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AN INTRAMOLECULAR HYDROGEN TRANSFER DURING THE CONVERSION OF D-GLUCOSE TO 2-(HYDROXYACETYL)-FURAN[a]

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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 D-fructose[1] and in substantially lower yields from D-glucose. The probable mechanism[2] for the

I ⇌ II → III → IV → V

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formation of V from D-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-D-glycero-2,3-hexodiulose and thence to V via the 4-eneose (IV). The mechanism is analogous to that proposed[2] 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 D-glucose than from I[1] probably stems from the fact that the aldose must first be converted to the ketose via the 1,2-enediol[4], 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 D-fructose was dissolved in 2 l of tritiated water (0.75 μc per mmole) which was 2 N in H_2SO_4 and heated for 2.0 hr at 100°. Chloroform extraction and sublimation gave 50 mg of V (mp = 79°, λ max = 270 nm, ϵ = 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 D-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-1 of the starting sugar[2], the results indicate that one of the carbon-bound hydrogens on this group, when it is derived from C-1 of D-glucose, arises from an intramolecular source and not from the solvent. To examine this possibility, D-glucose, specifically tritiated at C-2 was prepared by converting D-fructose-6-phosphate to D-glucose-6-phosphate-2-H^3 using phosphoglucose isomerase[3,5] in tritiated water, followed by treatment of the latter material with alkaline phosphatase[3]. The D-glucose-2-H^3 so obtained (40g) was diluted

with inert material to give 200 g of D-glucose-2-H^3 having a specific activity of 0.916 μc per mmole. This was treated with 2 l. of 2.0 N H_2SO_4 at 100° 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 μc per mmole respectively and were discarded since they could have been derived from small amounts of contaminating D-fructose-1-H^3 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 μc per mmole) 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 = 128-29°) having a TLC mobility identical to an authentic standard. After purification by sublimation (0.25 mm and 80°) 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 D-glucose to non-radioactive V in acidified tritiated water indicates that the intramolecular transfer is quantitative; the specific activity of the starting D-glucose-2-H^3 compared to the V obtained from it indicates a tritium isotope effect ($^{K}H/K_{H}3$) of 4.3 for the transfer. The most logical step for such a transfer to occur is in the isomerization of 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 occurring[8]. Although the enzymatic reactions were originally discussed in terms of a hydride shift mechanism[8] which is inconsistant with a 1,2-enediol intermediate, more recent mechanisms[9] 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 Barker[10] have recently reported a partial transfer from C-2 to C-1 during the interconversion of D-ribose-2-H^3 and D-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.

REFERENCES

1. R. E. Miller and S. M. Cantor, J. Am. Chem. Soc., 74, 5236 (1952).
2. E. F. L. J. Anet, Adv. Carbohyd. Chem. 19, 181 (1964), and references therein.
3. M. S. Feather and J. F. Harris, Carbohydrate Res., 15, 304 (1970).
4. J. C. Speck, Jr., Advan. Carbohyd. Chem., 13, 63 (1958).
5. Y. J. Topper, J. Biol. Chem., 225, 419 (1957).
6. M. S. Feather, V. Deshpande and M. J. Lybyer, Biochem. Biophys. Res. Comm., 38, 859 (1970).
7. A. S. Mildvan and I. A. Rose, Fed. Proc., 28, 534 (1969).
8. I. A. Rose and E. L. O'Connell, J. Biol. Chem., 236, 3086 (1961).
9. K. J. Schray and I. A. Rose, Biochemistry, 10, 1058 (1971), and references therein.
10. W. G. Gleason and R. Barker, Can. J. Chem., 49, 1432 (1971).