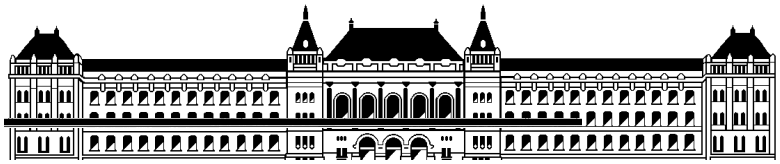

Budapest University of Technology and Economics

Structurally related compounds with common skeleton in the resolution processes

Ph.D. Theses

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1. Literature background

The separation of enantiomers is in the centre of undiminished interest of researchers since 160 years.
It was Pasteur, who showed in 1848, using the method of induced crystallisation of racemic compounds, that the strong tendency of conglomerate-forming compounds to form homochiral associates in racemic solutions makes feasible the separation of enantiomers. This method resulted in the crystallization of almost pure enantiomer from the solution of a racemic compound.
In 1998 Tamura and his research group had found during the resolution of compounds with racemic behaviour, that exists such way of crystallisítion when 90% of enantiomers' mixture is precipitated with low enantiomer purity, and the other enantiomer remains in the solution with high enantiomer purity.
In 1953 Pasteur had obtained enantiomers by separation of diastereomeric salts. In these cases the desired enantiomers were obtained using different chiral resolving agents (Quinotoxine and Cinchotoxine, respectively). Later the presence of L-tartaric acid in the first case and D-tartaric acid in the latter case was found in the crystallised diastereomeric salt. Thus, using structurally related resolving agents, the enantiomer recognition capability was different, although the difference between them was only a methoxygroup.
The recognition of Pasteur, concerning the separation of diastereomers was modified by Pope and Peachey who used half equivalent of resolving agent and half equivalent of an inorganic compound with similar character, thus a diastereomeric salt and a salt formed by the other enantiomer and the inorganic additive were separated.
A group of Dutch researchers improved this method (1998) using a mixture of chiral resolving agents.
Sakai and his research group found a correlation between the difference of the molecule lenghts of resolving agent and the racemic compound, and the purity of the enantiomer obtained (they showed that the maximum ee value could be reached if this difference is around zero).
These facts show that the best separation of enantiomers can be obtained if the structure of the resolving agent differs only slightly from the structure of the racemic compound.

2. Objectives

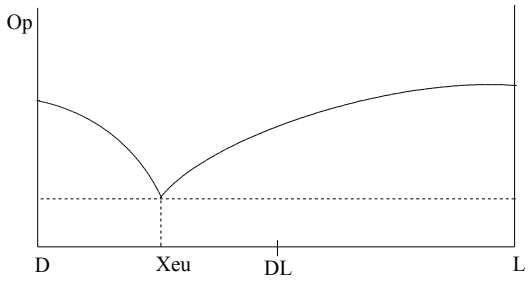
Based on the literature the questions occurred: under which conditions gives the structural similarity of the racemic compounds and the resolving agents an efficient enantiomer separation, and how the possibilities provided by this similarity could be generalised and approximated.
To obtain the answer, such experiments were designed in which the examined racemic compounds and the used resolving agents had an amino-group, eventually acylated or alkylated amino-group near to the phenyl-group in the α- or β-position. All the resolution processes were carried out in water for the good comparability.
Furthermore, our aim was to examine the influence of the partial replacement of the racemic compound or the resolving agent by an achiral compound of analogue structure, or the use of a mixture of resolving agents, respectively. We intended to examine the purification possibilities of non-racemic mixtures of enantiomers without using another chiral compound. This way we could examine further homo- and heterochiral interactions of related molecular structure.

3. Experimental and calculation methods

I have performd resolutions based on the separation of diastereomers using equimolecular or half equimolecular resolving agent, with and without achiral additives, as well as using mixture of chiral resolving agents.
The resolution processes were performed by dissolving the racemic compound and the resolving agent(s) separating the precipitated crystalls in hot water by filtration and then the enantiomers were deliberated. The process is characterized by the enantiomer excess (ee%), the yield (y%) and the resolvability (F= ee*y). The composition of enantiomer mixture in isomer is characterized by optical purity (OP), and with enantiomeric excess (ee), respectively. (The examined compounds are known, so the both can be used).

$$OP\ (\%) = \frac{[\alpha]^{t}_{\lambda,measured}}{[\alpha]^{t}_{\lambda,max.}} \cdot 100$$	$$ee(\%) = \frac{D - L}{D + L} \cdot 100$$
where OP (%) = optical purity $[\alpha]^{t}_{\lambda,measured}$= the optical rotation measured of the product $[\alpha]^{t}_{\lambda,max.}$= the optical rotation of the pure enantiomer	vhere ee (%)=enantiomeric purity D-L= enantiomeric excess D+L= the total enantiomeric composition

The efficiency of resolution can also be calculated from the enantiomer purity value at the eutectic composition on the biner phase diagram of a diastereomer salt. This value has to coincide with the experimental value obtained if the process is thermodinamically controlled and the salt pair is conglomerat forming.



$$F = \frac{1-2x_{eu}}{1-x_{eu}} = ee \cdot T$$

If these values are different it seems that the process is determined by the kinetic controll, or the enantiomer recongnition is occurred on another way.
The DSC measurements were performd on a TA Instruments DSC 2920 calibrated with indium) from 20°C to the melting temperature of the examined samples, with 5°C/min heating rate.
The optical rotations were determined with on a Perkin Elmer 241 polarimeter.

4. Theses

1. In the resolution of formyl-phenylalanine with phenylethylamine the kinetic control proved to be more significant, while the thermodynamic control was found dominant in the reaction with benzylamino-butanol in acetone, and in the resolution of acetyl-phenylalanine by phenylethylamine in the presence of phenoxyacetic acid.
   Concerning the examined compunds one can state that the kinetic control depends on the substituents of the racemic compounds, while the thermodynamic control has a great importance when the the separation is assisted by the solvent or the presence of another achiral compound.

2. Experiments verified that the presence of a structurally similar achiral or chiral compound can improve the results of a resolution.
   Substituting half of the reolving agent with an analogous (chiral or achiral) compound the results obtained can be improved compared to the results obtained with individual resolving agents.
   The achiral compound having structure similar to the racemic compound can improve the enantiomer separation or even it can make it possible if an appropriate resolving agent is used.

3. We estabilished, that the diastereomers obtained from resolutions, performd with structurally similar compounds, form either quasi conglomerates (homochiral) or quasi racemates (heterochiral), depending on the structure of the racemic compound (or its substituents). (The conglomerate/racemate ratio in the case of diastereomers is 17/83 which is in good correlation with the ratio observed in the case of enantiomers (10/90)). We have pointed out that the racemate- or conglomerate-like behaviour of enantiomer mixtures depend on the substituents of the racemic compound. It is also true for the case, when the separation is under kinetic control.

4. We have estabilished that the result of the resolution depends on the conglomerate- or racemate-like behaviour of enantiomer mixtures of the racemic compound. We observed a non-linear correlation between the enantiomeric purity of the product in the crystalline diastereomer salt and the enantiomeric purity of the resolving agent.

5. We discovered a linear correlation between the obtained results (average ee and average F values) and the relative lenghts of the resolving agent and enantiomer molecules.

6. We have estabilished that the purity of the enantiomer mixtures, obtained from the diastereomers (in the case of a resolution using structurally similar resolving agents), depends on the structure of the racemic compound, while the yield (the other factor of the efficiency) is determined by the structure of the resolving agent.

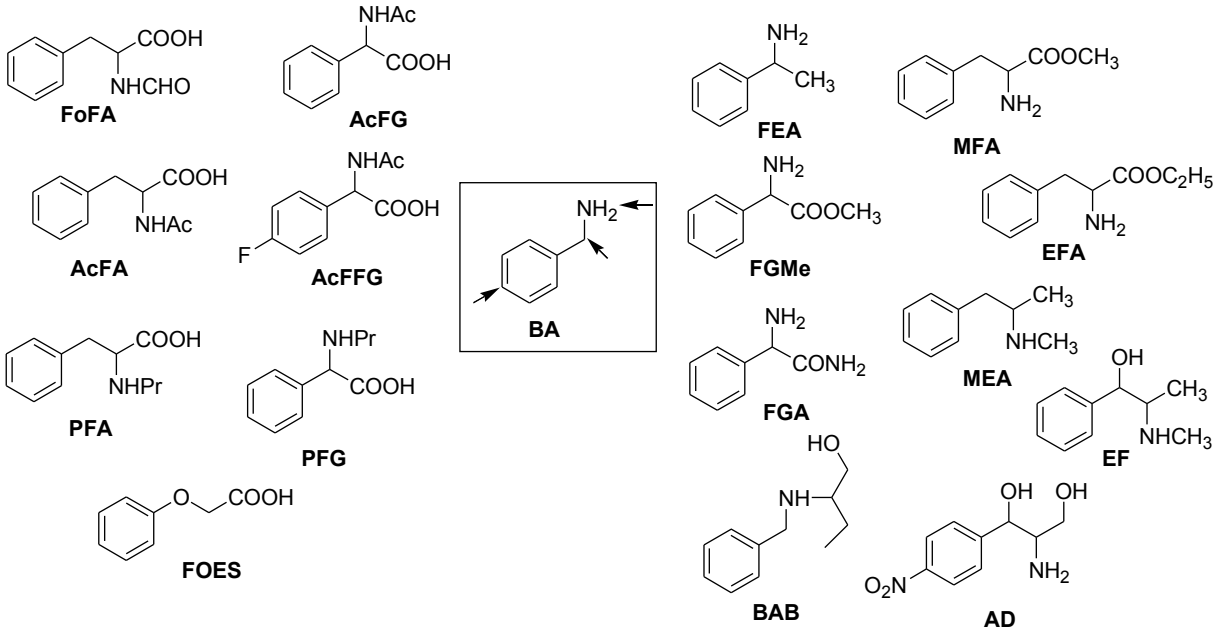
7. We determined an order for the enantiomer-recognition capability of the resolving agents, and a reagent-recognition capability of our racemic compounds respectively. In the case of the compounds examined, the acetyl group was found to be the most advantageous substituent of the racemic compound , while for resolving agents the methylester group is the most advantageous.

The order obtained can be considered certainly valid only for processes performd in water.

5. Short presentation of the results

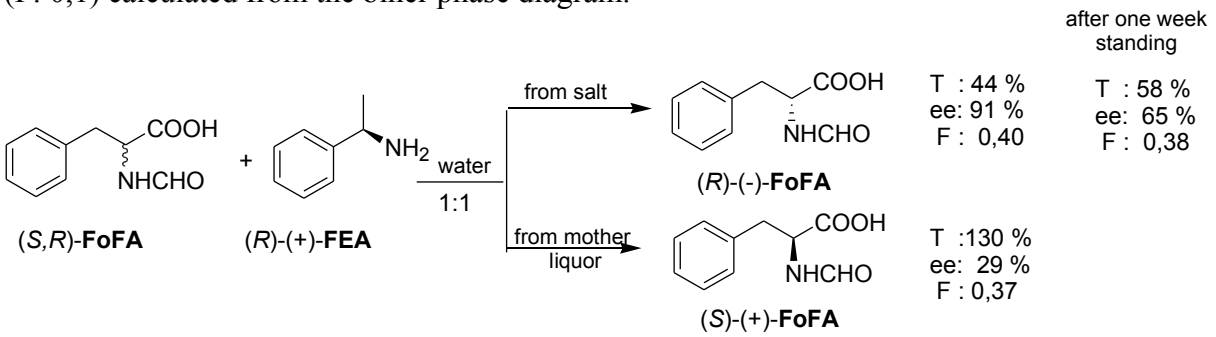
5.1 Resolution of structurally related racemic compounds with structurally related resolving agents in water.

In order to combine the advantages of different resolution methods, we had made experiments, in which the racemic compounds (chiral acids) are structurally related both with each other and the chiral bases used as resolving agents. The members of the two groups can be derived from benzylamine (**BA**).



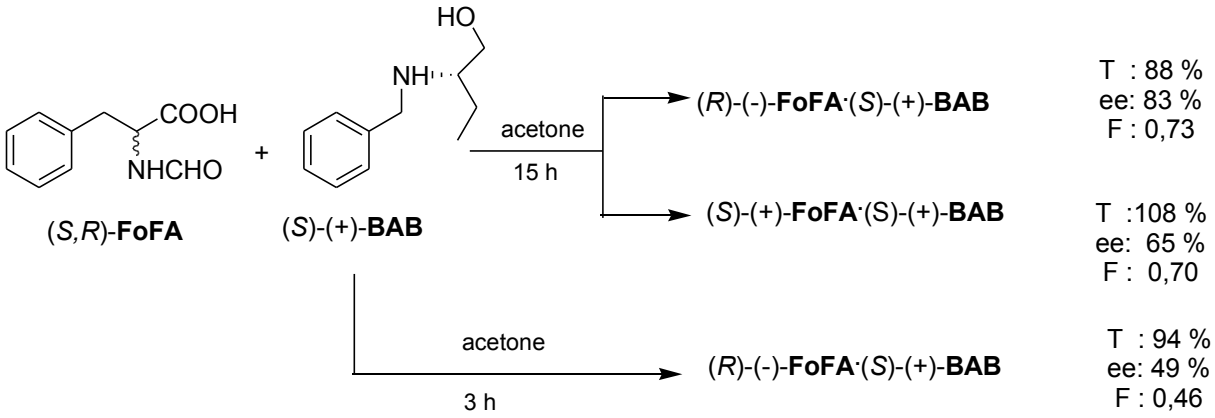
We have observed that at the crystallization of the diastereomers either the effect of kinetic control or the effect of thermodynamic control is predominant.

The *influence of kinetic control* is shown especially in the resolution of racemic FoFA with FEA. The results obtained from the resolution were more favourable than the expected results (F: 0,1) calculated from the biner phase diagram.



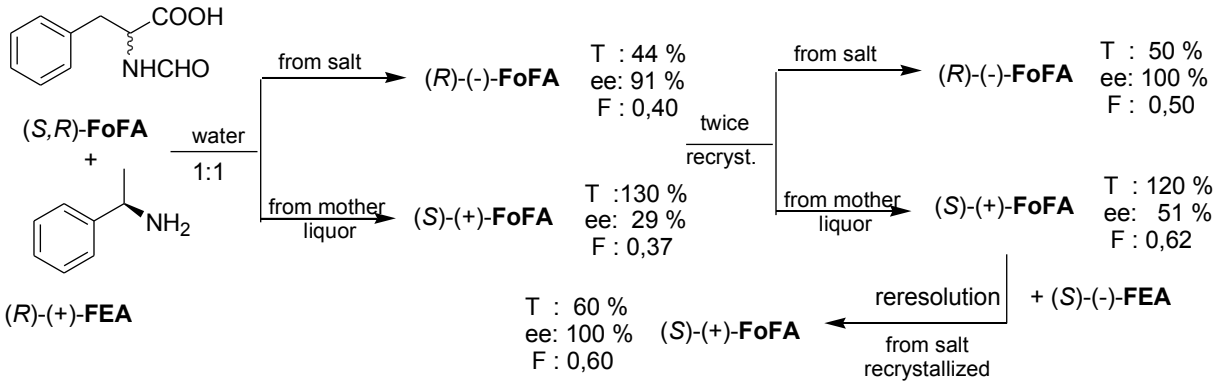
We have demonstrated, that this more effective separation is the result of a kinetic control. (The influence of the kinetic control were also observed at the purification of enantiomer mixtures of **PFA** and of **PFG** by fractioned precipitation)[12],[4],[2].

The influence of *thermodynamic control* has been shown especially at the resolution of racemic **FoFA** with the chiral **BAB**. In this case the expected value of F calculated from the biner phase diagram was 0.51 independently from the solvent. But the result obtained from the resolution was 0.1. Therefore we took into consideration the value of F: 0.73 obtained in acetone recently. It was presumable that in acetone the thermodynamic control determined the results obtained, but the change of the enantiomer purity in the time (in the diastereomer) refer to an intereaction between the resolving agent and acetone, which turned up the way of the resolution process observed using water as solvent. (The influence of thermodynamic control was also observed in the resolution of **AcFA** and **AcFG** by **FEA** in the presence of **FOES**) [2-3], [6-7], [10], [11].



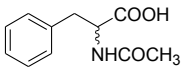
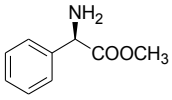
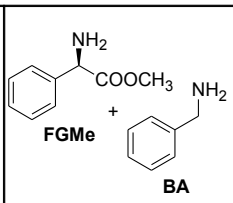
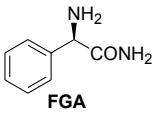
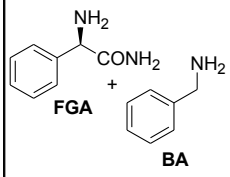
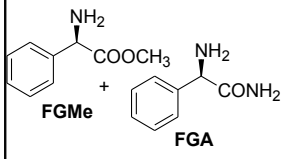
The enantiomer mixtures obtained were purified further by recrystallization of the diastereomers, by repeated resolution or by fractionated precipitation.

We obtained pure enantiomers by recrystallization (twice), or by repeated resolution, of the diastereomers obtained during the resolution of **FoFA** by **FEA** [5].

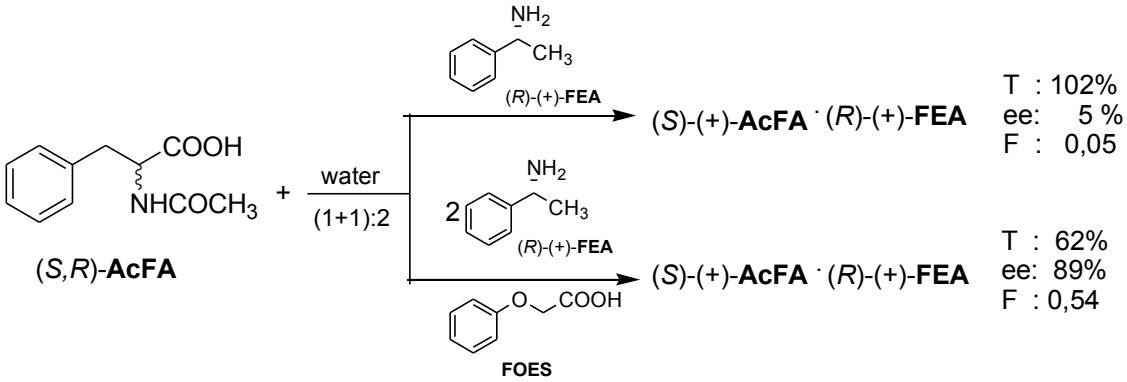


5.2 The efficiency of the resolution can be improved by replacing a part (half) of the resolving agent with a structurally similar, but achiral compound [2], [7], [11], [14] compared with the simple resolution.

We have demonstred that if the half of the resolving agent was replaced by a structurally similar, but achiral compound (not surprisingly we used benzylamine (**BA**)) the result of the separation was significantly improved. This effect was observed also in the case when we used a mixture of chiral resolving agents, too.

Racemic compound	 AcFA				
Resolving agent (the mixture)	 FGMe	 FGMe + BA	 FGA	 FGA + BA	 FGMe + FGA
ee (%)	55	95	74	100	100
F	0,26	0,18	0,43	0,81	0,83

*Replacing the half of the racemic compound (**AcFA**) with its achiral analogue reagent (**FOES**) the result of the resolution has improved significantly* [2], [5], [11].

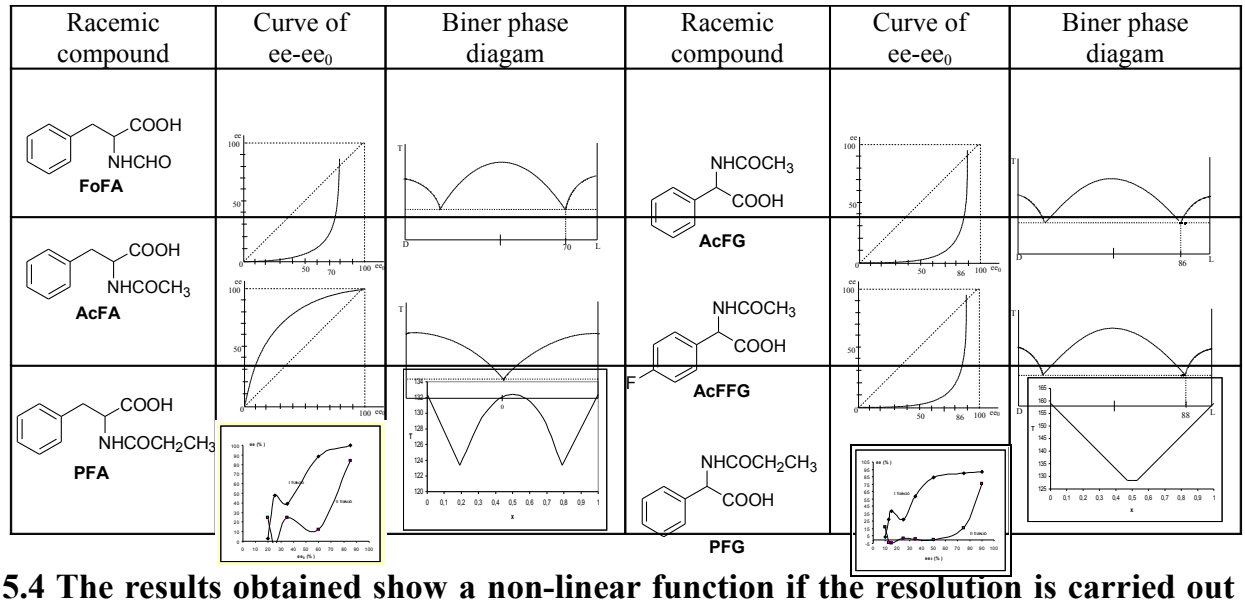


A product of only 5% *ee* was obtained when *N*-acetyl-phenylalanine (**AcFA**) was resolved with 1-phenylethylamine (**FEA**), but when the half part of the racemate was replaced by phenoxyacetic acid (**FOES**), the enantiomeric purity became quite high (*ee* 87%). In this case the stabilization of the thermodynamic equilibrium is very important. Although the replacement of the the half of the resolving agent with an achiral resolving agent was already applied by others, the replacement of the half of racemic compound with its analogue was not performed before us.

5.3 The conglomerate- or racemate-like behaviour of mixtures of enantiomers depends on the substituents of the racemic compound.

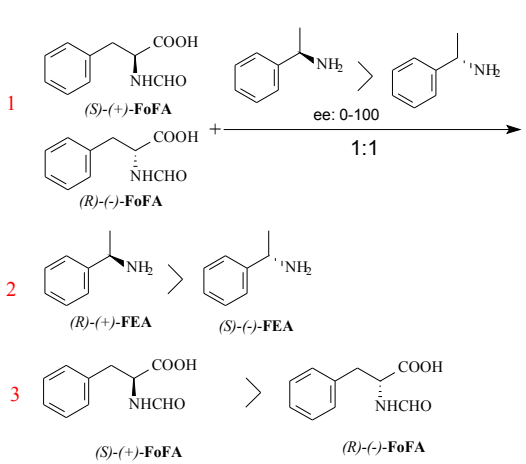
Based on the biner phase diagrams of mixtures of enantiomers we expected a conglomerate- or racemate-like behaviour. The examined enantiomer mixtures could have been purified by fractioned precipitation but not by recrystallization.

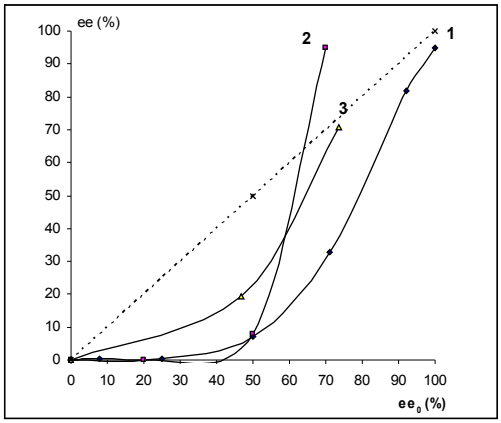
When the enantiomeric purity of the product obtained by recrystallization is plotted against the initial enantiomeric composition, the curves show a correlation with the biner phase diagrams in four cases. In the case of propionyl derivatives at low initial ee the phenomena observed at induced crystallisation was met. In this case, during the fractioned precipitation the kinetic control determines the enantiomer separation. Thus the conglomerate- or racemate-like behaviour of the mixtures of enantiomers depend on the substituents of the racemic compound [2], [5-6], [11-13].



5.4 The results obtained show a non-linear function if the resolution is carried out with the enantiomers' mixture of the resolving agent.

Whereas it was well-known that using mixtures of structurally similar resolving agent we can obtain better result (Dutch resolution) than in individual resolutions, but it has never been examined before what results can be obtained using resolving agent with "the most similar structure", i.e. the mixture of enantiomers (of the resolving agent) with different purity. It was considered evident, that the result of a resolution changes linearly with the purity of the enantiomers of the resolving agents. We have estabilished, however, a non-linear correlation in the case of the resolution of racemic **FoFA** by **FEA.** Appreciable enantiomer separation was only feasible when ee_0>50% although in this case half of the enantiomer purity available with pure enantiomer could be obtained and better results could be achieved if the racemic portion of the resolving agent was replaced by an achiral analogue, in our case by benzylamine (**BA**) [6-9], [12].

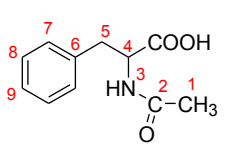




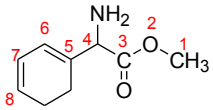
1. *resolution of rac* **FoFA** with (*R*)-**FEA** with various ee**.**
2. recrystallization of hemioxalates of **FEA.**
3. fractioned precipitation of enantiomer mixture of **FoFA**.

5.5 We were looking for a correlation between the results obtained (ee and F) and the differences of molecule lenghts of the resolving agents and the enantiomers as well.

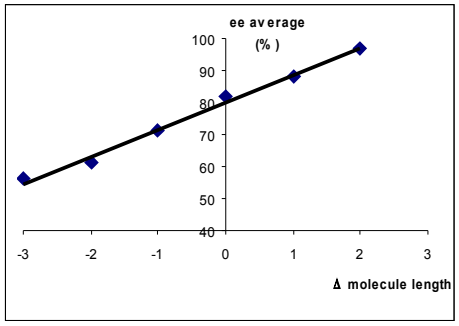
Sakai and his research group observed a correlation, namely the purity of the enantiomers obtained depended from the difference between the molecule lenghts of the resolving agents and of the enantiomers. Based on this observation, we found a linear correlation between the equal molecule lenghts differences of the resolving agents and the enantiomers (used in our experiences) and the obtained average values of ee and F [13].



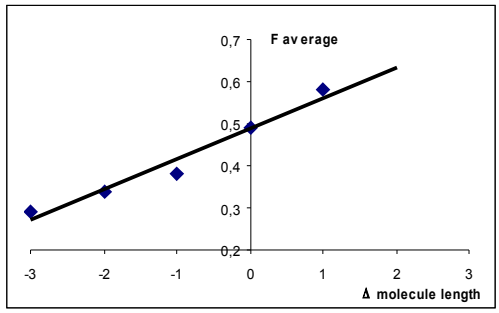
AcFA



FGMe



Δ	ee %	F
+2	97	0,31
+1	88	0,58
0	82	0,49
-1	71	0,38
-2	61	0,34
-3	56	0,29



Thus we can declare, that is not advantageous if the molecule length of the resolving agent is shorter than that of the enantiomer, and the presence of an achiral analogoue of the racemic compound can be favourable (this was observed in the case of the resolution of **AcFA** and **AcFG** with **FEA** when the presence of **FOES** made the separation of enantiomers possible).

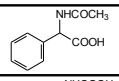
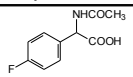
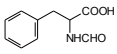
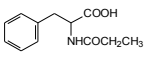
5.6 Our hypothesis that the behaviour of the obtained mixtures of diastereomers is very similar to the behaviour of the enantiomer mixtures, i.e. they become quasi racemate (racemate) or quasi conglomerate (conglomerate), respectively, was verified by our results obtained [5], [13].

Racemic compound	Resolving agent	The configuration of diastereomer *Enant.-res..agent*	ee (%)	F
FoFA	**FEA**	*R-R*	90,8	**0,40**
	FGMe	*R-R*	71,9	**0,39**
	FEA/FGMe	*R-R*	72,4	**0,29**
	FEA/BA	*R-R*	71,2	**0,24**
	FGMe/BA	*R-R*	71,1	**0,30**
AcFA	**FEA/FOES**	*S-R*	89,0	**0,55**
	FGME	*S-R*	55,0	**0,26**
	FGA	*S-R*	77,5	**0,43**
	FGMe/BA	*S-R*	95,0	**0,18**
	FGA/BA	*S-R*	100	**0,81**
	FGMe/FGA	*S-R*	100	**0,80**
AcFG	**FGMe**	*S-R*	78,7	**0,40**
	FGMe/BA	*S-R*	85,1	**0,55**
	FGMe/FEA	*S-R*	75,0	**0,60**
	FAEt	*R-S*	96,5	**0,31**
AcFFG	**FEA**	*S-R*	69,4	**0,28**
	FGMe	*S-R*	86,3	**0,59**
	FGMe/BA	*S-R*	77,5	**0,66**
PFG	**FGMe**	*S-R*	68,5	**0,24**
	FAEt	*R-S*	87,4	**0,29**

	FGMe	***S-R***	**43,3**	**0,29**
PFA	EF	***R-S***	**61,0**	**0,54**

Comparing the configuration of the diastereomer salts obtained I observed that in five cases the composition of the diastereomeric salts were heterochiral and in one case it was homochiral. So 83% of the examined recemic compounds have a racemate-like behaviour and 17% have a conglomerate-like behaviour. This shows a good correlation with the 90/10 ratio observed at the enantiomer mixtures. So, it is another evidence for the behaviour of the diastereomers being dependent on the structure (substituents) of the racemic compounds.

There is a good correlation between the eutectic compositions observed on the biner phase diagram of the enantiomer mixtures of the racemic compounds having racemate-like behaviour and the enantiomer purity obtained in their diastereomers (the highest enantiomer purity value reachable).

Racemic compound	ee_E (%) enant. mixture		Resolving agent	enantiomer in the diastereomer		average ee%	F
				config.	ee%		
	biner ph. 86	experim. 86	(*R*)-**FGMe** (*S*)-**FAEt**	*S* *R*	81 97	**89**	0,40 0,41
	88	86	(*R*)-**FEA** (*R*)-**FGMe**	*S* *R*	69 86	**77,5**	0,28 0,59
	70	69	(*R*)-**FEA** (*R*)-**FGMe**	*R* *R*	65 72	**68,5**	0,40 0,39
	**58**	**Kinetic control**	**(*R*)-**FGMe **(*R*)-**FGA **(*R,R*)-**AD **(*S,S*)-**EF	***S*** ***R*** ***R*** ***R***	**34** **63** **67** **61**	56	**0,29** **0,48** **0,54** **0,42**

5.7 We estabilished the order of the enantiomer-recognition ability of the resolving agents, as well as the reagent-recognition ability of our racemic compounds [13].

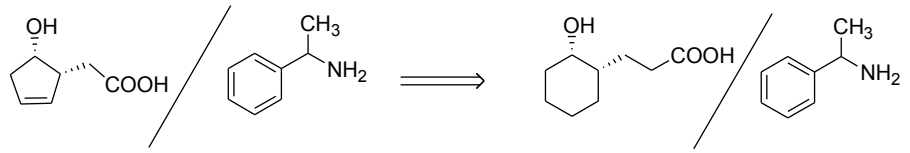
For arranging this order we have taken into consideration the number of resolving agents and mixtures used successfully (a), the average of enantiomeric purity obtained in the diastereomer salts (b), how many racemic compound could be separated with the given resolving agent (c), the average yield of the separation (d). We can estabilish that the most advantageous substituent in the racemic compound is the acetyl group, while at the resolving agents this is the methylester function.
This order is valuable exactly only in aqueous conditions.

Racemic compound	a x b	order
AcFA	7,4	1
AcFG	4,7	2
FoFA	3,5	3
PFA	2,4	4
AcFFA	2,3	5
PFG	**2,2**	6

Resolving agent	c x d	order
FGMe	5,48	1
FEA	3,38	2
FGA	2,96	3
AD	1,65	4
EF	1,44	5
FAMe	1,19	6
FAEt	**0,65**	7

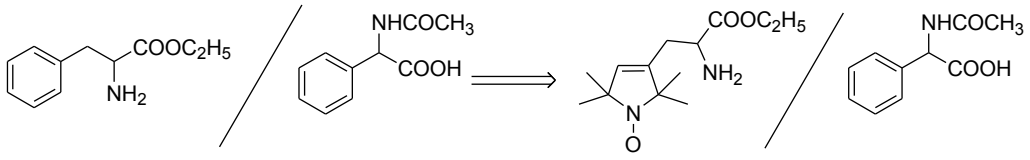
6. The application of the results

Our observations were applied successfully in many cases in the work of the research group. Structurally similar racemic acids were separated with the same resolving agent,[1]



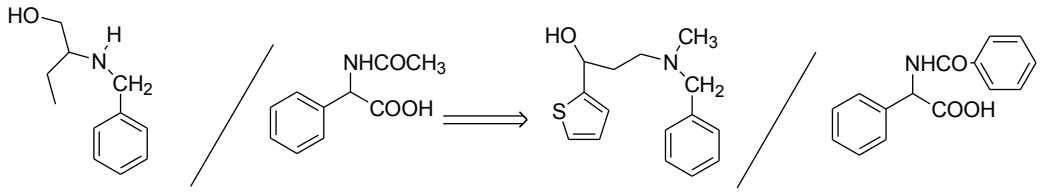
known diastereomer Related structure of diasztereomer

while structurally similar esters of aminoacids were separated with structurally related N-acetyl-amino-acid,[2]



known diastereomer Related structure of diasztereomer

and a racemic base structurally similar with one of our specific resolving agents was separated with an *N*-acyl-aminoacid[3].



known diastereomer Related structure of diasztereomer

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