ORGANIC LETTERS

2007
Vol. 9, No. 20
3909−3912

Synthesis of Stimuli-Responsive Cyclodextrin Derivatives and Their Inclusion Ability Control by Ring Opening and Closing Reactions

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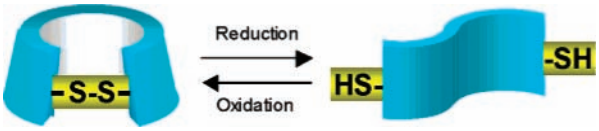
Received June 20, 2007

ABSTRACT



Novel stimuli-responsive cyclodextrins (CDs), in which a disulfide unit was inserted into the rings of permethylated α- and *β*-CDs, were synthesized. Their inclusion ability was controlled by the opening and closing of the ring based on dithiol−disulfide interconversions.

Cyclodextrins (CDs) have hydrophobic cavities into which organic molecules of appropriate size and shape can be incorporated mainly through hydrophobic interactions in aqueous solutions. The ability of CDs to form inclusion complexes with organic molecules has found applications in many areas.[1,2] Some effort to control the inclusion ability of CDs has been made by introducing stimuli-responsive units, such as photosensitive azobenzene units[3,4] and thermosensitive poly(*N*-isopropyl acrylamide) units,[5] to CD rings. For example, in the azobenzene-appended *γ*-CD, the inclusion ability was clearly changed by the *cis*-*trans* photoisomerization of the azobenzene moiety: the *cis* isomer showed higher inclusion ability toward (−)-borneol (K = 5790 M^{-1}) than that of the *trans* isomer (K = 2870 M^{-1}). Stimuli-responsive CDs, however, have been limited to those prepared by the modification of hydroxyl groups on the upper and/or lower rims of CDs. To the best of our knowledge, inclusion ability control by directly inserting a stimuli-responsive unit in the CD ring has not been reported yet. If this type of CD derivative is developed, one can more effectively control the inclusion ability by considerably changing the size and shape of the CD ring.

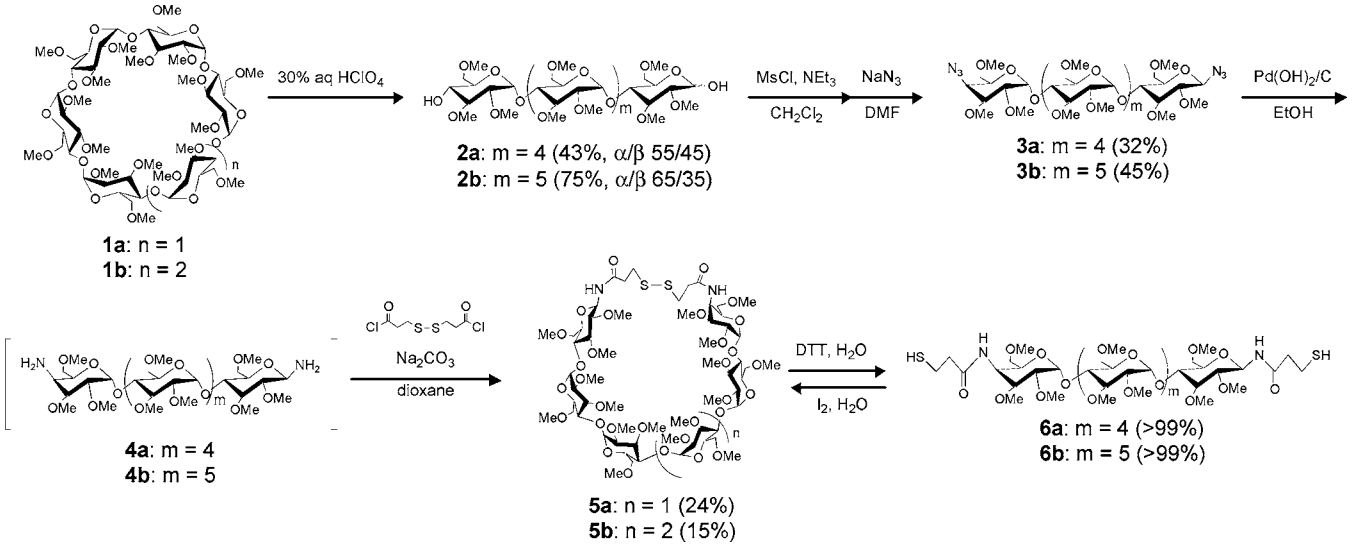
Herein, we report the synthesis of novel stimuli-responsive CD derivatives, in which a disulfide unit is inserted into permethylated α- and *β*-CD rings and the control of their inclusion ability by the opening and closing of the ring based on dithiol−disulfide interconversions.[6,7]

Stimuli-responsive CDs bearing disulfide units were synthesized from permethylated α- and *β*-CDs[8] in five reaction steps (Scheme 1): the ring opening of permethylated α- (or *β*-) CD by the cleavage of a single α-(1,4)-glucosidic bond,[8] mesylation of the terminal hydroxyl groups of the resulting maltohexaose (or maltoheptaose) derivative, replacement of the mesyloxy groups by azide groups, reduction of the azide groups,[9] and finally cyclization of the diamino

(1) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803−822.
(2) Szejtli, J.; Osa, T. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Eds.; Pergamon: Oxford, 1996; Vol. 3.
(3) Ueno, A.; Yoshimura, H.; Saka, R.; Osa, T. *J. Am. Chem. Soc.* **1979**, *101*, 2779−2780.
(4) Ueno, A.; Tomita, Y.; Osa, T. *Tetrahedron Lett.* **1983**, *24*, 5245−5248.
(5) Nozaki, T.; Maeda, Y.; Ito, K.; Kitano, H. *Macromolecules* **1995**, *28*, 522−524.
(6) Shinkai, S.; Inuzuka, K.; Miyazaki, O.; Manabe, O. *J. Org. Chem.* **1984**, *49*, 3440−3442.
(7) Shinkai, S.; Inuzuka, K.; Miyazaki, O.; Manabe, *J. Am. Chem. Soc.* **1985**, *107*, 3950−3955.
(8) Kikuzawa, A.; Kida, T.; Nakatsuji, Y.; Akashi, M. *J. Org. Chem.* **2005**, *70*, 1253−1261.

10.1021/ol701449v CCC: $37.00
Published on Web 09/05/2007

Scheme 1. Synthesis of Stimuli-Responsive CD Derivatives Bearing Disulfide Units



maltohexaose (or maltoheptaose) derivative with 3,3′-dithiopropionyl dichloride.[10] Reactions of **2a** and **2b** with mesyl chloride in the presence of triethylamine almost quantitatively yielded the corresponding mesylates. Without further purification, the mesylates were reacted with NaN_3 to produce **3a** and **3b** with a β-D-configuration at the terminal glucose C-1 position as main products. After the reduction of terminal azide groups using a $Pd(OH)_2/C$ catalyst, the resulting products **4a** and **4b** were reacted with 3,3′-dithiopropionoyl dichloride in the presence of excess Na_2CO_3 to yield the corresponding cyclic products **5a** (24% yield from **3a**) and **5b** (15% yield from **3b**), respectively. The structures of these CD derivatives were confirmed by NMR and mass spectrometry. In ^{1}H NMR spectra, the anomeric protons of **5a** and **5b** were observed as six and seven signals, respectively (Figure 1). Among the signals, a doublet at 4.88 ppm in **5a** and a doublet at 4.90 ppm in **5b** were assigned to protons with a β-D-configuration, based on the larger coupling constants (**5a**; J = 9.4 Hz, **5b**; J= 9.0 Hz). Compounds **5a** and **5b** were moderately soluble in water (**5a**: 8.8×10^{-2} mol/L, **5b**: 4.7×10^{-2} mol/L), but their water solubilities were lower than those of permethylated β-CD (1.7×10^{-1} mol/L) and γ-CD (3.0×10^{-1} mol/L).

The cleavage of S−S bonds of **5a** and **5b** was carried out in aqueous solutions with dithiothreitol (DTT) as a reductant at room temperature to give **6a** and **6b** in >99% yields, respectively. These reactions were monitored by ^{1}H NMR. Figure 2 shows the ^{1}H NMR spectral changes observed for **5a** upon addition of DTT. The intensity of anomeric proton signals from **5a** decreased with time, while the intensity of a newly appearing signal at 5.09 ppm, which was assigned to an anomeric proton of **6a**, increased with time. This observation indicates that the S−S bond of **5a** was cleaved to quantitatively give **6a**. In these reactions, the cleavage rate of the S−S bond was controlled by changing the DTT concentration: the cleavage reaction of **5a** (3.9 mM) in a 39 mM DTT solution was completed in 48 h, on the other hand, the reaction in a 117 mM DTT solution was completed within 24 h. The comparison of the S−S bond cleavage rate between **5a** and **5b** showed that the cleavage of **5b** bearing the larger ring was slower than that of **5a**. (The observed

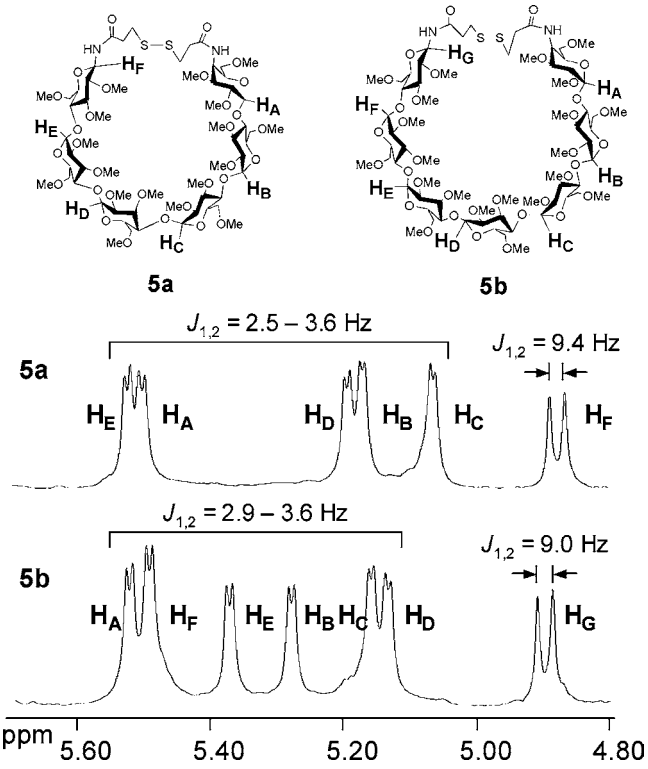


Figure 1. ^{1}H NMR spectra of anomeric protons of **5a** and **5b**.

(9) Chowdhary, M. S.; Hougt, L.; Richardson, A. C. *Carbohydr. Res.* **1986**, *147*, 49−58.
(10) Kida, T.; Michinobu, T.; Zhang, W.; Nakatsuji, Y.; Ikeda, I. *Chem. Commun.* **2002**, 1596−1597.

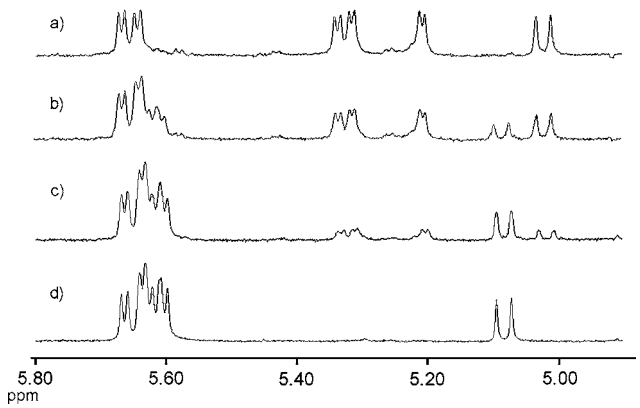


Figure 2. ^{1}H NMR spectral changes observed for host **5a** (3.9 mM) upon addition of DTT (117 mM) in D_2O at 25 °C: (a) 0 h, (b) 3 h, (c) 9 h, (d) 24 h.

pseudo-first-order rate constants for **5a** and **5b** in 117 mM DTT solution were $k_{5a} = 4.33 \times 10^{-5}$ s^{-1} and $k_{5b} = 3.50 \times 10^{-5}$ s^{-1}, respectively.)

Cyclization of **6a** and **6b** by oxidation of the dithiol was also studied. The stirring of **6a** in an iodine solution at room temperature for 3 h yielded **5a** (40%), together with several byproducts formed by the oligomerization of **6a** (Figure 3).

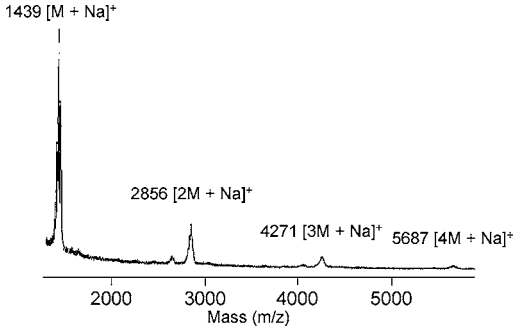


Figure 3. MALDI-TOF MS spectrum of the crude products obtained after cyclization of **6a**.

Similarly to **6a**, the cyclization of **6b** gave rise to **5b** in a moderate yield (30%), together with oligomeric byproducts (1643 [M + Na]$^+$, 3263 [2M + Na]$^+$, 4883 [3M + Na]$^+$, and 6503 [4M + Na]$^+$, respectively).

The inclusion ability of the CD derivatives **5a** and **5b** was examined by a UV−vis titration method using Basic Blue 7 (BB7) as a guest (Figure 4). UV−vis titrations were performed at 25 °C in phosphate buffer (pH 7.2). A solution of BB7 (3.0 mL, 2.0×10^{-5} M) was titrated in a quartz cell with increasing amounts of host stock solution (0.5 mL, 7.5×10^{-3} M) as follows: 0, 5, 10, 15, 20, 25, 30, 40, 50, 80, 100 μL. The absorbance of BB7 at 615 nm was decreased upon addition of host solution, indicating the formation of inclusion complex with BB7. The Job plots showed that the

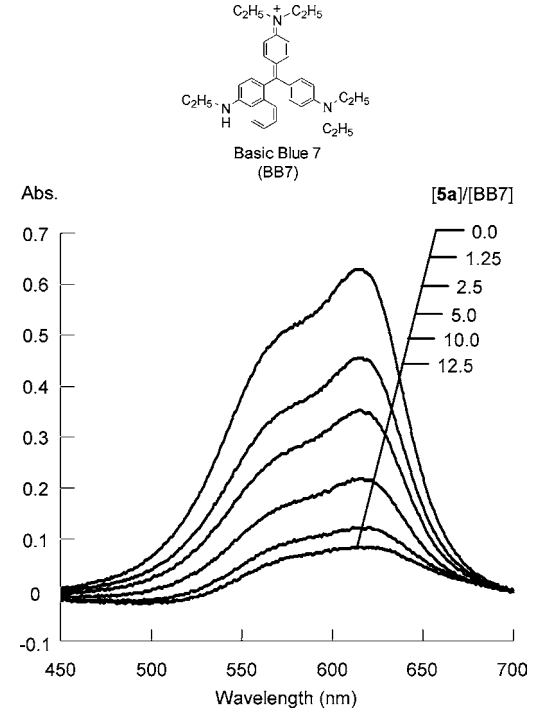


Figure 4. UV−vis spectral changes observed for guest BB7 (2.0×10^{-5} M) in phosphate buffer (pH 7.2) upon addition of host **5a** (7.5×10^{-3} M) at 25 °C.

hosts **5a** and **5b** formed a 1:1 complex with BB7 (see Supporting Information). Thus, the complexation of the host (H) with BB7 is expressed by eq 1

$$\mathrm{H} + \mathrm{BB7} \overset{K}{\rightleftharpoons} \mathrm{H{\bullet}BB7} \qquad (1)$$

The stability constant (K) was determined using a nonlinear least-squares method according to the curve fitting eq 2[11]

$$\Delta A = 1/2[\alpha([\mathrm{H}]_t + [\mathrm{BB7}]_t + 1/K) \pm \{\alpha^2([\mathrm{H}]_t + [\mathrm{BB7}]_t + 1/K)^2 - 4\alpha^2[\mathrm{H}]_t[\mathrm{BB7}]_t\}^{1/2}] \qquad (2)$$

where ΔA is the change in absorbance upon addition of host, α is the proportionality coefficient for the effective absorbance change caused by complex formation, $[\mathrm{H}]_t$ and $[\mathrm{BB7}]_t$ are the total concentrations of host and BB7, respectively (these values are corrected at each step).

Host **5a** showed higher inclusion ability toward BB7 ($K = 18\,000$ M^{-1}) than those of the host **5b** ($K = 12\,000$ M^{-1}) and permethylated β- ($K = 14\,000$ M^{-1}) and γ-CDs ($K = 15\,000$ M^{-1}). This result indicates that the BB7 molecule more closely fits the shape of the cavity of host **5a**. On the other hand, the inclusion ability of the open forms **6a** and **6b** toward BB7 was much lower (**6a**: $K = 7000$ M^{-1}, **6b**: $K = 6200$ M^{-1}), showing that the ring opening of the hosts **5a** and **5b** remarkably decreased the inclusion ability toward BB7.

(11) Hirose, K. *J. Inclusion Phenom.* **2001**, *39*, 193−209.

In conclusion, we developed novel types of stimuli-responsive CD derivatives by inserting a disulfide unit into permethylated CD skeletons. The inclusion ability of the CD derivatives was controlled by ring opening and closing. These novel compounds could be useful for constructing highly functional materials for drug delivery and tissue engineering. Extensive research in this direction is currently underway in our group.

Acknowledgment. This study was partially supported by Research Fellowships of the Japan Society for the Promotion of Science, a Grant-in-Aid for Scientific Research (No. 18550125) from the Japan Society of the Promotion of Science, and a grant from the Shonai Foundation for Science and Technology.

Supporting Information Available: Experimental procedure and ^{1}H and ^{13}C NMR spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701449V