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Resolution of *N*-methylamphetamine enantiomers with tartaric acid derivatives by supercritical fluid extraction

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Abstract—The resolution of *N*-methylamphetamine (MA) was carried out with the resolution agents *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid monohydrate (DBTA) and *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid (DPTTA). After partial diastereomeric salt formation, the unreacted enantiomers were extracted by supercritical fluid extraction (SFE). The effects of resolution agent molar ratio to the racemic mixture (mr), extraction pressure (*P*) and temperature (*T*) on the resolution efficiency were studied. The best chiral separation was obtained at a quarter of an equivalent resolution agent molar ratio for both resolution agents. Extraction conditions [pressure (100–200 bar), temperature (33–63 °C)] did not influence the resolution efficiency, which makes the enantiomer separation robust. In one extraction step, both enantiomers can be produced with high enantiomeric excess (ee) and remarkable yield (*Y*). Using DBTA as a resolution agent $ee_E = 83\%$, $Y_E = 45\%$ for the extract and $ee_R = 82\%$, $Y_R = 42\%$ for the raffinate were obtained.

1. Introduction

Due to the FDA's policy statement for the development of new stereoisomeric drugs chiral separation is becoming increasingly important in drug discovery.[1] Beside the industrial-scale crystallization processes there is a growing need to develop new, cost-effective and environmentally friendly technologies for the resolution of racemic compounds.

Supercritical fluids, especially carbon dioxide, can replace organic solvents as a reaction or separation media. The unique properties of carbon dioxide such as its relatively low critical conditions ($P_{krit} = 74$ bar, $T_{krit} = 31$ °C) and its ability to be easily removed from the products, offer new possibilities for producing pure enantiomers. Several studies have already proven the feasibility of enantioselective chemical[2–4] and biochemical[5–8] reactions in supercritical solvents.

The application of supercritical CO_2 as an extraction solvent in the separation of enantiomers on a preparative scale has been developed in our laboratory.[9] Bauza et al. have also presented the application of supercritical fluid extraction (SFE) for the separation of mandelic acid, phenylpropionic acid and phenylbutyric acid enantiomers on an analytical scale.[10,11] Kordikowsky et al. have used supercritical carbon dioxide as a precipitating agent during the resolution of ephedrine with mandelic acid. Diastereomeric salts were formed under supercritical conditions using the solution enhanced dispersion by supercritical fluids (SEDS) technique.[12]

Over the last 10 years, several racemic organic acids,[13] bases[14,15] and alcohols[16] have been resolved by SFE in our laboratory. In many cases the extraction pressure (*P*) or/and extraction temperature (*T*) strongly influenced the efficiency of the resolution.[13,14] However in a few cases the effects of these factors were not significant.[15,16] The design of an SFE resolution process requires the deep understanding of the influencing factors. For this purpose the resolution of *N*-methylamphetamine (MA) with two structurally similar resolution agents [*O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid monohydrate = DBTA and *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid = DPTTA] was studied by supercritical fluid extraction.

2. Results and discussion

The supercritical fluid extraction resolution process is shown in Scheme 1. The *racemic*-MA and the resolution

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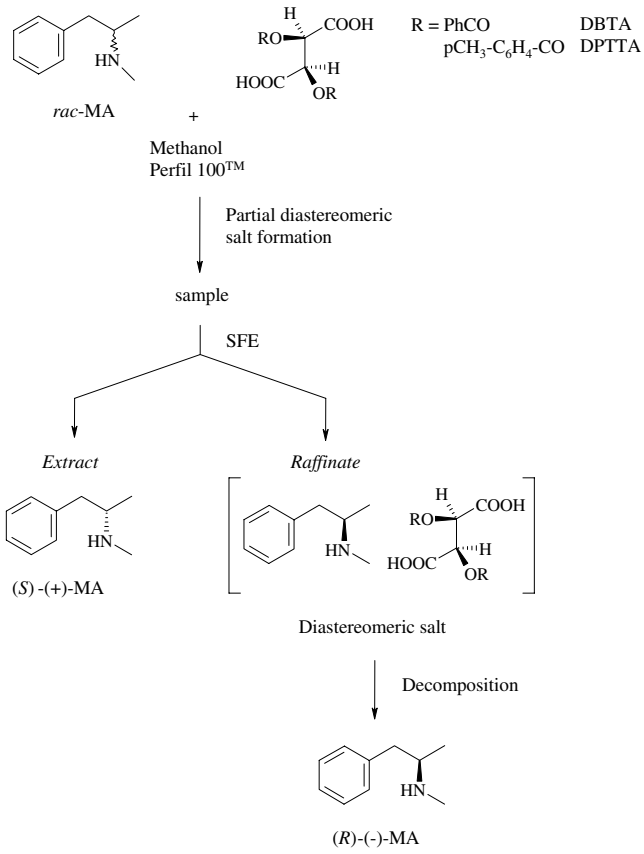

Scheme 1. Resolution of *N*-methylamphetamine by supercritical fluid extraction.

agent (DBTA or DPTTA) in less than one equivalent molar ratio were dissolved in methanol, after which the achiral support (Perfil 100™) was added to the solution. The solvent was then evaporated in vacuum. The solid sample was dried at room temperature for 1 h, and then transferred into an extractor vessel. A detailed description of the extraction unit has been given in previous work.[13] The free enantiomers were extracted with supercritical carbon dioxide in the range of 100–200 bar and 33–63 °C and then collected as an extract sample in the separator by pressure reduction of the solvent. The diastereomeric salts were insoluble in supercritical carbon dioxide and remained in the extractor as a raffinate. In all the experiments the extract was the (*S*)-(+)-enantiomer, the raffinate was the (*R*)-(−)-enantiomer in excess.

2.1. Effect of resolution agent molar ratio

According to our previous experience, by increasing the resolution agent to racemic mixture molar ratio (mr = mol resolution agent/mol racemate), the yield of the extract decreased but the chiral differentiation increased. Opposite tendencies were observed in the case of the raffinate. To determine the optimum resolution agent molar ratio, the resolution efficiency was described by the F parameter ($F = |ee_E Y_E| + |ee_R Y_R|$), where Y is the yield (mass of the extract (raffinate)/mass of the initial racemic compound) and ee is the enantiomeric excess (E and R subscripts represent the extract and the raffinate, respectively). The F parameter varied between 0 and 1.

To map the effect of the resolution agent molar ratio in the case of the resolution of *rac*-MA, several experiments were carried out in the range of $0 < mr < 0.5$. The results with standard deviances are shown in Figure 1. In both cases the F parameter passed through a maximum between 0.2 and 0.3 molar ratio, while the resolution efficiency reached its maximum when a half of the racemic amine was salified. In further experiments, the resolution agent/*rac*-MA ratio was optimized at 0.25. This optimal, condition is independent of the resolution agent (DBTA or DPTTA).

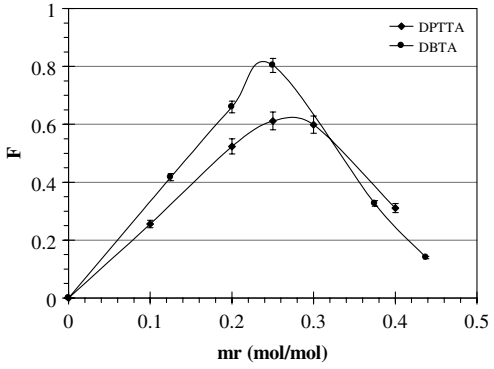

Figure 1. Effect of the resolution agent molar ratio on the F parameter ($P = 160$ bar, $T = 39$ °C).

Detailed experimental results at the optimal molar ratio are summarized in Table 1. Using DBTA gave better enantiomeric separation than DPTTA. In one resolution step the enantiomeric excesses are higher than 80% for the extract and raffinate.

Table 1. Results of the resolution at the optimal molar ratio ($P = 160$ bar, $T = 39$ °C)

Resolution agent	Extract		Raffinate		F
	ee (%)	Y (%)	ee (%)	Y (%)	
DPTTA	62	49.3	70	44.0	0.614
DBTA	85	47.3	83	48.2	0.804

2.2. Effects of extraction parameters

Two^2 full factorial experimental designs with three repetitions at the centre point were carried out on both resolution agents to study the effects of the extraction pressure (P) and temperature (T) on the resolution efficiency. The experimental settings and the obtained results are summarized in Table 2A and B.

The statistical evaluation of the experimental data was performed by Statistics for Windows® 6.0 software. This experimental design is suitable to fit the linear model given in Eq. 1 to the measured F parameter values (Fig. 2).

Table 2. Experimental results obtained by resolution of *rac*-MA with DPTTA (Panel A) and DBTA (Panel B) at 0.25 molar ratio at different extraction conditions

P (bar)	*T* (°C)	Extract		Raffinate		*F*
		ee (%)	*Y* (%)	ee (%)	*Y* (%)	
Panel A						
100	33	69	43.3	72	42.3	0.599
100	63	65	47.3	66	42.9	0.589
150	48	73	50.0	76	42.2	0.685
150	48	69	48.0	74	38.8	0.619
150	48	70	46.6	71	41.7	0.621
200	33	68	46.0	71	41.6	0.608
200	63	64	53.3	71	40.2	0.632
Panel B						
100	33	83	46.7	85	41.6	0.745
100	63	80	41.3	82	49.1	0.733
150	48	86	45.3	82	41.9	0.735
150	48	81	44.0	78	42.3	0.688
150	48	84	45.3	84	43.5	0.744
200	33	87	46.7	82	42.1	0.751
200	63	83	46.6	79	42.8	0.728

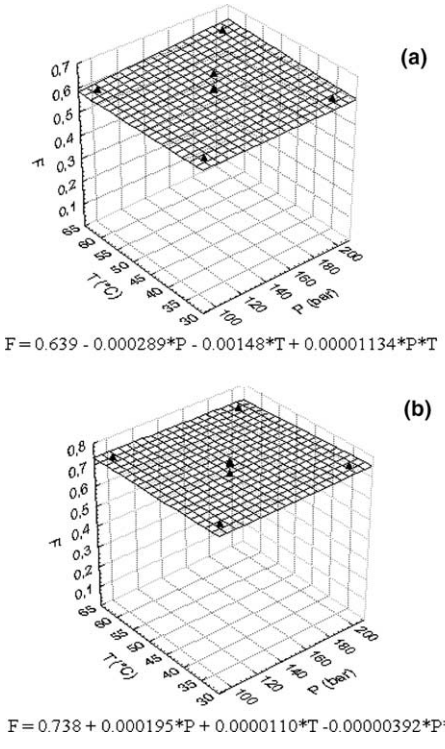

Figure 2. (a) Effect of extraction *P* and *T* on F by resolution with DPTTA. (b) Effect of extraction *P* and *T* on F by resolution with DBTA.

$$F = a + b^*P + c^*T + d^*PT, \quad (1)$$

where *a*, *b*, *c* and *d* are the regression coefficients.

According to the statistical analysis the curvature proved to be unimportant while the linear models were able to describe the experimental data. In both cases neither the pressure nor the temperature had a significant effect on the *F* parameter at 95% significancy level.

Although, the extraction pressure and temperature did not influence the resolution efficiency, they did determine the density of carbon dioxide and hence the solvent consumption. Fig. 3 shows typical extraction curves at 100 bar, 63 °C and 200 bar, 33 °C, where the extract yield (Y/Y_{max}, where Y_{max} is the maximum extract yield) is plotted as a function of the specific carbon dioxide consumption (m_{CO_2}). The CO_2 need of an extraction to reach the 99% extract yield can be calculated from the $Y/Y_{max} = 1 - \exp(-km_{CO_2})$ fitted function suggested by Brunner,[17] where *k* is a specific kinetic coefficient.

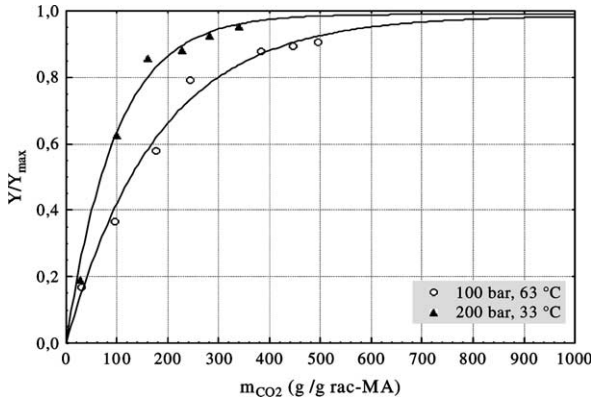

Figure 3. Typical extraction curves ($Y/Y_{max} = 1 - \exp(-0.0103 * m_{CO_2})$ at 200 bar, 33 °C; $Y/Y\,\max = 1 - \exp(-0.00558 * m_{CO_2})$ at 100 bar, 63 °C).

Increasing the solvent density improved the loading capacity of the solvent while the CO_2 consumption decreased from 820 g CO_2/g *rac*-MA at 100 bar 63 °C to 440 g CO_2/g *rac*-MA at 200 bar 33 °C.

2.3. Enantiomeric enrichment

Single extraction processes usually lead to breaking the racemic composition and providing partially resolved mixtures of enantiomers, with further purification still necessary to give pure enantiomers. Two methods [repeated resolution with DBTA resolution agent and partial salt formation with an achiral reagent (hydrochloric acid)] were used for the purification of the mixture of the MA enantiomers. Since MA enantiomers form conglomerates,[18] DBTA and hydrochloric acid were used in equivalent amounts with the pure enantiomeric part of the enantiomeric mixture. Both methods can be efficiently combined with the supercritical fluid extraction. Results of the subsequent purification steps are summarized in Table 3.

3. Conclusion

Supercritical fluid extraction is an efficient method for the separation of *N*-methylamphetamine enantiomers with DBTA and DPTTA resolution agents. Both enantiomers can be produced with high enantiomer selectivity and remarkable yield in a single extraction step.

Table 3. Enantiomeric enrichment of the enantiomeric mixture of MA by SFE ($P = 200$ bar, $T = 33$ °C)

Method	Starting mixture		Extract			Raffinate		
	Conf.	ee (%)	Conf.	Y (%)	ee (%)	Conf.	Y (%)	ee (%)
A	*R*	71	*S*	9.1	52	*R*	71	90
B	*S*	80	*S*	14.0	2	*S*	73.5	93

Method A: Repeated resolution with DBTA.
Method B: Partial salt formation with hydrochloric acid.

While using both resolution agents, the extraction pressure and temperature did not affect the resolution efficiency, which means the resolution is robust. The effects of the extraction conditions may depend on the stabilities of the diastereomeric salts in the supercritical solvent and, since the process is an extraction, on the contact time. The good solubility of MA in supercritical carbon dioxide and the great stabilities of the diastereomeric salts under the supercritical conditions could imply that the equilibria among the diastereomeric salts and free enantiomers formed during the sample preparation do not change under the extraction process.

The CO_2 consumption needed for the extraction of the free enantiomers decreased by increasing the solvent density. This fact suggests low extraction temperature and high extraction pressure conditions.

4. Experimental

4.1. Materials

Racemic *N*-methylamphetamine was prepared by Chinoin Pharmaceutical Ltd (Budapest). Resolution agents (*O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid monohydrate = DBTA, *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid = DPTTA) were purchased from Merck Ltd (Budapest). Other analytical grade reagents were obtained from Reanal Ltd (Budapest).The used CO_2 was 99.5% (w/w) pure and supplied by Messer Griesheim Hungaria Ltd, (Budapest).

4.2. General methods

Enantiomeric excess values of the samples were determined by optical rotatory measurements by Perkin Elmer 241 polarimeter according to prior calibration. The specific rotation of the optically pure (*R*)-*N*-methylamphetamine was $[\alpha]_D^{20} = -18.9$ (*c* 0.1, 1 M HCl).[19]

4.3. Resolution of *N*-methylamphetamine with *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid (DPTTA)

rac-MA (1.50 g, 10.1 mmol) and 0.97 g (2.52 mmol) DPTTA (mr = 0.25) were dissolved in 40 mL methanol after which 2.0 g Perfil 100™ was added to the solution. The solvent was evaporated in vacuum ($T = 40$ °C, $P = 20$ kPa) and the sample dried at room temperature for 1 h. The solid sample was put into the extractor vessel and extracted with supercritical carbon dioxide at 150 bar 48 °C. The extract was then collected in the separator {(*S*)-(+)-MA, 0.72 g, $Y_E = 48.0\%$, $[\alpha]_D^{20} = +13.1$ (*c* 0.1, 1 M HCl), $ee_E = 69\%$}.

The raffinate was suspended in 15 mL 2 M NaOH and 20 mL CH_2Cl_2 and stirred for 5 min. After filtering the support, the organic and aqueous phases were separated. The aqueous phase was extracted with 2×20 mL CH_2Cl_2. The collected organic phases were washed with 10 mL water and dried over Na_2SO_4. The solvent was evaporated in vacuum to give {(*R*)-(−)-MA, 0.58 g, $Y_R = 38.8\%$, $[\alpha]_D^{20} = -14.0$ (*c* 0.1, 1 M HCl), $ee_R = 74\%$}.

4.4. Resolution of *N*-methylamphetamine with *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid (DBTA)

rac-MA (1.50 g, 10.1 mmol) and 0.94 g (2.52 mmol) DBTA were dissolved in 40 mL methanol and 2.0 g Perfil 100™ then added to the solution. The solvent was evaporated in vacuum ($T = 40$ °C, $P = 20$ kPa) and the sample dried at room temperature for 1 h. The solid sample was transferred into the extractor vessel and extracted with supercritical carbon dioxide at 150 bar 48 °C. The extract was collected in the separator {(*S*)-(+)-MA, 0.68 g, $Y_E = 45.3\%$, $[\alpha]_D^{20} = +16.3$ (*c* 0.1, 1 M HCl), $ee_E = 86\%$}.

The raffinate was suspended in 15 mL 2 M NaOH and 20 mL CH_2Cl_2 and stirred for 5 min. After filtering the support, the organic and aqueous phases were separated. The aqueous phase was extracted with 2×20 mL CH_2Cl_2. The collected organic phase was washed with 10 mL water and dried over Na_2SO_4. The solvent was evaporated in vacuum to give {(*R*)-(−)-MA, 0.63 g, $Y_R = 41.9\%$, $[\alpha]_D^{20} = -15.6$ (*c* 0.1, 1 M HCl), $ee_R = 82\%$}.

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