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

Part I. Investigation of compounds with water, achiral alcohols and phenols

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Abstract

Thermal behaviour of O,O'-dibenzoyl-(2R,3R)-tartaric acid (DBTA), its monohydrate, and its potential supramolecular compounds with achiral alcohols and phenols were investigated with TG, DSC, EGD. The structural differences among the anhydrous DBTA, its monohydrate, and the supramolecular derivatives were investigated with X-ray powder diffraction. The thermal behaviour of DBTA-supramoleculars with isopropyl, *tert*-butyl, and 5-cyclohexyl alcohols is found to be similar to each other but essentially different from that of both DBTA and its monohydrate. On heating they melt and decompose between 60–180°C while they loose in one or two steps the bound alcohol. The thermal stability of the supramolecular compounds increases with the boiling point of the alcohol component. According to the X-ray powder diffraction patterns each supramolecular substance has different structure, that may also result in the different thermal stability of the compounds. The molar ratio of DBTA:achiral alcohol samples is 1:1.01–1:1.57 estimated from the corresponding mass losses. The XRD patterns of the prepared two DBTA-phenol materials are different from those of DBTA-achiral alcohol samples. The phenol compounds melt with slow mass losses and give an endothermic peak between 73–83°C but the melting point of the anhydrous DBTA cannot be observed. DBTA:phenol molar ratio is estimated to be 1:0.41 and 1:0.65 for phenol and 2-methylphenol, respectively.

Keywords: chiral complex, DSC, hydrate, optical resolution

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Introduction

Dibenzoyl-(2R,3R)-tartaric acid (DBTA) is a most frequently applied resolving agent for separating racemates via diastereoisomeric salt formation on laboratory and industrial scale [1–5]. Recently we have investigated the optical resolution of (N-alkyl)-pipecolic acid-anilides by tartaric acid (TA) and DBTA [6]. We found, despite of the basical character of the racemate and the acidic character of the resolving agent, that in 8 of 13 cases of the successful resolution processes, the precipitated product proved to be a supramolecular compound, not a real salt. According to this observation we have assumed that TA and DBTA can be used for the resolution of racemate compounds without basical character too. We tried our hypothesis on several alcohols and we observed that TA could not while DBTA could form supramolecular compounds with several chiral alcohols [7, 8]. We tried to find data in the literature about the complex forming properties of DBTA and we found that this question had not been investigated. In order to collect data from the complex forming ability of DBTA we decided to investigate different model supramolecular compounds of DBTA. In this publication we report on the results of reaction of DBTA with water, achiral alcohols and phenols.

Experimental

All chemicals were purchased from Merck.

Investigation of anhydrous DBTA and DBTA monohydrate

Dried anhydrous DBTA and DBTA monohydrate were stored for 16 days in air of well defined relative humidity then their thermal properties were measured by TG, DTG, DSC and EGD. In one case DBTA monohydrate was stored for 14 days in dried hexane. The anhydrous DBTA and DBTA monohydrate were analysed also with X-ray powder diffraction and investigated with a hot-stage microscope.

Investigation of DBTA – achiral alcohol supramolecular compounds

The DBTA – alcohol supramolecular compounds were prepared by dissolving 2–4.00 g of alcohol in 40 cm^3 dried *n*-hexane and suspending DBTA monohydrate in this solution in half molar equivalent ratio compared to the alcohol. After the reaction time (7 days), the solid phase was filtered out and dried in air for 24 h. The solid phases were analysed by TG, DTG, DSC, EGD, X-ray powder diffraction and hot-stage microscope.

Investigation of DBTA – phenol supramolecular compounds

The preparation and analysis of DBTA – phenol supramolecular compounds were similar to those of the DBTA – achiral alcohol compounds.

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 heatig rate of 8°C min^{-1}.

The diffraction patterns of DBTA, DBTA monohydrate and the compounds were measured with a FPM HZG-4 Diffractometer, Carl Zeiss, Jena, using CuK_α (λ=0.15405 nm) radiation and Ni filter. The speed of the goniometer was 1° min^{-1}.

The hot-stage microscopical analysis was carried out on a NU2 microscope, Carl Zeiss, Jena, between 20–200°C with a heating rate of 5°C min^{-1} using uncovered mount. Copies of the thermal curves and X-ray powder diffractograms of all the measured compounds can be requested from the authors (24 pages, size A4).

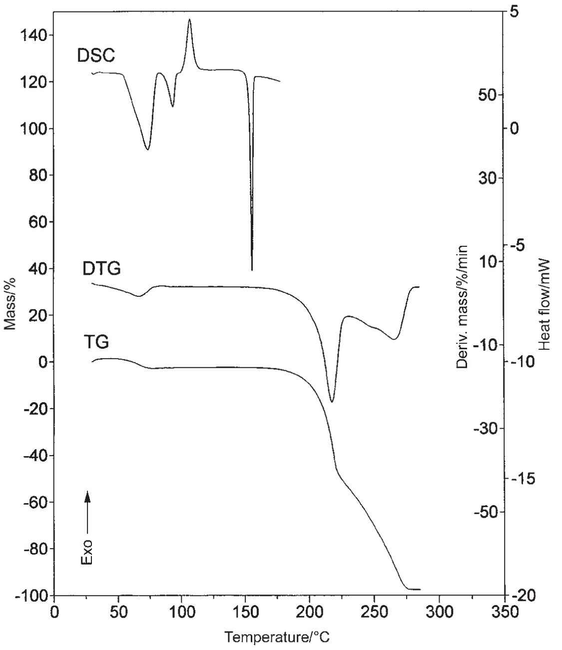


Fig. 1 TG, DTG, DSC curves of the dibenzoyl-(2R,3R)-tartaric acid monohydrate 1:1 supramolecular compound

Results and discussion

Investigation of anhydrous DBTA and DBTA monohydrate

Before investigating DBTA-alcohol and DBTA-phenol supramolecular compounds we measured, as a reference, the thermal and structural properties of DBTA and DBTA monohydrate.

The thermal behaviour of DBTA and DBTA monohydrate is very different. DBTA melted at 156°C then after reaching 180 °C it decomposed in two steps.

DBTA monohydrate lost its water of crystallisation between 50–80°C which can be seen as a step on the TG record. The measured water contents were less than calculated from the 1:1 DBTA:water ratio. Further mass loss occurs above 180°C when the DBTA decomposed in two steps, the first step took place between 180–225°C and the second step between 225–275°C.

The loss of the crystal water appears as an endothermic peak between 50–80°C on the DSC record. After the evaporation of the water of crystallisation, the structure

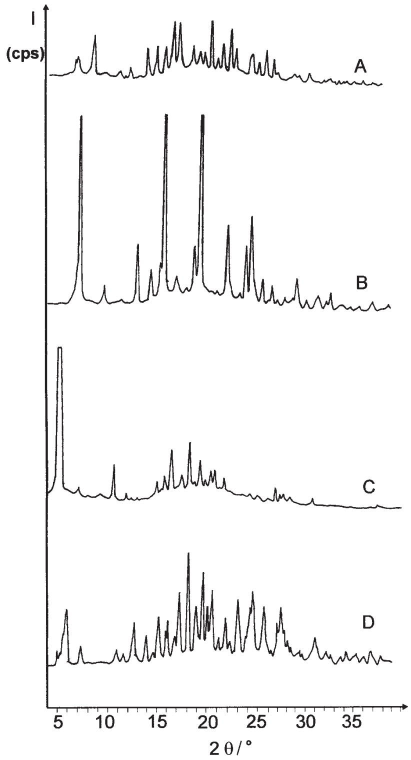


Fig. 2 Diffraction patterns of dibenzoyl-(2R,3R)-tartaric acid (A), dibenzoyl(2R,3R)-tartaric acid monohydrate (B), dibenzoyl-(2R,3R)-tartaric acid-4-*tert*-butylcyclohexanol 1:2 supramolecular compound (C) and dibenzoyl-(2R,3R)-tartaric acid-phenol 2:1 supramolecular compound (D)

breaks down which can be seen as a small endothermic peak at 94°C, then the crystal structure re-arranges at about 107°C, which is shown by a sharp exothermic peak. The melting of the anhydrous DBTA can be seen as a sharp endothermic peak at 156°C, increasing the temperature further results in the decomposition of DBTA.

The anhydrous DBTA and DBTA monohydrate not only have different thermal properties but different structures too, because their diffraction patterns are completely different.

We also investigated the hydration properties of DBTA and DBTA monohydrate. We stored DBTA and DBTA monohydrate under different degrees of relative humidity (Table 1). The measurements show that the hydrate contents of DBTA monohydrate remained under 4.78% so we could not reach the theoretical value of the 1:1 ratio. The dried anhydrous DBTA has the similar diffraction pattern as DBTA monohydrate after the hydration thereof the hydrate loss of DBTA monohydrate is reversible.

We investigated, with hexane as a model compound, the ability of DBTA to form supramolecular compound with apolar compounds. We stored DBTA monohydrate for 14 days in *n*-hexane but its thermal and structural properties did not change and it did not contain *n*-hexane according to the EGD measurement, so DBTA monohydrate is not able to form supramolecular compound with *n*-hexane.

Table 1 Summary of the hydrate contents of DBTA monohydrate

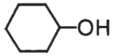
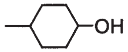
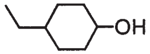
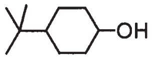
Compound	Circumstances	Water content/%
DBTA monohydrate	theoretical contents	4.78
DBTA monohydrate	initial measured contents	4.48
DBTA monohydrate	air of 58% rel. h (16 days)	4.36
DBTA monohydrate	air of 100% rel. h (16 days)	4.03
DBTA monohydrate	recrystallisation from water	4.02
DBTA monohydrate	in dried hexane (14 days)	3.94
Anhydrous DBTA	air of 58% rel. h (16 days)	4.34
Anhydrous DBTA	air of 100% rel. h (16 days)	4.39

Investigation of DBTA – achiral alcohol supramolecular compounds

We tried to form supramolecular compound with 9 achiral alcohols, and according to the thermal analysis 7 of 9 achiral alcohols formed supramolecular compounds with DBTA (Table 2). DBTA – achiral alcohol supramolecular compounds have very different thermal behaviour from DBTA monohydrate.

The thermal properties of the investigated DBTA – alcohol supramolecular compounds are very similar. On heating, they melt between 60–180°C while they lose the alcohol compound in one or two steps (Table 2, column 4, 5). Above 180°C DBTA decomposes in two steps. The compounds do not contain hydrate despite us-

Table 2 Thermoanalytical data of the measured DBTA-alcohol compounds

No.	Compound	EGD	TG1/%	TG2/%	∑TG/%	Molar ratio DBTA/ alc.	DSC/ °C	Supram. comp.
1	CH_3OH methanol	inorg.	3.82	–	3.82	–	70 endo 133 endo 149 endo	–
2	CH_3CH_2OH ethanol	inorg.	4.01	–	4.01	–	75 endo 113 exo 136 endo 151 endo	–
3	$(CH_3)_2CHOH$ *iso*-propyl-alcohol	organic	9.78	11.06	20.84	1:1.57	64 endo	+
4	$(CH_3)_3COH$ *tert*-butyl-alcohol	organic	3.02	14.38	17.40	1:1.01	84 endo	+
5	 cyclohexanol	organic	3.75	22.84	26.59	1:1.30	86 endo	+
6	 1-methyl-cyclohexanol	organic	6.83	25.20	32.03	1:1.48	80 endo	+
7	 4-methyl-cyclohexanol	organic	31.88	–	31.88	1:1.46	53 endo 74 endo 88 endo	+
8	 4-ethyl-caclohexanol	organic	29.20	–	29.20	1:1.15	72 endo 103 endo	+
9	 4-*tert*-butyl-cyclohexanol	organic	33.25	–	33.25	1:1.14	125 endo	+

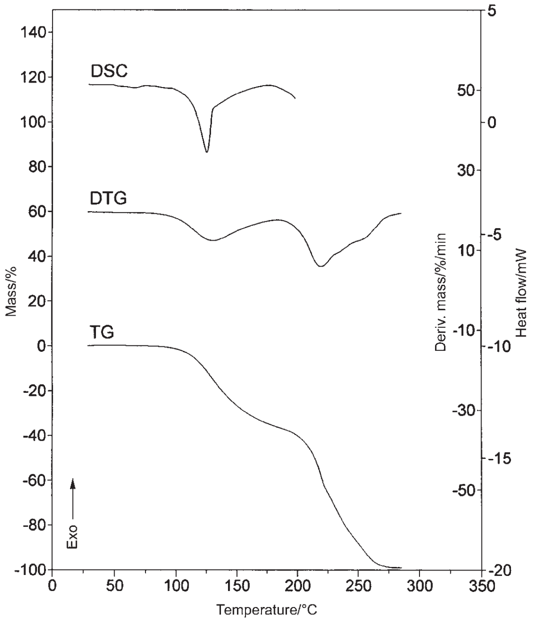


Fig. 3 TG, DTG, DSC curves of dibenzoyl-(2R,3R)-tartaric acid-4-*tert*-butyl-cyclohexanol 1:2 supramolecular compound

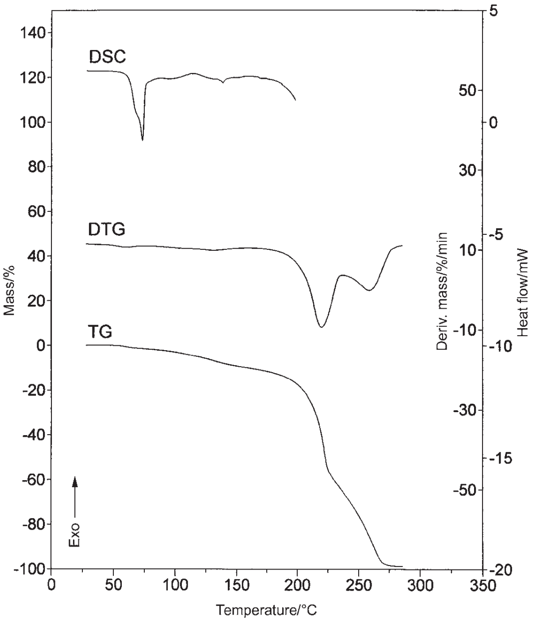


Fig. 4 TG, DTG, DSC curves of dibenzoyl-(2R,3R)-tartaric acid-phenol 2:1 supramolecular compound

ing DBTA monohydrate as a reacting agent. The alcohol displaces the water molecule in the crystal structure.

The primary alcohols with short straight alkyl chain (e.g. methanol, ethanol) do not form supramolecular compounds while the secondary aliphatic alcohols such as *iso*-propyl-alcohol (*i*-PrOH), *tert*-butyl-alcohol (*t*-BuOH) form supramolecular compounds. The supramolecular compound forming ability depends on the size and the structure of the alcohol.

The supramolecular compounds of *i*-PrOH and *t*-BuOH lose the alcohol components in two steps, the DBTA:alcohol molar ratio is between 1:1.01–1:1.57. On the DSC record the melting of a compound appears as a well-defined endothermic peak then the evaporation of the alcohol can be seen as a wider, irregular and poorly reperatable shape endothermic peak.

The bad reperatability arises from the type of the process when the surface of the melted compound intermittently solidifies and the alcohol evaporates across this layer.

The thermal stability (melting point) of the supramolecular compounds increase with the boiling point of the alcohol component.

We also managed to react some achiral cyclohexanols with DBTA monohydrate. The DBTA:alcohol molar ratio in the compounds are 1:1.14–1:1.48 close to the acyclic alcohols but does not reach the 1:2 molar ratio. The thermal properties of cyclohexanol supramolecular compounds do not differ substantially from the supramolecular compounds of the acyclic alcohols. First the melting point of the compound then the evaporation of the alcohol can be seen as endothermic peaaks on the DSC curve.

In cases of a multi-step endothermic effect the substance first melts and recrystallizes, then the new form melts again.

The thermal stability (melting point) of the supramolecular compounds increases with the boiling point of the cyclohexanol component. The supramolecular compound formation is stereoselective in the case of 4-alkyl-cylohexanols, the compound contains the *trans*-isomer in higher ratio than the initial composition, the *cis*-isomer enriches in the mother liquor [8].

Investigation of DBTA – phenol supramolecular compounds

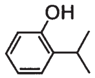
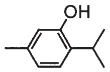
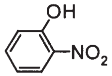
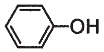
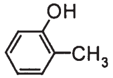
Among the investigated phenol-type compounds we found two supramolecular compounds (Table 3). It is important that thymol does not form supramolecular compound, in spite of the fact its saturated form (menthol) is able to form a supramolecular compound with high stability and stereoselectivity [7].

In these compounds the DBTA:phenol molar ratio is between 1:0.41–1:0.65 which is different from the DBTA – achiral alcohol supramolecular compounds. According to the TG analysis the DBTA:phenol molar ratio is close to 2:1.

The melting of the compounds gives a sharp endothermic peak on the DSC curve but the melting point of DBTA can not be seen.

The phenol compounds evaporate very slowly from the melted supramolecular compound partly because these compounds have higher boiling points than the cyclo-

Table 3 Thermoanalytical data of the measured DBTA – phenol supramolecular compounds

No.	Compound	EGD	TG1/%	TG2/%	∑TG/%	Molar ratio DBTA/ Ph.	DSC/ °C	Supram. comp.
10	 2-*iso*-propyl-phenol	inorg.	2.73	–	2.73	–	72 endo 95 endo 107 exo 156 endo	–
11	 thymol	inorg.	2.36	–	2.36	–	69 endo 95 endo 108 exo 156 endo	–
12	 2-nitro-phenol	inorg.	1.85	–	1.85	–	69 endo 95 endo 107 exo 156 enfo	–
13	 phenol	organic	1.59	8.18	9.77	1:0.41	73 endo	+
14	 2-methyl-phenol	organic	3.76	12.75	16.33	1:0.65	83 endo	+

hexanols. In the cases when the phenol compound did not form supramolecular compound with DBTA monohydrate we got back DBTA monohydrate.

Theoretical composition of the supramolecular compounds

According to the X-ray powder diffraction analysis all the supramolecular compounds have different structures resulting in different thermal stability of the compounds. We generated the X-ray powder diffraction patterns of compounds 5–7 from results of the single-crystal X-ray analysis [9]. Comparing the generated and the measured X-ray powder diffractograms we have observed that the respective diffraction patterns are similar to each other with different relative peak intensities. The theoretical DBTA:alcohol molar ratio which is estimated from the single-crystal X-ray analysis is an upper limit value because the polycrystalline supramolecular compounds always contained less alcohol than the strictly ordered single crystal.

The differences are caused by the preparation method. During preparation the alcohol is dissolved in hexane but DBTA monohydrate stays in the solid phase so the reaction is slow and diffusion-controlled while the single crystals of 5–7 supramolecular compounds were crystallized from the mother liquor after filtering the solid phase.

We have not been able to prepare single crystals of the DBTA – phenol supramolecular compounds but according to the thermal analysis and the X-ray powder diffraction patterns they have different properties than DBTA – achiral alcohol supramolecular compounds.

Conclusions

Our investigations have shown – taking into account the results of single-crystal XRD analysis that dibenzoyl-(2R,3R)-tartaric acid, depending on the structure of the guest molecule, forms supramolecular compounds of different stoichiometry and structure with alcohols. The theoretical DBTA:guest molar ratios are 1:2 for achiral alcohols, 1:1 for water and 2:1 for phenols. There are two reasons for the fact that, in the present series of experiments, the theoretical alcohol ratios could not be reached. Supramolecular compound formation in the investigated systems appears to be an equilibrium process, even if DBTA and the supramolecular compound are solid. This is supported by the finding that the structure of the products is substantially identical with that of single crystals containing the theoretical amount of alcohol, so the solid supramolecular compound can exist within a certain concentration range. Besides, in separate experiments we found that the actual composition of the solid supramolecular compound depend on the DBTA:alcohol initial ratio in the reaction mixture. The other reason for not reaching the theoretical amount of alcohol in the supramolecular compounds is the heterogeneous process of preparation requiring the diffusion of the guest compound into the solid host. DBTA monohydrate is a less stable structure than the supramolecular compounds of achiral alcohols or phenols because the latter displace the water of crystallization. It seems that the criterion for the supramolecular compound formation of achiral alcohols is a suitable, hydrophobic alkyl, cycloalkyl or aryl group. In case of a short alkyl chain (methanol, ethanol) the hydrophobic-hydrophobic interaction is too weak for stabilizing the supramolecular compound. The water is able to form a supramolecular compound, however it does not contain a hydrophobic group. On the other hand, it can donate two protons which is advantageous for DBTA, which is rich in proton acceptors but poor in proton donating groups. The difference between the H-bonding structures brings about the different supramolecular compound stoichiometry.

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