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Molecular Sugar Bowl: γ-Cyclodextrin with a Disaccharide Floor

Kazutaka Koga, Kanami Ishida, Tomonobu Yamada
De-Qi Yuan, and Kahee Fujita*

Faculty of Pharmaceutical Sciences, Nagasaki University, 1-14 Bunkyo Machi, Nagasaki 852-8131, Japan

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Abstract

A series of molecular sugar bowls composed of a γ-cyclodextrin wall and a trehalose floor have been synthesized by reacting 6A,6X-deoxy-6A,6X-dimercapto-γ-cyclodextrin and 6,6'-deoxy-6,6'-diiodotrehalose.

Keywords: γ-cyclodextrin, glycosides

Since the diphenylmethane-capped β-cyclodextrin [1] was first synthesized through the looper-walk reaction of diphenylmethane *p,p'*-disulfonyl dichloride with β-cyclodextrin, several other capped cyclodextrins have been successfully developed [2-17]. Such capped cyclodextrins demonstrated some interesting properties, such as the great enhancement and photo-induced change of guest-binding ability [1,3,4,17], energy transfer from the cap to the bound guest [2], intramolecular reaction of the cap moiety with the glucoside residue [6,11], etc. However, the caps reported so far are mainly aromatic species. On the other hand, many other cyclodextrin analogues have been developed by chemical synthesis or biochemical methods [18], but they are confined to mono-cyclic oligosaccharides or branched cyclic oligosaccharides. Recently, trehalose was transannularly bound to the primary side of β-cyclodextrin by two cysteamine tethers [19]. We report here the synthesis of a new class of bicyclic oligosaccharides – the sugar bowls **12** ~**14** which consist of a γ-cyclodextrin wall and a trehalose floor. The trehalose is tightly packed to the bottom of γ-cyclodextrin. It is supposed to provide an additional hydrophobic floor of the similar nature to that of cyclodextrin cavity and offer a possibility to mediate the guest-binding ability and also the catalytic property of cyclodextrin.

The preparation of the molecular sugar bowl **12** ~**14** is depicted in Scheme 1. Trehalose **1** was converted to the 6,6'-diiodide **2** in a yield of 75% by reacting with triphenyl phosphine/iodine followed by the treatment with sodium methoxide [20]. γ-Cyclodextrin was regioselectively capped by appropriate arenedisulfonyl chlorides to give **3** ~ **5** [21]. The corresponding dithiouronium salts **6** ~ **8** were synthesized from **3** ~ **5** by a slightly modified procedure for the preparation of mono-thiouronium salt of β-cyclodextrin [22]. The dithiols

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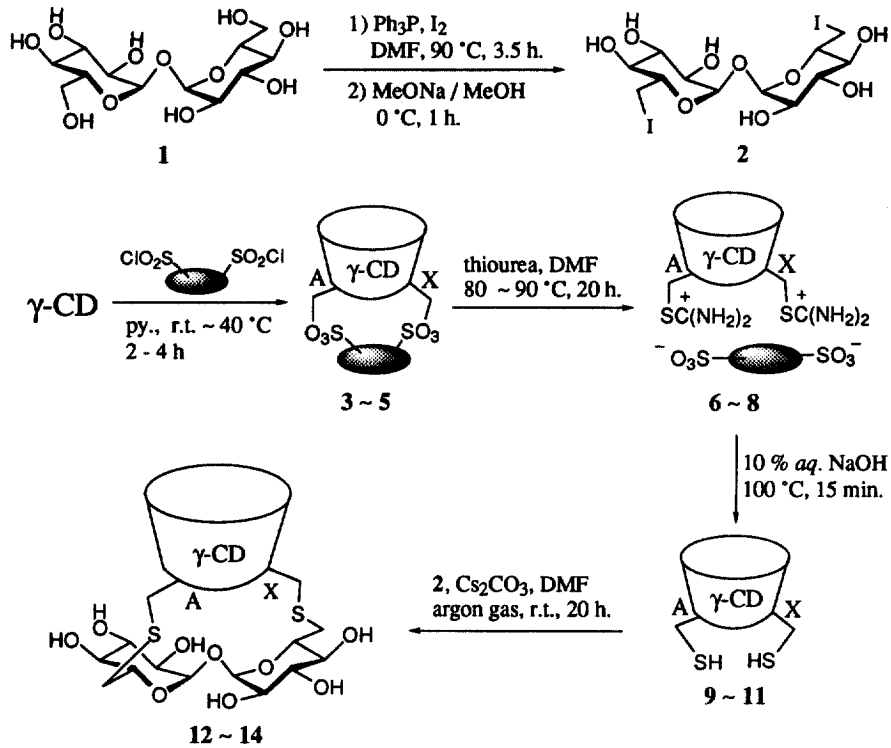
Scheme 1



compound	3, 6	4, 7	5, 8	9, 12	10, 13	11, 14
X	C	D	E	C	D	E

9 ~ 11 were generated by the treatment of **6 ~ 8** with *aq.* NaOH. The incorporation of the trehalose to the γ-cyclodextrin rim was accomplished by the reaction of **2** with **9 ~ 11**.

As a typical procedure for the preparation of the molecular sugar bowls, a solution of **6** (100 mg) in 10% *aq.* NaOH (5.7 mL) was stirred at 100 °C for 15 min, acidified to pH 3 with 1M hydrochloric acid and poured into acetone to give **9** as a white powder. The crude dithiol **9** was added to 10 mL of DMF and the insoluble material was removed by filtration. Cs_2CO_3 (935 mg) and 6,6'-dideoxy-6,6'-diiodotrehalose **2** (39.7 mg) were added to the filtrate and the resultant mixture was stirred at room temperature for 20 h. Then the reaction mixture was neutralised with 1M hydrochloric acid and poured into acetone to give a white powder, which was taken in water (50 mL) and applied to chromatography on reversed-phase column (Lobar Rp-18, size C, Merck) with the gradient elution from H_2O (1 L) to 30% *aq.* MeOH (1 L) to give a crude product. Further chromatography on Sephadex LH-20 with the elution of H_2O gave pure sugar bowl **12** in 15.6% yield (14.5 mg). By a similar procedure, the regioisomers

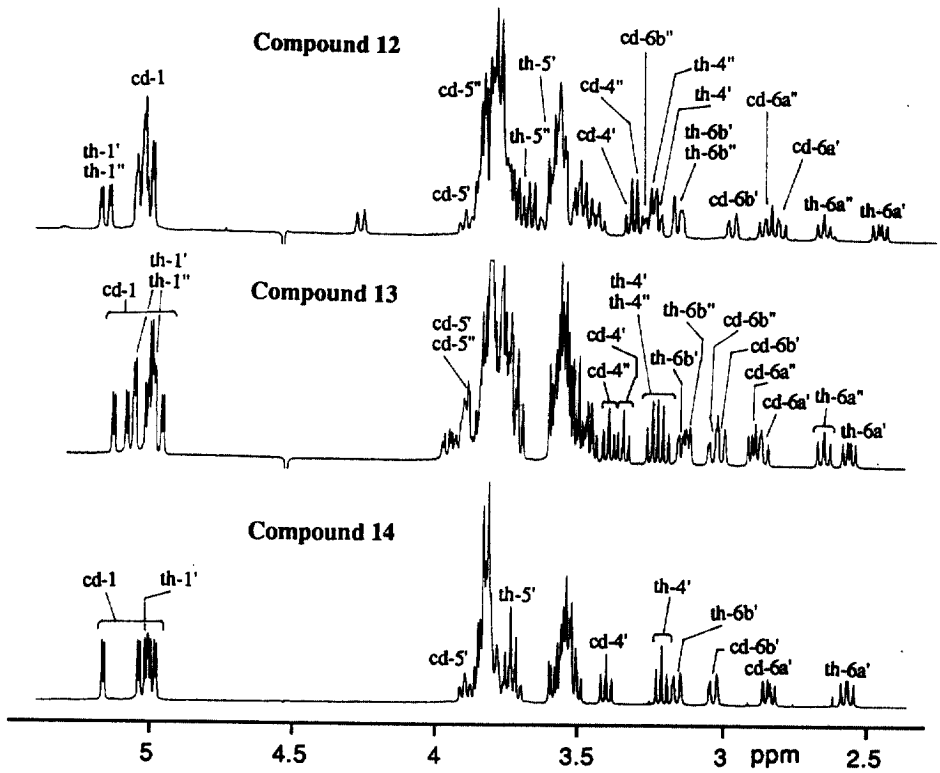


Figure 1 ^{1}H-NMR (500 MHz) spectra of the molecular sugar bowls **12** ~ **14** in D_2O

The spectra were assigned based on ^{1}H-^{1}H and ^{1}H-^{13}C COSY NMR experiments. For both the cyclodextrin and trehalose moieties (denoted as cd and th, respectively), the signals from one functional sugar unit are marked with primed numbers and those from the other functional sugar unit are represented by double primed numbers.

13 and **14** [23] were prepared from **7** and **8** in 13.5% and 14.4% yields, respectively. In the FAB-MS spectra, all the sugar bowls **12** ~ **14** showed the ion peaks at *m/z* 1635 and 1657 which were consistent with their pseudo molecular ions ($M + H^+$) and ($M + Na^+$). Their structure were also confirmed by NMR spectra (Figure 1 shows the ^{1}H-NMR spectra of **12** ~ **14**, the signals were assigned based on ^{1}H-^{1}H and ^{1}H-^{13}C-COSY experiments). The successful formation of the double sulfide-linkages between the cyclodextrin and the trehalose was clearly demonstrated by the high field chemical shifts ranging from 2.4 to 3.2 ppm for the protons and around 36 ppm for the carbons of the modified methylene groups.

The NMR spectra reflect some interesting difference in geometry among these compounds, though the exact conformation of these sugar bowls has not been obtained at this stage. As shown in Figure 1, compound **14**, which has the trehalose attached to the two glucosides separated by three sugar units, demonstrated only one type of modified glucoside for each of cyclodextrin and trehalose moieties. The methylene protons of trehalose resonate at 2.58 and 3.16 ppm while those of cyclodextrin locate at 2.85 and 3.04 ppm. All these signals splitted by different extent when the trehalose is attached to two glucosides separated

by two sugar sub-units (*i.e.* compound **13**). Especially the signals around 2.6 ppm relating to the two protons of the two trehalose methylene groups, are separated as a triplet and a doublet of doublet by 0.09 ppm. In the AC isomer **12**, the chemical shift difference of these two trehalose methylene protons are increased to 0.2 ppm. In addition, one of the methylene proton of the modified cyclodextrin glucoside is greatly shifted downfield to 3.27 ppm. These facts imply that while the sugar bowl **14** has a C_2 symmetry, **13** is asymmetric and the asymmetric nature of **12** is more apparent, which encases these sugar bowls into an interesting series of host candidates to study the asymmetric molecular recognition and catalysis.

Thus an efficient synthetic route to a new class of bicyclic oligosaccharides–the molecular sugar bowls has been worked out. Its application to α- and β-cyclodextrins, and research on the molecular recognition and catalytic properties of these sugar bowls are in progress.

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References and notes

[1] Tabushi I, Shimokawa K, Shimizu N, Shirakata H, Fujita K: J. Am. Chem. Soc. 1976; 98, 7855-7856.
[2] Tabushi I, Fujita K, Yuan LC: Tetrahedron Lett. 1977; 2503-2506.
[3] Ueno A, Yoshimura H, Saka R, Osa T: J. Am. Chem. Soc. 1979; 101, 2779-2780.
[4] Ueno A, Takahashi K, Osa T: J. Chem. Soc., Chem. Commun. 1981; 94-96.
[5] Tabushi I, Kuroda Y. Yokota K, Yuan LC: J. Am. Chem. Soc. 1981; 103, 711-712.
[6] Tabushi I, Yuan L C: J. Am. Chem. Soc. 1981; 103, 3574-3575.
[7] Tabushi I, Yamamura K, Nabeshima T: J. Am. Chem. Soc. 1984; 106, 5267-5270.
[8] Tabushi I, Nabeshima T, Fujita K, Matsunaga A, Imoto T: J. Org. Chem. 1985; 50, 2638-2643.
[9] Kato T, Nakamura Y: Heterocycles, 1988; 27: 973-979.
[10] Breslow R, Canary JW, Varney M, Waddell ST, Yang D: J. Am. Chem. Soc. 1990; 112, 5212-5219.
[11] Aquino AM, Abelt CJ, Berger KL, Darragh CM, Kelley SE, Cossette MV: J. Am. Chem. Soc. 1990; 112, 5819-5824.
[12] Yi G, Bradshaw JS, Rossiter BE, Rees SL, Petersson P, Markides KE, Lee ML: J. Org. Chem. 1993; 58, 2561-2565.
[13] Bonomo RP, Impellizzeri G, Pappalardo G, Rizzarelli E, Vecchio G: Gazz. Chim. Ital. 1993; 123: 593-595.
[14] Pikramenou K, Johnson KM, Nocera DG: Tetrahedron Lett. 1993; 3531-3534.
[15] Acquavella MF, Evans ME, Farraher SW, Nevoret CJ, Abelt CJ: J. Chem. Soc., Perkin Trans 2, 1995; 385-388.
[16] Yuan D-Q, Koga K, Yamaguchi M, Fujita K: Chem. Commun. 1996; 1943-1944.
[17] Yuan D-Q, Koga K, Fujita K, Yamaguchi M: Tetrahedron Lett. 1997; 7593-7596.
[18] Gattuso G, Nepogodiev SA, Stoddart JF: Chem. Rev. 1998; 98, 1959-1976.
[19] Cucinotta V, Grasso G, Vecchino G: J. Incl. Phenom. 1998; 31(1), 43-55.
[20] By the same procedure for the preparation of 6-perdeoxy-6-periodo-β-cyclodextrin: Ashton PR, Koniger R, Stoddart JF, Alker D, Harding VD: J. Org. Chem. 1996; 61: 903-908.
[21] Koga K, Kiyooka N, Yuan D-Q, Fujita K: to be published.
[22] Fujita K, Ejima S, Imoto T: J. Chem. Soc., Chem. Commun. 1984; 1277-1278.
[23] ^{13}C-NMR (125 MHz, D_2O), δ (ppm):
Compound **12**, 103.4 103.0, 102.6, 102.5, 102.3 and 101.5 (cd-1,1',1"); 92.5 (th-1',1"); 86.4 (cd-4'); 85.6 (cd-4"); 82.1, 81.6, 81.4, 81.3, 81.2 and 79.9 (cd-4); 74.2, 74.1, 74.0, 73.9, 73.8, 73.7, 73.5, 73.4, 73.3, 73.2, 73.1, 73.0, 72.9, 72.7, 72.2, 72.1, 71.3 and 70.7 (cd-2,2',2",3,3',3",5,5',5" and th-2',2",3',3",4',4",5',5"); 61.8, 61.4, 61.2 and 60.2 (cd-6); 38.0 (cd-6"), 35.1 (th-6'); 35.0 (th-6"); 34.0 (cd-6').
Compound **13**, 102.9, 102.7, 102.6, 102.3, 102.2, 101.9, 101.2 (cd-1,1',1"); 93.5 (th-1'); 93.4 (th-1"); 85.2 (cd-4'); 84.0 (cd-4"); 81.6, 81.4, 81.1, 80.8 and 80.2 (cd-4); 74.4, 74.1, 73.9, 73.8, 73.7, 73.6, 73.5, 73.3, 72.9, 72.8, 72.7, 72.6, 72.4, 72.3, 72.0, 71.9 and 71.2 (cd-2,2',2",3,3',3",5,5',5" and th-2',2",3',3",4',4",5',5"); 61.5, 61.2, 61.1, 60.9 and 60.6 (cd-6); 36.8 (cd-6'), 36.0 (th-6'); 35.6 (th-6"); 35.0 (cd-6").
Compound **14**, 102.3, 102.2, 101.8 and 101.5 (cd-1,1'); 93.3 (th-1'); 83.8 (cd-4'); 81.3, 80.6 and 80.5 (cd-4); 74.3, 73.6, 73.3, 73.2, 73.1, 72.9, 72.5, 72.3, 72.1 and 72.0 (cd-2,3,5 and th-2',3',4',5'); 61.3 and 61.06 (cd-6); 35.9 (th-6'); 35.7 (cd-6')