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Conformational Mobility in Chemically-Modified Cyclodextrins

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Abstract. The observation that per-2,6-*O*-methyl-3-*O*-benzoyl-α-cyclodextrin (**1**) displays some unusual conformational behaviour in solution has led to a detailed investigation by (dynamic) NMR spectroscopy of the equilibration process that occurs in solutions of per-2,3-*O*-benzoyl-α-cyclodextrin (**3**) and some related compounds (**7**–**9**) between conformational isomers with averaged C_6 and C_3 molecular symmetries in certain organic solvents such as benzene, dichloromethane, and chloroform. The solvent dependence of the conformational equilibrium is also reflected in a spread of values for the specific optical rotations for **3** from +9° in 1,1,2,2-tetrachloroethane, where there is a degenerate equilibrium between species with C_3 molecular symmetry, to +92° in acetone where a species with averaged C_6 symmetry is present.

Key words. Chemically-modified cyclodextrins, conformational analysis, NMR spectroscopy.

This paper is dedicated to the memory of Charles J. Pedersen whose seminal papers on crown ethers in the late 1960s captured the imagination of the senior author, encouraging him to effect (J. K. N. Jones, J. F. Stoddart, and W. A. Szarek, *Cand. J. Chem.* **47**, 3213 (1969)) the chemical modifications of α-cyclodextrin and β-cyclodextrin to 30- and 35-membered ring compounds containing 12 and 14 oxygen atoms, respectively. This early foray into the synthesis of oxygen-containing macrocycles was to lead directly to the incorporation of carbohydrates into chiral crown ethers (J. F. Stoddart, *Chem. Soc. Rev.* **8**, 85 (1979); *Top. Stereochem.* **17**, 207 (1987)), whilst preserving more than a passing interest (J. F. Stoddart, R. Zarzycki, *Rec. Trav. Chim. Pays-Bas* **107**, 515 (1988)) in one of Nature's most fascinating collection of compounds, the cyclodextrins, which share with Pedersen's wholly synthetic creations, the crown ethers, the ability to form inclusion complexes with other molecules and ions.

1. Introduction

Cyclodextrins (CDs) are a class of cyclic oligosaccharides composed of α-(1→4)-linked D-(+)-glucopyranose residues. They are designated by a Greek letter according to the number of residues. The commonly available CDs have 6, 7 and 8 D-glucopyranose units and are called α-, β- and γ-CD, respectively. In the 100 years [1] that have elapsed since they were first isolated by Villiers [2] they have been the subject of a large amount of research. It is well established that the D-glucopyranose units are in the $^4C_1$ chair conformation, and that the overall shape of the molecules is that of a truncated cone [3]. Their most characteristic feature – their ability to form inclusion complexes – is a direct consequence of this shape, and is being increasingly exploited in technological fields [4].

This paper is dedicated to the memory of the late Dr C. J. Pedersen.

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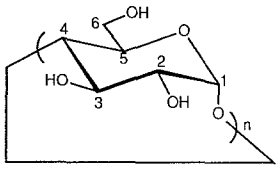


α-CD n = 6

β-CD n = 7

γ-CD n = 8

Numerous chemical modifications [5] of cyclodextrins have been performed with the aim of improving the complexing abilities and catalytic properties of the parent molecules [6]. To date, most of the research has concentrated on the modification of the primary face of cyclodextrins because of the relatively high reactivity of the C-6 hydroxyl groups. NMR spectroscopic studies carried out on the parent molecules are facilitated by the fact that rapid inter-residue motion results in NMR spectra which are qualitatively similar to that of one D-glucopyranose residue [7]. A large number of the chemically-modified CDs which have been prepared, maintain the original C_n molecular symmetry (n = number of glucose units) of the parent molecules, and therefore also give relatively simple NMR spectra. However, as the secondary faces of the molecules become [8] more amenable to synthetic elaboration, and the rigidifying effect of the circular network of intramolecular hydrogen bonds is removed, a range of conformationally-mobile CDs is revealed. In a series of elegant X-ray crystallographic studies carried out on per-methylated CDs, Harata [9] has shown that removal of the possibility of intramolecular hydrogen bonding [3] by per-methylation of CD molecules results in derivatives with drastically distorted cavities. In this paper, we wish to discuss the properties of some symmetrically-substituted CD derivatives which, as revealed by their unusually complex NMR spectra, exist in atypical conformations in solution.

2. Experimental

2.1. GENERAL SYNTHETIC PROCEDURES

Unless otherwise stated, chemicals were used as received. Prior to use, α-cyclodextrin was dried at 100°C, under high vacuum, in the presence of P_2O_5 for 24 hours. Literature procedures were employed for drying solvents. Column chromatography was carried out using Silica Gel 60 (Merck 7736 or 9385). Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. Microanalyses were performed by the University of Sheffield Microanalytical Service. Optical rotations were determined on a Perkin Elmer 141 polarimeter. Fast atom bombardment mass spectra (FABMS) were obtained using xenon and were performed on the Kratos MS 80 instrument with *m*-nitrobenzyl alcohol as the matrix. ^{1}H NMR spectra were recorded on (1) a Bruker WH 400 spectrometer (400.1 MHz) or (2) a Bruker AM 250 spectrometer (250.1 MHz). ^{13}C NMR spectra were recorded on (1) the Bruker WH 400 spectrometer (100.6 MHz) or (2) the Bruker AM 250 spectrometer (62.9 MHz). ^{19}F NMR spectra were recorded on a Bruker WP 80 SY spectrometer (74.9 MHz). All chemical shifts are quoted in ppm on the δ scale. All ^{1}H and ^{13}C NMR spectra were referenced to trimethylsilane (TMS) using either the solvent reference of internal TMS. ^{19}F NMR spectra were referenced to external

$CFCl_3$. In reporting the NMR chemical shift data, the superscripts A, B, C, and D are used to differentiate between different benzoyl and substituted-benzoyl groups.

2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F-Dodeca-O-benzoyl-α-cyclodextrin (Per-2,3-O-benzoyl-α-CD) (**3**) [12]

Potassium 2-propoxide in 2-propanol was prepared by adding clean potassium metal to distilled 2-propanol. This solution was titrated to determine the concentration of base. Per-2,3,6-*O*-benzoyl-α-cyclodextrin (1.22 g, 0.43 mmol) was added with stirring to distilled benzene (17 mL) under nitrogen and distilled 2-propanol (8.6 mL) was added. The resulting solution was cooled to 0°C and potassium 2-propoxide was added (3.03 mL of 0.847M solution, 2.58 mmol, i.e. 6 molar equiv.). The reaction mixture was allowed to warm up to room temperature and the solution was stirred at room temperature for 0.5 h. It was then neutralised with hydrochloric acid and the organic solvents were removed under vacuum. The resulting residue was shaken with ethanol-free chloroform (50 mL). The chloroform solution was washed with saturated aqueous chloride solution (3 × 30 mL) and dried ($MgSO_4$). Hexane was added to the chloroform solution until the product precipitated. This mixture was allowed to stand overnight and then it was filtered. The resulting cream coloured product was dried *in vacuo*. Column chromatography on silica gel using a gradient elution of chloroform to a chloroform/methanol mixture (9 : 1 v/v) achieved the purification of per-2,3-*O*-benzoyl-α-CD (**3**). (0.48 g, 51%); m.p. 209–210°C; (*Found*: C, 64.1; H, 4.9%; *m/z* (positive-ion FABMS), 2244 for $[M + Na]^+$. *Calc.* for $(C_{20}H_{18}O_7)_6$: C, 64.8; H, 4.9%; M, 2221); $[\alpha]_D + 71°$ (*c*, 1.2 in CH_3SOCH_3), $[\alpha]_D + 11°$ (*c*, 1.0 in $CHCl_3$) (Lit. [12] $[\alpha]_D + 96°$(*c*, 1.3 in CH_3SOCH_3), $[\alpha]_D + 9°$ (*c*, 1.1 in $CHCl_3$)); δ_H (400 MHz, CD_3COCD_3), 4.29 (12 H, *br m*, 5-H, 6b-H), 4.35 (6 H, *dd*, $J_{3,4}$,$J_{4,5}$8 Hz, 4-H), 4.63 (6 H, *dd*, $J_{5,6a} < 2$, $J_{6a,6b}$10 Hz, 6a-H), 5.04 (6 H, *dd*, $J_{1,2}$4, $J_{2,3}$10 Hz, 2-H), 5.52 (6 H, *d*, $J_{1,2}$4 Hz, 1-H), 6.14 (6 H, *dd*, $J_{2,3}$10, $J_{3,4}$8 Hz, 3-H), 6.96 (12 H, *t*, $J_{o,m}$, $J_{m,p}$8 Hz, C_m-H), 7.08 (12 H, *t*, $J_{o,m}$, $J_{m,p}$8 Hz, C_m-H), 7.29 (6 H, *t*, $J_{m,p}$8 Hz, C_p-H), 7.32 (6 H, *t*, $J_{m,p}$8 Hz, C_p-H), 7.45 (12 H, *d*, $J_{o,m}$8 Hz, C_o-H), and 7.60 (12 H, *d*, $J_{o,m}$8 Hz, C_o-H). δ_H (400 MHz, $CDCl_3$) 4.05 (3 H, *m*, $J_{4'5'}$9 Hz, 5′-H), 4.3–4.6 (12 H, *m*, 4-H, 6a′-H, 6b-H, 6b′-H), 4.7–4.9 (12 H, *m*, 2′-H, 4′-H, 5-H, 6a-H), 5.42 (3 H, *br s*, 1-H), 5.60 (3 H, *dd*, $J_{1,2}$3.5, $J_{2,3}$10 Hz, 2-H), 5.70 (3 H, *d*, $J_{1,2}$3.5 Hz, 1-H), 6.20 (3 H, *t*, $J_{2,3}$, $J_{3,4}$10 Hz, 3-H), 6.28 (3 H, *t*, 3′-H), 6.28 (6 H, *t*, C_m^D-H), 6.62 (6 H, *d*, $J_{o,m}$7.5 Hz, C_o^D-H), 6.86 (3 H, *t*, $J_{m,p}$7.5 Hz, C_p^D-H), 7.12 (6 H, *t*, $J_{o,m}$,$J_{m,p}$7.5 Hz, C_m^C-H), 7.24 (6 H, *t*, $J_{o,m}$, $J_{m,p}$8 Hz, C_m^A-H), 7.33 (6 H, *d*, $J_{o,m}$7.5 Hz, C_o^C-H), 7.35 (3 H, *t*, $J_{m,p}$7.5 Hz, C_p^C-H), 7.43 (3 H, *t*, $J_{m,p}$8 Hz, C_p^A-H), 7.47 (6 H, *t*, $J_{o,m}$, $J_{m,p}$8 Hz, C_m^B-H), 7.55 (3 H, *t*, $J_{m,p}$8 Hz, C_p^B-H), 7.98 (6 H, *d*, $J_{o,m}$8 Hz, C_o^B-H), and 8.10 (6 H, *d*, $J_{o,m}$8 Hz, C_o^A-H). δ_C (100 MHz, C_5D_5N) 62.4 (C-6), 73.0 (C-2), 73.4 (C-3), 73.6 (C-5), 77.9 (C-4), 98.0 (C-1), 128.2 and 128.3 (C_m), 129.9 and 130.1 (C_o), 132.7 and 133.1 (C_p). δ_C (100 MHz, $CDCl_3$) 52.3 and 64.7 (C-6, C-6′), 68.7 (C-2), 71.8 (C-5), 72.3 and 72.4 (C-3, C-3′), 73.4 and 73.5 (C-2′, C-5), 74.9 (C-4′), 77.9 (C-4), 94.5 (C-1′), 98.2 (C-1), 127.2 (C_m^D), 127.6 (C_i), 127.6 (C_m^A), 127.8 (C_m^C), 128.0 (C_m^B), 128.9 (C_i), 129.0 (C_o^D), 129.2 (C_i), 129.3 (C_o^C), 130.5 (C_o^A), 130.6 (C_i), 130.8 (C_o^B), 131.7 (C_p^D), 131.9 (C_p^A), 132.4 (C_p^C), and 132.6 (C_p^B).

2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F-Dodeca-O-benzoyl-6^A, 6^B, 6^C, 6^D, 6^E, 6^F-Hexa-O-p-toluenesulphonyl-α-cyclodextrin (Per-2-3-O-benzoyl-6-O-tosyl-α-CD) (**10**) [12]

Dry per-2,3-O-benzoyl-α-CD (**3**) (100 mg, 4.5×10^{-5} mol) was dissolved in pyridine (4.5 mL) under nitrogen. Freshly recrystallised *p*-toluenesulphonyl chloride (0.85 g, 4.5 mmol, 100 equiv.) was added to this solution. The reaction mixture was stirred overnight at room temperature. When the product was poured, with stirring, into ice/water, a fine white precipitate was formed. This precipitate was separated by fast (*ca.* 3000 rpm) centrifugation. The pyridine/water was decanted and the solid was dissolved in dichloromethane. Addition of light petroleum (bp. 60–80°C) to the solution reprecipitated the crude product which was again isolated by fast centrifugation followed by the decantation of the mother liquor. Subjecting the crude material to column chromatography on silica gel, using chloroform as the eluant, yielded a white solid that was characterised as per-2,3-*O*-benzoyl-6-*O*-tosyl-α-CD (120 mg, 85%); m.p. 155–156°C; (*Found*: C, 61.6; H, 4.58; S, 5.92%; *m/z* (positive-ion FABMS), 3168 for $[M + Na]^+$. *Calc.* for $(C_{27}H_{24}O_9S)_6$: C, 61.8; H, 4.61; S, 6.11%, M, 3145). $[\alpha]_D + 109°$ (*c*, 0.9 in $CHCl_3$) (Lit. [12] $[\alpha]_D + 104°$ (*c*, 1.1 in $CHCl_3$));δ_H (250 MHz, $CDCl_3$), 2.51 (18 H, *s*, Me), 3.95 (6 H, *dd*, $J_{3,4}9$, $J_{4.5}9$ Hz, 4-H), 4.40–4.67 (18 H, *m*, 5-H, 6a-H and 6b-H), 4.71 (6 H, *dd*, $J_{1,2}3.5$, $J_{2,3}10.5$ Hz, 2-H), 5.05 (6 H, *d*, $J_{1,2}3.5$ Hz, 1-H), 6.00 (6 H, *dd*, $J_{2,3}10.5$, $J_{3,4}9$ Hz, 3-H), 6.74 (12 H, *t*, $J_{o,m}$, $J_{m,p}8$ Hz, C_m-H), 6.81 (12 H, *t*, $J_{o,m}$, $J_{m,p}8$ Hz, C_m-H), 7.05 (12 H, *tt*, $J_{o,p}1.5$, $J_{m,p}8$ Hz, C_p-H), 7.08 (12 H, *dd*, $J_{o,m}$, $J_{o,p}1.5$ Hz, C_o-H), 7.27 (12 H, *dd*, $J_{o,m}8$, $J_{o,p}1.5$ Hz, C_o-H), 7.44 (12 H, BB′ of an AA′BB′ system, $J_{A,B}8$ Hz, C_m-H of tosylate), and 7.91 (12 H, AA′ of an AA′BB′ system, $J_{A,B}8$ Hz, C_o-H of tosylate). δ_C (63 MHz, $CDCl_3$) 22(Me), 69.0 (C-6), 70.0 (C-2), 71.0 (C-3), 71.8 (C-5), 78.5 (C-4), 98.5 (C-1), 127.4, 128.1, 129.3, 129.6, 130.1, 132.0, 132.4 (aromatic C—H), 127.7 (*C*—Me), 129.1, 132.9 (*C*—CO), 145.3 (C—SO_2), 164.3 and 165.8 (C=O).

2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F-Dodeca-O-benzoyl-6^A, 6^B, 6^C, 6^D, 6^E, 6^F-Hexa-O-methanesulphonyl-α-cyclodextrin (Per-2,3-O-benzoyl-6-O-mesyl-α-Cd) (**11**)

Dry per-2,3-*O*-benzoyl-α-CD (**3**) (100 mg, 0.045 mmol) was dissolved in dichloromethane (5 mL) containing freshly-distilled triethylamine (1 mL) at 0°C under nitrogen. Freshly distilled methanesulphonyl chloride (1 mL) was added over a period of 5 min. The colour of the solution turned bright yellow and a precipitate was formed. After stirring the solution for about 15 min, the solvents were removed under reduced pressure to give a pale yellow precipitate. An attempted recrystallisation using dichloromethane/hexane led to a precipitate, which was shown by TLC (chloroform/methanol, 9 : 1 v/v) to be mostly a side-product, presumably $Et_3NH^+MeSO_3^-$. It also gave a mother liquor which was enriched in the desired product. The mother liquors were removed under vacuum to give a white residue which was passed through a short chromatography column packed with silica gel using dichloromethane and then chloroform as an eluant. Removal of solvents under vacuum gave a white solid. The recrystallised product was dissolved in

dichloromethane (5 mL) and this solution was washed successively with hydrochloric acid (0.05M), dilute sodium bicarbonate, and water (all 3 × 5 mL). The resulting product was again further purified by passing it through a short chromatography column packed with silica gel using dichloromethane followed by chloroform as the eluants. Removal of solvents under vacuum gave a white solid which was characterised as per-2,3-*O*-benzoyl-6-*O*-mesyl-α-CD. (40 mg, 33%); m.p. 215–216°C; (*Found*: C, 56.3; H, 4.5; S, 7.3%; *m/z* (positive ion FABMS), 2712 for $[M + Na]^+$. $(C_{21}H_{20}O_9S)_6$ requires C, 56.3; H, 4.5; S, 7.1%; M, 2689). $[\alpha]_D + 97°$ (*c*, 0.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$), 3.26 (18 H, *s*, $-SO_2Me$), 4.15 (1 H, *dd*, $J_{3,4}$10, $J_{4,5}$10 Hz, 4-H), 4.65 (6 H, *m*, $J_{4,5}$10 Hz, 5-H), 4.79 (6 H, *d*, $J_{5,6b}$1.5, $J_{6a,6b}$11.5 Hz, 6b-H), 4.89 (6 H, *dd*, $J_{5,6a}$1.5, $J_{6a,6b}$11.5 Hz, 6a-H), 4.96 (6 H, *dd*, $J_{1,2}$3.5, $J_{2,3}$10.5 Hz, 2-H), 5.48 (6 H, *d*, $J_{1,2}$3.5 Hz, 1-H), 6.19 (6 H, *dd*, $J_{2,3}$10.5, $J_{3,4}$10 Hz, 3-H), 6.76 (12 H, *t*, $J_{o,m}$, $J_{m,p}$7.5 Hz, C_m-H), 6.81 (12 H, *t*, $J_{o,m}$, $J_{m,p}$7.5 Hz, C_m-H), 7.05 (6 H, *tt*, $J_{o,p}$1.5, $J_{m,p}$7.5 Hz, C_p-H), 7.07 (6 H, *tt*, $J_{o,p}$1.5, $J_{m,p}$7.5 Hz, C_p-H), 7.25 (12 H, *dd*, $J_{o,m}$7.5, $J_{o,p}$1.5 Hz, C_o-H), and 7.32 (12 H, *dd*, $J_{o,m}$7.5, $J_{o,p}$1.5 Hz, C_o-H).

2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^A, 6^B, 6^C, 6^D, 6^E, 6^F-Octadeca-O-p-fluorobenzoyl-α-cyclodextrin (Per-2,3,6-O-p-fluorobenzoyl-α-CD)

Dry α-CD (1.2 g, 1.2 mmol) was added with stirring to a solution of freshly distilled *p*-fluorobenzoyl chloride (12 mL, 14.4 g, 0.096 mol, i.e. 80 molar equiv.) in dry pyridine (50 mL) under nitrogen. When the resulting white suspension was heated to 100°C, a clear solution was obtained. This temperature was maintained for 4 days. The dark red mixture was poured, with stirring, into water (300 mL), to give a beige-coloured precipitate which was filtered. The filtered precipitate was subjected to column chromatography on silica gel with a gradient elution from dichloromethane to 5% methanol in dichloromethane. A second column was required in order to isolate a pure white solid which was characterised as per-2,3,6-*O*-*p*-fluorobenzoyl-α-CD. (2.4 g, 61%); m.p. 171–172°C; (*Found*: C, 61.1; H, 3.62%; *m/z* (positive-ion FABMS), 3192 for $[M + Na]^+$. $(C_{27}H_{19}O_8F_3)_6$ requires C, 61.4; H, 3.60%; M, 3169). $[\alpha]_D + 37°$ (*c*, 0.4 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$), 4.15 (6 H, *t*, $J_{3,4}$, $J_{4,5}$9 Hz, 4-H), 4.73 (6 H, *br d*, $J_{6a,6b}$11 Hz, 6b-H), 4.80 (6 H, *m*, 5-H), 4.84 (6 H, *dd*, $J_{1,2}$3, $J_{2,3}$10 Hz, 2-H), 5.01 (6 H, *br d*, $J_{6a,6b}$11 Hz, 6a-H), 5.52 (6 H, *d*, $J_{1,2}$3 Hz, 1-H), 6.15 (6 H, *dd*, $J_{2,3}$10, $J_{3,4}$9 Hz, 3-H), 6.55 (12 H, BB′ part of a AA′BB′X system, $J_{A,B} = J_{o,m}$9 Hz, $J_{B,X} = J_{m,F}$9 Hz, secondary benzoyl C_m-H), 6.58 (12 H, BB′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$9 Hz, $J_{B,X} = J_{m,F}$9 Hz, secondary benzoyl C_m-H), 7.16 (12 H, BB′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$9 Hz, $J_{B,X} = J_{m,F}$9 Hz, primary benzoyl C_m-H), 7.29 (12 H, AA′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$9 Hz, $J_{A,X} = J_{o,F}$6 Hz, secondary benzoyl C_o-H), 7.35 (12 H, AA′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$9 Hz, $J_{A,X} = J_{o,F}$6 Hz, secondary benzoyl C_o-H), and 8.15 (12 H, AA′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$9 Hz, $J_{A,X} = J_{o,F}$6 Hz, primary benzoyl C_o-H). δ_C (63 MHz, $CDCl_3$), 63.3 (C-6), 70.4 (C-2), 71.6 (C-3), 72.9 (C-5), 79.0 (C-4), 98.6 (C-1), 114.8 (*d*, $J_{C,F}$22 Hz, 2 × secondary benzoyl C_m), 115.8 ($J_{C,F}$22 Hz, primary benzoyl C_m), 124.1, 125.2, 125.8 (*d*, each $J_{C,F}$2.5 Hz, *C*—CO), 131.8, 132.2, 132.5 (*d*, each $J_{C,F}$9 Hz, C_o), 163.7, 165.0, 165.1 (C=O), 165.4, 165.7, and 166.0 (*d*, each

$J_{C,F}$255 hz, C—F). δ_F (75.4 MHz, $CDCl_3$), −105.4 (6 F, *tt*, $J_{o,F}$9, $J_{m,F}$6 Hz, secondary benzoyl F), −105.5 (6 F, *tt*, $J_{o,F}$9, $J_{m,F}$6 hz, secondary benzoyl F), and −106.0 (6 F, *tt*, $J_{o,F}$9, $J_{m,F}$6 Hz, primary benzoyl F).

2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F-Dodeca-O-p-fluorobenzoyl-α-cyclodextrin (Per-2,3-O-p-fluorobenzoyl-α-CD) (7)

Per-2,3,6-*O*-*p*-fluorobenzoyl-α-CD (50 mg, 1.6×10^{-5} mol) was dissolved in dry benzene (1 mL) and dry 2-propanol (1 mL). This solution was cooled to 0–5°C (ice-bath) under nitrogen. A solution of potassium 2-propoxide in 2-propanol (0.56 ml of a 0.17 M solution, 9.6×10^{-5} mol, i.e. 6 molar equiv.) was added and the reaction mixture was stirred at 0–5°C for 1 h. It was allowed to warm up to room temperature and then it was stirred for 1.5 h. The reaction mixture was neutralised with hydrochloric acid (*ca.* 0.1M) and the solvents were removed under reduced pressure to give a white residue. This crude product was subjected to column chromatography on silica gel using a gradient elution of dichloromethane to 10% methanol in dichloromethane to afford a white solid which was characterised as per-2,3-*O*-*p*-fluorobenzoyl-α-CD (13 mg, 34%); m.p. 304–305°C; (*Found*: C, 58.5; H, 4.59%; *m/z* (positive-ion FABMS), 2460 for $[M + Na]^+$. $(C_{20}H_{16}O_7F_2)_6$ requires C, 59.1; H, 3.97%; M, 2437); $[\alpha]_D + 10°$ (*c*, 0.2 in CH_3COCH_3); δ_H (250 MHz, CD_3COCD_3) 4.20–4.30 (12 H, *m*, 6a-H, 6b-H), 4.32 (6 H, *t*, $J_{3,4}$, $J_{4,5}$9 Hz, 4-H), 4.45 (6 H, *br s*, OH), 4.53 (6 H, *br d*, $J_{4.5}$9 Hz, 5-H), 4.91 (6 H, *dd*, $J_{1,2}$3.5, $J_{2,3}$10 Hz, 2-H), 5.54 (6 H, *d*, $J_{1,2}$3.5 Hz, 1-H), 6.05 (6 H, *dd*, $J_{2,3}$10, $J_{3,4}$9 Hz, 3-H), 6.77 (12 H, BB′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$ 9 Hz, $J_{B,X} = J_{m,F}$9 Hz, C_m-H), 6.81 (12 H, BB′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$ 9 Hz, $J_{B,X} = J_{m,F}$9 Hz, C_m-H), 7.45 (12 H, AA′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$ 9 Hz, $J_{A,X} = J_{o,F}$6 Hz, C_o-H), and 7.63 (12 H, AA′ part of an AA′BB′X system, $J_{A,B} = J_{o,m}$ 9 Hz, $J_{A,X} = J_{o,F}$6 Hz, C_o-H). δ_F (75.4 MHz, CD_3COCD_3) −106.8 (F, *tt*, $J_{o,F}$9, $J_{m,F}$6 Hz), and −107.5 (6 F, *tt*, $J_{o,F}$9, $J_{m,F}$6 Hz). The compound was only poorly soluble in $CDCl_3$, so the ^1H NMR spectrum recorded in this solvent exhibited a very poor signal/noise ratio. However, the general appearance of the spectrum was broad and complex, with the atypical doubling-up of expected resonances.

2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^A, 6^B, 6^C, 6^D, 6^E, 6^F-Octadeca-O-p-methoxybenzoyl-α-cyclodextrin (Per-2,3,6-O-p-methoxybenzoyl-α-CD)

Dry α-CD (1 g, 1.02×10^{-3} mol) was dissolved in distilled pyridine (50 mL). *p*-Methoxybenzoyl chloride (14 g, 0.082 mol, i.e. 80 molar equiv.) was added along with some more pyridine (20 mL). The reaction mixture was heated at 100°C for 4 days under nitrogen. It was then cooled and poured, with stirring, into ice/water (450 mL). The resulting beige coloured precipitate was filtered off and subjected to column chromatography on silica gel using a gradient elution of dichloromethane to chloroform. This chromatography achieved only a partial purification. Fractions corresponding to the major component were combined and the solvents were removed under vacuum to give a white solid that was characterised as per-2,3,6-*O*-*p*-methoxybenzoyl-α-CD. The isolated yield of the pure material after one column

was 1.0 g, 29%; m.p. 153–155°C; (*Found*: C, 63.4; H, 4.46%; *m/z* (positive-ion FABMS), 3410 for $[M + Na]^+$. $(C_{30}H_{28}O_{11})_6$ requires C, 63.8; H, 4.96%; M, 3387). $[\alpha]_D + 37°$ (*c*, 0.45 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$), 3.65 (36 H, *s*, 2 × OMe), 3.84 (18 H, *s*, OMe), 4.20 (6 H, *t*, $J_{3,4}$, $J_{4,5}$ 9 Hz, H-4), 4.77 (6 H, *m*, 5-H), 4.85 (6 H, *m*, 6b-H), 4.87 (6 H, *dd*, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, 2-H), 5.02 (6 H, *m*, $J_{6a,6b}$ 12 Hz, 6a-H), 5.51 (6 H, *d*, $J_{1,2}$ 3.5 Hz, 1-H), 6.19 (6 H, *dd*, $J_{2,3}$ 9, $J_{3,4}$ 10 Hz, 3-H), 6.31 (12 H, $(BB')^A$ of an $(AA'BB')^A$ system, $J_{o,m}$ 9 Hz, secondary benzoyl C_m^A-H), 6.34 (12 H, $(BB')^B$ of an $(AA'BB')^B$ system, $J_{o,m}$ 9 Hz, secondary benzoyl C_m^B-H), 6.96 (12 H, $(BB')^C$ of an $(AA'BB')^C$ system, $J_{o,m}$ 9 Hz, primary benzoyl C_m^C-H), 7.31 (12 H, $(AA')^A$ of an $(AA'BB')^A$ system, $J_{o,m}$ 9 Hz, secondary benzoyl C_o^A-H), 7.35 (12 H, $(AA')^B$ of an $(AA'BB')^B$ system, $J_{o,m}$ 9 Hz, secondary benzoyl C_o^B-H), and 8.11 (12 H, $(AA')^C$ of an $(AA'BB')^C$ system, $J_{o,m}$ 9 Hz, primary benzoyl C_o^C-H). δ_C (63 MHz, $CDCl_3$), 54.9 (2 × OMe), 55.3 (OMe), 63.2 (C-6), 70.5 (C-2), 71.4 (C-3), 72.6 (C-5), 79.0 (C-4), 98.6 (C-1), 112.6, 112.7, 113.8 (C_m), 120.8, 122.3, 122.5 (*C*—OMe), 131.5, 131.9, 132.0 (C_o), 162.3, 162,7, 163.3 (*C*—CO), 164.2, 165.6, and 165.9 (C=O).

2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F-Dodeca-O-p-methoxybenzoyl-α-cyclodextrin (Per-2,3-O-p-methoxybenzoyl-α-CD) (**8**)

Per-2,3,6-*O*-*p*-methoxybenzoyl-α-CD (100 mg, 0.0295 mmol) was dissolved in distilled 2-propanol (2 mL) and distilled benzene (3 mL) at 0–5°C (ice-bath) under nitrogen. A solution of postassium 2-propoxide in 2-propanol (0.32 mL of a 0.56M solution, 1.77×10^{-4} mol, 6 molar equiv.) was added and the solution was stirred at 0–5°C for 4 h before being allowed to warm to room temperature and then being stirred for a further 3 days. The reaction mixture was neutralised with hydrochloric acid (*ca.* 0.1M) and the solvents were removed under reduced pressure to give a white residue. This crude product was subjected to column chromatography on silica gel using a gradient elution of dichloromethane to 10% methanol in dichloromethane to give pure per-2,3-*O*-*p*-methoxybenzoyl-α-CD. (25 mg, 33%), m.p. 195–196°C; (*Found*: C, 61.9; H, 5.80%; *m/z* (positive-ion FABMS), 2604 for $[M + Na]^+$. $(C_{22}H_{22}O_9)_6$ requires C, 61.5; H, 5.45%; M, 2581); $[\alpha]_D + 19°$ (*c*, 0.9 in $CHCl_3$), $[\alpha]_D + 105°$ (*c*, 0.4 in CH_3COCH_3); δ_H (250 MHz, CD_3COCD_3), 3.74 36 H, *s*, 2 × OMe), 4.2–4.4 (18 H, *m*, 4-H, 5-H, 6b-H), 4.57 (6 H, *br d*, $J_{6a,6b}$ 9 Hz, 6a-H), 4.87 (6 H, *dd*, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, 2-H), 5.47 (6 H, *d*, $J_{1,2}$ 3.5 Hz, 1-H), 6.06 (6 H, *dd*, $J_{2,3}$ 10, $J_{3,4}$ 9 Hz, 3-H), 6.49 (12 H, *d*, $J_{o,m}$ 9.5 Hz, C_m^A-H), 6.57 (12 H, *d*, $J_{o,m}$ 9.5 Hz, C_m^B-H), 7.42 (12 H, *d*, $J_{o,m}$ 9.5 Hz, C_o^A-H), and 7.54 (12 H, *d*, $J_{o,m}$ 9.5 Hz, C_o^B-H). δ_H (250 MHz, $CDCl_3$), 3.55, 3.72, 3.75, 3.76 (each 9 H, *s*, OMe), 3.97 (3 H, *br m*, 5′-H), 4.2–4.5 (15 H, *m*, 5-H, 6a-H, 6b-H, 6a′-H, 6b′-H), 4.57–4.82 (9 H, *m*, 4-H, 4′-H, 2′-H), 5.30 (3 H, *br s*, 1′-H), 5.50 (3 H, *dd*, $J_{1,2}$ 3.5, $J_{2,3}$ 9 Hz, 2-H), 5.60 (3 H, *d*, $J_{1,2}$ 3.5 Hz, 1-H), 5.78 (6 H, $(BB')^D$ of an $(AA'BB')^D$ system, $J_{A,B} = J_{o,m}$ 9 Hz, C_m^D-H), 6.08 (3 H, *t*, $J_{2,3}$, $J_{3,4}$ 9 Hz, 3-H), 6.15 (3 H, *t*, $J_{2,3}$, $J_{3,4}$ 9 Hz, 3-H), 6.58 (12 H, *m*, $(BB')^C$ of an $(AA'BB')^C$ system, $J_{A,B} = J_{o,m}$ 9 Hz, C_m^C-H and 6 H, (AA') of an $(AA'BB')^D$ system, $J_{A,B} = J_{o,m}$ 9 Hz, C_o^D-H), 6.68 (6 H, $(BB')^A$ of an $(AA'BB')^A$ system, $J_{A,B} = J_{o,m}$ 9 Hz, C_m^A-H), 6.94 (6 H, $(BB')^B$ of an $(AA'BB')^B$ system, $J_{A,B} = J_{o,m}$ 9 Hz, C_m^B-H), 7.25 (6 H, $(AA')^C$ of an $(AA'BB')^C$ system, $J_{A,B} = J_{o,m}$ 9 Hz, C_m^C-H), 7.94 (6 H, $(AA')^B$ of an $(AA'BB')^B$ system,

$J_{A,B} = J_{o,m}$ 9 Hz, C_m^B-H), and 8.03 (6 H, $(AA')^A$ of an $(AA'BB')^A$ system, $J_{A,B} = J_{o,m}$ 9 Hz, C_m^A-H).

2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^D, 3^F, 6^A, 6^B, 6^C, 6^D, 6^E, 6^F-Octadeca-O-p-bromobenzoyl-α-cyclodextrin (Per-2,3,6-O-p-bromobenzoyl-α-CD)

Dry α-CD (500 mg, 0.51 mmol) was dissolved in distilled pyridine (20 mL) and *p*-bromobenzoyl chloride (9 g, 0.041 mol, i.e. 80 molar equiv.) added under an atmosphere of nitrogen. At room temperature a thick solid quickly formed which prevented stirring of the reaction mixture. However, this solid dissolved as the mixture was warmed up to 100°C and stirring was continued at this temperature for 3 days. The solution was cooled and poured into water (200 mL). This gave a copious amount of a brown precipitate which was separated by centrifugation. The solid was stirred with chloroform and the insoluble material was filtered. Column chromatography on silica gel, with dichloromethane as the eluent, afforded a pure sample of per-2,3,6-*O*-*p*-bromobenzoyl-α-CD (1.62 g, 74%); m.p. 191–192°C; *Found*: C, 45.5; H, 2.55; Br, 34.0%. $(C_{27}H_{19}O_8Br_3)_6$ requires C, 45.6; H, 2.67; Br, 33.8%. $[\alpha]_D + 49°$ (*c*, 1.0 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$), 4.14 (6 H, *t*, $J_{3,4}$, $J_{4,5}$ 9 Hz, 4-H), 4.71 (6 H, *br d*, $J_{4,5}$ 10 Hz, 5-H), 4.78 (6 H, *br dd*, $J_{5,6b}$ 4, $J_{6a,6b}$ 12 Hz, 6b-H), 4.85 (6 H, *dd*, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, 2-H), 5.01 (6 H, *br d*, $J_{5,6a} < 1$, $J_{6a,6b}$ 12 Hz, 6a-H), 5.54 (6 H, *d*, $J_{1,2}$ 3.5 Hz, 1-H), 6.15 (6 H, *dd*, $J_{2,3}$ 10, $J_{3,4}$ 9 Hz, 3-H), 7.08 (12 H, $(BB')^C$ of an $(AA'BB')^C$ system, $J_{A,B} = J_{o,m}$ 9 Hz, secondary benzoyl C_m^C-H), 7.13 (12 H, $(BB')^B$ of an $(AA'BB')^B$ system, $J_{A,B} = J_{o,m}$ 9 Hz, secondary benzoyl C_m^B-H), 7.15 (12 H, $(AA')^C$ of an $(AA'BB')^C$ system, $J_{A,B} = J_{o,m}$ 9 Hz, secondary benzoyl C_o^C-H), 7.22 (12 H, $(AA')^B$ of an $(AA'BB')^B$ system, $J_{A,B} = J_{o,m}$ 9 Hz, secondary benzoyl C_o^B-H), 7.64 (12 H, $(BB')^A$ of an $(AA'BB')^A$ system, $J_{A,B} = J_{o,m}$ 9 Hz, primary benzoyl C_m^A-H), and 7.99 (12 H, $(AA')^A$ of an $(AA'BB')^A$ system, $J_{A,B} = J_{o,m}$ 9 Hz, primary benzoyl C_o^A-H). δ_C (63 MHz, $CDCl_3$), 63.4 (C-6), 70.4 (C-2), 71.7 (C-3), 72.8 (C-5), 78.8 (C-4), 98.4 (C-1), 126.5, 127.7, 128.31 (C—Br), 128.33, 128.68, 128.70 (*C*—CO), 130.74, 130.98, 131.17 (C_o), 131.20, 131.39, 132.04 (C_m), 164.0 (CO), and 165.3 (2 × CO).

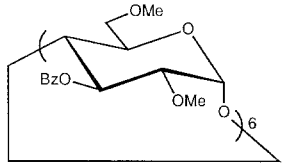
2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F-Dodeca-O-p-bromobenzoyl-α-cyclodextrin (Per-2,3-O-p-bromobenzoyl-α-CD) (**9**)

Per-2,3,6-*O*-*p*-bromobenzoyl-α-CD (500 mg, 0.117 mmol) was dissolved in benzene (10 mL) and distilled 2-propanol (5 mL). A solution of potassium 2-propoxide in 2-propanol (1.56 mL of 0.45M solution, 0.7 mmol, 6 molar equiv.) was added and the mixture was stirred at room temperature under nitrogen for 1 h. The reaction mixture was neutralised with hydrochloric acid (*ca.* 0.1M) and solvents were removed under reduced pressure to give a white residue. Column chromatography on silica gel with a gradient elution regime employing dichloromethane to 10% methanol in dichloromethane gave only a partial purification of the desired compound. Repeating this procedure achieved a complete separation of by-products and yielded per-2,3-*O*-*p*-bromobenzoyl-α-CD (170 mg, 46%); (*Found*: C, 45.3; H, 3.01%; *m/z* (positive-ion FABMS), 3191 for $[M + Na]^+$. $(C_{20}H_{16}O_7Br_2)_6$ requires C, 45.5; H, 3.05%; M, 3168); $[\alpha]_D + 14°$ (*c*, 0.9 in $CHCl_3$), $[\alpha]_D + 69°$ (*c*,

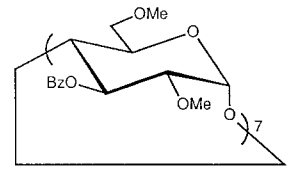
0.8 in THF); δ_H (400 MHz, d_8-THF), 4.11 (6 H, *br s*, 6b-H), 4.27 (6 H, *t*, 4-H), 4.40 (6 H, *m*, 5-H), 4.46 (6 H, *t*, 6b-H), 4.97 (6 H, *dd*, 2-H), 5.48 (6 H, *dd*, 1-H), 6.06 (6 H, *dd*, 3-H), 7.28 (12 H, $(BB')^A$ of an $(AA'BB')^A$ system, C_m^A-H), 7.38 (12 H, $(BB')^B$ of an $(AA'BB')^B$ system, C_m^B-H), 7.42 (12 H, $(AA')^A$ of an $(AA'BB')^A$ system, C_m^A-H), and 7.48 (12 H, $(AA')^B$ of an $(AA'BB')^B$ system, C_m^B-H). δ_H (400 MHz, $CDCl_3$), 3.91 (3 H, *m*, 5′-H), 4.13–4.45 (12 H, *m*, 6a-H, 6a′-H, 6b′-H, 4-H), 4.58–4.72 (12 H, *m*, 2′-H, 4′-H, 5-H, 6b-H), 5.29 (3 H, *br s*, 1-H), 5.52 (3 H, *dd*, 2-H), 5.57 (3 H, *d*, 1-H), 6.08 (3 H, *t*, 3′-H), 6.13 (3 H, *t*, 3-H), 6.37 (6 H, $(BB')^D$ of an $(AA'BB')^D$ system, C_m^D-H), 6.62 (6 H, $(AA')^D$ of an $(AA'BB')^D$ system, C_o^D-H), 7.14 (6 H, $(BB')^C$ of an $(AA'BB')^C$ system, C_m^C-H), 7.34 (6 H, $(AA')^C$ of an $(AA'BB')^C$ system, C_o^C-H), 7.50 (6 H, $(BB')^B$ of an $(AA'BB')^B$ system, C_m^B-H), 7.66 (6 H, $(BB')^A$ of an $(AA'BB')^A$ system, C_m^A-H), 7.78 (6 H, $(AA')^B$ of an $(AA'BB')^B$ system, C_o^B-H), 7.90 (6 H, $(AA')^A$ of an $(AA'BB')^A$ system, C_o^A-H), and 12.6 (*br s*, OH). δ_C (63 MHz, $CDCl_3$), 53.8, 59.0 (C-6 and C-6′), 68.5 (C-2), 71.6 (C-5′), 72.0, 73.0 (C-3, C-3′), 73.4, 74.6 (C-2′, C-5), 77.2 (C-4′), 77.5 (C-4), 94.1 (C-1′), 97.9 (C-1), 125.8, 127.1, 127.3, 128.3, 128.4 (C—Br and *C*—CO), 128.7 (three coincident resonances, C—Br and *C*—CO), 130.0, 130.5, 131.6, 131.9, 132.1 (C_o and C_m), 131.5 (three coincident signals, C_o and C_m), 162.9, 164.2, and 165.5 (C=O).

3. Results and Discussion

During the course of a research programme involving the synthesis of methylated CDs [10, 11], per-2,6-*O*-methyl-3-*O*-benzoyl-α-CD (**1**) and per-2,6-*O*-methyl-3-*O*-benzoyl-β-CD (**2**) were prepared [11]. The ^{1}H NMR spectrum of **2** shows a slight solvent dependence, whereas the effect of solvent on the ^{1}H NMR spectrum of the corresponding α-CD derivative (**1**) is greater.



1



2

The ^{1}H NMR spectrum of **1** was recorded (Figure 1) in $CDCl_3$. Extensive line broadening of signals was observed. When the spectra were recorded at elevated temperatures (50°C), the magnitude of the solvent effect was not so pronounced. By contrast, when the ^{1}H NMR spectrum of **1** was recorded in CD_2Cl_2, the only manifestation of unusual behaviour was observed in the broadening of the singlet for the 2-*O*-Me group. In C_6D_6 (Figure 2), however, the unusual behaviour was so pronounced that several resonances were observed for some protons while other signals were broadened to the extent that they could not be recognised. Although the spectrum recorded in CD_3SOCD_3 was well-resolved, the H-2 resonance and the 2-*O*-Me singlet were obscured by signals for HDO and residual CD_3SOCD_2H, respectively. The best solvent in which to record the ^{1}H NMR spectrum of **1** was

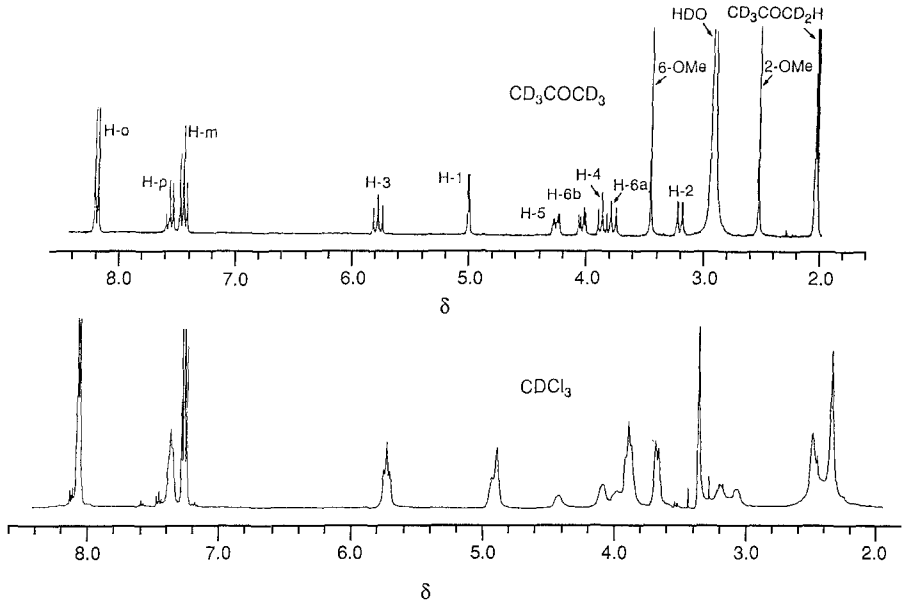


Fig. 1. ^{1}H NMR spectra of per-2,6-*O*-methyl-3-*O*-benzoyl-α-CD (**1**) in CD_3COCD_3 (250 MHz) and in $CDCl_3$ (400 MHz).

found to be CD_3COCD_3 (Figure 1). In this solvent, the resolution of signals was superior to that observed in all the other solvents examined. The resonances were well-dispersed and none of them were obscured by solvent peaks.

It was suspected that the atypical appearance of the spectra recorded in $CDCl_3$ and C_6D_6 might be the result of a slow equilibration process between diastereoisomeric conformations. All attempts to vindicate this hypothesis and identify conformational diastereoisomers by employing dynamic NMR spectroscopy were unsuccessful.

A similar phenomenon was observed [12] by Lehn *et al.* concerning the solvent dependence of the ^{1}H NMR (Figure 3) and ^{13}C NMR (Figure 4) spectra of

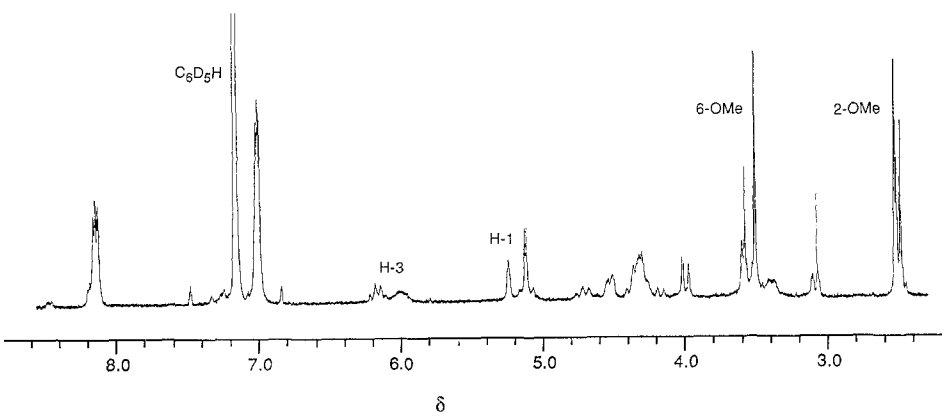


Fig. 2. ^{1}H NMR spectrum (250 MHz) of per-2,6-*O*-methyl-3-*O*-benzoyl-α-CD (**1**) in C_6D_6.

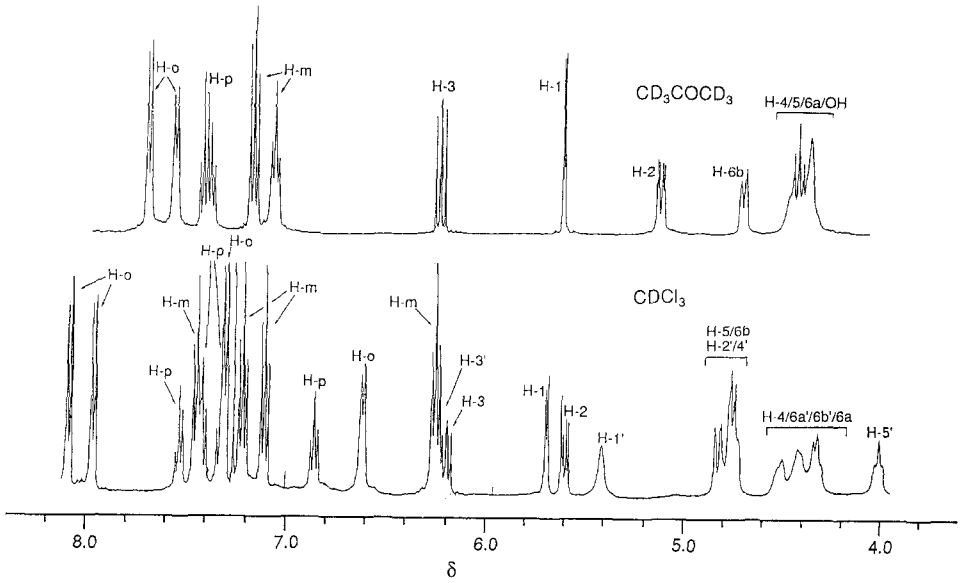


Fig. 3. ^{1}H NMR spectra (400 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in CD_3COCD_3 and $CDCl_3$.

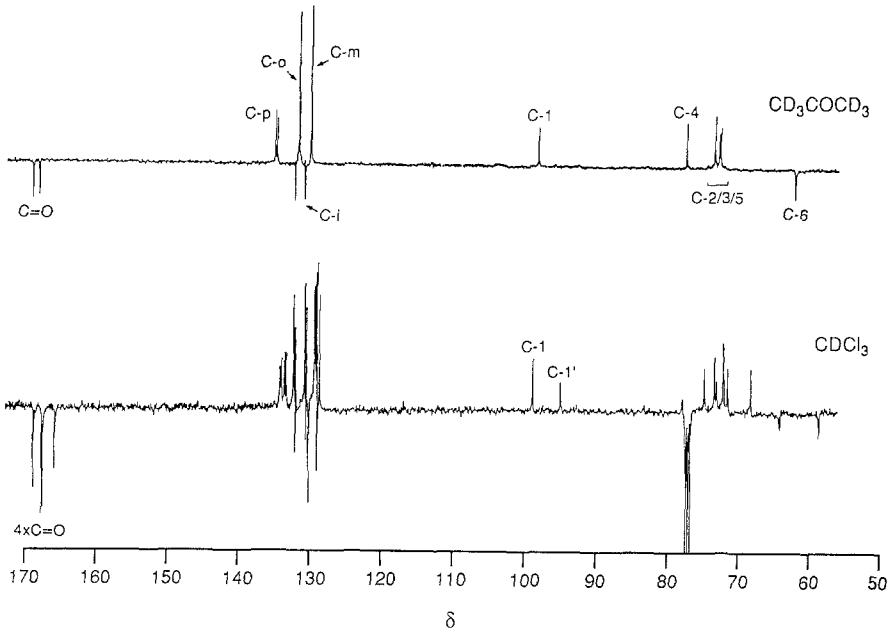
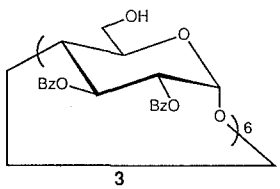


Fig. 4. ^{13}C NMR spectra (100 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in CD_3COCD_3 and $CDCl_3$.

per-2,3-*O*-benzoyl-α-CD (**3**). The assignments shown in Figures 3 and 4 were made by us using homonuclear difference decoupling and correlation (both H—H and C—H) spectroscopies.



3

The ^{1}H NMR spectrum of **3** in CD_3COCD_3 shows sharp resonances corresponding to an α-CD derivative with C_6 molecular symmetry. In $CDCl_3$ solution, however, the signals, although still quite well-resolved, are doubled-up in number. Furthermore, integration shows that the signals corresponding to any particular proton located in constitutionally identical environments are in an intensity ratio of 1 : 1. The initial, tentative explanation [12] of this unusual phenomena was that **3** undergoes a conformational change in $CDCl_3$ solution, which reduces its C_6 molecular symmetry by a factor of two, i.e. a species with averaged C_3 molecular symmetry (Figure 5) is present in $CDCl_3$ solution. Although the exact nature of this conformation was not discussed in detail by Lehn *et al.*, the importance of intramolecular hydrogen bonding in stabilising an atypical conformation was highlighted by IR spectroscopic data.

Since the conformational change undergone by **3** is more pronounced than that undergone by per-2,6-*O*-methyl-3-*O*-benzoyl-α-CD (**1**), a detailed investigation of **3** was initiated. It was anticipated that not only would a greater understanding of the conformational properties of **3** be achieved, but also that a general appreciation would be gained on how to induce drastic conformational changes into cyclodextrins as a result of simple chemical modifications. At the outset, two issues were addressed. They were the identification of (i) the nature of the conformational species in $CDCl_3$ solution and (ii) the factors which induce the phenomenon to occur. Both spectroscopic and synthetic studies were performed in order to bring a greater understanding to bear on this problem.

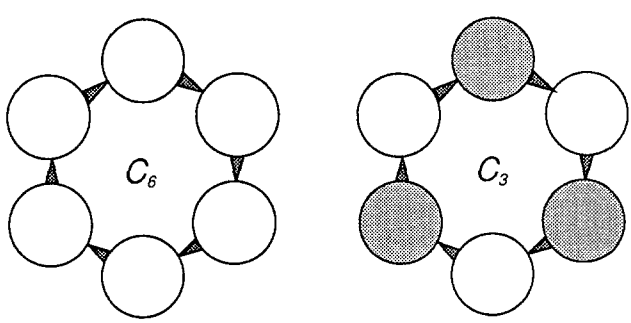


Fig. 5. Schematic representation of cyclodextrin derivatives with C_6 and C_3 symmetries (each circle represents a substituted D-glucopyranose ring and each arrow represents an α-1→4 glucosidic linkage).

The ^{1}H NMR spectrum of **3** was recorded in a wide range of solvents. In CD_3OD, CD_3SOCD_3 and C_5D_5N, well-resolved spectra consistent with α-CD derivatives with averaged C_6 molecular symmetry were observed. As expected, small chemical shift differences were evident in these polar solvents. ^{1}H NMR spectra were also recorded in CD_2Cl_2, C_6D_6, and $CDCl_2CDCl_2$ solutions. These spectra were all complex and signals were broad relative to those observed in the spectrum of **3** recorded in $CDCl_3$ solution under the same conditions. These observations supported the belief that there is an equilibrium established between conformational diastereoisomers in these solvents.

Two different types of gross conformational change can be identified. (i) The substituted D-glucopyranose residues might exist in $^4C_1$ or $^1C_4$ ring conformations or (ii) the relative orientations of contiguous D-glucopyranose units could be altered. The conformations of D-glucopyranose rings may be established by measuring the vicinal H—H coupling constants and applying the Karplus relationship [13]. Unfortunately, in all the solvents in which the unusual conformational behaviour is observed, the proton resonances are either too broad or they overlap with other resonances. As a result, the vicinal H—H coupling constants could not be determined for both of the resonances corresponding to any one particular ring proton.

An alternative method of determining the D-glucopyranose ring conformations is to measure the $^1J_{CH}$ coupling constants associated with the anomeric centre [14]. It has been shown that the magnitude of the coupling constant depends on the location of the anomeric proton in either an axial or an equatorial position. The two diastereoisomeric chair conformations of cyclodextrin D-glucopyranose rings in **3** – namely the $^4C_1$ and $^1C_4$ conformations – are associated with an equatorial and an axial anomeric proton, respectively. Values of this coupling constant observed for **3** are given in Table I along with appropriate literature values. The data recorded in this table for **3** in $CDCl_3$ solution indicate that the corresponding H-1 protons are in approximately equatorial positions on their respective D-glucopyranose rings. Since the values obtained are not exactly equal, it is possible that the ring conformations of the two D-glucopyranose units are not identical. However, such distortions are considered to be insignificant and could not possibly account for the conformational changes observed for this compound.

Table I. $^1J_{CH}$ Coupling constants of per-2,3-*O*-benzoyl-α-CD (**3**) at the anomeric centre.

Compound	$^1J_{CH}$ for anomeric centre (Hz)
α-D-Glucose[a]	169.5
β-D-Glucose[a]	162.0
α-CD[a]	168.5
Per-acetylated-α-CD[b]	177.5
Per-3,6-anhydro-β-CD[a,c]	164.0
Per-2,3-*O*-benzoyl-α-CD[c]	173.5, 169.0[b]
	172.0[d]

[a] Recorded in D_2O.
[b] Recorded in $CDCl_3$.
[c] Obtained using the INEPT pulse sequence.
[d] Recorded in C_5D_5N.

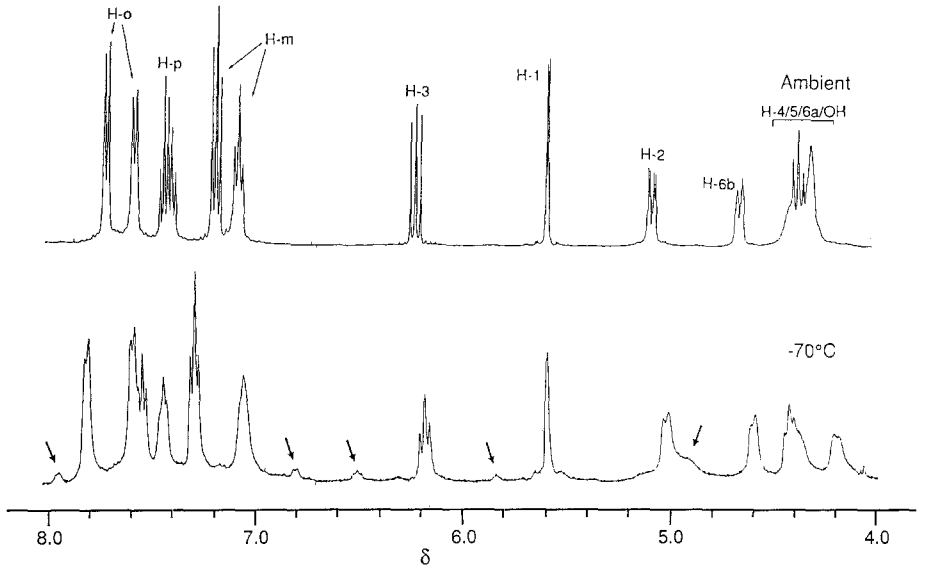


Fig. 6. ^{1}H NMR spectrum (400 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in CD_3COCD_3 recorded at ambient temperature and at −70°C.

In order to establish the existence of a conformational equilibrium in solution, a series of dynamic NMR spectroscopic studies were performed on **3**. Considering first of all solutions of **3**, which appear to comprise the averaged C_6 symmetrical species at room temperature, a CD_3COCD_3 solution of **3** was cooled to −70°C. This resulted (Figure 6) in a certain amount of line broadening and a number of additional resonances of low intensity, indicated with arrows in Figure 6, were identified. This line-broadening is unlikely to be a consequence of any increase in the viscosity of the solvent. In fact, it is believed to be a result of a conformational equilibration process involving a minor conformation. The presence of the additional resonances at low temperatures confirm the existence of this minor conformation.

The relatively low boiling point of CD_3COCD_3 limits the scope of the variable temperature NMR studies that can be performed in this solvent. Therefore, a CD_3SOCD_3 solution of **3** was employed for obtaining spectra above room temperature, because this solvent not only boils at a relatively high temperature (at *ca.* 190°C), it also gives similar spectroscopic results to those obtained in CD_3COCD_3. Warming a CD_3SOCD_3 solution of **3** to 60°C led (Figure 7) to a sharpening of the resonances in the spectrum, as a result of the decrease in viscosity of this solvent that occurs as the temperature is raised. The only difference noted in the spectra recorded at the two temperatures concerned the chemical shift of the OH resonance. Under ambient conditions, this proton resonates as a triplet at δ 4.85, a chemical shift characteristic [15] of a non-anomeric hydroxyl group hydrogen bonded to CD_3SOCD_3. On the other hand, the spectrum recorded at 60°C reveals the hydroxyl resonance as a double doublet at δ 4.65. Such a shift of a hydroxyl resonance to lower frequency with an increase in temperature is indicative [16] of hydrogen bond formation between the solute and the solvent. This hydrogen

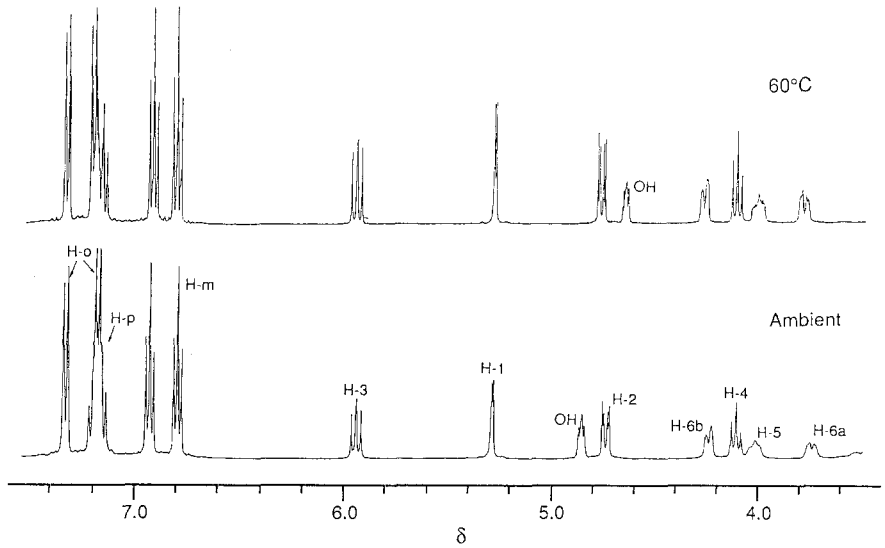


Fig. 7. ^{1}H NMR spectrum (400 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in CD_3SOCD_3 recorded at 60°C and at ambient temperature.

bonding interaction between **3** and the solvent is believed to be an important factor in stabilising the C_6 symmetrical structure of **3** in CD_3SOCD_3, and, by implication, in CD_3COCD_3, CD_3OD, and C_5D_5N as well.

When a $CDCl_3$ solution of **3** was warmed to 60°C, broadening of the ^{1}H NMR resonances was observed (Figure 8). However, the complexity of the spectrum, as reflected in the number of resonances, was not altered significantly. Cooling a

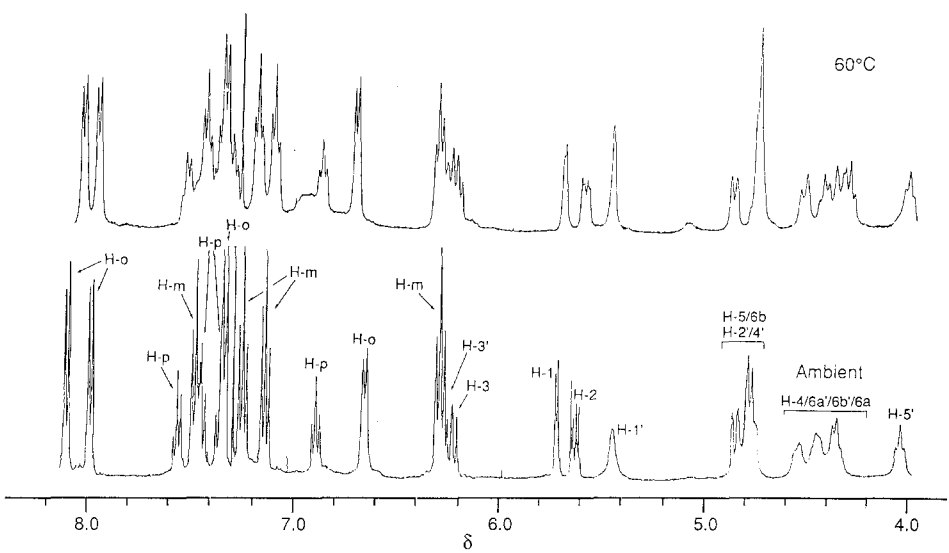


Fig. 8. ^{1}H NMR spectrum (400 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in $CDCl_3$ recorded at 60°C and at ambient temperature.

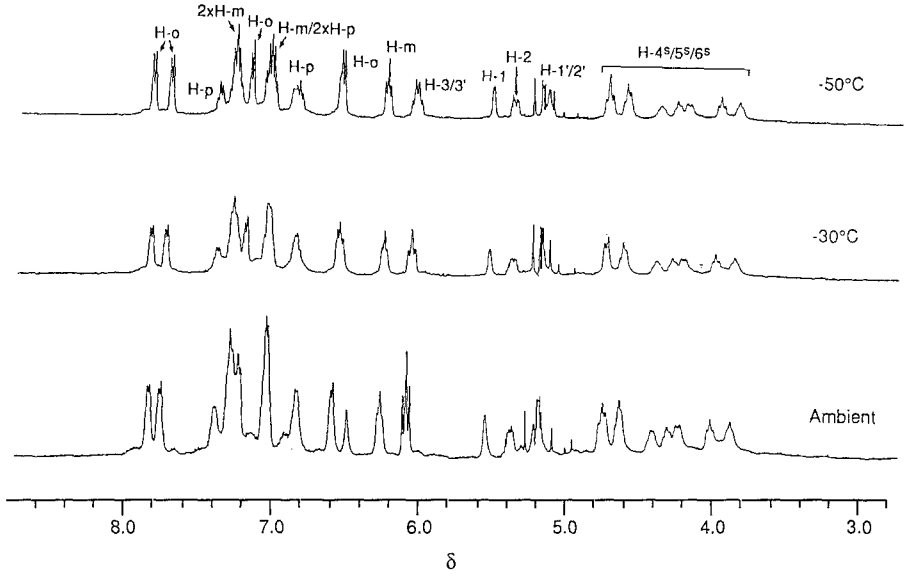


Fig. 9. ^{1}H NMR spectrum (400 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in CD_2Cl_2 at −50°C, at −30°C, and at ambient temperature.

$CDCl_3$ solution of **3** to −50°C also resulted in line broadening of all the resonances. However, in this instance, the phenomenon can be attributed to the increased viscosity of $CDCl_3$ at low temperatures.

Although the ^{1}H NMR spectrum of **3** in CD_2Cl_2 under ambient conditions (Figure 9) is both complex and broad – it resembles the ^{1}H NMR spectrum of **3** recorded in $CDCl_3$ in terms of the number of resonances, with the pair of doublets around δ 8 being diagnostic of the presence of the atypical conformational isomer – the resonances are not as well resolved. A tentative explanation for the appearance of this ^{1}H NMR spectrum was that the conformational equilibration process, which occurs in $CDCl_3$, is also occurring in CD_2Cl_2, although the rate of the equilibration is faster in CD_2Cl_2. Therefore it was anticipated that cooling the solution down would result in a better resolved ^{1}H NMR spectrum. As shown in Figure 9, this prediction was supported by our experimental observations. A well-resolved spectrum was obtained at −50°C and integration of the resonances at this temperature again revealed that the areas of peaks corresponding to a proton in a particular constitutional environment were in the ratio of 1 : 1. Warming up the solution above room temperature gave slightly broader spectra from which no further conclusions could be drawn.

The ^{1}H NMR spectrum of **3** in C_6D_6 under ambient conditions (Figure 10) was even broader than that obtained for **3** in CD_2Cl_2. As expected, the signals were dispersed over a much wider chemical shift range, with the characteristic high frequency pair of doublets for the atypical conformation resonating at δ 8.3 and δ 8.6. The broad and complex nature of the spectrum was again rationalised tentatively as being a consequence of a more rapid equilibration (relative to the rate in $CDCl_3$) between the two conformations. Because benzene freezes at 5°C, the

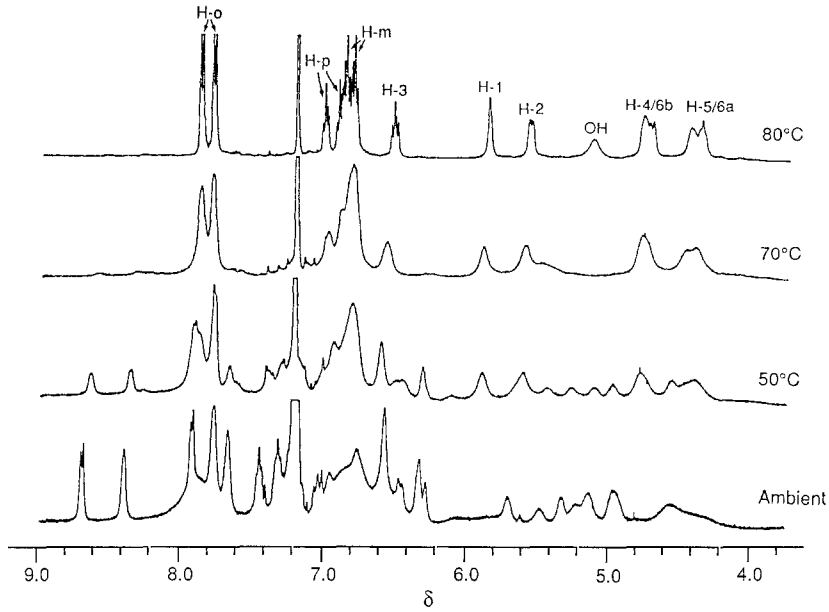


Fig. 10. ^{1}H NMR spectrum (400 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in C_6D_6 at 80°C, at 70°C, at 50°C, and at ambient temperature.

solution could not be cooled much below room temperature. Cooling the solution to 10°C did not result in any marked alteration in the appearance of the ^{1}H NMR spectrum. Warming the solution did, however, lead to changes in the spectrum. As the temperature was raised the number of peaks in the spectrum gradually diminished. This simplification in the ^{1}H NMR spectrum is most apparent by considering the two high frequency resonances at δ 8.3 and δ 8.6. Increasing the temperature of the solution leads to a decrease in the intensities of these peaks and eventually to their disappearance. The spectrum obtained at 80°C is characteristic of an α-CD derivative exhibiting the usual averaged C_6 molecular symmetry.

The existence of broad lines in the ^{1}H NMR spectra of **3** in CD_2Cl_2 and C_6D_6 at room temperature clearly reflects the existence of the same conformational process, i.e. an equilibration between two degenerate conformational states. Unfortunately, the low boiling point of CD_2Cl_2 and the high melting-point of C_6D_6 hinder the observation of a change with temperature, from a well-resolved but complex spectrum, to a well-resolved but simple spectrum. However, such a change could be achieved by recording the ^{1}H NMR spectra in $CDCl_2CDCl_2$.

The ^{1}H NMR spectrum of **3** in $CDCl_2CDCl_2$ recorded under ambient conditions showed substantial line-broadening, which probably results from the viscous nature of the solvent. Warming the solution led to a sharpening of the resonances, with the best resolution being achieved around 60°C. The spectrum at this temperature was partially assigned using homonuclear difference decoupling spectroscopy. These experiments succeeded in establishing two distinct resonances corresponding to constitutionally-identical protons on the disubstituted D-glucopyranose ring. These resonances were associated with two heterotopic H-3 protons, appearing as one

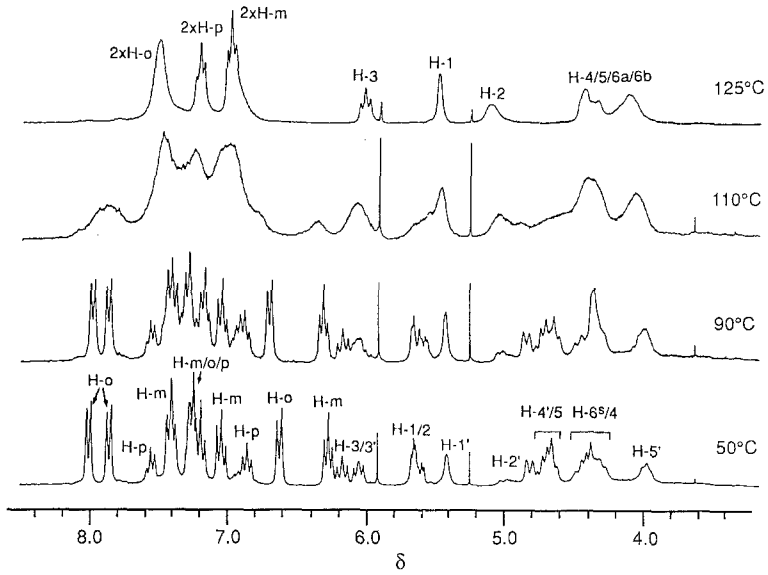


Fig. 11. ^{1}H NMR spectra (250 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in $CDCl_2CDCl_2$ at 125°C, at 110°C, at 90°C and at 50°C.

triplet at δ 6.21 ($J_{2,3} = J_{3,4} = 9.5$ Hz) and as another triplet of equal intensity at δ 6.07 ($J_{2,3} = J_{3,4} = 9.0$ Hz). In contrast to all of the ^{1}H NMR spectra of **3** recorded in pure solvents, this is the only spectrum in which resonances associated with constitutionally-identical protons have been resolved completely. Given the limited accuracy with which the vicinal H—H coupling constants can be measured, both heterotopic H-3 protons are associated with D-glucopyranose rings in the same $^4C_1$ chair conformation.

As the CD_2ClCD_2Cl solution was warmed up further, the spectra began to broaden, became featureless at 110°C and finally sharpened at 125°C to give a spectrum of the kind expected for an α-CD derivative with averaged C_6 molecular symmetry. Unfortunately, higher temperatures – and presumably better resolved spectra – could not be obtained because of the constraints imposed by the NMR spectrometer. These results helped to confirm the conclusion, based on the spectra recorded in CD_2Cl_2 (Figure 9) and C_6D_6 (Figure 10), that a degenerate equilibration process (Figure 12) is taking place between two equivalent conformations with C_3 molecular symmetry. In $CDCl_2CDCl_2$ at 50°C, this degenerate equilibration process is slow on the ^{1}H NMR time-scale, and hence, two sets of equal intensity resonances are observed, corresponding to two heterotopic D-glucopyranose residues. As the temperature is raised, the rates of inversion of the two degenerate conformers increases until, at 125°C, the rate is so rapid that averaged resonances are observed for the heterotopic D-glucopyranose residues. The free energy of activation for the process can be determined by considering the two heterotopic H-3 resonances which are separated by 30 Hz at 50°C ($\Delta\nu = 30$ Hz) and which coalesce at 110°C, i.e. $T_c = 110$°C. The free energy of activation for the degenerate equilibration process, calculated using the Eyring equation [17], is 19.4 kcal mol^{-1}.

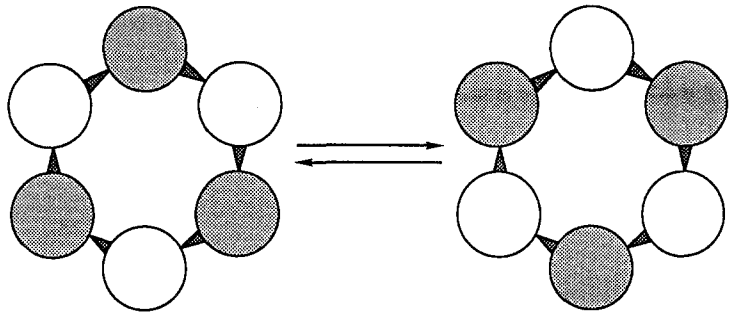


Fig. 12. A schematic representation of the degenerate equilibrium between two cyclodextrin derivatives with averaged C_3 molecular symmetry.

In all of the solvents, and under all of the conditions described above, the magnitudes of coupling constants (both $^3J_{HH}$ and $^1J_{CH}$) associated with the D-glucopyranose rings in **3** indicate that there is no significant distortion of their conformations from the normal $^4C_1$ chair. Therefore, the conformational behaviour of **3** must be associated with a discrete difference in the relative dispositions of the adjacent disubstituted D-glucopyranose residues around the torus of the α-CD derivative.

The relative orientations of two adjacent monosaccharide units in an oligosaccharide are defined [18] in terms of the glycosidic torsion angles, ϕ and ψ. A number of different procedures have been employed to determine these angles. One common method involves measuring vicinal carbon–proton coupling constants across the glycosidic linkage and relating the magnitude of this coupling constant to the relevant torsion angles by applying a 'Karplus-type' relationship [14, 19]. In cyclodextrin derivatives, the anomeric (C-1) and aglyconic (C-4) carbon atoms are also in vicinal relationships with respect to some of the endocylic protons, and so the problem becomes one of the identification and elimination of these endocyclic three-bond carbon–hydrogen couplings from the analysis.

In principle, there are a number of ways in which this can be achieved. Selective deuteration [20] of **3** was not considered to be a feasible method because of the difficulty associated with the synthesis of the deuterated analogue. The recording of a selectively-decoupled ^{13}C NMR spectrum proved to be inconvenient because of the inordinate length of time needed to acquire a spectrum with sufficient resolution. Identification of the small $^3J_{CH}$ coupling constants was achieved by recording the INEPT NMR spectrum of **3**. However, there was no way to establish which coupling constant corresponded to which vicinal carbon–proton pair. Finally, an attempt was made to apply the heteronuclear *J*-resolved technique of Bax and Freeman [21]. Unfortunately, this experiment met with only partial success. However, the vicinal coupling constant in CD_3COCD_3 relating to C-4′—O—C-1—H-1 was found to be 5.2 Hz. The corresponding torsion angle (ϕ) was thus calculated [22] to be 13°. This value is similar to one that was obtained for α-CD from X-ray crystallographic studies [3, 23]. The coupling constant corresponding to ψ (C-1—O—C-4′—H-4′) could not be measured because of the poor resolution of the H-4′ resonance. Overlapping signals and the broad nature of the ^1H NMR

Table II. Selected ^{13}C chemical shift data for per-2,3-*O*-benzoyl-α-CD (**3**).

Solvent	Resonances (ppm)			
	C-1	C-1′[a]	C-4	C-4′[a]
CD_3COCD_3	97.7	–	77.4	–
CD_3SOCD_3	96.7	–	76.5	–
C_5D_5N	98.0	–	77.9	–
$CDCl_3$	98.2	94.5	77.9	74.9
$CDCl_2CDCl_2$	98.2	94.7	77.5	75.0

[a] A prime (′) is normally used in cyclodextrin chemistry nomenclature to denote an adjacent glucopyranose residue. In this instance, the glucose units may be divided into two conformationally different types and the prime is used to distinguish between these units.

spectrum in $CDCl_3$ prevented any of the desired coupling constants from being determined for **3** dissolved in this solvent.

The glycosidic torsion angles have been determined in disaccharides and trisaccharides by measuring inter-residue nuclear Overhauser effects (NOEs) [24]. However, overlapping signals made such experiments unsuccessful in the present study.

Finally, recourse was made to the use of the proposed relationships between ^{13}C chemical shifts of anomeric and aglyconic carbon atoms and the glycosidic torsion angles. Such relationships have been discussed with reference to cyclodextrin systems [25], as well as to carbohydrates in general [26]. The relevant ^{13}C chemical shift data collected for **3** are given in Table II.

The magnitude of the torsion angle, ϕ, determined in CD_3COCD_3 suggests that the relative orientation of D-glucopyranose units obtained for this CD derivative in this solvent – and, by implication, in CD_3OD, CD_3SOCD_3, and C_5D_5N – is similar to that of the parent molecules. Therefore, average chemical shift values of *ca.* 97.5 ppm (C-1) and *ca.* 77.3 ppm (C-4) for these three solvents, are believed to be associated with the normal torsion angle values of *ca.* $+10°$. The different frequencies of the anomeric (especially C-1′) and aglyconic (especially C-4′) carbon atom resonances observed in $CDCl_3$ and $CDCl_2CDCl_2$ are believed to be associated with substantially different values for the appropriate torsion angles.

The relationships between ^{13}C chemical shifts and torsion angles are only semiquantitative at best and so must be applied to cyclodextrin derivatives with some caution. Also, the relationships [25] which have been established with particular reference to cyclodextrins were obtained from solid state ^{13}C NMR spectra of the parent molecules. In itself, of course, chemical modification causes alterations in ^{13}C chemical shift values, and further changes in these values may arise, in solution, from, for example, specific solvent effects [27]. With these reservations in mind, a consideration of the various relationships leads to the semiquantitative conclusion [26, 28] that a ± 2 ppm shift of the anomeric carbon corresponds to a change in ψ of $\pm 10°$, and a ± 2 ppm shift of the aglyconic carbon is associated with a change in ϕ of $\pm 5°$. Applying these approximate relationships to the changes in chemical shifts observed in the ^{13}C NMR spectra for **3** in $CDCl_3$ and in $CDCl_2CDCl_2$ resulted in the calculated torsion angle changes listed in Table III.

Table III. Changes in average values of ^{13}C chemical shifts in selected solvents.

Solvent	$\Delta\delta^{13}C^a$ (associated change in torsion angle)			
	C-1	C-1′	C-4	C-4′
$CDCl_3$	+0.7 ($\Delta\psi = 3.5°$)	−3.0 ($\Delta\psi' = -15°$)	+0.6 ($\Delta\phi = +1.5°$)	−2.4 ($\Delta\phi' = -6.0°$)
$(CDCl_2)_2$	+1.1 ($\Delta\psi = 5.5°$)	−2.8 ($\Delta\psi' = -14°$)	+0.2 ($\Delta\phi = +0.5°$)	−2.3 ($\Delta\phi' = -5.8°$)

[a] $\Delta\delta^{13}C = (\delta_{solvent} - \delta_{average}$ given in Table II) ppm.

Examination of molecular models indicates that such torsion angle changes are consistent with adjacent pairs of D-glucopyranose residues twisting relative to each other about their mutual glycosidic linkages. Such a twist results in the benzoate groups, of the residues with low frequency chemical shift values (those corresponding to C-1′ and C-4′), pointing further in towards the cavity than normal. The benzoate groups of the D-glucopyranose units which exhibit the higher frequency ^{13}C chemical shift values point further away from the cavity than is usual, and consequently, the C-6 hydroxyl groups on the same alternating D-glucopyranose rings are directed towards the centre of the cavity (Figure 13). The calculations suggest that the degree of the twist does not appear to be all that significant. Careful examination of molecular models indicates that changes in ψ' and ϕ' of the order $-30°$ to $-40°$ and a change in ψ and ϕ of the order $+30°$ to $+40°$ are required in order to produce the circular network of hydrogen bonds in **3** described by Lehn *et al.* [12]. The evidence for such a network is very strong. It is based on the O—H stretching frequency observed in the IR spectrum of **3** in $CHCl_3$ (ν O—H stretch, 3260 cm^{-1}), compared with that obtained on recording the IR spectrum in CH_3SOCH_3 (ν O—H stretch, 3430 cm^{-1}). This result was confirmed in the present investigation and extended to include pyridine (ν O—H stretch, 3400 cm^{-1}) as the solvent. By analogy with similar data obtained for calixarenes [29], the relatively

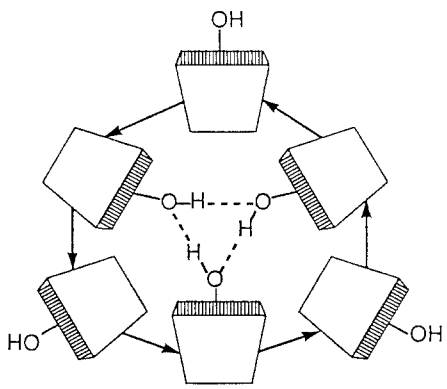


Fig. 13. Schematic representation of the unusual C_3 conformational isomer of **3** showing the relative tilt of the D-glucopyranose residues and circular network of intramolecular hydrogen bonds.

weak O—H stretch noted in the $CHCl_3$ solution probably reflects the presence of a strong intramolecular circular network of cooperative hydrogen bonds. It was also noted that, after shaking a $CDCl_3$ solution of **3** with D_2O and recording the ^1H NMR spectrum, there was no change in the spectrum. Thus, the weakening of the hydrogen bonding network caused by exchanging of H for D is clearly not sufficient to influence the nature of the degenerate conformations in the conformational equilibration process. Clearly, the quantitative uncertainties encountered in applying the chemical shift/torsion angle empirical relationships are such that only a qualitative interpretation can be placed on the data given in Tables II and III, i.e. that contiguous disubstituted D-glucopyranose residues are twisted relative to each other about their mutual glycosidic linkages.

The sensitivity of $[\alpha]_D$ values for cyclodextrins towards changes in D-glucopyranosidic torsional angles is well known [30]. Values of $[\alpha]_D$ for **3**, which were measured in a variety of solvents, are listed in Table IV. Thus, the large difference of $[\alpha]_D$ values recorded in acetone and chloroform must reflect significant changes in disubstituted D-glucopyranosidic torsional angles in **3** in these two solvents. No simple correlation could be achieved between these values and any of the well-known solvent polarity scales [31].

As a result of the spectroscopic and chiroptical studies performed in single solvents, much has been learnt about the conformational behaviour of **3**. In solvents such as methanol, acetone, pyridine, and DMSO, which readily participate in hydrogen bonding with hydroxyl groups, this α-CD derivative exhibits normal averaged C_6 molecular symmetry in which the disubstituted D-glucopyranose residues adopt the expected $^4C_1$ chair conformation. In solution, hydrogen bonds are presumably formed between these solvents and the free C-6 hydroxyl groups on the CD derivative. These intermolecular non-covalent bonds are undoubtedly important in stabilising the gross conformation of the molecule. However, in

Table IV. Chiroptical data for per-2,3-*O*-benzoyl-α-CD (**3**) in selected solvents.

Solvent	$[\alpha]^a_D$
Acetone	+92°
Pyridine	+90°
Ethyl acetate	+86°
Dimethylformamide	+78°
Dimethylsulphoxide[b]	+71°
Acetonitrile	+71°
1,4-Dioxan	+67°
Methanol	+52°
Tetrahydrofuran	+51°
Benzene	+42°
Dichloromethane	+34°
Chloroform[c]	+11°
1,1,2,2-Tetrachloroethane	+9°

[a] *c*, 0.3–1.2 at RT.
[b] Lit. [12] +96° (*c*, 1.3).
[c] Lit. [12] +9° (*c*, 1.1).

dichloromethane, chloroform, tetrachloroethane and benzene, a conformational equilibrium is established (Figure 12), between two degenerate conformations with averaged C_3 molecular symmetry. The reduction in symmetry must be associated with a relative twist in the orientation of adjacent disubstituted D-glucopyranose residues. Furthermore, one of the factors in stabilising the atypical conformation is a circular network of intramolecular cooperative hydrogen bonds (Figure 13) involving primary hydroxyl groups on a trio of alternating disubstituted D-glucopyranose residues.

Following the study of the conformational properties of **3** in pure solvents, an NMR spectroscopic investigation in a mixed solvent system comprised of CD_3COCD_3 and $CDCl_3$ was undertaken. An important point to note at the outset is that, despite being sparingly soluble in acetone, and readily soluble in chloroform, **3** is only just soluble in acetone/chloroform mixtures. Thus, addition of CD_3COCD_3 to a solution of **3** in $CDCl_3$ leads to the precipitation of the compound. Typical concentrations used in the mixed solvent investigations were 4–5 mg in 0.7 mL of solvent, compared with 15–20 mg of compound in the same volume of a pure solvent. In fact, the low solubilities meant that a ^{13}C NMR spectrum of **3** in $CD_3COCD_3/CDCl_3$ (1 : 1 v/v) with a good signal-to-noise ratio could not be obtained under routine conditions.

^1H NMR spectra of **3** in varying proportions of CD_3COCD_3 and $CDCl_3$ were recorded (Figure 14). In $CDCl_3/CD_3COCD_3$ (3 : 1 v/v), a spectrum was observed that was very similar to that obtained in pure $CDCl_3$. However, new peaks appeared, (marked with asterisks in Figure 14) at δ 7.40 (d), δ 7.00 (t), δ5.58 (d) and δ 5.08 (dd). Furthermore, some resonances which were overlapping in the

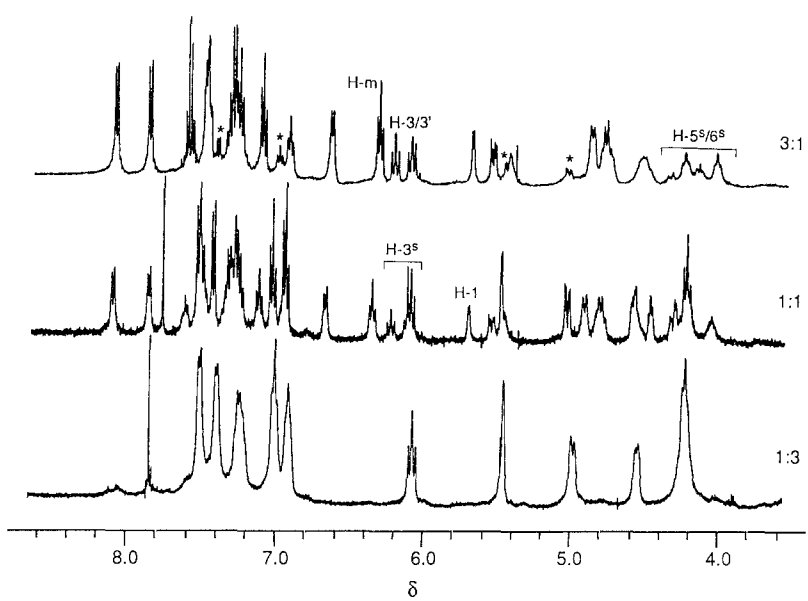


Fig. 14. ^1H NMR spectrum (400 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in $CDCl_3/CD_3COCD_3$ with v/v of 3 : 1, 1 : 1, and 1 : 3.

spectrum in pure $CDCl_3$ were well-resolved in the mixed solvent systems. In particular, the resonances in the regions δ 6.05–6.40 (H-3, H-3′, and H-m) and δ 4.0–4.6 (H-5 and H-6) were well separated. Measurements of the coupling constants involving the H-3 and H-3′ resonances showed them to be associated with D-glucopyranose rings in the $^4C_1$ chair conformation.

Employing $CDCl_3/CD_3COCD_3$ (1 : 3 v/v) as the solvent mixture gave a ^1H NMR spectrum (Figure 14) similar to that obtained in pure CD_3COCD_3. The only differences are that the spectrum is broader and that the characteristic peaks for the atypical conformation at *ca.* δ 8 are present. The ^1H NMR spectrum recorded in $CDCl_3/CD_3COCD_3$ (1 : 1 v/v) is well resolved and also extremely complicated. The relative proton count associated with the integral for the doublet at δ 5.70 (assigned to an anomeric proton) was equated with 1 H. On this basis, the integration of the disubstituted D-glucopyranose ring protons from δ 4.0–6.3 totalled 21 H and the integral corresponding to the benzoyl region (δ 6.30–8.20) equalled 30 H. The relative proton counts indicated by these integrals are consistent with the presence of three different types of disubstituted D-glucopyranose residues present in a ratio of 1 : 1 : 1.

The signals – a triplet and two overlapping triplets – between δ 6.05–6.30 integrate for 3 H and can be assigned to three different H-3 protons in a 1 : 1 : 1 ratio. All vicinal proton–proton coupling constants in this region were consistent with all of the disubstituted D-glucopyranose residues present adopting $^4C_1$ chair conformations.

Values of $[\alpha]_D$ for compound **3** in varying ratios of $CHCl_3$ and CH_3COCH_3 were recorded and an approximately linear relationship (Figure 15) was observed between the specific rotation and the percentage by volume of acetone, which turns out to be approximately equal to the percentages expressed as moles of acetone. Although a number of possible interpretations can be proposed to account for this

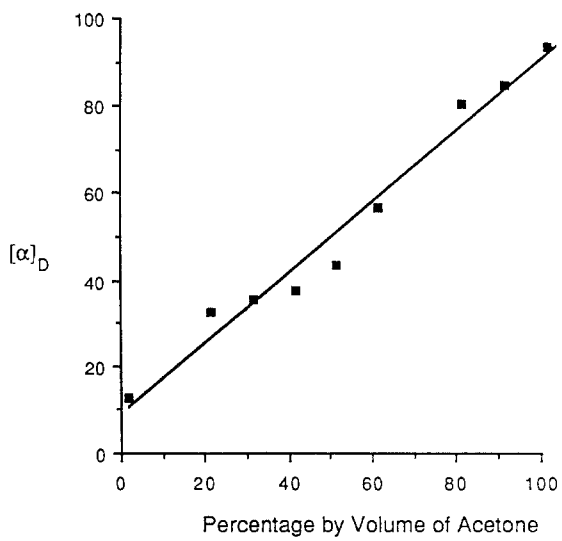


Fig. 15. Plot showing values of $[\alpha]_D$ for solutions of **3** in mixtures of $CHCl_3/CH_3COCH_3$.

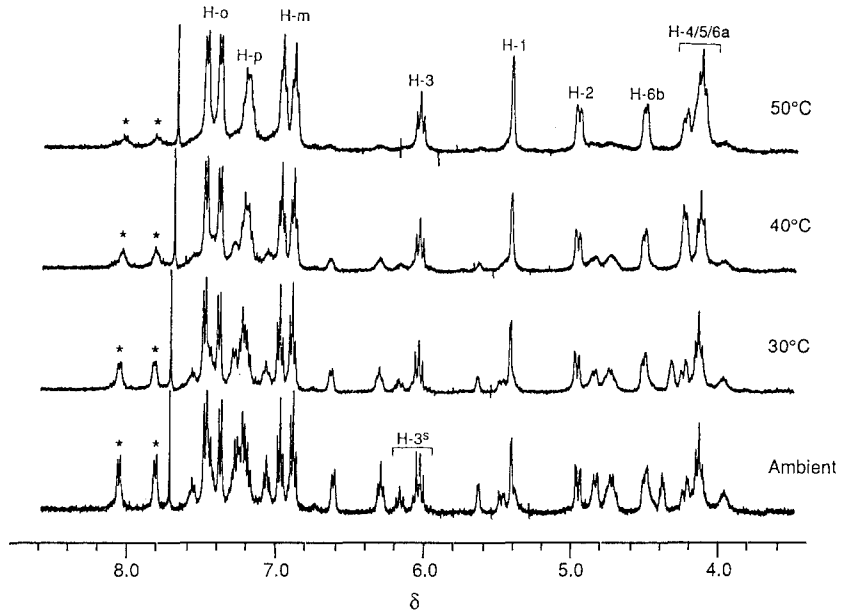


Fig. 16. ^{1}H NMR spectrum (400 MHz) of per-2,3-*O*-benzoyl-α-CD (**3**) in $CDCl_3/CD_3COCD_3$ (1 : 1 v/v) at 50°C, at 40°C, at 30°C and at ambient temperature.

observation, a particularly appealing one is that the linear nature of the relationship is a reflection of the presence in solution of a changing mixture of conformations with averaged C_6 and averaged C_3 molecular symmetries.

The rates of the conformational equilibration processes were investigated by variable temperature ^{1}H NMR spectroscopy in $CD_3COCD_3/CDCl_3$ (1 : 1 v/v). As shown in Figure 16, increasing the temperature of the solution caused many of the signals to 'disappear', e.g. the characteristic resonances for the degenerate conformations with C_3 molecular symmetry at δ 8.10 and δ 7.85 (indicated with asterisks in Figure 16) diminished gradually in intensity and eventually 'vanished'. Also, among the resonances (δ 6.05–6.30) for the H-3 protons, the triplet at δ 6.24 disappeared progressively as the temperature was raised. Furthermore, the quartet centred on δ 6.11 changed in its apparent multiplicity and eventually assumed a triplet character. At 50°C, the ^{1}H NMR spectrum indicates that an α-CD derivative with C_6 molecular symmetry is the predominant conformational isomer present in $CD_3COCD_3/CDCl_3$ (1 : 1 v/v).

The ^{1}H NMR spectra can be interpreted as showing the presence of an equilibrium between conformational isomers with C_3 and C_6 molecular symmetry, as shown schematically in Figure 17. Such a conclusion is consistent with the presence in solution of three different D-glucopyranose residues in a ratio of 1 : 1 : 1.

There is, of course, no fundamental reason why the ratio of $C_3 : C_6$ isomers must be 2 : 1. Changing the solvent ratio would be expected to alter the $C_3 : C_6$ isomer ratio, and it does. Thus, the peaks that were only just visible in the ^{1}H NMR spectrum (Figure 14) recorded in $CDCl_3/CD_3COCD_3$ (3 : 1 v/v) reflect the presence of a small amount of the C_6 conformation present in that solution.

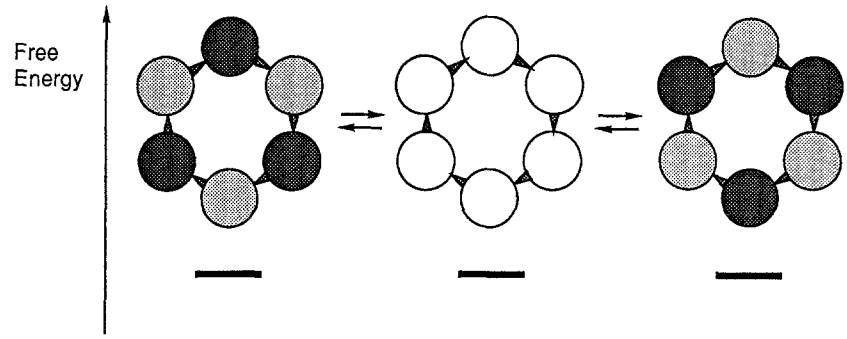


Fig. 17. Schematic energy level diagram representing the equilibration process occurring in $CDCl_3$/CD_3COCD_3 between different conformational isomers of per-2,3-*O*-benzoyl-α-CD (**3**).

The alteration in the appearance of the ^1H NMR spectra occurs over a short temperature range (*ca.* 25°). As a consequence, it can be assumed that there will be negligible changes in the values of the standard free enthalpies and standard free entropies for each of the states. Furthermore, it is apparent, from consideration of the well-known relationship for the standard free energy difference (ΔG^0) between two states (Equation 1), that the influence of ΔS^0 on ΔG^0 increases with a rise in temperature. And so the conformational equilibrium under consideration is probably most profitably analysed in terms of entropy factors.

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \tag{1}$$

A state containing a conformation with a symmetry number, σ, greater than unity, has its relative entropy reduced by a factor $R \ln \sigma$ [18]. This means that the entropy of the C_6 conformation is reduced relative to that of the C_3 conformation by a factor of $R \ln 2$. This factor is probably less important than the changes in entropy resulting from the different types of hydrogen bonding present in the two conformations. Thus, the C_6 conformation is believed to be stabilised by hydrogen bonds between acetone and the C-6 hydroxyl group. It is a highly solvated but flexible species and can thus be associated with a higher entropy. The C_3 conformation, however, is stabilised by relatively strong intramolecular hydrogen bonds, and, as a consequence, has a much lower entropy. Hence, the change from $C_3 \rightarrow C_6$ is asociated with a positive change in the standard free entropy ($+\Delta S^0$). Consideration of Equation 1 leads to the conclusion that an increase in temperature would mean that the free energy change for $C_3 \rightarrow C_6$ decreases relative to the free energy change for $C_6 \rightarrow C_3$. The outcome is shown schematically in Figure 18. As the temperature is raised, the free energy difference between the C_3 and C_6 conformations will continue to widen, increasing the population of the C_6 conformation even further.

In addition to the NMR spectroscopic experiments which have been performed, many attempts have been made to grow single crystals of **3** suitable for X-ray structural analysis. Clearly it is essential to pay particular attention to the type of solvent molecules present in the crystal lattice. Therefore, crystals were grown by the simple evaporation of the solvent from a solution of **3**. Evaporation of acetone leads to a powder, whereas evaporation of chloroform usually gives single crystals.

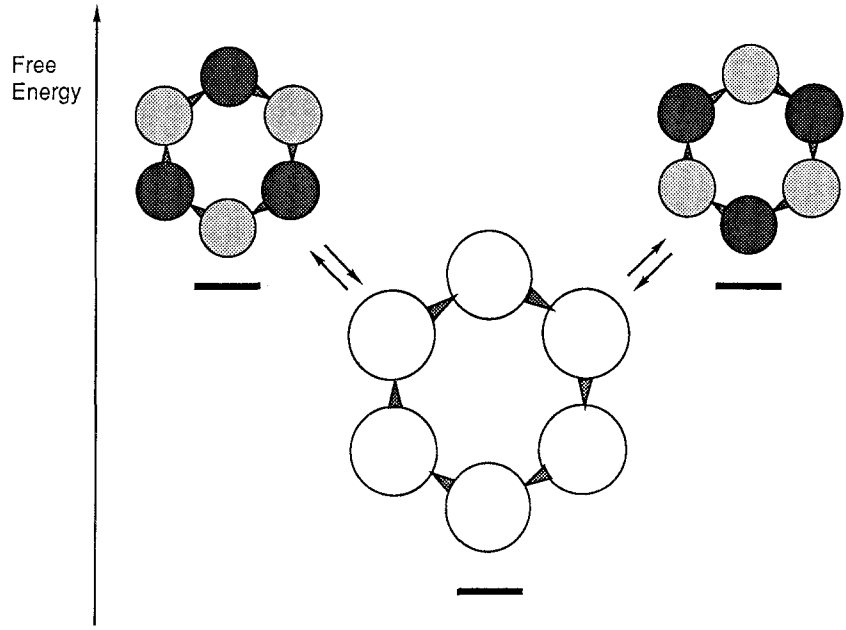


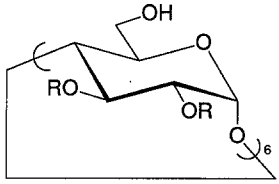
Fig. 18. Schematic representation of the effect of an increase in temperature on the equilibration process involving different conformational isomers (C_6 and C_3) of per-2,3-*O*-benzoyl-α-CD (**3**) (cf. Figure 17).

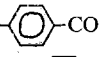
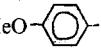
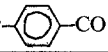
The practical problem of arresting the evaporation before it was complete meant that the crystals cracked quickly and became unsuitable for solid state structural analysis. Attempts to grow crystals using the vapour diffusion of hexane into a chloroform solution of **3** gave thin, intertwined needles. Good single crystals were eventually obtained by taking advantage of the poor solubility of the compound in chloroform/acetone mixed solvent systems. It was assumed that the precipitate which forms when acetone is added to a chloroform solution of **3** is a consequence of the C_3 conformation present in chloroform being 'insoluble' in acetone. Therefore, vapour diffusion of acetone into a chloroform solution of **3** was attempted and gave excellent single crystals which had a morphology similar to those obtained by the slow evaporation of a neat chloroform solution. Unfortunately, a preliminary crystallographic investigation [32] revealed that the unit cell contained in excess of 1000 non-hydrogen atoms (!) and could not be solved.

For many years, per-2,3-*O*-benzoyl-α-CD (**3**) remained the only well-defined example of a per-2,3-*O*-substituted CD derivative. However, the development of the *tert*-butyldimethylsilyl protecting group to block the primary face of CDs [8], has led to the synthesis of derivatives **4**–**6** (Table V). The experimental data given for these compounds suggest that they do not undergo any unusual conformational changes in chloroform solutions.

An attempt was made to prepare a number of substituted-benzoyl derivatives using the method described by Lehn *et al.* [12]. Examples of benzoyl groups were chosen containing, firstly, an electron withdrawing substituent (—F) in **7**, and secondly, an electron-donating substituent (—OMe) in **8**. The *p*-bromobenzoyl derivative **9** was also synthesised in the hope that the introduction of a heavy atom

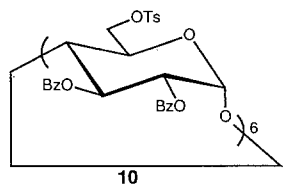
Table V. Per-2,3-*O*-substituted α-cyclodextrins and their conformational behaviour.



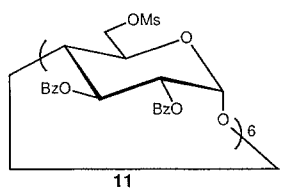
Compound	R	Conformational isomer present
4	Me	C_6
5	$PhCH_2$	C_6
6	CH_3CO	C_6
7	F-  -CO	C_3
8	MeO-  -CO	C_3
9	Br-  -CO	C_3

would aid X-ray crystallographic analysis. Slight modification of the established experimental procedure (see Experimental Section for exact details), making allowance for the different reactivity of the substituted benzoyl groups, enabled compounds **7**–**9** to be prepared in acceptable yields. ^{1}H NMR spectroscopy indicated that all three of these derivatives undergo a conformational change in $CDCl_3$, similar to that observed for per-2,3-*O*-benzoyl-α-CD (**3**).

Lehn *et al.* [12] had shown that completely functionalising the free C-6 hydroxyl groups results in derivatives which adopt conformations with averaged C_6 symmetry. This has been confirmed in the present investigation as a result of the synthesis of per-2,3-*O*-benzoyl-6-*O*-tosyl-α-CD (**10**) and per-2,3-*O*-benzoyl-6-*O*-mesyl-α-CD (**11**).



10



11

Single crystals of per-2,3-*O*-*p*-bromobenzoyl-α-CD (**9**), suitable for X-ray crystallographic analysis, were grown by vapour diffusion of acetone into a chloroform solution of the compound. The crystals are unstable in the absence of solvent and needed to be mounted in the mother liquor. Interestingly, the crystals completely failed to diffract X-rays! The reason for this surprising observation has tentatively been attributed to the glass-like structure of the crystal [32].

The investigations reported in this paper have clearly established that the groups at C-2 and C-3 play an important role in determining the conformational behaviour of compounds like **3**, **7**, **8**, and **9**. It might be expected that the removal of the

secondary face intramolecular hydrogen bonding network present in the parent cyclodextrins would render α-CD derivatives conformationally more flexible. However, the reason why benzoyl groups and *para*-substituted benzoyl groups should lead to atypical, but well-defined, conformational states is still unclear. It is likely that, as more chemical modifications of the secondary face of cyclodextrins are carried out, additional examples of unusual conformational behaviour will be uncovered. Indeed, in the fullness of time, it might transpire that the parent CDs and simple CD derivatives with their rigid, well-defined cavities will be the exceptional compounds.

Acknowledgements

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