RESOLUTION OF ALCOHOLS AND PURIFICATION OF ENANTIOMERIC MIXTURES

PH.D. THESIS

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1. INTRODUCTION

The living organism are bulit up from asymmetric molecules. They reacts in different way with the two mirror-image isomers (enantiomers) of a chiral molecule. The effect of a drug containing chiral centre depends on the applied stereoisomer. Further most of the industrial synthesis were achiral and racemic compounds were synthetized. Nowadays in most cases the resolution of the racemic compounds gives the effective stereoisomer. The current method in industrial resolution is based on the diastereomeric salt pair resolution. During this method diastereomer salt pair is produced from the racemic compound with a resolving agent and the salt pair is separated by fractional recrystallization. Generally in the first resolution step can not be achieved optically pure enantiomer and further separation of the enantiomeric mixture is needed. Compounds which do not contain acidic or basical function group can be resolved only with its derivative form with this method which makes this method difficult.

The TUB Department of Organic Chemical Technology for a long time past investigates the different preparative resolution methods. In my Ph.D. thesis I purposing the investigation of the direct resolution of racemic alcohols and the enantiomeric enrichment using achiral agents. As a model compounds I used different chiral alcohols (such as menthol,4-methil-2-penthanol, etc), α-phenylethylamine (PEA) and methamphetamine (MA)enantiomeric salt mixtures.

2. INVESTIGATED METHODS

TG and DTG analysis:

The Instrument is TA Instruments TGA 2050 Thermogravimetric Analyzer.

DSC analysis:

The instrument is TA Instruments DSC 2920 Modulated DSC.

Investigation of Thermomicroscope:

The instrument is type of NU2 hot-stage microscope.

Infrared Spectroscopy:

We got the spectrums on the type of Perkin Elmer FT-IR 1600 Series instrument.

Optical rotation measurement:

I measured the optical rotation on the type of Perkin Elmer 241 polarimeter.

NMR measurement:

The NMR spectrums carried out on type of Bruker AC 250 instrument.

Single-crystal X-ray diffraction analysis:

The data-collection was in room temperature on type of Rigaku AFC6S diffractometer and applied Cu-K_α ray.

3. THE SCIENTIFIC RESULTS OF DISSERTATION

1. We achieved enantiomeric separation (with diastereomeric supramolecular compound formation from hexaneous solution) with O,O'-di-para-(2*R*,3*R*)-tartaric acid (DPTTA) resolving agent in the case of *racemic-trans*-2-iodo-cyclohexanol and racemic-menthol **(4)**; with (*R*)-mandelic-benzylester in the case of *racemic*-menthol and *racemic*-4-methyl-2-penthanol and with (*R*)-mandelic-benzylester-oxalat in the case of *racemic*-4-methyl-2-penthanol (1. Table). We also studied the process of resolution with instrumental methods (IR, DSC, microscope).

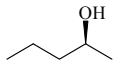
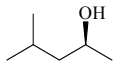
1. Table *Successful resolutions from solvent*

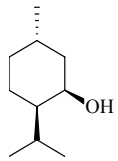
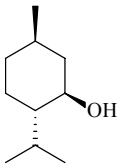
Alcohol/resolving-agent	menthol			4-methyl-2-penthanol			*trans*-2-iodo-cyclohexanol		
	Y (%)	e.e. (%)	S	Y (%)	e.e. (%)	S	Y (%)	e.e. (%)	S
DPTTA	-	-	-	-	-	-	71	61	0.43
R-(-)-mandelic-acid-bensylester	2.0	10.6	0.002	140.6*	4.19*	0.03*	-	-	-
R-(-)-mandelic-acid-bensylester-oxalat	-	-	-	102*	3.72*	0.04*	-	-	-

*:alcohol from hexaneous phase

2. We recognised that the enantiomeric mixtures can be separated via supramolecular-compound formation without solvent with the crystallisation of the racemic alcohol and the melted resolving agent **(5,6).** With this separation method the reaction time can be reduced on several hours and the result of the enantiomeric separation is more better than with the "solvent-process". We solved the resolution of *racemic*-menthol, *racemic*-neomenthol, *racemic*-2-penthanol and *racemic*-4-methyl-2-penthanol with O,O'-dibenzoyl-(2*R*,3*R*)-tartaric acid (DBTA) , and *racemic*-menthol with β-cyclodextrin. (*2. Table)*.

2. Table *Resolution of racemic alcohols with DBTA in melt*

Supramolecular compound of alcohols	Results of alcohol in solid phase		
	Y(%)	e.e.(%)	S
 *R*-(-)-2-penthanol	18.5 *63.2**	38.3 *20.1**	0.071 *0.126**
 *R*-(-)-4-methyl-2-penthanol	106 *91.0**	44.5 *28.1**	0.475 *0.255**

 (1*R*,2*R*,5*S*)-neomenthol	72.9	49.6	0.361
 (1*R*,2*S*,5*R*)-menthol	72.6 *45.0**	62.8 *83.0**	0.456 *0.370**

*: results of investigations from hexaneous solution

3. We observed the optimum of the resolution of the melt-crystallisation when we used 0.5 molequivalent resolving agent to the racemic alcohol compound while the maximum of the enantiomeric excess can be reached with less resolving agent (3. Table).

3. **Table** Enantiomeric separation of *racemic-menthol with diastereomeric crystallisation in melt, with different DBTA/menthol molar ratio*

DBTA mol:mol *racemic*-menthol*	Melt phases (+)-menthol			Supramolecular compound (-)-menthol		
	Y(%)	e.e.(%)	S	Y(%)	e.e.(%)	S
0.2	128.8	7.5	0.095	12.0	89.2	0.107
0.3	156.0	16.4	0.256	30.0	85.1	0.255
0.4	137.8	28.2	0.389	51.8	76.1	0.394
0.5	113.4	44.2	0.501	72.6	62.8	0.456
0.6	124.2	33.7	0.419	56.4	67.1	0.378
0.7	109.4	29.7	0.322	73.6	44.3	0.326

4. During our work we realised that in the case of DBTA more advantageous to produce supramolecular compound with the monohydrate form than the anhydrous form. If we sublimate a part of the melted SMC after the melt-crystallisation then we separate the diastereomeric compound from the residual we can increase significantly the efficiency of the enantiomeric separation. (4. Table).

4. **Table** *Comparison of resolution methods of DBTA-menthol via supramolecular compound*

Methods	**Y(%)**	**e.e.(%)**	**S**
DBTA.H_2O from solvent	45.0	83.0	***0.374***
DBTA.H_2O from melt	72.6	62.8	***0.456***
DBTA from melt	72.0	62.8	***0.452***
DBBS.H_2O from melt with plus water	70.4	67.1	***0.472***
From melt with sublimation DBTA.H_2O	85.6	67.8	***0.574***
From melt with sublimation DBTA	74.2	64.4	***0.509***

5. With the mixtures of analogous structured resolving agent (DBTA, DPTTA, (2*R*,3*R*)-tartaric acid) we can separate the enantiomers of *racemic*-menthol from hexaneous solution and also with melt-crystallisation and in the latter case the results of the separation are also more better. Using DBTA with itself not suitable resolving agent increases the efficiency of the resolution and causes synergic effect. (5.-*6. Tables*).

5. Table *Resolution of racemic-menthol with solid resolving agent-mixtures, in solvent*

Resolving agent-mixtures	Alcohols from solid phase		
	Y(%)	e.e.(%)	S
DBTA : DPTTA	-	-	-
(+)-DBTA : DPTTA	76.5	12.2	0.093
DBTA : DPTTA : TA	16.0	50.5	0.081

6. Table *Resolution of racemic-menthol with solid resolving agent-mixtures, in melt*

DBTA. H_2O mol	DPTTA mol	TA mol	Melt phases (+)-mentol			Supramolecular compound (-)-mentol		
			Y (%)	e.e. (%)	S	Y (%)	e.e. (%)	S
0.25	0.25	0	118.0	26.2	0.309	67.6	40.0	0.270
0.25	0	0.25	179.6	6.0	0.108	13.6	79.6	0.108
0.16	0.16	0.16	175	0.73	0.014	25	68.6	0.171
-	0.25	-	No crystallization					
-	-	0.25	No crystallization					

6. During the resolutions of racemic alcohols we didn't get pure enantiomers, only enantiomeric mixtures. We got better results with repeated-resolution when the amount of resolving agent equivalent with the enantiomeric excess. (7. *Table*).

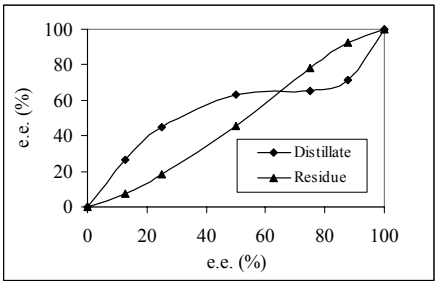
7. Table Repeated resolution of enantiomeric mixtures of menthol in melt phase *with diastereomeric crystallisation with different DBTA.H_2O molar ratio*

DBTA.H_2O mol:mol menthol enantiomeric micture	Initial enantiomeric excess mixture (-)-menthol	Melt phases (-)-menthol		Supramolecular compound (-)-menthol	
	e.e.(%)	Y(%)	e.e.(%)	Y(%)	e.e.(%)
0.50	63.8	49.1	40.6	45.6	94.4
0.65	63.8	29.3	10.4	60.3	92.0
	(+)-menthol	(+)-menthol		(-)-menthol	
0.60	28.8	68.8	41.4	20.7	16.4

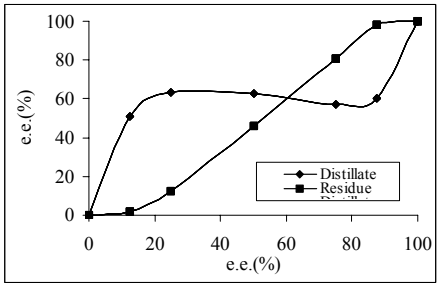
7. We worked out separation processes for difficultly separated enantiomeric mixtures which are using achiral dicarboxylic acid co-resolving agents. (oxalic acid, malonic acid, fumaric acid, phtalic acid) (1., 2., 3. Figures). **(1,2)**

1. Figure *The separation with distillation of the enantiomeric mixtures of α-phenylethylamine*

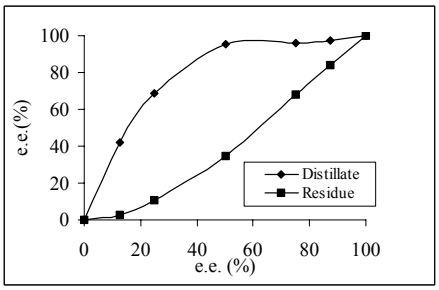
(*R*)-α-phenylethylammonium-oxalate



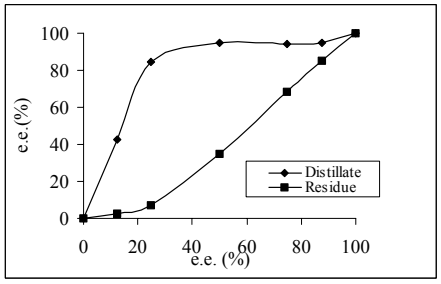
(*R*)-α-phenylethylammonium-malonate



(*R*)-α-phenylethylammonium-fumarate

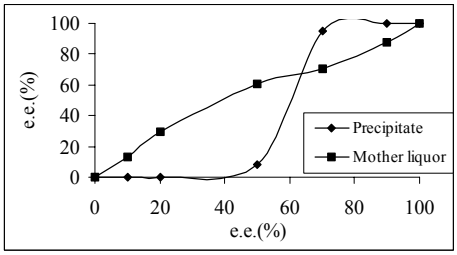


(*R*)-α-phenylethylammonium-phtalate

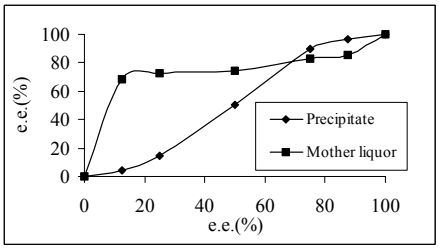


2. Figure *The separation with recrystallization of the enantiomeric mixtures of α-phenylethylamine*

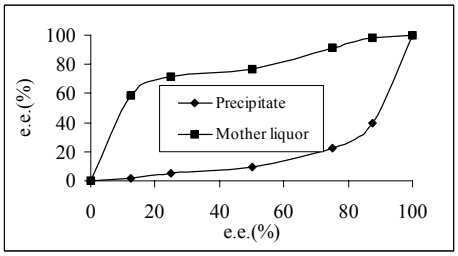
(*R*)-α-phenylethylammonium-oxalate



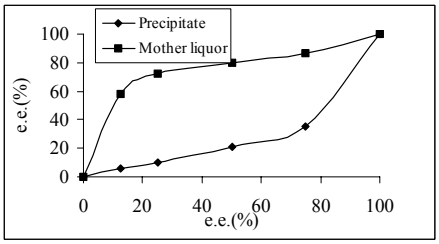
(*R*)-α-phenylethylammonium-malonate



(*R*)-α-phenylethylammonium-fumarate

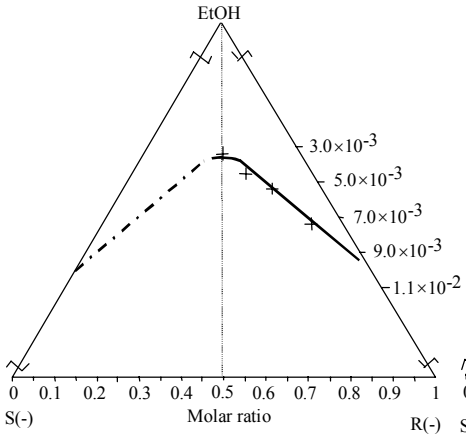


(*R*)-α-phenylethylammonium-phtalate

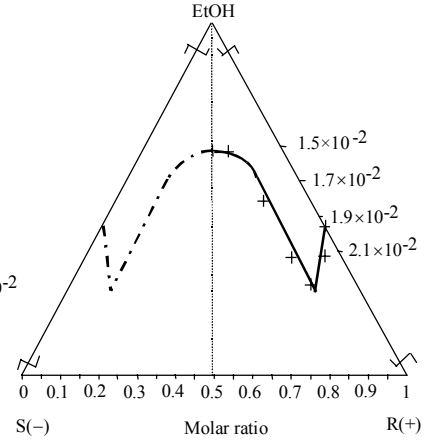


3. Figure *Solubility triangle-diagrams of the neutral salts of α-phenylethylamine*

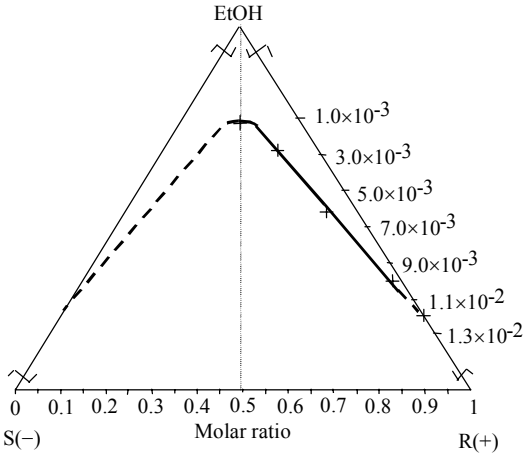
(*R*)-α-phenylethylammonium-phtalate



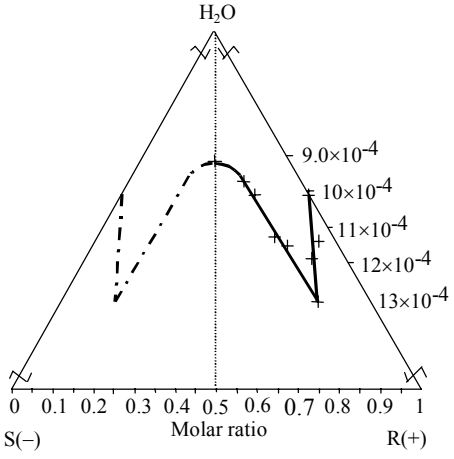
(*R*)-α-phenylethylammonium-malonate



(*R*)-α-phenylethylammonium-fumarate



(*R*)-α-phenylethylammonium-oxalate



8. We observed that we can separate purer enantiomeric mixtures from the initial mixture if we distillate the enantiomeric mixtures after partial salt formation, while we obtained better enantiomeric enrichment from the mother liquor during the crystallization of neutral salts. If the eutectic point of the enantiomeric mixture is far to pure enantiomer – like the salts of oxalic and malic acids- so the enantiomeric excess is higher in the residue, during the distillation if the initial enantiomeric excess is over then the eutectic point. The enantiomeric excess is also higher in the crystal during the recrystallization. In the case of the salts of fumaric and phtalic acids are achieved very high enantiomeric excess-increasement during the purifications.
9. We observed, that the curves of the distillate and the residue and the curves of the precipitated salt and mother liquor enantiomer composition cross each other at the same composition and the inflection points of

the IR spectums (C-H and C-N vibrations) of the enantiomeric mixtures and this is similar to the eutectic composition. (8. Table).

8. Table *Comparisation of eutectic composition with different methods*

Salts/ methods	(*R*)-α-phenylethylammonium-malonate e.e.(%)	(*R*)-α-phenylethylammonium-oxalate e.e.(%)
Distillation	59	65
Recrystallization	68	65
Solubility triangle-diagram	65	63
IR	63	65

10. We managed to separate conglomerate-type enantiomeric mixtures which can be difficultly separated such as N-methyl-amphetamine (MA) with achiral acidic agent –hidrochloride acid. **(3)** We observed that good separation results can be achieve among the eight purification methods if we use the achiral acidic agent in equivalent or in non-equivalent molar ratio in comparison to the basical compound according to the separation method. Based on this observation we came to the conclusion that efficient enantiomeric separation can be achieved if solid phase is present during the resolutions. (9., 10. Tables).

9. Table *Summary of the experiments with or without achiral salt forming agent*

	Mixture "A" (e.e.(%)=76.3)				Mixture "A" (e.e.(%)=76.3)				
Method	$[\alpha]_D^{20}$	e.e.(%)	m(g)	Y(%)	$[\alpha]_D^{20}$	e.e.(%)	m(g)	Y(%)	EEE
DISTILLATION									
Residue	-13.8	73.3	0.50	25.0	-	-	-	-	-
Distillate	-13.8	73.3	1.40	70.0					
EXTRACTION									
Organic phase	-13.8	73.3	1.20	60.0	-	-	-	-	-
Aqueous phase	-13.8	73.3	0.70	35.0					
CRYSTLLIZATION									
Precipitate	-	-	-	-	+17.7	93.6	0.83	41.5	53.0
Mother liquor					+10.8	60.3	1.15	57.5	-
SUBLIMATION									
Sublimate	-	-	-	-	+13.5	71.2	1.78	89.0	-
Residue					+18.5	97.9	0.21	10.5	14.0

10. Table *Summary of the experiments with non-equivalent amounts of achiral agent*

	Mixture "B" (e.e.(%)=76.1)					Mixture "C" (e.e.(%)=84.6)				
Methods	$[\alpha]_D^{20}$	e.e.(%)	m(g)	Y(%)	EEE	$[\alpha]_D^{20}$	e.e.(%)	m(g)	Y(%)	EEE
CRYSTALLIZATION										
Precipitate	17.9	94.9	1.60	80.0	99,8	+18.5	97.9	0.38	20	23.1
Mother liquor	-	0,9*	-	-	-	-	81.2*	-	-	.
DISTILLATION										
Residue	17.4	92.1	1.57	78.5	95,0	+18.1	95.6	0.40	20.0	22.6
Distillate	0.0	0.0	0.39	19.5	-	+15.4	81.7	1.55	77.5	-
STEAM DISTILLATION	-									
Residue	14.3	79.3*	-	82.5*	86,0	-	92.2*	-	20.0*	21.8
Distillate		75.3	0.35	17.5	-	+15.6	82.7	1.50	75.0	-
EXTACTION										
Organic phase	-13.9	73.8	0.36	18.0	-	+15.7	83.1	1.62	81.0	-
Aqueous phase		85.5*	-	82.0*	92,1	-	90.6*	-	19.0*	20.3

*: *calculated from the enantiomeric balance*

4. PUBLICATIONS

1. Dávid Kozma, Helén Simon, Csaba Kassai, Zoltán Madarász and Elemér Fogassy: Investigation of the Physicochemical Basis of Enantiomeric Enrichment: The Example of α-Phenylethylamine with Achiral Dicarboxylic Acids
   Chirality, 13, *29-33*. **2001**

2. Helén Simon, Csaba Kassai, Zoltán Madarász, Elemér Fogassy and Dávid Kozma: Enantiomerkeverékek királis ágens nélkül történő enantiomerdúsításának vizsgálata
   Magyar Kémiai Folyóirat, Vol. 107, *507-516*, **2001**

3. D. Kozma, H. Simon, Gy. Pokol and E. Fogassy: Enantiomeric Enrichment of Partially Resolved N-methyl-amphetamine
   J. Term. Anal. and Cal., Vol. 69, 409-416, **2002**

4. H. Simon, K. Marthi, Gy. Pokol, E. Fogassy and D. Kozma: O,O'-di-para-toluyl-(2*R*,3*R*)-tartaric acid as supramolekular resolving agent
   J. Term. Anal. and Cal.,Vol 74/1. 155-162, **2003**

5. H. Simon, Z. Vincze, K. Marthi, G. Lévai, Gy. Pokol, E. Fogassy and D. Kozma: Thermoanalitical study of O,O'-dibenzoyl-(2*R*,3*R*)-tartaric acid supramolekularcompounds Part IV.
   J. Term. Anal. and Cal. (Accepted for publication)

Patent:

6. Elemér Fogassy, Dávid Kozma and Helén Simon: Separation process for (-)-menthol
   Hungarian Patent, No: P 03 00458

5. LECTURES AND POSTERS

LECTURES:

1. *Helén Simon, Csaba Kassai, Zoltán Madarász, Dávid Kozma and Elemér Fogassy:* Separation of enantiomeric mixtures of α–phenyletylamine by partial salt formation followed by distillation
   XXII. Talks on Chemistry, 1-3. November **1999**, Szeged

2. *Helén Simon, Elemér Fogassy and Dávid Kozma:* The resolution of racemic alcohols with molecular complexes
   XXV. Talks on Chemistry, 28-30. October **2002**, Szeged

3. *Helén Simon, Elemér Fogassy and Dávid Kozma:* Investigation of racemic alcohols with molecular complexes
   Hungarian Chemical Society Chemists' Conference, 26-28. June **2003,** Hajdúszoboszló

4. Helén Simon, Elemér Fogassy and Dávid Kozma*:* O,O'-Dibenzoyl-(2*R*,3*R*)-tartaric acid as Supramolecular Compound Forming Resolving Agent
   15 th International Symposium on Chiral Discrimination October **2003,** Shiznoka- Japan (confirmed presenter)

POSTERS:

1. Helén Simon, Csaba Kassai, Zoltán Madarász, Dávid Kozma and Elemér Fogassy: Investigation of enantiomeric mixtures of α–phenyletylamine *Hungarian Chemical Society Chemists' Conference*, 22-24. Juni **1999**, Eger

2. Helén Simon, Csaba Kassai, Zoltán Madarász, Elemér Fogassy and Dávid Kozma: Investigation of the Physico-chemical Background of the Enantiomeric Enrichment *ISCD 12 - Chirality 2000*, 24-28. September **2000**, Chamonix- Mont Blanc France

3. Helén Simon, György Pokol, Elemér Fogassy and Dávid Kozma: Investigation of the enantiomeric enrichment of N-methamphetamine Hungarian Chemical Society Chemists' Conference, 27-29. June **2001**, Hajdúszoboszló