Novel Chiral Amide Hosts Derived from Mandelic Acid: A Marked Difference in Inclusion Abilities between Host Stereoisomers

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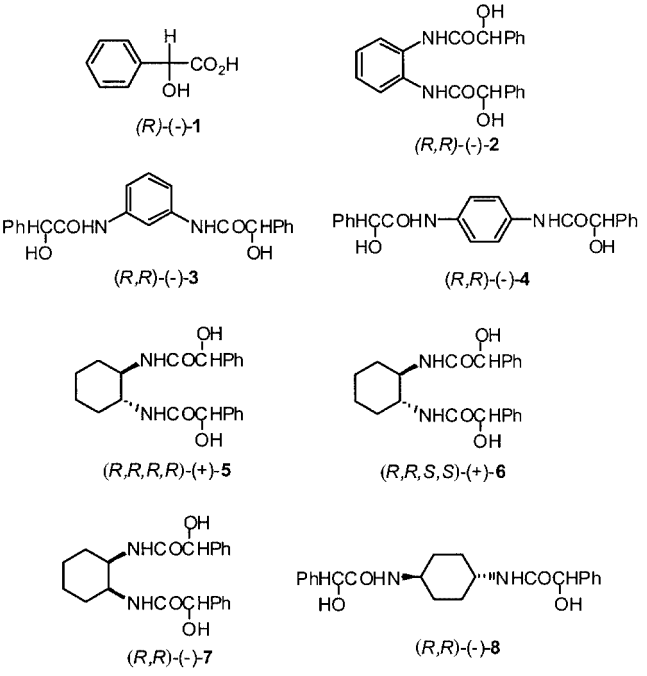
Novel chiral amide host compounds (**2**–**8**) have been synthesized from mandelic acid (**1**). A marked difference between the inclusion properties of analogous isomers such as **5** and **6** was observed. Host compounds **4** and **5** showed a relatively high chiral recognition in the optical resolution of guest compounds by inclusion crystallization.

Introduction

In recent years, there has been increasing interest in host-guest inclusion systems because of their potential applications in analytical, synthetic and material sciences.[1] Previously, we have designed chiral alcohol host compounds derived from tartaric acid, and found them to be very useful hosts for the optical resolution of racemic guests and for the enantioselective reaction of prochiral guests.[2] We have now designed and synthesized novel chiral amide host compounds (**2**−**8**) derived from mandelic acid (**1**), which have a rigid amide group connected to the benzene or cyclohexane framework, bulky phenyl substituents, and an OH group for possible hydrogen bonding to guest molecules. Of the phenylene-substituted host compounds, the *o*- and *p*-phenylene derivatives (**2**, **4**) showed a broad inclusion ability although the *m*-isomer **3** showed poor inclusion ability. The host compound (*R*,*R*,*R*,*R*)-(+)-**5** includes the greatest number of guest molecules, whereas the host (*R*,*R*,*S*,*S*)-(+)-**6** (the stereoisomer of **5**) showed little inclusion abilities.



Results and Discussion

The amide host compounds **2**−**4** were synthesized by the condensation reaction of (*R*)-(−)-mandelic acid and *o*-, *m*- and *p*-diaminobenzene, respectively, in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride hydrate[3] as a condensing agent. The amide host compounds **5** and **6** were prepared by the condensation reaction of (*R*,*R*)-(−)-*trans*-1,2-cyclohexanediamine with (*R*)-(−)-mandelic acid and (*S*)-(+)-mandelic acid, respectively, in the presence of *N*-hydroxysuccinic anhydride and dicyclohexylcarbodiimide (DCC) as a condensing agent according to the reported method.[4] The amide host compounds **7** and **8** were synthesized by the condensation reaction of (*R*)-(−)-mandelic acid with *cis*-1,2-cyclohexanediamine and *trans*-1,4-cyclohexanediamine, respectively, in the presence of *N*-hydroxysuccinic anhydride and dicyclohexylcarbodiimide (DCC) as a condensing agent. The yields, melting points and $[\alpha]_D$ value of these new host compounds are listed in Table 1.

The inclusion behavior of the host compounds **2**−**8** was studied. Of the *o*-, *m*- and *p*-phenylene-substituted host compounds (**2**−**4**), the *o*- and *p*-substituted hosts (**2** and **4**,

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Table 1. Yield, melting point and $[\alpha]_D$ value of new host compounds

Host	Yield [%]	Mp [°C]	$[\alpha]_D$ (*c*, solv.)
2	44	170−173	−72.8 (0.35, MeOH)
3	65	180−183	−33.7 (0.32, MeOH)
4	66	215−219	−27.0 (0.30, MeOH)
5	63	152−155	+3.7 (0.21, $CHCl_3$)
6	57	190−195	+108 (0.20, $CHCl_3$)
7	78	200−205	−84.6 (0.32, MeOH)
8	71	223−227	−82.6 (0.31, MeOH)

respectively) showed a higher inclusion ability for some typical guest compounds than the *m*-substituted host **3** (Table 2). A marked difference between the inclusion ability of analogous isomers (**5** and **6**) was observed. Host **5**, which was prepared from the condensation reaction between (*R*)-(−)-**1** and (*R*,*R*)-(−)-*trans*-1,2-cyclohexanediamine, took up all guest compounds tested, whereas host **6**, prepared from (*S*)-(+)-**1** and (*R*,*R*)-(−)-*trans*-1,2-cyclohexanediamine, included only two guest compounds (Table 2). The chirality of the stereogenic center of mandelic acid (**1**) is very important for inclusion complexation. The stereochemistry of *trans*-1,2-cyclohexanediamine is also important for stable inclusion, since the *cis* derivative **7** showed no inclusion properties. On the other hand, the 1,4-*trans* derivative **8** showed moderate inclusion properties, as shown in Table 2.

Table 2. Host-guest ratio of inclusion crystals[a]

Guest	2	3	4	5	6	7	8
MeOH	−[b]	−	−	2:1	−	−	−
Acetone	−	−	3:1	3:1	−	−	−
Cyclopentanone	1:1	−	1:1	1:1	−	−	−
Cyclohexanone	1:1	1:2	1:1	1:1	−	−	−
γ-Butyrolactone	−	−	−	1:2	−	−	−
THF	−	−	2:1	2:1	−	−	1:1
Dioxane	1:1	−	1:1	1:1	1:2	−	1:1
Acetonitrile	−	−	−	2:1	−	−	−
DMSO	1:1	−	2:1	1:1	1:1	−	1:1
DMF	1:1	−	2:1	1:1	−	−	−
Pyridine	−	−	1:1	1:1	−	−	1:1

[a] The host-guest ratios were determined by TG analysis.[b] No inclusion complexation occurred.

The results of optical resolution by one complexation with the host compounds **2**, **4**, **5**, **6** and **8** are summarized in Table 3. Racemic 2-methylcyclohexanone was partially resolved by complexation with host compound **2**. 3-Methylcyclohexanone was included in host compounds **2**−**4**, and was resolved most efficiently with host **4** in 44% *ee* after one complexation. The efficiency of the optical resolution of 2-methylcyclohexanone is much higher than that previously reported by using (*R*,*R*)-(−)-1,6-bis(2-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol as the optically active host compound.[5] Piperidine derivatives were resolved most efficiently by complexation with host **5**. For example, when a solution of a 1:4 mixture of **5** and (±)-2-ethylpiperidine in EtOAc was kept at room temperature for 12 h, 1:2 inclusion crystals of **5** and (+)-2-ethylpiperidine were formed as colorless needles. Four recrystallizations of the crystals from EtOAc gave pure inclusion crystals, which, upon heating in vacuo, gave (+)-2-ethylpiperidine of 100% *ee* in 21% yield by distillation. γ-Butyrolactone derivatives were also resolved by complexation with host **5**.

Table 3. Optical resolution of guest compounds by inclusion complexation

Guest	2	4	5	6	8
2-Methylcyclohexanone	17% *ee*	−[a]	−	−	−
3-Methylcyclohexanone	rac	44% *ee*	36% *ee*	−	−
2-Methylpiperidine	−	16% *ee*	29% *ee*	−	−
3-Methylpiperidine	−	rac	21% *ee*	18% *ee*	21% *ee*
2-Ethylpiperidine	−	36% *ee*	70% *ee*	−	−
3-Methyl-γ-butyrolactone	−	−	17% *ee*	−	−
3-Ethyl-γ-butyrolactone	−	−	32% *ee*	−	−

[a] No inclusion complexation occurred.

The chiral-discrimination properties of the new hosts are to a large extent due to their solid-state structures. A crystal of the 1:1 inclusion complex of (*R*,*R*)-(−)-**4** and (*R*)-2-ethylpiperidine suitable for X-ray analysis was obtained. The host molecule is characterized by an extended conformation of the central part with one intramolecular hydrogen bond: N15···O4 2.633(5), H15···O4 2.20 Å, angle N15−H15···O4 110.9° (Figure 1).

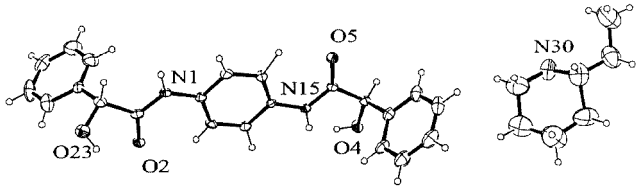

Figure 1. ORTEP diagram of the 1:1 complex of (*R*,*R*)-(−)-**4** and (*R*)-2-ethylpiperidine showing thermal ellipsoids at 30% probability level (significantly higher for the guest)

The host molecules form channels where the molecules of (*R*)-2-ethylpiperidine are included partially due to inter-

Table 4. Hydrogen bonding pattern

D−H	d(D−H)	d(H···A)	Angle	d(D···A)	A
O4−H4	0.82	2.14	118.44	2.633(5)	N15 intramolecular
O23−H23	0.82	2.23	146.64	2.951(4)	O4 [$-x+1, y-1/2, -z+1$]
N15−H15	0.86	2.07	152.11	2.860(4)	O2 [$-x+1, y+1/2, -z+1$]
N30−H30A	1.01	2.37	167.4	2.645 (5)	O4 [$-x, y+1/2, -z$]

actions between the hydrophobic groups of the host and guest. Additionally, a relatively strong intermolecular hydrogen bond can be postulated between N30 and O4 on the basis of a short donor···acceptor distance and the calculated position of the N30−H atom (for geometry see Table 4 and Figure 2). Such a structure promotes fast release of the guest from the hosting structure.

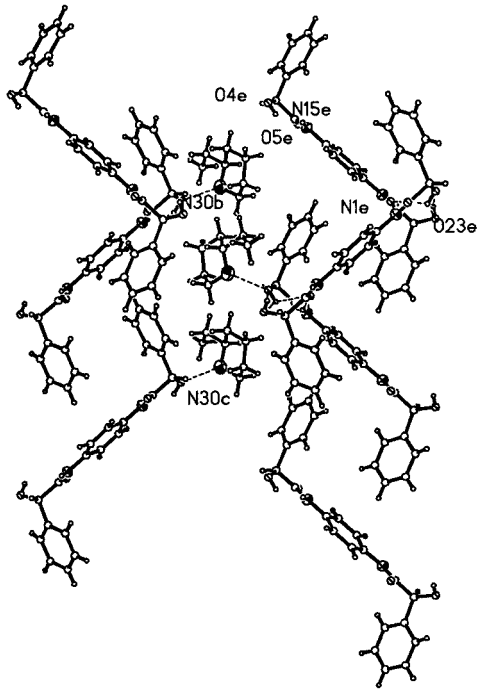

Figure 2. Crystal structure of the 1:1 complex between (*R*,*R*)-(−)-**4** and (*R*)-2-ethylpiperidine; the host molecules form channels containing hydrogen-bonded guest molecules

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded in $CDCl_3$ on a JEOL Lambda 300 spectrometer. IR spectra were recorded with a JASCO FT-IR 200 spectrometer. All melting points were determined using a Yanaco micro melting-point apparatus and are uncorrected. Optical rotations were determined with Jasco DIP 1000 polarimeter. The host-guest inclusion crystals were prepared by recrystallization of host compounds from the neat guest (solvent) solution; the host-guest ratios were determined by thermogravimetric analysis (TG).

Preparation of (*R*,*R*)-(−)-2-Hydroxy-*N*-[2-(2-hydroxy-2-phenylacetylamino)phenyl]-2-phenylacetamide (2). General Procedure: 4-[4,6-Dimethoxy-1,3,5-triazin-2-yl]-4-methylmorpholinium chloride hydrate (11.0 g, 39.9 mmol) was added to a mixture of (*R*)-(−)-mandelic acid (**1**; 25.0 g, 32.9 mmol) and *o*-phenylenediamine (1.8 g, 16.6 mmol) in MeOH (100 mL) at room temperature. After stirring for 6 h at room temperature, the MeOH was evaporated. The resulting residue was dissolved in EtOAc and washed successively with saturated sodium carbonate, water, 1 N HCl, water and brine and dried over $MgSO_4$. The crude product was purified by recrystallization from MeOH to give 2.72 g of **2** (44% yield) as colorless prisms [mp, 173−175 °C, $[\alpha]_D$ = −72.8° (*c* = 0.35, MeOH)]. IR (Nujol): $\tilde{\nu}$ = 3432 cm^{-1} (OH), 1661 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$), δ = 3.38 (d, *J* = 3 Hz, 2 H, CH), 4.95 (d, *J* = 3 Hz, 2 H, OH), 7.2−7.4 (m, 14 H, Ar), 8.51 (s, 2 H, NH) ppm. $C_{22}H_{20}N_2O_4$ (376.14): calcd. C 70.20, H 5.36, N 7.44; found C 70.23, H 5.54, N 7.52.

(*R*,*R*)-(−)-2-Hydroxy-*N*-[3-(2-hydroxy-1-phenylvinyloxyamino)phenyl]-2-phenylacetamide (3): Colorless prisms; m.p. 182−185 °C. $[\alpha]_D$ = −33.7 (*c* = 0.72, MeOH). IR (Nujol): $\tilde{\nu}$ = 3367 cm^{-1} (OH), 1665 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$), δ = 5.16 (d, *J* = 4 Hz, 2 H, CH), 5.75 (d, *J* = 4 Hz, 2 H, OH), 7.2−7.5 (m, 14 H, Ar), 8.95 (s, 2 H, NH) ppm. $C_{22}H_{20}N_2O_4$ (376.14): calcd. C 70.20, H 5.36, N 7.44; found C 70.18, H 5.66, N 7.55.

(*R*,*R*)-(−)-2-Hydroxy-*N*-[4-(2-hydroxy-1-phenylvinyloxyamino)phenyl]-2-phenylacetamide (4): Colorless prisms; m.p. 216−219 °C. $[\alpha]_D$ = −27.0 (*c* = 0.30, MeOH). IR (Nujol): $\tilde{\nu}$ = 3249 cm^{-1} (OH), 1613 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$), δ = 5.17 (d, *J* = 4 Hz, 2 H, CH), 6.00 (d, *J* = 4 Hz, 2 H, OH), 7.2−7.5 (m, 14 H, Ar), 9.31 (s, 2 H, NH) ppm. $C_{22}H_{20}N_2O_4$ (376.14): calcd. C 70.20, H 5.36, N 7.44; found C 70.10, H 5.61, N 7.65.

Preparation of (*R*,*R*)-(−)-2-Hydroxy-*N*-[2-(2-hydroxy-2-phenylacetylamino)cyclohexyl]-2-phenylacetamide (7). General Procedure: Dicyclohexylcarbodiimide (9.0 g, 43.8 mmol) was added to a stirred solution of (*R*)-(−)-mandelic acid (**1**; 5.3 g, 35.0 mmol), *cis*-1,2-cyclohexanediamine (2.0 g, 17.5 mmol) and *N*-hydroxysuccinic anhydride (5.0 g, 43.8 mmol) in anhydrous tetrahydrofuran (150 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue, dissolved in ethyl acetate, was washed successively with saturated sodium carbonate, water, 1 N HCl, water and brine and dried over $MgSO_4$. The crude product was purified by recrystallization from MeOH to give 5.2 g of **7** (78% yield) as colorless prisms [mp, 203−205 °C, $[\alpha]_D$ = −84.6 (*c* = 0.32, MeOH)]. IR (Nujol): $\tilde{\nu}$ = 3414 cm^{-1} (OH), 1685 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$), δ = 1.2−1.75 (m, 8 H), 3.37 (d, *J* = 3 Hz, 1 H), 3.49 (d, *J* = 3 Hz, 1 H), 3.66 (s, 2 H), 4.89 (d, *J* = 3 Hz, 1 H), 5.00 (d, *J* = 3 Hz, 1 H), 6.49 (d, *J* = 7.5 Hz, 1 H), 6.79 (d, *J* = 7.5 Hz, 1 H), 7.2−7.5 (m, 10 H) ppm. $C_{22}H_{26}N_2O_4$ (382.19): calcd. C 69.09, H 6.85, N 7.32; found C 69.33, H 7.01, N 7.59.

(*R*,*R*)-(−)-2-Hydroxy-*N*-[4-(2-hydroxy-1-phenylvinyloxyamino)cyclohexyl]-2-phenylacetamide (8): Colorless prisms, m.p. 224−227 °C. $[\alpha]_D$ = −82.6 (*c* = 0.31, MeOH)). IR (Nujol): $\tilde{\nu}$ = 3503 cm^{-1} (OH), 1640, 1623 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$), δ = 0.9−2.0 (m, 8 H), 3.37 (d, *J* = 3 Hz, 2 H), 3.74 (s, 2 H), 5.00 (d, *J* = 3 Hz, 2 H), 5.98 (br. s, 2 H), 7.2−7.4 (m, 10 H) ppm. $C_{22}H_{26}N_2O_4$ (382.19): calcd. C 69.09, H 6.85, N 7.32; found C 69.19, H 6.99, N 7.54.

Optical Resolution of 3-Methylcyclohexanone by Complexation with (*R*,*R*)-(−)-4: When a solution of (*R*,*R*)-(−)-**4** (1.0 g, 2.66 mmol) in (±)-3-methylcyclohexanone (4.0 g, 35.5 mmol) was kept at room temperature for 12 h, a 1:1 inclusion complex of (*R*,*R*)-(−)-**4** and (−)-3-methylcyclohexanone was formed as colorless prisms (1.05 g, 81% yield, no sharp m.p.). Heating the inclusion crystals at 180 °C/30 Torr gave (−)-3-methylcyclohexanone with 44% *ee* {0.11 g, $[\alpha]_D$ = −6.35 (*c* = 1.1, $CHCl_3$)} as a distillate. The optical purity of (−)-3-methylcyclohexanone was determined by comparison of the measured $[\alpha]_D$ value with the literature value.[6] An X-ray sample of the pure 1:1 complex of (*R*,*R*)-(−)-**4** and (−)-3-methylcyclohexanone was prepared by complexation of (*R*,*R*)-(−)-**4** with (−)-3-methylcyclohexanone of 100% *ee*.

Optical Resolution of 2-Ethylpiperidine by Complexation with (*R*,*R*,*R*,*R*)-(+)-5: A solution of a 1:4 mixture of (*R*,*R*,*R*,*R*)-(+)-**5** (1.5 g, 3.92 mmol) and (±)-2-ethylpiperidine (1.77 g, 15.7 mmol) in EtOAc (15 mL) was kept at room temperature for 12 h, forming 1:2 inclusion crystals of (*R*,*R*,*R*,*R*)-(+)-**5** and (+)-2-ethylpiperidine of 70% *ee* as colorless needles (1.99 g). Four recrystallizations of the inclusion crystals from EtOAc gave pure inclusion crystals (0.52 g). Heating the inclusion crystals at 180 °C/30 Torr gave (+)-2-ethylpiperidine of 100% *ee* {0.18 g, 21% yield, $[\alpha]_D = +11.3$ (c = 0.06, $CHCl_3$)} as a distillate. The optical purity of (−)-3-methylcyclohexanone was determined by ^{1}H NMR spectroscopy in the presence of (−)-bis(2-naphthol).[7]

X-ray Crystallographic Study of the 1:1 complex of (*R*,*R*)-(−)-4 and (*R*)-2-ethylpiperidine: A suitable crystal of dimensions 0.35 × 0.35 × 0.21 mm^3, covered by epoxy glue, was used for data collection on an Nonius BV Kappa CCD system at 283 K. Crystal data: a = 9.6110(4), b = 10.3610(4), c = 14.1490(6) Å, β = 103.1710(10)°; Z = 2, monoclinic space group $P2_1$, Mo-K_α radiation, λ = 0.7107 Å, $D_{calcd.}$ = 1.185 Mg·m^{-3}. A total of 3331 independent reflections were measured in the θ-range 2.18−21.97°. These were used for structure solution using SHELXS-97[8] and refinement with SHELXL-97.[9]. All non-H atoms were refined in the anisotropic mode. All non-hydroxyl hydrogens were placed geometrically and refined with a riding mode with U_{iso} constrained to 1.2 times that of the carrier atom. The positions of the N,O-protons were found from Δρ maps and refined without constraints. The position of the H30 proton, essential for host-guest binding, could not be found from difference maps. It was therefore placed geometrically and not refined. Final R_1 and wR_2 parameters are 0.0693 and 0.1789, respectively.

CCDC-209871 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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