Journal of Thermal Analysis and Calorimetry, Vol. 68 (2002) 679–685

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

Part III. SMC-s formation with chiral secondary alcohols

R. Illés[1], *Cs. Kassai*[2], *G. Pokol*[1], *E. Fogassy*[2] *and D. Kozma*[3*]

[1]Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, P.O.B. 91, H-1521 Budapest, Hungary
[2]Department of Organic Chemical Technology, Budapest University of Technology and Economics, P.O.B. 91, H-1521 Budapest, Hungary
[3]EGIS Pharmaceuticals, Budapest, Keresztúri út 30–38, H-1106, Hungary

Abstract

The enantioselectivity of the diastereomeric supramolecular compound (SMC) formation between O,O'-dibenzoyl-(2R,3R)-tartaric acid (DBTA) and chiral secondary alcohols was investigated. On the basis of TG measurements the DBTA:chiral alcohol molar ratio in the SMC-s is nearly 1:1. Among the investigated complexes the most stable SMC is *trans*-2-iodo-cyclohexanol-DBTA. The SMC forming capability and the enantioselectivity depends on the space filling of the alcohol side chain or ring. In the case of *trans*-2-halogen-cyclohexanols a relationship can be observed between the thermal stability of the SMC-s and the enantioselectivity of SMC forming.

Keywords: complex formation, enantiomer separation, enantioselectivity, optical resolution, tartaric acid

Introduction

Both on lab and on industrial scale the most frequently applied procedure for the separation of enantiomers from racemates is the optical resolution via diastereomer salt formation. During the resolution process, from the enantiomers having identical physical properties, diastereomer salts are prepared with the aid of a chiral resolving agent. The separation of the diastereomeric salts is based on their different physical properties and can be carried out by known preparative separation methods (e.g. fractional crystallization, distillation, sublimation) [1–4].

A large number of compounds cannot be resolved in this way because they do not contain an acidic or basic group. In this case the compound must be derivatized and the derivative can be resolved via diasteromeric salt formation. The other possibility for separating the enantiomers without derivatization is using chiral complex forming resolving agent.

---

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

1418–2874/2002/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

The resolution based on diastereomeric complex formation is the most advantageous because, in principle, every racemate can be resolved in this way and the same separation methods can be applied for separating the diastereomeric complexes as in the case of diastereomeric salts [5–10].

The most frequently applied resolving agents for separating bases via diastereomeric salt formation is tartaric acid and its derivative O,O’-dibenzoyl-(2R,3R)-tartaric acid (DBTA). Recently we observed that DBTA can be used as a diastereomeric supramolecular compound (SMC) forming resolving agent as well [11].

In this paper we continue the report on the thermoanalytical study of DBTA supramolecular compounds by the SMC-s of chiral secondary alcohols [12, 13]. Homologous series of secondary alcohols were applied as guest compounds in order to get detailed information about the supramolecular forming properties of DBTA.

Experimental

All chemicals were purchased from Aldrich except 5–10 which were synthesized by known organic methods [14].

General procedure for resolution of racemic alcohols with DBTA monohydrate

Finely powdered DBTA monohydrate (25 mmol) was suspended in the solution of 50 mmol of racemic-alcohol in 40 mL of hexane. 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 3×20 mL of CH_2Cl_2. The organic phase was evaporated and the alcohol component was purified by distillation then was analysed with chiral GC and polarimeter. The unreacted alcohol enantiomeric mixture can be obtained by fractional vacuum distillation of the hexaneous mother liquor.

Chiral GC analysis

A Hewlett Packard HP 5890/II instrument with FID detector was used for GC analysis. The column used was a 12 m×0.100 mm I.D. fused silica open tubular column coated with ChirasilDex chiral stationary phase at 0.15 μm film thickness [15]. The stationary phase was a methylsilicone polymer substituted with permethylated β-cyclodextrin via spacer. H_2 was used as carrier gas with 1 mL min^{-1} speed. The injection mode was split (1:160). The analysis temperature was adjusted to the volatility and selectivity of analytes. Compounds 8–10 were analysed as acetyl derivatives, the others without derivatization between 50–100°C.

Optical analysis

Optical rotation was measured with Perkin Elmer 241 polarimeter.

Thermal analysis

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

During the preparative resolutions solid DBTA monohydrate was reacted with the racemic mixture of secondary alcohols which had been dissolved in hexane. Using

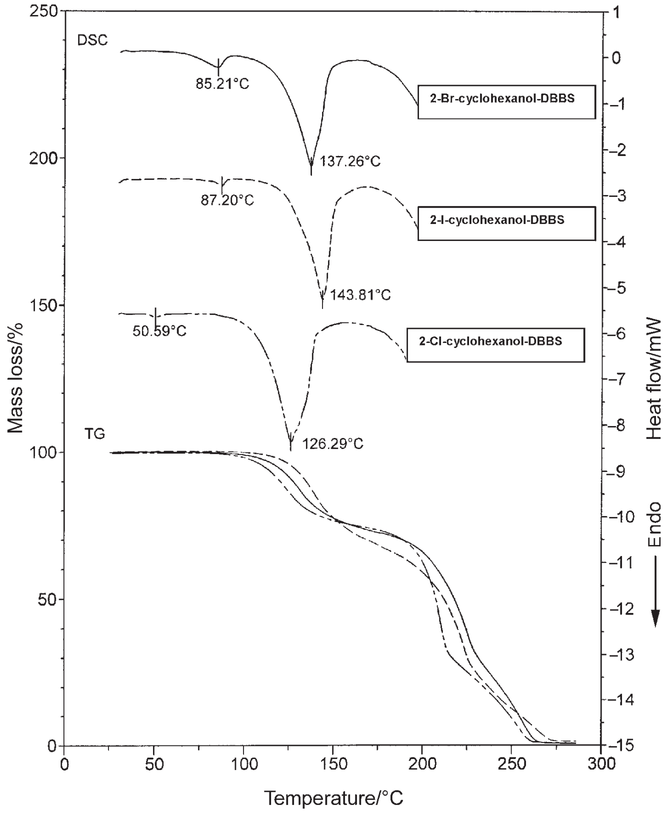


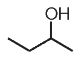
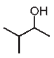
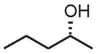
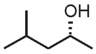
Fig. 1 DSC and TG curves of DBTA-*trans*-2-halogen-cyclohexanol supramolecular compounds

hexane as an inert solvent is not absolutely necessary to the SMC forming but it simplifies the separation of the SMC and the non-reacted alcohol enantiomer mixture.

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 complexed alcohol was distilled from the solid SMC. SMC was analyzed with thermoanalytical methods while the distillate was analyzed with chiral GC. The optical rotation of the distillate was measured with polarimeter to determine the absolute configuration of the alcohol enantiomer (the absolute configurations of the investigated alcohols are known from the literature [14]).

Figure 1 presents TG and DSC curves of DBTA: *trans*-2-halogen-cyclohexanol SMC-s as typical examples. The small endothermic DSC peaks below 100°C belong to structural transformations of the solid SMC-s. Melting and decomposition of the SMC-s (accompanied by the evaporation of the alcohol) take place above 100°C shown by large endothermic DSC peaks and the first mass loss step of the corresponding TG curves. Thermal decomposition of the remaining DBTA occurs above 175°C (the TG curves). The main characteristics of thermal behaviour of the other SMC-s were basicly similar.

Table 1 Diastereomeric SMC formation between DBTA monohydrate and secondary aliphatic alcohols

No.	Alcohol component	Alcohol in SMC/*w*%	Alcohol/DBTA molar ratio in SMC	SMC *m.p.*/ °C	Alcohol *e.e.* from SMC
1	 2-butanol	19.5	1.2 : 1	55	0
2	 3-methyl-2-butanol	18.2	0.98 : 1	59	0
3	 2-pentanol	27.7	0.86 : 1	75	0.20 (R)-(-)
4	 4-methyl-2-pentanol	23.4	1.1 : 1	105	0.28 (R)-(-)

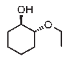
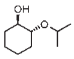
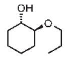
e.e.: enantiomeric excess

Diastereomeric SMC formation between DBTA monohydrate and secondary aliphatic alcohols

We found that DBTA reacts only with 2-butanols and 2-pentanols while the other chiral 2-alkanols which have longer side chain do not react with DBTA. The measured data are collected in Table 1. The thermal stability of the SMC-s of 1 and 2 with DBTA is rather low and these SMC-s are stable only in hexaneous solution. They slowly lose the alcohol components in air which can be seen as a decomposition of the crystals of the SMC resulting in the recovery of solid DBTA. The complex formation is not enantioselective in the case of 1 and 2.

The thermal stability of the SMC-s of 3 and 4 with DBTA is higher than that of 2-butanols. The reaction is enantioselective but the enantioselectivity is low. The SMC forming of 4 has the highest enantioselectivity and –at the same time– the thermal stability of the related SMC is the highest in this series. The thermal stabilities of the branched 2-alkanols are larger than those of the linear 2-alkanols. The host:guest molar ratio in the SMC-s which was measured by TG is nearly 1:1 which was found also characteristic to other chiral alcohol-DBTA SMC-s (previous papers [12, 13]).

Table 2 Diastereomeric SMC formation between DBTA monohydrate and *trans*-2-alkoxy-cyclohexanols

No.	Alcohol component	Alcohol in SMC/*w*%	Alcohol/DBTA molar ratio in SMC	SMC *m.p.*/°C	Alcohol *e.e.* from SMC
5	 *trans*-2-ethoxy-cyclohexanol	17.1	0.51 : 1	87	0.50 (1R,2R)-(-)
6	 *trans*-2-isopropoxy-cyclohexanol	20.5	0.58 : 1	112	0.15 (1R,2R)-(-)
7	 *trans*-2-propoxy-cyclohexanol	23.1	0.68 : 1	77	0.44 (1S,2S)-(+)

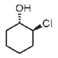
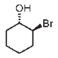
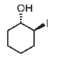
Diastereomeric SMC formation between DBTA monohydrate and trans-2-alkoxy-cyclohexanols

The crystallization of 5-7 with DBTA is slow in the hexaneous reaction mixture but yields more stable SMC-s than 1-4. Among the investigated trans-2-alkoxycyclohexanols only the 5-7 compounds from SMC with DBTA (Table 2). Alcohols having longer side chain than the propoxy group do not react with DBTA while trans-2-methoxy-cyclohexanol dissolves DBTA and no solid SMC forming can be observed. The thermal stability of 6-DBTA containing the branched side chin cyclohexanol derivative is the highest. The configuration of the SMC formation of 7 (1S,2S) is opposite to that of 5 and 6 (1R,2R). The trans-2-alkoxy-cyclohexanol-DBTA SMC-s contain less alcohol than calculated form 1:1 host:guest molar ratio.

Diastereomeric SMC formation between DBTA monohydrate and trans*-2-halogen-cyclohexanols*

The crystallization of 8–10 with DBTA is fast in the hexaneous reaction mixture. The SMC formation is enantioselective between all of the investigated *trans*-2-halohydrins and DBTA monohydrate (Table 3). The SMC-s enrich in the (1S,2S) enantiomer while the mother liquors enrich the (1R,2R) enantiomer. The thermal stability of halohydrin SMC-s is the highest among the investigated chiral cyclohexanols. Increasing the mass of the halogen atom in the host molecule increases the melting point (i.e., the stability) of the SMC and increases the enantioselectivity of the SMC forming. The most stable SMC is *trans*-2-iodo-cyclohexanol-DBTA where enantioselectivity of the SMC formation is the highest (*e.e.*=0.61). The *trans*-2-halogen-cyclohexanol-DBTA SMC-s contain less alcohol than the theoretical amount calculated from the 1:1 host:guest molar ratio.

Table 3 Diastereomeric SMC formation between DBTA monohydrate and *trans*-2-halogen-cyclohexanols

No.	Alcohol component	Alcohol in SMC/*w*%	Alcohol/DBTA molar ratio in SMC	SMC *m.p.*/ °C	Alcohol *e.e.* from SMC
8	 *trans*-2-chloro-cyclohexanol	24.6	0.87 : 1	126	0.35 (1S,2S)-(+)
9	 trans-2-bromo-cyclohexanol	26.3	0.71 : 1	137	0.56 (1S,2S)-(+)
10	 *trans*-2-iodo-cyclohexanol	30.1	0.68 : 1	144	0.61 (1S,2S)-(+)

Conclusions

We investigated the resolution of 10 secondary alcohols with DBTA via diastereomeric supramolecular compound formation. We found that DBTA can form SMC-s with several types of chiral secondary alcohols. The melting points of the aliphatic alcohols-DBTA SMC-s are rather low (55–105°C). SMC-s containing secondary alcohols with branched side chain are more stable (they have higher *m.p.*) than linear secondary alcohols. Cyclohexanols are more stable than aliphatic alcohols (*m.p.* is between 77–144°C). When the racemic alcohols reacted with DBTA, in most cases SMC forming was enantioselective. The enantioselectivity of the SMC forming and the configuration of the complexed alcohol enantiomer depend on the space filling of the host compound in a homologous series of alcohols. In the case of *trans*-2-halogen-cyclohexanols there is a correlation between the thermal stability of the SMC-s and the enantioselectivity of the SMC forming.

* * *

The authors are grateful for financial support from OTKA Foundation (grant numbers: T29251 (E. Fogassy), T31711 (D. Kozma)).

References

1 D. Kozma (ed.), Handbook of Optical Resolutions via Diastereomeric Salt Formation, CRC Press LLC, Boca Raton 2001.
2 S. H. Wilen, Resolving Agents and Resolutions in Organic Chemistry, Notre Dame Univ. Press., Notre Dame 1971.
3 E. L. Eliel and S. H. Wilen, Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., New York 1993, p, 153.
4 P. Newman, Optical Resolution Procedures for Chemical Compounds, Optical Resolution Information Center, Manhattan College, N. Y. Riverdale 1978–84.
5 D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo and A. Wonnacott, Helv. Chim. Acta, 70 (1987) 954.
6 E. Weber, C. Wimmer, A. L. Llamas-Saiz and C. Forces-Forces, J. Chem. Soc., Chem. Commun., (1992) 733.
7 M. C. Etter, Acc. Chem. Res., 23 (1990) 120.
8 F. Toda, K. Tanaka, L. Infantes, C. Foces-Foces, R. M. Claramunt and J. Elguero, J. Chem. Soc., Chem. Commun., (1995) 1453.
9 P. P. Korkas, E. Weber and G. Náray Szabó, J. Chem. Soc., Chem. Commun., (1995) 2229.
10 S. Hanessian, M. Simard and S. Roelens, J. Am. Chem. Soc., 117 (1995) 7630.
11 D. Kozma, Zs. Böcskei, Cs. Kassai, K. Simon and E. Fogassy, J. Chem. Soc., Chem. Comm., (1996) 753.
12 R. Illés, Cs. Kassai, G. Pokol, J. Madarász, E. Fogassy and D. Kozma, J. Therm. Anal. Cal., 61 (2000) 745.
13 Cs. Kassai, R. Illés, G. Pokol, J. Sztatisz, E. Fogassy and D. Kozma, J. Therm. Anal. Cal., 62 (2000) 647.
14 Cs. Kassai, Z. Juvancz, J. Bálint, E. Fogassy and D. Kozma, Tetrahedron, 56 (2000) 8355.
15 Cs. Kassai, J. Bálint, Z. Juvancz, E. Fogassy and D. Kozma, Synth. Comm., 31 (2001) 97.