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Resolution of racemic *trans*-1,2-cyclohexanediol with tartaric acid

Péter Molnár [a], Paul Thorey [a], György Bánsághi [a], Edit Székely [a,*], László Poppe [b], Anna Tomin [b], Sándor Kemény [a], Elemér Fogassy [b], Béla Simándi [a]

[a] Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, H-1521 Budapest, Hungary
[b] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary

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ABSTRACT

A simple method for the resolution of racemic *trans*-1,2-cyclohexanediol enantiomers is presented in this paper. The chiral discrimination was performed by tartaric acid via diastereomeric complex formation. The diastereomeric complexes were formed by adding the resolving agent to the racemic diol in a 0.5:1 molar ratio. The (2*R*,3*R*)-(+)-tartaric acid forms stable diastereomeric complex with (1*R*,2*R*)-(−)-cyclohexanediol. Supercritical carbon dioxide extraction was applied to the separation of the mixture of diastereomeric complexes and uncomplexed diol enantiomers. We found unexpected optimal conditions according to the 3^2 factorial design on the resolution efficiency within the studied range of the extraction pressure and temperature. In the best cases, the (1*S*,2*S*)- and (1*R*,2*R*)-diol enantiomers were obtained with $ee_{(1S,2S)} = 62\%$ and $ee_{(1R,2R)} = 93\%$ enantiomeric excess in one equilibrium stage, respectively.

1. Introduction

The applicability of supercritical fluid extraction (SFE) as an effective and green technique for enantioseparations is already known.[1–5] In these processes, diastereomeric salts or complexes of the racemic compounds and resolving agents are formed before the extraction step. The selected resolving agent is added in less than stoichiometric ratio to the racemic compound. The unreacted enantiomers are extracted with the supercritical solvent, and are collected as a powder after depressurization of the solution.

The *cis*- and *trans*-1,2-cyclohexanediols are the topic of many publications because of their importance as building blocks[6–12] or chiral auxiliaries.[13,14] The binary phase diagram for the *trans*-1,2-cyclohexanediol **1** enantiomers was determined by Leitão et al.[15] Several publications can be found in the literature dealing with the chiral derivatization or resolution of racemic *trans*-1,2-cyclohexanediol.[16–21] In a few cases, high enantiomeric purity was achieved. Lainé et al. resolved racemic *trans*-1,2-cyclohexanediol via the formation of dispiroketals. After removing the protecting auxiliary, the subsequent oxidation gave the corresponding diacetates of the diol in an enantiomeric excess (ee) of 95% and yield† of 36–45%.[22] Among the different optically active acids, Chatterjee et al. found that *O*-acetyl mandelic acid is a favourable agent for the esterification of the racemic *trans*-1,2-cyclohexanediol. The optical purity (op) and yields (*Y*) for the corresponding diol enantiomers were

$$op_{(1S,2S)-1} = 97\%, \quad Y_{(1S,2S)-1} = 46\%; \quad op_{(1R,2R)-1} = 96\%, \quad Y_{(1R,2R)-1} = 41\%, \text{ respectively.}[23]$$

Examples of enzyme-catalysed kinetic resolutions have been described in the literature.[24,25] Bódai et al. studied the kinetic resolution of the monoacetates of *trans*-1,2-cycloalkanediols by acylation with vinyl acetate.[26] Enantiomers of *trans*-1,2-cyclohexanediol were produced from their bisacetylated derivatives by enantioselective hydrolysis with recombinant lipases obtained from *Bacillus subtilis*.[27]

Apart from these techniques, asymmetric hydrogenation is an alternative method for producing cyclohexanediol enantiomers from cyclohexane-1,2-dione by using a cinchonidine-modified platinum catalyst.[28]

Among the aforementioned enantioseparation methods, the kinetic resolution of the diol by lipases gave the best ee values, although enzymatic transformation of the racemic compounds usually resulted in a complex mixture of more than two products, or required partial esterification before the kinetic resolution. In addition, the long reaction times (>24 h) and the considerable price of the enzymes are obvious disadvantages. Although the scale-up of the chiral derivatization or resolution techniques by non-enzymatic methods are more realizable, the ee values of the products are remarkably lower (<80%) in most of the cases. The chiral auxiliaries and selectors used were produced in laborious syntheses, which required different organic reagents and solvents in significant amounts, moreover, these enantioseparations are based on

* Corresponding author. Tel.: +36 1 463 2658/3096; fax: +36 1 463 3197.
E-mail address: sz-edit@mail.bme.hu (E. Székely).

† Yield is calculated in regard to the amount of the racemic compound.

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Nomenclature

a, *b*	constants in Brunner's equation
c, *d*	constants in the Hyperbolic equation
e, *f*	constants in the Parabolic diffusion model
g, *h*	constants in the Power law model
CO_2^{rel}	relative amount of carbon dioxide to the *rac*-**1**, g/g (Eq. (2.5))
ee	enantiomeric excess, %
F	resolution efficiency, separation efficiency, resolvability (Eq. (2.3))
m_{Extr}	mass of enantiomeric mixture in the extract
m_{Raff}	mass of enantiomeric mixture in the raffinate
m_{rac-1}	mass of the racemic *trans*-1,2-cyclohexanediol in the extractor
mr	molar ratio of the resolving agent (Eq. (2.4))
ee	enantiomeric excess, %
p	significance level of the experimental design
P	pressure, MPa
rac	racemic
rt	room temperature
$scCO_2$	supercritical carbon dioxide
T	temperature, °C
Y	yield, % regarding the amount of the racemic compound (Eqs. (2.1) and (2.2))
ρ	density of the supercritical carbon dioxide, g/ml

Subscripts

Extr	extract
Rac	racemic *trans*-1,2-cyclohexanediol
Raff	raffinate

covalent bond formation with the racemic compound. Therefore, additional process steps are required to form and remove the protecting/derivatizing agents from the diol, increasing the time and the organic solvent demands of the processes and decreasing the achievable yields.

Herein, we report a new and simple resolution for the enantiomers of *trans*-1,2-cyclohexanediol **1** by diastereomeric complex formation and subsequent supercritical fluid extraction, and show the influence of the extraction parameters on the resolution efficiency.

2. Results and discussion

2.1. Resolution of *trans*-1,2-cyclohexanediol enantiomers by supercritical fluid extraction

Tartaric acid and its derivatives are widely used as chiral agents in resolutions through diastereomeric complex or salt formation.[29–34] These compounds provide the advantages of wide availability and low cost as chiral agents. The resolution of racemic *trans*-1,2-cyclohexanediol **1** was first attempted with three compounds: *O*,*O*′-(−)-dibenzoyl-(2*R*,3*R*)-tartaric acid monohydrate **2**, *O*,*O*′-(−)-di-*p*-toluyl-(2*R*,3*R*)-tartaric acid **3** and tartaric acid **4**.

In general, the ratio of half a molar equivalent of resolving agent to the racemic compound gives the best separation efficiency (Pope–Peachy method[35]) in the resolutions, therefore the resolving agents and *rac*-**1** were reacted in 1:2 molar ratios in an ethanol solvent. The resolutions were performed according to the method described in Section 4.2. The results of the preliminary resolutions of *rac*-**1** are collected in Table 1. The yield (*Y*) and the resolution efficiency (*F*) are defined as follows:

$$Y_{Extr} = \frac{m_{Extr}}{m_{Rac}} \times \quad 100, \tag{2.1}$$

$$Y_{Raff} = \frac{m_{Raff}}{m_{Rac}} \times \quad 100, \tag{2.2}$$

$$F = Y_{Extr} \cdot ee_{Extr} + Y_{Raff} \cdot ee_{Raff} \tag{2.3}$$

where the subscripts 'Extr', 'Raff' and 'Rac' indicate the data corresponding to the extract, raffinate or to the racemic diol, respectively. The mass of the materials is signed by '*m*'. The concentration of the resolving agent is expressed by the term of molar ratio (*mr*), as follows:

$$mr = \frac{n_{resolving\ agent}}{n_{Rac}}, \tag{2.4}$$

where '*n*' is the molar amount of the compounds. The relative amount of the carbon dioxide (CO_2^{rel}) in the extractions was calculated according to the following term:

$$CO_2^{rel} = \frac{m_{CO_2}}{m_{Rac}}. \tag{2.5}$$

As a result of the rapid screening of resolving agents, tartaric acid **4** was found to be a suitable resolving agent for *trans*-1,2-cyclohexanediol. Successful resolutions were achieved with both of the pure tartaric acid enantiomers (2*R*,3*R*)-(+)-**4** and (2*S*,3*S*)-(−)-**4**, in accordance with the Marckwald principle. For lack of acidic or basic functional groups on the racemic compound, the resolution of *rac*-**1** by **4** is performed via diastereomeric complex formation.

The enantiomer of (1*R*,2*R*)-(−)-**1** was in excess in the more stable diastereomer with (2*R*,3*R*)-(+)-**4**. Kassai et al. reported that *O*,*O*′-(−)-dibenzoyl-(2*R*,3*R*)-tartaric acid **2** is a sufficient resolving agent for several racemic alcohols with a structure related to **1**; moreover, they found that the (*S*,*S*)-enantiomers of the alcohols were mainly in excess in the more stable supramolecular complexes.[36] In all cases, both the racemic alcohol and the resolving agent contain the two stereogenic centres at neighbouring carbon atoms. The Fisher and absolute configurations of the molecules are depicted in Scheme 1.

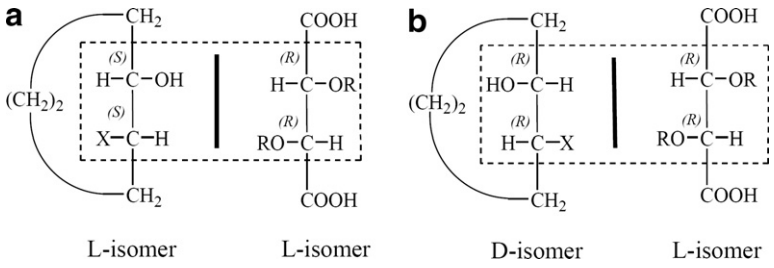
The configurations of the alcohol enantiomers in the more stable diastereomeric complexes with different resolving agents are collected in Table 2. Due to the absolute configurations, these molecule regions are mirror images of each other in certain diastereomers (Table 2, compounds **5**–**8**; Scheme 1a), and are not in a few other diastereomers (Table 2, compounds **1**, **9**, **10**; Scheme 1b). Although, molecules have the opposite structures according to the Fisher projection. Thus the (*R*,*R*)-alcohol:(*R*,*R*)-acid (D-alcohol:L-acid) conformation can be regarded as quasi racemic structures.

The observed phenomenon indicates that the structurally related racemic compounds cannot be resolved in every case with those resolving agents which have a similar chiral structure, even if the resolving agents have different substituents. Additionally, the configuration of the more stable diastereomeric complexes cannot be definitely predicted, even when structurally related racemic compounds and resolving agents are reacted.

The *trans*-2-halogen-cyclohexane-1-ols were successfully resolved with **2** via supercritical fluid extraction too, where the complex formation is based both on hydrogen bonds and dispersion interactions between the racemic compound and the resolving agent.[37] In the case of the resolution of *rac*-**1** with **4**, however, the complex formation should be based primarily on hydrogen-

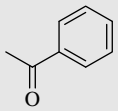
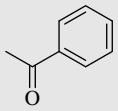
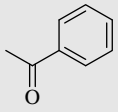
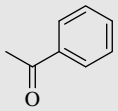
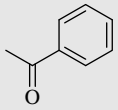
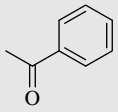
Table 1
Preliminary resolutions of *rac*-**1** with *O*,*O*′-(−)-dibenzoyl-(2*R*,3*R*)-tartaric acid monohydrate **2**, *O*,*O*′-(−)-di-*p*-toluyl-(2*R*,3*R*)-tartaric acid **3** and tartaric acid enantiomers **4**; P = 15 MPa, T = 48 °C, acid : *rac*-**1** molar ratio = 1:2, average value of $CO_2^{rel} = 770$ g/g

Run	Resolving agent	Extract		Raffinate		F
		ee_{Ext} (%)	Configuration	ee_{Raff} (%)	Configuration	
1	**2**	<1	(1*S*,2*S*)-**1**	<5	(1*R*,2*R*)-**1**	0.03
2	**3**	<1	(1*S*,2*S*)-**1**	<5	(1*R*,2*R*)-**1**	0.05
3	(2*R*,3*R*)-(+)-**4**	54.2	(1*S*,2*S*)-**1**	70.4	(1*R*,2*R*)-**1**	0.54
4	(2*S*,3*S*)-(−)-**4**	42.4	(1*R*,2*R*)-**1**	66.1	(1*S*,2*S*)-**1**	0.44



Scheme 1. Structures of different alcohol:resolving agent complexes according to the Fisher projection. The absolute configurations of the stereogenic centres are indicated by (*S*) or (*R*) and are incorporated within the dashed line. Vertical line represents the plane of the mirror. (a) No mirror image-shaped molecule regions. (b) Mirror image-shaped molecule regions.

Table 2
Configurations of different 2-substituted-cyclohexane-1-ol derivatives in the more stable diastereomeric complex formed with *O*,*O*′-(−)-dibenzoyl-(2*R*,3*R*)-tartaric acid monohydrate **2** or tartaric acid **4**

Racemic compound	X	R	Cahn–Ingold–Prelog configuration[a]	Fisher projection[a]
5	Cl		(1*S*,2*S*)-**5**:(2*R*,3*R*)-**2**	L-**5**:L-**2**
6	Br		(1*S*,2*S*)-**6**:(2*R*,3*R*)-**2**	L-**6**:L-**2**
7	I		(1*S*,2*S*)-**7**:(2*R*,3*R*)-**2**	L-**7**:L-**2**
8			(1*S*,2*S*)-**8**:(2*R*,3*R*)-**2**	L-**8**:L-**2**
9			(1*R*,2*R*)-**9**:(2*R*,3*R*)-**2**	D-**9**:L-**2**
10			(1*R*,2*R*)-**10** : (2*R*,3*R*)-**2**	D-**10**:L-**2**
1	OH	H	(1*R*,2*R*)-**1**:(2*R*,3*R*)-**4**	D-**1**:L-**4**

[a] The configurations given represent the alcohol:resolving agent stereochemistry of the more stable diastereomer.

bond formation. This shows that the cyclohexanol derivatives can be generally resolved by supercritical fluid extraction with tartaric acid or its derivatives.

A new process was developed for the enantioseparation of the racemic diol **1** by the formation of diastereomeric complexes with tartaric acid and subsequent supercritical carbon dioxide ($scCO_2$) extraction, as depicted in Figure 1. The resolution process is based on three steps. In the first step, a solid mixture is formed containing the uncomplexed diol enantiomers, the diastereomeric complexes and an inert support. This mixture is treated by supercritical carbon dioxide in the second step with a (1*S*,2*S*)-(+)-**1** rich enantiomeric mixture being extracted. The (1*R*,2*R*)-(−)-**1**

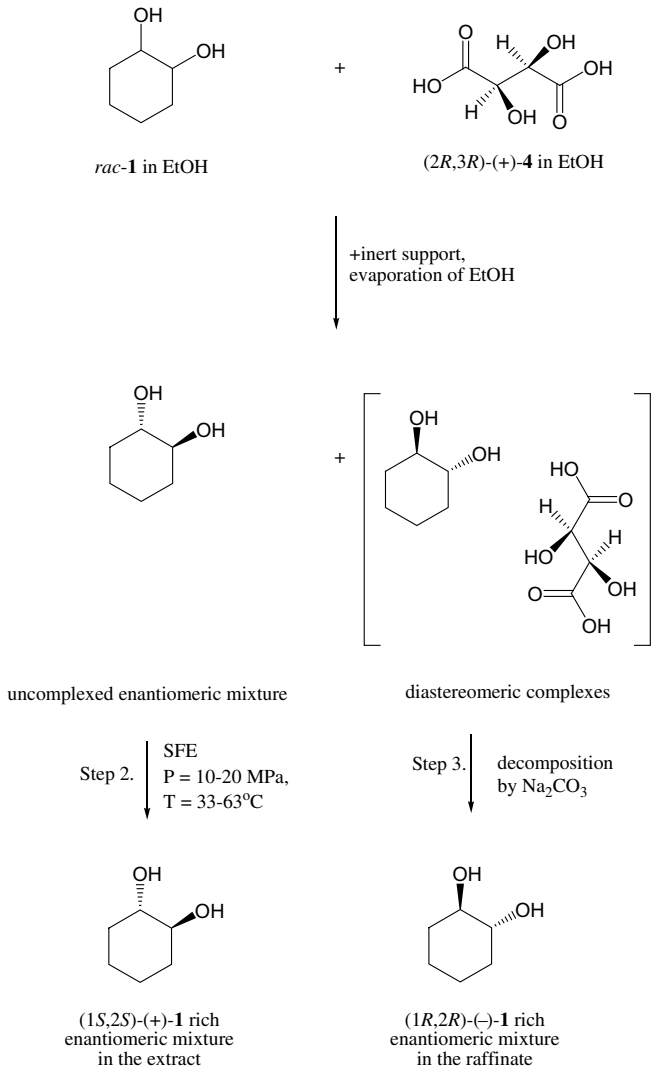


Figure 1. Resolution of racemic *trans*-1,2-cyclohexanediol **1** with (2*R*,3*R*)-(+)-tartaric acid **4** via diastereomeric complex formation and subsequent supercritical fluid extraction (SFE).

rich raffinate enantiomeric mixture is recovered after the decomposition of the remaining complexes in the last step.

Several empirical equations,[38] which are generally applicable to modelling the extraction kinetics, were tested to describe the extraction yields as a function of CO_2^{rel}. However, the Brunner's equation[39] gave a satisfactory value of R^2, and none of the equations used showed a reliable fit for the extraction data. The empirical equations and R^2 values of the fitted extraction curves are collected in Table 3. The yield data at two different settings of the extraction pressures and temperatures are shown in Figure 2.

Table 3
Fitted empirical equations and R^2 values on the extraction data of unreacted diol enantiomers

Fitting	Equation	R^{2a}	R^{2b}
Brunner	$Y_{Extr} = a \cdot (1 - \exp(-b \cdot CO_2^{rel}))$	0.988	0.984
Hyperbolic	$Y_{Extr} = c \cdot CO_2^{rel}/(1 + d \cdot CO_2^{rel})$	0.978	0.974
Parabolic diffusion	$Y_{Extr} = e + f \cdot (CO_2^{rel})^{1/2}$	0.941	0.943
Power law	$Y_{Extr} = g \cdot (CO_2^{rel})^{h}$	0.942	0.942

[a] Extraction at P = 10 MPa, T = 33 °C.
[b] Extraction at P = 15 MPa, T = 48 °C.

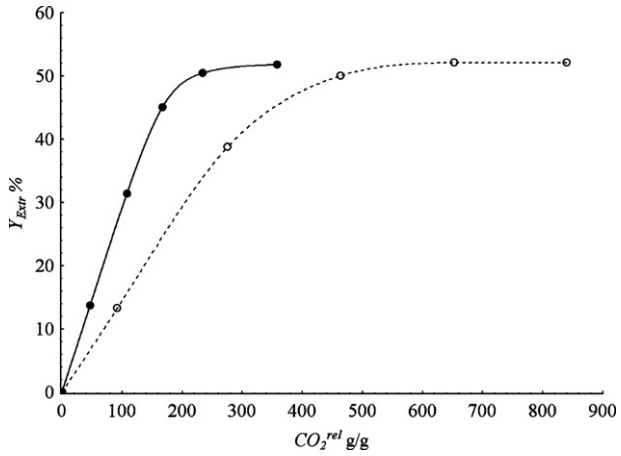


Figure 2. Extraction yield data of the unreacted diol enantiomers at P = 10 MPa, T = 33 °C (○); and P = 15 MPa, T = 48 °C, (●); mr = 0.50. Extraction points are linked by a spline fit.

The extraction data in Figure 2 indicate that the diastereomers formed are stable enough to allow the separation of the uncomplexed diol enantiomers and complexes by supercritical fluid extraction, moreover, all of the unreacted **1** enantiomers were dissolved by $scCO_2$. The stoichiometric ratio in the diastereomeric complex is diol:acid = 1:1.

2.2. Experimental design

Twelve resolutions were carried out within a full factorial 3^2 type experimental design at nine different combinations of the extraction pressure and temperature to study their influence on the values of the enantiomeric excess, yield and resolution efficiency and to quantify the effects of the extraction parameters with 0.05 significance level. All experiments were carried out at an mr = 0.50 ratio. Four repetitions were performed at the centre point. With this setup, the linear and quadratic effects of the pressure and temperature, as well as the effects of their interactions could be analysed statistically. The evaluation of the experimental data was performed by STATISTICA software (StatSoft, Inc., version 7.1). The factors and level values of the experimental design are collected in Table 4.

The linear (L) effects of the pressure and temperature were found to be significant for ee_{Extr}, ee_{Raff}, Y_{Extr} and Y_{Raff} and additionally, the enantiomeric excess and yield of the extracts were also influenced by the linear interaction of the pressure and temperature. The fitted surfaces of the experimental design are shown in Figure 3.

The extraction pressure and temperature have reverse effects on the enantiomeric excesses and yields of the extracts and raffinates. The minimum value of the ee_{Extr} = 38.7% as well as the maximum value of the ee_{Raff} = 93.1% were achieved at P = 20 MPa and T = 63 °C. We assume that a slight decomplexation of the diastereomers, under these conditions, plays a primary role on the values studied. The release of an enantiomeric mixture from the complex leads to a decrease in the purity of the extracts, although it enhances the purity of the raffinates. Thus, the yield of the extracts

Table 4
Factors and levels of the experimental design, mr = 0.50

Factor	Lowest level	Center level	Highest level
Pressure, MPa	10	15	20
Temperature, °C	33	48	63

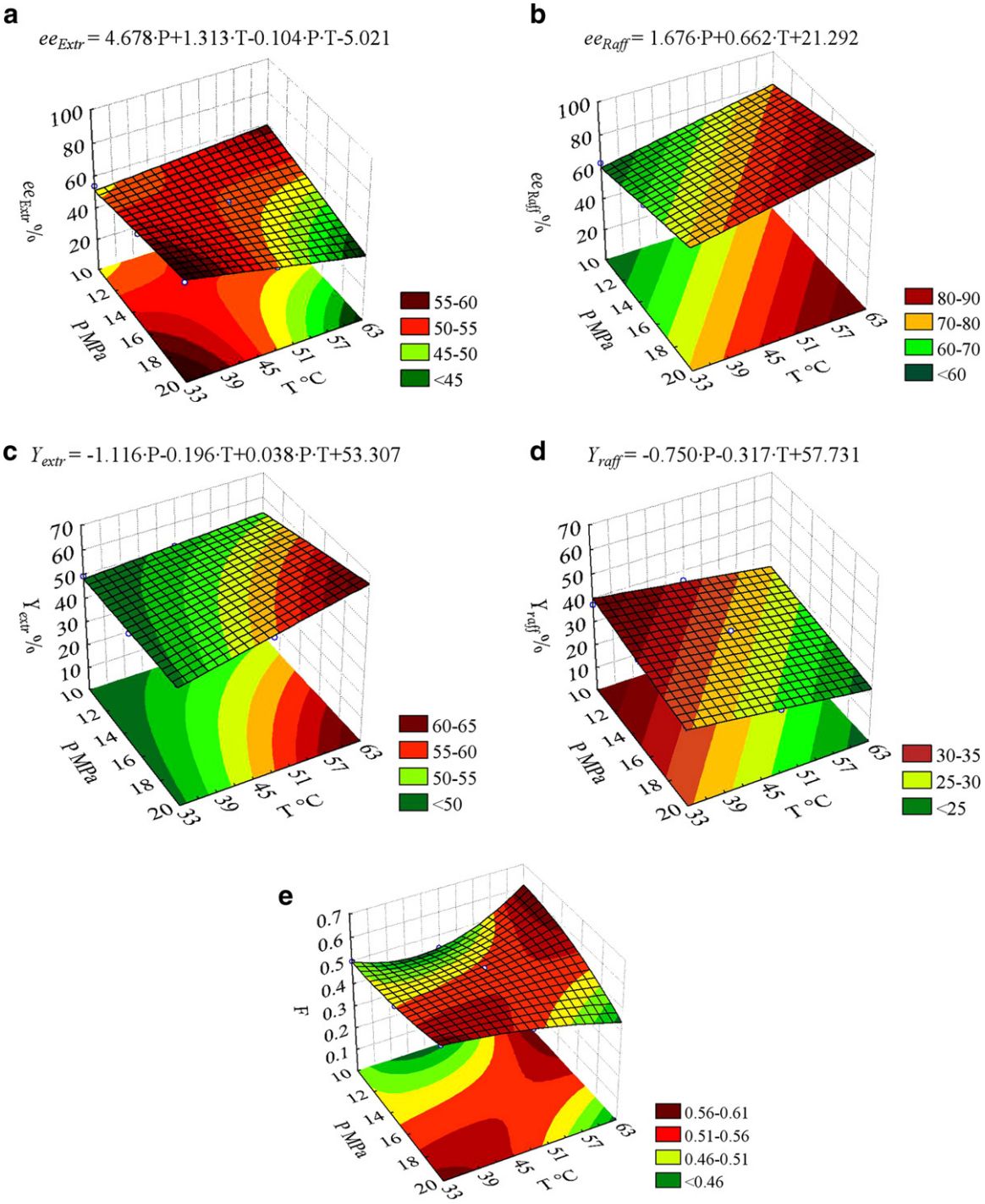


Figure 3. Fitted surfaces of the experimental design (a) ee_{Extr}; (b) ee_{Raff}; (c) Y_{Extr}; (d) Y_{Raff}; (e) F.

increases against the yield of the raffinates. As a result of the observed influences, the fitted surface of the resolution efficiency parameter is saddle-shaped, as shown in Figure 3e. It should be noted that no verifiable influence of the density of $scCO_2$ (ρ) on the F parameter was found, despite the density being clearly dependent on the pressure and temperature. The best resolutions ($F \cong 0.6$) within the range of the experimental design were achieved under the following conditions: P = 10 MPa, T = 63 °C, ρ = 0.275 g/ml, ee_{Extr} = 61.4%, ee_{Raff} = 91.9%, F = 0.61; or P = 20 MPa, T = 33 °C, ρ = 0.876 g/ml, ee_{Extr} = 62.1%, ee_{Raff} = 81.9%, F = 0.59; respectively. A lesser amount of CO_2 is necessary in the latter case. Significantly lower resolution efficiencies were achieved at P = 10 MPa, T = 33 °C, ρ = 0.738 g/ml, F = 0.50; and at P = 20 MPa, T = 63 °C, ρ = 0.705 g/ml, F = 0.44, respectively.

3. Conclusion

In this study, a new and effective process has been proposed for the resolution of *trans*-1,2-cyclohexanediol. This is the first resolution for *rac*-**1** which does not require formation of any new covalent bond. The separation of the enantiomers is performed by

molecular complex formation, most likely stabilized by hydrogen bonds. The enantiomeric mixtures were obtained over 60% ee for the extracted (1*S*,2*S*)-**1** and over 90% ee for the raffinate (1*R*,2*R*)-**1** enantiomers. The resolution of *trans*-1,2-cyclohexanediol with tartaric acid by SFE is a competitive technique with any already published methods due to the following advantages:

- short overall process time (<6 h), including the sample preparation, the extraction with $scCO_2$ and the decomposition step;
- the tartaric acid is a non-toxic, cheap and efficient resolving agent that does not require any structural modifications before use;
- the $scCO_2$—as a green solvent—is a suitable media for the separation of the uncomplexed enantiomers and diastereomeric complexes;
- organic solvent consumption is significantly reduced or can even be avoided;
- the tuning of the extraction parameters offers a simple way to influence the ee values in the extracts and raffinates as well.

We achieved the value of $F = 0.6$ as the maximum of the resolution efficiency in one equilibrium stage.

4. Experimental

4.1. Materials

Racemic *trans*-1,2-cyclohexanediol **1**, (2*R*,3*R*)-(+)-tartaric acid (2*R*,3*R*)-(+)-**4** and (2*S*,3*S*)-(−)-tartaric acid (2*S*,3*S*)-(−)-**4** were purchased from Sigma–Aldrich Corp., (Budapest), Hungary. Perfil P250™ as inert support (expanded and milled perlite for use as a filtering aid, specific surface area is 2.89 m^2/g) was kindly given by Baumit Co., (Budapest), Hungary. Carbon dioxide (99.5 w/w% pure) is the product of Linde Ltd, (Budapest), Hungary. Ethanol, methanol and trichloromethane were provided by Reanal Ltd, (Budapest), Hungary.

4.2. Methods

Racemic *trans*-1,2-cyclohexanediol **1** (1 g, 8.609 mmol) and (2*R*,3*R*)-(+)-tartaric acid (0.6463 g, 4.306 mmol) were dissolved separately in 15 ml of abs. ethanol and were combined. Inert support, Perfil P250™ was added (1.5 g) to the solution. The ethanol then was evaporated at 40–50 °C in 30 mbar vacuum. The solid sample was left to dry overnight at room temperature. The sample was extracted the next day under different conditions (P = 10–20 MPa, T = 33–63 °C) with approx. 660 g CO_2/g *rac*-**1**. The extractions were performed with a laboratory scale supercritical unit.[40] The (1*S*,2*S*)-(+)-**1** rich mixture was collected in the separator at 4 MPa and 40 °C. The raffinate was removed from the extractor and 40 ml of methanol was added to it, in order to dissolve the remaining diastereomeric complexes. After 1 h of stirring, the inert support was filtered and the methanol was evaporated at 40-50 °C in 30 mbar vacuum. The complex was decomposed by a saturated aqueous solution of Na_2CO_3 (6 ml) during the stirring for 15 min. The water then was evaporated from the residue at 70–80 °C in 30 mbar vacuum. The solid particles were crushed and 20 ml of trichloromethane was added to it. After 30 min of stirring, the sodium-tartrate salt was filtered out and the organic phase was evaporated. The product obtained contains the (1*R*,2*R*)-(−)-**1** in excess.

The enantiomeric excesses were determined by GC analysis with an Agilent 4890D chromatograph using Hydrodex-β-6-TBDPM (25 m × 0.25 mm × 0.25 μm film with permethylated β-cyclodextrin, Macherey & Nagel, No.: 21519/11) column. The analysis was performed at isotherm conditions (130 °C), carrier gas: hydrogen, head pressure: 12 psi, 1:50 split ratio, detector: FID at 250 °C, injector temperature at 250 °C.

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