and then analyzed by GLC. This analysis indicated complete conversion of the pyridine to pyridine *N*-oxide. GLC conditions: column, DB-210, temp 1, 60 °C; time 1, 5 min; rate 1, 20 °C/min; temp 2, 200 °C; time 2, 5 min; injector and detector temp, 250 °C; inlet pressure, 24 psi. Retention times: pyridine 2.7 min, pyridine *N*-oxide 12.6 min. Cyclohexanone was removed at room temperature and reduced pressure to give a very pale yellow liquid. Purification of the residue by flash chromatography on Kieselgel using 5-20% methanol in CH_2Cl_2 afforded pyridine *N*-oxide as a white crystalline solid (0.217 g, 97% yield), mp 60-65 °C (sealed tube) (lit.[24] mp 65-66 °C). ^1H NMR ($CDCl_3$): δ 7.27-7.38 (m, 3 H), 8.21-8.29 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 125.59 (C-4), 126.79 (C-3,5), 138.86 (C-2,6). Mass spectrum (EI, 70 eV): 96 (M + 1, 5), 95 (M^+, 100), 79 (52), 78 (12), 68 (9), 52 (29), 51 (18). Exact mass calcd for C_5H_5NO: 95.09.

i. **1-Adamantanol and Adamantane-1,3-diol.** To a cold (-10 °C), magnetically stirred solution of adamantane in 5 mL of cyclohexanone was added a solution of 0.25 M cyclohexanone dioxirane in cyclohexanone (50 mL, 12.5 mmol) and CH_2Cl_2 (25 mL). The progress of the reaction was followed by GLC. This analysis indicated conversion of adamantane to 1-adamantanol (42%) and adamantane-1,3-diol (57%) in 6 h. Traces of 1,3,5-trihydroxyadamantane and 1,3,5,7-tetrahydroxyadamantane were also observed. GLC conditions: column, DB-210; temp 1, 60 °C; time 1, 5 min; rate 1, 20 °C/min; temp 2, 200 °C; time 2, 5 min; injector and detector temp, 250 °C; inlet pressure, 24 psi. Retention times: adamantane, 5.9 min, 1-adamantanol, 10 min, adamantane-1,3-diol, 12.4 min. 1-Adamantanol: The mass spectrum was identical to that of an authentic sample.[25] Adamantane-1,3-diol: The mass spectrum was identical to that of an authentic sample.[25]

j. **7-Oxabicyclo[4.1.0]heptane.** To a cold (-20 °C, CO_2/CCl_4 bath), magnetically stirred solution of cyclohexene in 1 mL of cyclohexanone was added a solution of 0.25 M cyclohexanone dioxirane in cyclohexanone (6 mL, 1.5 mmol). The progress of the reaction was followed by GLC. This analysis indicated complete conversion (>99%) of the cyclohexene to cyclohexene oxide in 10 min. GLC conditions: column, DB-210; temp 1, 100 °C; time 1, 5 min; rate 20 °C/min; temp 2, 200 °C; time 2, 5 min; injector and detector temp, 250 °C; inlet pressure, 24 psi. Retention times: cyclohexene, 1.1 min, cyclohexene oxide, 4.9 min. The mass spectral data of the product were identical to those of an authentic sample of cyclohexene oxide.

k. ***cis*-4,5-Epoxyoctane.** To a cold (-20 °C, CO_2/CCl_4 bath), magnetically stirred solution of *cis*-4-octene (0.842 g, 0.75 mmol) in 1 mL of cyclohexanone was added a solution of 0.25 M cyclohexanone dioxirane in cyclohexanone (6 mL, 1.5 mmol). The progress of the reaction was followed by GLC. This analysis indicated that the *cis*-4-octene had been completely converted to the oxide in 10 min. GLC conditions: column, DB-210; temp 1, 100 °C; time 1, 5 min; rate 1, 20 °C/min; temp 2, 200 °C; time 2, 5 min; injector and detector temp, 250 °C; inlet pressure, 24 psi. Retention times: *cis*-4-octene, 1.4 min, *cis*-4-octene oxide, 6.7 min. The mass spectral data were identical to those of an authentic sample of the oxide.

l. ***trans*-4,5-Epoxyoctane.** The procedure used for the cis compound was followed. The time required for complete conversion of the *trans*-4-octene to the trans oxide was 1 h. Using the same GLC conditions the retention times were as follows: *trans*-4-octene, 1.3 min, *trans*-4-octene oxide, 6.3 min. Mass spectrum (EI, 70 eV): *m/z* 128 (M^+, 0.1), 113 (2), 110 (1), 99 (14), 85 (6), 81 (9), 72 (62), 57 (100), 56 (22), 55 (63), 43 (38), 41 (35). Exact mass calcd for $C_8H_{16}O$ 128.22.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health (Grant No. ES01984). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The Varian XL-300 NMR spectrometer was purchased with partial support from the National Science Foundation.

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Complexation of Chiral Glycols, Steroidal Polyols, and Sugars with a Multibenzenoid, Achiral Host As Studied by Induced Circular Dichroism Spectroscopy: Exciton Chirality Induction in Resorcinol-Aldehyde Cyclotetramer and Its Use as a Supramolecular Probe for the Assignments of Stereochemistry of Chiral Guests[1]

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Received July 5, 1991

Abstract: Resorcinol-dodecanal cyclotetramer **1** as an achiral host in chloroform forms hydrogen-bonded complexes with a variety of chiral di(poly)ols (**2**-**24**) including steroids and sugars. The complexation processes can be followed very conveniently by the induced circular dichroism (CD) spectroscopy. The binding constants as determined by CD titration increase in the order **15** (steroidal monool, $K = 8.7\ M^{-1}$) < **3**, **6**, and **8** (acyclic glycols, $(4.9-7.1 \times 10) < 9\alpha$, 10α, **12**, and **13** (cyclic glycols and steroidal diols, $(0.94-2.7) \times 10^2$) < **11** (steroidal triol, 6.9×10^2). This order reflects the extents of multiple host-guest hydrogen-bonding interactions. All of the resulting complexes exhibit CD with split Cotton effects as a result of exciton chirality induction in otherwise symmetric **1** upon binding of a chiral guest. The signs of split Cotton effects for complexes derived from glycols are correlated with the chiralities or absolute configurations of the guests, while those for sugar complexes are governed by the ring conformations (*C*1 or 1*C*) of sugar pyranoses. These results suggest that host **1** can be used as a novel, supramolecular probe for the assignments of stereochemistry of chiral guests.

Circular dichroism (CD) is specific to chiral molecules that absorb light. When a chiral molecule has two or more light-absorbing units (chromophores), exciton coupling therein results in split Cotton effects, the signs of which can be correlated with the absolute structure of the molecule. The stereochemistry of

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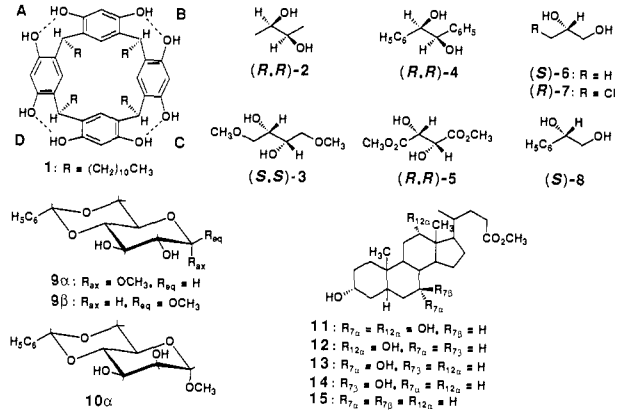
Chart I



chiral molecules can thus be elucidated via the *exciton chirality method*.[3] CD spectroscopy also finds unique application in the field of host–guest complexation. When a host is chiral but nonchromophoric (e.g., cyclodextrins) and a guest is achiral but chromophoric, only the host–guest complex is CD (induced CD) active.[4]

Resorcinol–dodecanal cyclotetramer **1** is a highly *rigid and symmetric* host compound having four hydrogen-bonding sites (A–D) which are linked together by a *m*-phenylene bridge. Host **1** has been shown to bind various di- and polyhydroxyl guests including sugars[5] via multiple hydrogen-bonding interactions in apolar organic media.[5–8] The complexation processes have so far been studied mostly by means of NMR spectroscopy.

The present work is concerned with the complexations of chiral di- and polyols. We report here that the induced CD spectroscopy[9] is a very powerful tool for elucidating such complexations, especially those involving complex natural products. In addition, binding of a chiral guest results in such an exciton chirality induction in the *multibenzenoid* host **1** as to reflect the stereochemistry of the guest. This opens the door to the use of **1** as a noncovalent, supramolecular probe for the assignment of stereochemistry of chiral di(poly)ols.

Results

Glycols. The interaction of host **1** with chiral glycols as guests was investigated by CD spectroscopy. The guests investigated include symmetrically disubstituted acyclic glycols such as (2*R*,3*R*)-2,3-butanediol [(*R*,*R*)-**2**], (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol [(*S*,*S*)-**3**], (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediol [(*R*,*R*)-**4**], and (2*R*,3*R*)-2,3-bis(methoxycarbonyl)-2,3-butanediol [dimethyl L-tartrate, (*R*,*R*)-**5**], monosubstituted acyclic glycols such as (2*S*)-1,2-propanediol [(*S*)-**6**], (2*R*)-3-chloro-1,2-propanediol [(*R*)-**7**], and (1*S*)-1-phenyl-1,2-ethanediol [(*S*)-**8**], and cyclic glycols such as methyl glycosides of 4,6-*O*-benzylidene-α-D-glucopyranose (**9α**), 4,6-*O*-benzylidene-β-D-glucopyranose (**9β**), and 4,6-*O*-benzylidene-α-D-mannopyranose

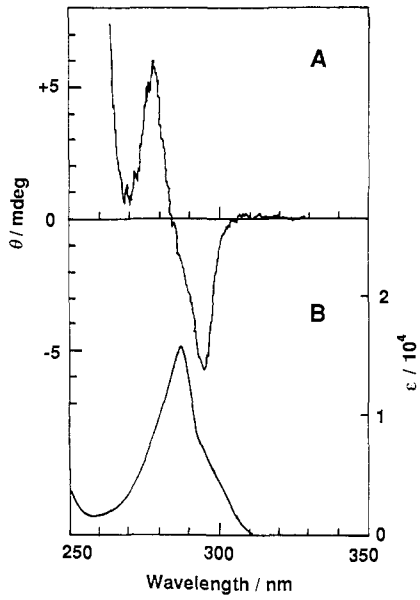


Figure 1. Induced circular dichroism spectrum (A) for a $CHCl_3$ solution (0.1-cm path length) of host **1** (1.0×10^{-3} M) and guest (*R*,*R*)-**4** (5.0×10^{-2} M) and electronic absorption spectrum (B) of **1** in $CHCl_3$. The rising-up of the CD spectrum at ≤270 nm is due to the intrinsic CD of the guest.[10]

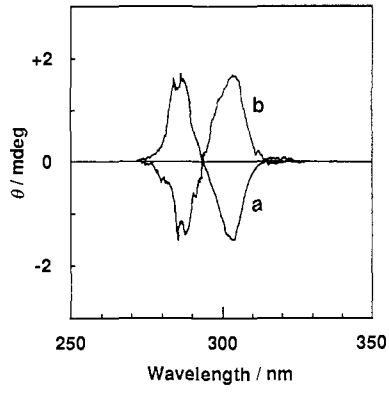


Figure 2. Induced circular dichroism spectra for $CHCl_3$ solutions (0.1-cm path length) of host **1** (1.0×10^{-3} M) and guest (*S*)-**8** (a) or (*R*)-**8** (b) (2.0×10^{-2} M).

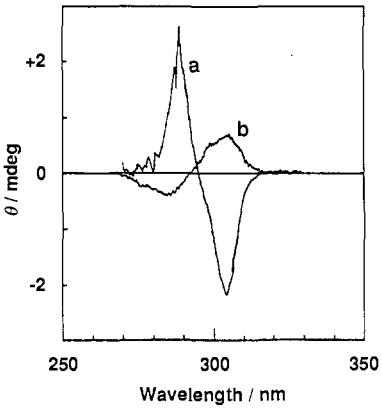


Figure 3. Induced circular dichroism spectra for $CHCl_3$ solutions (0.1-cm path length) of host **1** (1.0×10^{-3} M) and guest **9α** (a) or **10α** (b) (5.0×10^{-2} M).

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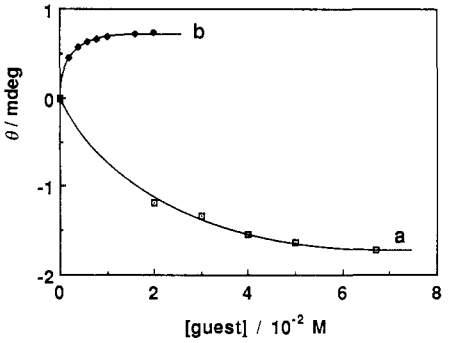


Figure 4. Correlations of observed ellipticities (θ) with [guest] at 25 °C for the complexation of host **1** (1.0×10^{-3} M) and guest (*S*)-**8** in $CHCl_3$ (0.1-cm path length) (a, at 305 nm) and that of host **1** (2.0×10^{-4} M) and guest **11** in $CHCl_3$ (0.5-cm path length) (b, at 302 nm).

(**10**α) (Chart I). Addition of any guest to a $CHCl_3$ solution of achiral macrocycle **1** (1.0×10^{-3} M with a 0.1-cm path length or 2.0×10^{-4} M with a 0.5-cm path length) resulted in appearance of an induced CD which occurred at or near the π–π^* transition band of **1** and exhibited split Cotton effects of a high degree of symmetry. The CD spectrum of complex **1**·(*R*,*R*)-**4**, as an example, is shown in Figure 1[10] together with the electronic absorption spectrum of host **1**. A pair of enantiomers, when both were available, gave a pair of CD spectra which were mirror images with each other, as illustrated in Figure 2 for the complexes of (*S*)-**8** and (*R*)-**8**.[10] Figure 3 shows the spectra for the complexes derived from glucoside and mannoside glycols **9**α and **10**α, which have opposite signs of Cotton effects. On the other hand, the α- and β-anomers of the glucoside glycols **9**α and **9**β gave the same signs of Cotton effects.

In Figure 4 are shown the observed ellipticities (θ) at 305 nm for solutions of host **1** (1.0×10^{-3} M) and varying amounts of guest (*S*)-**8** under the condition $[(S)\text{-}\mathbf{8}]_t/[\mathbf{1}]_t \geq 20$ (t = total). The correlation curve of a saturation behavior indicates a reversible host–guest complexation (eq 1). The titration data in Figure 4

$$\mathbf{1} + \text{guest} \overset{K}{\rightleftharpoons} \mathbf{1}\cdot\text{guest} \tag{1}$$

$$\frac{[\mathbf{1}]_t l}{100\theta} = \frac{1}{K[\theta]}\,\frac{1}{[\text{guest}]_t} + \frac{1}{[\theta]} \tag{2}$$

were satisfactorily analyzed by the Benesi–Hildebrand treatment[11] (eq 2, where l is the light path length (cm), K is the binding constant (M^{-1}), and $[\theta]$ is the molar ellipticity (deg·M^{-1}·cm^{-1}) for the complex).[3,12] Thus, plots of $[\mathbf{1}]_t l/100\theta$ vs $1/[(S)\text{-}\mathbf{8}]_t$ gave a straight line. From the slope and intercept were obtained K and $[\theta]$ for complex **1**·(*S*)-**8** at 25 °C. The 1:1 host–guest stoichiometry was previously confirmed from continuous-variation (Job) analyses of the ^{1}H NMR data for the complexation of diols including cyclic (racemic) glycols[7] and was reconfirmed here for that of acyclic glycols such as (*R*,*R*)-**2**; the data are shown in the Experimental Section. Similar CD titration was carried out for other selected guests, (*S*,*S*)-**3**, (*S*)-**6**, **9**α, and **10**α. In Table I are summarized the binding constants together with the signs and molar ($[\theta]$) or observed (θ) ellipticities[12] for the first (longer wavelength) and the second (shorter wavelength) components of split Cotton effects. The binding constants of guests (*R*,*R*)-**2** and racemic **6** were also obtained by the NMR method[7] (see the Experimental Section); $K_2 = 2.8 \times 10\ M^{-1}$ and $K_6 = 6.7 \times 10\ M^{-1}$ (Table I). The latter is in excellent agreement with that obtained by the CD titration ($K_{(S)\text{-}6} = 7.1 \times 10\ M^{-1}$; Table I). The binding constants obtained

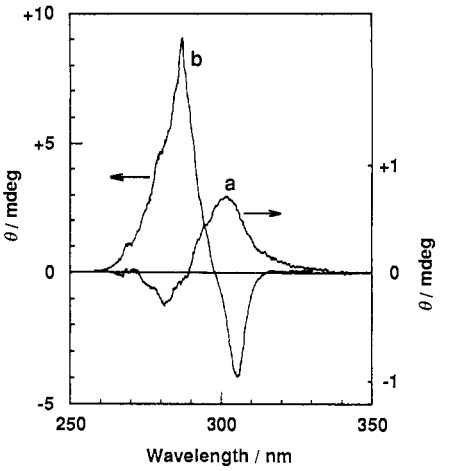
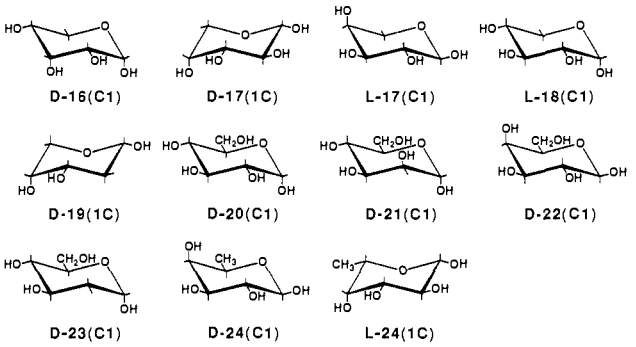


Figure 5. Induced circular dichroism spectra for $CHCl_3$ solutions (0.1-cm path length) of host **1** (1.0×10^{-3} M) and guest **11** (a) or **13** (b) (5.0×10^{-2} M).

Chart II



here for acyclic glycols and trans (**9**α) and cis (**10**α) cyclic glycols may be compared with those determined by ^{1}H NMR titration for other aliphatic diols ($(3.6\text{–}4.3) \times 10$), *trans*-1,2-cyclohexanediol (1.1×10^2), and *cis*-1,2-cyclohexanediol ($2.6 \times 10^2\ M^{-1}$).[7]

The present complexation is based on host–guest hydrogen bonding. Induced CD signals could be observed neither when the octaacetate derivative of **1**[5b] as host was used nor when the solvent was changed from chloroform to a more polar one such as acetone and chloroform–methanol (8:2). The binding of a simple, achiral alcohol such as 2-octanol was also confirmed by a competitive method.

Steroids and Sugars. It is for the complexation of complicated guests that the CD spectroscopy exerts its maximal usefulness. Cholic acid methyl ester (**11**) (Chart I) is a steroidal triol. The complexation of host **1** and guest **11** is suggested by ^{1}H NMR spectroscopy.[13] The formation of complex **1**·**11** in a reversible manner (eq 1) was convincingly evidenced by observing an induced CD (Figure 5) and a titration curve of the saturation type (Figure 4). Analysis of the latter according to eq 2 afforded the largest binding constant ($K_{11} = 6.9 \times 10^2\ M^{-1}$) obtained in this study.

Deoxy derivatives of **11** such as methyl esters of deoxycholic acid (**12**), chenodeoxycholic acid (**13**), and ursodeoxycholic acid (**14**) as diols as well as that of lithocholic acid (**15**) as a monool (Chart I) were similarly found to form complexes with host **1**. In Figure 5 is also shown the spectrum for complex **1**·**13**, which, in contrast to complex **1**·**11**, has first (longer wavelength) negative and second (shorter wavelength) positive Cotton effects. In fact, the signs of the Cotton effects depend on the numbers, location, and stereochemistry of the OH groups of steroidal guests **11**–**15** in a very complicated way (Table I). On the other hand, the binding constants (K) for **11**–**15** show a significant but reasonable

(10) Guests (*R*,*R*)-**4** and (*S*)-**8** in $CHCl_3$ show intrinsic CD ($[\theta]$, deg·M^{-1}·cm^{-1}): $+1.8 \times 10^3$ (268), $+1.9 \times 10^3$ (261), and $+1.3 \times 10^3$ (255 nm) for (*R*,*R*)-**4** and -2.9×10^2 (267), -3.7×10^2 (261), and -2.6×10^2 (255 nm) for (*S*)-**8**.

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(12) $\theta = [\theta]Cl/100$, where C is the concentration (M) of a CD-active compound. At saturation binding where $C = [\mathbf{1}]_t$ and hence $Cl = (1.0 \times 10^{-3}) \times 0.1 = (2.0 \times 10^{-4}) \times 0.5 = 10^{-4}$, $\theta_{sat} = 10^{-6}[\theta]$. When θ_{sat} is expressed in millidegrees, then $\theta_{sat} = 10^{-3}[\theta]$.

(13) Some methylene or methine proton resonances of guest **11** appear in a higher field (δ 0–−0.4) as a result of the benzene ring-current effects of host **1**. The methylene proton resonances, on the other hand, undergo almost no complexation-induced upfield shift.

Table I. Conformations and Chiralities of Guests and Signs of Split Cotton Effects, Molar ([θ]) or Observed (θ) Ellipticities, and Binding Constants (K) for Host–Guest Complexes[a]

guest	conformn[b]	R[b]	R'[b]	chirality	first Cotton[d,e] sign	first Cotton[d,e] [θ]	second Cotton[d,f] sign	second Cotton[d,f] [θ]	K (M^{-1})
(*R*,*R*)-**2**	E(−)	Me	Me	−	+	θ = +0.27	−	θ = −0.40	(2.8 × 10)[g]
(*S*,*S*)-**3**	E(+)	CH_2OMe	CH_2OMe	+	−	−1.3 × 10^3	+	+3.0 × 10^3	4.9 × 10
(*R*,*R*)-**4**	A(+)	Ph	Ph	+	−	θ = −5.9	+	θ = +5.7	
(*R*,*R*)-**5**	A(−)	CO_2Me	CO_2Me	−	+	θ = +1.8	−	θ = −1.1	
(*S*)-**6**	E(+)	Me	H	+	−	−1.2 × 10^3	+	+1.6 × 10^3	7.1 × 10 (6.7 × 10)[g]
(*R*)-**7**	E(+)	CH_2Cl	H	+	−	θ = −1.1	+	θ = +1.3	
(*S*)-**8**	E(+)	Ph	H	+	−	−2.1 × 10^3	+	+2.3 × 10^3	6.1 × 10
(*R*)-**8**	E(−)	Ph	H	−	+	θ = +1.6	−	θ = −1.4	
9α	*c*			+	−	−2.8 × 10^3	+	+3.0 × 10^3	9.4 × 10
9β	*c*			+	−	θ = −0.78	+	θ = +0.90	
10α	*c*			−	+	+1.2 × 10^3	−	−0.83 × 10^3	1.3 × 10^2
11					+	+0.78 × 10^3	−	−0.35 × 10^3	6.9 × 10^2
12					−	−2.3 × 10^3	+	+0.42 × 10^3	1.2 × 10^2
13					−	−4.3 × 10^3	+	+9.8 × 10^3	2.7 × 10^2
14					+	+14 × 10^3	−	−13 × 10^3	5.9 × 10
15					+	+28 × 10^3	−	−23 × 10^3	8.7

[a] In chloroform at 25 °C. [b] Refer to Scheme II. [c] Refer to Chart III. [d] Units: [θ], deg·M^{-1}·cm^{-1}; θ, mdeg. The experimental conditions for observing θ are [**1**] = 1.0 × 10^{-3} M with a 0.1-cm path length or 2.0 × 10^{-4} M with a 0.5-cm path length in the presence of a guest (5 × 10^{-2} M for **2**, **4**, **6**, **7**, and **9**β, 4 × 10^{-2} M for **5**, or 2 × 10^{-2} M for **8** (*R*)). Also see ref 12. [e] λ_{ext} = 295–305 nm. [f] λ_{ext} = 279–289 nm. [g] Obtained by ^{1}H NMR titration.

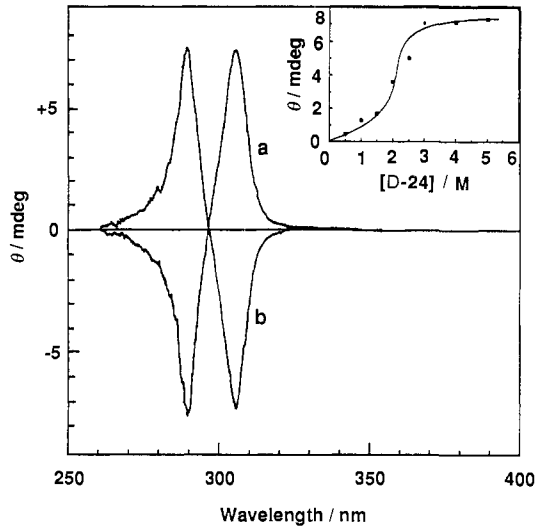


Figure 6. Induced circular dichroism spectra for complexes **1**·D-**24** (a) and **1**·L-**24** (b) in CCl_4 with a 0.5-cm path length. The complexes were prepared by extracting the sugars in water (5 M) into a CCl_4 solution of **1** (2.0 × 10^{-4} M). Insert: correlation of θ at 305 nm with [D-**24**] in source aqueous solutions.

dependence on the number of OH groups involved (Table I). It is also interesting to note an inverse correlation between *K* and [θ].

Induced CD spectroscopy also provides direct evidence for the extraction of sugars **16**–**24** (Chart II) from water to carbon tetrachloride upon formation of **1**·sugar complexes. Figure 6 shows the spectra for the enantiomeric complexes of D- and L-fucose (6-deoxygalactose, **24**) obtained by extracting the sugar in water ([**24**] = 5.0 M). In the inset of this figure are shown the observed ellipticities (θ) at 305 nm as a function of [D-**24**] in source aqueous solutions. The θ–[D-**24**] correlation reaches a plateau region at [D-**24**] ≈ 3 M. On the same ground was confirmed the extraction of other monosaccharides (5.0 M in water unless otherwise indicated) such as D-ribose (**16**), D- and L-arabinose (**17**), D-lyxose (**18**), 2-deoxy-D-ribose (**19**), D-glucose (**20**), D-mannose (**21**), D-galactose (**22**), and 2-deoxy-D-glucose (**23**). In every case, the induced CD was composed of split Cotton effects, the signs of which are shown in Table II, together with observed ellipticities (θ).

All of the D-hexoses **20**–**22** give the same signs of Cotton effects, first positive and second negative. This is, however, not the case for D-pentoses **16**–**18**: first positive and second negative for **16** and **18**, while first negative and second positive for **17**. Glucose (**20**) and deoxyglucose (**23**) give the same signs of Cotton effects, while ribose (**16**) and deoxyribose (**19**) show the opposite signs. Thus, at first glance, no simple correlation is possible between structures of sugars and the observed signs of Cotton effects. A second point of interest is the CD intensities. Previous studies[5a–c] indicate that there is remarkable selectivity in the extraction of sugars and that such sugars as **18** and **20**–**22** only have very low extractabilities. There is, however, no apparent correlation between extractabilities of sugars and CD intensities (θ) (Table II). This is not surprising since the CD intensity must depend on some geometrical factor(s) of the complex.

Table II. Conformations of Sugar Pyranoses and Signs of Split Cotton Effects and Observed Ellipticities (θ) for Complexes Thereof[a]

sugar	conformn	first Cotton sign	first Cotton θ[b,d]	second Cotton sign	second Cotton θ[c,d]
D-**16**	*C*1	+	+3.6	−	−2.4
D-**17**	1*C*	−	−5.5	+	+7.5
L-**17**	*C*1	+	+6.3	−	−6.9
D-**18**	*C*1	+	+3.8	−	−3.1
D-**19**	1*C*	−	−6.3	+	+4.9
D-**20**	*C*1	+	+0.37	−	−0.19
D-**21**	*C*1	+	+1.1	−	−0.71
D-**22**	*C*1	+	+3.2	−	−2.6
D-**23**	*C*1	+	+1.5	−	−0.50
D-**24**	*C*1	+	+7.3	−	−7.3
L-**24**	1*C*	−	−7.3	+	+7.3

[a] Sugar complexes were prepared by extracting a sugar in water (5 M unless otherwise indicated) into a carbon tetrachloride solution of host **1** (2.0 × 10^{-4} M). Galactose (**22**) was extracted from a 2.5 M aqueous solution. The CD spectra were taken directly for the CCl_4 extracts in a cell of a 0.5-cm path length at 25 °C. [b] In millidegrees. λ_{ext} = 302–308 nm. [c] In millidegrees. λ_{ext} = 281–290 nm. [d] See ref 12.

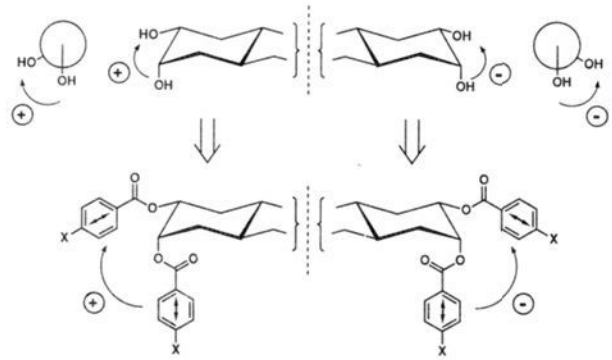
Discussion

Molecular Complexation and Induced CD. The induced CD technique has proved to be a very useful tool to elucidate the hydrogen-bonding interaction of multibenzenoid host **1** and chiral di(poly)ols in apolar organic media.[3,14] ^{1}H NMR spectroscopy is often used to detect host–guest complexation in solutions,[15] where complexation-induced shifts of particular resonances are followed.

(14) CD spectroscopy has been applied to elucidate the binding properties of chromophoric chiral guests. See, for examples: (a) Shinkai, S.; Arimura, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1987**, 1495–1496. (b) Ueno, A.; Suzuki, I.; Osa, T. *J. Am. Chem. Soc.* **1989**, *111*, 6391–6397.

(15) (a) Connors, K. A. *Binding Constant*; Wiley: New York, 1987; Chapter 5. (b) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386.

Scheme I



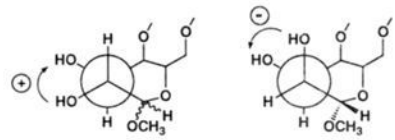
The shifts may be caused by chemical interactions such as hydrogen bonding[16] or by diamagnetic ring-current effects.[5-7,17] In order for this method to be successful, both host and guest must be relatively simple and must not be under such conditions as [host] ≫ [guest] or [guest] ≫ [host]; otherwise, the *particular* resonances in concern cannot be identified readily and/or, more seriously, they may develop with other resonances arising from all parts of free host, free guest, and complex. The NMR method indeed gives only indirect evidence for the complexation of steroid **11**. This is also true for the sugar complexations. The ^{1}H NMR signals for the ribose complex **1·16** could fortunately be assigned.[5b] Other sugar complexes, however, gave no distinct and assignable resonances for bound sugars. Their complexations were indirectly evidenced by reextracting them back into water.[5b]

In the present case, only host–guest complexes having chromophores in chiral environments are CD-active. As a consequence, they can be detected selectively even in the presence of large excess amounts of free host and free guest. Thus, the present results provide unambiguous evidence that macrocycle **1** forms molecular complexes with steroidal polyols **11**–**15**[18] and unprotected sugars **16**–**24** as well as simpler glycols **2**–**10** in $CHCl_3$ or CCl_4 solutions.

Chiral Exciton Coupling and Split Cotton Effects. CD signals with split Cotton effects are specific to chiral molecules containing two or more chromophores and arise from the so-called chiral exciton coupling.[3] The signs of split Cotton effects are correlated with the absolute structure of the molecule or, more strictly, the chirality of the transition moments. The chirality (or screw sense) is defined as positive (right-handed) or negative (left-handed) when the rotation (arrows) of two transition-moments (bold lines) is clockwise or counterclockwise, respectively, on going from the front one to the rear one (Scheme I). The rule[19] says that an exciton-coupled, bischromophoric system having a positive chirality shows first (longer wavelength) positive and second (shorter wavelength) negative Cotton effects. If the chirality is negative, the signs of split Cotton effects would be first negative and second positive.

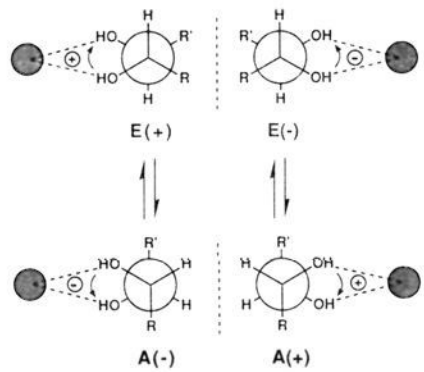
The *exciton chirality method*[3] has been applied to the elucidation of absolute configurations of cyclic diols, especially glycols (vicinal diols), via the corresponding para-substituted dibenzoate derivatives (Scheme I).[20] In the most stable conformation of an alkyl benzoate ester (–C^1–O–C^{2}O–Ar), the C^1–O and C^2–Ar bonds are trans with respect to the O–C^{2}O bond and are thus parallel to each other. The transition moments (bold lines), on the other hand, lie on the long axes of the benzene rings. Therefore, the chirality (arrows) of the two alcoholic C–O bonds is the same as that of the two transition moments. Thus, the sign (positive or negative) of the first (longer wavelength) Cotton effect is in accord with the chirality (positive or negative, respectively) of the molecule (dibenzoate chirality rule),[3] as shown in Scheme I for a pair of enantiomers of a cyclic glycol.

Chart III



9α, 9β 10α

Scheme II



Host **1** has a C_4 symmetry, its four equivalent benzene rings being fixed in a bowl conformation via four pairs of hydrogen-bonded OH groups.[21-23] The observation of split Cotton effects (Figures 1–3, 5, and 6) indicates that binding of a chiral guest to host **1** induces *asymmetric deformation* of the transition moments located in otherwise symmetrically arranged benzene rings.

Exciton Chirality Induction and Absolute Configuration of Chiral Glycols. Our previous ^{1}H NMR studies[7] indicate that cyclic glycols (*cis*- and *trans*-1,2-cyclohexanediol) undergo multiple hydrogen-bonding interactions with one of four binding sites of host **1** (A–D) composed of a pair of OH groups. In the present complexation, D-glucoside glycols **9**α and **9**β have a positive or clockwise chirality of the two C–OH bonds as shown in their Newman projections (Chart III). They give first negative and second positive Cotton effects (Table I). D-Mannoside glycol **10**α, on the other hand, has a negative or counterclockwise chirality (Chart III); it exhibits first positive and second negative Cotton effects.

The above correlation between absolute configurations and CD signs can be extended to acyclic glycols. In order for an acyclic glycol to undergo such a multiple hydrogen-bonding interaction at a binding site of host **1**, the two OH groups of the guest must be fixed in a syn-gauche conformation. There are two such conformations, pseudoequatorial (E) and pseudoaxial (A) (Scheme II; the shaded circle represents a binding site of host **1**). The former has bulky substituents (R and R′) in the pseudoequatorial

(16) (a) Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1090–1094. (b) Aoyama, Y.; Asakawa, M.; Yamagishi, A.; Toi, H.; Ogoshi, H. *Ibid.* **1990**, *112*, 3145–3151.

(17) (a) Vögtle, F.; Merz, T.; Wirtz, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 221–222. (b) Vögtle, F.; Müller, W. M.; Werner, U.; Losensky, H.-W. *Ibid.* **1987**, *26*, 901–903.

(18) For the lipophilic glucopyranoside binding with steroidal cyclodimers derived from cholic acid, see: (a) Bonar-Law, R. P.; Davis, A. P.; Murray, B. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1407–1408. For the host–guest type binding of steroid derivatives, see: (b) Carcanague, D. R.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 769–771. (c) Kumar, S.; Schneider, H.-J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 245–250. (d) Shimada, K.; Komine, Y.; Oe, T. *J. Liq. Chromatogr.* **1989**, *12*, 491–500. (e) Kawakami, H.; Yoshino, O.; Odashima, K.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 5610–5613.

(19) Harada, N.; Chen, S.-M. L.; Nakanishi, K. *J. Am. Chem. Soc.* **1975**, *97*, 5345–5352.

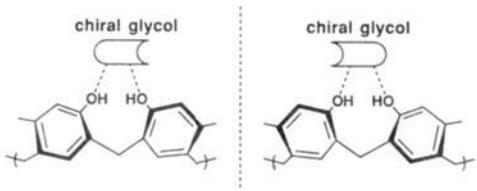
(20) Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1969**, *91*, 3989–3991.

(21) (a) Erdtman, H.; Högberg, S.; Abrahamsson, S.; Nilsson, B. *Tetrahedron Lett.* **1968**, 1679–1682. (b) Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498–4500. (c) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046–6050.

(22) For X-ray structures of O-substituted derivatives, see: (a) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229–2237. (b) Tucker, J. A.; Knobler, C. B.; Trueblood, K. N.; Cram, D. J. *Ibid.* **1989**, *111*, 3688–3699.

(23) Schneider, H.-J.; Guttes, D.; Schneider, U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 647–649. (b) Schneider, H.-J.; Karmer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442–6448. (c) Schneider, H.-J.; Guttes, D.; Schneider, U. *Ibid.* **1988**, *110*, 6449–6454.

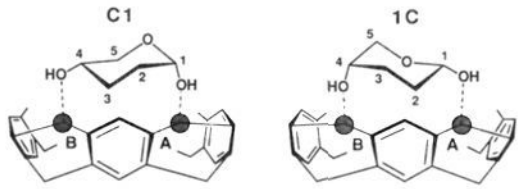
Chart IV



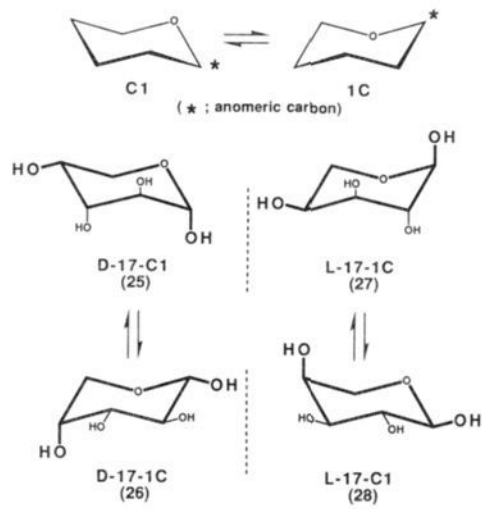
positions, while in the latter the substituents occupy pseudoaxial positions. In view of minimization of steric interactions at the hydrogen-bonding site, the guest would be more favorably bound in a pseudoequatorial conformation,[24] unless other factor(s) come into play. One case is when the substituents R and R′ are considerably bulky, as in the case of diphenyl glycol **4**; this guest may take a pseudoaxial conformation in order to avoid a significant phenyl–phenyl steric repulsion (judging from CPK models). Another case is when R and R′ can take part in the hydrogen-bonding interactions, as in the case of the diester or tartrate glycol **5**; this guest may also take a pseudoaxial conformation to allow a more extensive host–guest hydrogen-bond network involving the two ester groups.[25] The chirality (arrow) of the two C–OH bonds in a pseudoequatorial or pseudoaxial conformation depends on the absolute configuration of the glycol, either positive (clockwise) for an E(+) or A(+) conformation or negative (counterclockwise) for an E(−) or A(−) conformation (Scheme II). In Table I are summarized the expected conformations and chiralities of the glycols used in this study and the signs of split Cotton effects for complexes derived therefrom. There is indeed a correlation between them, but in an opposite sense to that found for the covalent dibenzoate systems (dibenzoate chirality rule): The sign of the first (longer wavelength) Cotton effect is opposite to the sign of chirality of the glycol. In terms of chirality transfer, the chirality of a guest glycol induces an opposite chirality in the multibenzenoid host **1**.

The chirality transfer seems to be based on the generation of a C_2 chirality upon binding of a chiral glycol, as schematically shown in Chart IV.[26] The elucidation of the precise mechanism, however, should be deferred until much information is available as to the structures of the present host–guest complexes and detailed nature of the hydrogen-bond network involving four (two from host and two from guest) OH groups. From a practical point of view, on the other hand, the observed correlation between structures and spectra suggests that host **1** can be used as a noncovalent, *supramolecular* CD probe for the assignments of absolute configurations of glycols. This is based on chirality transfer from guest to *multibenzenoid* host **1** via multiple host–guest hydrogen bonding. It is remarkable that multiple hydrogen bonding results in a conformational fixation, so that the present *exciton chirality induction* method is applicable to otherwise flexible glycols **2**–**8** including those having only one chiral center (**6**–**8**).[27] Attempts have been made of the use of metal complexes to fix conformation of acyclic glycols via chelation.[28] Quite

Chart V



Scheme III



recently, however, a simple procedure based on the exciton chirality method has been introduced for the assignment of stereochemistry in acyclic polyols.[29]

Exciton Chirality Induction and Ring Conformations of Sugars. The previous study[5b] indicates that sugars, e.g., ribose (**16**), are bound to host **1** in the form of α-pyranose. A simultaneous two-point hydrogen bonding involving the cis 1-OH and 4-OH groups of the guest and two adjacent binding sites A and B of the host is primarily responsible for the host–guest complexation (refer to structures in Chart V).[5b,7] The α-pyranose ring has two *possible conformations, C1 and 1C (Scheme III),*[30] *which are* interconvertible with each other by ring inversion. In Scheme III are shown all conformations of D- and L-α-arabinopyranose (**17**) as an example. D-**17**-*C*1 and L-**17**-1*C* are enantiomers as D-**17**-1*C* and L-**17**-*C*1 are; enantiomers thus have different conformations in this terminology. The bulky OH groups and the CH_2OH (in cases of hexoses **20**–**22**) or CH_3 (in the case of fucose (**24**)) group tend to occupy less hindered equatorial positions. These factors, coupled with the so-called anomer effect,[31] determine the relative stabilities of *C*1 and 1*C* conformations.[32] The more stable conformations thus evaluated for sugars **16**–**24**[33] are shown above as their structural formulas as well as in Table II. Inspection of Table II reveals a remarkable correlation between sugar conformations and CD signs. Sugars having the more stable *C*1 conformations exhibit first (longer wavelength) positive and second negative Cotton effects, while other sugars having the more stable 1*C* conformations show first negative and second positive Cotton effects.

(24) The pseudoequatorial conformation is also the preferred one for the chelated metal complexes of acyclic glycols: Dillon, J.; Nakanishi, K. *J. Am. Chem. Soc.* **1975**, *97*, 5417–5422.

(25) A simple diester such as (2*S*,4*S*)-2,4-diacetoxypentane was found to form a complex with host **1**, giving rise to an induced CD with split Cotton effects. This result indicates that the ester groups can participate in the present host–guest hydrogen-bonding interaction.

(26) Deformation of the benzene rings, however, is not necessarily compulsory. The chirality induction may simply be due to asymmetric hydrogen bonding with respect to the two OH groups of the host.

(27) For applications of dibenzoate chirality method to diols having a primary OH group, see ref 20. For an application of dibenzoate chirality method to acyclic diols, see: (a) McGahren, W. J.; Ellestad, G. A.; Morton, G. O.; Kunstmann, M. P.; Mullen, P. *J. Org. Chem.* **1973**, *38*, 3542–3544. (b) Harada, N.; Saito, A.; Gawronski, J.; Gawronska, K.; Sugioka, T.; Uda, H.; Kuriki, T. *J. Am. Chem. Soc.* **1991**, *113*, 3842–3850.

(28) (a) Nakanishi, K.; Schooley, D. A.; Koreeda, M.; Dillon, J. *J. Chem. Soc., Chem. Commun.* **1971**, 1235–1236. (b) Nakanishi, K.; Crouch, R.; Miura, I.; Dominguez, X.; Zamudio, A.; Villarreal, R. *J. Am. Chem. Soc.* **1974**, *96*, 609–611. (c) Dillon, J.; Nakanishi, K. *Ibid.* **1974**, *96*, 4057–4059. (d) Dillon, J.; Nakanishi, K. *Ibid.* **1974**, *96*, 4059–4061. (e) Dillon, J.; Nakanishi, K. *Ibid.* **1975**, *97*, 5409–5417.

(29) (a) Wiesler, W. T.; Nakanishi, K. *J. Am. Chem. Soc.* **1989**, *111*, 9205–9213. (b) Wiesler, W. T.; Nakanishi, K. *Ibid.* **1990**, *112*, 5574–5583. (c) Zhou, P.; Berova, N.; Nakanishi, K.; Knani, M.; Rohmer, M. *Ibid.* **1991**, *113*, 4040–4042.

(30) Reeves, R. E. *J. Am. Chem. Soc.* **1949**, *71*, 215–217; **1950**, *72*, 1499–1506.

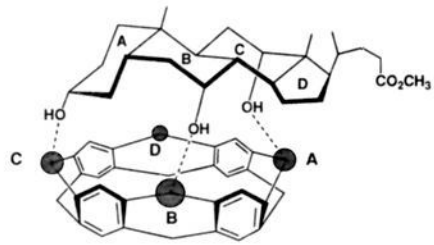
(31) (a) Edward, J. T. *Chem. Ind. (London)* **1955**, 1102–1104. (b) Wolfe, S.; Rank, A.; Tel, L. M.; Csizmadia, I. G. *J. Chem. Soc. B* **1971**, 136–145. (c) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527–548.

(32) The free energy differences between *C*1 and 1*C* conformations range from 0.10 (for α-ribopyranose with *C*1 being more stable) to 4.15 kcal/mol (for α-glucopyranose with *C*1 being more stable).[34]

(33) Angyal, S. J. *Aust. J. Chem.* **1968**, *21*, 2737–2746.

The above correlation can be explained by assuming that more stable conformations are also the conformations of sugars bound to host **1**.[34] As pointed out above,[5b] the cis 1-OH and 4-OH groups of a pyranose make the most important contribution to the binding process. If only 1-OH and 4-OH groups are taken into account for the sake of simplicity, any pyranose can be represented by one of four bold-lined structures **25**–**28** (Scheme III). Both *C*1 and 1*C* of a given sugar have one equatorial 1(4)-OH and one axial 4(1)-OH groups. They are, however, in an opposite arrangement for the two conformations. The axial OH and equatorial OH groups of a bound pyranose may induce different types of deformation of the benzene rings (transition moments). Therefore, the overall *chiralities* of deformation induced in host **1** upon binding of pyranoses **25** and **26** or **27** and **28** would be opposite to each other as if they were enantiomers, provided that the front side involving 2-C and 3-C and the rear side involving 5-C and ether oxygen of the pyranose are discriminated in the binding process. The actual deformation is not known but Chart V schematically illustrates the point. Structures **25** and **27** as well as **26** and **28** are enantiomers; they give rise to opposite chiralities. The following prediction can thus be made. It is the pyranose ring conformation (*C*1 or 1*C*) of the bound sugar that determines the chirality induced in the host and hence the signs of split Cotton effects. This is applicable to any sugar, whichever configuration (D or L) it may have and whichever stereochemistry (axial or equatorial) its 1-OH and 4-OH groups may be. This prediction is exactly what was observed (Table II). Host **1** can thus be used as a very novel, supramolecular probe for the assignments of ring conformations of sugar pyranoses.[35-37]

Molecular Recognition of Polyols. Cholic acid methyl ester (**11**) is a steroidal triol having equatorial 3-OH and axial 7- and 12-OH groups. Because of the cis A/B and trans B/C ring junctions, the three OH groups are nicely pointing to the same directions. In addition, they can undergo a three-point hydrogen-bonding interaction with the three binding sites (A–C) of host **1** (structure **29**),[38] as revealed by an examination of CPK molecular models. The binding constant of **11** ($K_{11} = 6.9 \times 10^2$ M^{-1}) is quite large. Its 7- and 12-deoxy diol derivatives **12** and **13** form less stable complexes with **1**; $K_{12} = 1.2 \times 10^2$ M^{-1} and $K_{13} = 2.7 \times 10^2$ M^{-1} (Table I). The 7,12-dideoxy monool **15** forms a far less stable complex; $K_{15} = 8.7$ M^{-1}.[39] These results demonstrate the importance of multipoint host–guest hydrogen-bonding interactions.[7] On the other hand, there is no simple correlation between structures and signs of split Cotton effects for the multipoint hydrogen-bonded complexes of steroids **11**–**15** (Table I). The stereoselectivities between steroid epimers **13** and **14** and sugar epimers **9**α and **10**α provide another interesting point. In both cases, the cis epimer (**13** and **10**α) having one axial and one equatorial OH groups are bound to **1** more firmly than the trans epimer (**14** and **9**α) having two equatorial OH's; the selectivities are $K_{13}/K_{14} = 4.7$ and $K_{10}/K_9 = 1.4$.



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The affinities of various guests to host **1** in homogeneous $CHCl_3$ solutions (Table I) follow the increasing order **15** (monool) < **3**, **6**, and **8** (acyclic diols) < **9**α, **10**α, **12**, and **13** (cyclic diols) < **11** (triol). A previous study using model diol and monool guests has revealed the geometrical requirements in terms of multifunctionality, rigidity, and stereochemistry for the multiple host–guest hydrogen bonding.[7] This study demonstrates that such principles in fact work fairly well for the discrimination of closely related polyalcoholic natural products.

Conclusions

A pair of benzene rings in host **1** are rigidly linked via the binding site composed of a pair of hydrogen-bonded OH groups. The chirality information of a bound guest is thus transmitted into an asymmetric deformation of the transition moments in the benzene rings. This deformation gives rise to an induced CD with split Cotton effects. The significance of the present induced CD spectroscopy is 2-fold. First, the chirality of the guest (absolute configuration for a glycol and ring conformation of a sugar) is correlated in a predictable way with the induced chirality in the host; the latter is reflected on the signs of split Cotton effects. This opens the door to the use of host **1** as a noncovalent, supramolecular probe for the assignments of stereochemistry of chiral di(poly)ols (*exciton chirality induction method*). Second, molecular complexation of such complex biomolecules as steroidal polyols and sugars can be followed very conveniently and sensitively. This suggests a potentiality of the induced CD spectroscopy in the rapidly growing area of molecular recognition of chiral natural products.[5,16b,18,40]

Further work is now under way to shed more light on the chirality induction in host **1** using a wider series of chiral guests including simpler alcohols, amines, and amino alcohols. Enantioselective guest binding to chiral derivatives of **1** is also an interesting extension of this work.

Experimental Section

Materials. Host **1** was prepared as described.[5b] Chiral guests **2**–**8** and **16**–**24** were commercial products of the highest grades. Steroidal esters **11**–**15** were obtained by the esterification of the corresponding acids with methanol in the presence of H_2SO_4 as catalyst and purified by means of column chromatography followed by recrystallization (two times) from either methanol or hexane–chloroform. Methyl glycosides **9**α, **9**β, and **10**α were prepared by the literature method[41] and purified by means of column chromatography followed by recrystallization from hexane–chloroform.

CD Spectra. CD spectra were obtained with a Jasco J-500C spectropolarimeter at 25 °C. For the determinations of binding constants, a series of $CHCl_3$ solutions containing host **1** (1.0×10^{-3} or 2.0×10^{-4}

(34) The host–guest hydrogen-bond energies involving 1-OH and 4-OH groups of a sugar would be similar for the *C*1 and 1*C* conformations, since both have one axial and one equatorial OH group. On the other hand, substituents on the 2-, 3-, or 5-position may cause a steric interaction with the host. This interaction would be more pronounced when the substituent is axial than when it is equatorial. It is, therefore, expected that the more stable conformation of a sugar having more substituents in the equatorial positions is preferred in the binding with the host.

(35) For CD spectroscopic studies on sugar benzoate derivatives, see: (a) Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1969**, *91*, 3989–3991. (b) Harada, N.; Sato, H.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1970**, 1691–1693. (c) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257–263. (d) Liu, H.-W.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5591–5593. (e) Liu, H.-W.; Nakanishi, K. *Ibid.* **1981**, *103*, 7005–7006. (f) Liu, H.-W.; Nakanishi, K. *Ibid.* **1982**, *104*, 1178–1185.

(36) CD spectroscopy has been applied to elucidate the stereochemistry of sugar derivatives. See, for examples: (a) Hargreaves, M. K.; Marshall, D. L. *Carbohydr. Res.* **1973**, *29*, 339–344. (b) Bukhari, S. T. K.; Guthrie, R. D.; Scott, A. I.; Wrixon, A. D. *Tetrahedron Lett.* **1970**, 3653–3656. (c) Johnson, A. W.; Smith, R. M.; Guthrie, R. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2153–2159. (d) Ganguly, A. K.; Sarre, O. Z.; Morton, J. *J. Chem. Soc., Chem. Commun.* **1969**, 1488–1489. (e) Mallas, A. K. *J. Am. Chem. Soc.* **1969**, *91*, 7505–7506. (f) Bukhari, S. T. K.; Guthrie, R. D. *Carbohydr. Res.* **1970**, *12*, 469–470. (g) Nutt, R. F.; Dickinson, M. J.; Holly, F. W.; Walton, E. *J. Org. Chem.* **1968**, *33*, 1789–1795. (h) Jenkins, S. R.; Arison, B.; Walton, E. *Ibid.* **1968**, *33*, 2490–2494. (i) Nutt, R. F.; Walton, E. *J. Med. Chem.* **1968**, *11*, 151–153.

(37) For a CD spectroscopic study on the complexation of sugars with a bis(phenylboric acid) derivative in water, see: Tsukagoshi, K.; Shinkai, S. *J. Org. Chem.*, in press.

(38) For this structure, each methyl group of guest **11** is a considerable distance away from the benzene rings of host **1**. This may be why there is no complexation-induced ^{1}H NMR upfield shift for the methyl groups.[13]

(39) Carcanague and Diederich[18b] studied the binding of carboxylic acid (not ester) derivatives of steroids **11**–**15** with a water-soluble cyclophane in aqueous methanol and found an essentially reverse selectivity as observed here.

(40) (a) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *J. Am. Chem. Soc.* **1987**, *109*, 2432–2434. (b) Tjivikua, T.; Ballester, P.; Rebek, J., Jr. *Ibid.* **1990**, *112*, 1249–1250. (c) Jeong, K. S.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *Ibid.* **1991**, *113*, 201–209.

(41) Evans, M. E. *Carbohydrate Res.* **1972**, *21*, 473–475.

M) and varying amounts of a guest were prepared in a cell of either 0.1 or 0.5-cm path length, respectively. The concentrations of guests were so chosen as to meet the Benesi-Hildebrand conditions ($[guest]_t/[host]_t > 10$; t = total) and cover a range of 10-90% (mostly 40-80%) complexation. The actual titration data for selected guests are as follows, [guest], mM (θ, mdeg): 20 (0.66), 25 (0.71), 30 (0.77), 40 (0.89), 50 (0.93) for (*S*,*S*)-**2**; 20 (1.19), 30 (1.33), 40 (1.54), 50 (1.63), 67 (1.71) for (*S*)-**8**; 2 (0.46), 4 (0.58), 6 (0.63), 8 (0.66), 10 (0.69), 16 (0.72), 20 (0.73) for **11**; 10 (5.43), 12 (5.90), 15 (6.47), 20 (7.86), 30 (9.29), 40 (10.14) for **14**; 10 (2.18), 12 (2.66), 14 (3.19), 20 (4.20), 25 (5.19), 40 (6.86), 50 (8.43), 80 (11.00). In every case, the Benesi-Hildebrand plots of $[1]_t l/100\theta$ vs $1/[guest]_t$ according to eq 2 gave a straight line with r (correlation coefficient) ≥ 0.98. The binding constants and molar ellipticities evaluated from the slopes and intercepts are summarized in Table I.[12]

Sugar extraction was performed as described.[5b] Thus, a two-phase mixture of a CCl_4 solution (20 mL) of host **1** (2.0×10^{-4} M) and an aqueous solution (2 mL) of a sugar (5 M for all sugars except for galactose (**22**) and 2.5 M for **22**) was vigorously stirred at room temperature for 24 h. The organic layer was carefully separated,[5b] taken in a cell of a 0.5-cm path length, and subjected to the measurements of CD spectra.

^{1}H NMR Study. The interaction of host **1** (1.0×10^{-2} M) and guest (*R*,*R*)-**2** or racemic **6** in $CDCl_3$ was investigated by means of ^{1}H NMR spectroscopy at 25 °C in exactly the same way with the same machine as described earlier.[7] The complexes **1·2** and **1·6** showed the methyl proton resonances at δ ca. -0.7 and -0.8, respectively. Binding constants of $K_2 = 2.8 \times 10$ M^{-1} and $K_6 = 6.7 \times 10$ M^{-1} were obtained from the dependence of extents of complexation on guest concentrations: $[\mathbf{1}\cdot\mathbf{2}]/[\mathbf{1}]_t = 0.175$, 0.355, 0.430, and 0.601 at $[\mathbf{2}]_t/10^{-2}$ M = 1.0, 2.0, 3.0, and 7.0, respectively; $[\mathbf{1}\cdot\mathbf{6}]/[\mathbf{1}]_t = 0.248$, 0.570, 0.640, and 0.698 at $[\mathbf{6}]_t/10^{-2}$ M = 1.0, 2.0, 3.0, and 5.0, respectively. ^{1}H NMR spectra were taken also for a series of solutions under conditions where $[\mathbf{1}]_t + [\mathbf{2}]_t$ was kept constant at 1.0×10^{-2} M. The continuous-variation (Job) plots of **[1·2]** vs mole fractions of **1** (f) showed a maximum at $f = 0.5$, indicating a 1:1 host:guest stoichiometry; $[\mathbf{1}\cdot\mathbf{2}]/10^{-4}$ M = 2.7, 3.7, 4.4, 4.8, 4.5, 3.8, and 3.1 at $f = 0.2$, 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8, respectively.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 02230212) from the Ministry of Education, Science, and Culture of the Japanese government. We are grateful to Dr. M. Kobayashi (Nagaoka University of Technology) for performing the molecular orbital calculation. We also thank Dr. Nobuyuki Harada (Tohoku University) for helpful discussions.

4-[(3,4-Dimethoxyphenyl)azo]pyridine: Two Different Pathways in the Acid Hydrolysis of the Two Methoxy Groups[‖,1]

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Received August 9, 1991

Abstract: The kinetics of hydrolysis of the two methoxy functions in the title compound **1** have been determined as a function of sulfuric acid concentration. Basicity constants for azo group protonation have been evaluated for **1** and several other (phenylazo)pyridines. The 4-OMe group in **1** hydrolyzes very readily in aqueous H_2SO_4 at 25 °C (half-life, seconds to minutes); the 3-OMe group also hydrolyzes, but more slowly (half-life, hours to days). The results extrapolate to a reactivity difference of 7000 in pure water. Both reactions exhibit maxima in the rate constant/percent H_2SO_4 profile. An excess acidity analysis of the rate data reveals that the origins of the deceptively similar rate profiles for the two methoxy functions are different, as are the reaction pathways for the hydrolyses. Hydrolysis of the 4-OMe group occurs via initial activation of the para position through azo protonation, followed by ipso ring carbon attack by three water molecules to give a positively charged intermediate, IH^+. Cleavage of the methoxy C-O bond in IH^+ leads to products. As the three water molecules are active participants in the bond making/breaking processes, either formation or decomposition of the intermediate may be rate-limiting (k_1, k_2 in Scheme I), depending on the log a_{H_2O} values of the medium. For the 3-OMe group, initial azo protonation is in competition with rate-determining ring carbon protonation, which is followed by fast water reaction with the resulting charged intermediate. Azo protonation inhibits the reaction by storing the substrate in an unreactive form, thus accounting for the decreasing reactivity at higher acidities (Figure 1). This is corrected for in the excess acidity treatment, yielding a linear plot (Figure 2). This linear plot is a direct consequence of the lack of requirement for water molecules in the rate-determining step of the 3-OMe hydrolysis. Conversely, the observed rate decrease for the 4-OMe group (Figure 1) results from depletion of the nucleophilic entity (water), which correlates with medium acidity in terms of rapidly diminishing log a_{H_2O} values; this, in turn, manifests in the downward curvature in the excess acidity plot (Figure 2). The totally different mechanisms for the reactions of the 3- and 4-OMe functions unraveled herein provide a framework for discussion of the hydrolyses of unactivated aromatic substrates in acidic media.

Alkyl aryl ethers are generally resistant to hydrolysis in acid media. Conventional cleavage methods include the Zeisel method[2] and treatment with a variety of reagents, such as anhydrous sulfonic acids,[3] Lewis acids,[4] and similar compounds; other methods[5] include phase-transfer catalysis.[6] However, the observations of Witt and Schmidt, published 100 years ago,[7] and kinetic studies by Bunnett and co-workers much later[8] demonstrate

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[‖] This paper is dedicated to Professor Joseph F. Bunnett on the occasion of his 70th birthday.

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0002-7863/92/1514-1358$03.00/0