

sodium hydroxide solutions in a 1:1 ratio. The data showed good fits to pseudo-first-order kinetics.

Spectral Measurements of pK_a 's. A 10–20- μL portion of a stock solution of the ketone in methanol (ca. 1×10^{-2} M) was added to 2.0 mL of a sodium hydroxide solution (0.001–0.66 M for **1a**; 0.01–0.075 M for **1b**; 0.15–1.0 M for **1c**) at constant ionic strength. The absorbances (288 nm for **1a**; 300 nm for **1b,c**) were extrapolated to zero time, and the pK_a 's were calculated from eq 3.

Ketonization of the Enols. The enol of 2-indanone was prepared under argon by mixing a 0.50 M solution of 2-indanone in methanol with a solution of sodium hydroxide (0.1 M, 2% methanol) in a 1:100 ratio. This solution was filtered through a micro-filtering disk and then mixed in a 1:50 ratio with acid (HCl) or buffer (acetate) with use of a HiTech SF-11 rapid-mixing apparatus and a Gilford Response spectrophotometer. The enols of 2-tetralone and 2-benzosuberone were prepared in a HiTech QP/SF stopped-flow apparatus. A methanol/water solution of ketone (2.2×10^{-3} M for **1b**; 1.2×10^{-3} M for **1c**) was mixed in a 1:1 ratio with sodium hydroxide (0.1 M for **1b**; 2.07 M for **1c**) by use of two syringes of the stopped-flow apparatus. After a delay of a few seconds to allow for formation of the enolate ion, this solution was rapidly mixed with a solution of acid or buffer. The decay in absorbance was monitored at 265 nm.

Acid-Catalyzed Enolization. The acid-catalyzed enolization of 2-indanone was monitored by adding 5.0 μL of an aqueous bromine solution (6.5×10^{-3} M) with a glass capillary to a solution of ca. 10^{-3} M 2-

indanone in HBr (0.01–0.09 M) and NaBr ($\mu = 0.1$ or 1.0). Extinction coefficients for the Br_2/HBr solutions were measured for each concentration of HBr. The decrease in absorbance was monitored at both 266 and 310 nm for approximately the first 5% disappearance of 2-indanone. The exact concentration of 2-indanone was determined spectrally before the addition of the bromine solution.

Enolization rate constants for **1a,b,c** were determined by HPLC monitoring the loss of ketone in aqueous HBr/ Br_2 solutions with 0.1–3% acetonitrile as cosolvent. A saturated solution of bromine in water (600 μL to 2.0 mL) was added to 50 mL of an aqueous solution of HBr (0.01–0.10 N, $\mu = 0.1$ for **1a**; 0.01–0.07 N, $\mu = 0.1$ for **1b**; 0.14–0.86 N, $\mu = 1.0$ for **1c**), followed by the addition of 50 μL of a 0.4–0.7 M solution of the ketone in acetonitrile. Aliquots of 2 mL of the reaction solution were taken at various time intervals (to 90% completion) and quenched with 3 mL of an aqueous solution of sodium thiosulfate (3.6–8.6 mM) and sodium acetate (0.1 or 1.0 M). 90–150- μL portion of the quenched mixture was injected into the HPLC, and the disappearance of ketone was monitored at 268 (**1a**) or 264 nm (**1b,c**) by use of a C_{18} column and 40% methanol (**1a**), 25% acetonitrile (**1b**), or 50% methanol (**1c**) as the eluting solvent.

Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Molecular Recognition and Stereoselectivity: Geometrical Requirements for the Multiple Hydrogen-Bonding Interaction of Diols with a Multidentate Polyhydroxy Macrocyclic¹

Yasuaki Kikuchi,[†] Yasushi Kato,[‡] Yasutaka Tanaka,[‡] Hiroo Toi,^{†,2} and Yasuhiro Aoyama^{*,†,2}

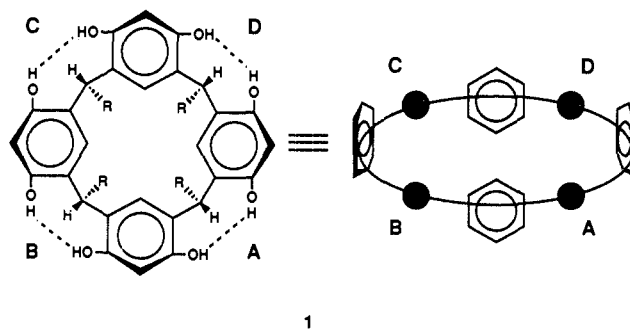
Contribution from the Department of Industrial Chemistry, Hachinohe National College of Technology, Tamonoki, Hachinohe, Aomori 031, Japan, and Department of Chemistry, Nagaoka University of Technology, Kamitomioka, Nagaoka, Niigata 940-21, Japan.

Received August 15, 1990

Abstract: Resorcinol–dodecanal cyclotetramer **1** in CDCl_3 forms hydrogen-bonded, 1/1 complexes with cyclohexanediols as well as with 2,4-pentane- and 2,5-hexanediol as their open-chain analogues and cyclohexanol and *cis*- and *trans*-4-*tert*-butylcyclohexanol. The affinities to **1** of cyclic diols ($K = (1.1\text{--}10) \times 10^2 \text{ M}^{-1}$ at 25 °C) are significantly larger than those of open-chain diols ($36\text{--}43 \text{ M}^{-1}$) and monools ($8\text{--}11 \text{ M}^{-1}$). Those of regio- and stereoisomers of cyclohexanediol depend on the configuration (axial–equatorial > diequatorial) and relative positions (1,4 \gg 1,2 > 1,3) of the two OH groups involved and decrease in the order *cis*-1,4 ($K = 1.04 \times 10^3$) > *cis*-1,2 (2.64×10^2) > *trans*-1,3 (1.81×10^2) > *trans*-1,4 (1.29×10^2) > *cis*-1,3 (1.24×10^2) > *trans*-1,2 ($1.06 \times 10^2 \text{ M}^{-1}$); the stereoselectivities are thus *cis*-1,4/*trans*-1,4 = 8.0, *cis*-1,2/*trans*-1,2 = 2.5, and *trans*-1,3/*cis*-1,3 = 1.5. The selectivities in the diol binding are discussed in terms of multiple hydrogen bonding of diol and **1**. The relatively large binding constant (K) for *cis*-1,4-diol with one axial and one equatorial OH group is attributed to an effective and simultaneous two-point hydrogen bonding of the two OH groups with two adjacent binding sites of **1** as a multidentate host.

The recent several years have seen a rather explosive development in molecular recognition based on hydrogen bonding.^{3–7} Much work has been concerned with the preorganized or oriented multipoint hydrogen-bonding fixation of *two-dimensional* and flat heteroaromatic guests such as nucleobases and related nitrogen heterocycles.⁶ Many other biorelevant molecules including sugars, steroids, alkaloids, and so on also have rigid and cyclic structures, but they are *three-dimensional*, giving rise to not only two-dimensional regiochemical but also three-dimensional stereochemical problems.

Resorcinol–dodecanal cyclotetramer **1** is what may be called a tetradentate host having four independent binding sites (A–D) composed of a pair of hydrogen-bonded OH groups on adjacent benzene rings. It is capable of selective *extraction* of sugars from



water into CCl_4 .⁷ A better understanding of the phenomenologically interesting selectivities observed, however, is hindered

[†]Hachinohe National College of Technology.

[‡]Nagaoka University of Technology.

(1) Molecular Recognition. 15. Part 14: Tanaka, Y.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* 1990, 63, 3343.

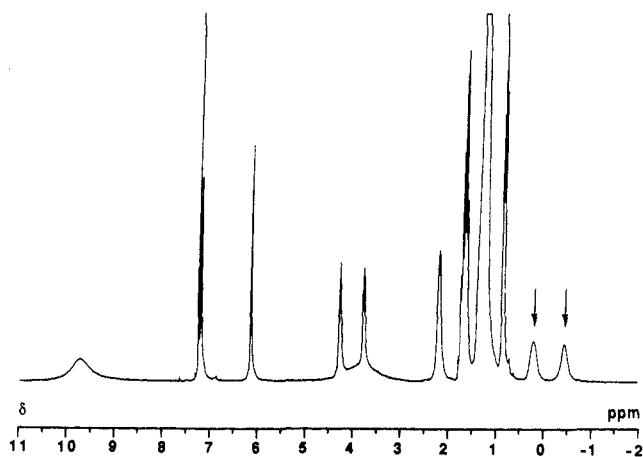


Figure 1. ^1H NMR spectrum of a CDCl_3 solution of **1** (1.0×10^{-2} M) and **4c** (3.0×10^{-2} M) at 25°C . Signals with marks are for the methylene protons on 2-C, 3-C, 5-C, and 6-C of bound **4c**.

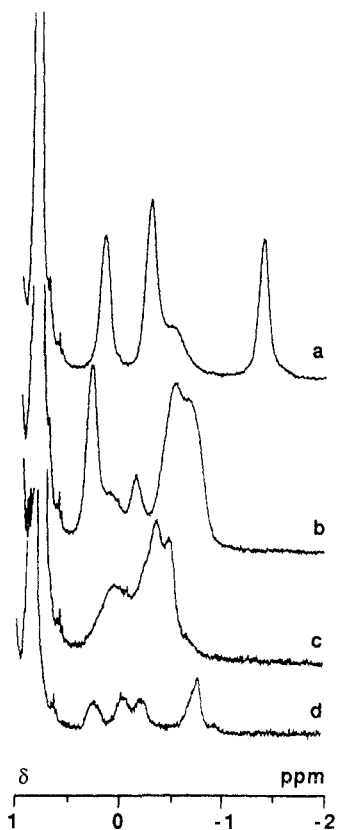


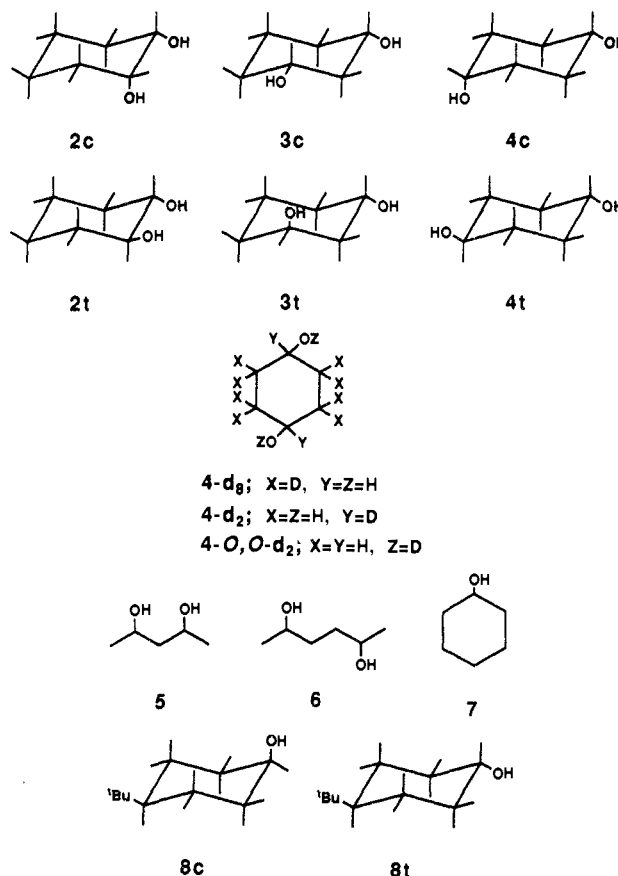
Figure 2. High-field portions of the ^1H NMR spectra of selected **1**-guest complexes in CDCl_3 at 25°C : a, **1-2c**; b, **1-3t**; c, **1-6**; d, **1-7**. The sharp absorption at δ 0.85 is for the methyl protons of host **1**.

by the lack of homogeneous binding data as well as by the lack of enough information as to the solvation/desolvation thermo-

dynamics for sugars in water. In the present work, we have investigated the interactions of **1**, as a multidentate but essentially two-dimensional host, and isomeric cyclohexanediols,⁸ as a family of simple and three-dimensional multifunctional guests. We report here on the geometrical requirements for the multiple host-guest hydrogen-bonding interactions in *homogeneous* solutions.

Results and Discussion

Complexation via Hydrogen Bonding. The interactions of host **1** and cyclohexanediols (*cis*- and *trans*-1,2- (**2c** and **2t**), -1,3- (**3c** and **3t**), and -1,4-cyclohexanediol (**4c** and **4t**), open-chain 1,3- and 1,4-diols (2,4-pentanediol (**5**) and 2,5-hexanediol (**6**)), and cyclic monools (cyclohexanol (**7**) and *cis*- and *trans*-4-*tert*-butylcyclohexanol (**8c** and **8t**)) were investigated by ^1H NMR spectroscopy. The spectrum at 25°C of a CDCl_3 solution of **1**



(1.0×10^{-2} M) and **4c** (0.5 – 5.0×10^{-2} M) as a representative of cyclic diol showed a pair of new resonances at higher fields (those with marks in Figure 1). These were readily assigned to the methylene protons on 2-C, 3-C, 5-C, and 6-C of **4c** bound with **1** on the basis of selective deuteration; such high-field signals were completely absent when 1,4-cyclohexanediol-2,2,3,3,5,5,6,6- d_8 (**4-d₈**, as a mixture of *cis* and *trans* isomers) was used in place of **4c** but present when the 1,4- d_2 or O,O- d_2 derivatives (**4-d₂** or **4-O,O-d₂**, respectively, as a mixture of *cis* and *trans* isomers) were employed. 2,5-Hexanediol (**6**) as a representative of open-chain diols was also shown to form a complex with host **1**. The high-field resonances (Figure 2) were assigned to the methyl protons on 1-C and 6-C and the methylene protons on 3-C and 4-C in a similar manner

(2) Present address: Section of Bioorganic Chemistry, Department of BioEngineering, Nagaoka University of Technology.

(3) (a) Rebek, J., Jr. *Science (Washington, D.C.)* **1987**, *235*, 1478. (b) Rebek, J., Jr. *Angew. Chem.* **1990**, *102*, 261; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245.

(4) (a) Aoyama, Y.; Yamagishi, A.; Asakawa, M.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 4076. (b) Aoyama, Y.; Asakawa, M.; Yamagishi, A.; Toi, H.; Ogoshi, H. *Ibid.* **1990**, *112*, 3145.

(5) Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2807.

(6) (a) Reference 3 and references cited therein. (b) Kelly, T. P.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. (c) Hamilton, A. D.; Van Engen, D. *Ibid.* **1987**, *109*, 5035. (d) Chang, S.-K.; Hamilton, A. D. *Ibid.* **1988**, *110*, 1318. (e) Bell, T. W.; Liu, J. *Ibid.* **1988**, *110*, 3673. (f) Muehldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *Ibid.* **1988**, *110*, 6561. (g) Adrian, J. C.; Wilcox, C. S. *Ibid.* **1989**, *111*, 8055. (h) Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek, J., Jr. *Ibid.* **1989**, *111*, 1090. (i) Zimmerman, S. C.; Wu, W. *Ibid.* **1989**, *111*, 8054.

(7) (a) Aoyama, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 634. (b) Aoyama, Y.; Tanaka, Y.; Sugahara, S. *Ibid.* **1989**, *111*, 5397.

(8) For examples of binding of organic hydroxyl compounds, see: (a) Moneta, W.; Baret, P.; Pierre, J.-L. *J. Chem. Soc., Chem. Commun.* **1985**, 899. (b) Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7120. (c) Kobino, K.; Takahashi, M.; Nishikawa, N.; Kakiuchi, K.; Tobe, Y.; Odaira, Y. *Tetrahedron Lett.* **1987**, *28*, 3825. (d) Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 4071. For a review on the incorporation of various compounds including alcohols in crystal lattices of host compounds, see: Toda, F. *Top. Curr. Chem.* **1987**, *140*, 43.

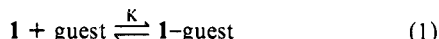
as above by use of 2,5-hexanediol-1,1,1,3,3,4,4,6,6,6- d_{10} and the 2,5- d_2 and *O,O*- d_2 derivatives.

The characteristic high-field absorptions for bound **4c** showed an integration of nearly 8 H at a sufficiently high concentration of **4c** (5.0×10^{-2} M) in accord with the above assignment, and their chemical shifts (δ 0.20 and -0.45 , Figure 1) were independent of [**4c**] in excess of **1**. The hydroxymethine proton resonance for free **4c** at δ 3.79, on the other hand, exhibited no change in the chemical shift in the presence of host **1**; its intensity, however, underwent such a reduction as to correspond to the formation of complexes **1-4c**. In fact, the intensity loss for this absorption and the intensity gain for the high-field resonances at δ 0.20 and -0.45 were always in a ratio of 2/8. The hydroxymethine proton resonance for bound **4c** could not be identified, probably due to overlap with resonances of host **1**. These results clearly indicate that the exchange between free **4c** and bound **4c** (refer to eq 1) is slow at room temperature compared with the NMR time scale; they give rise to distinct resonances with their *true* chemical shifts and integrations. This is, however, not the case in most previous examples of host-guest complexations,⁹ including those based on hydrogen bonding in apolar organic media,¹⁰ where the exchange between free and bound guest molecules is rather rapid to give concentration-dependent, averaged chemical shifts.

Other diols (**2-5**) and monools (**7** and **8**) exhibited similar behavior. Examination of ¹H NMR spectra indicates that what are characteristic of complex **1-4c** are generally true for other complexes, including those derived from monools; in every case, exchange between free and bound guest molecules is slow and all the ¹H resonances for bound guests except for those for the hydroxyl and hydroxymethine protons appear at higher fields. The high-field portions of the spectra of selected complexes are shown in Figure 2. The complexation-induced upfield shifts (1–3 ppm) for the C–H protons of bound guests as a result of the ring-current effects of the benzene rings of **1** are in accord with those for bound ribose,^{7b} glutaric acid,⁵ and methyl β -glucopyranoside.¹¹

The high-field NMR signals characteristic of complexation were not observed when either octaacetate of **1** or diacetate of diol **4c** or **6** was used in CDCl₃ or when **1** (1.0×10^{-2} M) and **4c** or **6** (3.0×10^{-2} M) were mixed in acetone- d_6 , a hydrogen bond breaking polar solvent. These results leave little doubt that hydrogen bonding between OH groups of **1** and diol is responsible for their complexation in CDCl₃.

Stoichiometry and Binding Constants. The appearance of distinct ¹H NMR signals for free and bound guest molecules without undergoing averaging allows a direct and accurate determination of [1-guest] in solution. Figure 3 shows the typical Job plots of [1-4c] vs mole fractions of **1** (f_1) for the complexation of **1** and diol **4c** under conditions where [**1**]_t + [**4c**]_t is kept constant at 1.0×10^{-2} M ($t = \text{total}$). The maximum occurs at $f_1 = 0.5$, indicating that the complex has a 1/1 (**1** to diol) stoichiometry (eq 1). The binding constant (K) is expressed in terms of the



$$K = \frac{[\mathbf{1}\text{-guest}]}{([\mathbf{1}]_t - [\mathbf{1}\text{-guest}])([\text{guest}]_t - [\mathbf{1}\text{-guest}])} \quad (2)$$

$$= \frac{C}{(1-C)(r-C)[\mathbf{1}]_t}$$

extent of complexation ($C = [\mathbf{1}\text{-guest}]/[\mathbf{1}]_t$) and the guest/host molar ratio ($r = [\text{guest}]_t/[\mathbf{1}]_t$), as in eq 2. In Figure 4 are shown the correlations of C and r for the complexations of **4c** and **6** with **1** under conditions of [**1**]_t = 1.0×10^{-2} M. The values of K calculated by eq 2, as summarized in Table I, are reasonably constant at different r 's (0.5–5.0).

The binding properties of other diols (**2c**, **2t**, **3c**, **3t**, **4t**, and **5**) and monools (**7**, **8c**, and **8t**) were analyzed in a similar manner.

(9) Diederich, F. *Angew. Chem.* **1988**, *100*, 372; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362.

(10) (a) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426. (b) Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek, J., Jr. *Ibid.* **1989**, *111*, 1090.

(11) Tanaka, Y.; S. Sutarto, Aoyama, Y. Unpublished results.

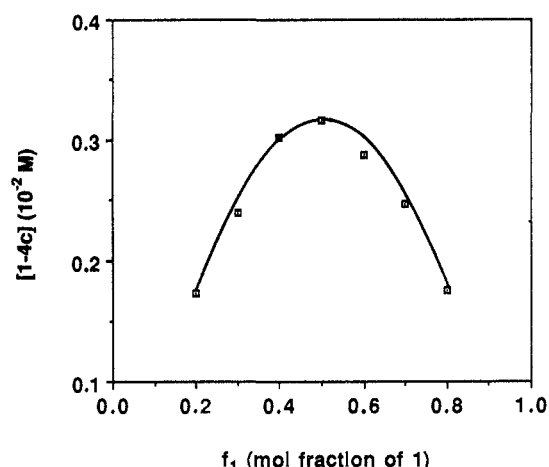


Figure 3. Job plots of [1-4c] vs mole fractions of **1** for the complexation of **1** and **4c** in CDCl₃ at 25 °C under conditions where [**1**]_t + [**4c**]_t is maintained at 1.0×10^{-2} M.

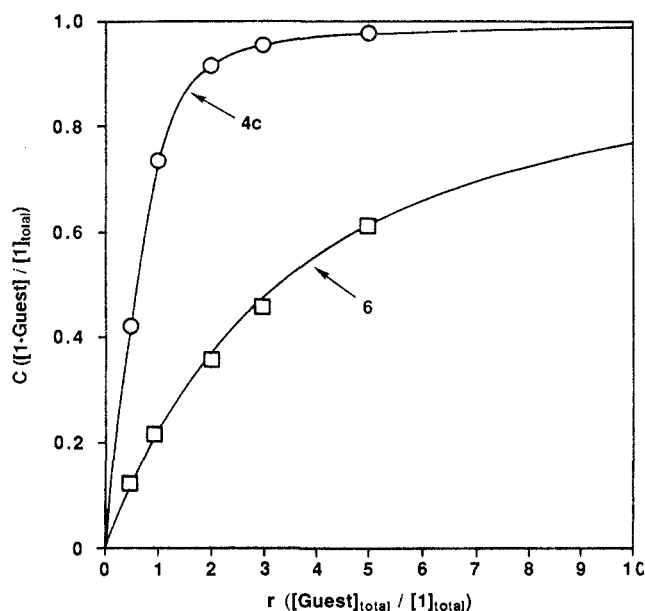


Figure 4. Correlations of the extents of complexation ($C = [\mathbf{1}\text{-guest}]/[\mathbf{1}]_t$) between **1** and **4c** or **6** in CDCl₃ at 25 °C and the host-guest molar ratios ($r = [\text{guest}]_t/[\mathbf{1}]_t$).

The dependencies of complexation on [guest] are illustrated in Figure 5 in the form of C - r correlations, and all the binding constants together with associated free energy changes are summarized in Table II. The solid lines in Figures 4 and 5 are theoretical ones based on the binding constants thus obtained. In Table II are also shown the configurations of the OH groups in cyclic diols and monools and the separations (O–O distances) of two OH groups in cyclic diols as evaluated from examination of CPK molecular models.

Selectivity. Inspection of Table II reveals several important points: (1) diols **2-6** have significantly higher affinities to **1** as compared with those of monools **7** and **8**; (2) the affinities of cyclic diols **2-4** are substantially higher than those of open-chain analogues **5** and **6**; (3) the *cis* stereoisomers are not necessarily bound more firmly with **1** than the *trans*, and the stereoselectivities in the binding of cyclic diols decrease in the order $4c/4t = 8.0^{12}$ ($\Delta\Delta G^\circ = 1.23$) \gg $2c/2t = 2.5$ ($\Delta\Delta G^\circ = 0.54$) $>$ $3t/3c = 1.5$ ($\Delta\Delta G^\circ = 0.23$ kcal/mol); (4) the lower affinity stereoisomers **4t**, **2t**, and **3c** have similar binding constants, while those of the higher affinity stereoisomers **4c**, **2c**, and **3t** depend on the separation (1,2-,

(12) This stereoselectivity is in accord with the α/β diastereoselectivity of ca. 30/1 (after correction for a concentration factor) in the extraction of ribopyranose with **1**.^{7b}

Table I. Analysis of the Binding of Diol with Host **1**^{a,b}

4c			6		
r	C	K (10 ³ M ⁻¹)	r	C	K (M ⁻¹)
0.497	0.421	0.957	0.500	0.124	37.6
0.985	0.735	1.11	0.942	0.218	38.5
1.982	0.915	1.01	2.010	0.359	33.9
2.981	0.955	1.05	2.969	0.458	33.6
4.995	0.977	1.06	4.961	0.625	38.4
av		1.04			36.4

^aIn CDCl₃ at 25 °C. [1]_t = 1.0 × 10⁻² M. ^br = [guest]_t/[1], C = [1-guest]/[1]_t, and K is calculated according to eq 2.

Table II. Geometrical Parameters of Guest Alcohols and Their Binding Constants (K) with Host **1**^a and Associated Free Energy Changes (ΔG°)

guest	config ^b of OH group(s)	O-O dist (Å) ^c	K ^d (M ⁻¹)	ΔG° ^e (kcal/mol)
2c	a, e	2.7	(2.64 ± 0.37) × 10 ²	-3.30 ± 0.08
2t	e, e	2.8	(1.06 ± 0.17) × 10 ²	-2.76 ± 0.09
3c	e, e	4.7	(1.24 ± 0.10) × 10 ²	-2.85 ± 0.05
3t	a, e	4.1	(1.81 ± 0.08) × 10 ²	-3.08 ± 0.04
4c	a, e	4.4	(1.04 ± 0.08) × 10 ³	-4.11 ± 0.04
4t	e, e	5.5	(1.29 ± 0.12) × 10 ²	-2.88 ± 0.05
5			42.9 ± 1.3	-2.23 ± 0.02
6			36.4 ± 2.5	-2.13 ± 0.04
7			11.0 ± 1.0	-1.42 ± 0.05
8c	a		7.8 ± 1.8	-1.22 ± 0.10
8t	c		8.4 ± 1.1	-1.26 ± 0.07

^aComplexation in CDCl₃ at 25 °C. ^bConfiguration; a and e stand for axial and equatorial, respectively. ^cFrom examination of CPK molecular models. ^dFrom eq 2. ^eAt 25 °C (298 K).

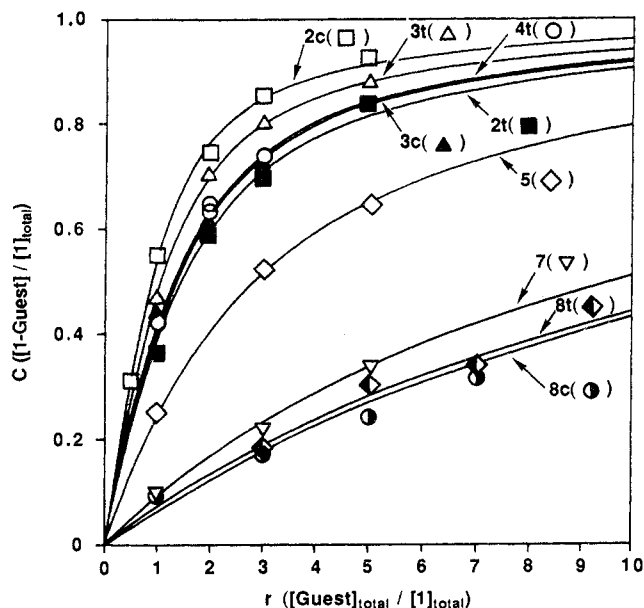


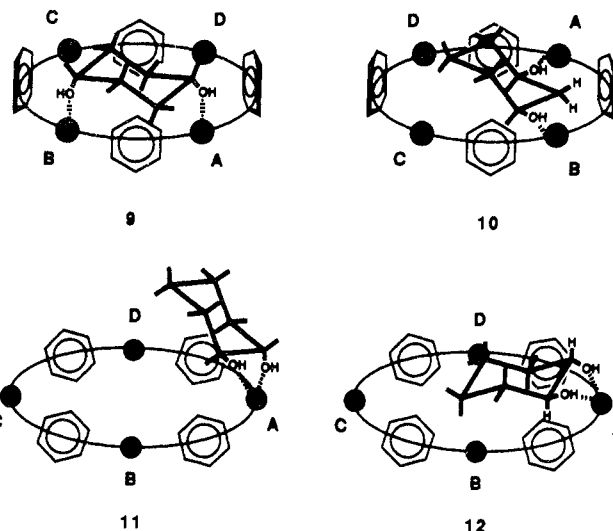
Figure 5. Correlations of the extents of complexation ($C = [1\text{-guest}]/[1]_t$) between **1** and a guest alcohol (**2c**, **2t**, **3c**, **3t**, **4t**, **5**, **7**, **8c**, or **8t**) in CDCl₃ at 25 °C and the host-guest molar ratios ($r = [1]_t/[1]_{\text{total}}$).

1,3-, or 1,4-) of the two OH groups involved; and (5) the cyclic *cis*-1,4-diol **4c** has an exceptionally large binding constant, and the associated free energy change (-4.11 kcal/mol) is more negative than 2 times that for the binding of monool reference **7** ($2 \times -1.42 = -2.84$ kcal/mol).

Item 1 points to the importance of multiple hydrogen bonding between **1** and a diol. Item 2 is understandable in terms of conformational flexibility of open-chain diols; two-point fixation of these must be accompanied by freezing of rotation around internal C-C bonds.¹³ The selectivity in the binding of regio- and stereoisomers of rigid cyclohexanediol, as summarized in items

3 and **4**, may be interpreted in terms of effectiveness of the multiple hydrogen bonding. The cyclohexane ring has a chair conformation as the most stable one. The skew-boat comes next; even that lies 5-6 kcal/mol above the chair.^{14,15} In view of this big energy difference, it is safely assumed that cyclohexanediols are bound with **1** also in a chair conformation. With reference to items **3** and **4**, the chair form of the separation-independent, low-affinity stereoisomers (**4t**, **2t**, and **3c**) have two equatorial OH groups, while that of the separation-dependent, high-affinity stereoisomers (**4c**, **2c**, and **3t**) have one axial and one equatorial OH group. A mere involvement of an axial OH group is not responsible for the observed higher affinities, since the binding constant of the conformationally fixed *cis* monool reference **8c** having an axial OH group is very close to those of the *trans* isomer **8t** having an equatorial OH group as well as parent cyclohexanol (**7**) (Table II).

Examination of CPK molecular models indicates that *cis*-1,4-diol **4c** with an O-O distance of 4.4 Å (Table II) allows a simultaneous two-point hydrogen-bonding involving both OH groups of **4c** and the adjacent A and B binding sites of host **1** (refer to structure **9**). This is not the case, however, for the *trans* isomer



4t, where the axial hydrogen (1-H or 4-H) interferes with such a two-point interaction. In the *cis*-1,3-diol **3c**, the separation of the two OH groups is long enough. They are, however, both in the equatorial positions.¹⁶ If they were to interact simultaneously with binding sites A and B, a severe steric interaction would be encountered between the benzene ring linking them and the axial 2-H of **3c** (refer to structure **10**). Such a steric interaction could be less pronounced when one OH group is in an axial position as in the *trans* isomer **3t**. In this case, however, the separation of two OH groups is too short; it seems, on the other hand, to be too long to allow their simultaneous interaction with one binding site A. Such an interaction is possible for 1,2-diol **2**. The dihedral angle and hence the strength of intramolecular hydrogen bonding of the two OH groups are almost the same for the *cis* (**2c**) and *trans* (**2t**) isomers.¹⁸ From the viewpoint of minimizing steric interaction, one may expect an *end-on* binding of the *trans* or the diequatorial isomer (**2t**) with **1** (refer to structure **11**). This seems to be not the case, however. Complexes **1-2t**, **1-2c**, and even **1-7**

(14) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1959**, *81*, 5727. (b) Howlett, K. E. *J. Chem. Soc.* **1957**, 4353. (c) Hazebroek, P.; Oosterhoff, L. J. *Discuss. Faraday Soc.* **1951**, *10*, 87. (d) Hendrickson, J. B. *J. Am. Chem. Soc.* **1961**, *83*, 4537.

(15) (a) Johnson, W. S.; Bauer, V. J.; Margrave, J. L.; Frisch, M. A.; Dreger, L. H.; Hubbard, W. N. *J. Am. Chem. Soc.* **1961**, *83*, 606. (b) Allinger, N. L.; Freiberg, L. A. *Ibid.* **1960**, *82*, 2393.

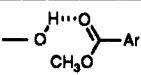
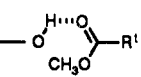
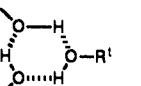
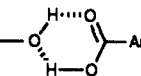
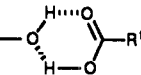
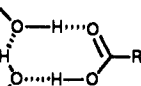
(16) Binding of *cis*-1,3-diol as a diaxial conformation remains a possibility. This is, however, unlikely in view of a severe steric interaction between two axial OH groups (1.9 kcal/mol).¹⁷

(17) Angyal, S. J.; McHugh, D. *J. Chem. Ind. (London)* **1955**, 947. (b) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; Chapter 8.

(18) Kuhn, L. P. *J. Am. Chem. Soc.* **1952**, *74*, 2492.

(13) For a recent discussion on this point, see ref 4b.

Table III. Selectivity Factors (K_2) and Associated Free Energy Changes (ΔG°_2) for Intramolecular Hydrogen Bonding (HB)

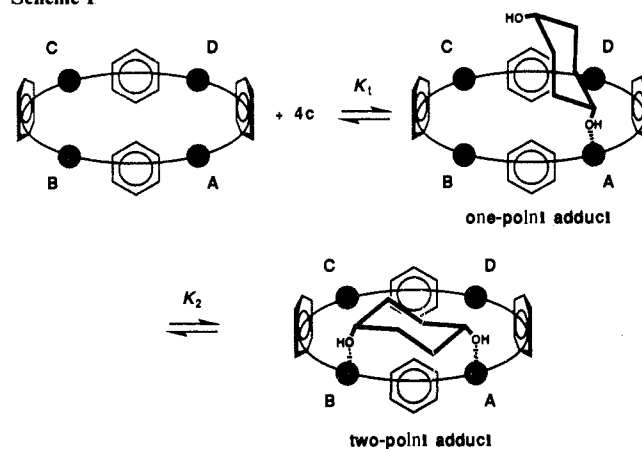
type of HB ^a	HB involved in complex	K_2^d (M ⁻¹)	$\Delta G^\circ_2^e$ (kcal/mol)	ref
	13^b (R = CH ₃)	9.5	-1.3	4b
	14^b (R = CH ₃)	42	-2.1	4a
	9^c	94	-2.7	this work
	13^b (R = H)	107	-2.7	4b
	14^b (R = H)	450	-3.5	4b
	15^c	1700, 3900	-4.4, -4.9	5

^aThe left- and right-hand sides are the binding sites of host and guest, respectively. Ar and R' stand for aromatic and aliphatic, respectively. ^bAT 15 °C (288 K). ^cAt 25 °C (298 K). ^d K_2 corresponds to the binding constant for the intramolecular hydrogen bonding in Scheme 1. ^e $\Delta G^\circ_2 = -RT \ln K_2$.

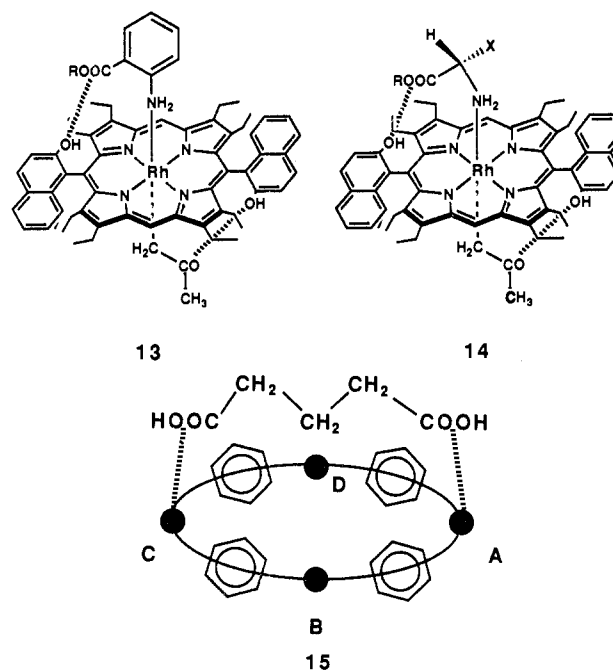
exhibit upfield-shifted ¹H NMR spectra (Figure 2) in a similar manner as complexes **1-4** and **1-3**, indicating that the protons on the cyclohexane ring of bound **2t**, **2c**, or **7** are close to the benzene rings of **1**. This may be a result of some kind of σ - π interaction, or other factors may come into play. Whatever the mechanistic details may be, if the cyclohexane ring of bound **2t** swings into the cavity of **1**, we have again a steric interaction between the benzene ring and the axial 1-H or 2-H of **2t** (refer to structure **12**).

In general, an equatorial OH group has geminal and cis vicinal hydrogen atoms that are axial; in addition, it lies approximately in the average plane of the cyclohexane ring, which must thus be forced in a closer proximity to the benzene rings to cause a more pronounced steric interaction. On the other hand, an axial OH group having geminal and cis vicinal hydrogen atoms in the equatorial positions avoids the cyclohexane ring and thus separates it from the benzene rings of **1** to reduce steric interactions between them. These model-building studies are summarized as follows. Multiple hydrogen bonding is difficult for diequatorial diols (**2t**, **3c**, and **4t**) irrespective of the separation of the two OH groups but is more favored for the axial-equatorial diols. The 1,4-diol **4c** would allow the two OH groups to interact separately with two binding sites of **1**, while the 1,2-diol **2c** would form a hydrogen-bond network involving the vicinal OH groups and one binding site of **1**; the multiple hydrogen bonding would be least effective for the *trans*-1,3-diol **3t** having an intermediate O-O distance. These expectations are consistent with what was observed, as summarized in items 3 and 4.

Deviation of free energy change from additivity, as indicated in item 5, is a general aspect of an effective multiple interaction. This is entropic in origin according to our detailed thermodynamic analysis of a two-point amino acid binding.^{4b} From a thermodynamic viewpoint, the formation of two-point adduct **1-4c** involves an intermolecular hydrogen bonding to give a one-point adduct followed by an intramolecular hydrogen-bonding to afford a two-point adduct (Scheme 1). If the binding constant of the first step (K_1) can be approximated to that (K_7) of monool reference **7**, then the selectivity for **4c** over **7** (K_{4c}/K_7) corresponds to the binding constant of the second step (K_2) with an associated free energy change of $\Delta G^\circ_2 = \Delta G^\circ_{4c} - \Delta G^\circ_7$. These analyses provide two ways of characterization of the present host-guest interaction in light of those in other systems. The first is the

Scheme I

magnitudes of ΔG°_2 , i.e., the free energy changes of intramolecular hydrogen bonding for the best bound guests. We have studied the formation of two-point adducts of amino acids and amino esters with a naphthol-functionalized Rhodium(III) porphyrin (refer to structures **13** and **14**)⁴ and those of dicarboxylic acids with the present host **1** (refer to structure **15**).⁵ In Table III are shown



the types of hydrogen bonding involved, the selectivity factors due to the hydrogen bonding (K_2), and the associated free energy changes ($\Delta G^\circ_2 = -RT \ln K_2$) for these systems and the present one. The variation in ΔG°_2 on going from simple monofunctional to bifunctional binding sites of host and guest is dramatic but reasonable. The second is the superiority of a two-point interaction in complex **1-4c** as compared with two independent one-point interactions. Let us assume that the thermodynamic parameters for the intermolecular hydrogen-bonding in step 1 (Scheme 1) are the same as those for the complexation of **1** and **7** and that the enthalpy changes for the intermolecular and intramolecular hydrogen-bonding interactions in steps 1 and 2, respectively, are the same.¹⁹ Then, the deviation of free energy change from additivity in item 5, $\Delta G^\circ_{4c} - 2(\Delta G^\circ_7) = -1.27$ kcal/mol, corresponds to the extent to which the intramolecular hydrogen bonding is entropically more favorable than the intermolecular hydrogen bonding; $\Delta G^\circ_{4c} - 2(\Delta G^\circ_7) = \Delta G^\circ_1 + \Delta G^\circ_2 - 2(\Delta G^\circ_7) = \Delta G^\circ_2 - \Delta G^\circ_7$

(19) This assumption is in fact approximately true for the intramolecular hydrogen-bonding interaction in adduct **13** (R = CH₃) and its intermolecular counterpart; see ref 4b.

$= -T\Delta S^\circ_2 - (-T\Delta S^\circ_7)$. The observed value (-1.27 kcal/mol) is in excellent agreement with that for the hydrogen bonding in adduct **13** ($R = CH_3$), where $\Delta S^\circ_{\text{intra}} = -5.3$ and $\Delta S^\circ_{\text{inter}} = -10.2$ cal/mol K so that $-T\Delta S^\circ_{\text{intra}} - (-T\Delta S^\circ_{\text{inter}}) = -1.5$ kcal/mol at 298 K.^{4b}

Conclusions

Polyhydroxy macrocycle **1** forms hydrogen-bonded 1/1 complexes with cyclohexanediols in a regio- and stereoselective manner. An important geometrical requirement for the multiple interaction of a cyclohexanediol with host **1** is the axial-equatorial orientation of two OH groups, the location or the separation of which then determines the effectiveness of multiple hydrogen bonding involving either two adjacent binding sites A and B or one site A of host **1**. On the other hand, multiple hydrogen bonding is not effective for cyclohexanediols having diequatorial OH groups irrespective of their location, presumably due to steric effects of the axial hydrogen atoms. Thus, the affinities to **1** decrease in the order **4c** (1,4-*cis*-a,e) > **2c** (1,2-*cis*-a,e) > **3t** (1,3-*trans*-a,e) > **4t** (1,4-*trans*-e,e) \cong **3e** (1,3-*cis*-e,e) \cong **2t** (1,2-*trans*-e,e) > **5** (open-chain-1,3) \cong **6** (open-chain-1,4) > **7** \cong **8c** \cong **8t** (monool), where a and e stand, respectively, for the axial and equatorial configurations. The stereoselectivities decrease in the order **4c/4t** \gg **2c/2t** > **3t/3c** as a consequence. A two-point interaction is significantly more favorable than two independent one-point interactions. This is the case at least for the best bound guest **4c**.

The present results provide a clue for a better understanding of the selectivities in the extraction of sugars.^{7b} Molecular recognition of other types of biomolecules having alcoholic OH groups, especially steroids, is also an interesting extension of this work.

Experimental Section

Macrocyclic host **1** and its octaacetate derivative were obtained as described.^{7b} 2,4-Pentanediol (**5**), 2,5-hexanediol (**6**), cyclohexanol (**7**), and *cis*- (**8c**) and *trans*-4-*tert*-butylcyclohexanol (**8t**) were commercial products of the highest grades.

1,2-Cyclohexanediols (2). *cis*-1,2-Cyclohexanediol (**2c**) was prepared by $KMnO_4$ oxidation of cyclohexene in water²⁰ and purified by recrystallization from *n*-hexane-ether: mp 97 °C (lit.²¹ mp 98 °C); purity 100% (by means of both gas chromatography (GC) and ¹H NMR analyses). *trans*-1,2-Cyclohexanediol (**2t**) was obtained by hydrolysis of cyclohexene oxide in HCO_2H-H_2O ²² and recrystallized from acetone: mp 104 °C (lit.²¹ mp 104 °C); purity 100% (GC and NMR).

1,3-Cyclohexanediol (3) and 1,4-Cyclohexanediol (4).²³ Stereoisomers in a commercially available sample were separated. Thus, a 3/2 mixture of *cis* (**3c**) and *trans* (**3t**) isomers was recrystallized from acetone to give crude crystals and mother liquid. The former was repeatedly recrystallized to give *cis*-diol **3c**: mp 84 °C (lit.²¹ mp 86 °C); ¹H NMR ($CDCl_3$) δ 3.76 (*CHOH*); IR (KBr) 3280 cm^{-1} (ν_{OH}); purity 100% (GC and NMR). From the mother liquid was recovered a 1/1 mixture of **3c** and **3t**. This mixture (31.7 g) was esterified with benzoyl chloride (95.9 g) and pyridine (65.0 g) in chloroform (150 mL) at room temperature for 24 h. The *trans*-dibenzoate (29.7 g, 34%) was obtained by chromatography on silica gel with chloroform as eluant, followed by recrystallization from methanol. A solution of *trans*-diester thus obtained (28.8 g) in ethanol (150 mL) saturated with HCl was refluxed for 72 h. Workup, chromatography on silica gel with methanol as eluant, and recrystallization from ether afforded *trans*-diol **4t** (5.1 g, 50%): mp 115 °C (lit.²¹ mp 117 °C); ¹H NMR ($CDCl_3$) δ 4.08 (*CHOH*); IR (KBr) 3260 cm^{-1} (ν_{OH}); purity 100% (GC and NMR).

A commercially available stereoisomer mixture of **4c** and **4t** was esterified with acetic anhydride and pyridine at room temperature for 24 h. The stereoisomer mixture of diacetate was recovered by chromatography on alumina with chloroform as eluant and was recrystallized from methanol to give *trans*-diacetate (31%) as crystals and mother liquid that was rich in *cis*-diacetate. The former was taken in an aqueous 6 N HCl, and the solution was refluxed for 5 h to achieve hydrolysis. Workup and repeated recrystallization from acetone gave *trans*-diol **4t** (88%): mp 140 °C (lit.²¹ mp 143 °C); ¹H NMR ($CDCl_3$) δ 3.63 (*CHOH*); IR (KBr) 3250 cm^{-1} (ν_{OH}); purity 100% (GC and NMR). The stereoisomer mixture of diacetate recovered from the mother liquid was hydrolyzed as above. The diol stereoisomer that resulted was subjected to repeated recrystallization from acetone to remove *trans*-diol **4c**. From the mother liquid containing sufficiently concentrated *cis* isomer was obtained a highly purified material of **4c** by recrystallization from acetone or *n*-hexane-acetone followed by careful visual selection of the well-developed needles of **4c**: mp 111 °C (lit.²¹ mp 112.4–112.8 °C); ¹H NMR ($CDCl_3$) δ 3.79 (*CHOH*); IR (KBr) 3290 cm^{-1} (ν_{OH}); purity 96.5% (GC) or 96.9% (NMR), the remaining 3.5 or 3.1% being the *trans* isomer **4t**.

Deuterated Compounds. 1,4-Cyclohexanediol-2,2,3,3,5,5,6,6-*d*₈ (**4-d**₈) was obtained as follows. A mixture of 1,4-cyclohexanedione (3.0 g) and D₂O (10 mL) containing a catalytic amount of DCl was stirred at 40 °C for 24 h. This procedure was repeated again for the residue obtained by workup. A solution of thus prepared deuterated diketone (3.0 g) in chloroform (50 mL) was added dropwise into $NaBH_4$ under stirring at room temperature. The mixture was stirred for 72 h, treated with a dilute aqueous HCl solution, and extracted with chloroform. The extract was dried over Na_2SO_4 , the solvent evaporated, and the residue recrystallized from acetone to give **4-d**₈: yield 55%; isotopic purity 77% (¹H NMR). Reduction of 1,4-cyclohexanedione (1.0 g) with $NaBD_4$ ²⁴ (0.38 g) in chloroform (40 mL) in a similar manner afforded 1,4-cyclohexanediol-1,4-*d*₂, which was recrystallized from acetone: yield 65%; isotopic purity 99%. A solution of 1,4-cyclohexanediol (**4**) in D₂O was stirred at room temperature for 3 h and the solvent removed. This procedure was repeated again for the residue obtained to give 1,4-cyclohexanediol-*O,O*-*d*₂ (**4-O,O-d**₂): yield 99%, isotopic purity 98%.

2,5-Hexanediol-1,1,1,3,3,4,4,6,6,6-*d*₁₀ (**6-d**₁₀), 2,5-hexanediol-2,5-*d*₂ (**6-d**₂), and 2,5-hexanediol-*O,O*-*d*₂ (**6-O,O-d**₂) were obtained in essentially the same ways as above and purified by chromatography on silica gel with chloroform as eluant. Yields and isotopic purities are as follows: 45 and 93% for compound **6-d**₁₀, 82 and 97% for compound **6-d**₂, and 99 and 98% for compound **6-O,O-d**₂.

¹H NMR Spectra and Evaluation of Binding Constants. A series of $CDCl_3$ solutions of **1** and a guest diol or monool in a sealed test tube were stirred at 25 °C for 24 h, and their ¹H NMR spectra taken with a JEOL-GX 270 spectrometer at 25 °C. The concentration of complex formed (**1-guest**, eq 1) was determined either directly by referring to the integrations for the high-field resonances characteristic of the complex or indirectly according to $[1-guest] = [guest]_1 - [guest]$; use of an internal standard (1,1,2,2-tetrachloroethane, δ 5.97) allowed us to evaluate $[guest]_1 - [guest]$ from the intensities of the hydroxymethine-proton resonance of free guest in the absence and presence of host **1**. Results of both procedures were in excellent agreement. Sample solutions for the titrations contained a fixed amount of **1** (1.0×10^{-2} M) and varying amounts of a guest ($(0.5-7.0) \times 10^{-2}$ M). The relationships between the extents of complexation ($C = [1-guest]/[1]_0$) and the molar ratios $r = [guest]_1/[1]_0$ are shown in Figures 4 and 5. The binding constants (K) were calculated according to eq 2 at different $[guest]_0$; the average values together with estimated errors are shown in Table 11. Sample solutions for continuous variations contained **1** and a guest, keeping $[1]_0 + [guest]_0$ constant at 1.0×10^{-2} M. The correlations between the concentrations of **1-guest** obtained and the mole fractions of **1** are shown in Figure 3.

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.

(20) Criegee, R.; Stanger, J. *Chem. Ber.* **1936**, *69*, 2753.

(21) *Encyclopaedia Chimica*; Kyoritsu Publishing: Tokyo, 1963.

(22) Cf.: *Organic Syntheses*; John Wiley & Sons: New York, 1943; Collect. Vol. II; pp 307, 308.

(23) Perrine, T. D.; White, W. C. *J. Am. Chem. Soc.* **1974**, *96*, 1542.

(24) Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 122.