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Synthesis of a Novel Class of Cyclodextrin-Based Nanotubes

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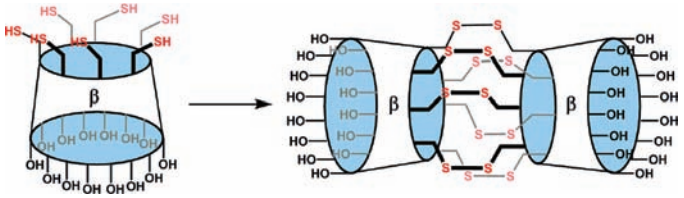
ABSTRACT



The synthesis and characterization of a novel class of structurally well-defined nanotubes from β-cyclodextrin are described. These new hosts were formed using disulfide linkages that substitute all the primary hydroxyl groups of a β-cyclodextrin. A deep and rigid hydrophobic channel with a size of more than 1.5 nm is found in the molecules. Because of their unique geometry and the potential biodegradability of the disulfide bond, this class of molecules could find broad applications in biology and other areas of research.

Cyclodextrins (CDs)[1] attract attention from different research fields because of their unique hydrophobic cavities which can host a range of organic compounds via noncovalent interaction. The building blocks of all natural CDs consist of the same α-glucopyranosyl unit which forms the wall of all cavities; therefore all CD cavities have the same height (7.9 Å). However, the cavity volumes differ according to the number of α-glucopyranosyl units involved in forming the host molecule. For example, α-CD constitutes six sugar units, generating a cavity with a fixed volume of 174 Å^3. The other two homologues, the β- and γ-CDs, which are formed with 7 and 8 sugar units, produce larger but still fixed cavity volumes of 262 and 424 Å^3, respectively. There has been considerable interest in developing chemistry to create novel hosts with increased volumes to augment CD's inclusion capability. Among the many strategies reported in the literature,[2] oligomerization of CD monomers[3] using linkers of variable nature is the most attractive because this creates linear or branched CD hosts with multiple cavities that have the potential to interact with guest molecules with high affinity and specificity by taking advantage of the cooperative effect.[4,5] Following Tabushi and Harada's pioneer work,[6] the syntheses of CD-based dimers,[7] trimers,[8] tetramers,[9]

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and pentamers[10] have been reported. The design and synthesis of such oligomeric CD hosts can be challenging depending on the chemical properties of linkers. Probably one of the simplest approaches is to use disulfide as a linker to bring together two CD molecules by taking advantage of the thiol−disulfide exchange which is a fundamental biological process. This method has been explored previously to prepare different CD-based "head to head", "head to tail", and "tail to tail" dimers (head: primary face, tail: secondary face) using one disulfide linkage.[7h−j] Recently, Kraus's group succeeded in preparing two duplexes of α-CD (Figure 1) using two and three disulfide linkages respectively.[11] They strategically placed the sulfur atoms at the $6^A,6^D$ or $6^A,6^C,6^E$ positions of α-CD and obtained dimers **1** and **2** in high yields.

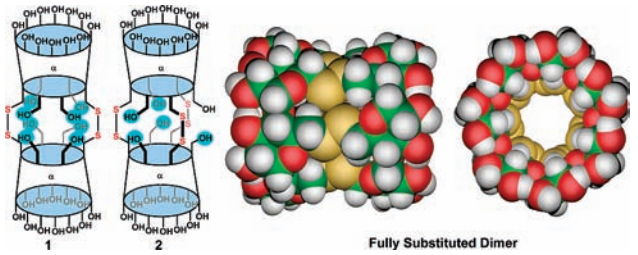

Figure 1. Structures of previously synthesized CD duplexes **1** and **2** containing 2−3 disulfide bonds and CPK models[12] of targeted duplexes fully substituted with disulfides.

One of the obvious advantages of using more than one linker to bridge CD molecules is that the resulting hosts such as **1** and **2** possess higher rigidity compared to those containing only one bridge. However, for incompletely substituted hosts like **1** and **2**, there are still some polar hydroxyl groups remaining, which make the middle zone of the molecules still hydrophilic. One of the most exquisite synthetic targets would be to replace all hydroxyl groups with disulfide linkages (Figure 1); this would allow us to obtain a novel class of molecules which are fully enclosed in the middle, thus effectively connecting the two hydrophobic cavities with an additional hydrophobic zone created by the fully encircled disulfide bonds. Molecular modeling showed that such molecules would possess a genuine tube which has a remarkable depth of more than 1.5 nm. To date, the synthesis of such a class of molecules has not yet succeeded. Because of their unique molecular topology, as well as of the presence of potentially biodegradable disulfide linkages,[13] this class of host molecules could have widespread applications in biology and areas involving molecular recognition.

The challenge to obtain such molecules is that the dimerization/thiol−disulfide exchange process could be very complex because of numerous possibilities to form disulfide bonds between two thiol groups located within the same CD molecule as well as across two CD molecules. In addition, the monomer can oligo- and polymerize to form a complex mixture. Indeed, recently, Chechik's group has studied the polymerization of a β-CD derived heptathiol (**5**) and they obtained large water-soluble nanocapsules cross-linked by disulfide linkages.[14] According to the molecular model and Kraus's work,[11a] the formation of disulfide linkages within the same CD molecules usually results in considerable distortion of the CD macrocycle, thus this would lead to the formation of CD intermediates with a higher energy owing to the presence of excessive amounts of torsional strains. If the total number of thiol groups within the same CD is an odd number, under basic conditions, this would result in an unpaired thiolate at any time, which should serve as a driving force to promote thiol−disulfide equilibrium, and ultimately, the intramolecular disulfide bonds would break in favor of the less strained intermolecular disulfide linkages. We believe that, after the formation of the first intermolecular disulfide linkage between two CDs, if a second disulfide bond could form between the pair, this would align the two CD molecules in the "head to head" orientation; this could promote the formation of other disulfide bonds between the two molecules; ultimately, the thiol−disulfide equilibrated process would favor the formation of the desired dimer, which should possess the least amount of torsional strains.

From our previous research, we had access to periodinated β-CD[15] (**3**, Scheme 1). We thought that compound **3** could be a good substrate to use because it can be converted to a molecule containing 7 thiol groups. Since the molecule had an odd number of thiols, it should be an ideal substrate to explore the scope of the thiol−disulfide equilibrium reaction. As shown in Scheme 1, we first replaced all iodides of compound **3** with potassium thioacetate in DMF. The intermediate thioacetate was not isolated but subjected to an peracetylation to afford the fully acetylated intermediate **4**, which was obtained in 76% yield by column chromatography on silica gel. To test the dimerization reaction, the peracetylated heptathiol **4** was first subjected to a Zémplen transesterification condition in methanol using sodium methoxide as the base under an argon atmosphere; the deacetylation finished within the first 30 min, and the solution became clear. The reaction was continued in the presence of a 1 M NaOH solution for 3 days under open

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(12) β-CD coordinates were obtained from the protein databank (http://www.pdb.org, 3M4E). All 6-OH's were replaced with thiols, and the resulting structure was minimized with an MM2 force field. The heptathiol was manually dimerized by forming 7 disulfide linkages, and the obtained dimer was minimized again. The obtained model has the following average dihedral angles: C4−C5−C6−S: −165°; C5−C6−S−S′: 165°; C6−S−S′−C6′: 115°; S−S′−C6′−C5′: 165°; S′−C6′−C5′−C4′: −165°.
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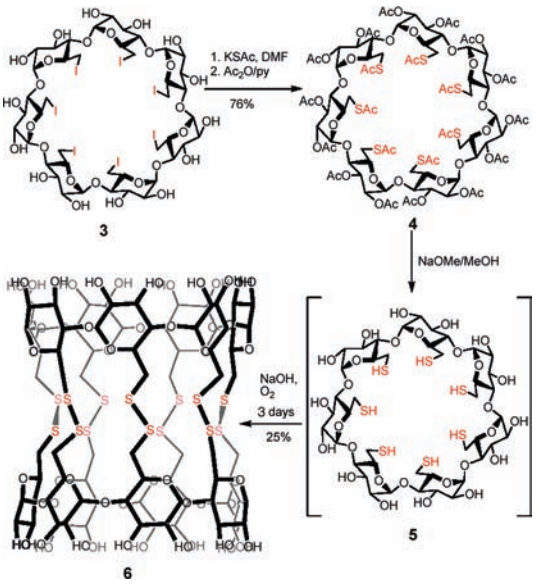
Scheme 1. Synthesis of Polyhydroxylated Dimer **6** from **3**



air with vigorous agitation. During this time, we observed the formation of a white precipitate, which was collected at the end of the reaction by centrifugation. The solid was repeatedly washed with water and methanol alternatively.

The 1D ^{1}H NMR spectrum of the precipitate in DMSO-d_6 revealed that broad signals were observed, but the simplicity of the ^{1}H NMR spectra suggested that the solid contained a simple or symmetrical compound; for example, a broad peak at 4.89 ppm was observed at 299 K (Figure 2a), which could be assigned to H-1's. When we heated the NMR solution to 360 K, we observed a dramatic change in resolution (Figure 2b); all signals became highly resolved. The broad resonance of anomeric protons appeared as a sharp doublet at 4.88 ppm (J = 3.7 Hz), and the remaining H-2, H-3, H-4, and H-5 also had the expected coupling patterns for an α-linked glucopyranoside. The two geminal protons H-6a and H-6b were found at 3.53, 3.28 ppm. A 1D ^{13}C NMR spectrum also revealed that the compound had only 6 types of carbons. Figure 2c shows the ^{1}H−^{13}C 2D HSQC NMR spectra recorded at 360 K, which revealed unambiguiously that the C-6 resonates at 39.96 ppm, confirming the attachment of a sulfur atom to the C-6 carbon. The simplicity of the NMR spectra of the isolated compound could also suggest the presence of a monomer, **5**. However, further characterization by high resolution ESI-QTOF mass spectrometry (Figure 3) confirmed the absence of monomer **5**, but the presence of dimer **6**, as a peak at m/z 2496.3448 was observed which correlates with the ammonium adduct of dimer **6** containing 7 disulfide linakges [$(C_{84}H_{126}O_{56}S_{14}$ + $NH_4)^+$, calculated: 2496.3440]. This is further confirmed by the presence of a doubly charged ammonium adduct peak (Figure 3). The isolated yield for dimer **6** was ~25% which was not optimized.

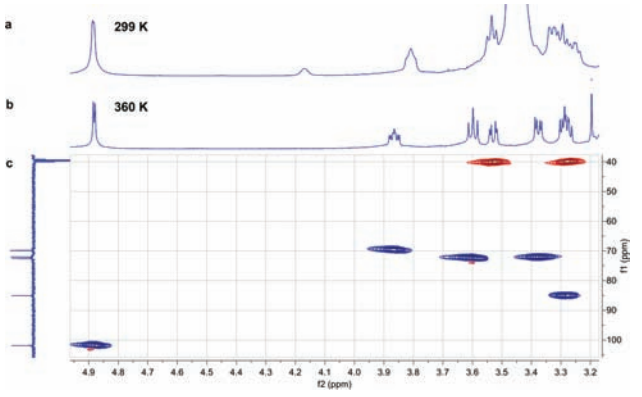


Figure 2. Varibale temperature 1D ^{1}H NMR spectra of dimer **6** recorded at (a) 299 K and (b) 360 K. (c) ^{1}H−^{13}C HSQC NMR spectra of **6** in DMSO-d_6 recorded at 360 K.

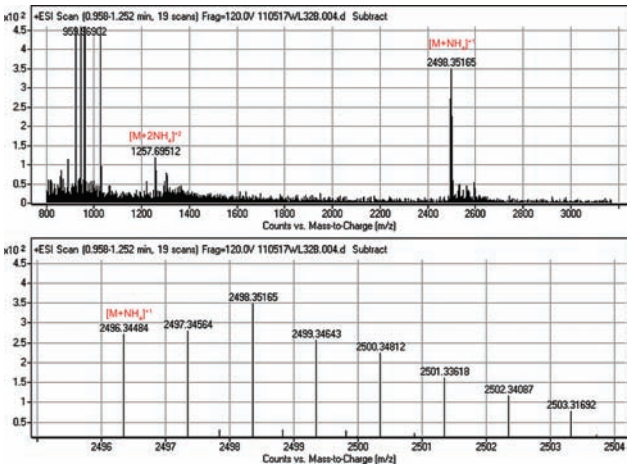


Figure 3. High resolution ESI-QTOF mass spectra of dimer **6**.

It is interesting to note that one of the polymerization procedures published by Chechik's group was also carried out using NaOH as a base, but they carried out the experiment in an extremely dilute concentration (50 mg in 500 mL of a 0.1 N NaOH solution). At basic pH, they did not observe the formation of a precipitate, but after neutralization with HCl, they indeed observed a slight precipitation which was not characterized.[14]

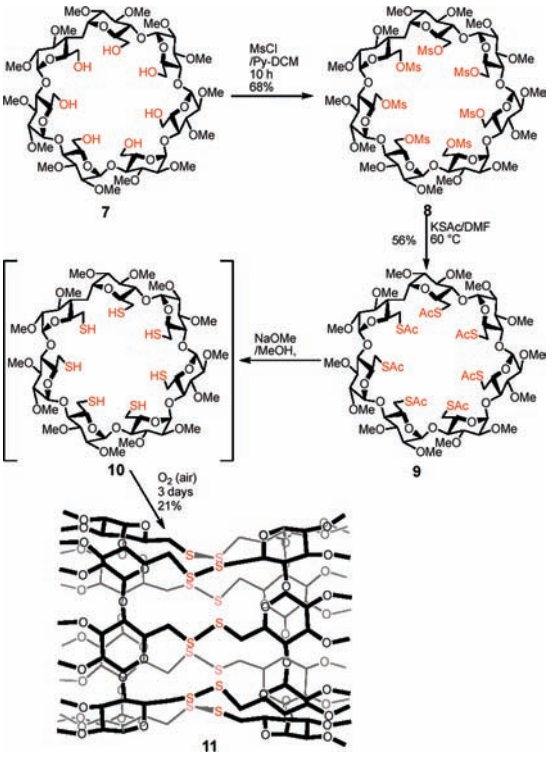
Compound **6** has an interesting structural feature because it has 28 hydroxyl groups separated into two groups of 14, and they are located at the very end of each side of the long hydrophobic channel. This provides a clear separation of polar and apolar groups in the molecule, which should provide it with unusual chemical and physical properties. We observed that dimer **6** had poor solubility in water, methanol, and chloroform, which could be well explained by its structural features.

To demonstrate the applicability of the methodology, we also designed another dimer **11** that had all the hydroxyl

groups protected with a methyl group. We expected the new target to have better solubility in organic solvents because it contains only apolar groups.

Thus, starting from heptol **7**,[16] we carried out a permesylation in a mixture of pyridine–dichloromethane (Scheme 2) to afford the permesylate **8** in 68% yield. All mesylates were displaced with potassium thioacetate to give the desired hepta-6-thioacetate **9** in 56% yield.

Scheme 2. Synthesis Route to Permethylated Dimer **11**



Compound **9** was subsequently subjected to an *in situ* deacetylation in methanol using sodium methoxide as a strong base, to provide the intermediate hepta-6-thiol **10** which was not isolated; after stirring in open air under basic conditions for another three days, dimerization readily occurred as we observed the formation of a new spot on TLC with an R_f 0.27 (hexane/acetone 3:2) and another major band below, which is probably due to oligo-/polymerization. The upper spot was isolated by column chromatography in 21% yield. Like the previously synthesized dimer **6**, the 1D ^{1}H and ^{13}C NMR spectra of compound **11** showed expected symmetry and simplicity as 7 types of sugar protons and 2 types of methyl groups were observed from the ^{1}H NMR spectra. The ^{13}C spectra also confirmed the existence of 8 types of carbon signals. This is further supported by high-resolution ESI-QTOF mass spectrometry which detected a peak at m/z 2893.7389, which correlates well with the expected value for the sodium adduct of $C_{112}H_{182}O_{56}S_{14}$: 2893.7381 $[M + Na]^+$.

Additionally, we also prepared another target, **12** (Figure 4), which possesses half the amount of hydroxyl groups of **6** and half the amount of methyl groups of **11**. This is realized by strategically placing a methyl group on the O-2 position of each glucopyranosyl unit. Target **12** should have interesting properties because it has balanced hydrophobic/hydrophilic groups. The analogous duplex **12** was synthesized in an analogous manner as **11** from per-6-*O*-*tert*-butyldimethylsilyl-3-*O*-methyl-β-CD (**13**)[16] (see Supporting Information).

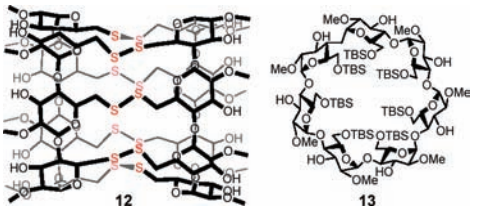


Figure 4. Structure of synthesized dimer **12** and its precursor **13**.

Preliminary studies showed that both compounds **11** and **12** were fully soluble in many common organic solvents including chloroform. However, they still have poor solubility in water.

In conclusion, we demonstrated that the thiol–disulfide exchange equilibrium can be applied to the synthesis of a novel class of fully enclosed β-CD dimers containing 7 disulfide linkages. This class of new hosts could find widespread utilities in many areas of research because of their uniquely deep hydrophobic pocket and molecular geometry.

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Supporting Information Available. Experimental procedures and related analytical data for compounds **4**–**6**, **8**–**11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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