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D_{3h}-Symmetrical Hydrogen-Bonding Unit as a Saccharide Recognition and Self-Assembling Module

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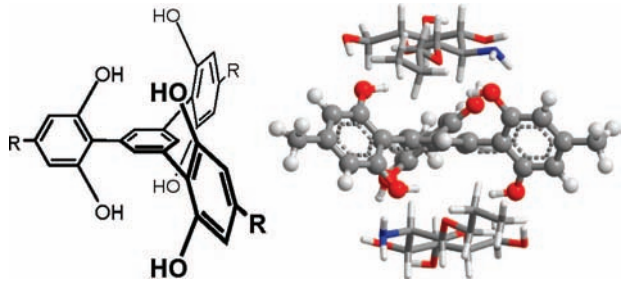
ABSTRACT



A D_{3h}-symmetrical triresorcinol module 1,3,5-tris(2,6-dihydroxy-4-pentylphenyl)benzene (3) was investigated in terms of its hydrogen-bonding ability for glycoside recognition and self-association. When 3 was treated with glycoside, corresponding changes were induced in ^{1}H NMR, UV, and CD spectra. The titration experiments indicated the participation of not only a 1:1 but also a 1:2 association of a glucosamine derivative guest. Self-association of 3 caused gelation with $CDCl_3$, and was studied by ^{1}H NMR and X-ray analysis.

Hydrogen bonding builds various kinds of natural and artificial supramolecular systems, and its proper design is essential for producing desirable functions. During our study of artificial host molecules for saccharide recognition,[1–4] we developed several types of effective designs in which plural hydrogen-bonding units such as phenols[5] and pyridines[6] are arranged in a rigid structure at appropriate distances. Among them, C_{3v}-symmetrical[2] triphenolic host **1** showed an interesting association behavior.[5] The host molecule binds glycosides with three phenolic hydroxy groups at intervals of ca. 4 to 6 Å from each other, and its recognition ability is considerably improved by fixing the hydroxy groups to the same side by inhibiting the phenol−benzene bonds (Figure 1). There is another method to keep the three hydroxy groups on one side of the same host skeleton, that is, by creating an additional symmetry plane corresponding to 180° rotation. Herein the D_{3h}-symmetrical host[7] 1,3,5-tris(2,6-dihydroxy-4-pentylphe-

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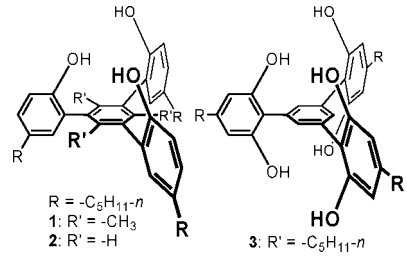


Figure 1. C_{3v}- and D_{3h}-symmetrical hosts **1**, **2**, and **3**.

nyl)benzene (**3**) was newly designed and synthesized to reduce the drawback caused by axial rotation. In addition, the bifacial molecule was found to form a self-assembling entity resulting in gelation in less-polar media.

The D_{3h}-symmetrical host molecule **3** was prepared as shown in Scheme 1. Commercially available 3,5-dimethoxybenzaldehyde (**4**) was subjected to react with *n*-butyllithium to give alcohol **5**,[8] which was reduced to 1,3-dimethoxy-5-pentylbenzene (**6**) with chlorotrimethylsilane-NaI.[9] The 2-position of **6** was lithiated, and treatment with trimethyl borate followed by hydrolysis gave 2,6-dimethoxy-4-pentylbenzeneboronic acid (**7**). Suzuki coupling of **7** and 1,3,5-triiodobenzene[10] with Buchwald's water-soluble ligand[11] yielded triarylated product **8**, and subsequent demethylation with an excess amount of BBr_3 afforded the targeted host molecule **3**. The demethylation needs to be performed at low temperature (−5 °C) to avoid direct electrophilic boronation on the central benzene ring.[12]

Saccharide recognition abilities were studied in $CDCl_3$ by treating **3** (1.0 mM) with an equimolar amount of glycoside: octyl β-(D and L)-glucopyranoside (**β-D-Glc** and **β-L-Glc**), octyl α-D-glucopyranoside (**α-D-Glc**), octyl α-(D and L)-mannopyranoside (**α-D-Man** and **α-L-Man**), octyl-β-D-galactopyranoside (**β-D-Gal**), octyl β-D-fructopyranoside (**β-D-Fru**), methyl β-D-ribofuranoside (**β-D-Rib**), and octyl β-D-2-amino-2-deoxyglucopyranoside[13] (**β-D-GlcNH$_2$**) (for their structures, see the Supporting Information). The last is a glucosamine derivative chosen as a basic substrate. When **3** was treated with **β-D-Glc**, some changes were observed in the ^{1}H NMR spectra because of host−guest association (Figure 2): (1) the signal for hydroxy protons of **3** appeared

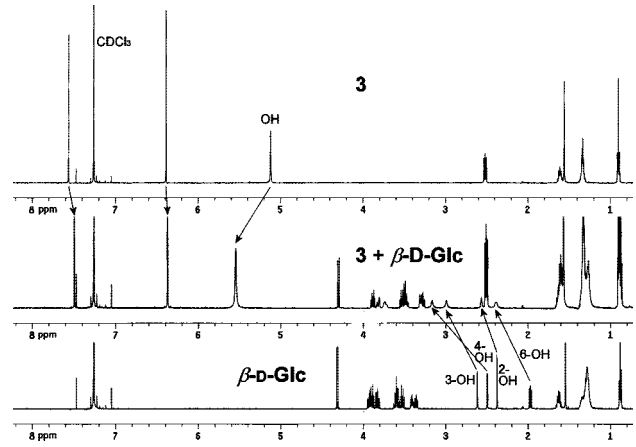
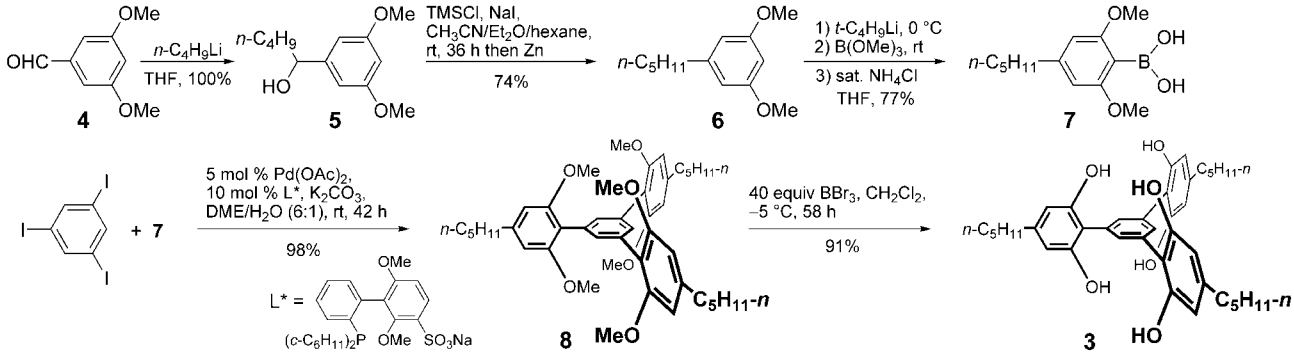


Figure 2. ^{1}H NMR spectra for **3** (top) and a mixture of **3** and **β-D-Glc** (middle) and **β-D-Glc** (bottom). Conditions: **3** (1.0×10^{-3} M) and/or **β-D-Glc** (1.0×10^{-3} M), $CDCl_3$, 23 °C, 500 MHz.

at 5.12 ppm as a singlet peak, and after addition of 1 equiv of **β-D-Glc**, this signal moved to 5.55 ppm with broadening; (2) the signals for glucoside OH protons also moved downfield; and (3) at the same time, upfield movement of the signal for the protons on the central benzene ring of **3** (from 7.56 ppm to 7.49 ppm) was observed. The downfield movement of signals for the OH protons on both **3** and **β-D-Glc** was caused by the formation of hydrogen bonding among the hydroxy groups, as in the case of glycoside recognition by **1**.[5] Titration experiments (see below) showed the increase in downfield movements of the signals for the four hydroxy protons in **β-D-Glc** in the order of 4- > 6- > 3- > 2-O*H*, probably because the 2-OH group suffers from steric hindrance by the octyl group at the 1-position. The upfield movement of the signal for the aromatic protons on the center ring of **3** was caused by the small enhancement of the anisotropic effect caused by the peripheral resorcinol

Scheme 1. Preparation of **3**[a]



[a]TMS = trimethylsilyl, DME = 1,2-dimethoxyethane.

rings. To fit with the glucoside effectively, **3** adjusts its conformation including the dihedral angles between the rings. When the dihedral angles increased, the anisotropic effect on the protons at the center ring was enhanced. The relatively stable structures generated by the Monte−Carlo method supported the increase in the dihedral angles resulting from host−guest association (Figure S1, Supporting Information). In variable-temperature ^{1}H NMR of the **3**/***β*-D-Glc** mixture cooled to −10 °C, no splitting of signals was observed to distinguish the two faces of **3**, therefore the axial rotation must be fast. The association of **3** with other kinds of glycosides also caused similar changes in ^{1}H NMR signals (Figure S2, Supporting Information). The δ values for O*H* and center-ring protons of **3** are summarized in Table 1.

Table 1. Movement of ^{1}H NMR Signals and Binding Constants for the Association between **3** and *n*-Octyl Glycosides

	δ (ppm)[a] values for protons in **3**		separated binding constant[b]
guest	O*H*	center ring	[M^{-1}]
none	5.12	7.56	
***β*-D-Glc**	5.55 (+0.43)	7.49 (−0.07)	$K_{11} = 245 \pm 7$[c]
***β*-L-Glc**	5.57 (+0.45)	7.49 (−0.07)	
α-D-Glc	5.45 (+0.33)	7.52 (−0.04)	
***β*-D-Gal**	5.46 (+0.34)	7.51 (−0.05)	
α-D-Man	5.98 (+0.86)	7.45 (−0.11)	$K_{11} = 2210 \pm 80$[c]
α-L-Man	5.96 (+0.84)	7.45 (−0.11)	
***β*-D-Fru**	5.76 (+0.64)	7.48 (−0.08)	$K_{11} = 1450 \pm 20$[d]
***β*-D-Rib**	5.34 (+0.22)	7.53 (−0.03)	
***β*-D-GlcNH$_2$**	not detected	7.44 (−0.12)	$K_{11} = 1010 \pm 20$,[d] $K_{12} = 440 \pm 20$[d]

[a] $\Delta\delta = \delta$(complex) − δ(**3**) values are shown in parentheses. ^{1}H NMR conditions: **3** (1.0×10^{-3} M), glycoside (1.0×10^{-3} M), $CDCl_3$, 23 °C. [b] K_{11} and K_{12} are binding constants for **3**/glycoside = 1:1 and 1:2 complexes, respectively. [c] Titration conditions: **3** (1.0×10^{-4} M), glycoside, $CDCl_3$, 23 °C. Obtained from the titration by ^{1}H NMR. [d] Titration conditions: **3** (1.0×10^{-4} M), glycoside, $CDCl_3$, 25 °C. Obtained from the titration by UV−vis spectroscopy.

Among them, ***β*-D-Man** caused the largest chemical shift movements for O*H* protons, and those for aromatic protons were comparable to the effects caused by ***β*-D-GlcNH$_2$**.

UV−vis and CD spectra of **3** also changed their shape at this glucoside recognition. In the UV−vis analysis of **3** (Figure 3a), remarkable hypochromism with a small blue shift was observed for the association with ***β*-D-Glc**, reflecting the weakening of the π-conjugate in **3** caused by axial rotation. In CD analysis, a mirror-image pair of induced CD bands was observed (Figure 3b) for the mixtures of **3** with ***β*-D-Glc** and

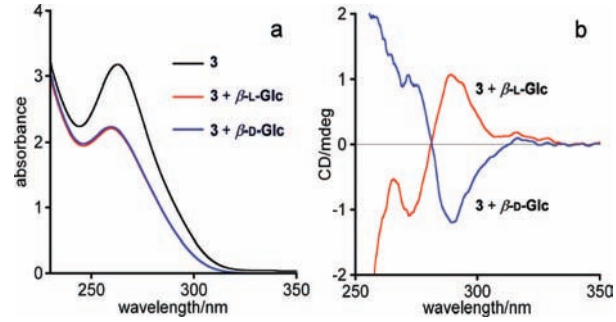


Figure 3. (a) Change in UV spectra of **3** with the absence (black) or presence of glucoside (red: ***β*-L-Glc**, blue: ***β*-D-Glc**). (b) Induced CDs of **3** associated with ***β*-L-Glc** (red) or ***β*-D-Glc** (blue). Conditions: **3** (1.0×10^{-3} M), L- or D-glucoside (2.0×10^{-3} M), $CDCl_3$, 25 °C, path length = 1 mm.

β*-L-Glc**, indicating the transfer of chirality from the guest saccharide to the axial chirality of the host. Job's plot was drawn for the chemical shifts in the ^{1}H NMR spectrum. The sum concentration [**3**] + [β*-D-Glc**] was fixed at 1.2×10^{-3} M, in which the influences of self-association for both the host and

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guest are very small (Figure S3, Supporting Information). The plot indicated that the stoichiometry of binding with **3**/***β*-D-Glc** is 1:1 under these conditions.

Next, ^{1}H NMR titration experiments were performed in $CDCl_3$. The concentration of **3** was fixed at 1.0×10^{-4} M at which the self-association is negligible, and glycosides ***β*-D-Glc** and **α-D-Man** were added. The titration curves obtained were fitted with the theoretical curve assuming 1:1 binding, and the binding constants (K_{11}) were 245 (vs ***β*-D-Glc**) and 2210 (vs **α-D-Man**) M^{-1} (Figures S4 and S5, Supporting Information). Thus, from a comparison with **2** ($K_a < 100$ M^{-1} with ***β*-D-Glc**), it was observed that the increase in symmetry C_{3v} to D_{3h} improved the binding abilities as a hydrogen-bonding module. Higher affinity for **α-D-Man** compared with ***β*-D-Glc** has also been observed for the case of the rigid C_{3v} host **1**.[5]

The structure of **3** may have potential to recognize two guest molecules on both of its sides. The basic saccharide, glucosamine derivative ***β*-D-GlcNH$_2$**, was found to associate with **3** in a 1:2 ratio. In spectroscopic analysis of the titration of **3** with ***β*-D-GlcNH$_2$**, a two-step change was observed in UV−vis and CD spectra (Figure S7a,b, Supporting Information). On the UV−vis spectrum, significant hypochromism was observed first, and red-shift took place next. On the CD spectrum, a negative band appeared around 290 nm first, and then turned into positive bands in the range 270−350 nm. Curve-fitting analysis of the titration curve indicated the presence of 1:1 and 1:2 associations between **3** and ***β*-D-GlcNH$_2$** (Figure S8, Supporting Information), and the separated association constants were obtained as $K_{11} = 1010$ M^{-1} and $K_{12} = 440$ M^{-1}.[14]

The triresorcinolic host **3** displayed its multiple hydrogen-bonding ability for self-association. This was demonstrated in the ^{1}H NMR spectra and as a gelation in $CDCl_3$. In ^{1}H NMR experiments with **3** at various concentrations in $CDCl_3$, downfield movement of the chemical shift δ(O*H*) for hydroxy protons became remarkable at greater than ca. 1×10^{-3} M. The plot of $\Delta\delta$(O*H*) against the concentration fitted well with the theoretical curve assuming simple dimerization, and K_{dim} was 22 ± 4 M^{-1} (Figure S9, Supporting Information). At the same time, the signal for the center-ring proton moved upfield, as in the cases of the association of **3** with glycosides (see above). The ESI-TOF-MS spectrum of **3** showed the signals for self-aggregated complexes up to hexamers (Figure S10, Supporting Information). Interestingly, when a $CDCl_3$ solution of higher concentration was kept at room temperature, gelation was observed;[15] coagel appeared at $>3.0 \times 10^{-3}$ M (>0.1% w/w), and gel at $>1.0 \times 10^{-1}$ M (>4% w/w) (Figure 4a). These organogels collapse into a clear solution by addition of one drop of MeOH, which disturbs the hydrogen bonding. Information about a crystal state of **3** was examined by X-ray analysis of hydrated

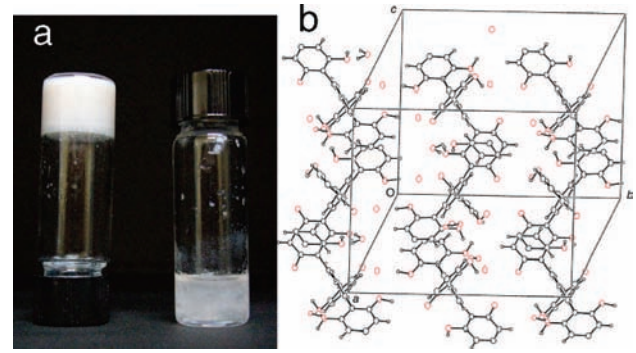

Figure 4. (a) (Left) Gel appeared from a 1.0×10^{-1} M solution in $CDCl_3$. (Right) Coagel appeared from a 1.0×10^{-2} M solution in $CDCl_3$. (b) Self-aggregation of **3** in a crystalline state. The pentyl groups are omitted for clarity.

crystals obtained from a CH_2Cl_2 solution (Figure 4b). In the crystal structure, a hydrogen-bonding network is built with hydroxy groups of **3** and included water molecules. First, a one-dimensional molecular column is formed along the *c*-axis with four hydroxy groups of **3** out of six. One water-mediated hydrogen bond was also recognized in this column. The other two hydroxy groups of **3** are used to form a network along the *b*-axis, mediated by included water molecules. This network arranges the one-dimensional column along the *b*-axis to form a two-dimensional layer structure. The layer structures are aligned along the *a*-axis with spacing due to the pentyl groups and water molecules. These structural characteristics may reflect the gelation properties of **3**.

In summary, D_{3h}-symmetric triresorcinol **3** was developed as a hydrogen-bonding host molecule. When it was treated with octyl glycosides in $CDCl_3$, host−guest association was observed in ^{1}H NMR and UV−vis analyses. The transfer of chirality from glycoside to **3** was observed in induced CD. The titration experiment showed that some of the 1:1 binding constants were comparable to those for fixed C_{3v} host **1**. It was also revealed that 1:1 and 1:2 associations occurred between **3** and the glucosamine derivative. Self-association of **3** caused formation of gel and crystals, and in the crystals multiple hydrogen bonds build columnar and layer structures as shown in Figure 4 b. The D_{3h}-symmetrical module is expected to be utilized in new host molecules and self-aggregating supramolecules.

Supporting Information Available: Experimental procedures and characterization of **3** and **5**−**8**, Figures S1−S10, and details of X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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