after 3 h, and **9H**$^+$ was precipitated with ether. (^{1}H NMR (CD_3CN): δ 6.68 (m, 2 H), 4.17 (br s, 2 H), 3.50 (br s, 2 H), 1.5-2.2 (m, 12 H), 1.35-1.5 (m, 2 H)). Deprotonation gave 23 mg of **9** (75% from **5**) as a white solid, mp 53-54 °C (after sublimation). ^{1}H NMR: δ 6.45 (m, 2 H), 3.40 (br s, 2 H), 2.91 (br s, 2 H), 1.48-2.3 (m, 12 H), 1.1-1.28 (m, 2 H). ^{13}C NMR: δ 130.8 (CH), 57.64 (CH), 55.53 (CH), 37.27 (CH_2), 25.43 (CH_2), 22.05 (CH_2), 19.23 (CH_2, half intensity). Empirical formula $C_{13}H_{20}N_2$ was established by high-resolution mass spectroscopy.

2,8-Diazatetracyclo[7.2.2.2^{3,7}.0^{2,8}]pentadecane (11). A mixture of 70 mg of **9** (0.34 mmol), 35 mg of K_2CO_3, 35 mg of 5% Pd on $BaCO_3$, and 8 mL of deaerated reagent-grade ethyl acetate were hydrogenated at atmospheric pressure. The H_2 uptake stopped after 9 mL of H_2 was taken up (~1 equiv). After filtration through Celite, bulb to bulb distillation gave 13 mg (19%) of **11** as a white solid, mp 37 °C. ^{1}H NMR: δ 2.92 (br s, 2 H), 2.77 (br s, 2 H), 2.0-2.4 (m, 3 H), 1.8-2.0 (m, 4 H), 1.5-1.8 (m, 10 H). ^{13}C NMR (CD_3CN): δ 55.3 (CH, bridgehead C), 54.2 (CH, bridgehead C), 38.5 (CH_2), 30.3 (CH_2), 24.5 (CH_2), 22.0 (CH_2), 20.5 (CH_2, half intensity).

2,8-Diazatetracyclo[7.3.2.2^{3,7}.0^{2,8}]hexadec-12-ene (10). To 0.23 g of **5** (1.83 mmol) in a flask with 10 mL of Et_2O was added 0.28 mL of HBF_4·Et_2O (~1 equiv) by syringe. The crude **5H**$^+$ was washed with 10 mL of ether, and 3 mL of CH_3CN followed by 0.22 mL of cycloheptadiene were added. After stirring for ~1 week at ambient temperature, the crude **10H**$^+$ was precipitated with ether. (^{1}H NMR (CD_3CN): δ 6.5 (m, 2 H), 4.07 (br s, 2 H), 3.55 (br s, 2 H), 1.2-2.2 (m, 16 H)). After stirring with 2 g of NaOH in 25 mL of Et_2O for 1 h, filtration, concentration, and recrystallization from Et_2O at -78 °C gave 32 mg of **10** (8% based on **5**) as a white solid, mp 52 °C. ^{1}H NMR: δ 6.15-6.35 (m, 2 H, olefinic H), 3.42 (br s, 2 H), 3.39 (br s, 2 H), 1.37-2.0 (m, 14 H), 1.06-1.33 (m, 2 H). ^{13}C NMR: δ 129.8 (CH, olefinic C), 59.8 (CH, bridgehead C), 57.0 (CH, bridgehead C), 36.7 (CH_2), 31.1 (CH_2), 20.4 (CH_2), 19.8 (CH_2, half intensity), 19.0 (CH_2, half intensity). Empirical formula $C_{14}H_{22}N_2$ was established by high-resolution mass spectroscopy.

2,8-Diazatetracyclo[7.3.2.2^{3,7}.0^{2,8}]hexadecane (12). A mixture of 150 mg of crude **10**, 33 mg of Pd on $BaCO_3$, 42 mg of K_2CO_3, and 15 mL of deaerated ethyl acetate were hydrogenated until H_2 uptake stopped (total uptake ~6 mL of H_2 in 2 h). After filtration through Celite and removal of solvent by rotary evaporation, 26 mg (17%) of **12** was obtained as a slightly yellow oil which was purified by bulb to bulb distillation. ^{1}H NMR: δ 2.98 (br s, 4 H), 1.4-2.2 (m, 20 H). ^{13}C NMR: δ 56.4 (CH, bridgehead C), 36.3 (CH_2), 20.6 (CH_2), 20.2 (half intensity). Empirical formula $C_{14}H_{24}H_2$ was established by high-resolution mass spectroscopy.

Electrochemical,[2] ESR,[2] PES,[7b] and UV[14] measurements were conducted as previously described. AM1 calculations were carried out on a VAX 8650, using program package AMPAC[10b] as modified by Timothy Clark.

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Molecular Recognition. 5.[1] Molecular Recognition of Sugars via Hydrogen-Bonding Interaction with a Synthetic Polyhydroxy Macrocycle[2]

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Contribution from the Department of Chemistry, Nagaoka University of Technology, Kamitomioka, Nagaoka, Niigata 940-21, Japan. *Received November 7, 1988*

Abstract: The resorcinol-aldehyde cyclotetramer **1a** as a lipophilic polar host solubilizes glycerol and water (neat liquids) and ribose (in an aqueous solution) as polar guests in CCl_4 upon formation of monomeric complexes **1a**·4(glycerol), **1a**·4H_2O, and **1a**·(ribose)·2H_2O, where ribose is bound highly selectively in the α-pyranose form. The extraction of 1,4-cyclohexanediol is also stereoselective, the cis isomer being extracted readily. A pair of hydrogen-bonded OH groups on adjacent benzene rings in **1a** provide the essential binding site for a guest OH group. While glycerol and H_2O are singly bound with such a binding site via hydrogen bonding, α-ribopyranose and *cis*-1,4-cyclohexanediol are doubly bonded with two binding sites separated by a metaphenylene bridge. Examination of CPK molecular models indicates that such a two-point **1a**-guest interaction is possible when the six-membered ring of a guest has cis OH groups on 1-C and 4-C, as in the case of α-ribopyranose and *cis*-1,4-cyclohexanediol. The extractabilities, or affinities to **1a**, of various aldopentoses, aldohexoses, and their deoxy derivatives decrease in the following order: fucose (6-deoxygalactose) > 2-deoxyribose > ribose > arabinose ≅ rhamnose (6-deoxymannose) ≫ galactose ≅ xylose ≅ lyxose ≅ mannose ≅ glucose. The affinities of sugars are governed by three factors: (1) the stereochemistry of the OH groups on 3-C and 4-C (cis ≫ trans), (2) the lipophilicity of the substituent on 5-C (CH_3 ≫ H ≫ CH_2OH), and (3) the nature of the substituent on 2-C (H > *cis*-OH > *trans*-OH, where cis and trans are with respect to the OH group on 3-C). Structural requirements for the formation of stable **1a**-sugar complexes are discussed in terms of maximization of favorable hydrogen-bonding interaction and minimization of unfavorable exposure of the sugar OH groups to bulk solvent.

The hydrogen bonding plays an essential role in biological informational interactions involving proteins, oligo- and polysaccharides, and nucleic acids. Molecular recognition of their constituents via the host-guest type interaction involving hydrogen bonding is a rapidly growing area. Much attention has been paid to the complexation of amino acids[3] and nucleobases and related

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(2) Preliminary accounts of this work: Aoyama, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 634.

(3) (a) Helgeson, R. C.; Koga, K.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 3021. (b) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *Ibid.* **1987**, *109*, 2432. (c) Aoyama, Y.; Yamagishi, A.; Asagawa, M.; Toi, H.; Ogoshi, H. *Ibid.* **1988**, *110*, 4076 and references cited therein.

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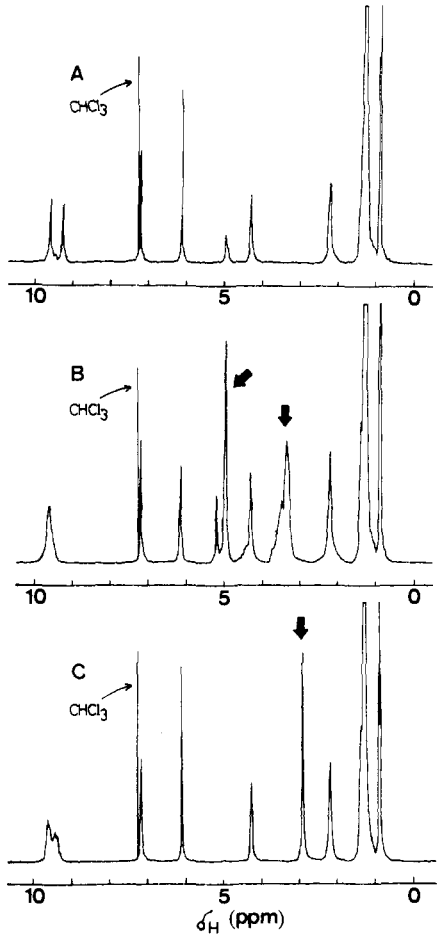
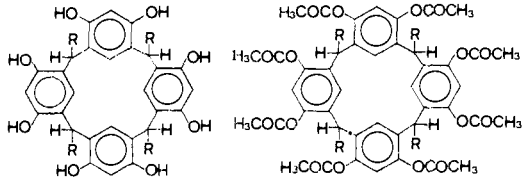


Figure 1. ^1H NMR spectra of **1a** (A), **1a**·4(glycerol) (B), and **1a**·$4H_2O$ (C) in $CDCl_3$ at room temperature. The signals with marks are for the guests incorporated.

nitrogen heterocycles.[4] On the other hand, we recently provided the first example of complexation of sugars in apolar organic media using a synthetic polyhydroxy macrocycle **1a** as a lipophilic polar host.[2,5] Sugars are polyhydroxy aldehydes (aldoses) or polyhydroxy ketones (ketoses) that constitute families of closely related stereoisomers. They exist actually as cyclic hemiacetals or hemiketals, either six-membered pyranoses or five-membered furanoses. Furthermore, the newly built asymmetric centers at 1-C can take either α- or β-configuration, giving rise to two anomers for both pyranoses and furanoses. The present work concerns the structure of the **1a**–ribose complex and the selectivity in the complexation of sugars with **1a**. We report here on the essential structural aspects of the **1a**–sugar complexation and the roles therein of various OH groups of sugars.

Results

Lipophilic Resorcinol–Aldehyde Cyclotetramers. Resorcinol–acetaldehyde and –benzaldehyde cyclotetramers (**1e** and **1f**)[6] have long been known.[7,10] They are scarcely soluble in apolar organic solvents but can be converted to soluble derivatives via acylation,[6] alkylation,[8] or silylation[8] of the OH groups. The acid-catalyzed reaction of resorcinol and dodecanal afforded a similar cyclotetramer **1a** as a monohydrate; **1a** showed good solubilities in apolar solvents such as CCl_4 and C_6H_6 and even in *n*-hexane. The condensation with shorter chain aldehydes, $CH_3(CH_2)_nCHO$ (n = 6, 4, 3, and 0), took place similarly and gave the corresponding cyclotetramers **1b**, **1c**, **1d**, and **1e**; among them **1b** and **1c** having



1a : R = $(CH_2)_{10}CH_3$
1b : R = $(CH_2)_6CH_3$
1c : R = $(CH_2)_4CH_3$
1d : R = $(CH_2)_3CH_3$
1e : R = CH_3
1f : R = C_6H_5

2 : R = $(CH_2)_{10}CH_3$

$n \geq 4$ were found to be soluble in CCl_4 and C_6H_6. Acetylation of **1a** afforded octaacetate **2**. Vapor pressure osmometry (VPO) indicated that **1a** is aggregated in $CHCl_3$ or C_6H_6, whereas **2** is monomeric. The ^1H (Figure 1A) and ^{13}C NMR spectra of **1a** in $CDCl_3$ indicate that the four benzene rings and four methine groups are equivalent.[11] The OH proton resonance appeared as two singlets of equal intensities at δ_H 9.60 and 9.28 and disappeared on deuteriation with D_2O. The IR spectrum of **1a** (1×10^{-1} M) in CCl_4 showed ν_{OH} at 3250 cm^{-1}. For comparison, 4-dodecylresorcinol (**3**) showed δ_H at 5.30 and 5.10 (OH) and ν_{OH} at 3600 cm^{-1} under the same conditions as for **1a**. The NMR spectra of **1b** and **1c** are essentially the same as those of **1a**.

Glycerol and Water Complexes. Vigorous stirring of a two-phase mixture of a CCl_4 solution of **1a** ($(1–2) \times 10^{-2}$ M, 4 vol) and glycerol ($HOCH_2CH(OH)CH_2OH$) or H_2O (neat, 1 vol) at 20 °C for 24 h resulted in transfer of the latter into the former solution, the stoichiometries **1a**/glycerol = **1a**/H_2O = 1/4 being established directly by ^1H NMR integration. When a 50% (mol/mol) aqueous solution of glycerol ([glycerol] = [H_2O] = 11 M) was used, only ca. 4 mol of H_2O was incorporated with little extraction of glycerol, indicating that the competition between H_2O and glycerol for the binding sites of **1a** is in favor of the former. The ^1H NMR spectra of the glycerol and water complexes at room temperature are shown in Figure 1, parts B and C, respectively. The guest signals with marks appear at δ_H 3.34 (CH, 20 H) and 4.98 (OH, 12 H) for bound glycerol and at 2.93 (8

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(5) 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) Kobiro, 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.

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

(7) Cram et al. have shown that derivatives of **1e** in which the OH groups on adjacent benzene rings were bridged by alkylation or silylation bind apolar molecules in organic solvents.[8] On the other hand, Schneider et al. have shown that the tetradeprotonated derivative of **1e** in alkaline media binds ammonium compounds.[9]

(8) (a) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826. (b) Cram, D. J.; Stewart, K. D.; Goldberg, I.; Trueblood, K. N. *Ibid.* **1985**, *107*, 2574. (c) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Kalleymeyn, G. W. *Ibid.* **1985**, *107*, 2575. (d) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *Ibid.* **1988**, *110*, 2229. (e) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Marti, K.; Sampson, R. M.; Kalleymeyn, G. W. *Ibid.* **1988**, *110*, 2554.

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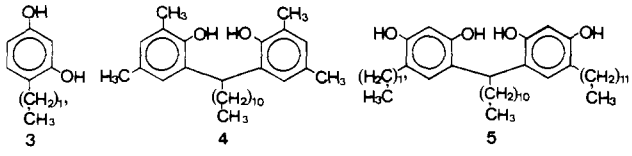
(10) Calixarenes are phenol–formaldehyde cyclocondensation oligomers: Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, *110*, 6153 and preceding papers in this series. For a review, see: Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161.

(11) The four benzene rings are not equivalent in octaacyl derivatives of **1**.[6] For X-ray structure, see: Nilsson, B. *Acta Chem. Scand.* **1968**, *22*, 732.

H) for bound water. Upon complex formation, the OH proton resonance of **1a** undergoes broadening with concomitant downfield shift of the higher field component. Variable-temperature studies of the water complex in $Cl_2DCCDCl_2$ indicated that the OH protons in **1a** (8 H) and bound H_2O (8 H) give distinct signals at room temperature as shown in Figure 1C, but they are no longer independent at higher temperatures. At 130 °C was observed an extensively broadened absorption ranging from δ_H 9.5 to 1.5 (OH, 16 H). The original spectrum (Figure 1C) was recovered on cooling the solution down to room temperature, the temperature induced structural changes thus being reversible.

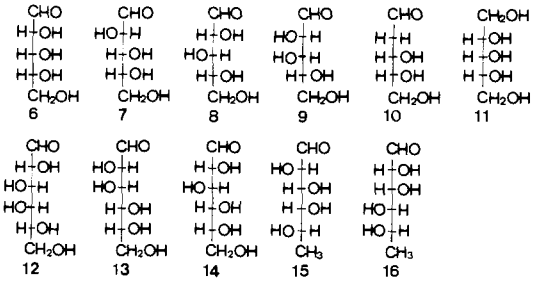
The glycerol complex **1a**·4(glycerol) in $CHCl_3$ is monomeric as such as shown by VPO, bound glycerol being readily and completely reextracted into D_2O and identified further by means of ^1H NMR spectroscopy.[12] The water complex **1a**·4H_2O was also formed upon prolonged exposure of **1a** (solid state) to (wet) air. Removal of bound water molecules from the tetrahydrate in vacuo at 80 °C was found to be stepwise and gave trihydrate (**1a**·3H_2O, δ_H 3.40 (OH in H_2O)) and dihydrate (**1a**·2H_2O, δ_H 3.75) until monohydrate (**1a**, δ_H 4.95 (Figure 1A)) resulted. Glycerol was also solubilized in CCl_4 when a lipophilic bisresorcinol, **5**, was used in place of **1a**. In marked contrast, no



3 **4** **5**

solubilization was observed when octaacetate **2**, a lipophilic resorcinol monomer, **3**, a lipophilic bisphenol, **4**, or dodecanol was used as the host. The OH proton resonance for compound **4** in $CDCl_3$ occurs at δ_H 5.62 (2 H), while compound **5** gives two separate signals at δ_H 7.42 (2 H) and 5.45 (2 H).

Ribose Complex. D-Ribose (**6**, in the Fischer projection formula), otherwise completely insoluble in CCl_4, was readily ex-



6 **7** **8** **9** **10** **11**

12 **13** **14** **15** **16**

tracted from a concentrated aqueous solution ([**6**] = 5.5 M) into a solution of **1a** in CCl_4. The resulting complex has a considerably enhanced solubility in CCl_4 ($\sim 4 \times 10^{-1}$ M) as compared with that of **1a** ($\sim 2 \times 10^{-2}$ M); it can be formulated as **1a**·ribose·2H_2O and is monomeric as such.[13] Involvement of two water molecules was suggested by ^1H NMR spectroscopy (vide infra). Two pieces of evidence suggested that the complexation of ribose in water and **1a** in CCl_4 to give the complex in the organic phase is a reversible process. First, ribose thus solubilized in CCl_4 could be completely reextracted into D_2O or H_2O[12] and analyzed by means of ^1H NMR spectroscopy, HPLC, and colorimetry[14] to give the molar ratio ribose/**1a** = 1. Second, the extents of solubilization of ribose in CCl_4 depended on [ribose] in the aqueous phase but not on [**1a**] in CCl_4; the molar ratios ribose/**1a** were lowered to approximately 0.7 (or 70% extraction based on **1a**), 0.5, 0.2, 0.05, and ~0 when $[ribose]_{aq}$ was lowered from 5.5 M to 3.2, 2.4, 1.6, 1.0, and 0.3 M, respectively.[15] The solubilization of ribose was

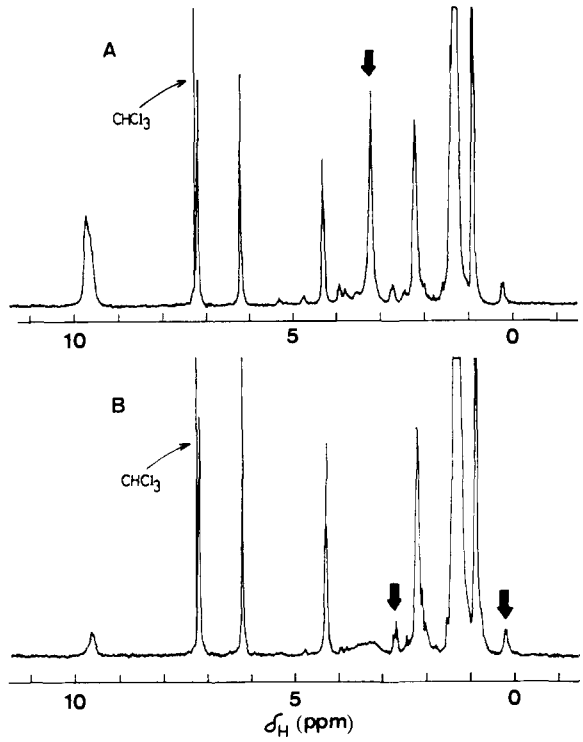
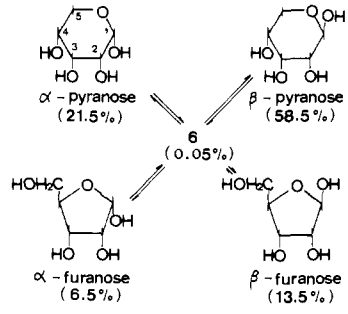


Figure 2. ^1H NMR spectra of **1a**·ribose·2H_2O (A) and **1a**·(ribose-d_4)·2D_2O (B) in $CDCl_3$ at room temperature. The latter complex was prepared by extracting ribose-d_4 from a D_2O solution. The signals with marks in A and B are for the OH protons of ribose and H_2O and the CH protons of ribose, respectively. Since the H–D exchange for the OH protons of **1a** is very slow and incomplete, spectrum B still shows some undeuteriated ArOH proton resonance.

Scheme I



observed also with **1b** or **1c** in place of **1a**, but never with **2**, **3**, **4**, **5**, calix[8]arene, or dodecanol; compound **5** is effective in the solubilization of glycerol (vide supra), but this is not the case for ribose.

The IR spectrum of the ribose complex **1a**·ribose·2H_2O showed no ν_{CO}. The ^{13}C NMR spectrum for a $CDCl_3$ solution under complete proton-decoupling conditions shows the sugar carbon resonances at δ_C 93.8, 71.7, 68.1, 67.8, and 65.0; this clearly indicates that bound ribose takes the pyranose form (refer to Scheme I for the structures and numbering),[16] although unam-

(12) Complete reextraction of the guests (glycerol and ribose) solubilized in CCl_4 into aqueous phase was confirmed by ^1H NMR spectroscopy; see the Experimental Section.

(13) After being dried thoroughly, the complex showed a molecular weight corresponding to a trimer, suggesting that loss of water molecule(s) induced aggregation of the complex; see the Experimental Section.

(14) Dubois, M.; Gilles, K. A.; Hamilton, J. K.; Rebers, P. A.; Smith, F. *Anal. Biochem.* **1956**, *28*, 350.

(15) The ^1H NMR spectroscopy suggests that **1a** which binds no ribose molecule exists as tetrahydrate (**1a**·4H_2O). Thus, the molar ratios which are dependent on $[ribose]_{aq}$ most likely reflect not particular host–guest stoichiometries but a competition between the ribose complex formation (**1a** + ribose + 2H_2O → **1a**·robise·2H_2O) and tetrahydrate complex formation (**1a** + 4H_2O → **1a**·4H_2O); ribose/**1a** = [**1a**·ribose·2H_2O]/([**1a**·ribose·2H_2O] + [**1a**·4H_2O]).

(16) The chemical shifts are in agreement with those reported for ribopyranose in D_2O:[17] δ_C 94.8 (1-C), 70.1 (2-C), 71.7 (3-C), 69.0 (4-C), 64.3 (5-C) for α-anomer; 95.3 (1-C), 72.6 (2-C), 72.6 (3-C), 70.0 (4-C), 64.3 (5-C) for β-anomer. Upon formation of the furanose ring, 4-C undergoes the most pronounced change in shielding;[18] δ_C (4-C) 82.8 for α-ribofuranose, 82.4 for β-ribofuranose, and 85.5 for β-phenylribofuranoside.

(17) Perlin, A. S.; Casu, B.; Koch, H. J. *Can. J. Chem.* **1970**, *48*, 2596.

Table I. Extractabilities of Various Sugars with **1a** (Molar Ratios of Sugars Extracted to **1a** Used)[a]

sugar	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
sugar/**1a**	0.5	0.1	vs[b]	vs[b]	0.8	vs[b]	vs[b]	vs[b]	vs[b]	1.0	0.1

[a] Sugars were extracted from an aqueous solution ([sugar] = 2.4 M) into a CCl_4 solution of **1a** ([**1a**] = 0.9×10^{-2} M) by vigorous stirring of these at 20 °C for 24 h. The sugars thus extracted were analyzed by means of HPLC and ^1H NMR spectroscopy after complete reextraction into H_2O or D_2O. [b] Very small; ≤ 0.03.

biguous determination of the configuration at 1-C requires further information (vide infra). The ^1H NMR spectrum for a $CDCl_3$ solution (Figure 2A) gives a complicated pattern. The marked signals at δ_H 3.21 and lower fields have an integration of 8 H. They do not appear in the spectrum (Figure 2B) for the ribose complex prepared by extracting ribose-d_4 from a D_2O solution; they are assigned to the OH protons in ribose (4 H) and two additional water molecules (4 H). As for the CH protons of ribose bound, two clearly distinguishable absorptions with marks in Figure 2B are observed at δ_H 2.68 and 0.19, both having an integration of 1 H. These, especially the latter, are considerably upfield shifted; ribose in D_2O or DMSO-d_6 exhibits CH proton resonances at δ_H ~5 (1-H) and 4–3 (2-, 3-, 4-, and 5-H). The ribose molecule in the complex must be close enough to the benzene rings of **1a** to be subject to their ring-current effects. The ribose complexes of **1b** and **1c** gave a ^1H NMR spectra quite similar to that of the **1a** complex. When dissolved in DMSO-d_6, however, the **1b**–ribose complex showed a *normal* ^1H NMR spectrum free from any ring-current effect of the benzene rings, indicating that the complex dissociated into free ribose and **1b** in this solvent.[19] The ^{13}C spectrum of this solution showed two sets of sugar carbon resonances in a ratio of ~10/1, the major one at δ_C 94.0, 71.3, 69.5, 67.4, and 60.7 and the minor one at 94.7, 72.1, 68.6, 68.2, and 63.5, which were identical with those for α- and β-ribopyranose in DMSO-d_6, respectively.[20] These results unambiguously demonstrate that ribose is bound with **1a–c** in CCl_4 highly selectively as α-ribopyranose; the selectivity α/β is approximately 10/1.[21] The ^{13}C resonances for ribose in the complex in $CDCl_3$ are now assignable in light of the reported assignments of α-ribopyranose in D_2O:[17] δ_C 93.8 (1-C), 71.7 (3-C), 68.1 (2-C), 67.8 (4-C), and 65.0 (5-C). The highly selective extraction of α-ribopyranose is significant, since ribose in water is a mixture of pyranose and furanose, for both of which the β-anomers are more stable and predominate over the α-anomers (Scheme I, where percent contents are shown in parentheses).[22]

The successful assignments of the ^{13}C resonances allow further assignments of CH proton resonances for ribose in the complex via ^1H–^{13}C correlation under selective proton-decoupling conditions. For example, the ^{13}C spectrum under selective irradiation of the proton at δ_H 2.68 showed the sole singlet signal at δ_C 71.7 (3-C or ribose bound), while other carbon resonances of the sugar and the host appeared as doublets or exhibited more complicated splittings. The proton at δ_H 2.68 is thus directly coupled with 3-C, and hence it is 3-H. In a similar manner was shown that the most shielded proton at δ_H 0.19 is 4-H, and 1-H and 2-H resonate respectively at δ_H ca. 2.2 and 1.1 although they give rise to no distinct signals in Figure 2B because of overlap with intense absorptions due to protons of the host.[23] The 5-H protons could not be assigned unambiguously by the present method.

Extraction of Sugars and Cyclohexanediols. The extraction of sugars or sugar alcohol (D-Adonitol, **11**) from water into CCl_4 containing **1a** (0.9×10^{-2} M) was carried out under similar conditions as above (i.e., stirring at 20 °C for 24 h), while keeping [sugar] in water constant at 2.4 M. The sugars investigated were aldopentoses [D-ribose (**6**), D-arabinose (**7**), D-xylose (**8**), and D-lyxose (**9**)], a 2-deoxyaldopentose [2-deoxy-D-ribose (**10**)], aldohexoses [D-galactose (**12**), D-mannose (**13**), and D-glucose (**14**)], and 6-deoxyaldohexoses [L-fucose (6-deoxy-L-galactose, **15**) and L-rhamnose (6-deoxy-L-mannose, **16**)]. None of them is otherwise soluble in CCl_4. The sugars extracted were completely reextracted into D_2O or H_2O and analyzed as above for ribose.[12] The molar ratios of sugars extracted to **1a** used can be taken as measures of their extractabilities or their affinities to **1a**, and are summarized in Table I.

Adonitol (**11**), the ribose-related sugar alcohol, shows a low affinity to **1a**, in marked contrast to parent ribose. There is a remarkable selectivity among aldopentoses including **10**, which may roughly be classified into moderate-to-high-affinity sugars (**6**, **7**, and **10**) and low-affinity sugars (**8** and **9**). This selectivity was also confirmed by competitive extractions; e.g., from an equimolar mixture of **6** and **8** in water ([**6**] = [**8**] = 1.6 M) was extracted **6** almost exclusively (**6**/**1a** = 0.3 and **8**/**1a** ≅ 0). This is rather surprising since **6** and **8** differ only in the configurations of the OH groups on 3-C. Similar competitions between **6** (standard) and **7** and between **6** and **10** showed the selectivities **7**/**6** = 1/4 and **10**/**6** = 2/1. These results indicate that the relative extractabilities are 1, 0.25, ~0, and 2 for **6**, **7**, **8**, and **10**, respectively; this is in agreement with their extractabilities in single extraction runs (Table I).

Although all of aldohexoses investigated (**12–14**) belong to low affinity sugars, their 6-deoxy derivatives **15** and **16** show high and moderate affinities, respectively.[24] The enhanced affinities of deoxysugars are consistent with a similar affinity-enhancement in going from **6** to **10**. On the other hand, a big different in the affinities of **15** and **16** may arise from the stereochemical requirement of the present host–guest association in a similar manner that determines the selectivity among aldopentoses.

1,4-Cyclohexanediol is highly soluble in water. An aqueous solution of this 1,4-diol (1.35 M) as a mixture of cis (53%) and trans (47%) isomers was extracted with CCl_4 in the absence and presence of **1a** (0.9×10^{-2} M). In its absence the resulting organic phase was 0.08 M in diol consisting of cis (54%) and trans (46%). In the presence of **1a**, more diol (0.48 M) was extracted, which consisted of cis (83%) and trans (17%). These results indicate that 1,4-cyclohexanediol is solubilized in CCl_4 upon complex formation with **1a**[25] and that the complexation is stereoselective, the cis isomer being complexed approximately 7 times more readily than the trans isomer.[26] 1,3-Cyclohexanediol as a mixture of cis (62%) and trans (38%) isomers was found to be solubilized with **1a** in CCl_4 in a similar manner. In marked contrast to the 1,4-diol, however, there was no stereoselectivity in the solubilization of the 1,3-diol; the compositions of stereoisomers of the 1,3-diol extracted in CCl_4 were cis (63%) and trans (37%) in the absence of **1a** and cis (64%) and trans (36%) in the presence of **1a**.

Discussion

Hydrogen Bonding. The equivalency of four benzene rings and four methine moieties in the NMR spectra indicates that **1a–c**

(18) Jones, A. J.; Grant, D. M.; Winkey, M. W.; Robins, R. K. *J. Am. Chem. Soc.* **1970**, *92*, 4078.

(19) The ^1H NMR spectrum of **1b**–ribose complex was taken because **1b** (uncomplexed) is readily soluble in DMSO, while **1a** is not.

(20) For ^{13}C data for β-ribopyranose in DMSO-d_6, see: Reuben, J. *J. Am. Chem. Soc.* **1984**, *106*, 6180.

(21) The true selectivity would be $\alpha/\beta \cong 30$ if corrected for the difference in the concentrations of α- and β-pyranose in water at equilibrium; $[\beta]_{aq}/[\alpha]_{aq} \cong 3$ (Scheme I). It was also shown independently that no epimerization of the anomeric center of ribopyranose took place under the conditions used.

(22) (a) Hayward, L. D.; Angyal, S. J. *Carbohydr. Res.* **1977**, *53*, 13. (b) *Carbohydrate*; Collins, P. M., Ed.; Chapman and Hall: New York, 1987.

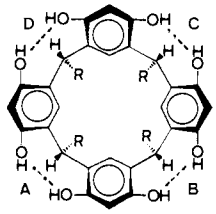
(23) The 2-H proton for complex **1b**–ribose could be observed as a distinct resonance.

(24) Since **1a** is achiral, use of D-enantiomers for **6–14** and L-enantiomers for **15** and **16** brings about no essential problem.

(25) The ^1H NMR resonances for 1,4-cyclohexanediol solubilized are considerably upfield shifted due to a ring-current effect of the benzene rings of **1a** in a similar manner as in **1a**–ribose complex.

(26) The concentrations of complexed *cis*- and *trans*-1,4-diol are $0.48 \times 0.83 - 0.08 \times 0.54 = 0.36$ M and $0.48 \times 0.17 - 0.08 \times 0.46 = 0.045$ M. The selectivity factor, 0.36/0.045 = 8, is corrected by a factor of 53/47 for the difference in the concentrations of cis and trans diol in the aqueous source solution or by a factor of 54/46 for the difference in their intrinsic solubilities in CCl_4.

has a symmetric macrocyclic skeleton. A large (~4 ppm) downfield shift for the OH protons and a significant shift to lower wavenumber in ν_{OH} (350 cm^{-1}) as compared with those for **3** can be taken as evidence that the OH groups in **1a–c** are hydrogen bonded. These observations, taken together, suggest that **1a–c** has a crown[6] or bowl-shaped conformation[8,9] with intramolecular hydrogen bonding between OH groups on adjacent benzene rings (refer to **17**).[27] There is little doubt that the hydrogen bonding



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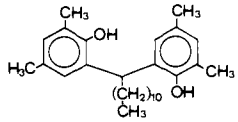

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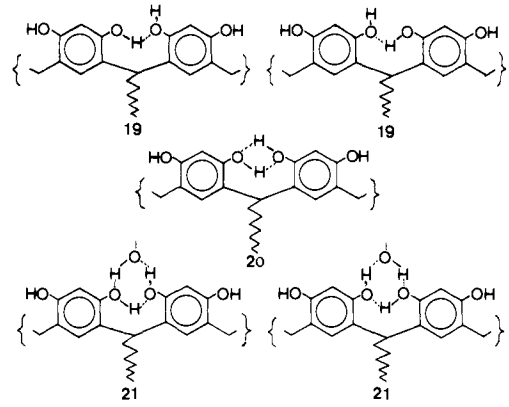
between OH groups of **1a** and those of the guests (glycerol, H_2O, and sugars) is responsible for the present host–guest association, since octaacetate **2** shows no affinity to the guests. The ^1H NMR spectrum of the complex **1a**–ribose shows an integration of 8 H for the OH protons of **1a**. The ^{13}C spectrum shows that ribose is bound as pyranose. The bound sugar can be readily reextracted into water or dissociated into free sugar simply by dissolving the complex in DMSO. These facts can be taken as evidence that we are observing host–guest *interaction* rather than *reaction* by formation of covalent bonds of acetal. The inhibition of otherwise ready aggregation of **1a** is reasonable since intermolecular hydrogen bonding of **1a** is in competition with the formation of monomeric **1a**–glycerol and **1a**–ribose complexes; their enhanced solubilities in CCl_4 may be due to effective insulation of the hydrogen-bonded OH groups of the host and guest from bulk solvent.

The 1:4 stoichiometry for the complexes **1a**–glycerol and **1a**–H_2O strongly suggests that a pair of hydrogen-bonded OH groups on adjacent benzene rings in **1a** provide the essential binding site and four such sites (refer to **17**) independently interact with small polar guests such as glycerol and H_2O. In fact, a lipophilic resorcinol monomer, **3**, which is unable to form such a pair, fails to solubilize glycerol to any detectable extent. On the other hand, a lipophilic bisresorcinol, **5**, readily solubilizes glycerol; the NMR spectrum suggests that **5** involves a weakly hydrogen-bonded OH pair (δ_H 7.42) together with two free OH groups (δ_H 5.45). An interesting case is lipophilic bisphenol **4**, which shows little affinity to glycerol. The NMR spectrum of **4** gives no sign of hydrogen-bonding interaction between the two OH groups (δ_H 5.62); **4** may take an anti conformation as shown in **18**. As far as the binding of glycerol and H_2O is concerned, the significance of the metacyclophane structure of **1a** seems to fix its conformation so as to allow effective intramolecular hydrogen bonding of the OH groups.

The ^1H NMR spectra of **1a–c** show two separate absorptions of equal intensities for the apparently equivalent OH protons (Figure 1A). The ^{13}C spectrum also shows two signals at δ_C = 150.57 and 150.35 for the aromatic carbons bearing OH groups. This seems to be significant, since it suggests that the intramolecular hydrogen bonding takes a nonsymmetric structure as shown in **19** and the tautomeric exchange 19 ⇌ 19′ is slow compared with NMR time scale. This may be due to instability of the transition state **20**, which involves a four-membered hydrogen-bonded ring system. The OH groups in **19** may interact with the guest OH group in such a way that one OH serves as a proton donor and the other as an acceptor; a six-membered ring results as a consequence as shown in **21**. This is only speculation but explains the significance of a pair of hydrogen-bonded OH groups in the host as the essential binding site. If a single OH group were to serve as both hydrogen donor and acceptor, a four-membered ring similar to that in **20** would result again. The extensive ^1H

(27) The tetradeprotonated tetraanion of **1e** was shown to possess strong hydrogen bonding between ArOH and adjacent ArO^- groups.[9]



19 19

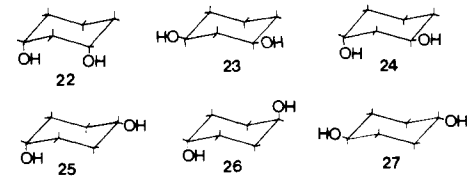
20

21 21

NMR line broadening for the OH protons in the water complex **1a**·4H_2O at 130 °C indicates that (1) no dissociation of the water molecules from **1a** takes place at 130 °C and (2) tautomeric shift in the hydrogen-bonding network (**21** ⇌ **21′**) is ready at higher temperatures, which results in rapid proton exchange.

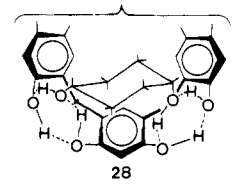
Two-Point Interaction in the Ribose and *cis*-1,4-Cyclohexanediol Complexes. The extraction of ribose is remarkable in two respects. First, ribose is extractable from an *aqueous* solution, indicating that the **1a**–ribose interaction competes favorably with the **1a**–H_2O and ribose–H_2O interactions. Since glycerol can not be extracted from an aqueous solution, the **1a**–ribose interaction must be considerably stronger than the **1a**–glycerol interaction. Second, ribose is extracted selectively in the α-pyranose form, although α-ribopyranose is not the most predominant form of ribose in water (Scheme I). The stoichiometry (**1a**·ribose·2H_2O) of the ribose complex suggests that the two binding sites out of four in **1a** (refer to **17**) interact with the guest sugar, the remaining two being occupied by water molecules. Such a two-point **1a**–ribose interaction explains not only the selectivity for α-ribopyranose (vide infra), the stability of the complex as referred to above, and the failure of **5** (having only one binding site) to bind ribose but also the characteristic upfield shifts of the ribose CH protons induced by a ring-current effect of the benzene rings of **1a**; a dual interaction necessarily places ribose in the vicinity of the cavity of **1a** with a consequence of enforced proximity of the guest sugar and benzene rings.

Examination of CPK molecular models provides an important clue to understand the present two-point host–guest interactions. The trimethylene chain in a 1,3-diol such as glycerol is somewhat shorter than required to allow a simultaneous interaction of the two terminal OH groups with two adjacent binding sites in **1a** (A and B in **17**), which are separated by a metaphenylene bridge. Another factor comes into play in the case of cyclohexanediol. The possible structures of the 1,3- and 1,4-diol are *cis*-(1,3)-aa (**22**), *cis*-(1,3)-ee (**23**), and *trans*-(1,3)-ae (**24**) for the former and



22 23 24

25 26 27



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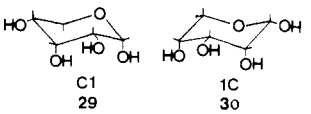
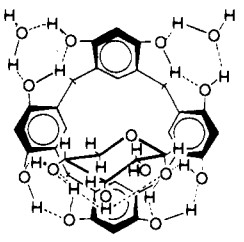
cis-(1,4)-ae (**25**), *trans*-(1,4)-aa (**26**), and *trans*-(1,4)-ee (**27**) for the latter, where a and e stand respectively for the axial and equatorial configurations of the OH groups. The two-point interaction seems to be difficult for all of them except for **25**. The two OH groups in *cis*-(1,3)-aa (**22**) are too close to separately interact with two different binding sites of **1a**. In **26**, they are

pointing in opposite directions. In **23**, **24**, and **27**, they may be appropriately separated. However, if two-point interaction were to occur for them, a severe steric interaction would be encountered between the benzene ring linking the two binding sites and the axial hydrogens on the cyclohexane ring. On the other hand, such a two-point interaction is possible for **25** as schematically shown in **28**; the separation of two OH groups is long enough, they are pointing in the same directions, and involvement of an axial OH group separates the cyclohexane ring from the benzene ring to reduce steric interactions between them. The model-building studies thus suggest that 1,3-diols essentially undergo a one-point interaction with **1a**, but dual or two-point interactions are possible for six-membered cyclic 1,4-diols having a chair conformation, provided that the OH groups are cis to each other. The extraction of 1,3-cyclohexanediol was experimentally found to be nonstereoselective. As for that of 1,4-cyclohexanediol and ribose, however, the cis isomers (i.e., α-anomer in case of ribopyranose) were extracted stereoselectively. It is well-known that pyranoses take a chair conformation. The agreement of the stereoselectivities observed and predicted based on models indicates that the two-point interaction involving the cis-OH groups on 1-C and 4-C is indeed an essential aspect which characterizes the **1a** complexes of 1,4-cyclohexanediol and α-ribopyranose.

α-Ribopyranose has two possible conformations, C1 (**29**) and 1C (**30**),[28] which are interconvertible by ring inversion. No information is available at present to decide which form is bound with **1a**.[29] Whichever of C1 and 1C is involved, CPK models for the **1a**–α-ribopyranose complex with a two-point interaction at 1-OH and 4-OH show that 1-H and 4-H are placed in the vicinity of benzene rings neighboring the two binding sites, as schematically shown in **31** where the conformation of the sugar is assumed to be C1.[30] This picture is consistent with the upfield shifts observed for the CH protons of bound ribose due to ring-current effects of the benzene rings; the upfield shifts are δ_H ca. 3, 2–3, 0.5–1.5, and 3–4 for 1-H, 2-H, 3-H, and 4-H, respectively.[31]



C1 29 1C 30



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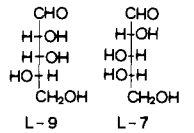
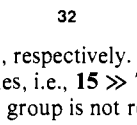
Selectivity in the Sugar Binding. Table I suggests that a factor governing the extractabilities of aldopentoses (**6**–**9**) including **10** is configuration of OH groups on 3-C (3-OH); in Fischer formulae they are directed to the right in the high-to-moderate-affinity sugars (**6**, **7**, and **10**) and to the left in the low-affinity sugars (**8** and **9**). On the other hand, the OH groups on 2-C (2-OH) play only a minor role; **10** (with no 2-OH) and **6** and **7** (with a 2-OH in opposite directions) are all extractable although to differing extents. The significance of the OH groups on 4-C (4-OH) is apparently not clear since D-series aldopentoses necessarily have 4-OH groups directed to the right, but it is made clearer by taking L-sugars into account. L-Lyxose (L-**9**) is a mirror image of D-lyxose



L-9 L-7

(**9**) and they must have identical affinities to **1a** since **1a** is achiral. On this basis, L-**9** is a low-affinity sugar; the difference between L-**9** and D-ribose (**6**) is only in the configuration of the 4-OH groups. Thus, inversion of configuration of D-ribose (**6**) at either 3-C (to give D-xylose (**8**)) or 4-C (to give L-lyxose) results in almost complete loss of affinity to **1a**. On the other hand, inversion of configuration at both 3-C and 4-C gives L-arabinose (L-**7**), a moderate-affinity sugar. Clearly, the governing factor is the relative configuration of 3-OH and 4-OH; **6**, **7**, and **10** owe their affinities to **1a** to the presence of *cis*-OH groups on 3-C and 4-C. A big difference in the affinities of two 6-deoxyaldopentoses (**15** and **16**) is understandable on the same ground; 3-OH and 4-OH are cis in **15**, while they are trans in **16**.

Formation of stable **1a**–sugar complexes in apolar media is attained by maximization of favorable **1a**–sugar interaction and minimization of unfavorable exposure of sugar OH groups to bulk solvent. The decreasing affinities in the order **10** > **6** > **7** illustrates the latter point. The 2-OH groups are not primarily responsible for the binding with **1a**. Under these circumstances, the best binding is provided when 2-OH is removed as in **10**. When it is present, the 2-OH–solvent contact would be greater for **7** (3-OH and 4-OH being trans) than for **6**, where *cis*-3-OH and -4-OH may be hydrogen bonded. The exocyclic CH_2OH group of an aldohexopyranose shows a similar effect in a more pronounced manner. Fucose (**15**), arabinose (**7**), and galactose (**12**) are closely related, where 3-OH and 4-OH are cis and 2-OH and 3-OH are trans. They differ in the substituents on 5-C of a pyranose ring as shown in **32**; R = CH_3, H, and CH_2OH for L-fucose, D-arabinose, and L-galactose, respectively. A remarkable difference in the affinities in this series, i.e., **15** ≫ **7** ≫ **12** (Table I), clearly indicates that the CH_2OH group is not responsible for the binding with **1a**, and the affinities are governed by lipophilicities of 5-substituents. In fact, **15** is the highest-affinity sugar investigated here and even **16** shows a moderate affinity though it has trans 3-OH and 4-OH.



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As in the case of 2-OH, the exposure of 3-OH to solvent may be minimized when it is cis to 4-OH. A rather rigorous requirement for cis stereochemistry of 3-OH and 4-OH may suggest that 3-OH plays a more positive role possibly by affecting the pK_a of 4-OH and also 1-OH via hydrogen-bonding interaction (refer to **31**).[33] A full interpretation of the significance of *cis*-3-OH will be postponed, however, until further information is available as to the structure of the sugar complex with unambiguous

(28) Thermodynamically, C1 is slightly more stable than 1C.

(29) Single crystals of the ribose complex suitable for X-ray analysis have not been obtained so far.

(30) The ^1H NMR spectrum of the ribose complex at room temperature (Figure 2A) shows sharp and single signals for the aromatic and methine products, although dissymmetry of structure **31** predicts nonequivalency of the benzene and methine moieties. This may simply be due to similar chemical shifts for the nonequivalent aromatic and methine protons, as also suggested by the ^1H NMR spectra for glycerol and water complexes (Figure 1, parts B and C), and hence does not necessarily mean that exchange between four binding sites (in an intramolecular sense) in **31** is rapid at room temperature. Even at −60 °C the ^1H NMR spectrum of the ribose complex showed no splitting of the protons in concern, although they were considerably broadened.

(31) The relative geometry of the benzene ring of **1a** and a particular proton of ribose bound can be evaluated from the upfield shift observed according to Johnson and Bovey.[32] If an assumption is made that the ribose proton in concern is right above the benzene ring without in-plane deviation, an upfield shift of 3 ppm, for example, indicates that the proton is ca. 2.4 Å above the benzene ring along the hexagonal axis. This is compatible with prediction based on CPK models.

(32) Johnson, C. E.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012.

(33) The pK_a of 4-OH may be lowered by backside hydrogen bonding with a cis-3-OH, allowing better hydrogen-bonding interaction with **1a**. The pK_a of 1-OH, on the other hand, is intrinsically lower than that of 4-OH owing to the presence of an additional electron-withdrawing group (ether oxygen). This may be why the hydrogen-bonding interaction of 1-OH with **1a** does not require crucial assitance of a cis-2-OH.

identification of the conformation (C1 or 1C) of bound pyranose, the hydrogen-bonding network therein, and the effect of pK_as of guest OH groups on the strength of hydrogen bonding. Use of 3-deoxysugars would also be interesting.

Summary

This work provides perhaps the first example of selective binding of sugars in apolar media. The present host **1a** has two essential features that lead to two-point fixation of sugars via the hydrogen-bonding interaction; a pair of hydrogen-bonded OH groups as the unit-binding site for a sugar OH group and availability of multiple binding sites which are separated by a *m*-phenylene bridge and are independent from each other. Ribose is bound with **1a** highly selectively in the form of α-pyranose as a results of discrimination between pyranose and furanose and between α- and β-anomers; this reflects rigorous molecular recognition or fitness of the two binding sites of **1a** and the *cis*-OH groups on 1-C and 4-C of α-ribopyranose. There is also a remarkable selectivity in the binding of various aldoses. Two requirements for effective binding are cis stereochemistry of 3-OH and 4-OH and lipophilicity of the sugar molecule as a whole. In particular, 2-OH and 5-CH_2OH (in cases of aldohexopyranoses) are not responsible for the binding with **1a** and they only reduce lipophilicities of sugar molecules. Hexoses show low affinities to **1a** on this ground, and deoxysugars with enhanced lipophilicities show higher affinities. Thus, affinities of sugars (substituent, stereochemistry of 3-OH and 4-OH) decrease in the order fucose (5-CH_3, cis) > 2-deoxyribose, ribose, and arabinose (5-H, cis) > rhamnose (5-CH_3, trans) ≫ galactose (5-CH_2OH, cis), xylose and lyxose (5-H, trans), and mannose and glucose (5-CH_2OH, trans); 2-deoxyribose (2-H) > ribose (2-OH cis to 3-OH) > arabinose (2-OH trans to 3-OH).

Experimental Section

General Procedures. ^{1}H NMR spectra at 270 MHz were taken on a JEOL JNM-GX 270 spectrometer for solutions in D_2O, $CDCl_3$, or $CDCl_3$–CCl_4; HDO (δ_H 4.75) in D_2O, $CHCl_3$ (δ_H 7.26) in $CDCl_3$, and $(CH_3)_4Si$ (δ_H 0.0) were used as internal references. ^{13}C NMR spectra at 68.7 MHz were obtained with the same machine for solutions in $CDCl_3$, DMSO-d_6, or D_2O where the solvents, $CDCl_3$ (δ_C 77.0) and DMSO-d_6 (δ_C 39.7), or external $(CH_3)_4Si$ (δ_C 0.0, for D_2O solutions) served as references. IR spectra were taken for CCl_4 solutions or KBr disks with a JASCO IR-810 spectrophotometer. MS spectra were recorded with a Shimadzu GCMS-6020 spectrometer. Vapor pressure osmometry (VPO) of compound **2** was carried out on a Corona-114 molecular weight apparatus with benzil as standard. Compound **2** in turn served as the standard in the VPO of other compounds. Elemental analyses were performed at the Microanalysis Center of Kyoto University. HPLC analyses of sugars were carried out with a JASCO apparatus equipped with an 830 RI detector on a column of μ-Bondapak CH (Waters) or PA-03 (Yamamura Chemical Research) with H_2O or CH_3CN–H_2O as eluant. Sephadex LH-20 was used for gel filtration and the components eluted with $CHCl_3$–CH_3OH (1:1) were detected by UV absorption at 280 nm. Sugars including a sugar alcohol (**6**–**16**), glycerol, and cyclohexanediols were commercial products. Glycerol and D-ribose deuteriated at the OH groups were obtained by H–D exchange reactions with D_2O. Thus, for example, a solution of ribose (1 g) in D_2O (4 mL) was stirred at room tempeature for 1 h. The excess D_2O was removed in vacuo at 80 °C and the residue was subjected to two additional cycles of dissolution in D_2O, stirring, and evaporation in vacuo to give ribose-d_4.

Macrocyclic Hosts (1a–c and 2). Into a solution of resorcinol (25.6 g, 0.23 mole and dodecanal (42.8 g, 0.23 mol) in ethanol (230 mL) was added 12 N hydrochloric acid (37 mL) at 0 °C. The mixture was stirred at 70 °C under nitrogen for 10 h. The precipitates which separated on cooling the mixture down to room temperature were recovered by filtration. A small amount of additional precipitates were obtained by addition of water to the filtrate. The precipitates were combined, washed thoroughly with hot water (80 °C, 10 L), dried, recrystallized twice from CH_3OH and then twice from hexane–acetone, and dried at 0.2 mmHg and 60 °C for 30 h to give compound **1a**[34] as a monohydrate as colorless needles (44.6 g (70%) after recrystallization from CH_3OH and 31.9 g (50%) after that from hexane–acetone): mp 270–271 °C dec; ^{1}H NMR ($CDCl_3$) δ_H 9.60 and 9.28 (each s, each 4 H, ArOH, disappeared on deuteriation), 7.20 and 6.10 (each s, each 4 H, ArH), 4.28 (t, 4 H, ArCRHAr), 2.21 and 1.29 (80 H, CH_2), 0.90 (t, 12 H, CH_3), 4.95 (br s, 2 H, H_2O, disappeared on deuteriation) (Figure 1A); ^{13}C NMR ($CDCl_3$) δ_C 150.57, 150.35, 124.90, 123.87, 102.86, 33.34, 33.19, 31.95, 29.81, 29.72, 29.40, 28.10, 22.69, 14.11; IR (CCl_4) 3250 cm^{-1} (ν_{OH}). Molecular weight by VPO for a C_6H_6 or $CHCl_3$ solution was 7066 (C_6H_6) or ca. 5000 ($CHCl_3$) (calcd 1124). Anal. Calcd for $C_{72}H_{112}O_8 \cdot H_2O$: C, 76.96; H, 10.22. Found: C, 76.92; H, 10.29. The reactions of resorcinol and $CH_3(CH_2)_nCHO$ (n = 6, 4, 3, and 0) were carried out similarly as above and gave compounds **1b**, **1c**, **1d**, and **1e**,[34] respectively; **1b** and **1c** were recrystallized twice from CH_3OH–H_2O and gave a ^{1}H NMR spectrum ($CDCl_3$) quite similar to that of **1a**, having split OH proton resonances at δ_H 9.58 and 9.32 for **1b** and 9.54 and 9.21 for **1c**.

A mixture of **1a** (21.1 g, 0.019 mol), acetic anhydride (102 g, 1.0 mol), and pyridine (4.0 g, 0.051 mol) was stirred at 80 °C under nitrogen for 13 h. The excess acetic anhydride and pyridine were removed in vacuo and the residue was taken in ether (500 mL). The ether solution was washed with aqueous $NaHCO_3$, H_2O, and aqueous NaCl. Workup and recrystallization from petroleum ether gave compound **2** as white needles (21.9 g, 80%): mp 132–132.5 °C; ^{1}H NMR ($CDCl_3$) δ_H 6.89 (s, 4 H, ArH), ca. 6 (very br, 4 H, ArH), 4.14 (t, 4 H, ArCRHAr), 2.16 (br s, 24 H, CH_3CO), 1.84 and 1.26 (80 H, CH_2), 0.88 (t, 12 H, CH_3); IR (KBr) 1762 cm^{-1} (ν_{CO}). Molecular weight by VPO for a C_6H_6 or $CHCl_3$ solution was 1445 (C_6H_6) or 1447 ($CHCl_3$) (calcd 1442). Anal. Calcd for $C_{88}H_{128}O_{16}$: C, 73.30; H, 8.95. Found: C, 73.39; H, 9.12. Gel filtration chromatography[35] of a crude sample of **2** prepared from a crude material of **1a** indicated the presence of two minor components, one (ca. 2% of **2**) being eluted before **2** and possibly the cyclopentamer and the other (<0.3% of **2**) being eluted after **2** and possibly the cyclotrimer. The yields of these products were higher when **1a** prepared under high-dilution conditions was used as substrate. Compound **2** obtained from **1a** purified by recrystallization was shown to be free from these byproducts.

1,1-Bis(2-hydroxy-3,5-dimethyl-1-phenyl)dodecane (4). A mixture of 2,4-xylenol (9.13 g, 75 mmol), dodecanal (6.88 g, 37 mmole, and 8 N HCl (24 mL) was stirred at room temperature for 24 h under nitrogen. The mixture was extracted with ether. The ether extract was washed with aqueous $NaHCO_3$ and then water. The ether was removed in vacuo and the residue recrystallized from hexane to give **4** as colorless needles (2.70 g, 18%): mp 118.0–118.5 °C; ^{1}H NMR ($CDCl_3$) δ_H 6.82 and 6.66 (each s, each 2 H, ArH), 5.62 (br s, 2 H, ArOH), 4.29 (t, 1 H, ArCRHAr), 2.21 and 2.07 (each s, each 6 H, $ArCH_3$), 2.00 and 1.24 (18 H, CH_2), 0.87 (t, 3 H, CH_3). Acetylation of **4** with acetic anhydride and pyridine afforded diacetate, which gave a satisfactory MS spectrum.

1,1-Bis(2,4-dihydroxy-5-dodecyl-1-phenyl)dodecane (5). A mixture of 4-dodecylresorcinol (1.0 g, 3.6 mmol), dodecanal (0.41 g, 2.2 mmole, and 6 N HCl (12 mL) in a mixed solvent of water (25 mL) and methanol (12 mL) was stirred at 40 °C for 3 h and at room temperature for 24 h under nitrogen. The mixture was neutralized by addition of aqueous $NaHCO_3$ and then extracted with ether. Workup and chromatography on silica with $CHCl_3$–ethyl acetate (1:1) as eluant gave **5** as colorless powders (0.48 g, 37%): mp 102.5–103.0 °C; ^{1}H NMR ($CDCl_3$) δ_H 7.42 and 5.45 (each br s, each 2 H, ArOH), 6.94 and 6.20 (each s, each 2 H, ArH), 4.16 (t, 1 H, ArCRHAr), 2.49 (m, 4 H, $ArCH_2$), 2.02, 1.54, and 1.25 (58 H, CH_2), 0.88 (t, 9 H, CH_3). Acetylation of **5** with acetic anhydride and pyridine afforded tetraacetate, which gave a satisfactory MS spectrum.

Glycerol and Water Complexes. A CCl_4 solution of **1a** ((1–2) × 10^{-2} M, 30 mL) and glycerol or H_2O (neat, 8 mL) was stirred vigorously at 20 °C for 24 h. The organic phase was separated, centrifuged, and filtered. The clear solution obtained was evaporated to give complex **1a**·4(glycerol) or **1a**·4H_2O. For the glycerol complex: ^{1}H NMR ($CDCl_3$) δ_H 9.60 (br s, 8 H, ArOH), 4.98 (s, 12 H, OH for glycerol), 3.34 (m, 20 H, CH for glycerol); CH protons of **1a** were very similar to those of **1a** uncomplexed (Figure 1B). Molecular weight by VPO for a $CHCl_3$ solution was 1497 (calcd for a **1a**·4(glycerol), 1474). For the water complex: ^{1}H NMR ($CDCl_3$) δ_H 9.65 and 9.38 (8 H, ArOH), 2.93 (s, 8 H, H_2O) (Figure 1C). The assignments were confirmed by use of the substrates deuteriated at OH groups, i.e., glycerol-d_3 and D_2O. A CCl_4 solution of the glycerol complex (5 mL) was stirred with D_2O (2 mL) for 48 h.[36] The ^{1}H NMR spectrum of the organic phase showed no absorption of glycerol. The NMR spectrum of the aqueous phase was identical with that of authentic glycerol in D_2O, indicating that glycerol solubilized in CCl_4 had been completely reextracted into D_2O. Glycerol

(34) 2,8,14,20-Tetraalkylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol; alkyl = undecyl (**1a**), heptyl (**1b**), pentyl (**1c**), butyl (**1d**), or methyl (**1e**).

(35) Gel filtration of **1a** was not successful since it was adsorbed on the column.

(36) Reextraction of glycerol and sugars is practically complete within a few hours.

was also solubilized in CCl_4 containing compound **5** with the molar ratio of glycerol/**5** ≅ 1, as evidenced by the ^1H NMR spectroscopy of the CCl_4 phase. On the other hand, no solubilization of glycerol was observed in the presence of compound **2**, **3**, **4**, or dodecanol in place of **1a** under otherwise identical conditions.

Ribose Complex. A two-phase mixture of a CCl_4 solution of **1a** ((1–2) × 10^{-2} M, 30 mL) and an aqueous solution of D-ribose (5.5 M, 5 mL) was stirred at 20 °C for 24 h. The organic layer was separated, centrifuged, and filtered as above to give a clear solution of **1a**·ribose·$2H_2O$: ^1H NMR ($CDCl_3$–CCl_4) is shown in Figure 2A; ^{13}C NMR ($CDCl_3$) δ_C 150.69, 150.22, 125.16, 123.32, 102.77, 33.03, 32.13, 32.08, 29.90, 29.70, 29.51, 28.07, 22.70, 14.09 (for the macrocyclic skeleton) and 93.8, 71.7, 68.1, 67.8, 65.0 (for ribose incorporated); IR (CCl_4) 3250 cm^{-1} with a shoulder at 3460 cm^{-1} (ν_{OH}). Molecular weight by VPO for a CCl_4 solution was 1272 (calcd for **1a**·ribose·$2H_2O$, 1292). After being dried in vacuo at 50 °C for 20 h, the complex showed a molecular weight (3866) corresponding to that of a trimer (calcd for 3(**1a**·ribose), 3768), suggesting that loss of water molecule(s) induced aggregation of the complex. The CCl_4 solution of the ribose complex obtained as above was stirred with H_2O or D_2O (4 mL) for 48 h.[36] The sugar reextracted into the aqueous phase was identified further by means of ^1H NMR spectroscopy; the amount of sugar reextracted as evaluated by NMR, HPLC, and colorimetry showed a good agreement to that of **1a** used, i.e., ribose/**1a** ≅ 1. Experimental details are shown below.

The ribose complexes of compounds **1b** and **1c** were obtained in a similar manner and gave the ^1H NMR spectra very similar to that of the **1a** complex; the **1b** complex showed the characteristic upfield-shifted resonance for 4-H of ribose at δ_H 0.22 and 2-H appeared as a distinct signal at 1.11.

Extraction of Sugars and Sugar Alcohol. A CCl_4 solution of **1a** (0.9 × 10^{-2} M, 30 mL) was stirred vigorously with an aqueous solution of a sugar or sugar alcohol (**6**–**16**, 2.4 M, 5 mL) in a sealed flask at 20 °C for 24 h. Stirring for 24 h was independently shown to be sufficient for the equilibrium to be attained; sugar in H_2O + **1a** in CCl_4 ⇌ sugar–**1a** complex in CCl_4. The organic phase was separated from the aqueous solution, centrifuged, and filtered to give a clear solution. The ^1H NMR spectrum of this solution gave only a rough estimate on the molar ratio of sugar/**1a** because of overlap of the protons of sugar and **1a**. For better analyses, the CCl_4 solution was stirred with D_2O (2–4 mL, containing a calculated amount of CH_3CO_2Na) or H_2O (2–4 mL) for 48 h,[36] and the two phases separated. In every case, the ^1H NMR spectrum of the CCl_4 phase left showed only signals for **1a**, indicating that the sugar solubilized in CCl_4 had been completely reextracted into the aqueous phase. The D_2O and H_2O solutions were directly analyzed by means of ^1H NMR spectroscopy and HPLC, respectively. The amount of sugar reextracted was evaluated comparison of a ^1H NMR integration ratio of the total sugar CH proton resonances (6 H for **6**–**9**, 7 H for **10**–**14**, and 8 H for **15** and **16**) to that of CH_3CO_2Na (3 H) added as integration standard and also by HPLC peak area after calibration using an authentic sample of the sugar. The sugar could also be analyzed by colorimetry.[14] The three analytical procedures gave similar results. Espeically, the NMR and HPLC results showed good agreements with each other. Approximate molar ratios of the amounts thus evaluated of sugars reextracted to that of **1a** used are summarized in Table I. Control runs under otherwise identical conditions for extraction and analysis indicated that no solubilization of ribose as a representative sugar takes place in the absence of **1a** or in the presence of **2**, **3**, **4**, **5**, calix[8]arene (using $CDCl_3$ as solvent), or dodecanol in place of **1a**.

Competitive Extraction of Sugars. Competitive-extraction runs were carried out similarly. Thus, for example, an aqueous solution of D-ribose (1.6 M) and D-xylose (1.6 M) was stirred with a CCl_4 solution of **1a** (0.9 × 10^{-2} M). The organic phase was separated and reextracted with H_2O as above. HPLC analysis of the H_2O extract on a column of PA-03 with CH_3CN–H_2O (83/17, 1.7 mL/min) as eluant indicated that almost exclusive extraction of ribose had taken place with molar ratios ribose/**1a** = 0.3 and xylose/**1a** ≅ 0; retention times were 5.5 and 7.3 min for ribose and xylose, respectively. A similar competition using an equimolar mixture of D-ribose and D-arabinose resulted in selective extraction of the former in a ratio ribose/arabinose = 4, as shown by HPLC analysis on PA-03 with CH_3CN–H_2O (83/17, 2.1 mL/min); retention times were 4.3 and 6.2 min, respectively, for ribose and arabinose. Since the HPLC separation of D-ribose and 2-deoxy-D-ribose was not satisfactory, the competition between these two sugars was analyzed by ^1H NMR spectroscopy, taking advantage of the characteristic signals for the 2-CH_2 protons (δ_H 2.0–1.4, 2 H), of the 2-deoxy sugar; from the relative integration of these protons was shown a selectivity factor of 2 favoring the deoxy sugar.

Extraction of Cyclohexanediols. An aqueous solution of 1,4-cyclohexanediol (1.35 M) as a mixture of cis (53%) and trans (47%) isomers was extracted with CCl_4 in the absence and presence of **1a** (0.9 × 10^{-2} M). The ^1H NMR spectrum of the organic phase in the presence of **1a** showed the signals for the diol solubilized which were considerably upfield-shifted (δ_H 0.13 and −0.47). The diol was reextracted into H_2O or D_2O and was analyzed by means of HPLC and ^1H NMR spectroscopy; the stereoisomer ratios were readily evaluated by NMR, taking advantage of the characteristic α-hydroxymethine protons (δ_H 3.78 and 3.61 for the cis and trans isomers, respectively). The authentic specimen of the trans isomer was obtained by fractional crystallization of a cis–trans mixture from acetone. The extraction of 1,3-cyclohexanediol was carried out and analyzed similarly.

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Registry No. 1a, 112247-07-1; **1a**·4(glycerol), 112247-09-3; **1a**·$4H_2O$, 112247-06-0; **1a**·ribose, 120578-29-2; **1a**·ribose·$2H_2O$, 120578-28-1; **1a**·(ribose-d_4)·$2D_2O$, 120578-32-7; **1b**, 120578-24-7; **1b**·ribose, 120578-30-5; **1c**, 120663-39-0; **1c**·ribose, 120663-41-4; **1d**, 120663-40-3; **1e**, 65338-98-9; **2**, 112247-08-2; **4**, 120578-25-8; **4** (diacetate), 120608-64-2; **5**, 120578-26-9; **5** (tetraacetate), 120578-33-8; **5**·glycerol, 120578-27-0; **6**, 50-69-1; **7**, 10323-20-3; **8**, 58-86-6; **9**, 1114-34-7; **10**, 533-67-5; **11**, 488-81-3; **12**, 59-23-4; **13**, 3458-28-4; **14**, 50-99-7; **15**, 2438-80-4; **16**, 3615-41-6; 1,3-$(HO)_2C_6H_4$, 108-46-3; $H_3C(CH_2)_{10}CHO$, 112-54-9; $H_3C(CH_2)_6CHO$, 124-13-0; $H_3C(CH_2)_4CHO$, 66-25-1; $H_3C(CH_2)_3CHO$, 110-62-3; H_3CCHO, 75-07-0; 2,4-$Me_2C_6H_3OH$, 105-67-9; 4-dodecylresorcinol, 24305-56-4; glycerol, 56-81-5; *cis*-1,4-cyclohexanediol, 931-71-5; *trans*-1,4-cyclohexanediol, 6995-79-5; *cis*-1,3-cyclohexanediol, 823-18-7; *trans*-1,3-cyclohexanediol, 5515-64-0.