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Intramolecular Glucosidation of 2-*O*-Hydroxyethyl-D-glucose

JAN ERIK HÖÖK and BENGT LINDBERG

Träkemiska avdelningen. Svenska Träforskningsinstitutet and Institutionen för Organisk kemi, Stockholms Universitet Stockholm, Sweden

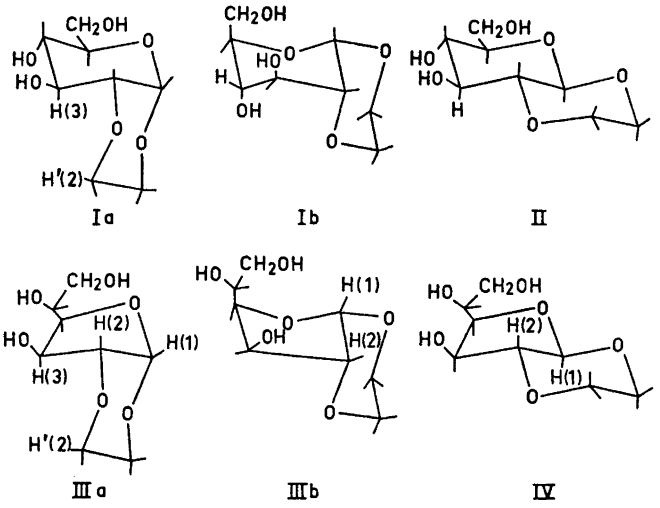
2-*O*-Hydroxyethyl-D-glucose undergoes intramolecular glucoside formation under acid conditions affording to two bicyclic D-glucopyranosides (I and II) and the bicyclic α-furanoside (III). The latter, 1,2-*O*-ethylene-α-D-glucofuranose, was also synthesised by another route, in order to confirm its structure.

Helferich and Werner[1] prepared the bicyclic 1,2-*O*-ethylene-α- and β-D-glucopyranosides from the corresponding 2-halogenoethyl-D-glucopyranosides by intramolecular etherification under alkaline conditions. It seemed probable that similar compounds should also be formed on intramolecular glucosidation of 2-*O*-hydroxyethyl-D-glucose. de Belder[2] has recently demonstrated that 1,2-*O*-(1-methylethylene)-α-D-glucopyranose and the corresponding α-D-glucofuranose are formed on acid hydrolysis of 2′-hydroxypropyl starch.

Methyl 2-*O*-hydroxyethyl-α- and β-D-glucopyranoside were available from a previous investigation,[3] and these, on acid hydrolysis, yielded 2-*O*-hydroxyethyl-D-glucose. When the latter substance was treated with hydrogen chloride in dimethylformamide, a mixture of several components was obtained as indicated by TLC and by GLC of the trimethylsilyl ether derivatives. One of the main components and a minor component were chromatographically indistinguishable from authentic samples of 1,2-*O*-ethylene-α-(I)- and β-D-glucopyranose (II), respectively.

The component present in the highest percentage was obtained crystalline, m.p. 218–220°, $[\alpha]_{578}$ −56° (water) after fractionation of the product on a silicic acid column. On periodate oxidation, one mole of oxidant was consumed and one mole of formaldehyde was formed, establishing a furanoside structure. Because of the low optical rotation, it was first believed to be the β-furanoside (IV).

The NMR spectrum of this substance in D_2O, showed *inter alia* a doublet at τ 4.55, $J_{1,2}$ 2.5 Hz. As no signals were observed at lower fields, this could safely be attributed to the anomeric proton. A six-membered ring, in the chair form, has a rather rigid structure and its conformation is only slightly modified when it is condensed with a five-membered ring.[4] Thus whereas the H(1)



and H(2) protons should be almost diaxial in IV, in IIIa or IIIb they should be close to equatorial-axial. Only the latter structure (III) is therefore compatible with the low coupling constant.[4]

The structure of the bicyclic furanoside was confirmed by its synthesis *via* another route. Treatment of D-glucose with 2-chloroethanol yielded a mixture of glucosides. On attempted fractionation of these on a column of strongly alkaline ion exchange resin,[5] cyclisation occurred. The mixture could, however, be fractionated on a silicic acid column. In addition to the α- and β-pyranosides, for which reference substances were available, a non-crystalline fraction, $[\alpha]_{578}$ +82° (water), was obtained. Methyl α- and β-D-glucofuranoside show $[\alpha]_D$ +115° and −78°, respectively, and it could therefore confidently be assumed that the fraction contained essentially the α-furanoside. On alkaline treatment, it gave a 70 % yield of 1,2-*O*-ethylene-α-D-glucofuranose (III), m.p. 218—220°, $[\alpha]_{578}$ −56°, in all respects indistinguishable from the bicyclic furanoside obtained on intramolecular glucosidation. The low optical rotation of this α-D-glucofuranoside is not really unexpected, considering that several other bicyclic α-D-glucofuranosides, *e.g.* 1,2-*O*-isopropylidene-α-D-glucofuranose, also have negative rotations.

The ratio of pyranosides to furanosides in the reaction product, as estimated from GLC of their trimethylsilyl ethers, was 1.0:2.5. When 2-*O*-hydroxyethyl-D-glucose (10 mg) in M sulphuric acid (5 ml) was treated at 100° for 18 h, III was formed in low yield but none of the other bicyclic compounds could be detected. It is conceivable that, under the conditions employed above, equilibrium for the intramolecular glucosidation reactions in dimethyl formamide and in water had not been established.

In the rigid bicyclic β-D-glucosides (II and IV), the anomeric effect is probably more pronounced than in the corresponding monocyclic β-D-glucosides. In the β-furanoside (IV), there is further an unfavourable *trans*-fusion between a five-membered and a six-membered ring. These effects

probably account for the low yield of II and the virtual absence of IV on intramolecular glucosidation.

Each of the bicyclic α-D-glucosides can occur in two conformations (Ia, Ib and IIIa, IIIb), in which their six-membered rings assume chair forms. From an inspection of models, it is evident that in the normal form, Ia, and the related furanoside, IIIa, there is a considerable steric interaction between the two hydrogen atoms, H(3) and H'(2). No such interactions are present in the alternative form, Ib, or in the related furanoside IIIb. In Ib there are strong interactions between the bulky, axial groups in the pyranose ring. In IIIb, however, the interactions between the substituents in the furanose ring seem to be less severe. A qualitative conformation analysis therefore indicates that the α-furanoside, III, should be the most stable and the β-furanoside, IV, the least stable of the 1,2-*O*-ethylene-D-glucoses, in agreement with the experimental results.

EXPERIMENTAL

Melting points are corrected. Evaporations were performed under reduced pressure at a bath temperature below 40°. TLC was performed on silica gel G (E. Merck, AG) and column chromatography on silicic acid (100 mesh. Mallinckrodt). GLC, of the trimethylsilylated sugars, was performed on columns containing 15 % (w/w) of BDS, on Chromosorb (100—120 mesh) at 160°, using a Perkin Elmer 800 Gas Chromatograph. NMR, in D_2O, was recorded on a Varian A60 spectrometer.

Intramolecular glucosidation of 2-O-hydroxyethyl-D-glucose. Methyl 2-*O*-hydroxyethyl-β-D-glucopyranoside [3] (1.1 g) was hydrolysed in M hydrochloric acid (15 ml) for 8 h at 100°, the solution neutralised with Dowex 3 (free base) and concentrated. The resulting syrup was dissolved in dimethylformamide (15 ml), containing 37 % aqueous hydrochloric acid (1 ml) and Drierite (2 g). The mixture was kept at 100°, with stirring, for 16 h and was then filtered and concentrated. The resulting syrup was fractionated on a silicic acid column (3.5 × 50 cm) using chloroform-ethanol, 3:1, as irrigant. The fractionation was followed by TLC in the same solvent system. The first fraction (400 mg), R_F 0.75, crystallised when concentrated. Recrystallisation from ethanol yielded pure *1,2-O-ethylene-α-D-glucofuranose* (III), m.p. 218—220°, $[\alpha]_{578}^{20}$ −56° (*c* 2.0, water). (Found: C 46.6; H 6.80; O 46.6. $C_8H_{14}O_6$ requires: C 46.6; H 6.84; O 46.6). Periodate oxidation was performed with 0.015 M aqueous solution of sodium metaperiodate at 20°. The periodate consumption [6] and the formation of formaldehyde [7] were followed spectrophotometrically, the latter after reaction with chromotropic acid. After 1 h, 0.95 moles of periodate had been consumed and 1.01 moles of formaldehyde formed. These values had not changed appreciably after 5 h.

The second fraction (200 mg) contained a mixture of I, R_F 0.62, and II, R_F 0.65, in the approximate ratio 10:1. The components I and II were chromatographically indistinguishable from authentic samples. It was not possible, by GLC, to separate I and II. The presence of some minor components, possibly dimers, was observed on GLC. No positive evidence for the presence of IV in the reaction mixture could be obtained.

Synthesis of 1,2-O-ethylene-α-D-glucofuranose (III). A mixture of D-glucose (6.5 g) and 2-chloroethanol (75 ml) was stirred at 45° until a homogeneous solution was obtained, Dowex 50 (H^+) (1 g) was added and stirring was continued, at the same temperature, for 15 min. The cooled product was filtered and concentrated to a syrup (7 g). This material (2 g) was fractionated on a silicic acid column (6.5 × 80 cm), using chloroform-ethanol, 3:1, as irrigant. The fractionation was followed polarimetrically and by TLC (same solvent system). The furanoside fraction (350 mg), R_F 0.50, had $[\alpha]_{578}^{20}$ +82° (*c* 2.0, water) and the pyranoside fraction (1.0 g), R_F 0.45, had $[\alpha]_{578}^{20}$ +90°. The conditions for the glucosidation reaction seemed to be close to optimal ones for furanoside formation. Higher temperatures or longer reaction times reduced the yield and also caused discolouration of the reaction mixture.

A solution of the furanoside fraction (250 mg) in a mixture of ethanol (15 ml) and 2 M aqueous sodium hydroxide (15 ml) was refluxed for 4 h, cooled, deionised with Dowex 50 (H^+) and Dowex 3 (free base) and concentrated. The remaining syrup crystallised spontaneously and after crystallisation from ethanol yielded pure III (145 mg), m.p. 218–220°, $[\alpha]_{578}^{20}$ −56° (*c* 2.0, water), indistinguishable (TCL, GLC, mixed m.p., IR) from the substance obtained from the internal glucosidation.

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