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SYNTHESIS, NMR, AND PRELIMINARY BINDING STUDIES OF A NEW CHIRAL MACROCYCLE FROM β-CYCLODEXTRIN

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ABSTRACT — *The reduction of per-O-diethylboryl β-cyclodextrin with ethyldiborane in the presence of 9-bora-bicyclo|3.3.1|-non-9-yl-mesylate afforded, after deboronation and acetylation, the 1,5-anhydro-D-glucitol derivative 4 (60%) and the new macrocyclic polyhydroxyether 3 (30%). The ^{1}H and ^{13}C n.m.r. spectra of 3 and the deacetylated derivative 1 have been studied. The ^{13}C T_1 values for 3 and 1 indicated a higher degree of internal motion in comparison to β-cyclodextrin. The binding ability of 3 has been investigated using Cram's picrate method.*

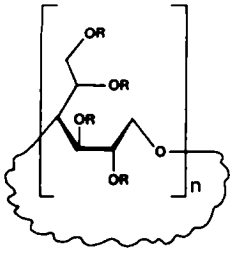
Cyclodextrins[1] and ionophores[2] can form complexes with a variety of guests: the former by hydrophobic interaction with neutral molecules, the latter by ion-dipole interaction with cations. In previous papers we reported on the reductive cleavage of some glycosides and disaccharides with the reagent system ethyldiborane/9-bora-bicyclo|3.3.1|-non-9-yl-mesylate (9-BBN-mesylate)[3,4] and, in a preliminary form, on the preparation of the cyclic polyhydroxy-ethers **1** and **2** by reduction of β- and α-cyclodextrin, respectively.[5] These modified cyclodextrins (**1** and **2**) can be considered macrocycles with a large hydrocarbon backbone incorporating functional groups with electron-donating ability similar to the natural ionophores.

We now report a full account of the reaction leading to **1** and **2** and give full details on the preparation and purification of **1**. Some n.m.r. studies on this compound and its acetylated derivative (**3**) are also reported. The improved synthetic and analytical procedures now developed for this macrocyclic polyhydroxy-ether (**1**) have allowed the study of some of its complexing properties.

RESULTS AND DISCUSSION

We have previously shown that methyl hepta-*O*-diethylboryl-β-maltoside is reduced with ethyldiborane/9-BBN-mesylate to give 1-*O*-methyl-4-*O*-(1-deoxy-D-glucitol-1-yl)-D-glucitol (cleavage **a**), and D-glucitol and 1,5-anhydro-D-glucitol (cleavage **b**).[4] Consequently, β-cyclodextrin (β-CD) could react with this reagent as indicated in Scheme I, giving a cyclic oligomer, by cleavage of seven C(1)-O(5) bonds (cleavage **a**), or seven molecules of 1,5-anhydro-D-glucitol, by cleavage of the seven C(1)-O(1) bonds (cleavage **b**). Alternatively all possible combinations of simultaneous cleavage **a** and **b** could be expected (**1a** + **6b**, **1b** + **6a**, etc.). The reaction has proven to be extremely sensitive to the structure of the substrate and to experimental conditions and small variations of these caused drastic changes in the composition of the reaction mixture as indicated by h.p.l.c.

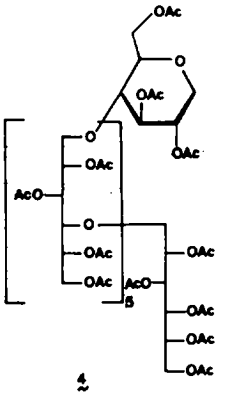
Thus, treatment of per-*O*-diethylboryl-β-cyclodextrin with ethyldiborane in the presence of a catalytic amount of 9-BBN-mesylate at 120°C gave a mixture with no distillable components. Analysis of the deboronated and acetylated reaction mixture by h.p.l.c. indicated the presence of a major reduction product (≈ 90%) and six minor by-products. Preparative h.p.l.c. gave, as the main product, an amorphous



1 n = 7 R = H

2 n = 6 R = H

3 n = 7 R = Ac



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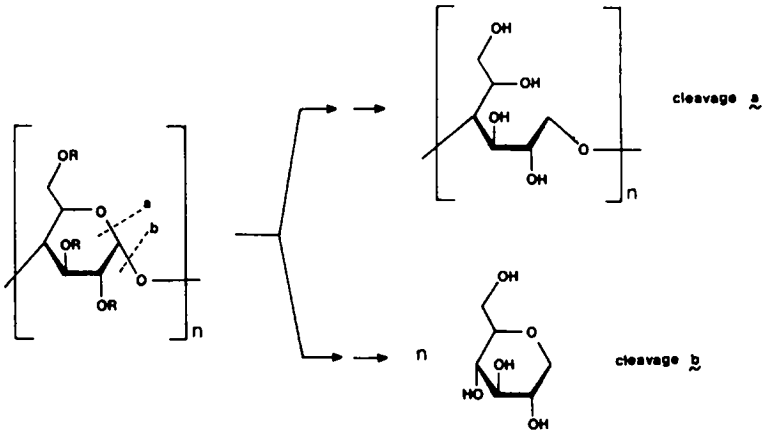
solid, the structure of which was established as 4,[6] resulting from six a cleavages and one b cleavage of the parent β-CD.

When the reaction was carried out using increasing amounts of 9-BBN mesylate a different distribution of final products could be observed. Thus when an approximately equimolecular amount of catalyst was used two major products, 4 and 3 *(see below)* were formed. A further increase of the proportion of catalyst resulted in an increasing of the concentration of the minor by-products. The best experimental conditions for the preparation of macrocycle 3 were found when the reaction was carried out by treating of per-*O*-diethylboryl-β-cyclodextrin (0.6 mmol) first with ethyl diborane at room



Scheme I

temperature, with subsequent evaporation of the triethylboron, and then with 9-BBN-mesylate (0.46 mmol) at 120°C. H.p.l.c. analysis of the mixture after deboronation and acetylation indicated the presence of two major products, one of them being 4. Careful separation by colum chromatography yielded, in addition to product 4, a slower-moving product to which structure 3 was assigned. The ^{13}C n.m.r. spectrum of 3 showed only six signals indicating that the product was a symmetric molecule. Deacetylation of 3 gave 1, the ^{13}C n.m.r. spectrum of which showed only six sharp signals. The ^{1}H n.m.r. spectrum recorded at 300 MHz (in DMSO-d_6), contained four broad signals attributable to OH, and a very complex group of signals between δ 3.3 and 3.8. The f.a.b. mass spectrum showed peaks at m/z 1171 (100%, $|M+Na|^+$), 1149 (50%, $|M+H|^+$), 1193 (20%, $|M+2Na-H|^+$), 1007 (30%, $|M+Na-164|^+$) and 985 (15%, $|M-163|^+$).

The ^{1}H n.m.r. spectrum of 1, in contrast to that of β-cyclodextrin, revealed a considerable dependence on the temperature. The spectrum recorded at 22°C and 300 MHz (in D_2O) consisted of very broad bands which sharpened as the temperature was increased. At 80°C the line width was comparable to that observed in the spectrum of β-cyclodextrin at 22°C. This clearly indicates a certain degree of internal motion in compound 1. Table 1 gives the ^{1}H n.m.r. data of 1 and 3. The ^{1}H n.m.r. spectrum of 3 recorded by using benzene-d_6 as the solvent, in contrast to that of the polyhydroxy-ether 1, showed practically no dependence on temperature in the range 20°-60°C, suggesting a smaller degree of internal motion in this molecule. The small differences observed between the coupling constant values of the peracetylated derivative 3 and the corresponding values of 1 can be attributed to a slightly different average conforma-

Table 1. ^{1}H data of the macrocyclic polyhydroxy ether 1 and of its peracetylated derivatives 3 (δ scale, J in Hz)

	1 [a]	3 [b]
H-1a	-	4.12
H-1b	-	4.12
H-2	3.95	5.60
H-3	3.78	5.70
H-4	3.50	4.15
H-5	3.87	5.57
H-6a	3.75	4.79
H-6b	3.64	4.47
$J_{2,3}$	5.0	4.6
$J_{3,4}$	3.5	5.0
$J_{4,5}$	6.1	5.3
$J_{5,6a}$	3.6	2.9
$J_{5,6b}$	6.2	7.2
$J_{6a,6b}$	-11.8	-12.4

a) Spectrum registered at 300 MHz and 80°C in D_2O. Dioxane as internal reference.
b) Spectrum registered at 300 MHz and 50°C in benzene-d_6. TMS as internal reference.

tion, since no significant differences are observed in the coupling constant values when the cyclodextrins are peracetylated.[7]

Table 2 contains the ^{13}C chemical shift data of compounds 1 and 3. The signal multiplicities were obtained by the APT technique and the assignments were made by using low-power selective proton decoupling. The ^{13}C spin-lattice relaxation times of 1 as well as those of its peracetylated derivative (3) were measured in view of the internal motion exhibited by 1 as revealed by the temperature dependence of its ^{1}H n.m.r. spectrum. Table 3 shows the observed T_1 values for these two compounds. The differences in the spin-lattice relaxation times of the carbon atoms C-2, C-3, C-4 and C-5 of 1 confirm the existence of a certain degree of internal motion. It should be mentioned that the T_1 values of carbon atoms C-2, C-3, C-4 and C-5 of cyclodextrins, whose skeletons do not exhibit any internal motion, are identical within experimental error.[8] On the other hand, the much smaller differences observed in the T_1 values of C-2, C-3, C-4 and C-5 in 3 are in agreement with the lesser degree of internal motion revealed by its ^{1}H n.m.r. spectrum. The fact that slightly smaller T_1 values were observed for compound 1 when the measurements were carried out in DMSO-d_6 instead of

Table 2. ^{13}C chemical shifts of the macrocyclic polyhydroxy ether 1 and of its peracetylated derivative 3 (δ scale) [a]

Carbon atom	1		3
	D_2O [b]	DMSO-d_6 [c]	Benzene-d_6 [c]
C-1	74.1	73.5	71.2
C-2	71.6	70.6	71.1
C-3	71.4	70.1	71.0
C-4	81.3	81.5	78.5
C-5	72.3	71.7	70.9
C-6	63.3	62.6	63.0

a) Spectra registered at 50°C.
b) Dioxane as internal reference.
c) TMS as internal reference.

Table 3. ^{13}C proton-decoupled spin-lattice relaxation times, T_1 (sec), of the macrocyclic polyhydroxy ether 1 and of its peracetylated derivative 3 [a]

Carbon atom	1		3
	D_2O [b]	DMSO-d_6 [c]	Benzene-d_6 [c]
C-1	0.17	0.10	0.12
C-2	0.28	0.15	0.18
C-3	0.27	0.15	0.21
C-4	0.24	0.20	0.20
C-5	0.34	0.22	0.21
C-6	0.24	0.14	0.13

a) The measurements were carried out at 50°C.

in D_2O can be partly attributed to the lower viscosity of the DMSO-d_6 solution. It could also be due to differences in the intermolecular hydrogen bonding of the hydroxy groups of 1 with the two solvents, as has been demonstrated by circular dichroism measurements of cyclodextrins.[9]

Binding abilities of 3 were assessed by solvent extraction of aqueous solution of Li^+, Na^+, K^+, Rb^+, Cs^+,

$MeNH_3^+$ and $PhCH(CH_3)NH_3^+$ picrates with chloroform using Cram's method.[10] Under these experimental conditions only Li^+ (K_a = 82,000 M^{-1}) and $PhCH(CH_3)NH_3^+$ (K_a = 380 M^{-1}) were bound. The absorption maxima of the corresponding picrates in the organic phase indicated a 1:1 stoichiometry for the complexes.[10,11] Although compound **3** has not a crown structure, it can bind selectively lithium with an association constant of the orden of magnitude as reported[12] for 14-crown-4 and 15-crown-5 and higher than those reported for some carbohydrate containing crown-compounds.[13]

EXPERIMENTAL

General methods. All experiments with borylated compounds were carried out under argon. Column chromatography was performed on silica gel Merck 60 (70-230 mesh). H.p.l.c. of the acetylated mixtures was carried out on a column of 15 cm lenght and 4 mm internal diameter packed with Hibar EC Lichrosorb RP-18 previously treated with a 4.9×10^{-3} molar solution of α-cyclodextrin in 35% w/w methanol-water, washed with 1:1 THF-methanol. A flow-rate of 1 ml/min with 36% w/w methanol-water as mobile phase was used. ^1H and ^{13}C n.m.r. spectra were recorded at 300 MHz and 75 MHz using a Varian XL-300 spectrometer. Spin-lattice relaxation times were determined by the inversion-recovery technique using a non-linear least-square fitting procedure. Optical rotations were measured using a Perkin-Elmer 141 polarimeter.

Reduction of per-*O*-diethylboryl-β-cyclodextrin. A stirred mixture of per-*O*-diethylboryl-β-cyclodextrin[14] (1.62 g, 0.62 mmol) and ethyldiborane[15] (1.56 g, 25.5 mmol, H^-) was kept at room temperature for 3 days. Evaporation at 20°C/12 torr removed ≃ 0.47 g of triethylboron. Then 9-BBN-mesylate[16] (0.1 g, 0.46 mmol) was added and the mixture heated to 120°C for 4 h. The solution was cooled to room temperature and the excess ethyldiborane was destroyed by bubbling ethylene through the solution. The volatile components were removed *in vacuo*. No material could be distilled from the residue (1.13 g) at 150°C/10^{-3} torr. Methanol (90 mL) was added to the residue and the mixture was heated to boiling. Methanol was removed and propane-1,3-diol (6 mL) was added to the residue and the volatiles distilled off (70°C bath/10^{-3} torr). The propane-1,3-diol treatment was repeated to give a boron-free residue to which ethanol was added and distilled off. Pyridine (10 mL) and acetic anhydride (10 mL) were added to the residue and the mixture stirred overnight at room temperature. Concentration of the solution gave 1.38 g of a peracetylated mixture. H.p.l.c. analysis indicated two main components and six by-products. Column chromatography (1 g) on silica gel (hexane-ethylacetate 1:11) eluted first pure **4** (0.35 g) and second a mixture of **4** and **3** (0.5 g). This fraction was rechromatographied and the composition of each fraction tested by h.p.l.c. It yielded 0.3 g of pure **4** and 0.15 g of pure **3** as a no crystalline solid; $|\alpha|_D^{20}$ + 45.7 (c 0.5, chloroform). ^1H and ^{13}C n.m.r. data for **3** are given in Tables 1 and 2. (Found: C, 51.0; H, 6.32. Calcd. for $C_{98}H_{140}O_{63}$: C, 50.6; H, 6.02).

To a solution of **3** (0.3 g) in absolute methanol (5 mL) sodium methoxide (0.2 mL, 1M) was added. The solution became warm and compound **1** precipitated as a highly hygroscopic white solid (0.14 g, 98%); $|\alpha|_D^{20}$ + 22.4 (c 0.24, water). For ^1H and ^{13}C n.m.r., *see Tables 1 and 2*. (Found: C, 43.8; H, 7.62. Calcd. for $C_{42}H_{84}O_{35}$: C, 43.9; H, 7.37).

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