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Highly Convergent Synthesis of C_3- or C_2-Symmetric Carbohydrate Macrocycles

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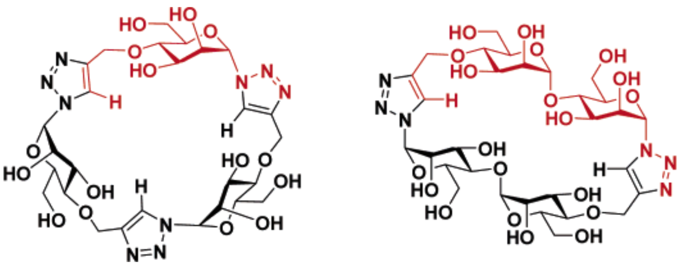
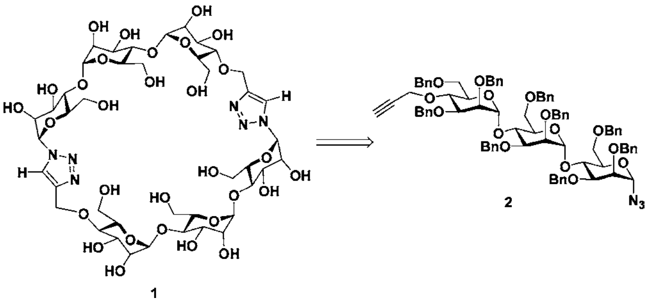
ABSTRACT



A highly convergent strategy for the synthesis of C_3- or C_2-symmetric oligosaccharide macrocycles is reported. Molecular modeling indicates these macrocycles possess sterically congested cavities. Weak host–guest interactions are observed that should be beneficial for applications such as functionalized molecular pores.

Macrocycles are important building blocks in supramolecular chemistry, exemplified in their diverse applications as molecular pores,[1] artificial receptors,[2] and components in complex supramolecular architectures.[3] Although an extensive array of macrocycle structures have been reported, few examples offering the potential for selective functionalization exist. In cases where water solubility is needed, the number of available choices becomes even smaller.

Of the water-soluble macrocycles, the cyclodextrins (CDs) offer amphiphilic character along with sites for manipulation in the form of hydroxyl groups. However, these natural products are under-utilized in supramolecular chemistry because the selective functionalization of the macrocycle is often prohibitively challenging.[4] Advances in this area allow for partial control over the placement of functionality, but the traditionally lengthy total synthesis of CDs is the only approach that enables completely regioselective functional group placement. These efforts usually suffer from the use of low-yielding cycloglycosylation reactions to form the macrocycle.[5]



As an alternative approach, we recently disclosed the synthesis of a CD analogue **1** derived from a trisaccharide **2** that displayed an anomeric azide and a 4-propargyl ether at the opposing terminus.[6] Upon exposure of this intermediate

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(1) (a) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743. (b) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621.

(2) (a) Bell, T. W.; Hext, N. M. *Chem. Soc. Rev.* **2004**, *33*, 589. (b) Goswami, S.; Mukherjee, R.; Ray J. *Org. Lett.* **2005**, *7*, 1283.

(3) (a) Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1959. (b) Elemans, J. A. A. W.; Rowan, A. E.; Nolte, R. J. M. *Ind. Eng. Chem. Res.* **2000**, *39*, 3419.

(4) Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977.

(5) Gattuso, G.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1919.

(6) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638.

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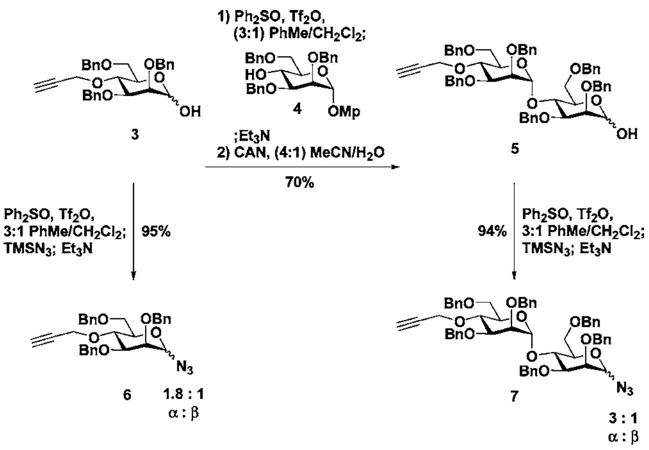
to conditions for Cu(I)-catalyzed[7] Huisgen cycloaddition and subsequent deprotection, a cyclodimer was isolated that complexed 8-anilino-1-naphthalene sulfonate with an association constant similar to that of β-cyclodextrin. Since the trisaccharide **2** is synthesized from its constituent monosaccharides, one can place synthetic handles onto the molecule to allow for selective functionalization. This strategy should allow for the placement of substituents at any position on the periphery of the macrocycle via interchange of protecting groups within its monosaccharide building blocks.

Of the common natural CDs, properties such as host–guest interactions, water solubility, and cavity size change dramatically as the number of sugars increases from six (α-CD) to eight (γ-CD).[8] This trait provides researchers with another property that can be tuned for a specific application. Given the importance of such tunability, work began toward variations of our original trisaccharide-based macrocycle that utilized a monosaccharide or a disaccharide building block. Herein the synthesis and complexing ability of carbohydrate macrocycles are reported starting from an appropriately protected monosaccharide or disaccharide.

These studies were initiated by synthesizing a monosaccharide that contained the requisite anomeric azide and 4-propargyl ether moieties (Scheme 1). The fully functionalized monosaccharide **6** was accessed in one step from hemiacetal **3**.[6] Activation of hemiacetal **3** with Ph_2SO and Tf_2O at −45 °C allowed for capture by trimethylsilyl azide to afford a 95% yield of monosaccharide **6** (1.8:1 α:β), whose anomers were separated cleanly by flash column chromatography.

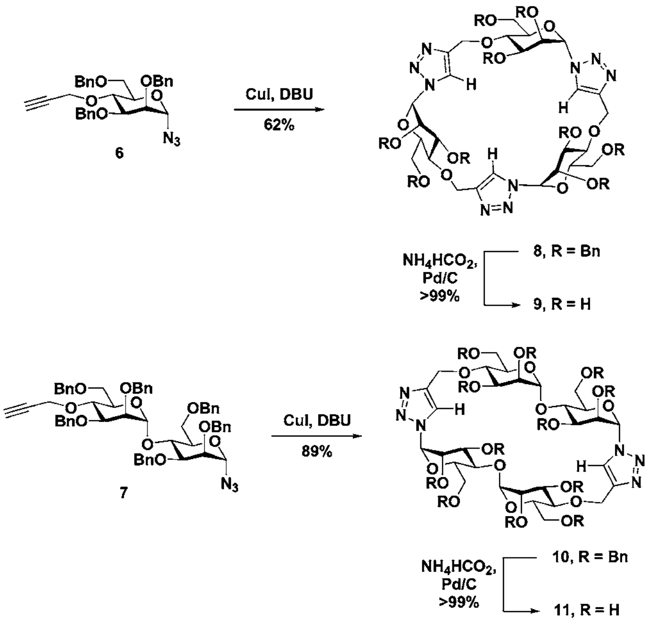
Scheme 1. Synthesis of Fully Functionalized Saccharides



The corresponding disaccharide **7** based upon α-(1,4) linked mannose units was synthesized in a similar manner (Scheme 1). Donor **3** glycosylated mannose acceptor **4** under dehydrative glycosylation conditions[9] followed by anomeric deprotection of the newly formed disaccharide to furnish a 70% yield of hemiacetal **5** over the two steps. The azide moiety was installed under the same conditions that were employed for the monosaccharide substrate to give a 94% yield of disaccharide **7** (3:1 α:β). The anomers were again separated cleanly by flash column chromatography.

With the azide and alkyne substituents appended to the monosaccharide and disaccharide substrates **6** and **7**, it was found that the conditions for Cu(I) catalysis employed for the trisaccharide cyclodimer worked for these compounds as well (Scheme 2). Exposure of monosaccharide **6** to CuI and DBU for 20 h afforded cyclotrimer **8** in 62% yield, with the remainder constituting a mixture of tetramer through hexamer byproducts as evidenced by MALDI-TOF mass spectrometry. Cyclotrimer **8** offers a unique characteristic in that it possesses C_3 symmetry, in contrast to the pseudo-C_2 symmetry of trisaccharide based cyclodimer **1**.[10]

Scheme 2. Sequential [3 + 2] Cycloadditions and Deprotection



Similarly, upon exposure of the disaccharide substrate **7** to the Cu(I) conditions for 18 h, cyclodimer **10** was formed cleanly in 89% yield (Scheme 2). Considering the possibility of oligomerization of the disaccharide, this high yield may be due to a presumably curved topology of the disaccharide building block that could facilitate cyclization in preference to oligomerization.

The deprotection of the benzyl groups was effected via transfer hydrogenolysis with NH_4HCO_2 and Pd/C in a solvent mixture of 2:2:1 EtOAc/EtOH/H_2O for both macrocycles **8** and **10**. This solvent combination afforded good solubility

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[7] (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

[8] Saenger, W.; Jacob, J.; Gessler, K.; Steiner, T.; Hoffmann, D.; Sanbe, H.; Koizumi, K.; Smith, S. M.; Takaha, T. *Chem. Rev.* **1998**, *98*, 1787.

[9] Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

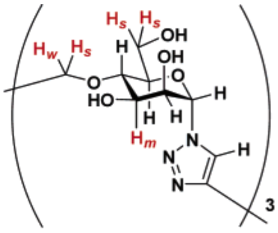
[10] We only observe ^1H and ^{13}C resonances for the repeat unit of the monosaccharide cyclotrimer and disaccharide cyclodimer.

of both macrocycles as the polarity of the substrates changed from nonpolar to polar during the removal of the hydrophobic protecting groups. The crude reaction mixture was purified by dialysis to give >99% yield of the desired macrocycles **9** and **11** from **8** and **10**, respectively. Although fully benzyl protected saccharides were used, orthogonal protecting groups could allow for facile post-cyclization site-selective modification.

CDs display an amphiphilic character with a cone-like hydrophobic cavity. A myriad of small molecules have been shown to bind within the nonpolar cavity of CDs.[11] Likewise, trisaccharide-based cyclodimer **1** was shown to bind a functionalized naphthalene fluorophore. However, for applications such as molecular pores, the binding of small organic molecules to macrocycle cavities can be a deleterious property. Because of our interest in such applications, the propensity of macrocycles **9** and **11** to form host−guest complexes was examined. Physical models of macrocycles **9** and **11** indicated that such a hydrophobic cavity could exist for these compounds but also suggested that the cavity shapes differ significantly from those observed for CDs.

Further investigation of the cavity shape was performed using the Molecular Operating Environment (MOE) software.[12] The structures of α-CD, *β*-CD, monosaccharide cyclotrimer **9**, disaccharide cyclodimer **11**, and trisaccharide cyclodimer **1** were input into MOE, and the energy was minimized using the MMFF94 force field. The modeling predicted a toroidal cavity shape for the CDs and a distorted shape for macrocycles **1**, **9**, and **11**. Trisaccharide cyclodimer **1** was predicted to have a well-defined and open cavity that should allow for guest binding. However, macrocycles **9** and **11** were predicted to have cavities with nontoroidal shapes and sterically restricted openings that could make guest binding more difficult.

Nonetheless, the ability of macrocycles **9** and **11** to function as hosts in supramolecular complexes was investigated using ^{1}H NMR shift titration. Upon screening a variety of small molecules that are known to bind with CDs, it was found that guests with six and five-membered aromatic rings such as benzoic acid and pyrrole did not bind to macrocycles **9** and **11**, presumably due to the small cavities of **9** and **11**. These results demonstrate a contrast between macrocycles such as CDs and trisaccharide cyclodimer **1** that bind small aromatic molecules and macrocycles **9** and **11** that seem unable to bind these guests. Simple alkanols such as 1-propanol and 1-butanol were also tried as guests in order to minimize steric interactions between the macrocyclic hosts and the guest, but the saturated hydrocarbon chains did not provide measurable complexation-induced shifts (CIS). These results led us to try 2,4-hexadiyne-1,6-diol **12** (Figure 1). This water-soluble diyne has been shown to form complexes with both α-CD and *β*-CD as determined by ^{1}H NMR shift titration.[13] The reported association constants for (1:1) complexes with these hosts are 580 ± 20 and 18 ± 2 M^{-1}, respectively.

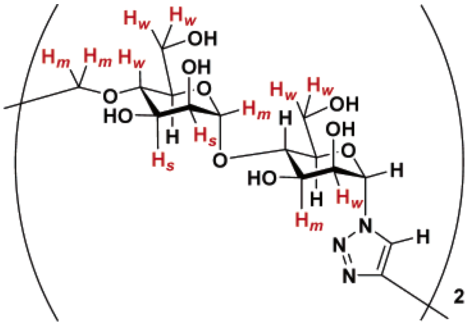


9

12

Figure 1. NOEs (shown in red) observed for resonances of cyclotrimer **9** upon irradiation of 2,4-hexadiyne-1,6-diol methylene protons (shown in blue). (*s* = strong, *m* = medium, *w* = weak).

Upon titrating the monosaccharide cyclotrimer **9** with the 2,4-hexadiyne-1,6-diol guest **12** in D_2O, an association constant of 8.8 ± 1.5 M^{-1} was calculated by nonlinear regression analysis. When the same procedure was done using the disaccharide cyclodimer **11**, we found an association constant of 10.4 ± 1.1 M^{-1} as compared to 18 ± 2 M^{-1} for *β*-CD. To further verify that diyne **12** was forming a complex with these macrocycles, NOESY1D spectra were obtained in D_2O for (10:1) mixtures of the diyne with each of the two macrocyclic hosts. Irradiation of the singlet resulting from the methylene protons of the diyne guest **12** showed NOEs to several signals on the monosaccharide cyclotrimer **9** (Figure 1). Since the NOESY1D pulse sequence was utilized, only a qualitative estimate of the enhancements is reported (*s* = strong, *m* = medium, *w* = weak). Similar NOEs were observed when the same experiment was performed using the disaccharide cyclodimer host **11** (Figure 2). Enhancement of signals from protons on both the secondary (2° OH side) and primary (1° OH side) rims of the macrocycles strongly supports the assertion that the diyne threads through the macrocycles.



11

12

Figure 2. NOEs (shown in red) observed for resonances of cyclodimer **11** upon irradiation of 2,4-Hexadiyne-1,6-diol methylene protons (shown in blue). (*s* = strong, *m* = medium, *w* = weak).

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[11] Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875.

[12] *Molecular Operating Environment*, version 2004.03; Chemical Computing Group: Montreal, Canada, 2004.

[13] Huuskonen, J.; Buston, J. E. H.; Scotchmer, N. D.; Anderson, H. L. *New J. Chem.* **1999**, *23*, 1245.

The intermolecular NOEs observed for both **9** and **11** with the diyne guest provides good evidence that the hosts are in close proximity to the guest on the NMR time scale. Although these data suggests a complex is forming between the host and guest for these two macrocycles, the association constants for these interactions are small. As is predicted by molecular modeling, this is likely due to the steric interactions encountered by guest molecules attempting to enter the small angular cavities of macrocycles **9** and **11**. Therefore, these macrocycles should be ideal for applications such as molecular pores in which the binding of small molecule guests is generally undesirable.[14]

In summary, we have developed a convergent method for the efficient construction of carbohydrate-based macrocycles whose tendency against the binding of small molecules complements our cyclodextrin analogue **1**. Computational modeling indicates that these macrocycles have small cavities with openings that are too sterically demanding for most small organic molecules to enter. The installation of orthogonal protecting group handles should allow for the site-selective manipulation of these new macrocycles providing for their use in a wide array of applications for supramolecular chemistry. Studies toward the selective functionalization of these macrocycles are currently underway.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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