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Role of Methanol in Chiral Combinations of Host–Guest Molecules in the Inclusion Crystal: Structure Determination by X-Ray Crystallography

Fumio Toda,[*a] **Koichi Tanaka,**[a] **Ikuko Miyahara,**[b] **Shohei Akutsu**[b] **and Ken Hirotsu**[*b]

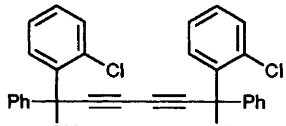
[a] *Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama, Ehime 790, Japan*
[b] *Department of Chemistry, Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan*

(*S*,*S*)-(−)-1,4-bis[3-(*o*-chlorophenyl)-3-hydroxy-3-phenyl-1-propynyl]benzene (**2**) and (*S*,*S*)-(−)-9,10-bis[3-(*o*-chlorophenyl)-3-hydroxy-3-phenyl]anthracene (**3**) include one enantiomer of racemic guest compound when the complexation is carried out in toluene, but include the other enantiomer and MeOH in a 1 : 1 : 1 ratio when the complexation is carried out in MeOH; the X-ray crystal structure of a 1 : 1 : 1 complex of **3**, (*S*)-(+)-2-methylpiperidine and MeOH is reported, and preparation of the new chiral host compound (**3**) is also described.

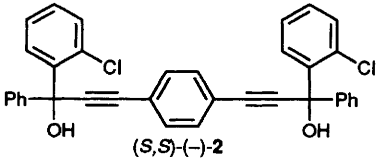
Optically active diacetylenic diols, (*S*,*S*)-(−)-1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol **1**[1,2] and (*S*,*S*)-(−)-1,4-bis[3-(*o*-chlorophenyl)-3-hydroxy-3-phenyl-1-propynylbenzene **2**,[3] have been reported to be useful as chiral hosts for the optical resolution of various guest compounds by an enantioselective inclusion complexation. We report the interesting result that **2** and the newly prepared chiral host, (*S*,*S*)-(−)-9,10-bis[3-(*o*-chlorophenyl)-3-hydroxy-3-phenyl]-anthracene **3** include one enantiomer of racemic guest compound in the absence of MeOH, but include the other enantiomer together with a MeOH molecule in the presence of MeOH.

For example, when a solution of **3** (0.5 g, 0.76 mmol) and (±)-2-methylpiperidine **4** (0.15 g, 1.52 mmol) in toluene (5 ml) was kept at room temperature for 12 h, a 1 : 1 inclusion crystal of **3** and (−)-**4** was formed as yellow prisms (mp not clearly defined), which upon distillation at 150°C/20 mmHg gave (−)-**4** of 71% ee [0.05 g, 67% yield, $[\alpha]_D$ −3.2 (*c* 0.12, MeOH)]. However, when the above complexation was carried out in MeOH (5 ml), a 1 : 1 : 1 inclusion crystal of **3**, (*S*)-(+)-**4** and MeOH was formed as yellow prisms (mp not clear), which upon distillation at 150°C/20 mmHg gave (*S*)-(+)-**4** of 62% ee [0.5 g, 67% yield, $[\alpha]_D$ +2.8 (*c* 0.11, MeOH)].

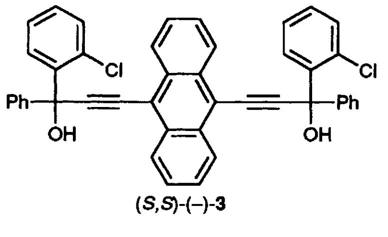
In the absence and presence of MeOH, **3** included (*R*)-(−)- and (*S*)-(+)-enantiomers of **4**, respectively, although the MeOH molecule is also included together with the (*S*)-(+)-guest in the latter case. Similarly, **3** included the (−)-enantiomer of methyl alanate **6** in the absence of MeOH and its (+)-enantiomer together with MeOH in the presence of MeOH (Table 1). In the case of phenylethylamine **5**, a 1 : 1 : 1 complex of **3**, (+)-**5** and MeOH was formed when the complexation was carried out in MeOH and (+)-**5** of 58% ee was obtained from the complex in 82% yield by distillation *in vacuo*, although no complexation occurred in toluene (Table 1).



(*S*,*S*)-(−)-**1**



(*S*,*S*)-(−)-**2**



(*S*,*S*)-(−)-**3**

4

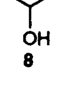
$\underset{NH_2}{PhCHMe}$

5

$\underset{NH_2}{MeCHCO_2Me}$

6

7



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The host **2** also showed a similar tendency. Complexation of **2** and (±)-4-hydroxycyclopent-2-enone **7** in toluene gave a 1 : 2 inclusion complex of **2** and (+)-**7**, from which (+)-**7** of 38% ee was obtained in 72% yield by distillation *in vacuo*. When the complexation was carried out in MeOH, a 1 : 1 : 1 complex of **2**, (−)-**7** and MeOH was obtained, from which (−)-**7** of 42% ee was obtained in 44% yield by distillation *in vacuo*. In the case of 3-acetylcyclohex-2-enol **8**, a 1 : 1 : 1 complex of **2**, (−)-**8** and MeOH was obtained when the complexation was carried out in MeOH, from which (−)-**8** of 58% ee was isolated in 55% yield by distillation. However, when the complexation was carried out in toluene, a 1 : 1 complex of **2** and (±)-**8** was obtained. Upon treatment of **2** with **4** and **5** in MeOH no complex was formed, although inefficient enantioselective complexation occurred in toluene (Table 1).

However, host **1**, which has no substituent between the two acetylenic moieties, showed a different behaviour from that of **2** and **3**. Complexation experiments of **1** with **4** or **8** in toluene and MeOH gave almost the same result in each case (Table 1).

MeOH plays a very interesting role, changing the chiral combination of host and guest in the inclusion crystal. The MeOH can also be replaced by EtOH. For example, complexation of **2** and (±)-**7** in EtOH gave a 1 : 1 : 1 complex of **2**, (−)-**7** and EtOH (mp 70–75°C), which upon distillation *in*

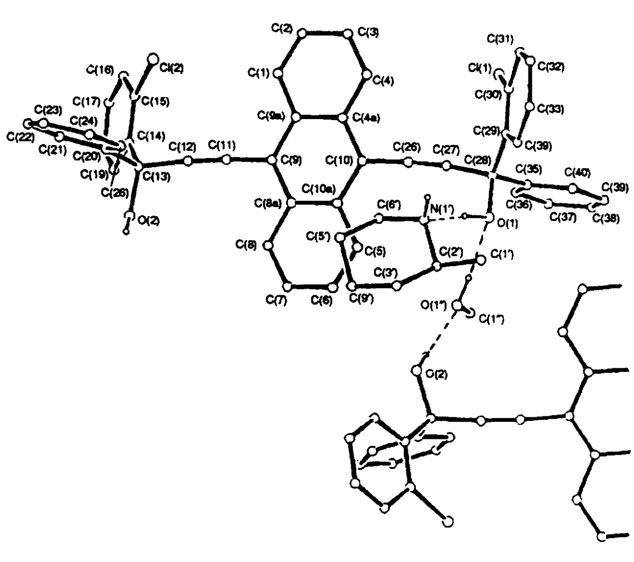

Fig. 1 X-ray structure of a 1 : 1 : 1 complex of **3**, (*S*)-(+)-**4** and MeOH showing hydrogen bond network: O(2)···O(1") = 2.712(7), O(1")···O(1) = 2.871(6) and O(1)···N(1') = 2.773(6) Å

Table 1 Optical resolution of guest compounds by inclusion complexation with chiral hosts in toluene and MeOH[a]

		Host					
		1		2		3	
Guest	Solvent	Inclusion complex h : g : s (mp/°C)	Isolated guest (%, % ee)^b	Inclusion complex h : g : s (mp/°C)	Isolated guest (%, % ee)^b	Inclusion complex h : g : s (mp/°C)	Isolated guest (%, % ee)^b
4	$PhCH_3$	1 : 1 : 0 (118–120)	(±)-**4** (15, 0)	1 : 1 : 0 (95–96)	(−)-**4** (68, 26)	1 : 1 : 0 —^{e}	(−)-**4** (67, 71)
	MeOH	1 : 1 : 0 (118–120)	(±)-**4** (43, 0)	1 : 1 : 0 (95–96)	(−)-**4** (60, 32)	1 : 1 : 1 —^{e}	(+)-**4** (67, 62)
5	$PhCH_3$	—^{c}	—	1 : 1 : 0 (113–114)	(+)-**5** (74, 14)	—^{c}	—
	MeOH	—^{c}	—	—^{c}	—	1 : 1 : 1 —^{e}	(+)-**5** (82, 58)
6	$PhCH_3$	—^{c}	—	—^{c}	—	1 : 1 : 0 —^{e}	(+)-**6** (90, 20)
	MeOH	—^{c}	—	—^{c}	—	1 : 1 : 1 —^{e}	(−)-**6** (77, 39)
7	$PhCH_3$	—^{c}	—	1 : 2 : 0 (86–94)	(+)-**7** (72, 38)	1 : 2 : 0 —^{e}	(±)-**7** (63, 0)
	MeOH	—^{c}	—	1 : 1 : 1 (91–95)	(−)-**7** (44, 42)	—^{c}	—
8	$PhCH_3$	1 : 2 : 0 (147–148)	(+)-**8** (86, 40)	1 : 1 : 0 (132–134)	(±)-**8** (73, 0)	—^{d}	—
	MeOH	1 : 2 : 0 (147–148)	(+)-**8** (79, 66)	1 : 1 : 1 —^{e}	(−)-**8** (55, 58)	—^{d}	—

[a] Complexations were carried out by recrystallizing host (0.5 g) and its twice molar amounts of guest from the solvent (5 ml). In the case of the complexation with **7** in alcohols, host (0.5 g) and its twice molar amounts of **7** were recrystallized from alcohols (2 ml). [b] Optical purities of **4**, and **5** and **6** were determined by measurement of ^1H NMR spectra in the presence of the chiral shift reagent **2** or **3**[2] and $Eu(hfc)_3$, respectively. Optical purities of **7** and **8** were determined by HPLC on the chiral solid phase Chiralcel OC and OJ, respectively.† [c] No complexation occurred. [d] No complexation experiments were carried out. [e] Mp not clearly defined.

vacuo gave (−)-**7** of 78% ee in 80% yield. However, sterically larger alcohols than EtOH such as PrOH and BuOH did not display the same behaviour.

In order to determine the role of MeOH, the X-ray crystal structure of the 1 : 1 : 1 complex of **3**, optically pure (*S*)-(+)-**4** and MeOH was analysed. X-ray analytical data† disclosed that MeOH and one guest molecule are assembled between two hosts, and a hydrogen bond network, host(1)–OH···MeOH···host(2)–OH···guest–NH is constructed (Fig. 1).‡ The MeOH molecule which is sandwiched between the two phenyl rings of two hosts plays a steric role, widening the space between the two hosts so that the guest can be accommodated in the space. Although (*S*)-(+)-**4** can be accommodated in the chiral space, the other enantiomeric guest (*R*)-(−)-**4** can not. This is the reason for the enantioselective inclusion of guests by the chiral host compound.

Unfortunately, however, inclusion crystals which were formed in the absence of MeOH are not suitable for X-ray analysis. Therefore, it is not clear why the other enantiomeric guest is included in the inclusion crystal in the absence of MeOH. In that case, the space of the guest cavity of hosts **2** and **3** is probably different to that formed in the presence of MeOH, wherein the other enantiomeric guest is fitted.

The new chiral host compound **3** [mp 202–203 °C, $[\alpha]_D$ −91.8 (*c* 1.0, MeOH)] was prepared as yellow prisms in 34% yield from optically pure 1-(*o*-chlorophenyl)-1-phenylprop-3-yn-1-ol† and 9,10-dibromoanthracene in the presence of $PdCl_2(PPh_3)_2$ and Et_3N,[5] by a similar procedure to that used for the preparation of **2**.[3]

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Footnotes

† Chiralcel OC and OJ are available from Daicel Chemical Industries Ltd., Himeji, Japan.

Crystal data: orthorhombic, *a* = 18.143(3), *b* = 16.312(3), *c* = 14.519(4) Å; ρ_{calc} = 1.222 g cm^{-3}; *Z* = 4 in space group $P2_12_12_1$, 4244 reflections with $2\theta < 50.0$ were recorded on a four-circle diffractometer using graphite-monochromated Mo-Kα radiation. Of these, 2784 with $I > 3\sigma(I)$ were judged as observed. The structure was solved using SHELX-86 [G. M. Sheldrick: Program for the automatic solution of crystal structures. University of Gottingen, Germany, 1986]. Full-matrix least-squares refinement with anisotropic temperature factors for non-hydrogen atoms and isotropic hydrogens converged to *R* = 0.055 and R_w = 0.079. $(\Delta/\sigma)_{max}$ = 0.26 for non-H and 0.37 for H-atoms, $\Delta\rho_{max}$ = 0.38 and $\Delta\rho_{min}$ = −0.32 eÅ^{-3}. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‡ X-ray crystal structure was drawn according to the method: C. K. Johnson, ORTEP, Oak Ridge National Laboratory Report, ORNL-TM-3794.

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