CH-π Interaction as an Important Driving Force of Host-Guest Complexation in Apolar Organic Media. Binding of Monools and Acetylated Compounds to Resorcinol Cyclic Tetramer As Studied by ^{1}H NMR and Circular Dichroism Spectroscopy

Kenji Kobayashi,[†,1] Yuji Asakawa,[†] Yasuaki Kikuchi,[‡] Hiroo Toi,[†,1] and Yasuhiro Aoyama*[,†,1]

Contribution from the Department of Chemistry, Nagaoka University of Technology, Kamitomioka, Nagaoka, Niigata 940-21, Japan, and Department of Industrial Chemistry, Hachinohe National College of Technology, Tamonoki, Hachinohe, Aomori 031, Japan

Received October 23, 1992

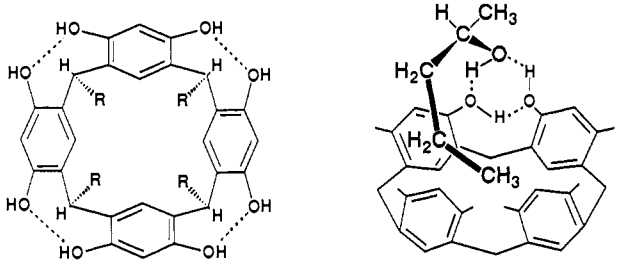
Abstract: The CH-π interaction plays an important role in the complexation involving resorcinol cyclic tetramer **1** in chloroform. Thus, host **1** binds simple monools **4–10** via a cooperation of CH-π and hydrogen-bonding interactions, where the binding constants at 298 K (up to 13 M^{-1}) increase with increasing chain lengths (from ethyl through propyl to butyl) as well as branching in the aliphatic moiety of the guests. In addition, the largest complexation-induced ^{1}H NMR upfield shift for a bound guest occurs at the terminal methyl group, which must therefore be deeply incorporated in the aromatic cavity of the host. The complexes derived from chiral secondary alcohols **10–17** including terpenes and steroids exhibit induced circular dichroism as a result of guest-to-host chirality transfer which is mediated by the CH-π interaction. Borneol (**14**) having three methyl groups to allow a multipoint CH-π interaction forms a particularly stable complex (K = 54 M^{-1}). The acetyl group in a guest is significantly complexation-promoting. This is primarily due to enhanced CH-π interaction involving the polarized C-H bonds of the acetyl group. The binding constants for selected guests are K = 35, 12, 4, and 1 M^{-1} for 3-oxo-1-butanol (simple alcohol having an acetyl group), bornyl acetate (monoacetate having a bulky and highly branched aliphatic moiety), 2,4-diacetoxypentane (simple diacetate), and cholestane (bulky hydrocarbon), respectively.

Introduction

Resorcinol cyclic tetramer **1** (Chart I) is a multidentate host having a bowl-shaped cavity made up of four highly electron-rich benzene rings. It is capable of multiple hydrogen-bonding fixation of such guests as diols,[2,3] sugars,[3,4] and dicarboxylic acids[5] in apolar organic media. The complexation can be conveniently followed by either ^{1}H NMR or circular dichroism (CD) spectroscopy. The former takes advantage of the ring-current effects of the benzene rings of the host, which result in significant complexation-induced upfield shifts of the ^{1}H NMR signals for bound guest.[2,4,5] The latter owes its usefulness to the generation of induced chirality in the multibenzenoid cavity of the host upon binding of a chiral guest.[3] Thus, the benzene rings play phenomenologically important roles in the detection of host-guest complexes. However, their essential contribution to the host-guest complexation still remains to be elucidated.[6]

In the present work, we investigated the interaction of host **1** with various monools and some nonalcoholic derivatives, focusing upon the effects of apolar parts of the guests. We report here that (1) there is indeed a substantial contribution of the guest-host aliphatic-aromatic interaction so that the present monool complexation should be described as a cooperation of CH-π and hydrogen-bonding interactions and (2) the polarized C-H bonds of the acetyl group allow a better CH-π interaction.

Chart I



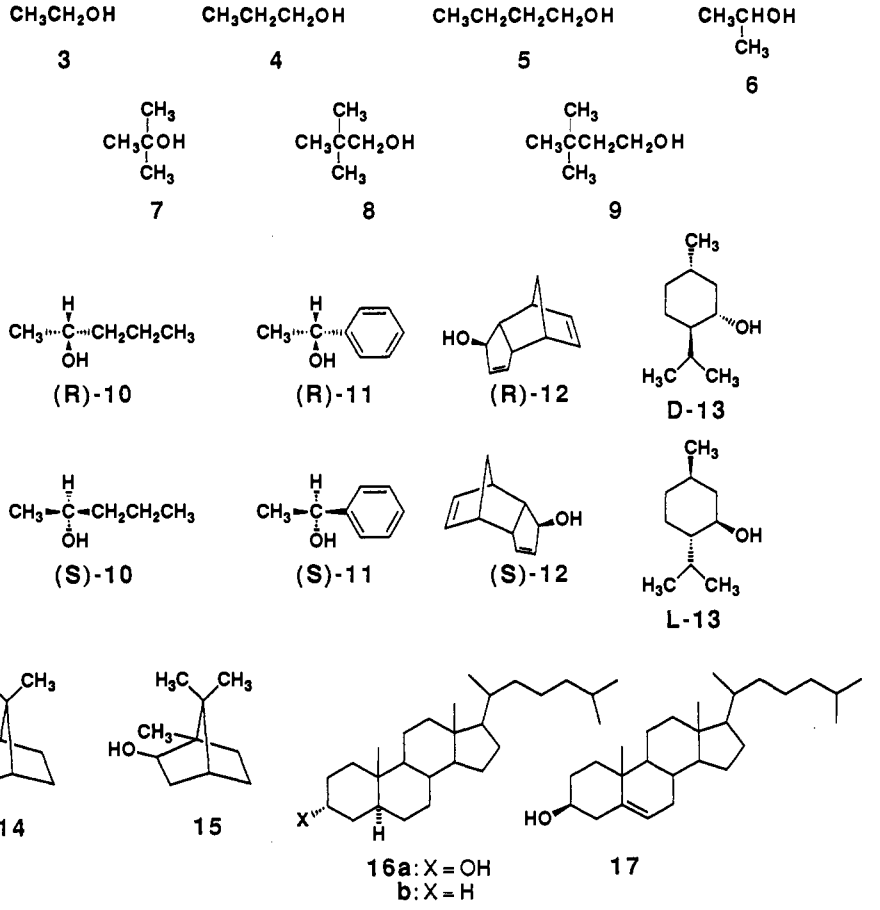
Results and Discussion

^{1}H NMR Study on the Complexation of Simple Monools. The ^{1}H NMR spectrum for a $CDCl_3$ solution of host **1** (10 mM) and 2-pentanol (**10**, Chart II) (150 mM) showed upfield-shifted resonances for bound guest. The respective signals were assigned as shown in Figure 1A by using selectively deuteriated derivatives

† Nagaoka University of Technology.
‡ Hachinohe National College of Technology.
(1) Present address: Section of Bioorganic Chemistry, Department of BioEngineering, Nagaoka University of Technology.
(2) Kikuchi, Y.; Kato, Y.; Tanaka, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1349-1354.
(3) Kikuchi, Y.; Kobayashi, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 1351-1358.
(4) (a) Aoyama, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 634-635. (b) Aoyama, Y.; Tanaka, Y.; Sugahara, S. *J. Am. Chem. Soc.* **1989**, *111*, 5397-5404. (c) Tanaka, Y.; Ubukata, Y.; Aoyama, Y. *Chem. Lett.* **1989**, 1905-1908. (d) Tanaka, Y.; Khare, C.; Yonezawa, M.; Aoyama, Y. *Tetrahedron Lett.* **1990**, *31*, 6193-6196. (e) Kurihara, K.; Ohto, K.; Tanaka, Y.; Aoyama, Y.; Kunitake, T. *J. Am. Chem. Soc.* **1991**, *113*, 444-450.
(5) Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2807-2808.
(6) For previous reports on the complexation of apolar guests by neutral aromatic hosts in halogenated solvents, see: (a) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1986**, *108*, 4230-4232. (b) Canceill, J.; Lacombe, Collet, A. *C. R. Acad. Sci., Ser. II* **1987**, *304*, 815-818. (c) Canceill, J.; Cesario, M.; Collet, A.; Guilhem, J.; Lacombe, L.; Lozach, B.; Pascard, C. *Angew. Chem.* **1989**, *101*, 1249-1251; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1246-1248. (d) Collet, A.; Dutasta, J.-P.; Lozach, B. *Bull. Soc. Chim. Belg.* **1990**, *99*, 617-633.

0002-7863/93/1515-2648$04.00/0

Chart II



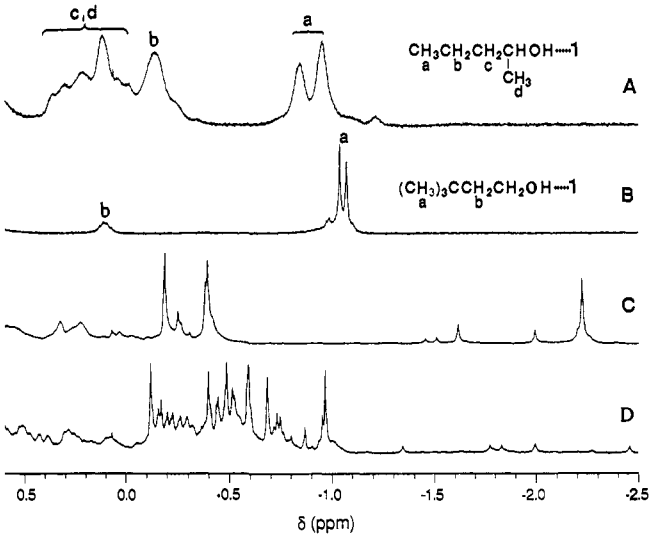


Figure 1. High field portions of the ^1H NMR spectra of complexes of **1**·**10** (A), **1**·**9** (B), **1**·**14** (C), and **1**·**15** (D) in $CDCl_3$. The sample solutions were prepared by adding guest **10** (150 mM), **9** (50 mM), **14** (100 mM), or **15** (100 mM) to a $CDCl_3$ solution of host **1** (10 mM).

such as $CH_3CH(OD)CH_2CH_2CH_3$, $CH_3CD(OH)CH_2CH_2CH_3$, $CD_3CH(OH)CD_2CH_2CH_3$, and $CD_3CH(OH)CH_2CH_2CH_3$. The complexation-induced shifts (CIS; positive value indicates an upfield shift) as a result of the ring-current effects of the benzene rings of the host increase in the order 1-CH_3 and 3-CH_2 (1.4–1.5) < 4-CH_2 (1.6) < 5-CH_3 (1.8–1.9 ppm).[7] The otherwise flexible propyl group in bound 2-pentanol could stay away from the host in order to minimize steric interactions between them. Clearly, however, this is not the case. It swings over into the aromatic cavity of the host, as schematically shown in structure **2** (Chart I).

Host **1** (10 mM) also forms complexes with other simple alcohols. The guests investigated are ethanol (**3**), 1-propanol (**4**), 1-butanol (**5**), 2-propanol (**6**), 2-methyl-2-propanol (*tert*-butanol, **7**), 2,2-dimethyl-1-propanol (neopentanol, **8**), and 3,3-dimethyl-1-butanol (**9**) (Chart II). In every case except for **3**,[9] bound guest exhibited characteristic upfield-shifted resonance(s), as typically shown in Figure 1B for the complex derived from guest **9**. The integrations for these resonances changed with changing [guest], while the chemical shifts remained unaffected, as in the case of diol binding.[2] Thus, the exchange between free guest and complex is slow as compared with NMR time scale even in the present case of relatively weak monool complexation. The 1:1 host–guest stoichiometry was confirmed by the continuous-variation (Job) plots in a usual manner.[2] The binding constants (K) for guests **3**–**10** were obtained by evaluating the integrals of the characteristic methyl-proton resonances for free and bound guests. In Table I are summarized the chemical shift and CIS data as well as K's for the complexes at 298 K. The relative binding abilities of the guests were also evaluated by a competitive method; **4** (0.6), **5** (1), **6** (0.3), **7** (0.5), **8** (1, standard),

(7) For comparison, the largest CIS's for other guests bound to host **1** are ~2.1 (CH_2 of *cis*-1,4-cyclohexanediol in $CDCl_3$),[2] ~3 (1-H of ribose in $CDCl_3$),[4b] ~3 ($CH_2CH_2CH_2$ of glutaric acid in $CDCl_3$),[5] 3.6 (OCH_3 of methyl β-D-glucopyranoside in $CDCl_3$) (Kikuchi, Y.; Tanaka, Y.; Sutarto, S.; Kobayashi, K.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.*, in press), 2.5 (4- and 5-CH_2 of *cis*-1,2-cyclohexanediol in D_2O),[8] and 1.6 ppm (5-CH_3 of fucose in D_2O).[8]

(8) Kobayashi, K.; Asakawa, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* in press.

(9) Ethanol (**3**) does not exhibit any notable upfield shift in the presence of host **1**. This does not necessarily indicate, however, that **3** is not bound to **1**. It might be due to rapid exchange between free and bound forms of the particular guest **3** or due to the short chain-length in guest **3**, which is not sufficient to place the terminal methyl group deeply in the cavity of **1**.

Table I. Binding Constants (K) for the Complexation of Host **1** with Various Guests[a] and Chemical Shifts (δ_{CH_3}) as Well as Complexation-Induced Upfield Shifts ($\Delta\delta_{CH_3}$)[b] for the Methyl Groups of Bound Guests

guest	3[c]	4	5	6	7	8	9	10	23	24	25
K[d] (M^{-1})		2	4	0.6	2	3	13	4	35	13	12
K_{rel}		0.7	1.3	0.2	0.7	1[f]	4.3	1.3	12	4.3	4.0
δ_{CH_3}[e]		−0.21	−0.53	+0.11	−0.26	−0.91	−1.03	−0.85 −0.96	−0.40	g	g
$\Delta\delta_{CH_3}$ (ppm)		1.15	1.47	1.04	1.47	1.82	1.95	1.77 1.88	2.59		

[a] In $CDCl_3$ with [**1**] = 10 mM at 298 K. The K's for guests **4**–**10** were determined by direct binding assay, while those for guests **23**–**25** were obtained by competition (see Experimental Section for detail). [b] Relative to free guest in $CDCl_3$. [c] The methyl-proton resonance undergoes no shift in the presence of host **1**. [d] Errors are within ±25%. [e] Broad singlet for **4**, **5**, and **23**. Very broad singlet for **6**. A number of sharp resonances for **7**, **8**, and **9** (refer to Figure 1B); δ_{CH_3} refers to the most intense one. A couple of broad resonances for **10** (refer to Figure 1A). [f] Standard. [g] Not observed probably because of overlap with the resonance of the host.

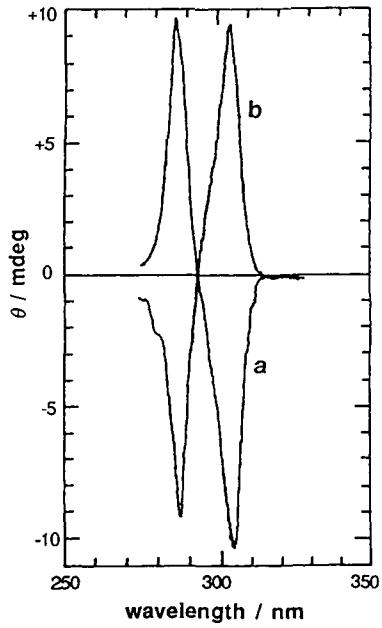


Figure 2. Induced circular dichroism spectra for $CHCl_3$ solutions (0.1-cm path length) of host **1** (1.0 mM) and guest (*R*)-**12** (a) or (*S*)-**12** (b) (100 mM).

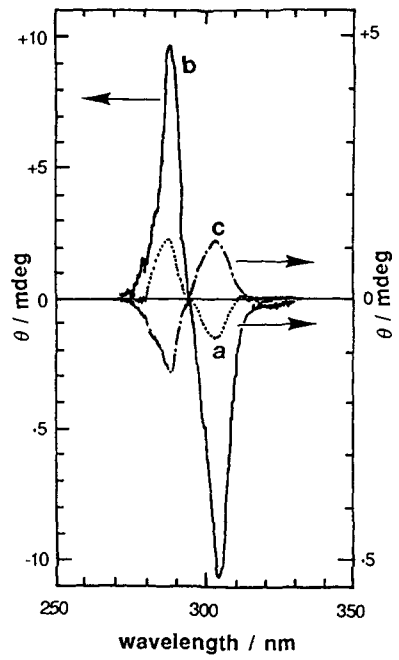


Figure 3. Induced circular dichroism spectra for $CHCl_3$ solutions (0.1-cm path length) of host **1** (1.0 mM) and guest L-**13** (a), **14** (b), or **17** (c) (100 mM).

9 (3.5), and **10** (1). These values are in good agreement with K_{rel}'s obtained by direct binding assay (Table I).

There is a rather big span in K's for otherwise closely related monools **3**–**9**. The binding constants increase with increasing chain lengths, i.e., in the order **3** < **4** < **5** and **7** < **8** < **9**. The binding constants also increase with increasing branching, i.e., in the order **3** < **6** < **7**, **4** < **8**, and **5** < **9**. Clearly, steric effects of the alkyl groups are not important factors. It is also interesting to note that the variation in K's roughly parallels that in CISs for the terminal methyl groups. The overall trends in Table I indicate again that the alkyl groups, bulkier and more branched ones in particular, in guest alcohols promote host–guest complexation by being incorporated in the aromatic cavity of the host.

CD Study on the Complexation of Secondary Chiral Monools. Host **1** also forms complexes with chiral alcohols. The guests investigated include simple secondary alcohols such as (*R*)- and (*S*)-2-pentanol [(*R*)-**10** and (*S*)-**10**] and (*R*)- and (*S*)-1-phenylethanol [(*R*)-**11** and (*S*)-**11**], a tricyclic secondary alcohol (3*R*)- and (3*S*)-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ol [(*R*)-**12** and (*S*)-**12**], terpenes such as D- and L-menthol (D-**13** and L-**13**) and epimeric borneol (**14**) and isoborneol (**15**), and steroids such as epicholestanol (**16a**) and cholesterol (**17**) (Chart II). Every chiral guest in Chart II exhibited complexation-induced highly upfield-shifted ^1H NMR resonances whose CISs were independent of [guest], as above. They were, however, too complicated to be assigned unless in simpler cases. The actual spectra for borneol (**14**) and isoborneol (**15**) are shown in Figure 1C,D. Under these circumstances, the circular dichroism (CD) spectroscopy provides an alternative and very convenient method to follow the complexation. Since host **1** is chromophoric but achiral and a guest is chiral but nonchromophoric, only resulting host–guest complexes are (induced) CD active.[3]

A $CHCl_3$ solution of host **1** (1.0 mM) and an above guest exhibited CD with split Cotton effects. Enantiomers (*R*)-**10** and (*S*)-**10**, (*R*)-**11** and (*S*)-**11**, (*R*)-**12** and (*S*)-**12**, and D-**13** and L-**13** gave spectra which were mirror images to each other, as shown in Figure 2 for (*R*)-**12** and (*S*)-**12**. The spectra for the complexes derived from L-menthol (L-**13**), borneol (**14**), and cholesterol (**17**) as for other typical examples are shown in Figure 3. In Figure 4 are shown Θ/Θ_{sat} or the extents of complexation for solutions of host **1** (1.0 mM) and varying amounts of such guests as (*S*)-**11**, L-**13**, **14**, and **17** under conditions of $[guest]_t/[1]_t \geq 10$ (t = total) at 298 K; Θ is the observed ellipticity for the first Cotton effect at 304 ± 1 nm and Θ_{sat} is the extrapolated one at saturation binding. The titration curves of a saturation behavior indicate a reversible host–guest complexation and were satisfactorily analyzed by the Benesi–Hildebrand treatment. The binding constants obtained are summarized in Table II, together with the signs and molar or observed ellipticities of the first or longer wavelength and the second or shorter wavelength Cotton effects. The binding constant of 6 M^{-1} for guest (*R*)-**10** is in reasonable agreement with the NMR-determined binding constant of 4 M^{-1} for racemic **10** (Table I). In Table II are also

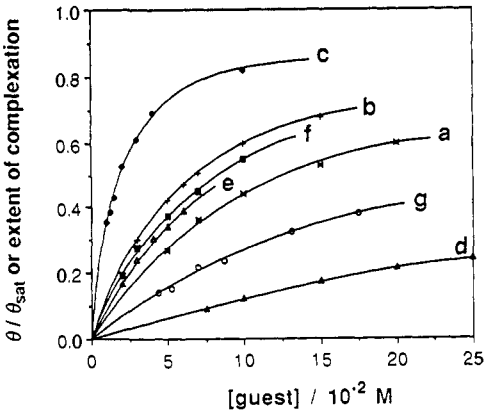


Figure 4. Correlations of Θ/Θ_{sat} with [guest] at 298 K for the complexation of host **1** (1.0 mM) and guest (*S*)-**11** (a), L-**13** (b), **14** (c), **16b** (d), **17** (e), **21** (f), or (*R*,*R*)-**27a** (g) in $CHCl_3$ (0.1-cm path length); Θ is the observed ellipticity of the first Cotton at 304 ± 1 nm and Θ_{sat} is the extrapolated ellipticity at saturation binding.

Table II. Configurations of Hydroxymethine or Acetoxymethine Carbon and Signs of Optical Rotation for Chiral Guests and Signs of Split Cotton Effects, Molar ([θ]) or Observed (θ) Ellipticities, and Binding Constants (*K*) for Host–Guest Complexes[a]

			first Cotton[c,d]		second Cotton[c,e]		
guest	configuration	sign of optical rotation[b]	sign	[θ] or θ	sign	[θ] or θ	*K* (M^{-1})
(*R*)-**10**	*R*	–	–	[θ] = –0.95	+	[θ] = +0.97	6
(*S*)-**10**	*S*	+	+	θ = +0.40	–	θ = –0.45	
(*R*)-**11**	*R*	+	–	[θ] = –3.9	+	[θ] = +4.5	8
(*S*)-**11**	*S*	–	+	[θ] = +4.0	–	[θ] = –4.2	8
(*R*)-**12**	*R*	–	–	θ = –10.3	+	θ = +9.7	
(*S*)-**12**	*S*	+	+	θ = +9.5	–	θ = –9.2	
D-**13**	*S*	+	+	θ = +1.1	–	θ = –1.3	15
L-**13**	*R*	–	–	[θ] = –1.3	+	[θ] = +1.7	15
14	*S*	–	–	[θ] = –13.1	+	[θ] = +11.9	54
15	*R*	–	+	[θ] = +1.2	–	[θ] = –1.0	24
16a	*R*	+	–	[θ] = –2.8	+	[θ] = +3.4	10
16b		+	–	[θ] = –4.3	+	[θ] = +5.4	1
17	*S*	–	+	[θ] = +2.5	–	[θ] = –2.8	11
18		+	+	θ = +1.1		*f*	
21	*S*	–	–	[θ] = –5.5	+	[θ] = +5.0	12
(*S*)-**26a**	*S*	+	+	[θ] = +6.2	–	[θ] = –4.8	3
(*R*,*R*)-**27a**	*R*,*R*	–	–	[θ] = –31	+	[θ] = +29	4
28a	*R*,*S*	+	+	θ = +0.86	–	θ = –0.50	

[a] In $CHCl_3$ at 298 K. [b] Refers to $[\alpha]_D^{25}$. [c] Units: [θ], 10^3·deg·M^{-1}·cm^{-1}; θ, mdeg. The experimental conditions for observing θ are [**1**] = 1.0 mM with a 0.1-cm path length in the presence of a guest (100 mM for (*S*)-**10**, (*R*)-**12**, (*S*)-**12**, and D-**13**, 300 mM for **18**, 50 mM for **21**, or 200 mM for **28a**). For the relation of [θ] and θ, see Experimental Section. [d] λ_{ext} = 304 ± 1 nm. [e] λ_{ext} = 287 ± 1 nm. [f] The second Cotton effect could not be observed because of the overlapping intrinsic CD for guest **18**.

shown the absolute configurations of the OH-carrying asymmetric carbons and the signs of optical rotation of the guests.

Examination of Table II again reveals a big span in the binding constants for the present secondary alcohol guests. Bulkier aliphatic moieties as in guest **14** might suppress host–guest complexation for steric reasons. Actually, however, they tend to lead to more stable complexes. The ^1H NMR spectrum for the complex of the highest affinity guest **14** shows three sharp and upfield-shifted resonances assignable to the three methyl groups (Figure 1C). The CIS for one of them at δ –2.23 is as large as ~3 ppm, indicating its deep incorporation into the aromatic cavity of host **1**. On the other hand, the lowest-affinity guest **10** exhibits the largest CIS of 1.8–1.9 ppm for the 5-CH_3 group (Figure 1A and Table I).

(10) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA 1983.

Chart III

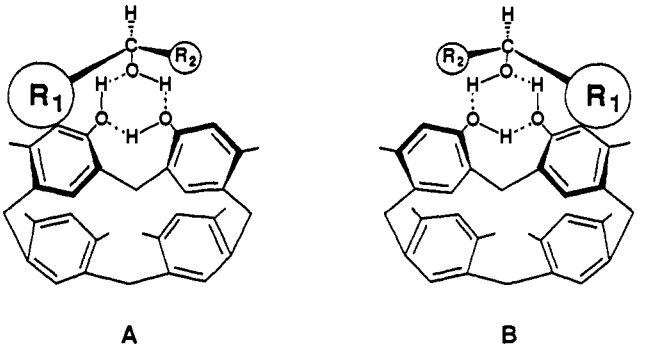
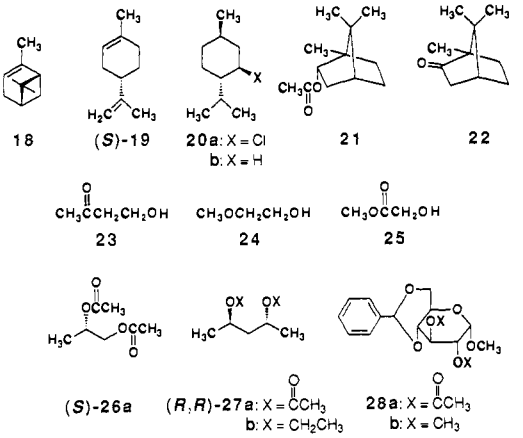


Chart IV



Multichromophoric chiral molecules exhibit CD with split Cotton effects as a result of exciton coupling.[10] The appearance of induced CD suggests that a local C_2 chirality is generated in host **1** upon binding of a chiral guest.[3] The direction of the chiral deformation, i.e., A or B in Chart III, then determines the signs of the Cotton effects.[11] It is important here to refer to the fact that the OH group in a guest is not necessarily essential for the chirality induction in the host. Thus, such chiral hydrocarbons as cholestane (**16b**, Chart II) and α-pinene (**18**) (Chart IV) in a large excess amount are effective in inducing CD (Table II). Analysis of the titration data for guest **16b** (Figure 4) gave a binding constant of K = 1 M^{-1} (Table II). Such chiral guests as (*S*)-limonene [(*S*)-**19**] and L-menthyl chloride (**20a**) (Chart IV), on the other hand, failed to give induced CD. Although the suggested hydrocarbon complexation still remains to be further characterized, it is essential that the interaction of the present host and a sufficiently bulky and conformationally fixed polycyclic hydrocarbon guest such as **16b** and **18** results in some kind of chiral deformation of the former.

Importance of the CH–π Interaction. The NMR and CD results presented above clearly indicate that there is an attractive force between the aliphatic and aromatic moieties of guest and host, respectively. This attractive force most probably derives from an attractive aliphatic–aromatic or CH–π *interaction*, possibly assisted by solvophobic forces.[12] The term "CH–π interaction" is used here only to emphasize that aliphatic and aromatic moieties are involved. It may belong to the general class of the van der Waals interactions. Characterization of this interaction, however, should be deferred until further information is available.

(11) Examination of various chiral alcohols indicates that the signs of split Cotton effects are more or less correlated with the absolute configuration of the chiral hydroxymethine carbon. Borneol (**14**) and isoborneol (**15**) are exceptions in this respect. Details will be reported elsewhere.

(12) In view of good solubilities of the present guests in chloroform, solvophobic effects, if any, would play only a minor role. However, this point must await experimental information, since it is known that the mixing of isobutane with carbon tetrachloride is substantially endothermic (ca. 0.9 kcal/mol in ΔH). We are grateful to the referee for this suggestion.

The CH–π interaction involving aliphatic CH moieties is well documented[13] as either a conformation-controlling intramolecular process or a crystal-structure controlling intermolecular force, especially for inclusion complexes of calixarene derivatives.[14] In solutions in organic media, solvent molecules come into play as a competitor.[14g,15] Generally, thus, the van der Waals interaction if any provides only a very weak binding force in solutions. However, there are several previous reports on the binding of apolar guests by neutral aromatic hosts in halogenated solvents.[6,16] In fact, Collet et al. have shown that halomethanes and hydrocarbon isobutane can be incorporated fairly strongly in a size-selective manner in a *desolvated* cavity of the cryptophane host, leading to "van der Waals molecules".[6] The aromatic cavity of host **1** is undoubtedly open to solvation. The present finding indicates that when coupled with hydrogen-bonding (vide infra) the CH–π interaction involving even an unactivated aliphatic hydrocarbon moiety and highly electron-rich dialkyldihydroxybenzene rings provides a substantial driving force for intermolecular host–guest association in apolar organic media.[17] In aqueous solutions, the *apolar* interaction is much more evident. There are a couple of recent examples of the CH–π interaction involving either highly electron-rich aromatic rings of a host[17] or highly polarized C–H bonds in a guest in water.[18] Its signifcance, however, is often spurred because of concurrent solvophobic, i.e., hydrophobic effects.

Cooperation of Hydrogen-Bonding and CH–π Interactions. The involvement of host–guest hydrogen-bonding in the complexation of monool guests **4–17** was confirmed by examining the ^{1}H NMR behaviors of nonalcoholic reference compounds such as cholestane (**16b**) and *trans*-1-isopropyl-4-methylcyclohexane (**20b**) (Chart IV). They did not give any distinct upfield-shifted resonances in the higher field ($\delta < 0$) under conditions of [**1**] = 10 mM and [**16b** or **20b**] = 200 mM. In addition, no resonance of **16b** or **20b** (10 mM) underwent upfield shift in the presence of an equimolar amount of **1** (vide infra). Thus, the present host–guest complexes should be described as multipoint adducts involving the OH–OH hydrogen-bonding and the CH–π interactions, as schematically shown in structure **2** for adduct **1**·**10** (Chart I). Their relative contributions can also be estimated. If it is assumed that all the secondary alcohols **10–17** (Chart II) form a similar hydrogen bond with the host, the free energy changes for the complexation of the lowest-affinity guests **10** (K = 4 M^{-1} from NMR titration (Table I) and 6 M^{-1} from CD titration (Table II)) provide an upper limit for the contribution of hydrogen bonding (HB);

$$-\Delta G°_{HB} \leq -\Delta G°(\mathbf{10}) = RT \ln K(4\text{–}6) = \sim 1 \text{ kcal/mol (298 K)}$$

The selectivity for a bulkier alcohol relative to **10** then gives a lower limit for the contribution of CH–π interaction;

$$-\Delta G°_{CH\text{–}\pi} \geq \Delta\Delta G°[\mathbf{X}/\mathbf{10}] = RT \ln K_X/K_{10} = 0.3\text{–}1.4 \text{ kcal/mol for } \mathbf{X} = \mathbf{11} \text{ and } \mathbf{13\text{–}17}.$$

Thus, for the binding of borneol (**14**), the highest affinity guest, $-\Delta G°_{CH\text{–}\pi} \geq 1.4$ kcal/mol is comparable with or even greater than $-\Delta G°_{HB} \leq 1$ kcal/mol. In relevance to this, it is interesting to note that non-hydroxyl derivatives of **14** such as bornyl acetate (**21**; K = 12 M^{-1} and $-\Delta G°$ = 1.5 kcal/mol) and camphor (**22**) (Chart IV) can also be bound to host **1** (vide infra).

It is also interesting at this point to reevaluate the previously studied complexation of *cis*-1,4-cyclohexanediol ($K = 1.04 \times 10^3$ M^{-1} and $-\Delta G°$ = 4.11 kcal/mol)[2] and glutaric acid ($K = 1.2 \times 10^5$ M^{-1} and $-\Delta G°$ = 6.9 kcal/mol).[5] The enhanced stability of their complexes should indeed primarily be ascribed to oriented host–guest two-point hydrogen-bonding, judging from the relatively small K observed and CH–π contribution estimated even for best-bound one-point guest **14**. Nevertheless, the *selectivity* in the diol,[2] dicarboxylic acid,[5] and sugar complexation[4] could be controlled by the CH–π interaction. The best-fit multipoint hydrogen-bonded host–guest complexes have enforced CH–π proximity.

The cooperation of hydrogen bonding and CH–π interactions (referring to structure **2**) explains not only the 1:1 host–guest stoichiometry[2-5] but also the chain-length dependence of both CISs and K's for simple alcohols (Table I).[19] An examination of CPK molecular models indicates that the terminal methyl group of 1-butanol hydrogen-bonded to the host as in structure **2** can reach the bottom of the aromatic cavity. In the case of 1-propanol, however, the separation of 1-OH and 3-CH_3 groups seems to be not long enough for the latter to be deeply bound in the cavity. It is also important to note that the complexes derived from epimers **14** and **15** have opposite signs of split Cotton effects (Table II) and remarkably different ^{1}H NMR spectra (Figure 1C,D). Thus, the configuration of the OH group governs the actual mode of incorporation of the aliphatic bornyl moiety in the cavity.[11] This is consistent with the concurrent polar (hydrogen bonding) and apolar (CH–π) interactions.

The dual interaction in the binding of alcoholic guests to host **1** bears a remarkable relevance to the biological sugar–protein complexation. X-ray crystallography[20] indicates that sugars are always bound to proteins via a collaboration of the hydrogen bonding between sugar OH groups and polar moieties of the protein and the stacking or even sandwiching[20e] of sugar CH moieties with aromatic amino acid side chains such as the indole ring of the tryptophan residue.

Enhanced CH–π Interaction of the Acetyl Group. Host **1** also forms complexes with 3-oxo-1-butanol (**23**), ethylene glycol monomethyl ether (**24**), and methyl glycolate (**25**) (Chart IV). They are oxo/oxa analogs of parent 1-butanol (**5**), having the same or similar chain-length as **5**. The binding constants obtained by a competitive method are K = 35, 13, 12, and 4 M^{-1} for **23**, **24**, **25**, and **5**, respectively (Table I). The oxygen functionalities introduced, especially the carbonyl group, might stabilize the complexes by forming an additional hydrogen bond to the host. This is, however, not the case since there is practically no difference in K's for methyl ether **24** and methyl ester **25**. Thus, the

(13) Nishio, M.; Hirota, M. *Tetrahedron* **1989**, *45*, 7201–7245.

(14) (a) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005–1007. (b) Ungaro, R.; Pochini, A.; Andreetti, G. D.; Domiano, P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 197–201. (c) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B. L. *J. Org. Chem.* **1986**, *51*, 3581–3584. (d) Bott, S. G.; Coleman, A. W.; Atwood, J. L. *J. Chem. Soc., Chem. Commun.* **1986**, 610–611. (e) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Marverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229–2237. (f) Andreetti, G. D.; Ori, O.; Ugozzoli, F.; Alfieri, C.; Pochini, A.; Ungaro, R. *J. Incl. Phenom.* **1988**, *6*, 523–536. (g) Soncini, P.; Bonsignore, S.; Dalcanale, E.; Ugozzoli, F. *J. Org. Chem.* **1992**, *57*, 4608–4612. (h) Atwood, J. L.; Bott, S. G.; Jones, C.; Raston, C. L. *J. Chem. Soc., Chem. Commun.* **1992**, 1349–1351. For reviews, see: Andreetti, G. D.; Ugozzoli, F. In *Calixarenes, A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Ed.; Kluwer Academic Publishers: Dordrecht, 1991; pp 87–123.

(15) (a) Diederich, F.; Dick, K.; Griebel, D. *J. Am. Chem. Soc.* **1986**, *108*, 2273–2286. (b) Diederich, F. *Angew. Chem.* **1988**, *100*, 372–396; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386.

(16) For the encapsulation of relatively small guests in carcerand hosts, see: (a) Cram, D. J.; Stewart, K. D.; Goldberg, I.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2574–2575. (b) Tanner, M. E.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1990**, *112*, 1659–1660. (c) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167–2172 and references cited therein.

(17) A highly water-soluble tetrasulfonate derivative of host **1** binds relatively hydrophobic sugars in water. The driving force of this complexation is more likely due to attractive guest–host CH–π interaction rather than a simple hydrophobic effect (ref 8).

(18) Petti, M. A.; Shepodd, T. L.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825–6840.

(19) A similar selectivity was observed in the gas-phase complexation involving cavitand derivatives of host **1** (R = C_6H_{13}): Dalcanale, E.; Vincenti, M. presented at Workshop on Calixarenes and Related Compounds, Mainz, 1991. Cf.: Vincenti, M.; Dalcanale, E.; Soncini, P.; Guglielmetti, G. *J. Am. Chem. Soc.* **1990**, *112*, 445–447.

(20) (a) Phillips, D. C. *Sci. Am.* **1966**, *215*, 78–90. (b) Chipman, D. M.; Sharon, N. *Science* **1969**, *165*, 454–465. (c) Quiocho, F. A.; Vyas, N. K. *Nature* **1984**, *310*, 318–386. (d) Vyas, N. K.; Vyas, M. N.; Quiocho, F. A. *Nature* **1987**, *327*, 635–638. (e) Vyas, N. K.; Vyas, M. N.; Quiocho, F. A. *Science* **1988**, *242*, 1290–1295. (f) Quiocho, F. A.; Wilson, D. K.; Vyas, N. K. *Nature* **1989**, *340*, 404–407. (g) Bundle, D. R. *Pure Appl. Chem.* **1989**, *61*, 1171–1180. (h) Lemieux, R. U. *Chem. Soc. Rev.* **1989**, *18*, 347–374. (f) Sharon, N.; Lis, H. *Chem. Britain* **1990**, 679–682.

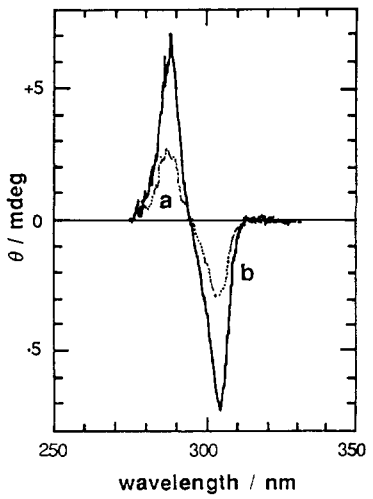


Figure 5. Induced circular dichroism spectra for $CHCl_3$ solution (0.1-cm path length) or host **1** (1.0 mM) and guest **21** (a) (100 mM) or (*R*,*R*)-**27a** (b) (87 mM).

complexation-promoting effects of the acetyl group in oxy ketone **23** must be primarily ascribed to the polarized methyl group (C–H$^{\delta+}$) activated by the carbonyl moiety.[21] This methyl group probably allows a better CH–π interaction, as compared with that in guest **5**, with the highly electron-rich dialkyldihydroxybenzene rings of the host. In accord with this, bound oxy ketone **23** shows the ^{1}H NMR resonance for the acetyl–methyl protons at δ –0.40; this corresponds to a CIS of 2.59 ppm, which is larger than any of those for nonactivated methyl groups in simple monools **4**–**10** (Table I). This NMR result also confirms that ketone **23** is bound as such and not as enol.

Complex formation was also detected for diacetates of some chiral diols such as (*S*)-1,2-diacetoxypropane [(*S*)-**26a**], (2*R*,4*R*)-2,4-diacetoxypentane [(*R*,*R*)-**27a**], and methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**28a**). The resulting complexes exhibited induced CD with split Cotton effects, as typically shown in Figure 5 for (*R*,*R*)-**27a**. In marked contrast, the corresponding alkoxy derivatives such as (*R*,*R*)-**27b** and -**28b** were CD-silent. The binding constants obtained by CD titration as above (Figure 4 for (*R*,*R*)-**27a**) are $K_{26a} = 3$ and $K_{27a} = 4$ M^{-1}, which are significantly smaller than those for parent diols; K = 71 and 42.9 M^{-1} for 1,2-propanediol[3] and 2,4-pentanediol,[2] respectively.

A more essential difference between alcoholic and nonalcoholic guests lies in the kinetic aspect of the complexation. As referred to above, every alcoholic guest which is bound to host **1** via multiple interaction involving the hydrogen bonding exhibits definite complexation-induced ^{1}H NMR upfield shifts (Figure 1), irrespective of the magnitude of K; the exchange between free guest and complex is slow as compared with NMR time scale. On the other hand, hydrogen bonding is not involved or only plays a minor role in the complexation of acetates **26a**, **27a**, and **28a** and chiral hydrocarbons **16b** and **18**; the exchange between free guest and complex in this case is fast so as only to give averaged NMR signals. When such a guest is present in a large excess amount to allow substantial complexation of the host, *observed* CISs for the guest were too small to be detected. Bornyl acetate (**21**) is remarkable in this respect. It binds to host **1** (K = 12 M^{-1}, Table II) more strongly than simple monools **4**–**8** and **10** (Table I). The resulting complexes not only exhibits induced CD (Figures 4 and 5) but also shows highly upfield-shifted ^{1}H NMR resonances, whose CISs are independent of [**21**] in a similar manner as in the case of parent borneol (**14**) (Figure 1C).[22] Thus, the multipoint CH–π interaction involving the bornyl moiety stabilizes the complex at least partly by significantly slowing down the decomplexation rate.

(21) The pK_a of acetone is ~20.

(22) Similar upfield-shifted ^{1}H NMR resonances were observed for the complex of camphor (**22**). Guest **22** in an excess amount shows an intrinsic and intense CD at ~300 nm. This prevented induced CD for the camphor complex from being observed.

Concluding Remarks

The formation of *hydrogen-bonded* complexes between host **1** and monool guests in chloroform actually involves a substantial contribution (up to ca. 1.4 kcal/mol) of the attractive guest–host CH–π interaction. Bulkier and more branched alkyl groups and the polarized CH_3 moiety in the acetyl group are complexation-promoting. The significance of the present CH–π interaction is 3-fold. First, it gives rise to a sizable selectivity that arises from the difference in aliphatic hydrocarbon moieties of the guests. This may also be true for the more stable diol,[2,3] dicarboxylic acid,[5] and sugar complexes.[4] They have *enforced* CH–π proximity as a result of multiple host–guest hydrogen-bonding. Second, the CH–π interaction mediates the chirality transfer from guest to host. Asymmetric incorporation of alkyl groups of a chiral secondary alcohol in the cavity generates a chiral deformation or a local C_2 chirality in the latter. The chirality thus induced in the host gives characteristic CD spectra. Very weak complexation of chiral hydrocarbon guests can be sensitively detected in this manner. Third, enhanced CH–π interaction involving polarized C–H bonds provides a general strategy for the binding of polar but nonhydroxylic compounds, especially acyl derivatives, in organic media. Further work, particularly on gas-phase binding, solvent effects including guest–solvent interactions, H/D isotope effects, and thermodynamics, is definitely required in order to reveal detailed nature of the present *CH*–π interaction, i.e., whether it, in the form of the general van der Waals interaction, is based on dispersion forces as a result of dipolar interactions or some other factor(s) come into play.

Experimental Section

Materials. Host **1** was prepared as described.[4b] All of the alcohols **3**–**17** and **23**–**25** except (*R*)- and (*S*)-**12**, **15**, and **16a**, ketone **22**, and hydrocarbons **16b** and **18**–**20** were commercial products of the highest grades. Chiral hydrocarbons **16b**, **18**, and **19** were carefully purified by means of column chromatography on silica gel with pentane as eluant to remove oxygen-functionalized impurities. Tricyclic dienol **12** was obtained and resolved according to a literature method.[23] Isoborneol (**15**) was prepared by the reduction of camphor (**22**) with lithium tri-*sec*-butylborohydride in THF[24] and purified by recrystallization from a mixture of petroleum ether and hexane. Epicholestanol (**16a**) was similarly obtained by the reduction of cholestanone and purified by recrystallization from ethanol. The epimeric (diastereomeric) purities of these were almost 100% as judged by ^{1}H NMR and/or gas chromatographic analyses. Acetates **21**, (*S*)-**26a**, (*R*,*R*)-**27a**, and **28a** and ethers **27b** and **28b** were obtained, respectively, by the acetylation (acetic anhydride and pyridine) and alkylation (NaH and alkyl iodide in DMF) of parent alcohols[3] in usual manners. The products were purified by means of column chromatography on silica gel followed by recrystallization in case of **28a** and **28b** from ether–hexane and hexane, respectively.

Deuteriated Derivatives of Racemic 2-Pentanol (10). 2-Pentanol-*O-d* was obtained (68%) by the repeated (three times) H–D exchange of compound **10** (10 g) in D_2O (10 mL) for 24 h. 2-Pentanol-*2-d* was prepared (64%) by the reduction of 2-pentanone (4.1 g) with $NaBD_4$ (1.0 g) in D_2O (20 mL) for 24 h. 2-Pentanol-*1,1,1,3,3-d*$_5$ was obtained (65%) as follows. A solution of 2-pentanone (10 g) and NaOD (0.1 g) in D_2O (20 mL) was stirred at room temperature for 24 h. This procedure was repeated two more times for the organic layer that separated upon addition of brine. The pentadeuteriated ketone thus prepared was reduced with $NaBH_4$ (2.1 g) in H_2O (20 mL) for 24 h. Workup gave the pentadeuteriated alcohol. 2-Pentanol-*1,1,1-d*$_3$ was obtained (58%) by the Grignard

(23) (a) Tanaka, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1987**, 271–272. (b) Tanaka, S.; Inomata, K.; Ogasawara, K. *Chem. Lett.* **1989**, 359–362.

(24) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159–7161.

reaction of butanal (2.0 g) with CD_3MgI prepared from CD_3I (5.0 g) and Mg (0.92 g) in diethyl ether.

^{1}H NMR Spectroscopy. ^{1}H NMR spectra were taken at 298 K with the same machine as described earlier.[2] Upon binding to host **1** in $CDCl_3$, alcoholic guests **3–10** exhibited characteristic upfield-shifted ^{1}H NMR resonances, which represented nonaveraged, intrinsic signals for the resulting complexes. The concentration of the complex was evaluated by referring to the integration for the terminal methyl-proton resonance which was readily assigned. Sample solutions for continuous variations contained host **1** and compound **9** as a representative guest, keeping $[\mathbf{1}]_t + [\mathbf{9}]_t$ constant at 20 mM. Plots of $[\mathbf{1}\cdot\mathbf{9}]$ vs mole fractions of **1** (f) showed a maximum at $f = 0.5$, indicating a 1/1 host/guest stoichiometry $[\mathbf{1}\cdot\mathbf{9}]$/mM = 0, 0.72, 1.04, 1.18, 1.26, 1.21, 1.06, 0.85, and 0 at f = 1.0, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, and 0, respectively.

Sample solutions for the determination of binding constants contained a fixed amount of host **1** (10 mM) and varying amounts of guest (10–100 mM). The binding constants were calculated according to $K = [\text{complex}]/[\mathbf{1}][\text{guest}]$, where $[\mathbf{1}] = [\mathbf{1}]_t - [\text{complex}]$ and $[\text{guest}] = [\text{guest}]_t - [\text{complex}]$, respectively ($t$ = total), and [complex] was evaluated as above. The K values shown in Table I are the averages of those obtained at least four different guest concentrations. Some typical data are as follows. For guest **8**, K = 2.8, 2.9, 2.8, 2.8, and 2.6 M^{-1} at $[\mathbf{8}]_t$ = 10, 20, 40, 60, and 100 mM, respectively, and $K_{av} = 2.8 \pm 0.2$ M^{-1}. For guest **9**, K = 15, 14, 13, and 11 M^{-1} at [**9**] = 20, 30, 40, and 50 mM, respectively, and $K_{av} = 13 \pm 2$ M^{-1}. Competitive guest binding using a ternary system of host **1** (10 mM), a guest alcohol (50 mM), and standard guest (**8** in most cases and **9** in some cases) (50 mM) was also carried out by referring to the integrations for the respective methyl-proton resonances for the resulting two complexes.

The binding of oxy ketone **23** was analyzed in a similar manner as above. On the other hand, the methyl-proton resonances for the complexes derived from methyl ether **24** and methyl ester **25** could not be detected probably because of overlap with the intense resonances of the host. Under these circumstances, the binding constants for guests **23–25** were evaluated by another competitive method using a ternary system of the host (10 mM), guest **X** (**X** = **23–25**) (100 mM), and standard guest **8** (100 mM). The concentration of complex **1·8** is readily known from the integration of the methyl-proton resonance thereof and [**1**] is obtained according to $K_8 = [\mathbf{1}\cdot\mathbf{8}]/[\mathbf{1}][\mathbf{8}] = 3$ M^{-1} (Table I), where $[\mathbf{8}] = [\mathbf{8}]_t - [\mathbf{1}\cdot\mathbf{8}]$. The binding constant for guest **X** is calculated according to $K_X = [\mathbf{1}\cdot\mathbf{X}]/[\mathbf{1}][\mathbf{X}]$, where $[\mathbf{1}\cdot\mathbf{X}] = [\mathbf{1}]_t - [\mathbf{1}] - [\mathbf{1}\cdot\mathbf{8}]$ and $[\mathbf{X}] = [\mathbf{X}]_t - [\mathbf{1}\cdot\mathbf{X}]$.

CD Spectroscopy. CD spectra were obtained with a JASCO-J-500C spectropolarimeter at 298 K. For the determination of binding constants, a series of $CHCl_3$ solutions containing host **1** (1.0 mM) and varying amounts of a guest were prepared in a cell of 0.1-cm path length. The concentrations of guest were so chosen as to meet the Benesi–Hildebrand conditions ($[\text{guest}]_t/[\text{host}]_t \geq 10$). The intrinsic CD for unsaturated guest alcohols extended into the 290-nm region, where the second Cotton effect for the derived complexes appeared. The contribution of intrinsic CD was subtracted computationally. In every case, the Benesi–Hildebrand plots of $[\mathbf{1}]_t l/100\Theta$ vs $1/[\text{guest}]_t$ (according to $[\mathbf{1}]_t l/100\Theta = 1/K[\Theta]\cdot 1/[\text{guest}]_t + 1/[\Theta]$ gave an excellent straight line; l is the light path length (cm). The binding constants (K) and molar ellipticities ($[\Theta]$) evaluated from the slopes and intercepts are summarized in Table II. At saturation binding, $\Theta_{sat} = [\Theta][\mathbf{1}]_t l/100 = 10^{-6}[\Theta]$. When Θ is expressed in millidegrees, then $\Theta_{sat} = 10^{-3}[\Theta]$. Figure 4 shows some typical correlations of Θ/Θ_{sat} vs $[\text{guest}]_t$. The actual titration data for other guests are as follows, $[\text{guest}]_t$, mM (Θ regardless of the sign, mdeg): 50 (0.23), 70 (0.28), 80 (0.31), 100 (0.39), 120 (0.40) for (*R*)-**10**; 23 (0.54), 30 (0.64), 40 (0.87), 50 (0.94), 60 (1.04) for **16a**; 50 (0.75), 60 (0.84), 72 (1.04), 100 (1.34), 150 (1.77) for **26a**.

Acknowledgment. We are grateful to Dr. K. Awano (Nagaoka National College of Technology) for the generous gift of compounds (*R*)-**12** and (*S*)-**12**. We also thank Professors K. Nakanishi (Columbia University), R. Ungaro (University of Parma), J. L. Sessler (University of Texas at Austin), and J. L. Atwood (University of Alabama) for helpful comments.