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Note

Multiple tritylation: a convenient route to polysubstituted derivatives of cyclomaltohexaose

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Regioselective multiple substitution of the cyclomalto-oligosaccharides (cyclodextrins, CDs) has received considerable attention[1–10], in order to obtain compounds for use as models of enzymic catalysts[1,2] and to enhance their abilities in molecular recognition[3]. Tabushi *et al.*[4,5] have designed ligands for the AB, AC, and AD sulphonation of cyclomaltoheptaose (βCD), but, even with these highly specific complexes, the yields were of the order of 10–15%. For less exacting, but more widely used substituents, such as naphthylsulphonyl, tosyl, or trityl, attempts to poly-substitute the CDs gave < 10% of the desired compounds only after extensive chromatography[6–9]. However, for cyclomaltohexaose (αCD), 23% of the symmetrical $6^A,6^C,6^E$-tri-*O*-trityl derivative was obtained[10]. This method allows the synthesis of tri- and tetra-substituted derivatives of αCD in gram quantities with yields of 15–30%, and with only flash chromatography being used in the purification stage. The stereoisomers obtained are shown in Fig. 1, and designated according to Stoddart and co-workers[11].

As in the work of Boger *et al.*[10], 3.3 equiv. of trityl chloride were added to a solution of αCD in dry pyridine, but at a higher temperature (70° *vs.* 55°) and for longer times of reaction (36 h *vs.* 24 h). The crude mixture was then treated with iodomethane–sodium hydride in *N,N*-dimethylformamide. Flash chromatography then gave the ACE isomer (23%, R_F 0.34), the ABC isomer (21%, R_F 0.14), and a mixture (22%, R_F 0.25) of the ABD and ABE isomers. Boger *et al.*[10] recorded the ^{13}C-n.m.r. spectra of two non-symmetrical products and comparison with our data suggests that the second spectrum corresponds to the impure ABC isomer.

When the molar ratio of trityl chloride:αCD was increased to 4.5:1 and the time of reaction to 72 h, methylation and flash chromatography gave the three possible tetrasubstituted products: ABDE (25%, R_F 0.61), ABCD (15%, R_F 0.55), and ABCE (32%, R_F 0.48).

For all of the compounds obtained, the ^{1}H-n.m.r. spectra are complex and sensitive to the solvent. It is probable that ring current effects associated with the phenyl

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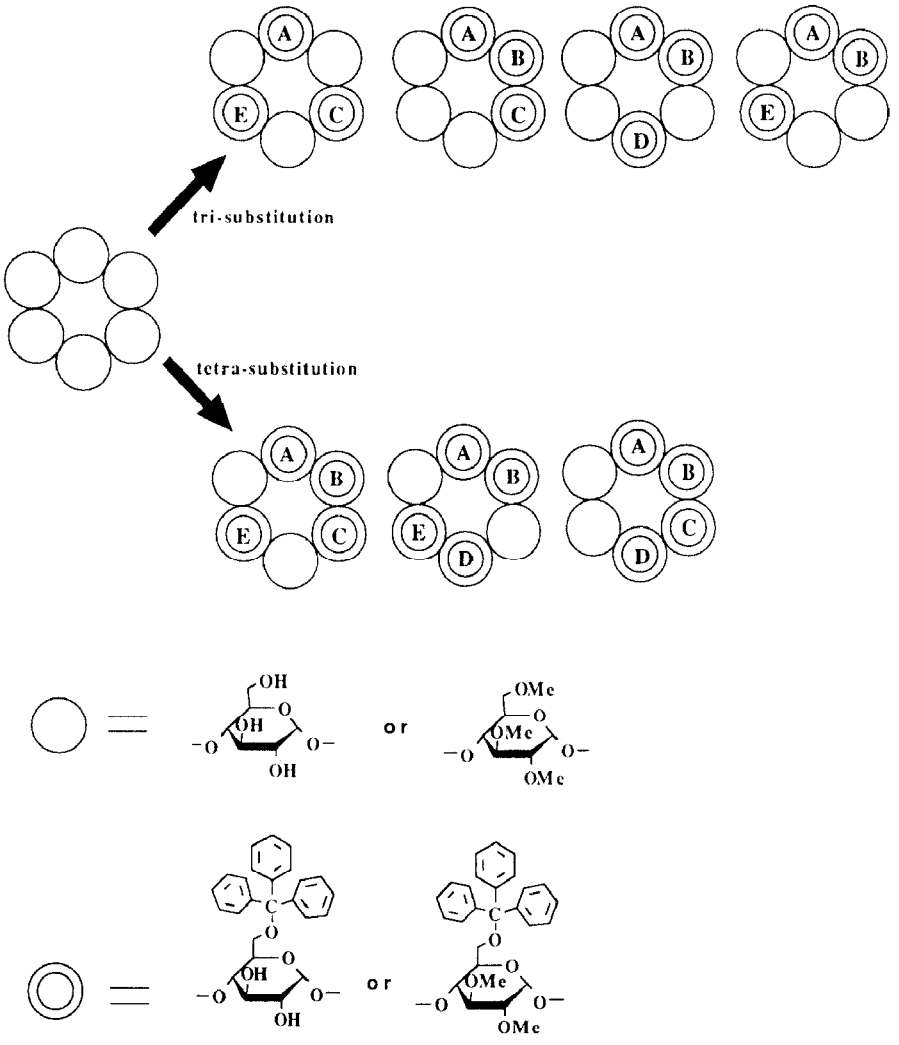

Fig. 1. Schematic representation of the tri- and tetra-substitution of αCD.

groups cause large shifts in the H-1 resonances. In consequence, the H-1 resonances for the symmetrical ACE compound are found at 4.92 and 5.23 p.p.m. (in CD_3COCD_3). Fig. 2 shows the ^{1}H-n.m.r. spectra of the region for anomeric protons.

EXPERIMENTAL

Commercial compounds were used without purification, except where otherwise stated. Cyclomaltohexaose (αCD, Fluka) was dried at 0.1 mmHg and 120° for 24 h. Pyridine and *N,N*-dimethylformamide were freshly distilled over CaH_2. During work-up, the aqueous-washed organic solutions were dried over Na_2SO_4. T.l.c. was performed

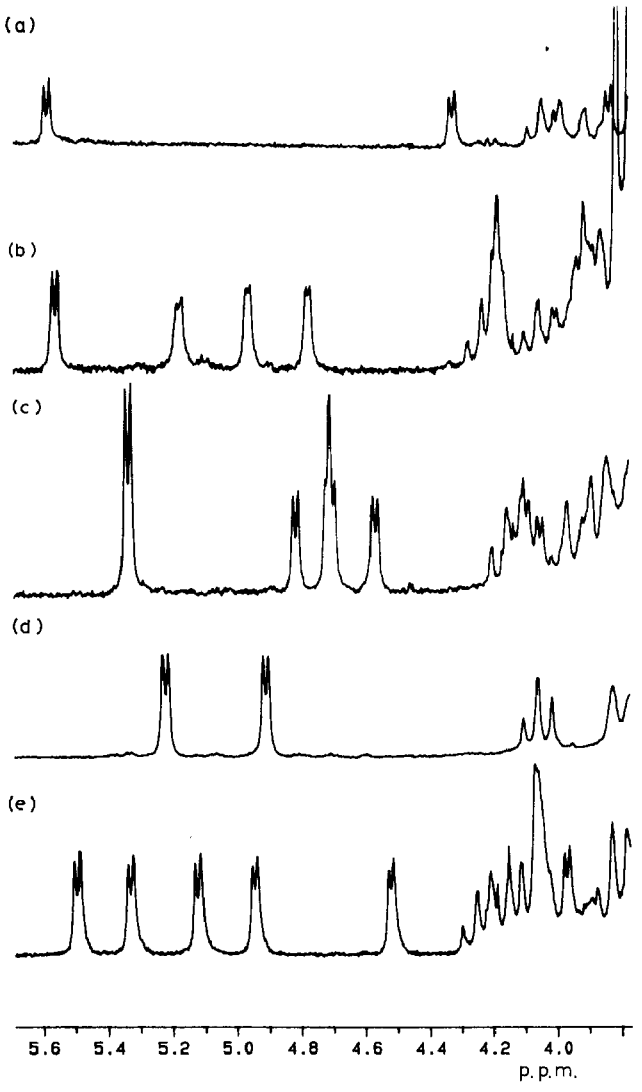

Fig. 2. ^{1}H-N.m.r. spectra (200 MHz) of the region for anomeric protons of the methylated tri- and tetra-*O*-trityl derivatives of αCD: (a) $6^A,6^B,6^D,6^E$; (b) $6^A,6^B,6^C,6^D$; (c) $6^A,6^B,6^C,6^E$; (d) $6^A,6^C,6^E$; (e) $6^A,6^B,6^C$ (see Experimental).

on Silica Gel F_{254} (Merck) with detection by charring with H_2SO_4. N.m.r. spectra (^{1}H, 200 MHz; ^{13}C, 50 MHz) were recorded with a Bruker AC 200P spectrometer for solutions in acetone-d_6.

Procedure for trisubstitution. — To a solution of dry αCD (4.0 g, 4.11 mmol) in anhydrous pyridine (150 mL) was added trityl chloride (3.9 g, 13.57 mmol). The stirred solution was kept for 36 h at 70°, then poured into water (600 mL), and the precipitate was collected and dried. To a solution of the crude product (6.8 g) in dry *N,N*-dimethylformamide (200 mL) was added sodium hydride (9.6 g, 60% dispersion in

mineral oil). The mixture was stirred for 1 h, MeI (12 mL, freshly distilled) was added slowly, the temperature was kept at $<35°$, and the mixture was stirred for 4 h. Excess of NaH was destroyed by the addition dropwise of MeOH, water (500 mL) was added, the mixture was extracted with ether, the extract was washed with water and dried, the solvent was evaporated, and the residue was subjected to flash chromatography (*tert*-butyl methyl ether–heptane, step gradient: 60:40→75:25), to give the following compounds.

Pentadeca-*O*-methyl-6^A,6^C,6^E-tri-*O*-tritylcyclomaltohexaose (1.81 g, 23%), R_F 0.34 (*tert*-butyl methyl ether–heptane, 7:3). ^{13}C-N.m.r. data: δ 144.59, 129.00, 127.83, 127.10 (aromatic), 99.78, 97.63 (C-1), 86.40 (Ph_3C), 82.72, 82.16, 82.01, 81.71, 81.52, 81.12 (C-2,3,4), 71.54, 71.00 (C-5), 71.34, 63.11 (C-6), 61.13, 60.86 (MeO-3), 58.17, 57.94, 57.18 (MeO-2,6).

Anal. Calc. for $C_{108}H_{132}O_{30}$: C, 67.91; H, 6.97. Found: C, 68.20; H, 6.94.

Pentadeca-*O*-methyl-6^A,6^B,6^C-tri-*O*-tritylcyclomaltohexaose (1.65 g, 21%), R_F 0.14. ^{13}C-N.m.r. data: δ 145.44, 145.29, 145.08, 129.83, 129.69, 128.96, 128.61, 127.94 (aromatic), 100.63, 99.83, 99.51, 99.21, 98.00, 97.36 (C-1), 87.17, 86.86 (Ph_3C), 83.88, 83.67, 82.59, 82.36, 81.72, 79.29, 78.49, 77.20, 73.22, 72.45, 72.07, 71.55 (C-2,3,4,5), 71.84, 63.98 (C-6), 63.98, 62.07, 61.93, 61.64, 61.23, 60.09, 59.56, 59.40, 59.22, 59.00, 58.77, 58.47, 58.11, 57.48 (MeO-2,3,6).

Anal. Found: C, 67.90; H, 7.05.

Procedure for tetrasubstitution. — A solution of αCD (4.0 g, 4.11 mmol) in anhydrous pyridine (60 mL) at 70° was stirred with trityl chloride (5.32 g, 18.50 mmol) for 48 h, then concentrated under reduced pressure. A solution of the residue in $CHCl_3$ was washed with water, dried, and concentrated. To a solution of the crude solid (8.6 g) in dry *N,N*-dimethylformamide (250 mL) was added NaH (15.2 g, 60% dispersion in mineral oil), the mixture was stirred for 1 h at room temperature, MeI (23.6 mL, freshly distilled) was added dropwise, and the temperature of the mixture was kept below 35° for 4 h. Excess of NaH was destroyed by MeOH, the solution was diluted with H_2O (600 mL) and extracted with ether, the extract was dried, the solvent was evaporated, and the residue was subjected to flash chromatography (ethyl acetate–heptane, 45:55) to give the following compounds.

Tetradeca-*O*-methyl-6^A,6^B,6^D,6^E-tetra-*O*-tritylcyclomaltohexaose (2.20 g, 25%), R_F 0.61 (ethyl acetate–heptane, 6:4). ^{13}C-N.m.r. data: δ 144.99, 129.70, 129.41, 128.82, 128.45, 127.79 (aromatic), 98.62, 97.82, 97.08 (C-1), 86.69, 86.46 (Ph_3C), 83.84, 83.49, 82.73, 82.50, 81.88, 74.91 (C-2,3,4), 72.99, 72.11, 70.85 (C-5), 71.18, 62.17 (C-6), 61.96, 61.27, 60.87, 59.92, 59.47, 58.46, 57.41 (MeO-6,2,3).

Anal. Calc. for $C_{126}H_{144}O_{30}$: C, 70.77; H, 6.79. Found: C, 70.66; H, 6.87.

Tetradeca-*O*-methyl-6^A,6^B,6^C,6^D-tetra-*O*-tritylcyclomaltohexaose (1.32 g, 15%), R_F 0.55. ^{13}C-N.m.r. data: δ 144.35, 144.09, 128.88, 127.15 (aromatic), 96.93, 96.32, 95.61 (C-1), 86.38, 86.15, 86.03 (Ph_3C), 83.54, 83.24, 82.68, 76.10, 72.89, 72.47, 71.21 (C-2,3,4,5), 71.50, 62.60 (C-6), 61.20, 60.67, 60.51, 60.13, 59.24, 58.95, 58.46, 57.95, 57.85 (MeO-6,2,3).

Anal. Found: C, 70.73; H, 6.62.

Tetradeca-*O*-methyl-6^A,6^B,6^C,6^E-tetra-*O*-tritylcyclomaltohexaose (2.84 g, 32%), R_F 0.48. ^{13}C-N.m.r. data: δ 145.54, 145.24, 145.13, 144.98, 132.01, 129.67, 129.45, 128.64, 128.45, 127.75 (aromatic), 99.87, 99.64, 99.06, 97.70 (C-1), 86.97, 86.91, 86.80 (Ph_3C), 83.52, 83.22, 82.89, 82.71, 82.37, 82.26, 82.02, 81.87, 81.43, 80.69, 80.26, 79.73 (C-2,3,4), 73.51, 72.73, 72.33, 72.18, 71.83 (C-5), 72.06, 68.31, 64.80, 63.73, 63.12 (C-6), 61.87, 61.50, 61.38, 61.27 (MeO-3), 59.16, 59.02, 58.85, 58.64, 58.53, 58.15, 57.59 (MeO-2,6).

Anal. Found: C, 70.51; H, 6.78.

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