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THE ABSENCE OF PROTON EXCHANGE DURING THE CONVERSION OF HEXOSE TO 5-(HYDROXYMETHYL)-2-FURALDEHYDE[a]

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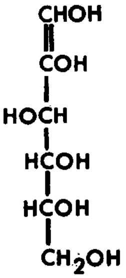
3-Deoxyglycosuloses such as III have been proposed as intermediates in the alkaline degradation of sugars to saccharinic acids, dehydration reactions leading to the formation of 2-furaldehyde derivatives[1] and in the decomposition of Amadori products[1,2]. It has been suggested[3] that, in a substantial portion of the dehydration reaction pathway, III participates by undergoing reversible equilibration with II (cis form) which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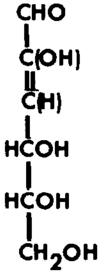
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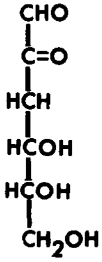
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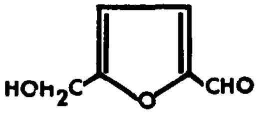
IV

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undergoes further dehydration between C-3 and C-4 to form the 3,4-dideoxy-glycosulos-3-ene followed by its conversion to 5-(hydroxymethyl)-2-furaldehyde (IV).

Although III is usually considered to arise from the hexose 1,2-enediol (I) via either the cis or trans enolic form (II), a recent report[4] indicates that III could arise alternately from D-glucose via a 2 → 3 hydride shift mechanism. We have attempted to access the importance of III, formed by either mechanism, in the overall dehydration reaction. The former possibility was investigated by converting both D-fructose and D-glucose to IV in acidified deuterium oxide solution. The possibility of III, formed via a 2,3 hydride shift, as a reaction intermediate was examined by preparation and characterization of D-glucose-2-H^2 and its subsequent conversion to IV in aqueous acid. In either case, the amount of deuterium incorporated at position 3 of IV would be expected to reflect the importance of III as a reaction intermediate.

Both D-hexoses were converted to IV in deuterium oxide 0.0285N in sulfuric acid by heating at 250° for 90 seconds. IV was obtained in crude form by ether extraction and was converted to the furoic acid by mild air oxidation[5] prior to isolation as 5-(hydroxymethyl)-2-furoic acid. After esterification with diazomethane, deuterium incorporation measurements were made by n.m.r. spectrometry at 60 MH_z using chloroform-d solutions at a concentration of 150 g. per 1. Using an authentic sample of methyl 5-(hydroxymethyl)-2-furoate the ring protons appeared as doublets centered at δ 7.75 (relative to tetramethyl silane), J3.5H_z (C-3) and at δ 6.96, J3.5H_z (C-4) and the carbon bound hydroxymethyl protons as a singlet at δ 5.05. In the case of the furoic acid isolated during the above experiments the signal intensities from the protons at these three positions were compared with one another and with the methyl ester protons at δ 4.19, and, no deuterium incorporation could be detected in the IV derived from either hexose.

D-Fructose-6-phosphate was converted to crystalline D-glucose-6-phosphate specifically deuterated at C-2 using the phosphohexose isomerase reaction in deuterium oxide solution essentially as described by Topper[6]. After digestion with alkaline phosphatase, chromatographically pure D-glucose-2-H^2 was isolated in an overall yield of 15%. The α-pentaacetate of this material was chromatographically identical to α-D-glucose pentaacetate and its n.m.r. spectrum in chloroform-d showed the anomeric proton as a singlet at δ 6.23 instead of the normally observed[7] doublet, thus confirming its strucutre as D-glucose-2-H^2. The IV derived from this compound was, again, devoid of carbon bound deuterium. The recovery of unreacted D-glucose-2-H^2 at the end of the experiment further showed that deuterium loss did not occur by a reversible equilibration of the sugar with solvent protons.

Anet[3] has suggested that, for the dehydration of D-fructose at 100° in 0.02N oxalic acid, about 50% of the total IV formed could have arisen via II (cis form) without prior equilibration, but that a substantial amount of IV is formed via III. Since the experiments described in this report were done at 250°, the conversion of D-fructose to IV was repeated at the conditions used by Anet[3] in his studies on the dehydration reaction, i.e. in 0.02N oxalic acid at 100°. IV was isolated and the deuterium incorporation measurements made as described above. No measurable deuterium incorporation could be detected.

Using the above figures, which are accurate to ±0.1 atom of deuterium per molecular position, we cannot substantiate the presence of 3-deoxyglucosulose as a major reaction intermediate. Yet to be considered is the possibility that III is a minor contributor to the reaction, i.e. being responsible for less than 20% of the total yield or that III could be formed by an as yet unconsidered mechanism. The formation of III by hydride shift mechanisms seems unlikely however, and, it is noteworthy in this respect that the suggestions that Amadori products give rise to

III by a 1,3 hydride shift mechanism has recently been refuted.[8]

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