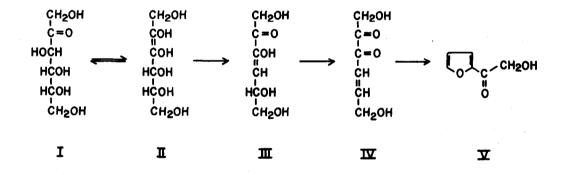
AN INTRAMOLECULAR HYDROGEN TRANSFER DURING THE CONVERSION OF D-GLUCOSE TO 2-(HYDROXYACETYL)-FURAN^a Donald W. Harris and Milton S. Feather Department of Agricultural Chemistry, University of Missouri, Columbia, Mo. 65201

(Received in USA 25 August 1972; received in UK for publication 23 October 1972)

Both 5-(hydroxymethyl)-2-furaldehyde and 2-(hydroxyacetyl)-furan (V) are produced from hexoses on treatment with aqueous mineral acid at elevated temperatures. V Is produced in yields of less than 1% from \underline{D} -fructose¹ and in substantially lower yields from \underline{D} -glucose. The probable mechanism² for the



^aContribution from the Missouri Agricultural Experiment Station. Journal Paper No. <u>6475</u>. formation of V from <u>p</u>-fructose (I) is shown below and involves the conversion of the ketose (I) to the 2,3-enediol (II) which undergoes dehydration to the enolic form (III) of 4-deoxy-<u>p</u>-glycero-2,3-hexodiulose and thence to V via the 4-eneose (IV). The mechanism is analogous to that proposed² for the formation of 2-furaldehydes from hexoses, a reaction which is similar to the one considered here and which has had considerable experimental verification^{2,3}. The fact that V is produced in much lower yield from <u>p</u>-glucose than from I¹ probably stems from the fact that the aldose must first be converted to the ketose via the 1,2-enediol⁴, followed by subsequent decomposition through intermediates II - IV.

As part of our studies on the mechanism of sugar dehydration reactions, we have attempted to evaluate the above pathway with respect to the extent of equilibration of I with II as well as that of III with its keto form, by performing the conversions in acidified tritiated water followed by a determination of the amount and position of carbon bound isotope acquired. Thus, 200 g of <u>p</u>-fructose was dissolved in 2 1 of tritiated water (0.75 µc per mmole) which was 2 <u>N</u> in H₂SO₄ and heated for 2.0 hr at 100°. Chloroform extraction and sublimation gave 50 mg of V (mp = 79°, λ max = 270 nm, \in = 13,500) having a TLC mobility on silica gel HF, using chloroform-acetic acid (9:1) as irrigant, identical to an authentic sample. Similar treatment of <u>p</u>-glucose gave about 5 mg of V which was isolated by preparative TLC and identified by its TLC flow rate and UV spectrum. The V obtained from either source was essentially devoid of any carbon bound tritium, having less than 6% the activity of the solvent.

Since it is generally conceded that the hydroxymethyl carbon atom of V corresponds to C-l of the starting sugar², the results indicate that one of the carbon-bound hydrogens on this group, when it is derived from C-l of <u>p</u>-glucose, arises from an intramolecular source and not from the solvent. To examine this possibility, <u>p</u>-glucose, specifically tritiated at C-2 was prepared by converting <u>p</u>-fructose-<u>6</u>-phosphate to <u>p</u>-glucose-6-phosphate-2-H³ using phosphoglucose isomerase^{3,5} in tritiated water, followed by treatment of the latter material with alkaline phosphatase³. The <u>p</u>-glucose-2-H³ so obtained (40g) was diluted

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with inert material to give 200 g of D-glucose-2-H³ having a specific activity of 0.916 μ c per mmole. This was treated with 2 1. of 2.0 <u>N</u> H₂SO₄ at 100⁰ for 3 hr and the resulting V isolated by chloroform extraction. This procedure was repeated 9 times and each sample, which constituted about 5 mg, was separately isolated and a 2 mg sample counted. The first 2 samples had specific activities of 1.56 and 0.54 μ c per mmole respectively and were discarded since they could have been derived from small amounts of contaminating D-fructose-1-H³ which could have been present in the preparation as a result of the preparative process. Samples 4-9, all of which were labeled to the same extent, (average specific activity = 0.21 μ c per manole) were pooled, diluted with 200 mg of inert V and recrystallized from hexane to give a preparation having a specific activity of 2.52 x 10^{-2} µc per mmole. This material, on periodate oxidation, gave 2-furoic acid (mp = 128-29⁰) having a TLC mobility identical to an authentic standard. After purification by sublimation (0.25 mm and 80⁰) this material had a specific activity of 7.49 x 10^{-4} µc per mmole, or less than 3.0% the activity of the V from which it was obtained, thus indicating that the tritium had migrated from C-2 of the D-glucose to the carbon atom corresponding to C-1 during the dehydration.

The conversion of \underline{D} -glucose to non-radioactive V in acidified tritiated water indicates that the intramolecular transfer is quantitative; the specific activity of the starting \underline{D} -glucose-2-H³ compared to the V obtained from it indicates a tritium isotope effect (K H/K_H³) of 4.3 for the transfer. The most logical step for such a transfer to occur is in the isomerization of \underline{D} -glucose to I during the reaction. Transfer reactions of this type have been observed during biological transformations involving isomerase enzymes, some of which effect a complete transfer of hydrogen from C-2 of the aldose to C-1 of the ketose^{6,7} and some only a partial transfer with some solvent exchange occurring⁸. Although the enzymatic reactions were originally discussed in terms of a hydride shift mechanism⁸ which is inconsistant with a 1,2-enediol intermediate, more recent mechanisms⁹ have been presented which are based on the presence of 1,2-enediols, indicating that such isomerizations would involve a transfer of a proton rather than a hydride ion. Gleason and Barker¹⁰ have recently reported a partial transfer from C-2 to C-1 during the interconversion of \underline{P} -ribose-2-H³ and \underline{P} -arabinose in alkaline solution and discussed this in terms of a hydride shift mechanism. It cannot be stated with certainty whether the transfer observed here involves a hydride shift or a proton transfer, but the results suggest that aldose-ketose isomerizations, particularly those occurring in acid solution merit further investigation.

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