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THERMOANALYTICAL STUDY OF O,O'-DIBENZOYL-(2R,3R)-TARTARIC ACID SUPRAMOLECULAR COMPOUNDS

Part II. Investigation of the resolution of racemic alcohols

Cs. Kassai[1]*, R. Illés*[2]*, G. Pokol*[2]*, J. Sztatisz*[2]*, E. Fogassy*[1] *and D. Kozma*[1*]

[1]Department of Organic Chemical Technology, Budapest University of Technology and Economics, Budapest, H-1521 Műegyetem rkp. 3, POB 91
[2]Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, H-1521 Budapest, Szt. Gellért tér 4., Hungary

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Abstract

The resolution of three chiral alcohols with O,O'-dibenzoyl-(2R,3R)-tartaric acid (DBTA) via diastereoisomeric supramolecular compound formation was investigated with thermoanalytical methods. On the basis of TG measurements the DBTA:chiral alcohol molar ratio in the compounds is 1:1 which agrees with the results of single-crystal X-ray diffraction analysis. The DBTA – chiral alcohol supramolecular compounds have different supramolecular structure than the DBTA – achiral alcohol supramolecular compounds. The supramolecular compounds containing cyclohexanols have higher thermal stability than the compounds containing acyclic aliphatic alcohols. The amount of unreacted DBTA monohydrate in the solid phase can be determined both with DSC and with TG measurements.

Keywords: crystallization, inclusion complex, optical resolution

Introduction

The most frequently applied procedure for the separation of enantiomers from racemates is the optical resolution via diastereoisomer formation [1–5]. During the process, from the enantiomers having identical physical properties, diastereoisomers are prepared with the aid of a chiral resolving agent. The separation of the diastereoisomers is based on their different physical properties (e. g. fractional crystallization, distillation, sublimation).

The interaction between the racemate and the resolving agent can bring about covalent bonding (covalent diastereoisomers), salt bonding (diastereoisomeric salts) or secondary bonding (diastereoisomeric complexes). The resolution based on dia-

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

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stereoisomeric complex formation is most advantageous because, in principle, every racemate can be resolved by this way. The secondary bonding energy between the resolving agent and the racemate is weaker than the covalent or salt bonding energy, so this procedure needs the least energy for obtaining the enatiomers with the best yield. However, the resolutions based on complex forming are not frequently used because generally applicable complex forming resolving agents have not yet available despite of several efforts [6–11] (Fig. 1).

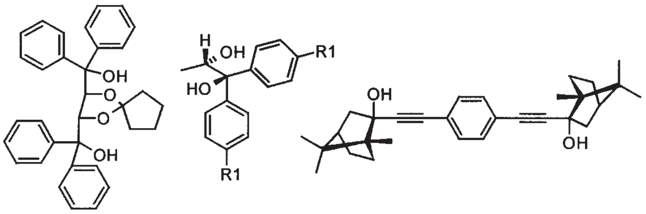


Fig. 1 Diastereoisomeric complex forming resolvig agents

Recently we observed that O,O'-dibenzoyl-(2R,3R)-tartaric acid (DBTA) being a frequently applied agent for resolutions via diastereoisomeric salt formation, can be used as a diastereoisomeric supramolecular compound forming resolving agent as well [12, 13] (Fig. 2).

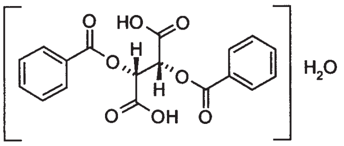


Fig. 2 O,O'-dibenzoyl-(2R,3R)-tartaric acid monohydrate

DBTA can behave as a proton donor or proton acceptor and its aromatic rings can take part in hydrophobic interactions. Therefore DBTA itself can, without any further derivation, resolve racemates via diastereoisomeric supramolecular compound formation.

In this paper we report on the thermoanalytical investigation of DBTA – chiral alcohol compounds, formed in the resolution of three racemic alcohols.

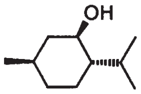
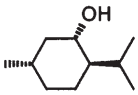
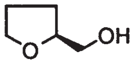
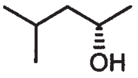
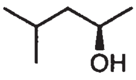
Experimental

All chemicals were purchased from Merck.

General procedure for resolution of racemic alcohols with DBTA and DBTA monohydrate

Finely powdered DBTA or DBTA monohydrate was suspended in the solution of 1–4.00 g of racemic-alcohol in 40 ml of hexane. After standing one week at room temperature the solid phase was filtered then heated in a sublimation equipment at 80°C in vacuum in the case of menthol. The other alcohols reacted similarily except they were distilled instead of sublimation. The enantiomeric enrichment was calculated from the specific optical rotation. The experimental results are summarised in Table 1.

Table 1 Resolution of racemic alcohols via diastereoisomeric supramolecular compound formation

Sample	Initial mass/g			Initial molar ratio	Supram. comp.	Sublimate/Distillate		
	DBTA	DBTA H_2O	Alcohol	DBTA Alc.	Mass/g	Mass/g	$[\alpha]_D^{20}$	e. e.
								
			(1R,2S,5R)-menthol		(1S,2R,5S)-menthol			
M1	2.3		1.00	1 : 1	2.58	0.36	–21.80	0.436
M2	2.3		4.00	1 : 4	1.83	0.39	–21.60	0.432
M3[*]	–	2.4	4.00	1 : 4	1.90	0.11	–44.63	0.892
								
			(R)-tetrahydrofurfuryl alcohol		(S)-tetrahydrofurfuryl alcohol			
T1	3.5		1.00	1 : 1	1.17	0.15	+0.50	0.03
T2	1.75		1.00	1 : 2	2.56	0.11	+2.00	0.12
T3[*]	3.5		4.00	1 : 4	4.75	0.73	+4.19	0.24
T4		3.69	2.00	1 : 2	5.11	0.51	+0.14	0.08
T5		1.84	2.00	1 : 4	2.04	0.22	+3.65	0.21
								
			(R)-4-methyl-2-pentanol		(S)-4-methyl-2-pentanol			
P1	3.50		1.00	1 : 1	4.27	0.90	–2.20	0.06
P2	3.50		2.00	1 : 2	4.12	0.95	–7.06	0.21
P3	3.50		4.00	1 : 4	3.39	0.81	–10.22	0.30
P4		3.69	1.00	1 : 1	3.91	0.68	–9.74	0.28
P5[*]		3.69	2.00	1 : 2	4.10	0.91	–9.54	0.28

[*] Investigated also with hot stage microscope

Thermal and optical analysis

DSC curves were recorded and integrated with DuPont 1090B Thermal Analysis System. Samples of 5.0–5.5 mg were run in open aluminium pans under flowing argon ($10\ \mathrm{l\ h^{-1}}$) with a heating rate of $5°\mathrm{C\ min^{-1}}$. The temperature range of thermal decomposition was determined by thermogravimetric measurements which was carried out on the same system under flowing air ($10\ \mathrm{l\ h^{-1}}$) with a heating rate of $10°\mathrm{C\ min^{-1}}$ in open pans. The melting processes were observed on a NU-10 microscope (Carl Zeiss, Jena). The optical rotation was measured with Perkin Elmer 241 polarimeter.

The specific optical rotation of the alcohols: $[\alpha]_D^{20}=-50$ (c=10; EtOH), (1R,2S,5R)–menthol; $[\alpha]_D^{20}=+17$ (c=1; $CHCl_3$), (S)–THFA; $[\alpha]_D^{20}=-34.22$ (c=1; no solvent), (R)-4-methyl-2-pentanol.

Results and discussion

During the preparative resolutions we reacted the solid supramolecular compound forming agent with the *racemic* mixture which had been dissolved in an inert solvent (Fig. 3).

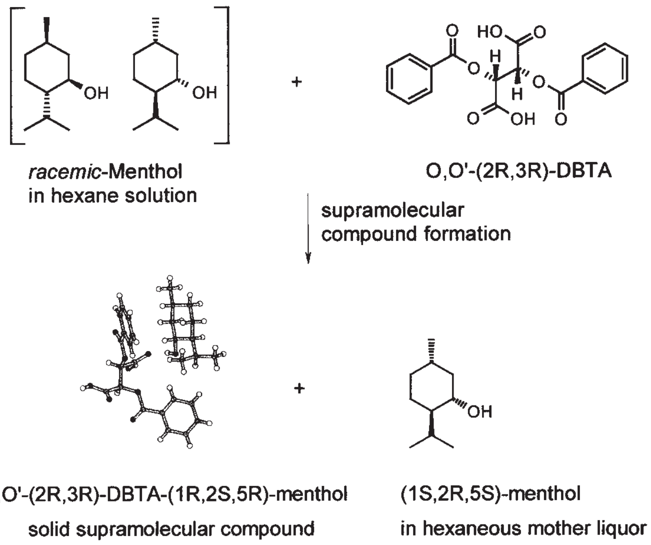


Fig. 3 Resolution of menthol with O,O'-dibenzoyl-(2R,3R)-tartaric acid via diastereoisomeric supramolecular compound

We used hexane as the inert solvent since DBTA does not dissolve in hexane but the investigated alcohols do.

After the expiration on the reaction time (7 days) the solid compound was separated with filtration from the mother liquor. The compound was dried in air for 24 h then the menthol was sublimated in vacuo while the other alcohols were distilled from the solid supramolecular compound. During reaction the suspended material clots into a sticky mass then in a few hours the material begins to recrystallize.

Before the investigation of the supramolecular compounds we studied the thermal properties of the anhydrous DBTA and DBTA monohydrate and DBTA supramolecular compounds with achiral alcohols and phenols which is reported in a separate paper [14].

The investigation of DBTA – menthol supramolecular compounds

racemic-Menthol was reacted with different molar ratio of DBTA applying both anhydrous and monohydrate forms (Table 1). In all experiments we managed to get a well-defined crystalline compound. Increasing the amount of the alcohol decreases the yield of the supramolecular compound because the solubility of DBTA increases with the amount of the alcohol component. Using anhydrous DBTA the obtainable optical purity was not effected by the applied molar ratio. Despite of the applied 1:1 initial molar ratio, the reaction was not complete, the solid phase consisted of the supramolecular compound and the unreacted DBTA which was proven by the DSC measurements. Using DBTA monohydrate the obtainable optical purity was twice higher.

The melting process of sample M3 was observed with the aid of hot stage microscope.

The investigated supramolecular compound was clear and consisted of well-defined prismatic crystals. By the effect of the heat at about 90°C the edge of the crystals started to round and its surface became rugose then from 100°C the smaller crystals began to melt. The whole mass of the supramolecular compound melted at 110°C. The melt lost its clarity and became brown at 200°C.

The TG and DSC measurements are nearly the same in the case of the compounds with different optical purity, the slow mass loss begins at 50 and its maximum is between 150–180°C where the alcohol distillation from the melted compound is the fastest (Figs 4–7).

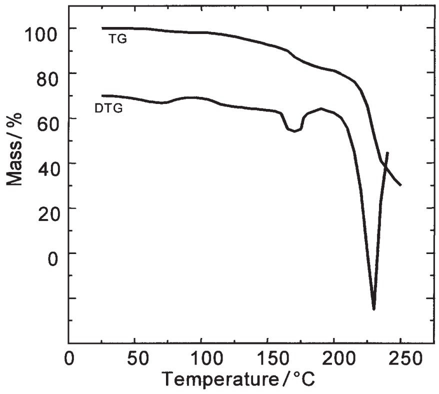


Fig. 4 TG and DTG curves of M1 supramolecular compound

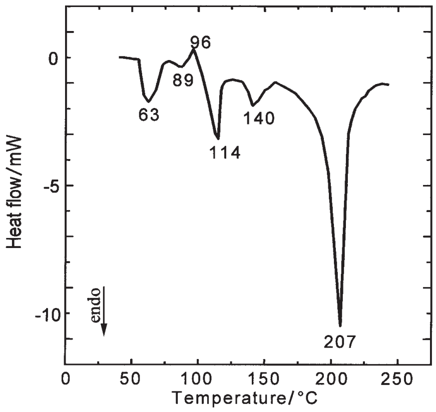


Fig. 5 DSC curve of M1 supramolecular compound

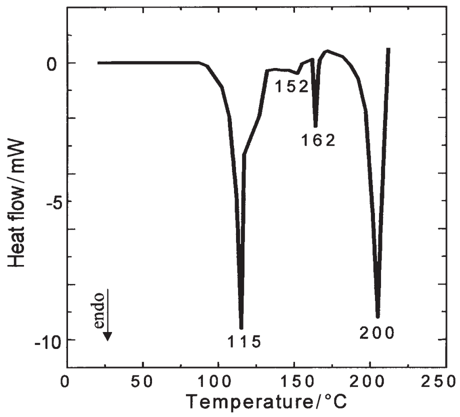


Fig. 6 DSC curve of M2 supramolecular compound

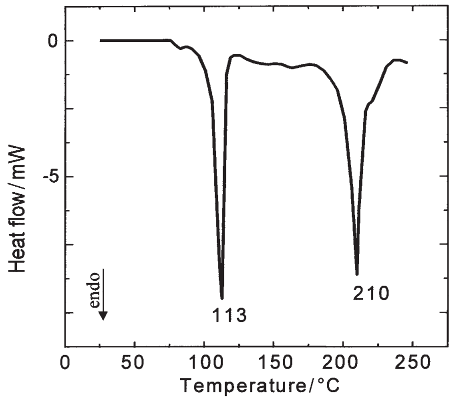


Fig. 7 DSC curve of M3 supramolecular compound

The supramolecular compounds do not contain water even though DBTA monohydrate was applied as a supramolecular compound forming agent, the alcohol completely displaces the water in the compound.

If not all the DBTA was reacted, a mixture of the supramolecular compound and the unreacted DBTA monohydrate can be observed. In these cases we observed the step of the evaporation of the residue of the water of crystallization between 50–90°C. The melting point of the pure supramolecular compound can be seen as a well-defined endothermic peak between 113–116°C then the evaporation of the alcohol from the melted supramolecular compound gives a broad endothermic peak between 130–170°C. In cases when unreacted DBTA monohydrate remains in the solid phase its phase transition peaks can be seen on the DSC curve near the peaks of the supramolecular compound. The decomposition of DBTA begins above 180, the maximum of the endothermic peaks is between 205–219°C. The DBTA:menthol molar ratio is nearly 1:1 in the supramolecular compound. We got the same host:guest molar ratio from the single-crystal X-ray diffraction analysis of the supramolecular compound [13].

The investigation of DBTA-tetrahydrofurfuryl alcohol supramolecular compounds

The resolution of the *racemic*-tetrahydrofurfuryl alcohol (THFA) with DBTA in most cases yielded a product with poor optical purity (Table 1). In some cases DBTA or DBTA monohydrate dissolved in the hexane phase and gave no solid compound. The THFA is incorporated in the supramolecular compounds mainly with S configuration while the mother liquor is enriched in the R configuration. Increasing the DBTA:alcohol molar ratio the obtainable optical purity increases. The product with highest optical purity can be obtained with anhydrous DBTA with DBTA:alcohol 1:4 molar ratio. The obtained optical purity of the THFA reaches 24% after evaporating the alcohol from the supramolecular compound. Applying DBTA monohydrate the highest optical purity was 21% with 1:2 DBTA:alcohol molar ratio.

The melting process of sample T3 was observed with the aid of hot stage microscope.

The supramolecular compound did not show a well-grown crystals as in the case of menthol. The supramolecular compound melted at 45–50 but smaller crystals remained in the melt to 80°C. Between 80–180°C the melt did not change significantly but the drops became smaller and its clarity was gradually lost.

According to the TG and DSC measurements the supramolecular compound lost its alcohol component slowly and gradually between 60–185°C. The mass loss started at 60, and its rate increased to 150–160 then at 190–195°C gave a minimum, then with the decomposition of DBTA began to grow again. The calculated DBTA:alcohol molar ratios from the results of the measurements in this case are also around 1:1. According to the DSC measurements the melting of the compound began around 50–60, the end of the endothermic peak is between 73–75°C. The evaporation of the alcohol gave a broad endothermic peak between 90–185 and after 195°C the endothermic peak of the decomposition of DBTA can be observed.

The investigation of DBTA–4–methyl–2–pentanol supramolecular compounds

Starting from the racemic composition, resolution of 4-methyl-2-pentanol was possible in all cases but the optical purity of the alcohol compound obtained from the supramolecular compound was not high, between 6–30% (Table 1). In each case well-defined crystal supramolecular compounds were evolved. The product with the highest optical purity can be obtained using 1:4 DBTA:alcohol initial molar ratio. Applying anhydrous DBTA 30% optical purity can be achieved. Nearly the same optical purity (27–28%) can be achieved by the use of DBTA monohydrate with 1:2 DBTA:alcohol initial molar ratio.

The melting process of sample P5 was observed with the aid of hot stage microscope.

The supramolecular compound contained clear long prism shaped crystals. Increasing the temperature from 92 the shapes of the crystals began to round and the whole crystal mass melted at 110°C. The effect of further heating till 180°C did not cause significant changes.

According to the calculated values of TG and DTG measurements the DBTA:alcohol molar ratio is around 1:1 in the supramolecular compound. We got the same molar ratio from the single-crystal X-ray diffraction analysis [15]. The mass loss of the supramolecular compound began at about 70, then up to 180°C the alcohol component evaporated in small steps. Above 200°C began the decomposition of DBTA. The melting of the supramolecular compound gave a broad endothermic peak between 100–110 on the DSC record, then at about the boiling point of the alcohol component at 134°C a small endothermic peak can be found. The peak which belongs to the melt of the supramolecular compound is not sharp since the compound also contains a small amount of hydrate and the endothermic peak of the water evaporation overlaps with the peak belonging to the melt of the supramolecular compound. The melting of the unreacted DBTA gives an endothermic peak between 125–155 then above 180°C the decomposition of DBTA begins.

Conclusions

In the present work we investigated the resolution of three chiral alcohols with DBTA via diastereoisomeric supramolecular compound formation with thermoanalytical methods. We observed that in all cases DBTA formed supramolecular compounds with one chiral alcohol, unlike the DBTA – achiral alcohol compounds where the ratio was 1:2. The resolution was more efficient when we used DBTA monohydrate rather than anhydrous DBTA in spite of the fact that the alcohol displaced all water of crystallization in the supramolecular compounds, so the monohydrate phase appears to be more accessible for the preferred alcohol enantiomer.

The supramolecular compounds lost the alcohol component in the 60 to 185°C temperature range and its melting temperatures were in the same range. The thermal stability (melting point) of the compounds is different, the cyclohexanol compounds have higher stability than ones containing acyclic aliphatic alcohols. After the evolution of the alcohol the decomposition of the DBTA started above 185°C.

The selection of the appropriate initial molar ratio is essential for the optimal utilization of the supramolecular compound forming resolving agent. With other analytical methods (e.g. NMR, IR, optical rotation measurement) it is not possible to determine the presence and the quantity of the unreacted DBTA monohydrate because of the similar properties of the unreacted DBTA and the supramolecular compound. The amount of unreacted DBTA monohydrate in the solid phase can be determined both with DSC and with TG measurements. The thermal measurements can be applied for planning and optimizing the practical resolution procedures.

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