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Bisthiocyclomalto-oligosaccharides with trehalosyl and octyl links: their synthesis for dual-cavity inclusion

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Abstract

6,6′-Dithio-α,α-trehalose has been prepared, and its thiolate dianion reacted with 6^1-*O*-*p*-tolylsulfonylcyclomaltoheptaose to form the trehalosyl-linked thiocyclodextrin dimer **5**. Another cyclodextrin dimer (**6**) having the more flexible octyl link was similarly synthesised. Formation of a 1:1 complex with Methyl Orange at pH 4 by dual-cavity inclusion was confirmed for **5** and **6**.

Keywords: Cyclodextrin; Thiotrehalose; Inclusion

1. Introduction

Cyclodextrins (cyclic malto-oligosaccharides) are well known as host molecules in aqueous environments [1]. Two improvements on their behaviour have been the subject of research: the increase in the capacity of cyclodextrins to include large and complex guest molecules, and the increase in the host–guest association constants which in virtually all cases are no better than 10^4. Extension of the cavity with multiple groups, for example by methylation [2] or by means of more extended modification [3a,3b], has resulted in favourable interactions with guest molecules, which derive from larger effective cavity size. Another approach has been to link two cyclodextrin molecules, which may then cooperate to host larger than usual guest molecules with association constants approaching those of antibody complexes [3b–5]. The link between the cyclodextrin units is obviously important, since its length or rigidity, for example, will affect complexation.

Previous biscyclodextrins have had aromatic or disulfide links. An expectation for a dual cavity might be that it would show selectivity as a receptor deriving from different, and fairly stable, relative orientations of the component cavities. Such a possibility might be brought about by a link, for example a sugar unit, having definite conformations.

α,α-Trehalose, in view of its crystallographic 'concave' conformation as well as its symmetry, has already been recognised as a potential building block for macrocycles in host–guest chemistry [6]. We have synthesised 6,6′-dithio-α,α-trehalose (**4**) and used it to form a relatively rigid saccharide

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link between two cyclomaltoheptaose (β-cyclodextrin) molecules. The methodology is similar to that already used by us to synthesise branched cyclodextrins, where the key step is a displacement reaction by sugar thiolate on 6-monosulfonylated cyclodextrin [7]. In this synthesis, the use of α,α-trehalose dithiolate produced a trehalosyl-linked cyclodextrin dimer, 6-*S*-(6^{I}-deoxycyclomaltoheptaos-6^{I}-yl)-6-thio-α-D-glucopyranosyl 6-*S*-(6^{I}-deoxycyclomaltoheptaos-6^{I}-yl)-6-thio-α-D-glucopyranoside (**5**).

2. Results and discussion

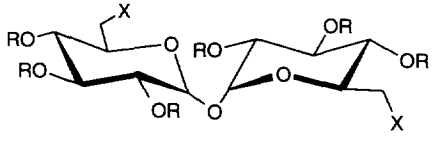
Derivative chemistry of α,α-trehalose relies largely on its molecular symmetry, which makes it possible to sulfonylate trehalose with similar selectivity to that of methyl α-D-glucopyranoside, and obtain the 6,6′-di-*p*-toluenesulfonate [8]. Displacement of the sulfonate group, to obtain the acetylated 6,6′-dithiobenzoate (**2**), was carried out on the acetylated sulfonate (**1**) in 1,3-dimethyl-2-oxohexahydropyrimidine. A similar reaction, but using thioacetate in dimethylformamide, gave the octaacetate (**3**) of 6,6′-dithiotrehalose. The free sugar (**4**) was obtained by deesterification of derivative **2** or **3**.

We tried to purify this air-sensitive dithio sugar as a disulfide, a method employed for 6-thiosucrose [9]. In this case there was also the possibility, as indicated by molecular modelling, of formation of an intramolecular 6,6′-disulfide. Aerial oxidation of dilute solutions, as well as oxidation with bromine, was used. The former reaction was monitored with 5,5′-dithiobis(2-nitrobenzoic acid) [10], an indicator normally used in amino acid chemistry. However, examination of the products from air and bromine oxidation indicated that they were probably polymeric mixtures. Elution from thin-layer chromatograms, even after acetylation, was not possible under conditions employed for the other trehalose derivatives, and ^{1}H NMR spectra showed several anomeric proton signals.

The disodium salt of dithiotrehalose was prepared from the octaacetate **3** and used directly for iodide-catalysed reaction with 6^{I}-*O*-*p*-tolylsulfonylcyclomaltoheptaose. This produced the trehalosyl-linked biscyclodextrin **5**. The disodium salt of octanedithiol was similarly used to produce the flexibly linked dimer **6**.

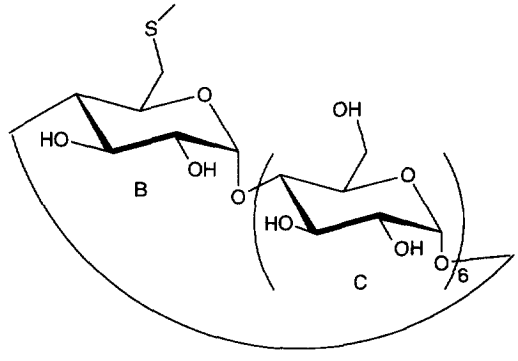
The FAB mass spectrum of **5** was obtained after permethylation, and showed a pattern for loss of from one to six methylated "anhydroglucose" units in vari-methylated groups beginning at *m/z* 3254 for $[M+H]^{+}$ ($C_{96}H_{158}O_{77}S_2$). Methylated "anhydroglucose" oligomers are probably lost by double glycosidic cleavages [11]. Other and more prominent peaks were observed at *m/z* 1853 (methylated dithiotrehalosyl-cyclodextrin fragment) and 1424 (methylated 6-thiocyclomaltoheptaosyl fragment).

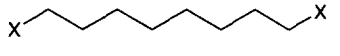
The NMR spectra of **5** and **6** were interpreted by means of 2D C–H correlation, as well as by comparison with the NMR spectra of glucopyranosyl-branched thiocyclodextrins. The shielding effect of the sulfur atoms is seen for the CH_2S carbons of



A

1 R = Ac, X = OTs
2 R = Ac, X = SBz
3 R = Ac, X = SAc
4 R = H, X = SH
5 R = H, X =





6 X as for 5

A, B, and C refer to the NMR assignments

rings A,B of **5** at 38.0 and 39.5 ppm, respectively. These were differentiated by assuming greater mobility for the trehalose linkage atoms as compared with those of the cyclodextrin torus, and applying an inversion recovery pulse sequence.

With the thioglucopyranosyl-branched cyclodextrins which we have previously synthesised, the sugar branches, although they dramatically increase solubility as compared with the natural cyclodextrin and thereby also make possible more effective guest solubilisation, do not noticeably modify either binding ability or mode of binding [7,12]. The thiotrehalose-linked cyclodextrin dimer **5**, however, was expected to show 1:1 binding of a suitably proportioned guest molecule which would fill both its cavities. Methyl Orange is a convenient guest to confirm such 1:1 binding [13]. As described previously for cyclomaltohexaose (α-cyclodextrin) and cinnamic acid, where a 2:1 (host:guest) complex is possible, deviation from linearity is observed in the "double reciprocal" plot of absorbance change with cyclodextrin molarity at relatively high host concentrations [14]. This non-linearity does not appear when the cyclodextrin dimer **5** complexes with Methyl Orange (Fig. 1). This is because the dual cavity includes both ends of the dye, making 2:1 complexation impossible even at high host-to-guest ratio[1]. A similar plot was obtained for the second dimer (**6**) with Methyl Orange. The apparent [16] association constants for the complexes obtained from these plots were: $K_a = 1 \times 10^5\ M^{-1}$ for the dimer **5** with Methyl Orange at pH 4, and $K_a = 1.5 \times 10^5\ M^{-1}$ for the dimer **6** (correlation coefficient > 0.9)[2].

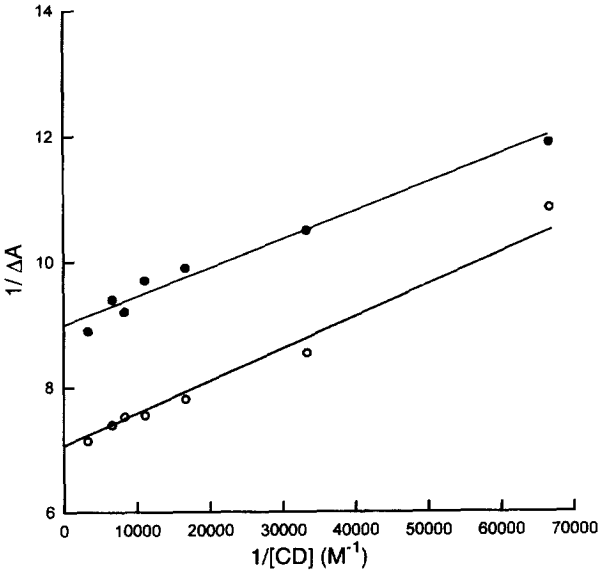


Fig. 1. Plots of reciprocal of molar concentration of cyclodextrin dimers **5** (○) and **6** (●) against reciprocal of absorbance change at λ 480 nm for Methyl Orange at pH 4.

These values may be compared with that obtained by Matsui and Mochida for the 1:1 complex of Methyl Orange with β-cyclodextrin under the same conditions ($K_a = 4 \times 10^2$) [13] to show that there is some advantage in the dual-cavity structures. The binding constants are much smaller than those for complexation by some other dimers with suitable guests, which may exceed 10^{10}, since the match between Methyl Orange and **5** or **6** is not optimal. Also, there is apparently no advantage in the rigid structure of the thiotrehalosyl-linked dimer for such a guest.

Although Methyl Orange confirms dual-cavity inclusion by the new dimers, larger and more complex guests will be needed to elicit any contrasting complexation behaviour. A more detailed study of complexation by these cyclodextrin dimers will be published elsewhere.

3. Experimental

General methods.—TLC was performed on precoated plates of Silica Gel 60 (Merck) by elution with 2-butanone–MeOH–water (4:1:1) (unless otherwise stated), and treatment with 5% H_2SO_4 in EtOH followed by heating.

For fast atom bombardment mass spectroscopy the methylated sample [17] was dissolved in MeOH and applied to a glycerol–thioglycerol target matrix. Analysis (by M-Scan Ltd) was done with a VG AUTOSPEC spectrometer operating at $V_{acc} = 8$ kV and a Cs ion gun operating on 30 kV at an emission current of 1 μA.

Concentrations of free thiol were monitored with 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB) as follows: thiol solution (50 μL) was added to DTNB solution (100 μL, 0.1 M) in phosphate buffer (1 mL, pH 8) and absorbance measured at 412 nm.

2,2′,3,3′,4,4′-Hexa-O-*acetyl-6,6′-di*-S-*benzoyl-6,6′-dithio*-α,α-*trehalose* (**2**).—Hexa-*O*-acetyl-6,6′-di-*O*-*p*-tolylsulfonyl-α,α-trehalose (**1**) [8] (1 g, 1.2 mmol)

[1]We have observed non-linearity with the drug clofazimine as a guest [15].

[2]The apparent K_a value is the sum of the different K_a values for the various anionic and tautomeric forms of Methyl Orange. Methyl Orange has a pK_a of 3.4 and, therefore, at the pH of our measurements (pH 4) exists in an equilibrium between basic and acidic forms.

in 1,3-dimethyl-2-oxohexahydropyrimidine (25 mL) was treated with sodium thiobenzoate (from 0.35 mL, 3 mmol, of thiobenzoic acid) at 80 °C (36 h). The solvent was removed in vacuo (0.4 mbar), and the product caused to solidify by addition of ice–water. Recrystallisation from MeOH gave compound **2** (0.64 g, 70%); mp 126–128 °C; $[\alpha]_D^{20}$ +141° (*c* 0.1, acetone). ^{1}H NMR (270 MHz, Me_2SO-d_6): δ 7.90 (d, 4 H, *J* 7 Hz, *o*-H), 7.71 (t 2 H, *J* 7 Hz, *p*-H), 7.68 (t, 4 H, *m*-H), 5.32 (t, 2 H, $J_{2,3}$ 10.5, $J_{3,4}$ 9.5 Hz, H-3,3′), 5.21 (d, 2 H, $J_{1,2}$ 3.7 Hz, H-1,1′), 5.03 (t, 2 H, $J_{4,5}$ 9.5 Hz, H-4,4′), 5.04 (dd, 2 H, H-2,2′), 3.92 (m, 2 H, $J_{5,6a}$ 2.5, $J_{5,6b}$ 4 Hz, H-5,5′), 3.44 (dd, 2 H, $J_{6a,6b}$ 14 Hz, H-6a,6a′), 3.22 (dd, 2 H, H-6b,6b′), 2.09–1.94 (m, 18 H, *Me*COO). ^{13}C NMR (68 MHz, Me_2SO-d_6): δ 190.1 (*C*OS), 169.6–169.1 (*C*OO), 135.90–126.9 (Ar), 90.6 (C-1,1′), 70.3–68.9 (C-2,2′,3,3′,4,4′,5,5′), 29.1 (C-6,6′), 20.3–20.1 (*Me*CO). Anal. Calcd for $C_{38}H_{42}O_{17}S_2$: C, 54.67; H, 5.07; S, 7.68. Found: C, 54.40; H, 5.03; S, 7.34.

2,2′,3,3′,4,4′-Hexa-O-*acetyl-6,6′-di*-S-*acetyl-6,6′-dithio-α,α-trehalose* (**3**).—Compound **1** [8] (1 g, 1 mmol) was dissolved in a solution of potassium thioacetate (0.3 g, 2.6 mmol) in DMF (60 mL) and the solution heated at 70 °C under nitrogen for 36 h. Evaporation of the solvent in vacuo and addition of ice–water gave the product, which was recrystallised twice from EtOH to obtain compound **3** (0.7 g, 90%); mp 153–155 °C; $[\alpha]_D^{20}$ +125° (*c* 0.1, acetone). ^{1}H NMR (270 MHz, Me_2SO-d_6): δ 5.29 (t, 2 H, $J_{2,3}=J_{3,4}=9.8$ Hz, H-3,3′), 5.15 (d, 2 H, $J_{1,2}$ 3.5 Hz, H-1,1′), 5.01 (dd, 2 H, H-2,2′), 4.96 (t, 2 H, $J_{4,5}$ 9.7 Hz, H-4,4′), 3.73 (dd, 2 H, $J_{5,6a}$ 2, $J_{5,6b}$ 4 Hz, H-5,5′), 3.20 (dd, 2 H, $J_{6a,6b}$ 14 Hz, H-6a,6a′), 2.94 (dd, 2 H, H-6b,6b′), 2.33 (s, 6 H, MeCOS), 2.04–1.98 (m, 18 H, MeCOO). ^{13}C NMR (68 MHz, Me_2SO-d_6): δ 169.7–169.4 (Me*C*O), 90.6 (C-1,1′), 70.3 (C-3,3′), 69.5 (C-5,5′), 69.2 (C-4,4′), 68.9 (C-2,2′), 29.1 (C-6,6′), 20.3–20.1 (*Me*COO), 15.0 (*Me*COS). Anal. Calcd for $C_{28}H_{38}O_{17}S_2$: C, 47.32; H, 5.39; S, 9.02. Found: C, 46.90; H, 5.37; S, 9.30.

6,6′-Dithio-α,α-trehalose (**4**).—Compound **2** (1 g, 1.2 mmol), dissolved in the minimum of dry acetone, was added to a solution of NaOMe (3 molar equiv) in MeOH (25 mL). After reaction under N_2 (30 min), the pH was adjusted to 7 by addition of Amberlite IR-120 (H^+-form) resin. After acidification with 1 M HCl and filtration, the solvent was removed in vacuo, and addition of ice-cold acetone precipitated the air-sensitive product **4** (0.4 g); mp 112 °C (dec); $[\alpha]_D^{20}$ +120° (*c* 0.1, water); ν_{max}^{KBr} 2584 cm^{-1} (SH); which was not further purified. The compound was similarly prepared by deacylation of **3**. Anal. Calcd for $C_{12}H_{22}O_9S_2$: C, 38.49; H, 5.92; S, 17.13. Found: C, 37.49; H, 6.40; S, 15.99.

*6-S-(6^I-Deoxycyclomaltoheptaos-6^I-yl)-6-thio-α-*D*-glucopyranosyl 6-S-(6^I-deoxycyclomaltoheptaos-6^I-yl)-6-thio-α-*D*-glucopyranoside* (**5**).—6,6′-Dithio-α,α-trehalose octaacetate (**3**) (1 g, 1.4 mmol), dissolved in dry acetone (6 mL), was added to a solution of NaOMe (3.5 mmol) in MeOH (20 mL). The solution was kept under N_2 (1 h), while thiol-deacetylation was monitored (DTNB). Then 6^I-*O*-*p*-tolylsulfonylcyclomaltoheptaose [7] (5.4 g, 4.2 mmol) and NaI (0.15 g) in dry DMF (40 mL) were added through a pressure-equalising funnel. The reaction solution was heated to 70 °C. After 36 h, TLC showed disappearance of the sulfonate (R_f 0.33) and appearance of product (R_f 0.03). Solvents were removed in vacuo and the product precipitated by addition of dry MeOH. After filtration the colourless powder was stirred with MeOH overnight and then washed with acetone to give **5** (1.6 g, 45%); mp 168–172 °C (dec); $[\alpha]_D^{20}$ +99° (*c* 0.15, water). ^{1}H NMR (500 MHz, Me_2SO-d_6): δ 5.54 (bm, OH-2A,2B,2C, OH-3A,3B,3C), 4.86 (d, 1 H, $J_{1,2}$ 6 Hz, H-1A), 4.83 (d, 1 H, $J_{1,2}$ 6 Hz, H-1B), 4.79 (d, 6 H, $J_{1,2}$ 5.7 Hz, H-1C), 4.3 (bm, OH-6C), 3.9–3.5 (m, H-2A,3A,5A,2B,3B,4B,5B,3C, 5C,6C) 3.4–2.6 (m, H-2C,4C,6B,6A). ^{13}C NMR (125.7 MHz, Me_2SO-d_6): δ 106.0 (m, C-1B, C-1C, C-1′C, C-1″C), 97.0 (C-1A), 88.3 (C-4B), 85.7 (C-4C), 77.5–76.0 (m, C-2A,2B,2C,3A,3B,3C,4A,5A, 5B,5C), 64.1 (C-6C), 39.5 (C-6B), 38.0 (C-6A). Anal. Calcd for $C_{96}H_{158}O_{77}S_2 \cdot 5H_2O$: C, 42.1; H, 6.23; S, 2.4. Found: C, 41.7; H, 6.29; S, 3.0.

*1,8-Di(6^I-thiocyclomaltoheptaos-6^I-*S*-yl)octane* (**6**).—The disodium salt of 1,8-octanedithiol was prepared by addition of the dithiol (0.5 g, 2.8 mmol) to NaOMe (from 0.1 g, 4.6 mmol, Na) in dry MeOH, followed by evaporation of the solvent. The disodium salt was redissolved in anhydrous DMF (10 mL) and 6^I-*O*-*p*-tolylsulfonylcyclomaltoheptaose [7] (11.85 g, 9.2 mmol), dissolved in DMF (10 mL), was added under N_2. The solution was maintained at 60 °C for 36 h, when TLC showed the formation of product (R_f 0.45). Solvent was removed in vacuo to a final volume of 5 mL. Addition of MeOH caused formation of a hygroscopic precipitate. This was filtered off and washed with MeOH, then acetone, and finally MeOH to obtain **6** (pure by TLC) (2.65 g 48%);

mp 210–219 °C (dec); $[\alpha]_D^{20}$ +157° (*c* 0.1, H_2O). ^1H NMR (500 MHz, Me_2SO-d_6): δ 5.5 (bm, OH-2A,2B,2C,3A,3B,3C), 5.02 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1B), 4.92 (d, 1 H, $J_{1,2}$ 4 Hz, H-1″C), 4.82 (bd, 5 H, $J_{1,2}$ 4 Hz, H-1C), 4.25 (bm, OH-6C), 4.2–3.6 (m, H-2B,3B,4B,5B,3C,6C), 3.58 (bd $J_{4,5}$ 9 Hz, H-5C), 3.34 (bt, $J_{3,4}$ 9 Hz, H-4C), 3.30 (q, $J_{2,3}$ 9.6 Hz, H-2C), 2.96 (dd, 1 H, $J_{5,6a}$ 2, $J_{6a,6b}$ 13 Hz, H-6aB), 2.75 (dd, 1 H, $J_{5,6b}$ 6 Hz, H-6bB), 2.53 (t, 2 H, $J_{\alpha,\beta}$ 7 Hz, H_α), 1.48 (m, 2 H, H_β), 1.30 (bm, 2 H, H_γ), 1.24 (m, 2 H, H_δ). ^{13}C NMR (68 MHz, D_2O): δ 101.9 (C-1B,1C), 81.9 (C-4B,4C), 73.9 (C-3B,3C), 72.1 (C-2B,2C), 71.9 (C-5B,5C), 64.0 (C-6C), 35.2–30.0 (m, C-6B, CH_2). Anal. Calcd for $C_{92}H_{154}O_{66}S_2$: C, 46.43; H, 6.48; S, 2.69. Found: C, 45.91; H, 6.29; S, 2.97.

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