Per-2,3-O-alkylated β-cyclodextrin duplexes connected with disulfide bonds

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ABSTRACT

Per-2,3-di-O-methyl- and per-2,3-di-O-allyl-β-cyclodextrin duplexes held by two disulfide bonds between their primary faces have been prepared. Permethylation significantly increased the solubility of the cyclodextrin duplexes in a wide range of solvents from water to chlorinated hydrocarbons. Per-2,3-di-O-methylated duplexes are able to form inclusion complexes with organic molecules in aqueous solutions, yet the stability constants are lower by 4–5 orders of magnitude as compared to analogous non-alkylated β-cyclodextrin duplexes.

KEYWORDS

cyclodextrins; inclusion complexes; disulfide bonds

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Introduction

Complexation of molecules and ions, both organic and inorganic, by receptors with high affinity and selectivity in aqueous environment plays a key role in various biological processes. Chemists gave rise to a broad range of synthetic analogues that were designed to mimic these processes. Within macrocyclic receptors operating in aqueous media, cyclodextrins (CDs) play important role due to their abilities to form host–guest complexes with a wide range of organic molecules, yet the stabilities of such complexes are relatively low compared to those found in nature (1).

We have recently reported host molecules consisting of two cyclodextrin macrocycles connected with two or three disulfide bonds in a head-to-head manner (2–5). These macrocyclic tubular receptors, coined cyclodextrin duplexes, possess significantly enlarged cavities (300–740 Å³) as compared to native CDs and are capable of formation of inclusion complexes with a wide range of organic molecules in aqueous media with high binding affinities ($K_a \sim 10^5–10^9$ M⁻¹). We intended to further explore this concept by modification of the peripheries of the duplexes in order to (i) improve their solubilities in aqueous solutions and to (ii) further modulate their binding properties, selectivities in particular, by specific interactions of the peripheral substituents with guest compounds. We presumed that permethylation of all secondary hydroxyls at both peripheries of the duplexes could lead to much higher solubility as deduced from the known effect of permethylation of native CDs (6). Furthermore, we intended to introduce suitable reactive moieties, such as allyl groups, that could be later converted to various functional groups such as carboxyls or amines and, in this way, increase binding affinities and selectivities by electrostatic interactions (7).

In this paper, we report synthetic methodology allowing preparation of β-CD duplexes permethylated and perallylated at secondary hydroxyls and a preliminary assessment of the binding properties of the former.
Results and discussion

Synthesis

Due to the relative lability of disulfide bonds we presumed that modifications of the peripheral hydroxyl groups should be done prior to dimerisation. The strategy to synthesise the target peralkylated duplexes requires that primary hydroxyl groups be selectively protected first, leaving the secondary hydroxyls free for subsequent alkylation, with protective groups that are amenable to selective cleavage at O6' and O6'' positions. We used recently described procedure for the chemoselective desilylation at O6' and O6'' positions of per[(2,3-di-O-alkyl-6-tert-butyldimethylsilyl)-β-cyclodextrin (8). Thus, the synthesis started with the introduction of tert-butyldimethylsilyl (TBDMs) protective groups on the primary rim of β-CD, followed by methylation at the secondary rim (9, 10). Then, the cleavage with DIBAL-H afforded diol 3. Conversion of the free hydroxyl groups of compound 3 into mesyl group using methanesulfonyl chloride and triethylamine in dry dichloromethane allowed the isolation of the corresponding dimesylated compound 5 in 81% yield. Next, compound 5 was reacted with potassium thioacetate to give the protected disulfanyl derivative 7 in 90% yield. The five remaining TBDMS groups were then removed by the treatment with BF₃·Et₂O in dry DCM to provide disulfanyl derivative 9 (64%) which was hydrolysed by sodium hydroxide solution under argon atmosphere to give the key disulfanyl derivative 11 (82%). Analogous procedure was used to prepare per[(2,3-di-O-allyl)-β-CD derivatives 6, 8, 10 and 12; reversing the order of thiolation–desilylation reactions (c and d, Scheme 1) in the course of preparation of perallylated products allowed somewhat higher yield in the desilylation (c) step.

Next we performed a series of air-promoted oxidations of the disulfanyl derivative 11. We found that the distribution of resulting monomeric and dimeric species is highly influenced by the reaction conditions – the solvent system in particular. First we applied conditions that were similar to our recently published reports on non-alkylated cyclodextrin duplexes (2, 4, 5). Air oxidation of the disulfanyl derivative 11 was performed at 1 and 10 mM concentrations of compound 11 in the mixture of ethanol/H₂O (1:1) using ammonium bicarbonate buffer at pH 9. The reaction vessels were sealed with rubber septa that were punctured with needles to allow slow diffusion of air oxygen. The reactions were completed within five days as revealed by monitoring with TLC and by MALDI-MS analysis. In both cases the analysis revealed formation of intramolecular disulfide 13 as the major product that was accompanied with trace amounts of dimeric products. Moreover, at 10 mM concentration the formation of oligomeric and polymeric products was observed. We then explored other solvents; water, methanol, ethanol, tetrahydrofuran and dioxane yielded intramolecular disulfide 13 as the major product, whereas the use of chlorinated solvents such as dichloromethane, tetrachloromethane and dichloroethane increased the yield of dimeric species to about 50%, as estimated after staining the spots on TLC with phosphomolybdcic acid. No significant difference in product distribution was observed when compared across the series of these chlorinated solvents. Hence, the least volatile dichloroethane with triethylamine as a base was chosen as it diminished the reduction of volume due to evaporation of solvent within 5 days of reaction time. Addition of methanol (2% v/v) to the reaction mixture suppressed formation of trace amounts of a precipitate of intermediates in the course of reaction. Under these conditions, a mixture of both possible isomers of duplexes 15 and 17 was obtained after chromatography on silica gel in total yield of 64%, whilst intramolecular disulfide was obtained in 28% yield.

The per[(2,3-di-O-allyl)-β-CD analogue 12 showed even higher propensity for intramolecular disulfide formation. In contrast to the permethylated analogue 11, compound 12 exclusively gave intramolecular disulfide 14 in non-polar media; duplex species could only be isolated in polar media such as methanol. Thus, oxidation of compound 12 with air oxygen in methanol in the presence of sodium hydroxide as a base afforded a mixture of intramolecular disulfide 14 (58%) and dimeric species 16 or 18 (14%).

In addition to the variation of solvents, we attempted the use of a template to direct the oxidation reaction towards the dimeric product in a similar manner as reported for non-methylated α-CD duplex (2). Thus, the oxidation of disulfanil derivative 11 was carried out at 1 mM concentration of compound 11 in aqueous solution in ammonium bicarbonate buffer at pH 9 in the presence of 0.5 and 1 equivalents, respectively, of 1,14-tetradecanedioic acid as the template. In contrast to the previously observed (2) effect, after 48 h of reaction time the reaction yielded only intramolecular disulfide 13.

The NMR analyses revealed that both possible isomers 15 and 17 of methylated duplexes (coined (4)‘eclipsed’ and ‘non-eclipsed’) were present in the mixture. Their separation by HPLC could not be achieved under similar conditions as for non-methylated analogues (4). Interestingly, the analogous perallylated duplex was present as a single isomer 16 or 18; however, we were unable to attribute the one of the two possible structures to the product by means of NMR analysis.

The propensity for the formation of intramolecular disulfide at the expense of dimeric species was also observed earlier in the oxidation of 2,3,6-per-O-methylated...
Table 1. Results of ITC study. Stability constants for analogous complexes with non-methylated duplex are shown in the right column for comparison.

| entry | guest compd | \( K \pm \sigma \) M\(^{-1}\) | \( \Delta H^\circ \pm \sigma_{\Delta H} \) kcal-mol\(^{-1}\) | \( \Delta S^\circ \pm \sigma_{\Delta S} \) kcal-mol\(^{-1}\) | \( \Delta G^\circ_{\text{obsd}} / \Delta G^\circ_{\text{calcd}}^{[a]} \) kcal-mol\(^{-1}\) | \( \Delta G^\circ_{\text{obsd}} / \Delta G^\circ_{\text{calcd}}^{[a]} \) kcal-mol\(^{-1}\) |
|-------|-------------|----------------------------|------------------|------------------|-------------------|-------------------|
| 1     | 19          | \( 3.86 \pm 0.28 \times 10^4 \) | \(-6.36 \pm 0.29 \) | \(-0.1 \pm 0.33 \) | \(-6.26 / -7.6 \) | \(-10.97 / -8.4 \) |
| 2     | 20          | \( 2 \times 10^3 \) | \( \text{nd}^{[b]} \) | \( \text{nd}^{[b]} \) | \(-4.5 / -6.7 \) | \(-10.83 / -7.7 \) |
| 3     | 21          | \( 2 \times 10^3 \) | \( \text{nd}^{[b]} \) | \( \text{nd}^{[b]} \) | \(-4.5 / -8.2 \) | \(-10.35 / -8.3 \) |
| 4     | 22          | \(< 10^2 \) | \( \text{nd}^{[b]} \) | \( \text{nd}^{[b]} \) | \( > -2.73 / -7.7 \) | \(-7.58 / -7.7 \) |

Note. Titrations were carried out in 5 mM phosphate buffer at pH 7.0;
[a] binding affinities calculated with AutoDock Vina (\(^1\)) program;
[b] \( \Delta H^\circ \) (and consequently \( \Delta S^\circ \)) could not be determined unambiguously due to the high correlation of fitting parameters. Duplex-OH refers to non-methylated analogue reported in our earlier paper (\(^2\)).

disulfanyl \( \alpha \)-CD (\(^11\)). Disruption of the hydrogen bonds between the secondary hydroxyls by their methylation allows deformations of the cyclodextrin macrocycle to occur through the rotations about the glycosidic bonds. Consequently, this allows the sulfur-bearing glucose unit to tilt with its primary carbon towards the centre of the macrocycle diminishing the strain in the intramolecular disulfide bridge which is likely to arise in non-methylated hydrogen-bonded analogue.

All isolated duplexes exhibit remarkable solubilities in non-polar media such as chlorinated hydrocarbons, ethers as well as in more polar solvents such as alcohols. Moreover, methylated duplexes 15 and 17 are well soluble in water.

**Complexation studies**

Recently, we reported that \( \beta \)-cyclodextrin duplexes showed very high binding affinities to shape-compatible organic guest molecules (\(^4\)). We therefore intended to use the same set of guest compounds to test complexation abilities of the methylated \( \beta \)-cyclodextrin duplexes 15 and 17. Since isomers 15 and 17 could not be separated, we used them as a mixture supposing that the complexation properties of the individual isomers will be similar. We observed such behaviour with analogous non-alkylated duplexes (\(^4\)) where the binding affinities of the individual isomers were indistinguishable. We used the same methods and conditions as described earlier (\(^4\)), i.e. isothermal titration calorimetry (ITC) performed in phosphate-buffered aqueous solutions. However, for most of these guest compounds the binding constant turned out to be too low to be safely determined by ITC with respect to the usable concentrations of host and guest compounds. These were limited by the solubilities of guest compounds in water as well as by the dilution heats produced by both host and/or guest at given concentration in the course of titrations. Thus, only guest compounds 19–21 (Figure 1) lent themselves to the determination of binding constants with duplexes 15 and 17 (Table 1). The most stable complex with methyl orange 19 reveals apparent stability constant \( 3.9 \times 10^8 \) M\(^{-1}\), which is about four orders of magnitude lower as compared to non-methylated analogue (\(^4\)) (\( 1.1 \times 10^8 \) M\(^{-1}\)). Similar trend was observed with other guest compounds as well - binding affinities for these guests were lower by 4–5 orders of magnitude in comparison to the non-methylated \( \beta \)-cyclodextrin duplexes (Duplex-OH, right column; (\(^4\)). Unambiguous determination of \( \Delta H^\circ \) and consequent calculation of \( \Delta S^\circ \) terms could be only achieved with ligand 19; in other cases high correlation of fitting parameters precluded determination of their reliable estimates.

We performed a series of NMR experiments to shed light on the structure of the most stable complex of mixture of duplexes 15 and 17 with methyl orange 19 in D\(_2\)O. Only limited data could be extracted from these experiments due to the significantly less favourable dispersion of 14 sets of proton and carbon signals of glucose units as compared to the CD\(_3\)OD solution of duplexes used for structural assignment. Nevertheless, the 2D-NOESY experiment (see ESI) indicates NOE between aromatic protons of the guest and H-5 protons of the duplexes. Interactions are likely to occur also to H-3 protons of the CD skeleton; however, these could not be safely distinguished from H-4 protons due to extensive overlaps. Collectively, the
NMR data support the inclusion mode of complexation of methyl orange 19 by duplexes.

We computed binding energies of complexes of the duplex 15 with a series of ligands 19–22 using AutoDock Vina program (12). Model of the ‘eclipsed’ isomer of per(2,3-di-O-methyl)-β-CD duplex 15 was constructed (Figure 2) using crystal co-ordinates of the non-methylated β-cyclodextrin to which methyl groups were added. Two units were connected by disulfide bonds linking C6'-C6'' and C6''-C6'' atoms and the geometry was optimised by molecular mechanics (MMFF94 force field). This model was used as an input structure for docking, whereas the input coordinates of ligands were obtained either from crystal structures (when they were available) or by in silico modelling them on a semi-empirical level (PM6). The initial geometry optimisation of structures of the ligands is of lesser importance since they are subjected to conformational changes in the course of the docking process. In striking contrast to complexes with non-methylated cyclodextrin duplex in which the same calculation procedures were applied (4), the calculations of stabilities of complexes of duplex 15 yielded (Table 1) overestimated values in all cases. This is assumed to be due to the rigid body docking model implemented in AutoDock Vina in which the receptor structure is fixed. In case of methylated duplex 15, the algorithm may underestimate the entropy loss upon binding by the flexible macrocycle. Satisfactory agreement (± 2 kcal mol⁻¹) was obtained for ligands 19 and 20, whereas larger discrepancy was found in the calculation of binding affinity of the complex with ligands 21 and 22.

One of the early evidence of the reduced binding potential of per(2,3,6-tri-O-methyl)-β-CD with respect to the native β-CD was reported by Gelb and Schwarz (13). In that study on the complexation of amino-adamantane derivatives by per(2,3,6-tri-O-methyl)-β-CD, methyl substituents lowered binding constants by two orders of magnitude with respect to native β-CD. Interestingly, binding affinities remained virtually unchanged for methyl orange (5100 vs. 4500 M⁻¹). In the case of duplexes 15 and 17, the loss of binding potential for methyl orange was also less significant than for the other guests when compared with non-methylated duplexes. This may indicate a favourable role of dipole–dipole interactions of the negatively charged anion with primary hydroxyl groups (14), as has also been specifically observed for sulfonate anion (15). Wenz recently reported (16) a systematic study on the effect of various patterns of methylation of hydroxyls present on the β-cyclodextrin skeleton on its complexation properties. He found that permethylation of the secondary hydroxyls of β-CD led to a significant reduction of the binding affinities, presumably to the loss of entropy caused by disruption of hydrogen bonds supporting the circular shape of the macrocycle. Such effect may play important role in complexation properties of duplex species as well.
Scheme 1. (a) DiBAL-H, Toluene, −40 °C (R = Me) or −9–0 °C (R = allyl); (b) MsCl, Et₃N, DCM, 0–25 °C; (c) CH₃COSK, DMF, 60 °C; (d) BF₃·Et₂O, DCM, 0–25 °C; (e) NaOH, EtOH/H₂O (R = Me) or MeOH (R = allyl), RT; (f) Et₃N, 2% MeOH in DCE (R = Me) or NaOH/MeOH (R = allyl), RT.
Conclusions

We have synthesised cyclodextrin duplexes linked by two disulfide bonds which are permethylated and parallayed at the secondary hydroxyl groups. Although conditions for dimerisation could be found, in particular the disulfanyl derivative 12 tends to prefer intramolecular disulfide bond formation upon oxidation, as compared to the non-alkylated analogue (4). For both precursors 11 and 12, the course of the reaction is strongly dependent on the used solvent. The permethylated duplexes 15 and 17 display very high solubilities in both polar and non-polar solvents, from water to alcohols to chlorinated hydrocarbons. It was found that per-2,3-di-methylated duplexes are able to form inclusion complexes with organic molecules in aqueous solutions with, however, significantly reduced binding affinities to the guest compounds that were earlier shown (4) to form very stable complexes with non-alkylated duplexes.

Experimental section

General

The NMR spectra were measured on Bruker AVANCE-600 instrument (1H at 600.13 MHz and 13C at 150.9 MHz) with a cryoprobe in CDCl3 or CD3OD at 25 °C. Spectra in CDCl3 were referenced to TMS (1H) or solvent peak (13C, using δ(CDCl3) = 77.0 ppm). Spectra in CD3OD were referenced to solvent peak (using δ(H) (MeOD) = 3.31 ppm; δ(C(MeOD) = 49.0 ppm). Partial structural assignment of proton and carbon signals was achieved combining 1D-1H and 13C-spectra (APT) with homonuclear 2D-h,h-CoSy, 2D-h,h-ToCSy, 2D-h,h-roeSy peak (using δH = 77.0 ppm). Spectra in CD3OD were referenced to solvent peak (using δH (MeOD) = 3.31 ppm; δC(MeOD) = 49.0 ppm). The NMr spectra were measured on Bruker AVANCe-600 instrument (1h at 600.13 Mhz and 13C at 150.9 Mhz) with a cryoprobe in CDCl3 or CD3oD at 25 °C. Spectra in CDCl3 were referenced to TMS (1H) or solvent peak (13C, using δ(CDCl3) = 77.0 ppm). Spectra in CD3OD were referenced to solvent peak (using δH (MeOD) = 3.31 ppm; δC(MeOD) = 49.0 ppm). Partial structural assignment of proton and carbon signals was achieved combining 1D-1H and 13C-spectra (APT) with homonuclear 2D-h,h-CoSy, 2D-h,h-ToCSy, 2D-h,h-roeSy.

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The toluene phase was separated and residue was washed with water and aqueous sodium carbonate then dried with anhydrous MgSO4 and concentrated to afford a colourless solid, which was purified by column chromatography on silica gel. Elution with EtOAc–hexane (1:1) furnished major product diol 1 (1.37 g, 61% yield) as colourless solids. Analytical data were in accordance with the published literature (8).

6IV, 6V, 6VI, 6VII, 7I, 7II, 7III, 7IV, 7V, 7VI, 7VII-tetradeca-O-allyl-β-cyclodextrin (5): To a solution of diol 3 (1.68 g, 0.883 mmol) and triethylamine (1.23 mL, 8.8 mmol) in anhydrous DCM (42 mL) at 0 °C under argon atmosphere mesyl chloride (0.420 mL, 5.4 mmol) was added dropwise, and the reaction mixture was further stirred for 1 h while allowing to warm up slowly to room temperature. The reaction mixture was neutralised with saturated NaHCO3 (5 mL), then it was diluted with DCM (20 mL) and washed with H2O (2 × 20 mL). The organic layer was washed with water, dried over MgSO4, and concentrated to furnish the dimesylated compound 4 (1.47 g, 81% yield) as a colourless solid. Analytical data were in accordance with the published literature (8).

6II, 6III, 6IV, 6V, 6VI, 6VII-Penta-O-tert-butylidemethylsilyl-2I, 2II, 2III, 2IV, 2V, 2VI, 2VII, 3I, 3II, 3III, 3IV, 3V, 3VI, 3VII-tetradeca-O-methyl-β-cyclodextrin (3): Compound 2 (122 mg, 48.9 μmol) was dissolved in 0.8 mL of dry toluene. 1.5 M solution of DIBAL-H in toluene (195 μL, 0.293 mmol) was added dropwise at −9 °C under argon. The mixture was stirred for 1.5 h, the bath being allowed to warm up slowly to 0 °C. The reaction was monitored by TLC in toluene–acetone (95:5). After completion of the reaction it was quenched with 1 M HCl (1 mL) and washed with ethyl acetate. The organic layer was washed with water, dried over MgSO4 and the solvent was evaporated. Purification by column chromatography (isocratic elution hexane–diethyl ether 4:1) gave compound 4 as a white material (91 mg, 82% yield). HRMS (MALDI): m/z calcd for C114H196O35Si5 [M + Na]+: 2288.230, found 2288.2324; elemental analysis (%) calcd for C114H196O35Si5: C 60.39, H 8.71; found C 60.18, H 8.77. 1H-NMR, see Table S1; 13C-NMR, see Table S3.
6,6'-Di-O-methanesulfonfyl-6,6',6',6',6',6',6',6'-penta-O-tert-butylidimethylsilyl-2', 2''', 2''', 2''', 2', 2', 2', 2', 2', 2', 2', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3', 3'.
and degassed by means of a triple vacuum–argon cycle. Then a degassed 1 M aqueous solution of NaOH (1.76 mL, 1.76 mmol) was added into the mixture and allowed to react for 3 h at room temperature under argon. After completion of reaction the solution was neutralised with TFA then evaporated to dryness under vacuum. The residue was purified by column chromatography (silica gel, DCM–methanol 92:8) to furnish compound 11 (201 mg, 82%, calcd for DCM solvate). HRMS (MALDI), m/z calcd for C_{56}H_{98}O_{35}S_{2} [M + Na]^+: 1385.5324, found 1385.5312; elemental analysis (%) calcd for C_{56}H_{98}O_{35}S_{2}: 3CH_2Cl_2: C 43.79, H 6.48; found C 43.64, H 6.31. \(^{1}H\)-NMR, see Table S2; \(^{13}C\)-NMR, see Table S4.

6,6^IV^-Dideoxy-6^IV^-disulfanyl-2^I, 2^II, 2^III, 2^IV, 2^V, 2^VI, 2^VII, 3^I, 3^II, 3^III, 3^IV, 3^V, 3^VI-tetradeca-O-allyl-β-cyclo-dextrin (12): Compound 10 (105 mg, 57.9 μmol) was dissolved in methanol (8 mL) and the mixture was degassed by means of triple vacuum/argon cycle. A degassed 1 M aqueous solution of sodium hydroxide (0.58 mL; 0.58 mmol) was added, and the mixture was allowed to react for 2 h at room temperature under argon atmosphere. Then the solution was acidified with 1 M aqueous acetic acid to pH 7 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, isocratic elution DCM–methanol 95:5) to yield the product 12 (71 mg, 71%) as a colourless amorphous material. HRMS (MALDI): m/z calcd for C_{84}H_{126}O_{33}S_{2} [M + Na]^+: 1749.7515 found, 1749.7537; elemental analysis (%) calcd for C_{84}H_{126}O_{33}S_{2}: C 58.39, H 7.35; found C 58.36, H 7.40. \(^{1}H\)-NMR, see Table S1; \(^{13}C\)-NMR, see Table S3.

Oxidative dimerisation of disulfanyl derivative 11: Compound 11 (200 mg, 0.124 mmol, calcd for DCM solvate) was dissolved in dichloroethane–methanol (98:2, 160 mL) and triethylamine (21 μL, 0.150 μmol) was added at room temperature. The reaction mixture was vigorously stirred at room temperature in a loosely stoppered flask with daily monitoring by TlC (etoAc–acetone–h_{2}O–etoh 17:3:3:3). After the oxidation reaction had finished (5 days), the mixture was evaporated to dryness and purified by column chromatography on silica gel to provide the intramolecular disulfide 14 (30 mg, 58%) and duplex (16 or 18) (7 mg, 14%).

Intramolecular disulfide 14: (24 mg, 71%) as a white material. HRMS (MALDI): m/z calcd for C_{84}H_{126}O_{33}S_{2} [M + Na]^+: 1749.7515 found, 1749.7537; elemental analysis (%) calcd for C_{84}H_{126}O_{33}S_{2}: C 58.45, H 7.24; found C 58.73, H 7.54. \(^{1}H\)-NMR, see Table S1; \(^{13}C\)-NMR, see Table S3.

Duplex: HRMS (MALDI): m/z calcd for C_{168}H_{248}O_{66}S_{4} [M + Na]^+: 3472.4825, found 3472.4871; elemental analysis (%) calcd for C_{168}H_{248}O_{66}S_{4}: C 58.45, H 7.24; found C 57.81, H 6.78. \(^{1}H\)-NMR, see Table S1; \(^{13}C\)-NMR, see Table S3.

Supplemental material

Supplemental data for this article can be accessed online here: http://dx.doi.org/10.1080/10610278.2016.1164860

Disclosure statement

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