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Optical Resolution of Racemic Alcohols via Diastereoisomeric Supramolecular Compound Formation with *O*,*O*′-Dibenzoyl-(2*R*,3*R*)-tartaric Acid

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Abstract—*O*,*O*′-Dibenzoyl-(2*R*,3*R*)-tartaric acid (DBTA) forms a hydrogen bonded supramolecular compound with alcohols. The supramolecular compound formation is enantioselective for a large number of chiral alcohols, therefore DBTA can be used as resolving agent, also for compounds having no basic group. The condition of the complex formation is that the guest molecule should contain a proton donating group and a fitting aliphatic chain or cycloalkane ring. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

When a racemate contains a basic or an acidic group, its optical resolution can always be accomplished by diastereoisomeric salt formation as among the large number of basic or acidic resolving agents, usually at least one effective resolving agent can be found.[1,2]

The optical resolution of alcohols is more complicated. The enantiomers can be separated after derivatization (diastereoisomeric ester, or a diastereoisomeric salt) or, in one step, by complex formation. The one-step process would be the most practical way but until now a generally applicable, easily available complex forming resolving agent has not been found. Several research groups have tried to find complex forming resolving agents, usually by derivatizing the salt forming resolving agents,[3–12] but these resolving agents can only be applied for the resolution of a small number of racemates on a laboratory scale and unfortunately they are not available in bulk quantities.

Recently we have observed that the basic (*N*-alkyl)-pipecolic acid anilides can form supramolecular compounds with *natural* (2*R*,3*R*)-tartaric acid (TA) and with its benzoyl derivative *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid (DBTA).[13]

Based on this observation we have assumed that TA and DBTA may also be used for the resolution of racemic compounds without basic character. This can be interesting not only from a theoretical point of view, but also from a practical viewpoint since TA and DBTA are the two most frequently used, widely available and inexpensive acidic resolving agents.

Results and Discussion

The stability of a supramolecular compound is determined by the number of the weak interactions. The good complex forming ability of DBTA arises from a number of factors. Although the carboxylic acid groups of DBTA can donate protons for hydrogen bonding, it can also behave as a proton acceptor due to the 8 oxygen atoms it contains. The benzoyl groups can take part in hydrophobic interactions while the other part of the molecule contains polar hydrophilic groups.

Coordinative metal complexes of DBTA are also known to have been used for optical resolution,[12] but the diastereoisomeric supramolecular compound forming properties of DBTA have not yet been investigated.

Supramolecular compound forming properties of TA and DBTA were pre-tested with five chiral alcohols and it was found that the resolution is only possible with DBTA, while TA did not interact with those alcohols. The preliminary experiments showed a more efficient enantiomeric separation using DBTA monohydrate than anhydrous DBTA, so subsequently that was used.[16] Among the tested racemic alcohols the resolution of menthol showed the highest

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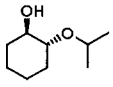
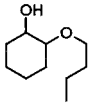
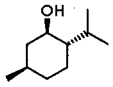
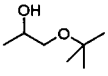
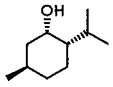
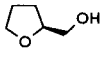
Table 1. Summary of the resolution results (The yield is related to the half amount of the racemate. *S*=e.e.× yield.[14] The configurations of the main isomers were identified by optical rotatory measurements.[15])

No.	Compound#	From crystalline phase			No.	Compound#	From crystalline phase		
		e.e.	Yield	S			e.e.	Yield	S
1		0	0.48	0	**12**		0.61	0.71	0.433
2		0	0.59	0	**13**		No solid phase		
3		0.20	0.63	0.126	**14**		0.50	0.74	0.370
4		0.28	0.91	0.255	**15**		0.15	0.60	0.090
5		0.05	0.19	0.009	**16**		0.44	0.66	0.290
6		0	0.11	0	**17**		0	0.46	0
7		0.07	0.66	0.046	**18**		0.83	0.45	0.374
8		0	0.93	0	**19**		No complex formation		
9		0.10	0.34	0.034	**20**		No complex formation		
10		0.35	0.74	0.259	**21**		No solid phase		
11		0.56	0.63	0.353	**22**		0.21	0.55	0.115

The configuration of the enriched enantiomer is shown in the table.

stereoselectivity, so for the systematic investigation alcohols with related structures were selected.

During optical resolutions, the diastereoisomers are generally separated by fractional crystallization which usually requires solvents. The selection of the appropriate solvents is not only a time- and labour-consuming process but the results with different solvents are hardly comparable. We developed a generally applicable process for the separation of diastereoisomeric supramolecular compounds by the use of hexane as semi-inert solvent. Hexane dissolves the alcohols but it does not dissolve the DBTA-monohydrate and the DBTA-alcohol supramolecular compound. The applied process is simple, generally applicable and the results are comparable.

The alcohol was dissolved in hexane and DBTA-monohydrate was suspended in this solution (one molar equivalent of DBTA-monohydrate was reacted with two molar equivalents of alcohol because we supposed that the molar ratio in the supramolecular compound is 1:1, and half the amount of the unreacted enantiomer remains in the mother liquor). The formation of the supramolecular compound by recrystallization of the solid phase starts on the solid–liquid interface and at room temperature, without stirring last about 1 week.

After filtration, the alchol enriched in one enantiomer can be obtained from the mother liquor and the other one from the solid compound. The enantiomericaly enriched alcohol which was a part of the supramolecular compound can be recovered by distillation or sublimation.

The results of 22 experiments are summarised in Table 1 (the homologous compounds are listed one after the other). By the comparison of the resolution results of the homologous compounds the following conclusions can be drawn:

1. Supramolecular compound formation in *trans*-selective in the case of 2-substituted cyclohexanols (e.g. menthol (**18**) forms a supermolecular compound while *iso*-menthol (**19**) does not). Supramolecular compound

formation is also *trans* selective for the achiral 4-alkyl-cyclohexanols.[17]
2. Among aliphatic secondary alcohols, 2-pentanols (**3**,**4**) form enantioselective supramolecular compounds with DBTA.
3. The 2-alkyl-cyclohexanols having a group larger than isopropyl do not interact with DBTA (**20**).
4. In the case of *trans*-2-alkoxy-cyclohexanols the enantioselectivity and the configuration of the alcohol in the supramolecular compound also depends on the size of the alkoxy group (**13**–**17**).
5. The enantioselectivity in the case of 2-alkyl-cyclohexanols depends on the size of the alkyl group. For 2-methyl- and 2-ethyl-cyclohexanols the *S*,*S*-*trans* isomer was incorporated into the supramolecular compound while menthol (**18**) incorporated with the opposite configuration.[17]
6. *trans*-2-Halogen-cyclohexanols form supramolecular compounds of *S*,*S* configuration (**10**–**12**). The enantioselectivity increases with the size of the halogen atom.

Experimental

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. The stationary phase was a methyl-silicone polymer substituted with permethylated β-cyclodextrin via spacer.[18] H_2 was used as carrier gas with 1 ml/min speed. The injection mode was split (1:160). The analysis temperature was adjusted to the volatility and selectivity of analytes. Several analytes were analysed in free form, but a few samples required derivatization with TFAA according to standard procedure.[19] Compounds **10**–**12** were analysed as acetyl derivatives, the others without derivatization between 323–373 K. The IR measurements were made by a Perkin–Elmer FT-IR 1600. The NMR spectra were taken on a Bruker AC 250 FT-NMR. All spectra were measured in $CDCl_3$ solution and chemical shift values are expressed in ppm from TMS (0.0 ppm) in the case of ^{13}C NMR from $CDCl_3$ (77.0 ppm) as internal standard on δ scale. All chemicals were purchased from Aldrich except **10**–**17** which were synthesized by known organic methods.[20]

General procedure for preparing DBTA-alcohol supramolecular compounds

50 mmol of alcohol was dissolved in 20–40 ml of hexane and in this solution 25 mmol of DBTA monohydrate was suspended. After 1 week standing at room temperature the solid supramolecular compound was filtered off and dried in air. 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. The mother liquor was distilled, the first fraction was hexane, the second fraction was the unreacted alcohol enantiomeric mixture.

Preparation of *trans*-2-chloro-cyclohexanol (10) from cyclohexene-oxide

To a cooled and stirred 37% aqueous HCl solution (17.8 ml, 0.153 mol) was added dropwise cyclohexene-oxide (5.00 g, 51 mmol). The solution was allowed to warm up to room temperature and was extracted with 3×20 ml of CH_2Cl_2. The organic phase was washed with 2×20 ml of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by distillation (83–86°C/15 Hgmm). Yield 5.52 g (80%). IR [cm^{-1}], 3358; 2939; 2861; 1450; 1073. ^1H NMR, 1.25–1.45 (m, 3H); 1.55–1.85 (m, 3H); 2.08–2.18 (m, 1H), 2.18–2.30 (m, 1H); 2.90–2.97 (m, 1H); 3.45–3.60 (m, 1H); 3.65–3.82 (m, 1H). ^{13}C NMR, 23.6, 25.2, 32.9, 34.8, 66.7, 74.7. Anal. calcd for $C_6H_{11}ClO$: C 53.54, H 8.24, Cl 26.34, found: C 53.61, H 8.21.

Preparation of *trans*-2-bromo-cyclohexanol (11) from cyclohexene-oxide

To a cooled and stirred 48% aqueous HBr solution (38 ml, 0.153 mol) was added dropwise cyclohexene-oxide (5.00 g, 51 mmol). The solution was allowed to warm up to room temperature and was extracted with 3×20 ml of CH_2Cl_2. The organic phase was washed with 2×20 ml of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by distillation (93–94°C/15 Hgmm). Yield 7.36 g (80%). IR [cm^{-1}], 3385; 2938; 2860; 1449; 1072. ^1H NMR, 1.18–1.48 (m, 3H); 1.65–1.95 (m, 3H); 2.08–2.20 (m, 1H), 2.28–2.40 (m, 1H); 2.55–2.60 (m, 1H); 3.55–3.67 (m, 1H); 3.85–3.98 (m, 1H). ^{13}C NMR, 23.7, 26.2, 33.4, 35.8, 61.0, 74.7. Anal. calcd for $C_6H_{11}BrO$: C 40.25, H 6.19, Br 44.62, found: C 40.17, H 6.24.

Preparation of *trans*-2-iodo-cyclohexanol (12) from cyclohexene-oxide

To a stirred aqueous KI (25.4 g, 0.153 mol/50 ml H_2O) solution was added cyclohexene-oxide (5.00 g, 51 mmol). To the cooled KI-solution was added dropwise aqueous H_2SO_4 solution (4 ml of 98% H_2SO_4/20 ml H_2O). The solution was allowed to warm up to room temperature and was extracted with 4×20 ml of CH_2Cl_2. The organic phase was washed with 3×20 ml of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by distillation (107–111°C/15 Hgmm). Yield 10.21 g (81%). mp=43°C, IR [cm^{-1}], KBr, 3405; 2933; 2853; 1447; 1066. ^1H NMR, 1.20–1.60 (m, 4H); 1.80–1.92 (m, 1H); 1.95–2.20 (m, 2H), 2.30 (broad s, 1H), 2.35–2.50 (m, 1H); 3.60–3.72 (m, 1H); 3.98–4.10 (m, 1H). ^{13}C NMR, 24.3, 27.8, 33.6, 38.4, 43.1, 75.7. Anal. calcd for $C_6H_{11}IO$: C 31.88, H 4.90, I 56.14, found: C 31.92, H 4.85.

Preparation of *trans*-2-methoxy-cyclohexanol (13) from cyclohexene-oxide

Cyclohexene-oxide (5.00 g, 51 mmol) was dissolved in 15 ml of MeOH then 1.00 g (19 mmol) of NaOMe was added. The solution was refluxed for 6 h, then 30 ml of H_2O was added, extracted with 3×10 ml of CH_2Cl_2. The

organic phase was dried over $MgSO_4$, the solvents were evaporated and the residue was purified by distillation (80–82°C/15 Hgmm). Yield 5.10 g (77%). IR [cm^{-1}], 3440; 2933; 2861; 1452; 1102. ^1H NMR, 0.95–1.40 (m, 4H); 1.65–1.80 (m, 2H); 1.90–2.20 (m, 1H), 2.85–3.00 (m, 1H); 3.12 (s, 1H); 3.42 (s, 4H). ^{13}C NMR, 23.6, 23.7, 28.8, 31.9, 55.9, 73.0, 84.6. Anal. calcd for $C_7H_{14}O_2$: C 64.58, H 10.84, found: C 64.49, H 10.79.

Preparation of *trans*-2-ethoxy-cyclohexanol (14) from cyclohexene-oxide

Cyclohexene-oxide (5.00 g, 51 mmol) was dissolved in 15 ml of EtOH and into this solution 1.00 g (15 mmol) of NaOEt was added. The solution was refluxed for 6 h, then 30 ml of H_2O was added, extracted with 3×10 ml of CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvents were evaporated and the residue was purified by distillation (82–84°C/15 Hgmm). Yield 5.64 g (77%). IR [cm^{-1}], 3446; 2973; 2933; 2863; 1450; 1107. ^1H NMR, 1.05–1.40 (m, 7H); 1.60–1.85 (m, 2H); 1.93–2.20 (m, 2H), 2.95–3.10 (m, 1H); 3.17 (s, 1H); 3.33–3.55 (m, 2H); 3.63–3.85 (m, 1H). ^{13}C NMR, 15.3, 23.7, 24.2, 29.1, 32.0, 63.8, 73.2, 83.1. Anal. calcd for $C_8H_{16}O_2$: C 66.63, H 11.18, found: C 66.58, H 11.24.

Preparation of *trans*-2-isopropoxy-cyclohexanol (15) from cyclohexene-oxide

Na (1.20 g, 52 mmol) was dissolved in 30 ml of iPrOH and was added cyclohexene-oxide (5.00 g, 51 mmol). The solution was refluxed for 12 h then 30 ml of H_2O was added, extracted with 2×30 ml of CH_2Cl_2. The organic phase was dried over $MgSO_4$, solvents were evaporated and the residue was purified by distillation (96–104°C/15 Hgmm). Yield 3.93 g (49%). IR [cm^{-1}], 3446; 2970; 2933; 2862; 1451; 1075. ^1H NMR, 1.05–1.40 (m, 10H); 1.65–1.80 (m, 2H); 1.90–2.15 (m, 2H), 2.90–3.20 (m, 2H); 3.30–3.47 (s, 1H); 3.67–3.85 (m, 1H). ^{13}C NMR, 21.9, 23.4, 23.7, 24.0, 30.0, 31.8, 69.2, 73.2, 80.9. Anal. calcd for $C_9H_{18}O_2$: C 68.31, H 11.47, found: C 68.22, H 11.40.

Preparation of *trans*-2-propoxy-cyclohexanol (16) from cyclohexene-oxide

Na (1.40 g, 61 mmol) was dissolved in 30 ml of PrOH and was added cyclohexene-oxide (5.00 g, 51 mmol). The solvent was refluxed for 6 h and 60 ml of H_2O was added, extracted with 3×50 ml of CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvents were evaporated and the residue was purified by distillation (73–76°C/15 Hgmm). Yield 3.85 g (48%). IR [cm^{-1}], 3424; 2935; 2861; 1451; 1086. ^1H NMR, 0.80–1.00 (m, 3H); 1.00–1.40 (m, 4H); 1.45–1.80 (m, 4H), 1.90–2.20 (m, 2H); 2.91 (s, 1H); 2.95–3.08 (m, 1H); 3.20–3.50 (m, 2H); 3.50–3.70 (m, 1H). ^{13}C NMR, 10.1, 22.9, 23.5, 23.8, 28.8, 31.7, 70.0, 73.1, 83.0. Anal. calcd for $C_9H_{18}O_2$: C 68.31, H 11.47, found: C 68.25, H 11.43.

Preparation of *trans*-2-butoxy-cyclohexanol (17) from cyclohexene-oxide

Na (1.20 g, 52 mmol) was dissolved in 30 ml of *n*-BuOH and was added cyclohexene-oxide (5.00 g, 51 mmol). The solution was refluxed for 5 h then 60 ml of H_2O was added, extracted with 3×50 ml of CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvents were evaporated and the residue was purified by distillation (107–108°C/15 Hgmm). Yield 7.10 g (81%). IR [cm^{-1}], 3440; 2933; 2863; 1451; 1101. ^1H NMR, 0.80–1.00 (m, 3H); 1.00–1.45 (m, 6H); 1.45–1.80 (m, 4H), 1.85–2.15 (m, 2H); 2.85–3.07 (m, 1H); 3.14 (s, 1H); 3.20–3.49 (m, 2H); 3.52–3.72 (m, 1H). ^{13}C NMR, 13.5, 19.0, 23.6, 23.9, 28.8, 31.8, 31.9, 68.2, 73.3, 83.2. Anal. calcd for $C_{10}H_{20}O_2$: C 69.72, H 11.70, found: C 69.77, H 11.65.

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ethoxy-cyclohexanol (**14**), $[\alpha]_D^{20}$=negative, measured: $[\alpha]_D^{20}$=−41.2 (c=2; CH_2Cl_2), (1*R*,2*R*)-*trans*-propoxy-cyclohexanol (**16**), $[\alpha]_D^{20}$=negative, measured: $[\alpha]_D^{20}$=+38.7 (c=2; CH_2Cl_2), (1*R*,2*R*)-*trans*-isopropoxy-cyclohexanol (**15**), $[\alpha]_D^{20}$=−85.6 (c=2; CH_2Cl_2), measured: $[\alpha]_D^{20}$=−14.0 (c=2; CH_2Cl_2), Hoenig, H.; Seufer-Wasserthal, P. *Synthesis* **1990**, *12*, 1137; (1*S*,2*S*)-*trans*-2-iodo-cyclohexanol (**12**), $[\alpha]_D^{23}$=+33.1 (c=2.5; $CHCl_3$), measured: $[\alpha]_D^{23}$=+22.9 Fukuzawa, T.; Shimoji, Y. Hashimoto, T. *Tetrahedron Asymmetry* **1996**, *7*, 1649; (1*R*,2*S*,5*R*)-(−)-Menthol (**18**) $[\alpha]_D^{20}$=−50 (c=10; EtOH), measured: $[\alpha]_D^{20}$=−41.6 (c=10; EtOH), CAS: [2216-51-5]; (*S*)-2-cyclohexene-1-ol (**22**), $[\alpha]_D^{20}$=+130.6 (c=1.21; $CHCl_3$), measured: $[\alpha]_D^{20}$=−26.9 (c=1.21; $CHCl_3$), Fukuzawa, T.; Hashimoto, T. *Tetrahedron Asymmetry* **1993**, *4*, 2323.

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