BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLÁH DOCTORAL SCHOOL

NEW RECOGNITIONS IN THE PROCESSES OF DIASTEREOMERIC SALT RESOLUTION

Summary of PhD Thesis

Author:
Zsolt Szeleczky

Supervisor:
Prof. Dr. Elemér Fogassy

Consultant:
Dr. Emese Pálovics

Department of Organic Chemistry and Technology

2015

1. *Structure and results of PhD thesis*

The production of enantiopure compounds by methods which are based on crystallization seems to be an obsolete technology compared to asymmetric synthesizes and chromatographic resolutions, however the majority of enantiopure pharmaceutical agents are still prepared this way industrially. [1] It is known, that the separation of enantiomeric mixture could be accomplished between every kind of two phases which are based on formation of homo- and heterochiral associates and their diastereomeric interactions, that was named the self-disproportionation of enantiomers (SDE) by *Soloshonok* et al.[2] According to *Pasteur*'s observation, the separation of enantiomers could be accomplished, if the racemic compound reacts with the appropriate chiral compound, so-called the resolving agent (and maybe with achiral additive).[3] Then the associates with diastereomeric interaction are formed, which can be separated with crystallization due to the different chemical and physical properties (for example solubility). After the decomposition of separated diastereomers, the corresponding enantiomeric mixture and regenerated resolving agent can be produced. Usually, pure enantiomers can only be obtained by further purification of these enantiomeric mixtures. The structure of my PhD thesis can be seen on Figure 1.

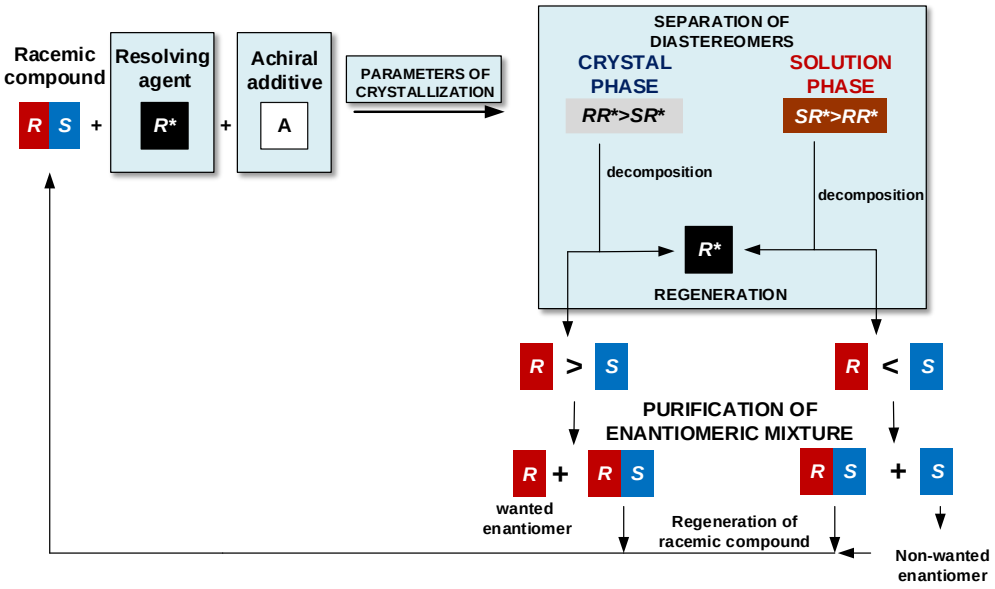

Figure 1. Route to the pure enantiomers via diastereomeric salt resolution

1.1 *Resolving agent*

During the elaboration of a new resolving method the first step is the selection of the resolving

[1] Murakami, H., From Racemates to Single Enantiomers – Chiral Synthetic Drugs over the last 20 Years. In *Novel Optical Resolution Technologies*, Sakai, K.; Hirayama, N.; Tamura, R., Eds. Springer Berlin Heidelberg: 2007; Vol. 269, pp 273-299.
[2] Soloshonok, V. A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. E., *Chemical Society Reviews* **2012,** *41*, 4180-4188.
[3] Pasteur, L., *Comptes rendus de l'Académie des Science* **1853**, 26, 162.

agent. In some experiments that is performed with trial-and-error manner, but thermoanalytic and conformation-based methods can help with the selection. Regarding that we wanted to know if there is any kind of initial characteristic of the racemic molecule whereby we can select the ideal resolving agent. If there is a self-disproportionation of enantiomer mixtures there can be an arrangement during formation of diastereomeric associates, and so during the distribution of the diastereomer pairs between the two phases.

Formerly, approaching this we examined the interactions of structurally related compounds, as there is structural analogy between the compounds which forms the diastereomer we expect, that a reaction mixture like this acts as an enantiomer mixture. Investigating the resolution of structurally analogues compounds it turned out that interestingly the eutectic composition of the racemic compound appears in the statistic average of the enantiomer mixture's enantiomer purity. [4] Following that, we wanted to examine the same concept regarding structurally non-related resolutions. When resolutions were carried out with structurally non-related resolving agents (45 examples), similar correlation was observed between the average purity of the enantiomeric mixtures obtained after resolution (ee_{DIA} :78%) and the eutectic composition of the racemic compounds (ee_{EUrac} : 73%). Accordingly, the composition of diastereomeric salt must depend on eutectic composition of racemic compounds. But in the case of mixture of chiral compounds, the role of resolving agent cannot be excluded. As it turned out, there is similarly proper correspondence. When the eutectic composition of the resolving agent was higher than that of the racemic compound (29 examples), the parity was even higher between the average purity of enantiomeric mixtures (ee_{DIA} :80%) and the average eutectic composition of the resolving agents (ee_{EUres} : 78%). [S1,S5,S6]

Although we know well that the diastereomeric salt resolution depends on many parameters, firstly we tried to confirm our initial hypothesis, that the behavior or self-disproportionation of enantiomeric mixture determines the final result of the resolution, with the statistics having large size of sample. After all we wanted to study our hypothesis with sole systematic resolutions. Therefore, we studied the racemic mandelic acid (**MA**) and its derivates, the 2-chloromandelic acid (**CMA**) and the *O*-acetylmandelic acid (**AMA**), diastereomeric salt resolution with amino acids including 3-(aminomethyl)-5-methylhexanoic acid (Pregabalin) (**PG**), phenylalanine (**Phe**) in free state in respect of crystallization time. In this particular series of resolutions, we have found that the eutectic composition of either the racemic compound or the resolving agent may influence the purity of the enantiomeric mixture under kinetic or thermodynamic control. [S2-S3]

As we uses average data before, *Sakai* et al. carried out experiments with 1-aryl-1-alkylamine and 2-hydroxycarboxylic acid, proving through reverse resolution processes the significance of the

[4] Pálovics, E.; Schindler, J.; Faigl, F.; Fogassy, E., Behavior of Structurally Similar Molecules in the Resolution Processes. In *Comprehensive Chirality*, Carreira, E. M.; Yamamoto, H., Eds. Elsevier: Amsterdam, 2012; pp 91-95.

relative length between the racemic and the resolving agent molecules. They defined molecule length as the number of atoms from the α atom to the end of the molecule. Following 20 resolutions, they concluded that the highest quality separation is achievable through the utilization of a resolving agent with the same molecule length as the racemic molecule.[5] However, under our previous observation, higher resolvability could be achieved through using a resolving agent with a molecule length significantly different from that of the racemic molecule. In order to clarify the antilogy, results of 49 diastereomeric salt resolution were catalogued by our workgroup. Most of these resolutions have been put into industrial use now and the results were produced under optimal conditions. Considering the large quantity and diversity of these resolutions, the statistical conclusions based on this sample could be scientifically justified. According to this study, it seems using an absolute molecule length difference of zero or 3 to 6 produces the best resolutions.[S12]

Dutch researchers found that the application of a mixture of resolving agents with similar characteristics may lead to more efficient enantiomeric separations than the sole application of a given resolving agent (Dutch resolution).[6] We applied mixtures of amino acids with non-basic side chain and isoelectric point of c.a. 6 as the resolving agent. (*S*)-Phenylalanine [(*S*)-**Phe**] and (*S*)-3-(aminomethyl)-5-methylhexanoic acid [(*S*)-pregabalin] [(*S*)-**PG**] were chosen for α- and γ-amino acid, respectively The aspartame (L-aspartyl-L-phenylalanine methyl ester) [(*S*,*S*)-**AP**], which incorporates a β-amino acid moiety. Mandelic acid (**MA**) was chosen as the racemic compound. Under the series of resolution experiment with the mixtures of amino acids we noticed that the mixture that was structurally similar the most resulted the best separation. Also, a significant improvement in the efficiency of the resolution was observed when the resolution of mandelic acid was accomplished with a mixture of the structurally related (*S*)-phenylalanine and (*S*)-alanine.[S4]

1.2 Achiral additive

Apart from resolving agent using achiral additive could affect the final result of diastereomeric salt resolution. Based on our previous studies, the resolution efficiency can also be improved by using achiral additives with a similar structure to either the racemic compound or the resolving agent. First of all, in the sphere of amphoteric resolving agents we investigated amphoteric achiral additives, such as glycine (**Gly**), β-alanine (**beta-Ala**) and γ-aminobutyric acid (**GABA**) with similar structures to the corresponding resolving agent (Figure 2.) According to the results, the efficiency of mandelic acid (**MA**) resolution could also be improved by applying structurally related amphoteric achiral additives along with the corresponding resolving agents.[S4]

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[5] Sakai, K.; Sakurai, R.; Nohira, H., New Resolution Technologies Controlled by Chiral Discrimination Mechanisms. In *Novel Optical Resolution Technologies*, Sakai, K.; Hirayama, N.; Tamura, R., Eds. Springer Berlin Heidelberg: 2007; Vol. 269, pp 199-231.

[6] Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J., *Angewandte Chemie International Edition* **1998**, *37*, 2349-2354.

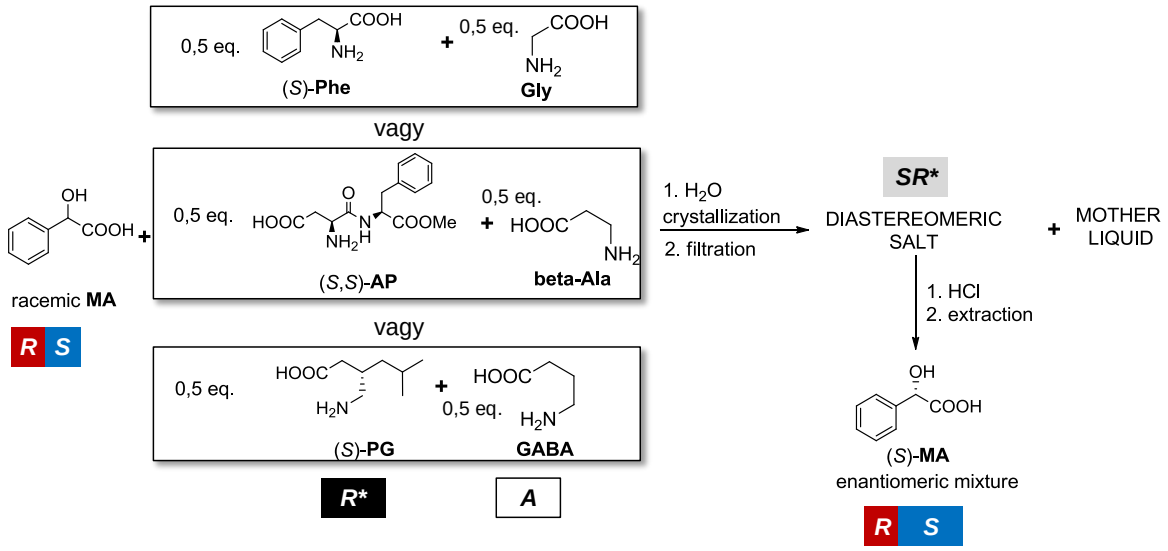


Figure 2. Using achiral amino acid additives

The pH of solution could be influenced with using inorganic acid or base, which are particular achiral additives. Due to their amphoteric character, the ionization state of amino acids varies with pH. They could be in protonated form, zwitterionic form or deprotonated form depending on the pH. Because of this feature of amino acids, we studied the pH-dependency of mandelic acid resolution using (*S*)-phenylalanine or (*R*)-pregabalin as resolving agent. In the case of both resolutions we discovered that best resolvability value can be achieved if we set nearly the same initial pH values as the pK_a of the carboxyl group of the resolving agent (Figure 3.; Figure 4.).

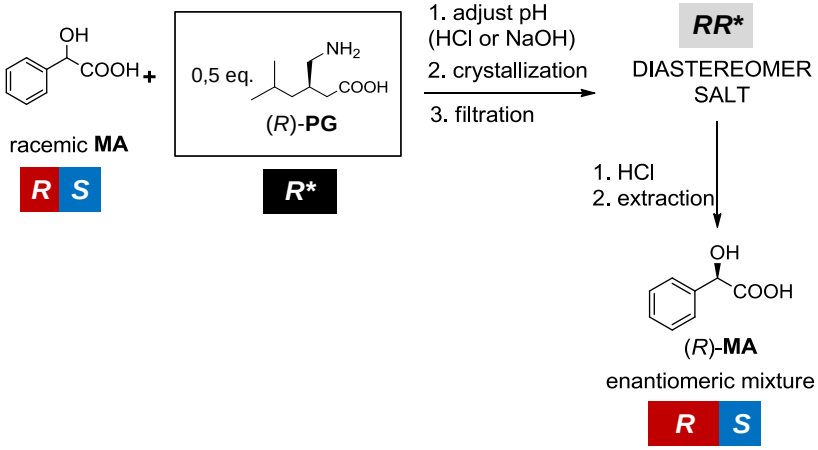


Figure 3. pH-dependency of the MA resolution with (*R*)-PG

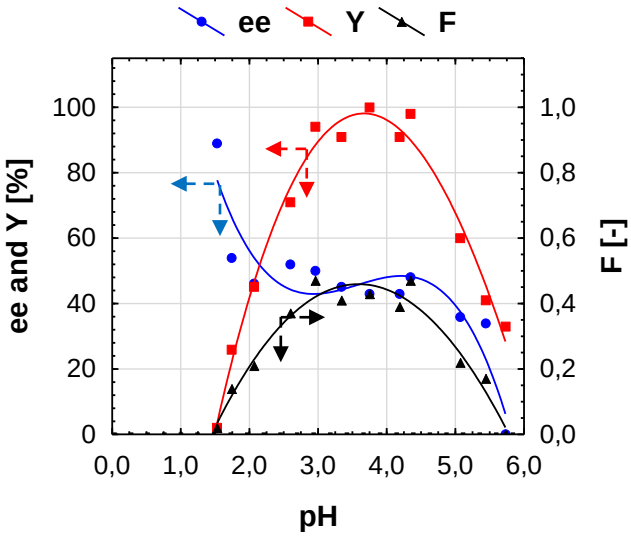


Figure 4. Enantiomeric purity (*ee*), yield (Y) and resolvability (F) of mandelic acid isolated from crystalline diastereomers in function of pH

Not only acids and bases could be applied as achiral additive, but also compounds which have not chemical characteristics. This type of compound are the solvates or compounds which are similar to solvates but not solvents. We applied this concept successfully in the resolution of a pharmaceutical

ingredient. The enantioseparation of racemic amlodipine via diastereomeric salt formation could be accomplished with solvate formation. In previous procedures, dimethylsulfoxide, dimethyl-formamide and dimethylacetamide were appropriate solvate forming solvent. According to our procedure we also achieved good separation in acetone applying mixture of thiourea and urea which are structurally related to previous solvate compounds. Furthermore, we developed a method for purification of amlodipine enantiomeric mixtures.

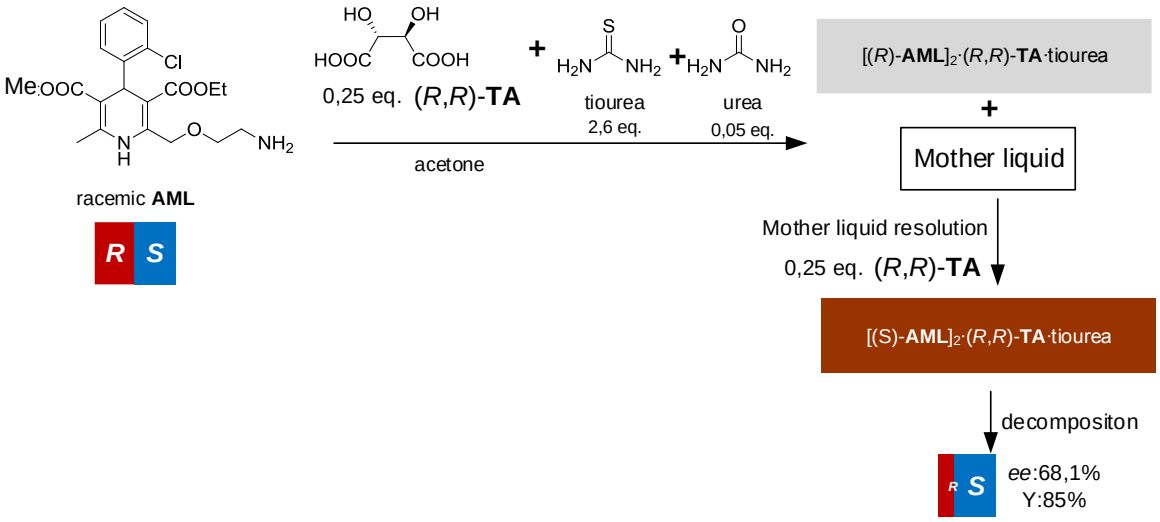


Figure 5. Diastereomeric salt resolution of amlodipine

1.3 Parameters of crystallization

Application of ultrasound to crystallization is a well-known method, although, there are just a few examples of the usage of ultrasound in the field of diastereomeric salt resolution.[7] It is known that manipulation of ultrasound effect can be achieved by changing ultrasound-related parameters such as frequency, duration, power and so forth. Consequently, our aim was the studying the effect of ultrasound duration and power on the composition of crystalline diastereomer and the results of optical resolutions. Our model was the resolution of racemic 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]tiazole [tetramisole] [**TET**] with (*R*,*R*)-dibenzoyl-tartaric acid [(*R*,*R*)-**DBTA**] as resolving agent. Comparative experiments were carried out using crystallization times of 5-30 minutes without ultrasound irradiation. Ultrasound experiments were carried out using duration times of 5-30 minutes and at 4.3W; 6.5W and 11.0W power. Without ultrasound the thermodynamic control decreased the enantiomeric purity of tetramisole isolated from crystalline diastereomer (Figure 7). However, the application of ultrasound could prevent the decrease of enantiomer excess. It seems that the effect of thermodynamic control predominate over the effect of kinetic control and it causes lower enantiomeric purity, and then the application of ultrasound can result efficient separation because of inhibition of crystallization of the less soluble diastereomer.

[7] Brave, I. J.; Chen, L.; Wei, P. C. P.; Hung, J.; Sun, C., *Tetrahedron* **2013,** *69*, 2834-2843.

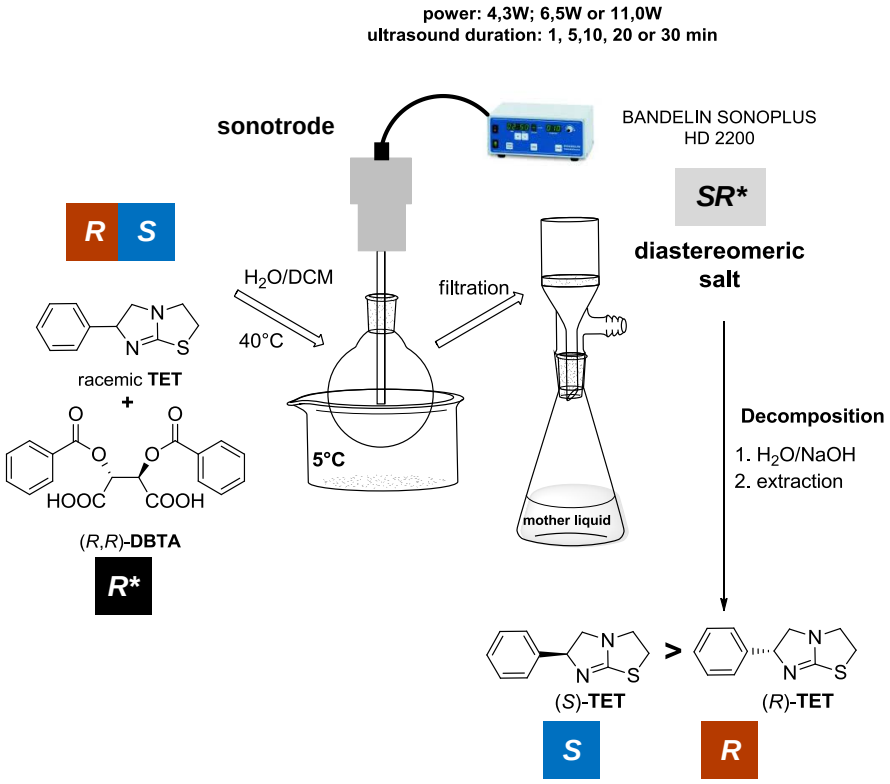


Figure 6. Schematic figure of ultrasound-assisted resolutions

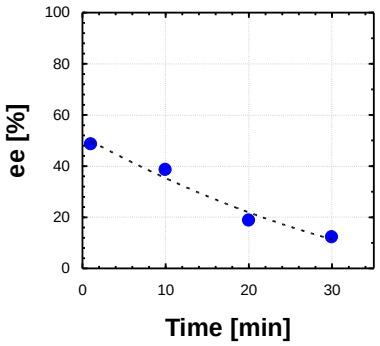


Figure 7. Enantiomeric purity of tetramisole isolated from crystalline diastereomers in function of crystallization time without ultrasound

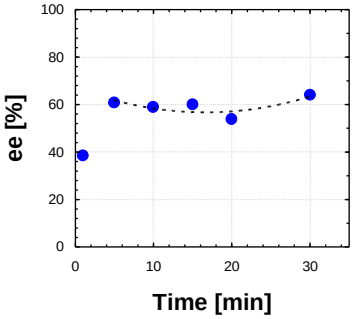


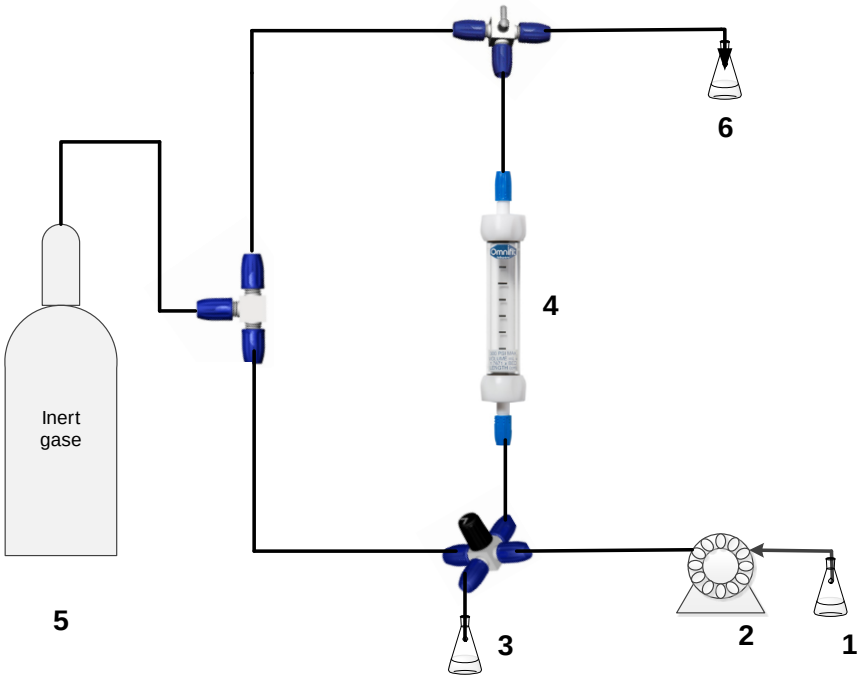
Figure 8. Enantiomeric purity of tetramisole isolated from crystalline diastereomers in function of crystallization time with ultrasound irradiation

1.4 Separation of diastereomers and regeneration of resolving agent

The diastereomeric salt resolutions usually are batch processes in the pharmaceutical industry. This method needs a lot of apparatus and time. We wanted to develop a new resolution process which has less demands for these. In the case of using a stirred tank reactor with filter basket to the crystallization process, number of apparatuses could be decreased. Because after the separation of the diastereomeric salt and mother liquid the decomposition of diastereomeric salt could be achieved in the crystallization reactor. If the resolving agent precipitated in conditions of decomposition while the enantiomeric mixture from crystalline diastereomer get to the solution phase, the recycling of resolving agent could be possible in the same reactor, and that we named the detention in a cage. The resolving agent could be applied as fixed catalysis bed. According to the concept, we used the calcium salt of (*R*,*R*)-dibenzoyl-tartaric acid monodimethylamide as a resolving agent in the resolution of hydrochloride salt of *treo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol. The resolving agent was placed on a nutsche filter and then the solution of racemic compound was reacted with this layer. After the fast crystallization, diastereomeric salt which stayed on the filter was decomposed and the resolving agent precipitated

above the filter. This resolving agent can be reused in the next resolution experiment. The crystallization processes were monitored by RAMAM spectroscopy and we determined the end points of crystallizations.

Considering the result of nutsche filter resolutions, we designed and constructed a fixed bed crystallization column in laboratory size. The mixing and the removing of mother liquids were accomplished by inert gas-inlet (Figure 9.). We named this new resolution method as „resolving agent in a cage".



1. Feeder **2.** Peristaltic pump **3.** Picker **4.** Crystallization column **5.** Gase reservoir **6.** Gase diversion

Figure 9. Scheme of appliance for method named „resolving agent in a cage"

2. Experimental methods

Conventional methods of preparative organic chemistry were used in resolutions. Ultrasonic irradiation was accomplished with a high-intensity ultrasonic probe (Bandelin Sonoplus HD 2200). Raman monitoring measurement was accomplished with Labram dispersion Raman spectrometer. The stoichiometry of the diastereomers was determined by ^{1}H NMR spectroscopy. The enantiomeric excess values were determined by chiral HPLC measurement (Gilson instrument, Phenomenex Lux® column) or by specific rotation determining. Optical rotations were determined using a Perkin-Elmer 241 polarimeter.

3. *Theses*

1. In the diastereomeric salt resolution, we found relationship between the enantiomeric purity of enantiomeric mixture isolated from the crystalline diastereomer and the behavior of enantiomeric mixtures of diastereomer components and even the molecule length difference of racemic and resolving agent. Either the eutectic composition of racemic compounds or the eutectic composition of resolving agent may determine the enantiomeric purity of enantiomeric mixture isolated from crystalline diastereomer. We made suggestion on the field of the process of optimal resolving agent selection according to which good separation are expected by using resolving agent which have high eutectic composition. **[S1,S5,S6,S9]**

2. We proved that when eutectic composition of racemic compounds or eutectic composition of resolving agent determines the composition of crystalline diastereomeric salt under the kinetic control, then in the case of thermodynamic control the eutectic composition of the other component determines the composition of crystalline diastereomeric salt. So the optimal enantioseparation can be provided by selection of the crystallization time.**[S2,S3]**

3. α-amino acid, γ-amino acid and β-amino acid moiety containing amphoteric compounds are suitable for the resolution of racemic acids as a resolving agent and with the application of their mixtures more efficient enantiomeric separation can be achieved compared with the given sole resolving agent. **[S4,S8,S10]**

4. With application of the mixture of α-amino acid, γ-amino acid, β-amino acid moiety containing amphoteric compounds and structurally related achiral amino acids more efficient enantiomeric separation can be achieved in the resolution of racemic acids compared with the given sole resolving agent. **[S4,S8]**

4. *Application of scientific results*

Our conclusions in the field of eutectic composition and molecule length can help preparative chemists with the selection of the ideal resolving agent. Our successful experiments with amphoteric resolving agent extend the group of possible resolving agents and show that the application of resolving agent mixtures can be also beneficial in the order to achieve better separation. Co-application of achiral additives and resolving agents can result better separation.

In my opinion, developing a resolving method the systematic search of achiral additives cannot be ignored because the price of this much lower than chiral compounds'. The solvate-like achiral additives should be examined in every optical resolution when solvate is produced. In the field of amphoteric resolving agent, we showed that the set of the appropriate pH leads to significant improvement of the separation. When the effect of thermodynamic control predominate over the

effect of kinetic control and it causes lower enantiomeric purity, and then the application of ultrasound can result efficient separation. Based on the method named „resolving agent in a cage" new resolution processes can be developed that need less apparatuses and time.

5. Publications

Full scientific publications related to the PhD Thesis:

[S1] Pálovics, E.; Szeleczky, Z.; Fődi, B.; Faigl, F.; Fogassy, E. Prediction of the efficiency of diastereomer separation on the basis of behaviour of enantiomer mixtures *RSC Advances* **2014**, 4, 21254-21261. **IF:3,840**

[S2] Szeleczky, Z.; Bagi, P.; Pálovics, E.; Fogassy, E. The Effect of SDE on the Separation of Diastereomeric Salts - A Case Study for the Resolution of Mandelic Acid Derivatives with Pregabalin *Tetrahedron: Asymmetry* **2014**, 25, 1095-1099. **IF: 2,155**

[S3] 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. **IF:2,155**

[S4] 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. **IF:2,155**

Proceedings related to the PhD Thesis:

[S5] Pálovics, E.; Szeleczky, Z.; Bagi, P.; Faigl, F.; Fogassy, E. Regularities between Separations of Enantiomeric and Diastereoisomeric Mixtures. Prediction of the Efficiency of Diastereomeric/Enantiomeric Separations on the Basis of Behaviour of Enantiomeric Mixtures *Periodica Polytechnica* **2015,** 59/1, 26-37. **IF: 0,296**

[S6] Pálovics, E., Szeleczky, Z.; Faigl, F.; Fogassy, E. "*New trends and strategies in the chemistry of advanced materials*." (Muntean, S. G., Tudose, R., ed.) 74. **2013**.

Other scientific publications related to the PhD Thesis:

[S7] Pálovics, E. Szeleczky, Z.; Faigl, F.; Fogassy, E. Amfoter karakterű vegyületek a reszolválás folyamataiban *Műszaki Szemle* **2013**, 61, 34-35. **IF:0**

[S8] Szeleczky, Z.; Fődi, B.; Pálovics, E.; Fogassy, E. Amfoter karakterű rezolválóágensek vizsgálata *Műszaki Szemle* **2013**, 62, 1-7. **IF:0**

[S9] Pálovics, E. Szeleczky, Z.; Fődi, B.; Faigl, F.; Fogassy, E. Kódolja-e a királis vegyületek tulajdonsága az enantiomerfelismerést? *Műszaki Szemle* **2013**, 62, 23-30. **IF:0**

Patent related to the PhD Thesis:

[S10] Fogassy, E. Pálovics, E.; Szeleczky, Z. Reszolválási eljárás amfoter karakterű vegyületek körében, Hungarian Patent No. 120027

Submitted manuscripts related to the PhD Thesis:

[S11] Szeleczky, Z.; Semsey, S.; Bagi, P.; Pálovics, E.; Faigl, F.; Fogassy, E. Selecting Resolving Agents in Respect of Their Eutectic Compositions *Chirality* (submitted)

[S12] Szeleczky, Z.; Bagi, P.; Semsey, S.; Fődi, B.; Pálovics, E.; Faigl, F.; Fogassy, E. An Aspect of Selecting Resolving Agents – The Role of Differences in Molecule Length in Diastereomeric Salt Resolutions *Separation Science and Technology* (submitted)

Other publication:

[S13] Szeleczky, Z. Enzyme catalysed kinetic resolution of trans-1,2-cyclohexanediol in a continuous high pressure reactor *Periodica Polytechnica* **2011**, *55/1*, 44. **IF: 0,269**

Oral presentations:

[S14] Szeleczky, Z.; Utczás, M.; Vida, L.; Simándi, B.; Székely, E. Transz-1,2-ciklohexándiol enzimkatalizált kinetikus reszolválása szuperkritikus szén-dioxidban, *XXXIII. Kémiai Előadói Napok*, Szeged, Hungary, 25-27th October 2010

[S15] Utczás, M., Székely, E.; Forró, E.; Tasnádi, G.; Monek, É.; Szeleczky, Z.; Szőllősy, Á.; Fülöp, F.; Simándi, B. Enzim katalizált reszolválás szuperkritikus szén-dioxidban, *MTA Vegyipari Műveleti Munkabizottsági ülés*, Veszprém, Hungary, 26th April 2012

[S16] Utczás, M.; Székely, E.; Forró, E.; Tasnádi, G.; Monek, É.; Szeleczky, Z.; Szőllősy, Á.; Fülöp, F.; Simándi, B. Enzimkatalizált reszolválások szuperkritikus szén-dioxidban, *Szuperkritikus Oldószerek Műveleti és Analitikai Alkalmazása '12*, Budapest, Hungary, 22th May 2012

[S17] Szeleczky, Z.; Pálovics, E.; Fogassy, E. Amfoter karakterű vegyületek alkalmazása reszolváló ágensként, *XXXV. Kémiai Előadói Napok*, Szeged, Hungary, 29-31th October 2012

[S18] Szeleczky, Z.; Pálovics, E.; Fogassy, E. Amfoter karakterű vegyület alkalmazása reszolválóágensként, *Tudomány Hete '12*, Dunaújváros, Hungary, 12-17th November 2012
(The abstract of presentation was printed in *Műszaki Szemle* **2013**, 62, 23-30.)

[S19] Pálovics, E.; Szeleczky, Z.; Faigl, F.; Fogassy, E. Correlations between separations of enantiomeric- and diastereomeric mixtures, *13th Edition Timisoara's Academic Days*, Timisoara, Romania, 13-14th June 2013

[S20] Szeleczky, Z.; Fődi, B.; Pálovics, E.; Fogassy, E. Amfoter karakterű reszolválóágensek vizsgálata, *XIX. Nemzetközi Vegyészkonferencia*, Baia Mare, Romania, 21-24th November 2013

[S21] Pálovics, E.; Szeleczky, Z.; Fődi, B.; Fogassy, E. Kódolja-e a királis vegyületek tulajdonsága az enantiomerfelismerést?, *XIX. Nemzetközi Vegyészkonferencia*, Baia Mare, Romania, 21-24th November 2013

[S22] Fődi, B.; Szeleczky, Z.; Pálovics, E.; Fogassy, E. Újszerű reszolváló ágensek és technológiák alkalmazása a diasztereomer sóképzéses reszolválásban, *XXXVII. Kémiai Előadói Napok*, Szeged, Hungary, 3-5th November 2014

[S23] Fődi, B.; Szeleczky, Z.; Pálovics, E.; Fogassy, E. Újszerű reszolváló ágensek és technológiák alkalmazása a diasztereomer sóképzéses reszolválásban, *Tudományos Hét 2014*, Dunaújváros, Hungary, 10-14th November 2013

[S24] Pálovics, E.; Szeleczky, Z.; Faigl, F.; Fogassy, E. Hogyan befolyásolják az enantiomer-felismerést a királis rendszerekben lejátszódó kölcsönhatások? *XX. Nemzetközi Vegyészkonferencia*, Cluj-Napoca, Romania, 6-9th November 2013

Posters:

[S25] Szeleczky, Z.; Utczás, M.; Simándi, B.; Székely, E. *Transz*-1,2-ciklohexándiol enzimkatalizált kinetikus reszolválása, *Műszaki Kémiai Napok '10*, Veszprém, Hungary, 27-29th April 2010

[S26] Szeleczky, Z.; Pálovics, E.; Fogassy, E. Resolution of mandelic acid with aspartame, *15th Austrian Chemistry Days*, Graz, Austria, 23-26th September 2013

[S27] Szeleczky, Z.; Pálovics, E.; Fődi, B.; Tóth, G.; Fogassy E. Chiral discrimination in diastereomeric salt formation, *Chirality 2014*, Prague, Czech Republic, 27-30th July 2014

[S28] Pálovics, E.; Szeleczky, Z.; Faigl, F.; Fogassy E. Prediction of efficiency of resolution processes based on the regularities observed and encoded in properties of racemic compounds and resolving agents, *New trends and strategies int he chemistry of advanced materials with relevance in biological systems, technique and environmental protection new trends and strategies int the chemistry of advanced*, Timisoara, Romania, 5-6th June 2014

[S29] Pálovics, E.; Szeleczky, Z.; Faigl, F.; Fogassy, E. Prediction of the efficiency in resolution processes, *5th EuCheMS Chemistry Congress*, Istambul, Turkey, 31th Augustus 2014

[S30] Tóth, G.; Szeleczky, Z.; Pálovics, E.; Fogassy, E. Development of high-throughput method for optimization of diastereomeric salt resolution, *12th International Conference "Students for Students"*, Cluj-Napoca, Romania, 22-26th April 2015