

## **THERMOANALYTICAL STUDY OF O,O'-DIBENZOYL-(2R, 3R)-TARTARIC ACID SMC Part IV. SMC formation in melt**

*H. Simon*<sup>1</sup>, *Z. Vincze*<sup>1</sup>, *K. Marthi*<sup>2</sup>, *G. Lévai*<sup>3</sup>, *Gy. Pokol*<sup>3</sup>, *E. Fogassy*<sup>1</sup>  
and *D. Kozma*<sup>1\*</sup>

<sup>1</sup>Department of Organic Chemical Technology, Budapest University of Technology and Economics, Budapest, Műegyetem rkp. 3, P.O. Box 91, H-1521 Hungary

<sup>2</sup>Research Group for Technical Analytical Chemistry, Hungarian Academy of Sciences, Budapest University of Technology and Economics, Budapest, Szt. Gellért tér 4, H-1521, Hungary

<sup>3</sup>Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, Budapest, Szt. Gellért tér 4, H-1521, Hungary

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### **Abstract**

It has been shown that optical resolution via supramolecular compound (SMC) formation with O,O'-dibenzoyl-(2R,3R)-tartaric acid (DBTA) can be performed not only by the previously described way (i.e. in hexaneous solution), but also without a solvent, in the melt of the racemate. The resolution of racemic menthol and neomenthol was investigated by preparative and thermoanalytical methods. The resolution in melt is not only simpler and faster, but the efficiency of the resolution has proved to be higher in the case of the menthol. The neomenthol forms no SMC with DBTA in hexaneous solution, but in melt we were able to obtain a SMC and to perform a resolution.

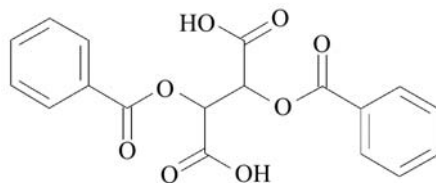
### **Introduction**

O,O'-dibenzoyl-(2R,3R)-tartaric acid monohydrate (DBTA) is one of the most frequently used resolving agents for optical resolution of racemic bases via diastereoisomeric salt formation [1, 2]. It has been found that DBTA can serve also as a diastereomeric supramolecular compound (SMC) forming resolving agent for the preparative scale resolution of a large number of alcohols [3–6] (Scheme 1).

During optical resolutions, the diastereomers are usually separated by fractional crystallization with the aid of a solvent. We developed a generally applicable process for the separation of SMC-s using hexane as semi-inert solvent [7]. Hexane dissolves the alcohols but it does not dissolve DBTA and the DBTA-alcohol supramolecular compound.

\* Author for correspondence: E-mail: david@oct.bme.hu

The racemate is dissolved in hexane and DBTA is suspended in this solution. The formation of the SMC starts on the solid-liquid interface by recrystallization of the solid phase. Without stirring lasts about one week at room temperature [7].



Scheme 1 DBTA

In this paper we report the SMC formation in melt, without solvent, which proved to be simpler and faster. Additionally, the efficiency of the resolution could also be improved.

## Experimental

All chemicals were purchased from Aldrich.

### *Resolution of racemic menthol with DBTA monohydrate in melt*

10 g (0.064 mol) of racemic menthol was mixed with finely powdered DBTA monohydrate (Table 1). The mixture was gently heated on water-bath until a clear melt was formed. After cooling back to room temperature the stirred melt solidified. The solid was suspended in 15 mL hexane and filtered. The filtered SMC was dissolved in saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution, extracted three times with 20 mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was evaporated and the alcohol component was purified by distillation then analysed with a polarimeter. The unreacted alcohol could be obtained by fractional vacuum distillation of the hexaneous mother liquor. Results are summarised in Table 1.

### *Resolution of racemic neomenthol with DBTA monohydrate in melt*

0.85 g (0.0054 mol) of racemic neomenthol was mixed with 1.02 g (0.0027 mol) DBTA monohydrate. The mixture was gently heated on water bath until a clear melt formed. After cooling back to room temperature the stirred melt solidified. The solid was suspended in 5 mL hexane and filtered. The filtered SMC was dissolved in aqueous NaOH, extracted three times with 20 mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was evaporated and the alcohol component was purified by distillation.

$$m: 0.31 \text{ g } (Y=72.9\%), [\alpha]_{\text{D}}^{20} = -10.41 \text{ (} c=10, \text{ EtOH), } ee=0.496$$

The unreacted alcohol was obtained by fractional vacuum distillation of the hexaneous mother liquor.

$m$ : 0.54 g ( $Y=127.0\%$ ),  $[\alpha]_D^{20}=+5.66$  ( $c=10$ , EtOH),  $ee=0.269$

Optical rotation was measured with a Perkin Elmer 241 polarimeter.

The TG and DTG curves were recorded on a TA Instruments TGA 2050 thermogravimetric analyzer. Samples of 5.5–6.5 mg were analyzed in open platinum pans under flowing air ( $10 \text{ L h}^{-1}$ ) between 25–300°C with a heating rate of  $10^\circ\text{C min}^{-1}$ .

DSC curves were recorded with a TA Instruments 2920 Modulated DSC. Samples of 3.0–4.0 mg were analyzed in open aluminium pans under flowing argon ( $10 \text{ L h}^{-1}$ ) between 20–200°C with a heating rate of  $5^\circ\text{C min}^{-1}$ .

A Leitz microscope (type Dialux 20) equipped with a Mettler hot stage (type FP82HT) was used to check visually the formation of the SMC.

## Results and discussion

The resolution of menthol by SMC formation in hexane with DBTA is quite efficient ( $S=0.374$ ) [7], but very slow. In our attempt to find a better way to perform the resolution, we tried the resolution in melt, because of the low melting point of racemic menthol ( $m.p.$ : 33°C).

The mixture of DBTA and racemic menthol is a thick suspension (containing some molten menthol) at room temperature. Just above room temperature menthol melts and this melt dissolves DBTA. After obtaining a clear liquid phase, the stirred melt was allowed to cool back to room temperature. The process resulted in a white solid, having quite a different appearance from the starting suspension. From this solid the unreacted menthol and the SMC were separated and the menthol enantiomers were liberated as described in the Experimental section. The experiments were performed with different molar ratios. The results are summarised in Table 1.

**Table 1** SMC formation in melt with different molar ratio of racemic menthol and DBTA

$MR$	Non-reacted menthol				Menthol from SMC				
	$m/g$	$Y/\%$	$[\alpha]_D^{20}$	$ee$	$m/g$	$Y/\%$	$[\alpha]_D^{20}$	$ee$	$S$
0.2	6.4	128.8	+3.7	0.08	0.6	12.0	-44.6	0.89	0.107
0.3	7.8	156.0	+8.2	0.16	1.5	30.0	-42.5	0.85	0.255
0.4	6.9	137.8	+14.1	0.28	2.6	51.8	-38.0	0.76	0.394
0.5	5.7	113.4 155.0*	+22.1	0.44 0.24*	3.6	72.6 45.0*	-31.4	0.63 0.83*	0.456 0.37*
0.6	6.2	124.2	+16.8	0.34	2.8	56.4	-33.6	0.67	0.378
0.7	5.5	109.4	+14.9	0.30	3.7	73.6	-22.1	0.44	0.326

$MR$ : molar ratio of DBTA : menthol;

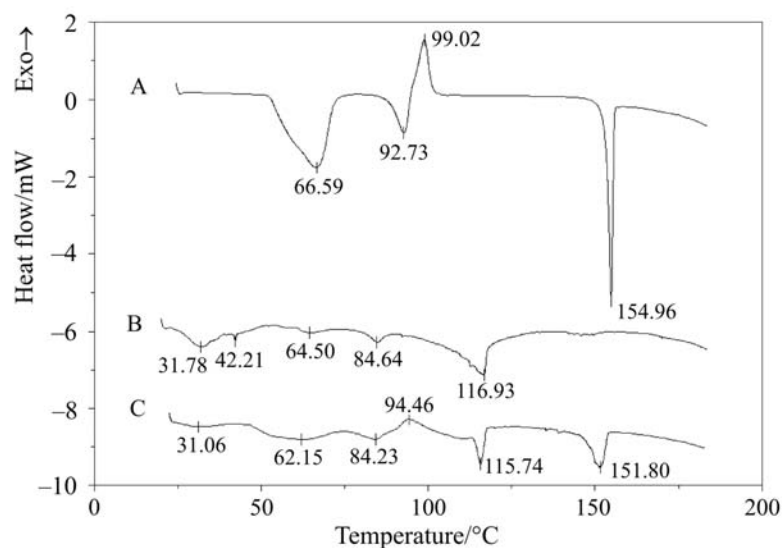
$S$  (efficiency of the resolution) =  $(Y \cdot ee)/100$ ; \* results of experiment in hexane

It can be seen that the enantiomeric excess of menthol, liberated from the SMC was higher using smaller amounts of DBTA, but the efficiency of the resolution was the best by using 2:1 ratio DBTA : menthol, which is in accordance with observation that (–)-menthol forms SMC with DBTA at a 1:1 molar ratio [8, 9]. The efficiency of the resolution proved to be higher, than in hexane. It is not possible to reach a very high enantiomeric excess in one resolution step, this is why the preparative scale SMC formation was tried not only from racemic menthol, but also from enantiomeric mixtures of menthol. The result of such experiments are summarised in Table 2.

By repeating the resolution with SMC formation from melt, very high enantiomeric excess could be achieved.

To get a better understanding of the SMC formation between DBTA and menthol, we studied this process under a microscope and by DSC.

For the DSC measurement DBTA and (–)-menthol was mixed in a molar ratio of 1:1 and heated slowly with  $2.5^{\circ}\text{C min}^{-1}$  (Fig. 1). The first endothermic peak at  $31.5^{\circ}\text{C}$  corresponds to the melting of menthol; the second one with a minimum at  $67^{\circ}\text{C}$  belongs to the evaporation of water. After the loss of water the complex formation starts. The SMC crystallizes at  $90^{\circ}\text{C}$ . At slightly higher temperatures after the crystallization the complex starts to melt, giving a large endothermic peak at  $116^{\circ}\text{C}$ . Heating further the menthol evaporates at about  $145^{\circ}\text{C}$ . When the molar ratio of the DBTA: (–)-menthol was 2:1, which means one molar equivalent amount of unreacted DBTA, the DSC curve is similar to the previously described with the addition of an endothermic peak corresponding to the melting point of DBTA. Figure 2 shows thermo micrographs made at 63, 68 and at  $113^{\circ}\text{C}$ .



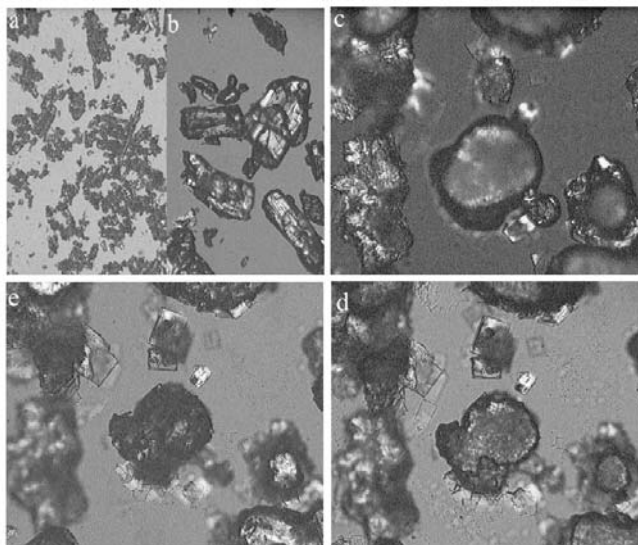
**Fig. 1** DSC curves of a – DBTA monohydrate, b – DBTA: (–)-menthol (1 :1) and c – 2:1 mixture

**Table 2** SMC formation in melt with non-racemic menthol

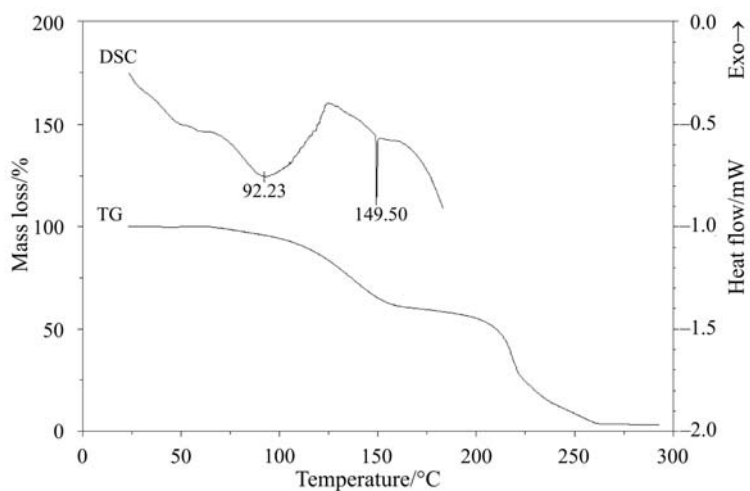
<i>MR</i>	Starting menthol			Non-reacted menthol			Menthol from SMC				
	$[\alpha]_D^{20}$	<i>ee</i>	<i>m/g</i>	<i>m/g</i>	<i>Y/%</i>	$[\alpha]_D^{20}$	<i>ee</i>	<i>m/g</i>	<i>Y/%</i>	$[\alpha]_D^{20}$	<i>ee</i>
0.50	-31.9	0.64	5.7	2.8	49.1	-20.3	0.41	2.7	45.6	-47.2	0.94
0.65	-31.9	0.64	5.8	1.7	29.3	-5.2	0.10	3.5	60.3	-46.0	0.92
0.60	+14.4	0.29	27.6	18.3	68.8	+20.7	0.42	5.6	20.7	-8.2	0.16

MR: molar ratio of DBTA: menthol

We were not able to resolve racemic neomenthol with DBTA in hexaneous suspension. From melt using the same way as for the menthol quite an efficient resolution ( $S=0.34$ ) was attainable. It can be seen from the DSC curve (Fig. 3) that the melt recrystallizes between 115–135°C (by that time the uncomplexed neomenthol enantiomer has already evaporated), then the complex rapidly decomposes, and the complexed enantiomer evaporates. At 150°C only DBTA remains, which can be seen from the sharp melting peak.



**Fig. 2** Pictures of a – DBTA at room temperature, b – menthol at room temperature and their (1 : 1) mixture c – at 63°C, d – at 68°C and e – at 113°C



**Fig. 3** DSC and TG curves of DBTA : racemic neomenthol (1 : 2)

## Conclusions

DBTA can form SMC-s with menthol and neomenthol in the melt. This process is simpler than the one carried out in hexaneous solution and can result in a more effective resolution of the alcohol enantiomers or it can provide enantiomer separation in such cases when it proved to be unsuccessful in hexane.

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## References

- 1 D. Kozma (Ed.), Handbook of Optical Resolutions via Diastereomeric Salt Formation, CRC Press LLC, Boca Raton 2001.
- 2 P. Newman, Optical Resolution Procedures for Chemical Compounds, Optical Resolution Information Center, Manhattan College, N.Y. Riverdale 1978–1984.
- 3 D. Kozma, Zs. Böcskei, Cs. Kassai, K. Simon and E. Fogassy, *J. Chem. Soc. Chem. Com.*, (1996) 753.
- 4 R. Illés, Cs. Kassai, Gy. Pokol, E. Fogassy and D. Kozma, *J. Therm. Anal. Cal.*, 68 (2002) 679.
- 5 D. Kozma, H. Simon, Gy. Pokol and E. Fogassy, *J. Therm. Anal. Cal.*, 68 (2002) 409.
- 6 H. Simon, K. Marthi, Gy. Pokol, E. Fogassy and D. Kozma, *J. Therm. Anal. Cal.*, 74 (2003) 155.
- 7 Cs. Kassai, Z. Juvancz, J. Bálint, E. Fogassy and D. Kozma, *Tetrahedron*, 56 (2000) 8355.
- 8 R. Illés, Cs. Kassai, Gy. Pokol, J. Madarász, E. Fogassy and D. Kozma, *J. Therm. Anal. Cal.*, 61 (2000) 745.
- 9 Cs. Kassai, R. Illés, Gy. Pokol, J. Sztatisz, E. Fogassy and D. Kozma, *J. Therm. Anal. Cal.*, 62 (2000) 647.