PROTON EXCHANGE DURING THE CONVERSION OF HEXOSE INTO 5-HYDROXYMETHYL-2-FURALDEHYDE
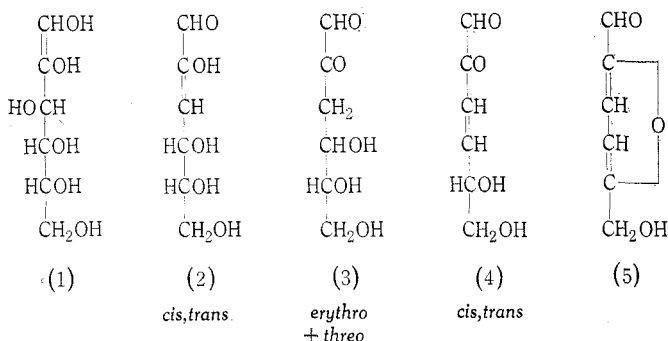
By E. F. L. J. Anet*

Feather and Harris[1] have reported that when hexoses are treated with acid in deuterium oxide solution to form 5-hydroxymethyl-2-furaldehyde (5), less than 10% deuterium is incorporated at position 3 of (5); and that therefore the 3-deoxy-glycosuloses (3)† do not participate (<20%) in the dehydration of hexoses to (5).

Because they have ignored isotope effects, in particular the primary kinetic isotope effect, this extension of their results, to the reaction with water as a solvent may not be justified.
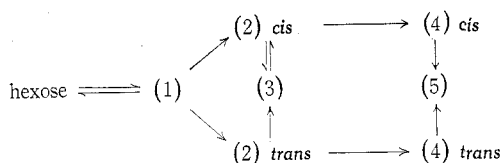
Scheme 1.—Mechanism of formation of 5-hydroxymethyl-2-furaldehyde.[2] In H_2O, 38% of (5) arises from (3) and 10% from (4) trans.

If the rate-limiting step of the reaction (2) → (3) (Scheme 1, see[2]) involves, as expected, the formation of a C–H bond, then the rate should show a primary

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† Before international rules of nomenclature were formulated several names were in use for some of the compounds in this communication: (3) are 3-deoxyhexos-2-uloses (formerly, 3-deoxyhexosones, "3-deoxyglucosone" etc.); (4) are 3,4-dideoxyhex-3-enos-2-uloses (3,4-dideoxyhexosulos-3-enes, 3,4-dideoxy-Δ^3-hexosones, 3,4-didehydro-3,4-dideoxyhexosuloses). Specific compounds require the addition of a configurational prefix such as D-erythro.

1 Feather, M. S., and Harris, J. F., Tetrahedron Lett., 1968, 5807.

2 Anet, E. F. L. J., Aust. J. Chem., 1965, 18, 240; Adv. Carbohyd. Chem., 1964, 19, 181.

kinetic isotope effect, i.e. k_D/k_H is usually more than 6.[3] On changing the solvent from H_2O to D_2O, if the rate of the competitive reaction (2) → (4) is not affected,* the total amount of (3) formed should decrease by a factor of c. 6. The proportion of (5) arising from (3), found to be 38% in H_2O,[2] will become < 7%. Therefore the results of Feather and Harris[1] (< 20%) are not in disagreement with the previous mechanism.[2]

Similarly, if a primary kinetic isotope effect slows the reaction (1) → hexose, when D_2O is the solvent, the concentration of (1) will rise; thus the rates of formation and the concentrations of (2), (4), and (5) will also increase. If no other isotope effects are present the increase will be equal (those of (4) *trans* and (5) are c. 1·6 higher, see Table 1). The faster overall rate for the reaction in D_2O could possibly be due to a higher concentration of the acyclic form of D-fructose and/or to specific acid catalysis.

TABLE 1

PRODUCTS FROM D-FRUCTOSE HEATED IN OXALIC ACID 0·01M AT 100°

Expressed as mmol/mol D-fructose

Conditions	(3)	(4) *trans*	(5)	(5)/(3)	(5)/(4) *trans*
H_2O, 135 min	1·4	0·35	6·5	4·6	18·5
D_2O, 135 min	0·8	0·60	10·6	13·3	17·7
H_2O, 220 min	2·1	0·45	10·6	5·0	23·8
D_2O, 220 min	1·4	0·70	17·4	12·4	25·0

The concentration of (3) will not be c. 6 times lower in D_2O than in H_2O because the rate of formation of (2) is higher, and because (3) will enolize more slowly since one of the hydrogen atoms of the methylene group at C3 is replaced by a deuterium atom.

The results from the following experiments indicate that the above isotope effects are probably operative in the acid-catalysed formation of 2-furaldehydes from sugars. The reaction is too complex to be treated in a more exact manner, but it is obvious that the part played by (3) is altered by changing the solvent from H_2O to D_2O, in contrast to that of (4) *trans* (see Table 1).

Experimental

Solutions (20 ml) of D-fructose (0·3M) in H_2O or D_2O containing oxalic acid (0·01M) were heated at 100° for 135 or 220 min and cooled. The reaction mixtures were treated with 2,4-dinitrophenylhydrazine (2% in 30% perchloric acid) for 3 min and filtered. The precipitates were washed with 15% perchloric acid, then with water, and dried. The resulting mixtures of hydrazones were dissolved in tetrahydrofuran and determined by t.l.c.[4] The t.l.c. plates (20 by 20 cm) were coated with silica gel, and the adsorbent was cut to give a separate strip for each

* The reactions hexose → (1) → (2) → (4) → (5) are probably not subject to primary kinetic isotope effects because the formation or rupture of C–D bonds are unlikely to be involved as rate-controlling steps,[3] at least in the early stages of the dehydration. Other isotope effects may cause changes in the rates of these reactions.

[3] Westheimer, F. H., *Chem. Rev.*, 1961, **61**, 265.

[4] Anet, E. F. L. J., *J. Chromat.*, 1962, **9**, 291.

applied spot. After development with toluene–ethyl acetate (1:1 for derivatives of (3) and 3:1 for those of (4)) for 15 cm the plates were air-dried and the required hydrazones scraped off. The hydrazones were eluted with tetrahydrofuran and determined from the absorbances at 435 nm.

The t.l.c. plates were normally air-dried before development when the derivatives from the D-*erythro* and D-*threo* isomers of (3) were not resolved, but by equilibrating the plates at 70% relative humidity before development the two isomers were clearly separated. The ratios of the isomers did not appear to vary for the different treatments.

The rates of formation of (5) were followed by examining smaller volumes of D-fructose solutions heated in ampoules (1 ml) for various times. The cooled ampoules were smashed, the contents diluted with water, and the absorbances of free (5) read at 284 nm (ϵ 16500). The rates were first order up to 4 hr.