# O,O'-DI-*p*-TOLUOYL-(2*R*,3*R*)-TARTARIC ACID AS SUPRAMOLECULAR RESOLVING AGENT

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## Abstract

O,O'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid (DPTTA) was investigated as supramolecular complex (SMC) forming resolving agent with three racemic alcohols (menthol, 4-methyl-2-pentanol, *trans*-2-iodo-cyclohexanol) by preparative scale experiments and thermoanalytical measurements. Despite the very small structural difference (two methyl groups) between the O,O'-dibenzoyl-(2*R*,3*R*)-tartaric acid (DBTA) and DPTTA, their SMC forming properties with water and racemic alcohols is very different. While DBTA forms SMC with all the three investigated alcohols, DPTTA forms SMC only with *trans*-2-iodo-cyclohexanol. DPTTA binds the guest compound less strongly and the stoichiometry of the SMC is also different. The weaker interactions resulted in less effective optical resolutions. The results of these investigations remind us, that in optical resolutions during the chiral discrimination process the weaker interactions have a determining role, since DBTA and DPTTA have the possibility to form the same strong (O–H···O and N–H···O) hydrogen bond network.

**Keywords:** complex formation, enantiomer separation, O,O'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid, optical resolution, enantioselectivity

## Introduction

Optical resolution via diastereomeric salt formation is the most frequently applied procedures for the separation of enantiomers on a large scale. With the aid of a chiral resolving agent the enantiomers that have identical physical properties, are transformed into diastereomeric compounds. These can be separated because they have different physical properties [1–2]. Compounds having neither acidic nor basic groups cannot be resolved this way. They are usually resolved via diasteromeric salt formation after derivatization with a bifunctional acid or base or without derivatization by using a chiral complex forming resolving agent [3–9]. Since the derivatization process is tedious, it seems reasonable to perform the resolution via the formation of complexes.

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We have described earlier that O,O'-dibenzoyl-(2*R*,3*R*)-tartaric acid (DBTA) can be used as a diastereomeric supramolecular compound (SMC) forming resolving agent [10]. We have investigated the role of the guest compounds during the SMC formation, by reacting the DBTA with more than 30 racemates [11–15].

In this study we investigate the effect of a small structural change in the host compound, using O,O'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid (DPTTA).



DBTA                    DPTTA
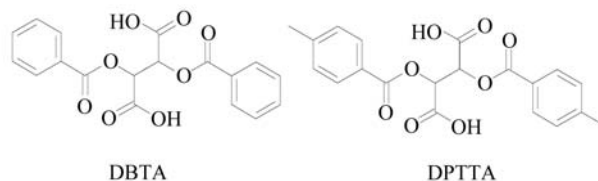
## Experimental

All chemicals were purchased from Aldrich.

### General procedure for resolution of racemic alcohols with DPTTA monohydrate

4.00 g of racemic-alcohol was dissolved in 40 mL of hexane, half molar equivalent amount of finely powdered DPTTA monohydrate was suspended in the solution (in case of menthol: 4.94 g; 4-methyl-2-pentanol: 7.56; *trans*-2-iodo-cyclohexanol: 3.42 g DPTTA were used). After standing one week without stirring at room temperature the solid phase was filtered and 15–20 mg of the SMC was analysed with TG, DSC and EGD. The solid supramolecular compound was dissolved in aqueous $Na_2CO_3$ solution, extracted by three times with 20 mL portions of $CH_2Cl_2$. The organic phase was evaporated and the alcohol component was purified by distillation. It was then analysed with a polarimeter. The unreacted alcohol enantiomeric mixture can be obtained by fractional vacuum distillation of the hexaneous mother liquor. Results are summarised in Table 1.

### Optical analysis

Optical rotations were measured with Perkin Elmer 241 polarimeter.

### Thermal analysis

The TG and DTG curves were recorded with a TA Instruments TGA 2050 thermogravimetric analyzer. Samples of 5.5–6.5 mg were analyzed in open platinum pans under flowing air (10 L h$^{-1}$) between 25–300°C with a heating rate of 10°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 L h$^{-1}$) between 20–200°C with a heating rate of 5°C min$^{-1}$.

EGD measurements were recorded with a DuPont 916 thermal evolution analyzer with Chromel–Alumel thermocouple and hydrogen flame ionisation detector. Samples of 5.0–6.0 mg were analyzed between 20–300°C under nitrogen flow (1.8 L h$^{-1}$) with a heating rate of 8°C min$^{-1}$.

## Results and discussion

The resolution by SMC formation was performed with DPTTA in the same way as with DBTA: the solid host was suspended in the hexaneous solution of the racemate. In this study we used the following three racemic alcohols that gave the most efficient resolution with DBTA.

menthol          4-methyl-2-pentanol          *trans*-2-iodo-cyclohexanol
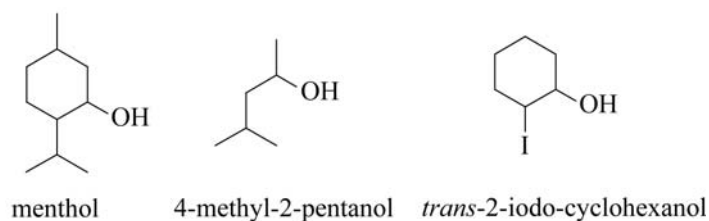
The results of the resolutions are summarised in Table 1.

All the solid phases and the DPTTA were analysed by thermoanalytical methods. For the better comparison in the Figures the thermal curves of DPTTA are always shown together with the corresponding DBTA curves.

Both DBTA and DPTTA exist in monohydrate form and were used as such. The loss of the crystal water in case of DBTA appears as an endothermic peak between 50–80°C on the DSC record (Fig. 1). After the evaporation of the water, the structure
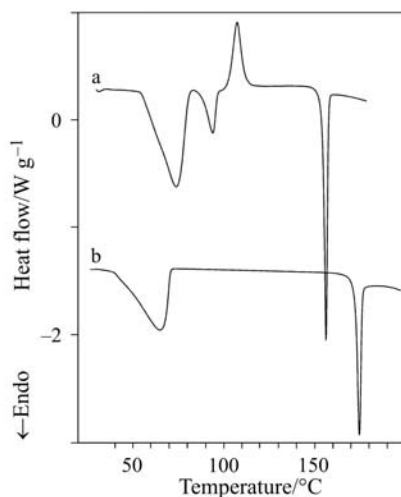


**Fig. 1** DSC curves of a – DBTA and b – DPTTA

**Table 1** Results of the preparative experiments

| Racemate | Hexaneous phase | | | | Solid phase | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $M$/g | $Y$ | $[\alpha]_D^{20}$ | e.e. | $M$/g | $Y$ | $[\alpha]_D^{20}$ | e.e. | $S^*$ |
| **I** | 2.58 | 1.28 (1.55)** | +0.228 | 0.0046 (0.24)** | 0.32 | 0.16 (0.45)** | −0.237 | 0.0047 (0.83)** | 0.00076 (0.37)** |
| **II** | 3.90 | 1.95 (1.09)** | −1.60 | 0.09 (0.23)** | 0 | 0 (0.91)** | 0 | 0 (0.28)** | 0 (0.25)** |
| **III** | 1.51 | 0.75 (1.00)** | −9.29 | 0.28 (0.48)** | 2.28 | 1.14 (0.71)** | +7.30 | 0.22 (0.61)** | 0.25 (0.43)** |

*The efficiency (0<$S$<1) of the optical resolution has been defined as the product of the enantiomeric excess (0<e.e.<1) and the yield (0<$Y$<1) [$Y$=2 for the racemate, $Y$=1 for one enantiomer] : $S$=e.e.$Y$.
**Results of the experiments with DBTA [12]

breaks down, which can be seen as a small endothermic peak at 94°C, then the crystal structure re-arranges at about 107°C, as indicated by a sharp exothermic peak. The water free DBTA melts at 156°C. The DPTTA lost the water at a lower temperature, shows no trace of structural re-arrangement and melts at 176°C.

The only difference in the molecular structure of DBTA and DPTTA is the presence or absence of two methyl groups in para position on the phenyl group. The hydrogen donor and acceptor atoms are the same in both compounds.

Despite this high similarity, the water complexing ability of the two compounds is very different. As can be concluded from the thermal measurements, in case of DBTA monohydrate the water is an essential part of the crystal structure. The DPTTA monohydrate binds the water less strongly, the loss of the water makes no substantial change in its structure. The anhydrous DPTTA melts at higher temperature than DBTA, which indicates higher stability.

The same tendency can be observed for all the investigated alcohols.

By reacting DPTTA with menthol no complex formation was observed. The poor resolution can be due to some chiral interaction on the surface of the host compound. The small amounts of menthol presumably evaporate at about 40°C together with the crystal water (Fig. 2). The SMC with DBTA lost the menthol only at 113°C. It is very interesting that though the DPTTA melts at 175°C – like in case of DPTTA obtained from the monohydrate – an endothermic peak was observed at 144°C, which indicates a polymorphic transition. Investigations with a hot stage microscope have shown that melting can be observed at this temperature at the edges of the crystals, followed by crystallization.

4-methyl-2-pentanol forms no SMC with DPTTA. The DSC curve of the solid phase of the preparative experiment is almost identical with the DPTTA mono-
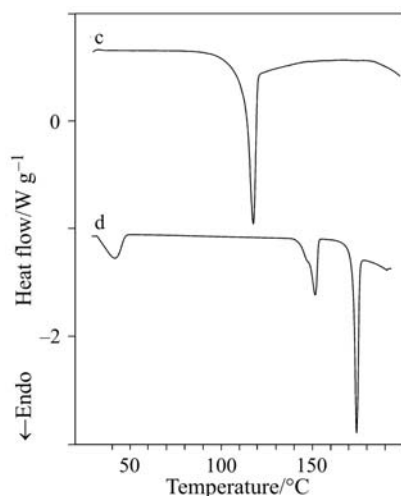


**Fig. 2** DSC curves of the solid phase from the preparative SMC forming experiments of c – enthol-DBTA and d – DPTTA
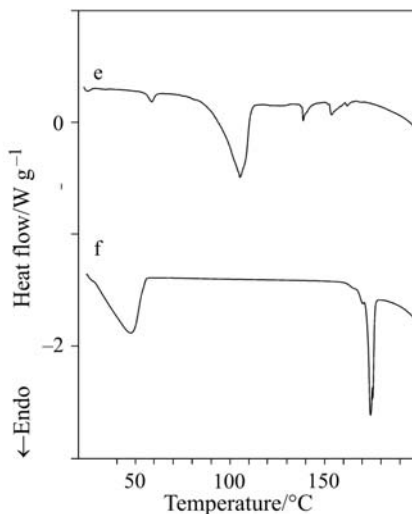
**Fig. 3** DSC curves of the solid phase from the preparative SMC forming experiments of e – 4-methyl-2-pentanol – DBTA and f – DPTTA
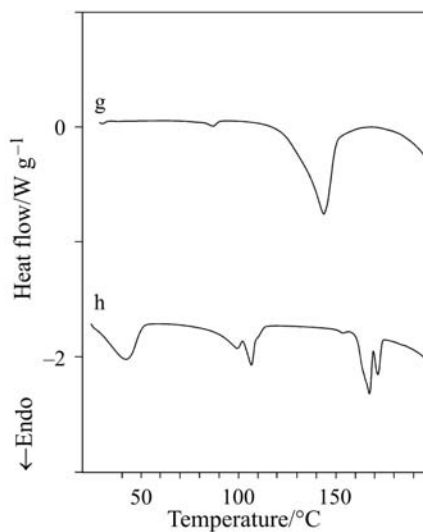


**Fig. 4** DSC curves of the solid phase from the preparative SMC forming experiments of g – *trans*-2-iodo-cyclohexanol – DBTA and h – DPTTA. The TG curve for the DPTTA SMC shows a mass loss of 23.5%

hydrate (Fig. 3). The only difference is a small shoulder at 165–170°C, which indicates some contamination from the experiment, which somewhat decreases the melting point.

TG-MS results have shown that the first endothermic peak (which was assigned to the loss of water from DPTTA) belongs to the evolution of water and hexane. The

binding of hexane on these samples might be the reason why the DPTTA that remained from the SMC formation attempts with menthol and 4-methyl-2-pentanol formed different polymorphic modifications. Attempts to prepare these modifications without any alcohol were fruitless, no hexane was found to be bound to DPTTA even after several months of reaction time.

*Trans*-2-iodo-cyclohexanol forms a supramolecular compound with DPTTA, as indicated by both the preparative and the thermoanalytical experiments. The SMC of the DPTTA with *trans*-2-iodo-cyclohexanol contains also water that leaves the crystal lattice at 40°C (Fig. 4). That is a very important difference because the SMC-s with DBTA never contain water; although both host compounds were always applied as monohydrates. The *trans*-2-iodo-cyclohexanol leaves the complex with DPTTA at lower temperature than in case of SMC with DBTA. From the TG curve 23.5% mass loss can be seen which corresponds to 2:1 DPTTA: alcohol molar ratio, which is different from the SMC-s of chiral alcohols with DBTA, where the ratio is 1:1 [12–14].

## Conclusions

Despite the very small structural difference (two methyl groups) DBTA and DPTTA have different SMC forming properties with water and racemic alcohols. While DBTA forms SMC-s with all the three investigated alcohols (menthol, 4-methyl-2-pentanol, *trans*-2-iodo-cyclohexanol), DPTTA reacts only with *trans*-2-iodo-cyclohexanol. This SMC of DPTTA binds the guest compound less strongly, and the stoichiometry of the SMC is also different. The looser interaction resulted in less effective optical resolution. This is in agreement with previous findings, i.e. in optical resolutions during the chiral discrimination process the weaker interactions have a determining role.

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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 1978–84.

3  M. C. Etter, Acc. Chem. Res., 23 (1990) 120.

4  S. Hanessian, M. Simard and S. Roelens, J. Am. Chem. Soc., 117 (1995) 7630.

5  P. P. Korkas, E. Weber and G. Náray Szabó, J. Chem. Soc., Chem. Commun., (1995) 2229.

6  E. Weber, C. Wimmer, A. L. Llamas-Saiz and C. Forces-Forces**,** J. Chem. Soc., Chem. Commun., (1992) 733.

7  D. Kozma, H. Simon, Gy. Pokol and E. Fogassy, J. Therm. Anal. Cal., 69 (2002) 409.

 8  D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo and A. Wonnacott, Helv. Chim. Acta,
    70 (1987) 954.
 9  F. Toda, K. Tanaka, L. Infantes, C. Forces-Forces, R. M. Claramunt and J. Elguero, J. Chem.
    Soc., Chem. Commun., (1995) 1453.
10  D. Kozma, Zs. Böcskei, Cs. Kassai, K. Simon and E. Fogassy, J. Chem. Soc. Chem. Comm.,
    (1996) 753.
11  R. Illés, Cs. Kassai, Gy. Pokol, J. Madarász, E. Fogassy and D. Kozma, J. Therm. Anal. Cal.,
    61 (2000) 745.
12  Cs. Kassai, R. Illés, Gy. Pokol, J. Sztatisz, E. Fogassy and D. Kozma, J. Therm. Anal. Cal.,
    62 (2000) 647.
13  Cs. Kassai, Z. Juvancz, J. Bálint, E. Fogassy and D. Kozma, Tetrahedron, 56 (2000) 8355.
14  Cs. Kassai, J. Bálint, Z. Juvancz, E. Fogassy and D. Kozma, Synth. Comm., 31 (2001) 97.
15  R. Illés, Cs. Kassai, Gy. Pokol, E. Fogassy and D. Kozma, J. Therm. Anal. Cal., 68 (2002) 679.