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Note

Synthesis of $2^1,3^1$-*O*-(propane-1,2-diyl)- and $2^1,3^1$-*O*-(3-hydroxypropane-1,2-diyl)-cyclomaltoheptaose

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Abstract

$2^1,3^1$-*O*-(Propane-1,2-diyl)cyclomaltoheptaose has been prepared from 2-*O*-allylcyclomaltoheptaose by mercuration in trifluoroacetic acid, followed by reduction with sodium borohydride. 2-*O*-(2,3-Epoxypropyl)cyclomaltoheptaose, prepared from 2-*O*-allylcyclomaltoheptaose by oxidation with dimethyldioxirane, was converted into $2^1,3^1$-*O*-(3-hydroxypropane-1,2-diyl)cyclomaltoheptaose by treatment with trifluoroacetic acid. Both derivatives containing fused 1,4-dioxane rings are mixtures of stereoisomers, in which the methyl and hydroxymethyl group, respectively, that is linked to this ring, occupies an axial or an equatorial position. © 1997 Elsevier Science Ltd.

Keywords: Cyclodextrins; 1,4-Dioxane rings fused to sugar residues

1. Introduction

The cyclodextrins can include non-polar substances into their cavities. They are widely used in pharmaceutics and in analytical chemistry [1]. Modification by substitution may improve their solubility or specificity for different guest compounds. We have reported on the synthesis of a number of monosubstituted derivatives of cyclomaltoheptaose (β-cyclodextrin, β-CD) [2–4]. Crystal structures of β-CD derivatives monoalkylated on O-2 or O-6 contain chains of associated molecules in which the substituent in one molecule is inserted into the cavity of the next molecule in the chain [5–7].

In the cyclodextrins the opening on the secondary hydroxyl side is wider than the opening on the primary hydroxyl side, and is obviously preferred for the entry and insertion of a guest molecule. Modification on the secondary side by rigid substituents, which can not themselves be included, may therefore lead to hosts with increased guest selectivity. We now report on the synthesis of two such β-CD

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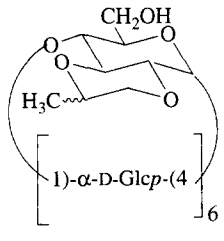
derivatives, in which a 1,4-dioxane ring is fused to the 2- and 3-positions in one of the α-D-glucopyranosyl residues.

2. Results and discussion

2-*O*-Allyl-β-CD [4] was used as starting material. Mercuration–demercuration of monoallyl ethers of vicinal diols is known to give 1,4-dioxane derivatives [8], and demercuration is accomplished by reduction with sodium borohydride in alkaline solution [9]. When the mercuration reaction was performed in aqueous solution, the demercuration yielded the previously known 2-hydroxypropyl-β-CD [3] as the main product, although now as a mixture of diastereoisomers. When, however, the mercuration with mercuric acetate was performed in trifluoroacetic acid, the subsequent demercuration yielded $2^1,3^1$-*O*-(propane-1,2-diyl)-cyclomaltoheptaose (**1**). The ^{13}C NMR spectrum of the crude product showed, *inter alia*, a signal at δ 16.2 and a weaker signal at δ 15.9, assigned to the isomers with equatorial and axial methyl group, respectively. The reaction product was methylated, hydrolyzed, reduced with sodium borodeuteride, acetylated and investigated by electron impact GLC–MS. A mixture of acetylated 2,3,6-tri-*O*-methyl-D-glucitol and another component in the approximate ratio 6:1 was obtained. The latter (**2**), from its mass spectrum, derived from a 2,3-*O*-(propane-1,2-diyl)-α-D-glucopyranosyl residue in the β-CD derivative. Some typical fragments are indicated in the formula. The $2^1,3^1$-*O*-(propane-1,2-diyl)-β-CD was crystallized from water. The molecular weight, 1174.5, as determined by FABMS, and its mobility on TLC, were the same as observed for 2-*O*-allyl-β-CD, but only the latter reacted rapidly with aqueous permanganate.



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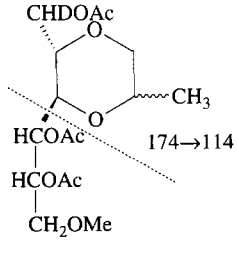

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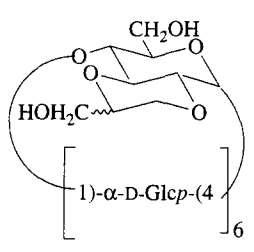
The other intramolecular cyclization started from 2-*O*-(2,3-epoxypropyl)-β-CD, prepared from 2-*O*-allyl-β-CD by oxidation with dimethyldioxirane. Attempted cyclization by treatment with aqueous sodium hydroxide yielded 2-*O*-(2,3-dihydroxpropyl)-β-CD which, except for being a mixture of diastereoisomers, was identical with a previously prepared sample [7]. When 2-*O*-(2,3-epoxypropyl)-β-CD was treated with trifluoroacetic acid at room temperature, however, cyclization occurred and amorphous $2^1,3^1$-*O*-(3-hydroxypropane-1,2-diyl)-cyclomaltoheptaose (**3**) was obtained. It had $M = 1190.4$, as determined by FABMS. Methylation analysis, as described for $2^1,3^1$-*O*-(propane-1,2-diyl)-β-CD, gave, *inter alia*, two components (7 and 8% respectively) with almost identical mass spectra, which were in agreement with that expected for the alditol derivative (**4**) from a $2^1,3^1$-*O*-(3-hydroxypropane-1,2-diyl)-α-D-glucopyranosyl residue. A substance related to **3**, namely, methyl 2,3-*O*-(3-hydroxypropane-1,2-diyl)-α-D-glucopyranoside, has been prepared by similar methods [10].



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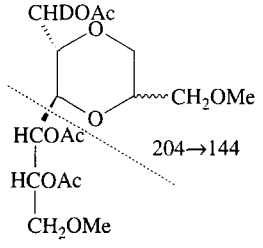

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There are indications that some intermolecular etherification occurs on heating of 2-*O*-(2,3-epoxypropyl)-β-CD in a vacuum, but this has to be investigated further.

3. Experimental

General methods.—TLC was performed on Kieselgel 60 F_{254}, using freshly prepared 1-PrOH–EtOAc–H_2O–conc. aq ammonia (6:1:3:1) as solvent. The spots were developed by spraying with Vaugh's reagent [1 g $Ce(SO_4)_2$, 24 g $(NH_4)_2MoO_4$, 50 mL conc. H_2SO_4, 450 mL H_2O], followed by moderate heating. Column chromatography was performed on silica gel, using the solvent system 1-PrOH–toluene–H_2O–conc. aq ammonia (6:1:3:1). Mass spectra were recorded with a FAB VG 7070E-HF instrument at Mass Spectroscopy Service Laboratory of the University of Minnesota; a matrix of glycerol and TFA was used. ^{13}C NMR spectra of solutions in D_2O were recorded at 70 °C on a Jeol GSX-270 instrument,

using acetone (δ 31.00) as internal standard. Methylation analyses were performed as previously described [11]. The crystalline β-CD derivatives were used in hydrated state as starting materials.

As partial hydration of cyclodextrins is a general phenomenon and can change rapidly and continuously [12], elemental analyses are nearly useless and are not given.

Mercuration in water – demercuration of 2-O-allyl-β-CD.—Mercuric acetate (14 mg, 47 μmol) in water (100 mL) was added to a solution of 2-*O*-allyl-β-CD (50 mg, 38 μmol) in water (1 mL). After 1 h at 24 °C 3 M NaOH (100 mL), containing $NaBH_4$ (1 mg), was added, the solution kept at 24 °C for 8 h, neutralized with H_2SO_4, concentrated, and fractionated by preparative TLC. The main product was 2-*O*-(2-hydroxypropyl)-β-CD (R_f 0.20), and only traces of the cyclization product (R_f 0.34) were observed.

Mercuration in TFA – demercuration of 2-O-allyl-β-CD.—Mercuric acetate (500 mg, 1.57 mmol) in TFA (10 mL) was added to a solution of 2-*O*-allyl-β-CD (1 g, 0.76 mmol) in TFA (20 mL), and the solution was kept for 1 h at 24 °C. The solution was then concentrated to dryness under reduced pressure at 24 °C, cooled with ice, dissolved in 3 M NaOH (11 mL) containing $NaBH_4$ (60 mg), and kept for 12 h at 60 °C. The solution was then desalted by successive treatments with Dowex 50 (H^+) (30 g), Dowex 1X2 (HCO_3^-) (20 g), Dowex 50 (10 g), and Dowex 1X2 (10 g). Silica gel (5 g) was added and the water removed under reduced pressure. The solid was added to the top of a silica gel column (50 g), and chromatography gave amorphous $2^1,3^1$-*O*-(3-hydroxypropane-1,2-diyl)-β-CD (600 mg, 60%). An aqueous solution of the product crystallized (300 mg, m.p. 295, decomp.). MS: m/z 1175.5 $(M + H)^+$.

2-O-(2,3-epoxypropyl)-β-CD.—An excess of a freshly prepared solution of dimethyldioxirane [13] in acetone (20 mL) was added to a suspension of 2-*O*-allyl-β-CD (975 mg, 0.75 mmol) in water (30 mL) and the mixture stirred at 24 °C for 1 h. The acetone was evaporated, the solution freeze dried, and the residue crystallized from water (5 mL), yielding the title compound (800 mg), m.p. 295 °C (decomp.), R_f 0.25. MS: m/z 1191.3 $(M + H)^+$.

$2^1,3^1$-O-(3-hydroxypropane-1,2-diyl)-β-CD (**3**).—A solution of 2-*O*-(2,3-epoxypropyl)-β-CD (1 g, 0.84 mmol) in TFA was kept for 7 h at 24 °C, and then concentrated at the same temperature under reduced pressure. 1-PrOH (10 mL) was added, the mixture concentrated to dryness, dissolved in water (100 mL), treated with Dowex 1X2 (HCO_3^-) (30 g), concentrated together with silica gel (5 g), and fractionated on a silica gel column (100 g). The title compound was obtained as an amorphous powder (R_f 0.25, 740 mg, 74%). MS: m/z 1191.4 $(M + H)^+$.

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