Sugar Recognition by Triethylbenzene-based C_3-Symmetric Hosts†

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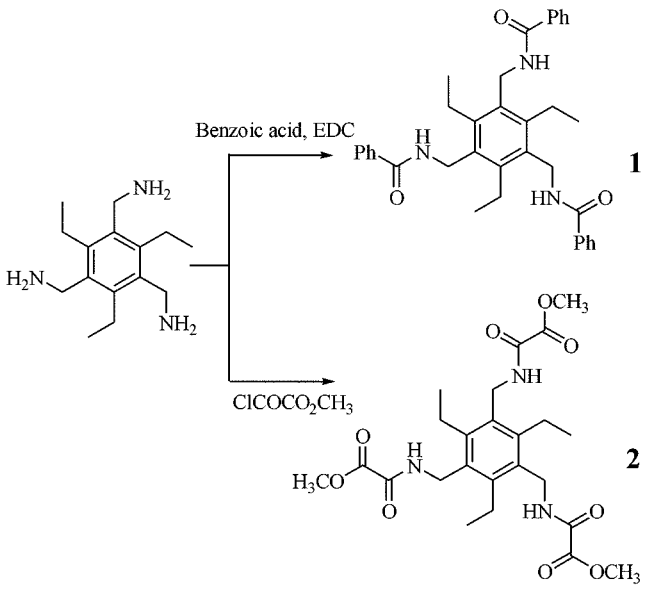
Carbohydrate recognition through noncovalent interactions is one of the challenging goals of biomimetic and supramolecular chemistry.[1] This is attributed to the structural diversity of sugars and to their important roles in biological processes.[2] As revealed by the X-ray crystal structures of carbohydrate-protein complexes,[3] the most effective approach to carbohydrate recognition is to surround the polar hydroxyl groups with complementary hydrogen bonding groups and place aromatic surfaces against carbohydrate CH moieties. Despite considerable effort in developing artificial carbohydrate receptors, there are only a few effective hydrogen-bonding receptors for sugars in organic solvents reported to date and anomeric-selective and diastereoselective artificial receptors for monosaccharides are in a much earlier stage of development.[4]

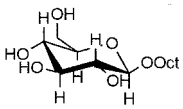
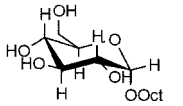
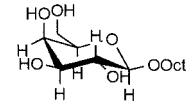
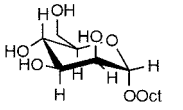
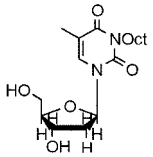
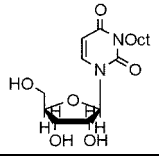
This paper describes the synthesis of conformationally rigid triethylbenzene-based hosts (**1**, **2**) having H-bond donors and acceptors and their binding properties toward sugar derivatives. Placing three ethyl groups on the 2, 4 and 6 positions of the central benzene ring of **1** and **2** would result in orienting the three amide or methoxycarbonyl amide groups in the same direction, respectively.[5] Treatment of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene[6] with benzoic acid in the presence of EDC or methyl chlorooxaacetate in the presence of DIPEA afforded C_3-symmetric tris-(amides) **1** and **2**, respectively, as shown in Scheme 1.[7]



Scheme 1. Synthetic scheme for triethylbenzene-based tripodal hosts **1** and **2**.

Addition of glycosides to **1** or **2** in $CDCl_3$ caused downfield shifts of the NH resonances of the hosts, indicating the formation of intermolecular hydrogen bonds between the NH's of the host and OH's of sugars. Analysis of the ^{1}H NMR titration data gives the binding constants listed in Table 1. The striking characteristic of **1** and **2** is their highly diastereoselective recognition of glycosides (entry 3 *vs.* 1, 2, 4) combined with moderate anomer-selective recognition of glucopyranosides (entry 1 *vs.* 2). **1** and **2** show higher affinity for both α-D-mannopyranoside and D-glucopyranosides than for β-D-galactopyranoside. The stereochemical arrangement of OH groups on C-3, C-4 and C-5 of Glc is the

Table 1. Binding constants of **1** and **2** with guests[a]

entry	guest structure	name	K_a (M^{-1})	
			1	**2**
1		β-Glc	710	1540
2		α-Glc	250	330
3		β-Gal	16	4
4		α-Man	860	2000
5		Thymidine	< 1	13
6		Uridine	15	13

[a] ^{1}H NMR titration of 1.0 mM of [**H**] in $CDCl_3$ at 300 K. Chemical shift of NH of hosts was monitored after each addition of guests.

†Dedicated to Prof. Y. H. Kim on the occasion of his 65th birthday.

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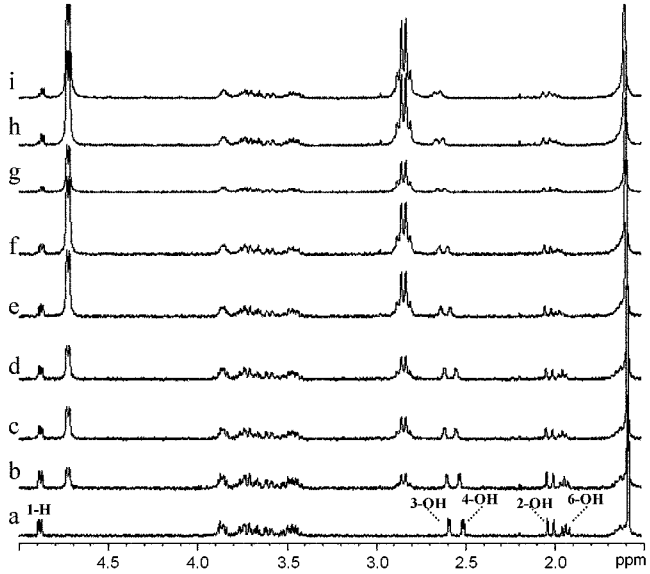

Figure 1. ^{1}H NMR reverse titration spectra of α-Glc with **1** in $CDCl_3$ at 300 K. (a) only α-Glc (b) 0.4 eq (c) 0.8 eq (d) 1.2 eq (e) 1.6 eq (f) 2.0 eq (g) 2.4 eq (h) 2.8 eq (i) 3.2 eq of **1** were added.

same as that of Man, and this arrangement is particularly well recognized by hosts. Gal, the epimer of Glc at C-4, is weakly bound, indicating that the stereochemistry at C-4 is crucial in binding to hosts. In contrast, the stereochemistry at C-2 and C-1 is less important. These selectivities would result from the preorganized host structure.[8] Comparing to the previous oxazoline-based C_3-symmetric hosts with rigid oxazoline groups as H-bonding acceptors, the current system shows much higher diastereoselectivity for glycosides as mentioned above; while more rigid C_3-symmetric tris(oxazoline) hosts show moderate anomeric selectivity (α- *vs.* β-D-glucopyranoside) and diastereoselectivity (β-D-galactopyranoside *vs.* D-glucopyranosides), **1** and **2** display moderate anomeric selectivity (α- *vs.* β-D-glucopyranoside) and enhanced diastereoselectivity (β-D-galactopyranoside *vs.* D-glucopyranosides and α-D-mannopyranoside).[8b] It is not surprising that not only the number of hydrogen bonding sites in the substrates but also geometrical complementarity between the hydrogen-bond sites of host and guest affect the binding affinities of substrates (entry 1-4 *vs.* 5-6).

Table 2. Complexation-induced shifts (CIS) of guests upon addition of **1**[a]

	$\Delta\delta_{max}$ of CIS (δ of free ligand) in ppm		
	α-Glc	β-Glc	α-Man
1-H	−0.118 (4.88)	−0.047 (4.30)	−0.645 (4.84)
2-OH	+0.094 (2.01)	ND[b]	ND[b]
3-OH	+0.345 (2.58)	ND[b]	ND[b]
4-OH	+0.785 (2.50)	ND[b]	ND[b]
6-OH	+0.424 (1.93)	ND[b]	ND[b]

[a] ^{1}H NMR reverse titration of 1.0 mM of [**G**] in $CDCl_3$ at 300 K. Extrapolated to maximum complex formation from the CIS values. [b] Not determined because the peak shifts are not well observed during titration.

To clearly observe the intermolecular hydrogen bonding patterns between host and guest, reverse titration was performed in acid-free chloroform (Figure 1). The complexation-induced shifts (CIS) of the 1-H, 2-OH, 3-OH, 4-OH, and 6-OH resonances of *n*-octyl-α-D-glucopyranoside (α-Glc) were determined. The assignments of the resonances of the four hydroxyl protons were made on the basis of a reference article.[9] Upon addition of **1**, all the OH protons of α-Glc moved downfield while the anomeric proton of α-Glc was shifted to the upfield region.

Downfield shifts of OH protons of α-Glc suggest intermolecular H-bonding interactions between α-Glc and **1**. Upfield shifts of the anomeric protons of α-Glc, β-Glc and α-Man implies that the anomeric proton comes into contact with the aromatic surfaces of **1**. The CIS values for the complex are determined by extrapolation to maximum complexation and listed in Table 2. The maximum chemical shift changes of OH protons at the 3, 4, and 6 positions of α-Glc are larger than that of the 2-OH proton. This is probably caused by the stronger interactions of **1** with 3, 4, and 6-OH of α-Glc compared to 2-OH of α-Glc. The larger upfield shift of 1-H of α-Man, compared to α-Glc, also implies that 1-H of α-Man is in closer contact with aromatic surfaces of **1**, leading to a higher affinity.

The anomeric selectivity and diastereoselectivity for sugars can be explained by molecular modeling study (Figure 2).[10] In comparison with three intermolecular H-

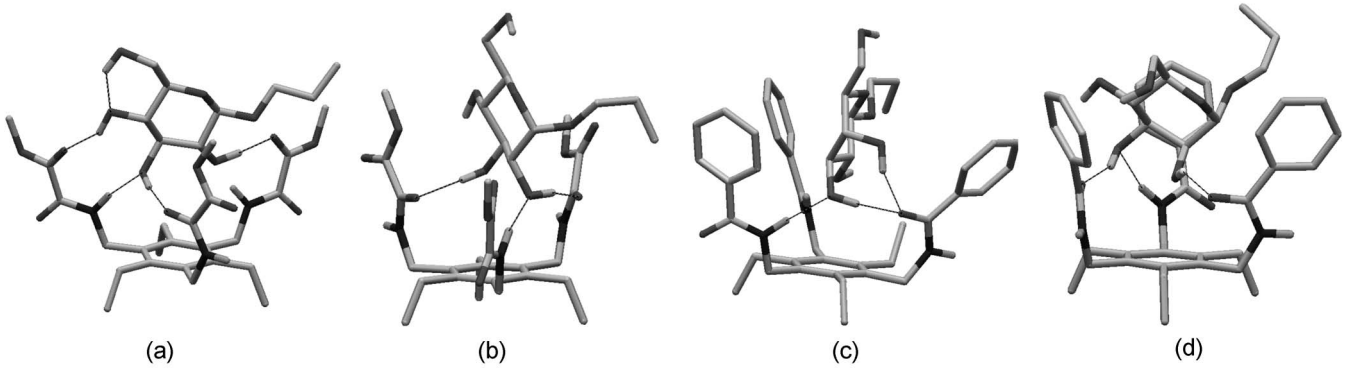

Figure 2. Minimized structures for the complexes between hosts and guest: (a) **2** and β-Glc four intermolecular H-bonds (AAAD···DDDA), (b) **2** and α-Glc, three intermolecular H-bonds (AAD···DDA), (c) **1** and β-Gal, three intermolecular H-bonds (AD···DDA), (d) **1** and α-Man, three intermolecular H-bonds (AAD···DDA) (A = H-bond acceptor, D = H-bond donor).

bonds between **2** and α-Glc, four intermolecular H-bonds are involved in the complex between **2** and β-Glc, as shown in Figure 2(a) and (b). The difference in the number of intermolecular H-bonds is a possible cause of the anomer-selectivity of **2** for β-Glc. Similarly, diastereoselectivity of **1** for α-Man over β-Gal is most likely to result from the slight energetic difference in the intermolecular hydrogen bonding patterns, as illustrated in Figure 2(c) and (d).

In conclusion, we have developed triethylbenzene-based tripodal tris(amides) as anomer-selective and diastereo-selective receptors toward sugars and nucleosides. ^{1}H NMR spectroscopic studies and computer modeling provide plausible binding modes in solution.

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7. Compound **1**: mp 254-257 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.75 (m, 15H, Ar*H*), 5.95 (br, 3H, N*H*), 4.73 (d, J = 4.2 Hz, 6H, ArCH_2N), 2.84 (q, J = 7.5 Hz, 6H, ArCH_2CH$_3$), 1.29 (t, J = 7.5 Hz, 9H, ArCH$_2$*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 144.7, 134.1, 132.3, 131.7, 128.7, 127.0, 38.7, 23.2, 16.7; MS (FAB$^+$, *m*-NBA) *m/z* 562 (M+1).
Compound **2**: mp 182-186 ^{o}C (*dec*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (br, 3H, N*H*), 4.57 (d, J = 4.8 Hz, 6H, ArCH_2N), 3.93 (s, 9H, CO_2C*H*$_3$), 2.70 (q, J = 7.6 Hz, 6H, ArCH_2CH$_3$), 1.23 (t, J = 7.6 Hz, 9H, ArCH$_2$*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 155.9, 144.8, 131.2, 53.8, 38.3, 23.2, 16.3; MS (FAB$^+$, *m*-NBA) *m/z* 508 (M+1).
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