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Mixed acetals of cyclodextrins. Preparation of hexakis-, heptakis- and octakis[2,6-di-*O*-(methoxydimethyl)methyl]-α-, β- and γ-cyclodextrins

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Abstract

The proton-catalyzed addition of 2-methoxypropene to α-, β- and γ-cyclodextrins resulted in hexakis-, heptakis-, and octakis[2,6-di-*O*-(methoxydimethyl)methyl]-α-, β- and γ-cyclodextrins, but no reaction was observed of CD-s with 2,2-dimethoxypropane. The mixed acetal-type compounds can be alkylated under basic conditions. The preparation of hexakis(3-*O*-benzyl)-α-cyclodextrin demonstrates the synthetic value of this methodology. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Carbonyl compounds generally, acetone and its acetals or enolethers particularly, react with diols in the presence of an acid catalyst to give cyclic acetals.[1] These type of acetals are especially important derivatives in the field of carbohydrates. Hexopyranosides give mainly 4,6-*O*-acetals,[2] but their vicinal cis-diols furnish dioxolane-type five-membered cyclic acetals.[3] The formation of dioxolane-type rings from vicinal trans-diequatorial diols is also known, but only few derivatives having this type of ring-system were prepared. Their preparation needs also certain consideration: i.e., methyl α-D-glucopyranoside reacts with acetone to give exclusively the 4,6-*O*-isopropylidene derivative. The case is similar also using 2,2-dimethoxypropane as a reagent, the amount of methyl 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranoside is ca. 1.5–14%,[4] but with 2-methoxypropene its proportion is higher than 70%.[5] In the case of xylopyranosides it is easy to obtain the 2,3-*O*-isopropylidene derivatives, such as benzyl 2,3-*O*-isopropylidene-,[6] methyl 2,3-*O*-isopropylidene-,[7] methyl 2,3-*O*-isopropylidene-1-thio-,[8] and ethyl 2,3-*O*-isopropylidene-1-thio-β-D-xylopyranoside.[9] These compounds were produced in 65–75% yields, using 2-methoxypropene as a reagent, and the 3,4-*O*-isopropylidene isomers were the minor components, usually present in $< 15\%$.

It was also observed that methyl 4,6-di-*O*-methyl-α-D-[10] and phenyl 4,6-di-*O*-methyl-β-D-glucopyranoside[11] reacted very easily even with 2,2-dimethoxypropane to result in the 2,3-*O*-isopropylidene derivatives. This observation shows that the absence of a 4,6-*O*-isopropylidene moiety increases the flexibility of the pyranoside ring, and the 2,3-trans-diequatorial hydroxyl groups form the cyclic acetals.[12]

It is also to be mentioned that the hexopyranosides react with 2-methoxypropene, as well as with 2,2-dimethoxypropane at the primary OH group giving (methoxydimethyl)methyl ethers,[13] which are more acid-sensitive than the methoxymethyl ethers. These mixed acetals are very useful starting materials because the free OH group(s), if it (they) is (are) present, can be readily alkylated under alkaline conditions.[13]

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2. Results and discussion

Actually, the preparation of partially substituted cyclodextrins has raised a lot of synthetic and structural problems; their synthesis is more difficult than those of the simple monosaccharide derivatives,[15] although each of the α-D-glucopyranosyl units is chemically equivalent. Therefore, a synthetic approach producing homogenous compounds can be very valuable in this field.

Considering the possibility of the development of the synthesis of a dioxolane ring[2–9] from vicinal trans-diequatorial hydroxyl groups, as well as the easy formation of (methoxydimethyl)methyl ethers at the primary OH groups[13] (and very rarely also at the secondary OH groups[14]), the conversion of cyclodextrins [α-CD (**1**), β-CD (**2**) and γ-CD (**3**)] into dioxolane-acetal or (methoxydimethyl)methyl ether derivatives can be regarded as a promising procedure obtaining partially substituted CD derivatives.

Earlier experiments showed that the best yields either for the dioxolane-type isopropylidene acetals,[16] or for the (methoxydimethyl)methyl ethers[13] could be obtained when neat 2,2-dimethoxypropane was employed in large excess. Unfortunately, the cyclodextrins (**1**–**3**) could not be dissolved in this reagent. Therefore, the cyclodextrins (**1**–**3**) were dissolved in *N*,*N*-dimethylformamide, the solutions were diluted with the reagent (50 equiv), and then the catalyst was added. However, no reaction could be detected even at 70 °C (Fig. 1).

A completely different behavior was observed when 2-methoxypropene was the reagent. To increase the solubility of the cyclodextrins, a suspension in a very small amount of *N*,*N*-dimethylformamide was used, the reagent was added to the reaction mixture, and the reaction was initiated by a catalytic amount of *p*-toluenesulfonic acid. A complete dissolution of the cyclodextrins occurred in an exothermic process, and multicomponent reaction mixtures were detected by TLC. If the reaction temperature was high, the main product was a polymer, formed from the reagent. By cooling to room temperature the amount of the polymer could be reduced, but the reaction pattern did not change. The product (**4**–**6**) having the highest chromatographic mobility proved to be the main component in each case, to be isolated in 30–40% yield.

All three cyclodextrin derivatives (**4**–**6**) showed very similar ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra there were two OCH_3 signals at 3.25–3.15 ppm, and four CH_3 singlets appeared at 1.45–1.15 ppm. The ^{13}C NMR spectra showed more information about the structure of the isolated compounds. In the sugar-skeleton region, six signals were found showing a symmetrical structure of the compounds. With the help of the J-ECHO spectra the C-1 (**4**, 102.34; **5**, 102.34; and **6**, 102.65 ppm) signals, as well as the C-6 (**4**, 59.33; **5**, 59.32; and **6**, 59.65 ppm) resonances could be assigned. In the anomeric region the spectra of all three compounds contained two additional signals (**4**, 102.21, 99.72; **5**, 102.21, 99.73; and **6**, 102.31 and 99.72 ppm). These signals could be assigned to the acetalic carbon atoms of the mixed acetals. COSY, HMBC and HETCOR measurements allowed a complete structure assignment, and thus compounds **4**–**6** were identified as hexakis-, heptakis- and octakis[2,6-di-*O*-(methoxydimethyl)methyl]-α- (**4**), -β- (**5**) and γ-cyclodextrins (**6**). It is to be noted that the bulky (methoxydimethyl)methyl ether groups caused ~ -2ppm α-shifts, and this observation made the position of the secondary O–C(CH_3)$_2$–OCH_3 group questionable. HETCOR measurements of compound **4** showed $^3J_{CH}$ couplings between C_q (102.2 ppm) and H-2 (3.79 ppm), and couplings were also detected between O*H*-3 (4.64 ppm) and C-4 (83.8 ppm), as well as between O*H*-3 and C-2 (72.0 ppm). These results clearly demonstrated that the O–C(CH_3)$_2$–OCH_3 groups were located at C-2 and C-6. Because the chemical shift values of all three acetals are nearly the same, we are convinced that the assignments are also correct in the β- and γ-CD compounds.

These acetal derivatives are acid-labile compounds; during chromatographic separation, a small amount of triethylamine was added to the eluent system. The pure compounds are microcrystalline substances, which start to decompose at room temperature after standing for

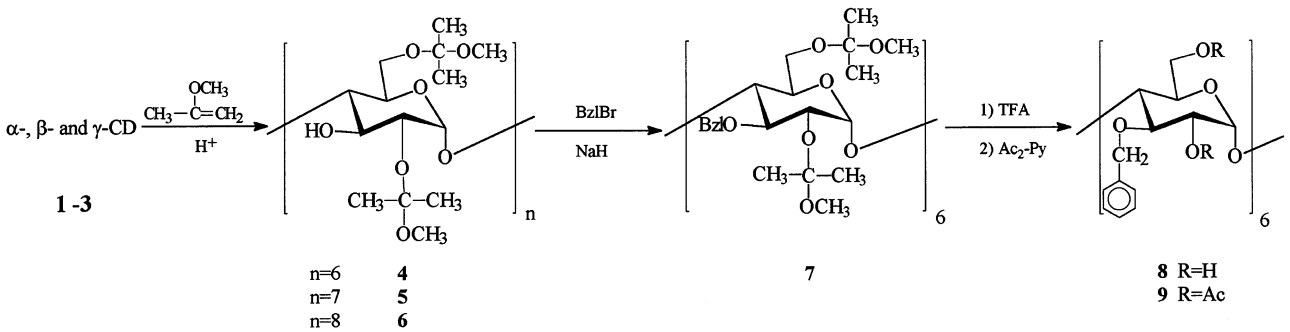

Fig. 1.

Table 1
^{13}C NMR data of substituted cyclodextrin derivatives

	4	5	6	8[a]
C-1	102.34	102.34	102.65	103.47
C-2	72.04	72.00	72.45	74.81
C-3	71.21	71.20	71.65	80.89
C-4	83.79	83.79	83.90	82.97
C-5	70.65	70.66	70.93	74.21
C-6	59.33	59.32	59.65	62.09
$CH_3O-C(CH_3)_2-O-2$	102.21	102.21	102.31	
$CH_3O-C(CH_3)_2-O-6$	99.72	99.73	99.72	
$CH_3O-C(CH_3)_2-O-2$	50.07	50.12	50.12	
$CH_3O-C(CH_3)_2-O-6$	48.50	48.49	48.41	
4 x CH_3	25.21 24.97 24.67 24.29	25.22 25.0 24.71 24.33	25.01 25.01 24.63 24.27	
Ph–CH2–				75.62
Aromatic				139.59 129.40 129.26 128.70

[a] Measured in CD_3OD, all others in $CDCl_3$.

1–2 days, but they are rather stable at −20 °C, and can be stored for 1–2 months without a remarkable decomposition.

The mixed acetal of the α-cyclodextrin (**4**) was benzylated under the Brimacombe conditions (DMF, NaH)[17] to furnish hexakis[3-*O*-benzyl-2,6-di-*O*-(methoxydimethyl)methyl]-cyclomaltohexaose (**7**). Removal of the acetal groups upon mild-acid hydrolysis[18] gave the hitherto unknown hexakis(3-*O*-benzyl)-cyclomaltohexaose (**8**).

To confirm the presence of the *O*-benzyl group at C-3, compound **8** was acetylated and the ^{1}H NMR spectrum of the fully substituted **9** was assigned. The low-field quartet at 4.83 ppm ($J_{1,2}$ 4.0 and $J_{2,3}$ 9.8 Hz) was ordered to H-2. Similarly, H-6a and H-6b resonated also at low fields (4.46 and 4.28 ppm) demonstrating that the two-acetyl groups were located at C-2 and C-6.

Compound **8** is considered as a valuable intermediate to synthesize partially protected cyclodextrin derivatives. The ^{13}C NMR spectral data of compounds **4**–**6** and **8** are collected in Table 1.

3. Experimental

General.—NMR spectra were recorded at 25 °C with Bruker WP 200 SY (^{1}H, 200 MHz; ^{13}C, 50.3 MHz), Bruker AM-360 (^{1}H, 360 MHz; ^{13}C, 75.0 MHz) and Bruker Avance DRX 500 (^{1}H, 500.13 MHz; ^{13}C, 125.76 MHz) instruments for solutions in $CDCl_3$ (internal Me_4Si) or in CD_3OD. Proton chemical shifts (δ) are given in ppm relative to the signal for internal Me_4Si ($CDCl_3$). Carbon chemical shifts were referenced to the solvent signal. Mass spectra were obtained with a PerSeptive Biosystems MALDI-TOF instrument. 2,5-Dihydroxybenzoic acid was used as a matrix. Column chromatography was performed on Kieselgel 60 (E. Merck, 230 mesh) and the fractions were monitored by TLC on Kieselgel 60 F_{254} (E. Merck) by detection with UV light and then charring with H_2SO_4. Unless noted otherwise, optical rotations were measured for solutions in $CHCl_3$ at 20 °C with a Perkin–Elmer 241 polarimeter, using a 10 cm (1 mL) cell. Concentration of solutions was performed at 30 °C.

Protocol for acetalization.—Cyclodextrin (2.5 mmol) was suspended in dry *N*,*N*-dimethylformamide (20 mL), and was stirred with 4 Å molecular sieves (2.0 g) and with *p*-toluenesulfonic acid (10 mg) for 1 h at rt. To the reaction mixture, 2-methoxypropene (14 mL, 146 mmol) was added dropwise during 30 min. After stirring for 1 h, additional *p*-toluenesulfonic acid (70 mg) was added to the reaction mixture, and stirring was continued for 96 h. The mixture was filtered through a Celite pad and the filtrate was neutralized by Et_3N. The solution was evaporated and the residue was purified twice by column chromatography on Kieselgel 60 (150 g), using 2:1 CH_2Cl_2–acetone, containing 0.5% of Et_3N.

Hexakis[2,6-di-O-*(methoxydimethyl)methyl]-α-cyclodextrin* (**4**).—Microcystalline solid. Yield: 1.65 g (36%; 0.90 mmol); $[\alpha]_D$ +54.01° (*c* 0.48, $CHCl_3$); R_f 0.65 (95:5:0.5 CH_2Cl_2–MeOH–Et_3N); ^{1}H NMR: δ 4.84 (d, 1 H, $J_{1,2}$ 3.04 Hz, H-1), 4.64 (s, 1 H, OH-3), 4.09 (t, 1 H, $J_{3,4}$ 9.57 Hz, H-3), 3.82 (m, 1 H, $J_{5,6a}$ 2.22 Hz, H-5), 3.79 (dd, 1 H, $J_{4,5}$ 9.75 Hz, H-4), 3.36 (s, 3 H, OCH_3-2), 3.14 (s, 3 H, OCH_3-6); ^{13}C NMR: see Table 1. Anal. Calcd for $C_{84}H_{156}O_{42}$: C, 54.88; H, 8.55. Found: C, 55.02; H, 8.61.

Heptakis[2,6-di-O-*(methoxydimethyl)methyl]-β-cyclodextrin* (**5**).—Microcrystalline solid. Yield: 2.26 g (42.3%; 1.05 mmol); $[\alpha]_D$ +54.87° (*c* 0.15, $CHCl_3$); R_f 0.60 (94:6:0.5 CH_2Cl_2–MeOH–Et_3N); ^{13}C NMR: see Table 1. Anal. Calcd for $C_{98}H_{182}O_{49}$: C, 54.88; H, 8.55. Found: C, 54.69; H, 8.62.

Octakis[2,6-di-O-*(methoxydimethyl)methyl]-γ-cyclodextrin* (**6**).—Solid powder. Yield: 1.98 g (32.3%; 0.81 mmol); $[\alpha]_D$ +61.81° (*c* 0.52, $CHCl_3$). R_f 0.65 (93:7:0.5 CH_2Cl_2–MeOH–Et_3N); ^{13}C NMR: see Table 1. Anal.

Calcd for $C_{112}H_{208}O_{56}$: C, 54.88; H, 8.55. Found: C, 54.67; H: 8.41.

Hexakis[3-O-benzyl-2,6-di-O-(methoxydimethyl)-methyl]-α-cyclodextrin (**7**).—To a solution of **4** (303 mg, 1.65×10^{-4} mol) in dry DMF (3 mL) was added NaH (48 mg, 2 mmol) and stirred for 1 h at rt. To the chilled reaction mixture, BnBr (214 μL, 1.8 mmol) was added and stirred for overnight at rt. The usual work-up procedure resulted in a syrupy product which was purified by column chromatography (4:1 CH_2Cl_2–acetone) to give **7** (333 mg; 85%); $[\alpha]_D + 20.61°$ (*c* 0.32, $CHCl_3$); R_f 0.55 (4:1 CH_2Cl_2–acetone); ^{13}C NMR: δ 101.64 (C_2–O–*C*), 99.87 (C_6–O–*C*), 80.0 (C-3), 75.54 (*C*H_2–Ph), 72.0 (C-5), 60.0 (C-6), 49.77 (C_2–OCO*C*H_3), 48.50 (C_6–OCO*C*H_3), 25.39, 24.82, 24.82, 24.49 (4 × *C*H_3). Anal. Calcd for $C_{126}H_{192}O_{42}$: C, 63.62; H, 8.14. Found: C, 63.26; H, 8.09.

Hexakis(3-O-benzyl)-α-cyclodextrin (**8**).—Compound **7** (238 mg, 0.1 mmol) was dissolved in 90% aq trifluoroacetic acid (5 mL) and the solution was kept for 15 min at rt, then concentrated. The residue was chromatographed (80:20:3 CH_2Cl_2–MeOH–water) to yield syrupy **8** (124 mg, 82%, 0.08 mmol); $[\alpha]_D + 13.26°$ (*c* 0.34, MeOH); R_f 0.53 (80:20:3 CH_2Cl_2–MeOH–water); ^{13}C NMR: see Table 1; MALDI-TOF-MS: *m*/*z* 1535.62 [M + 23]. Anal. Calcd for $C_{78}H_{96}O_{30}$: C, 61.89; H, 6.39. Found: C, 62.02; H, 6.41.

Hexakis(2,6-di-O-acetyl-3-O-benzyl)-α-cyclodextrin (**9**).—Acetic anhydride (0.5 mL) was added to a stirred solution of compound **8** (50 mg, 0.033 mmol) in anhyd pyridine (0.5 mL) at 0 °C. The ice-bath was removed and the mixture was stirred for 24 h at rt. Concentration and subsequent column chromatographic purification of the residue gave **9** (58 mg, 87%, 0.029 mmol); $[\alpha]_D + 131.56°$ (*c* 0.18 $CHCl_3$); R_f 0.45 (17:3 CH_2Cl_2–acetone); ^1H NMR (360 MHz): δ 7.30–7.18 (m, 5 H, aromatic), 5.12 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.83 (q, 1 H, $J_{2,3}$ 9.8 Hz, H-2), 4.76 (AB-quartet, 2 H, C*H*$_2$–Ph); 4.46 (d, 1 H, J_{6a6b} 12.0 Hz, H-6*a*), 4.28 (dd, 1 H, $J_{5,6b}$ 5.6 Hz, H-6*b*), 4.13 (m, 1 H, H-5), 4.08 (t, 1 H, $J_{3,4}$ 9.0 Hz, H-3), 3.70 (t, 1 H, $J_{4,5}$ 9.0 Hz, H-4), 2.07 and 1.41 (2s, 6 H, O*Ac*-2,6).

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