Formation of Methyl α-L-Arabinopyranoside on Alkaline Treatment of Methyl α-L-Arabinofuranoside

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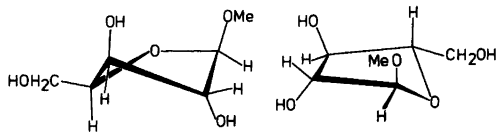
On treatment of methyl α-L-arabinofuranoside with alkali, some methyl α-L-arabinopyranoside is formed. A possible mechanism for this reaction is proposed. Some aspects of the alkaline hydrolysis of glycosides are discussed.

Although alkyl glycosides are considered to be stable to alkali, they are hydrolysed and degraded under drastic conditions, *e.g.* strong alkali and 170 °C. An investigation of anomeric methyl aldopyranosides [1] demonstrated that the anomer in which OH-2 and the aglycone are *trans*-disposed was most reactive, indicating that the intermediate formation of the 1,2-anhydropyranose is of major importance. When OH-2 and the aglycone are equatorial in the most stable chair form (*e.g.* $^4C_1$ for methyl β-D-glucopyranoside) the glycoside has to assume the alternate conformation ($^1C_4$) before reaction can occur. The relative rates for alkaline hydrolysis of the *trans*-glycopyranosides therefore depend upon the free-energy differences between the two chair forms. Studies of other pyranosides [2] supported this assumption but demonstrated that other routes for the alkaline hydrolysis may also be significant.

Methyl aldofuranosides in which OH-2 and the aglycone are *trans*-disposed reacted much faster that the corresponding pyranosides.[3] The β-D-xylofuranoside and the β-D-glucofuranoside were considerably more reactive than the α-L-arabinofuranoside and the β-D-galactofuranoside. The conformations of the methyl aldofuranosides in aqueous solution have recently been investigated by Angyal,[4] by examination of their ^{1}H NMR spectra. He found that the β-D-xylo- (*1*) and β-D-glucofuranosides assume the $^3T_2$ conformation and that the α-L-arabino- (*2*) and β-D-galactofuranosides assume the E_0 conformation. As the energy differences between the different twist and envelope forms are small, this means that the furanoside will occupy a segment of the pseudorotational itinerary, centered around the conformation indicated.[5] Cyr and Perlin,[6] who studied the conformations of the methyl aldofuranosides by examining their ^{13}C NMR spectra, arrived at similar results.



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In the favoured $^3T_2$ conformation of methyl β-D-xylofuranoside (*1*) and methyl β-D-glucofuranoside, OH-2 and the aglycone are pseudoaxial. In methyl α-L-arabinofuranoside (*2*) and methyl β-D-galactofuranoside, in the favoured E_0 conformation, the aglycone takes up a pseudoaxial and OH-2 an isoclinal orientation. The favoured conformation of the two former furanosides is therefore closer to the transition state for the formation of a 1,2-anhydrofuranose, and the higher reactivity of these furanosides is thus comprehensible.

An unexpected result was the observation that some methyl β-D-xylopyranoside was formed on alkaline treatment of methyl β-D-xylofuranoside.[3] Unidentified neutral components were also formed in low yields on alkaline treatment of other furanosides. Although part of these products could have been impurities in the starting material which had become enriched, it seemed more likely that they were actually reaction products. This problem has now been reinvestigated for the alkaline hydrolysis of methyl α-L-arabinofuranoside (*2*).

The purity of the starting material *2* was checked by GLC of its triacetate. The isomeric methyl-L-arabinosides were well-separated from *2* on the columns used and it was concluded that the sample contained about 0.2% of the β-furanoside, 0.1% of the β-pyranoside and virtually no (<0.1%) α-pyranoside. After treatment with 2.65 M aqueous sodium hydroxide at 170 °C for 10 h, 20% of neutral material was recovered, most of which (93%) consisted of unchanged *2*. After partial removal of this by successive crystallisations, the remainder yielded raw crystals of the main neutral reaction product, methyl α-L-arabinopyranoside (*4*), in about 2% yield calculated on the amount of starting material. Recrystallisation gave pure *4* in 0.3% yield. The sample was indistinguishable from authentic material (optical rotation, m.p., mixed m.p., ^{1}H and ^{13}C NMR, GLC-MS of the triacetate). Considering that the α-pyranoside is also degraded during the reaction, at about one third of the rate of the furnoside, the actual amount of pyranoside formed should be greater than 2%.

In a series of experiments, the amounts of *2* and *4* after different reaction times were determined by GLC (Fig. 1). First order kinetics with respect to *2*

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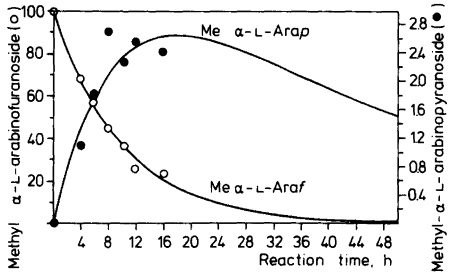
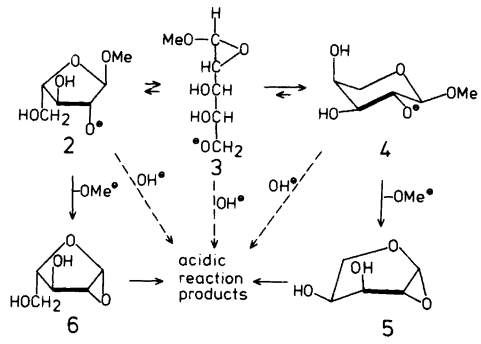


Fig. 1. Percentages of remaining starting material and of methyl α-L-arabinopyranoside on alkaline treatment of methyl α-L-arabinofuranoside. The curves are theoretically derived from calculated reaction constants.



Scheme 1.

and *4*, respectively, were assumed for the rate determining steps, namely:

$2 \xrightarrow{k_1} 4$

$4 \xrightarrow{k_2}$ degradation products

$2 \xrightarrow{k_3}$ degradation products

The value for k_2, $6{,}4 \times 10^{-6}$ s^{-1} was taken from Ref. 1, and those for k_1, 1.2×10^{-6} s^{-1} and k_3, 26 $\times 10^{-6}$ s^{-1}, were determined by regression analysis. A comparison between the observed points and the calculated yield curves (Fig. 1) shows that the agreement is not very good for *4*. This is most probably due both to uncertainties in the analyses and to deviations from the assumed pseudo-first order kinetics. The maximum yield of *4*, however, seems to be approximately 2.6%.

The most reasonable mechanism by which *4* is formed seems to be a nucleophilic attack of O^--2 upon C-1, but which cleavage of the linkage between C-1 and the ring oxygen, yielding the epoxide *3* (Scheme 1). This is rapidly opened during the reaction conditions, in part by intramolecular reaction with O^--5 and formation of pyranoside (*4*). The two consecutive inversions at C-1 result in an unaltered configuration. The previously observed formation of methyl β-D-xylopyranoside[3] from *1* should be quite analogous. Moreover, the formation of levoglucosan[3] from methyl β-D-glucofuranoside probably proceeds *via* methyl β-D-glucopyranoside.

Summing up, it can be assumed that *2* reacts through the pathways indicated in Scheme 1. The formation of *4* has now been demonstrated and that *5* is an intermediate was indicated by indirect evidence.[1,2] The assumption of the analogous 1,2-anhydro-β-L-arabinofuranoside (*6*) seems to be reasonable. Furthermore, a direct attack of a hydroxyl ion on C-1, with release of the aglycon, cannot be excluded. Any alkaline hydrolysis of the glycosidic links will result in formation of arabinose, the fast degradation of which into acids is well-known.

The alkaline hydrolysis of the methyl *trans*-glycosides is only 2.5 – 10 times faster than that of the *cis*-glycosides. One of the mechanisms by which the latter may react involves intermediate formation of an acyclic 1,2-epoxide with retention of the aglycone, as discussed above for the furanosides. This may account for the relatively high reactivity of these glycosides.

Experimental. Methyl α-L-arabinofuranoside was synthesised *via* its tribenzoate as described for the D-enantiomer by Wright and Khorana.[7] Both the benzoate and the free arabinoside were crystallised three times. Methyl α-L- and β-L-arabinopyranosides were prepared by a Koenigs-Knorr synthesis[8] and a Fischer synthesis,[9] respectively.

Quantitative GLC analyses of acetylated glycosides were performed by using packed columns of 3% SP-2340 on 100/200 Supelcoport, and 5% EGS on Chromosorb W. The mass spectrometer, Finnigan type 1020, was coupled to a GLC capillary column containing OV 225.

The alkaline treatments were carried out as described earlier.[2] However, in the kinetic series, performed on a 200 mg scale, pentaerythritol (300 mg) was added as an internal standard to the reaction mixture after the heating. The hydrolysates were deionised as described earlier,[2] and concentrated to dryness.

In the kinetic series, the dry residues were acetylated with acetic anhydride – pyridine, 1:1, before analysis, as were also small aliquots from the product of the preparative experiment.

In the preparative experiment, *2* (10 g) in 2.65 *M* aqueous sodium hydroxide (100 ml) was heated at 170 °C for 10 h. The solution was deionised and concentrated. The neutral product (2.0 g), which

according to GLC analysis contained unchanged *2* as the main component and approximately 6% *4*, was fractionated by crystallisations from ethyl acetate. Pure *4* (30 mg) was isolated and showed m.p. 131 – 134 °C and $[\alpha]_D^{22}$ +17°, in good agreement with published values.[9]

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