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Sugar recognition by C_3-symmetric oxazoline hosts

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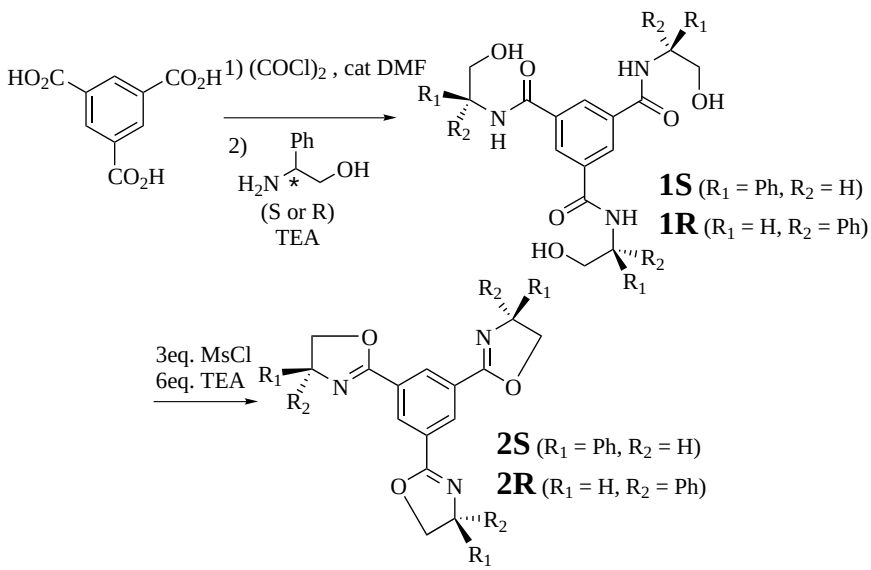
Abstract—C_3-Symmetric tris(oxazoline) derivatives (**2***S*,**2***R*) were designed to complex sugars and alcohols in nonpolar organic solvent through complementary intermolecular hydrogen-bonding interactions. ^{1}H NMR titration demonstrated that the C_3-symmetric hosts were capable of anomer-selective recognition for *n*-octyl-D-glucopyranoside. ^{1}H NMR data revealed intermolecular hydrogen bonds between **2***S* and glucopyranosides. © 2001 Elsevier Science Ltd. All rights reserved.

Carbohydrate recognition through non-covalent interactions is one of the challenging goals of biomimetic and supramolecular chemistry.[1] This is ascribed to the complex structural diversity of carbohydrates and to their important roles in biological regulation.[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 efforts in the development of artificial carbohydrate receptors, there are only a few effective hydrogen-bonding receptors for sugars in organic solvents reported to date and anomeric-selective artificial receptors for monosaccharides are far less developed.[4]

We describe here oxazoline-based C_3-symmetric hosts having three oxazoline nitrogens as H-bonding acceptors and a central phenyl group as a π-donor for CH-π interactions, and focus on the anomer-selective recognition for octyl-D-glucopyranoside in chloroform.

C_3-Symmetric chiral tris(oxazoline) derivatives were synthesized from 1,3,5-benzenetricarboxylic acid as shown in Scheme 1.[5] Treatment of triacid with oxalyl



Scheme 1. Synthetic scheme for oxazoline derivatives **2***S* and **2***R*.

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chloride under cat. DMF in dichloromethane afforded triacid chloride which was subsequently added to amino alcohol to give rise to tris(amides) in good yield. Reaction of the resulting amide with mesyl chloride in the presence of TEA afforded the desired tris(oxazolines).[6]

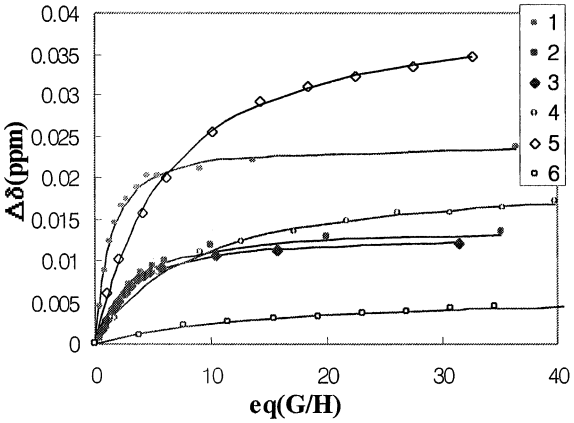
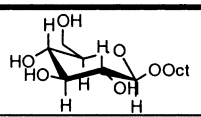
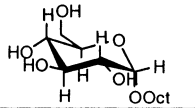
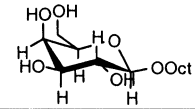
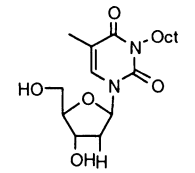
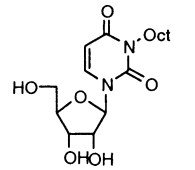
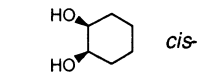


Figure 1. ^{1}H NMR titration curves between host **2***S* and guests in $CDCl_3$ at 295 K. $[H]_0 = 1.5$ mM, **1** = *n*-octyl-β-D-glucopyranoside, **2** = *n*-octyl-α-D-glucopyranoside, **3** = *n*-octyl-β-D-galactopyranoside, **4** = *N*-octylthymidine, **5** = *N*-octyluridine, **6** = *cis*-1,2-cyclohexanediol.

^{1}H NMR titration in $CDCl_3$ shows a dramatic downfield shift of aromatic protons at the center of the host **2***S*, which may be caused by the decrease of charge density in a nitrogen lone pair (Fig. 1). This results from intermolecular H-bonding interactions between H-bond acceptor N of host and H-bond donor OH of guest.

Curve fitting of the host signals to a 1:1 binding isotherm gave apparent binding constants listed in Table 1. The 1:1 binding ratio was confirmed by a Job's plot (Fig. 2). The binding constants between **2***S* and *n*-octyl-D-glucopyranoside were found to be 270 for α anomer and 1120 for β anomer. Although the binding affinity of **2***S* is weaker than that of Mazik's C_3-symmetric polypyrimidine receptors due to the decreased number of the H-bonding donors and acceptors in **2***S*,[7a] the selectivity between α and β anomers increases from 1.1 to 4.1 (β/α) presumably because of the steric interactions of the phenyl substituents in the oxazoline rings. The binding affinity of **2***S* to *n*-octyl-β-D-galactopyranoside is four times weaker than to *n*-octyl-β-D-glucopyranoside. This anomeric selectivity and diastereoselectivity for sugars are mostly likely to result from the slight energetic difference in the intermolecular H-bonding patterns due to the varying degree of steric interaction between sugars and **2***S*. *cis*-1,2-Cyclo-

Table 1. Binding constants between hosts and guests[a]

entry	guest structure	name	K_a (M^{-1})	
			2S	2R
1		β-D-Glucose	1120(±42)	1190(±120)
2		α-D-Glucose	270(±46)	310(±18)
3		β-D-Galactose	250(±20)	250(±22)
4		Thymidine	60(±15)	30(±18)
5		Uridine	80(±23)	62(±25)
6		*cis*-1,2-Cyclohexanediol	40(±13)	

[a] ^{1}H NMR titration of 1.5 mM of [**2**] in $CDCl_3$ at 295 K.

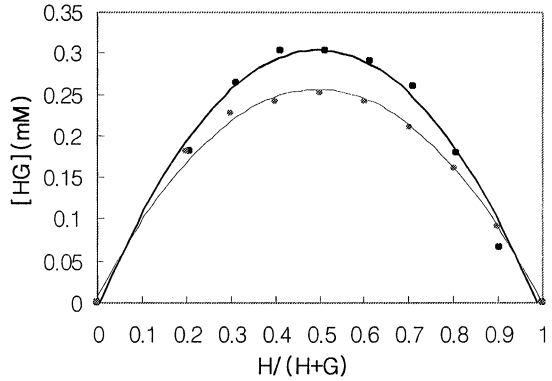


Figure 2. Job's plot between host **2***S* and D-glucopyranosides at 295 K. [H]+[G] = 1.0 mM, each in 500 μL. Rectangular and circle represent β-glucopyranoside and α-glucopyranoside, respectively.

hexanediol, *N*-octylthymidine and *N*-octyluridine with fewer numbers of hydroxyl groups show weaker binding affinities to the host, which implies that not only geometrical complementarity of H-bonding partners but also the number of H-bonds are crucial in H-bond based molecular recognition system.

In order to elucidate the intermolecular binding mode, we performed inverse ^{1}H NMR titrations of **2***S* with sugar guests in $CDCl_3$ (Table 2). Resonance changes in OH protons of sugar derivatives were compared upon addition of 0.3 equiv. of **2***S* to each sugar guest. In particular, 3-OH and 4-OH protons of β-D-glucopyranoside show the more pronounced changes compared to those of α-anomer. This implies that those protons of β-D-glucopyranoside are more strongly involved in H-bonds with **2***S* than those of α-anomer. Furthermore, inverse ^{1}H NMR titration experiments show that 1-H and 5-H of α- or β-D-glucopyranoside experience upfield shifts upon addition of **2***S*, which indicates that these protons are likely to be placed in the shielding region of the aromatic ring of the host due to the hydrogen bonding interactions. However, since hosts **2***S* and **2***R* give essentially the same binding constants for both α- and β-isomers of the sugar derivatives, the chirality of the hosts turns out to have no effect on the chiral discrimination.

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

	$\Delta\delta_{max}$ of CIS (δ of free ligand) in ppm		
	α-Glc	β-Glc	β-Gal
1-H	−0.168 (4.85)	−0.042 (4.29)	−0.061 (4.25)
2-OH	+0.286 (1.96)	+0.033 (2.38)	+0.291 (2.37)
3-OH	+1.45 (2.52)	+0.907 (2.63)	+0.726 (2.60)
4-OH	+1.24 (2.44)	+0.795 (2.52)	+0.436 (2.76)
6-OH	+0.084 (1.88)	+0.021 (1.97)	+0.149 (2.08)

[a] ^{1}H NMR reverse titration of 1.5 mM of $[G]_0$ in $CDCl_3$ at 295 K. Extrapolated to maximum complex formation from the CIS values.

Calculated structures revealed three intermolecular H-bonds between three oxazoline nitrogens of **2***S* and three OH groups in the 2,4,6-positions of β-D-glucopyranoside (AAA···DDD).[8] In contrast, only one H-bond is shown in the complex between **2***S* and α-D-glucopyranoside due to the steric hindrance between phenyl groups of **2***S* and axial OR in the anomeric position of α-D-glucopyranoside (Fig. 3). In addition, 1-H and 5-H of β-D-glucopyranoside are directed toward the central phenyl surface of **2***S* as shown in Fig. 3 (a). This is in accordance with inverse ^{1}H NMR titration experiments in which those protons show upfield shifts upon addition of increasing amounts of **2***S*. In the case of complexation of **2***S* with β-D-galactopyranoside, only two H-bonds are observed as expected from its weaker binding affinity to **2***S* compared to the complexation with β-D-glucopyranoside.

In conclusion, we have developed benzene-based tripodal tris(oxazolines) as artificial receptors for sugars and alcohols. This is one of the rare examples of anomer-selective molecular recognition of alkylglycosides by noncovalent interactions.[4f]

Acknowledgements

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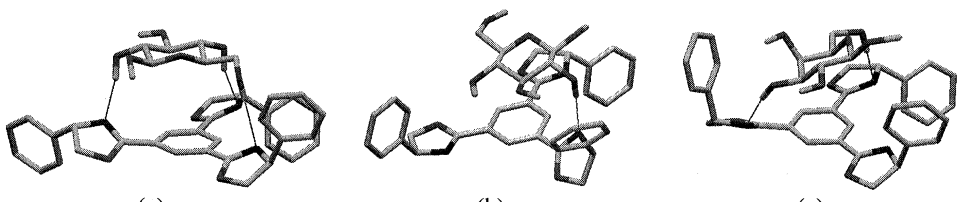

Figure 3. Minimized structures between **2***S* and guests; (a) **2***S* and β-Glc, three intermolecular H-bonds (AAA···DDD) (b) **2***S* and α-Glc, one intermolecular H-bond (A···D) (c) **2***S* and β-Gal, two intermolecular H-bonds (AA···DD). Hydrogens except OHs are omitted for clarity.

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5. During this work, Ahn et al. reported oxazoline homologues as artificial receptors for alkylammonium ions: Kim, S.-G.; Ahn, K. H. *Chem. Eur. J.* **2000**, *6*, 3399–3403.
6. Typical experimentals and characterizations for each compound are as follows:
   1,3,5-Tris[2-[4-(*S*)-phenyl-1,3-oxazoline]]benzene (**2***S*):
   To a solution of 100 mg (0.176 mmol) of **1***S* in 5 mL of CH_2Cl_2 were added 0.17 mL of TEA and 50 μL (0.64 mmol) of MsCl at 0°C under N_2. Resulting white suspension was stirred at rt under N_2 for additional 30 h to afford a clear solution. Volatile residues were evaporated. A yellowish solid was purified by silica-gel column chromatography to afford a white solid which was recrystallized in 0.5 mL of CH_2Cl_2 by diffusion of diethyl ether (95% yield).
   ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (s, 3H, central Ar*H*), 7.22 (m, 15H, Ar*H* of L-Phe), 5.34 (dd, $J=10$ Hz, 8 Hz, 3H, -CH_2O), 4.74 (dd, $J=10$ Hz, 8 Hz, 3H, -CH_2O), 4.22 (t, $J=8$ Hz, 3H of C**H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9, 142.4, 131.6, 129.2, 128.9, 128.1, 127.1, 75.5, 70.7; MS (FAB$^+$, *m*-NBA) 514 (M+1, 100%); $[\alpha]_D^{28}=-54.22$ ($c=0.050$, CH_2Cl_2).
   1,3,5-Tris[2-[4-(*R*)-phenyl-1,3-oxazoline]]benzene (**2***R*):
   All characteristics are the same as that of **2***S* except $[\alpha]_D^{19}=+59.44$ ($c=0.065$, CH_2Cl_2).
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