Tubular duplex α-cyclodextrin triply bridged with disulfide bonds: synthesis, crystal structure and inclusion complexes†

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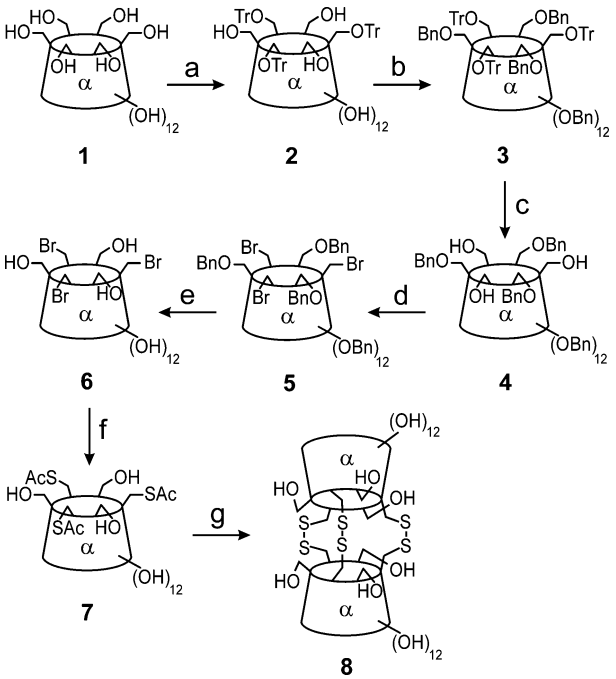
Received (in Cambridge, UK) 10th March 2009, Accepted 20th April 2009
First published as an Advance Article on the web 7th May 2009
DOI: 10.1039/b904933a

Template-free oxidative dimerization of 6^{I}, 6^{III}, 6^{V}-trisulfanyl-α-cyclodextrin proceeds with a remarkable efficiency (≥ 94%) yielding an unprecedented duplex α-cyclodextrin triply bridged with disulfide linkages whose structure has been confirmed by X-ray analysis.

Tubular architecture in the molecular world has always tempted researchers across various scientific fields from biology to chemistry to physics. Aside from the prominent class of carbon nanotubes,[1] the design and synthesis of their organic analogues[2–4] gave rise to a broad range of nanotubular structures endowed with desirable properties. Most organic nanotubes have been prepared by supramolecular self-assembly of smaller components in solution or solid state. Covalent bonding of building blocks constituting the tubular structure has been much less explored,[5–8] most likely due to difficulties associated with the control over the irreversible distribution of kinetically stable (by)products.

Relatively rigid cyclodextrin macrocycles are potentially useful components for the covalent synthesis of nanotubular structures, the template-directed statistical crosslinking of α-cyclodextrins being the most prominent example.[8] We have recently reported the synthesis of a chemically homogeneous α-cyclodextrin dimer consisting of a pair of α-cyclodextrin macrocycles covalently linked with *two* disulfide bonds at their primary rims.[9] The apparently smooth course of dimerization, easily controllable by the concentration of the starting material, suggested that disulfide bonds are nearly ideal linking groups for this purpose. In this communication, we describe an unprecedented template-free dimerization of trifunctionalized α-cyclodextrin derivative leading to a duplex α-cyclodextrin connected with *three* symmetrically placed disulfide bonds. The synthetic study is corroborated with an X-ray analysis and preliminary physico-chemical studies of the product.

The synthesis (Scheme 1; for more details see ESI†) commenced with a selective protection of three primary hydroxylic groups at $C6^{I}$, $C6^{III}$ and $C6^{V}$ positions of α-cyclodextrin with bulky trityl groups.[10] Benzylation of the remaining hydroxylic groups of trityl derivative **2** gave rise to compound **3**, this was followed by the removal of trityl groups with trifluoroacetic acid to furnish triol **4**. Subsequently, the remaining free primary hydroxylic groups were transformed into bromides and the protecting benzyl groups of the corresponding tribromide **5** were removed by hydrogenation using palladium on charcoal as a catalyst in a mixture of DMF and ethanol. Reaction of tribromide **6** with potassium thioacetate in DMF at room temperature gave rise to the acetylated trisulfanyl derivative **7**. Dimerization *via* oxidation of thiol groups could be carried out conveniently under aerobic conditions using the derivative **7**, the protecting acetyl groups being cleaved *in situ*. Thus, a 9 mM solution of compound **7** in 1 M aqueous ammonia was allowed to react in the presence of air oxygen for 24 hours. Subsequent analysis of the reaction mixture by NMR and ESI-MS revealed the *formation of a sole product* whose structure was attributed to the dimer **8**. No by-products such as intramolecular disulfides or larger cyclic and linear oligomers were observed in the reaction mixture. Simple work-up by evaporation of the solvent and removal of traces of ammonia with ion-exchanger allowed the isolation of the dimer **8** in a 94% preparative yield.



Scheme 1 Synthesis of α-cyclodextrin duplex **8**; (a) TrCl, pyridine, 75 °C, 18 h, 20%; (b) BnCl, NaH, DMSO, rt, 4 h, 95%; (c) TFA, MeOH, CH_2Cl_2, rt, 4 h, 90%; (d) CBr_4, PPh_3, DMF, 60 °C, 18 h, 92%; (e) H_2, 40 bar, Pd/C, DMF–EtOH, rt, 4 h, 91%; (f) CH_3COSK, DMF, rt, 18 h, 92%; (g) 1 M NH_4OH, O_2, rt, 24 h, 94%.

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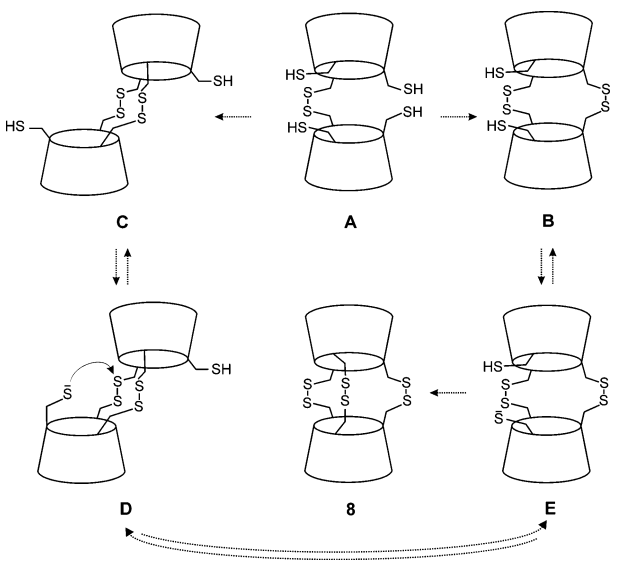
† Electronic supplementary information (ESI) available: Synthetic procedures, tables of ^{1}H and ^{13}C NMR chemical shifts, ^{1}H and ^{13}C NMR spectra, details of the determination of association constants of inclusion complexes by ITC including selected thermograms, and X-ray experimental data. CCDC 723533. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b904933a

Taking into account the low yields usually encountered[5–7,11,12] in analogous dimerization reactions, the quantitative formation of the duplex **8** is remarkable. Tentatively, it can be ascribed to the dynamic nature of the disulfide bond;[13] the oxidative dimerization reaction is envisaged to proceed *via* singly bridged intermediate **A** (Scheme 2) which can provide, upon further oxidation, two stereoisomers **B** and **C** designated, using Breslow's terminology,[11] as occlusive and aversive, respectively. Whilst stereoisomer **B** is a direct precursor of the duplex **8**, the aversive isomer **C** cannot close the last disulfide bond in an intramolecular manner and would be a precursor of further oligomerization (not observed at the investigated concentration). Since molecular modeling suggests that both putative isomers **B** and **C** can be formed without significant strain and should be thus abundantly present in the reaction mixture, it is plausible that the aversive isomer **C**—after deprotonation to **D**—undergoes intramolecular thiol–disulfide exchange producing the "correct" stereoisomer **E**, which is subsequently oxidized to the desired duplex **8**. An analogous mechanism may also be operative to reform oligomeric species which might arise.

The structure of the duplex **8** was unequivocally confirmed by X-ray analysis of its single crystal (Fig. 1) grown by diffusion of acetone vapors into the aqueous solution of **8**.‡ The analysis reveals that all glucose units are in normal $^4C_1$ chair conformation and no significant departures from the usual glucosyl torsion angles[14] φ and ψ are observed (mean values $\varphi = 108.0 \pm 6.2^\circ$; $\psi = 130.5 \pm 7.0^\circ$). Dihedral angles of the disulfide bonds span from 81° to 90° suggesting a near-optimal conformation. The geometry analysis reveals that neither the cyclodextrin macrocyles nor the disulfide bonds undergo significant distortion upon dimerization accounting for the presumed high thermodynamic stability of the duplex **8**.

The length of the tube expressed as the mean internuclear distance between the most proximal oxygen atoms of the hydroxylic groups located at the opposite peripheries of the duplex (regardless of their assignment to particular glucose units) amounts to 13.3 Å. The minimal inner diameter of the tube defined as the minimal internuclear distance between opposite sulfur atoms is 4.3 Å. In the crystal lattice, the duplexes are packed in a colinear fashion along the crystallographic *c*-axis forming channels partially filled with water molecules.



Scheme 2 Proposed conversion pathways of stereoisomeric intermediates to duplex.

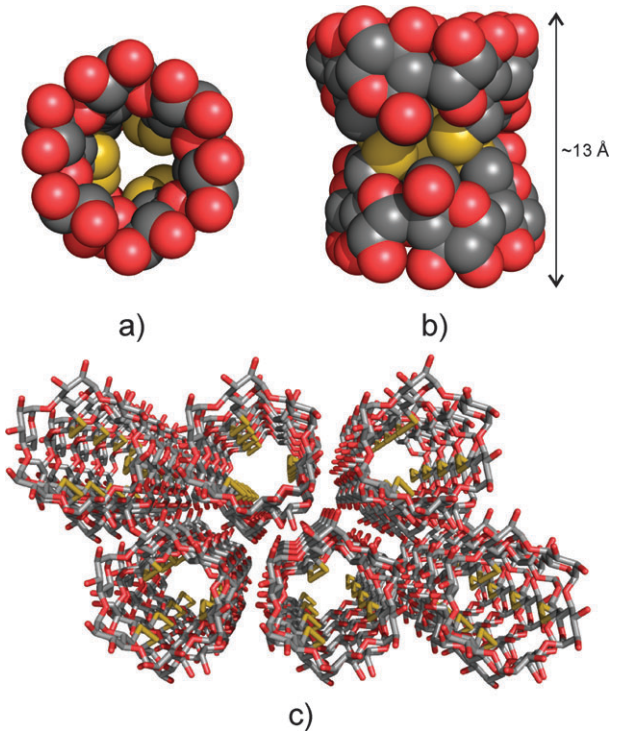


Fig. 1 Crystal structure of the α-cyclodextrin duplex **8**; (a) top-down and (b) side views of space-filling representation; (c) packing along *c*-axis. Hydrogens have been omitted for clarity. Solvent molecules have been removed with PLATON/SQUEEZE program.[18] Color code: dark grey: C, red: O, yellow: S.

In the crystal structure, all three disulfide bonds of **8** are oriented in a right-handed screw sense indicating a chirality transfer from the cyclodextrin macrocycle. Chirality of the disulfide bonds in duplex **8** is also observed in its aqueous solution as evidenced by CD spectrum (Fig. 2) displaying two bands with maxima at 222 and 269 nm, respectively, attributed to disulfide chromophores.

Native cyclodextrins are known to form inclusion complexes with shape-compatible organic molecules in aqueous solutions.[15] Duplex **8**, being well-soluble in water (up to 10^{-2} M), can be expected to be a good host for long aliphatic alkyl chains. Thus, the ability of duplex **8** to form complexes with α,ω-alkanediols (C_{11}–C_{13}) and 1-undecanol as model compounds was studied by isothermal titration calorimetry in aqueous solutions. Binding constants (Table 1) increase with the length of the alkyl chain from 4.9×10^5 M^{-1} for 1,11-undecanediol to 2.1×10^7 M^{-1} for 1,13-tridecanediol. 1-Undecanol binds to the dimer **8** with higher propensity ($K_a = 3 \times 10^6$ M^{-1}) compared to the corresponding 1,11-undecanediol. The binding constants of complexes of α,ω-alkanediols and **8** are about 2–4 orders of magnitude higher as compared to complexes of native α-cyclodextrin[15] and comparable to those of the doubly bridged duplex.[9]

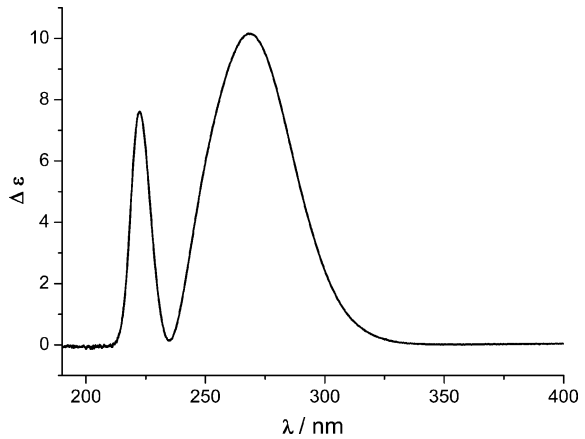


Fig. 2 CD spectrum of duplex **8** recorded in aqueous solution at 1.5 mM concentration. Values of $\Delta\varepsilon$ have been normalized to one disulfide bond.

Table 1 Thermodynamic parameters of the complex formation of **8** with α,ω-alkanediols and 1-undecanol as determined by ITC in aqueous solutions[a]

Guest	K/M^{-1}	ΔH°/kcal mol^{-1}	$T\Delta S^\circ$/ kcal mol^{-1}
$OH(CH_2)_{11}OH$	$(4.88 \pm 0.09) \times 10^5$	-13.5 ± 0.2	-5.7 ± 0.2
$OH(CH_2)_{12}OH$	$(6.13 \pm 0.14) \times 10^6$	-15.2 ± 0.2	-6.0 ± 0.2
$OH(CH_2)_{13}OH$	$(2.08 \pm 0.05) \times 10^7$	-15.4 ± 0.2	-5.4 ± 0.2
$CH_3(CH_2)_{10}OH$	$(2.99 \pm 0.11) \times 10^6$	-13.7 ± 0.2	-4.9 ± 0.2

[a] All titrations were carried out at 298.15 K using ten injections. Each titration was repeated three times and the raw data were averaged prior to the fitting procedure.[9] Experimental details including selected thermograms can be found in ESI†.

In conclusion, we have prepared a duplex α-cyclodextrin composed of two parent α-cyclodextrin macrocycles triply connected with disulfide bonds. The demonstrated high efficiency of the template-free dimerization step ($\geq 94\%$) is presumed to be the consequence of the dynamic nature of the disulfide bond allowing the convergence of all competing intermediates into the duplex **8**, and calling for a much broader exploitation in the design of organic nanotubes. The tubular species described herein is distinguished by chemical homogeneity, precisely defined length, rigid structure and, in contrast to other[5–7,9,12] covalently bonded tubular molecules constructed from macrocyclic building blocks, very small voids in its walls. The long cavity of the duplex **8** allows the inclusion of alkyl chains with high binding constants (up to 2.1×10^7 M^{-1} for 1,13-tridecanediol) and may thus find applications in supramolecular self-assembly of rotaxanes, catenanes[16] and other mechanical devices. Moreover, the unique capability of disulfide bonds to be cleaved by reducing thiols might open access to an external stimuli-controlled release of the included guest, as demonstrated very recently in β-cyclodextrin disulfide-cross-linked polymeric nanocapsules.[17]

The authors thank Lucie Bednárová for measurements of CD spectra. Financial support from the Institute (Z40550506) and grant agencies (GA AVČR, IAA400550810; GA ČR, 203/06/1550; MŠMT OC172 and 0021620857) is greatly acknowledged.

Notes and references

‡ *Crystal data for dimer* **8**: $C_{72}H_{114}O_{54}S_6{\cdot}(C_3H_6O){\cdot}11(H_2O)$; $M_r = 2292.25$; $\rho_{calcd} = 1.462$ g cm^{-3}; crystal dimensions $0.4 \times 0.3 \times 0.1$ mm; triclinic, $P\bar{1}$ (no. 1); $a = 13.7086(2)$ Å, $b = 13.7560(2)$ Å, $c = 16.0247(2)$ Å; $\alpha = 81.3890(10)^\circ$, $\beta = 81.6130(10)^\circ$, $\gamma = 61.0206(7)^\circ$; $V = 2604.30(6)$ Å^3; $Z = 1$, $T = 150$ K, 73 040 reflections collected, 20 107 unique ($R_{int} = 0.044$). $R = 0.056$, w$R(F^2) = 0.157$; PLATON/SQUEEZE[18] tool was used to correct the data of **8** for the presence of the disordered solvent molecules. More details can be found in ESI†.

1 *Carbon Nanotubes*, ed. A. Jorio, G. Dresselhaus, M. S. Dresselhaus, Springer, Berlin, Heidelberg, 2008.
2 D. T. Bong, T. D. Clark, J. R. Granja and M. R. Ghadiri, *Angew. Chem., Int. Ed.*, 2001, **40**, 988.
3 D. Pasini and M. Ricci, *Curr. Org. Synth.*, 2007, **4**, 59–80.
4 N. Sakai, J. Mareda and S. Matile, *Acc. Chem. Res.*, 2005, **38**, 79.
5 A. Ikeda and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 1994, 2375.
6 (*a*) G. V. Zyryanov and D. M. Rudkevich, *J. Am. Chem. Soc.*, 2004, **126**, 4264; (*b*) V. G. Organo, A. V. Leontiev, V. Sgarlata, H. V. R. Dias and D. M. Rudkevich, *Angew. Chem., Int. Ed.*, 2005, **44**, 3043.
7 T. Gottschalk, B. Jaun and F. Diederich, *Angew. Chem., Int. Ed.*, 2007, **46**, 260.
8 A. Harada, J. Li and M. Kamachi, *Nature*, 1993, **364**, 516.
9 L. Kumprecht, M. Buděšínský, J. Vondrášek, J. Vymětal, J. Černý, I. Císařová, J. Brynda, V. Herzig, P. Koutník, J. Závada and T. Kraus, *J. Org. Chem.*, 2009, **74**, 1082.
10 C. C. Ling, A. W. Coleman and M. Miocque, *Carbohydr. Res.*, 1992, **223**, 287.
11 R. Breslow and S. Chung, *J. Am. Chem. Soc.*, 1990, **112**, 9659.
12 D. Q. Yuan, K. Koga, I. Kouno, T. Fujioka, M. Fukudome and K. Fujita, *Chem. Commun.*, 2007, 828.
13 P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J. L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652.
14 W. Saenger, J. Jacob, K. Gessler, T. Steiner, D. Hoffmann, H. Sanbe, K. Koizumi, S. M. Smith and T. Takaha, *Chem. Rev.*, 1998, **98**, 1787.
15 M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875.
16 G. Wenz, B. H. Han and A. Muller, *Chem. Rev.*, 2006, **106**, 782.
17 L. C. Jones, W. M. Lackowski, Y. Vasilyeva, K. Wilson and V. Chechik, *Chem. Commun.*, 2009, 1377.
18 A. L. Spek, *PLATON—A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands, 2008.