The First Successful Crystallographic Characterization of a Cyclodextrin Dimer: Efficient Synthesis and Molecular Geometry of a Doubly Sulfur-Bridged β-Cyclodextrin**

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Abstract: β-Cyclodextrin is transannularly disulfonylated at the 6^A- and 6^B-positions, and then converted to the corresponding 6^A,6^B-diiodide and 6^A,6^B-dithiol. Cross-coupling of the latter two species yields a single head-to-head-coupled β-cyclodextrin dimer **5** with two sulfur linkers at adjacent 6-methylene carbons. NMR and X-ray analysis revealed the *trans*-type ("aversive") linkage of both β-cyclodextrin units. In the solid-state structure of **5**·5 MeOH·23 H_2O, the undistorted cyclodextrin macrocycles feature almost parallel ring planes pointing away from each other, leaving **5** with a "handcuff-like" appearance of approximate C_2 symmetry. This work represents the first successful crystallographic study on a cyclodextrin dimer.

Keywords: cross-coupling · cyclodextrins · molecular structure · sulfide-bridges · X-ray diffraction

Introduction

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 confined by their C_n symmetry and limitations in cavity size, shape, flexibility, and hydrophobicity. Bridging two or more CD units together provides a promising way to alter both the binding ability and guest selectivity. In the pioneering works, Tabushi synthesized a doubly bridged β-CD dimer with two ethylenediamine spacers,[2] and Fujita found that the two CD moieties of disulfide-bridged β-CD could cooperate in the binding of ethyl orange, yielding an association constant about 220 times that of β-CD.[3] Breslow et al. demonstrated that the same CD dimer selectively bound appropriate "ditopic guests" almost as strongly as antigen–antibody binding.[4] Large varieties of CD dimers have been synthesized in which two CD units are linked on either their primary or secondary face by single or double linkers ranging from single atoms to oligopeptide segments.[5] Heterodimers,[6] -trimers,[7] and -tetramers[8] have also been reported. The *cis* forms of doubly bridged CD dimers were found to bind appropriate guests with very high affinities and shape selectivities.[9] Nolte et al. demonstrated that, depending on the nature of linkers, CD dimers can bind tetrakis(sulfophenyl)porphyrin to form 1:1 *syn*-, *syn-/anti*-, and 2:2 (crossed double-zigzag-type) complexes.[10] CD dimers were found to have sequence-selective binding ability toward peptides and to disrupt protein aggregation.[11] Catalytic functionalities within the linker or on the rims of a dimer may result in strong catalysis. For example, the La^{III} complex of a bipyridyl-bridged β-CD dimer has been used to significantly enhance the hydrolysis of phosphodiesters,[12] thiazolio-appended CD dimers were used to promote benzoin condensation,[13] Se–Se-bridged CD dimers were used to effect glutathione peroxidase-like activity,[14] CD-sandwiched metalloporphyrin has been used to catalyze the epoxidation of alkene,[15] metalloporphyrin-based CD tetramers have been used to demonstrate site-specific oxidation of steroids,[16] and β-carotene[17] and, quite recently, EDTA–Ce^{IV}-bridged CD dimers have been used to amplify luminol chemiluminescence,[18] among many others.

Undoubtedly, three-dimensional structural information on the CD oligomers is very important for understanding the

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process of molecular recognition by CD dimers.[19] Unfortunately, we know surprisingly little about the spatial structures of CD oligomers in spite of the many efforts directed to their synthesis and properties. We do not even have enough knowledge to make a convincing judgment on the most fundamental aspects of the large host molecules: do the two or more CD cavities distort or not upon being bridged? How are they spatially arranged? In the following we report a highly efficient synthesis of a new β-CD dimer with two very short sulfur linkers and its unequivocal structural characterization through NMR analysis. Single-crystal X-ray-diffraction analysis was employed for the first time to obtain structural information on a CD dimer and it successfully afforded a clear image of the solid-state structure of the doubly sulfur-bridged β-CD dimer.

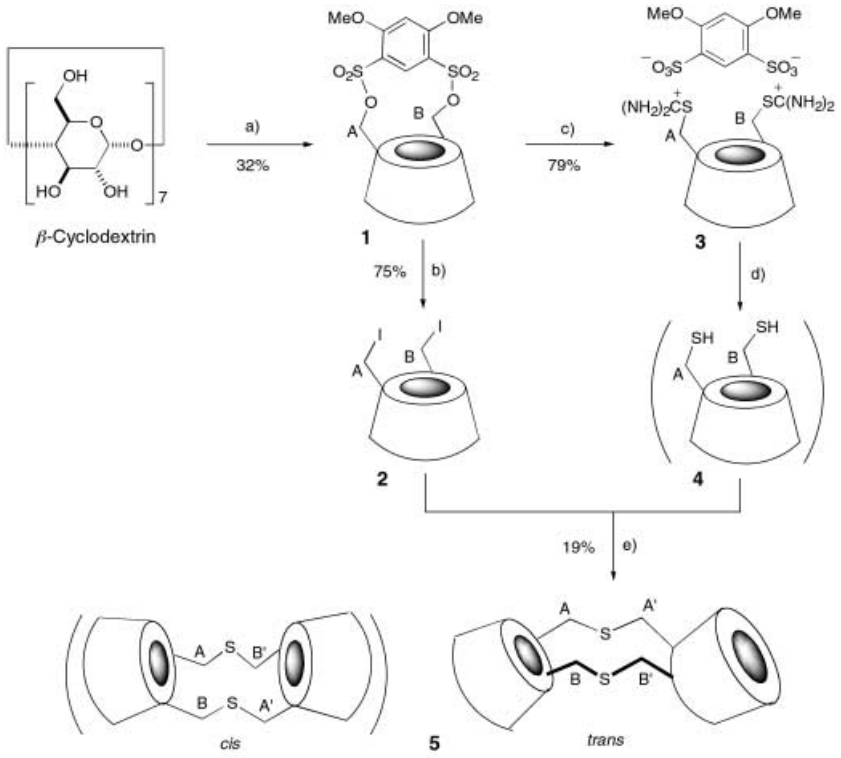
Results and Discussion

The synthetic approach to the doubly bridged CD dimer is depicted in Scheme 1. β-CD was selectively activated by employing the "looper's walk" method.[20] Treatment of β-CD with 4,6-dimethoxy-1,3-benzenedisulfonyl chloride in dry pyridine afforded the $6^A,6^B$-capped CD **1**,[21] whose yield is clearly dependent on the molar ratio of capping reagent to CD. Utilization of the capping reagent in 50% excess ensured a good yield of the capped product **1**, usually ranging from 30 to 40%. Compound **1** was converted to the corresponding $6^A,6^B$-diiodide **2** by stirring a mixture of **1** and KI in DMF at 80 °C. Treatment of **1** with thiourea in DMF gave the thiouronium salt **3** in 79% yield. This was treated with 0.25 N aqueous NaOH, and the generated $6^A,6^B$-dithiol **4** was collected by precipitation with acetone. The crude $6^A,6^B$ dithiol **4** was used in the following reaction without further purification. Reaction of the dithiol **4** and diiodide **2** was carried out in DMF in the presence of Cs_2CO_3 at room temperature and under an argon atmosphere. Reversed-phase chromatography of the reaction mixture afforded the doubly bridged β-CD dimer **5** in 19% yield. The FAB-MS spectrum showed the molecular peak $[M^+]$ at $m/z = 2266.1$, consistent with the expected structure of a doubly bridged β-CD dimer with two sulfur linkers (calcd $C_{84}H_{136}O_{66}S_2^+$: 2266.2).

In principal, two isomeric head-to-head β-CD dimers may be formed in the course of the cross-coupling reaction, with either a *cis*-type linkage across the glucose $6^A,6^{B'}$- and $6^B,6^{A'}$-positions, or alternatively a *trans* connection of the $6^A,6^{A'}$ and $6^B,6^{B'}$ type. Both isomers retain C_2 symmetry, yet differ substantially in their molecular shapes: the *cis* isomer is expected to adopt a compact, occlusive geometry ("clamshell"),[9] whereas the *trans* compound should be characterized by an extended, aversive appearance ("loveseat").[9] However, NMR spectra of the isolated product indicate the presence of only a single isomer, the alternative form was not recognized from the fractions of column chromatography.

Both the ^{1}H and ^{13}C NMR spectra of **5** (Figure 1) maintain the basic pattern of β-CD, the weaker signals shifted out from the normal ones are related to the modified sugar residues. Partial assignment of the spectra based on 2D COSY experiment reveals only two sorts of functional glucosides; this confirms the C_2 symmetry of the dimer. Both of them demonstrated significant upfield shifts for their methylene geminal protons (up to the range of 2.75 – 3.25 ppm), a moderate upfield shift for H-4 and small to moderate downfield shifts for H-5, but trivial shifts for H-1, H-2and H-3. 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. Apart from the modified units, no other glucosides showed meaningful shifts. These observations suggest that no apparent distortion should have occurred in the hydrophobic cavities of the doubly bridged CD dimer.

The assignment of the bridging mode (*cis*- or *trans*- with respect to the ring containing both linkers) of the dimer is attempted by using NMR tech-



Scheme 1. Synthesis of the doubly bridged β-CD dimer **5**. a) 1.5 equiv 4,6-dimethoxy-1,3-benzenedisulfonyl chloride, dry pyridine, 40 °C, 2.5 h. b) KI, DMF, 80 °C, 4.5 h. c) Thiourea, DMF, 90 °C, 20 h. d) 0.25 N aqueous NaOH, 90 °C, 10 min; $NaBH_4$, RT, 10 min. e) Cs_2CO_3, DMF, Ar gas, RT, 66 h.

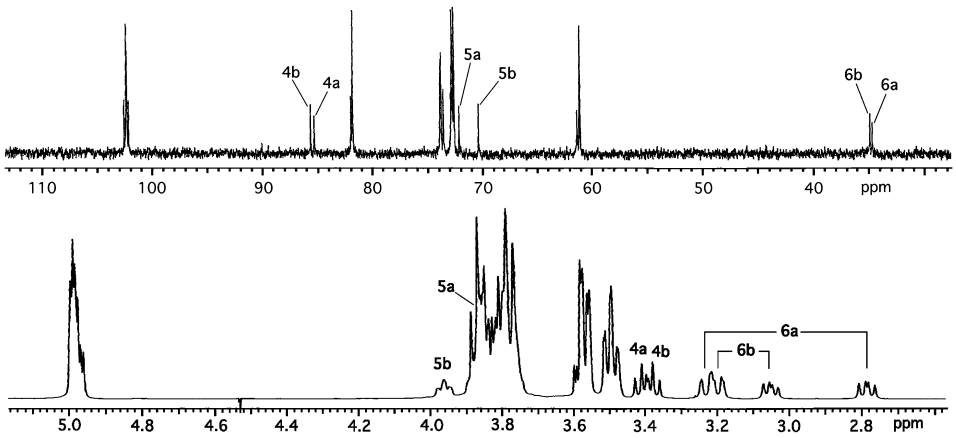


Figure 1. ^{1}H and ^{13}C NMR spectra of β-CD dimer **5** (D_2O, CH_3CN int.).

niques. In the *cis* structure, each sulfur atom bridges the "A" glucoside of one CD moiety and "B" glucoside of another, that is, the two sorts of modified sugar residues are correlated by one sulfur atom. This correlation is expected to be probed by the HMBC (heteronuclear multiple bond correlation) method.[22] In the *trans* isomer, each sulfur connects one pair of equivalent sugar residues, thus no HMBC signals are expected to appear between the two sorts of modified sugar residues. As shown in Figure 2, no cross-signals were observed between the two sorts of modified methylene groups; this suggests a *trans* structure for dimer **5**. This assignment is confirmed by the result of single-crystal X-ray diffraction.

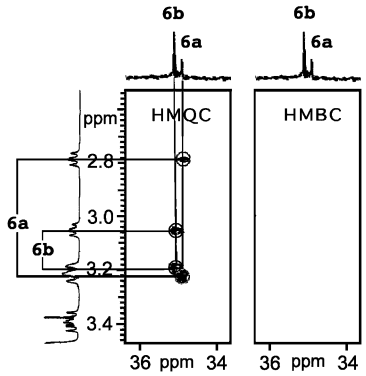


Figure 2. HMQC and HMBC spectra of **5** (only the modified methylene part is shown for clarity). No HMBC crossed islands appeared between 6a and 6b; this suggests a *trans*-structure for **5**.

Solid-state structure analysis of 5: Single crystals of **5** were obtained after chromatographic purification as described above. Low-temperature X-ray analysis revealed a crystal composition of $\mathbf{5}\cdot 5\,MeOH\cdot 23\,H_2O$, the molecular and crystal structures are displayed in Figure 3, unequivocally establishing the *trans*-type linkage of the β-CD moieties and the approximate C_2 symmetry of **5**. The β-CD dimers are packed in a herringbone-like fashion forming individual cavities that are blocked by adjacent CD rings and thus do not form tube-like channels. The β-CD cavities are partially filled with four and five water molecules of crystallization, the other water molecules and methanol fill interstitial positions between the macrocycles. All hydroxyl groups and oxygen atoms participate in the formation of a three-dimensional hydrogen-bonding network in the crystal lattice.

For the dimeric β-CD unit a few relevant geometry descriptors are listed in Table 1, a comprehensive list of atomic coordinates and all bond length and angles—all of which are within standard ranges for organic compounds—may be obtained from the data deposited with the Cambridge Crystallographic Data Centre (see Experimental Section). The molecular geometry of **5** is characterized by an almost coplanar alignment of the $C6^{A}$-S-$C6^{A'}$ and $C6^{B}$-S-$C6^{B'}$ fragments within the sulfur linkages, with the shape of an elongated planar hexagon. Within this linkage, the O6-C5-C6-S dihedral angles invariably adopt (−)-*gauche* arrangements, yet the calculated values for the C5-C6-S-C6′ torsion angles differ significantly at both positions (approx. 75° and −130°, cf. Table 1).

Table 1. Selected geometry parameters for the dimeric β-CD unit as calculated from the solid-structure of $\mathbf{5}\cdot 5\,MeOH\cdot 23\,H_2O$.

Linkage		A–A′	B–B′
torsion angles [°]	O5-C5-C6-S	−45.7	−68.9
	C5-C6-S-C6′	−128.1	75.5
	C6-S-C6′-C5′	−133.6	76.1
	S-C6′-C5′-O5′	−44.5	−67.2
CD unit		I	II
tilt angle[a]	τ [°]	103 ± 8	104 ± 9
ring diameter[b]	r [Å]	9.86 ± 0.26	9.85 ± 0.47
ring puckering[c]	d [Å]	0.12 ± 0.06	0.06 ± 0.03
inclination[d]	[°]	2.9	2.9

[a] Angle between the least-squares best-fit mean plane of the macrocycle (defined by all intersaccharidic O4 atoms) and the mean plane of the pyranose rings (atoms O5 and C1–C5); values of $\tau > 90°$ indicate outward tilting of the C2 and C3 side of the glucoses; parameter averaged over all glucose residues. [b] Average O4–O4‴ separations within the CD macrocycles. [c] Average deviation of all O4–atoms of the CD macrocycles from planarity. [d] Angle between the least-squares best-fit mean ring planes (all O4 atoms) of both linked β-CD units.

Both linked β-CD-rings feature almost parallel mean ring planes with a relative inclination of only 2.9°; the centers of the two cavities being 13.6 Å apart. The geometries of the β-CD units are within the usual ranges observed for these compounds and their complexes[24, 25] (tilt angles τ[25] of the glucose residues in relation to the macroring of approx. 105°, ring diameters of about 9.9 Å). As evidenced by their Cremer–Pople parameters[26] Q, Θ, and ϕ, all glucose units adopt standard $^{4}C_1$ chair conformations ($Q \approx 0.563 \pm 0.018$ Å, $\Theta \approx 4 \pm 2°$, ϕ is not significant). Out of the total of ten 6-CH_2OH groups six adopt *gauche–trans* (*gt*) arrangements with O5-C5-C6-O6-torsion angles of $\omega \approx +60°$, the remaining four are in *gauche–gauche* (*gg*) orientations ($\omega \approx -60°$) and

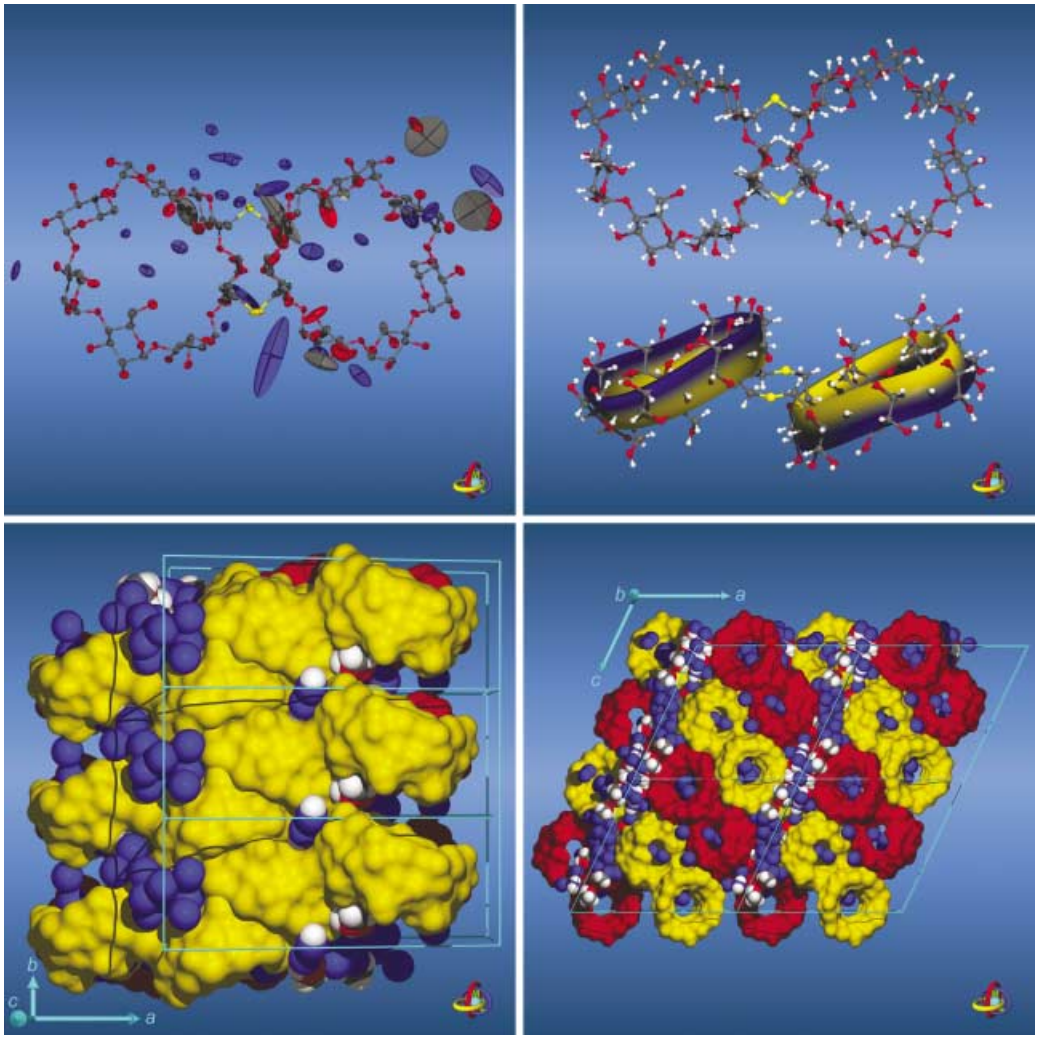


Figure 3. Solid-state structure of **5**·5 MeOH·23 H_2O. Top left: Molecular geometry and anisotropic 50% probability ellipsoids for the non-hydrogen atoms of the asymmetric unit; for clarity the water oxygen atoms are colored blue. Top right: Front- and side-view ball-and-stick-type models displaying the sulfur linker between the two β-CD units. The ribbon model (the black edge of which corresponds to the side of the CDs carrying the secondary 2- and 3-OH groups, while the yellow rim corresponds to the primary 6-CH_2OH groups) clearly shows the *trans*-relationship between both CD rings. Bottom left: As represented by their yellow contact-surfaces,[23] the β-CD-dimers are stacked in the crystal lattice in a herringbone-like fashion (1·3·1 unit cells, viewed down the *c*-axis). Bottom right: The stacks of CDs are arranged in layers as indicated by alternating red and yellow surfaces (2·1·2 unit cells, view down the *b*-axis); each β-CD cavity is occupied by four or five water molecules, the rest of the waters of crystallization and the methanol molecules occupy interstitial positions between the macrocycles; water molecules (blue spheres) and methanol are represented as CPK-type solid spheres.

no disorder was observed. The linked CD macrocycles feature almost identical over-all shapes, their backbones being superimposable with an average deviation of only 0.22 Å in their atomic positions (non-hydrogen atoms except for all O6 atoms).

Conclusion

A short and efficient synthesis of a new β-CD dimer has been presented, in which two β-CD units are connected in a head-to-head fashion with a very short sulfur linker. Of the two isomers expected to emerge from the cross-coupling reaction, only the *trans*-type compound was isolated while the *cis*-type compound was not detected. X-ray analysis unequivocally established the *trans*-type linkage of the CD moieties of **5** in a zigzag shape. The molecular geometry of **5** is characterized by an almost parallel arrangement of the mean ring planes of the two undistorted CD rings fused together through an elongated planar hexagon consisting of the $C6^{A}$-S-$C6^{A'}$ and $C6^{B}$-S-$C6^{B'}$ fragments within the sulfur linkages. The *trans* dimer opens up the possibility of specifically forming inclusion complexes with potential guest molecules of 1:2 stoichiometry. Moreover, the rather rigid linkage and the "handcuff-like" shape of the dimeric host molecule with two separated cavities may allow included guest molecules and their long-range interactions at well-defined distances to be studied.

Experimental Section

General: β-CD was obtained from the Japan Maize Products Co. Ltd. and used without further purification. 4,6-Dimethoxy-1,3-benzenedisulfonyl chloride was synthesized by chlorosulfonation of 1,3-dimethoxybenzene.[27]

Pyridine and DMF were dried over 4 Å molecular sieves. Other solvents and chemicals were of reagent grade and used as received from commercial sources. Reversed-phase column chromatography was performed on a Merck prepacked Lobar column (LiChroprep® RP-18, Size B or C). NMR spectra were recorded on a Varian Unity plus 500 spectrometer, and D_2O was used as solvent. Chemical shifts were referenced to acetonitrile (internal standard, $\delta_H = 1.98$ ppm, $\delta_C = 1.70$ ppm). FAB-MS spectra were recorded on a JEOL JMS-HX110 spectrometer.

$6^A,6^B$-(4,6-dimethoxy-1,3-benzenedisulfonyl)-β-cyclodextrin (1): 4,6-Dimethoxy-1,3-benzenedisulfonyl chloride (2.50 g, 9.23 mmol) was added to a solution of β-CD (6.33 g, 5.58 mmol) in dry pyridine (500 mL). The mixture was stirred at 40 °C for 2.5 h. After the reaction had been quenched by adding water (5 mL), the solvent was removed in vacuo. The residue was taken into 10% aqueous MeOH solution (1 L) and filtered, and the filtrate was then subjected to reversed-phase Lobar column chromatography with gradient elution from 10–40% aqueous methanol (1 L for each). The 20 mL fractions containing the capped CD were combined and evaporated. Lyophilization of the residue afforded the desired product **1** (2.52 g, 32%).

$6^A,6^{A'}$:$6^B,6^{B'}$-bis(thia)-bis($6^A,6^B$-dideoxy-β-cyclodextrin) (5): KI (3.90 g, 23.5 mmol) was added to a solution of the capped CD **1** (3.19 g, 2.29 mmol) in dry DMF, and the resultant mixture was stirred at 80 °C for 4.5 h. After removal of the solvent in vacuo, the residue was taken into 35% aqueous MeOH solution and filtered. Chromatography of the filtrate on a reversed-phase Lobar column with gradient elution from 10–40% aqueous methanol (1 L for each) gave $6^A,6^B$-diiodo-β-CD **2** (2.31 g, 75%).

Alternatively, the capped CD **1** (0.5 g, 0.36 mmol) was treated with thiourea (0.55 g, 7.2 mmol) in DMF at 90 °C for 20 h. The product was precipitated with acetone (0.2 L) and purified by Lobar column chromatography. Eluting the column with a gradient from 100% H_2O–10% aqueous MeOH (1 L for each) yielded the $6^A,6^B$-dithiouronium salt **3** (0.44 g, 79%). This (0.15 g, 0.10 mmol) was dissolved in aqueous NaOH solution (0.25 N, 2.5 mL) and stirred at 90 °C for 10 min. The solution was cooled down to RT, and $NaBH_4$ (25 mg, 0.66 mmol) was added. Ten minutes later, the reaction solution was acidified to pH 3 with 1 N HCl while being cooled with ice-water bath, then acetone (300 mL) was added to precipitate the dithiol **4**. The crude dithiol **4** was dried in vacuo, taken into DMF (6 mL), and filtered. Diiodide **2** (0.15 g, 0.11 mmol) and cesium carbonate (0.13 g, 0.4 mmol) were added to the filtrate. The mixture was degassed, stirred at RT for 66 h under argon, neutralized with 1 N HCl followed by addition of acetone (300 mL) to precipitate the CD species. Chromatography of the precipitate on a reversed-phase Lobar column (gradient elution from 100% H_2O to 40% aqueous MeOH, 1 L for each) gave the pure CD dimer **5** (41 mg, 19% based on engaged dithiouronium salt **3** or 16% based on the capped CD **1**). FAB-MS: *m/z*: 2266.1 [M^+] (calcd 2266.2 for $C_{84}H_{136}O_{66}S_2^+$). ^1H and ^{13}C NMR are given in Figure 1. Cooling the NMR sample solution (30 mg in 0.6 mL D_2O, CH_3CN as internal standard) to 5 °C yielded single crystals suitable for X-ray diffraction.

Solid-state structure of $5\cdot 5MeOH\cdot 23H_2O$: A suitable single crystal of **5** with dimensions $0.52\times 0.24\times 0.16$ mm was sealed in a tube and subjected to X-ray analysis on a Siemens CCD three-circle diffractometer with graphite-monochromated radiation $Mo_{K\alpha}$ ($\lambda = 0.71073$ Å) at low temperature $T = 100(2)$ K. The electron density of the solvent in the crystal lattice was approximated through molecules of water and methanol. Analysis of the structure and the hydrogen-bonding network in the crystal lattice yielded 23 additional water molecules and five molecules of methanol (presumably from chromatographic purification) per dimeric β-CD unit. Structure parameters were determined as follows: $M_r = 2840.61\ g\,mol^{-1}$ ($C_{84}H_{136}O_{66}S_2\cdot 5CH_3OH\cdot 23H_2O$), monoclinic, space group $C2$, $a = 35.557(2)$, $b = 12.3387(5)$, $c = 31.543(2)$ Å, $\beta = 115.272(4)$, $V = 12514.3(12)$ Å^3, $Z = 4$, $\rho = 1.508\ g\,cm^{-1}$, $\mu(Mo_{K\alpha}) = 0.167\ mm^{-1}$, $F(000) = 5888$, Θ range 0.71–25.31°, with limiting indices $-42 \le h \le 42$, $-14 \le k \le 14$, and $-37 \le l \le 37$. Of the 72505 reflections collected 22474 were independent ($R_{int} = 0.0740$). The structure was solved by direct methods (SHELXS-97)[28] and successive Fourier synthesis. Refinement (on F^2) was performed by the full-matrix least-squares method with SHELXL-97.[28] $R(F) = 0.0823$ for 18524 reflections with $I > 2\sigma(I)$, $\omega R(F^2) = 0.2382$ for all 22474 reflections ($\omega = 1/[\sigma^2(F_o^2) + (0.1670P)^2 + 23.4030P)]$; in which $P = (F_o^2 + 2F_c^2)/3$). All non-hydrogen atoms (except for one methanol oxygen atom) were refined anisotropically (reflections 22474/parameters 1663/restraints 6). Hydrogen atoms were considered in calculated positions with the $1.2\,U_{eq}$ value of the corresponding bound atom.

CCDC-190090 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

Molecular graphics were generated by using the *MolArch*$^+$ program.[30]

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