A DETAILED INVESTIGATION OF THE ACID-CATALYSED FORMATION OF ACETALS FROM ACETONE AND D-GLUCITOL

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ABSTRACT

The acid-catalysed acetonation of D-glucitol has been studied in detail. The true complexity of the reaction, giving the 1,2- and 3,4-monoacetals, the 1,2:3,4-, 3,4:5,6-, and 1,2:5,6-diacetals, and the 1,2:3,4:5,6-triacetal, has been shown. These studies have been carried out mainly by gas–liquid chromatographic techniques, and have shown that, with acetone, the primary hydroxyl group at C-1 is more reactive than that at C-6. The structures of the various acetals have been verified by p.m.r. spectroscopy.

INTRODUCTION

The first product reported from the acetonation of D-glucitol was the triacetal isolated by Speier[1] in 1895 by a direct condensation of acetone and D-glucitol in the presence of 1% of hydrogen chloride. Later workers studying this condensation have been able to isolate mono- and di-acetals. Pressman *et al.*[2] obtained the triacetal by sulphuric acid catalysis, but by using zinc chloride as catalyst they isolated the 1,2-mono- and 1,2:5,6-di-*O*-isopropylidene-D-glucitols. Moreover, by further acetonation of the diacetal they were able to obtain the triacetal identical to that first obtained by Speier[1] and so concluded that the triacetal might have the 1,2:3,4:5,6 structure. Bourne *et al.*[3] subjected the above triacetal to partial, acid hydrolysis and isolated 3,4-mono- and 3,4:5,6-di-*O*-isopropylidene-D-glucitol as crystalline products and inferred the presence of 1,2:3,4-di-*O*-isopropylidene-D-glucitol in a syrupy mixture by degradative and paper-chromatographic methods.

The structures of the isopropylidene glucitols which have been isolated were determined classically; subsequent proton magnetic resonance studies have shown that there is no rearrangement during graded, acid hydrolysis of the acetals of D-mannitol[4], and we have now been able to show that the same is true for isopropylidene acetals of D-glucitol.

Additional evidence for the structure of the 1,2- and 3,4-acetals was that the isomers behaved as predicted[5] during ionophoresis in molybdate buffer.

DISCUSSION AND RESULTS

Condensation using zinc chloride

Under anhydrous conditions, zinc chloride acts as a Lewis acid, and the catalytic effect is fairly mild compared to that of concentrated mineral acids.

The only crystalline products isolated from direct condensation of acetone and D-glucitol are the 1,2-mono-, the 1,2:5,6-di-, and the tri-*O*-isopropylidene-D-glucitols. The 1,2-acetal has now been characterised as its crystalline bis(benzeneboronate) in addition to the known tetraacetate and tetrabenzoate. In addition to these acetals, Pressman *et al.*[2] obtained a syrup which settled out before the diacetal crystallised, and which approximated to a diacetal (by elemental analysis); from the low consumption of periodate they concluded that this diacetal could not contain free, vicinal hydroxyl groups. However, in our hands, the syrup obtained at the same point in the reaction was shown to be mainly uncrystallised 1,2:5,6-di-*O*-isopropylidene-D-glucitol. Analysis of the zinc chloride-catalysed reaction by paper chromatography did not yield any further information, whereas thin-layer chromatography (silica gel, butanone saturated with water) revealed three fractions which proved to be the mono-, di-, and tri-acetals. Gas–liquid chromatography, however, showed up the true complexity of this reaction, revealing six products (Fig. 1) after a period of 3 h when the reaction was at equilibrium.

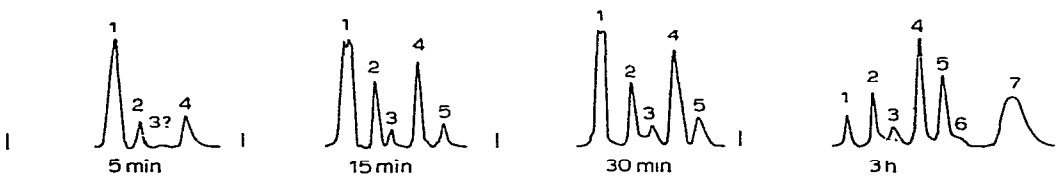


Fig. 1. Progress of the reaction of D-glucitol and acetone in the presence of anhydrous zinc chloride, analysed by g.l.c. 1, D-Glucitol; 2, 1,2-mono-; 3, 3,4-mono-; 4, 1,2:5,6-di-; 5, 1,2:3,4-di-; 6, 3,4:5,6-di-; 7, 1,2:3,4:5,6-tri-acetals.

The reaction was studied by quenching samples at intervals and analysing these by g.l.c. Quenching of the reaction after 5 min showed the presence of two products which, by comparison with standards, were evidently 1,2-mono- and 1,2:5,6-di-*O*-isopropylidene-D-glucitol. Further analysis of the reaction at 15 min, 30 min, and 3 h showed increasing complexity until finally there were six products.

By consideration of the products after reaction for 5 min, it can be seen that the 1,2-mono- and the 1,2:5,6-di-acetal are present in approximately equal amounts, suggesting that there is extremely rapid, initial attack at the primary hydroxyl group followed by cyclisation. The 1,2-monoacetal is present during direct synthesis, but indirect synthesis of the 5,6-monoacetal has shown that this was not detected in the initial and later stages of direct synthesis; the retention value of the per(trimethylsilyl ether) of the 5,6-monoacetal differs from those of all the other acetals.

From this, we may conclude that initial ring formation must be primarily at

HO-1 and HO-2 followed by a rapid formation of the ring at HO-5 and HO-6. As the reaction proceeds, the 3,4-monoacetal is formed together with the 1,2:3,4-and 3,4:5,6-diacetals and the triacetal. By consideration of the relative amounts, the 1,2:5,6-diacetal is finally the second most-abundant acetal and from this it might well be concluded that initial ring formation between HO-1 and HO-2 enhances the reactivity of HO-6 or HO-5 and so promotes the formation of the 5,6-ring. This may either be due to the increased dissolution of the D-glucitol following monoacetal formation or a combination of this effect and conformational effects. It is also possible that intramolecular hydrogen-bonding contributes to the enhanced reactivity.

Condensation using mineral acids

(*a*) *Anhydrous* N,N-*dimethylformamide and hydrogen chloride gas.* — Under anhydrous conditions with equimolar quantities of acetone and D-glucitol, the major product is 1,2-*O*-isopropylidene-D-glucitol with only minor amounts of other acetals (Figs. 2 and 3). This supports the hypothesis that there is initial cyclisation at HO-1 and HO-2.

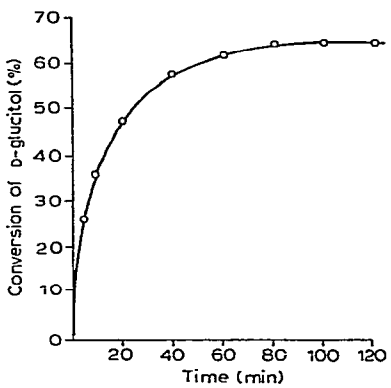


Fig. 2. Progress of the hydrogen chloride (1.11M) catalysed reaction of D-glucitol (1 mol.) and acetone (1 mol.) in anhydrous *N,N*-dimethylformamide at 25°, analysed by g.l.c.

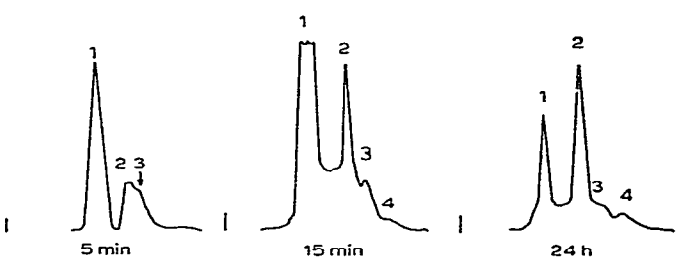


Fig. 3. Progress of the hydrogen chloride (1.11M) catalysed reaction of D-glucitol (1 mol.) and acetone (1 mol.) in anhydrous *N,N*-dimethylformamide at 25°, analysed by g.l.c. Compounds numbered as in Fig. 1.

There is thus a difference between this homogeneous reaction and the heterogeneous, zinc chloride-catalysed reaction in which there is rapid formation of the di- and tri-acetals. This may be due to the fact that, in the zinc chloride-catalysed reaction, D-glucitol is only slightly soluble and it is the soluble portion that reacts preferentially with the excess acetone.

(*b*) *Sulphuric acid.* — The interesting feature of this catalyst is the very rapid formation of triacetal. After reaction for 30 sec (Fig. 4), virtually no D-glucitol remains, and the amounts of mono- and di-acetals are very low.

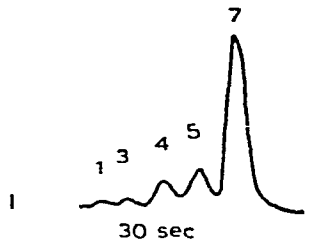


Fig. 4. Progress of the sulphuric acid catalysed reaction of D-glucitol and acetone, analysed by g.l.c. Compounds numbered as in Fig. 1.

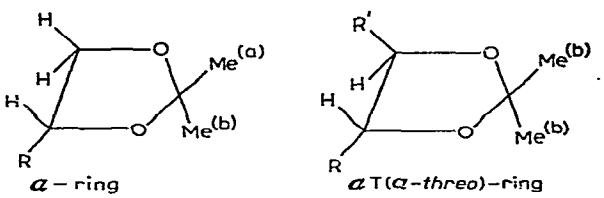
Partial, acid hydrolysis of the triacetal

This work has verified the previous report[3] that the 3,4-mono- and 3,4:5,6-di-*O*-isopropylidene acetals can be isolated as pure, crystalline products from the partial, acid hydrolysis of the 1,2:3,4:5,6-triacetal. Additionally, impure 1,2:3,4-di-acetal has now been isolated from the reaction, and indeed this diacetal is the main, initial product of hydrolysis, as shown by the g.l.c. analysis.

Confirmation of structures by p.m.r. spectroscopy

P.m.r. spectroscopy was used to investigate the environments of the methyl groups in the isopropylidene acetals. The analysis is based on that previously used for other isopropylidene acetals[4].

The 1,2-acetal exhibited equal strength peaks at τ 8.74 and 8.72 which may be assigned to the protons of $Me^{(a)}$ and $Me^{(b)}$, respectively.



The 1,2:5,6-diacetal gave an identical spectrum in terms of peak positions and strengths for the protons of the methyl groups, since there are two $Me^{(a)}$ and two $Me^{(b)}$ groups. On the other hand, there was a single sharp peak at τ 8.73 for the 3,4-acetal; this

αT(α-*threo*)-ring contains two $Me^{(b)}$ groups. The 1,2:3,4:5,6-triacetal has two $Me^{(a)}$ and four $Me^{(b)}$ groups, and it showed signals of relative strength 1:2 at τ 8.73 and 8.70, respectively, with the signal at τ 8.70 slightly shouldered on the downfield side due to the slightly different environments of the $Me^{(b)}$ groups in the 3,4-ring and the two α-rings. The 3,4:5,6-diacetal had signals of relative strength 1:3 at τ 8.74 and 8.73, respectively, due to one $Me^{(a)}$ and three $Me^{(b)}$ groups, with the peak at τ 8.73 slightly shouldered on the upfield side due to the different environments of the α-ring $Me^{(b)}$ compared to that of the two $Me^{(b)}$ groups of the 3,4-ring.

General observations

The mass spectra of the isopropylidene acetals of D-glucitol provided additional evidence of the structures assigned to them, as will be reported later.

Thus we have shown that, in the initial stages of the reaction between D-glucitol and acetone, the 1,2-acetal is preferred to the 3,4- and 5,6-acetals. Moreover, during hydrolysis of the triacetal, the 5,6-ring is the least stable. Clearly, there are steric and/or electronic factors which account for this difference in behaviour between the 1,2 and 5,6 terminal-glycol groups of D-glucitol. Perhaps the explanation lies in the observation[6] that, in the crystal, D-glucitol has a sickle-shaped, carbon–carbon backbone, rather than a planar, extended zig-zag one.

In earlier papers[7], we have shown that the reaction of D-glucitol with various aldehydes gives rise initially to the 2,3-acetals and not to acetals involving primary positions. This behaviour is now shown to be quite different from that of acetone. Our results with D-glucitol find a parallel in the isopropylidenation and benzylidenation of *erythro*- and *threo*-1,2,3-butanetriols[8].

EXPERIMENTAL

Gas–liquid chromatography was usually carried out on a modified Perkin–Elmer Fractometer with a flame-ionisation detector. The stationary support in all cases was Celite. P.m.r. spectra were recorded on a Varian HA 60-IL spectrometer. The solvent was methyl sulphoxide-d_6 with tetramethylsilane as an internal standard ($\tau = 10.00$).

1,2-Mono- and 1,2:5,6-di-*O*-isopropylidene-D-glucitol were prepared according to the method of Pressman *et al.*[2] (Experiment 1). The 3,4-mono-, 3,4:5,6-di-, 1,2:3,4:5,6-tri-, and syrupy mixture of the 3,4:5,6- and 1,2:3,4-di-acetals were prepared according to the method of Bourne *et al.*[3].

On ionophoresis in molybate buffer[5], the 1,2-acetal had the same mobility as D-glucitol, whereas the 3,4-acetal was non-migratory.

1,2-O-Isopropylidene-D-glucitol bis(benzeneboronate). — A solution of the monoacetal (50 mg) and benzeneboronic anhydride (47 mg) in methanol (2 ml) was evaporated. The residue was extracted with light petroleum (b.p. 60–80°), and the extract yielded the bis(benzeneboronate); after several recrystallisations from light petroleum (b.p. 60–80°), the product (51 mg) had m.p. 103–104°, $[\alpha]_D^{26}$ +7.7° (*c* 2.0, pyridine) (Found: C, 64.1; H, 6.1; B, 5.5. $C_{21}H_{24}B_2O_6$ calc.: C, 64.0; H, 6.1; B, 5.5%). There were strong absorptions at 1610[9a], 1450[9b], and 1360[9b] cm^{-1} (KBr disc), characteristic of a benzeneboronate.

5,6-O-Isopropylidene-D-glucitol. — 2,4-*O*-Benzylidene-5,6-*O*-isopropylidene-D-glucitol (5 g, m.p. 183–183.5°; lit.[10] m.p. 179°), prepared from 2,4-*O*-benzylidene-D-glucitol[11], was dissolved in dry methanol, and palladium black (5 g) was added. Hydrogenation was carried out at 4–6 atmospheres at room temperature until no further hydrogen was taken up. The catalyst was filtered off under nitrogen, and the filtrate was evaporated to a colourless syrup which crystallised but which could not be recrystallised. G.l.c. showed it to be pure and different from any other monoisopropylideneglucitol. The compound decomposed rapidly, yielding acetone and D-glucitol, so that no satisfactory elemental analysis was obtained; the product had m.p. 46–48°, $[\alpha]_D^{25}$ +10.8° (*c* 1.05, pyridine).

Investigation of the syrupy diacetal described (Experiment 1) by Pressman et al.[2]. — The syrupy product (1 g), which separated from light petroleum prior to crystallisation of the 1,2:5,6-diacetal, was freeze-dried and dissolved in pyridine (20 ml) cooled in ice, and benzoyl chloride (1.5 ml) was slowly added over 15 min. The mixture was left at room temperature for 24 h and then poured into ice–water to give a syrup which crystallised. Two recrystallisations from ethanol afforded 3,4-di-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-glucitol (1.01 g), m.p. and mixed m.p. 134–134.5°; lit.[2] m.p. 134–135°.

Reaction between D-glucitol and acetone. — (*a*) *In the presence of anhydrous zinc chloride.* Experiment 1[2] was repeated (0.005 × the original scale), aliquots were removed, and the reaction was quenched by addition of aqueous sodium hydroxide after 5, 15, and 30 min, and 3 h. The samples were evaporated to dryness and extracted with pyridine. The extracts were dried and aliquots were converted into the per(trimethylsilyl ethers) in the usual way[12]. These were analysed by g.l.c. using a 10% PPE column at 173° (Fig. 1).

Standard *O*-isopropylidene-D-glucitols gave the following results (retention values relative to D-glucitol): 1,2-monoacetal, 1.24; 3,4-, 1.38; 5,6-, 1.58; 1,2:5,6-diacetal, 1.48; 1,2:3,4-, 1.77; 3,4:5,6-, 1.92; 1,2:3,4:5,6-triacetal, 2.23.

(*b*) *In anhydrous* N,N-*dimethylformamide containing hydrogen chloride.* D-Glucitol (10 g, 1 mol.) was dissolved in *N*,*N*-dimethylformamide containing absorbed hydrogen chloride gas. Acetone (4.035 ml, 1 mol.) was added and the solution made up to 100 ml with *N*,*N*-dimethylformamide. The final reaction medium was 1.11M in acid.

Samples were removed at intervals and analysed by gas–liquid chromatography, using a 5% Apiezon K column at 195° (Figs. 2 and 3).

(*c*) *In the presence of sulphuric acid.* D-Glucitol (1 g) and acetone (10 ml) were mixed, and conc. sulphuric acid (0.2 ml) was added with swirling. The D-glucitol immediately went into solution and, after given periods, aliquots were withdrawn and neutralised. The aliquots were evaporated to yield a syrupy solid which was extracted with pyridine (1 ml). The pyridine solution (0.2 ml) was used to prepare the *O*-trimethylsilyl derivatives which were analysed by g.l.c., using a 5% Apiezon K column at 195° (Fig. 4).

Standards showed the following retention values: D-glucitol, 1.00; 1,2-mono-

acetal, 1.10; 3,4-monoacetal, 1.32; 1,2:5,6-diacetal, 1.84; 1,2:3,4-diacetal, 2.29; triacetal, 2.79.

Samples taken at 15, 20, 30, and 60 min, and 3 h showed no changes in the number of constituents but a higher proportion of tri-*O*-isopropylidene-D-glucitol while the others decreased.

Partial, acid hydrolysis of tri-O-isopropylidene-D-glucitol — Tri-*O*-isopropylidene-D-glucitol (3.23 g) was dissolved in ethanol (80 ml) containing 5M hydrochloric acid (1.6 ml), and the mixture was left at room temperature. Samples (1 ml) were withdrawn, quenched with M sodium hydroxide (1 ml), and analysed as the per(trimethylsilyl ethers) on 5% Apiezon K at 195°.

The initial stages were the most interesting and showed that the main, initial product of hydrolysis was a compound which was shown by comparison with standards to be 1,2:3,4-di-*O*-isopropylidene-D-glucitol.

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