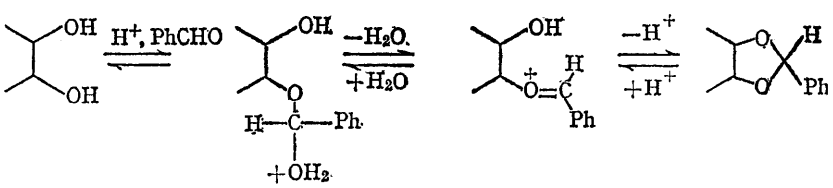
Observations on Cyclic Acetal Formation and Migration

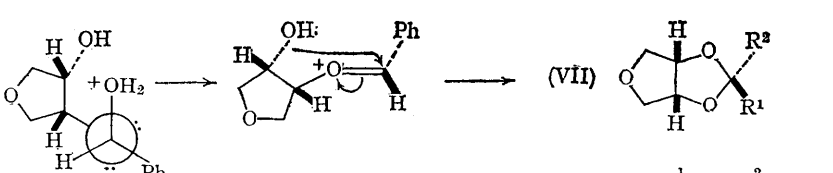
By F. S. AL-JEBOURY, N. BAGGETT, A. B. FOSTER, and J. M. WEBBER
(*The Chemistry Department, The University, Birmingham*)

LITTLE is known of the course of the acid-catalysed reaction of aldehydes with polyhydric alcohols although the molecular situation at equilibrium is well documented.[1]

Benzylidenation of 1,4-anhydroerythritol under homogeneous conditions[2] at 25—30° in nitromethane containing toluene-*p*-sulphonic acid was conveniently followed by observing the appearance of the benzyl proton signals in the n.m.r. spectrum. Under suitable conditions, there was rapid development of a signal at relatively high field (τ 4·96, 6% of tetramethylsilane in chloroform as external reference) followed by the slow appearance of a signal at τ 4·67 paralleled by diminution in intensity of the first signal. At equilibrium, the two signals were of comparable integrated area. For reasons detailed elsewhere,[3] the benzylidene derivatives (VII, *endo*-Ph) and (VIII, *exo*-Ph), both of which have been isolated crystalline,[2,3] have been associated with the high- and low-field benzyl proton signals (τ 4·96 and 4·67) respectively. Similar results were observed when dimethylformamide or t-butyl alcohol was used as solvent and also with cyclohexane-*cis*-1,2-diol. The



(I) (II) (III) (IV)



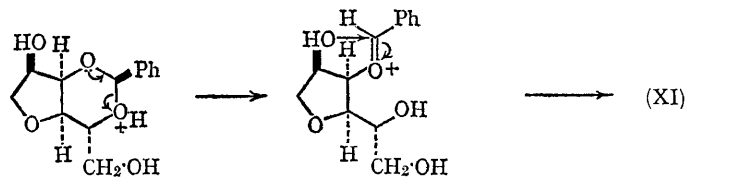
(V) (VI)

(VII) R^1=H, R^2=Ph
(VIII) R^1=Ph, R^2=H

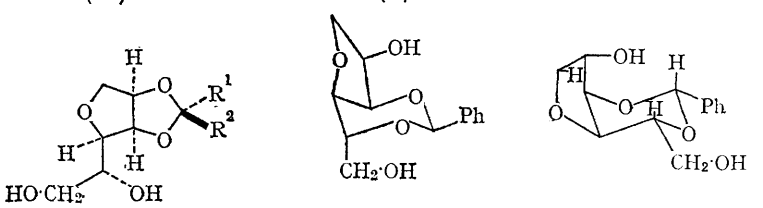
[1] J. A. Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.
[2] N. Baggett, A. B. Foster, J. M. Webber, D. Lipkin, and B. E. Phillips, *Chem. and Ind.*, 1965, 136.
[3] N. Baggett, K. W. Buck, A. B. Foster, M. H. Randall, and J. M. Webber, *Proc. Chem. Soc.*, 1964, 118; *J. Chem. Soc.*, 1965, 3394.

selective formation of isomer (VII) reflects initial kinetic control.

Acid-catalysed benzylidenation may be represented[4] by the sequence (I) → (IV) and if, as seems reasonable, the loss of water from the protonated hemiacetal (II) is followed by rapid cyclization of the oxonium ion (III) then the steric result in the kinetic phase can be rationalized. Loss of water from the preferred conformation (V) of one enantiomorph of the protonated hemiacetal



(IX) (X) (XI)



(XIII) (XIV)

(XI) R^1=H,R^2=Ph
(XII) R^1=Ph,R^2=H

(or of the alternative structure with H and H_2O^+ attached to the acetal carbon atom interchanged) derived from 1,4-anhydroerythritol affords the transoid oxonium ion (VI) in which the hydroxyl group is well placed for nucleophilic attack on the upper side of the acetal carbon atom to afford the benzylidene derivative (VII, *endo*-Ph). On the other hand, substantial rotation about the C–O$^+$ bond would be necessary to allow similar attack from the opposite side of the acetal carbon atom to afford isomer (VIII, *exo*-Ph).

The retention of configuration at the glycosidic centre in the acid-catalysed conversion[5] of methyl 3,6-anhydro-α-D-glucopyranoside into the α-furanoside may be explained by a mechanism closely similar to that detailed above.

Oxonium ions of the type (III) will also be formed in acid-catalysed acetal migrations and, providing that 1,3-dioxolan derivatives are formed, a steric result related to that described above should occur. Dissolution of 1,4-anhydro-3,5-*O*-benzylidene-D-mannitol (m.p. 143°, $[\alpha]_D$ + 42° in H_2O) in acetic acid causes rearrangement to a 2,3-*O*-benzylidene derivative[6] of unknown stereochemistry. It was found that at 25—30° in dimethylformamide containing toluene-*p*-sulphonic acid the low-field benzyl proton signal (τ 4·35) of the 3,5-*O*-benzylidene derivative was replaced by one at relatively high field (4·54) for the known[6] 2,3-acetal (m.p. 94—95°, $[\alpha]_D$ − 96° in H_2O) which may be assigned[3] the structure (XI, *endo*-Ph). Prolonged exposure of compound (XI) to acid caused equilibration of the 2,3-*O*-benzylidene group as indicated by the appearance of a second benzyl proton signal at relatively low field (τ 4·35) corresponding to the hitherto unknown isomer (XII, *exo*-Ph) (m.p. 111—112°, $[\alpha]_D$ − 40° in H_2O) isolated after chromatography on silica gel. A clear parallel is provided with the benzylidenation of 1,4-anhydroerythritol.

1,4-Anhydro-3,5-*O*-benzylidene-D-mannitol would be expected[1] to have an "O"-inside structure (XIII) with an *eq.* phenyl and an *ax.* hydroxymethyl group rather than an "H"-inside structure (XIV) with *eq.* phenyl and hydroxymethyl groups. Because of deshielding effects[3] each structure would have a benzyl proton signal at relatively low field. However, only the transoid oxonium

[4] *Cf.* J. T. Edward, *Chem. and Ind.*, 1955, 1102.
[5] W. N. Haworth, L. N. Owen, and F. Smith, *J. Chem. Soc.*, 1941, 88.
[6] R. E. Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 2858.

ion (X) derived from the appropriately protonated 3,5-*O*-benzylidene compound (IX) with the "O"-inside structure would recyclize to give the actually observed first product, *viz.* the 2,3-*O*-benzylidene acetal (XI, *endo*-Ph), whereas the corresponding sequence with the "H"-inside structure would give isomer (XII, *exo*-Ph). Thus, in certain cases, the steric result of acetal migrations may provide information about structure and conformation not otherwise easily obtainable.

Other acetal migrations are being studied.

(*Received, April 21st*, 1965.)