The first topologically controlled synthesis of doubly bridged β-cyclodextrin dimers

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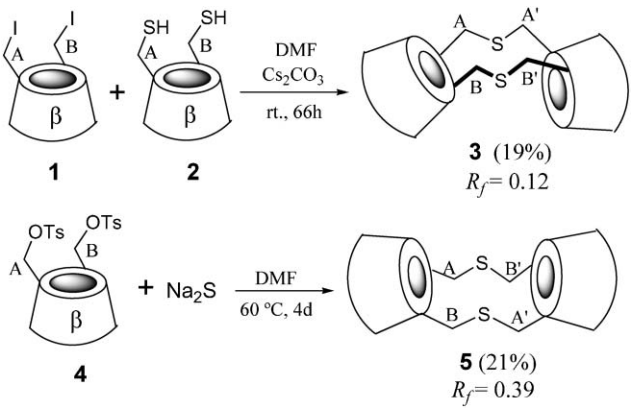
Reaction $6^A,6^B$-di(*O*-tosyl)-β-cyclodextrin with Na_2S in DMF gave the *cis*-dimer of β-cyclodextrin in 21% isolated yield while the *trans*-dimer was not detected.

Exciting achievements have been witnessed with cyclodextrins (CDs) as artificial hosts in many of the most actively pursued research fields, such as drug delivery systems, molecular sensing technologies, biomimetic recognition, and catalysis.[1] However, the recognition ability of native CDs is greatly restricted by their C_n symmetry and limitations in cavity size, shape, flexibility, and hydrophobicity. Bridging two CD units together by a suitable tether may theoretically double the free energy changes of binding and therefore provides a promising way to alter both the binding ability and guest selectivity.[2] For this reason, research on CD dimers has been actively pursued[3] since the first report on the increased binding ability of disulfide-bridged β-CD dimer.[4] However, the single tether can not effectively prevent the linked CD rings from twisting around it, and enables many conformations other than that required for the binding of a "ditopic guest". Therefore, even better binding abilities can be realized by bridging two CDs with two linkers. Tabushi *et al.*[5] prepared a β-CD dimer with two diamine-linkers by stepwise reactions of ethylenediamine with a capped CD. Breslow *et al.* described a stepwise synthesis of bent β-CD dimers with two different linkers, S–S and naphthalene,[6] and demonstrated that the *cis*-dimer ("occlusive") binds appropriate ditopic guest very strongly ($K_a > 4 \times 10^{11}$ M^{-1}) while the *trans*-dimer ("aversive") does not allow the two CD moieties to work cooperatively. Unfortunately, the *cis*-dimers, though topologically suitable for strong binding, are very difficult to synthesize because the thermodynamically favorable *trans*-dimers usually predominate in the competing dimerisations. Even more difficult is to clarify the topological aspects of the dimers. Recently, we described the synthesis of a *trans*-dimer (**3**) of β-CD by cross-coupling $6^A,6^B$-diiodo-β-CD (**1**) and $6^A,6^B$-dithio-β-CD (**2**), and the X-ray structure of the dimer.[7] Herein we report a facile synthesis of the *cis*-dimer (**5**) by the reaction of $6^A,6^B$-di(*O*-tosyl)-β-CD **4** and Na_2S. This reaction, although very simple, presented quite interesting *topological preference* and may reflect the importance of *weak interaction for generating selectivity*.

Dimer **5** was synthesized simply by heating $6^A,6^B$-di(*O*-tosyl)-β-CD **4**[8] (0.77 g, 0.53 mmol) and sodium sulfide (46 mg, 0.59 mmol) in DMF (5 mL) at 60 °C for 4 d (Scheme 1).



Scheme 1 Synthesis of CD dimers doubly bridged by sulfur atoms.

Chromatography of the reaction mixture on a reversed-phase column (Lobar Rp-18, size B, gradient elution 0–50% aq. CH_3OH) and then on a BioGel P-2 column (eluted with 10% aq. CH_3OH) afforded the doubly bridged β-CD dimer **5** (128 mg, 21% from **4**).

Dimer **5** showed the pseudo-molecular ion peak at m/z = 2287 (M + Na) in its FAB-MS spectrum. Its ^1H and ^{13}C NMR spectra (Fig. 1, only proton spectra are shown) are obviously different from those of dimer **3**. Partial assignment of the spectra based on a 2D COSY experiment reveals only two types of functional glucoside units. Both of them demonstrated significant upfield shifts for their methylene geminal protons, a moderate upfield shift for H-4 and moderate downfield shifts for H-5. Other protons were also subjected to some shifts but their assignments were not attempted. The ^{13}C NMR spectrum demonstrated remarkable upfield shifts for C-6, small upfield shifts for C-5, and downfield shifts for C-4 of the modified sugar units. This chemical shift pattern is in good agreement with the replacement of the primary hydroxyl groups by alkyl thiols. These facts implied that compound **5** is an isomer of **3**. Since the *trans*-structure of **3** has been unambiguously determined by X-ray crystallographic characterization,[7] dimer **5** should have the *cis*-structure. The large R_f value supported the *cis*-structure in which the polar primary hydroxyl groups may be situated in the center of the molecule. Direct spectroscopic evidence for the *cis*-structure came from detailed NMR examination.†

The two dimers differ in bridging mode. The *cis*-dimer **5** has each sulfur atom bridging two different types of methylene groups while the *trans*-isomer **3** has each sulfur atom bridging two identical methylene groups. Therefore, the *cis*-isomer **5** is expected to display heteronuclear multiple bond correlation (HMBC)[9] between the two types of modified methylene groups but the

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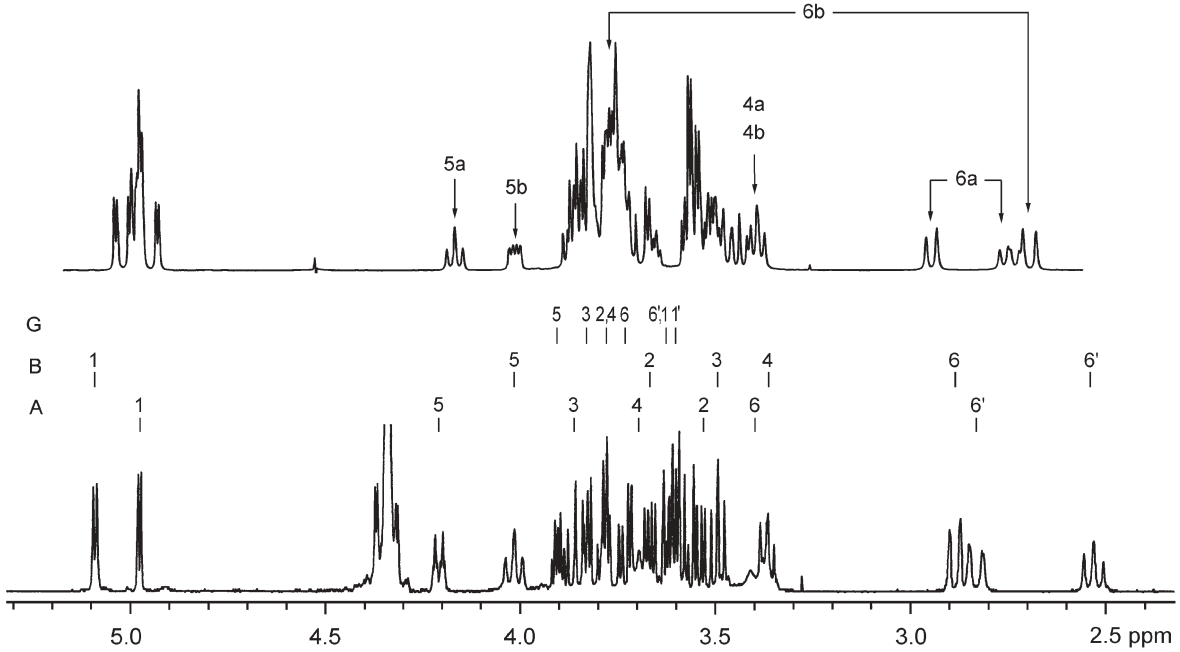


Fig. 1 ^{1}H NMR spectra of the CD dimer **5** (top) and compound **6** (bottom) in D_2O. Assignments were made based on 2D NMR experiments. The letters a and b in the top spectrum denote the different modified sugar units but do not reflect their sequence.

trans-isomer **3** should not. As shown in Fig. 2, cross-signals were clearly observed between the two types of modified methylene groups. This result strongly supports the *cis*-structure of dimer **5**.

In order to further confirm the structural assignment, a thorough spectroscopic characterization of the bridged part was attempted. Dimer **5** was first converted to compound **6** by enzymatic degradation followed by reduction with borohydride to eliminate the interference of unmodified glucoside units (Scheme 2). Only the S-bridge units remained in **6** together with two terminal glucitol residues (*m*/*z* = 1009 (M + H)). The NMR spectra of **6**, although still complicated, clearly displayed the C_2 symmetry. COSY experiments allowed the extraction of all the ^{1}H and ^{13}C signals related to each sugar unit. The sequence of the sugars linked by glycoside bonds was unambiguously determined by the strong HMBC correlations of H-1^{A}–C-4^{G}, H-4^{G}–C-1^{A} and H-4^{A}–C-1^{B}. Finally, the strong cross signals relating H-6^{A}–C-6^{B} and H-6^{B}–C-6^{A} correlations in HNBC spectra of **6** suggested the two triose chains be double-bridged by two unsymmetrical but identical 6^{A}-S-6^{B} linkers.

Based on the above observations, it can be safely concluded that dimer **5** has the *cis*-geometry. In principle, both dimers **3** and **5** are expected to form in the reaction. Although close attention was paid, dimer **3** was not found from the chromatography fractions. This strongly suggests that, in contrast to the cross-coupling of **1** and **2**, the reaction of 6^{A},6^{B}-ditosyl-β-CD and Na_2S greatly favors the formation of the *cis*-dimer. This selectivity is somewhat surprising since the *cis*-/*trans*- ratio was not expected to be far beyond a factor of 2, based on literature data[10] reported for relating compounds! The reaction process includes the *substitution* of one tosylate group of **4** by S^{2-} to generate two regioisomeric intermediates and the *coupling* of the latter (Scheme 3). Homo-coupling of both intermediates leads to the same *cis*-dimer while cross-coupling between the two intermediates results in the *trans*-dimer. Although some selectivity was recognized in the

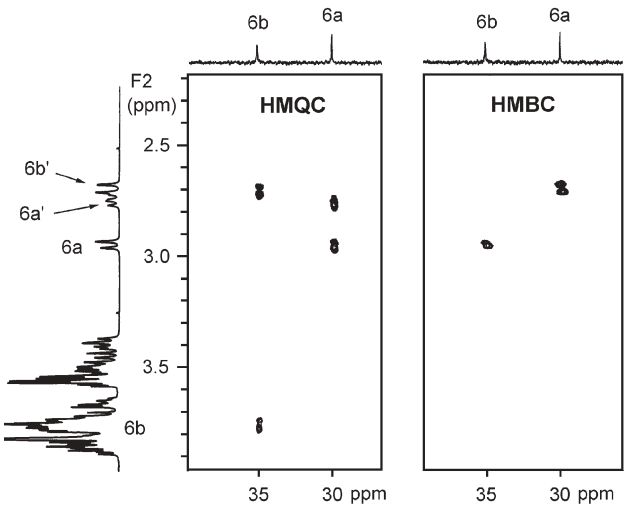
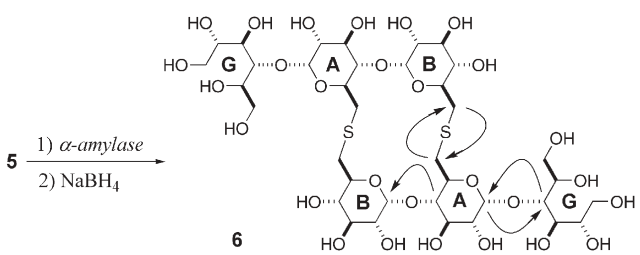
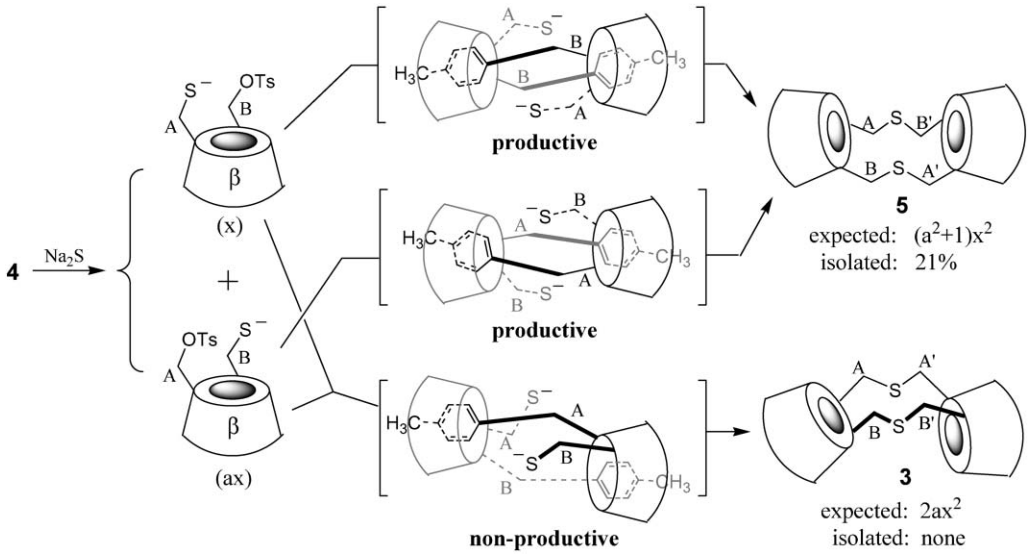


Fig. 2 ^{1}H–^{13}C HMQC and HMBC NMR spectra of the CD dimer **5** (only the modified methylene part is shown for clarity).



Scheme 2 Enzymatic degradation of dimer **5**. The arrays denote strong H → C correlations observed in the HMBC spectra.



Scheme 3 Host–guest interactions may induce topological preference in the syntheses of CD dimers. The letters x and ax refer to the yields of the two intermediates. Given both the substitution and coupling steps have the same yields and the couplings are simply governed by chance, the expected total yield of the dimers from the ditosylate **4** is calculated to be $(x + ax)^2 = x^2 + a^2x^2 + 2ax^2$ where the term $(x^2 + a^2x^2)$ corresponds to the homo-coupling while the term $2ax^2$ results from the cross-coupling.

substitution reactions of similar disubstituted CD derivatives,[10] the selectivity that might occur in the first step can hardly account for the general results of the reaction since even assuming a high 10-times preference for one regioisomer, the *trans*-dimer should amount to one fifth that of the *cis*-dimer and should be detectable. An inclusion complex formation of the intermediates prior to coupling may reasonably account for the exclusive formation of the *cis*-dimer. The two isomeric intermediates form one hetero- and two homo-dimeric complexes. The homo complexes locate the thiolate group of each CD near the tosylate group of the counterpart CD and reactions can readily occur to generate the *cis*-topology. The cross complexation, however, generates a *non-productive* complex in which the thiolate groups are situated far from the tosylate groups. Although no direct spectroscopic evidence has been gathered, such complex formation of the intermediates should reasonably occur since similar complex structure was observed in solutions of azobenzene-substituted α-CDs,[11] and CD derivatives bearing a hydrophobic substituent proved to aggregate to form dimers, oligomers or polymers, by insertion of the substituent into the cavity of another molecule.[12]

In conclusion, this paper describes that the reaction of $6^A,6^B$-di(*O*-tosyl)-β-CD and Na_2S produced the *cis*-dimer of β-CD with high selectivity. The topological preference of this reaction is deduced to originate from a weak intermolecular host–guest interaction of the intermediates.

Notes and references

† "*cis*-" or "*trans*-" is referred to the ring containing the two linkers.

^{13}C NMR data of **5** (D_2O, CH_3CN int.): δ 102.6, 102.3, 102.2, 100.1 (1a), 85.0 (4a, 4b), 82.0, 81.8, 81.6, 81.4, 79.5 (5b), 75.8, 74.2, 74.0, 73.9, 73.8, 73.7, 73.4, 73.1, 73.0, 72.9–72.6 (6 peaks), 72.5, 72.4, 61.4, 61.3, 61.2, 61.1, 61.0, 35.3 (6b), 30.0 ppm (6a).

Conversion of **5** to **6**: A mixture of **5** (60 mg) and α-amylase (EC 3.2.1.1 from *Aspergillus oryzae*, Sigma) (81 mg) in 0.2 M acetate buffer solution (6 mL, pH 5.6) containing 0.02 M $CaCl_2$ was kept for 6 d at 40 °C. After being heated for 10 min in a boiling water-bath, the mixture was membrane-filtered (cellulose acetate, 3.0 μm), diluted to 20 mL with water, and chromatographed on a reversed-phase column (Lobar Rp-18, size B, eluted with a gradient of 0–50% aq. CH_3OH). The obtained product and $NaBH_4$ (10 mg) were dissolved in water (10 mL) and stirred overnight at rt. Chromatography of the reaction mixture on a reversed-phase column (Lobar Rp-18, size B) and subsequently on Sephadex LH-20 afforded the pure compound **6** (13 mg, 48%). ^{13}C NMR (D_2O, CH_3CN int.): unit A: δ 99.5 (1), 70.8 (2), 72.0 (3), 72.2 (4), *ca.* 74.0 (5), 32.1 (6); unit B: 98.7 (1), 72.2 (2), 76.3 (3), 71.4 (4), 68.5 (5), 28.8 (6); unit G, 62.4 (1), 71.2 (2), 70.0 (3), 81.3 (4), 72.2 (5), 62.0 ppm (6).

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