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Note

Heptakis[6-*S*-(2,3-dihydroxypropyl)-6-thio] cyclomaltoheptaose and its sulfone: water-soluble β-cyclodextrin derivatives having modified polarity

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In continuation of our work [1] on chain extension in cyclomaltoheptaose (β-CD), we decided to elaborate on an interesting concept which has recently been advanced by Ling and Darcy [2]. These authors considered that the volume of the hydrophobic cavity of cyclodextrins might be expanded by appropriate chain elongation at the C-6 positions and so become suitable for inclusion complexing of guest molecules of larger size, or for accommodating more than one guest molecule of a given size, thereby increasing the scope of host–guest interaction. They synthesized the 6-*S*-hydroxyethylated 6-thiocyclodextrins **1**–**3**, reasoning that insertion of the hydrophobic fragments $-S-CH_2CH_2-$ in the primary carbinol groups might serve the purpose stated. Upon entry of a guest molecule, these conformationally mobile ethylthio chains might arrange themselves in preferred orientations so as to increase the effective size of the cavity. For the cyclomaltooctaose derivative **3**, spectroscopic evidence could be adduced that such is indeed the case [2]. Unfortunately, **3** alone showed sufficient solubility in water (0.9 g per 100 mL) to command practical interest in this regard, whereas **1** and **2** were stated to be only slightly soluble in water. We thought that the much more readily available and industrially important β-cyclodextrin should be derivatizable so as to furnish compounds closely analogous to **2** but with a practical degree of solubility. With this in mind

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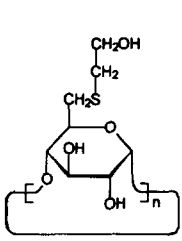
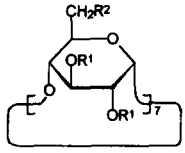
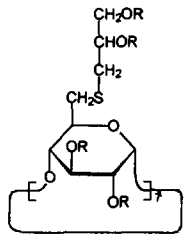
we proceeded to synthesize the heptakis[6-*S*-(2,3-dihydroxypropyl)-6-thio]cyclomaltoheptaose (**9**) and the corresponding heptakis-sulfone **11**.



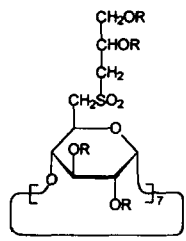
1 n = 6
2 n = 7
3 n = 8



4 R^1 = Ac, R^2 = OH
5 R^1 = Ac, R^2 = OTf
6 R^1 = Ac, R^2 = I
7 R^1 = H, R^2 = I



8 R = Ac
9 R = H



10 R = Ac
11 R = H

The attachment of 2,3-dihydroxypropylthio groups at the C-6 positions of β-CD was achieved in three procedural variations, involving nucleophilic displacement with 3-mercapto-1,2-propanediol (1-monothioglycerol) in the 6-trifluoromethanesulfonate **5** and the 6-deoxy-6-iodo derivatives **6** and **7** of cyclomaltoheptaose, respectively. Crystalline triflate **5**, not previously described, was prepared in 90% yield from conveniently available [1,3] heptakis(2,3-di-*O*-acetyl)cyclomaltoheptaose (**4**). The triflate is reasonably stable, can be stored for some months without deterioration, and may well prove suitable as a substrate for a variety of useful substitution reactions including, for example, reactions with *C*-nucleophiles [4]. With 1-monothioglycerol in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) it reacted completely within 5 min at room temperature. The displacement product was not isolated as such but was directly *O*-acetylated in its diol chains, to furnish the peracetylated derivative **8** in good yield (68%). The same product **8** was obtained in analogous fashion from heptakis(2,3-di-*O*-acetyl-6-deoxy-6-iodo)cyclomaltoheptaose (**6**). The yield was only moderate (38.5%), but this disadvantage is at least partly offset by the circumstance that the preparation [1,5] of stable, indefinitely storable **6** from commercial β-cyclodextrin involves less expenditure in work and materials than that of the triflate **5**. The most straightforward and attractive procedure in terms of yield and labor was reaction of heptakis(6-deoxy-6-iodo)cyclomaltoheptaose (**7**) [5,6] with thioglycerol and DBU in *N,N*-dimethylformamide (15 h at room temperature), followed by in situ peracetylation, which gave **8** in 77% yield.

Zemplén deacetylation of **8** quantitatively yielded the crystalline target compound **9**, heptakis[6-*S*-(2,3-dihydroxypropyl)-6-thio]cyclomaltoheptaose. Its solubility in water was 5.1 g per 100 mL, more than five times that of **3**; on a molar basis, the solubility of **9** (0.0289 mol L^{-1}) was enhanced 1.8-fold over that of β-CD (0.0159 mol L^{-1}). These data make it a promising candidate for the study of inclusion complexing phenomena of potential interest for practical applications.

Oxidation of **8** with a threefold excess of 3-chloroperoxybenzoic acid in chloroform solution occurred readily during 20 min at room temperature and gave the corresponding sulfone, heptakis[6-(2,3-diacetoxypropylsulfonyl)-2,3-di-*O*-acetyl-6-deoxy]cyclomalto-

heptaose (**10**). The crystalline product was obtained in 90% yield after the 3-chlorobenzoic acid formed and unconsumed peroxy acid had been completely removed from the crude reaction mixture by simple ether extraction. When instead of such extraction the mixture was, for the same purpose, subjected to column chromatography, separation of the acids was incomplete and **10** emerged as a crystalline adduct containing 7 molecules of 3-chlorobenzoic acid per cyclodextrin molecule, as indicated by ^{1}H and ^{13}C NMR spectra and elemental analysis.

Zemplén deacetylation of **10** gave the heptakis-tetraol **11** in 92% yield as a crystalline material whose solubility in water, 11 g per 100 mL, was more than twice as high as that of the thio ether **9**, and on a molar basis (0.0533 mol L^{-1}) showed a 3.5-fold enhancement over β-CD. It is to be expected that differing polarities and steric requirements of the substituent chains will vary the inclusion complexing behavior of these two new cyclodextrin derivatives, and a comparative investigation of this aspect is underway.

The new compounds **5** and **8–11** were shown by their NMR spectra to be uniformly heptasubstituted derivatives of β-CD. Thus, each ^{13}C spectrum exhibited a single set of signals for the cycloheptaose carbon atoms. The FAB mass spectra accorded with the calculated molecular weights, with the molecular ion producing a strong peak (56% for **5**) or even the base peak (for **8–10**). However, because of the use of racemic 1-monothioglycerol in the synthesis, **8–11** were expected to be mixtures of diastereomers with respect to the configuration of C-2 in the side chains that were randomly incorporated. The expectation was borne out by the presence of doubled ^{13}C signals due to slight chemical-shift differences for C-6 of the sugar, and C-1 and C-2 in the appended propyl chains, in **9**, **10**, and **11** [1]. An unusual feature which probably was also due to the presence of diastereomeric monosaccharide units was the shape of the anomeric proton signal for **8** at 5.07 ppm (correlated by HETCOR with C-1 at 96.9 ppm). It had the appearance of a narrow triplet but presumably consisted of two partially overlapping doublets. Molecular models suggest that in one of the side-chains secondary carbinol configurations the acetyl carbonyl group comes closer to H-1 than in the other, so that a small shielding difference may be explicable.

1. Experimental

*Heptakis(2,3-di-*O*-acetyl-6-*O*-trifluoromethylsulfonyl)cyclomaltoheptaose* (**5**).—A solution of heptakis-2,3-diacetate **4** [1,3] (1.85 g, 7.52 mequiv of monosaccharide units) in 1,2-dichloroethane (15 mL, freshly distilled from P_2O_5) was prepared and set aside. Triflic anhydride (1.8 mL, 1.5 molar equiv per glucose unit) was introduced by syringe into a sealed vessel containing a chilled (−15 °C) solution of dry pyridine (0.9 mL, 1.5 molar equiv) in dry 1,2-dichloroethane (20 mL). The flocculent precipitate was magnetically stirred for 5 min, and then the prechilled solution of **4** was rapidly added. The mixture was stirred at −15 to −10 °C for 30 min, at 0 °C for 2 h, and at 25 °C for 1.5

[1] In **11**, the C-3 signal of the chain was also doubled. The spectrum of **8** was not sufficiently resolved to show all these small effects.

h, after which **4** (R_f 0.3) was completely replaced by **5** (R_f 0.7; TLC with 30:5:4 EtOAc–MeOH–H_2O). The solution was cooled again (0 °C) and washed with 5% HCl (2 × 25 mL), aq $NaHCO_3$ solution, and water (all ice-cold), dried (Na_2SO_4), treated with activated carbon and Celite, filtered, and evaporated at low temperature. The almost colorless syrup obtained turned into an off-white solid during evaporation of several small portions of added CCl_4. The pulverized material was then triturated with some ether and hexane and brought to dryness in vacuo (to remove all of the CCl_4), giving **5** (2.52 g, 89%; in a 300-mg run the yield was 92%), mp 124–125 °C (dec), $[\alpha]_D$ +83.8° (*c* 0.93, $CHCl_3$); FABMS: *m/z* 2670 (M^+ + Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.28 (t, $J_{2,3} \approx J_{3,4} \approx 8.4$ Hz, H-3), 5.10 (d, $J_{1,2}$ 3.8 Hz, H-1), 4.87 (dd, $J_{1,2}$ 3.8, $J_{2,3}$ 9.5 Hz, H-2), 4.80 (m, 2 H, H-6,6′), 4.20 (m, H-5), 3.74 (t, $J_{3,4} \approx J_{4,5} \approx 8.6$ Hz, H-4), 2.09 and 2.06 (2 s, 3 H each, 2 OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.2 (2 CO), 118.5 (q, *J* 319 Hz, CF_3), 97.5 (C-1), 76.8 (C-4), 74.0 (C-6), 70.0, 69.8, 69.6 (C-2,3,5), 20.8 and 20.7 ($COCH_3$). Anal. Calcd for $C_{77}H_{91}F_{21}O_{63}S_7$ (2647.9): C, 34.93; H, 3.46; S, 8.48. Found: C, 34.99; H, 3.81; S, 8.13.

Heptakis{6-S-[(2R,S)-2,3-diacetoxypropyl]-2,3-di-O-acetyl-6-thio}cyclomaltoheptaose (**8**).—(A) *From triflate* **5**. A mixture of **5** (378 mg, 1 molar equiv of monosaccharide units), 1-monothioglycerol (268 mg, ≈ 2.5 molar equiv), and DBU (350 mg, 2.5 molar equiv) in dry oxolane (25 mL) was allowed to react at room temperature. Compound **5** (R_f 0.7) was completely consumed after 5 min, and several slower spots ($R_f \approx$ 0.3–0.1) were observed, presumably representing **8** and products of deacetylation; there was also a spot for remnant thioglycerol (R_f 0.6) and one for an unidentified substance (R_f 0.4). This pattern did not change during 4 h at room temperature, or after boiling of a test sample for 5 min (TLC with 30:5:4 EtOAc–MeOH–H_2O). The solvent was evaporated and replaced by $CHCl_3$, and the solution then washed twice with 5% HCl, once with aq $NaHCO_3$, and with water, dried (Na_2SO_4), and evaporated to give a colorless foam (230 mg) of the slow-moving products. (The substances of R_f 0.6 and 0.4 remained in the aqueous phase.) The foam was acetylated overnight with acetic anhydride (4 mL) and pyridine (2 mL), with addition of a catalytic amount of 4-dimethylaminopyridine, after which TLC showed a single spot for **8**, R_f 0.42 (EtOAc, double irrigation). Processing of the mixture by treatment with excess MeOH, and evaporation with several portions of added MeOH followed by toluene gave crude **8** (285 mg, 67%) as a colorless foam.

(B) *From iodo derivative* **6**. Compound **6** (356 mg, 1 molar equiv of monosaccharide units) was treated exactly like **5** as described in (A). After 20 min, **6** was completely consumed and the same pattern of products was seen and remained unchanged during 4 h (TLC with 30:5:4 EtOAc–MeOH–H_2O). The solution was decanted from a water-soluble, oily deposit which had been formed, and was processed, and the product acetylated as described in (A). There was obtained 162 mg (38.5%) of crude **8**, R_f 0.73 (10:1 EtOAc–EtOH), identical (NMR) with **8** from (A).

(C) *From iodo compound* **7**. To a solution of **7** (272 mg, 1 molar equiv of monosaccharide units) in dry DMF (5 mL) was added 1-monothioglycerol (540 mg, 5 equiv) and DBU (450 mg, 3 equiv). The mixture was allowed to stand at room temperature for 15 h. Acetic anhydride (8 mL), pyridine (4 mL), and a catalytic quantity of 4-dimethylaminopyridine were then added, and after 7 h the mixture was processed

by taking it up in $CHCl_3$ (100 mL) and washing the solution several times with 5% HCl followed by aq $NaHCO_3$ and water. Evaporation of the dried (Na_2SO_4) solution gave a colorless syrup which showed a strong spot identical with that of **8** from A and B, accompanied by a faster spot due to acetylated thioglycerol (TLC both with EtOAc and 10:1 EtOAc–EtOH). The material was purified by column chromatography on SiO_2 with EtOAc as eluent, to give **8** as a colorless syrup that crystallized on trituration with ether–hexane; yield, 325 mg (77.4%).

(D) *Purification and characterization.* Although the crude products from A (285 mg) and B (129 mg) gave single spots on "normal" TLC, they proved difficult to crystallize, and very heavy spotting revealed the presence of traces of faster and more slowly migrating impurities. They were therefore jointly chromatographed on a column (18 × 2 cm) of SiO_2 by development with 20:1 EtOAc–EtOH, and the pooled, pure and almost-pure fractions (340 mg, 82% recovery) were rechromatographed by use of EtOAc. Thus was obtained pure **8**, mp 83–84 °C (from ether–hexane), $[\alpha]_D$ +88° (*c* 1, $CHCl_3$), R_f 0.72 (10:1 EtOAc–EtOH); FABMS: *m/z* 2966 (96%, $M^+ + Na$); ^1H NMR (300 MHZ, $CDCl_3$): δ 5.2 (m, 2 H, H-2,3), 5.07 (t, 1 H, H-1), 4.80 (m, 1 H, H-5), 4.36 (m, 1 H, H-3 of thioglyceryl), 4.1 (m, 2 H, H-2,3′ of thioglyceryl), 3.86 (t, *J* 8.3 Hz, H-4), 3.06 and 2.79 (2 m, 2 H each, CH_2–S–CH_2), 2.07–2.04 (4 s, 12 H, 4 OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.6, 170.6, 170.2, 169.5 (4 CO), 96.9 (C-1), 78.6 (C-4), 71.8 (double peak, C-2 of thioglyceryl), 71.0 (C-3), 70.8 (C-2), 70.6 (C-5), 64.1 (C-3 of thioglyceryl), 34.2 and 34.0 (C-1 of thioglyceryl and C-6), 21.0–20.8 (4 $COCH_3$). Anal. Calcd for $C_{119}H_{168}O_{70}S_7$ (2942.7): C, 48.57; H, 5.75; S, 7.63. Found: C, 48.53; H, 5.56; S, 7.37.

Heptakis{6-S-[(2R,S)-2,3-dihydroxypropyl]-6-thio}cyclomaltoheptaose (**9**).—To a solution of **8** (158 mg) in ab MeOH (25 mL) was added a catalytic amount of NaOMe in MeOH. After about 12 min a solid precipitate began to appear, and after 1.5 h the supernatant solution was free from **8** (TLC). Ether was added to increase the amount of precipitate which was then isolated by filtration and washed with ether to give 94 mg (99%) of crystalline **9**, mp 192–195 °C (dec), $[\alpha]_D$ +106° (*c* 1, water); solubility in water: 51 mg mL^{-1} (= 0.0289 mol L^{-1}); FABMS: *m/z* 1787 (base peak, $M^+ + Na$); ^1H NMR (300 MHz, D_2O): δ 5.16 (d, $J_{1,2}$ 2.6 Hz, H-1), 3.96 (m, 3 H), 3.71 (m, 2 H), 3.61 (m, 2 H), 3.31 (d, 1 H, *J* 13 Hz), 3.03 (ddd, 1 H, *J* 2.5, 8.5, and 11.0 Hz), 2.91 (ddd, 1 H, *J* 2.5, 5.0, and 13.5 Hz), 2.79 (septet, 1 H, *J* 5.5, 7.5, and 13.3 Hz). ^{13}C NMR (75.4 MHz, D_2O with Me_2SO-d_6 as internal reference): δ 103.2 (C-1), 85.7 (C-4), 74.4 (C-3), 73.5, 73.3 [C-2(*R*) and C-2(*S*) of thioglyceryl], 72.6 (C-2), 72.4 (C-5), 66.0 (C-3 of thioglyceryl), 37.6, 37.5 and 35.5, 35.3 (double peaks for C-1 of thioglyceryl and C-6). In Me_2SO-d_6 as solvent, all signals were shifted slightly (by ≈ 1 ppm) to lower values.

Heptakis{6-[2(R,S)-2,3-diacetoxypropylsulfonyl]-2,3-di-O-acetyl-6-deoxy}cyclomaltoheptaose (**10**).—3-Chloroperoxybenzoic acid (800 mg, purity 50–60%; Aldrich Chemical Co.) was added portionwise at room temperature to a stirred solution of **8** (320 mg) in $CHCl_3$ (40 mL). After 20 min all of the **8** (R_f 0.6) had been replaced by **10** (R_f 0.5, single spot in TLC with EtOAc). The mixture was left for 1 h without observable change, then concentrated to dryness. The solid residue was triturated exhaustively with portions of ether (4 × 25 mL), filtered, and washed again with ether. The vacuum-dried,

crystalline product **10** (310 mg, 90%) had mp 140–141 °C, $[\alpha]_D$ +56° (*c* 1, $CHCl_3$), FABMS: *m/z* 3190 (base peak, $M^+ + Na$). Its spot on TLC was UV-negative, and its NMR spectra showed no trace of contamination by aromatic acid. ^1H NMR (300 MHz, acetone-d_6): poorly resolved multiplets integrating to a total of 12 H for sugar ring and alkylsulfonyl chain at δ 5.68 (1 H), 5.35 (2 H), 4.90 (1 H), 4.62 (1 H), 4.39 (2 H), 4.18 (1 H), 3.90 (2 H), and 3.68 (2 H), and singlets at 2.06, 2.05, 2.04, and 2.03 totalling 12 H for 4 OAc. ^{13}C NMR (75.4 MHz, acetone-d_6): δ 170.7, 170.0 (more intense peaks, 2 CH_3CO on sugar ring), 170.95, 170.90 and 170.4, 170.3 (less intense double peaks, CH_3CO on diol chain), 97.7 (C-1), 78.4 (C-4), 71.0, 70.7 (C-2,3), 68.5 (C-5), 66.4, 66.1 [C-2(*R*) and C-2(*S*) of diacetoxypropylsulfonyl], 64.9, 64.8 (double peak for C-3 of diacetoxypropylsulfonyl), 57.1, 56.9 (double peak for C-1 of diacetoxypropylsulfonyl), 55.3 (C-6), 21.0, 20.9, 20.9, 20.7 (4 $COCH_3$). (Assignments aided by HETCOR) Anal. Calcd for $C_{119}H_{168}O_{84}S_7$ (3166.6): C, 45.13; H, 5.34; S, 7.07. Found: C, 45.25; H, 5.24; S, 6.74.

Adduct with 3-chlorobenzoic acid.—Compound **8** (320 mg) was oxidized exactly as described above. However, the dry residue obtained upon evaporation of the solvent from the reaction mixture was not extracted with ether; instead, it was subjected to chromatography on a column (25 × 2 cm) of SiO_2 by use of EtOAc as eluent. Foreruns contained aromatic acid (R_f 0.75, non-charring after ethanolic H_2SO_4 spray; detected under UV light), and the fractions containing the oxidation product (R_f 0.5, charring, but also UV-positive) yielded a colorless syrup which on trituration with ether turned into a white solid (230 mg), mp 93–96 °C, $[\alpha]_D$ +45° (*c* 1, EtOAc). According to the NMR spectra it was an adduct of **10** with 7 molecules of 3-chlorobenzoic acid, but under the conditions of FAB mass spectrometry the complex dissociated completely and showed the molecular ion of **10** at *m/z* 3191 ($M^+ + Na$) as the base peak. The ^1H NMR data (300 MHz, acetone-d_6): δ 7.98 (s), 7.97 (d), 7.65 (d), and 7.53 (t), jointly integrating to 4 H, for *m*-Cl-C_6H_4-CO_2H; the remainder of the spectrum was indistinguishable from that of pure **10**. The ^{13}C NMR data (75.4 MHz, acetone-d_6): 166.4 (aroyl CO), 134.8 and 133.5 (C-1,3 of *m*-Cl–C_6H_4–CO_2), 133.6, 131.1, 130.1, and 128.8 (C-2,4,5,6 of *m*-Cl–C_6H_4–CO_2); the remainder of the spectrum was identical with that of pure **10**. The product did not liberate I_2 from a solution of KI in acetone and hence did not contain peroxy acid. Anal. Calcd for $C_{168}H_{203}Cl_7O_{98}S_7$ (4262.5): C, 47.34; H, 4.80; S, 5.26. Found: C, 47.95; H, 4.85; S, 4.72.

Heptakis{6-deoxy-6-[(2R,S)-2,3-dihydroxypropylsulfonyl]}cyclomaltoheptaose (**11**). —A solution of **10** (300 mg, free from *m*-chlorobenzoic acid) in abs MeOH (65 mL) was treated at room temperature with a catalytic amount of NaOMe in MeOH. A solid precipitate of **11** appeared and was isolated after 2 h and washed with ether; yield, 104 mg (92%); mp 205–208 °C, $[\alpha]_D$ +81° (*c* 1, water). Solubility in water: 44 mg/0.4 mL (= 0.0553 mol L^{-1}). ^{13}C NMR data (75.4 MHz, in D_2O with the Me_2SO-d_6 signal as internal reference): δ 103.0 (C-1), 84.6 (C-4), 74.1 (C-3), 73.5 (C-2), 73.4 (C-5), 68.2, 68.0 [C-2(*R*) and C-2(*S*) of dihydroxypropylsulfonyl], 66.1 (C-3 of dihydroxypropylsulfonyl), 59.5, 59.1 and 56.1, 56.0 (C-1 of dihydroxypropylsulfonyl and C-6). The ^1H NMR spectrum (D_2O) exhibited signals at δ 5.15 (1 H), 4.6–4.2 (2 H), and 4.1–3.6 (13 H) which were insufficiently resolved for analysis. Anal. Calcd for $C_{63}H_{112}O_{56}S_7$ (1990.0): C, 38.02; H, 5.67. Found: C, 38.13; H, 5.87.

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