SEPARATION OF N-METHYLAMPHETAMINE ENANTIOMERS BY SUPERCRITICAL FLUID EXTRACTION

Ildikó Kmecz[*a], Béla Simándi[a], Edit Székely[a], Elemér Fogassy[b]

[a]Budapest University of Technology and Economics, Department of Chemical Engineering
1521 Budapest, Muegyetem rakpart 3.
[b]Budapest University of Technology and Economics, Department of Organic Chemical Technology
1521 Budapest, Muegyetem rakpart 3.
e-mail: kmetz@mail.bme.hu, Fax: +36-1-463-3197

Separation of N-methylamphetamine enantiomers was carried out using O,O'-di-p-toluoyl-(2R,3R)-tartaric acid as a resolution agent in less than equivalent molar ratio. After the partial diastereomeric salt formation, the unreacted enantiomers were extracted with supercritical carbon dioxide. The effects of the resolution agent molar ratio, extraction pressure and temperature on the resolution efficiency were studied. The maximal chiral separation was obtained at quarter of an equivalent resolution agent molar ratio. Changing of the extraction pressure (100-200 bar) and temperature (33-63 °C) has no significant effect on the resolution efficiency, which makes the separation robust. In one extraction step both enantiomers can be produced with high optical purity and remarkable yield (OP_E = 68 %, Y_E = 45 % for the extract and OP_R = 70 %, Y_R = 40 % for the raffinate).

INTRODUCTION

Preparation of biologically active compounds in many cases leads to racemic final product, which contains the enantiomers in 1:1 ratio. These enantiomers often show different biological effects, usually one of them has the required therapeutic activity, and the other is inactive or responsible for the toxic side effect. Therefore production of pure enantiomers is getting more and more importance in the pharmaceutical and pesticide industries.

The commonly used resolutions are based on fractional crystallization of the diastereomeric salts from the proper solvent [1]. Many racemic compounds can be resolved by this way successfully, but this method has several disadvantages. The final products contain solvent residuals and the great solvent consumption leads to economical and environmental problems. So the aim of the researchers is to find environmentally friendly and efficient processes.

Supercritical fluid extraction (SFE) is a new alternative for separation of the enantiomers, which was developed in our laboratory. Resoluiton by SFE is also based on diastereomeric salt formation and the resolution agent is used in less than equivalent molar ratio. The separation can be achieved by the extraction of the free enantiomers from the side of the more stable diastereomeric salts with supercritical carbon dioxide. Previously we found that several racemic acids [2,3] can be resolved by this method, but until now only a few organic bases [4] were tested.

The aim of this study was to extend the applicability of this process for other organic bases. The studied model compound was the N-methylamphetamine (MA) which is an intermediate of Jumex (antiparkinson agent). The resolution of racemic-MA with O,O'-di-p-toluoyl-

tartaric acid (DPTTA) is described in the literature [5] so DPTTA was used as a resolution agent in our work.

MATERIALS AND METHODS

Materials

Racemic N-methylamphetamine was prepared by CHINOIN Pharmaceutical Ltd. (Budapest). The O,O'-di-p-toluoyl-(2R,3R)-tartaric acid resolution agent was purchased from Merck Ltd. (Budapest). Other analytical grade reagents were obtained from Reanal Ltd. (Budapest). Carbon dioxide (99.5 %(w/w) pure) was supplied by Messer Griesheim Ltd. (Budapest, Hungary).

Methods

The resolution method is shown in Figure 1. The racemic-MA and the DPTTA, which was used in less than equivalent molar ratio, were dissolved in methanol and achiral support material (perfil) was added to the solution. The solvent was evaporated in vacuum. The solid sample was dried at room temperature for 1 hour and then was filled into the extractor vessel. Detailed description of the extractor unit is given in previous work [2]. The free enantiomers were extracted with supercritical carbon dioxide in the range of 100-200 bar, and 33-63 °C and were collected as extract samples in the separator by pressure reduction of the solvent. The diastereomeric salts were insoluble in supercritical carbon dioxide, and remained in the extractor as raffinate. After the decomposition of the diastereomeric salts, the optical purity values of the extract and the raffinate were calculated from the optical rotation measured by Pelkin Elmer 241 polarimeter. The specific rotation of the pure enantiomers is known form the literature [5].

In all experiments the extract was reached in the S-(+)-enantiomer, and the raffinate contained the R-(-)-enantiomer in excess.
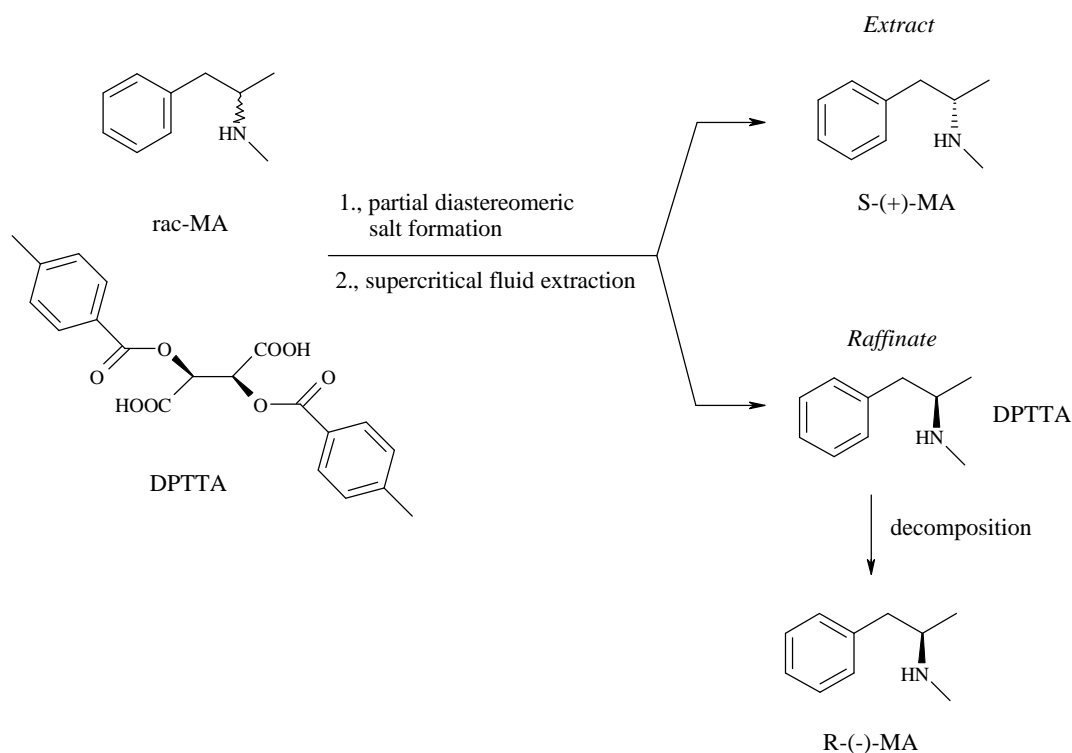
Figure 1: Resolution of racemic-MA by supercritical fluid extraction.

RESULTS AND DISCUSSION

To map those effects, which may have influence on the efficiency of the resolution, the resolution agent molar ratio (mol resolution agent/mole racemic base) and the extraction pressure and temperature were examined. In all experiments the resolution efficiency is described by the F parameter ($F = OP_E*Y_E + OP_R*Y_R$, where Y is the yield = mass of the extract (raffnate)/mass of the initial racemic compound, and OP is the optical purity. E and R subscripts represent the extract and the raffinate, respectively). The F parameter is varied between 0 and 1.

Effect of resolution agent molar ratio

To study the effect of the amount of the resolution agent on the resolution efficiency the molar ratio was varied in the range of 0.1-0.4. The measured optical purity values with the standard deviances and the yield for the extract and the raffinate are shown in Figure 2a., and Figure 2b., respectively.
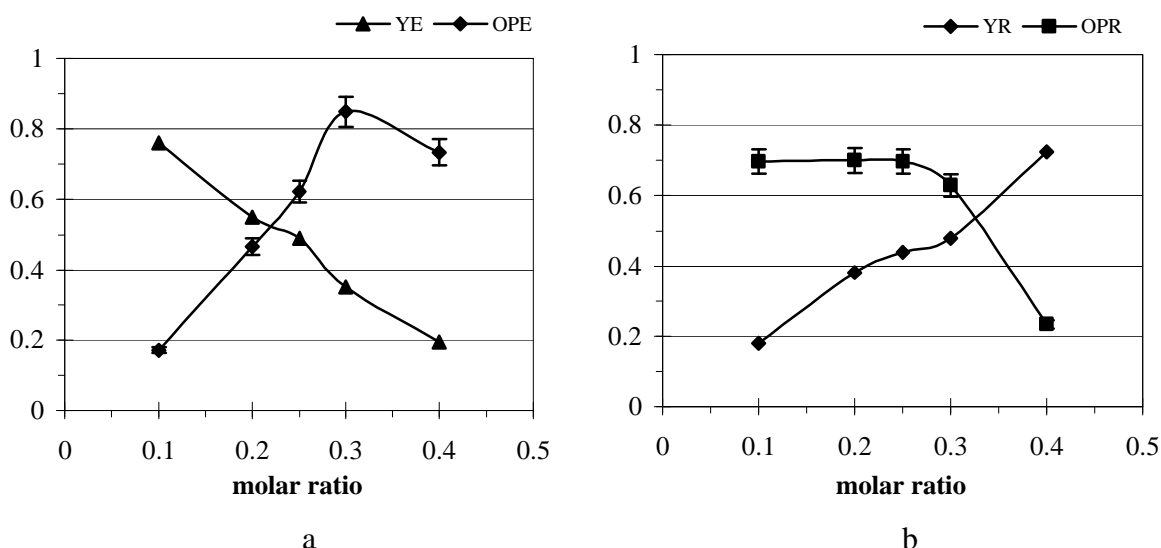

Figure 2: Effect of the resolution agent molar ratio on the yield and optical purity for the extract (a) and the raffinate (b).

As it can be seen in Figure 2a. by increasing the resolution agent molar ratio the optical purity of the extract increases and passes through a maximum, while the yield decreases almost linear. The opposite tendencies were observed in case of the raffinate (Figure 2b.).

Figure 3. shows the changes of F parameter as a function of molar ratio. The F parameter has a slight maximum between 0.25 and 0.30 molar ratio. Further experiments were carried out at 0.25 resolution agent/racemic-MA molar ratio.
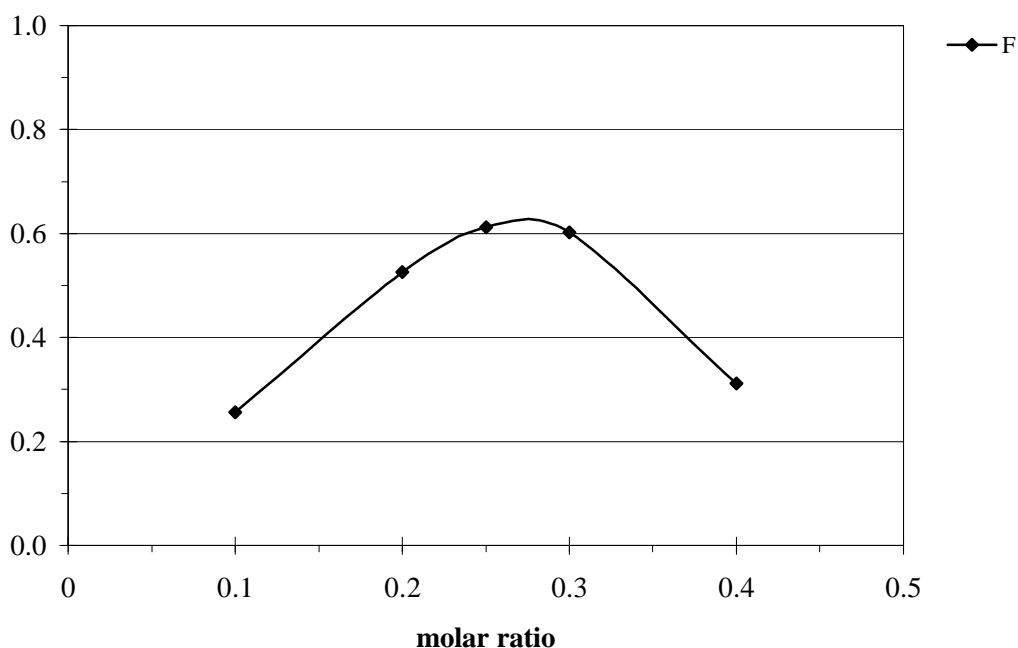
Figure 3: Effect of molar ratio on the resolution efficiency by resolution of racemic-MA.

Effect of the extraction parameters

2^2 full factorial experimental design, with three repetitions in the center point, was carried out to determine the effects of extraction pressure (100, 150, 200 bar) and temperature (33, 48, 63 °C). The obtained results are summarized in Table 1. The F parameter was used as dependent variable. This experimental design is suitable to estimate the linear effects of pressure, temperature and their linear combination, and a linear model is fitted to the experimental data. The applicability of the fitted model is checked by curvature calculation.

Table 1: Effect of the pressure (P) and temperature (T) on the yield, optical purity and the F parameter at 0.25 DPTTA / racemic-MA molar ratio.

P (bar)	T (°C)	Extract		Raffinate		F
		Y_E (%)	OP_E (%)	Y_F (%)	OP_F (%)	
100	33	43.3	68.5	42.3	71.7	0.60
100	63	47.3	64.8	42.9	65.7	0.59
150	48	50.0	72.7	42.2	76.2	0.68
150	48	48.0	69.1	38.8	74.1	0.62
150	48	46.6	69.5	41.7	71.1	0.62
200	33	46.0	68.1	41.6	70.7	0.61
200	63	53.3	64.3	40.2	71.4	0.63

The Pareto diagram (Figure 4.) shows the results of the statistical analysis of the experimental data. It is obvious from the diagram that neither the pressure nor the temperature has significant effect on the F parameter at $p=0.05$ significance level. The fitted linear model describes very well the experimental data, because the curvature is also not significant.
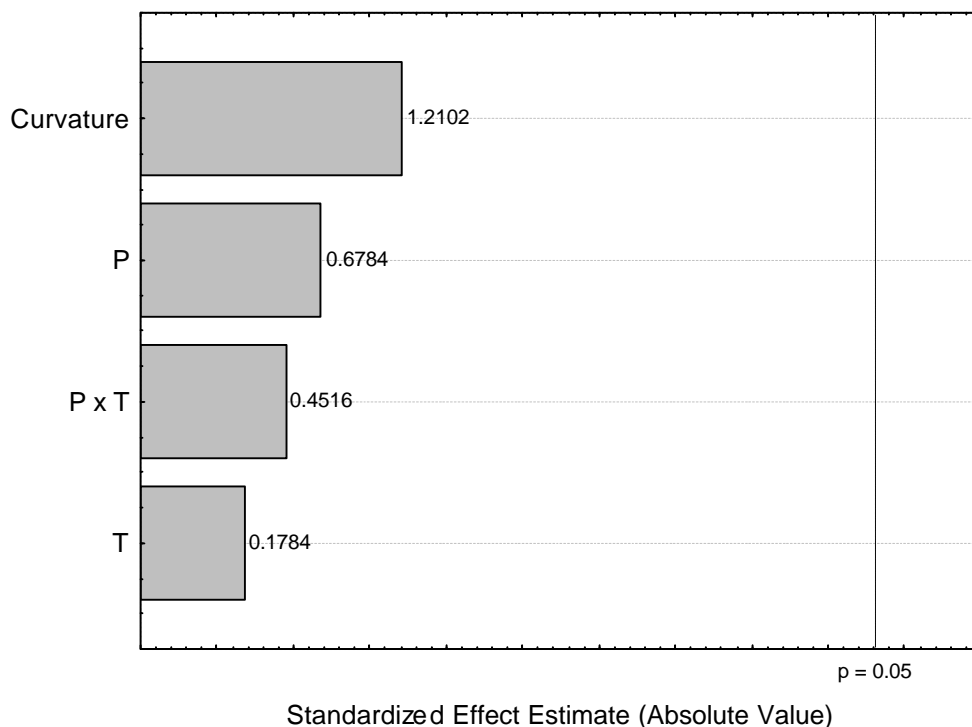

Figure 4: Pareto diagram of the effects of the extraction parameters (P, T) on the F parameter by resolution of racemic-MA.

However, varying the extraction pressure and temperature the density of the carbon dioxide is changed, which has influence on the loading capacity. Increasing the solvent density improves the loading capacity, and the carbon dioxide consumption decreases from ~400 g/g MA at 100 bar, 63 °C to ~100 g/g MA at 200 bar, 33 °C.

CONCLUSION

Supercritical fluid extraction proved to be an efficient method for the resolution of racemic-MA with DPTTA as a resolution agent. In one extraction step both enantiomers can be produced with high enantioselectivity and remarkable yield (OP = 68 %, Y = 45 % for the extract and OP = 70 %, Y = 40 % for the raffinate) at 0.25 resolution agent/racemic-MA molar ratio. The extraction parameters have no significant effect on the resolution efficiency. But the extraction pressure and temperature may influence the loading capacity of the carbon dioxide, and the carbon dioxide consumption is four times higher at 100 bar, 63 °C than at 200 bar, 33 °C. These results suggest low extraction temperature and high extraction pressure conditions.

The solvent free final products and the environmentally benign solvent make this process competitive with the conventional method.

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ACKNOWLEDGEMENT