 min, resulting in (R)-**ETO** enantiomer mixture of 99% enantiomer purity (**Scheme 12**). In the case of room temperature stirring, the product was received with low yield and low optical purity (~ee: 40%), which indicates the almost simultaneous crystallization of the two diastereomers [37].
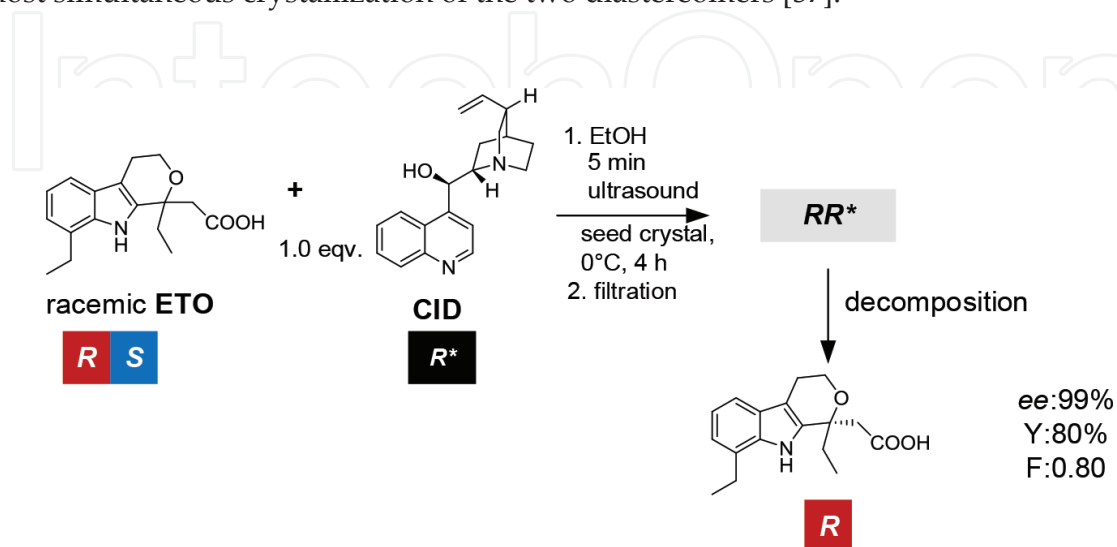
Scheme 12. Resolution of etodolac with the application of ultrasound.
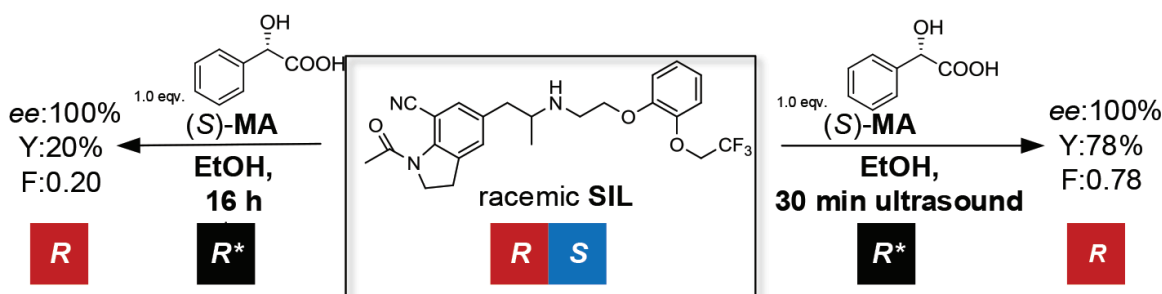
Scheme 13. Resolution of silodosin intermediate.

The resolution of the intermediate of silodosin (**SIL**) was carried out with (*S*)-mandelic acid (**MA**) during sonication (for 30 min) by Sun et al. They found a threefold increase in the yield. The ultrasound intensified the separation of the more stable diastereomer, ensuring fast crystallization in case of resolution based on salt formation (**Scheme 13**) [38].

The resolution of the racemic 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole (**TET**) was carried out with (*R,R*)-dibenzoyl-tartaric acid ((*R,R*)-**DBTA**) in water/dichloromethane non-miscible solvent mixture [36].

Comparative experiments were executed to determine the effect of the ultrasound treatment compared with conventional stirring. The racemic tetramisol was dissolved in the mixture of dichloromethane and water at 40°C. The resolving agent, 0.3 mol equivalent (*R,R*)-**DBTA**, was dissolved in dichloromethane at 40°C, and then the solutions were unified and cooled to 5°C. The speed of the magnetic stirrer was 500 rpm. The ultrasound treatment was carried out for 1, 5, 10, 15, 10 and 30 min, using a Bandelin Sonopuls HD 2200 apparatus, with 4.3, 6.5 and 11.0 W powers. After the appearance of the first crystal, the diastereomeric salt was allowed to crystallize for different times, that is for 1, 10, 20 and 30 min, followed by filtration. The diastereomeric salt was analyzed with chiral HPLC (**Figure 13**).

By filtrating the formed diastereomeric salt after 1 min of crystallization, (*S*)-tetramisol ((*S*)-**TET**) of 48% enantiomer purity could be separated with a yield of 91% (**Figure 14**).

By increasing the time of the crystallization, the enantiomer purity of the recoverable enantiomeric mixture decreases, while the yield increases. When the time of the crystallization was 30 min, the enantiomer purity decreased to 12%. The efficiency of resolution (F) values shows a significant decrease with increasing crystallization time (from 0.44 to 0.12). This is the beneficial effect of the kinetic control.

Immediate crystal precipitation was observed in the course of the application of ultrasound. When applying ultrasound of 4.3 W power, after 1 min an enantiomer purity of 39% and a yield of 84% were reached. By increasing the time of the sonication, the enantiomeric mixture of tetramisol could be separated from the diastereomeric salt with an *ee* between 54 and 64% and the yield was between 78 and 93%. The efficiency of resolution increased from 0.43 to 0.55 in course of sonication for 5–30 min (**Figure 15**). The use of ultrasound of 6.5 and 11.0 W power, respectively, resulted in almost the same *ee*, Y and F values after 30 min of sonication. Practically, the enantiomer purity was constant during the sonication.
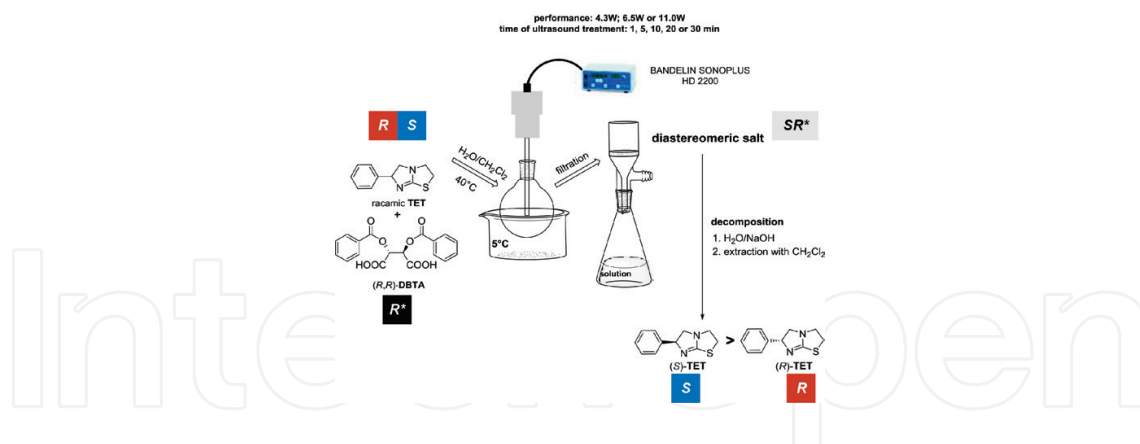
Figure 13. Schematic illustration of the experiments carried out with the application of ultrasound.

Figure 14. Enantiomer purity (A), yield (B) and efficiency of resolution value (C) of the enantiomeric mixture of tetramisol separated from the diastereomeric salt, in the function of the crystallization time, without the application of ultrasound (average values of three parallel experiments).
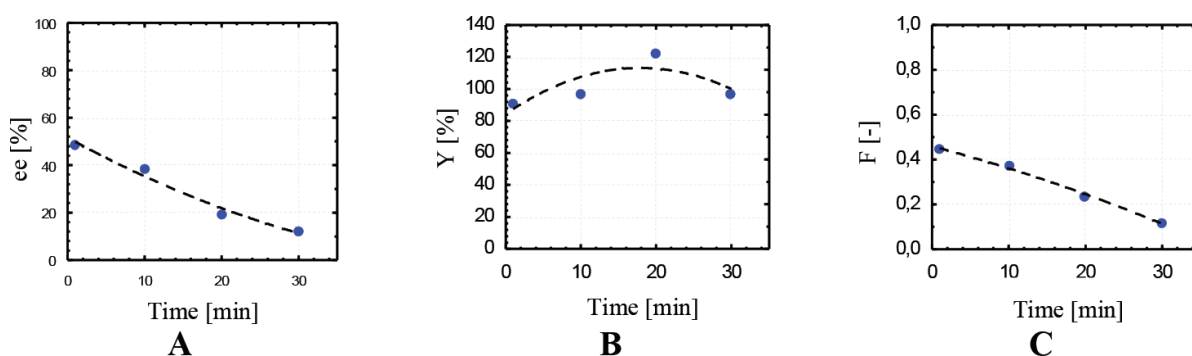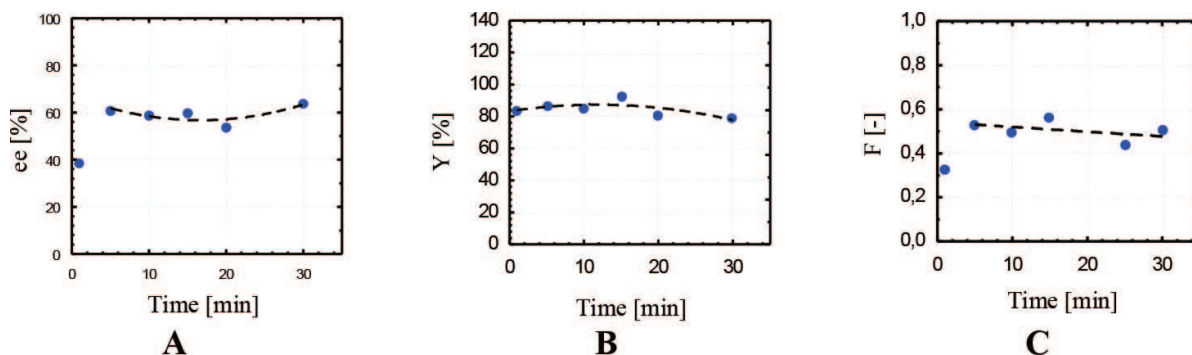

Figure 15. Enantiomer purity (A), yield (B) and efficiency of resolution value (C) of the enantiomeric mixture of tetramisol separated from the diastereomeric salt, in the function of the crystallization time, with the application of ultrasound of 4.3 W (average values of three parallel experiments).

6. Conclusion

One of the possibilities for the separation of mixtures of chiral compounds (for both enantiomers and diastereomers) is their non-linear distribution between two phases.

It is noteworthy that the result of the crystalline segregation can be essentially changed by the set of appropriate pH value. The recent recognition of the effect of the kinetic control

combined with ultrasound treatment, leading to a time-independent stabilization and amelioration of the result of the separation, is also remarkable.

The equilibriums can also be significantly affected by the formation of solvate molecules or with the built-in of non-solvent molecules of similar molecular architecture to the crystalline structure during the formation of the solid phase.

Acknowledgements

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References

[1] Newman P. Optical resolution procedures of chiral compounds 1-3. New York: Resolution Information Center. 1978-1984

[2] Wilen SH. Resolving agents and resolutions in organic cehemistry. In: Eliel EL, Allinger NL, editors. Topics in Stereochemistry. Vol. 107. New York: Wiley-Interscience; 1972

[3] Jaques J, Collet A, Wilen SH. Enantiomers, Racemates, and Resolutions, John Wiley & Sons, Inc., New York, Chichester, Brisbane, Toronto 1981

[4] Faigl F, Kozma D. Optical Resolution via Complex Formation with O,O′-Dibenzoyltartaric Acid, in Enantiomer Separation: Fundamentals and Practical Methods Chapter 3. (Edited by Toda, F.), Kluwer Academic Publishers, Dordrecht, Hollandia, 2004. p. 73

[5] Fogassy E, Nógrádi M, Pálovics E, Schindler J. Resolution of Enantiomers by Non-Conventional Methods Synthesis. 2005;**10**:1555

[6] Fogassy E, Nógrádi M, Kozma D, Egri G, Pálovics E, Kiss V. Optical resolution methods. Organic and Biomolecular Chemistry. 2006;**16**:3011

[7] Faigl F, Fogassy E, Nógrádi M, Pálovics E, Schindler J. Strategies in optical resolution (a practical guide). Tetrahedron: Asymmetry. 2008;**4**:519

[8] Sheldon RA. Chirotechnology: Industrial Synthesis of Optically Active Compounds. New York: Marcel Dekker; 1993

[9] Wilen SH, Collet A, Jaques J. Strategies in optical resolutions. Tetrahedron. 1977;**33**:2725

[10] Kobayashi Y, Kodama K, Saigo K. Supramolecular Architecture Consisting of an Enantiopure Amine and an Achiral Carboxylic Acid: Application to the Enantioseparation of Racemic Alcohols. Organic Letters. 2004;**17**:2941

[11] Pálovics E, Szeleczky Z, Faigl F, Fogassy E. In: Muntean SG, Tudose R, editors. Correlations between Separations of Enantiomeric- and Diastereomeric Mixtures, New Trends and Startegies in the Chemistry of Advanced Materials. 2013. pp. 74-79

[12] Pálovics E, Szeleczky Zs, Fődi B, Faigl F, Fogassy E. In How is the enantiomeric recognition influenced by the interactions of chiral systems? New trends and startegies in the chemistry of advanced materials with relevance in biological systems, technique and environmental protection. (Ed. Tudose R); 2015. pp. 14-16

[13] Pálovics E, Szeleczky Z, Fődi B, Faigl F, Fogassy E. Prediction of the efficiency of diastereomer separation on the basis of the behaviour of enantiomeric mixtures. RSC Advances. 2014;**4**:21254-21261

[14] Szeleczky Z, Bagi P, Pálovics E, Fogassy E. The effect of the eutectic composition on the outcome of kinetically and thermodynamically controlled resolutions that are based on the formation of diastereomers. Tetrahedron: Asymmetry. 2015;**26**:377-384

[15] Pálovics E, Schindler J, Faigl F, Fogassy E. Behavior of structurally similar molecules in the resolution processes. In: Carreira EM, Yamamoto H, editors. Comprehensive Chirality. Amsterdam: Elsevier; 2012. pp. 91-95

[16] Szeleczky Zs, Semsey S, Bagi P, Pálovics E, Faigl F, Fogassy E. Selecting resolving agents in respect of their eutectic compositions. Chirality: The pharmacological biological and chemical consequences of molecular asymmetry. 2016;**28**(3)**:**230-234

[17] Szeleczky ZS, Bagi P, Pálovics E, Faigl F, Fogassy E. The pH-dependency of diastereomeric salt resolutions with amphoteric resolving agents. Journal of Chemical Research-Synopses. 2016;**40**(**1**):21-25

[18] Szeleczky Zs, Kis-Mihály E, Semsey S, Pataki H, Bagi P, Pálovics E, Gy M, Gy P, Fogassy E, Madarász J. Effect of ultrasound-assisted crystallization in the diastereomeric salt resolution of tetramisole enantiomers in ternary system with O,O'-dibenzoyl-(2R,3R)-tartaric acid. Ultrasonics Sonochemistry. 2016;**32**:8-17

[19] Zhong N, Zhao X, Ma H, Chen Y. WO Patent 2007/0096661

[20] Jang SY, Kim S, Yun S, Bang HJ, Kim HK, Suh KH. Method for preparing (S)-(-)-amlodipine or a salt thereof and an intermediate used therein WO Patent 2008/100023. Chemical Abstracts. 2008;**149**:274860

[21] Bereczki L, Pálovics E, Bombicz P, Pokol G, Fogassy E, Marthi K. Optical resolution of N-formylphenylalanine succeeds by crystal growth rate differences diastereomeric salts. Tetrahedron:Asymmetry. 2007;**18**:260-264

[22] Szeleczky Z, Bagi P, Fődi B, Semsey S, Pálovics E, Faigl F, Fogassy E. Non-linear effects in the enantiomeric separation of mandelic acid using the mixtures of amphoteric resolving agents. Tetrahedron:Asymmetry. 2015;**26**:721-731

[23] Fogassy E, Faigl F, Ács M, Grofcsik A. Equilibrium-model of optical resolution via diastereomeric salt formation. Journal of Chemical Research. 1981;**11**:346-347

[24] Fogassy E, Faigl F, Ács M, Simon K, Kozsda É, Podányi B, Czugler M, Reck G. Structural studies on optical resolution via diasteroisomeric salt formation-enantiomer separation for cis-permethrinic acid[cis-2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclo-propane-carboxylic acid]. Journal of the Chemical Society, Perkin Transactions. 1988;**2**:1385-1392

[25] Bálint J, Egri G, Kiss V, Gajáry A, Juvancz Z, Fogassy E. Unusual phenomena during the resolution of 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline(FTHQ): thermodynamic-kinetic control. Tetrahedron: Asymmetry. 2002;**12**:3435-3439

[26] Sakai K, Sakurai R, Hirayama N. Chiral discrimination controlled by the solvent dielectric constant. Tetrahedron: Asymmetry. 2004;**15**:1073-1076

[27] Sakai K, Sakurai R, Akimoto T, Hirayama N. Molecular mechanism of dielectrically controlled optical resolution (DCR). Organic and Biomolecular Chemistry. 2005;**3**:360-365

[28] Shitara H, Shintani T, Kodama K, Hirose T. Solvent-Induced Reversed Stereoselectivity in Reciprocal Resolutions of Mandelic Acid and erythro-2-Amino-1,2-diphenylethanol. Journal of Organic Chemistry. 2013;**78**:9309-9316

[29] Sakurai R, Sakai K, Kodama K, Yamaura M. Dielectrically controlled resolution (DCR) of 3-aminopiperidine via diastereomeric salt formation with N-tosyl-(S)-phenylalanine. Tetrahedron: Asymmetry. 2012;**23**:221-224

[30] Sakai K, Sakurai R, Nohira H, Tanaka R, Hirayama N. Practical resolution of 1-phenyl-2-(4-methylphenyl)ethylamine using a single resolving agent controlled by the dielectric constant of the solvent. Tetrahedron: Asymmetry. 2004;**15**:3495-3500

[31] Kitamoto Y, Suzuki K, Morohashi N, Sakai K, Hattori T. Switching of the Diastereomer Deposited during the Crystallization of N-[(S)-1-Phenylethyl]-2′-carbamoyl-1,1′-binaphthalene-2-carboxylic Acid: Investigation of the Mechanism of Dielectrically Controlled Resolution. Journal of Organic Chemistry. 2013;**78**:597-605

[32] Kodama K, Kimura Y, Shitara H, Yasutake M, Sakurai R, Hirose T. Solvent-induced chirality control in the enantioseparation of 1-phenylethylamine via diastereomeric salt formation. Chirality. 2011;**23**:326-332

[33] Gizur T, Törley J, Fogassy E, Bálint J, Egri G, Demeter Á. Process for preparing tamsulosin hydrochloride. WO Patent 2004022532; Chemistry Abstract. 2004;**253341**:140

[34] Blackmond DG, Klussmann M. Spoilt for choice: assessing phase behavior models for the evolution of homochirality. Chemical Communications. 2007:3990-3996

[35] Nemák K, Ács M, Jászay ZM, Kozma D, Fogassy E. Study of the diastereomers formed formed between pipecolic acid N-alkylanilides and 2R,3R-tartaric acid or O,O'-dibenzoyl-2R,3R-tartaric acid. Do the tartaric acids form molecular complexes instead of salts during optical resolutions? Tetrahedron. 1996;**52**:1637-1642

[36] Szeleczky Zs. New recognition int he processes of diastereomeric salt resolution. PhD Thesis, Budapest University of Technology and economics, 2015, https://repozitorium.omikk.bme.hu/bitstream/handle/10890/1494/tezis_eng.pdf?sequence=4&isAllowed=y

[37] Ge L, Zhao Q, Yang K, Liu S, Xia F. Optical Resolution and Optimization of (R,S)-Propranolol Using Dehydroabietic Acid Via Diastereomeric Crystallization. Chirality. 2015;**27**:131-136

[38] Chou S, Tseng C, Chang L. Exploration of an Efficient Method for Optical Resolution of Etodolac. Journal of the Chinese Chemical Society. 2001;**48**:229-234