of a cation-anion ion pair of $K_{as} \approx 0.3$ M^{-1},[26] can be used to estimate $k_{-1} = 6 \times 10^8$ to 7×10^9 s^{-1} for collapse of $BH^{+\cdot}$-CH_2COSEt by proton transfer to give $B{\cdot}CH_3COSEt$, so in the presence of a general acid of $pK_{BH} = 7.5$, the thiol ester enolate has an estimated lifetime ($1/k_{-1}$) from 10^{-9} to 10^{-10} s. If an enzyme provides stabilization of the thiol ester enolate relative to the thiol ester,[12a] then the lifetime of such carbanions in an enzyme active site may well be even longer than 10^{-9} s. These results provide evidence against the suggestion that enzyme-catalyzed Claisen condensation and related reactions proceed by concerted mechanisms[5,6,8] that are enforced, because in the presence of an acidic amino acid residue at the enzyme the intermediate enolate cannot exist for the time of even a single bond vibration (ca. 10^{-13} s).[6]

Enzyme catalysts often act to stabilize reactive carbanion intermediates,[12a,34] and the primary barrier which must be lowered in order for enzymatic catalysis of deprotonation at the α-carbonyl position of simple ketones and thiol esters to occur is the thermodynamic barrier to the formation of these unstable enolates.[12a] The 1.5-2.5-unit difference between the pK_a of a simple ketone and that of a simple thiol ester shows that protein catalysts must overcome a 2-3 kcal/mol larger thermodynamic barrier in order to deprotonate the latter carbon acid.

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Highly Cooperative Binding of Alkyl Glucopyranosides to the Resorcinol Cyclic Tetramer Due to Intracomplex Guest-Guest Hydrogen-Bonding: Solvophobicity/Solvophilicity Control by an Alkyl Group of the Geometry, Stoichiometry, Stereoselectivity, and Cooperativity

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Abstract: The resorcinol cyclic tetramer (**1**) binds methyl and *n*-octyl glucopyranosides via hydrogen-bonding in apolar organic media. The complexation behaviors of these two alkyl glucosides are markedly different from each other. Methyl glucoside (**2**), which is otherwise insoluble in $CHCl_3$ or CCl_4, is solubilized in that solvent upon formation of a 2:1 (host to guest) sugar-encapsulation complex with a remarkable β/α anomer selectivity. Octyl glucoside (**3**), on the other hand, is soluble in $CHCl_3$ and is bound to host **1** to give a 1:4 (host to guest) complex with only a low anomer selectivity. The four guest molecules are bound at the four unit hydrogen-bonding sites of the host with an exceptionally high cooperativity that arises from intracomplex guest-guest hydrogen-bonding involving the 5-CH_2OH and 2-OH groups of the adjacent glucoside molecules. The way to achieve a maximal hydrogen-bond network is discussed in terms of solvophobicity/solvophilicity control by an alkyl group of the geometry, stoichiometry, stereoselectivity, and cooperativity.

Introduction

Complexation of sugar derivatives in apolar organic media is a rapidly growing area of molecular recognition.[1] Unprotected monosaccharides can be solubilized in an apolar solvent upon formation of lipophilic complexes with a suitable host such as the resorcinol cyclic tetramer (**1**).[1a] Host **1** has a symmetric bowl-shaped aromatic cavity and four independent hydrogen-bonding sites (A-D) composed of a pair of OH groups. Lipophilic sugar derivatives such as sugar glycosides having a long alkyl chain can also be used as guests; they undergo complexation in homogeneous solutions.[1b] Both solubilization and homogeneous complexations are promoted by the hydrogen-bonding interaction. It is not well understood, however, how the polar host-guest interaction is affected by the solvophobicity/solvophilicity or the polar/apolar balance of the guest.

In the present work, we have studied the complexation of host **1** with methyl glucopyranoside (**2**) and *n*-octyl glucopyranoside (**3**) (Chart I). The methyl and octyl derivatives are insoluble or solvophobic and soluble or solvophilic, respectively, in an apolar solvent such as $CHCl_3$. We report here that the octyl derivative exhibits a remarkable cooperativity due to intracomplex guest-guest hydrogen-bonding. It is also shown that the difference in the intrinsic solubilities of **2** and **3** results in a dramatic alteration of their complexation behaviors.

Results

Solubilization of Methyl Glucopyranoside. Methyl β-D-glucopyranoside (2β), otherwise completely insoluble in CCl_4, was

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(1) (a) Aoyama, Y.; Tanaka, Y.; Sugahara, S. *J. Am. Chem. Soc.* **1989**, *111*, 5397. (b) Bonar-Law, R. P.; Davis; Murray, B. A. *Angew. Chem.* **1990**, *102*, 1497; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1407. (c) Greenspoon, N.; Wachtel, E. *J. Am. Chem. Soc.* **1991**, *113*, 7233. (d) Kikuchi, Y.; Kobayashi, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 1351.

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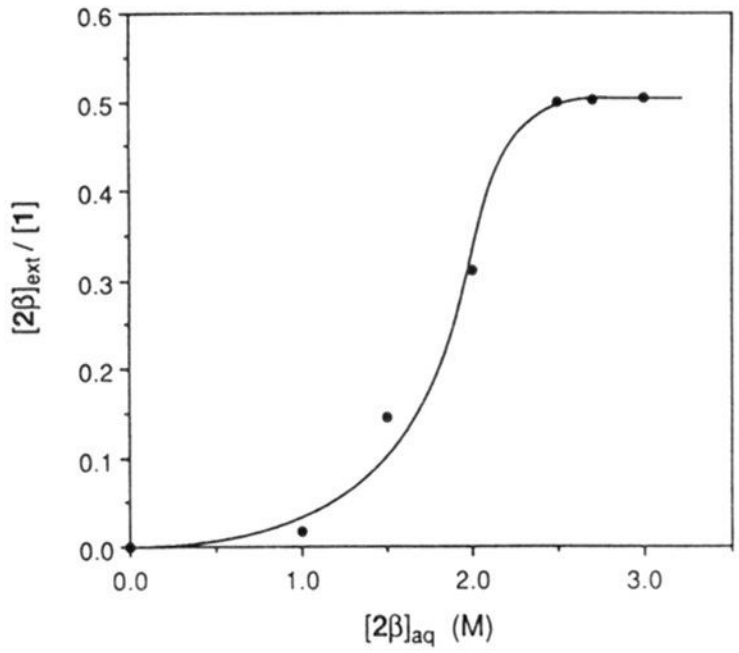
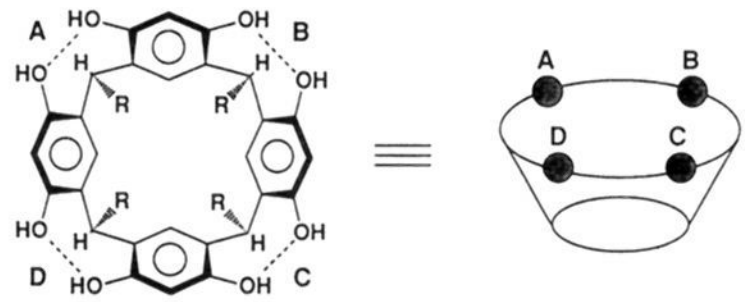
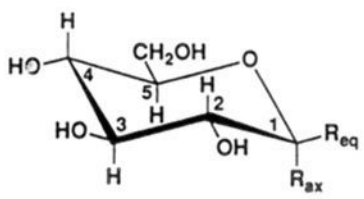


Figure 1. Molar ratios of glucoside **2**β extracted into CCl_4 ($[\mathbf{2}\beta]_{ext}$) to host **1** (10 mM) as a function of [**2**β] in source aqueous solutions.

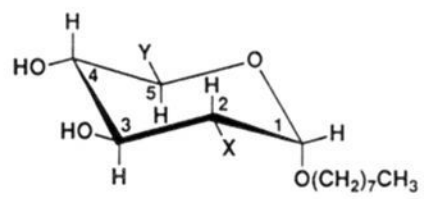
Chart I



1; R = $(CH_2)_{10}CH_3$



2α; R_{ax} = OCH_3, R_{eq} = H
2β; R_{ax} = H, R_{eq} = OCH_3
3α; R_{ax} = $O(CH_2)_7CH_3$, R_{eq} = H
3β; R_{ax} = H, R_{eq} = $O(CH_2)_7CH_3$



4α; X = OH, Y = H
5α; X = H, Y = CH_2OH

readily extracted from an aqueous solution (2.7 M, 2 mL) into a CCl_4 solution of host **1** (10 mM, 2 mL). Glucoside **2**β thus solubilized in CCl_4 could be completely reextracted into D_2O for further identification by means of ^1H NMR, indicating that neither hydrolysis of **2**β nor its isomerization to the α anomer **2**α had taken place. The molar ratios of **2**β solubilized in CCl_4 to **1** depend on [**2**β] in the aqueous phase and reach a saturation or plateau region at $[\mathbf{2}\beta]_{aq} \geq 2.5$ M, where $[\mathbf{2}\beta]/[\mathbf{1}] = 0.5$ (Figure 1). The complex can thus be formulated as 2(**1**)·**2**β. This was also supported by molecular weight determination by means of vapor pressure osmometry. The solubilization of **2**β into $CHCl_3$ was also achieved in essentially the same manner.

The ^1H NMR spectrum of the present 2:1 host–guest complex in $CDCl_3$ shows very complicated resonances for the hydroxyl and aromatic protons of host **1** and characteristically upfield-shifted resonances for the CH protons of bound **2**β (Figure 2A): δ –0.03 (CH_3), 1.95 (1-H), 2.30 (2-H), 2.43 (4-H), 2.66 (3-H), 2.80 (5-H), and 3.09 and 3.60 (6-H). The extents of upfield shifts[2] are small for 6-H (0.31 ppm), moderate and rather constant for 2-, 3-, 4-, and 5-H (0.80–0.93 ppm), and very large for 1-OCH_3 (3.58 ppm) and 1-H (2.40 ppm). The present complexation between an achiral chromophoric host **1** and a chiral nonchromophoric guest **2**β was also confirmed by observing an induced circular dichroism (CD)

(2) Relative to the chemical shifts for **2**β in D_2O: δ 3.55 (CH_3), 4.35 (1-H), 3.23 (2-H), 3.46 (3-H), 3.35 (4-H), 3.69 (5-H), and 3.40 and 3.91 (6-H).

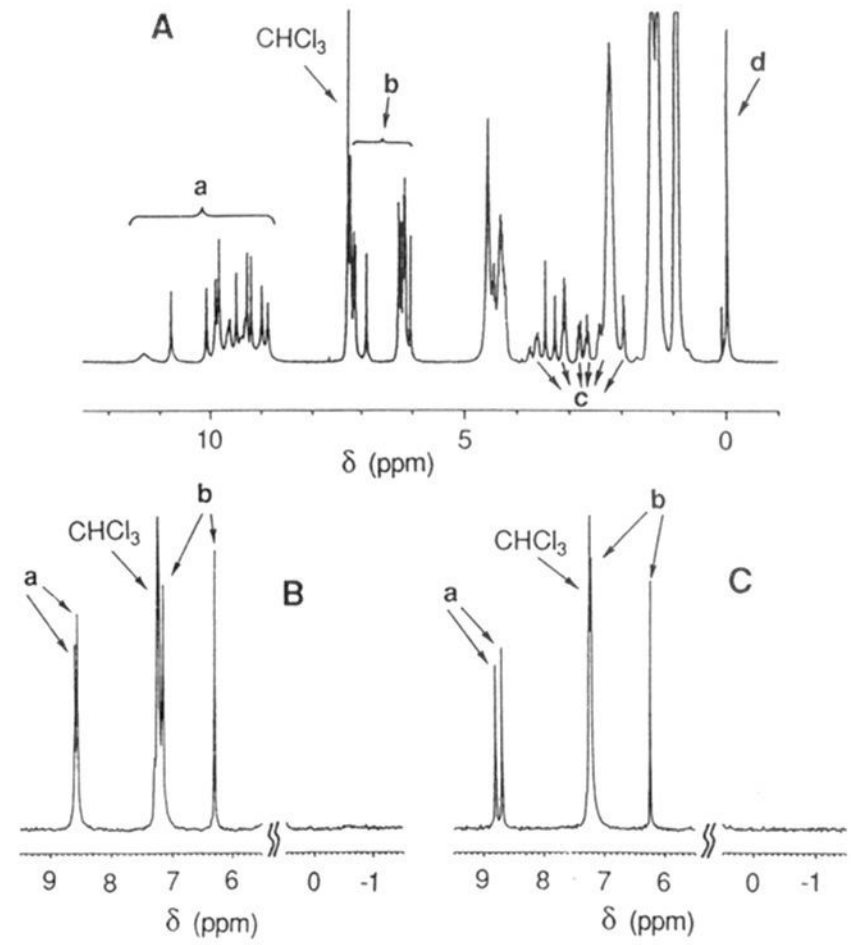


Figure 2. ^1H NMR spectra of complexes 2(**1**)·**2**β (A), **1**·4(**3**α) (B, lower- and higher-field portions only), and **1**·4(**3**β) (C, lower- and higher-field portions only) in $CDCl_3$. Assignments: a (OH of host **1**), b (aromatic H of host **1**), c (A, ring C–H of guest **2**β), and d (A, OCH_3 of guest **2**β). The sample solutions for the last two complexes were prepared by adding glucoside **3**α or **3**β (80 mM) to a $CDCl_3$ solution of host **1** (1.0 mM).

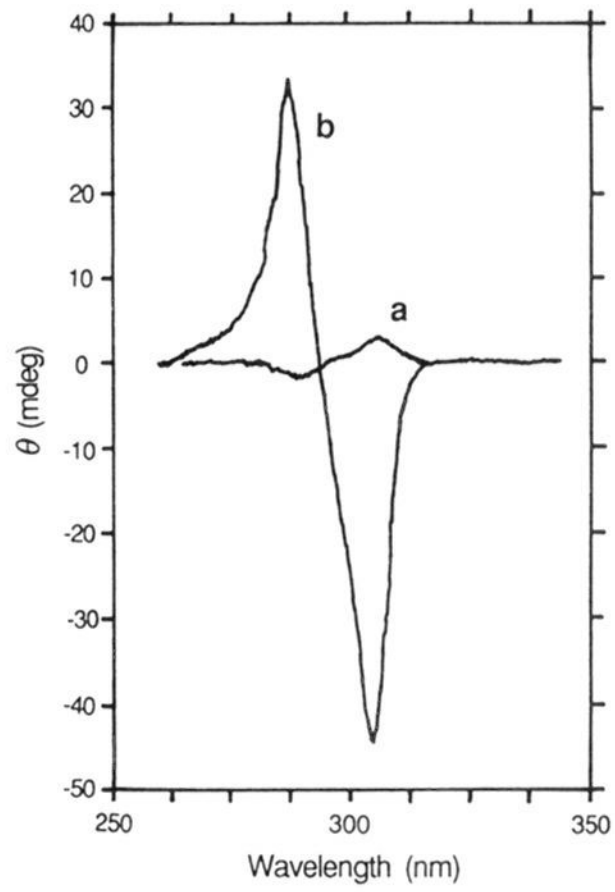


Figure 3. Circular-dichroism spectra of complexes **1**–**2**α (a) and **1**–**2**β (b) in CCl_4 in a cell of 0.5-cm path length at 25 °C. The sample solutions were prepared by extracting glucoside **2**α or **2**β (5 M) in water into CCl_4 containing host **1** (0.2 mM).

with split Cotton effects (Figure 3).[3]

In marked contrast to β-glucopyranoside **2**β, the α anomer **2**α showed a surprisingly lower affinity to **1**. Even at higher glucoside concentrations (≥2.5 M) where the binding of **2**β was in the saturation range, that of **2**α was just detected by ^1H NMR and CD spectroscopy (Figure 3). The striking selectivity for **2**β over

(3) See ref 1d for the induced-CD characterization of the complexes of host **1** with chiral glycols, steroidal polyols, and unmodified sugars in $CHCl_3$.

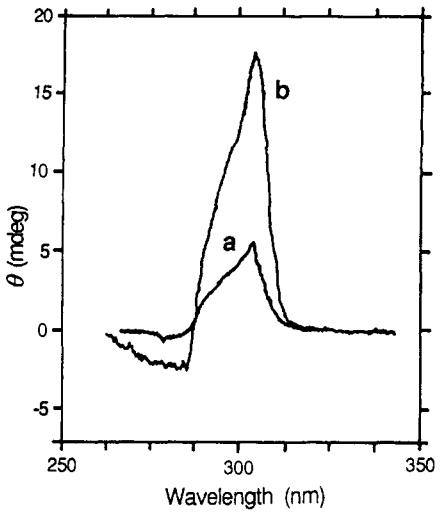


Figure 4. Circular-dichroism spectra of complexes **1**·4(3α) (a) and **1**·4(3β) (b) in $CHCl_3$ in a cell of 0.1-cm path length at 25 °C. The sample solutions were prepared by adding glucoside 3α or 3β (80 mM) to a $CHCl_3$ solution of host **1** (1.0 mM).

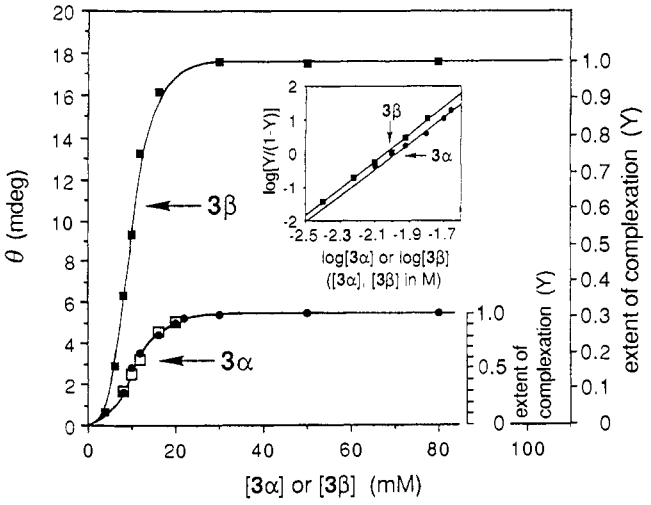


Figure 5. Correlations of the observed ellipticities (θ) at 305 nm with [3α] or [3β] for the complexation of host **1** (1.0 mM) and guest 3α or 3β in $CHCl_3$ at 25 °C. Extents of complexation ($Y = \theta/\theta_{sat}$) are also shown. The solid lines are theoretical ones based on eq 2 and $K = 1.9 \times 10^8$ M^{-4} for 3α or 3.2×10^8 M^{-4} for 3β. Open squares in the Y–[3α] correlation represent extents of complexation evaluated by the ^1H NMR method for the complexation of host **1** (1.0 mM) and guest 3α in $CDCl_3$ at 25 °C. Inset: Hill plots of log $[Y/(1 - Y)]$ vs log [3α] or log [3β] according to eq 1.

2α was also confirmed by competition; from an equimolar mixture of 2α and 2β in water ([2α] = [2β] = 2.0 M) was extracted 2β almost exclusively ([2β]/[1] = 0.4 and [2α]/[1] ≈ 0.01).[4]

Homogeneous Complexation of Octyl Glucopyranoside. *n*-Octyl α- (3α) and β-D-glucopyranoside (3β) are *soluble* in $CHCl_3$. They also form complexes with host **1** (1.0 mM), as confirmed again by observing induced CD (Figure 4). Plots of CD intensities (observed ellipticities) at 305 nm as a function of [3α] or [3β] gave a sigmoidal binding isotherm (25 °C) (Figure 5). This is characteristic of a cooperative binding process. Vapor pressure osmometry for guest 3β (true mol wt 292) in $CHCl_3$ indicated that molecular weight somewhat depends on concentration. The observed (average) molecular weights at various concentration ranges are 3.5×10^2 (1.2-mer) (6–13 mM), 4.5×10^2 (1.5-mer) (13–25 mM), 6.9×10^2 (2.4-mer) (25–50 mM), and 4.7×10^2 (1.6-mer) (6–50 mM). These results indicate that guest **3** is

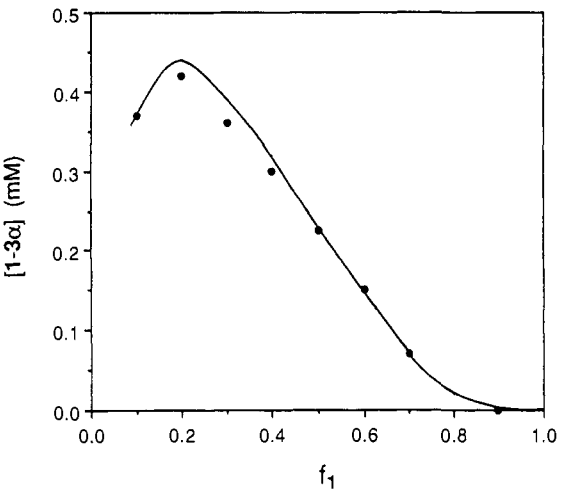


Figure 6. Job plots of the concentrations of complex **1**–3α vs mole fractions of host **1** (f_1) for the complexation of **1** and 3α in $CDCl_3$ at 25 °C under conditions where [**1**] + [3α] is maintained at 10 mM. The solid line is a theoretical one based on eq 2 and $K = 1.9 \times 10^8$ M^{-4}.

essentially monomeric at concentrations lower than 10 mM and that it undergoes slight aggregation at higher concentrations to give a dimer or trimer at best, even at [3β] = 50 mM. Thus, the sigmoidal titration curve for 3β in Figure 5 cannot be explained in terms of (reversed) micelle formation for 3β, with a critical micelle-forming concentration at ~4 mM.

The complexation of **1** and 3α or 3β can also be followed by ^1H NMR spectroscopy. The ^1H NMR spectrum of host **1** free from complexation in $CDCl_3$ shows a pair of broad singlets (δ 9.60 and 9.28) and a pair of sharp singlets (δ 7.20 and 6.10) for the hydroxyl and aromatic protons, respectively.[1a] In the presence of guest **3**, another set of corresponding resonances for the host–guest complex appears: a pair of sharp singlets at δ 8.60 and 8.53 (OH) and a pair of sharp singlets at δ 7.16 and 6.30 (aromatic H) for 3α and a pair of sharp singlets at δ 8.81 and 8.70 (OH) and a pair of sharp singlets at δ 7.18 and 6.26 (aromatic H) for 3β. Thus, the OH protons and the higher-field component of the aromatic protons undergo upfield and downfield shifts, respectively, upon binding of guest 3α or 3β. In Figure 2B,C are respectively shown the actual spectra in these and higher-field regions for homogeneous $CDCl_3$ solutions of host **1** in the presence of a sufficiently excess amount (80 equiv) of guest 3α or 3β to ensure a 100% complexation. It is also noteworthy that there are no characteristically upfield-shifted resonances for bound guest in the higher-field region (≤0 ppm) (Figure 2B,C).

The observation of distinct sets of ^1H NMR resonances for free host **1** and complex **1**–**3** allows direct evaluation of [**1**] and [**1**–**3**] by integration. The extents of complexation (Y), evaluated in this manner, for **1** (1.0 mM) and varying amounts of 3α are also shown in Figure 5 (open squares). Thus, the NMR titration curve fits very well with the CD titration curve. In Figure 6 are shown the so-called continuous-variation (Job) plots of [**1**–3α] vs mole fractions of **1** (f_1) under conditions where $[1]_t + [3\alpha]_t$ is maintained at 10 mM (t = total). The maximum occurs at $f_1 = 0.2$, indicating that complex **1**–3α has a novel 1:4 (**1** to 3α) stoichiometry. The complexation of **1** and 3β showed similar Job plots.

The cooperativity in the binding of four molecules of guest **3** can be evaluated by analyzing the sigmoidal CD titration curves (Figure 5) on the basis of the so-called Hill equation (eq 1),[5] where

$$\log [Y/(1 - Y)] = n \log [3] + \log K \qquad (1)$$

$Y = \theta/\theta_{sat}$ is the extent of complexation (Figure 5), K is the binding constant, and n (Hill coefficient) is the measure of cooperativity.[6]

(4) Distinction of 2α and 2β in D_2O, after reextraction, could be readily made by means of ^1H NMR spectroscopy: $\delta(CH_3)$ 3.40 for 2α and 3.55 for 2β.

(5) Equation 1 is derived from the expression $Y = K[3]^n/(1 + K[3]^n)$, which corresponds to the equilibrium **1** + *n*(**3**) ⇌ **1**·*n*(**3**).

(6) Connors, K. A. *Binding* Constants; John Wiley: New York, 1987; pp 78–86.

Hill plots of log $[Y/(1-Y)]$ vs log $[\mathbf{3}\alpha]$ or log $[\mathbf{3}\beta]$, according to eq 1 and assuming $[\mathbf{3}] = [\mathbf{3}]_t$, gave a straight line (inset of Figure 5) with a slope of $n = 3.9$ for $\mathbf{3}\alpha$ or 4.0 for $\mathbf{3}\beta$. Thus, the CD (titration) and NMR (Job plots) results are consistent with each other; four molecules of guest $\mathbf{3}\alpha$ or $\mathbf{3}\beta$ are bound to host **1** in a highly cooperative manner ($n \approx 4$) (eq 2). The intercepts

$$\mathbf{1} + 4(\mathbf{3}) \overset{K}{\rightleftharpoons} \mathbf{1}\cdot 4(\mathbf{3}) \qquad (2)$$

of the Hill plots give the binding constants $K = 0.6 \times 10^8$ M^{-4} for $\mathbf{3}\alpha$ and 1.6×10^8 M^{-4} for $\mathbf{3}\beta$. These values, however, should be corrected because, strictly, $[\mathbf{3}] \neq [\mathbf{3}]_t$ under the concentration range $[\mathbf{3}]_t/[\mathbf{1}]_t = 4$–22 (Figure 5). The true values were obtained directly by the equation $K = [\mathbf{1}\cdot 4(\mathbf{3})]/[\mathbf{1}][\mathbf{3}]^4$ where $[\mathbf{1}] = [\mathbf{1}]_t - [\mathbf{1}\cdot 4(\mathbf{3})]$ and $[\mathbf{3}] = [\mathbf{3}]_t - 4[\mathbf{1}\cdot 4(\mathbf{3})]$; $K = 1.9 \times 10^8$ (from the CD titration data) or 1.8×10^8 M^{-4} (from the NMR titration data) for $\mathbf{3}\alpha$ and 3.2×10^8 M^{-4} (CD) for $\mathbf{3}\beta$. The solid lines in Figures 5 and 6 are theoretical ones based on these binding constants and the 1:4 stoichiometry (eq 2).

n-Octyl α-D-xylopyranoside ($\mathbf{4}\alpha$) and α-2-deoxy-D-glucopyranoside ($\mathbf{5}\alpha$) (Chart I) as references behaved quite differently from glucoside **3**. Xylose and 2-deoxyglucose are derivatives of glucose, lacking the 5-CH_2OH and 2-OH groups, respectively. The ^1H NMR spectra for $CDCl_3$ solutions of host **1** and guest $\mathbf{4}\alpha$ or $\mathbf{5}\alpha$ in various guest/host molar ratios showed no change in the host–proton (OH and aromatic H) resonances, characteristic of the **1**–**3** complexation (Figure 2B,C). The only sign for a weak host–guest complexation was the complexation-induced shifts of the guest–proton resonances, but with very low intensities, at δ +0.2 to –0.7. CD spectroscopy gave similar results. Even under conditions ([**1**] = 1.0 mM and [guest] = 20 mM) where the binding of glucosides $\mathbf{3}\alpha$ and $\mathbf{3}\beta$ was almost in the saturation range (Figure 5), that of xyloside $\mathbf{4}\alpha$ and 2-deoxyglucoside $\mathbf{5}\alpha$ was just detected at best; the observed ellipticities (θ/mdeg) were 0.17 (305 nm) for $\mathbf{4}\alpha$ and ~0 for $\mathbf{5}\alpha$, as compared with $\theta = 5.01$ for $\mathbf{3}\alpha$ and 17.43 for $\mathbf{3}\beta$ under otherwise identical conditions (Figure 5).

The relative binding abilities of **3**, **4**, and **5** were evaluated by competitive binding. It was found that addition of an equimolar (to $\mathbf{3}\alpha$ or $\mathbf{3}\beta$) amount of $\mathbf{4}\alpha$ or $\mathbf{5}\alpha$ to a binary system of **1** and $\mathbf{3}\alpha$ or $\mathbf{3}\beta$ in $CHCl_3$ or $CDCl_3$ resulted in practically no change or only a slight reduction in the amount of complex $\mathbf{1}\cdot 4(\mathbf{3}\alpha)$ or $\mathbf{1}\cdot 4(\mathbf{3}\beta)$, which was readily evaluated by ^1H NMR (Figure 2B,C) or CD (Figure 4) spectroscopy. For example, the CD intensity at 305 nm for a ternary system of **1** (1.0 mM), $\mathbf{3}\beta$ (20 mM), and $\mathbf{4}\alpha$ or $\mathbf{5}\alpha$ (20 mM) in $CHCl_3$ was ≥97% or ~95%, respectively, of that for the binary system of **1** (1.0 mM) and $\mathbf{3}\beta$ (20 mM).[7] These results indicate that the binding of xyloside $\mathbf{4}\alpha$ and 2-deoxyglucoside $\mathbf{5}\alpha$ is practically too weak to compete with glucoside **3**. In other words, host **1** shows a remarkable selectivity for **3** over **4** and **5**, despite their apparent close structural similarity.

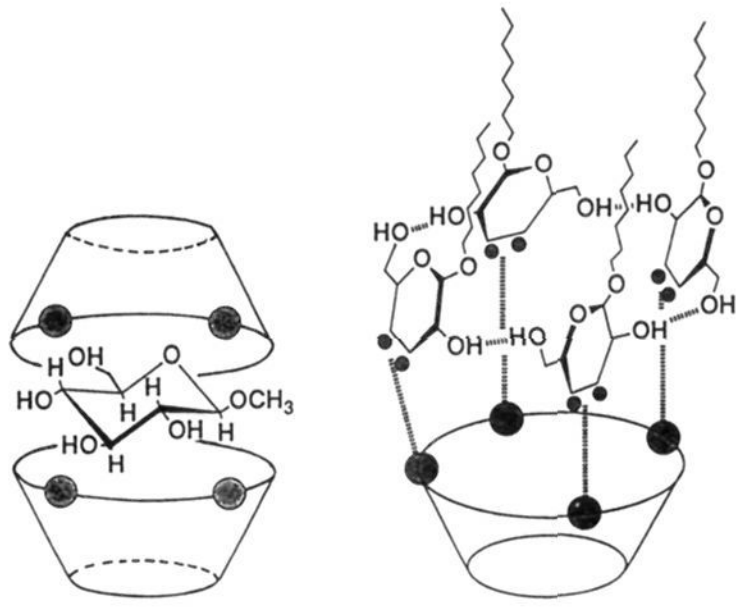
Discussion

Sandwichlike Encapsulation of Methyl Glucopyranoside. Glucopyranose, an aldohexose, has 2-OH, 3-OH, 4-OH, and 5-CH_2OH groups in an all-trans or zigzag configuration, a situation where the multiple hydrogen-bonding interaction with host **1** having a multiple but essentially two-dimensional binding site is least favorable. In fact, glucose is one of the least-readily-extractable sugars.[1a] The 2:1 (host to guest) stoichiometry observed for complex $\mathbf{1}$–$\mathbf{2}\beta$ indicates that two molecules of host **1** are required to encapsulate guest $\mathbf{2}\beta$, thereby giving rise to a lipophilic complex soluble in CCl_4 or $CHCl_3$. A possible structure for the complex is schematically shown in **6** in Chart II (hydrogen bonds are not shown because of uncertainty).

The methyl group may promote the extraction of guest $\mathbf{2}\beta$ either by enhancing the lipophilicity as compared with that of parent glucopyranose[1a] or by stabilizing the resulting complex via a guest–host, methyl–aromatic, CH–π interaction.[8,9] The methyl

(7) Similar competitive binding experiments indicated that the CD intensity for the mixture of **1** (1.0 mM) and $\mathbf{3}\beta$ (20 mM) was again little affected by *n*-octyl glycosides of other aldopentoses such as α-D-ribo- and α-D-arabinopyranose (20 mM), giving ≥97% of the original intensity.

Chart II



6 7

group may also cause steric hindrance. The essential role(s) of the methyl group and the origin(s) of the remarkable β/α anomer selectivity associated therewith are not clear at present. Probably, the extraction-promoting or -inhibiting effect(s) of the methyl group would depend on its stereochemistry, equatorial in the β anomer $\mathbf{2}\beta$ or more crowded axial in the α anomer $\mathbf{2}\alpha$. There is indeed good NMR indication that guest $\mathbf{2}\beta$ is tightly packed in the encapsulation complex $2(\mathbf{1})\cdot\mathbf{2}\beta$ (structure **6**). First, a close proximity of the methyl group of bound $\mathbf{2}\beta$ and a benzene ring of host **1** is evidenced by a very large (3.58 ppm) upfield shift of the methyl protons, together with their strong ^1H–^{13}C NOE correlation with the aromatic 5-C. Second, movement of guest $\mathbf{2}\beta$ in the 2:1 complex **6** must be frozen. This is indicated by the extensive splittings of the hydroxyl and aromatic proton resonances for the host (Figure 2A); the 16 hydroxyl H's and the 8 aromatic 2-H's as well as 5-H's are thus rendered nonequivalent in the presence of an unsymmetrical guest $\mathbf{2}\beta$ in a *fixed* geometry.

Cooperative Binding of Octyl Glucopyranoside. The 1:4 stoichiometry observed for octyl glucoside **3** (eq 2) leaves little doubt that the four unit hydrogen-bonding sites (A–D)[1a,1d,10,11] of the host are involved in the cooperative binding of guest $\mathbf{3}\alpha$ or $\mathbf{3}\beta$. Such a high cooperativity as observed here (Hill coefficient ≈ 4) has no precedent.[12] A typical biological example of cooperative processes is the binding of four molecules of O_2 to hemoglobin; this exhibits a Hill coefficient of 2.8.[13] The positive or homotropic cooperativity in the present system may arise either from allosteric conformational change in the binding sites[12] or from intracomplex guest–guest attractive interaction. The latter is much more plausible, in view of the rigid nature of host **1** and the structural

(8) Kobayashi, K.; Asakawa, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* following paper in this issue.

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requirement of the guests for cooperativity discussed below.

The plausible hydrogen-bond network in complex **1**·4(**3**) is schematically shown in structure **7** in Chart II (small circles on the pyranose rings stand for 3-OH and 4-OH groups, and dotted lines represent hydrogen bonds). There are two essential interactions. One is host–guest hydrogen-bonding between a unit-binding site of the host and the glycolic 3-OH and 4-OH groups of the guest with the octyl group, the most lipophilic part of the molecule, being extended into bulk solvent. The glycol binding with host **1** has been extensively studied.[1d,11] The other is guest–guest hydrogen-bonding, as the source of cooperativity, between the 5-CH_2OH and 2-OH groups of two adjacent molecules of bound **3**.

Structure **7** of a C_4 symmetry is compatible not only with the ^1H NMR results (simple aromatic proton resonances for the host and lack of any notable upfield shifts for the bound guest;[14] Figure 2B,C) but also with the low anomer selectivity between **3**α and **3**β ($K_{3\beta}/K_{3\alpha} = 1.7$). Most importantly, structure **7** is consistent with the stability and cooperativity in complex **1**·4(**3**). That *both* the 5-CH_2OH and 2-OH groups of glucoside **3** play essential roles is evidenced by the low binding abilities and lack of cooperativity for xyloside **4**α and 2-deoxyglucoside **5**α. In referring to structure **7**, each guest molecule has two additional guest–guest hydrogen bonds involving these groups. In the course of successive binding of four molecules of **3**, the first-, the second- and third-, and the fourth-introduced ones have zero, one, and two such hydrogen bonds. The binding constants thus increase in the order $K_1 < K_2 = K_3 < K_4$. Although quantitative evaluation is not easy, this intracomplex guest–guest hydrogen-bonding must be a sizable interaction, since the 1:4 stoichiometry (eq 2) indicates that four molecules of glucoside **3** are *simultaneously* bound to host **1** as a result of an exceptionally high cooperativity ($n \approx 4$).

Conclusions

The present work shows how host **1** having an essentially two-dimensional multidentate binding site interacts with an alkyl glucopyranoside having a three-dimensional arrangement of the OH groups in apolar organic media. The main conclusion here is that the way to achieve a maximal hydrogen-bond network depends dramatically on whether or not the guest glucoside is intrinsically soluble in the medium. Methyl glucoside (**2**) is solvophobic or otherwise insoluble in apolar media. In order for this guest to be solubilized, the OH groups must be insulated from the bulk solvent by undergoing an extensive hydrogen-bonding interaction with the host. This results in a guest-promoted clustering of the host to give a compact 2:1 (host to guest) sugar-encapsulation complex with a remarkable β anomer selectivity. In the homogeneous binding of octyl glucoside (**3**), a solvophilic or soluble guest, on the other hand, potential guest–guest hydrogen-bonding becomes more important. This results in a highly cooperative host-induced aggregation of the guest to give a 1:4 (host to guest) complex.

The implication of this work may be 2-fold. First, the mode (geometry, stoichiometry, stereoselectivity, and cooperativity) of polar host–guest interaction of an otherwise highly hydrophilic compound can be altered completely by its lipophilic modification via alkylation. Second, in reference to the cooperative binding of glucoside **3**, direct sugar–sugar interaction can provide a source of high selectivity in molecular recognition of sugars. Recent work suggests that direct oligosaccharide–oligosaccharide interactions on the cell surfaces play an essential role in intercellular recognition.[15]

(14) Xyloside **4**α and 2-deoxyglucoside **5**α could not form the structure corresponding to **7**. They would only be weakly bound in a *usual* manner in the cavity of host **1** so as to give rise to complexation-induced upfield shifts, as observed.

Experimental Section

Materials. Host **1** was prepared as described.[1a] Methyl α- (**2**α) and β-D-glucopyranoside (**2**β) and *n*-octyl β-D-glucopyranoside (**3**β) were commercial products. Other octyl glycosides were obtained according to a slight modification of the literature method,[16] i.e., by the glycosidation of the corresponding monosaccharides with octanol in the presence of HCl (1.25% by weight) at 50 °C for 3 days. The products were purified by column chromatography (silica gel) with acetone as eluant, followed by recrystallization from hexane–acetone, hexane–ether, or hexane: *n*-octyl α-D-glucopyranoside (**3**α), mp 68.0–68.5 °C, $\delta_{1\text{-}C}$ 99.2; α-D-xylopyranoside (**4**α), mp 65.5–67.5 °C, δ 98.8; α-2-deoxy-D-glucopyranoside (**5**α), mp 101.5–102.0 °C, δ 97.8; α-D-ribopyranoside, mp 96.5–97.0 °C, δ 100.2; α-D-arabinopyranoside, mp 114.0–114.5 °C, δ 99.1. The α configuration for each glycoside was confirmed by ^{13}C NMR spectroscopy.[17] The yields were ~40% for **3**α and 10–20% for other glycosides.

Instruments and Measurements. ^1H and ^{13}C NMR spectra, respectively, at 270 and 68.7 MHz were taken on a JEOL JNM-GX 270 spectrometer at 25 °C for $CDCl_3$ solutions. The OH proton resonances were assigned on the basis of deuteriation. The CH proton resonances for bound **2**β were assigned by means of ^1H–^1H and ^1H–^{13}C COSY and ^1H–^1H NOESY correlations. Vapor pressure osmometry for guest **3**β and complex **1**·**2**β in $CHCl_3$ at 35 °C was performed on a Corona-114 molecular weight apparatus with benzil (mol wt 210) and the octaacetate derivative of **1**[1a] (1442) as standards, respectively. CD spectra were obtained with a JASCO J-500C spectropolarimeter at 25 °C for a series of $CHCl_3$ solutions containing host **1** (1.0 mM) and varying amounts of **3**β or **3**β in a cell of 0.1-cm path length. Referring to Figure 5, the ratio of observed ellipticity to that at saturation (θ/θ_{sat}) represents the extent of complexation (Y). The binding constant was calculated according to $K = [\text{complex}]/[\mathbf{1}][\text{guest}]^4$, where $[\text{complex}] = [\mathbf{1}]_t(\theta/\theta_{sat})$, $[\mathbf{1}] = [\mathbf{1}]_t - [\text{complex}]$, and $[\text{guest}] = [\text{guest}]_t - 4[\text{complex}]$ (t = total). The K values shown in the text are the averages of those obtained at six different guest concentrations. For guest **3**α, $K = 1.9 \times 10^8$, 2.4×10^8, 2.2×10^8, 1.5×10^8, 1.5×10^8, and 1.7×10^8 M^{-4} at $[3\alpha]_t = 8$, 10, 12, 16, 20, and 22 mM, respectively, and $K_{av} = (1.9 \pm 0.5) \times 10^8$ M^{-4}. For **3**β, $K = 1.8 \times 10^8$, 2.4×10^8, 3.0×10^8, 2.9×10^8, 4.7×10^8, and 4.6×10^8 M^{-4} at $[3\beta] = 4$, 6, 8, 10, 12, and 16 mM, respectively, and $K_{av} = (3.2 \pm 1.4) \times 10^8$ M^{-4}. The binding constant for **3**α was also obtained in exactly the same manner by treating the NMR titration data (Figure 5); $K = 2.1 \times 10^8$, 1.8×10^8, 1.6×10^8, 1.9×10^8, and 1.6×10^8 M^{-4} at $[3\alpha] = 8$, 10, 12, 16, and 20 mM, respectively, and $K_{av} = (1.8 \pm 0.3) \times 10^8$ M^{-4}.

Extraction. A two-phase mixture of a CCl_4 or $CHCl_3$ solution of host **1** (10 mM, 50 mL) and an aqueous solution of guest **2**β (2.7 M, 10 mL) was stirred at 30 °C for 12 h. The organic phase was separated from the mixture, centrifuged, and filtered to give a clear solution, as in the case of sugar extraction.[1a] Removal of the solvent gave complex **2**(**1**)·**2**β: ^{13}C NMR ($CDCl_3$) δ_C 14.1, 22.5, 30.1, 31.4–33.9, 101.6–106.5, 122.6–125.4, 149.5–151.5 for the macrocyclic skeleton and 54.5 (CH_3), 59.8 (6-C), 68.5 (4-C), 72.1 (2-C), 75.1 (3-C), 75.8 (5-C) for **2**β incorporated; 1-C was not assignable due to overlap with resonances of **1**. Molecular weight by vapor pressure osmometry for a $CHCl_3$ solution was 2.4×10^3 (calcd for **2**(**1**)·**2**β 2182). The ^1H NMR spectrum is shown in Figure 2A. The molar ratio **2**β:**1** was evaluated by ^1H NMR integration for the characteristic methyl group of **2**β, either directly for the complex in $CDCl_3$ or after reextraction of **2**β back into D_2O.

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Registry No. **2**α, 97-30-3; **2**β, 709-50-2; **3**α, 29781-80-4; **3**β, 29836-26-8; **4**α, 144467-14-1; **5**α, 144467-15-2.

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