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A Rigid C_{3V}-Symmetrical Host for Saccharide Recognition: 1,3,5-Tris(2-hydroxyaryl)-2,4,6-trimethylbenzenes

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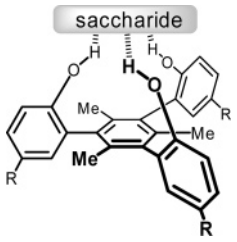
ABSTRACT



A rigid C_{3V}-symmetrical host molecule, *syn*-1,3,5-tris(2-hydroxy-5-pentylphenyl)-2,4,6-trimethylbenzene, was readily obtained via Suzuki coupling and thermal atropisomerization. The host molecule effectively associated with various saccharides by multipoint hydrogen bonds, whereas its *anti*-atropisomer and analogue lacking in methyl groups showed much weaker association with saccharides. Thermodynamic analyses suggested that the difference of the association strength was caused by entropic factors.

Hydrogen bonding is one of the fundamental noncovalent interactions working for assemblies of various natural and artificial molecules.[1] In artificial hydrogen-bonding assemblies, it is essential to design proper arrangement of hydrogen-bonding functionalities on proper frameworks to make the interaction effective. We have investigated a series of host molecules bearing multipoint hydrogen-bonding moieties for recognition of saccharides and nucleobases.[2] Herein we wish to report the development of a host molecule, *syn*-1,3,5-tris(2-hydroxy-5-pentylphenyl)-2,4,6-trimethylbenzene (**1-syn**), which has three phenolic OH groups arrayed on a very rigid C_{3v}-symmetrical framework (Figure 1). Recently, various kinds of C_{3v}-symmetrical host molecules have been developed, for example, by using frameworks of hexaethylbenzene and its analogues,[3,4] and 1,3,5-triarylbenzenes.[5,6] Although the 1,3,5-triaryl-2,4,6-trimethylbenzene framework of **1-syn** would be promising for its higher rigidity and symmetry, little has been known about its advantage in molecular recognition.[5]

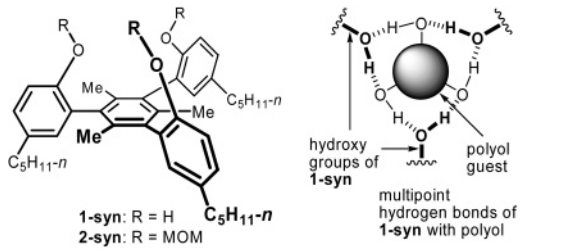


Figure 1. (Left) A C_{3v}-symmetrical host molecule **1-syn** and MOM-derivative **2-syn**. (Right) Plausible multipoint hydrogen bonds of **1-syn** with a polyol guest.

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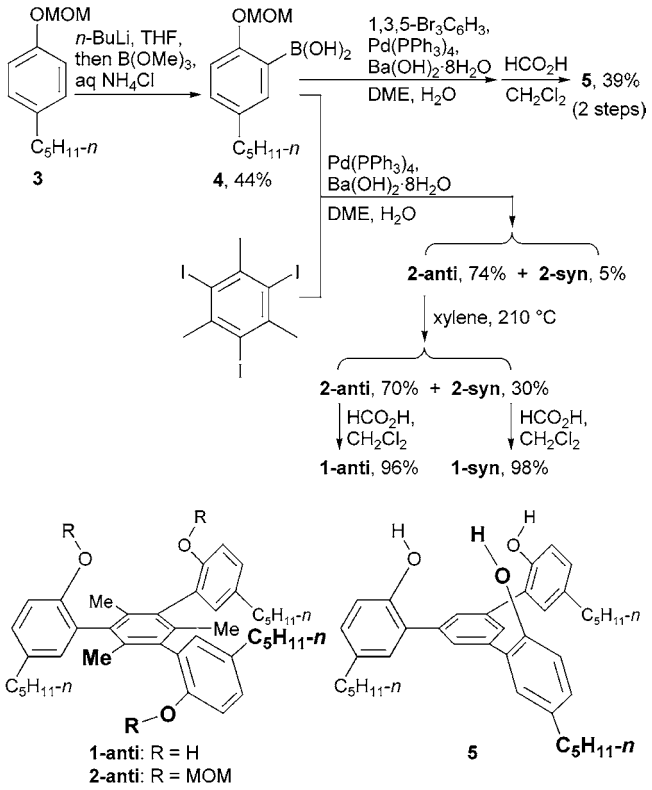
When the structure of **1-syn** was examined with its CPK model, the three phenolic rings were found to be no longer rotatable about the phenol-benzene bonds because of steric hindrance of the three methyl groups on the center benzene ring. The three oxygen atoms of the OH groups stand at intervals of ca. 4−6 Å, which is too far to form intramolecular hydrogen bonding efficiently. On the other hand, intermolecular association with polyols would be preferred because of the multipoint hydrogen bonding (Figure 1). From the thermodynamic viewpoint, the high symmetry and rigidity of **1-syn** would be favorable to form host−guest complexes without suffering entropic loss caused by restructuring. Taking into account these merits, we decided to develop **1-syn** as a host molecule for recognition of saccharides.

The targeted C_{3v}-symmetrical host molecule **1-syn** was prepared straightforwardly in the way described in Scheme 1. *p*-Pentylphenol was protected by methoxymethyl (MOM)

Scheme 1. Synthesis of **1-syn**, **1-anti**, and **5**



group to give **3**, which was derivatized to boronic acid **4** via *ortho*-lithiation. Suzuki coupling of **4** with 2,4,6-triiodomesitylene[7] afforded triarylated mesitylene as a mixture of atropisomers **2-syn** and **2-anti** in 5% and 74% yield, respectively. The desired atropisomer is **2-syn**, so the major product **2-anti** had to be isomerized to **2-syn**. Fortunately, when **2-anti** was heated to 210 °C in xylene for 3 h, partial isomerization to **2-syn** occurred. On TLC analysis (silica gel, CH_2Cl_2/hexane = 2:1), R_f values for **2-syn** and **2-anti** were 0.15 and 0.73, respectively. By column chromatography (silica gel, hexane/AcOEt = 10:1), **2-syn** (30%) and recovered **2-anti** (70%) were easily separated. The conversion yield was quantitative, so theoretically most of **2-anti** can be converted to **2-syn** by repeating this thermal isomerization. Acidic deprotection of the MOM groups on **2-syn** and **2-anti** yielded **1-syn** and **1-anti**, respectively, which also have very different R_f values on TLC (silica gel, CH_2Cl_2, R_f = 0.06 for **1-syn** and 0.65 for **1-anti**). The great differences of R_f values between **1-syn** and **1-anti** and between **2-syn** and **2-anti** probably reflect the fitness of the tripodal structure of **1-syn** and **2-syn** for interacting with the surface of silica gel. As the CPK model predicted, the steric hindrance of the three methyl groups on the center benzene ring is enough to inhibit easy atropisomerization,[5] since no change was observed under conditions such as 2 months at room temperature for **1** and **2**, at 80 °C in DMSO-d_6 for **2-syn**, at 160 °C in mesitylene for 6 h for **2-anti**, and at 100 °C in 1,4-dioxane for 6 h for **1-anti** in the presence of *t*-BuOK. To study the effect of the methyl groups in **1** for molecular recognition, non-methyl analogue **5** was prepared by a similar procedure from **4** and 1,3,5-tribromobenzene. In the case of **5**, no separation of ^{1}H NMR signals caused by atropisomerization was observed in $CDCl_3$ even at −40 °C, because the rotation about the phenol-benzene bond is fast in **5**.

The self-association tendencies of **1-syn**, **1-anti**, and **5** were evaluated using ^{1}H NMR analyses in $CDCl_3$. At a dilute concentration, the signal of the O*H* protons of **1-syn** was observed as one sharp singlet peak. When the concentration of **1-syn** increased, the O*H* signal significantly moved downfield with broadening (Figure S1A). The relationship between the chemical shift of the O*H* signal and the concentration of **1-syn** fit with the theoretical curve assuming self-dimerization ($K_{dim} = 1.3 \pm 0.8 \times 10^2$ M^{-1}). When **1-anti** was subjected to a similar NMR experiment, two kinds of O*H* signals were observed: the one is the signal of the two O*H* protons on the upper side of the triarylbenzene framework shown in Scheme 1, and the other is the signal of the one O*H* proton on the opposite lower side. According to the

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increase of the concentration of **1-anti**, the former signal moved a little downfield with significant broadening, while the latter scarcely changed (Figure S1B). The K_{dim} for **1-anti** was estimated at ca. 10 M^{-1}, which is considerably smaller than that for **1-syn**. These results indicate that the association strength depends on the number of OH groups on one side of the triarylbenzene framework to make multipoint hydrogen bonds efficiently. For non-methyl analogue **5**, the downfield change of the chemical shift of three O*H* protons was also small (Figure S1C) and the K_{dim} was estimated at ca. 3 M^{-1}; thus the free rotation of the phenol moieties weakens the association.

When **1-syn** (2.5×10^{-3} M) was mixed with an equimolar amount of octyl β-D-glucopyranoside (***β*-Glc**) in $CDCl_3$, the ^{1}H NMR signals of the O*H* protons on both **1-syn** and ***β*-Glc** significantly moved downfield with broadening (Figure 2).

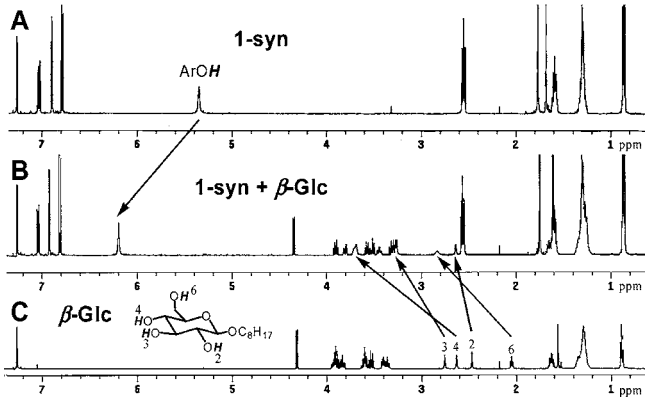

Figure 2. ^{1}H NMR spectra of (A) **1-syn** (2.5×10^{-3} M), (B) **1-syn** (2.5×10^{-3} M) + ***β*-Glc** (1.0 equiv), and (C) ***β*-Glc** (2.5×10^{-3} M) in $CDCl_3$, 22 °C, 500 MHz.

By contrast, in the cases of **1-anti** and **5** in a similar ^{1}H NMR experiment, such movement and broadening were very small. Upon association with ***β*-Glc**, the two O*H* protons on **1-anti** became diastereotopic and the separation of ^{1}H NMR signals was observed. Between **1-syn** and a series of alkyl glycosides soluble in $CDCl_3$, the binding constants were calculated on the basis of ^{1}H NMR titration (Table 1). The titration curves fit with the theoretical curves assuming 1:1 association (for ***β*-Glc**, see Figure S2) within the range of concentration at which the self-associations both of **1-syn** and of the glycosides were negligible. Among the glycosides examined, octyl α-D-mannopyranoside (**α-Man**) was found to associate with **1-syn** most strongly. This is possibly because of the structural fitness for multipoint hydrogen-bonding between **1-syn** and **α-Man** and/or because of the relatively weak intramolecular hydrogen-bonding in **α-Man**.[8] Other kinds of the glycosides also showed good association with **1-syn**. On the other hand, the associations of **1-anti** and **5** with ***β*-Glc** and methyl β-D-ribofranoside (***β*-Rib**) were very weak (K_a < 100 M^{-1}). Thus, the C_{3v} structure of **1-syn** is suitable not only for the self-association but also for the saccharide recognition. The binding strength between **1-syn**

Table 1. Association of **1-syn**, **1-anti**, and **5** with Glycosides Studied by ^{1}H NMR Experiments

host	glycoside[a]	K_a (M^{-1})[b]	ΔG (kJ mol^{-1})[b]	$\Delta\delta$(host-O*H*)[c] (ppm)
1-syn	***β*-Glc**	$6.3 \pm 0.2 \times 10^3$	−22	+0.85
	α-Glc	$2.4 \pm 0.1 \times 10^3$	−19	+0.80
	***β*-Man**	$1.5 \pm 0.3 \times 10^4$	−24	+1.24
	α-Man	$3.3 \pm 0.2 \times 10^4$	−25	+1.49
	***β*-Gal**	$2.4 \pm 0.1 \times 10^3$	−19	+0.80
	***β*-Fru**	$1.1 \pm 0.1 \times 10^4$	−23	+1.13
	***β*-Rib**	$1.8 \pm 0.5 \times 10^3$	−18	+1.03
1-anti	***β*-Glc**	<100[d]		+0.16 (2H), +0.01 (1H)
	***β*-Rib**	<100[d]		
5	***β*-Glc**	<100[d]		+0.15
	***β*-Rib**	<100[d]		

[a] **Glc** = octyl D-glucopyranoside, **Man** = octyl D-mannopyranoside, **Gal** = octyl D-galactopyranoside, **Fru** = octyl D-fructopyranoside, **Rib** = methyl D-ribofuranoside. [b] Conditions: host (1.0×10^{-4} M), titrated with glycoside, $CDCl_3$, 22 °C. [c] Conditions: host (2.5×10^{-3} M) with or without glycoside (1.0 equiv), $CDCl_3$, 22 °C. Downfield movement of δ(host-O*H*) is shown. [d] Because curve-fitting analysis was not available as a result of the self-association of both the host and glycoside, K_a values were estimated from the slope in the initial stage of the titration plot.

and saccharides is comparable to that for many other hydrogen-bonding host molecules previously reported,[2,4,9] although **1-syn** has a much simpler structure and is much more available with ease.

For the association of **1-syn** with ***β*-Rib** in $CDCl_3$, the thermodynamic parameters were $\Delta H = -35$ kJ mol^{-1}, $T\Delta S = -17$ kJ mol^{-1}, and $\Delta H/T\Delta S = 2.1$ (300 K) obtained by van't Hoff plot. For comparison, the ratios $\Delta H/T\Delta S$ were estimated for **1-anti** and **5** at 1.2 and 1.2 (300 K), respectively, for the same guest.[10] These results suggest that the differences of the binding constants are mainly due to the contribution of entropic factors. Probably less symmetry in **1-anti** and less rigidity in **5** caused entropic loss when they associate with saccharide. The high rigidity and symmetry of **1-syn** are necessary for efficient saccharide recognition. For high efficiency and easy availability, the framework of **1-syn** is also attractive as tridentate ligands and triacidic catalysts, and investigations for versatility of the architectures are now underway.

Supporting Information Available: Figures S1 and S2 and experimental details for the syntheses and analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) In the cases for **1-anti** and **5**, the accurate values for ΔH and $T\Delta S$ could not be acquired because of ambiguity about $\Delta\delta_{sat}$(host-O*H*), ^{1}H NMR downfield movement of δ(host-O*H*) at the saturating point. The ratio $\Delta H/T\Delta S$ was estimated from a tentative van't Hoff plot by assuming $\Delta\delta_{sat}$(host-O*H*) values varied from 0.7 to 2 ppm. For **1-syn**, $\Delta\delta_{sat}$(host-O*H*) value was calculated as 1.0 ppm from the titration curve.